# CARDIOLOGY PHARMACY

## PREPARATORY REVIEW AND RECERTIFICATION COURSE

**2023**

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# American College of Clinical Pharmacy and American Society of Health-System Pharmacists

# Cardiology Pharmacy Preparatory Review and Recertification Course

# American College of Clinical Pharmacy and American Society of Health-System Pharmacists

# Cardiology Pharmacy Preparatory Review and Recertification Course

2023 Edition


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**Continuing Pharmacy Education:**
The American College of Clinical Pharmacy and the American Society of Health-System Pharmacists are accredited by the Accreditation Council for Pharmacy Education as a provider of continuing pharmacy education. The Universal Activity Numbers are 2023 ACCP/ASHP Cardiology Pharmacy Preparatory Review and Recertification Course: Primary Prevention of Cardiovascular Disease and Public Health: 0217-9999-23-080-H01-P; Dyslipidemia: 0217-9999-23-081-H01-P; Blood Pressure Management in Adult Patients: 0217-9999-23-082-H01-P; Stable Atherosclerotic Disease 0217-9999-23-083-H01-P; Anticoagulation: 0217-9999-23-084-H01-P; Arrhythmias: 0217-9999-23-085-H01-P; Drug-Induced Cardiovascular Disease and Drugs to Avoid in Cardiovascular Disease: 0217-9999-23-086-H01-P; Chronic Heart Failure: 0217-9999-23-087-H01-P; Decompensated Heart Failure: 0217-9999-23-088-H01-P; Heart Transplant and Mechanical Circulatory Support: 0217-9999-23-089-H01-P; Acute Coronary Syndrome: 0217-9999-23-090-H01-P; Cardiovascular Emergencies: 0217-9999-23-091-H01-P; Pulmonary Arterial Hypertension: 0217-9999-23-092-H01-P; Specialized Topics in Cardiovascular Disease: 0217-9999-23-093-H01-P; Translation of Evidence: 0217-9999-23-094-H99-P; Principles of Cardiology Pharmacy Practice Administration: 0217-9999-23-095-H04-P. All Cardiology Pharmacy Preparatory Review and Recertification Course sessions are application-based activities.

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# Program Goals and Target Audience

The Cardiology Pharmacy Preparatory Review and Recertification Course is designed to help pharmacists who are preparing for the Board of Pharmacy Specialties certification examination in Cardiology Pharmacy as well as those seeking a general review and refresher on disease states and therapeutics. The program goals are as follows:

1. To present a high-quality, up-to-date overview of cardiovascular disease states and therapeutics; review cardiology pharmacy practice management techniques; and review biostatistical principles and literature evaluation methods relevant to cardiology pharmacy practice;
2. To provide a framework to help attendees prepare for the specialty certification examination in cardiology pharmacy practice; and
3. To offer participants an effective learning experience using a case-based approach with a strong focus on the thought processes needed to solve patient care problems in each therapeutic area.

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# Primary Prevention of Cardiovascular Disease and Public Health

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**Learning Objectives**

1. Identify the pharmacotherapeutic agents that reduce the risk of developing cardiovascular disease (CVD).
2. Develop a treatment plan that incorporates lifestyle modifications and evidence-based pharmacotherapy to reduce the risk of an index cardiovascular event for a given patient scenario.
3. Develop a tobacco cessation treatment plan for a patient who requests assistance for a quit attempt.
4. Evaluate a given patient scenario to determine CVD risk and recommend appropriate lipid therapy.
5. Determine appropriate patients to recommend initiation of aspirin therapy for the primary prevention of CVD.
6. Counsel a patient on appropriate complementary and alternative pharmacotherapeutic agents to optimize CVD risk reduction, including vitamin D and omega-3 fatty acids.

**Abbreviations in This Chapter**

| | |
|---|---|
| ACC | American College of Cardiology |
| ADA | American Diabetes Association |
| AHA | American Heart Association |
| ASCVD | Atherosclerotic cardiovascular disease |
| BMI | Body mass index |
| CHD | Coronary heart disease |
| CRP | C-reactive protein |
| CV | Cardiovascular |
| CVD | Cardiovascular disease |
| DBP | Diastolic blood pressure |
| HDL | High-density lipoprotein cholesterol |
| HTN | Hypertension |
| LDL | Low-density lipoprotein cholesterol |
| MI | Myocardial infarction |
| MOA | Mechanism of action |
| NNT | Number needed to treat |
| O3FA | Omega-3 fatty acid |
| PCE | Pooled cohort equations |
| SBP | Systolic blood pressure |
| TG | Triglycerides |
| USPSTF | U.S. Preventive Services Task Force |

**Self-Assessment Questions**

*Answers and explanations to these questions can be found at the end of this chapter.*

1. A 63-year-old white man (body mass index [BMI] 32 kg/m$^2$) with no known allergies presents to the medication management clinic for a cardiovascular (CV) risk reduction assessment. His blood pressure is 152/94 mm Hg averaged over two separate readings and heart rate is 72 beats/minute. He denies tobacco use. Laboratory tests show potassium (K) 4.3 mEq/L, serum creatinine (SCr) 0.89 mg/dL, hemoglobin A1C (A1C) 7.1%, total cholesterol (TC) 175 mg/dL, high-density lipoprotein cholesterol (HDL) 42 mg/dL, and low-density lipoprotein cholesterol (LDL) 135 mg/dL. His calculated atherosclerotic cardiovascular disease (ASCVD) score using the pooled cohort equations (PCE) is 30%, and his optimal ASCVD risk is 7.5%. The patient takes lisinopril 10 mg daily for his blood pressure. The patient participates in shared decision-making and wishes to undertake aggressive risk reduction efforts. In addition to lifestyle modifications, which group of additional medications would best be added to this patient's daily regimen?
   A. Atorvastatin 80 mg daily, chlorthalidone 12.5 mg daily, metformin 500 mg twice daily.
   B. Aspirin 81 mg daily, atenolol 50 mg daily, atorvastatin 10 mg daily.
   C. Atorvastatin 40 mg daily, metformin 500 mg twice daily.
   D. Aspirin 81 mg daily, atorvastatin 40 mg daily, metformin 500 mg twice daily.

2. A 68-year-old female patient has a 40 pack-year history and currently smokes 20 cigarettes daily with the first cigarette within 10 minutes of waking daily. She has a medical history of anxiety and is working to taper and discontinue clonazepam 0.5 mg twice daily for generalized anxiety disorder. Which smoking cessation plan would be most appropriate for this patient?
   A. Varenicline 0.5 mg daily for 3 days; then 0.5 mg twice daily for 4 days; then 1 mg twice daily.
   B. Nicotine patch 21 mg/day topically and bupropion extended release (XL) 150 mg orally twice daily.

C. Nicotine patch 14 mg/day topically.

D. Nicotine patch 14 mg/day topically and nicotine gum 2 mg every 1–2 hours as needed.

3. A 65-year-old woman with type 2 diabetes currently takes metformin 1000 mg twice daily and liraglutide 1.8 mg daily. Her A1C is 8.4%. Which would best reduce her CV risk?

   A. Glipizide 2.5 mg daily.

   B. Empagliflozin 10 mg daily.

   C. Repaglinide 1 mg before meals.

   D. Saxagliptin 2.5 mg daily.

4. A patient with a BMI of 32 kg/m$^2$ has discussed the role of various obesity management strategies with her provider. She has no clinically significant concomitant disease states aside from a history of hypertension (HTN) and epilepsy. Her current medications include amlodipine 10 mg daily, lisinopril 20 mg daily, and carbamazepine 600 mg daily. According to your clinical assessment, which is most appropriate for this patient to use for weight loss?

   A. Phentermine.

   B. Orlistat.

   C. Naltrexone/bupropion.

   D. Semaglutide.

5. A 48-year-old man with a medical history of HTN (blood pressure 125/78 mm Hg) taking ramipril 5 mg daily is being considered for statin therapy. His current lipid panel includes TC 180 mg/dL, HDL 40 mg/dL, and LDL 125 mg/dL. His calculated ASCVD score using the PCE is 6.8%. He has no other CV risk factors. Which is the best recommendation for this patient regarding statin therapy?

   A. Initiate atorvastatin 10 mg daily.

   B. Initiate rosuvastatin 20 mg daily.

   C. Initiate pravastatin 40 mg daily.

   D. Statin therapy is not currently indicated.

6. A 38-year-old woman (BMI 24 kg/m$^2$) asks how much she should exercise. She currently has a desk job and has "not exercised in years." Her father recently had a myocardial infarction (MI), so she is motivated to begin exercising. Her medical history is noncontributory. Her ASCVD score using the PCE is less than 1%. Which is the best recommendation for this patient?

   A. No changes are currently needed because her ASCVD score is low.

   B. No changes are currently needed because she is younger than 40.

   C. Recommend 150 minutes of moderate activity per week or 75 minutes of vigorous activity per week.

   D. Recommend 150 minutes of moderate activity per week only if she begins to gain weight.

7. A 70-year-old woman (BMI 21 kg/m$^2$) presents to your interdisciplinary atrial fibrillation transitions clinic with newly diagnosed atrial fibrillation. Her medical history includes HTN (blood pressure 150/85 mm Hg) and hypothyroidism (controlled). She drinks 1 glass of wine at dinner each night and says she otherwise "eats a low-salt diet." She walks every day and denies symptoms of anxiety. In addition to optimizing her HTN regimen and evaluating for possible obstructive sleep apnea, which would be best to recommend to reduce her risk of atrial fibrillation and HTN?

   A. Eliminate all alcohol from diet.

   B. Eliminate all fats from diet.

   C. Limit potassium and sodium intake to 2400 mg each per day.

   D. Eat 6–11 servings of carbohydrates, 3–5 servings of vegetables, and 2–4 servings of fruit daily.

8. A 50-year-old man with a history of HTN and asthma asks whether he should take omega-3 fatty acids (O3FAs) to reduce his risk of MI and stroke. He has no known history of ASCVD, and his family history is noncontributory. Which is the best recommendation for this patient?

   A. Initiate O3FA 1 g daily.

   B. Initiate omega-3 carboxylic acid 2 g twice daily.

   C. Initiate icosapent ethyl 2 g twice daily.

   D. O3FAs are not recommended for primary prevention of ASCVD in this patient.

## I. INTRODUCTION

A. Background:
   1. CVD was responsible for 19.1 million deaths globally in 2020.
   2. CVD remains the leading cause of death in adults in the United States.
      a. In 2019, coronary heart disease (CHD) was the leading cause of CVD death (41.3%).
      b. Stroke accounted for 17.2% of CVD deaths in 2019.
   3. Use of population-based strategies and affordable cost-effective interventions may reduce morbidity and mortality throughout the world.
      a. Most in U.S. with myocardial infarction (MI) have at least 1 risk factor for CVD prior to event
      b. Increasing a patient's number of "ideal" CV health factors has been associated with reduced incidence of ASCVD events

B. Campaigns and efforts to reduce the development and progression of CVD continue.
   1. Healthy People 2020
   2. Million Hearts Initiative by U.S. Department of Health and Human Services
   3. Million Hearts Cardiovascular Risk Reduction Model
   4. American Heart Association (AHA): Make the Effort to Prevent Heart Disease with Life's Simple 7
      a. Defined model of "ideal cardiovascular health"
      b. "Life's Simple 7"
         1. Manage blood pressure.
         2. Control cholesterol.
         3. Reduce blood glucose.
         4. Get active.
         5. Eat better.
         6. Lose weight.
         7. Stop smoking.
      c. The 2018 Cardiovascular Health Promotion Series from Journal of American College of Cardiology may assist clinicians in facilitating targeted care to patients towards this goal.

C. 2019 ACC/AHA Guideline on the Primary Prevention of Cardiovascular Disease provides recommendations on aspirin, physical activity, tobacco use, team-based care, shared decision making, and social determinants of health to organize care for the primary prevention patient
   1. Team-based care is suggested to improve risk factor control
   2. Shared decision making is important to facilitate patient engagement and improve overall health
   3. Social determinants should be assessed to prevent ASCVD risk escalation and development

## II. ATHEROSCLEROTIC CARDIOVASCULAR DISEASE RISK FACTORS

A. Age, Sex, Race/Ethnicity
   1. Prevalence of CVD increases with age in men and women.
   2. CVD death is more common in men than in women overall, though it tends to be higher in non-Hispanic black women than in non-Hispanic black men.
   3. Age-adjusted death rates for CHD are higher in non-Hispanic black women than in non-Hispanic white or Hispanic women.

B. Family History
   1. Shared genetic predisposition and lifestyle habits

2. Paternal occurrence of early myocardial infarction (MI) increases the risk for male children by 200% and for female children by 70% (Circulation 2001;104:393-8). In this study, parental MI in those younger than 60 years conferred a greater risk of CVD than did parental MI at older ages.

C. Hypertension
   1. Increases risk of CHD in a log-linear relationship
   2. Those with HTN likely to develop atherosclerotic cardiovascular disease (ASCVD) 5 years earlier than in normotensive peers
   3. Every systolic blood pressure (SBP) increase of 20 mm Hg is associated with a 2-fold increase in CVD death.
   4. Every diastolic blood pressure (DBP) increase of 22 mg Hg is associated with a 2-fold increase in CVD death.
   5. Increased prevalence in men to age 64; then increased prevalence in women
   6. Remains underrecognized, with almost one of every six individuals unaware of diagnosis
   7. Key prevalence rates in various populations:
      a. Patients 60 years and older: 67.2%
      b. Patients 8–17 years of age: 11%
      c. Non-Hispanic black men: 45%
      d. Non-Hispanic black women: 46.3%

D. Hyperlipidemia
   1. Cholesterol deposits in the endothelial lining of arterial vessels are the primary cause of atherosclerosis.
   2. The 2013 American College of Cardiology/American Heart Association (ACC/AHA) blood cholesterol guideline recommendations suggest that more than 45 million Americans without ASCVD will benefit from statin initiation, given expected rates of high cholesterol.
   3. The 2018 ACC/AHA blood cholesterol guidelines suggest further tailoring of recommendations to patient-centered decision making.
   4. Low HDL is associated with an increased risk of ASCVD, but this is not a current therapy target because pharmacologic interventions to raise HDL have not been proven beneficial.

E. Diabetes
   1. More than 37 million adults have diabetes: 28.7 million individuals diagnosed (including 28.5 million adults), 8.5 million undiagnosed.
   2. Relative risk of CHD is 1.38 times higher, and for CHD death, risk is 1.86 times higher for each decade an individual lives with diabetes.
   3. In those with diabetes studied in Framingham Heart Study, body habitus further increased ASCVD rates.
      a. Women with a normal weight and diabetes had a 54.8% incidence of ASCVD compared with women with obesity, who had a 78.8% incidence of ASCVD.
      b. Men with normal weight and diabetes had a 78.6% rate of ASCVD compared with men with obesity, who had an 86.9% incidence.
   4. In adults with diabetes older than 65, 68% die of heart disease and 16% die of stroke.

F. Tobacco Use
   1. Almost one in three ASCVD deaths in adults older than 35 are attributable to smoking or secondhand smoke exposure.
   2. Mortality is 3 times higher for U.S. smokers than for those who never smoked.
   3. Both smoking and smokeless tobacco increase the risk of all-cause mortality and are established risk factors for ASCVD.
   4. ASCVD risk increases with low overall cigarette primary and secondary exposures.

5. Smoking rates are inversely associated with family income: 20.2% making less than $35,000, 14.1% making $35,000–$74,000, 10.5% making $75,000–$99,900, and 6.2% making at least $100,000. This original statistic is from 2015; the new statistic is from 2020 (CDC Burden of Cigarette Use in the U.S.).
6. Since the U.S. Surgeon General's report in 1965, age-adjusted rate of smoking has declined from 51% to 14.1% (CDC Current Cigarette Smoking Among Adults in the United States) for men and from 34% to 11.0% (CDC Current Cigarette Smoking Among Adults in the United States) for women, showing the success of public health interventions.
7. Smoking cessation decreases ASCVD risk after 1 year, and risk returns to that of nonsmokers after 10 years of discontinuation, whereas stroke risk returns to that of nonsmokers within 2–5 years after discontinuation.
8. Electronic cigarettes (e-cigarettes) are now used by 1 in 20 individuals in United States.
9. User rates of disease development in those who use e-cigarettes compared with those who do not use e-cigarettes or any tobacco products (Vindhyal 2019):
    a. 56% more likely to have MI
    b. 30% more likely to have cerebrovascular accident (CVA)
    c. 25% more likely to have coronary artery disease
    d. 55% greater rates of depression

G. Physical inactivity
1. Approximately 1 in 3 U.S. adults do not engage in leisure time physical activity.
2. Less than 28% of high school aged teens meet AHA recommendations for performing 60 minutes of exercise daily.

H. Obesity
1. Obesity prevalence increased from 30.5% (1999–2000) to 41.9% (2019–2022) in the United States.
2. Worldwide, the percentage of overweight or obese adults increased to 41.8% of males and 41.8% of females as of 2017 (CDC National Health Statistics Reports).
3. The Global Burden of Disease study statistical model suggests Pacific Island countries have the greatest mortality rate associated with high body-mass index (BMI).

## III. RISK ASSESSMENT TOOLS AND CALCULATORS

A. INTERHEART Study: Showed that risk factors account for over 90% of population risk of first MI. Commonly recognized risk factors for developing CVD are noted in Table 1.

**Table 1.** Risk Factors for Developing CVD

| Modifiable Risk Factors | Nonmodifiable Risk Factors |
|---|---|
| Obesity | Age (male ≥ 45 yr; female ≥ 55 yr) |
| Cocaine use, amphetamine use | Sex |
| Tobacco exposure | Family history/premature CVD in first-degree relative (< 55 yr in male relative, < 65 yr in female relative) |
| Dietary intake | Ethnicity |
| Physical inactivity | |
| Blood pressure | |
| Blood glucose elevation | |
| Abnormal cholesterol | |

CVD = cardiovascular disease.

B. Predictive Risk for Individuals: May be used to guide clinical decisions of preventive interventions intensity
   1. Critical component in primary prevention of ASCVD
   2. Identifies patients who may have greater net benefit and lower number needed to treat to obtain benefit from use of statins or anti-hypertensive therapies.
   3. Relative risk reduction in CV events is 25%–33% for drug treatment with HTN or high cholesterol.

C. Risk Prediction Charts: May underestimate CV risk in individuals who have already had a CV event or in those with actual high CV risk who have:
   1. Established coronary artery disease/CVD and have had recent revascularization procedures
   2. Evidence of left ventricular hypertrophy or hypertensive retinopathy
   3. Familial hypercholesterolemia or baseline LDL 190 mg/dL or greater.
   4. Elevated blood pressure
   5. Type 1 or 2 diabetes
   6. Renal dysfunction or failure

D. 2019 ACC/AHA Primary Prevention Guidelines: Assessing ASCVD Risk
   1. The 10-year ASCVD risk estimate should begin a patient-centered discussion about risk-reducing strategies and should not be the sole reason for initiating pharmacotherapy (e.g., lipid therapy or blood pressure management).
   2. Clinicians should routinely assess traditional CV risk factors and calculate 10-year ASCVD risk using the pooled cohort equations (PCE) for adults 40-75 years of age.
   3. It is reasonable to assess traditional ASCVD risk factors at least every 4-6 years in adults age 20-39 years.
   4. It is reasonable to use risk-enhancing factors (Box 1) to guide decisions about preventive interventions in adults at borderline (5% to less than 7.5%) or intermediate (7.5% to less than 20%) 10-year ASCVD risk.
   5. It is reasonable to measure a coronary artery calcium score to guide risk discussions in adults at intermediate (7.5% to less than 20%) or selected adults at borderline (5% to less than 7.5%) 10-year ASCVD risk if the risk-based decision remains uncertain.
   6. Estimation of lifetime or 30-year ASCVD risk may be considered for adults age 20-39 years and those age 40-59 years with a 10-year risk less than 7.5%.

E. ACC/AHA Pooled Cohort Equations (PCE) (2013)
   1. All risk estimate calculators have inherent limitations and must be interpreted in the context of patient-specific circumstances.
   2. PCE are best validated in non-Hispanic whites and non-Hispanic blacks living in the United States.
   3. PCE may underestimate risk in chronic inflammatory conditions (e.g., autoimmune diseases, HIV) or in those at socioeconomic disadvantage.
   4. PCE may overestimate risk at higher socioeconomic status or in those with continued access to preventive services.
   5. PCE may be less well calibrated in more modern populations than in the older cohorts from which these equations were derived. Therefore, consideration of risk-enhancing factors is recommended for those at borderline or intermediate risk (Box 1).
   6. Although PCE are generally recommended, clinicians may consider using an alternative risk assessment tool if that tool is validated in a population similar to an individual patient being assessed (see next section).

F. Other Risk Calculators:
   1. Framingham general CVD risk calculator
      a. Third National Cholesterol Education Panel Adult Treatment Panel (2002) guidelines recommended use for patients without ASCVD or a risk equivalent and two or more traditional risk factors in routine clinical practice: Patients with a 10-year risk greater than 20% of death or definite MI were deemed at high risk of CVD.
      b. First risk scoring system to be incorporated into a national guideline to guide treatment decisions
      c. Updated in 2008 to evaluate 8 parameters to predict total CVD
      d. Estimated risk of CVD is expected to be higher with this score than with other scores that only predict CHD.
      e. Incorporates eight variables to predict seven end points
         i. Variables: Age, sex, TC, HDL, SBP, active treatment for blood pressure, diabetes, current smoker
         ii. End points: CHD death, nonfatal MI, angina, fatal or nonfatal stroke, transient ischemic attack (TIA), intermittent claudication, heart failure
   2. Reynolds CVD risk score (2007)
      a. Includes family history of MI and high-sensitivity CRP as variables, developed from 24,000 women without diabetes and 10,000 men from the Nurses' Health Study in 2007 and the Physicians' Health Study in 2008
      b. Shown to more accurately predict risk of CV events in white and black women than the Framingham and ATP (Adult Treatment Panel) III risk scores, likely because of better calibration to populations without diabetes. In addition, may be more predictive in patients who have a positive family history and elevated high-sensitivity CRP than Pooled Cohort Equation
      c. Uses eight (in women)/seven (in men) variables to estimate risk of four end points
         i. Variables: Age, TC, HDL, SBP, diabetes on the basis of A1C (women only), current smoking status, parent with MI before age 60, serum high sensitivity-CRP
         ii. End points: CV death, nonfatal MI, nonfatal stroke, coronary revascularization
   3. Million Hearts Longitudinal ASCVD Risk Assessment Tool (2017)
      a. Developed by Million Hearts and the Centers for Medicare & Medicaid Services to assess a value-based payment approach toward reducing the 10-year predicted risk of ASCVD
      b. Replaced by the ACC/AHA PCE risk calculator
   4. QRISK3 (2018)
      a. Risk assessment calculator most recently updated in 2018 (QRISK3) (available online)
      b. Calculates 10-year risk of MI or stroke for adults age 25-84 years
      c. Externally validated
      d. Developed in a UK population and intended for use in the UK
      e. Recommended by the UK National Institute for Health and Care Excellence
      f. Incorporates 20 variables to predict two end points
         i. Variables: Age (25-84 years), sex, ethnicity, UK postcode (optional), smoking status, diabetes, family history, chronic kidney disease (CKD), atrial fibrillation, HTN treatment, rheumatoid arthritis, systemic lupus erythematosus, severe mental illness, use of atypical antipsychotic medication, regular steroid use, erectile dysfunction, cholesterol/HDL ratio, SBP, standard deviation of at least the two most recent SBP readings, BMI
         ii. End points: MI or stroke

G. Lifetime Risk Assessment
   1. May be useful for describing ASCVD risk in patients younger than 50 years who may have high rates of lifetime risk, though low rates of 10-year risk.
   2. ASCVD Risk Calculator (http://static.heart.org/riskcalc/app/index.html#!/baseline-risk) may assist clinicians on long-term consequences of one or more elevated risk factors.

3. Risk factors that enhance risk and require additional discussion include:
   a. Premature ASCVD family history
   b. Primary hypercholesterolemia
   c. Metabolic syndrome
   d. Chronic kidney disease
   e. Chronic inflammatory conditions (psoriasis, HIV/AIDS, rheumatoid arthritis)
   f. History of premature menopause prior to age 40
   g. History of pregnancy-associated conditions that increase later ASCVD risk
   h. High-risk race/ethnicities
   i. Lipid biomarkers
4. After completing initial assessment and risk score calculation, may wish to consider additional assessment through the following tests to guide therapy
   a. High sensitivity-CRP
   b. Coronary artery calcium score
   c. Ankle-brachial index
   d. Family history of CVD

H. Summary Table of Risk Calculator modality with calculated outcome measures (Table 2)

**Table 2.** Summary and Characteristics of Risk Score

| Risk Calculator | Endorsement | Outcome |
|---|---|---|
| Framingham General CVD Risk Calculator<br>https://www.mdcalc.com/framingham-coronary-heart-disease-risk-score | ATP III (2001) and NLA (2014) | 10-year risk of definite MI or death |
| Pooled Cohort Equations Risk Calculator<br>https://tools.acc.org/ascvd-risk-estimator-plus/#!/calculate/estimate/ | ACC/AHA (2013)<br>2018 AHA/ACC Multisociety Guideline on the Management of Blood Cholesterol | 10-year and lifetime ASCVD risk (coronary death or nonfatal MI, or fatal or nonfatal stroke) |
| QRISK3 (2018)<br>https://qrisk.org/three/ | National Institute for Health and Care Excellence (2014, 2016) | 10-year risk of MI or stroke |
| Reynolds Risk Score (2008)<br>https://www.mdcalc.com/reynolds-risk-score-cardiovascular-risk-women | Not included in national guidelines | 10-, 20- and 30-year risk of MI, stroke, or revascularization |

ASCVD = atherosclerotic cardiovascular disease; ATP = Adult Treatment Panel; MI = myocardial infarction; NLA = National Lipid Association.

## IV. LIPID THERAPY FOR PRIMARY PREVENTION

A. Lifestyle modification is the cornerstone of initial intervention.
   1. Heart-healthy diet
   2. Regular exercise
   3. Maintain healthy weight.
   4. Smoking cessation

B. U.S. Preventive Services Task Force (USPSTF) Recommendations (2022):
   1. Adults 40–75 years of age who have one or more CVD risk factors (dyslipidemia, diabetes, HTN, or smoking) and an estimated 10-year CVD risk of 10% or greater should have statin therapy initiated.
      a. Because of limited data directly comparing the effects of different statin intensities on health outcomes, moderate-intensity statin therapy seems reasonable for primary prevention in most individuals. (Table 3 lists relative-potency and available strengths for this therapy class.)
   2. Adults 40–75 years of age who have one or more CVD risk factors and an estimated CVD risk of 7.5% to less than 10% should be selectively offered a statin.
      a. The benefit of initiating a statin in this group is smaller than in patients with a CVD risk of 10% or greater.
      b. Patient values and preferences should be considered.
   3. Evidence is insufficient to recommend for or against initiating a statin in adults 76 and older.

C. 2018 AHA/ACC Guidelines and 2019 ACC/AHA Primary Prevention Guidelines
   1. Patients age 20-75 years with severe primary hypercholesterolemia (LDL 190 mg/dL or greater) are indicated for high-intensity statin therapy (regardless of 10-year ASCVD risk). After therapy with high-intensity statin for 4-12 weeks:
      a. If LDL reduction is less than 50% and/or LDL is 100 mg/dL or greater, ezetimibe is reasonable.
      b. If LDL remains greater than or equal to 100 mg/dL while taking a maximally tolerated statin and ezetimibe, adding a proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitor can be considered (or if baseline LDL was 220 mg/dL or higher and on-treatment LDL is 130 mg/dL or higher).
   2. For patients age 40-75 years with diabetes and LDL of 70-189 mg/dL, a moderate-intensity statin should be initiated regardless of 10-year ASCVD risk. It is reasonable to prescribe high-intensity statin therapy with a goal of reducing LDL by at least 50% in adults with diabetes and several ASCVD risk factors (Box 1 and Box 2). It may be reasonable to add ezetimibe to maximally tolerated statin therapy to achieve a reduction in LDL by 50% or more in patients with diabetes and an ASCVD risk of 20% or higher.
   3. Age-based recommendations for certain groups without diabetes include:
      a. Age 0-19 years: Lifestyle modifications to prevent or reduce ASCVD risk.
      b. Age 20-39 years: Estimate lifetime risk to encourage lifestyle to reduce ASCVD risk; consider statin if patient has a family history of premature ASCVD and LDL 160 mg/dL or higher.
      c. Age older than 75 years: Clinical assessment and risk discussion:

**Box 1.** Risk-Enhancing Factors for Clinician-Patient Risk Discussion According to ACC/AHA Guidelines

| |
|---|
| Family history of premature ASCVD (males younger than 55 years, females younger than 65 years) |
| LDL 160-189 mg/dL |
| Metabolic syndrome |
| Chronic kidney disease (eGFR 15-59 mL/minute/1.72 $m^2$) |
| History of early menopause or preeclampsia |
| Chronic inflammatory disorders (e.g., psoriasis, rheumatoid arthritis, lupus, HIV/AIDS) |
| High-risk ethnic groups (e.g., South Asian ancestry) |
| Elevated triglyceride values greater than 175 mg/dL |
| Apolipoprotein B greater than or equal to 130 mg/dL |
| High-sensitivity C-reactive protein greater than or equal to 2.0 mg/dL |
| Ankle-brachial index less than 0.9 |
| Lipoprotein (a) greater than or equal to 50 mg/dL |

**Box 2.** Diabetes-Specific Risk Enhancers According to the ACC/AHA Guidelines

| |
|---|
| Long duration (≥ 10 years of type 2 diabetes or ≥ 20 years for type 1 diabetes) |
| Albuminuria ≥ 30 mcg albumin/mg creatinine |
| eGFR < 60 mL/minute/1.73 $m^2$ |
| Retinopathy |
| Neuropathy |
| Ankle-brachial index < 0.9 |

4. For adults age 40-75 years with an LDL of 70-189 mg/dL and without diabetes, it is recommended to calculate a 10-year ASCVD risk to determine appropriate therapy:
    a. If risk is less than 5% (low risk): Emphasize lifestyle to reduce risk factors.
    b. If risk is 5%-7.4% (borderline risk): Assess for risk-enhancing factors (Box 1); presence of risk-enhancing factors may justify initiation of moderate-intensity statin.
    c. If risk is 7.5%-19.9% (intermediate risk): A moderate-intensity statin should be recommended after a risk discussion. LDL should be reduced by at least 30%, and, for optimal ASCVD risk reduction, LDL should be reduced by at least 50%. Presence of risk-enhancing factors favors initiation or intensification of statin therapy.
        i. If risk decision is still uncertain, consider measuring a coronary artery calcium score.
    d. If risk is 20% or greater: Initiate statin therapy to reduce LDL by 50% or more.
5. Assess adherence and percent response to LDL-lowering therapies and lifestyle changes with repeat lipid measurement 4-12 weeks post-statin start, and repeat every 3-12 months as needed.
6. Older adults (older than 75)
    a. Data are limited with modern background therapy.
    b. Usually appropriate to continue statin therapy if well tolerated
    c. Concern about statin-associated dementia largely disproven
    d. Patients older than 75 are at a several-fold increased risk of fatal ASCVD events compared with younger patients.
        i. 29.7 (age older than 75) versus 17.8 (age 71-75 years) ASCVD events per 1000 patient-years
        ii. 8.5 (age older than 75) vs. 2.5 (age 71-75) fatal ASCVD events per 1000 patient-years
    e. Number needed to treat (NNT) to prevent one event in 5 years (based on 20% or 40% relative risk reduction [RRR]) decreases with advancing age because of increased risk of ASCVD events:
        i. Age 79 years: NNT 14 (40% RRR) or 27 (20% RRR)
        ii. Age 70 years: NNT 21 (40% RRR) or 42 (20% RRR)
        iii. Age 60 years: NNT 38 (40% RRR) or 75 (20% RRR)
        iv. Age 50 years: NNT 78 (40% RRR) or 156 (20% RRR)
        v. Age 40 years: NNT 200 (40% RRR) or 400 (20% RRR)
    f. STAREE trial ongoing to assess statins for primary prevention in older adults; expected to be completed in 2023

**Table 3.** Relative LDL-Lowering Efficacy of Statins and Statin-Based Therapies[a]

| Atorva (mg) | Fluva (mg) | Pitava (mg) | Lova (mg) | Prava (mg) | Rosuva (mg) | Ezetimibe/ Simva (mg) | Simva (mg) | %↓ LDL |
|---|---|---|---|---|---|---|---|---|
| — | 20–40 | *1* | 10–20 | | — | — | 5-10 | 30 |
| *10* | *80* | *2* | *40* | *40* | — | — | *20* | 38 |
| *20* | — | *4* | *80* | *80* | *5* | *10/10* | *40* | 41 |
| **40** | — | — | — | — | *10* | **10/20** | — | 47 |
| **80** | — | — | — | — | **20** | **10/40** | — | 55 |
| — | — | — | — | — | **40** | — | — | 63 |

[a]Bold type denotes high-intensity statin; lowers LDL by ≥ 50%; Italic type denotes moderate-intensity statin; lowers LDL by 30% to < 50%; and regular type denotes low-intensity statin; lowers LDL by < 30%.

Atorva = atorvastatin; Fluva = fluvastatin; Lova = lovastatin; Pitava = pitavastatin; Prava = pravastatin; Rosuva = rosuvastatin; Simva = simvastatin.

Adapted from: Stone NJ, Robinson J, Lichtenstein AH, et al. 2013 ACC/AHA guidelines on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults. Circulation 2014;129(suppl 2):S1-45.

**Patient Case**

1. Which best represents a moderate-intensity statin dose?
   A. Lovastatin 20 mg daily.
   B. Pravastatin 40 mg daily.
   C. Fluvastatin 40 mg daily.
   D. Atorvastatin 40 mg daily.

## V. DIET MODIFICATION (RECOMMENDATIONS SUMMARIZED IN TABLE 4)

A. Adherence to a healthy lifestyle offsets genetic factors associated with increased ASCVD risk.

B. Focus has changed from the impact of dietary patterns on surrogate health markers to the impact on CV and metabolic health outcomes.

C. Dietary fat and CVD relationship has been investigated over the past 40 years.

D. Saturated Fats: Raise LDL
   1. Increased dietary intake yields increases in LDL, decreases in HDL, and increases in coronary disease rates.
   2. *Trans* fatty acids come from the partial hydrogenation of unsaturated oils.
   3. n-6 polyunsaturated fatty acids and monounsaturated fatty acids lower TC, LDL, and TG.
   4. The 2020–2025 dietary guidelines for Americans recommend that no more than 10% of calories come from saturated fats and recommend avoiding all *trans* fats.

E. Systematic Review: Reducing/changing dietary fat reduced the incidence of combined CV events by 16% and CV mortality by 9% but did not affect total mortality with a minimum 2-year diet change.
   1. In trials studying the effect of reducing saturated fat and replacing it with carbohydrates, serum cholesterol was reduced by 5%.
   2. No significant reduction in CVD events

F. 2013 AHA/ACC Guideline on Lifestyle Management to Reduce CV Risk
   1. Emphasis should be on the intake of whole grains, vegetables, and fruits.
   2. Low-fat dairy products, lean meats (poultry, fish), legumes, nuts, and non-tropical vegetable oils should be included.
   3. Processed meats, sweets, and sugar-sweetened beverages should be limited.
   4. Saturated fat calories should be limited to 5%–6% of total calories.
   5. *Trans* fats should be avoided.
   6. Salt intake should not exceed 2400 mg of sodium daily.

G. 2019 ACC/AHA Guideline on Primary Prevention of Cardiovascular Disease
   1. Promoting a healthy lifestyle (including diet) throughout life is the most important way to prevent ASCVD, heart failure, and atrial fibrillation.
   2. Recommend a diet high in vegetables, fruits, legumes, nuts, whole grains, fish, and vegetables or lean animal protein to reduce ASCVD risk.
   3. Avoid *trans* fats.
   4. Replacing saturated fats with mono- and polyunsaturated fats can help reduce ASCVD risk.
   5. A diet low in cholesterol and sodium can help reduce ASCVD risk.
   6. Minimize consumption of processed meats, refined carbohydrates, and sweetened beverages to reduce ASCVD risk.
   7. Potential barriers to attaining a heart-healthy diet should be assessed and considered, including food access and economic factors that affect patient adherence.
   8. Table 4 summarizes the expected effects of dietary and lifestyle modification on blood pressure.

H. 2020 USPSTF Guideline on Behavioral Counseling, Diet, and Exercise for CV Prevention in Adults with CV Risk Factors
   1. Reduce saturated fats, sodium, sweets, and added sugar.
   2. Increase fruits, vegetables, whole grains, and fish and other healthy fats.
   3. Promote Dietary Approaches to Stop Hypertension (DASH) and Mediterranean diets.
   4. Behavioral change approach includes setting goals, active self-monitoring, addressing barriers, and motivational interviewing.

I. 2022 USPSTF guideline on behavioral counseling interventions to promote a healthy diet and physical activity for CVD prevention in adults without CVD risk factors
   1. For adults 18 and older, the decision to offer or refer for behavioral counseling interventions to promote a healthy diet and physical activity should be an individual one.
   2. Considers patient motivations and goals, activity level and ability, circumstances, and preferences

J. 2021 American Heart Association Scientific Statement: Dietary Guidance to Improve CV Health
   1. Organized into "10 features" as follows:
      a. Adjust energy intake and expenditure to achieve and maintain a healthy body weight.
      b. Eat plenty of fruits and vegetables, and choose a wide variety.
      c. Choose foods made mostly with whole grains rather than refined grains.
      d. Choose healthy sources of protein.
         i. Mainly protein from plants (legumes, nuts)
         ii. Fish and seafood
         iii. Low- or fat-free dairy products instead of full-fat dairy products
         iv. If meat or poultry is desired, choose lean cuts and avoid processed forms.
      e. Use liquid plant oils instead of tropical oils (coconut, palm, palm kernel) or animal fats (butter, lard) and partially hydrogenated fats.

   f. Choose minimally processed foods instead of ultra-processed foods.
   g. Minimize intake of beverages and foods with added sugars.
   h. Choose and prepare foods with little or no salt.
   i. If you do not drink alcohol, do not start; if you choose to drink alcohol, limit intake.
   j. Adhere to this guidance regardless of where food is prepared or consumed.
2. Statement also advises caution with plant-based meat alternatives because many are ultra-processed and contain added sugars, saturated fats, and preservatives.
3. Advises at least 150 minutes of moderate-intensity physical activity per week

K. 2020–2025 Dietary Guidelines for Americans
1. Added sugars should be less than 10% of daily calories.
2. Saturated fats should be less than 10% of calories.
3. Sodium intake should be less than 2300 mg/day.
4. Alcohol – See text that follows.
5. 85-15 guide: 85% of calories should come from nutrient-dense foods (vegetables, fruits, whole grains, dairy, healthy proteins), and 15% of calories are available for other uses (about 250–350 calories for most Americans).

L. Mediterranean and DASH Diets: Emphasize fruits, vegetables, and healthy fats (fish, nuts, and extra-virgin olive oil) and improve surrogate markers and clinical outcomes

M. Dietary potassium intake:
1. Increased dietary potassium intake has been associated with reduced rates of HTN and stroke.
2. Intake of 1380 mg potassium chloride is associated with systolic bp reductions of 2 mm Hg in normotensive patients and up to 4-5 mm Hg for hypertensive patients.
   a. Effect magnified in blacks and those with high-sodium diets.
   b. May be mediated by changes in the sodium/potassium index.
3. Goal intake is 3500 mg (World Health Organization) to 4700 mg (2015 Dietary Guidelines Advisory Committee), primarily from food sources, including fruits, vegetables, meats, fish, soy, selected dairy products.

N. PREDIMED Study
1. Original publication of primary prevention evaluation: 7447 patients at high CV risk in three arms: Mediterranean diet supplemented with extra-virgin olive oil, Mediterranean diet with mixed nuts, and low-fat diet control group
2. Combined CV death, nonfatal MI, and stroke end point was significantly reduced by 30% in both arms of the Mediterranean diet compared with the low-fat diet arm (trial was terminated early at 4.8 years median follow-up)
3. As the result of randomization procedure errors, the study was republished June 2018 to reflect omitting 1588 patients whose trial-group assignments were known or thought to have departed proper randomization processes
4. In both the original and republished study, CVD in Mediterranean diet groups was reduced by approximately 30% when compared to the control group
5. Stroke and myocardial infarction reductions were primary drivers of combined endpoint reduction

O. Alcohol Use
   1. The 2020–2025 dietary guidelines for Americans recommend moderate intake if alcohol is consumed only by adults of legal drinking age.
      a. Up to one drink per day for women
      b. Up to two drinks per day for men
      c. Consistent with 2019 ACC/AHA primary prevention guidelines
      d. The 2020 Dietary Guidelines Advisory Committee concluded that "no evidence exists to relax current Dietary Guidelines for Americans recommendations, and there is evidence to tighten them for men such that recommended limits for both men and women who drink would be 1 drink per day on days when alcohol is consumed."
      e. Despite this conclusion from the advisory committee, the 2020–2025 dietary guidelines for Americans continue previous recommendations (2 drinks/day for men and 1 drink/day for women).
      f. As stated earlier, the 2021 AHA scientific statement recommends that people who do not already consume alcohol do not start. The statement also does not support starting alcohol intake to improve CV health.
   2. One alcoholic drink-equivalent is defined as 14 g (0.6 fl oz) of pure alcohol.
   3. To calculate drink-equivalents, multiply the volume in ounces by the alcohol content in percent and divide by 0.6 oz of alcohol per drink-equivalent.
      a. About 12 oz of beer, 5 oz of wine, or 1.5 oz of liquor
   4. Excessive drinking is defined as:
      a. High-risk drinking: Consuming 4 or more drinks on any day or 8 or more drinks per week for women and 5 or more drinks on any day or 15 or more drinks per week for men
      b. Binge drinking is consuming 4 or more drinks for women or 5 or more drinks for men within about 2 hours.
      c. Any alcohol consumption by pregnant women or those younger than 21 years
      d. Excessive drinking is responsible for 1 in 10 deaths among working-age adults age 20–64.
   5. Individuals who should avoid alcohol consumption:
      a. Those taking certain prescription or over-the-counter medications
      b. Those recovering from alcoholism or who cannot control alcohol intake
      c. Those who are driving, planning to drive, or participating in other activities that require skill, coordination, and alertness
      d. Women who are pregnant or may become pregnant
   6. Combined use of caffeine and alcohol are not recognized as safe by the U.S. Food and Drug Administration (FDA) and should be avoided.
   7. Alcohol has several important consequences for CV health:
      a. Alcohol consumption may be responsible for 16% of HTN, and risk of HTN increases by 40% if patient consumes more than 14 standard drinks per week.
      b. Limiting daily alcohol consumption helps reduce blood pressure.
      c. Regular alcohol use is strongly linked to an increased incidence of atrial fibrillation.
      d. Regular alcohol use also increases risk of obstructive sleep apnea, obesity, metabolic syndrome, unexplained left ventricular hypertrophy, and heart failure

**Table 4.** Recommended Lifestyle Modifications

| Modification | Recommendation | Expected SBP Impact: Hypertension | Expected SBP Impact: Normotension |
|---|---|---|---|
| Weight reduction | Maintain a normal body weight (BMI 18.5–24.9 kg/m$^2$)<br>Expect 1 mm Hg reduction for each 1-kg reduction in body weight | -5 mm Hg | -2/3 mm Hg |
| Adopt DASH eating plan (includes substantial potassium intake) | Consume a diet rich in fruits, vegetables, and low-fat dairy products with a reduced content of saturated and total fat | -11 mm Hg | -3 mm Hg |
| Reduce dietary sodium intake | Reduce sodium intake to ≤ 2400 mg/day<br>Reducing sodium intake further to ≤ 1500 mg/day is associated with greater BP reduction<br>Reducing sodium intake by at least 1000 mg/day will lower BP if desired daily sodium intake goal is not achieved | -5/6 mm Hg | -2/3 mm Hg |
| Enhanced potassium intake from dietary sources | Target: 3500-5000 mg/day, preferably by a diet rich in potassium (certain fruits and vegetables) | -4/5 mm Hg | -2 mm Hg |
| Physical activity | Engage in regular aerobic physical activity such as brisk walking (at least 30 min/day most days of the week)<br>90-150 min/week at 65-75% heart rate reserve | -5/8 mm Hg | -2/4 mm Hg |
| Moderation of alcohol consumption | Limit intake to:<br>Men: 2 drinks/day (total: 24 oz of beer, 10 oz of wine, or 3 oz of 80-proof whiskey)<br>Women and those with lower body weight: 1 drink/day (total: 12 oz of beer, 5 oz of wine, 1.5 oz of 80-proof whiskey) | -4 mm Hg | -3 mm Hg |

BMI = body mass index; BP = blood pressure; DASH = Dietary Approaches to Stop Hypertension; oz = ounce; SBP = systolic blood pressure.

From: Whelton PK, Carey RM, Aronow WS, et al. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA guideline for the prevention, detection, evaluation, and management of high blood pressure in adults: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. J Am Coll Cardiol 2018;71:e127-e248

**Patient Case**

2. A 52-year-old male patient asks for recommendations to improve his CV risk through diet interventions. He asks which dietary interventions would improve his overall health. Which is the best response?
   A. Consume a diet high in animal proteins.
   B. Limit unsaturated fats to 5%-6% of dietary intake.
   C. Eliminate all sodium intake.
   D. Eliminate *trans* fat intake.

## VI. PHYSICAL ACTIVITY

A. Physical activity protects against CVD, reduces CV morbidity and mortality, and reduces risk factor development (HTN and obesity).

B. Sedentary lifestyle approaches smoking as a leading cause of preventable death.

C. 2008 Physical Activity Guidelines for Americans Issued by U.S. Health and Human Services: Describe major research of health benefits of physical activity. Recommendations are supported by AHA and American College of Sports Medicine 2011 recommendations.

1. Some physical activity is better than none.
2. Additional benefits are reaped because the amount of physical activity increases through higher intensity, greater frequency, and/or longer duration for most health outcomes.
3. Recommended activity levels:
    a. At least 30 minutes of moderate-intensity physical activity 5 days each week
    b. Vigorous aerobic activity for 25 minutes 3 days per week
    c. Some combination of options a and b
    d. All regimens should incorporate two or three sessions of resistance training each week.

D. 2018 Physical Activity Guidelines Advisory Committee Scientific Report further documents health benefits in increasing physical activity and increases flexibility in the ways to achieve the health benefits.

E. 2019 ACC/AHA Guideline of the Primary Prevention of Cardiovascular Disease
1. Adults should be encouraged to optimize physically active lifestyle at all healthcare encounters.
2. Adults should engage in a minimum of 150 minutes weekly of moderate-intensity (3.0–5.9 metabolic equivalents, or miles per hour) or 75 minutes weekly of vigorous-intensity (≥ 6 metabolic equivalents, or miles per hour) aerobic physical activity to reduce ASCVD risk.
3. Any amount of moderate- or vigorous-intensity physical activity can be beneficial to reduce risk of ASCVD.
4. Patients who are overweight or who have obesity may require 200-300 minutes/week of physical activity to maintain weight loss after 1 year.
5. Decreasing sedentary behavior may reduce ASCVD risk.

F. USPSTF Guideline on Behavioral Counseling, Diet, and Exercise for CV Prevention
1. Guidelines for adults with and without CV risk factors advise at least 150 minutes per week of moderate-intensity physical activity.
2. Behavioral change approach includes setting goals, active self-monitoring, addressing barriers, and motivational interviewing.

## VII. SMOKING CESSATION

A. About 4%–6% of the smoking population succeed annually.

B. 2019 ACC/AHA Guideline on Primary Prevention of Cardiovascular Disease suggests:
1. All adults should be assessed at each interaction for tobacco use.
2. Patient status for tobacco use should be recorded as a vital sign to facilitate tobacco cessation efforts.
3. All adults who use tobacco should strongly be advised to quit.
4. Behavioral intervention plus pharmacotherapy combination is recommended for greatest quit rate success.
5. All persons should avoid secondhand smoke exposure to reduce ASCVD risk.

C. 2021 USPSTF Guidelines
1. Recommend that clinicians ask all adults about tobacco use, advise them to stop using tobacco, and provide behavioral interventions and FDA-approved pharmacotherapy for cessation to non-pregnant adults who use tobacco
2. Recommend that clinicians ask all pregnant women about tobacco use, advise them to stop using, and provide behavioral interventions for cessation in pregnant women using tobacco
3. Insufficient evidence to assess balance of benefits and harms of pharmacotherapy interventions for tobacco cessation in pregnant women

4. Insufficient evidence to assess the balance of the benefits and harms of e-cigarettes for tobacco cessation. USPSTF recommends directing patients using tobacco to other tobacco cessation interventions with proven effectiveness and established safety.

**Box 3.** 5 A's Model for Treating Tobacco Use

| |
|---|
| Ask about tobacco use |
| Advise to quit |
| Assess willingness to make a quit attempt |
| Assist in quit attempt |
| Arrange follow-up |

Adapted from: Barua RS, Rigotti NA, Benowitz NL, et al. 2018 ACC expert consensus decision pathway on tobacco cessation treatment: a report of the American College of Cardiology Task Force on Clinical Expert Consensus Documents. J Am Coll Cardiol 2018;72:3332-65.

D. U.S. Public Health Service Clinical Practice Guideline Suggestions
   1. Brief treatment is effective.
   2. Seven first-line medications (five nicotine and two non-nicotine) increase long-term abstinence rates.

E. American Thoracic Society (ATS) Guidelines for Initiating Pharmacologic Treatment for Tobacco Dependence (2020)
   1. Cessation increases significantly if pharmacologic therapy is used.
   2. Categorizes medications as follows:
      a. Controllers: Delayed onset of effect; reduce the frequency and intensity of the impulse to smoke
      b. Relievers: Rapid onset of effect; helps relieve the impact of cue-based cravings
   3. Recommendations:
      a. Varenicline first line over bupropion
      b. Varenicline plus nicotine replacement is favored over varenicline alone.

F. Medications for Smoking Cessation
   1. Bupropion sustained release (SR): 150 mg orally every morning x 3 days; then 150 mg orally twice daily started 1–2 weeks before quit date
      a. Minimum 8 hours between doses/avoid bedtime dosing (insomnia)
      b. Contraindicated in patients with:
         i. Seizure disorder
         ii. History of anorexia nervosa or bulimia
         iii. Simultaneous discontinuation of alcohol, sedatives, or benzodiazepines
         iv. Monoamine oxidase inhibitor use in past 14 days
      c. Use in pregnancy: Animal testing has shown adverse effects to the fetus, though use in humans may have benefits that outweigh negative outcomes.
      d. Precautions: Patients younger than 18 years, using with other medications that lower seizure threshold
      e. Treatment duration is 7–12 weeks, with up to 6 months of maintenance therapy in selected patients.
      f. Adverse events: Insomnia, dry mouth, dizziness, nervousness, seizures (0.1% risk), neuropsychiatric symptoms (rare)
   2. Varenicline
      a. Available as 0.5- and 1-mg tablets
      b. Dosing: 0.5 mg daily in the morning on days 1–3, then 0.5 mg twice daily on days 4–7, then 1 mg orally twice daily thereafter for weeks 2–12. An additional 12-week course may be used. May start up to 35 days before quit date

   c. Dose adjustment required for a creatinine clearance less than 30 mL/minute/1.73 $m^2$: 0.5 mg orally daily for days 1–3; then maximum dose 0.5 mg orally twice daily thereafter
   d. Black box warning removed December 2016 regarding neuropsychiatric events
   e. Adverse events: Nausea, sleep disturbances, constipation, neuropsychiatric symptoms
3. Second-line Drugs for smoking cessation (non-FDA labeled)
   a. Nortriptyline 75–100 mg orally daily for 6–12 weeks in cessation trials
   b. Clonidine 0.15–0.45 mg orally daily in cessation trials. Monitor for dry mouth, dizziness, hypotension
4. Nicotine gum: Available as 2- and 4-mg over-the-counter medication
   a. Dose is based on how soon after awakening patients require their first cigarette (within 30 minutes, 4 mg, more than 30 minutes, 2 mg).
      i. Weeks 1–6: 1 piece every 1–2 hours
      ii. Weeks 7–9: 1 piece every 2–4 hours
      iii. Weeks 10–12: 1 piece every 4–8 hours
   b. Maximum: 24 pieces/day
   c. Chewing process: Chew and "park" when peppery taste/tingling sensation appears; resume after taste dissipates. Discontinue use after around 30 minutes.
   d. Avoid food/beverage for 15 minutes before or during use.
   e. Precautions: Avoid use within 14 days of MI, underlying arrhythmias, angina pectoris, temporomandibular joint disease
   f. Adverse events: Mouth/jaw soreness, hiccups, dyspepsia, salivation
5. Nicotine inhaler: Available in 10-mg cartridge that delivers a 4-mg inhalation
   a. Dose: 6–16 cartridges/day: Start with 1 cartridge every 1–2 hours.
      i. Puff continuously for 20 minutes.
      ii. Initially, use at least 6 cartridges daily.
      iii. Inhale to back of throat or puff in short breaths.
   b. Same precautions as for nicotine gum
   c. Adverse effects: Mouth and throat irritation, cough, headache, hiccups
6. Nicotine lozenge: Available in 2- or 4-mg lozenge
   a. Dosing for weeks 1–12 same as for nicotine gum
      i. Maximum dose is 20 lozenges/day.
      ii. Allow to dissolve slowly over 10–30 minutes.
      iii. Use for up to 12 weeks.
   b. Same precautions as for other nicotine preparations.
   c. Adverse effects: Nausea, hiccups, cough, heartburn
7. Nicotine nasal spray
   a. Available as a 10-mg/mL aqueous solution
   b. Dosing: One or two doses/hour (8–40 doses/day)
      i. One dose is 2 sprays (1 spray in each nostril) – Each spray delivers 0.5 mg of nicotine.
      ii. Do NOT sniff/swallow/inhale through the nose as spray is administered.
   c. Same precautions as for other nicotine preparations except that those with underlying chronic and nasal disorders and reactive airway disease should use caution
   d. Adverse events: Nose and throat irritation, rhinitis, tearing, sneezing, headache
8. Nicotine patch
   a. Available as 7-, 14-, and 21-mg patches
   b. Dosing is based on the number of cigarettes/day (may be increased for use of chewing tobacco).
      i. 10 or more cigarettes/day: 21 mg/day for 28–42 days, then 14 mg/day for 14 days, then 7 mg for 14 days
      ii. Fewer than 10 cigarettes/day: 14 mg/day for 42 days, then 7 mg/day for 14 days

   c. Rotate patch sites daily.
   d. May wear for 16 hours each day.
   e. Nighttime wear increases patient sleep disturbances for 8–10 weeks
   f. Precautions are similar to those for other nicotine products.
9. Combination medication options may include the following, which have improved cessation rates compared with either therapy alone:
   a. Bupropion SR plus nicotine patch
   b. Bupropion SR plus nicotine lozenge or gum
   c. Varenicline plus nicotine patch, lozenge, or gum
10. Counseling and medication are more effective either intervention alone.

G. Cognitive-Behavioral Therapy: Improves success of quit attempt

H. Other Nonpharmacologic Therapies with Minimal Evidence
   1. Hypnosis
   2. Acupuncture

I. Relative Effectiveness of Pharmacotherapy vs. Nicotine-Replacement Therapy (NRT)
   1. EAGLES trial randomized 8144 smokers in a 1:1:1:1 fashion to varenicline 1 mg twice daily, bupropion 150 mg twice daily, nicotine patch 21 mg per day with taper, or placebo.
   2. Varenicline was associated with higher abstinence rates than placebo (OR 3.61; 95% CI, 3.07-4.24), nicotine patch (OR 1.68; 95% CI, 1.46-1.93), and bupropion (OR 1.75; 95% CI, 1.52-2.01).
   3. Bupropion was associated with higher abstinence rates than placebo (OR 2.07; 95% CI, 1.75-2.45).
   4. Nicotine patch was associated with higher abstinence rates than placebo (OR 2.15; 95% CI, 1.82-2.54).
   5. Rates of moderate-severe neuropsychiatric adverse events were low and did not differ by group.
   6. Rates of major adverse CV events were also low and did not differ by group.
   7. Continuous abstinence rates:
      a. Varenicline 33.5% (weeks 9-12) and 21.8% (weeks 9-24)
      b. Bupropion 22.6% (weeks 9-12) and 16.2% (weeks 9-24)
      c. Nicotine patch 23.4% (weeks 9-12) and 15.7% (weeks 9-24)
      d. Placebo 12.5% (weeks 9-12) and 9.4% (weeks 9-24)

**Patient Cases**

3. Which recommendation for nicotine replacement is most appropriate for a 38-year-old man who wishes to stop smoking after a 10 pack-year history? He states he smokes his first cigarette about 1 hour after awakening each day and uses about 20 cigarettes each day.
   A. Nicotine 14-mg patches: 1 daily for 6 weeks, then 7-mg patches daily for 2–4 weeks.
   B. Nicotine 7-mg patches: 1 daily for 6 weeks, then discontinue.
   C. Nicotine 21-mg patches: 1 daily for 2 weeks, then 14-mg patches daily for 2–4 weeks, then 7 mg patches daily for 2 weeks, then discontinue.
   D. Nicotine gum 4 mg 1 or 2 pieces every 1–2 hours for 6 weeks, then taper.

4. A 31-year-old patient presents to the pharmacy with a prescription for bupropion. The patient informs you that she plans to quit smoking. The new prescription is appropriately dosed, and the patient has no contraindications to therapy. Which counseling point is most appropriate for this patient?
   A. Avoid bedtime dosing and allow at least 8 hours between doses because it may cause insomnia.
   B. Patients may gain weight while taking this medication.
   C. Take the medication for up to 1 year.
   D. Start the medication 1 month before the anticipated quit date.

5. A 42-year-old woman presents to the pharmacy with a desire to quit smoking. Her medical history is noncontributory. Her social history includes 2 pack/day smoking, with the first cigarette smoked within 15 minutes of awakening. She has not previously tried any smoking cessation products, given that this is her first quit attempt. The patient has commercial prescription insurance. Which initial smoking cessation treatment is most appropriate at this time to augment the cognitive behavioral support she is receiving from 1-800-QUIT NOW?
   A. Nicotine 21 mg 24-hour patch daily for 12 weeks.
   B. Nicotine 14 mg 24-hour patch daily for 6 weeks, then 7 mg/day for 2 weeks.
   C. Nicotine gum 2 mg 1 piece every 1–2 hours for 6 weeks, then taper.
   D. Varenicline 0.5 mg orally daily for 3 days, then 0.5 mg twice daily for 4 days, then 1 mg twice daily for 2-12 weeks.

J. Smokeless Tobacco
   1. Treatments for smokeless tobacco differ, in part, because of differing characteristics of its use.
   2. Normal dip or chew contains 2–3 times the nicotine content of a cigarette (average cigarette nicotine content is 1.8 mg).
   3. Nicotine absorption takes longer: Smokeless tobacco nicotine absorption takes up to 30 minutes for dopamine release to occur.
   4. Nicotine absorption from smokeless tobacco continues for up to 60 minutes after tobacco is removed from mouth.
   5. Behavioral therapy (identifying triggers, modifying behaviors) in addition to nicotine replacement therapy appears to be most effective.
   6. Doses for nicotine replacement therapy are often higher than those for cigarette smokers and are based on cans or pouches of tobacco used per week. Dosing suggestions are reflected in Table 5.

**Table 5.** Nicotine Patch Dosing Instructions for Smokeless Tobacco Cessation

| Cans/Pouches per Week | Starting Dose/Duration | Taper Instructions |
|---|---|---|
| > 3 | Up to 42-mg patches daily for 4–6 weeks | Taper by 7- to 14-mg steps every 2–4 weeks |
| Two or three | Up to 21-mg patches daily for 4–6 weeks | Taper by 7- to 14-mg steps every 2–4 weeks |
| < 2 | 14-mg patches daily for 4–6 weeks | Taper by 7- to 14-mg steps every 2–4 weeks |

7. Nicotine lozenge dosing instructions are based on time to first use and number of cans or pouches per week (monotherapy may not be as effective).
    a. First use within 30 minutes of awakening or more than 3 cans or pouches weekly, 4-mg lozenge (1 or 2 lozenges every 1–2 hours) up to 20 per day for up to 12 weeks
    b. First use after 30 minutes of awakening if less than 3 cans or pouches weekly, 2-mg lozenge (1 or 2 lozenges every 1–2 hours) up to 20 per day for up to 12 weeks
8. Nicotine gum dosing instructions are based on time to first use and number of cans or pouches per week (monotherapy may not be as effective).
    a. First use within 30 minutes of awakening or more than 2 cans or pouches weekly, 4-mg gum (1 or 2 pieces every 1–2 hours) up to 10–12 pieces/day for up to 12 weeks
    b. First use after 30 minutes of awakening if less than 2 cans or pouches weekly, 2-mg gum (1 or 2 pieces every 1–2 hours) up to 10–12 pieces/day for up to 12 weeks
9. Combination therapy options combine nicotine patches with gum or lozenges for improved success in quit attempts.
10. Varenicline and bupropion SR currently have no data supporting use for smokeless tobacco cessation attempts.
11. A randomized trial of e-cigarettes versus NRT in combination with behavioral support has shown a potential role in quit efforts.
    a. 886 people in the UK National Health Service were randomized to NRT (single- or combination-product use) versus an e-cigarette with a standardized 18-mg/mL nicotine liquid starter pack. Both arms were supported with 4 weeks of behavioral intervention.
    b. Primary outcome measure: 1-year abstinence rate
    c. E-cigarette group abstinence rate was 18.0%, NRT group abstinence rate was 9.9% (relative risk 1.83; CI, 1.30–2.58; $p<0.001$)
    d. Rates of continued e-cigarette use at 1 year were significant (96.6% of arm), which may be problematic with unknown long-term exposure to e-cigarette products.
12. Additional reports of lung injury from e-cigarettes and vaping products have been reported in the past 24 months –use cannot be recommended as an alternative or replacement for nicotine at this time.

## VIII. WEIGHT MANAGEMENT/OBESITY

A. Background and Definitions
    1. Obesity prevalence in the United States was 41.9% from 2017 to March 2020.
        a. Between 1999 and March 2020, obesity prevalence in the United States increased from 30.5% to 41.9%.
        b. The prevalence of severe obesity increased from 4.7% to 9.2% during the same period.
    2. The cost associated with medical care for obesity was estimated at $173 billion (estimated cost in 2019 dollars).
        a. Adults with obesity incurred medical costs $1861 higher than adults of normal weight.
        b. Individuals with class III obesity (BMI ≥ 40 kg/m$^2$) incur 81% more costs than normal-weight adults.

3. National Health Interview Survey and 1996 Medical Expenditure Panel Survey show that the prevalence of CVD is proportional to the BMI.
    a. 20% of normal-weight individuals have CVD.
    b. 28% of overweight individuals have CVD.
    c. 39% of individuals with obesity have CVD.
4. A clinically significant weight loss of 5%–10% of starting weight improves CVD risk factors.
5. Type 2 diabetes, HTN, dyslipidemia, metabolic syndrome, CVD, osteoarthritis, cancer, and sleep apnea have been ameliorated with weight reduction.
6. Waist circumference is an independent predictor of risk of:
    a. CVD
    b. Type 2 diabetes
    c. Dyslipidemia
    d. HTN
    e. All-cause mortality
7. Table 6 below demonstrates weight classification by BMI and waist circumference: this may be used to express one's ASCVD risk as compared to a normal weight individual with a normal waist circumference.
8. Waist circumference should be measured in all patients with a BMI less than 35 kg/m$^2$ because it may be more useful in patients with central adiposity.
    a. Elevated waist circumference defined as:
        i. 40 inches or greater in men
        ii. 35 inches or greater in women
    b. Combining BMI and waist circumference may be a more appropriate strategy for assessing CV risk related to obesity.

**Table 6.** Weight Classification by BMI and Waist Circumference

| | | **Disease Risk Relative to Normal Weight and Waist Circumference** | |
|---|---|---|---|
| **Classification** | **Body Mass Index (kg/m$^2$)** | **Men < 40 in (102 cm) Women < 35 in (88 cm)** | **Men > 40 in (102 cm) Women > 35 in (88 cm)** |
| Underweight | < 18.5 | | |
| Normal weight | 18.5–24.9 | | |
| Overweight | 25–29.9 | Increased | High |
| Obese class I | 30–34.9 | High | Very high |
| Obese class II | 35–39.9 | Very high | Very high |
| Obese class III | ≥ 40 | Extremely high | Extremely high |

Information from: NHLBI Obesity Education Initiative Expert Panel. The Information from: NHLBI Obesity Education Initiative Expert Panel on the Identification, Evaluation, and Treatment of Overweight and Obesity in Adults. The practical guide: identification, evaluation, and treatment of overweight and obesity in adults. National Institutes of Health and National Heart, Lung and Blood Institute. October 2000:1-94. (NIH Publication 00-4084).

B. 2019 ACC/AHA Guideline on the Primary Prevention of Cardiovascular Disease
    1. Weight loss is recommended to improve ASCVD risk profile in those who are overweight or obese.
    2. Comprehensive lifestyle modifications, counseling, and calorie restriction are recommended to achieve and maintain weight loss.
    3. BMI calculation is recommended at least annually.
    4. Measurement of waist circumference is reasonable to stratify those patients who may be at higher cardiometabolic risk.

C. Obesity and CVD
   1. Associated with increased risk of morbidity and mortality and reduced life expectancy
   2. May affect cardiac structure and function because of increased amounts of adipose tissue, altered metabolic profile, and increased metabolic demand
   3. Individuals with obesity tend to have increased cardiac output and reduced systemic peripheral resistance compared with normal-weight individuals.
   4. Meaningful weight loss (at least 5% initial weight) may improve blood pressure, LDL, TG, and glucose and/or may delay onset of diabetes.

D. Drugs Associated with Weight Gain
   1. Drug-induced weight gain is a modifiable risk factor. Table 7 identifies common therapies that are associated with weight gain, and suggestions for weight neutral or negative alternatives.
   2. Weight gain may be neutral in near-term but may increase weight over extended long-term use.

**Table 7.** Drugs Associated with Weight Gain and Alternative Drug Options

| Drugs Causing Weight Gain | Weight Neutral or Loss Alternatives |
|---|---|
| **Diabetes Drugs** | |
| Insulin<br>Sulfonylureas (glyburide and glipizide)<br>Meglitinides<br>Thiazolidinediones | Glimepiride, metformin, DPP4 inhibitors, acarbose, GLP-1 agonist, pramlintide, SGLT2 inhibitors |
| **Psychiatric Drugs** | |
| Antidepressants (SSRIs, TCAs, MAOIs, mirtazapine)<br>Antipsychotics (clozapine, olanzapine, and risperidone)<br>Anticonvulsants (valproic acid, gabapentin, carbamazepine)<br>Lithium | Fluoxetine, bupropion<br>Aripiprazole, quetiapine, ziprasidone<br>Lamotrigine, topiramate, zonisamide |
| **Antihypertensive Drugs** | |
| Nonselective β-blocker (namely propranolol)<br>α-Adrenergic blockers (prazosin, clonidine) | ACE inhibitors, ARBs, calcium channel blockers, selective β-blockers |

ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; GLP-1 = glucagon-like peptide-1; MAOI = monoamine oxidase inhibitor; SGLT2 = sodium glucose cotransporter-2; SSRI = selective serotonin reuptake inhibitor; TCA = tricyclic antidepressant.

Information from: Hollander P. Anti-diabetes and anti-obesity medications: effects on weight in people with diabetes. Diabetes Spectrum 2007;20:159-65; Malone M. Medications associated with weight gain. Ann Pharmacother 2005;39:2046-55.

E. Management of Weight Loss/Treatment of Obesity (See Figure 1 for summary graphic of this management algorithm.)
   1. Diet, exercise, and behavioral modification therapies should be included in all weight management approaches.
   2. Pharmacotherapy and bariatric surgery should be considered adjunctive therapies to behavior change and increased physical activity.
   3. Pharmacotherapy may be indicated at a BMI greater than 30 $kg/m^2$ (or a BMI greater than 27 $kg/m^2$ with comorbidity).
   4. Bariatric surgery may be considered at a BMI greater than 35 $kg/m^2$ with comorbidity or at a BMI greater than 40 $kg/m^2$.
   5. Bariatric surgery reduces mortality and improves glycemic control, lipid panels, and blood pressure.
   6. The Swedish Obese Subjects study was a nonrandomized, prospective, controlled study of 2010 individuals with obesity who underwent bariatric surgery and 2037 matched controls who received usual care.

a. Median follow-up was 14.7 years.
b. 11% of the population had diabetes.
c. CV death was reduced in the intervention arm (adjusted hazard ratio [HR] 0.47; 95% confidence interval [CI], 0.29–0.76, p=0.002), showing continued benefit from ongoing care post-surgery.

F. Goals for Weight Loss
1. Goal of 5%–10% weight loss from baseline within 6 months is beneficial.
2. Initial step: Participate in comprehensive lifestyle program for at least 6 months.
a. Focus on lower-calorie dietary intake, increased physical activity, and behavioral strategies.
b. Average weight loss of up to 8 kg within 6 months for programs that incorporate all three strategies; socioeconomic context also needs to be considered when establishing a strategy

G. Nonpharmacologic Therapies for Obesity
1. Energy deficit must be created to reach weight-loss goals.
a. Option 1: Limit intake to 1200–1500 kcal/day for women and 1500–1800 kcal/day for men, with body weight adjustments.
b. Option 2: Use formula to estimate an individual's daily energy intake and then develop a 500- to 750-kcal/day reduction to achieve a 30% energy deficit. Examples include the World Health Organization formula and the Harris-Benedict equation.
c. Restrict or eliminate a certain group or type of foods to reduce energy intake.
2. Develop and maintain physical activity to maintain weight loss and prevent regaining of weight (see Physical Activity section).
3. Cognitive-behavioral therapy to modify thoughts and beliefs regarding weight, behaviors for successful weight loss with face-to-face meetings and ongoing support
4. Sleep
a. National Sleep Foundation–recommended sleep duration is 7–9 hours each night.
b. Sleeping less than 6 hours per night appears to be an emerging risk factor for obesity.

H. Pharmacotherapy for Obesity
1. There are currently five FDA-approved medications for obesity management: liraglutide, semaglutide, naltrexone/bupropion, orlistat, and phentermine/topiramate.
2. May be considered for individuals who:
a. Do not achieve a 5% minimum weight loss after a 6-month comprehensive intervention
b. Have a BMI of 30 $kg/m^2$ or greater
c. Have a BMI of 27–29.9 $kg/m^2$ with at least one additional risk factor for developing CVD
3. Liraglutide (3 mg daily)
a. MOA: Acts at proopiomelanocortin (POMC) neurons to cause satiety by glucagon-like peptide-1 receptor
b. FDA indicated as adjunct to reduced-calorie diet and physical activity for weight loss in BMI 30 $kg/m^2$ or higher or BMI 27 $kg/m^2$ or higher with at least one additional weight-related comorbidity (with or without diabetes)
c. Associated with a 5.6-kg weight loss at 1 year (or 5.4% weight loss)
d. Black box warning: Thyroid C-cell tumors in rodents; human relevance has not been determined. Warnings: May cause acute pancreatitis, acute gall bladder disease, renal impairment; may increase heart rate
4. Semaglutide (2.4 mg once weekly)
a. MOA: Acts at POMC neurons to cause satiety by glucagon-like peptide-1 (GLP-1) receptor
b. FDA indicated as an adjunct to a reduced-calorie diet and increased physical activity in patients with a BMI of 30 $kg/m^2$ or greater or 27 $kg/m^2$ or greater with at least one weight-related comorbid condition (e.g., HTN, diabetes, dyslipidemia)

   c. STEP trials assessing weight-loss efficacy versus placebo at 68 weeks
      i. STEP 1: 12.5% weight loss (or 12.7 kg)
      ii. STEP 2: 6.2% weight loss (or 6.1 kg)
      iii. STEP 3: 10.5% weight loss (or 10.6 kg)
   d. Semaglutide versus liraglutide RCT:
      i. STEP 8: 15.8% (semaglutide) versus 6.4% (liraglutide) weight loss at 68 weeks (-15.3 kg vs. -6.8 kg weight loss)
      ii. Although not yet incorporated into professional guidelines, STEP 8 suggests semaglutide is more effective than liraglutide for weight loss.
   e. Black box warning: Thyroid C-cell tumors in rodents; human relevance has not been determined. Warnings: May cause acute pancreatitis, acute gallbladder disease, hypoglycemia, acute kidney injury, heart rate increase
5. Phentermine (Ionamin 30–37.5 mg/day):
   a. Mechanism of action (MOA): Stimulates hypothalamus to release norepinephrine, resulting in appetite suppression
   b. Associated with a 3%–5% weight loss
   c. Adverse effects: Mean blood pressure and heart rate elevations, headache, insomnia, palpitations, ischemic CV events, euphoria, diarrhea, dry mouth, urticarial, impotence
   d. Avoid in patients with anxiety disorders, serious structural cardiac abnormalities, cardiomyopathy, serious arrhythmias, other serious cardiac problems that increase risk of sudden cardiac death, monoamine oxidase inhibitor use, pregnancy, breastfeeding, hyperthyroidism, history of drug abuse
   e. Has been identified by AHA as an agent that may be directly toxic to myocardium
   f. Use caution in patients with mild HTN and other CV conditions that may be exacerbated by increased blood pressure or heart rate.
   g. Approved for short-term use only (3 months)
6. Phentermine/topiramate (3.75 mg of phentermine/23 mg of topiramate extended release starting dose, increase to 15 mg of phentermine/92 mg of topiramate extended release daily maximum dose)
   a. MOA: GABA receptor modulator that releases norepinephrine (addiction potential)
   b. Associated with a greater than 5% weight loss at 1 year
   c. Teratogenic: Obtain negative pregnancy test at baseline and monthly thereafter.
   d. Precautions: Monitor for depression, glaucoma, cognitive impairment
   e. Avoid using with monoamine oxidase inhibitors.
   f. REMS (Risk Evaluation and Mitigation Strategies) program
7. Naltrexone/bupropion (16 mg/180 mg twice daily):
   a. MOA: Dopamine and norepinephrine reuptake inhibitor that acts at POMC neurons to increase satiety and opioid antagonist
   b. Moderate weight loss (8.2%–11.5% at 1 year) potential
   c. Black box warning: Monitor for suicidal behavior and ideation.
   d. Avoid dosing with high-fat meals; contraindicated in patients with uncontrolled HTN, seizure disorders, anorexia nervosa or bulimia, drug or alcohol withdrawal and patients taking monoamine oxidase inhibitors
8. Orlistat (60–120 mg three times daily, over-the-counter 60-mg dose, Rx 120 mg dose)
   a. MOA: Pancreatic and gastric lipase inhibitor that blocks absorption of one-third of fat calories and is excreted unchanged
   b. Associated with a 3% weight loss at 1 yr
   c. Take with multivitamin, may cause gastrointestinal (GI) events with high-fat diet, contraindicated with narrow therapeutic index drugs (levothyroxine, warfarin, antiepileptic drugs)

9. Lorcaserin
    a. MOA: Serotonin active agent that activates the serotonin-2c receptor
    b. On February 13, 2020, the FDA requested that the manufacturer voluntarily withdraw immediate- and extended-release lorcaserin from the U.S. market because of cancer signal in a safety trial.
    c. No additional monitoring is recommended at this time for patients who have taken lorcaserin.

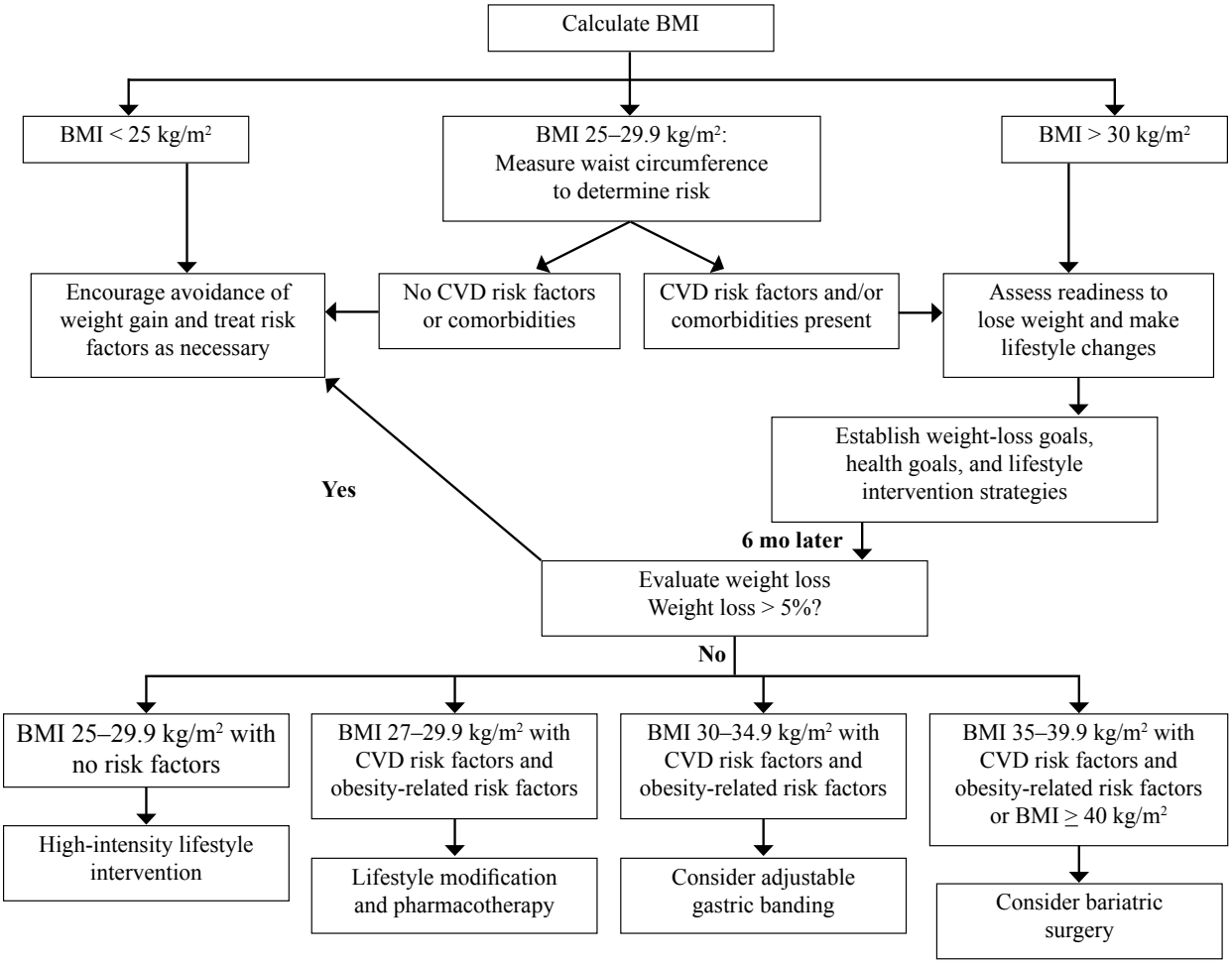


**Figure 1.** General approach to obesity management.

Information adapted from: Jensen MD, Ryan DH, Apovian CM, et al. 2013 AHA/ACC/TOS guideline for the management of overweight and obesity in adults: a report of the American College of Cardiology/American Heart Association task force on practice guidelines and the Obesity Society. Circulation 2014;129(25 suppl 2):S102-38.

**Table 8.** Agent Selection for Obesity Medications

| Concomitant Medical Condition | Avoid Medications | Suggested Medications |
|---|---|---|
| **Uncontrolled hypertension or history of heart disease** | Phentermine and diethylpropion (sympathomimetic agents) | Orlistat |
| **Type 2 diabetes** | | GLP-1 agonist or SGLT2 inhibitors |
| **Seizure history** | Phentermine, naltrexone/bupropion | |
| **Depression** | | Phentermine/topiramate, phentermine, orlistat |

## IX. DIABETES MANAGEMENT

A. Background
   1. CVD is a major cause of morbidity and mortality in patients with diabetes.
   2. 1.9 million U.S. adults older than 20 have been given a diagnosis of diabetes.
   3. Patients with diabetes have a:
      a. 3-fold increase in CV mortality compared with age-matched individuals without diabetes
      b. 2-fold increase in overall mortality compared with age-matched individuals without diabetes
   4. In 2008, the FDA issued drug development recommendations for companies to ensure that new and existing therapies did not increase CV risk.
   5. The European Medicines Agency issued similar recommendations in 2012.
   6. The FDA released a new guidance document in March 2020 updating the 2008 recommendations. Updated formal recommendations have not yet been released.
   7. CV safety profiles may be used to facilitate the most appropriate medication selection and management.
   8. ADA 2022 Standards recognize the risks associated with clinical inertia and need for shared decision making.
   9. Prediabetes is associated with an increased CV risk, so regular screening for and treatment of modifiable risk factors for CVD are suggested.
      a. Self-management education and support programs may assist patients with prediabetes with strategies to prevent the progression of, or delay the development of, diabetes.
   10. ADA 2022 Standards Section 10: Cardiovascular Disease and Risk Management was endorsed by the American College of Cardiology.
      a. CV risk factors should be assessed annually:
         i. Obesity/overweight
         ii. HTN
         iii. Dyslipidemia
         iv. Smoking
         v. Family history of premature coronary disease
         vi. CKD
         vii. Albuminuria
      b. Blood pressure targets address role of individualized targets (Table 9).
         i. In patients with diabetes and HTN with a 10-year ASCVD risk of less than 15%, treat to target 140/90 mm Hg.
         ii. In patients with diabetes and HTN with existing ASCVD or a higher 10-year ASCVD risk of 15% or greater, treat to target of less than 130/80 mm Hg if it can safely be attained.
         iii. In pregnant patients with diabetes and HTN, a blood pressure target of 110-135/85 mm Hg or less is recommended.
         iv. All patients with diabetes and HTN should monitor blood pressure at home.
         v. Recommendations from ADA differ from 2017 ACC/AHA recommendations for patients with diabetes.
         vi. ACC/AHA recommends goal blood pressure less than 130/80 mm Hg for adults with diabetes and HTN.

**Table 9.** 2022 ADA Guidelines Goal BP Values for Patients with Diabetes (goals vary)

| Patient Population | Goal BP (mm Hg) |
|---|---|
| People with diabetes and HTN with ASCVD risk 15% or more (a higher target of < 140/90 may be appropriate if the lower value cannot be obtained). If lower risk for ASCVD with 10-year ASCVD risk < 15%, BP goal is <140/90[a] | < 130/80 |
| Pregnancy with diabetes[a] | 110-135/85 |
| In adults both with and without diabetes having a urine albumin excretion < 30 mg/24 hr (or equivalent) whose BP is consistently > 140/90 mm Hg[b] | ≤ 140/90 |
| In adults both with and without diabetes having a urine albumin excretion ≥ 30 mg/24 hr (or equivalent) whose BP is consistently > 130/80 mm Hg[b] | ≤ 130/80 |

[a]American Diabetes Association. 10. Cardiovascular disease and risk management: Standards of Medical Care in Diabetes-2022. Diabetes Care 2022;45:S144-S174 .

[b]KDIGO clinical practice guideline for the management of blood pressure in chronic kidney disease. Kidney Int Suppl 2012;2:341-2.

CKD = chronic kidney disease.

c. ASCVD risk calculator (Risk Estimator Plus) use is incorporated as a component of risk assessment and to elucidate treatment plans (http://tools.acc.org/ASCVD-Risk-Estimator-Plus).
d. Aspirin use in primary prevention was updated to reflect newer data (see section on aspirin in primary prevention for full discussion).
e. ADA-European Association for the Study of Diabetes (ADA-EASD) recommendations outline useful medications with proven cardiovascular benefit in those persons with ASCVD.
f. In patients with type 2 diabetes, consideration of comorbidities (ASCVD, HF, CKD), hypoglycemic risk, cost, adverse effects, and weight impact should be weighed with therapy selections.

B. Pharmacotherapy Recommendations:
1. First-line therapy depends on comorbidities, patient-centered treatment factors, and management needs and usually includes metformin and comprehensive lifestyle modifications. (Note: this is a change from past guidelines, which recommended metformin first line.)
2. Other medications (GLP-1 receptor agonist, sodium-glucose cotransporter-2 [SGLT2] inhibitors) with or without metformin according to glycemic needs are appropriate initial therapy for individuals with type 2 diabetes with, or at high risk of, ASCVD, HF, and/or CKD.
3. Among patients with type 2 diabetes and established ASCVD or indicators of high CV risk, established CKD, or HF, an SGLT2 inhibitor and/or a GLP-1 receptor agonist with demonstrated CVD benefit is recommended independent of baseline A1C, A1C target, and metformin use and in consideration of patient-specific factors.
4. Patients with documented ASCVD or indicators of high risk should be offered an SGLT2 inhibitor or GLP-1 receptor agonist that have demonstrated CVD benefit.
5. Patients with heart failure with reduced ejection fraction (HFrEF) (with or without diabetes) should be prescribed an SGLT2 inhibitor.
6. Patients with CKD (with or without diabetes) should be considered for SGLT2 inhibitor therapy. GLP-1 receptor agonist with proven CVD benefit may be used if SGLT2i is not tolerated or is contraindicated.
7. Patients with ASCVD and diabetes or diabetes with several CV risk factors should be considered for SGLT2 inhibitor therapy to prevent new-onset HFrEF.
8. Other patients at risk of developing HFrEF should be considered for SGLT2 inhibitor therapy.

C. Select Medications That May Reduce CV Risk in Type 2 Diabetes
1. Pioglitazone: Studied for secondary prevention in patients post-stroke and those with documented CVD
a. May worsen HF by inducing sodium-water retention

2. Liraglutide: Studied in the LEADER trial
    a. Included adult patients with at least one risk factor for CVD older than 60 and patients with documented CVD older than 50
    b. Assigned patients to liraglutide 1.8 mg daily or placebo for mean follow-up 3.8 years follow-up to 1 degree end point of first major adverse CV event
    c. Liraglutide reduced primary major adverse CV events from 14.9% to 13.0% (HR 0.87; 95% CI, 0.78–0.97; p=0.01) compared with placebo.
    d. CV death and all-cause mortality were reduced more significantly than were nonfatal MI and nonfatal stroke.
3. Empagliflozin:
    a. EMPA-REG OUTCOME trial, which included 7020 patients with diabetes and CVD, found reduced primary composite outcome of CV death, nonfatal MI, or nonfatal CVA from 12.1% to 10.5% (HR 0.86; 95% CI, 0.74-0.99; p=0.04) with empagliflozin.
    b. Finding was driven by the reduction in CV mortality (reduced from 5.9% to 3.7%).
    c. Beneficial findings noted within first 30–60 days of study, sustained throughout median 3.1 years of follow-up
    d. Of importance, empagliflozin did not reduce individual rates of MI or stroke
    e. Reduced heart failure hospitalizations by 35%, including in patients with no history of heart failure
    f. Has FDA indication for reducing CV mortality
    g. EMPEROR-Reduced trial, which included 3730 patients with HFrEF (with or without diabetes) for a median of 16 months, found a 25% reduction in CV death or HF hospitalization (NNT 19).
    h. Outcome driven by a 31% reduction in HF hospitalization (NNT 20); no mortality benefit observed
    i. Lack of mortality benefit may be because of lack of power (smaller and shorter follow-up than in DAPA-HF). Subsequent prespecified meta-analysis of DAPA-HF and EMPEROR-Reduced found a 13% reduction in all-cause mortality.
    j. EMPEROR-Preserved trial, which included 5988 patients with HF with preserved EF (HFpEF) (with or without diabetes) for a median of 26 months, found a 21% reduction in CV death or HF hospitalizations (NNT 31). Outcome driven by a 29% reduction in HF hospitalizations (NNT 32), no mortality benefit observed. Empagliflozin became the first medication to reduce CV death and HF hospitalizations in patients with HFpEF. FDA updated labeling to reduce risk of CV death and HF hospitalization in adults (previous labeling specified HFrEF).
4. Canagliflozin:
    a. CANVAS trial included 10,142 participants with type 2 diabetes, average age 63 years; 66% had established CVD
    b. Randomization to canagliflozin or placebo for 3.6 years.
    c. Canagliflozin significantly reduced CV composite outcome (HR 0.86; 95% CI, 0.75-0.97; p<0.001 for noninferiority, p=0.02 for superiority).
    d. Did not reduce individual outcomes of CV death, MI, or stroke
    e. Benefit driven by 33% reduction in heart failure hospitalization
    f. Increased risk of lower limb amputation in CANVAS trial, but not observed in CREDENCE trial
    g. FDA recently softened wording of amputation risk; no longer a black box warning but still a warning
    h. Risk of amputation seems higher in older patients with several comorbidities.
    i. CREDENCE included 4401 patients with eGFR 30-90 mL/minute/1.72 $m^2$ and diabetes for a median of 2.6 years.
    j. CREDENCE found reduction in renal outcomes, including onset of end-stage renal disease. No effect on mortality

5. Dapagliflozin:
    a. DECLARE TIMI 58 included 17,160 patients (10,186 without CVD).
    b. Randomization to dapagliflozin or placebo for 4.2 years
    c. Therapy was noninferior to placebo for major adverse CV events; did not reduce major adverse CV events (8.8% vs. 9.4% placebo, p=0.17)
    d. No effect on individual outcomes of MI or stroke
    e. Reduced heart failure hospitalizations, including in patients with no history of heart failure
    f. DAPA-HF trial, which included 4744 patients with HFrEF (with or without diabetes) for a median of 18 months, found a 26% reduction in composite of CV death or worsening heart failure (NNT 21), as well as reductions in: heart failure hospitalization (NNT 20), CV death (NNT 53), and all-cause mortality (NNT 44)
    g. DAPA-CKD trial, which included 4304 adults (with or without diabetes) and eGFR 25-75 mL/minute/1.72$^2$ for median 2.4 years, found reduction in renal outcomes, included onset of end-stage renal disease
    h. Also observed reduction in heart failure hospitalization or CV death (NNT 56) and all-cause mortality (NNT 48)
    i. Dapagliflozin was granted FDA indication for reducing the risk of CV death and heart failure hospitalization in patients with HFrEF.
6. Ertugliflozin (VERTIS-CV [diabetes and ASCVD]) and sotagliflozin (SOLOIST-WHF [HFrEF hospitalization and diabetes] and SCORED [diabetes with CKD and CV risk factors]) have also recently been associated with reductions in heart failure hospitalizations across heterogeneous patient populations.
7. A summation of CV effects by drug class may be found in Table 10.

**Table 10.** CV Effects Noted by Therapeutic Drug Class

| Drug | Action | Weight Effects | Causes Hypoglycemia | ASCVD CV Effects | HF CV Effects |
|---|---|---|---|---|---|
| Biguanides (metformin) | Lower glucose by increasing peripheral tissue sensitivity to insulin | Modest weight loss | Minimal risk of hypoglycemia | Potential benefit | Neutral |
| Sulfonylureas | Increase insulin production at pancreas | Weight increase | Significant risk of hypoglycemia | CV mortality, nonfatal MI, and mortality risk increased with monotherapy/ neutral | Neutral |
| Meglitinides | Insulin secretagogues | Weight increase | Modest risk of hypoglycemia | Unknown effects on CV system/no improvement in CV outcomes | Unknown |

**Table 10.** CV Effects Noted by Therapeutic Drug Class (*Cont'd*)

| Drug | Action | Weight Effects | Causes Hypoglycemia | ASCVD CV Effects | HF CV Effects |
|---|---|---|---|---|---|
| Thiazolidinediones | Peroxisome proliferator–activated receptor agonist to increase glucose use and decrease glucose production in peripheral tissue | Weight increase | Low risk of hypoglycemia | Pioglitazone reduced composite morbidity/mortality end point in patients with type 2 DM Rosiglitazone may be associated with increased risk of MI, though CV and all-cause mortality link is unclear | All agents contraindicated for use in HF NYHA classes III and IV. Use caution and close monitoring for signs and symptoms of edema or HF when treating with these agents |
| GLP-1 receptor agonists | Augment insulin response based on glucose, regulate postprandial glucagon secretion, slow gastric emptying, and increase satiety | 5.4%–12.5% reduction in body weight compared with placebo (higher weight reductions more closely associated with semaglutide) | Minimal risk of hypoglycemia | Liraglutide approved for CVD benefit > semaglutide > exenatide extended release Large CV outcome trials with semaglutide in obesity ongoing | Neutral |
| Dipeptidyl peptidase 4 inhibitors (DPP-4) | Block destruction of incretin | Weight neutral | Low risk of hypoglycemia | Potential risk: saxagliptin, alogliptin | Potential risk: saxagliptin, alogliptin |
| α-Glucosidase inhibitors | Competitively block α-glucosidase and prevent complex carbohydrate digestion | | Low risk of hypoglycemia | Shown in clinical trials to reduce HTN and CV events | No data |
| Sodium-glucose cotransporter-2 inhibitors | Reduce renal glucose reabsorption and lower blood glucose concentrations | 1- to 2-kg weight reduction | Minimal risk of hypoglycemia | None have shown reduction in MI or stroke. Empagliflozin reduced CV death in one trial | Empagliflozin, canagliflozin, dapagliflozin, ertugliflozin, and sotagliflozin show benefit |
| Pramlintide | Amylin analog that is cosecreted with insulin to regulate blood glucose by slowing gastric emptying, reducing post-meal hyperglycemia | 1.5-kg weight reduction | Significant hypoglycemia in combination with insulin use | No CV data supporting benefit | No data |
| Bromocriptine | Dopamine-2 receptor agonist that reduces plasma glucose, A1C, and TG | | Low risk of hypoglycemia | Reduced first CV event composite end point at 1 yr | No data |

DM = diabetes; HF = heart failure; NYHA = New York Heart Association.

D. Meta-analysis of 7435 patients showed a pooled CVD relative risk of 1.18 for each 1% increase in A1C.

E. Lifestyle modification is a cornerstone of long-term diabetes management and CVD prevention efforts.

F. Various diets have been effective for weight loss in individuals with diabetes in short-term evaluations for up to 2 years' duration:
   1. Low-fat diets
   2. Mediterranean diets
   3. Low-carbohydrate diets
   4. DASH
   5. Reduction of saturated fat, trans fat, increased dietary n-3 fatty acids, viscous fiber, and plant stanols/sterols intake

G. Moderate Weight Loss of 5% of Body Weight: Improves insulin resistance, reduces blood pressure

H. Action for Health in Diabetes (Look AHEAD) trial, which evaluated intensive dietary intervention and exercise therapy on CV morbidity and mortality in patients with type 2 diabetes, was discontinued for clinical futility in 2013 (9.6 years' median follow-up). No benefit in reducing overall CV risk was noted.

I. Statin therapy remains a significant intervention to reduce CV risk in patients with diabetes.
   1. See Lipid Therapy section for recommendations on statin therapy for patients with diabetes.
   2. See Omega-3 Fatty Acids section for recommendations on O3FAs (including icosapent ethyl) for patients with diabetes.

J. Statin therapy has been identified as a potential contributor to blood glucose increases, according to clinical trial data.
   1. JUPITER trial reported a less than 1% absolute increase (but a 27% relative risk increase) in the rosuvastatin group diagnosis of diabetes.
   2. High-dose atorvastatin associated with higher glucose concentrations in the PROVE-IT TIMI 22 substudy; atorvastatin associated with a statistically significant increased risk of developing A1C of greater than 6% in those with and without diabetes
   3. Meta-analysis review and epidemiologic data led to the effect of statins on incident diabetes being added to statin labels by the FDA. It remains unclear how statin therapy affects glucose concentrations with existing diabetes.
   4. The HOPE-3 trial found no excess cases of diabetes or cancer in patients receiving rosuvastatin 10 mg daily or placebo for primary prevention.
   5. The CV benefits of statins are generally thought to outweigh the risk of new-onset diabetes.

**Patient Case**

6. A 51-year-old female patient (height 68 inches, weight 89 kg, BMI 29.8 kg/m$^2$) who has had diabetes since age 46 presents for an annual medication review and wellness check today. Her blood pressure is 138/72 mm Hg, heart rate is 88 beats/minute, and microalbumin is 19 mg/mmol. A fasting laboratory panel completed today shows TC 160 mg/dL, TG 200 mg/dL, HDL 45 mg/dL, LDL 78 mg/dL, A1C 9.5%, SCr 1.23 mg/dL, and K 4.5 mEq/L. She stopped smoking at age 40. Her current medication profile includes metformin 1000 mg twice daily, rosuvastatin 40 mg daily, and lisinopril 40 mg daily. Which intervention will best improve this patient's A1C and CV risk factors?
   A. Lose 5–8 kg with lifestyle modification.
   B. Start O3FA 1 g daily.
   C. Start ezetimibe 10 mg daily.
   D. Start aspirin 81 mg daily.

## X. HYPERTENSION

This topic is covered in depth in the chapter on blood pressure management.

## XI. DYSLIPIDEMIA

This topic is covered in depth in the chapter on dyslipidemia.

## XII. ASPIRIN

MOA: Irreversibly inactivates cyclooxygenase-1, blocking the production of thromboxane $A_2$ and inhibiting platelet aggregation. Daily doses of aspirin 75-100 mg largely leave cyclooxygenase-2 intact, allowing prostaglandin production to continue, and aspirin is not considered a nonsteroidal anti-inflammatory drug.

A. Historical Trials
   1. Aspirin has been around for hundreds of years and is readily available in many stores and homes.
   2. Two key studies in the 1980s brought the idea of aspirin for primary prevention to the forefront.
   3. British Doctors Trial (1988)
      a. Randomized 5139 British male physicians to aspirin 500 mg daily or no aspirin (control) for 6 years of follow-up
      b. Vascular deaths were similar in aspirin (4.3%) and control (4.6%).
      c. Aspirin was associated with fewer TIAs (15.9 vs. 27.5 per 10,000 patient-years, $p<0.05$).
      d. Peptic ulcer was 58% higher in aspirin group.
      e. Authors concluded results were not encouraging, though noted the confidence intervals were wide for stroke, MI, and vascular death composite
   4. Physicians' Health Study (1989)
      a. Randomized 22,071 healthy male physicians to aspirin 325 mg every other day or placebo for a median follow-up of 60.2 months
      b. Rates of death similar between groups (RR 0.96; 95% CI, 0.80-1.14; p=0.64)
      c. Aspirin associated with reduction in MI (RR 0.56; 95% CI, 0.45-0.70; $p<0.00001$)
      d. More GI bleeding (RR 1.77; 95% CI, 1.07-2.94; p=0.04) and total bleeding (RR 1.32; 95% CI, 1.25-1.40; $p<0.00001$); 2-fold higher incidence of hemorrhagic strokes with aspirin (n=23 vs. n=12)
   5. Subsequent trials continued to show mixed results, with some (e.g., HOT and WHS) finding ischemic benefit, whereas others (e.g., PPP and AAA) did not.
   6. Of importance, almost every subsequent trial has shown an increased risk of bleeding, and no major trial has ever shown reduced all-cause mortality with aspirin for primary prevention.
   7. Given these uncertainties, it was important to assess aspirin for primary prevention in a modern population.

B. Recent Trials
   1. ARRIVE (2018)
      a. Randomized 12,546 patients with several CV risk factors at moderate CV risk to aspirin 100 mg daily or placebo for a median follow-up of 5.1 years
      b. Primary outcome of MI, stroke, CV death, unstable angina, or TIA similar between groups (HR 0.96; 95% CI, 0.81-11.3; p=0.6038)
      c. Rates of individual components of primary outcome similar between groups
      d. Aspirin associated with a 2-fold increase in GI bleeding (HR 2.11; 95% CI, 1.36-3.28)

2. ASCEND (2018)
    a. Randomized 15,480 patients with diabetes and no known history of CVD to aspirin 100 mg daily or placebo for a mean follow-up of 7.4 years
    b. Primary outcome (original) of MI, stroke, or CV death similar between groups (RR 0.92; 95% CI, 0.82-1.03)
    c. Primary outcome (modified) of MI, stroke, TIA, or CV death lower in aspirin group (RR 0.88; 95% CI, 0.79-0.97; p=0.01; NNT 91)
    d. Rates of major bleeding (RR 1.29; 95% CI, 1.09-1.53; p=0.003; NNH 112) and serious GI bleeding (RR 1.36; 95% CI, 1.05-1.75; NNH 200) higher in aspirin group
3. ASPREE (2018)
    a. Randomized 19,114 older, community-dwelling adults without known CVD to aspirin 100 mg daily or placebo for a median follow-up of 4.7 years
    b. Rates of primary outcome of death, dementia, or persistent physical disability similar between groups (HR 1.01; 95% CI, 0.92-1.11)
    c. All-cause death higher in aspirin group (HR 1.14; 95% CI, 1.01-1.29)
    d. Rates of other cardiovascular outcomes similar between groups
    e. Aspirin associated with increased major hemorrhage (HR 1.38; 95% CI, 1.18-1.62; NNH 98), intracranial bleeding (HR 1.50; 95% CI, 1.11-2.02; NNH 271), and upper GI bleeding (HR 1.87; 95% CI, 1.32-2.66; NNH 233)
4. Systematic review & meta-analysis (2019)
    a. Included 13 trials with 164,225 patients
    b. Aspirin associated with 11% reduction in CV death, MI, and stroke (NNT 265)
    c. Aspirin associated with a 43% increase in major bleeding (NNH 210)

C. Guidelines
1. ESC primary prevention guidelines (2016)
    a. Antiplatelet therapy is not recommended in individuals without CVD because of the increased risk of major bleeding (class III, LOE B).
    b. Antiplatelet therapy (e.g., with aspirin) is not recommended for people with diabetes who do not have CVD (class III, LOE A).
2. USPSTF guidelines 2022
    a. For adults 40–59 years of age with an estimated 10% or greater 10-year CVD risk, the decision to initiate low-dose aspirin should be an individual one (grade C).
        i. Recommend initiation of aspirin in those with a 10% or greater CVD risk at a younger age (40 instead of 50).
        ii. The net benefit of aspirin in this group is small.
        iii. Individuals who are not at increased risk of bleeding and who are willing to take low-dose aspirin daily are more likely to benefit.
    b. Aspirin should not be initiated in adults 60 and older for primary prevention (grade D).
    c. For eligible patients who choose to start aspirin, data suggest that the benefit of aspirin decreases as age increases. Therefore, patients and clinicians should consider stopping aspirin use around age 75.
3. ACC/AHA primary prevention guidelines (2019)
    a. Low-dose aspirin (75-100 mg orally daily) may be considered for the primary prevention of ASCVD among selected adults age 40-70 years who are at higher ASCVD risk but not at increased bleeding risk (Class IIb, LOE A).
    b. Low-dose aspirin (75-100 mg orally daily) should not be administered on a routine basis for the primary prevention of ASCVD among adults older than 70 (Class III: harm, LOE B).

   c. Low-dose aspirin (75-100 mg orally daily) should not be administered for the primary prevention of ASCVD among adults of any age who are at increased risk of bleeding (Class III: harm, LOE C).
   d. Aspirin should be used infrequently for routine ASCVD primary prevention because of the absence of a net benefit (not graded).
4. ADA diabetes standards (2021)
   a. Aspirin therapy (75-162 mg/day) may be considered as a primary prevention strategy in those with diabetes who are at increased CV risk, after a comprehensive discussion with the patient on the benefits compared with increased risk of bleeding (A).
5. ESC guidelines (2021)
   a. In patients with diabetes at high or very high CVD risk, low-dose aspirin may be considered for primary prevention in the absence of clear contraindications.
      i. Recommendation is based on the ASCEND trial's modified primary end point of CV death, MI, stroke, and TIA (12% RRR, NNT 91) over 7.4 years. Of importance, the NNH for major bleeding was 111 (29% relative increase).
      ii. Rates of the original primary end point (CV death, MI, stroke) were similar between groups.
      iii. Rates of individual outcomes of CV death, MI, stroke, and TIA were also similar between groups.
      iv. This is a change from the 2016 wording (above).
   b. Antiplatelet therapy is not recommended in individuals with low/moderate CV risk because of increased risk of major bleeding.

D. Summary
1. Aspirin for primary prevention has been recommended for decades.
2. Aspirin's benefit for primary prevention mainly derives from older trials whose populations may not represent current practice.
3. Since the late 1980s, there have been many advances in lipid therapy, HTN goals, smoking cessation therapy, glycemic control, weight loss, and lifestyle modifications.
4. Recent trials with modern background therapy have shown lower-than-anticipated CV event rates, which may have contributed to decreased ischemic benefit with aspirin for primary prevention.
5. Aspirin for primary prevention may be considered in adult patients who are 40–59 years of age with an estimated 10% or greater 10-year CVD risk and who are not at an increased risk of bleeding. A dose of 81 mg/day is reasonable in those who choose to start treatment. For adults 60 and older, use of aspirin as primary prevention is not recommended.
6. Additional research is needed in patients with non-obstructive coronary artery disease who are not at increased risk of major bleeding and who do not have an independent indication for oral anticoagulation.

**Patient Cases**

7. A 52-year-old woman with diabetes, HTN, and obesity presents to your CV risk reduction clinic. Her current medications include atorvastatin 40 mg daily, empagliflozin 25 mg daily, lisinopril 20 mg daily, and metformin 1000 mg twice daily. A recent lipid panel includes LDL 80 mg/dL and TG 220 mg/dL. Her A1C is 7.8%. She asks about taking fish oil. Which would be most appropriate for this patient?
   A. Administer O3FA 1 g daily.
   B. Administer omega-3 carboxylic acid 2 g twice daily.
   C. Administer icosapent ethyl 2 g twice daily.
   D. O3FAs are not indicated in this patient.

8. A 63-year-old man with HTN, hyperlipidemia, and former tobacco use presents to his primary care physician for a routine wellness check. His BMI is 28 kg/m$^2$, blood pressure is 145/87 mm Hg, and calculated 10-year CV risk is 13% (using Framingham score) and 17% (using PCE). Which is the best recommendation for aspirin in primary prevention for this patient?
   A. Initiate aspirin 81 mg daily.
   B. Initiate aspirin 325 mg every other day.
   C. Initiate aspirin 325 mg daily.
   D. Aspirin for primary prevention is not indicated in this patient.

## XIII. COMPLEMENTARY AND ALTERNATIVE PHARMACOTHERAPEUTIC AGENTS

Definition: *Complementary and alternative medicine* is defined as a group of diverse and medical and health care systems, practices, and products that are not generally considered part of conventional medicine.

A. A 2007 National Health Interview Survey found that the top 5 most commonly used complementary and alternative medicine therapies (aside from prayer) were natural products (fish oil, glucosamine, echinacea, flaxseed), deep breathing, meditation, chiropractic and osteopathic care, and massage therapy.

B. Data are limited for patterns for use of complementary and alternative medicine for CVD treatment and prevention in the United States.

C. Garlic:
   1. Placebo-controlled trial showed no difference in cholesterol parameters after 24 weeks of therapy comparing three garlic preparations.
   2. May reduce blood pressure in hypertensive patients but not normotensive patients (10–12 mm Hg systolic reduction/6–9 mm Hg diastolic reduction)
   3. Current evidence is insufficient to delineate a therapeutic benefit from regular use compared with placebo for reducing CV risk of morbidity and mortality.

D. USPSTF 2022 Recommendations
   1. To prevent CVD
      a. Insufficient evidence to assess benefits-harms for use of multivitamins to prevent CVD
      b. Evidence is insufficient to assess benefit-harm for use of single or paired supplements aside from beta-carotene and vitamin E to prevent CVD, including:
         i. Vitamin A
         ii. Vitamin C

iii. Vitamin D without or with calcium
iv. Selenium
v. Folic acid with or without vitamin B12
vi. Vitamins B3 and B6

2. Use of beta-carotene or vitamin E to prevent CVD is not recommended by the USPSTF because of increased harm.
3. Vitamin D supplementation at 2000 IU daily compared with placebo in 2018 VITAL trial.
   a. 25,871 patients in two-by-two factorial design with primary outcome measure of myocardial infarction, stroke, or cardiovascular death.
   b. Primary outcome occurred in 396 patients vs. 409 placebo patients (HR 0.97; 95% CI, 0.85–1.12; p=0.69), no secondary outcomes were different between groups.
   c. Authors concluded vitamin D 2000 units/day supplementation did not affect cardiovascular disease development.
   d. 2019 meta-analysis of 21 trials (including VITAL) and 83,291 patients found no difference with vitamin D compared with placebo for reducing major adverse CV events (RR 1.00; 95% CI, 0.95-1.06; p=0.85).
   e. Secondary outcomes did not differ.
   f. Results were consistent across subgroups (including vitamin D dosage and calcium administration).

E. Omega-3 Fatty Acids (products summarized in Table 11)
   1. 18.8 million U.S. adults reported consumption of a fish oil supplement within 30 days (2012).
   2. Around 25% of participants in the U.S. National Health and Nutrition Examination Survey (1999-2014) had TG of at least 150 mg/dL.
   3. Many observational and mendelian trials have described TG as a modifiable risk factor to reduce residual CV risk.
   4. Populations consuming diets high in fish appear to have lower CHD risk.
   5. Two main types of O3FAs are found in fish: eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA).
   6. EPA may reduce inflammatory markers, reduce lipid oxidation, and scavenge free radicals.
   7. DHA is associated with neurologic tissue and is structurally different from EPA.
   8. O3FA products
      a. Efficacy
         i. Lowers TG by 26%–45%
         ii. May raise LDL by 45% when TG concentrations are very high
         iii. Raises HDL by 11%–14%
      b. MOA: Unknown. Possibly inhibits acyl-CoA:1,2 diacylglycerol acyltransferase, increases hepatic β-oxidation, or reduces TG hepatic synthesis
      c. Adverse effects: GI (e.g., burping, taste perversion, dyspepsia); at more than 3 g/day, inhibition of platelet aggregation, bleeding
      d. Used to treat hypertriglyceridemia as an adjunct to diet in adults with TG concentrations of 500 mg/dL or greater
      e. Dose: 4 g/day as a single dose or in two divided doses
   9. Icosapent ethyl
      a. Efficacy
         i. Lowers TG by 33%
         ii. Does not appear to increase LDL
      b. MOA: Eicosapentaenoic acid, the active metabolite of icosapent ethyl, may reduce hepatic very-low-density lipoprotein (VLDL)-TG synthesis and secretion and increases TG clearance from circulating VLDL particles.

c. Adverse effects: Arthralgia
d. Used to treat hypertriglyceridemia (500 mg/dL or greater) as an adjunct to diet
e. Dose: 2 g twice daily

10. Omega-3 carboxylic acid
    a. Efficacy
        i. Lowers TG by 30%
        ii. May raise HDL by 5%
        iii. May raise LDL by 25%
    b. MOA: Not fully understood
    c. Adverse effects: Diarrhea
    d. Used to treat hypertriglyceridemia (500 mg/dL or greater) as an adjunct to diet
    e. Dose: 2 g (2 capsules) or 4 g (4 capsules) once daily

F. Recent Trials: Low-dose O3FAs
    1. Omega-3 Treatment Trialists' Collaboration Meta-Analysis (2018)
        a. Systematic search of randomized controlled clinical trials comparing O3FAs with placebo or active control with at least 500 patients and at least a 1-year follow-up
        b. Identified 10 trials with 77,917 participants; 8 of 10 trials at low risk for selection bias (except for open-label trials)
        c. EPA and DHA doses highly variable across trials
        d. No difference in outcomes of nonfatal MI or CHD death, stroke, revascularization, or any major vascular event
        e. Of importance, meta-analysis conducted before the publication of ASCEND, VITAL, REDUCE-IT, and STRENGTH trials
    2. ASCEND (2018)
        a. Randomized 15,48 adults with diabetes but without known CVD to 1 g of O3FA (460 mg of EPA, 380 mg of DHA) versus 1 g of placebo (olive oil) for a median of 7.4 years
        b. Primary outcome of MI, stroke, TIA, or CV death similar between groups (RR 0.97; 95% CI, 0.87-1.08; p=0.55)
        c. Rates of individual components of primary outcome were similar between groups.
        d. Rates of all-cause mortality and CV death were also similar between groups.
    3. VITAL (2019)
        a. Randomized 25,304 adults without known CVD to 1 g of O3FA (460 mg of EPA, 380 mg of DHA) versus 1 g of placebo (olive oil) for a median of 5.3 years
        b. Primary outcome of MI, stroke, or CV death similar between groups (HR 0.92; 95% CI, 0.80-1.06; p=0.24)
        c. Rates of individual components of primary outcome similar between groups
        d. Exception: MI appeared lower in O3FA group (HR 0.72; 95% CI, 0.59-0.90). However, authors noted there was no adjustment for multiple hypothesis testing; hence, this outcome should be considered exploratory.
    4. Summary
        a. According to the meta-analysis of around 77,000 patients and two subsequent trials of over 40,000 patients total, there is scant evidence that 1 g of O3FA provides any worthwhile CV benefit.

G. Recent Trials: High-Dose O3FAs
    1. REDUCE-IT (2019)
        a. Randomized 8179 patients to icosapent ethyl 2 g twice daily versus placebo (mineral oil) for a median of 4.9 years

b. Patients required to have established CVD or to have diabetes with at least one additional risk factor
c. Required to have LDL 41-100 mg/dL and TG 150-499 mg/dL and receive stable dose of statin (TG later amended to 200-499 mg/dL)
d. About 70% were secondary prevention, and 30% were primary prevention.
e. Icosapent ethyl reduced primary outcome of CV death, MI, stroke, revascularization, or unstable angina compared with placebo (HR 0.75; 95% CI, 0.68-0.83; p<0.001; NNT 21).
f. Icosapent ethyl also associated with significant reductions in CV death (NNT 112), fatal or nonfatal MI (NNT 39), and fatal or nonfatal stroke (NNT 112)
g. Rates of all-cause mortality were similar between groups.
h. Atrial fibrillation was more common with icosapent ethyl (5.4% vs. 3.9%).

2. EVAPORATE (2020)
a. Randomized 64 patients to icosapent ethyl 2 g twice daily or placebo (mineral oil)
b. Primary outcome was change in coronary artery plaque progression at 18 months.
c. Icosapent ethyl associated with reductions in several plaque-type volumes (range -1% to -34%)
d. However, mineral oil associated with significant increases in multiple plaque-type volumes (range +1% to +109%)
e. Has led to concern that positive results of REDUCE-IT may partly be the result of a potentially harmful effect of mineral oil control

3. STRENGTH (2020)
a. Omega-3 carboxylic acid (75% EPA, 25% DHA) versus placebo (corn oil) for a median follow-up of 3.5 years before being terminated for futility
b. Required to have LDL less than 100 mg/dL and TG 180-499 mg/dL and to receive stable dose of statin
c. Rate of primary end point of CV death, MI stroke, revascularization, or unstable angina similar between groups (HR 0.99; 95% CI, 0.90-1.09; p=0.84)
d. Rates of individual components of primary outcome similar between groups
e. Rates of individual components of primary outcome were similar between groups, as was all-cause mortality.
f. Atrial fibrillation was more common with omega-3 carboxylic acid (HR 1.69; 95% CI, 1.29-2.21).

4. Controversies and uncertainty with high-dose O3FAs
a. Several hypotheses have been proposed to explain the positive results of REDUCE-IT compared with the lackluster results of other efforts.
i. High-dose, high-purity EPA composition of icosapent ethyl
ii. Predominantly secondary prevention population (rather than primary prevention)
iii. Requiring elevated TG at study entry
b. However, STRENGTH shared these characteristics, making these explanations less plausible.
c. Some have called for a trial comparing icosapent ethyl with corn oil placebo to definitively answer the question.

H. Guideline Recommendations
1. 2019 ESC lipid guidelines
a. Statins are first drug of choice to reduce CV risk in high-risk individuals with TG above 200 mg/dL (class I, LOE B).
b. In high-risk patients with TG 145-499 mg/dL despite statin therapy, addition of icosapent ethyl 2 g twice daily should be considered (class IIa, LOE B).

2. ACC/AHA guidelines:
a. 2019 ACC/AHA primary prevention guidelines make no recommendations (for or against) O3FAs to reduce CV risk.

b. 2018 ACC/AHA lipid guidelines (and past ACC/AHA lipid guidelines) similarly make no recommendations regarding (for or against) O3FAs to reduce CV risk.

3. 2022 ADA guidelines
   a. In patients with ASCVD or other CV risk factors taking a statin with controlled LDL but elevated TG values (135–499 mg/dL), the addition of icosapent ethyl can be considered to reduce CV risk.

I. Summary
   1. Many trials have assessed O3FAs for the prevention of CVD, and O3FAs are widely taken as nonprescription supplements.
   2. Several trials have failed to detect any meaningful benefit in CV risk reduction with 1 g of O3FA.
   3. 1 g of O3FA daily should not be recommended to reduce CV risk.
   4. According to currently available evidence, icosapent ethyl 2 g twice daily is the only O3FA product to demonstrate reductions in CV events with modern background therapy
   5. However, some controversy exists with icosapent ethyl, and additional data are needed to clearly identify its place in therapy.

**Table 11.** Comparison of FDA approved omega-3 products

| Product | Omega-3-Acid Ethyl Esters | Icosapent Ethyl | Omega-3 Carboxylic Acids | Omega-3 Acid Ethyl Esters A |
|---|---|---|---|---|
| Brand name | Lovaza | Vascepa | Epanova | Omtryg |
| FDA indication | TG reduction in adults with severe TG elevation | TG reduction in adults with severe TG elevation FDA approval for primary prevention in patients with diabetes and two CV risk factors for patients already taking maximally tolerated statin with TG ≥ 150 mg/dL | TG reduction in adults with severe TG elevation | TG reduction in adults with severe TG elevation |
| Primary prevention end point benefit | No | Yes, in patients who meet the FDA indication for primary prevention use | No | No |
| Daily dosing | 4 g | 2 g BID | 2–4 g daily | 4 g daily |
| Omega-3 content | 465 mg of EPA and 375 mg of DHA | 1 g of icosapent ethyl | 850 mg of EPA and DHA combined | 465 mg of EPA and DHA combined |

BID = twice daily; DHA = docosahexaenoic acid; EPA = eicosapentaenoic acid.

## XIV. TRANSITIONS OF CARE

A. Significant opportunities exist for optimizing CV risk reduction during transitions of care.

B. It is unlikely that all CV risk factors will be fully optimized in all patients at time of hospital discharge.

C. Pharmacists can play a pivotal role in facilitating effective transitions of care by ensuring appropriate discharge medication reconciliation, counseling patients (as appropriate), and recommending appropriate follow-up.

D. Examples of follow-up that pharmacists may be uniquely suited to assist with include:
    1. Recommending repeat lipid panel 4–12 weeks after intensification of lipid therapy
    2. Reassessing blood pressure control in 2–4 weeks in patients with HTN
    3. Ensuring appropriate laboratory follow-up (e.g., basic metabolic panel) in patients starting angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, angiotensin receptor-neprilysin inhibitors, mineralocorticoid receptor antagonists, and/or SGLT2 inhibitors
    4. Reassessing glycemic control at follow-up and/or rechecking A1C in 3 months
    5. Outlining future stepwise intensification of HTN, lipid therapy, glycemic control, and other CV risk factors to be considered at follow-up

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## ANSWERS AND EXPLANATIONS TO PATIENT CASES

**1. Answer: B**

Low-intensity statins lower LDL by less than 30%. Moderate-potency therapies (e.g., pravastatin 40 mg daily) lower LDL by 30%–50% from baseline (Answer B is correct). Answer A (lovastatin 20 mg daily) and Answer C (fluvastatin 40 mg daily) are low-intensity statins. Answer D (atorvastatin 40 mg daily) is a high-intensity statin.

**2. Answer: D**

The 2013 ACC/AHA guideline on lifestyle modification to reduce CV risk states that eliminating *trans* fat intake, whenever possible, and saturated fats to a goal of 5%–6% of dietary intake is preferred, with no more than 30% of daily calories sourced from fats (Answer D is correct). Of note, the 2020–2025 dietary guidelines recommend limiting saturated fat to less than 10% of daily calories. Answer B is incorrect because it refers to unsaturated fats rather than saturated fats. Protein from plants (e.g., nuts, legumes) and lean animal protein (fish) are generally considered healthy protein sources. Some animal protein (e.g., red meat) may increase the risk of CVD (Answer A is incorrect). Sodium should be limited to 2400 mg/day to reduce the risk of HTN and improve hypertensive control (Answer C is incorrect). Of note, the 2020–2025 dietary guidelines recommend a sodium intake of less than 2300 mg/day, which is slightly different from the AHA recommendation.

**3. Answer: C**

This patient's nicotine requirement best approximates the 21-mg patch/day requirement for use (Answer C is correct). If he used fewer than 10 cigarettes/day, 7- or 14-mg patches might be appropriate (Answers A and B are incorrect). Because he smokes his first cigarette about 1 hour after awakening, the correct dose of nicotine gum or lozenge would be 2 mg every 1-2 hours for 6 weeks and then taper (Answer D is incorrect).

**4. Answer: A**

Answer A is correct because bupropion may cause insomnia and should be taken in the morning with at least 8 hours between doses (when dosing twice daily); bedtime dosing should be avoided. Answer B is incorrect because bupropion is an appetite suppressant that may cause weight loss. Answer C is incorrect because the medication should only be taken for 7-12 weeks or up to 6 months in some patients. Answer D is incorrect because bupropion should be started 1-2 weeks before the anticipated quit date.

**5. Answer: D**

Answer A is the correct starting dose (21 mg/day) but has an incorrect taper. The patient should receive the 21-mg/day patch for 6 weeks and then taper. Answer B is incorrect because she should start with the 21-mg patch, and Answer C is incorrect because she should start with the 4-mg starting dose on the basis of when she has her first cigarette. Answer D is the correct dose; the patient has no contraindications to therapy and has prescription insurance. In all cases, combining pharmacologic therapy with cognitive behavioral therapy improves efficacy.

**6. Answer: A**

Answer A is an almost 10% intentional weight loss, which significantly reduces A1C and CV risk factors. Omega-3 fatty acid 1 g daily as studied in the ASCEND and VITAL trials failed to reduce CV outcomes (Answer B is incorrect). Ezetimibe can be considered as adjunct therapy in patients with severe primary hypercholesterolemia (LDL 190 mg/dL or higher at baseline) with an inadequate response to statin therapy. However, adding ezetimibe would likely not provide meaningful benefit because this patient is taking rosuvastatin 40 mg daily with LDL 78 mg/dL and has no history of ASCVD (Answer C is incorrect). Finally, adding aspirin would not modify this patient's A1C or provide significant CV benefit (Answer D is incorrect).

**7. Answer: C**

The ASCEND (100% diabetes) and VITAL (13% diabetes) trials failed to show benefit with O3FA 1 g daily for the prevention of major adverse CV events in patients without CVD (Answer A is incorrect). The STRENGTH trial similarly did not find benefit with omega-3 carboxylic acid 2 g twice daily (Answer B is incorrect). The REDUCE-IT trial did find a reduction in major adverse CV events in patients with elevated TG taking maximally tolerated statins. About 30% of patients were a primary prevention cohort. Icosapent ethyl is FDA indicated in patients with diabetes, elevated TG, and several CV risk factors (Answer C is correct; Answer D is incorrect).

**8. Answer: D**

This patient represents a "typical" patient from the ASCEND trial, which assessed aspirin 100 mg daily versus placebo for the primary prevention of CVD. The rates of the primary end point of CV death, MI, unstable angina, stroke, or TIA were similar between groups. Aspirin was associated with a 2-fold increase in GI bleeding. Admittedly, the event rate overall was lower than anticipated, speaking not only to the limitations of CV risk calculators, but also to how other modern therapies have lowered CV risk. Although this patient certainly has CV risk factors (uncontrolled HTN and obesity), aspirin seems unlikely to benefit him according to the ASCEND trial (Answer D is correct; Answers A-C are incorrect). He should be counseled on lifestyle modifications (including diet and exercise), his antihypertensive regimen should be optimized, and he should be considered for statin therapy, given intermediate risk (on the basis of PCE score) and several CV risk factors.

## ANSWERS AND EXPLANATIONS TO SELF-ASSESSMENT QUESTIONS

**1. Answer: A**

This patient's problem list includes HTN, obesity, and diabetes because of an A1C greater than 6.5% and a Pooled Cohort Equation risk score of 30% for a 10-year calculated risk of a CV event. The ACC/AHA guidelines recommend at least a moderate-intensity statin for patients with diabetes age 40-75 years. They also state that a high-intensity statin is reasonable for patients with several risk factors. Because this patient has a high ASCVD score and several CV risk factors, a high-intensity statin would be reasonable. In addition, his blood pressure is not at goal; hence, adding another agent (and/or titrating lisinopril) would be reasonable. Finally, because the patient has diabetes, he should be initiated on metformin 500 mg twice daily (Answer A is correct). Although he is certainly at high risk, many of his risk factors are modifiable (obesity, HTN, lipids, glycemic control), and his optimal ASCVD risk is 7.5%. As such, it would be best to focus on addressing his modifiable risk factors and then reassess CV risk to determine whether aspirin is appropriate for this patient (the ACC/AHA guidelines and ESC guidelines do not recommend routine aspirin for primary prevention). Answer B is incorrect because it recommends aspirin, and β-blockers are not recommended as first-line antihypertensive agents. Answer C does not address glycemic control. Answer D recommends aspirin and does not address HTN.

**2. Answer: A**

Varenicline would be appropriate for this patient because bupropion use is contraindicated in patients who are also discontinuing benzodiazepine use, making Answer A correct and Answer B incorrect. Because she smokes more than 10 cigarettes daily, the appropriate starting dose of nicotine patch is 21 mg/hour (Answer C is incorrect). Because she smokes her first cigarette within 30 minutes of awakening, nicotine gum 4 mg would be appropriate (Answer D is incorrect)

**3. Answer: B**

Glipizide and repaglinide may improve glycemic control but have not been shown to reduce the risk of future CV events (Answers A and C are incorrect). Empagliflozin was shown to reduce the risk of heart failure hospitalization in the EMPA-REG OUTCOME trial, including in patients without a history of heart failure, as well as to reduce CV death (Answer B is correct). Saxagliptin was found to increase the risk of heart failure hospitalization in SAVOR-TIMI 53 but did not otherwise increase CV events (Answer D is incorrect).

**4. Answer: D**

Phentermine should be avoided in patients with a history of HTN or other serious cardiac disease (Answer A is incorrect). Although orlistat would otherwise be reasonable, it should be avoided with narrow therapeutic index medications such as carbamazepine because of uncertain absorption (Answer B is incorrect). Naltrexone/bupropion should be avoided in patients with a history of seizures (Answer C is incorrect). Semaglutide would be reasonable to help with weight loss and would not interact with the patient's comorbidities or other medications (Answer D is correct)

**5. Answer: D**

The ACC/AHA primary prevention guidelines state that patients at borderline risk (ASCVD score 5% to less than 7.5%) may qualify for a moderate-intensity statin if risk-enhancing factors are present. The 2022 USPSTF guidelines for statin use do not recommend initiation of statin therapy unless the 10-year CVD risk is 10% or greater in patients 40–75 years of age with at least one CVD risk factor. Answer B is incorrect because it is a high-intensity statin. Given that this patient does not appear to have any risk-enhancing factors, he would not currently qualify for statin therapy (Answer D is correct; Answers A and C are incorrect). However, he should be counseled on appropriate lifestyle modifications, and his ASCVD risk should reassessed at routine intervals (the guidelines suggest every 4-6 years).

**6. Answer: C**

The ACC/AHA primary prevention guidelines recommend 150 minutes weekly of moderate-intensity activity or 75 minutes weekly of vigorous-intensity activity (Answer C is correct). Of note, the guidelines also recommend that an active lifestyle should be encouraged at all health care encounters and that any level of physical activity reduces CV risk (Answers A, B, and D are incorrect). These recommendations are very similar to the USPSTF guidelines, which recommend 90-180 minutes/week of moderate to vigorous physical activity.

**7. Answer: A**

Alcohol consumption significantly increases the risk of HTN and atrial fibrillation (even if only drinking 1 standard drink per day). Alcohol also increases the risk of obstructive sleep apnea, obesity, metabolic syndrome, unexplained left ventricular hypertrophy, and heart failure (Answer A is correct). The ACC/AHA and USPSTF guidelines recommend a low-sodium Mediterranean diet that is typically characterized by fish, fruits, vegetables, nuts, legumes, and whole grains. Although *trans* fats should be eliminated from the diet, some fats are believed to be heart healthy (e.g., those found in vegetables, fish, and nuts) (Answer B is incorrect). Sodium should be limited to less than 2400 mg/day; however, increasing dietary potassium intake to about 3500-4700 mg daily may reduce the risk of HTN and stroke; also, foods high in potassium include certain fish, fruits, and vegetables (Answer C is incorrect). Answer D is incorrect because it does not address alcohol consumption; does not include fish, nuts, and legumes; and potentially minimizes intake of nutrient-dense foods.

**8. Answer: D**

The VITAL and ASCEND trials assessed O3FA 1 g daily in patients without CVD and failed to show CV benefit (Answer A is incorrect). The STRENGTH trial similarly failed to show CV benefit with omega-3 carboxylic acid 2 g twice daily in patients without CVD. Although the REDUCE-IT trial observed reduction in major adverse CV events with icosapent ethyl 2 g twice daily, patients were required to have established CVD or to have diabetes with several risk factors. In addition, patients were required to have elevated TG and be taking maximally tolerated statin therapy. This patient does not fit the criteria of REDUCE-IT (Answer C is incorrect). Although this patient should be encouraged to follow appropriate lifestyle modifications, there is no evidence that routinely prescribing O3FAs for the prevention or treatment of ASCVD provides meaningful benefit (Answer D is correct).

# Dyslipidemia

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# Dyslipidemia

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**Learning Objectives**

1. Describe the role of cholesterol and lipoproteins in the development of atherosclerotic cardiovascular disease (ASCVD).
2. Evaluate a patient's ASCVD risk by appropriately using the 10-year ASCVD Risk Pooled Cohort Equations and optional risk enhancers.
3. Establish goals of therapy for the management of blood cholesterol, including statin intensity, and create a monitoring plan for patients receiving lipid-lowering therapies.
4. Develop an appropriate treatment regimen for patients who are statin intolerant or unable to achieve goals of therapy on maximally tolerated statin therapy according to the 2018 Guideline on the Management of Blood Cholesterol and the 2022 Expert Consensus Decision Pathway on the Role of Nonstatin Therapies for LDL-Cholesterol Lowering in the Management of Atherosclerotic Cardiovascular Disease Risk.
5. Identify appropriate indications for the use of triglyceride-lowering therapies to manage hypertriglyceridemia.
6. Evaluate the needs of special populations (e.g., those with diabetes, older adults, those with kidney disease), and adapt treatment strategies to optimize outcomes.

**Abbreviations in This Chapter**

| | |
|---|---|
| ABI | Ankle-brachial index |
| ApoB | Apolipoprotein B |
| ASCVD | Atherosclerotic cardiovascular disease |
| CAC | Coronary artery calcium |
| CHD | Coronary heart disease |
| CK | Creatine kinase |
| DHA | Docosahexaenoic acid |
| eGFR | Estimated glomerular filtration rate |
| EPA | Eicosapentaenoic acid |
| FH | Familial hypercholesterolemia |
| GERD | Gastroesophageal reflux disease |
| HDL-C | High-density lipoprotein cholesterol |
| hs-CRP | High-sensitivity C-reactive protein |
| HTN | Hypertension |
| LDL-C | Low-density lipoprotein cholesterol |
| Lp(a) | Lipoprotein(a) |
| mAbs | Monoclonal antibodies |
| O3FA | Omega 3 fatty acids |
| PCE | Pooled Cohort Equation |
| siRNA | Small interfering RNA |
| TC | Total cholesterol |
| TG | Triglycerides |
| VLDL | Very-low-density lipoprotein |

**Self-Assessment Questions**

*Answers and explanations to these questions can be found at the end of this chapter.*

1. A 44-year-old white woman presents to her primary care provider for her annual physical examination. Over the past 6 months, she has had increased fatigue and has gained about 10 lb with no changes in her lifestyle. Her only medication is loratadine 10 mg/day. Her fasting lipid panel shows total cholesterol (TC) 231 mg/dL, low-density lipoprotein cholesterol (LDL-C) 155 mg/dL, high-density lipoprotein cholesterol (HDL-C) 54 mg/dL, and triglycerides (TG) 112 mg/dL. Her calculated 10-year atherosclerotic cardiovascular disease (ASCVD) risk score is 1.2%. Which is the best recommendation at this time?
   A. Initiate atorvastatin 10 mg/day.
   B. Initiate rosuvastatin 20 mg/day.
   C. Obtain a high-sensitivity C-reactive protein (hs-CRP).
   D. Obtain a thyroid panel.

2. A 57-year-old African American woman with hypertension (HTN) and dyslipidemia presents to her primary care provider with a concern of increased thirst and urination. Her medications include lisinopril 20 mg/day, amlodipine 10 mg/day, chlorthalidone 12.5 mg/day, and atorvastatin 10 mg/day. Her laboratory results show a hemoglobin A1C (A1C) of 7.7%, TC 184 mg/dL, LDL-C 103 mg/dL, HDL-C 41 mg/dl, and TG 202 mg/dL. Including her new diagnosis of diabetes, her 10-year ASCVD risk score is 22%. Which is the best recommendation at this time?
   A. Add fenofibrate 145 mg/day.
   B. Add niacin extended release 500 mg/night.
   C. Increase atorvastatin to 40 mg/day.
   D. Continue atorvastatin 10 mg/day.

3. A 43-year-old white man with HTN and heterozygous familial hypercholesterolemia presents to your lipid clinic for evaluation of statin intolerance. He reports bilateral muscle aches in his legs with atorvastatin (10 mg, 40 mg), rosuvastatin (5 mg), and pravastatin (20 mg). His fasting laboratory results show TC 267 mg/dL, LDL-C 200 mg/dL, HDL-C 38 mg/dL, and TG 143 mg/dL. Which is the best recommendation to achieve at least a 50% reduction in LDL-C?
   A. Initiate colesevelam 1.875 g every 12 hours.
   B. Initiate evolocumab 140 mg subcutaneously every 2 weeks.
   C. Initiate gemfibrozil 600 mg twice daily.
   D. Initiate fluvastatin extended release (XL) 20 mg/day.

*Questions 4 and 5 pertain to the following case.*

4. A 51-year-old white man presents with diabetes mellitus, HTN, hypertriglyceridemia, and a history of acute pancreatitis. He denies using tobacco but drinks 4–6 beers/day. His current medication regimen is as follows: lisinopril 20 mg/day, chlorthalidone 50 mg/day, amlodipine 10 mg/day, rosuvastatin 20 mg/day, metformin 1000 mg twice daily, and insulin glargine 28 units at bedtime. Although he still has obesity (body mass index [BMI] 38 kg/m$^2$), he reports a 5-lb weight loss over the past month by very-low dietary fat and avoidance of carbohydrates, as well as caloric reduction. Fasting laboratory results show A1C 6.9%, TC 157 mg/dL, LDL-C 78 mg/dL (directly measured), HDL-C 38 mg/dL, and TG 1054 mg/dL. Renal and hepatic function remain within normal limits. He shares with you that he is frustrated with taking "all of these pills every day." Which best describes potential secondary causes that may be contributing to his hypertriglyceridemia?
   A. Alcohol consumption, poorly controlled diabetes, amlodipine.
   B. Alcohol consumption, rosuvastatin, weight loss.
   C. Obesity, alcohol consumption, chlorthalidone.
   D. Obesity, poorly controlled diabetes, metformin.

5. In addition to nonpharmacologic recommendations, which treatment option is best for his TG?
   A. Add fenofibrate 145 mg/day.
   B. Add niacin extended release 500 mg/night.
   C. Add omega-3 fatty acids 1 g/daily.
   D. Increase rosuvastatin to 40 mg/day.

6. A 64-year-old African American man with stage 4 chronic kidney disease (estimated glomerular filtration rate [eGFR] 20 mL/minute/1.73 m$^2$), HTN, and hyperlipidemia is being treated with simvastatin 20 mg/ezetimibe 10 mg daily. After a recent hospitalization for acute renal failure, he is being referred to begin hemodialysis three times a week. Fasting laboratory results show TC 129 mg/dL, LDL-C 64 mg/dL, HDL-C 47 mg/dL, and TG 90 mg/dL. According to the Kidney Disease: Improving Global Outcomes (KDIGO) guidelines, which is the most reasonable way to address his hyperlipidemia?
   A. Continue simvastatin 20 mg/ezetimibe 10 mg daily.
   B. Change to simvastatin 20 mg daily (discontinue exetimibe).
   C. Discontinue simvastatin/ezetimibe.
   D. Change to ezetimibe 10 mg daily (discontinue simvastatin).

7. A 54-year-old white man with allergic rhinitis and HTN presents for an annual wellness visit. His current medications include loratadine 10 mg/day and hydrochlorothiazide 25 mg/day. He does not use tobacco products and reports 1 or 2 alcoholic drinks per week. He exercises five times a week (running and cycling) and follows a Mediterranean-style diet. Fasting laboratory results show TC 189 mg/dL, LDL-C 126 mg/dL, HDL-C 45 mg/dL, and TG 90 mg/dL. His calculated 10-year ASCVD risk score is 5.6% but he is very concerned about his risk of heart disease. Which risk-enhancer should you consider at this time?
   A. Screen for albuminuria.
   B. Perform ankle-brachial index measurement.
   C. Evaluate family history of premature ASCVD.
   D. Obtain a serum calcium concentration.

8. A 54-year-old South Asian man with diabetes mellitus, HTN, dyslipidemia, and gastroesophageal reflux disease (GERD). He is a current smoker. His current medications include lisinopril 20 mg/day, amlodipine 10 mg/day, pravastatin 40 mg/day, and

omeprazole 20 mg/day. Fasting laboratory results show glucose 109 mg/dL, TC 197 mg/dL, LDL-C 128 mg/dL, HDL-C 37 mg/dL, and TG 166 mg/dL. His non-HDL is 160 mg/dL. According to the 2018 cholesterol management guidelines, which would be most appropriate in this patient?

A. Add fenofibrate 145 mg/day.
B. Change pravastatin to atorvastatin 40 mg/day.
C. Increase pravastatin to 80 mg/day.
D. Add ezetimibe 10 mg/day.

9. A 68-year-old white woman with HTN, a history of transient ischemic attack (1 year ago), and hyperlipidemia recently had an acute myocardial infarction (MI) for which she received two drug-eluting stents. She presents to the clinic today for a follow-up 2 months after the MI. Her medications include metoprolol succinate 50 mg/day, lisinopril 20 mg/day, furosemide 20 mg/day, atorvastatin 20 mg/day, omeprazole 20 mg/day, aspirin 81 mg/day, and clopidogrel 75 mg/day. She achieved a 35% reduction in her LDL-C, but she has previously not tolerated higher doses of atorvastatin or rosuvastatin because of myalgia. Fasting laboratory results show TC 157 mg/dL, LDL-C 83 mg/dL, HDL-C 48 mg/dL, and TG 132 mg/dL. Which is the best recommendation at this time to further reduce her risk of recurrent events?

A. Add alirocumab 75 mg subcutaneously every 2 weeks.
B. Add ezetimibe 10 mg/day.
C. Add niacin extended release 500 mg/night.
D. Add icosapent ethyl 2 g twice daily.

10. A 78-year-old white man with HTN presents for a cardiovascular (CV) risk assessment. His medications include lisinopril 20 mg/day, chlorthalidone 12.5 mg/day, and aspirin 81 mg/day. Fasting laboratory results show A1C 5.3%, TC 203 mg/dL, LDL-C 136 mg/dL, HDL-C 44 mg/dL, and TG 115 mg/dL. His vital signs include blood pressure 134/76 mm Hg, and his BMI is 27 kg/m$^2$. His CAC is 120. He is a nonsmoker and drinks 1 glass of red wine nightly. His calculated 10-year ASCVD risk score is 36.9%. Which is the best recommendation at this time regarding the use of statin therapy in this patient?

A. Consider additional risk markers (e.g., hs-CRP) before recommending statin therapy.
B. Discuss with the patient the potential risk-benefit of statin therapy and consider a low-intensity statin, given his age.
C. Engage in a patient-provider discussion and recommend a moderate- or high-intensity statin.
D. Initiate high-intensity statin therapy because his CAC is greater than 100.

## I. ROLE OF SERUM CHOLESTEROL AND LIPOPROTEINS IN THE DEVELOPMENT OF ASCVD

A. Cholesterol: A lipid molecule that is biosynthesized (primarily in the liver) or obtained through diet that is an essential component of animal cell membranes and used in the biosynthesis of steroid hormones and bile acids.

B. Lipoprotein carriers: Responsible for transporting cholesterol, TG, and phospholipids throughout the body because cholesterol is minimally soluble in water and requires a hydrophilic carrier in plasma.
   1. ApoB acts as a ligand for LDL receptors, which allows the delivery of cholesterol into the cells, removing cholesterol from the blood.
      a. ApoB-containing lipoproteins include chylomicrons, very-low-density lipoproteins (VLDLs), intermediate-density lipoproteins, lLDLs, and lipoprotein(a) [Lp(a)].
      b. Retention of ApoB-containing lipoproteins in the subendothelial is the primary cause and initiator of atherosclerosis; these are therefore often called "atherogenic lipoproteins."
      c. LDL is the dominant form of atherogenic cholesterol (>90%), VLDL is the main carrier of TG, and chylomicrons transport dietary fat and are less certainly atherogenic.
   2. High-density lipoprotein cholesterol (HDL-C) is the only major lipoprotein that does not contain ApoB. The major protein component of HDL-C is ApoA1. HDL-C is a key participant in reverse cholesterol transport, which moves cholesterol from peripheral tissues back to the liver. HDL-C is then transfered to VLDL or LDL-C by cholesteryl ester transfer protein (CETP). Low serum concentrations of HDL-C are associated with increased ASCVD risk; however, HDL-C should not be used as a target of drug therapy, given the lack of data to support benefit with HDL-raising therapies.
   3. Non-HDL represents all potentially atherogenic cholesterol and is calculated by subtracting HDL-C from TC. Although non-HDL appears to be a better predictor of ASCVD risk than LDL-C, few clinical trials have included non-HDL goals as a target of therapy.
   4. Lipoprotein(a) is a lipoprotein subclass consisting of an LDL-like particle that is highly inheritable and an independent risk factor for ASCVD and aortic stenosis. Its role as a target of therapy is unclear but rapidly evolving. Only aspirin, proprotein convertase subtilisin/kexin type 9 (PCSK9) monoclonal antibodies (mAbs), small interfering RNA (siRNA) molecules, lipoprotein apheresis, and niacin reduce Lp(a) concentrations, but the clinical significance of this is unclear.

C. Triglycerides
   1. Three fatty acids esterified to a glycerol molecule found in all lipoproteins but primarily chylomicrons and (VLDL); used as an energy source.
   2. Elevated TG concentrations are commonly the result of insulin resistance and strongly associated with increased ASCVD risk; however, the role of TG as an independent risk factor and its direct role in disease development is evolving.

## II. MEASUREMENT OF CHOLESTEROL

A. Initial measurement of a patient's lipid profile helps assess ASCVD risk and should be done in all adults 20 years and older who are not on lipid therapy to document baseline cholesterol values.
   1. Friedewald formula: LDL-C = (TC) – (TG/5) – (HDL-C)
   2. Non-HDL = (TC) – (HDL-C)

B. Fasting vs. Nonfasting Measurement
   1. Generally fasting or nonfasting lipid profile can be used for ASCVD risk assessment.
   2. Initial fasting measurement is recommended in individuals with family history of premature ASCVD or genetic hyperlipidemia.

3. If the initial nonfasting profile shows TG greater than 400 mg/dL, a repeat fasting measurement is recommended.
4. The Martin/Hopkins estimation is preferred over the Friedewald equation when LDL-C is less than 100 mg/dL and TG 150–400 mg/dL.

C. Other Direct Cholesterol Measurements
1. To improve accuracy, direct measurement of LDL-C is reasonable if the initial value is less than 70 mg/dL.
2. ApoB has a relative indication for use in patients if baseline TG concentrations are greater than 200 mg/dL. ApoB less than 90 mg/dL is desirable.
3. Lipoprotein(a) is also not routinely recommended; however, recent drug development has renewed interest in Lp(a) measurement, particularly in high-risk patients (family or personal history of premature unexplained ASCVD) or on nonstatin medications (PCSK9-mAbs, siRNA molecules).

D. Repeated measurements to assess adherence to therapy and percentage response (to medication and/or lifestyle) are recommended 4–12 weeks after initiation or change and should be repeated every 3–12 months as clinically indicated.

## III. LIFESTYLE THERAPIES TO REDUCE ASCVD RISK

A. Lifestyle therapies (diet, weight control, physical activity, and tobacco avoidance) are recommended for the general public, those at risk of ASCVD, and those with ASCVD.

B. Diet
1. Follow a dietary pattern high in fruits, vegetables, whole grains, low-fat dairy, low-fat poultry, fish, legumes, non-tropical vegetable oils, and nuts.
2. Limit intake of sugar, low-calorie sweeteners, refined grains, *trans* fat, saturated fat, sodium, red meat, and processed meats.
3. High- and low-carbohydrate dietary patterns are NOT recommended; rather, plant-based and Mediterranean diets are encouraged.
4. Of note, a Mediterranean diet supplemented with either mixed nuts or extra virgin olive oil reduced the incidence of major CV events in the PREDIMED study. This was primarily driven by a reduction in the risk of stroke.
5. Caloric intake should be reduced to avoid weight gain and/or to promote weight loss.

C. Physical Activity in Adults: At least 150 minutes per week of moderate-intensity or 75 minutes per week of vigorous-intensity aerobic physical activity, in bouts of 10 minutes or more, is encouraged to reduce ASCVD risk.

D. Other Lifestyle Therapies: Avoid smoking (and other forms of tobacco), use moderate to no alcohol consumption (2 drinks/day or less for men and 1 drink/day or less for women).

E. More detailed information is provided in the 2019 ACC/AHA Guideline on the Prevention of Cardiovascular Disease.

## IV. OVERVIEW OF CHOLESTEROL GUIDELINES

**Patient Cases**

1. A 47-year-old African American woman who self-initiated lifestyle therapies for the past 12 months presents for further treatment. She has longstanding HTN and asthma and was recently (1 year ago) given a diagnosis of diabetes. Her medications are albuterol, lisinopril, amlodipine, and metformin. Her vital signs include blood pressure 126/88 mm Hg. Her laboratory results are as follows: TC 184 mg/dL, LDL-C 107 mg/dL, HDL-C 55 mg/dL, and TG 112 mg/dL. Her PCE estimated 10-year ASCVD risk is 6.0%. According to the 2018 cholesterol management guideline, which is the most appropriate next step for this patient?
   A. Initiate a low-intensity statin because her 10-year risk is less than 7.5%.
   B. Initiate a moderate-intensity statin because she has diabetes and no diabetes-specific risk enhancers.
   C. Initiate a high-intensity statin because she has diabetes and at least one diabetes-specific risk enhancer.
   D. Continue lifestyle therapies and do not initiate statin therapy.

2. According to the 2018 cholesterol management guidelines, which is best described as a moderate-intensity statin dose?
   A. Pravastatin 20 mg/day.
   B. Lovastatin 20 mg/day.
   C. Atorvastatin 40 mg/day.
   D. Rosuvastatin 10 mg/day.

A. 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA Guideline on the Management of Blood Cholesterol (aka 2018 Cholesterol Management Guideline)
   1. This 2018 guideline updates the 2013 guideline incorporating recommendations of the National Lipid Association (NLA), previous focused updates to the 2013 guideline, and newly available randomized controlled trials.
   2. Emphasis is on heart-healthy lifestyle for all, particularly younger individuals. Further supported by updated U.S. Preventive Services Task Force in late 2020.
   3. Four statin benefit groups (will be discussed in more detail later in chapter):
      a. Clinical ASCVD: History of acute coronary syndrome, MI, stable or unstable angina, coronary or arterial revascularization, stroke, transient ischemic attack, or peripheral arterial disease
      b. Primary severe hypercholesterolemia (LDL-C 190 mg/dL or greater)
      c. Patients with diabetes age 40-75 and LDL-C of 70-189 mg/dL
      d. Primary prevention (in select patients after assessment with PCE to estimate 10-year ASCVD risk)
   4. First-line therapy for patients with clinical ASCVD continues to be high-intensity (or maximally tolerated) statin therapy.
   5. In patients at very high risk (i.e., recurrent ASCVD events) and in whom LDL-C remains greater than 70 mg/dL, adding non-statins for further LDL-C reduction is reasonable. This recommendation incorporates findings from IMPROVE-IT (with ezetimibe) and ODYSSEY OUTCOMES and FOURIER (with the PCSK9 monoclonal antibody therapies alirocumab and evolocumab, respectively) trials. This recommendation has since been expanded upon further with the 2022 Expert Consensus Decision Pathway on the Role of Nonstatin Therapies for LDL-Cholesterol Lowering in the Management of Atherosclerotic Cardiovascular Disease Risk.
   6. Provide further guidance on clinician-patient risk discussion in patients for primary prevention and to guide statin intensity in those with diabetes with risk enhancers.
   7. Increase emphasis on repeated lipid measurements (reassessment as mentioned in section II).

B. 2022 Expert Consensus Decision Pathway on the Role of Nonstatin Therapies for LDL-Cholesterol Lowering in the Management of Atherosclerotic Cardiovascular Disease Risk
   1. Updated guidance for the use of newly FDA approved nonstatin therapies bempedoic acid, inclisiran, and evinacumab
   2. Reintroduced LDL-C goals as a means of assessing optimal lipid lowering therapy and guiding the addition of nonstatin therapy

C. Additional guidelines/statements are available from the European Society of Cardiology (2019), Veteran Affairs/Department of Defense (2020), American Association of Clinical Endocrinologists (2020), United States Preventive Services Task Force (2022), American Diabetes Association (2023).

## V. RISK ASSESSMENT BASED ON 2018 CHOLESTEROL MANAGEMENT GUIDELINES

A. For primary prevention of ASCVD in those with diabetes, further risk assessment should be used to guide therapy. Evaluation of major ASCVD risk factors, calculation of 10-year ASCVD risk using the PCE, and identification of risk-enhancers guide clinician-patient risk discussions. In patients age 40-75 years, these and other patient-specific factors (i.e., drug interactions, frailty, cost) determine medication eligibility, initiation and intensity. However, certain patients should be initiated on a statin without the need for further risk assessment:
   1. Patients age 20-75 with LDL-C 190 mg/dL or greater (high-intensity statin indicated)
   2. Patients age 40-75 with diabetes and LDL-C 70 mg/dL or greater (moderate-intensity statin recommended, with risk stratification for high-intensity statin)

B. Major ASCVD Risk Factors
   1. Age older than 45
   2. Current cigarette smoking
   3. Dysglycemia (diabetes)
   4. Diagnosis of hypertension: 130/80 mm Hg or greater or on antihypertensive therapy
   5. Low HDL-C
      a. Less than 40 mg/dL in males
      b. Less than 50 mg/dL in females
   6. Elevated LDL-C of 160 mg/dL or greater or non-HDL of 190 mg/dL or greater
   7. Family history, given difficulty in defining and varying attribution to patient's personal risk is not as helpful. Commonly defined as premature history of coronary heart disease (first-degree male relative < 55 years or first-degree female < 65 years)

C. Pooled Cohort Equation (PCE) for ASCVD Risk Estimation
   1. PCE estimates the 10-year risk of nonfatal MI or CHD death, or fatal or nonfatal stroke in individuals 40–79 years of age.
   2. Using PCE to estimate lifetime ASCVD risk may be considered in adults 20–59 years of age without clinical ASCVD or high short-term risk. Lifetime ASCVD risk score is more appropriate for emphasizing the importance of therapeutic lifestyle changes than for initiating lipid-lowering therapy.
   3. Based on cohort studies of racially and geographically diverse populations
   4. Essentially replaced the traditional Framingham Risk Score
   5. Useful to assess ASCVD risk for primary prevention, but should not be used in patients with clinical ASCVD or elevated LDL-C 190 mg/dL or greater
   6. Does not include all races/ethnicities, so may over/underestimate risk in non-white and non–African American groups

7. Pooled Cohort Equations and ASCVD Risk Estimator Plus Application: (http://tools.acc.org/ASCVD-Risk-Estimator-Plus/#!/calculate/estimate/): Allows PCE assessment of 10-year and lifetime ASCVD risk and includes additional risk enhancers and advice
    a. Age
    b. Sex
    c. Race (white, African American, other)
    d. Systolic blood pressure
    e. TC
    f. HDL-C
    g. LDL-C
    h. Diabetes
    i. Smoking status (current, former, never)
    j. Treatment for HTN
    k. The new estimator plus includes advice on statin and aspirin use.

D. Recommendations Regarding Use of Optional Risk Markers
1. Consider in patients for whom a risk-based decision remains uncertain after appropriate quantitative assessment.
    a. Recommended for clinician-patient discussion in patients age 40-75 with LDL-C 70-189 mg/dL and PCE indicating "borderline" (5% to less than 7.5%) or "intermediate" (greater than 7.5% to less than 20%) risk
    b. After risk discussion, patients with borderline risk may be initiated on a moderate-intensity statin if additional risk enhancers are present.
    c. After risk discussion plus risk enhancers with or without a CAC, patients with intermediate risk may be initiated on a moderate-intensity statin to reduce LDL-C by 30%-49%.
2. Consider an upward revision in ASCVD risk if:
    a. Borderline primary hypercholesterolemia (LDL-C 160-189 mg/dL)
    b. TG concentrations are persistently 175 mg/dL or greater (three repeated measures)
    c. History of premature ASCVD in a first-degree relative (parents and siblings only) before age 55 (male relatives) or 65 (female relatives)
    d. High-risk ethnicity (i.e., South Asian ancestry)
    e. Comorbidities:
        i. Chronic kidney disease (eGFR 15-59 mL/minute/1.73 $m^2$ with or without albuminuria; not receiving dialysis or a previous kidney transplant)
        ii. Premature menopause (younger than 40)
        iii. History of gestational diabetes or preeclampsia
        iv. Chronic inflammatory diseases (HIV/AIDS, rheumatoid arthritis, psoriasis)
        v. Metabolic syndrome
    f. Specific measurements, if available:
        i. Ankle-brachial index (ABI) less than 0.9
        ii. Lipoprotein(a) 50 mg/dL or greater (125 nmol/L)
        iii. hs-CRP (2.0 mg/L or greater)
        iv. Apolipoprotein B (ApoB) 130 mg/dL or greater (corresponds to an LDL-C 160 mg/dL or greater)
3. Coronary artery calcium (CAC) score can be measured if uncertainty remains after risk assessment. Measured in Agatston units
    a. Guidelines recommend in patients at intermediate or borderline risk but uncertain whether to start a statin
    b. CAC score of zero: Indicates low ASCVD risk (may be able to withhold statin if no other high-risk features unless the patient has diabetes, a family history of premature CHD, or a history of cigarette smoking). Consider rechecking in 5–10 years.

c. CAC score 1-99: Reasonable to initiate statin if age 55 and older.
d. CAC score of 100 or greater: Statin therapy recommended
e. No usefulness in patients already treated with statins

4. The following risk markers are NOT recommended for routine use in clinical practice at this time because of uncertainty about their use:
   a. Carotid intima-media thickness
   b. Cardiorespiratory fitness

**Patient Case**

*Questions 3 and 4 pertain to the following case.*

A 51-year-old white man presents for a CV risk assessment. He smokes 1 pack/day but denies drinking alcohol. His medical history includes GERD, HTN, and hyperlipidemia. His medications include lisinopril 10 mg/day, amlodipine 10 mg/day, and omeprazole 20 mg/day. His family history significant for a grandfather who died of a stroke at age 78. His blood pressure today is 130/84 mm Hg, and fasting laboratory results show a TC 208 mg/dL, LDL-C 140 mg/dL, HDL-C 42 mg/dL, and TG 130 mg/dL.

3. Which best depicts this patient's estimated 10-year ASCVD risk using PCE?
   A. 4.5%.
   B. 12.2%.
   C. 22%.
   D. 29%.

4. Which is the best recommendation regarding further identification of risk-enhancing factors and need for statin therapy?
   A. No further evaluation is warranted, given the patient's "low risk."
   B. No further evaluation is warranted, given the patient's "borderline risk."
   C. Evaluate for risk-enhancing factors, given the patient's "intermediate risk."
   D. Obtain a CAC to determine whether statin therapy is indicated.

## VI. TREATMENT BUILT ON STATINS

A. Statin Dosing (Table 1)
   1. Randomized clinical trial data support the use of fixed doses of high-intensity statins in the highest-risk patients (e.g., clinical ASCVD).
      a. TNT: 10,001 patients with CHD and LDL-C less than 130 mg/dL. Atorvastatin 80 mg/day was superior to atorvastatin 10 mg/day in reducing major CV events by 22%, but no difference in mortality was observed.
      b. PROVE-IT: 4162 patients less than 10 days post-acute coronary syndrome. Atorvastatin 80 mg/day was superior to pravastatin 10 mg/day in reducing mortality and major CV events by 16%.
   2. Randomized clinical trial data support the use of fixed-dose moderate intensity statins in individuals deemed "at risk" who are most likely to benefit from statin therapy.
      a. WOSCOPS: 6595 patients with hyperlipidemia. Pravastatin 40 mg/day was superior to placebo in reducing nonfatal MI or death from CHD by 31%.
      b. AFCAPS/TexCAPS: 5608 patients with hyperlipidemia. Lovastatin 20–40 mg/day was superior to placebo in reducing first major coronary event (including fatal and non-fatal) by 37%.

3. The Cholesterol Treatment Trialists' (CTT) Collaboration completed a meta-analysis comparing more intensive doses with less intensive doses (or control) of statin for their reduction in major adverse CV events.
    a. 26 trials, with over 170,000 participants, and at least 2 years (4.8 median) of follow-up were included.
    b. Reduction in LDL-C (by each 1 mmol/L or 38.67 mg/dL) results in a 21% relative risk reduction in major vascular events.
4. Age cutoffs in guidelines merely reflect the inability to determine the magnitude of benefit in individuals younger than 40 or older than 75 because of a lack of representation in clinical trials.

**Table 1.** Statin Intensity

| Statin Name | Low Intensity (LDL- C Reduction: ~30%) | Moderate Intensity (LDL- C Reduction: ~30%–50%) | High Intensity (LDL- C Reduction: ~>50%) |
|---|---|---|---|
| Atorvastatin | | 10 mg (20 mg) | 80 mg (40 mg) |
| Rosuvastatin | | 10 mg (5 mg) | 40 mg (20 mg) |
| Simvastatin | 10 mg | 20–40 mg | |
| Pravastatin | 10–20 mg | 40 mg (80 mg) | |
| Lovastatin | 20 mg | 40 mg (80 mg) | |
| Fluvastatin XL | 20–40 mg | 80 mg (40 mg twice daily for immediate release) | |
| Pitavastatin | | 1–4 mg | |

B. General Approach to Initiating Statin Therapy
    1. Laboratory assessment
        a. Obtain a lipid panel and ensure baseline hepatic function is normal.
        b. Evaluate for secondary causes, especially when TG is 500 mg/dL or greater, LDL-C is greater than 190 mg/dL, or the patient has an unexplained elevation in hepatic enzymes.
    2. Age assessment
        a. If 75 years of age or younger and without contraindications or drug-drug interactions that may influence statin safety, initiate indicated statin intensity based on specific statin benefit group and provide healthy lifestyle counseling.
        b. If older than 75 years of age but high-intensity was otherwise indicated, in the absence of drug interactions or contraindications, high-intensity is reasonable. Moderate-intensity is also reasonable, given patient preference/concerns or frailty (not automatically decreased because of age). Continue high-intensity in patients who tolerate it. In patients who exhibit functional decline, increasing frailty, and limited life expectancy, it is reasonable to stop statin because future benefits are limited.
        c. In patients 76–80 years of age with an LDL-C between 70 and 189 mg/dL, a CAC may be considered to rule out the need for statin therapy.
    3. Monitoring: Obtain a repeat lipid panel within 4–12 weeks. No need for routine monitoring of liver function tests (LFTs) or creatine kinase (CK)

C. Statin Benefit Group Overview (Figure 1)
    1. Clinical ASCVD
        a. Recommendations divided into VERY high risk and NOT very high risk (Table 2)
        b. VERY high-risk defined as a history of multiple major ASCVD events or one major ASCVD event and multiple high-risk conditions (Criteria listed in Table 2)
        c. VERY high-risk: Initiate a high-intensity statin.

d. NOT at very high-risk and age older than 75: Continue high-intensity if patient is already taking it, otherwise initiate either moderate- or high-intensity
e. NOT at very high risk and age 75 or younger: High-intensity or maximal tolerated
f. Particularly in patients initiated on statins at the time of a first ASCVD event, multiple medication changes are likely to have occurred simultaneously and increased complexity of medication regimens, requiring extra care.
    i. It is recommended that transitions of care support be provided to these patients (i.e., discharge counseling, 24–48 hours follow-up phone calls to review medications, early postdischarge follow-up with comprehensive medication management).
    ii. Management plans to evaluate tolerability and efficacy of statin in 4–12 weeks.
    iii. In all patients who do not achieve desired LDL-C reduction, consider adding additional therapy to maximally tolerated statin. Nonstatin therapies are discussed in greater detail later in chapter.

**Table 2.** Very High-Risk of Future ASCVD Events

| Category | Criteria |
|---|---|
| Major ASCVD events | Recent ACS (previous 12 months)<br>History of MI<br>History of ischemic stroke<br>Symptomatic PAD (claudication with ABI less than 0.85 or previous pulmonary arterial disease revascularization or amputation) |
| High-risk conditions | Age ≥65 years<br>Heterozygous FH<br>History of HF<br>Prior elective CABG or PCI<br>DM<br>HTN<br>CKD (eGFR 15-59 mL/min/1.73 $m^2$)<br>Current smoking<br>Persistently elevated LDL-C ≥100 mg/dL despite maximally tolerated statin and ezetimibe |

ACS = Acute Coronary Syndrome, ASCVD = Atherosclerotic Cardiovascular Disease, CABG = coronary artery bypass graft, CKD = chronic kidney disease, DM = diabetes, FH = familial hypercholesterolemia, HF=heart failure, HTN=hypertension, MI = myocardial infarction, PAD= peripheral arterial disease, PCI = percutaneous coronary intervention.

2. LDL-C of 190 mg/dL or greater
    a. Age 20-75: Start with maximally tolerated statin with goal of greater than 50% reduction in LDL-C.
    b. In all patients who do not achieve desired LDL-C reduction, consider adding additional therapy to maximally tolerated statin.
3. Patients with diabetes
    a. In patients with diabetes age 40-75, a moderate-intensity stain is indicated unless they have several ASCVD risk factors (or more than a 20% 10-year risk of ASCVD), in which case a high-intensity statin is indicated.
    b. In patients with diabetes age 20-39 years, with diabetes-specific risk enhancers that are independent of other risk factors, it is reasonable to start a statin:
        i. Long duration (10 years or more for type 2 diabetes or 20 years or more for type 1 diabetes)
        ii. Albuminuria
        iii. eGFR less than 60 mL/minute/1.73 $m^2$
        iv. Retinopathy
        v. Neuropathy
        vi. ABI less than 0.9
4. Primary prevention
    a. Age 0-19 years: Lifestyle therapies unless diagnosis of familial hypercholesterolemia (statin)
    b. Age 20-39 years: Lifestyle therapies alone unless family history of premature ASCVD and LDL-C of 160 mg/dL or more (statin)
    c. Age 40-75:
        i. In high-risk patients (PCE 10-year ASCVD risk of 20% or greater): Statin to reduce LDL-C by 50% or greater
        ii. In patients with "borderline risk" (from 5% to less than 7.5%) and "intermediate risk" (from 7.5% to less than 20%), evaluate risk enhancers with or without CAC (discussed in the previous text) to guide statin use. If statin therapy is favored, then a target LDL-C reduction of 30% -49% is desired.
        iii. In patients at "low risk" (less than 5%): Emphasize lifestyle therapies.
    d. Age older than 75: Patient-provider risk discussion

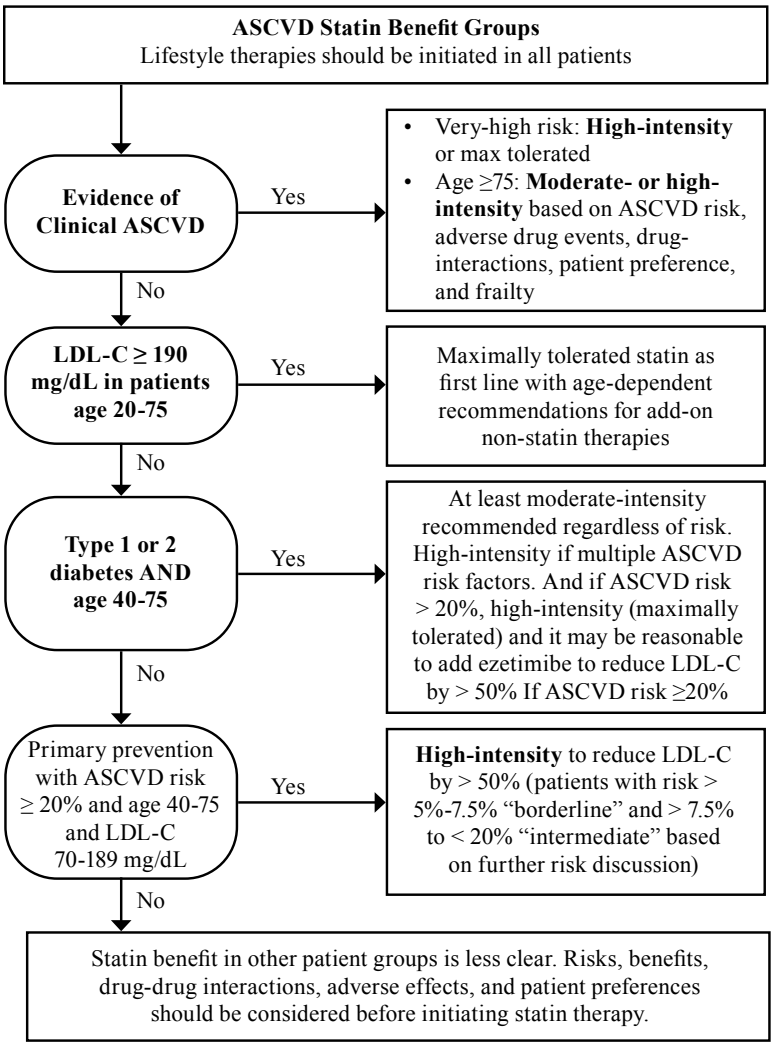


**Figure 1.** Statin benefit groups overview.

Reference: Grundy SM, Stone NJ, Bailey AL, et al. 2018 ACC/AHA/AACVPR/AAPA/ABC/ACPM/ADA/AGS/ APhA/ASPC/NLA/ PCNA guideline on the management of blood cholesterol: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Clinical Practice Guidelines. J Am Coll Cardiol 2018 Nov 10. [Epub ahead of print]. Available at https://www.acc.org/latest-in-cardiology/ten-points-to-remember/2018/11/09/14/28/2018-guideline-on-management-of-blood-cholesterol.

## VII. MANAGEMENT OF ELEVATED TRIGLYCERIDES

A. General
   1. Elevated TG concentrations appear to be a biomarker of increased ASCVD risk, but their role as a causal factor in the development of atherosclerosis and ASCVD remains debatable.
   2. Elevated TG concentrations account for around 10% of all cases of acute pancreatitis (arbitrarily defined as greater than 1000 mg/dL), whereas alcohol abuse and gallstones account for at least 80% of cases.
   3. Clinical studies showing reduced pancreatitis with TG-lowering therapies are limited to secondary prevention in patients who already had a first incidence of pancreatitis.
   4. Nonpharmacologic measures (e.g., weight loss, alcohol avoidance, reduction in sugar/carbohydrate intake, physical activity, improving glycemic control) should be recommended in all patients with elevated TG concentrations.

5. The 2021 ACC Expert Consensus Decision Pathway on the Management ofASCVD Risk Reduction in Patients With Persistent Hypertriglyceridemia updated the 2018 cholesterol management guideline because pharmacotherapy for reducing TG was not recommended at the time given the lack of clinical evidence supporting clinical outcome efficacy.
6. Updates included consideration of either an LDL-C risk-based approach or a TG risk-based approach in select patient subgroups discussed below. Table 4 shows relative effect lipid-lowering medications on TG concentration reduction.
7. The TG risk-based approach is based on the results of the REDUCE-IT trial and USA-subgroup analysis (REDUCE-IT USA), which were not available at the time of the 2018 cholesterol management guideline publication. These results showed that in patients with clinical ASCVD and persistently elevated TG (135–499 mg/dL), adding icosapent ethyl 2 g twice daily to background statin therapy significantly reduced major adverse CV events and all-cause mortality in the USA subgroup. Findings are discussed in further detail later in the chapter.

B. Treatment of Elevated TG
   1. Moderate hypertriglyceridemia (fasting 150 mg/dL or greater or nonfasting TG 175-499 mg/dL):
      a. Adults 20 years of age and older: Recommend lifestyle therapies, identification of secondary causes (Table 3)
      b. Adults 40–75 years of age with ASCVD 20% or higher: Use this as an indication for initiating or intensifying the statin. For ASCVD risk 5% to less than 20%, may consider statin initiation or intensification.
      c. Adults 50 years of age or older with diabetes and one or more ASCVD high-risk features per REDUCE-IT trial criteria: Consider icosapent ethyl
      d. High-risk features defined as any of the following: Men 55 years of age or older and women 65 years of age or older, cigarette smoker or stopped smoking within 3 months, hypertension (blood pressure 140 mm Hg or more systolic or 90 mm Hg or more diastolic) or on antihypertensive medication, HDL-C 40 mg/dL or less for men or 50 mg/dL or less for women, Hs-CRP more than 3.0 mg/L, renal dysfunction - creatinine clearance (CrCL) greater than 30 and less than 60 mL/min, retinopathy, albuminuria, ABI less than 0.9 without symptoms of intermittent claudication
      e. Adults with clinical ASCVD: Patients with an LDL-C less than 70 mg/dL may consider icosapent ethyl. Patients with an LDL-C 70–99 mg/dL may also be considered for icosapent ethyl or intensification of LDL-C risk-based approach or both. Patients at VERY high risk, or LDL-C 100 mg/dL or higher should prioritize an LDL-C risk-based approach.
   2. Severe hypertriglyceridemia (fasting TG 500 mg/dL or greater):
      a. Chylomicrons, which impart pancreatitis risk, are elevated in addition to VLDL (atherogenic).
      b. Adults 40–75 years of age with ASCVD risk 5% or greater, clinical ASCVD, or diabetes: Address reversible causes and initiate or intensify statin therapy. Then consider fibrate or prescription omega-3 fatty acids (icosapent ethyl or omega-3 acid ethyl esters) to reduce risk of pancreatitis and low-fat diet if persistent TG greater than 500 mg/dL
      c. Adults 20–39 years of age or 40–75 years of age with ASCVD risk less than 5%: Consider fibrate or prescription omega-3 fatty acids to reduce risk of pancreatitis and low-fat diet if persistent TG greater than 500 mg/dL
      d. Fenofibrate is preferred over gemfibrozil because of better safety and fewer drug interactions
   3. TG 1000 mg/dL or greater (also “severe”):
      a. Implement very low fat diet (10%–15% of calories) and avoid refined carbohydrates and alcohol.
      b. Implement very low-fat diet (avoid refined carbohydrates and alcohol).
      c. Consider statin initiation or intensification in appropriate patients as noted with TG greater than 500 mg/dL.
      d. Consider fibrate (fenofibrate preferred) or prescription omega-3 fatty acids (icosapent ethyl or omega-3 acid ethyl esters) to reduce risk of pancreatitis.

**Table 3.** Common Secondary Causes of Elevated LDL-C and TG

| Cause | Increase LDL-C | Increase TG |
|---|---|---|
| Medications | Glucocorticoids, amiodarone, diuretics, cyclosporine | Oral estrogens, glucocorticoids, bile acid sequestrants, protease inhibitors, retinoic acid, anabolic steroids, immunosuppressive drugs (cyclosporine, tacrolimus, sirolimus), atypical antipsychotics, tamoxifen, raloxifene, β-blockers, thiazide and loop diuretics, propofol, L-asparaginase, bexarotene, cyclophosphamide, interferons |
| Dietary influences | Saturated or *trans* fats, weight gain, anorexia | History of alcohol abuse or alcohol excess; diets high in saturated fat, sugar, or high-glycemic index food; sedentary lifestyle; total parenteral nutrition with lipid emulsions |
| Disease states and medical conditions | Nephrotic syndrome, biliary obstruction, hypothyroidism, obesity, pregnancy | Poorly controlled diabetes, hypothyroidism, obesity, pregnancy, nephrotic syndrome, chronic renal failure, lipodystrophies, Cushing syndrome, gycogen storage disease, acute hepatitis, rheumatoid arthritis, psoriasis, systemic lupus erythematosus, multiple myeloma sepsis, obesity/weight gain, metabolic syndrome |

**Table 4.** Effect of Lipid-Lowering Medications on TG

| Medication | % Decrease in TG |
|---|---|
| Statins | 10–30 |
| Fibrates | 30–50 |
| Immediate-release niacin | 20–50 |
| Extended-release niacin | 10–30 |
| Ezetimibe | 5–10 |
| Omega-3 fatty acids | 20–50 |
| PCSK9 monoclonal antibodies | 0–17 |

**Patient Case**

5. A 46-year-old African American woman who was recently (3 months ago) hospitalized for acute pancreatitis (TG greater than 2000 mg/dL) is referred to you for management of hypertriglyceridemia. Her other medical history includes HTN, which is well controlled. Her estimated 10-year ASCVD risk is 5.1%. Since her hospitalization, she has lost 10 lb by reducing her intake of simple carbohydrates and walking for 30 minutes five times a week. She is concerned because her weight loss has plateaued in recent weeks. She does not use tobacco or alcohol. Her medications include amlodipine 10 mg/day, losartan 100 mg/day, and a multivitamin. Today's fasting laboratory results show TC 210 mg/dL, LDL-C (not calculated), HDL-C 39 mg/dL, and TG 1058 mg/dL. Which is the best treatment recommendation at this time?

   A. Continue diet, exercise, and weight loss only.

   B. Initiate bempedoic acid 180 mg/day.

   C. Initiate ezetimibe 10 mg/day.

   D. Initiate fenofibrate 145 mg/day.

## VIII. STATINS

A. Dosing (Table 1)
B. Efficacy
   1. First-line therapy for reducing atherogenic lipoproteins and ASCVD risk
   2. Reduces coronary events, stroke, coronary revascularization, CV-related and total mortality (primary and secondary prevention)
   3. Reduces LDL-C 24%–60%
   4. Reduces TG 10%–30%
   5. Raises HDL-C 5%–15%
   6. Does not reduce Lp(a)

C. Mechanism of Action: Inhibits HMG-CoA reductase, an enzyme responsible for converting HMG-CoA to mevalonate, which is the rate-limiting step in the production of cholesterol, leading to increased hepatic LDL receptors and increased clearance of LDL-C

D. Adverse Effect Profile/Monitoring
   1. Obtain lipid profile 4–12 weeks after initiation; then every 3–12 months
      a. The 2018 cholesterol management guideline supports routine lipid monitoring, which is based on randomized controlled trial evidence, to confirm that the percent reduction in LDL desired is achieved and to objectively assess adherence to statin therapy.
      b. A post hoc analysis of the JUPITER study showed that only 46% of participants achieved the expected 50% or greater reduction in LDL while taking rosuvastatin 20 mg/day. This supports the variability in individual responses to statin therapy and the need for lipid monitoring.
   2. Statin intolerance
      a. Defined as one or more adverse effects associated with statin therapy
      b. Complete intolerance – inability to tolerate any dose of statin therapy
      c. Partial intolerance – inability to tolerate the dose necessary to achieve therapeutic objectives
      d. At least two statins must be tried, one at the lowest approved dose to achieve therapeutic goal
      e. Statin-associated muscle symptoms (SAMS) is the most common
      f. Estimated to occur in 5%–30% of patients, and may vary across populations and settings
   3. Statin-associated muscle symptoms
      a. Definition of SAMS:
         i. Myalgia – Unexplained muscle achiness or soreness, often without CK elevation
         ii. Myopathy – Muscle "weakness" and sometimes associated with CK elevation
         iii. Myositis – Muscle inflammation confirmed by muscle biopsy and/or magnetic resonance imaging
         iv. Rhabdomyolysis – CK elevation 10 x upper limit of normal with myoglobinuria or acute renal failure; very rare
      b. More likely to occur with moderate-high intensity statin doses
      c. Rule out other causes, such as recent initiation of a strenuous exercise program, hypothyroidism, alcohol use, obesity, diabetes, vitamin D deficiency, and drug interactions
      d. More common in older adults, frequent exercisers, small body frame, and chronic kidney disease
      e. Usually resolves with decrease in statin dose, statin discontinuation, changing to another statin, or every-other-day statin administration; therefore in most cases, rechallenge is recommended when SAMS are not severe in nature.
         i. Recent N of 1 trials have suggested statin muscle intolerance is associated with a nocebo effect (SAMSON, StatinWISE)

f. Guidelines do not recommend coenzyme Q10 supplementation for the treatment of SAMS. Randomized controlled trials have shown mixed efficacy, but it appears safe.

3. Elevated hepatic transaminases
   a. Transient elevations that usually resolve with time
   b. LFTs at baseline before initiating statin therapy
   c. Routine monitoring is not recommended. LFTs should be obtained if symptoms of hepatotoxicity are present.
   e. Routine monitoring is not recommended.
4. Increased risk of new-onset type 2 diabetes
   a. Appears to be a dose-dependent effect
   b. Much more likely to occur in individuals with risk factors for diabetes
      i. Metabolic syndrome
      ii. Fasting glucose 100 mg/dL or greater
      iii. BMI greater than 30 kg/m2
      iv. A1C greater than 6%
   c. Further analysis of the JUPITER trial showed that patients without risk factors for diabetes had no increased risk of developing diabetes.
   d. The risk-benefit ratio of statin use in patients with diabetes should take into consideration its metabolic effects.
5. Contraindications
   a. Acute liver failure or decompensated cirrhosis
   b. Nursing mothers
6. Pharmacokinetics (Table 5)
7. Select drug-drug interactions (Table 6)
8. Adults with chronic kidney disease (CKD)
   a. Patients with CKD have increased risk of ASCVD.
      i. In a meta-analysis of over 1.4 million people, there was a linear increase in cardiovascular mortality seen with decreasing estimated glomerular filtration rate (eGFR) below a threshold eGFR of 75 mL/min/1.73 $m^2$.
      ii. The Alberta cohort, which followed more than 1 million individuals for more than 4 years, demonstrated risk of ASCVD to be greater than 10% over 10 years.
   b. 2018 Cholesterol Management Guidelines recommendations in CKD
      i. eGFR 15–59 mL/min/1.73 $m^2$ is used as a risk-enhancing factor when determining need for initiation of moderate-intensity statin (with or without ezetimibe – SHARP) in patients 40–75 years of age with LDL-C 70–189 mg/dL with ASCVD risk greater than 7.5%
      ii. It may be reasonable to continue statin therapy in patients who are being initiated on dialysis.
      iii. Initiation of statin therapy for primary prevention in patients already requiring dialysis is not recommended (Class III-no benefit, LOE B–R).
   c. 2013 KDIGO guidelines recommendations
      i. All adults 50 years of age and older with CKD (stage 1–4) should be managed with statin, largely moderate intensity, based on dosing used in the few RCT of patients with eGFR less than 60 mL/min/1.73 $m^2$ establishing safety.
      ii. Reasonable to continue therapy (statins or statin/ezetimibe combinations) in patients who are already receiving and being started on dialysis
      iii. In adults with dialysis-dependent CKD, KDIGO recommends avoiding initiation of statins or statin/ezetimibe combinations.
   d. Neither current guideline specifically addresses if high-intensity statin is reasonable to initiate or continue in patients with CKD (or who develop CKD) and have a compelling indication (i.e., ASCVD).

i. The 2021 ACC/AHA Guideline for Coronary Artery Revascularization states pretreatment with high-intensity statin in patients with CKD undergoing angiography is a "best practice" because high-dose statins reduce the occurrence of contrast-induced acute kidney injury.

e. Pharmacokinetic data suggest no dosage adjustment is inherently indicated for atorvastatin (across all eGFR ranges) while rosuvastatin at no higher then moderate-intensity if eGFR is less than 30 mL/min/1.73 $m^2$ is reasonable (Table 7).

f. Differing dosing recommendations combined with limited inclusion of CKD patients in outcomes based clinical trials of statins require careful considerations with treatment on this high-risk special population.

9. Use in women
   a. Consider premature menopause and history of pregnancy-associated disorders in risk assessment.
   b. Women of childbearing age receiving statins should be counseled to use contraception.
   c. Women who plan to become pregnant should discontinue the statin 1–2 months before pregnancy or as soon as pregnancy is discovered.
   d. As of July 2021, FDA requested downgrading statin contraindication in pregnancy because of a data review in which there was limited data suggesting fetal harm. This would allow statin use in highest-risk patients such as homozygous familial hypercholesterolemia (FH) with prior ASCVD and allow risk-benefit discussions.
   e. In most patients, statins should continue to be avoided in pregnancy and in breastfeeding women.
10. HIV and chronic inflammatory disorders (e.g., psoriasis, lupus, rheumatoid arthritis, etc.) are considered a risk-enhancing factor in favor of statin therapy.

**Patient Case**

6. A 57-year-old white man presents to a general cardiology clinic reporting angina during his daily walk that resolves with rest. His medical history includes coronary artery disease, HTN, and hyperlipidemia. His medications include aspirin 81 mg/day, lisinopril 20 mg/day, metoprolol succinate 100 mg/day, isosorbide mononitrate 60 mg/day, and simvastatin 40 mg/day (myalgia reported with both atorvastatin and rosuvastatin). The cardiologist decides to add ranolazine 500 mg twice daily. Which is the best recommendation regarding treatment of his hyperlipidemia at this time?

   A. Continue simvastatin 40 mg/day.

   B. Decrease simvastatin to 20 mg/day.

   C. Increase simvastatin to 80 mg/day.

   D. Change to lovastatin 40 mg/day.

**Table 5.** Pharmacokinetic Differences Between Statins

| Statin | Bioavailability (%) | Half-Life (hr) | Metabolism | Prodrug? | Solubility |
|---|---|---|---|---|---|
| Atorvastatin | 14 | 14 | 3A4 | No | Lipophilic |
| Fluvastatin | 24 | 3 | 2C9 | No | Lipophilic (slightly less than atorvastatin) |
| Lovastatin | < 5 | 2–3 | 3A4 | Yes | Lipophilic |
| Pitavastatin | 51 | 12 | 2C9, 2C8 | No | Lipophilic |
| Pravastatin | 17 | 1.5–2 | N/A | No | Hydrophilic |
| Simvastatin | < 5 | 2 | 3A4 | Yes | Lipophilic |
| Rosuvastatin | 20 | 20 | 2C9 | No | Hydrophilic |

N/A = not applicable.

**Table 6.** Select Drug-Drug Interactions with Statins

| | Lovastatin | Pravastatin | Simvastatin | Fluvastatin | Pitavastatin | Atorvastatin | Rosuvastatin |
|---|---|---|---|---|---|---|---|
| Amiodarone | Daily dose NTE 40 mg | | Daily dose NTE 20 mg | | | | |
| Amlodipine | Daily dose NTE 20 mg | | Daily dose NTE 20 mg | | | | |
| Boceprevir | CI | | CI | | | Daily dose NTE 40 mg (boceprevir) | |
| Colchicine | Use with caution | Use with caution | Use with caution | Use with caution | Use with caution | Use with caution | Use with caution |
| Cyclosporine | CI | Daily dose NTE 20 mg | CI | Daily dose NTE 20 mg | | CI | Daily dose NTE 5 mg |
| Danazol | Daily dose NTE 20 mg | | CI | | | | |
| Diltiazem, verapamil | Daily dose NTE 20 mg | | Daily dose NTE 10 mg | | | | |
| Dronedarone | Daily dose NTE 20 mg | | Daily dose NTE 10 mg | | | | |
| Erythromycin, clarithromycin, telithromycin | CI | Daily dose NTE 40 mg (clarithromycin) | CI | | Daily dose NTE 1 mg (erythromycin) | Daily dose NTE 20 mg (clarithromycin) | |
| Gemfibrozil | CI | | CI | Use with caution | Use with caution | | Daily dose NTE 10 mg |
| Grapefruit juice (> 1 quart per day) | Avoid use | | Avoid use | | | Avoid excess quantities (> 1.2 L/day) | |
| Itraconazole, ketoconazole, posaconazole, fluconazone | CI | | CI | Daily dose NTE 20 mg BID (fluconazole) | | Daily dose NTE 20 mg (itraconazole) | |
| Nefazodone | CI | | CI | | | | |
| Niacin | Avoid doses of niacin ≥ 1 g/day | Avoid doses of niacin ≥ 1 g/day | Avoid doses of niacin ≥ 1 g/day | Avoid doses of niacin ≥ 1 g/day | Avoid doses of niacin ≥ 1 g/day | | Avoid doses of niacin ≥ 1 g/day |
| HIV protease inhibitors | CI | | CI | | | CI with tipranavir plus ritonavir. Daily dose NTE 20 mg (saquinavir plus ritonavir, darunavir plus ritonavir, fosamprenavir or fosamprenavir plus ritonavir) Daily dose NTE 40 mg (nelfinavir) | Daily dose NTE 10 mg (lopinavir/ ritonavir or atazanavir/ ritonavir) |
| Ranolazine | NTE 20 mg | | Daily dose NTE 20 mg | | | | |
| Rifampin | | | | | Daily dose NTE 2 mg | | |
| Voriconazole | CI | | CI | | | | |

BID = twice daily; CI = contraindicated; NTE = not to exceed.

**Table 7.** Dosing of Statin Agents in Chronic Kidney Disease

| Statin | Dosing by eGFR (mL/min/1.73 m$^2$) in mg from package insert | | | Comments | Dose Recommended by KDIGO Guidelines[a] |
|---|---|---|---|---|---|
| | 30–59 (CKD stage 3) | 15–29 (CKD stage 4) | < 15 or HD | | |
| Atorvastatin | 10–80 | 10–80 | 10–80 | No dosage adjustment recommended | 20 mg/day |
| Fluvastatin | 10–80 | 10–40 | 10–40 | Doses > 40 mg not studied in severe renal impairment | 80 mg/day |
| Lovastatin | 20–80 | 10–40 | 10–40 | Labeling cautions against doses > 20 mg when CrCl < 30 mL/min/1.73 m$^2$ | Not studied |
| Pitavastatin | 1–2 | 1–2 | 1–2 | Avoid 4 mg based on PK. | 2 mg/day |
| Pravastatin | 20–80 | 10–80 | 10–80 | Labeling recommends initial dose of 10 mg if significant renal impairment | 40 mg/day |
| Simvastatin[b] | 20–80 | 5–40 | 5–40 | Labeling recommends initial dose of 5 mg if CrCl < 30 mL/min/1.73 m$^2$ | 40 mg/day (ezetimibe/simvastatin 10/20 mg/day[d]) |
| Rosuvastatin | 5–40 | 5–10 | Unknown | — | 10 mg/day |

[a]Kidney Disease: Improving Global Outcomes. KDIGO clinical practice guidelines for lipid management in chronic kidney disease. Kidney Int 2013;3:1-56.

[b]The 80-mg simvastatin dose should be reserved for patients who have been taking simvastatin 80 mg long term (e.g., ≥ 12 mo) and who have no evidence of muscle toxicity.

[c]No data available; cannot recommend.

[d]The SHARP trial showed simvastatin 20 mg/day plus ezetimibe 10 mg/day reduced major CV events compared with placebo; however, this was driven by a reduction only in ischemic stroke and revascularization, not MI or coronary death.

CrCl = creatinine clearance; eGFR = estimated glomerular filtration rate; HD = hemodialysis; PK = pharmacokinetic.

## IX. ROLE OF NON-STATIN THERAPIES

A. 2022 ACC Expert Consensus Decision Pathway on the Role of Nonstatin Therapies for LDL-Cholesterol Lowering in the Management of Atherosclerotic Cardiovascular Disease Risk
   1. Clinician-patient shared decision-making
      a. Adherence to statin therapy and lifestyle modifications
         i. Monitor statin response to assess whether desired percent LDL-C reduction is achieved by obtaining a lipid panel.
         ii. Consider non-statins that significantly lower atherogenic lipoproteins (LDL and non-HDL).
      b. Statin intolerance
      c. Potential risk reduction
      d. Potential risk of adverse effects or drug-drug interactions
      e. Discussion of out-of-pocket costs
      f. Invite patient to ask questions, express values, and collaborate to develop treatment and monitoring plan.

2. Recommended non-statin interventions
    a. Ezetimibe
    b. PCSK9 mAbs
    c. Bile acid sequestrants
    d. Bempedoic Acid
    e. Inclisiran
    f. Referral to lipid specialist and/or dietitian

B. Patient Groups Who May Be Considered for Non-statin Therapy
1. Patients with clinical ASCVD at VERY high risk (defined previously) and patients with clinical ASCVD and clinical diagnosis or genetic confirmation of familial hypercholesterolemia receiving maximal statin therapy: LDL-C goal reduction of greater than 50% and LDL-C 55 mg/dL or less (or non-HDL-C 85 mg/dL or less)
2. Patients with clinical ASCVD considered NOT at very high risk and patients with clinical ASCVD with baseline LDL-C greater than 190 mg/dL without clinical diagnosis or genetic confirmation of familial hypercholesterolemia, receiving maximal statin therapy: LDL-C goal reduction of greater than 50% and LDL-C 70 mg/dL or less (or non-HDL-C 100 mg/dL or less)
3. Patients without clinical ASCVD and with baseline LDL-C greater than 190 mg/dL receiving maximal statin therapy: LDL-C goal reduction of greater than 50% and LDL-C 100 mg/dL or less (or non-HDL-C 130 mg/dL or less)
4. Patients with or without diabetes (without ASCVD but risk of 20% or greater) receiving maximally tolerated statin therapy but less than a 50% reduction in LDL-C (and LDL greater than 70 mg/dL or non-HDL greater than 100 mg/dL): Consider adding ezetimibe or bile acid sequestrants (if TG less than 300 mg/dL) if ezetimibe-intolerant.
5. Guidance for treatment selection.
    a. Addition of ezetimibe or PCSK9 mAb should be considered first based on patient characteristics or preferences.
    b. Ezetimibe is often preferred for patients requiring less than 25% additional LDL-C reduction, have recent acute coronary syndrome, for cost considerations, or easier administration (oral).
    c. In the highest risk patient groups, the combination PCSK9 mAb/ezetimbe may be reasonable in order to reach LDL-C targets.
    d. Addition of bempedoic acid or inclisiran (as a substitute for PCSK9 mAb) are alternative options if goal is still not achieved or as patient preference.
    e. Bile acid sequestrants have a modest benefit for increased glycemic control that may be beneficial in diabetics as an alternative to ezetimibe, but they should be avoided in those with TG concentrations above 300 mg/dL.
    f. If still not at goal, referral to lipid specialist and dietitian
    g. Patients with homozygous familial hypercholesterolemia: may consider evinacumab, lomitapide, and/or LDL apheresis under care of lipid specialist
6. Treatment for adults with statin intolerance (statin benefit groups previously defined):
    a. Adults with clinical ASCVD or LDL-C of 190 mg/dL or greater
        i. First line: Ezetimibe and/or PCSK9 mAb
        ii. Second line: Bempedoic acid or inclisiran
    b. Adults without ASCVD and with or without diabetes
        i. First line: Ezetimibe
        ii. Second line: Bile acid sequestrants
        iii. Third line: Bempedoic acid

7. If persistent hypertriglyceridemia, refer to the 2021 ACC Expert Consensus Decision Pathway on the Management of ASCVD Risk Reduction in Patients With Persistent Hypertriglyceridemia for consideration of icosapent ethyl for CV risk reduction

## X. CHOLESTEROL ABSORPTION INHIBITOR

A. Ezetimibe (also available as ezetimibe/simvastatin and ezetimibe/bempedoic acid)
   1. Dosing: 10 mg orally once daily

B. Efficacy
   1. Reduces coronary events, stroke, and CHD mortality when added to statin therapy in the setting of acute MI (IMPROVE-IT), but benefit remains unknown in patients with stable CHD or for primary prevention
   2. Reduces LDL-C 18% (monotherapy); 25% (combined with statin)
   3. Reduces TG 5%–10%
   4. Raises HDL-C 1%–5%

C. Mechanism of Action: Inhibits cholesterol absorption from the small intestine by inhibiting Niemann-Pick C1-like 1 on intestinal epithelial cells decreasing hepatic stores of cholesterol and increasing systemic LDL clearance

D. Adverse Effect Profile/Monitoring
   1. Gastrointestinal (GI) upset
   2. Not recommended in patients with moderate/severe hepatic impairment. Slightly higher risk of elevated hepatic transaminases when used in combination with statin therapy
   3. Drug-drug interactions
      a. Avoid use with cyclosporine, which can increase ezetimibe concentrations.
      b. Monitor use with cholestyramine, which can decrease ezetimibe concentrations. Take either 2 hours before or 4 hours after BAS.

## XI. PCSK9 MONOCLONAL ANTIBODIES (MABS)

A. Alirocumab, Evolocumab
   1. Dosing:
      a. Alirocumab: Initial dose of 75 mg subcutaneously every 2 weeks and may be increased to 150 mg subcutaneously every 2 weeks; may also be given 300 mg subcutaneously every 4 weeks
      b. Evolocumab: 140 mg subcutaneously every 2 weeks; may also be given 420 mg subcutaneously every 4 weeks
      c. For adults with homozygous hypercholesterolemia, the starting doses are higher (150 mg and 420 mg for alirocumab and evolocumab, respectively)

B. Efficacy
   1. Reduces LDL-C up to 60% in statin-treated patients
   2. Indicated for heterozygous and homozygous familial hypercholesterolemia or clinical ASCVD
   3. Reduces non-fatal cardiovascular events when used in combination with statin therapy in secondary prevention population (evolocumab in FOURIER and alirocumab in ODYSSEY OUTCOMES)
   4. A significant reduction in all-cause mortality was found in the ODYSSEY OUTCOMES trial; however, this was an exploratory outcome and was not supported by a significant reduction in CV death.

C. Mechanism of action: Inhibits PCSK9, an enzyme that facilitates the degradation of LDL receptors in the liver, which allows LDL receptor recycling, increasing the number of available LDL receptors on the liver to remove LDL-C from the blood

D. Adverse effect profile/monitoring: Injection-site reactions

E. Cost
   1. Cholesterol management guidelines value statement on PCSK9 mAbs
      a. Initial value statement from 2018 Cholesterol Management Guidelines identified PCSK9 mAbs as a low value in terms of cost effectiveness based on pricing at that time.
      b. As cost of PCSK9 mAbs was reduced, 2019 NLA statement updated cost analysis for reasonable cost effectiveness in high-risk patients (e.g., ASCVD, familial hypercholesterolemia, etc.)
      c. The 2022 Expert Expert Consensus Decision Pathway on the Role of Nonstatin Therapies did not provide an updated specific cost-value statement but focuses on shared decision-making to consider the additional LDL-C lowering desired, costs, patient preferences, frequency and route of administration, and convenience.
      d. Price points of these medications are changing, so value in quality-adjusted life-years needs to be evaluated as changes in benefits and costs occur.
      e. Updated cost analyses from the ODYSSEY OUTCOMES and FOURIER using reducing pricing revealed PCSK9 mAbs are "high" to "intermediate" value in these high-risk populations (less than about $50,000 to $100,000 per QALY).
   2. There are many resources available for patients to receive reduced or no-cost medications, including PCSK9 inhibitors. Programs are often complex and difficult for most patients to manage independently. Therefore, it is important for pharmacists to engage patients and teams to ensure affordability of prescribed regimens on an individual basis (out-of-pocket expenses), because cost is a common barrier of adherence.

**Patient Case**

7. A 69-year-old woman with a history of MI, diabetes, HTN, and GERD is referred to your lipid clinic because of statin intolerance. She reports myalgias with rosuvastatin and pravastatin (40 mg), liver enzyme elevations with atorvastatin, and GI upset with ezetimibe. Her medications include metformin 1000 mg twice daily, amlodipine 10 mg/day, lisinopril 10 mg/day, and omeprazole 20 mg/day, and she is currently tolerating pravastatin 20 mg/day. Today's fasting laboratory results show TC 238 mg/dL, LDL-C 110 mg/dL, HDL-C 44 mg/dL, and TG 421 mg/dL. Which is the best recommendation at this time to further reduce her ASCVD risk?

   A. Add colesevelam 1.875 g twice daily.

   B. Add evolocumab 140 mg subcutaneously every 2 weeks.

   C. Add fenofibrate 145 mg/day.

   D. Add omega-3 fatty acids 4 g/day.

## XII. BILE ACID SEQUESTRANTS

A. Cholestyramine, Colestipol, Colesevelam

B. Efficacy
   1. Reduces coronary events and CHD mortality (primary prevention)
   2. Reduces LDL-C 15%–26%
   3. Raises HDL-C 3%–6%
   4. Raises TG up to 10%
   5. Drug of choice for pregnant patients

C. Mechanism of Action: Bind to bile acids to disrupt enterohepatic recirculation of bile acids. Liver is stimulated to convert hepatocellular cholesterol to bile acids.

D. Adverse Effect Profile/Monitoring
   1. GI upset
   2. Constipation
   3. Drug-drug interactions: May decrease absorption of other drugs, including warfarin, β-blockers, levothyroxine, and thiazide diuretics. Administer other medications 1–2 hours before or 4 hours after administering the bile acid sequestrants.
   4. Contraindications: TG concentrations greater than 300 mg/dL

## XIII. NICOTINIC ACID (NIACIN)

A. Niacin Formulations (Table 8)

**Table 8.** Niacin Formulations

| Drug Form | Brand Name | Dose Range (g) |
|---|---|---|
| Immediate release | Niacin | 1.5–3 |
| Immediate release | Niacor | 1.5–6 |
| Extended release | Niaspan | 1–2 |
| Sustained release | Slo-Niacin | 1–2 |

B. Efficacy
   1. Does not reduce coronary events when used in combination with statins in patients with well-controlled LDL-C concentrations (AIM-HIGH, HPS2-THRIVE)
   2. Reduces LDL-C 15%–26%
   3. Reduces TG 20%–50%
   4. Raises HDL-C 15%–26%

C. The 2018 cholesterol management guidelines do not recommend niacin because of demonstrated lack of CV benefit when combined with statin therapy with controlled LDL-C. Concerns regarding safety also contributed to this recommendation.
   1. Contraindications: Liver disease, gout, active peptic ulcer disease

**Patient Case**

8. A 34-year-old woman with a history of heterozygous familial hypercholesterolemia recently tested positive for pregnancy. She takes atorvastatin 40 mg/day and ezetimibe 10 mg/day. Which is the best recommendation at this time?
   A. Continue atorvastatin; discontinue ezetimibe.
   B. Continue ezetimibe; discontinue atorvastatin.
   C. Discontinue both atorvastatin and ezetimibe; initiate alirocumab 75 mg subcutaneously every 2 weeks.
   D. Discontinue both atorvastatin and ezetimibe; initiate colesevelam 1.875 g twice daily.

## XIV: ATP-CITRATE LYASE (ACL) INHIBITOR

A. Bempedoic acid (also available as ezetimibe/bempedoic acid)
   1. Dosing: 180 mg orally once daily

B. Efficacy
   1. Phase II and III trials alone or in combination with statins or ezetimibe/bempedoic acid reduces LDL-C by around 23%-30% (CLEAR Tranquility, Serenity, Wisdom, and Harmony Trials).
   2. The Phase 3 CLEAR Outcomes trial evaluated bempedoic acid in patients with, or at high risk of, ASCVD who were statin intolerant. Bempedoic acid significantly reduced a 4-component MACE by 13%, myocardial infarction by 23%, and coronary revascularization by 19% compared to placebo.
   3. In February 2020, bempedoic acid was FDA approved for treatment of adults with heterozygous FH or established ASCVD in addition to statin therapy who require additional lowering of LDL-C.

C. Mechanism of Action: Targets cholesterol biosynthesis pathway in liver, inhibiting ATP-citrate lyase (ACL) upstream of HMG-CoA reductase.

D. Adverse Effect Profile/Monitoring
   1. 1%-10%: Upper respiratory tract infection, muscle spasms, hyperuricemia (consequent to inhibited renal organic anion transporter 2), back pain, abdominal pain, bronchitis, anemia, elevated liver enzymes
   2. Less than 1%: Tendon rupture (0.5%)
   3. Drug Interactions: Do not exceed dose of 20 mg with simvastatin or 40 mg with pravastatin (increased risk of myopathy)

## XV. SMALL INTERFERING RNA MOLECULE (siRNA)

A. Inclisiran
   1. Dosing: 284 mg subcutaneously initially, followed by a repeat dose again at 3 months, and then every 6 months
      a. Administered by a healthcare professional

B. Efficacy
   1. Phase 2 trials show inclisiran 300 mg administered as subcutaneous injection at baseline, 3 months, and then every 6 months to have sustained lowering up to 6 months with reduced LDL-C by 52.6%, PCSK9 levels by 69.1%, and hsCRP by 16.7%.

2. Phase 3 randomized controlled trials examined dose of 284 mg at 0, 3, and every 6 months and examined long-term (540 days) LDL-C lowering and safety.
    a. ORION-10 was conducted in the United States with adults with ASCVD and LDL-C greater than 70 mg/dL. Enrolled 1561 patients with baseline LDL-C of 104 mg/dL and reduced by 52.3% ($p<0.001$). Mild injection site reactions were more frequent in inclisiran-treated patients.
    b. ORION-11 (Europe and South Africa) also included additional high-risk patients with similar outcomes.
    c. Both studies also demonstrated siRNA ability to reduce TC (33.1%), ApoB (43.1%), non-HDL (47.4%), TG (12.6%), and Lp(a) (25.6%), as well as increase HDL-C by 5.1%.
3. In December 2021, inclisiran was FDA approved for treatment of adults with heterozygous FH or clinical ASCVD in addition to statin therapy who require additional lowering of LDL-C.
4. The results of the ongoing clinical outcome trial, HPS-4/TIMI 65/ORION-4 trial, with target enrollment of 15,000 participants with ASCVD, is not expected for several years.

C. Mechanism of Action: siRNAs interfere with translation of PCSK9 by interfering with expression of specific genes through posttranscriptional gene silencing. Ultimately, this increases number of LDL receptors and decreases LDL-C.

D. Adverse Effect Profile/Monitoring
    1. 1–10%: Injection-site reactions, bronchitis, upper respiratory tract infection

## XVI. FIBRATES

A. Fenofibrate, Gemfibrozil

B. Efficacy
    1. Reduces coronary events as monotherapy vs. placebo (Helsinki Heart Study, VA-HIT, FIELD) but does not reduce coronary events when used in combination with statins (ACCORD-LIPID, PROMINENT)
    2. Reduces LDL-C 5%–20% (may vary depending on TG concentrations)
    3. Reduces TG 30%–55%
    4. Raises HDL-C 18%–22%

C. Mechanism of Action: Activates lipoprotein lipase and reduces ApoCIII, resulting in increased lipolysis

D. Adverse Effect Profile/Monitoring
    1. Dyspepsia, gallstones, myalgia, increased hepatic transaminases
    2. LFTs at baseline; then every 3 months for 12 months; then only when clinically indicated
    3. Evaluate renal function before initiating fenofibrate, within 3 months after initiation, and then every 6 months thereafter.
    4. Drug-drug interactions
        a. Can increase the risk of myalgia in patients taking statin therapy (less with fenofibrate)
        b. May increase the international normalized ratio in patients taking warfarin therapy
    5. Contraindications
        a. Severe renal or hepatic disease
        b. Gemfibrozil should be used cautiously with statins because of increased risk of adverse drug events or rhabdomyolysis.

E. Fibrates are primarily viewed as TG-lowering therapies. They are NOT recommended in the 2018 cholesterol management guidelines for further reduction in LDL-C because of lack of clinical efficacy.

## XVII OMEGA-3 FATTY ACIDS (O3FA)

A. Omega-3 Acid Ethyl Esters, Icosapent Ethyl, Omega-3 Carboxylic Acids (Table 9)

**Table 9.** Prescription-Only Formulations of Omega-3 Fatty Acids

| Formulation | EPA (mg) | DHA (mg) | TG | LDL-C | HDL-C |
|---|---|---|---|---|---|
| Omega-3 acid ethyl esters | 465 | 375 | ↓ 26%–45% | ↑ 45%[a] | ↑ 11%–14% |
| Icosapent ethyl | 1000 | — | ↓ 33% | NS | NS |
| Omega-3 carboxylic acids | 500–600 | 150–250 | ↓ 30% | NS | ↑ 5% |

[a]Only an issue when TG concentrations are very high in patients not taking statin therapy, and thought to be an increase in less atherogenic LDL (larger particle size). The increase in LDL is also accompanied by a significant 40% reduction in VLDL cholesterol.

DHA = docosahexaenoic acid; EPA = eicosapentaenoic acid; NS = not significant.

B. Efficacy
   1. Polyunsaturated fatty acids that exist in three forms: α-linolenic acid (found in plants), EPA (eicosapentaenoic acid), and docosahexaenoic acid (DHA); both EPA and DHA are found in fish and other marine animals
   2. Used for the treatment of hypertriglyceridemia in patients with TG concentrations of at least 500 mg/dL in doses of 2–4 g daily given typically in two divided doses (see below for FDA-approved indications for prescription products)
   3. Available over the counter as a dietary supplement in various formulations and often contain low amounts of actual EPA and DHA
      a. FDA-approved indications:
         i. Adjunct to diet to reduce TG concentrations in patients with TG of 500 mg/dL or greater
         ii. Icosapent ethyl: In addition to above, in December 2019, approved as add-on to maximally tolerated statin to reduce risk of CV events in at-risk adults with TG 150 mg/dL or greater
      b. Omega-3 fatty acid formulations available by prescription only (see Table 9)
   4. Evidence to support the assertion that O3FA administration reduce the risk of CV events or mortality was historically limited to clinical trials conducted in specific populations (e.g., advanced heart failure, Japanese patients with hyperlipidemia) and using specific O3FA formulations.
      a. The ASCEND trial of fish oil supplements in 15,480 patients with diabetes for primary prevention showed no benefit (7.4 years of follow-up).
      b. Icosapent ethyl at a dose of 4 g daily was studied in the 2019 REDUCE-IT trial.
         i. Included 8179 patients with clinical ASCVD or diabetes and additional risk factors
         ii. All patients taking a maximally tolerated statin with persistent hypertriglyceridemia (135-499 mg/dL)
         iii. Primary outcome CV death, myocardial infarction, stroke: 17.2% vs. 22.0% (95% CI, 0.68-0.83)
         iv. Outcome difference observed despite modest reduction in TG concentrations (-39.0 mg/dL vs. 4.5 mg/dL)
         v. Bottom line: May be a role for prescription icosapent ethyl in patients with ASCVD and diabetes or high-risk conditions taking maximally tolerated statin with persistent moderate hypertriglyceridemia
         vi. REDUCE-IT USA, a subgroup analysis of 3146 patients randomized in the United States, showed reductions in primary composite end point and all-case mortality: 18.2% versus 24.7% (95% CI, 0.59–0.80) and 7.2% versus 9.8% (95% CI, 0.55–0.90), respectively.
      c. In 2020, results of the EVAPORATE trial indicated that icosapent ethyl 4 g/day reduced plaque value (as measured by computed tomography angiography). Results are thought to explain and support the benefit seen in the REDUCE-IT trial.

d. In 2020, the STRENGTH trial, evaluating the carboxylic acid formulation of EPA/DHA (O3CA) in statin treated adults with high CVD risk and elevated TG (180–500 mg/dL), was terminated early when interim analysis revealed low probability of benefit. There were noted to be significantly higher incidence of atrial fibrillation and gastrointestinal side effects as well. Results further support that formulation and ratios of O3FA may be relevant to benefit.

C. Mechanism of Action: Not well understood, but likely related to a reduction in VLDL-TG synthesis in the liver and an increase in TG clearance from circulating VLDL particles

D. Adverse Effect Profile/Monitoring
   1. GI upset (burping, diarrhea)
   2. Atrial fibrillation (icosapent ethyl)
   3. Doses above 3 g/day may inhibit platelet aggregation and increase risk of bleeding
   4. Contraindications: Hypersensitivity to fish

## XVIII. ORPHAN DRUGS

A. Lomitapide
   1. Efficacy
      a. Reduces LDL-C by 40%
      b. Indicated for homozygous familial hypercholesterolemia
      c. Dose: 5 mg once daily; may titrate to 60 mg/day
   2. Mechanism of action: A selective microsomal TG protein inhibitor preventing the formation of ApoB-containing particles
   3. Adverse effect profile/monitoring
      a. GI symptoms
      b. Box warning for risk of hepatotoxicity: Causes significant LFT elevations and increases hepatic fat (only available through a Risk Evaluation and Mitigation Strategy program)
      c. Avoid use with moderate or strong cytochrome P450 (CYP) 3A4 inhibitors.

B. Evinacumab
   1. Efficacy
      a. Reduces LDL-C by 49%
      b. Indicated for homozygous familial hypercholesterolemia
      c. Dose: 15 mg/kg intravenous infusion administered monthly
   2. Mechanism of action: Human monoclonal antibody that inhibits angiopoietin-like protein 3; promotes VLDL processing and clearance upstream of LDL formation
   3. Adverse effect profile/monitoring
      a. Flu-like symptoms
      b. Avoid in pregnancy

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## ANSWERS AND EXPLANATIONS TO PATIENT CASES

**1. Answer: B**
Low-intensity statin therapy is not recommended except in those who cannot tolerate moderate- to high-intensity statin therapy, making Answer A incorrect. This patient has diabetes, which places her in one of the four statin benefit groups, making Answer D incorrect. Estimation of the 10-year ASCVD risk is needed in patients with diabetes to determine the appropriate statin intensity. Because this patient's risk score is less than 7.5%, a moderate-intensity statin is indicated, making Answer C incorrect and Answer B correct.

**2. Answer: D**
Pravastatin 20 mg and lovastatin 20 mg are considered low-intensity statins, making Answers A and B incorrect. Atorvastatin 40 mg is considered a high-intensity statin, making Answer C incorrect. Only rosuvastatin 10 mg would be considered a moderate-intensity statin, making Answer D correct.

**3. Answer: B**
Using patient-specific factors (age 51 years, male, white, TC 208 mg/dL, HDL-C 42 mg/dL, LDL-C 140 mg/dL, systolic blood pressure 130 mm Hg, a smoker, receiving HTN treatment), his 10-year risk using PCE is 12.2% (Answer B is correct; Answers A, C, and D are incorrect). Furthermore, this patient can be categorized as "intermediate risk."

**4. Answer: C**
This patient's PCE estimated risk identifies him as having "intermediate risk," making Answers A and B incorrect. Measurement of CAC is only indicated when the decision whether to initiate a statin is unclear, after assessing for risk-enhancing factors. Risk-enhancing factors have not yet been evaluated; therefore, this should be performed next, making Answer C correct and D incorrect.

**5. Answer: D**
Although continuing the patient's diet, exercise, and weight loss would remain a key component of the strategy to reduce her TG concentrations, she would be unlikely to reach acceptable TG concentrations to reduce her pancreatitis risk, making Answer A incorrect. Bempedoic acid and ezetimibe minimally affects TG concentrations, making Answers B and C incorrect. If a moderate intensity statin were listed as an option, this would be reasonable to consider, because they significant lower TG concentrations. However, given her history of acute pancreatits and her TG level of 500–1000 mg/dL, a targeted TG lowering therapy is preferred.. Fenofibrate would reduce her TG by 30%–50%, making Answer D correct.

**6. Answer: B**
Ranolazine inhibits CYP3A4, which is an important metabolic pathway for select statins, including lovastatin, simvastatin, and atorvastatin. Continuing simvastatin at the current dose of 40 mg/day would increase the patient's risk of statin-related adverse effects, making Answer A incorrect. Decreasing simvastatin to 20 mg/day would be consistent with the current recommendations to minimize the risk of adverse effects, making Answer B correct. Simvastatin 80 mg/day was removed from the market by the FDA because of concerns for a higher risk of statin-related adverse effects, making Answer C incorrect. Changing to lovastatin 40 mg/day would also increase the risk of adverse effects, making Answer D incorrect.

**7. Answer: B**
This patient is at very high risk of recurrent ASCVD, given her history of MI, age, HTN, and diabetes; therefore, high-intensity statin therapy is indicated. Because she cannot tolerate statins at higher doses, non-statins should be considered. She also has a history of intolerance to first-line non-statin pharmacotherapy with ezetimibe. Bile acid sequestrants can reduce atherogenic lipoprotein burden but are contraindicated in patients with TG concentrations greater than 300 mg/dL, making Answer A incorrect. Although this patient has elevated TG concentrations, the combination of fenofibrate or omega-3 fatty acids with statin therapy would not further reduce ASCVD risk (Answers C and D are incorrect). According to the 2018 cholesterol management guidelines, a PCSK9 mAb should be considered, making Answer B correct.

**8. Answer: D**
Despite the FDA request to downgrade the contraindication of statins in pregnancy, they still should be avoided if possible, making Answer A incorrect. It may be a risk discussion if prior ASCVD events had occurred, but short term discontinuation of statins likely confers low risk. Ezetimibe is pregnancy category C, suggesting animal studies have shown increased risk; however, human studies are not available, making Answer B incorrect. Currently, there are no data with using PCSK9 mAbs in pregnancy, making Answer C incorrect. Bile acid sequestrants are pregnancy category B and are preferred in pregnant women, making Answer D correct.

## ANSWERS AND EXPLANATIONS TO SELF-ASSESSMENT QUESTIONS

**1. Answer: D**
This patient's calculated 10-year ASCVD risk score is only 1.2%, so initiating statin therapy at this time is not indicated, making Answers A and B incorrect. Although obtaining additional risk markers (e.g., hs-CRP) can be useful for patients deemed at intermediate ASCVD risk, they are less useful in patients whose 10-year ASCVD risk is exceedingly low, making Answer C incorrect. Furthermore, her unexplained weight gain and fatigue suggest she is hypothyroid, a common secondary cause of hyperlipidemia. The patient has signs and symptoms consistent with hypothyroidism, including unexplained weight gain and increased fatigue. Therefore, ordering a thyroid panel would be best, making Answer D correct.

**2. Answer: C**
Fibrates reduce TG concentrations but have limited efficacy in lowering LDL-C. Furthermore, current guidelines do not support the routine addition of fibrates because data are lacking to support a clinical benefit, making Answer A incorrect. Niacin may slightly worsen glycemic control; it is also not recommended by the current guidelines as add-on therapy because of limited data to support a clinical benefit and safety concerns, making Answer B incorrect. This patient has newly diagnosed diabetes, and her estimated 10-year ASCVD risk is high at 22%; therefore, a high-intensity statin is recommended, making Answer C correct. Atorvastatin 10 mg/day (Answer D) is only a moderate-intensity statin, and several clinical trials (e.g., TNT and PROVE-IT) have shown greater benefit with higher-intensity statins in similar patients.

**3. Answer: B**
This patient belongs to the primary hypercholesterolemia statin benefit group because he has severe hypercholesterolemia (LDL-C 190 mg/dL or greater). Because of his history of not tolerating several statins at various doses, non-statin therapies are warranted. Colesevelam and gemfibrozil would only minimally reduce LDL-C, making Answers A and C incorrect. With the patient's extensive history of statin intolerance and minimal reduction of LDL-C at this dose, fluvastatin would not be recommended, making Answer D incorrect. The 2018 cholesterol management guidelines recommend ezetimibe or, alternatively, a PCSK9 mAb to further lower LDL-C, making Answer B correct.

**4. Answer: C**
Improving glycemic control can improve TG concentrations, but this patient already has well-controlled diabetes with an A1C of 6.9%, making Answers A and D incorrect. Certain medications can increase TG concentrations, but chlorthalidone (a thiazide diuretic) is the only such medication he takes. Amlodipine, rosuvastatin, and metformin are not associated with increasing TG concentrations, making Answers A, B, and D incorrect. Alcohol consumption alone increases the risk of pancreatitis and can cause an increase in TG concentrations. Obesity is also associated with increased TG concentrations. As such, Answer C is correct.

**5. Answer: A**
Because his TG concentration exceeds 1000 mg/dL, and to help reduce his risk of recurrent pancreatitis, TG-lowering lifestyle modifications and drug therapy are indicated. In addition to abstaining from alcohol, a fibrate should be added to his statin therapy. Fenofibrate significantly reduces TG concentrations and is a once-daily medication, which may be best for this patient, given his pill burden, making Answer A correct. Niacin is not recommended by the guidelines and, it could worsen his glycemic control, making Answer B incorrect. The most effective dose of omega-3 fatty acids for lowering TG is 4 g/day, making Answer C incorrect. Although statins can lower TG at higher doses, he already takes a high-intensity statin, and increasing rosuvastatin would probably not provide much additional TG lowering, making Answer D incorrect.

**6. Answer: A**
Dosing of statins in CKD is not without controversy. With regard to this patient, who has well-controlled lipids on simvastatin/ezetimibe presumably for the primary prevention of ASCVD, both the 2013 KDIGO guidelines and 2018 Multi-society Guidelines for Management of Blood Cholesterol state it is reasonable to continue current statin therapy (with or without ezetimibe) in patients being initiated on dialysis. Guidelines specifically reference the SHARP trial (which evaluated simvastatin/ezetimibe vs. placebo) to support this, because greater than 30% of patients progressing during trial to dialysis. Answer A is correct. Stopping simvastatin/ezetimibe (either component or both) is not thought to be necessary from a standpoint of safety; therefore, Answers B, C, and D are incorrect.

**7. Answer: C**

This patient exercises regularly and reports no signs or symptoms of peripheral arterial disease; also, he does not use tobacco products. Therefore, this patient would probably have no evidence of peripheral arterial disease, making an ankle-brachial index screening less useful (Answer B is incorrect). Answer A is incorrect because albuminuria screening is not currently recommended, given lack of evidence. Answer D is incorrect because CAC scores, NOT serum calcium, may be used as a risk enhancer in patients with a moderate ASCVD risk. Asking about his family history of ASCVD would be a simple and cost-effective method to further characterize his overall ASCVD risk, making Answer C correct.

**8. Answer: B**

Given that this patient has diabetes and several ASCVD risk factors (smoking, South Asian ethnicity, undiagnosed metabolic syndrome and HTN), a high-intensity statin is reasonable according to the 2018 cholesterol management guidelines. His current pravastatin dose is insufficient, and increasing it to 80 mg/day would only provide an additional 7% reduction in LDL-C and is not high-intensity statin therapy, making Answer C incorrect. Ezetimibe may be used but should be preferred in patients who are taking the maximally tolerated statin, which this patient is not (Answer D is incorrect). Although his TG concentrations are slightly elevated, this is not an indication for fenofibrate, and adding fenofibrate would unlikely achieve the non-HDL-C goal, making Answer A incorrect. Atorvastatin 40 mg/day is a high-intensity statin and would most likely result in recommend LDL-C reduction, making Answer B correct.

**9. Answer: A**

This patient has not yet achieved the desired 50% reduction in baseline LDL-C because she cannot tolerate more potent statins; therefore, additional therapy is indicated. Icosapent ethyl would not help the patient achieve her LDL-C goal; however, it is indicated when TG are greater than 150 mg/dL, and because this patient's TG are 132 mg/dL, Answer D is incorrect. This patient would be considered at VERY high risk given 2 ASCVD events in less than 2 years, and her LDL-C remains above 55 mg/dL while receiving maximally tolerated statins. Better data exist for use of PSCK9 inhibitors, specifically alirocumab, in this setting (ODYSSEY OUTCOMES); therefore, Answer A is correct. Ezetimibe is orally administered and is more economical; it may have to be considered in some patients. However, Answer A is a better option than Answer B, as a reduction of greater than 25% is necessary to reach LDL-C goal of 55 mg/dL or less. Niacin is not recommended because of safety concerns and its demonstrated lack of clinical benefit when added to statin therapy, making Answer C incorrect.

**10. Answer: C**

This patient's 10-year ASCVD risk is 36.9%; therefore, no further laboratory assessment is needed, and Answer A is incorrect. Because studies of high-intensity statins are limited in adults older than 75, the 2018 guidelines on management of blood cholesterol recommend moderate- or high-intensity statin therapy after a patient-clinician discussion, making Answer C correct. Low-intensity statins are only indicated in patients who do not tolerate moderate- or high-intensity, making Answer B incorrect. Measurement of CAC is not helpful in patients with clinical ASCVD and is only potentially helpful in risk discussion in patients with intermediate- or moderate-risk primary prevention, making Answer D incorrect.

# Blood Pressure Management in Adult Patients

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**Learning Objectives**

1. Develop an optimal pharmacologic treatment plan for a patient with hypertension (HTN) according to practice guidelines and clinical trial evidence.
2. Demonstrate appropriate drug selection and blood pressure goals for the treatment of HTN according to concomitant conditions and compelling indications.
3. Devise an evidence-based treatment strategy for resistant HTN to achieve blood pressure goals.
4. Construct appropriate drug therapy plans for the treatment of hypotension and/or antihypertensive drug related adverse events.

**Abbreviations in This Chapter**

| | |
|---|---|
| ABPM | Ambulatory blood pressure monitoring |
| ADR | Adverse drug reaction |
| ASCVD | Atherosclerotic cardiovascular disease |
| CAD | Coronary artery disease |
| CKD | Chronic kidney disease |
| CV | Cardiovascular |
| CVD | Cardiovascular disease |
| DBP | Diastolic blood pressure |
| GDMT | Guideline-directed medical therapy |
| HBPM | Home blood pressure monitoring |
| HF | Heart failure |
| HTN | Hypertension |
| ICH | Intracerebral hemorrhage |
| MI | Myocardial infarction |
| NSTEMI | Non–ST-segment elevation myocardial infarction |
| OH | Orthostatic hypotension |
| RCT | Randomized controlled trial |
| SBP | Systolic blood pressure |
| TIA | Transient ischemic attack |

**Self-Assessment Questions**

*Answers and explanations to these questions can be found at the end of this chapter.*

1. R.P. is a 58-year-old Japanese-American woman with a history of hypertension (HTN) and osteoarthritis. Her medications include acetaminophen 3 g/day, amlodipine 10 mg/day, lisinopril 40 mg/day, and aspirin 81 mg/day. Her vital signs include blood pressure 136/85 mm Hg (with similar repeat) and heart rate 86 beats/minute. Her total cholesterol (TC) is 180 mg/dL, high-density lipoprotein cholesterol (HDL) 45 mg/dL, and low-density lipoprotein cholesterol (LDL) 115 mg/dL. Her current 10-year atherosclerotic cardiovascular disease (ASCVD) risk is 14.3%. Which is the next best step for R.P. at this time?
   A. Add chlorthalidone 12.5 mg/day.
   B. Increase lisinopril to 80 mg/day.
   C. Add atenolol 50 mg/day.
   D. Make no medication changes at this visit.

*Questions 2 and 3 pertain to the following case.*

A.M. is a 32-year-old woman (height 66 inches, weight 70 kg) with type 1 diabetes and HTN. Her blood pressure has been difficult to control, with her SBP over 170 mm Hg at times. Her current medication regimen is as follows: ramipril 10 mg/day, chlorthalidone 25 mg/day, amlodipine 10 mg/day, ethinyl estradiol 20 mcg/norethindrone 1 mg daily (for the past 5 years), and insulin as directed. Her vital signs today include blood pressure 146/82 mm Hg, repeated blood pressure 142/80 mm Hg; heart rate 82 beats/minute; and body mass index (BMI) 24.5 kg/m$^2$. A.M. would prefer not to take any more drugs, if possible.

2. Which is the best clinical plan for A.M.?
   A. No change in therapy is warranted at this time.
   B. Advise weight loss, and recheck her blood pressure in 3 months.
   C. Change chlorthalidone to hydrochlorothiazide.
   D. Discuss changing her contraceptive method.

3. Six months later, A.M. and her husband are ready to have children. Which is the best therapeutic plan for A.M.?
   A. No change in therapy is warranted at this time.
   B. Discontinue ramipril and replace with labetalol.
   C. Increase chlorthalidone to 50 mg/day.
   D. Discontinue all antihypertensive therapy.

4. D.W. is a 50-year-old African American man being discharged from the hospital after an acute non–ST-segment elevation myocardial infarction (NSTEMI). His medical history is significant for HTN. He was taking hydrochlorothiazide 25 mg/day before hospitalization. An echocardiogram before discharge reveals a left ventricular ejection

fraction of more than 60%. His vital signs include blood pressure 150/94 mm Hg and heart rate 80 beats/minute. Which is best for managing his HTN?

A. Discontinue hydrochlorothiazide and add diltiazem.
B. Continue hydrochlorothiazide and add metoprolol.
C. Discontinue hydrochlorothiazide and add losartan.
D. Continue hydrochlorothiazide and add losartan.

5. T.J. is a 45-year-old White woman with a history of type 2 diabetes treated with glipizide 5 mg/day. She presents to the clinic for a routine follow-up of her diabetes. Her vital signs today include blood pressure (average of two readings) 134/84 mm Hg and heart rate 70 beats/minute. Her laboratory results are as follows: sodium (Na) 140 mEq/L, potassium (K) 4.0 mEq/L, chloride (Cl) 102 mEq/L, bicarbonate 28 mEq/L, blood urea nitrogen 14 mg/dL, serum creatinine (SCr) 1.0 mg/dL, and 24-hour urine albumin 36 mg/24 hours. At her last visit, her blood pressure was 136/85 mm Hg. Which is best to manage her HTN at this time?

A. No changes are needed; her blood pressure is at goal.
B. Begin lifestyle modifications and add amlodipine 5 mg/day.
C. Begin lifestyle modifications and add lisinopril 5 mg/day.
D. Begin lifestyle modifications and add atenolol 25 mg/day.

6. R.P. is a 65-year-old Hispanic man who is following up for his periodic checkup. He has a history of an ischemic stroke 1 year ago but remains ambulatory and living independently. After his stroke, he began monitoring his blood pressure at home, which he has done reliably on a verified home blood pressure monitoring (HBPM) device. He remains anxious of healthcare settings since his stroke. Three months ago, his office blood pressure was 134/90 mm Hg, and he was advised to decrease his salt intake. Today, he proudly reports that his HBPM readings are consistently in the low 120s/70s since he modified his diet. However, his clinic blood pressure is 146/88 mm Hg with similar repeat. Which is the next best step for R.P.?

A. He has masked HTN; initiate lisinopril.
B. He may have white-coat HTN; order ambulatory blood pressure monitoring (ABPM).
C. His HBPM skills need improvement; schedule a class for him.
D. No action is needed; his HBPM readings are at goal.

7. An 81-year-old woman with ASCVD (NSTEMI with 4-vessel coronary artery bypass grafting 7 years ago), HTN, and chronic kidney disease (CKD) presents with dizziness on standing. Last week, she almost fell after getting out of bed. She has tried increasing her fluid and salt intake, but this has not helped. Today, her blood pressure is 138/74 mm Hg and heart rate is 60 beats/minute while sitting; 1 minute later, she stands, and her blood pressure is 115/70 mm Hg and heart rate is 76 beats/minute. She takes metoprolol tartrate 50 mg twice daily, lisinopril 20 mg/day, aspirin 81 mg/day, and atorvastatin 40 mg/day. Which is the next best step in treating this patient's blood pressure?

A. Start midodrine 2.5 mg three times daily.
B. Discontinue all of her antihypertensive drugs.
C. Start droxidopa 100 mg three times daily.
D. Lower her metoprolol dose to 25 mg twice daily.

8. A 54-year-old man presents to the clinic for a follow-up of his hypertensive drug regimen. His medical history is significant for HTN and coronary artery disease (CAD). To control his blood pressure, he takes amlodipine 10 mg/day, lisinopril 40 mg/day, and chlorthalidone 25 mg/day. Today in the clinic, his vital signs include blood pressure 154/96 mm Hg and heart rate 55 beats/minute, and his laboratory results are all within normal values. Which would best manage this patient's HTN?

A. Change chlorthalidone to hydrochlorothiazide.
B. Increase amlodipine to 15 mg/day.
C. Add spironolactone 25 mg/day.
D. Discontinue lisinopril and start losartan 25 mg/day.

## I. HYPERTENSION

An updated national hypertension (HTN) guideline was released in November 2017: Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults (2017 American College of Cardiology [ACC]/AHA HTN guideline). As seen in the text that follows, it superseded various guidelines (except, perhaps, some comorbidity-specific guidelines) that were previously used in practice since the last national guideline was released in 2002. The aim of the new guideline was to answer four questions on HTN in adults:

1. Is there evidence that self-directed monitoring of blood pressure and ABPM are superior to office-based measurement of blood pressure by a health care worker for:
   a. Preventing adverse outcomes for which high blood pressure is a risk factor
   b. Achieving better blood pressure control
2. What is the optimal target for blood pressure lowering during antihypertensive therapy in adults?
3. In adults with HTN, do various antihypertensive drug classes differ in their comparative benefits and harms?
4. In adults with HTN, does initiating treatment with antihypertensive pharmacologic monotherapy versus initiating treatment with two drugs (including fixed-dose combination therapy), either of which may be followed by adding sequential drugs, differ in comparative benefits and/or harms on specific health outcomes?

To support its recommendations, the guideline used class of recommendation and level of evidence (as denoted in parenthesis behind the recommendations in this chapter).

Class (strength) of Recommendation

- I: Strong, benefit >>> risk
  - It is recommended, indicated, useful, effective, beneficial
- IIa: Moderate, benefit >> risk
  - It is reasonable, can be useful/effective/beneficial
- IIb: Weak, benefit ≥ risk
  - May be reasonable, may be considered
  - Usefulness/effectiveness is unknown, unclear, uncertain, or not well established
- III [no benefit]: Moderate, benefit = risk
  - It is not recommended, indicated, useful, effective, beneficial
- III [harm]: Strong, risk > benefit
  - Potentially harmful, causes harm
  - Associated with excess morbidity or mortality

Class (quality) of Evidence

- Level A
  - High-quality evidence from more than one randomized trial
  - Randomized controlled trial (RCT), meta-analysis of high-quality RCT
  - One or more RCTs corroborated by high-quality registry studies
- Level B-R (randomized)
  - Moderate-quality evidence from one or more RCTs
  - Meta-analysis of moderate-quality RCTs
- Level B-NR (nonrandomized)
  - Moderate-quality evidence from one or more well-designed, well-executed nonrandomized, observational or registry studies; meta-analysis of such studies
- Level C-LD (limited data)
  - Randomized or nonrandomized observational or registry studies with limitations of design or execution; meta-analysis of such studies
- Level C-EO (expert opinion)
  - Consensus of expert option on clinical experience

This new guideline was endorsed by various national organizations in the United States, including:

- American College of Cardiology (ACC)
- American Heart Association (AHA)
- American Academy of Physician Assistants (AAPA)
- Association of Black Cardiologists (ABC)
- American College of Preventive Medicine (ACPM)
- American Geriatrics Society (AGS)
- American Pharmacists Association (APhA)
- American Society of Hypertension (ASH)
- American Society for Preventive Cardiology (ASPC)
- National Medical Association (NMA)
- Preventive Cardiovascular Nurses Association (PCNA)

Major Practice Guidelines:

- Joint National Committee on Prevention, Detection, and Treatment of High Blood Pressure (JNC) 7 (2002) – Previous national (U.S.) HTN guideline
- Kidney Disease: Improving Global Outcomes (KDIGO) Clinical Practice Guideline for the Management of Blood Pressure in Chronic Kidney Disease (2021)
- Recommendations from former JNC 8 panel (December 2013) – Guideline not sanctioned by the National Heart, Lung, and Blood Institute or any major practice organization
- International Society of Hypertension Global Hypertension Practice Guidelines (2020)
- AHA/ASA Guideline for the Management of Patients with Spontaneous Intracerebral Hemorrhage (2022)
- AHA/ACC/ASH Treatment of Hypertension in Patients with Coronary Artery Disease (2015)
- American Diabetes Association (ADA) Standards of Medical Care in Diabetes (2023)
- AHA/ACC/HFSA Guideline for the Management of Heart Failure (2022)

A. Definition: Blood pressure should be categorized as normal, elevated, or stage 1 or 2 HTN to prevent and treat high blood pressure (I, B-NR).

| BP Category | SBP (mm Hg) | | DBP (mm Hg) |
|---|---|---|---|
| Normal | < 120 | And | < 80 |
| Elevated | 120–129 | And | < 80 |
| Hypertension | | | |
| Stage 1 | 130–139 | Or | 80–89 |
| Stage 2 | ≥ 140 | Or | ≥ 90 |

DBP = diastolic blood pressure.

B. Prevalence
   1. In adults (age 20 and older) in the United States with blood pressure 130/80 mm Hg or greater or receiving antihypertensive therapy (Circulation 2023;147:e93-e621):
      a. Overall: 122.4 million (46.7%)
         i. Males: 62.8 million (50.4%)
         ii. Females: 59.6 million (43%)

b. Prevalence increases with age.

| Age (yr) | Males and Females (%) |
|---|---|
| 20–44 | 28.5 |
| 55–64 | 58.6 |
| 65+ | 76.5 |

c. Prevalence is highest in non-Hispanic Black people.
   i. Males: 55.8%
   ii. Females: 56.9%

2. In 2020, 119,997 individuals died because of high blood pressure.
   a. Age-adjusted death rate principally attributed to high blood pressure: 29.1 per 100,000
   b. The death rate attributable to HTN increased by 54.8% in 2010–2020.
3. From 2018 to 2019, estimated direct and indirect costs of high blood pressure were $52.2 billion.

C. Risks Associated with HTN
1. The relationship between blood pressure and cardiovascular disease (CVD) events is continuous, consistent, and independent of other risk factors.
2. For people 40–70 years of age, each increment of 20 mm Hg in SBP or of 10 mm Hg in diastolic blood pressure (DBP) doubles the risk of CVD across the range of 115/75–185/115 mm Hg.
3. Target-organ damage
   a. Heart
      i. Left ventricular hypertrophy
      ii. Angina or myocardial infarction (MI)
      iii. Coronary revascularization
      iv. HF
         (a) Reduced ejection fraction (HF*r*EF)
         (b) Preserved ejection fraction (HF*p*EF)
   b. Brain: Stroke or transient ischemic attack (TIA)
   c. CKD
   d. Peripheral arterial disease
   e. Retinopathy
4. The 10-year ASCVD risk should be calculated using the ACC/AHA Pooled Cohort Equations for those without established ASCVD (calculator available online at http://tools.acc.org/ascvd-risk-estimator-plus/).

D. Screening and Management of CVD Risk Factors: Screening and management of modifiable CVD risk factors are recommended in patients with HTN.
1. Modifiable risk factors
   a. Current cigarette smoking, secondhand smoking
   b. Diabetes mellitus
   c. Dyslipidemia
   d. Overweight/obesity
   e. Physical inactivity/low fitness
   f. Unhealthy diet

2. Relatively fixed risk factors
    a. CKD
    b. Family history
    c. Increased age
    d. Low socioeconomic/educational status
    e. Male sex
    f. Obstructive sleep apnea
    g. Psychosocial stress

E. Benefits of Lowering Blood Pressure by Initiating Antihypertensive Medications
1. Associated with relative risk reductions in the incidence of:
    a. Stroke: 35%–40%
    b. MI: 20%–25%
    c. HF: Greater than 50%
    d. In patients with a blood pressure of 140/90 mm Hg or higher and additional cardiac risk factors, achieving a sustained 12-mm Hg reduction in SBP for 10 years will prevent one death for every 11 patients treated. For CVD or other target-organ damage, only nine patients would require such a blood pressure reduction to prevent a death.
2. Fewer individuals at high CVD risk would need to be treated to prevent a CVD event (i.e., lower number needed to treat) than would those at low CVD risk.
3. The higher the CVD risk, the greater the benefit of blood pressure reduction.

F. Etiology
1. Essential HTN: 90% (no identifiable cause)
2. Screening for specific forms of secondary HTN is recommended when certain clinical indications and physical examination findings are present or in adults with resistant HTN (I, C-EO).
    a. Drug-resistant/induced HTN
    b. Abrupt onset of HTN
    c. Onset of HTN at age younger than 30 years
    d. Exacerbation of previously controlled HTN
    e. Disproportionate target-organ damage for degree of HTN
    f. Accelerated/malignant HTN
    g. Onset of diastolic HTN in older adults (age 65 and older)
    h. Unprovoked or excessive hypokalemia
3. If an adult with sustained HTN screens positive for a form of secondary HTN, refer to a physician with expertise in that form of HTN for diagnosis and treatment (IIa, C-EO).
4. Identifiable secondary causes of HTN
    a. Common causes (see Table 1)
        i. Primary aldosteronism
            (a) Screening is recommended for patients with resistant HTN, hypokalemia (spontaneous or substantial), incidentally discovered adrenal mass, family history of early-onset HTN, or stroke at a young age (younger than 40 years) (I, C-EO).
            (b) Use of the plasma aldosterone/renin activity ratio is recommended when adults are screened for primary aldosteronism (I, C-EO).
            (c) In adults with HTN and a positive screening test for primary aldosteronism, referral to a HTN specialist or endocrinologist for further evaluation and treatment is recommended (I, C-EO).

ii. Renal artery stenosis
   (a) Medical therapy is recommended for adults with atherosclerotic renal artery stenosis (I, B-NR).
      (1) No RCT to date has shown a clinical advantage of renal artery revascularization over medical therapy.
      (2) The recommended medical approach is optimal management of HTN with an antihypertensive regimen that includes a renin-angiotensin-system blocker, in addition to LDL reduction with a high-intensity statin, smoking cessation, hemoglobin A1C (A1C) reduction in patients with diabetes mellitus, and antiplatelet therapy.
   (b) For adults with renal artery stenosis for whom medical treatment has failed (refractory HTN, worsening renal function, and/or intractable HF) and those with non-atherosclerotic disease, including fibromuscular dysplasia, it may be reasonable to refer them for consideration of revascularization (angioplasty and/or stent placement) (IIa, C-EO).

iii. Obstructive sleep apnea
   (a) Continuous positive airway pressure (CPAP) improves obstructive sleep apnea.
   (b) Studies of the effects of CPAP on blood pressure have shown only small effects on blood pressure (e.g., reductions of 2–3 mm Hg), with results depending on
      (1) Patient adherence to CPAP use
      (2) Severity of obstructive sleep apnea
      (3) Presence of daytime sleepiness in study participants

**Table 1.** Common Secondary Causes of HTN

| Common Cause | Clinical Indications | Physical Examination Findings and Screening Tests |
|---|---|---|
| Drug or alcohol induced | • Sodium-containing antacids<br>• Caffeine<br>• Nicotine<br>• Alcohol<br>• NSAIDs<br>• Oral contraceptives<br>• Cyclosporine<br>• Sympathomimetics<br>• Cocaine, amphetamines, and other illicit drugs<br>• Neuropsychiatric agents<br>• Erythropoiesis-stimulating agents<br>• Clonidine withdrawal<br>• Herbal agents | Physical Findings<br>Fine tremor, tachycardia, sweating (cocaine, ephedrine, MAOIs); acute abdominal pain (cocaine)<br><br>Screening Tests<br>Urinary drug screen (illicit drugs) |
| Obstructive sleep apnea | • Resistant HTN<br>• Snoring<br>• Fitful sleep<br>• Breathing pauses during sleep<br>• Daytime sleepiness | Physical Findings<br>Obesity, Mallampati class III–IV; loss of normal nocturnal BP decrease<br><br>Screening Tests<br>Berlin Questionnaire; Epworth Sleepiness Scale score; overnight oximetry |

**Table 1.** Common Secondary Causes of HTN (*Cont'd*)

| Common Cause | Clinical Indications | Physical Examination Findings and Screening Tests |
|---|---|---|
| Primary aldosteronism | • Resistant HTN<br>• HTN with hypokalemia<br>• HTN and muscle cramps or weakness<br>• HTN and incidentally discovered adrenal mass<br>• HTN and obstructive sleep apnea<br>• HTN and family history of early-onset HTN or stroke | Physical Findings<br>Arrhythmias (with hypokalemia); especially atrial fibrillation<br><br>Screening Tests<br>Plasma aldosterone-renin ratio under standardized conditions |
| Renal parenchymal disease | • UTIs<br>• Obstruction, hematuria<br>• Urinary frequency and nocturia<br>• Analgesic abuse<br>• Family history of polycystic kidney disease<br>• Elevated SCr<br>• Abnormal urinalysis | Physical Examination<br>Abdominal mass (polycystic kidney disease); skin pallor<br><br>Screening Tests<br>Renal ultrasound |
| Renovascular disease | • Resistant HTN<br>• HTN of abrupt onset or worsening or increasingly difficult to control<br>• Flash pulmonary edema<br>• Early-onset HTN, especially in women | Physical Findings<br>Abdominal systolic-diastolic bruit; bruits over other arteries, femoral<br><br>Screening Tests<br>Renal duplex Doppler ultrasound; MRA; abdominal CT |

CT = computed tomography; HTN = hypertension; MAOI = monoamine oxidase inhibitor; MRA = magnetic resonance angiography; NSAID = nonsteroidal anti-inflammatory drug; UTI = urinary tract infection.

Adapted from table 13 *in*: Whelton PK, Carey RM, Aronow WS. 2017 ACC/AHA/AAPA/ABC/ ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA guideline for the prevention, detection, evaluation, and management of high blood pressure in adults: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. Hypertension 2017 Nov 13. [Epub ahead of print]

b. Uncommon causes
    i. Pheochromocytoma/paraganglioma
    ii. Cushing syndrome
    iii. Hypothyroidism
    iv. Hyperthyroidism
    v. Aortic coarctation (undiagnosed or repaired)
    vi. Primary hyperparathyroidism
    vii. Congenital adrenal hyperplasia
    viii. Mineralocorticoid excess syndromes other than primary aldosteronism
    ix. Acromegaly

**Patient Case**

1. A 46-year-old White woman is new to your clinic. While shopping recently, she took her blood pressure at an automatic blood pressure station, which informed her that her blood pressure is "too high." Today, her blood pressure is 144/90 mm Hg, with similar repeat. She takes no prescription medications, though over the counter, she takes an appetite suppressant, St. John's wort, and ibuprofen 400 mg twice daily. For the past week, she has also taken pseudoephedrine 30 mg twice daily for a cold. She drinks "at least" 4 cups of coffee daily, 2 diet sodas/day, and 2 or 3 alcoholic drinks every evening. Although she has no symptoms of illness or of feeling bad, she has difficulty falling asleep at night. Her laboratory test results today are normal. Her BMI is 30.2 kg/m$^2$. Which is the best intervention for this patient's HTN?

   A. Initiate exercise and ask her to return in 1 month.

   B. Initiate lisinopril 10 mg/day and ask her to return in 1 month.

   C. Discontinue her over-the-counter medications (with appropriate alternatives), decrease coffee and soda intake, lower her alcohol intake to 1 drink/day, and ask her to return in 1 month.

   D. Discontinue her coffee and alcohol intake, initiate lisinopril 10 mg/day, and ask her to return in 1 month.

c. Drugs with the potential to impair blood pressure control
   i. Alcohol
      (a) Limit to 1 drink or less per day for women.
      (b) Limit to 2 drinks or less per day for men.
   ii. Amphetamines
      (a) Discontinue or reduce dose.
      (b) Consider behavioral therapy.
   iii. Antidepressants (serotonin-norepinephrine reuptake inhibitors, tricyclic antidepressants)
      (a) Consider alternative agents.
      (b) Avoid tyramine with monoamine oxidase inhibitors (MAOIs).
   iv. Herbal supplements: Avoid use.
   v. Atypical antipsychotics
      (a) Limit use and consider alternative agents, when possible.
      (b) Consider behavioral therapy.
   vi. Caffeine
      (a) Limit to less than 300 mg/day.
      (b) Avoid use with uncontrolled HTN.
   vii. Decongestants
      (a) Use for shortest duration possible.
      (b) Consider alternative therapies.
   viii. Immunosuppressants (e.g., cyclosporine, tacrolimus)
   ix. Oral contraceptives
      (a) Low-dose estrogen or progestin-only
      (b) Consider alternative form (intrauterine device).
   x. Nonsteroidal anti-inflammatory drugs (NSAIDs)
      (a) Avoid systemic NSAIDs, if possible.
      (b) Consider alternative analgesics.
   xi. Recreational drugs: Avoid/discontinue use.
   xii. Systemic corticosteroids
      (a) Avoid/limit use.
      (b) Consider alternative routes (inhaled, topical), when feasible.
   xiii. Angiogenesis inhibitor (e.g., bevacizumab) and tyrosine kinase inhibitors (e.g., sunitinib, sorafenib): Initiate or intensify antihypertensive therapy.

**Patient Case**

2. M.P., a 52-year-old Asian woman, presents to the clinic to discuss her heartburn symptoms. Her primary care physician has been running late, and she was rushed back to her examination room a few minutes ago. Her blood pressure is 144/84 mm Hg. She has no history of HTN, and the only drug she takes is over-the-counter famotidine. Which is the next best action to take for M.P.?

   A. Recheck her blood pressure after she has been seated quietly for 5 minutes.

   B. Initiate hydrochlorothiazide 12.5 mg/day.

   C. Initiate lisinopril 10 mg/day.

   D. Her blood pressure is not of concern because she does not have HTN.

G. Measurement of Blood Pressure: Proper methods are recommended to accurately measure, document, diagnose, and manage blood pressure (I, C-EO).
   1. Properly prepare the patient.
      a. Relaxed, seated, feet flat on the floor, back supported for at least 5 minutes
      b. Avoid caffeine, exercise, and smoking for at least 30 minutes.
      c. No talking, bare arm for cuff
   2. Use proper technique for blood pressure measurement.
      a. Validated device
      b. Support patient's arm, position cuff at the midpoint of the sternum; use correct cuff size (bladder encircles 80% of arm).
   3. Take the proper measurements needed for the diagnosis and treatment of HTN.
      a. At first visit, record blood pressure in both arms; use the higher reading; separate readings by 1–2 minutes.
      b. Inflate cuff 20–30 mm Hg above palpated radial pulse; deflate cuff by 2 mm Hg per second.
   4. Properly document accurate blood pressure readings.
      a. Record SBP and DBP using the nearest even number.
      b. Note the time of the most recent blood pressure medication taken.
   5. Average the readings, two or more readings on two more occasions
   6. Provide blood pressure readings to the patient verbally and in writing.

H. Alternative Methods for Blood Pressure Measurement
   1. Out-of-office blood pressure measurements are recommended to confirm the diagnosis of HTN and titrate blood pressure–lowering medication, with telehealth or clinical interventions (I, A).
      a. HBPM:
         i. Patient training should occur under medical supervision.
         ii. Devices should be automated and validated with appropriate cuff size. Memory should be available to store readings.
         iii. While measuring readings at home, the patient should follow the same technique as used in the office (remain still, sit correctly, take several readings, record readings).
      b. ABPM:
         i. Patients wear a portable blood pressure–measuring device on their non-dominant arm for 24 hours.
         ii. Blood pressure during daily activities and during sleep
         iii. Devices should meet validation standards.
         iv. Systolic ABPM predicts stroke and other cardiovascular (CV) outcomes independently of office blood pressure monitoring.

v. Blood pressures taken in various settings and with various devices should correspond (see Table 2). Example: If an office blood pressure goal is less than 130/80 mm Hg
   (a) 24-hour mean blood pressure should be less than 125/75 mm Hg.
   (b) Mean daytime blood pressure less than 130/80 mm Hg
   (c) Mean nighttime blood pressure less than 110/65 mm Hg

**Table 2.** Corresponding BP Values

| **Corresponding BP values** | | | | |
|---|---|---|---|---|
| If the Clinic BP is: | 120/80 | 130/80 | 140/90 | 160/100 |
| Then the corresponding BP, in the respective setting, should be: | | | | |
| HBPM | 120/80 | 130/80 | 135/85 | 145/90 |
| Daytime ABPM | 120/80 | 130/80 | 135/85 | 145/90 |
| Nighttime ABPM | 100/65 | 110/65 | 120/70 | 140/85 |
| 24-Hour ABPM | 115/75 | 125/75 | 130/80 | 145/90 |

ABPM = ambulatory blood pressure monitoring; BP = blood pressure; HBPM = home blood pressure monitoring.

Adapted from: table 11 *in*: Whelton PK, Carey RM, Aronow WS. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA guideline for the prevention, detection, evaluation, and management of high blood pressure in adults: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. Hypertension 2017 Nov 13. [Epub ahead of print]

vi. The USPSTF issued a statement on screening for high blood pressure in adults in October 2015, which was updated in April 2021.
   (a) For patients with an elevated blood pressure in the office, clinicians should confirm the HTN diagnosis with readings outside the clinical setting (24-hour ABPM or HBPM readings).
   (b) Clinicians should screen adult patients 18 and older without an HTN diagnosis for HTN using office blood pressure measurement with confirmation from readings outside the clinical setting.
   (c) Will help decrease the number of patients with a false diagnosis of HTN because of short-term elevations in blood pressure (e.g., from stress, pain, or caffeine intake), white-coat HTN, or errors in blood pressure measurement
   (d) Outside confirmation may not be needed in all cases.
      (1) Very high blood pressure (higher than 180/110 mm Hg)
      (2) Patients with signs of end-organ damage
      (3) Patients with HTN because of an underlying condition (e.g., CKD)

2. Automated oscillometric blood pressure (AOBP) measurement
   a. AOBP devices take many consecutive blood pressure readings in the office with the patient sitting and resting alone.
   b. Proper technique is still necessary.
   c. Compared with conventional manual office measurements, a decreased white-coat response usually occurs with AOBP devices.
   d. AOBP devices can be programmed to automatically obtain and average three or more readings to satisfy the criteria for several consecutive measurements.

I. White-Coat vs. Masked HTN
   1. White-coat HTN: Office blood pressure is 130/80–160/100 mm Hg after a 3-month trial of lifestyle modification but with daytime ABPM or HBPM blood pressure less than 130/80 mm Hg.
      a. In adults with an untreated SBP greater than 130 mm Hg but less than 160 mm Hg or DBP greater than 80 mm Hg but less than 100 mm Hg, it is reasonable to screen for white-coat HTN using either daytime ABPM or HBPM before diagnosing HTN (IIa, B-NR).

b. In adults with white-coat HTN, periodic monitoring with ABPM or HBPM is reasonable to detect transition to sustained HTN (IIa, C-LD).
c. In adults being treated for HTN with office blood pressure readings not at goal and HBPM readings suggestive of a significant white-coat effect, confirmation by ABPM can be useful (IIa, C-LD).
d. In adults receiving multidrug therapies for HTN and office blood pressure measurements within 10 mm Hg above goal, it may be reasonable to screen for white-coat effect with HBPM (IIb, C-LD).

2. Masked HTN: Office blood pressure is 120–129/less than 80 mm Hg after a 3-month trial of lifestyle modification; daytime ABPM or HBPM blood pressure of 130/80 mm Hg or greater
   a. In adults with untreated office blood pressure measurements that are consistently 120–129 mm Hg for SBP or 75–79 mm Hg for DBP, screening for masked HTN with HBPM (or ABPM) is reasonable (IIa, B-NR).
   b. It may be reasonable to screen for masked uncontrolled HTN with HBPM in adults being treated for HTN and office readings at goal, in the presence of target-organ damage or increased overall CVD risk (IIa, C-EO).
   c. In adults being treated for HTN with elevated HBPM readings suggestive of masked uncontrolled HTN, confirmation of the diagnosis by ABPM may be reasonable before intensification of antihypertensive drug treatment (IIa, C-EO).

J. Patient Evaluation
   1. Primary HTN
      a. Gradual increase in blood pressure, with slow rate of blood pressure rise
      b. Lifestyle factors present that favor higher blood pressure
      c. Family history of HTN
   2. Secondary HTN
      a. Blood pressure lability, episodic pallor dizziness (pheochromocytoma)
      b. Snoring, hypersomnolence (obstructive sleep apnea)
      c. Prostatism (CKD caused by post-renal urinary tract obstruction)
      d. Muscle cramps, weakness (hypokalemia)
      e. Weight loss, palpitations, heat intolerance (hyperthyroidism)
      f. Edema, fatigue, frequent urination (kidney disease or failure)
      g. History of coarctation repair
      h. Central obesity, facial rounding, easy bruising (Cushing syndrome)
      i. Medication or substance use/abuse
      j. Absence of family history of HTN
   3. Laboratory and diagnostic testing
      a. Basic testing
         i. Fasting blood glucose
         ii. Complete blood cell count
         iii. Lipid profile
         iv. SCr with estimated glomerular filtration rate (eGFR)
         v. Serum sodium, potassium, calcium
         vi. Thyroid-stimulating hormone
         vii. Urinalysis
         viii. Electrocardiogram
      b. Optional testing
         i. Echocardiogram
         ii. Uric acid
         iii. Urinary albumin/creatinine ratio

K. Blood Pressure Goals for Patients with HTN (Table 3)
   1. For adults with confirmed HTN and known CVD or 10-year ASCVD event risk of 10% or greater, a blood pressure target of less than 130/80 mm Hg is recommended (I; SBP: B-R, DBP: C-EO).
   2. For adults with confirmed HTN without additional markers of increased CVD risk, a blood pressure target of less than 130/80 mm Hg may be reasonable (IIb; SBP: B-NR, DBP: C-EO).

**Table 3.** BP Thresholds for and Goals of Pharmacologic Therapy in Patients with HTN According to Clinical Condition

| Clinical Condition | BP Threshold, mm Hg | BP Goal, mm Hg |
|---|---|---|
| Clinical CVD or 10-year ASCVD risk ≥10% | ≥130/80 | <130/80 for all |
| No clinical CVD and 10-year ASCVD risk <10% | ≥140/90 | |
| Diabetes mellitus[a] | ≥130/80 | |
| Chronic kidney disease | ≥130/80 | |
| Chronic kidney disease after renal transplantation | ≥130/80 | |
| Heart failure | ≥130/80 | |
| Stable ischemic heart disease | ≥130/80 | |
| Secondary stroke prevention | ≥140/90 | |
| Secondary stroke prevention (lacunar) | ≥130/80 | |
| Peripheral arterial disease | ≥130/80 | |
| Older persons (≥65 years; noninstitutionalized, ambulatory, community-living) | ≥130 (SBP) | <130 (SBP) |

[a]According to the 2017 ACC/AHA HTN guideline; 2018 ADA guideline does not agree.

ASCVD = atherosclerotic cardiovascular disease; CVD = cardiovascular disease.

   3. Select clinical trials and meta-analysis that compare blood pressure goals:
      a. "Systolic Blood Pressure Reduction and Risk of Cardiovascular Disease and Mortality: Systematic Review and Network Meta-analysis" – 2017
         i. Assessed the association of mean achieved SBP levels with the risk of CVD and all-cause mortality in adults with HTN treated with antihypertensive therapy. Trials were not prospective comparisons of particular blood pressure goals but values achieved during individual trials.
         ii. Over 144,000 patients from 42 trials were included.
         iii. Linear associations between mean achieved SBP and risk of CVD and mortality were seen (Figure 1).
            (a) Major CVD: Lowest risk was at 120–124 mm Hg, compared with
               (1) 130–135 mm Hg: hazard ratio (HR) 0.71 (95% confidence interval [CI], 0.60–0.83)
               (2) 140–144 mm Hg: HR 0.58 (95% CI, 0.48–0.72)
               (3) 150–154 mm Hg: HR 0.46 (95% CI, 0.34–0.63)
               (4) Greater than 160 mm Hg: HR 0.36 (95% CI, 0.26–0.51)
            (b) All-cause mortality: Lowest risk was at 120–124 mm Hg, compared with
               (1) 130–135 mm Hg: HR 0.73 (95% CI, 0.58–0.93)
               (2) 140–144 mm Hg: HR 0.59 (95% CI, 0.45–0.77)
               (3) 150–154 mm Hg: HR 0.51 (95% CI, 0.36–0.71)
               (4) Greater than 160 mm Hg: HR 0.47 (95% CI, 0.32–0.67)

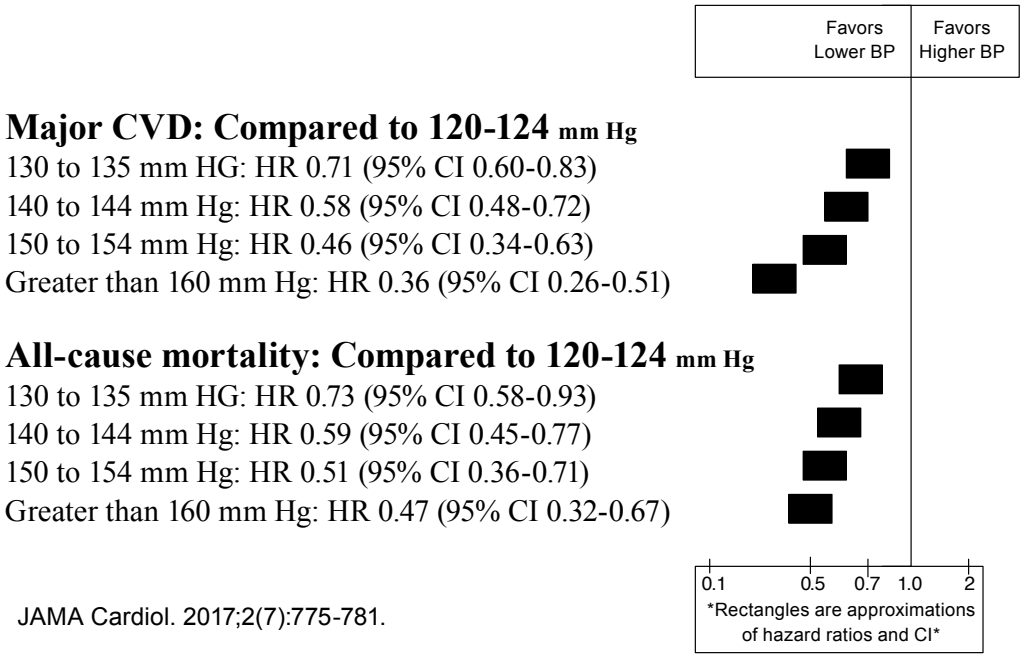


**Figure 1.** Major cardiovascular disease and all-cause mortality associated with more intensive reductions in systolic blood pressure.

CVD = cardiovascular disease.

iv. Authors concluded that reducing SBP to levels below historically recommended goals (based on guidelines preceding the 2017 ACC/AHA guideline) could significantly reduce CVD and all-cause mortality.

b. "A Randomized Trial of Intensive versus Standard Blood-Pressure Control" (SPRINT trial) – 2015
   i. More than 9300 people 50 and older without diabetes or previous stroke/TIA with SBP of 130–180 mm Hg with increased CV risk (clinical or subclinical CVD other than stroke, CKD, 10-year Framingham risk of 15% or higher, age 75 and older) randomized to SBP target of less than 120 mm Hg or less than 140 mm Hg (based on automated office blood pressure monitoring)
   ii. Intensive control reduced the primary outcome of composite MI, acute coronary syndrome, acute decompensated HF, death from CV causes (1.65% per year vs. 2.19% per year; HR 0.75; 95% CI, 0.64–0.89; $p<0.001$) with number needed to treat of 61. Benefits also occurred in patients older than 75.
   iii. Increased rates of hypotension, syncope, electrolyte abnormalities, and acute kidney injury/failure occurred in the intensive arm. Number needed to harm was 100 for hypotension.
   iv. The SPRINT trial excluded patients with diabetes, cerebrovascular disease, symptomatic HF or reduced left ventricular ejection fraction, and advanced renal dysfunction (eGFR less than 20 mL/minute/1.73 $m^2$ or end-stage renal disease); thus, extrapolation of findings to these groups is limited.
   v. Individualized decision-making is pertinent and must consider risk-benefit as well as patient preference and quality of life (e.g., adding another medication, potential adverse drug reactions [ADRs]).
   vi. Follow-up data, including post-trial observations from the "Final Report of a Trial of Intensive versus Standard Blood-Pressure Control," suggest benefit after 3.33 years in the intensive treatment arm (N Engl J Med 2021;384:1921-30); however, HF rates no longer differed between groups.

c. ACCORD BP (Action to Control Cardiovascular Risk in Diabetes blood pressure trial) – 2010
    i. RCT that enrolled over 4700 patients with type 2 diabetes who had CVD or at least two additional risk factors for CVD. Patients were assigned to either intensive therapy (goal SBP less than 120 mm Hg) or standard therapy (goal SBP less than 140 mm Hg).
    ii. Baseline blood pressure was 139/76 mm Hg. Goals were reached in both groups. Mean attained blood pressure at 1 year in the intensive group was 119.3 mm Hg, and mean attained blood pressure in the standard therapy group was 133.5 mm Hg.
        (a) After a 4.7-year follow-up:
            (1) No significant difference in the rate of the primary composite outcome (nonfatal MI, nonfatal stroke, or death from CV causes) between the intensive and standard therapy groups (1.87% vs. 2.09%; HR 0.88; 95% CI, 0.73–1.06)
            (2) No difference in all-cause mortality (1.28% vs. 1.19%) or in death from CV causes (0.52% vs. 0.49%) between the intensive and standard therapy groups
            (3) Intensive therapy was associated with significant reductions in the annual rates of total stroke and nonfatal stroke (0.32% vs. 0.53%; HR 0.59; 95% CI, 0.39–0.89).
            (4) Serious adverse events from antihypertensive drugs (e.g., hypotension, syncope, bradycardia, electrolyte abnormalities, angioedema, and renal failure) occurred significantly more often in the intensive therapy group than in the standard therapy group (3.3% vs. 1.3%).
        (b) Trial affected blood pressure goals in ADA standards of medical care in diabetes.
d. STEP study group
    i. RCT of 8511 Chinese patients with HTN 60–80 years of age. Patients were assigned to an intensive blood pressure target (110–130 mm Hg) or standard target arm (130–150 mm Hg).
    ii. At 1 year, mean SBP was 127.5 mm Hg and 135.3 mm Hg in the intensive and standard arms, respectively.
    iii. After a 3.34-year follow-up, intensive treatment was favored over standard treatment:
        (a) Primary outcome events were 3.5% compared with 4.6% (HR 0.74; 95% CI, 0.60–0.92; p=0.007).
        (b) Individual outcomes of stroke (HR 0.67, 0.47–0.97), acute coronary syndrome (HR 0.67, 0.47–0.94), and acute decompensated HF (HR 0.27, 0.08–0.98) significantly improved with intensive blood pressure treatment.
        (c) Hypotension was higher in the intensive treatment arm, but other safety and renal outcomes did not differ significantly between the two groups.

L. Blood Pressure Treatment
1. Blood pressure treatment strategies according to blood pressure level and ASCVD risk (Figure 2; Table 3)
    a. Use of blood pressure–lowering medications is recommended for secondary prevention of recurrent CVD events in patients with clinical CVD and an average SBP of 130 mm Hg or greater or an average DBP of 80 mm Hg or greater and for primary prevention in adults with an estimated 10-year ASCVD risk of 10% or greater and an average SBP of 130 mm Hg or greater or an average DBP of 80 mm Hg or greater (I; SBP: A, DBP: C-EO).
    b. Use of blood pressure–lowering medication is recommended for primary prevention of CVD in adults with no history of CVD and with an estimated 10-year ASCVD risk of less than 10% and an SBP of 140 mm Hg or greater or a DBP of 90 mm Hg or higher (I, A).

**Patient Case**

3. A 50-year-old African American woman with dyslipidemia presents to your clinic for blood pressure assessment. When she participated in a health fair the past week, she was told her blood pressure was "too high." She has smoked for the past 35 years but has recently considered quitting. Her blood pressure today an average of 154/94 mm Hg and heart rate is 72 beats/minute. She takes vitamin D supplementation daily, fish oil, and acetaminophen as needed. Laboratory tests show TC 230 mg/dL, HDL 35 mg/dL, LDL 155 mg/dL, SCr 0.9 mg/dL, K 4.0 mEq/L, and Na 141 mEq/L. Her BMI is 26.0 kg/m$^2$. Her 10-year ASCVD risk is 15.2%. Which is the next best action?

   A. Treat with education on diet and exercise only.

   B. Treat with education on diet and exercise, and initiate metoprolol succinate 25 mg/day.

   C. Treat with education on diet and exercise, and initiate chlorthalidone 12.5 mg/day.

   D. Treat with education on diet and exercise, and initiate chlorthalidone 12.5 mg/day and amlodipine 5 mg/day.

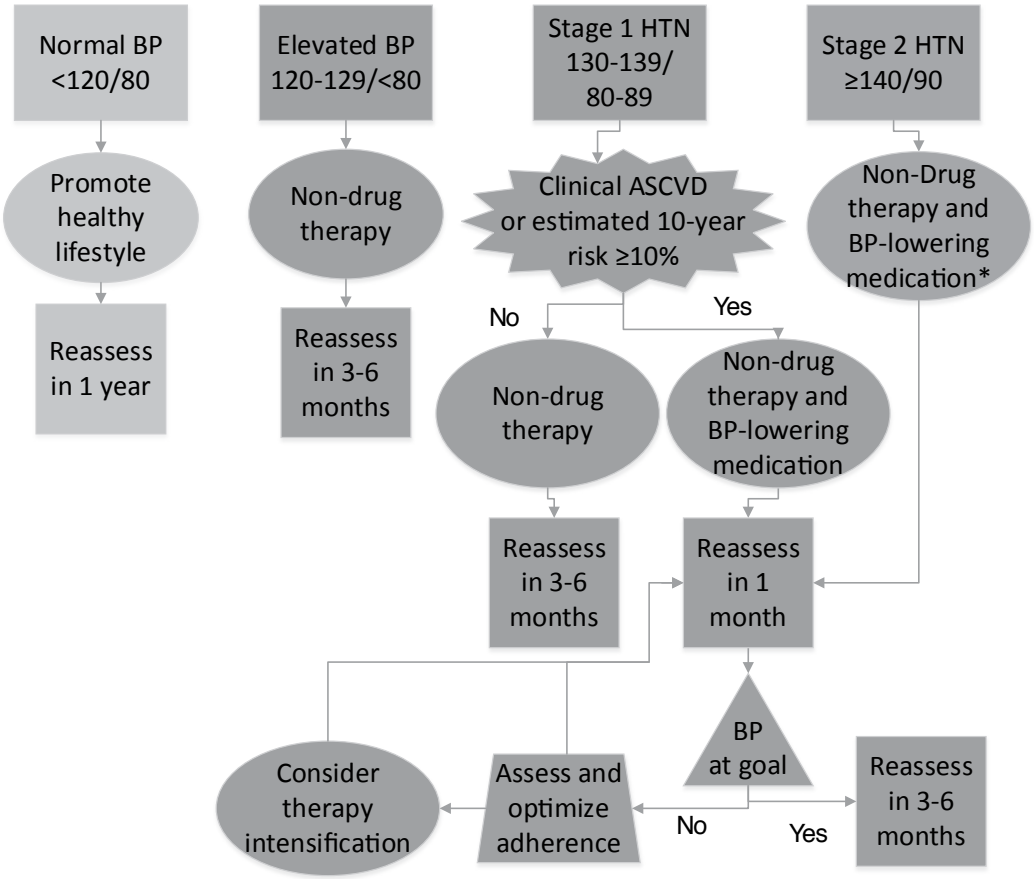


**Figure 2.** BP treatment strategies according to BP level and ASCVD risk.

*Initiation of antihypertensive drug therapy with two first-line agents of different classes, either as separate agents or in a fixed-dose combination, is recommended in adults with stage 2 HTN and an average blood pressure of greater than 20/10 mm Hg above their blood pressure target.

ASCVD = atherosclerotic cardiovascular disease; BP = blood pressure.

c. Initial blood pressure follow-up
   i. Adults with an elevated blood pressure or stage 1 HTN who have an estimated 10-year ASCVD risk of less than 10% should be treated with nonpharmacologic therapy and have a repeat blood pressure evaluation within 3–6 months (I, B-R).
   ii. Adults with stage 1 HTN who have an estimated 10-year ASCVD risk of 10% or higher should initially be treated with a combination of nonpharmacologic and antihypertensive drug therapy and have a repeat blood pressure evaluation in 1 month (I, B-R).
   iii. Adults with stage 2 HTN should be evaluated by or referred to a primary care provider within 1 month of the initial diagnosis, have a combination of nonpharmacologic and antihypertensive drug therapy (with two agents of different classes) initiated, and have a repeat blood pressure evaluation in 1 month (I, B-R).
   iv. For adults with a very high average blood pressure (e.g., SBP of 180 mm Hg or greater or DBP of 110 mm Hg or greater), evaluation followed by prompt antihypertensive drug treatment is recommended (I, B-R).
   v. For adults with a normal blood pressure, a repeat evaluation every year is reasonable (IIa, C-EO).

2. Nonpharmacologic therapies (lifestyle modifications) (Table 4)

**Table 4.** Recommended Lifestyle Modifications

| Modification | Recommendation | Approximate SBP Reduction |
|---|---|---|
| Weight reduction | Maintain a normal body weight (BMI 18.5–24.9 kg/m$^2$) | 5–20 mm Hg per 10-kg weight loss |
| Adopt DASH eating plan (includes substantial K intake) | Consume a diet rich in fruits, vegetables, and low-fat dairy products with a reduced content of saturated and total fat | 8–14 mm Hg |
| Reduce Na intake | Reduce Na intake to ≤ 2400 mg/day<br>Reducing Na intake further to ≤ 1500 mg/day is associated with greater blood pressure reduction<br>Reducing Na intake by at least 1000 mg/day will lower blood pressure if desired daily Na intake goal is not achieved | 2–8 mm Hg |
| Physical activity | Engage in regular aerobic physical activity such as brisk walking (at least 30 min/day most days of the week) | 4–9 mm Hg |
| Moderation of alcohol consumption | Limit consumption to:<br>Men: 2 drinks/day (24 oz of beer, 10 oz of wine, or 3 oz of 80-proof whiskey)<br>Women and those of lower body weight: 1 drink/day | 2–4 mm Hg |

BMI = body mass index; DASH = Dietary Approaches to Stop Hypertension.

3. Principles of drug therapy
   a. For initiation of antihypertensive drug therapy, first-line agents include thiazide diuretics, calcium channel blockers (CCBs), and angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin receptor blockers (ARBs) (I, A).
      i. Choice of initial therapy: Monotherapy versus combination therapy
         (a) Initiating antihypertensive drug therapy with a single antihypertensive drug is reasonable in adults with stage 1 HTN and a blood pressure goal of less than 130/80 mm Hg with dosage titration and sequential addition of other agents to achieve the blood pressure target (IIa, C-EO).

(b) Initiating antihypertensive drug therapy with two first-line agents of different classes, either as separate agents or in a fixed-dose combination, is recommended in adults with stage 2 HTN and an average blood pressure greater than 20/10 mm Hg above their blood pressure target (I, C-EO).

ii. First-line agents

(a) ACEIs: Benazepril, captopril, enalapril, fosinopril, lisinopril, moexipril, perindopril, quinapril, ramipril, trandolapril

(1) Mechanism of action – Prevent conversion of angiotensin I to angiotensin II (potent vasoconstrictor) by competitive inhibition of ACE. Results in lower blood pressure secondary to lower concentrations of angiotensin II, increased plasma renin activity, and reduced aldosterone secretion

(2) Evidence

(A) PROGRESS study (randomized trial of a perindopril-based blood pressure–lowering regimen among 6105 individuals with previous stroke or TIA)

(B) ANBP2 study (comparison of outcomes with ACEIs and diuretics for HTN in older adults)

(3) Clinical use

(A) Indications to use ACEIs first line

- Non–African American patients
- Albuminuria – Reduce the progression of nephropathy and diabetic and non-diabetic albuminuria
- HF or left ventricular dysfunction with a left ventricular ejection fraction of 40% or less
- CAD, post-MI
- Recurrent stroke prevention – Reduced recurrence when used in combination with thiazide-type diuretics

(B) Recommended as add-on therapy for African American patients

(C) Contraindications

- Pregnancy
- Angioedema
- Concomitant aliskiren administration

(4) Important ADRs

(A) Increasing SCr – Limited increase of as much as 30% above baseline is acceptable. This becomes the patient's new baseline SCr concentration.

- Patient may have a new baseline SCr concentration after initiation of an ACEI.
- Increased risk of acute renal failure in patients with severe bilateral renal artery stenosis

(B) Hyperkalemia

(C) Angioedema – Occurs 2–4 times more often in African Americans

(D) Cough, dry (11% with 2.5% discontinuation)

(5) Dosing and monitoring

(A) Simultaneous use of an ACEI, ARB, and/or renin inhibitor can be harmful and is not recommended to treat adults with HTN (III [harm], A).

(B) Consider avoiding in women during childbearing years.

(C) Consider initiating at a lower-than-average dose if the patient is an older adult, is receiving concomitant diuretic therapy, or has renal impairment.

(D) Reassess SCr and K 1–2 weeks after initiation or dose titration.

(E) Monitor K closely, especially if renal impairment exists or another K-sparing drug or K supplement is used.

(b) ARBs (azilsartan, candesartan, eprosartan, irbesartan, losartan, olmesartan, telmisartan, valsartan)
  (1) Mechanism of action – Selective, competitive angiotensin II receptor type 1 receptor antagonist, reducing the end-organ responses to angiotensin II. Results in decreased total peripheral resistance (afterload) and cardiac venous return (preload). Reduction in blood pressure occurs independently of the status of the renin-angiotensin system.
  (2) Evidence: CV morbidity and mortality in the LIFE study (Losartan Intervention for Endpoint Reduction in Hypertension): A randomized trial against atenolol
  (3) Clinical use
    (A) Indications to use ARBs first line
      • Non–African American patients
      • Albuminuria – Reduce the progression of nephropathy and diabetic and non-diabetic albuminuria
      • HF or left ventricular dysfunction with left ventricular ejection fraction of 40% or less
      • CAD
      • Recurrent stroke prevention – Reduce recurrence when used in combination with thiazide-type diuretics
    (B) Recommended as add-on therapy for African American patients
    (C) Contraindications
      • Pregnancy
      • Do not co-administer with aliskiren.
    (D) Increased risk of acute renal injury with bilateral renal artery stenosis
    (E) Angioedema (ARB-induced or idiopathic) – Although ARBs may be considered alternative therapy for patients who have developed angioedema while taking an ACEI, patients have also developed angioedema with ARBs, and extreme caution is advised when substituting an ARB for a patient with HTN who has had angioedema associated with ACEI use. Must weigh risk-benefit of use; consider other agents, if possible
  (4) Important ADRs – Similar to those with ACEIs except for cough
    (A) Increasing SCr – Limited increase of as much as 30% above baseline is acceptable. This becomes the patient's new baseline SCr value.
    (B) Hyperkalemia
    (C) Angioedema – Less than with ACEIs
  (5) Dosing and monitoring
    (A) Simultaneous use of an ACEI, ARB, and/or renin inhibitor can be harmful (i.e., can worsen renal function and/or hyperkalemia) and is not recommended to treat adults with HTN (III [harm], A).
    (B) Consider avoiding in women during childbearing years.
    (C) Monitor SCr and K values 7–10 days after initiation or titration.
    (D) Monitor K closely, especially if renal impairment exists or another K-sparing drug or K supplement is used.

(c) Thiazide and thiazide-type diuretics (chlorthalidone, hydrochlorothiazide, indapamide, metolazone)
  (1) Mechanism of action – Act on the kidneys to reduce sodium reabsorption in the distal convoluted tubule. By impairing sodium transport in the distal convoluted tubule, natriuresis and concomitant water loss are induced.

(2) Evidence
   (A) Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT)
   (B) Prevention of stroke by antihypertensive drug treatment in older people with isolated systolic HTN: Final results of the Systolic Hypertension in the Elderly Program (SHEP)
   (C) Medical Research Council (MRC) trial of treatment of mild HTN: Principal results
   (D) Hypertension in the Very Elderly Trial (HYVET)

(3) Clinical use
   (A) Option as first-line therapy for most patients with HTN, either alone or in combination with one of the other drug classes (ACEIs, ARBs, CCBs)
   (B) Enhances the efficacy of multidrug regimens
   (C) Chlorthalidone preferred to hydrochlorothiazide by ACC/AHA 2017 HTN guideline.
      • Chlorthalidone has been compared in a large observational comparative cohort study (JAMA Intern Med 2020;180:542-51) to hydrochlorothiazide and while no advantage on major adverse cardiovascular events was seen, chlorthalidone was associated with a significantly higher risk of hypokalemia (HR, 2.72; 95% CI, 2.38–3.12), hyponatremia (HR, 1.31; 95% CI, 1.16–1.47), acute renal failure (HR, 1.37; 95% CI, 1.15–1.63), chronic kidney disease (HR, 1.24; 95% CI, 1.09–1.42), and type 2 diabetes mellitus (HR, 1.21; 95% CI, 1.12–1.30), which emphasizes the need for diligent monitoring with this agent.
      • The Diuretic Comparison Project (N Engl J Med 2022;387:2401-410) randomized 13,523 patients in a 1:1 ratio to be changed from hydrochlorothiazide to chlorthalidone or to continue hydrochlorothiazide. No difference between the two arms was found for the primary outcome of major CV events (HR 1.04; 95% CI, 0.94–1.16). Major CV events were defined as stroke, nonfatal MI, urgent coronary revascularization because of unstable angina, HF hospitalization, and non–cancer-related death. More hypokalemia occurred in the chlorthalidone group than in the hydrochlorothiazide group (HR 1.38; 95% CI, 1.19–1.60).
   (D) Contraindication – Anuria

(4) Important ADRs
   (A) Electrolyte abnormalities (hypokalemia, hyponatremia, hypomagnesaemia)
   (B) Hyperuricemia

(5) Dosing and monitoring
   (A) Monitor SCr, Na, K, and magnesium 7–10 days after initiation or titration. Patients taking metolazone will need to be more closely monitored because of the enhanced diuretic effect, particularly if used with loop diuretics.
   (B) Chlorthalidone efficacy was evaluated in patients with uncontrolled HTN and an eGFR of 15 to less than 30 mL/minute/1.73 $m^2$ (N Engl J Med 2021;385:2507-19). A total of 160 patients were randomized to chlorthalidone or placebo. At baseline, mean 24-hour ambulatory SBP values were 142.6 mm Hg and 140.1 mm Hg in the chlorthalidone and placebo groups, respectively. Patients were taking 3.4 plus or minus 1.4 antihypertensive medications at baseline and had a mean GFR of 23.2 plus or minus 4.2 mL/minute/1.73 $m^2$. At 12 weeks, patients had reductions of -11 mm Hg and -0.5 mm Hg from baseline blood pressure in the chlorthalidone and placebo groups, respectively.

**Patient Case**

4. A 66-year-old African American man with a history of dyslipidemia and HTN presents for a routine check-up. His blood pressure readings are 140/72 mm Hg (repeat 138/70 mm Hg). He currently takes atorvastatin 20 mg/day, lisinopril 20 mg/day, and hydrochlorothiazide 25 mg/day. His heart rate was 54 beats/minute (repeat 55 beats/minute), SCr 1.1 mg/dL (CrCl [ideal body weight] 72 mL/minute), K 4.2 mEq/L, and Na 139 mEq/L. Which change, if any, would be best for his medication regimen?
   A. Discontinue lisinopril.
   B. Initiate amlodipine 5 mg daily.
   C. Initiate verapamil extended release 120 mg daily.
   D. Discontinue hydrochlorothiazide.

(d) CCBs
  (1) Dihydropyridines (amlodipine, felodipine, isradipine, nicardipine, nifedipine, nisoldipine)
    (A) Mechanism of action – Act by relaxing the smooth muscle in the arterial wall, decreasing total peripheral resistance, and hence reducing blood pressure
    (B) Evidence
      • ALLHAT
      • Benazepril plus amlodipine or hydrochlorothiazide for HTN in high-risk patients (ACCOMPLISH trial)
      • Prevention of CV events with an antihypertensive regimen of amlodipine, adding perindopril as required versus atenolol, adding bendroflumethiazide as required, in the Anglo-Scandinavian Cardiac Outcomes Trial-Blood Pressure Lowering Arm (ASCOT-BPLA): A multicenter RCT
      • Effects of intensive blood pressure lowering and low-dose aspirin in patients with HTN: Principal results of the Hypertension Optimal Treatment (HOT) randomized trial
    (C) Clinical use
      • Option as first-line therapy for most patients with HTN
      • Potent blood pressure lowering
      • Improve anginal symptoms
    (D) Important ADRs
      • Peripheral edema
      • Orthostasis
      • Reflex tachycardia
    (E) Dosing and monitoring – Initiate at a low dose for older adult patients.
  (2) Non-dihydropyridines (diltiazem, verapamil)
    (A) Mechanism of action – Act as a potent vasodilator of coronary vessels, increasing blood flow and decreasing the heart rate by strong depression of atrioventricular (AV) node conduction. In addition, act as a potent vasodilator of peripheral vessels, reducing peripheral resistance and afterload. They have negative inotropic effects.
    (B) Evidence
      • Principal results of the Controlled Onset Verapamil Investigation of Cardiovascular End Points (CONVINCE) trial
      • A CCB (verapamil) versus a non-CCB treatment strategy for patients with stable CAD: INVEST: An RCT
      • Randomized trial of effects of CCBs compared with diuretics and β-blockers on CV morbidity and mortality in HTN: Nordic Diltiazem (NORDIL) study

(C) Clinical use:
- Option as first-line therapy for most patients with HTN
- Used for HTN in patients with concomitant conditions (e.g., atrial fibrillation or stable angina) who would benefit from these medications

(D) Contraindications
- Heart block
- Sick sinus syndrome

(E) Important ADRs
- Bradycardia
- Heart block
- Constipation

(F) Dosing and monitoring
- Potent CYP3A4 and P-glycoprotein inhibitors; sources of potentially serious drug-drug interactions
- Do not use with concomitant HF*r*EF (left ventricular ejection fraction less than 40%).
- Use with caution in patients receiving concomitant atrioventricular nodal-blocking agents.
- Other important drug-drug interactions to be mindful of include (but are not limited to) ivabradine, colchicine, dofetilide (contraindicated with verapamil), and ranolazine.

iii. Secondary antihypertensive agents

(a) Aldosterone antagonists (eplerenone, spironolactone)

(1) Mechanism of action – Inhibit the effect of aldosterone by competing for intracellular aldosterone receptors in the cortical collecting duct. This decreases Na and water reabsorption while decreasing K secretion.

(2) Evidence
(A) Efficacy of low-dose spironolactone in subjects with resistant HTN
(B) Role of spironolactone in the treatment of patients with refractory HTN

(3) Clinical use
(A) Resistant HTN
(B) Patients with HTN and HF*r*EF or HF*p*EF

(4) Contraindications
(A) Anuria
(B) Acute renal insufficiency – Avoid if eGFR is 30 mL/minute/1.73 $m^2$ or less.
(C) Hyperkalemia – Avoid if K is 5.0 mEq/L or more.

(5) Important ADRs
(A) Hyperkalemia
(B) Gynecomastia and mastodynia with spironolactone

(6) Dosing and monitoring:
(A) Monitor SCr and K within 1 week of initiation of titration of spironolactone and regularly thereafter.
(B) Measure serum potassium before initiating eplerenone therapy, within the first week, and at one month after the start of treatment or dose adjustment.
(C) When used with concomitant HF*r*EF, monitor SCr and K on day 3, day 7, and monthly for the first 3 months after initiation or titration and periodically thereafter.

(b) $\alpha_1$-Blockers (doxazosin, prazosin, terazosin)

(1) Mechanism of action – Selective $\alpha_1$-antagonists reduce blood pressure by decreasing total peripheral resistance and venous return. Selective $\alpha_1$-blockade produces vasodilation and reduces preload and afterload during rest and exercise.

(2) Evidence – ALLHAT showed a 25% higher rate of combined CVD and a 2-fold higher rate of HF than in the diuretic arm.
(3) Clinical use
(A) In general, reserved for hypertensive male patients with concomitant benign prostatic hyperplasia
(B) Usually viewed as fourth- or fifth-line agent for HTN
(4) Important ADRs – Dizziness and orthostatic hypotension (OH)
(5) Dosing and monitoring: Start with a very low dose. The patient should consider taking the first dose at night while in bed. Titrate slowly over time as needed.

(c) β-Blockers
(1) Types
(A) Cardioselective: Atenolol, betaxolol, bisoprolol, metoprolol tartrate, metoprolol succinate
(B) Combined α- and β-receptor blockers: Carvedilol, labetalol
(C) Cardioselective and vasodilatory: Nebivolol
(D) Non-cardioselective: Nadolol, propranolol
(E) Intrinsic sympathomimetic: Acebutolol, penbutolol, pindolol
(2) Mechanism of action – Selective ($\beta_1$ only) or nonselective ($\beta_1$ and $\beta_2$) receptor blocker results in negative inotropic and chronotropic actions. Some β-blockers (e.g., pindolol, acebutolol) have intrinsic sympathomimetic activity, meaning they can exert low-level agonist activity at the β-adrenergic receptor while acting as a receptor site antagonist. Agents without intrinsic sympathomimetic activity are usually used for HTN. Carvedilol and labetalol also have $\alpha_1$-blocking activity, and nebivolol also has nitric oxide–mediated vasodilating properties.
(3) Evidence
(A) ACC Foundation/AHA guidelines since the 1980s
(B) Not considered first line for essential HTN because of the lack of positive outcome data; however, are adjunctive agents when patients with HTN have indications for β-blockade
(4) Clinical use
(A) Indications
- HF or left ventricular systolic dysfunction with left ventricular ejection fraction of 40% or less – (Metoprolol succinate, carvedilol, bisoprolol first line with other appropriate GDMT)
- Post-MI (within first 3 years) – First line
- β-Blockers with $\alpha_1$-blocking activity are likely more effective antihypertensive agents than are β-blockers without this mechanism.

(B) Contraindications
- Sinoatrial or AV node dysfunction
- Decompensated HF
- Severe bronchospastic disease

(5) Important ADRs
(A) Bradycardia – Adjust doses for symptomatic bradycardia only.
(B) Heart block – Adjust doses or discontinue therapy for greater than first-degree heart block.
(C) Bronchospastic disease
(D) Exercise intolerance
(E) Sexual dysfunction
(F) Fatigue

(6) Dosing and monitoring
(A) Relative contraindications include hypotension and bronchospastic lung disease.
(B) Monitor heart rate regularly.
(C) Taper shorter-acting agents rather than abruptly discontinuing them to avoid rebound anginal and hypertensive effects.

(c) Other diuretics (other than thiazides)
(1) Loops (bumetanide, furosemide, torsemide)
(A) Mechanism of action – Act by reversibly binding to the Na, K, Cl cotransport mechanism on the luminal side of the ascending loop of Henle, thereby inhibiting the active reabsorption of these ions
(B) Clinical use: HTN management for patients with HF and CKD, using scheduled twice-daily dosing
(C) Contraindication – Anuria
(D) Important ADRs
- Electrolyte abnormalities (hypokalemia, hyponatremia, hypomagnesemia)
- Dehydration/hypovolemia

(E) Dosing and monitoring: Monitor SCr, Na, K, and magnesium 7–10 days after initiation or titration.
(F) Approximate dose equivalence (oral)
- Furosemide 40 mg
- Bumetanide 1 mg
- Torsemide 10–20 mg
- Ethacrynic acid 25–50 mg (may be useful for patients with allergic reactions to other loop diuretics caused by sulfa moiety)

(2) K-sparing (amiloride, triamterene)
(A) Mechanism of action – Block the epithelial Na channel on the lumen side of the kidney collecting tubule. Na channel blockers directly inhibit Na entry into the Na channels.
(B) Evidence: Effect of amiloride, or amiloride plus hydrochlorothiazide, compared with hydrochlorothiazide on glucose tolerance and blood pressure (PATHWAY-3)
(C) Clinical use: Typically used in combination with thiazide-type diuretic for K balance
(D) Contraindications
- Anuria
- Hyperkalemia
- Severe renal or hepatic disease

(E) Important ADR – Hyperkalemia
(F) Dosing and monitoring
- Avoid in patients with a CrCl of less than 10 mL/minute/1.73 $m^2$.
- Monitor SCr and K 7–10 days after initiation or titration.

(d) Central $\alpha_2$-androgenic agonist and other centrally acting drug (clonidine, methyldopa, guanfacine)
(1) Mechanism of action – Stimulate $\alpha_2$-receptors in the brain, which decreases sympathetic outflow, cardiac output, and peripheral vascular resistance, lowering blood pressure and heart rate
(2) Clinical use
(A) May be useful for resistant HTN
(B) Clonidine may be beneficial for hypertensive urgency.
(C) Methyldopa can be used in pregnancy.

(3) Important ADRs
(A) Dizziness and OH
(B) Drowsiness
(C) Dry mouth
(D) AV block, bradycardia (clonidine)
(4) Dosing and monitoring
(A) Clonidine: Rebound HTN possible if withdrawn too quickly, especially if taking concomitant β-blocker (except for carvedilol and labetalol, because of unopposed α-stimulation)
(B) Avoid in patients with HF.

(f) Direct renin inhibitor (aliskiren)
(1) Mechanism of action – Direct renin inhibition, decreasing plasma renin activity and inhibiting the conversion of angiotensinogen to angiotensin I
(2) Evidence
(A) No outcomes data available for aliskiren monotherapy
(B) ALTITUDE study (Aliskiren Trial in Type 2 Diabetes Using Cardiovascular and Renal Disease Endpoints) – Terminated early. This is not a HTN trial, per se, but it does show the risk of adverse reactions.
• Aliskiren added to ACEI or ARB therapy in patients with type 2 diabetes and renal impairment compared with a placebo add-on
• Increased adverse events (nonfatal stroke, renal complications, hyperkalemia, and hypotension) and no apparent benefits among patients randomly assigned to aliskiren group
(3) Contraindications
(A) Pregnancy
(B) Patients with diabetes when used in combination with ACEIs or ARBs because of increased risk of renal impairment, hyperkalemia, and hypotension
(C) Avoid use in combination with cyclosporine or itraconazole.
(D) Avoid concurrent use with ACEIs or ARBs in patients with renal impairment (creatinine clearance [CrCl] less than 60 mL/minute/1.73 $m^2$).
(4) Important ADRs
(A) Angioedema
(B) Hyperkalemia if used concomitantly with ACEI
(5) Dosing and monitoring
(A) Consider avoiding in women during childbearing years.
(B) High-fat meals decrease absorption substantially.
(C) Patients with renal insufficiency were excluded from trials.

(g) Direct vasodilators (hydralazine, minoxidil)
(1) Mechanism of action – Direct-acting smooth muscle relaxants that act as a vasodilator primarily in arteries and arterioles
(2) Clinical use
(A) May be useful for resistant HTN
(B) Usually viewed as fourth- or fifth-line agent for HTN
(3) Important ADRs
(A) Hydralazine
• Tachycardia (consider use with β-blocker)
• Drug-induced lupus-like syndrome
• Headache

(B) Minoxidil
- Tachycardia (consider use with β-blocker)
- Fluid retention (consider use with loop diuretic)
- Pericardial effusion
- Hirsutism

(4) Dosing and monitoring
(A) Hydralazine – Two to four times daily
(B) Minoxidil – One or two times daily

b. Follow-up after antihypertensive initiation
i. Adults initiating a new or adjusted drug regimen for HTN should have a follow-up evaluation of adherence, response to treatment, and monitoring for adverse drug events at monthly intervals until control is achieved (I, B-R).
ii. Follow-up and monitoring after initiation of drug therapy for HTN control should include systematic strategies to help improve blood pressure, including use of HBPM, team-based care, and telehealth strategies (I, A).

M. Landmark Trials Comparing Antihypertensive Therapies
1. Primary outcomes in high-risk hypertensive patients randomly assigned to receive ACEI or CCB versus diuretic: Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) – 2002
a. More than 33,000 individuals, 55 and older, with HTN and one additional risk factor
b. Participants were randomly assigned to receive chlorthalidone 12.5–25 mg/day (n=15,255), amlodipine 2.5–10 mg/day (n=9048), or lisinopril 10–40 mg/day (n=9054).
c. Primary outcome was combined fatal coronary heart disease or nonfatal MI, analyzed by intention to treat.
d. No differences were found in the primary coronary heart disease outcome or mortality between the thiazide-type diuretic chlorthalidone, the ACEI lisinopril, or the CCB amlodipine.
e. Original authors' conclusion: Thiazide-type diuretics are superior in preventing one or more major forms of CVD and are less expensive.
f. Study limitations include the following:
i. Atenolol was added as a second drug (may not be the most appropriate).
ii. Mean SBPs were higher in the amlodipine arm (0.8 mm Hg; p=0.03) and the lisinopril arm (2 mm Hg; p<0.001) than in the chlorthalidone arm.
iii. New-onset diabetes mellitus was higher in the chlorthalidone arm.
2. Benazepril plus amlodipine or hydrochlorothiazide for HTN in high-risk patients (ACCOMPLISH) trial – 2008
a. Enrolled over 11,500 patients with HTN at high risk of a CV event who were randomly assigned to initial combination therapy with benazepril (20 mg/day) plus either amlodipine (5 mg/day) or hydrochlorothiazide (12.5 mg/day)
b. Despite prior antihypertensive therapy in 97% of the patients, mean baseline blood pressure was 145/80 mm Hg.
c. Benazepril was increased to 40 mg/day in both groups at 1 month. If goal blood pressure was not attained, the amlodipine dose was increased to 10 mg/day and the hydrochlorothiazide dose to 25 mg/day.
d. The primary end point (composite of death from CV causes, nonfatal MI, nonfatal stroke, hospitalization for angina, resuscitation after sudden cardiac death, or coronary revascularization) was the time to the first event.

e. The data and safety monitoring board terminated the trial early at a mean follow-up of 36 months when a substantial disadvantage associated with the hydrochlorothiazide arm was noted and the prespecified stopping rule was exceeded.
f. The primary end point was achieved significantly less often in the benazepril/amlodipine group (9.6% vs. 11.8%; HR 0.80; 95% CI, 0.72–0.90).
g. The mean office blood pressure was slightly (about 1 mm Hg) but significantly lower in the benazepril/amlodipine group (131.6/73.3 mm Hg compared with 132.5/74.4 mm Hg). The clinical benefits with the benazepril/amlodipine combination likely cannot be explained by better blood pressure control alone.

N. HTN with Comorbidities
1. Stable ischemic heart disease (SIHD)
a. Heart disease is the most common form of target-organ damage associated with HTN.
b. In adults with SIHD and HTN, a blood pressure target of less than 130/80 mm Hg is recommended (I; SBP: B-R, DBP: C-EO).
c. Adults with SIHD and HTN should be treated with medications (e.g., guideline-directed medical therapy [GDMT] with β-blockers, ACEIs, or ARBs) for compelling indications (e.g., previous MI, stable angina) as first-line therapy, with other drugs added as needed to further control HTN (I; SBP: B-R, DBP: C-EO) (Figure 3).
d. In adults with SIHD with angina and persistent uncontrolled HTN, adding dihydropyridine CCBs to GDMT β-blockers is recommended (I; SBP: B-NR).
e. In adults who have had an MI or acute coronary syndrome, it is reasonable to continue GDMT β-blockers beyond 3 years as long-term therapy for HTN (IIa, B-NR).
f. β-Blockers and/or CCBs may be considered to control HTN in patients with CAD (without HF*r*EF) who had an MI more than 3 years ago and have angina (IIb, C-EO).

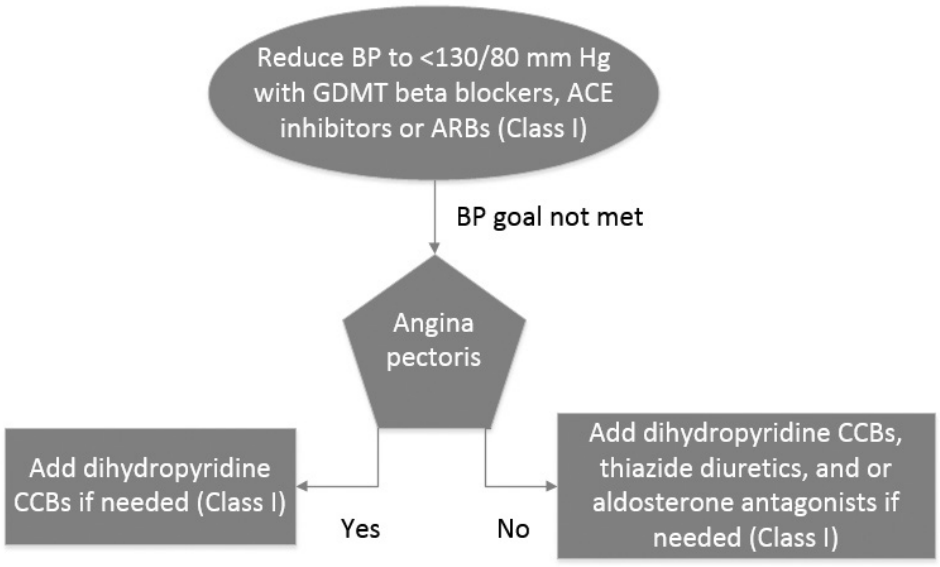


**Figure 3.** Hypertension treatment in patients with stable ischemic heart disease.
GDMT = guideline-directed medical therapy.

**Patient Case**

5. B.B is a 69-year-old woman (height 64 inches, weight 64 kg) with New York Heart Association class III HF*r*EF (ejection fraction 30%). Her blood pressure today is 138/88 mm Hg (138/86 mm Hg on repeat) and heart rate is 56 beats/minute. Laboratory test results today are as follows: SCr 1.1 mg/dL (CrCl [adjusted body weight] 44 mL/minute/1.73 $m^2$), K 3.7 mEq/L, and Na 143 mEq/L. She takes carvedilol 25 mg twice daily, enalapril 10 mg twice daily, and furosemide 40 mg twice daily. Her primary care physician asks you which medication, if any, should be added to her regimen next. Which is the best response?

   A. No further medications are indicated because her blood pressure is controlled.

   B. Start spironolactone 12.5 mg/day.

   C. Discontinue carvedilol and start metoprolol succinate 50 mg/day.

   D. Start amlodipine 5 mg/day.

2. HF
   a. HTN is one of the most important modifiable risk factors for both HF*p*EF and HF*r*EF.
   b. Individuals with HTN have a much higher risk of developing HF than do normotensive men and women. Long-term treatment of both systolic and diastolic HTN reduces the risk of HF by around 50%.
   c. HTN is an important contributor to acute decompensated HF.
   d. 2017 ACC/AHA HTN guidelines
      i. In adults at increased risk of HF, the optimal blood pressure in those with HTN should be less than 130/80 mm Hg (I; SBP: B-R, DBP: C-EO).
      ii. Adults with HF*r*EF and HTN should be prescribed GDMT titrated to attain a blood pressure of less than 130/80 mm Hg.
      iii. Non-dihydropyridine CCBs are not recommended in the treatment of HTN in adults with HF*r*EF (III [no benefit], B-R).
      iv. In adults with HF*p*EF with symptoms of volume overload, diuretics should be prescribed to control HTN (I, C-EO).
      v. In adults with HF*p*EF and persistent HTN after managing volume overload, ACEIs or ARBs and β-blockers should be titrated to attain an SBP of less than 130 mm Hg (I, C-EO).
   e. 2022 AHA/ACC/HFSA Guideline for the Management of Heart Failure
      i. In patients with stage A HF and HTN, blood pressure should be controlled in accordance with GDMT for HTN to prevent symptomatic HF (1, A).
         (a) The SPRINT trial showed that patients with increased CV risk (defined as age older than 75, established vascular disease, chronic renal disease, or a Framingham Risk Score greater than 15%), control of blood pressure to a goal SBP of less than 120 mm Hg was associated with a significantly reduced incidence of HF and CV death.
      ii. In patients with HF*r*EF and HTN, titration of GDMT to the maximally tolerated target dose is recommended (1, A).
      iii. Patients with HFpEF and HTN should have medications titrated to attain blood pressure targets in accordance with published clinical practice guidelines to prevent morbidity (1, C-LD).

**Patient Case**

6. A 60-year-old White man with type 2 diabetes is new to your clinic. Today, his blood pressure is 155/78 mm Hg with repeat 151/73 mm Hg, and heart rate is 80 beats/minute. He is intolerant of two different ACEIs because of cough. He takes metformin 850 mg three times daily, glipizide 10 mg twice daily, hydrochlorothiazide 25 mg/day, and omeprazole as needed. Laboratory test results are as follows: SCr 1.5 mg/dL (CrCl [ideal body weight] 54 mL/minute/1.73 $m^2$), A1C 6.8%, K 4.0 mEq/L, and microalbumin/creatinine 98.2 mg/g. His BMI is 31.6 $kg/m^2$. Which is best to initiate for his elevated blood pressure?
   A. Spironolactone 12.5 mg/day.
   B. Amlodipine 2.5 mg/day.
   C. Losartan 25 mg/day.
   D. Metoprolol succinate 25 mg/day.

3. Diabetes mellitus
   a. Most patients with diabetes are affected by HTN, and HTN is a risk factor for macro- and microvascular complications. Because CVD is the No. 1 killer of, and main source of morbidity in, patients with diabetes, controlling CV risk factors such as HTN in patients with diabetes is of utmost importance.
   b. 2017 ACC/AHA HTN guideline
      i. In adults with diabetes mellitus and HTN, antihypertensives should be initiated at a blood pressure of 130/80 mm Hg or higher with a treatment goal of less than 130/80 mm Hg (I, SBP: B-R, DBP: C-EO).
      ii. In adults with diabetes mellitus and HTN, all first-line classes of antihypertensive agents (i.e., diuretics, ACEIs, ARBs, and CCBs) are useful and effective (I, $A^{SE}$).
      iii. In adults with diabetes mellitus and HTN, ACEIs or ARBs may be considered in the presence of albuminuria (IIb, B-NR).
   c. ADA standards of medical care in diabetes 2023:
      i. Evidence grading system
         (a) A
            (1) Clear evidence from well-conducted, generalizable RCTs that are adequately powered
            (2) Supportive evidence from well-conducted RCTs that are adequately powered
         (b) B
            (1) Supportive evidence from well-conducted cohort studies
            (2) Supportive evidence from a well-conducted case-control study
         (c) C
            (1) Supportive evidence from poorly controlled or uncontrolled studies
            (2) Conflicting evidence with the weight of evidence supporting the recommendation
         (d) E
            (1) Expert consensus
            (2) Clinical experience
      ii. Recommendations
         (a) All patients with diabetes and HTN should monitor their blood pressure at home (A).
         (b) Blood pressure should be measured at all routine clinical visits. Patients with an elevated blood pressure (SBP 120–129 mm Hg and DBP less than 80 mm Hg) should have their blood pressure readings confirmed using several readings, including measurements on a separate day, to diagnose HTN (A).

(c) For patients with diabetes and HTN, blood pressure targets should be individualized through a shared decision-making process that addresses CV risk, potential adverse effects of antihypertensive medications, and patient preferences. (B)
(d) People with diabetes and HTN qualify for antihypertensive drug therapy when their blood pressure is persistently elevated (130/80 mm Hg or greater). The on-treatment target blood pressure goal is less than 130/80 mm Hg if it can safely be attained (B).
(e) In pregnant patients with diabetes and preexisting HTN who are treated with antihypertensive therapy, a blood pressure target of 110–135/85 mm Hg is suggested to reduce the risk of accelerated maternal HTN (A).
(f) For patients with a blood pressure greater than 120/80 mm Hg, use lifestyle intervention consisting of weight loss if overweight or obese; a Dietary Approaches to Stop Hypertension (DASH)-style eating pattern, including reducing sodium and increasing potassium intake; moderation in alcohol intake; and increased physical activity. (A)
(g) Patients with a confirmed office-based blood pressure of 130/80 mm Hg or greater qualify for initiation and titration of pharmacologic therapy to achieve the recommended blood pressure goal of less than 130/80 mm Hg (A).
(h) Patients with a confirmed office-based blood pressure of 160/100 mm Hg or greater should, in addition to lifestyle therapy, have prompt initiation and timely titration of two drugs or a single-pill combination of drugs shown to reduce CV events in patients with diabetes (A).
(i) Treatment for HTN should include drug classes shown to reduce CV events in patients with diabetes: ACEIs or ARBs are recommended first-line therapy for hypertension in people with diabetes and coronary disease (A).
(j) Multidrug therapy is usually required to achieve blood pressure targets. However, combinations of ACEIs and ARBs and combinations of ACEIs or ARBs with direct renin inhibitors should not be used (A).
(k) An ACEI or ARB, at the maximum tolerated dose indicated for blood pressure treatment, is the recommended first-line treatment for HTN in patients with diabetes and a urinary albumin/creatinine ratio of greater than or equal to 300 mg/g creatinine (A) or 30–299 mg/g creatinine (B). If one class is not tolerated, the other should be substituted (B).
(l) For patients treated with an ACEI, ARB, or diuretic, SCr/eGFR and serum potassium concentrations should be monitored at least annually (B).
(m) Patients with HTN who are not meeting blood pressure targets on three classes of antihypertensive medications (including a diuretic) should be considered for aldosterone antagonist therapy (B).

4. CKD (GFR less than 60 mL/minute/1.73 $m^2$ or the presence of albuminuria)
   a. 2017 ACC/AHA HTN guidelines
      i. Adults with HTN and CKD should be treated to a blood pressure goal of less than 130/80 mm Hg (I, SBP: B-R, DBP: C-EO).
      ii. In adults with HTN and CKD (stage 3 or higher or stage 1 or 2 with albuminuria [300 mg/day or greater, or 300 mg/g or greater albumin/creatinine ratio or the equivalent in the first morning void]), treatment with an ACEI reasonable to slow kidney disease progression (IIa, B-R) (Figure 4).
      iii. In adults with HTN and CKD (stage 3 or higher or stage 1 or 2 with albuminuria [300 mg/day or greater, or 300 mg/g or greater albumin/creatinine ratio or the equivalent in the first morning void]), treatment with an ARB may be reasonable if an ACEI is not tolerated (IIb, C-EO).
      iv. In patients without albuminuria (greater than/equal to 300 mg/d or 300 mg/g creatinine), usual first-line medications can be used.

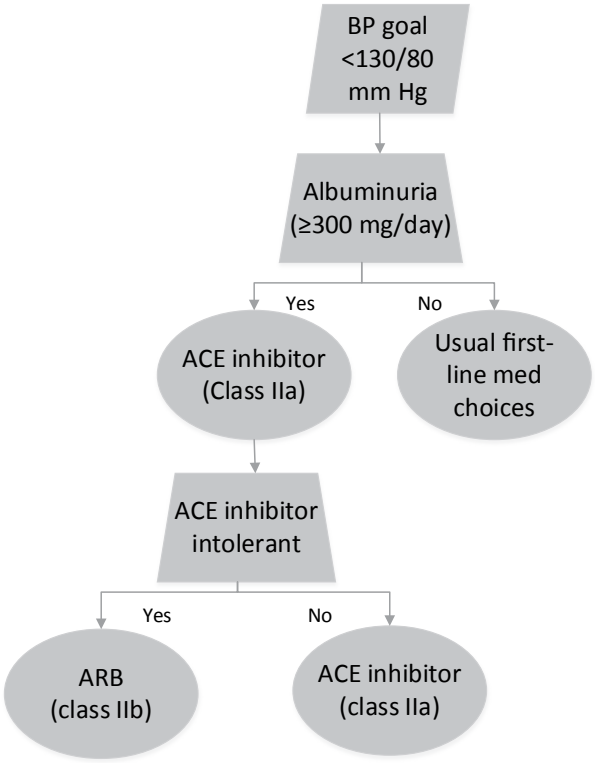


**Figure 4.** Hypertension treatment for patients with hypertension and chronic kidney disease.

b. KDIGO guidelines
    i. Suggest that adults with CKD and high blood pressure be treated with a target SBP of less than 120 mm Hg, when tolerated, using standardized office blood pressure management (weak recommendation), but individualization is key because potential benefits and harms may vary with CKD stage, presence of diabetes, individuals with SBP 120–129 mm Hg, patients with very low baseline DBP (e.g., <50 mm Hg), particularly in the presence of coronary artery disease, and in the very old (e.g., >85 years) or very frail.
    ii. ACEIs/ARBs preferentially suggested for people with CKD and high blood pressure, with variable levels of evidence depending on eGFR and albuminuria level (particularly strong evidence for those with heavy albuminuria)
        (a) ACEIs or ARBs should be administered at maximally recommended doses to achieve the benefits described because the proven benefits were achieved in trials using these doses.
        (b) Mineralocorticoid receptor antagonists are effective for refractory hypertension but may cause decline in kidney function or hyperkalemia, particularly among those with low eGFR (consider K binders).

c. A limited increase in SCr of as much as 30% above baseline is acceptable with ACEIs and ARBs.

5. Kidney transplantation
    a. After kidney transplantation, it is reasonable to treat patients with HTN to a blood pressure goal of less than 130/80 mm Hg (IIa, SBP: NR, DBP: C-EO).
    b. After kidney transplantation, it is reasonable to treat patients with HTN with a CCB on the basis of improved GFR and kidney survival (IIa, B-R).

6. Cerebrovascular disease
    a. Acute intracerebral hemorrhage (ICH)
        i. In adults with ICH who present with an SBP of greater than 220 mm Hg, it is reasonable to use continuous intravenous drug infusion and close blood pressure monitoring to lower SBP (IIa, C-EO).
        ii. In patients with spontaneous ICH of mild to moderate severity presenting with SBP of 150–220 mm Hg, acute lowering of SBP to a target of 140 mm Hg with the goal of maintaining it in the range of 130–150 mm Hg is safe and may be reasonable for improving functional outcomes (IIb, B-R).
        iii. In patients with spontaneous ICH (mild to moderate severity) presenting with SBP greater than 150 mm Hg, acute lowering of SBP to less than 130 mm Hg is potentially harmful (III [harm], B-R).
    b. Acute ischemic stroke (less than 72 hours)
        i. Thrombolysis
            (a) Adults with acute ischemic stroke and elevated blood pressure who are eligible for treatment with intravenous tissue plasminogen activator should have their blood pressure slowly lowered to less than 185/110 mm Hg before thrombolytic therapy is initiated (I, B-NR).
            (b) In adults with an acute ischemic stroke, blood pressure should be less than 185/110 mm Hg before administration of intravenous tissue plasminogen activator and should be maintained below 180/105 mm Hg for at least the first 24 hours after initiating drug therapy (I, B-NR).
            (c) Initiating or reinitiating antihypertensive therapy during hospitalization in patients with a blood pressure greater than 140/90 mm Hg who are neurologically stable is safe and reasonable to improve long-term blood pressure control, unless contraindicated (IIa, B-NR).
        ii. No thrombolysis
            (a) In patients with a blood pressure of 220/120 mm Hg or greater who did not receive intravenous alteplase or endovascular treatment and have no comorbid conditions requiring acute antihypertensive treatment, the benefit of initiating or reinitiating treatment of HTN within the first 48–72 hours is uncertain. It may be reasonable to lower blood pressure by 15% during the first 24 hours after onset of stroke (IIb, C-EO).
            (b) In patients with a blood pressure less than 220/120 mm Hg who did not receive intravenous thrombolysis or endovascular treatment and do not have a comorbid condition requiring acute antihypertensive treatment, initiating or reinitiating treatment of HTN within the first 48–72 hours after an acute ischemic stroke is not effective to prevent death or dependency (III [no benefit], A).
    c. Secondary stroke prevention
        i. In patients who experience a stroke or TIA and HTN not currently restricting dietary sodium, it is reasonable to recommend reducing sodium intake by at least 1 g/day (2.5 g/day of sodium) to reduce the risk of CVD events, including stroke (IIa, B-R).
        ii. In patients with HTN who experience a stroke or TIA, treatment with a thiazide diuretic, ACEI, or ARB is useful for lowering blood pressure and reducing recurrent stroke risk (I, A).
        iii. In patients with HTN who experience a stroke or TIA, an office blood pressure goal of less than 130/80 mm Hg is recommended for most patients to reduce the risk of recurrent stroke and vascular events (1, B-R).
        iv. Individualized drug regimens that consider patient comorbidities, agent pharmacologic class, and patient preference are recommended to maximize drug efficacy (1, B-NR).
        v. In patients without a history of HTN who experience a stroke or TIA and have an average blood pressure of 130/80 mm Hg or greater, antihypertensive medication treatment can beneficial to reduce the risk of recurrent stroke, ICH, and other vascular events (2a, B-R).

7. Peripheral arterial disease: Adults with HTN and PAD should be treated similarly to patients with HTN without peripheral arterial disease (I, B-R).
8. Atrial fibrillation, valvular heart disease, and aortic disease
    a. For patients with atrial fibrillation, treatment of HTN with an ARB can help prevent the recurrence of atrial fibrillation (IIa, B-R).
    b. In adults with asymptomatic aortic stenosis, HTN should be treated with pharmacotherapy, starting at a low dose and gradually titrating as needed (I, B-R).
    c. In patients with chronic aortic insufficiency, treating systolic HTN with agents that do not slow the heart rate (i.e., avoid β-blockers) is reasonable (IIa, C-EO).
    d. In patients with thoracic aortic disease, β-blockers are the preferred antihypertensive agents (I, C-EO).

O. Special Patient Groups
1. Racial and ethnic treatment differences
    a. In Black adults with HTN but without HF or CKD, including those with diabetes mellitus, initial antihypertensive treatment should include a thiazide-type diuretic or CCB (I, B-R).
    b. Two or more antihypertensive medications are recommended to achieve a blood pressure target of less than 130/80 mm Hg in most adults with HTN, especially in Black adults with HTN (I, C-LD).
    c. Integration of health promotion by trusted individuals within the Black community and specialty pharmacists as was demonstrated in the BARBER Trials (Am Heart J 2009;157:30-6; N Engl J Med 2018;378:1291-301) can improve blood pressure control.
2. Treatment differences with respect to male and female sex
    a. In the SPRINT trial, there was no evidence of an interaction between sex and treatment effect.
    b. CVD outcomes did not differ significantly between men and women in a large meta-analysis (31 RCTs with about 100,000 men and 90,000 women with HTN).
    c. Adverse effects
        i. Antihypertensive adverse effects were noted twice as often in women as in men in the TOMHS study.
        ii. ACEI-induced cough and CCB edema were more common in women than in men.
        iii. Women were more likely to have hypokalemia and hyponatremia and less likely to have gout with diuretics.
    d. Pregnancy
        i. Women with HTN who become pregnant, or are planning to become pregnant, should be transitioned to methyldopa, nifedipine, and/or labetalol during pregnancy (I, C-LD).
        ii. Women with HTN who become pregnant <u>should not</u> be treated with ACEIs, ARBs, or direct renin inhibitors (III [harm], C-LD).
3. Older individuals
    a. Treatment of HTN with a SBP treatment goal of less than 130 mm Hg is recommended for non-institutionalized ambulatory community-dwelling adults (65 and older) with an average SBP of 130 mm Hg or greater (I, A).
    b. For older adults (65 and older) with HTN and a high burden of comorbidity and limited life expectancy, clinical judgment, patient preference, and a team-based approach to assess risk-benefit is reasonable for decisions regarding intensity of blood pressure lowering and choice of antihypertensives (IIa, C-EO).
    c. In adults with HTN, blood pressure lowering is reasonable to prevent cognitive decline and dementia (IIa, B-R).
4. Surgical procedures
    a. In patients with HTN undergoing major surgery who have been taking β-blockers chronically, β-blockers should be continued (I, B-R).

b. Patients with intraoperative HTN should be treated with intravenous medications until oral medications can be resumed (I, C-EO).
c. In patients with HTN undergoing planned elective major surgery, it is reasonable to continue medical therapy for HTN until surgery (IIa, C-EO).
d. In patients with HTN undergoing major surgery, discontinuation of ACEIs or ARBs perioperatively may be considered (IIb, B-NR).
e. In patients with planned elective major surgery and an SBP of 180 mm Hg or greater or DBP of 110 mm Hg or greater, deferring surgery may be considered (IIb, C-LD).
f. For patients undergoing surgery, abrupt preoperative discontinuation of β-blockers or clonidine can be harmful (III [harm], B-NR).
g. β-Blockers should not be initiated on the day of surgery in β-blocker–naive patients (III [harm], B-NR).

5. Hypertensive crises, emergencies, and urgencies (see Cardiovascular Emergencies chapter)

**Patient Case**

7. A 58-year-old Hispanic woman with CAD and type 2 diabetes presents to the clinic with her HBPM readings. She is frustrated because her blood pressure is still not at goal. She takes chlorthalidone 25 mg/day, lisinopril 40 mg/day, amlodipine 10 mg/day, and metoprolol tartrate 25 mg twice daily. She tried terazosin but had to discontinue it because of dizziness. Her blood pressure today is 148/79 mm Hg with repeat 145/81 mm Hg and heart rate is 58 beats/minute. Laboratory test results are as follows: SCr 1.2 mg/dL (CrCl [adjusted body weight] 51.8 mL/minute/1.73 $m^2$), K 3.6 mEq/L, and Na 142 mEq/L. Her BMI is 27.5 $kg/m^2$ and ejection fraction is 45%. Which regimen change, if any, would be best for this patient?

A. Initiate spironolactone 25 mg/day.
B. Discontinue chlorthalidone and start spironolactone 25 mg/day.
C. Increase metoprolol to 50 mg twice daily.
D. No change in her current regimen is warranted.

P. Resistant HTN

1. Evaluation of resistant HTN
   a. Confirm treatment resistance:
      i. Office SBP/DBP of 130/80 mm Hg or greater and patient taking three or more antihypertensive medications, including a long-acting CCB, an ACE inhibitor or ARB, and a diuretic, at maximal or maximally tolerated doses. OR
      ii. Office SBP/DBP less than 130/80 mm Hg but patient requires four or more antihypertensive medications
   b. Exclude pseudoresistance.
      i. Ensure accurate office blood pressure measurements.
      ii. Assess for nonadherence/confirm adherence to prescribed regimen.
      iii. Obtain home blood pressure readings or ABPM readings to exclude white-coat effect.
   c. Screen for secondary causes of HTN and treat, if possible (see Table 1).
      i. Primary aldosteronism
      ii. Renal parenchymal disease
      iii. Renal artery stenosis
      iv. Pheochromocytoma
      v. Obstructive sleep apnea
      vi. Cushing syndrome

vii. Coarctation of the aorta
viii. Other endocrine disorders

2. Management of resistant HTN: Progress to next step if blood pressure remains uncontrolled
   a. Step 1
      i. Exclude causes of HTN: secondary causes, white-coat effect, medication nonadherence
      ii. Maximize lifestyle interventions: low-sodium diet (<2400 mg/day), at least 6 hours/night of uninterrupted sleep, weight loss, exercise)
      iii. Optimize three-drug regimen of CCB, RAS inhibitor, and diuretic (appropriately dosed for renal function) at maximally tolerated doses.
   b. Step 2: Substitute optimally dosed thiazide diuretic (chlorthalidone or indapamide) for previous diuretic
   c. Step 3: Add mineralocorticoid (aldosterone) receptor antagonist: spironolactone or eplerenone
   d. Step 4
      i. If heart rate ≥70 beats/min, add β-blocker
      ii. If β-blocker is contraindicated, add central α1-agonist (clonidine or guanfacine)
   e. Step 5: Add hydralazine and titrate to maximal dose (use concomitantly with a β-blocker and diuretic)
   f. Step 6: Substitute minoxidil for hydralazine and titrate
   g. Step 7: Refer to HTN specialist or ongoing clinical trial

Q. Chronotherapy in HTN Management
   1. It has been unclear whether there is CV benefit with taking antihypertensive medications at nighttime compared with in the morning.
      a. Two prospective trials (the MAPEC and the Hygia Chronotherapy trials) found a decrease in CV events when antihypertensive medications were taken at nighttime compared with in the morning.
      b. Conversely, the HARMONY (Hellenic-Anglo Research into Morning or Night Antihypertensive Drug Delivery) trial found no difference in 24-hour blood pressures on the basis of timing of medications.
      c. In addition, in the setting of some limitations, the publishing journal of the Hygia Chronotherapy Trial printed an Expression for Concern and recommended interpreting results and conclusions with caution.
   2. CV outcomes in adults with HTN with evening compared with morning dosing of usual antihypertensives in the UK (TIME study): a prospective, randomised, open-label, blinded-end point clinical trial – 2022
      a. Enrolled 21,204 patients diagnosed with HTN and taking at least one antihypertensive medication
      b. Participants were randomly assigned to take their blood pressure medications in the evening (n=10,503) or morning (n=10,601).
      c. Primary outcome was a composite of vascular death or hospitalization for nonfatal MI or nonfatal stroke.
      d. No difference was found between the evening and morning groups (3.4% vs. 3.7%; HR 0.95; 95% CI, 0.83–1.10).
   3. Currently, because findings from the Hygia Chronotherapy Trial were not replicated in the TIME trial, timing of when patients take blood pressure medications is likely best when it is most convenient for them.

R. Improving HTN Control
   1. Adherence
      a. In adults with HTN, dosing of antihypertensives once daily rather than several times daily improves adherence (I, B-R).
      b. Use of combination pills rather than free individual components can improve adherence to antihypertensive therapy (IIa, B-NR).

2. Effective behavioral and motivational strategies to achieve a healthy lifestyle (i.e., tobacco cessation, weight loss, moderation in alcohol intake, increased physical activity, reduced Na intake, and eating a healthy diet) are recommended for adults with HTN (I, C-EO).
3. Team-based and technology-assisted care
    a. A team-based care approach (including pharmacists) is recommended for adults with HTN (I, A).
    b. Use of the electronic health record (EHR) and registries helps identify patients with undiagnosed or undertreated HTN (I, B-R).
    c. Use of the EHR and registries helps guide quality improvement efforts designed to improve HTN control (I, B-R).
    d. Telehealth strategies can be useful adjuncts to interventions shown to reduce blood pressure for adults with HTN (IIa, A).
4. Quality of care
    a. Using performance measures, in combination with other quality improvement strategies, at patient-, provider-, and system-based levels is reasonable to facilitate optimal HTN control (IIa, B-NR).
    b. Using quality improvement strategies at the health system, provider, and patient levels to improve identification and control of HTN can be effective (IIa, B-R).
    c. Financial incentives paid to providers can help achieve improvements in treatment and management of patient populations with HTN (IIa, B-R).
    d. Health system financing strategies (e.g., insurance coverage and copayment benefit design) can help facilitate improved medication adherence and blood pressure control in patients with HTN (IIa, B-NR).
5. Plan of care: Every adult with HTN should have a clear, detailed, and current evidence-based plan of care that ensures the achievement of treatment and self-management goals, encourages effective management of comorbid conditions, prompts timely follow-up with the health care team, and adheres to CVD GDMT (I, C-EO).
6. Transitions of care
    a. HTN is estimated to affect 75% of all hospitalized patients.
    b. Evidence suggests lack of communication to patients when medication therapy is changed from home to hospital or hospital to home.
    c. Optimal transitioning from hospital to home is especially relevant for HTN, despite the lack of published research.
    d. Pharmacists can play a major role in the four factors of optimal transition:
        i. Presence of knowledgeable hospital clinicians
        ii. Antihypertensive medication reconciliation at discharge
        iii. Patient information transfer between clinicians
        iv. Patient and family education

**Patient Case**

8. A 63-year-old White man was admitted to the hospital last week with a STEMI and discharged after stent placement. He now takes prasugrel 10 mg/day, aspirin 81 mg/day, enalapril 2.5 mg/day, and metoprolol succinate 12.5 mg/day. His blood pressure is 105/70 mm Hg with similar repeat, heart rate is 65 beats/minute, and ejection fraction is 50%. He has no OH symptoms but asks whether his blood pressure is too low. Which is the best response to the patient's inquiry?

    A. His blood pressure is too low; discontinue metoprolol succinate.

    B. His blood pressure is too low; discontinue enalapril.

    C. Reassure him that his blood pressure should be this low; no changes are needed.

    D. Reassure him that there is no concern for his blood pressure; no changes are needed.

## II. HYPOTENSION

A. Definition
   1. No specified blood pressure reading is considered too low in asymptomatic patients not taking antihypertensive therapy. As long as the patient has no symptoms (e.g., dizziness, fatigue, syncope), there is no concern.
   2. Overtreatment with antihypertensive therapy can cause hypotension.
      a. There is no evidence of benefit from an SBP less than 110 mm Hg, and the risk of adverse effects increases with unnecessary drugs.
      b. If blood pressure is this low, consider tapering therapy unless therapy has benefits beyond blood pressure lowering, such as medications used to treat reduced left ventricular function.

B. Orthostatic Hypotension: Sustained reduction of at least 20 mm Hg in SBP or of 10 mm Hg in DBP within 3 minutes of standing or head-up tilt testing
   1. Prevalence and risk factors
      a. Among patients 65 and older, the prevalence is about 16%.
         i. Increases as patients age
         ii. In older adults, OH has been identified as an independent predictor of mortality.
      b. Risk factors for OH
         i. Age
         ii. Comorbid conditions
         iii. Number of drugs used (particularly antihypertensive agents)
         iv. Major CV events have been associated with OH, and OH is a risk factor for syncope and falls.
   2. Healthy response
      a. About 700 mL of venous blood goes to the peripheral circulation on standing, which causes a transient decrease in cardiac output and blood pressure.
      b. The baroreflex-mediated compensatory sympathetic system activates with a decrease in parasympathetic activation, which increases heart rate and vascular resistance to restore cardiac output and blood pressure.
   3. Response with concomitant conditions
      a. When the autonomic system fails to trigger these compensatory mechanisms, OH can occur.
      b. Peripheral damage of the autonomic nerves (e.g., by diabetes or Parkinson disease) commonly contributes to OH.
      c. Autoimmune and neurodegenerative autonomic dysfunction can cause more pronounced OH, but this rarely occurs.
      d. Older adults are especially prone to OH because their compensatory mechanisms diminish over time. Baroreflex sensitivity, heart rate response, and vasoconstriction become blunted as patients age.
   4. Symptoms of OH
      a. Dizziness, fatigue, dim or blurred vision, pain in the back of the neck/shoulders
      b. Occur within a few seconds of standing
      c. These symptoms are not present in the supine position and should be relieved after sitting or lying down.
      d. Symptoms are usually worse on awakening because of nighttime pressure natriuresis, making morning orthostatic measurements sensitive to detecting OH.
   5. Evaluation
      a. Measure blood pressure at both 1 minute and 3 minutes of standing after the patient has been supine for at least 5 minutes. This helps determine whether there is an immediate decrease in blood pressure, when patient falls are most likely to occur, and if there is delayed onset of blood pressure lowering.

b. Measure heart rate at each of these periods because there is a compensatory mechanism for the heart rate to increase with certain types of OH.
c. Diagnosis may require several measurements.

6. Goals of therapy: Decrease the patient's symptoms, improve functional status, and decrease the risk of falls and syncope (the goal is not to achieve a certain blood pressure target).
7. Treatment
   a. Nonpharmacologic therapy
      i. Eliminate or lower the dose of any offending agents (e.g., α-blockers).
      ii. Increase fluid and salt intake.
      iii. Avoid standing too quickly.
      iv. Initiate exercise.
      v. Use of abdominal binder or compressive waist-high stockings
      vi. Raise head of bed 6–9 inches.
   b. Pharmacologic therapy
      i. Fludrocortisone increases intravascular volume.
      ii. Adrenergic agent hypertensives (e.g., midodrine, pyridostigmine, pseudoephedrine, atomoxetine)
      iii. Fludrocortisone or midodrine can be used in patients who are not hypertensive. Midodrine can be used in combination with either fludrocortisone or pseudoephedrine if monotherapy is ineffective.
      iv. Droxidopa – Structural analog of norepinephrine. No study has shown a treatment effect beyond 2 weeks; hence, this agent's place in therapy is uncertain.
   c. Patients with OH and HTN
      i. 2.5 times higher risk of falls in older adult patients with OH and HTN than in patients with OH without HTN
      ii. Continue antihypertensive therapy in patients with OH and HTN because adequately controlling blood pressure does not increase the risk of OH.
      iii. Use caution to avoid volume depletion and rapid-dose titration of antihypertensive drugs.
      iv. Antihypertensive agents should be initiated at low doses and titrated slowly.
      v. ACEIs or ARBs may be beneficial in these patients because of improved blood pressure regulation and cerebral blood flow.

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## ANSWERS AND EXPLANATIONS TO PATIENT CASES

**1. Answer: C**

This patient is taking many medications and other substances that can either increase blood pressure or make blood pressure control difficult. The herbal supplements, NSAID, and decongestant should be discontinued because they are likely contributing to her elevated blood pressure. In addition, she is drinking more alcohol and coffee/soda (caffeine intake is greater than 300 mg/day) than recommended. Once these agents have been discontinued, her blood pressure may return to goal (Answer C is correct). Although improving her exercise is certainly recommended, it will not likely result in her achieving her blood pressure goal if the other agents are not discontinued (Answer A is incorrect). The patient may not need antihypertensive therapy once the agents that increase her blood pressure are stopped, making Answers B and D incorrect.

**2. Answer: A**

At least two blood pressure readings should be obtained to assess blood pressure accurately. A blood pressure measurement is likely inaccurate if the patient has not been seated quietly for at least 5 minutes (Answer A is correct). Therapy can be determined after accurate blood pressure readings have been obtained (Answers B and C are incorrect). This patient may have undiagnosed HTN (Answer D is incorrect).

**3. Answer: D**

The threshold for pharmacologic treatment in this patient is greater than 130/80 mm Hg because her ASCVD risk is greater than 10%. Answer D is correct because the patient's average blood pressure is 20/10 mm Hg or greater over her blood pressure goal, and the 2017 ACC/AHA HTN guidelines recommend initiating two different blood pressure–lowering medications. Because the patient's BMI is near goal, diet and exercise only will not get her blood pressure to goal (Answer A is incorrect). Although thiazide-type diuretics are a recommended first-line therapy, a single agent will not likely get her blood pressure to goal (Answer C is incorrect). β-Blockers are not a first-line therapy because she currently has no compelling indication for metoprolol (e.g., acute coronary syndrome, HF) (Answer B is incorrect).

**4. Answer: B**

An additional antihypertensive agent should be initiated because the patient's blood pressure is not at goal (less than 130/80 mm Hg). Amlodipine would provide blood pressure–lowering effects to help him reach his blood pressure goal (Answer B is correct). Lisinopril and hydrochlorothiazide should not be discontinued at this time because this would result in more elevated blood pressure readings (Answers A and D are incorrect). Verapamil would not be the best agent to start at this time because the patient's heart rate is ranging from 54 to 56 beats/minute. In addition, the patient does not have a concomitant condition (atrial fibrillation, stable angina) to make this a compelling medication to initiate (Answer C is incorrect).

**5. Answer: B**

Because this patient has New York Heart Association III HF*r*EF and an ejection fraction less than 40%, an aldosterone antagonist is recommended, making Answer B correct. The new blood pressure goal for patients with HF*r*EF is less than 130/80 mm Hg, making Answer A incorrect. Carvedilol is a more potent blood pressure–lowering β-blocker than metoprolol succinate, making Answer C incorrect. Guideline-directed therapy should be initiated before other antihypertensive drugs for patients with HF*r*EF, making Answer D incorrect.

**6. Answer: C**

Additional treatment is needed because the patient's blood pressure is above goal (goal is less than 130/80 mm Hg). Angiotensin receptor blockers are the best replacement medications for ACEIs in this patient because he has microalbuminuria (Answer C is correct). The patient has no comorbidity that would necessitate a β-blocker at this time (Answer D is incorrect). Although spironolactone and amlodipine are potent blood pressure–lowering drugs that he may eventually need, his microalbuminuria dictates that an ARB be used next (Answers A and B are incorrect).

**7. Answer: A**

This patient has resistant HTN, which is the inability to reach goal blood pressure with three optimally dosed antihypertensive medications from three different drug classes (including a diuretic) or when blood pressure control is achieved but requires four or more

medications. Spironolactone is beneficial for resistant HTN (Answer A is correct). Therapy change is needed because her blood pressure remains above goal (goal is less than 130/80 mm Hg) (Answer D is incorrect). Metoprolol should not be increased because of her heart rate (Answer C is incorrect). Discontinuing chlorthalidone could further increase her blood pressure (Answer B is incorrect).

**8. Answer: D**

The blood pressure goal for patients with CVD is less than 130/80 mm Hg, making Answer C incorrect. Although his blood pressure need not be less than 110 mm Hg, he is having no consequences such as adverse effects from over-treatment. The ACEIs are a class I recommendation for patients with ASCVD and diabetes or CKD unless contraindicated. β-Blocker therapy is also a class I recommendation for patients who have had an MI within the past 3 years, unless contraindicated, making Answers A and B incorrect. Answer D is correct because ACEIs and β-blockers have evidence of benefit beyond blood pressure lowering in patients with ASCVD, like this patient. Because he is asymptomatic, no change in therapy is needed.

## ANSWERS AND EXPLANATIONS TO SELF-ASSESSMENT QUESTIONS

**1. Answer: A**

This patient's blood pressure goal is less than 130/80 mm Hg. Once adherence to her current therapy is confirmed, chlorthalidone is the preferred thiazide diuretic and a first-line option, and is appropriate at this time (Answer A is correct). The HTN guidelines support the use of a long-acting calcium channel blocker and inhibitor of the renin-angiotensin-aldosterone system, plus a diuretic to control blood pressure. Increasing the dose of an ACEI or adding a β-blocker is not preferable at this time (Answers B and C are incorrect). Answer D is not correct as the patient's blood pressure goal is <130/80 mm Hg and a medication change is warranted.

**2. Answer: D**

Oral contraceptives, specifically estrogen, may increase blood pressure, and risk can increase with duration of use. An alternative contraceptive without estrogen would less likely contribute to the patient's HTN (Answer D is correct). Answers A and B are incorrect because her blood pressure requires better control, but weight loss is unlikely to help because her BMI is normal. Answer C is incorrect because hydrochlorothiazide is not more potent than chlorthalidone.

**3. Answer: B**

Angiotensin-converting enzyme inhibitor therapy is contraindicated in pregnancy, and discontinuing ramipril is the most important next step, making Answers A and C incorrect. Answer D is incorrect because this patient will require very good blood pressure control during her pregnancy, and her blood pressure has a history of becoming very elevated. Labetalol is a good choice because it is a preferred antihypertensive drug in pregnancy (Answer B is correct).

**4. Answer: B**

With this patient's history, his goal blood pressure is less than 130/80 mm Hg, and his NSTEMI is a compelling reason to have a β-blocker as part of his antihypertensive regimen. In general, African American patients do not respond as well as White patients when β-blockade is used as monotherapy; however, β-blockers should still be used in this population, especially when a compelling indication exists. Maintaining his hydrochlorothiazide regimen increases the likelihood of adequate blood pressure control because African Americans typically respond well to diuretic therapy, bearing in mind that most people require two or more drugs to attain adequate blood pressure control (Answer B). The regimens without a β-blocker are inappropriate because of the patient's medical history of an acute MI. Therapy consisting of losartan (Answers C and D) or diltiazem (Answer A) is inferior to β-blockade in this patient population.

**5. Answer: C**

For adults both with and without diabetes having a urine albumin excretion of 30 mg/24 hours (or equivalent) whose blood pressure is consistently higher than 130/80 mm Hg, the blood pressure target is less than 130/80 mm Hg. The presence of albuminuria is a compelling reason to include an ACEI in the absence of any contraindication. Lisinopril initiated at a low dose of 5 mg/day is appropriate, given this patient's mildly elevated blood pressure (Answer C). Although amlodipine (Answer B) could get the patient to her goal blood pressure, it has not shown renal-protective effects. Similarly, this patient has no compelling indication for a β-blocker; therefore, an atenolol-based regimen (Answer D) is less desirable than the ACEI regimen. Additional drug therapy is warranted because she has microalbuminuria (Answer A).

**6. Answer: B**

White-coat HTN occurs when office blood pressure readings are 130/80–160/100 mm Hg while daytime ABPM or HBPM readings are less than 130/80 mm Hg. In adults being treated for HTN with office blood pressure readings not at goal and HBPM readings suggestive of a significant white-coat HTN, confirmation by ABPM can be useful (Answer B is correct). Answer A is incorrect because masked HTN is when office blood pressure readings are at goal while HBPM readings are above goal. Answer C is incorrect because he has reliably been taking his blood pressure at home for the past year on a verified HBPM device. Answer D is incorrect because his office readings are above his blood pressure goal of less than 130/80 mm Hg; thus, his home readings need to be verified (action is required).

**7. Answer: D**

This patient no longer has a class I indication for a β-blocker because her NSTEMI was more than 3 years ago. Metoprolol is likely contributing to her OH and lack of appropriate chronotropic response to standing. Current ACC/AHA guidelines call for a goal SBP of less than 130 mm Hg for noninstitutionalized ambulatory community-dwelling adults older than 65; however, clinical judgment must be used to assess risk-benefit in decisions regarding intensity of blood pressure lowering and choice of antihypertensive agents. Lowering her metoprolol dose will likely improve her OH and is unlikely to profoundly increase her blood pressure (Answer D is correct). Answer B is incorrect because if all of her antihypertensive medications were discontinued, she could become hypertensive, and lisinopril is recommended because she has ASCVD and CKD. Answers A and C are incorrect because additional medications to treat OH should not be initiated until her antihypertensive regimen is optimized.

**8. Answer: C**

The diagnosis of resistant HTN is made when a patient takes three optimally dosed antihypertensive medications from three different drug classes (including a diuretic, if possible) or when blood pressure control is achieved but requires four or more medications. Appropriate treatment in this patient would be to add spironolactone to his regimen (Answer C is correct). Hydrochlorothiazide is not more potent than chlorthalidone and would not result in greater blood pressure lowering (Answer A is incorrect). Increasing the amlodipine beyond 10 mg daily exceeds typical dosing and is not appropriate (Answer B is incorrect). Losartan is no more potent than lisinopril; thus, making that change would not result in greater blood pressure lowering (Answer D is incorrect).

# Stable Atherosclerotic Disease

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**Learning Objectives**

1. Recommend patient-specific pharmacologic therapy for the management of stable ischemic heart disease (SIHD).
2. Differentiate between the antianginal options for a patient with refractory angina.
3. Develop an optimal pharmacologic regimen and monitoring plan for patients with peripheral arterial disease (PAD) considering individual patient symptomatology and characteristics.
4. Develop an evidence-based pharmacologic regimen for secondary prevention of ischemic stroke and transient ischemic attack (TIA).
5. Recommend risk factor modification strategies to prevent a recurrent event for patients with SIHD, PAD, and ischemic stroke/TIA.

**Abbreviations in This Chapter**

| | |
|---|---|
| ABI | Ankle-brachial index |
| ACEI | Angiotensin-converting enzyme inhibitor |
| ALI | Acute limb ischemia |
| ASCVD | Atherosclerotic cardiovascular disease |
| CAD | Coronary artery disease |
| CCB | Calcium channel blocker |
| CKD | Chronic kidney disease |
| CV | Cardiovascular |
| DAPT | Dual antiplatelet therapy |
| DES | Drug-eluting stent |
| DM | Diabetes mellitus |
| HFrEF | Heart failure with reduced ejection fraction |
| HLD | Hyperlipidemia |
| HTN | Hypertension |
| IC | Intermittent claudication |
| LVEF | Left ventricular ejection fraction |
| MALE | Major adverse limb events |
| MI | Myocardial infarction |
| PAD | Peripheral arterial disease |
| PCI | Percutaneous coronary intervention |
| SIHD | Stable ischemic heart disease |
| SPP | Skin perfusion pressure |
| TBI | Toe-brachial index |
| $TcPO_2$ | Transcutaneous oxygen pressure |
| TIA | Transient ischemic attack |

**Self-Assessment Questions**

*Answers and explanations to these questions can be found at the end of this chapter.*

1. A 62-year-old man with a medical history of hypertension (HTN), diabetes mellitus (DM), and chronic angina presents to his cardiologist for a routine follow-up. He received a drug-eluting coronary stent to the right coronary artery 10 months ago and states he is feeling well and has no complaints. Current medications include aspirin 81 mg daily, ticagrelor 90 mg twice daily, metoprolol 50 mg twice daily, atorvastatin 40 mg daily, metformin 500 mg twice daily, and nitroglycerin 0.4-mg tablets sublingually as needed for chest pain. Blood pressure is 150/88 mm Hg, heart rate is 62 beats/minute, and low-density lipoprotein cholesterol (LDL) is 125 mg/dL; other laboratory values are within normal limits. Which is the most appropriate therapy for this patient?
   A. Amlodopine 5 mg daily.
   B. Lisinopril 10 mg daily.
   C. Ranolazine 500 mg twice daily.
   D. Metoprolol 100 mg twice daily.

2. A 60-year-old man with stable ischemic heart disease (SIHD), HTN, hyperlipidemia (HLD), and mild depression presents with angina on exertion. His medications include aspirin 81 mg daily, nitroglycerin 0.4 mg sublingually as needed for chest pain, atorvastatin 20 mg daily, citalopram 40 mg daily, and chlorthalidone 25 mg daily. His blood pressure is 158/92 mm Hg and heart rate is 68 beats/minute. Laboratory values are within normal limits. Which would best treat his angina?
   A. Lisinopril 10 mg daily.
   B. Ranolazine 500 mg twice daily.
   C. Verapamil 120 mg daily
   D. Carvedilol 6.25 mg twice daily.

3. A 68-year-old woman presents to the cardiologist with complaints of chest pain on exertion. Her medical history is significant for coronary artery disease (CAD), HTN, and HLD. Her medications are metoprolol 50 mg twice daily, aspirin 81 mg daily, isosorbide mononitrate 60 mg daily, and atorvastatin 40 mg daily. Her vital signs include heart rate

60 beats/minute and blood pressure 100/58 mm Hg. Laboratory values are within normal limits. Which would best control her angina?

A. Give amlodopine 5 mg daily.
B. Increase metoprolol to 100 mg twice daily.
C. Give ranolazine 500 mg twice daily.
D. Give lisinopril 5 mg daily.

4. A 64-year-old man with a history of CAD, HTN, and HLD had a coronary artery stent placed 4 years ago. The patient now has chronic stable angina that occurs after walking 2–3 blocks. No lesions are detected on his coronary angiogram that are amenable to further intervention. His heart rate is 58–62 beats/minute and blood pressure is 142/78 mm Hg. Current medications include aspirin 81 mg daily, atorvastatin 40 mg at bedtime, metoprolol 50 mg twice daily, ramipril 10 mg daily, and tadalafil as needed. Which intervention will be of most benefit for his angina?

A. Add isosorbide mononitrate 60 mg daily.
B. Add diltiazem 180 mg daily.
C. Increase metoprolol to 100 mg twice daily.
D. Add amlodipine 5 mg daily.

5. A 72-year-old woman with a history of several TIAs, HTN, and gastroesophageal reflux disease (GERD) while taking lisinopril, hydrochlorothiazide, and omeprazole presents to her physician. She finds it difficult to pay for her medications each month. Which is the best antithrombotic regimen to prevent stroke in this patient?

A. Warfarin with target international normalized ratio (INR) 2.5.
B. Prasugrel 10 mg daily.
C. Clopidogrel 75 mg daily.
D. Aspirin 81 mg daily.

*Questions 6 and 7 pertain to the following case.*

A 68-year-old man with a medical history of HTN and dyslipidemia recently underwent a routine ankle-brachial index (ABI) assessment, which revealed 0.75 in the right leg and 0.62 in the left leg. He comes to the clinic today for a routine follow-up appointment. Relevant laboratory results include LDL 85 mg/dL, total cholesterol 171 mg/dL, high-density lipoprotein cholesterol 52 mg/dL, and triglycerides 168 mg/dL. His blood pressure is 125/69 mm Hg. His home medications include lisinopril 10 mg daily, metoprolol succinate 50 mg daily, and furosemide 40 mg daily. He recently lost his job and has no current health insurance; thus, he is concerned about the cost of medications.

6. According to the American Heart Association/American College of Cardiology (AHA/ACC) guidelines, which would best reduce this patient's risk of cardiovascular (CV) disease and cerebrovascular disease?

A. Aspirin 81 mg daily.
B. Aspirin 81 mg daily and clopidogrel 75 mg daily.
C. Vorapaxar 2.08 mg daily.
D. Warfarin titrated to an INR of 2.5.

7. Which lipid-lowering regimen would be most appropriate for this patient?

A. Atorvastatin 80 mg daily.
B. Pravastatin 40 mg daily.
C. Rosuvastatin 5 mg daily.
D. Simvastatin 80 mg daily.

8. A 72-year-old woman with documented peripheral arterial disease (PAD), DM, and HTN reports to the clinic for a follow-up. She has participated in a structured exercise program with improvement in her claudication symptoms; however, she continues to have symptoms, limiting her quality of life. Her current medications include aspirin 81 mg daily, ramipril 10 mg daily, and insulin glargine 38 units daily. Which would best minimize her claudication symptoms?

A. B-complex vitamin.
B. Cilostazol.
C. Pentoxifylline.
D. Warfarin.

## I. INTRODUCTION – ATHEROSCLEROTIC DISEASE

A. Chronic and progressive disease that can occur in multiple arterial vascular beds

B. Leading cause of mortality worldwide. Patients often have polyvascular disease (16%–28%), which incrementally increases the risk of mortality, myocardial infarction (MI), and stroke.

C. Atherosclerosis is the most common underlying pathogenesis in ischemic heart disease (IHD), cerebrovascular disease, resulting in non-cardioembolic ischemic stroke or transient ischemic attack (TIA), or peripheral arterial disease (PAD).

D. Risk factor modification is a major component of treatment for all three disease processes.
   1. Adequate control of hypertension (HTN), hyperlipidemia (HLD), and diabetes (DM); smoking cessation; eating a healthy diet; getting regular exercise; and getting annual influenza vaccinations are central to treatment.
   2. Recommendations for specific atherosclerotic disease states are based on major guidelines.

**Table 1.** Atherosclerotic Diseases

| | **Stable Ischemic Heart Disease** | **Peripheral Arterial Disease** | **Cerebrovascular Disease (stroke/TIA)** |
|---|---|---|---|
| Smoking cessation | **Class 1 rec:** Referral to special programs and pharmacotherapy is recommended | | |
| | Strong dose-response risk exists between number of cigarettes smoked and CV risk in SIHD | Tobacco is a strong RF for development and progression of PAD | Important independent RF for first ischemic stroke and associated with increased risk of silent brain infarctions |
| Diabetes[a] | Goal A1C < 7% is appropriate, and < 6.5% may be acceptable if it can safely be achieved. A1C < 8% may be appropriate for patients with extensive comorbid conditions or advanced macrovascular complications<br><br>Treatment is recommended according to current DM guidelines with emphasis on SGLT2 inhibitors and GLP-1 RA agents | | |
| | In patients with SIHD, type 1 DM is associated with a 10-fold increase in CV events in patients with SIHD; patients with type 2 DM have a 2–6 times higher risk of death from CV causes than patients without DM | DM increases risk of CLI, amputation, and death in patients with PAD. A1C goal < 6.5% with lower adjusted odds of major amputations compared with A1C > 6.5% and is especially important in patients with CLI | 60%–70% of patients with established cerebrovascular disease have pre- or overt DM<br><br>DM is associated with increased risk of first ischemic stroke |
| HTN[b] | **Class 1 rec:** Goal < 130/80 mm Hg | | |
| | Treatment with GDMT such as ACEIs, ARBs, and ß-blockers is first line. DHP CCPs, thiazides, MRAs, etc., are added if needed for additional BP control or anginal symptom control | Patients with PAD are often under-represented in HTN clinical trials. There is no evidence that any one class of antihypertensives is superior | Treatment with a thiazide, ACEI, or ARB is first line considering the presence of comorbidities and patient preference<br><br>If not previously treated for HTN and average office BP ≥ 130/80 mm Hg, medication can reduce risk of recurrent stroke |

**Table 1.** Atherosclerotic Diseases *(Cont'd)*

| | Stable Ischemic Heart Disease | Peripheral Arterial Disease | Cerebrovascular Disease (stroke/TIA) |
|---|---|---|---|
| Hyperlipidemia[c] | **Class 1 rec:** High-intensity statin to goal LDL < 70 mg/dL (<55 mg/dL if very high risk[d]) or decrease in LDL ≥ 50% of baseline in patients ≤ 75 yr<br>**Class 2a rec:** Addition of ezetimibe or PCSK9 inhibitor in very high-risk[d] patients taking maximally tolerated statins with LDL ≥ 70 mg/dL or non-HDL ≥ 100 mg/dL<br>**Class 1 rec:** Add ezetimibe to statin to attain LDL < 70 mg/dL for stroke prevention[e] | | |
| | Statins have been shown to reduce the risk of ASCVD in several major clinical trials of patients at high risk of adverse CV events, including SIHD | Statins improve CV outcomes and reduce adverse limb-related outcomes, including worsening claudication, new CLI or revascularization, and new amputation | Atorvastatin 80 mg if LDL > 100 mg/dL to reduce risk of recurrent stroke in those with no known CAD[e] |
| Annual influenza vaccination | **Class 1 rec** for patients with SIHD and PAD | | |
| | Associated with reduced risk of mortality in patients with IHD; NNT = 122 to prevent one death during one flu season | Observational studies show reduced CV event rates among patients with CVD, including PAD | Not discussed in guidelines, but evidence supports benefit of vaccine to reduce risk of stroke[f] (Lee KR 2017) |

[a]American Diabetes Association (ADA). 9. Pharmacologic approaches to glycemic treatment: standards of medical care in diabetes-2021. Diabetes Care 2021;44(suppl 1):S111-S124.

[b]2017 ACC/AHA multisociety guideline for the prevention, detection, evaluation, and management of high blood pressure in adults. J Am Coll Cardiol 2018;71:e127-e248.

[c]2018 AHA/ACC multisociety guideline on the management of blood cholesterol. Circulation 2019;139:e1082-e143; 2022 ACC expert consensus decision pathway on the role of nonstatin therapies for LDL-cholesterol lowering in the management of atherosclerotic cardiovascular disease risk: a report of the American College of Cardiology Solution Set Oversight Committee. J Am Coll Cardiol 2022;80:1366-418.

[d]Very high risk includes a history of several major ASCVD events or one major ASCVD event and several high-risk conditions.

[e]2021 guideline for the prevention of stroke in patients with stroke and transient ischemic attack: a guideline from the American Heart Association/American Stroke Association. Stroke 2021;52:e364-e467.

[f]Lee KR, Bae JH, Hwang IC, Kim KK, Suh HS, Ko KD. Effect of Influenza Vaccination on Risk of Stroke: A Systematic Review and Meta-Analysis. Neuroepidemiology. 2017;48(3-4):103-110.

ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; ASCVD = atherosclerotic cardiovascular disease; BP = blood pressure; CAD = coronary artery disease; CCB = calcium channel blocker; CLI = critical limb ischemia; CV = cardiovascular; CVD = CV disease; DHP = dihydropyridine; DM = diabetes; GDMT = guideline-directed medical therapy; GLP-1 RA = glucagon-like peptide-1 receptor agonist; HTN = hypertension; IHD = ischemic heart disease; MRA = mineralocorticoid receptor antagonist; NNT = number needed to treat; PAD = peripheral arterial disease; PCSK9 = proprotein convertase subtilisin/kexin type-9; rec = recommendation; RF = risk factor; SGLT2 = sodium-glucose cotransporter 2; SIHD = stable ischemic heart disease; TIA = transient ischemic attack.

Information from: 2012 ACCF/AHA multisociety guideline for the diagnosis and management of patients with stable ischemic heart disease. J Am Coll Cardiol 2012;60:e44-e164; 2016 AHA/ACC guideline on the management of patients with lower extremity peripheral artery disease: J Am Coll Cardiol 2017;69:1465-508; 2021 guideline for the prevention of stroke in patients with stroke and transient ischemic attack: a guideline from the American Heart Association/American Stroke Association. Stroke 2021;52:e364-e467.

This table adapted from: Rogers KC, Chilbert MR. Stable atherosclerotic disease. In: Jackevicius C, Patterson JH, eds. Cardiology Self-Assessment Program, 2021 Book 1. Atherosclerotic Heart Disease. American College of Clinical Pharmacy, 2021:57-90.

## II. CORONARY HEART DISEASE AND STABLE ISCHEMIC HEART DISEASE

A. Background

1. *Coronary heart disease* is a general term that encompasses the various phases that patients may cycle between over several decades. These phases include asymptomatic disease, stable ischemic heart disease (SIHD), unstable angina, non–ST-segment elevation myocardial infarction (MI), and ST-segment elevation MI.
2. Around 20.1 million Americans 20 years and older have coronary heart disease, which accounts for 42.1% of the deaths attributable to cardiovascular (CV) disease.
3. The prevalence of coronary heart disease is higher in males (8.3%) than in females (6.2%).

4. More than 11 million Americans 20 and older have chronic angina.
5. Chest pain is the second most common concern of adults presenting to the ED, with more than 6.5 million visits each year; women 65 and older account for most of the visits.
6. Approximately 33% of patients with a history of CAD self-report at least one anginal episode each month, with 23% experiencing symptoms daily or weekly. Of those reporting daily or weekly angina, 56% are taking at least two antianginals.
7. Chest pain is the most common symptom of coronary artery disease (CAD) in both women and men, and women are more likely to present with associated symptoms such as nausea, shortness of breath, and fatigue.

B. Normal Physiology
   1. Anatomy
      a. Large epicardial coronary arteries – Serve mainly as conductance vessels with little resistance to myocardial blood flow
      b. Intramyocardial arterioles – Dense network of blood vessels that supply the basal flow of oxygen and nutrients to the myocardium; capable of vasodilation and constriction in response to changes in tone such as exercise, changes in blood pressure, and emotional stress
      c. Normal coronary blood flow is controlled by the heart's requirement for oxygen.
   2. Determinants of myocardial oxygen supply and flow
      a. Arterial oxygen content – Normally fixed; determined by oxygen saturation and extraction and lumen size of coronary arteries
      b. Coronary blood flow – Determined by lumen cross-sectional area and arteriolar tone
      c. Control of tone is affected by protective surface of vascular endothelium and agents that affect its intact and functional status (e.g., nitric oxide, endothelin, shear stress, cigarettes, HTN, HLD).
      d. Diastole – Coronary artery blood flow occurs during diastole, resulting in oxygen and nutrients perfusing the cardiac tissue. This is normally equal between epicardial and endocardial layers.
      e. Coronary vasospasm – Acute spasm from Prinzmetal (variant) angina or cocaine-induced spasm reduces blood flow, especially in areas of atherosclerotic lesions
   3. Determinants of myocardial oxygen demand
      a. Heart rate – Tachycardia can increase myocardial oxygen demand.
      b. Contractility – Increases in force of contractility can increase myocardial oxygen demand.
      c. Myocardial wall tension – Directly related to the size of the ventricular cavity and blood pressure and indirectly on muscle mass. Increased pressure or enlargement of the left ventricle will increase myocardial oxygen demand.
   4. Ischemia or angina is related to an imbalance between myocardial oxygen supply and demand.

C. Pathophysiology
   1. Atherosclerotic cardiovascular disease (ASCVD) – Plaques obstruct blood flow in large epicardial vessels, decreasing lumen size and increasing resistance in the intramyocardial vessels.
   2. Autoregulation – When critically narrowed, the arterioles dilate in an effort to maintain oxygen supply and prevent ischemia at rest.
   3. Mismatch of oxygen supply and demand – During increases in myocardial oxygen demand (e.g., exercise, HTN, tachycardia) in the setting of atherosclerotic obstructions, the arterioles are incapable of further dilation, and the response is insufficient to provide oxygen to the myocardium; ischemia occurs and patients have angina.
   4. Atherosclerosis is a progressive disease, and as plaque encroaches into more of the lumen of the coronary arteries, it may become a more vulnerable plaque capable of rupture, causing an acute coronary syndrome.
      a. With rupture or erosion of a plaque, the endothelium is exposed to circulating blood.
      b. This activates both platelet aggregation and the coagulation cascade which can lead to an occlusive thrombus.

5. Risk factors for atherosclerotic disease include cigarette smoking, HLD, HTN, DM, obesity, physical inactivity, age, and premature family history.

D. Effects of Ischemia
   1. Mechanical – Failure of normal muscle contraction and relaxation may lead to transient left ventricular (LV) failure, angina, or necrosis.
   2. Biochemical – Ischemia leads to anaerobic energy use, which can lead to impaired cell membrane function and decreased force of contraction.
   3. Electrical – Ischemia can lead to repolarization abnormalities, ischemia, infarction, and lethal arrhythmias.

E. Clinical Presentation of Chronic Stable Angina or SIHD (Table 2)

**Table 2.** Clinical Presentation of SIHD

| Nature of Pain | Location of Pain | Associated Symptoms | Onset and Duration | Precipitating Factors | Relieving Factors |
|---|---|---|---|---|---|
| Pressure, heaviness, crushing, burning, tightness, aching | Substernal, above diaphragm, may radiate but less common in SIHD | Nausea, vomiting, SOB, diaphoresis, anxiety, dyspnea, lightheadedness<br><br>More likely in patients with DM, women, and older adults; often called "anginal equivalents" | 0.5–20 min, typically builds gradually over several minutes; sudden onset of severe chest pain suggests other etiologies such as aortic dissection | Exercise, postprandial, cold weather, sex, emotional stress | Rest, sublingual NTG |

DM = diabetes; NTG = nitroglycerin; SIHD = stable ischemic heart disease; SOB = shortness of breath.

F. Classification of Angina
   1. Cardiac-related angina (1) occurs with a characteristic quality, location, and duration; (2) is provoked by exertion or emotional stress; and (3) is relieved by nitroglycerin or rest.
   2. Possible cardiac-related angina meets only two of the criteria described in No. 1.
      a. Anginal equivalents – Some patients may have symptoms that are not typically characteristic of cardiac angina such as shortness of breath, anxiety, weakness, indigestion, and heartburn.
      b. Patients more likely to present in with associated symptoms include women, individuals with diabetes, and older adults.
   3. Non-cardiac chest pain meets none or only one of the characteristics of cardiac angina.
   4. Canadian Cardiovascular Society Classification System – Subjective classification of symptoms (Box 1)

**Box 1.** Grading of Angina Pectoris by the Canadian Cardiovascular Society Classification System

| |
|---|
| **Class I:** Ordinary activity (e.g., walking, climbing stairs) does not cause angina. Angina occurs with strenuous, rapid, or prolonged exertion |
| **Class II:** Slight limitation of ordinary activity. Angina occurs when walking or climbing stairs rapidly, walking uphill, or exertion that occurs after meals, or in the cold, or after emotional stress, or only during the few hours after awakening. Angina occurs when walking > 2 blocks or climbing more than one flight of stairs at a normal pace under normal conditions |
| **Class III:** Marked limitation of ordinary activity. Angina occurs when walking 1–2 blocks on the level and climbing one flight of stairs at a normal pace under normal conditions |
| **Class IV:** Inability to carry on any physical activity without discomfort. Anginal symptoms occur at rest |

Available at Canadian Cardiovascular Society (CCS). Canadian Cardiovascular Society Grading of Angina Pectoris. Available at https://ccs.ca/app/uploads/2020/12/Ang_Gui_1976.pdf.

G. Physical Examination – Best to evaluate during an acute episode of angina; often normal or nonspecific otherwise, but can help identify risk factors for ASCVD

H. Differential Diagnosis – Other diseases may precipitate ischemia either through increasing myocardial oxygen demand or decreasing oxygen supply and should be ruled out when evaluating patients with SIHD (Table 3).

**Table 3.** Comorbid Conditions Associated with Ischemia

| Increases Myocardial Oxygen Demand | Decreases Myocardial Oxygen Supply |
|---|---|
| Hypothermia | Anemia |
| Hyperthyroidism | Hypoxemia (i.e., pneumonia, asthma, COPD, OSA, pulmonary HTN) |
| Sympathomimetic toxicity (i.e., cocaine) | Sympathomimetic toxicity (i.e., cocaine) |
| Severe uncontrolled HTN | Sickle cell disease |
| Hypertrophic cardiomyopathy | Hypertrophic cardiomyopathy |
| Aortic stenosis | Aortic stenosis |
| Sustained tachycardia | Polycythemia |
| Anxiety | |

COPD = chronic obstructive pulmonary disease; HTN = hypertension; OSA = obstructive sleep apnea.

I. Diagnostic Procedures (Table 4)

**Table 4.** Diagnostic Procedures for Evaluating Patients with SIHD

| Test | Overview | Benefits | Limitations/Disadvantages |
|---|---|---|---|
| ECG | 12-lead electrical recording of the heart | Noninvasive, first-line evaluation for all patients presenting with chest pain; ischemic abnormalities increase probability of accurately diagnosing underlying heart disease | Usually normal in SIHD unless recorded during acute episode of chest pain but a negative ECG does not exclude the diagnosis of ischemia; serial ECGs should be performed when ACS is suspected |
| Exercise stress test | Monitors heart with ECG, BP, HR, and angina symptoms while patient exercises on a treadmill or stationary bicycle | Noninvasive, easy, and provides fast results, widely available; can determine extent of myocardial damage, cause of angina, and safe level of exercise in patient with established CAD | Some medications such as AV nodal blockers, digoxin, and caffeine can interfere with results; some patients with comorbidities cannot walk on treadmill (e.g., amputees, fraility, marked obesity, patients with PAD, severe HF). Less sensitive and specific in women |
| Pharmacologic stress imaging | For patients unable to safely walk on a treadmill; pharmacologic agents such as dobutamine, adenosine, and regadenoson are used to increase blood flow to normal arteries while decreasing flow at sites of stenosis. Uses ECHO or myocardial perfusion scintigraphy for imaging | Widely available functional test; can be used to define severity of ischemia and aid in risk stratification | Adverse drug events can occur with agents used in the test, including dobutamine, which may cause ventricular arrhythmias, adenosine/regadenoson may cause SOB or bronchospasm, chest pain, flushing; some medications such as AV nodal blockers, digoxin, and caffeine can interfere with results |

**Table 4.** Diagnostic Procedures for Evaluating Patients with SIHD *(Cont'd)*

| Test | Overview | Benefits | Limitations/Disadvantages |
|---|---|---|---|
| Nuclear stress imaging (also known as myocardial perfusion imaging), including rest/stress positron emission tomography (PET) or single-photon emission computed tomography (SPECT) | Similar to exercise stress test but uses radioactive substances (e.g., thallium, sestamibi) to image (with gamma camera) areas of heart muscle that are not getting enough oxygen at rest and/or during exercise on treadmill or induced by medications | Widely available functional test; allows for detection of perfusion abnormalities, measures of LV function; can determine extent of myocardial damage, cause of angina, and safe level of exercise in patient with established CAD; avoids use of contrast dye | Exposure to ionizing radiation; same adverse drug events as pharmacologic stress test can occur |
| Cardiac CTA | CT scan with dye allows 3-D images of heart, permitting identification of coronary artery anatomy | Noninvasive; can be used to evaluate graft patency; without dye can be used to measure calcium score | Exposure to ionizing radiation, contrast agents can induce nephropathy especially in patients with reduced renal function; some patients have contrast allergy; not as widely available, cost. Not recommended in patients with prior revascularization. Some patients may be unable to cooperate with breath-hold instructions. β-Blockers are often administered to achieve a target HR for imaging |
| Cardiac magnetic resonance (CMR) imaging | Evaluates major coronary vessels to detect and localize myocardial ischemia and infarction. Defines structural cardiac abnormalities and evaluates LV function and can determine myocardial viability | Noninvasive; can evaluate valves and pericardium and identify presence of other abnormalities such as tumors, myocardial edema, and microvascular obstruction to help differentiate between acute and chronic MI or other causes of chest pain such as myocarditis | Difficult for patients with claustrophobia, contraindicated in patients with metallic implants (e.g., pacemakers, defibrillators, infusion pumps, cochlear implants); gadolinium contrast agents are contraindicated in patients with severe renal dysfunction (GFR < 30 mL/min/1.73 $m^2$), not widely available, cost |
| Cardiac catheterization | Contrast dye is injected into catheter placed in femoral or radial arteries to visualize coronary artery anatomy | Highly accurate diagnosis of significant coronary lesions | Invasive, contrast-induced nephropathy, some patients have contrast allergy, exposure to radiation, microvascular disease not detectable, cost |

ACS = acute coronary syndrome; AV = atrioventricular; BP = blood pressure; CAD = coronary artery disease; CT = computed tomography; CTA = computed tomographic angiography; ECG = electrocardiogram; ECHO = echocardiogram; GFR = glomerular filtration rate; HF = heart failure; HR = heart rate; LV = left ventricular; PAD = peripheral arterial disease.

Montalescot G, Sechtem U, Achenbach S, et al. 2013 ESC guidelines on the management of stable coronary artery disease. Eur Heart J 2013; 34:2949-3003.

J. Goals of SIHD (see Figure 1)

1. Goals: Reduce risk of an ischemic event, reduce ischemia symptoms, increase physical function, slow progression of atherosclerosis, and improve quality of life.
2. Risk factor modification includes smoking cessation; control of HTN, HLD, and DM; exercise; weight management; and influenza vaccination.
   a. Blood pressure goal: Less than 130/80 mm Hg for those with known CV disease or ASCVD risk of 10% or greater. (class 1)

b. Specific agents to consider should be based on patient comorbidities and characteristics and may include angiotensin-converting enzyme inhibitors (ACEIs) and β-blockers as first line with other agents such as thiazide diuretics or calcium channel blockers (CCBs) or aldosterone antagonists as needed. (class 1)
c. In patients with type 2 DM and ASCVD, a sodium-glucose cotransporter-2 (SGLT2) inhibitor or glucagon-like peptide-1 (GLP-1) receptor agonist with proven CVD benefit should be part of the glucose-lowering regimen.

K. Pharmacologic Therapy for SIHD (see Figure 1)
1. Antiplatelets – Indicated in patients with coronary heart disease unless contraindicated (see Figure 2)
a. Aspirin dose: 75–162 mg/day (class 1)
b. Decreases CV events by about one-third
c. Clopidogrel 75 mg/day can be used if patients have an allergy to or cannot tolerate aspirin (class 1).
i. Clopidogrel, evaluated in the 1996 CAPRIE trial, significantly reduced the incidence of stroke, MI, or CV death compared with aspirin in patients with a history of MI, stroke, or symptomatic PAD.
ii. The absolute benefit of clopidogrel was small (5.32% vs. 5.83%; p=0.043; absolute risk reduction [ARR] = 0.5%; number needed to treat [NNT] = 200), and there was an increased risk of GI bleeds with clopidogrel but not more intracranial bleeds.
d. Dual antiplatelet therapy (DAPT) with aspirin and clopidogrel may be reasonable in patients with SIHD at high risk (class 2b).
i. The 2006 CHARISMA trial showed no benefit with DAPT in reducing the risk of MI, stroke, or death. However, in post hoc analyses, patients with documented prior MI, ischemic stroke, or peripheral arterial disease (PAD) had better outcomes.
ii. The 2015 PEGASUS-TIMI 54 trial evaluated a largely SIHD population with a history of MI in the prior 1–3 years and one other major CV risk factor, randomizing patients to ticagrelor 90 mg twice daily plus aspirin, ticagrelor 60 mg twice daily plus aspirin, or aspirin alone. Although the primary end point of MI, CV death, and stroke was reduced in both DAPT arms, TIMI (Thrombolysis In Myocardial Infarction) minor and major bleeding significantly increased, as did bleeding leading to discontinuation of the study drug. Intracranial hemorrhage and fatal bleeding rates were similar among groups.
iii. The 2019 THEMIS trial compared the combination of ticagrelor and aspirin with aspirin alone in 19,220 patients with SIHD and type 2 DM. Patients with a previous MI or stroke were not included in this trial. The primary efficacy outcome (composite of CV death, MI, or stroke) was lower in the DAPT group (7.7% vs. 8.5%; hazard ratio [HR] 0.90; 95% confidence interval [CI], 0.81–0.99; p=0.040). The lower incidence was mainly driven by a reduction in MI and stroke. However, the risk of TIMI major bleeding was higher in the DAPT group (2.2% vs. 1.0%; HR 2.32; 95% CI, 1.82–2.94; p<0.001). In addition, discontinuation rates were higher with ticagrelor than with placebo (34.5% vs. 25.4%), mainly because of a greater frequency of bleeding and dyspnea. The small absolute risk reduction in ischemic events must be weighed against the increase in bleeding in determining which patients should use this combination.
e. Prasugrel and ticagrelor are not currently indicated in SIHD as an alternative to aspirin, nor are they recommended post-percutaneous coronary intervention (PCI) in patients with SIHD at this time undergoing elective PCI. However, several trials evaluating a shorter duration of DAPT after PCI that included patients with SIHD did use a DAPT regimen consisting of ticagrelor. Risk-benefit should be weighed individually.
f. DAPT duration after PCI depends on several factors (see Figure 2).

g. Transitions of care: Patients undergoing revascularization for SIHD are often admitted for outpatient elective PCI. It is important that these patients be adequately educated on their DAPT regimen. Interventionalists often choose a DAPT regimen on the basis of several clinical factors, including ischemic risk (e.g., type of stent, length and diameter of stent, location of stent, prior PCI procedures, comorbidities), as well as the patient's bleeding risk (e.g., prior bleeds, need for oral anticoagulant [OAC], age, history of GI bleeding, renal function). There is typically no "one-size-fits-all" regimen. Therefore, when educating patients on DAPT, it is important to know the exact recommendation so that it can be communicated to the patient clearly in writing and verbally. Educating the patient on the importance of adherence, signs and symptoms of bleeding, avoidance of OTC medications (NSAIDs), excessive alcohol, etc., is key to reducing adverse events.

2. Anticoagulation
   a. In patients with IHD both coagulation and platelet pathways are amplified. Use of antithrombotic agents therefore seems rational and has been the subject of clinical evaluation.
   b. Meta-analysis by Anand and Yusuf in 2003 evaluated varying intensities of oral anticoagulant (OAC) with warfarin with or without aspirin.
      i. Low-intensity OAC plus ASA (INR <2.0) had no benefit vs. ASA alone and increased bleeding.
      ii. High-intensity OAC (INR 2.8-4.8) significantly decreased total mortality, MI, and stroke compared with ASA alone but also significantly increased major bleeding.
      iii. Moderate-intensity OAC (INR 2.0-3.0) nonsignificantly decreased recurrent ischemic events by 16% vs. ASA alone while statistically increasing major bleeding.
      iv. Moderate-high intensity OAC with ASA statistically reduced the combined endpoint of CV death/MI/stroke by 16% compared with ASA alone with no difference in major bleeding.
   c. In October 2018, the FDA approved the addition of the direct oral anticoagulant (DOAC), rivaroxaban 2.5 mg BID to aspirin 100 mg daily to reduce the risk of CV death, MI, and stroke in patients with CAD and PAD based on the COMPASS trial.
      i. Rivaroxaban 2.5 mg BID plus ASA 100 mg reduced the absolute rate of composite primary endpoint of CV death, MI, and stroke by 1.3% (4.1% vs. 5.4%; HR 0.76, 95% CI 0.66-0.86, p<0.001) at a cost of 1.2% (3.1% vs. 1.9%; HR 1.70, 95% CI 1.40-2.05, p<0.001) increase in major bleeding compared to ASA alone.
         (a) Patients considered at high risk of bleeding were excluded from COMPASS.
         (b) There was no difference in fatal or intracranial hemorrhage between groups.
         (c) Most of the increased bleeding events with rivaroxaban and aspirin were in the GI tract.
      ii. In the subgroup of patients with CAD, which was 91% of the total study population, the combination resulted in an ARR in the primary outcome of 2% compared with ASA alone (4% vs. 6%; HR 0.74, 95% CI 0.65-0.86, p<0.0001) while causing a 1.2% absolute risk increase in major bleeding (3.1% vs. 1.9%; HR 1.66, 95% CI 1.37-2.03, p<0.0001).
      iii. Small absolute risk reduction must be weighed against increase in bleeding. Who should be treated with combination therapy with rivaroxaban 2.5 mg BID plus ASA 100 mg daily needs to be further elucidated to identify those patients with highest ischemic risk and lowest bleeding risk.
      iv. In a separate subgroup analysis, which should be considered hypothesis-generating, COMPASS investigators risk-stratified the patients enrolled according to risk scores and identified patients at highest risk to include those with polyvascular disease, DM, heart failure, and renal insufficiency. Authors stated that the combination of rivaroxaban and aspirin reduced the incidence of serious vascular events by 25% (4.48% vs. 5.95%; HR 0.75; 95% CI, 0.66–0.85) at the cost of a nonsignificant 34% increase in severe bleeding (1.34; 95% CI, 0.96–1.88).

d. The addition of rivaroxaban or any DOAC agent to aspirin in stable ASCVD patients is not currently guideline recommended therapy in the United States, however the 2019 European Society of Cardiology guidelines recommend the addition of low-dose rivaroxaban (class 2a) to aspirin 100 mg daily in patients considered at high risk for ischemic events (e.g., post MI greater than 1 year or multivessel CAD) without an increased risk of bleeding (e.g., history of intracranial hemorrhage, recent gastrointestinal bleeding or anemia, extreme old age or frailty, estimated glomerular filtration rate less than 15 mL/min).

**Patient Case:**

1. A 65-year-old man with chronic stable angina undergoes PCI and receives a DES in his mid-circumflex artery. His medications before PCI include aspirin 81 mg daily, metoprolol 25 mg twice daily, and atorvastatin 20 mg daily. Laboratory values post-heart catheterization are within normal limits; blood pressure is 156/89 mm Hg and heart rate is 78 beats/minute. According to the 2021 ACC/AHA guidelines for coronary artery revascularization, which antiplatelet regimen is most appropriate for this patient?

   A. Aspirin 81 mg daily and ticagrelor 90 mg twice daily for 1 month.

   B. Aspirin 81 mg daily and clopidogrel 75 mg daily for 6 months.

   C. Aspirin 325 mg daily and ticagrelor 90 mg twice daily for 3 months.

   D. Aspirin 325 mg daily and clopidogrel 75 mg daily for 12 months.

3. β-Blockers
   a. Initial therapy for relief of symptoms in patients with SIHD (class 1)
   b. In patients with SIHD with normal LV function who have had an acute coronary syndrome or MI continued for at least 3 years and in patients with a left ventricular ejection fraction (LVEF) of 40% or less with heart failure or a prior MI (limited to bisoprolol, carvedilol, or metoprolol succinate) (class 1). In addition, β-blockers may be considered as chronic treatment for anginal symptoms in patients with coronary or other vascular disease, or for blood pressure control.
   c. Pharmacologic effects (see Table 5)
      i. Decreases heart rate, contractility, afterload, and blood pressure (decreases oxygen demand)
      ii. Indirectly improves perfusion in areas of ischemia by prolonging diastole (increases oxygen supply)
      iii. Decreases LV wall stress may improve subendocardial blood flow (increased oxygen supply).
      iv. β-Blockers also are associated with reduced ventricular arrhythmias and remodeling.
      v. Unopposed α stimulation, however, may lead to coronary vasoconstriction; thus, avoid or use cautiously in patients with proven vasospasm or with recent cocaine or methamphetamine use.
   d. Initiate at the lowest dose and titrate slowly to relief of angina symptoms.
   e. Dose the β-blocker to a targeted heart rate of 55–60 beats/minute.
   f. All β-blockers appear to be equally efficacious; individual choice should be based on cardiac selectivity, adverse effects, and comorbid conditions such as heart failure with reduced ejection fraction (HFrEF), for which the only indicated β-blockers include bisoprolol, carvedilol, and metoprolol succinate. (Table 5)

**Table 5.** Properties of β-Blockers

| Agent | Selectivity | Intrinsic Sympathomimetic Activity | Usual Dose | Adverse Effects |
|---|---|---|---|---|
| Acebutolol | β1 | Yes | 200–600 mg twice daily | Fatigue, exercise intolerance, lethargy, sleep disturbances, impotence, depression<br>CNS symptoms more common with higher degree of lipophilicity (e.g., propranolol) |
| Atenolol | β1 | No | 50–200 mg daily | |
| Betaxolol | β1 | No | 10–20 mg daily | |
| Bisoprolol | β1 | No | 5–20 mg daily | |
| Carvedilol | None | No | 25–50 mg twice daily | |
| Esmolol (intravenous) | β1 | No | 50–300 mcg/kg/min | |
| Labetalol | None | Yes | 200–600 mg twice daily | |
| Metoprolol | β1 | No | 50–200 mg twice daily | |
| Nadolol | None | No | 40–80 mg daily | |
| Pindolol | None | Yes | 2.5–7.5 mg three times daily | |
| Propranolol | None | No | 20–80 mg twice daily | |
| Timolol | None | No | 10–60 mg daily (divided once or twice daily) | |
| **Relative Contraindications:** Vasospastic angina, severe depression, uncontrolled DM, severe bronchospasm, severe PAD | | | | |
| **Absolute Contraindications:** Severe bradycardia, severe hypotension, sick sinus syndrome, high-degree AV block, severe unstable LV failure | | | | |

CNS = central nervous system; DM = diabetes mellitus

g. Avoid abrupt discontinuation because this could cause worsening of angina or MI.
h. No data analyses show decreased mortality with β-blockers in SIHD except in patients post-acute coronary syndrome or with HFrEF; however, β-blockers reduce the frequency and duration of angina.
i. Place in therapy: May be considered beyond 3 years for patients with CAD if needed for HTN or angina (class 2a). Only a class 1 indication for first 3 years post-acute coronary syndrome
j. Contraindications: Severe bradycardia (heart rate less than 50 beats/minute), high-degree atrioventricular block (without pacemaker), sick sinus syndrome (without pacemaker), unstable decompensated heart failure

4. CCBs
   a. Pharmacologic effects (see Table 6)
      i. Decrease coronary vascular resistance and increase coronary blood flow (increase oxygen supply)
      ii. Coronary vasodilation at sites of stenosis (increase oxygen supply)
      iii. Negative inotropy, to varying degrees; occurs with nifedipine much more than with amlodipine and felodipine (decrease oxygen demand); non-dihydropyridines with the most negative inotropic effects
      iv. Decrease heart rate (verapamil and diltiazem only) and decrease systemic vascular resistance and arterial blood pressure (decrease oxygen demand)
      v. Dihydropyridines may cause reflex tachycardia and an increase in myocardial oxygen demand.
      vi. Other adverse effects include headache, dizziness, palpitations, flushing, vasodilation, and edema.

**Table 6.** Pathophysiologic Effects on Myocardial Oxygen Supply and Demand

| | Oxygen Supply | Oxygen Demand | | | |
|---|---|---|---|---|---|
| | Coronary Blood Flow | Heart Rate | Arterial Pressure | Venous Return | Myocardial Contractility |
| **β-Blockers** | — | ↓ | ↓ | — | ↓ |
| **DHP CCB** | ↑ | ↑ | ↓ | — | ↓ |
| **Non-DHP CCB** | ↑ | ↓ | ↓ | — | ↓ |
| **Nitrates** | ↑ | ↑— | ↓ | ↓ | — |
| **Ranolazine** | — | — | — | — | — |

↑ = increased supply/demand; ↓ = decreased supply/demand; — = neutral, or no effect on supply/demand; CCB = calcium channel blocker; DHP = dihydropyridine.

b. Place in therapy
   i. Instead of β-blocker therapy when unacceptable adverse effects emerge, if β-blockers are contraindicated, or if treating vasospastic angina (class 1).
   ii. Short-acting dihydropyridines (nifedipine, nisoldipine) can exacerbate angina in patients with fixed lesions; they have been associated with increased CV events in patients with HTN and should be avoided (except in slow-release formulations).
   iii. Use CCBs with caution in patients with severe aortic valve stenosis.
   iv. In combination (dihydropyridines) with β-blockers when initial treatment with β-blockers is inefficient (class 1).
   v. Optional for treatment of angina or HTN in patients with CAD.

c. Contraindications for non-dihydropyridines: HFrEF, severe bradycardia, high-degree atrioventricular block (without pacemaker), sick sinus syndrome (without pacemaker)

d. Avoid dihydropyridines in HFrEF (amlodipine has neutral effects on mortality and is often used to manage HTN or SIHD).

5. Nitrates

a. Pharmacologic effects (see Table 6)
   i. Endothelium-dependent vasodilation; dilates epicardial arteries and collateral vessels (increase oxygen supply)
   ii. Decreases left ventricular volume because of decreased preload mediated by venodilation (decrease oxygen demand)
   iii. Can cause a reflex increase in sympathetic activity and can increase heart rate and contractility and therefore increased myocardial oxygen demand in some patients

b. Place in therapy
   i. As needed sublingual tablets or spray nitrate is necessary to relieve effort or rest angina. (class 1)
   ii. In addition, as needed nitrates can be used before exercise to avoid ischemic episodes.
   iii. Long-acting nitrates such as isosorbide mononitrate dosed once daily can be used as initial therapy if β-blockers are contraindicated or inefficient, or as a substitute for unacceptable adverse effects to β-blockers (class 1). However, nitrates are better add-on treatment because they produce a greater effect when combined with β-blockers or CCBs. In addition, combination therapy avoids the lack of coverage during the nitrate-free period.

iv. Nitrates are preferred in patients with vasospastic angina.
v. Adverse effects: Headache, hypotension, dizziness, flushing, reflex tachycardia, and methemoglobinemia
vi. Nitrate-free interval necessary to avoid tachyphylaxis
vii. No evidence that nitrates reduce mortality in SIHD

c. Contraindications: Hypertrophic obstructive cardiomyopathy, inferior wall or right ventricular MI, severe aortic valve stenosis, avanafil within 12 hours, sildenafil and vardenafil within 24 hours, tadalafil within 48 hours. All manufacturers of PDE-5 inhibitors list concomitant nitrates as a contraindication.

6. Combination therapy
   a. Non-dihydropyridine CCBs may be added to β-blocker therapy to achieve heart rate goals in patients with continued angina (however, caution is advised because the combination can cause heart block).
   b. β-Blockers added to dihydropyridines can attenuate the reflex tachycardia.
   c. A scheduled nitrate is useful in conjunction with a β-blocker or non-dihydropyridine CCB (blunting the reflex sympathetic tone with nitrate therapy).
7. Ranolazine
   a. Pharmacologic effects (see Table 6)
      i. Antianginal effects are not fully known. Inhibits the late phase of the inward sodium channel in ischemic myocytes during repolarization, reducing intracellular sodium concentrations. This reduction in sodium concentrations leads to reduced calcium influx, which decreases ventricular tension and myocardial oxygen consumption.
      ii. Increases "oxygen efficiency"
   b. Place in therapy
      i. Use in combination with β-blockers, CCBs, or nitrates when initial management with these drugs is unsuccessful (class 2a) or if blood pressure or heart rate is too low to add these drugs.
      ii. Initial dose: 500 mg twice daily, increasing to 1000 mg twice daily, depending on symptoms
      iii. Avoid in patients with moderate-severe hepatic impairment.
      iv. Discontinue if acute renal failure occurs in patients with severe renal impairment (creatinine clearance [CrCl] less than 30 mL); monitor renal function in patients with moderate to severe renal failure.
   c. Important points
      i. No significant effects on heart rate or blood pressure; thus, bradycardia and hypotension are not of concern
      ii. Adverse effects: Constipation, dizziness, nausea, headache, dyspnea, peripheral edema
      iii. Prolongs the QT interval in a dose-related manner but does not increase the risk of proarrhythmia. However, caution should be used with other QT-prolonging medications (e.g., azoles, macrolides, fluroquinolones, citalopram, escitalopram, other antiarrhythmic agents, chlorpromazine, droperidol, ondansetron, haloperidol, thioridazine, etc.) in patients with congenital long QT syndrome or acquired QT interval prolongation.
   d. Dosing considerations (Table 7)

**Table 7.** Ranolazine Considerations

| Clinical Factors | Do Not Exceed 500 mg BID of Ranolazine | Use with Caution | Ranolazine Contraindicated |
|---|---|---|---|
| Moderate 3A inhibitors (e.g., diltiazem, verapamil, erythromycin, fluconazole) | ✓ | | |
| Strong 3A inhibitors (e.g., ketoconazole, itraconazole, clarithromycin, nefazodone, nelfinavir, ritonavir, indinavir, saquinavir, etc.) | | | ✓ |
| Liver cirrhosis | | | ✓ |
| CYP 3A inducers (e.g., rifampin, rifabutin, phenytoin, phenobarbital, carbamazepine, St. John's wort) | | | ✓ |
| Moderate to severe renal impairment (CrCL <60mL/min) – monitor renal function periodically as acute renal failure has occurred in some patients with severe renal failure. | | ✓ | |
| Drugs that prolong QT interval (e.g., antiarrhythmics, erythromycin, ciprofloxacin, ketoconazole, thioridazine, ziprasidone) | | ✓ | |
| Patients with long QT syndrome or acquired QT interval prolongation | | ✓ | |

8. Additional therapies
    a. ACEIs
        i. Decrease CV events in patients with coronary heart disease (and no LV dysfunction) at high risk of subsequent CV events
        ii. Should be considered in patients who also have an LVEF of 40% or less, HTN, DM, and/or chronic kidney disease (CKD) (class 1)
        iii. Consider using in lower-risk patients with a mildly reduced or normal LVEF in whom CV risk factors are well controlled and revascularization has been performed.
    b. Angiotensin receptor blockers: Recommended as an alternative to ACEIs in patients who also have an LVEF of 40% or less, HTN, DM, and/or CKD or who cannot tolerate an ACEI (e.g., cough or angioedema) (class 1)
    c. Lipid-lowering therapy (see Chapter 2: Dyslipidemia)
        i. Counsel on healthy lifestyle habits.
        ii. Lipid panel, baseline hepatic transaminases; consider secondary causes of dyslipidemia, evaluate for conditions that may influence statin safety
        iii. Moderate or high-intensity statin therapy if without contraindications, drug-drug interactions, or history of statin intolerance (class 1)

**Patient Cases**

*Questions 2 and 3 pertain to the following case.*

A 65-year-old man with chronic stable angina received a DES in his mid-circumflex artery 2 years ago. His medical history includes HTN, HLD, SIHD, and DM. His medications include aspirin 81 mg daily, metoprolol 25 mg twice daily, metformin 1000 mg twice daily, and atorvastatin 20 mg daily. Blood pressure is 156/89 mm Hg and heart rate is 90 beats/minute. He states that he continues to have one or two episodes of angina per week when climbing more than two flights of stairs. Pertinent laboratory results are potassium (K) 4.2 mEq/L, serum creatinine (SCr) 1.0 mg/dL, low-density lipoprotein cholesterol (LDL) 105 mg/dL, and hemoglobin A1C (A1C) 7.0%; other laboratory values are within normal limits.

**Patient Cases *(Cont'd)***

2. Which is the most appropriate adjustment to this patient's medical regimen to improve his angina symptoms?
   A. Add amlodipine 5 mg daily.
   B. Add sublingual nitroglycerin as needed.
   C. Increase metoprolol to 50 mg twice daily.
   D. Increase atorvastatin to 40 mg daily.

3. In addition, which other pharmacologic modifications would be best to recommend at the same time to improve this patient's CV risk?
   A. Increase atorvastatin to 80 mg daily and add lisinopril 5 mg daily.
   B. Add ranolazine 500 mg twice daily and clopidogrel 75 mg daily.
   C. Discontinue metoprolol and add clopidogrel 75 mg daily.
   D. Add amlodipine 5 mg daily and ranolazine 500 mg twice daily.

4. A 64-year-old woman with SIHD, HTN, HLD, and CKD presents with complaints of angina after walking 1 block. Her medications include aspirin 81 mg daily, amlodipine 10 mg daily, metoprolol succinate 50 mg daily, and rosuvastatin 20 mg daily. Her heart rate is 58 beats/minute and blood pressure is 100/60 mm Hg. Pertinent laboratory values include K 4.1 mEq/L, SCr 1.4 mg/dL, and CrCl 52 mL/minute/1.73 $m^2$. Which is the most appropriate recommendation to treat this patient's angina?
   A. Increase metoprolol succinate to 100 mg daily.
   B. Change amlodipine to diltiazem.
   C. Add ranolazine 500 mg twice daily.
   D. Add lisinopril 5 mg daily.

9. Nonpharmacologic therapy
   a. Revascularization
      i. PCI: No clinical trials have shown a survival benefit of PCI over optimal medical therapy (OMT) in SIHD. PCI may be indicated in certain patients with SIHD with refractory angina despite OMT and significant stenoses (class 1). In addition, some patients who have a clinical indication for CABG but are poor surgical candidates may benefit from PCI over OMT alone. The risk-benefit should be weighed on an individual basis.
         – The ISCHEMIA trial adds to the knowledge gained from previous trials (COURAGE, BARI 2D) that evaluated an invasive strategy with PCI or CABG plus OMT and lifestyle changes compared with OMT and lifestyle changes alone in 5179 patients with stable CAD and moderate or severe myocardial ischemia on stress testing. Patients with a clear indication for CABG such as left main disease or ejection fraction less than 35% were excluded. The ISCHEMIA trial showed that invasive measures did not reduce the overall rate of the primary outcome of MI, CV death, hospitalization for unstable angina, heart failure, or resuscitation for cardiac arrest (HR 0.93; 95% CI, 0.80 to 1.08). In addition, no significant differences in secondary outcomes of CV or all cause mortality, MI, cardiac arrest, or stroke were noted between groups. Which patients should receive PCI or coronary artery bypass grafting remains a decision between the patient and the interventionalist and depends on the patient's clinical symptoms, quality of life, failure of OMT, and comorbidities, as well as the extent of obstructive disease. However, starting with medications and lifestyle modifications, including smoking cessation, should remain of utmost importance for most patients with SIHD.

ii. CABG may be indicated in certain patients with SIHD with refractory angina despite OMT and significant stenoses (class 1). This may include those who cannot be treated with PCI such those with a significant left main disease or lesions considered anatomically complex, those with ischemic cardiomyopathy, and those with triple vessel disease.
iii. In some patients with SIHD and multivessel disease, revascularization with either CABG or PCI may be reasonable to lower the risk of CV events, including death, spontaneous MI, and urgent revascularizations (class 2a).

b. Enhanced external counterpulsation – Uses inflatable cuffs on lower extremities to cause a synchronized increase of venous return during diastole. May be helpful in refractory angina (class 2b); treatment courses are up to 7 weeks or longer and are contraindicated in PAD, decompensated heart failure, and severe aortic regurgitation
c. Spinal cord stimulation – At T1 to T2 level in refractory angina; few data available but may be helpful in some patients (class 2b)
d. Transmyocardial revascularization – Percutaneous procedure or in conjunction with CABG in refractory, incapacitating angina with no other feasible options (class 2b). Involves drilling a series of laser channels from outside the heart into the heart chambers. Angiogenesis as well as destruction of nerve fibers are postulated to occur, which alleviates pain.

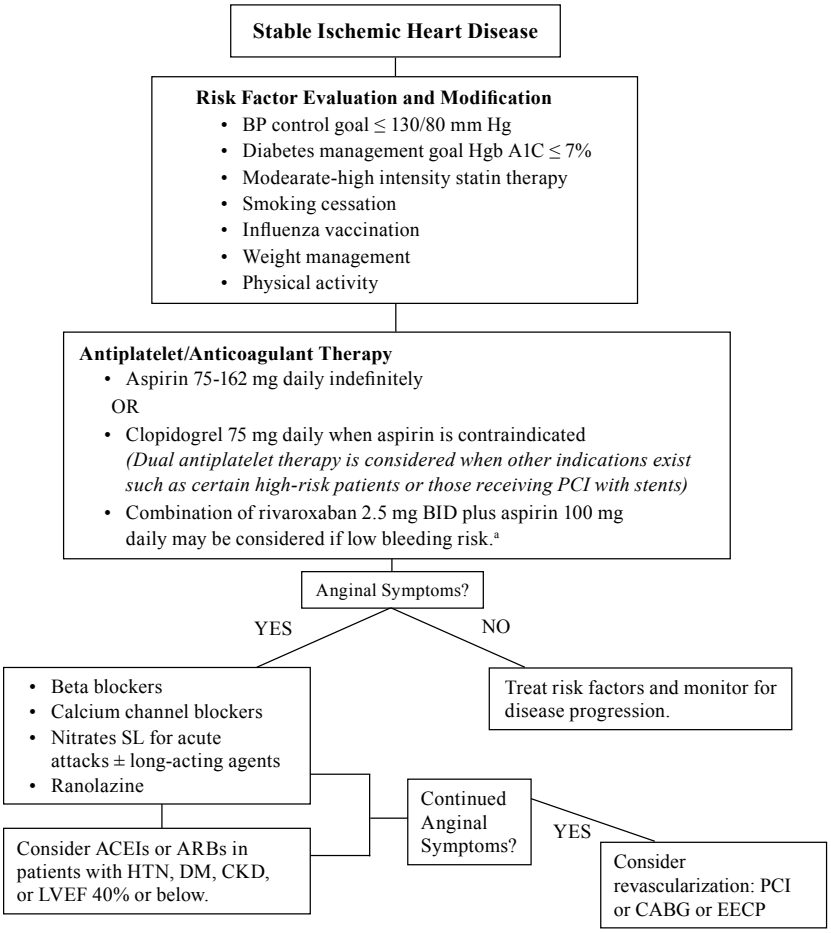


**Figure 1.** General approach to SIHD management.

[a]Combination therapy with rivaroxaban and aspirin based on COMPASS trial; not guideline recommended therapy at this time.

ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; BID = twice daily; BP = blood pressure; CABG = coronary artery bypass graft; DM = diabetes mellitus; EECP = enhanced external counterpulsation; HTN = hypertension; IHD = ischemic heart disease; LVEF = left ventricular ejection fraction; PCI = percutaneous coronary intervention; SIHD = stable ischemic heart disease

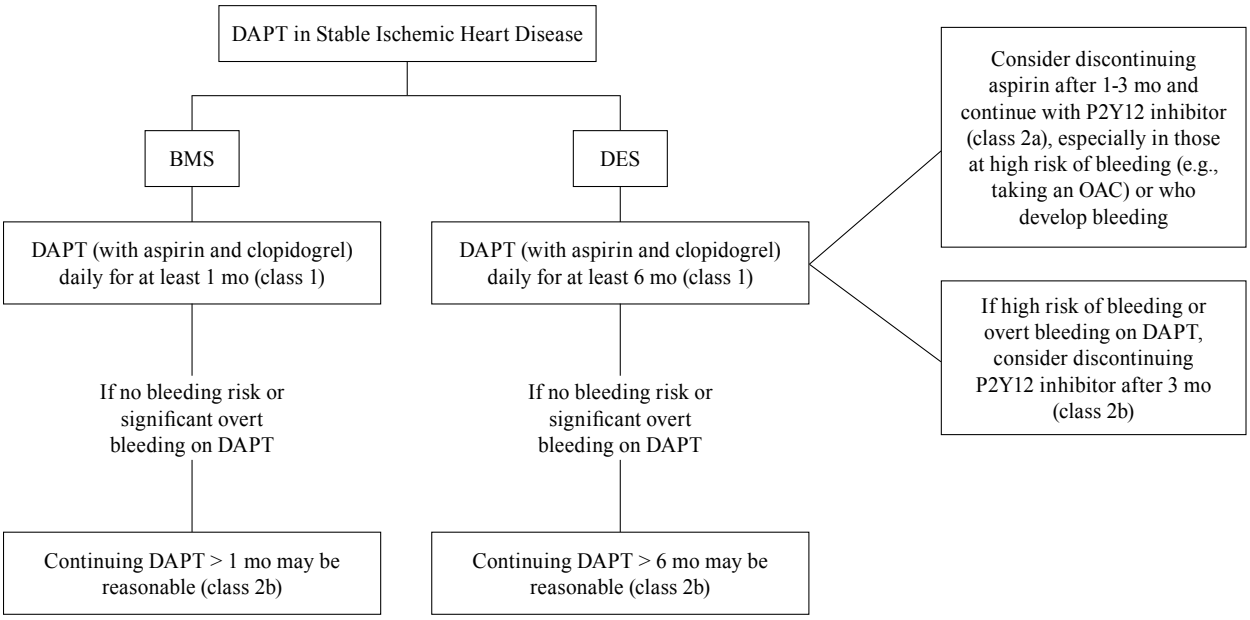


**Figure 2**. Dual antiplatelet therapy in stable ischemic heart disease.

BMS = bare metal stent; DAPT = dual antiplatelet therapy; DES = drug-eluting stent; OAC = oral anticoagulant.

For additional detailed information, see Lawton JS, Tamis-Holland JE, Bangalore S, et al. 2021 ACC/AHA/SCAI guideline for coronary artery revascularization: a report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. Circulation 2022;145:e18-e114.

## III. ATHEROSCLEROTIC (NON-CARDIOEMBOLIC ISCHEMIC) STROKE OR TRANSIENT ISCHEMIC ATTACK

A. Background
   1. Ischemic stroke refers to brain, spinal cord, or retinal cell death caused by infarction based on neuroimaging and/or clinical evidence.
   2. Around 795,000 patients have a new or recurrent stroke each year with approximately 87% of ischemic etiology.
   3. Prevalence increases with age in both men and women but women have a higher lifetime prevalence than men.
   4. Stroke accounted for about 1 of every 19 deaths in 2019 in the United States.
   5. Leading cause of serious long-term disability
   6. Transient ischemic attack (TIA) is a neurological episode caused by ischemia in the brain, spinal cord, or retina without causing an acute infarction. Signs and symptoms typically are transient and last less than 24 hours.
      a. Around 240,000 patients experience TIAs eash year.
      b. Short-term risk of stroke, hospitalizations for CVD events, and death are increased after a TIA with risk of stroke.
   7. Patients who survive the initial high-risk period following a TIA have a 10-year stroke risk of 19% and a combined 10-year stroke, MI, or vascular death risk of 43%.
   8. Short-term risk of stroke, hospitalizations for CVD events, and death are increased after a TIA with risk of stroke.

B. Common Risk Factors: HTN, DM, dyslipidemia, obesity, physical inactivity, tobacco, increased age, other atherosclerotic disease such as cardiac disease or PAD.
   1. The risk of future strokes or TIAs can be reduced using appropriate secondary prevention strategies.
   2. In the INTERSTROKE study, five main risk factors accounted for up to 90% of the population-attributable risk of both ischemic and hemorrhagic strokes: HTN, physical inactivity, diet, smoking, and abdominal obesity.
   3. Targeting several risk factors such as antihypertensive therapy, antiplatelets, and statins, together with improved diet and exercise has additive benefits in reducing subsequent cerebrovascular events.

C. Antiplatelet Therapy
   1. Antiplatelet therapy is recommended over OAC to reduce the risk of recurrent atherosclerotic stroke, TIA, and other CV events (class 1).
   2. Antiplatelet therapy reduces the relative risk of MI, death and stroke by around 22%.
   3. Single antiplatelet therapy (SAPT) options after a TIA or atherosclerotic stroke:
      a. Aspirin 50–325 mg daily (class 1)
      b. Aspirin 25 mg plus extended-release dipyridamole 200 mg twice daily (class 1): At least as effective as aspirin but usually less well tolerated secondary to gastrointestinal symptoms and headaches
      c. Clopidogrel 75 mg daily (class 1)
   4. Clopidogrel is the drug of choice for patients who are allergic to aspirin.
   5. DAPT with aspirin plus clopidogrel when initiated within 12-24 hours and at least within 7 days of onset of a minor ischemic stroke or high-risk TIA and for continuation for 21–90 days and followed by SAPT (class 1).
      a. In the CHANCE trial, the primary outcome of ischemic or hemorrhagic stroke was reduced in patients who were treated within 24 hours of a TIA or minor stroke with aspirin 75 mg for 21 days and clopidogrel 300-mg load followed by 75 mg daily for 90 days with similar rates of bleeding.
      b. Similarly, the POINT trial evaluated the early combination of clopidogrel (600-mg loading dose followed by 75 mg daily) and aspirin (50–325 mg daily; dose site–dependent; however, 162 mg daily for 5 days followed by 81 mg daily was recommended) compared with aspirin alone in 4881 patients with minor ischemic stroke or high-risk TIA. The trial was terminated early because of the lower risk of major ischemic events with DAPT (5% vs. 6.5%; HR 0.75; 95% CI, 0.59–0.95; p=0.02) as well as the higher risk of major hemorrhage (0.9% vs. 0.4%; HR 2.32; 95% CI, 1.10–4.87; p=0.02) at 90 days compared with aspirin alone.
      c. In a pooled analysis of both CHANCE and POINT, authors found that early and short-term treatment with clopidogrel plus aspirin reduced the risk of major ischemic events within the first 3 weeks but not out to 90 days, with more frequent, but not statistically different, major bleeding in the DAPT group.
      d. The THALES trial randomized patients with a mild to moderate acute noncardioembolic stroke or TIA to 30 days of treatment with aspirin plus ticagrelor, or aspirin alone. The primary outcome of stroke or death occurred in 6.6% of the aspirin alone group and 5.5% in the DAPT group of ticagrelor plus aspirin (HR 0.83; 95% CI, 0.71–0.96; p=0.02). This was mostly driven by a reduction in ischemic stroke. Severe bleeding rates were higher in the DAPT group compared to the aspirin alone group (0.5% vs. 0.1%; p=0.001). In addition, there was no difference in the secondary outcome of disability between groups (p=0.61).
      e. The short-term use of DAPT in mild to moderate stroke or TIA may be beneficial in reducing the incidence of recurrent stroke, but use must be weighed against the increased risk of major bleeding.
      f. A recent network meta-analysis compared DAPT regimens including clopidogrel and ASA to ticagrelor and ASA in the prevention of recurrent stroke or death. Data from 5517 patients in clopidogrel arm and 5859 in the ticagrelor arm found both DAPT regiments were superior to aspirin alone, but there was no statistically significant difference between the two DAPT regimens. Both DAPT regimens had higher rates of bleeding than ASA alone. This suggests that DAPT with ticagrelor is a reasonable alternative to ASA and clopidogrel if there is clopidogrel intolerance or failure.

6. With a recent (less than 24 hours) minor-moderate stroke, high-risk TIA, or symptomatic intra- or extracranial stenosis (30% or greater), DAPT with ticagrelor and aspirin for 30 days may be considered (class 2b) but may increase the risk of bleeding events, including intracranial hemorrhage.
7. The continuous use of DAPT with aspirin plus either clopidogrel or ticagrelor is not recommended long term (more than 90 days) for secondary prevention of a stroke because of the potential to increase the risk of hemorrhage (class 3).
8. In addition, the combination of triple antiplatelet therapy with aspirin, clopidogrel, and dipyridamole is not recommended because of the significantly increased risk of bleeding and lack of difference in stroke outcomes in the TARDIS trial.
9. For patients who have had a stroke or TIA while receiving aspirin, increasing the aspirin dose to reduce the risk of subsequent strokes or TIAs has no known benefit (Class 2b). Although alternative antiplatelet agents may be considered, these agents have not been adequately studied in this setting.
10. Other $P2Y_{12}$ antiplatelet agents are not currently recommended as secondary prevention for TIA or ischemic stroke. Prasugrel was found to increase the risk of strokes in patients in clinical trials and is contraindicated in patients with a history of TIA or stroke. In the SOCRATES trial, ticagrelor was not superior to aspirin in reducing the rate of stroke, MI, or death at 90 days in patients with a nonsevere ischemic stroke or high-risk TIA who did not receive thrombolysis. Bleeding rates were similar in both groups but more patients discontinued ticagrelor due to minor bleeding events.
11. In a stroke outcomes substudy of the COMPASS trial, rivaroxaban 2.5 mg twice daily plus aspirin resulted in a small but significant reduction in an annualized rate of stroke (0.5% vs. 0.8%; HR 0.58; 95% CI, 0.44–0.76; $p<0.0001$) compared to aspirin alone. In those with a history of stroke greater than 1 month prior to randomization, a 67% relative risk reduction in subsequent strokes occurred in the combination group versus the aspirin alone group ($p=0.01$). Rates of bleeding were similar between those with a prior history of stroke versus those without ($p=0.19$). It is important to note that patients with a recent ischemic stroke or previous hemorrhagic or lacunar strokes were excluded in the COMPASS trial due to the risk of intracranial hemorrhage. The 2021 guidelines state that the role of DOACs in combination with antiplatelets for secondary stroke prevention is unanswered, and no recommendations are provided.

D. Lipid Management and Stroke Risk Reduction
   1. Atorvastatin 80 mg daily (or another high-intensity statin) is indicated in patients with ischemic stroke with no known CAD and LDL greater than 100 mg/dL (class 1).
   2. Goal LDL of less than 70 mg/dL is recommended using a statin plus ezetimibe, if needed, to reduce the risk of major CV events (class 1).
   3. Add a PCSK9 inhibitor to a statin plus ezetimibe for those who still have an LDL greater than 70 mg/dL if considered at very high risk (e.g., stroke plus other major ASCVD risk factor or stroke plus several high-risk conditions) (class 2a).
   4. Obtain a lipid profile 4–12 weeks after statin initiation or dose adjustment and every 3–12 months thereafter to assess adherence and/or safety.
   5. Use of icosapent ethyl 2 g twice daily is reasonable to reduce the risk of recurrent stroke in patients with fasting TG of 135–499 mg/dL and LDL of 41–100 mg/dL who are already taking moderate- to high-intensity statins, who have an A1C less than 10%, and who have no history of pancreatitis, atrial fibrillation, or severe heart failure (class 2a).
   6. In patients with severe hypertriglyceridemia (TG 500 mg/dL or greater), identify and address the cause and implement a very low-fat diet, consumption of omega-3 fatty acids, avoidance of refined carbohydrates and alcohol, and fibrates, if needed, to prevent pancreatitis (class 2a).
   7. Moderate- to high-intensity statins are recommended for patients with or without evidence of additional ASCVD and regardless of LDL concentration (class 1) when stroke or TIA is presumed to be caused by atherosclerosis as recommended by the guidelines for the management of blood cholesterol.

8. Other risk factor modification evaluation and screening after TIA or stroke should include optimal treatment for diabetes, obesity, diet, and physical activity. In addition, tobacco cessation; reduction in heavy alcohol use, if applicable; and evaluation for obstructive sleep apnea should be considered in patients with or without evidence of additional ASCVD and regardless of LDL concentration (class 1) when stroke or TIA is presumed to be caused by atherosclerosis.
9. Moderate- or high-intensity statin therapy if without contraindications, drug-drug interactions, or history of statin intolerance (class 1)
10. Nonstatin therapies such as ezetemibe or PCSK-9 inhibitors are recommended in patients with a history of ischemic stroke or TIA and should be utilized as appropriate.

E. HTN Therapy – High prevalence of HTN in patients with ischemic stroke
   1. For most neurologically stable patients, the goal blood pressure is less than 130/80 mm Hg (class 1). For patients with intracranial large artery atherosclerosis, a systolic blood pressure goal of less than 140 mm Hg may be appropriate (class 1).
   2. Drugs of choice: ACEIs, angiotensin receptor blockers, thiazide diuretics, or a combination of ACEIs and a thiazide. (class 1)
   3. Optimal regimen is unknown at this time, but therapy should be individualized to the patient for whom specific agents may be indicated (e.g., CAD, DM, CKD). The magnitude of blood pressure lowering seems to be more important for risk reduction than the individual agent used.
   4. In patients without a history of HTN whose average office blood pressure is 130/80 mm Hg or greater, antihypertensives can be beneficial (class 2a).

**Patient Case**

5. A 62-year-old woman with a history of HTN, HLD, and asthma was initiated on aspirin 325 mg daily for a recent TIA. Within days, she experienced urticaria and itching. Which would be the most appropriate antiplatelet regimen for preventing stroke in this patient?
   A. Decrease the aspirin dose to 81 mg daily.
   B. Change to aspirin 25 mg plus extended-release dipyridamole 200 mg twice daily.
   C. Give clopidogrel 75 mg daily.
   D. Give warfarin to a target INR of 2.5.

## IV. PERIPHERAL ARTERIAL DISEASE OF THE LOWER EXTREMITIES

A. Background
   1. Common CV disease affecting more than 200 million people worldwide 40 and older with significant morbidity and mortality yet often unrecognized and underdiagnosed
   2. Disorder of the arteries, other than cerebral and coronary, including femoropopliteal-tibial, aortoiliac, and infrapopliteal arteries, with the lower extremities affected more commonly
   3. Patients with PAD have a higher rate of CV events than patients with CAD or cerebrovascular disease.
   4. Approximately two-thirds of patients with PAD also have CAD and one-third have cerebrovascular disease.
   5. Studies have suggested that patients with PAD are often less likely to receive appropriate risk factor modification therapy compared with patients with CAD or cerebrovascular disease.

B. Pathophysiology
   1. A narrowing of the arterial lumen of lower-extremity arteries because of atherosclerosis. Similar to coronary atherosclerosis, PAD is a progressive disease that develops over many years and can be asymptomatic, or can manifest with symptoms of ischemic pain with increased skeletal muscle oxygen demand or as an acute ischemic event because of plaque rupture.
   2. Risk factors include age 65 and older, DM, HLD, HTN, cigarette smoking, history of known atherosclerotic disease in another vascular system (coronary, carotid, renal, mesenteric artery stenosis, or abdominal aortic aneurysm), or a family history of PAD.

C. Definitions
   1. Stable PAD – Patients without an endovascular or surgical peripheral artery procedure within the previous 6 months and without current signs of critical limb ischemia
   2. Intermittent claudication (IC) – Classic symptom of PAD that occurs in about one-third of patients with PAD. Pain, fatigue, cramping, and discomfort occur with exertion in the lower extremities (thighs, hips, or calves) and are relieved with rest. Symptoms occur as a result of ischemia because of occlusive atherosclerotic lesions in the setting of increase blood flow demand.
   3. Chronic limb-threatening ischemia (CLTI) – Also referred to as critical limb ischemia or chronic limb ischemia, CLTI is characterized by a severe, chronic (2 weeks or more) duration of ischemia/pain at rest, nonhealing ulcers or gangrene. A primary complication of PAD associated with a 30% rate of major lower limb amputations and a 25% mortality rate at 1 year
   4. Acute limb ischemia (ALI) – A medical emergency characterized by acute onset of severe pain usually less than 2 weeks' duration caused by severe hypoperfusion of the limb. Patients have pain, pulselessness, cold limbs, numbness, and paralysis. Patients with ALI are placed into one of three categories:
      a. Viable – No immediate threat; patient still has audible arterial and venous Doppler pulses; no sensory loss or muscle weakness
      b. Threatened – Mild to moderate sensory or motor loss, no arterial Doppler pulse but patient has an audible venous pulse
      c. Irreversible – Major tissue loss and/or permanent nerve damage, profound muscle weakness and sensory loss, paralysis, completely inaudible venous or arterial Doppler pulses
   5. Tissue loss – Either minor, nonhealing ulcer, focal gangrene, or pedal ischemia or major, defined as nonfunctional foot that is nonsalvageable, extending above the transmetatarsal region

D. Patient Presentation
   1. Many patients (more than 50%) with chronic PAD are asymptomatic; however, patients' symptoms can range from discomfort on exertion, diminished walking ability, to gangrene. Although IC is a classic symptom of PAD, not all patients with PAD have IC; therefore, IC cannot be used alone to diagnose PAD.
   2. Physical examination findings that increase likelihood of PAD include abnormal lower extremity pulses, vascular bruit, nonhealing wounds or gangrene in the extremities, and other signs such as interarm BP variability 15 mmHg or greater.
   3. Nonspecific signs of PAD on physical exam may include leg numbness or weakness, coolness in leg or foot, unhealing sores on lower extremities, discoloration in skin or hair loss on extremities, shiny or waxy appearance to skin on extremities.

E. Classification of Severity of PAD (see Table 8)

**Table 8.** PAD Classification Systems

| **Fontaine Classification** | | **Rutherford Classification** | | |
|---|---|---|---|---|
| Stage | Symptoms | Grade | Category | Symptoms |
| I | Asymptomatic | 0 | 0 | Asymptomatic |
| IIa | Non-disabling IC | I | 1 | Mild claudication |
| | | I | 2 | Moderate claudication |
| IIb | Disabling IC | I | 3 | Severe claudication |
| III | Ischemic rest pain | II | 4 | Ischemic rest pain |
| IV | Ulceration or gangrene | III | 5 | Minor tissue loss |
| | | III | 6 | Major tissue loss |

IC=intermittent claudication.

From Aboyans V, Ricco JB, Bartelink MEL, et al. 2017 ESC guidelines on the diagnosis and treatment of peripheral arterial diseases, in collaboration with the European Society for Vascular Surgery (ESVS). Eur J Vasc Endovasc Surg 2017 Aug 26. pii: S1078-5884(17)30454-9. doi: 10.1016/j.ejvs.2017.07.018. [Epub ahead of print]

F. Screening and Diagnosis (Table 9 and Table 10)
   1. Patients 65 and older or at risk of PAD should be screened with a comprehensive history and physical examination and asked about presence of symptoms or poor wound healing.
   2. Physical examination: Palpation of lower-extremity pulses including the dorsalis pedis and posterior tibial pulses, auscultation for femoral bruits, and inspection of feet and legs
   3. Blood pressure measurement in both arms; an inter-arm difference greater than 15–20 mm Hg suggests subclavian artery stenosis
   4. Ankle-brachial index (ABI)
      a. Simple, noninvasive, gold standard test for PAD with good sensitivity and specificity (90% or more)
      b. Resting ABI – While lying supine, the systolic blood pressure is measured in the brachial arteries of both arms and the dorsalis pedis and posterior tibial arteries of the legs with a standard cuff and a continuous-wave Doppler device. The ABI is calculated by dividing the highest ankle SBP by the highest arm SBP.
      c. Exercise ABI – Treadmill exercise test with ABI
      d. ABI values (Table 11)
   5. Other screening tests (see Table 10)

**Table 9.** Recommendations for PAD Screening[a]

| Patient Groups | Screening or Evaluation | Class of Recommendation |
|---|---|---|
| Patients at increased risk but no history or physical findings of PAD | Assess Symptoms: Comprehensive medical history, assess exertional leg symptoms, walking impairment, ischemic rest pain, nonhealing wounds | 1 |
| | Physical Examination: Palpation of lower extremity pulses, auscultation for femoral bruits, inspections of legs and feet | 1 |
| | Diagnosis: Resting ABI is reasonable due to a high prevalence of abnormal ABI in asymptomatic PAD patients with risk factors | 2a |
| Patients with a history or physical findings of PAD | Resting ABI with or without segmental pressures and waveforms | 1 |
| | Noninvasive BP measurement in both arms – interarm differences of >15–20 mmHg is abnormal and suggestive of subclavian artery stenosis | 1 |
| Patients with PAD and ABI >1.4 | TBI – to evaluate for PAD in patients with noncompressible arteries | 1 |
| Patients with exertional symptoms and normal or borderline resting ABI (>0.90 and ≤1.40) | Exercise treadmill ABI – objectively measures symptom limitations and aids in diagnosis in lower extremity PAD | 1 |
| Patients with PAD and abnormal resting ABI (≤0.90) | Exercise treadmill ABI – to objectively assess functional status | 2a |
| In setting of nonhealing wounds or gangrene and either:<br>• normal ABI (1.00–1.40)<br>• borderline ABI (0.91–0.99)<br>• abnormal ABI (≤0.90)<br>• noncompressible arteries (ABI >1.40 and TBI ≤0.70) | Perfusion assessment measures: TBI with waveforms, $TcPo_2$, or SPP – to aid in diagnosis of CLTI | 2a |

ABI = ankle-brachial index; BP = blood pressure; CLTI = chronic limb-threatening ischemia; SPP = skin perfusion pressure; TBI = toe-brachial index; $TcPo_2$ = transcutaneous oxygen pressure

[a]Information from Gerhard-Herman MD, Gornik HL, Barrett C, et al. 2016 AHA/ACC guideline on the management of patients with lower extremity peripheral artery disease: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. J Am Coll Cardiol 2017;69:e71-126.

**Table 10.** Diagnostic Tests[a]

| Test | Overview | Benefits | Limitations |
|---|---|---|---|
| ABI | Doppler probe and sphygmomanometer used to determine SBP at arms (brachial artery) and ankle (posterior tibial and dorsalis pedis arteries) in supine position to determine pressure at ankle; the higher of these two values is used in calculation | Quick<br>Cost effective<br>Noninvasive<br>Good validity as first line diagnostic test<br>Results predict patient and limb survival and wound healing | Noncompressible pedal arteries (common in diabetics and/or advanced CKD) may prevent accurate measurement of ABI |
| Exercise Treadmill ABI | Time to onset of symptoms, muscles affected and total walking time is determined<br>Questions are posed to the patient to determine the type of symptoms that occur during exercise (e.g., atypical limb discomfort, IC, joint pain)<br>After exercise, ABIs in each leg are calculated every minute until results reach preexercise baseline. This provides data on the significance of functional limitation caused by the disease<br>>20% decrease in pressure immediately after exercise confirms an arterial etiology of symptoms | Provides the most data on the degree of functional limitation<br>Useful when resting ABI results are normal; tool to determine response to therapy | Costly, time-consuming, and not as readily available |
| TBI | Similar to ABI but cuff is placed on each large toe vs. ankles<br>Score <0.7 typically considered diagnostic for PAD | Useful to diagnose PAD when ABI is >1.40 (noncompressible arteries cause an artificial elevation of ABI)<br>Noninvasive | |
| Duplex Ultrasound | Provides imaging of the vessel and data regarding blood flow velocity | Noninvasive<br>Provides data on localization and severity of disease | Arterial calcification can reduce accuracy<br>Reduced detection in distal arteries when proximal stenosis is present |
| CTA | Determines anatomy and degree of stenosis<br>Data can be used to determine whether a patient is a candidate for vascular intervention | Noninvasive<br>Alternative to MRA, especially in those for whom MRA is contraindicated | Iodinated contrast and ionizing radiation are required<br>Not recommended for routine screening |
| MRA | Magnetic imaging is used to determine anatomic location and degree of stenosis | Nonivasive<br>Contrast is not administered | Patients need to remain completely still<br>Cannot be used in patients with metallic implants<br>Disease may be overestimated because of turbulent flow in lower extremities<br>Expensive |

CKD = chronic kidney disease; IC = intermittent claudication; MRA = magnetic resonance angiography; SBP = systolic blood pressure; TBI = toe-brachial index;

[a]Modified from: Table 4.3 *in* Watson K, Pincus KJ. Peripheral arterial disease. In: Dong BJ, Elliott DP, eds. Updates in Therapeutics®: Ambulatory Care Pharmacy Preparatory Review and Recertification `

Information from: Gerhard-Herman MD, Gornik HL, Barrett C, et al. 2016 AHA/ACC guideline on the management of patients with lower extremity peripheral artery disease: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. J Am Coll Cardiol 2017;69:e71-126.

**Table 11.** ABI Values

| ABI Value | Description | Comment |
|---|---|---|
| ≤0.90 | Abnormal | Diagnostic for PAD |
| 0.91–0.99 | Borderline | Exercise ABI needed to confirm diagnosis |
| 1.00–1.40 | Normal | If symptomatic: Exercise ABI<br>If Asymptomatic: Rules out PAD |
| >1.40 | Noncompressible | TBI needed to confirm diagnosis |

**Patient Case:**
*Questions 6 and 7 pertain to the following case.*
A 49-year-old man with obesity and a history of DM, HTN, and gouty arthritis has bilateral calf pain with his daily walk. He describes the pain as "crampy and achy" that is relieved when he sits down to rest. He has a 30 pack-year history of smoking but quit 6 months ago when he was given a diagnosis of diabetes. On physical examination, his feet are cool to the touch, and his dorsalis pedis and posterior tibial pulses are diminished. His blood pressure is 149/82 mm Hg, and laboratory results are A1C 8.5% and LDL 135 mg/dL. His home drugs include metformin 1000 mg twice daily, gabapentin 100 mg three times daily, amlodipine 5 mg daily, and colchicine as needed.

6. Which would best evaluate PAD in this patient?
   A. ABI.
   B. No evaluation required.
   C. Toe-brachial index (TBI).
   D. Treadmill exercise test.

7. Which best describes this patient's risk factors for PAD?
   A. Age, gout, and HTN.
   B. Diabetes, smoking, and HTN.
   C. HTN, peripheral neuropathy, and smoking.
   D. Diabetes, smoking, and peripheral neuropathy.

G. Treatment of PAD (see Figure 3)
   1. Risk factor modification
      a. Smoking cessation (class 1)
         i. Patients who are smokers or former smokers should be asked about their smoking status at each visit.
         ii. Patients who use tobacco should be advised to quit at each visit and should be offered help in developing a smoking cessation plan, which may include the following:
            (a) Pharmacotherapy (varenicline, bupropion, and/or nicotine replacement)
            (b) Behavioral treatment
            (c) Referral to a smoking cessation program
      b. Lipid management (See Dyslipidemia chapter)
         i. Moderate- and high-intensity statins for CV risk reduction in patients with atherosclerotic PAD (class 1) to a goal LDL less than 70 mg/dL or a decrease in LDL 50% or greater of baseline in those 75 years and younger. Addition of ezetimibe or PCSK-9 inhibitor in very high risk patients on maximally tolerated statins with LDL 70 mg/dL or greater or non–high density lipoprotein cholesterol 100 mg/dL or greater.

ii. Statins improve symptoms such as walking distance and reduce mortality, stroke, and CV events.
iii. Evidence from the FOURIER trial found that in the 3642 patients with stable PAD (defined as having IC, ABI less than 0.85, or a history of piror vascular procedures), evolocumab significantly reduced the primary composite end point (hospital admission of ACS, coronary revascularization, or CV death) as well as the risk of major adverse limb events (MALE) in patients receiving moderate- or high-intensity statin therapy.
iv. Current guidelines for PAD do not include recommendations for PCSK-9 inhibitors; however, the 2018 lipid guidelines aptly consider PAD as ASCVD; therefore, patients with PAD should appropriately be treated with moderate- to high-intensity statins with the addition of PCSK-9 inhibitors or ezetimibe in patients (class 2a) or other appropriate non-statin therapies as indicated.

c. Diabetes management – Major risk factor for PAD and is associated with a worse prognosis, including progression to CLTI, amputation, and death
i. Goal: A1C less than 7%. Patients with A1C concentrations less than 6.5% have a lower age-adjusted odds of major amputation than patients with A1C concentrations greater than 9.5%. Glycemic control may reduce limb-related adverse events (class 1).
ii. A1C less than 8% may be appropriate for patients with extensive comorbid conditions or advanced macrovascular complications.
iii. Treatment should be determined by current diabetes management guidelines. SGLT2 inhibitors and glucagon-like peptide 1 receptor agonist agents may be considered.
iv. Regular foot examinations are recommended.
v. ABI is recommended in diabetic patients at risk of PAD.

d. HTN management – Treat HTN to reduce the risk of MI, stroke, heart failure, and CV death (class 1).
i. Goal: Less than 130/80 mm Hg
ii. Goal of less than 130/80 mm Hg may be reasonable in patients with previous MI, stroke, or TIA or CAD risk equivalents such as PAD, carotid stenosis, or abdominal aortic aneurysm.
iii. Drugs of choice
(a) There is no evidence that any one class is superior to another in reducing CV disease outcomes in patients with PAD.
(b) β-Blockers - Many studies have shown that β-blockers do not worsen claudication symptoms or impair functional status and may be considered if other compelling indications exist.
(c) ACEIs/angiotensin receptor blockers - Can reduce the risk of CV ischemic events in patients with PAD (class 2a)

e. Influenza vaccination: Patients with PAD should receive an annual vaccine to reduce CV events (class 1).

2. Antiplatelet therapy – Reduce MI, stroke and death in patients with symptomatic (class 1) PAD or asymptomatic patients (class 2a) with ABI of 0.90 or less
a. Aspirin 75–325 mg daily alone (class 1); consider bleeding risk before using a dose higher than 81 mg daily
b. Clopidogrel 75 mg daily alone (class 1); typically as an alternative to aspirin. CAPRIE trial showed the benefit of clopidogrel compared with aspirin in CV risk reduction and similar rates of bleeding events in patients with symptomatic atherosclerotic disease of whom around 34% had symptomatic PAD; however, the reduced primary end point was mainly driven by the effect in those with PAD. In the overall study, clopidogrel was superior to aspirin for major adverse cardiovascular events with an 8.7% relative risk reduction (5.32 vs. 5.83%, p=0.043). In the PAD subgroup, the effect for clopidogrel was more prominent at 23.8% (3.71% vs. 4.86%, p=0.0028).

c. Ticagrelor – EUCLID trial – Double-blind, event-driven trial that evaluated 13,885 patients with symptomatic PAD and ABI of 0.80 or less or who had received prior revascularization of the lower limbs more than 30 days before randomization to ticagrelor 90 mg twice daily or clopidogrel 75 mg daily for 30 months. Primary composite efficacy outcome (CV death, MI, or ischemic stroke) did not differ between groups. Major bleeding was similar between groups. More patients discontinued ticagrelor prematurely than clopidogrel ($p<0.001$), mainly because of minor bleeding and dyspnea. At this time, ticagrelor is not recommended in the guidelines for the treatment of PAD, but it could be considered an alternative to clopidogrel according to this study. Of interest, patients who were homozygous for loss-of-function alleles to clopidogrel were excluded from this study. This study was published after the AHA/ACC guidelines; therefore, no recommendations are provided at this time for ticagrelor in PAD. The European Society of Cardiology (ESC) guidelines, published after EUCLID, continue to recommend aspirin or clopidogrel as the SAPT in symptomatic patients with PAD.

d. In asymptomatic patients with a borderline ABI of 0.91–0.99, the benefit of antiplatelet therapy with aspirin or clopidogrel is unclear (class 2a AHA/ACC guidelines but class 3 per ESC guidelines).

e. DAPT is not well established in PAD and should only be used in patients with other indications such as those receiving cardiac stents. DAPT may be considered in patients at a particularly high risk of CV ischemic events if they are not at a high risk of bleeding (class 2b).
   i. CHARISMA trial substudy of patients with PAD showed that DAPT with aspirin plus clopidogrel was no better than aspirin alone in the 3096 patients with PAD. Rates of severe, fatal, or moderate bleeding did not differ, but the rate of minor bleeding was increased with clopidogrel (34.4% vs. 20.8%: OR 1.99; 95% CI, 1.69–2.34; p=0.001).
   ii. A subgroup analysis of 1143 patients (only 5% of total population) with prior MI and PAD at baseline in the PEGASUS-TIMI 54 trial had a significant reduction in major adverse cardiovascular events with the DAPT group consisting of ticagrelor 60 mg twice daily plus aspirin. Patients receiving DAPT also had a decreased risk of major adverse limb events (HR 0.65; 95% CI, 0.44–0.95; p=0.026). DAPT therapy with ticagrelor increased TIMI major bleeding in patients with or without PAD by only 0.12%.
   iii. A prespecified analysis of 1687 patients with PAD (8.8% of the population) from the THEMIS trial found that DAPT with ticagrelor plus aspirin significantly reduced the risk of MALE by 55% (HR 0.45; 95% CI, 0.23-0.86) compared with aspirin alone. There was a significant increase in major bleeding with DAPT in this trial, which suggests that the combination of ticagrelor and aspirin should be used with caution and more data are needed to fully understand which patients with PAD would benefit from this therapy.
   iv. DAPT, typically for 1 month, may reduce the risk of limb-related events such as repeat revascularization in patients who have undergone lower-extremity revascularization (class 2b).
   v. Vorapaxar – The overall net benefit of the protease-activated receptor-1 antagonist is uncertain, and the AHA/ACC PAD guidelines give it a class 2b recommendation. Vorapaxar was evaluated in the TRA 2 P-TIMI 50 trial, which included 3787 patients with PAD. Vorapaxar did not reduce the primary composite end point but did significantly reduce the rate of hospitalization because of ALI and revascularization but at a significantly increased risk of moderate or severe bleeding. Vorapaxar is U.S. Food and Drug Administration (FDA) indicated in patients with PAD when added to existing antiplatelet therapy, but its clinical usefulness is uncertain and is rarely used in clinical practice. Dose at 2.08 mg daily with aspirin and/or clopidogrel; note that triple therapy significantly increases bleeding risk. Currently, no data support vorapaxar use with other antiplatelet agents such as ticagrelor or prasugrel. Contraindicated in patients with history of stroke, TIA, or intracerebral hemorrhage

f. Prasugrel – There are no published data on the use of prasugrel in PAD at this time.

3. Oral anticoagulation
    a. In October 2018, the FDA approved the addition of the DOAC, rivaroxaban 2.5 mg BID to aspirin 100 mg daily to reduce the risk of CV death, MI, and stroke in patients with CAD and PAD based on the COMPASS trial.
        i. In the subgroup of patients with PAD (defined as previous peripheral bypass surgery or angioplasty, limb or foot amputation, IC with objective evidence of PAD, previous carotid artery revascularization, or asymptomatic carotid artery stenosis of at least 50% or CAD with ABI less than 0.90), which included 27% of the population, the combination of rivaroxaban plus aspirin reduced the absolute rate of composite primary endpoint of CV death, MI, and stroke by 2% (5% vs. 7%; HR 0.72, 95% CI 0.57-0.90; p=0.0047) and MALE, which included amputations by 1% (1% vs 2%; HR 0.54, 95% CI 0.35-0.82; p=0.0037)
        ii. The combination therapy resulted in an absolute increased risk of major bleeding by 1% (3% vs. 2%; HR 1.61, 95% CI 1.12-2.31; p=0.0089). Of note, patients at high risk of bleeding were excluded from COMPASS, which may have underestimated the true bleeding risk in a more general population of patients with PAD.
        iii. Small absolute benefits in major adverse cardiac events should be carefully weighed with bleeding risks when initiating this therapy in patients with stable vascular disease.
        iv. A subsequent analysis of the patients in the COMPASS PAD population showed that patients who had a MALE, including amputation, have a reduced rate of hospitalization and death in the following 12 months while taking the combination of rivaroxaban 2.5 mg twice daily and aspirin 100 mg daily.
        v. See section on stable ischemic heart disease regarding discussion of the open label extension of the COMPASS trial.
    b. Current guidelines published prior to the COMPASS trial state that providers should not use oral anticoagulants in patients with PAD to reduce the risk of CV ischemic events because studies have shown no benefit and increased mortality and increased bleeding (class 3).
4. Symptom alleviation – Agents that reduce PAD symptoms
    a. Cilostazol 100 mg twice daily – Nonselective phosphodiesterase type 3 inhibitor that results in vasodilation of the peripheral arteries and inhibits platelet aggregation; recommended to improve claudication symptoms; mainly walking distance (class 1)
        i. Adverse effects include headache, diarrhea, dizziness, and palpitations. Does not increase bleeding when added to aspirin and clopidogrel
        ii. Contraindicated in HFrEF of any severity because of increased risk of arrhythmias and death
    b. Pentoxifylline 400 mg three times daily is not effective for claudication and not recommended (class 3).
    c. Chelation therapy and homocysteine lowering are not beneficial for claudication (class 3).
5. Structured exercise therapy – Supervised and structured exercise programs are recommended to reduce leg pain and improve functional status and quality of life in patients with PAD (class 1).

H. Revascularization – For patients with severe IC causing limited mobility
    1. Endovascular revascularization – Generally preferred first line; strategies include angioplasty, stents, and atherectomy
    2. Surgical revascularization – Reserved for patients in whom endovascular procedures are not beneficial; generally avoided in younger patients
    3. In CLTI, revascularize as soon as possible to minimize tissue loss.
    4. For ALI, administer heparin unless there is a contraindication; consider catheter-based thrombolysis if there is a salvageable limb.
    5. Use of single antiplatelet therapy (class 1) or DAPT (class 2b) with a thienopyridine is recommended post-revascularization procedures.

6. The CASPAR trial of patients undergoing below-knee bypass grafting showed no benefit of DAPT with aspirin and clopidogrel, compared with aspirin alone, with respect to limb or systemic outcomes. There were no significant differences between rates of severe bleeding.
7. Edoxaban – The small ePAD study showed no difference in the safety and efficacy of DAPT with edoxaban plus aspirin compared with clopidogrel plus aspirin for 3 months in 203 patients post-endovascular treatment. There was no statistically significant difference in major bleeds.
8. VOYAGER-PAD evaluated the safety of 2.5 mg twice daily rivaroxaban plus aspirin 100 mg daily for decreasing major thrombotic vascular events in patients undergoing lower-extremity revascularization procedures. Approximately two-thirds of patients underwent endovascular revascularization and one-third surgical revascularization. A statistically significant reduction in the primary outcome (composite of ALI, major amputation, MI, ischemic stroke, or CV death) occurred with the OAC plus aspirin group compared to the aspirin alone group (p=0.009), although this was driven by the surgical revascularization group only. International Society on Thrombosis and Haemostasis (ISTH) major bleeding occurred more with the rivaroxaban plus aspirin group (p=0.007).
9. The AHA/ACC guidelines state that the usefulness of anticoagulation after lower extremity autogenous vein or prosthetic bypass is uncertain (class 2b). The slightly more recent ESC guidelines state that after endovascular revascularization, either aspirin or clopidogrel can be added to OAC (either warfarin or a DOAC) for 1 month if the bleeding risk is low (class 2a) but that an OAC alone may be considered if the bleeding risk is high (class 2a). Using an OAC and SAPT for more than 1 month is an option in patients with high ischemic risk or if there is another indication for long-term SAPT (class 2b).

I. Management of ALI
   1. Patients may present with an ischemic, cold, painful leg caused by an arterial occlusion of less than 2 weeks duration.
   2. Unfractionated heparin is initiated acutely to slow or stop thrombus propagation.
   3. Patients who recently received UFH prior to onset of ALI and have a decreased platelet count may have suspected heparin-induced thrombocytopenia. Use of a direct thrombin inhibitor is recommended.
   4. Catheter-based thrombolysis may be considered in patients with ALI if the limb is considered salvageable.

**Patient Case:**
A 49-year-old man with obesity and a history of DM, HTN, and gouty arthritis has bilateral calf pain with his daily walk. The pain, which he describes "crampy and achy," is relieved when he sits down to rest. He has a 30 pack-year history of smoking but quit 6 months ago when he was given a diagnosis of diabetes. On physical examination, his feet are cool to the touch, and his dorsalis pedis and posterior tibial pulses are diminished. His blood pressure is 149/82 mm Hg, and laboratory results include A1C 8.5% and LDL 135 mg/dL. His home drugs include metformin 1000 mg twice daily, gabapentin 100 mg three times daily, amlodipine 5 mg daily, and colchicine as needed.

8. According to the AHA/ACC guidelines, which would best reduce this patient's risk of cardio- and cerebrovascular disease?
   A. Aspirin 81 mg daily.
   B. Aspirin 81 mg daily and clopidogrel 75 mg daily.
   C. Ticagrelor 90 mg twice daily.
   D. Vorapaxar 2.08 mg daily with aspirin 81 mg daily.

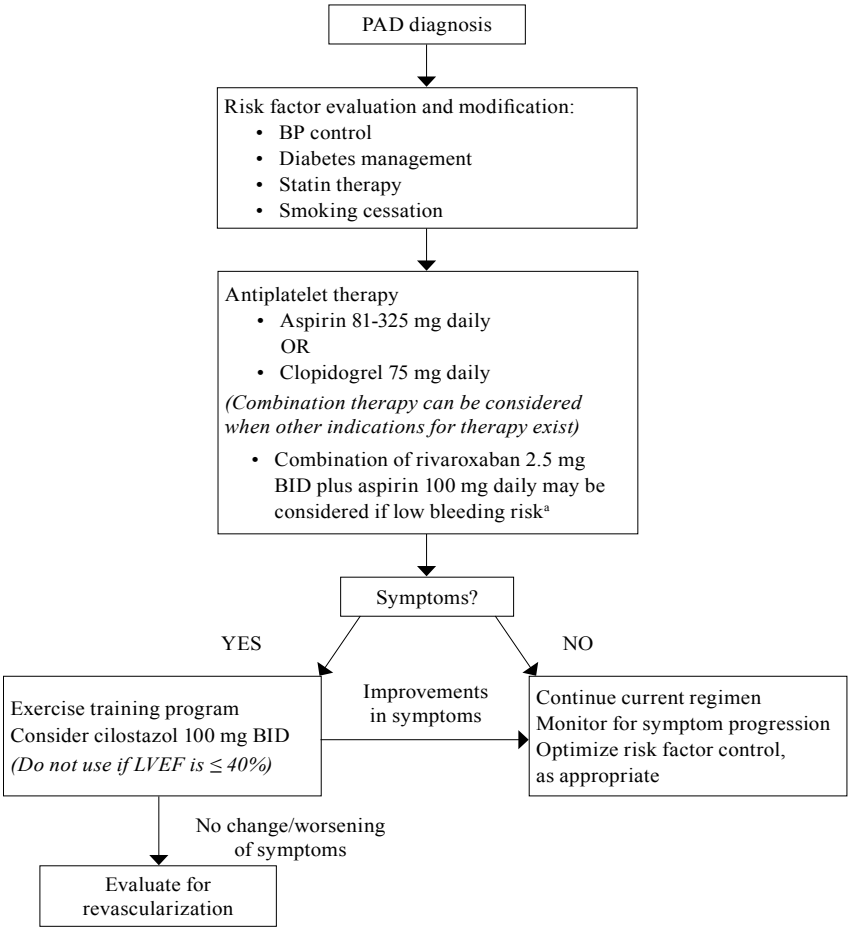


**Figure 3.** General approach to peripheral arterial disease management.

[a]Combination therapy with rivaroxaban and aspirin based on COMPASS trial; not guideline recommended therapy at this time.

BID = twice daily; LVEF = left ventricular ejection fraction; PAD = peripheral arterial disease.

Information from: Watson K, Pincus KJ. Peripheral arterial disease. In: Bainbridge JL, Cardone K, Cross LB, et al., eds. Updates in Therapeutics®: Ambulatory Care Pharmacy Preparatory Review and Recertification Course, 2014 ed. Lenexa, KS: American College of Clinical Pharmacy, 2014:85-106.

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## ANSWERS AND EXPLANATIONS TO PATIENT CASES

**1. Answer: B**

The 2021 ACC/AHA guidelines for coronary revascularization recommend that patients with SIHD undergoing PCI with a DES receive DAPT with aspirin 81 mg daily (Answers C and D are incorrect) and clopidogrel (Answers A and C are incorrect) as the $P2Y_{12}$ antagonist for at least 6 months (Answer B is correct). Dual antiplatelet therapy can be considered for more than 6 months in patients who are not at high risk of bleeding and who have tolerated 6 months of DAPT, which would allow Answer D as an option except that the aspirin dose is too high, making it incorrect. A shorter duration of DAPT of 1–3 months may be considered with continuation of the $P2Y_{12}$ inhibitor in some patients. Answer A is incorrect, however, because it recommends DAPT for only 1 month, which would be more appropriate for a patient receiving a BMS.

**2. Answer: C**

In patients with angina, the ACC/AHA recommends β-blockers as first-line therapy. This patient currently takes low-dose metoprolol, and his blood pressure and heart rate are not well controlled to targets of less than 130/80 mm Hg and 55–60 beats/minute; thus, his metoprolol dose can be increased (Answer C is correct). Adding amlodipine could help his angina and blood pressure but would not lower his heart rate and could have negative consequences through its mechanism of reflex tachycardia (Answer A is incorrect). Patients with angina should have a prescription for sublingual nitroglycerin; however, sublingual nitroglycerin alone would not help reduce this patient's blood pressure or heart rate, which is contributing to the patient's increased myocardial oxygen demand (Answer B is incorrect). This patient would benefit from moderate- to high-intensity statin therapy; however, increasing his statin would not directly improve his anginal symptoms (Answer D is incorrect).

**3. Answer: A**

Other risk factor modifications should be considered in patients with SIHD. This patient should receive moderate- to high-intensity statin therapy because he is in the known ASCVD risk category; therefore, his atorvastatin dose should be at least 40–80 mg daily. Adding an ACEI in patients with SIHD is a class 1 recommendation in patients with DM (Answer A is correct). Adding ranolazine is not recommended because the patient currently receives one antianginal, and an adjustment was just made to improve angina (Answers B and D are incorrect). Use of DAPT with clopidogrel is not recommended in SIHD unless other comorbidities warrant it, making Answers B and C incorrect.

**4. Answer: C**

This patient's blood pressure and heart rate are at target levels and are too low to tolerate any increase in current metoprolol or the addition of another antihypertensive agent like lisinopril (Answers A and D are incorrect). Adding ranolazine to regimens for patients currently taking two or three antianginals whose blood pressure and heart rate will not tolerate titration of other antianginals is appropriate (Answer C is correct). Even though this patient has CKD, the use of ranolazine is acceptable as long as SCr and blood urea nitrogen are periodically monitored. Changing amlodipine to diltiazem would offer no advantage for anginal control and could cause an adverse drug event with the combination of diltiazem and metoprolol (Answer B is incorrect).

**5. Answer: C**

This patient probably has a true allergy to aspirin. Patients with a history of asthma, nasal polyps, or chronic sinusitis are more likely to have an adverse event to aspirin. Therefore, she should be changed to a non–aspirin-containing produce (Answers A and B are incorrect) such as clopidogrel (Answer C is correct). Warfarin and other oral anticoagulants are not recommended for secondary prevention of non-cardioembolic ischemic stroke (Answer D is incorrect).

**6. Answer: A**

The ABI is the first-line test for most individuals at risk of PAD or in whom PAD is suspected (Answer A is correct). This is because the ABI is inexpensive, noninvasive, and readily accessible in many physicians' offices. Further evaluation is needed at this time because of the worrisome PAD symptoms and because PAD cannot be diagnosed on the presence of symptoms alone (Answer B is incorrect). The TBI test would not be indicated at this time because the patient has not undergone an ABI evaluation yet. TBI is used when the ABI is greater than 1.40 which is indicative of of absent pedal pulses or noncompressible vessels. The TBI test is beneficial when the resting ABI is normal but there is still concern

for disease. Treadmill testing is costly, time-consuming, and not as readily available; therefore, it is not required at this time (Answer D is incorrect).

**7. Answer: B**

As with other atherosclerotic disorders, diabetes, smoking, and HTN are risk factors for PAD (Answer B is correct). Although age increases the risk of CV disease and PAD, gout is not a risk factor (Answer A is incorrect). Peripheral neuropathy, a common complication of diabetes, does not increase the risk of PAD (Answers C and D are incorrect).

**8. Answer: A**

Although ticagrelor can reduce the risk of events according to the recently published EUCLID trial, the AHA/ACC offers no recommendation for initial antiplatelet regimens other than aspirin or clopidogrel as single therapy (Answer C is incorrect; Answer A is correct). Dual antiplatelet therapy with aspirin and clopidogrel would be considered only for an individual with PAD after lower-extremity endovascular or surgical revascularization or if the patient had another indication such as receiving a DES after an MI (Answer B is incorrect). Vorapaxar has an indication for PAD; however, the net clinical benefit is uncertain because of the higher risk of bleeding and lack of clinical benefit in clinical trials. The AHA/ACC guidelines give this agent a class 2b recommendation (Answer D is incorrect).

## ANSWERS AND EXPLANATIONS TO SELF-ASSESSMENT QUESTIONS

**1. Answer: B**

This patient has no complaints of angina; however, his blood pressure is not at the ideal goal of less than 130/80 mm Hg, according to the 2012 ACC/AHA guidelines for patients with SIHD and the 2015 ACC/AHA/American Society of Hypertension (ASH) blood pressure guidelines for patients with CAD. Therefore, additional antihypertensive therapy is appropriate for this patient. Angiotensin-converting enzyme inhibitors are recommended in patients with SIHD who also have HTN, DM, LVEF of 40% or less, or CKD as long as there are no contraindications (class 1). Therefore, lisinopril (Answer B) would be the most appropriate therapy at this time to control his blood pressure as well as provide CV-protective events. Amlodopine and metoprolol as well as antianginals are good agents in patients with SIHD for HTN; however, because this patient has no angina at this time and his heart rate is in the low 60s, these agents would provide no added benefit (Answers A and D are incorrect). Ranolazine would not be indicated because the patient has no angina (Answer C is incorrect).

**2. Answer: D**

β-Blockers are considered first-line, initial therapy for the treatment of ischemic heart disease to control angina symptoms (Answer D is correct). Although ACEIs are recommended in patients with SIHD who also have HTN (like this patient) to prevent MI and death, they would not adequately control his anginal symptoms (Answer A is incorrect). He should eventually be initiated on an ACEI if his blood pressure tolerates. Non-dihydropyridine CCBs and ranolazine are not recommended as first-line treatment of anginal symptoms but are considered when β-blockers are not tolerated, are ineffective alone, or are contraindicated (Answers B and C are incorrect). In addition, ranolazine would not help control his blood pressure and has the potential for additive effects on QT prolongation when administered in conjunction with citalopram.

**3. Answer: C**

Ranolazine is the best option to treat chest pain in this patient with stable angina because the patient's vital signs show a low blood pressure and low heart rate (Answer C is correct). Ranolazine has no effect on blood pressure and heart rate and would not cause a further decrease in blood pressure or heart rate. Because of the patient's vital signs, increasing metoprolol or adding amlodipine would not be good options (Answers A and B are incorrect), even though both of these treatment modalities would be appropriate. Adding lisinopril, although recommended to reduce mortality in patients with SIHD, would do little to treat the acute symptoms of angina (Answer D is incorrect).

**4. Answer: D**

This patient currently receives a β-blocker for angina and an ACEI to reduce his CV risk and treat his HTN. The patient has a prescription for tadalafil as needed, which prevents using a nitrate to treat his angina (Answer A is incorrect). His heart rate is on the lower side, which prohibits increasing the β-blocker or adding a non-dihydropyridine CCB (Answers B and C are incorrect). Using amlodipine to help with his angina symptoms as well as reduce his blood pressure to less than 130/80 mm Hg is appropriate (Answer D is correct).

**5. Answer: D**

According to the AHA/ASA guidelines on stroke prevention, aspirin, the combination of aspirin 25 mg and extended-release dipyridamole 200 mg twice daily, and clopidogrel 75 mg are acceptable for initial therapy. Typically, patients are initiated on aspirin 81 mg daily for secondary prevention unless the patient has contraindications, which this patient appears not to have (Answer D is correct). The choice should be individualized depending on patient risk factors, costs, and other issues like potential drug-drug interactions. Therefore, warfarin is incorrect because it is not recommended in this situation (Answer A is incorrect). Prasugrel is contraindicated in patients with a history of TIA/stroke (Answer B is incorrect), and clopidogrel would not be best because the patient takes omeprazole, and clopidogrel is more expensive than aspirin (Answer C is incorrect).

**6. Answer: A**

The AHA/ACC guidelines give both aspirin and clopidogrel as single therapy a class 1 recommendation for patients with symptomatic PAD (Answer A is correct). Dual antiplatelet therapy with aspirin and clopidogrel would be considered only for an individual with PAD

after lower-extremity endovascular or surgical revascularization (Answer B is incorrect). Dual antiplatelet therapy would also be used in an individual with PAD who required DAPT for another indication, such as receiving a coronary artery stent. Vorapaxar is indicated as a concomitant therapy to antiplatelets; however, the agent's clinical benefit is uncertain (Answer C is incorrect). In addition, this patient has no insurance, so cost should be considered. There is no evidence that warfarin would reduce this patient's risk of CV events (Answer D is incorrect).

**7. Answer: A**

According to the patient's risk classification, he should receive high-intensity statin therapy regardless of his LDL concentration. According to the 2013 ACC/AHA blood cholesterol guidelines, atorvastatin 80 mg daily is the only option listed that qualifies as high-intensity statin therapy (Answer A is correct). Pravastatin 40 mg daily and rosuvastatin 5 mg daily are considered moderate-intensity therapies (Answers B and C are incorrect). Simvastatin 80 mg should not be used because of the increased risk of adverse effects, and the maximal recommended daily dosage is 40 mg (Answer D is incorrect).

**8. Answer: B**

Of the pharmacologic therapies evaluated to reduce IC symptoms, cilostazol has the most compelling data (Answer B is correct). The efficacy of B-complex vitamins in reducing homocysteine concentrations has not been shown, and B-complex vitamins are not recommended (Answer A is incorrect). Cilostazol is more effective than pentoxifylline, whose effect is marginal and is not recommended by the AHA/ACC guidelines (Answer C is incorrect). Warfarin therapy plays no role in reducing IC symptoms (Answer D is incorrect).

# Anticoagulation

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**Learning Objectives**

1. Recommend a patient-specific pharmacotherapy plan to reduce the risk of stroke in patients with atrial fibrillation (AF).
2. Devise an evidence-based pharmacotherapy plan for preventing and treating venous thromboembolism (VTE).
3. Analyze the need for anticoagulation in patients with AF or VTE.
4. Determine appropriate reversal strategies for patients at risk of bleeding, or actively bleeding while receiving anticoagulation therapy.
5. Determine appropriate selection and dosing of anticoagulant therapy on the basis of patient-specific factors and drug interactions.
6. Evaluate literature and clinical implications of data for patients receiving anticoagulant agents.

**Abbreviations in This Chapter**

| | |
|---|---|
| ACC | American College of Cardiology |
| ACCP | American College of Chest Physicians |
| AF | Atrial fibrillation |
| AHA | American Heart Association |
| CRNM | Clinically relevant nonmajor |
| DOAC | Direct oral anticoagulant |
| DVT | Deep venous thrombosis |
| FFP | Fresh frozen plasma |
| LMWH | Low-molecular-weight heparin |
| MI | Myocardial infarction |
| NVAF | Nonvalvular atrial fibrillation |
| PCC | Prothrombin complex concentrate |
| 4PCC | Four-factor prothrombin complex concentrate |
| PE | Pulmonary embolism |
| P-gp | P-glycoprotein |
| PRBC | Packed red blood cell |
| t-PA | Tissue plasminogen activator |
| UFH | Unfractionated heparin |
| VKA | Vitamin K antagonist |
| VTE | Venous thromboembolism |

**Self-Assessment Questions**

*Answers and explanations to these questions may be found at the end of this chapter.*

*Questions 1–3 pertain to the following case.*

N.T. is a 68-year-old woman (height 63 inches, weight 58 kg) who presents to the hospital with atrial fibrillation (AF). After her heart rate is controlled with metoprolol, she is asymptomatic. She also has hypertension, type 2 diabetes, osteoarthritis, and depression. Her current medications include metoprolol 100 mg twice daily, lisinopril 10 mg daily, acetaminophen 1000 mg three times daily, metformin 500 mg twice daily, and citalopram 20 mg daily. Her heart rate is currently 82 beats/minute and blood pressure is 130/88 mm Hg. Her serum creatinine (SCr) is 0.8 mg/dL and creatinine clearance (CrCl) is 60 mL/minute/1.73 $m^2$; she has normal hepatic function.

1. Which best depicts N.T.'s $CHA_2DS_2$-VASc and HAS-BLED scores?
   A. $CHA_2DS_2$-VASc score of 2 and a HAS-BLED score of 1.
   B. $CHA_2DS_2$-VASc score of 4 and a HAS-BLED score of 2.
   C. $CHA_2DS_2$-VASc score of 5 and a HAS-BLED score of 4.
   D. $CHA_2DS_2$-VASc score of 4 and a HAS-BLED score of 1.

2. Which is the most appropriate stroke prevention strategy for N.T.?
   A. Aspirin 325 mg once daily.
   B. Rivaroxaban 20 mg once daily.
   C. Apixaban 2.5 mg twice daily.
   D. Edoxaban 30 mg once daily.

3. N.T. was initiated on dabigatran and 3 months later is involved in a motor vehicle accident, resulting in an intracranial hemorrhage. Which is the most appropriate reversal strategy for N.T.?
   A. Protamine.
   B. Fresh frozen plasma (FFP).
   C. Idarucizumab.
   D. Andexanet alfa.

*Questions 4–6 pertain to the following case.*

M.R. is a 51-year-old woman (height 65 inches, weight 98 kg, body mass index 36 kg/$m^2$) who presents to the emergency department with pain, swelling, and redness in her right leg up into her thigh. She also has some shortness of breath and pain in the middle of her chest.

She reports that she had a hysterectomy about 2 weeks ago and has not been moving around much at home in the past 2 weeks. On physical examination, her right leg is warmer than the left and tender to touch. Her cardiac examination appears normal, with vital signs of heart rate of 80 beats/minute, blood pressure 146/96 mm Hg, respiratory rate 20 breaths/minute, and $O_2$ saturation 92% on room air. Her initial laboratory information includes a positive D-dimer, a negative troponin, and a CrCl of 65 mL/minute/1.73 $m^2$. Duplex ultrasonography detects a right femoral-popliteal deep venous thrombosis (DVT), and a computed tomography (CT) angiogram reveals a pulmonary embolism (PE). Her other conditions include hypertension, diabetes mellitus, and dyslipidemia. She also reports smoking 1 pack/day of cigarettes for the past 30 years. Her current medications include lisinopril 10 mg daily, chlorthalidone 25 mg daily, metformin 1000 mg twice daily, pravastatin 40 mg daily, and hydrocodone 5 mg/acetaminophen 500 mg every 6 hours as needed for pain.

4. Which best depicts M.R.'s number of venous thromboembolism (VTE) risk factors?
   A. 3.
   B. 4.
   C. 5.
   D. 6.

5. Which statement regarding M.R.'s outpatient therapy is most accurate?
   A. Despite having a PE, M.R. has a low risk of 30-day mortality and can be treated as an outpatient.
   B. The presence of a positive D-dimer represents a large thrombus burden and dictates that M.R. be admitted to the hospital.
   C. M.R. should be admitted to the hospital because patients with a PE have high risk of 30-day mortality.
   D. Because M.R. had a negative troponin, she can safely be treated as an outpatient.

6. Which is the most appropriate treatment strategy for M.R.?
   A. Enoxaparin 100 mg every 12 hours and dabigatran 150 mg twice daily; after 5 days, enoxaparin can be discontinued.
   B. Rivaroxaban 15 mg twice daily for 7 days, followed by 20 mg once daily.
   C. Enoxaparin 100 mg every 12 hours for 5 days; then initiate edoxaban 60 mg once daily.
   D. Unfractionated heparin (UFH) 4000-unit bolus, followed by 1000 units/hour and warfarin 7.5 mg to an international normalized ratio (INR) of 2.0–3.0, discontinuing UFH when a therapeutic INR is reached.

7. W.R. (weight 100 kg) is admitted for treatment of DVT with a PE. He is given an 8000-unit bolus of UFH and initiated on an infusion of 1800 units/hour. Twelve hours into the infusion, he begins to vomit blood. Which is the most appropriate dose of protamine for W.R.?
   A. 80 mg.
   B. 50 mg.
   C. 31.5 mg.
   D. 18 mg.

8. N.Z. is a 76-year-old man recently hospitalized for a heart failure exacerbation with significant fluid overload and severely restricted mobility. His other medical conditions include hypertension, coronary artery disease with a myocardial infarction (MI) 8 years ago, VTE 2 years ago, dyslipidemia, osteoarthritis, and gastroesophageal reflux disease. His medications before admission are lisinopril 20 mg daily, furosemide 40 mg daily, metoprolol succinate 100 mg daily, aspirin 81 mg daily, atorvastatin 80 mg daily, acetaminophen 1000 mg three times daily, and ranitidine 150 mg daily. On admission, furosemide was changed to 40 mg intravenously daily, and his recently increased metoprolol dose is reduced back to 50 mg daily. N.Z.'s current CrCl is 58 mL/minute/1.73 $m^2$. The team is discussing the potential need for prophylaxis of VTE. Which would be most appropriate for N.Z.?
   A. Enoxaparin 40 mg subcutaneously daily for 10 days.
   B. Apixaban 2.5 mg twice daily for 35 days.
   C. UFH 5000 units subcutaneously twice daily for 10 days.
   D. Rivaroxaban 10 mg daily for 35 days.

## I. STROKE PREVENTION IN NONVALVULAR ATRIAL FIBRILLATION

A. Introduction
   1. Atrial fibrillation (AF) is the most common sustained cardiac dysrhythmia, affecting 2.7–6.1 million Americans.
   2. Incidence increases with age.
      a. Around 1% of patients with AF are younger than 60 years of age.
      b. Around 12% of patients with AF are 75–84 years of age.
      c. More than one-third of patients with AF are 80 years of age and older.
   3. Accounts for more than 500,000 hospital discharges annually in the United States and significant health care costs

B. Pathophysiology
   1. Etiology
      a. Typically related to structural heart disease such as coronary artery disease, heart failure, or other cardiogenic issues such as hypertension
      b. Valvular heart disease
      c. Noncardiogenic causes: Hyper- or hypothyroid disease, acute infection, excessive alcohol intake, post-surgery, and PE
   2. Rhythm
      a. AF is supraventricular tachyarrhythmia.
      b. Incomplete conduction of supraventricular impulses
      c. Conduction through the atrioventricular node is erratic and is revealed by the electrocardiogram as an irregularly irregular rhythm.
   3. Thrombosis
      a. Incomplete conduction of supraventricular impulses creates a lack of atrial contraction.
      b. Incomplete emptying of the cardiac chambers during systole increases the rate of blood pooling in the atria, most notably in the left atrial appendage.
      c. Ninety percent of thromboses occur in the left atrial appendage and 10% in the left atrium.
      d. Blood stasis is associated with the increased formation of mural thrombi, which may cause arterial embolization, or stroke, if dislodged by a return to normal sinus rhythm or by the shearing forces from turbulent blood flow through the chambers.

C. Definitions
   1. Paroxysmal AF: AF terminates spontaneously or with intervention within 7 days.
   2. Persistent AF: Continuous AF that is sustained more than 7 days
   3. Longstanding persistent AF: Continuous AF for more than 12 months
   4. Permanent AF: Decision of the patient and clinician to stop further attempts to restore and/or maintain normal sinus rhythm and remain in AF
   5. NVAF: When discussing the role of direct oral anticoagulants (DOACs), NVAF represents patients without moderate or severe mitral stenosis and those with mechanical heart valves, including patients receiving transcatheter aortic valve replacement (without AF).
      a. The INVICTUS trial (n=4531) demonstrated an increase in stroke, systemic embolism, MI, or vascular death in patients receiving rivaroxaban compared to vitamin K antagonist (VKA) (8.2% vs. 6.5%; $p<0.001$) in patients with rheumatic heart disease (mitral stenosis).

D. Stroke
   1. NVAF increases the risk of stroke by 5-fold compared with patients without AF.
   2. AF is responsible for 15%–20% of all strokes.

3. Risk stratification (only for patients with NVAF)
   a. The $CHA_2DS_2$-VASc score is primarily used and referred in the guidelines to determine the risk of stroke for patients with NVAF. The $CHADS_2$ score is included for reference because many trials referred to used the $CHADS_2$ score instead of the $CHA_2DS_2$-VASc.
   b. $CHADS_2$ score
      i. 6 possible points based on risk factors (Table 1)
      ii. Risk of ischemic stroke is 1.9%–18.2%, depending on score (Table 2).
      iii. Limited by ability to determine who is truly at low or intermediate risk because those with scores of 0 or 1 suggest a risk of approximately 2%–3% (Table 2)
   c. $CHA_2DS_2$-VASc score
      i. 9 possible points based on risk factors (Table 1)
      ii. Adds risk factors of age 65–74, female sex, and history of other vascular disease
      iii. Improves predictive value of who is truly at low risk (score of 0 = 0% risk) and intermediate risk (score of 1 = 1.3% risk)
      iv. Guidelines from the American Heart Association (AHA)/American College of Cardiology (ACC)/Heart Rhythm Society, the European Society of Cardiology, and the American College of Chest Physicians (ACCP) all recommend using the $CHA_2DS_2$-VASc score to determine the need for anticoagulant therapy in patients with NVAF (Table 3; Table 4).

**Table 1.** Risk Stratification for Ischemic Stroke in Patients with NVAF

| $CHADS_2$ Score | | $CHA_2DS_2$-VASc Score | |
|---|---|---|---|
| Congestive heart failure[a] | 1 | Congestive heart failure[a] | 1 |
| Hypertension | 1 | Hypertension | 1 |
| Age ≥ 75 | 1 | Age ≥ 75 | 2 |
| Diabetes mellitus | 1 | Diabetes mellitus | 1 |
| Previous stroke or TIA or thromboembolism | 2 | Previous stroke or TIA or thromboembolism | 2 |
| | | Vascular disease (prior MI, PAD, aortic plaque) | 1 |
| | | Age 65–74 | 1 |
| | | Sex category (female) | 1 |

[a]Heart failure as a risk factor represents those with an ejection fraction ≤ 40% or patients with recent decompensated heart failure requiring hospitalization, irrespective of ejection fraction.

MI = myocardial infarction; NVAF = nonvalvular atrial fibrillation; PAD = peripheral arterial disease; TIA = transient ischemic attack.

**Table 2.** Adjusted Stroke Rate per Year Based on $CHADS_2$ and $CHA_2DS_2$-VASc Scores

| Score | $CHADS_2$ Adjusted Stroke Rate (%/year) | $CHA_2DS_2$-VASc Adjusted Stroke Rate (%/year) | Risk Category |
|---|---|---|---|
| 0 | 1.9 | 0 | Low |
| 1 | 2.8 | 1.3 | Intermediate |
| 2 | 4.0 | 2.2 | High |
| 3 | 5.9 | 3.2 | |
| 4 | 8.5 | 4.0 | |
| 5 | 12.5 | 6.7 | |
| 6 | 18.2 | 9.8 | |
| 7 | — | 9.6 | |
| 8 | — | 6.7 | |
| 9 | — | 15.2 | |

**Table 3.** Guideline Recommendations for Antithrombotic Therapy in Patients with NVAF Based on $CHA_2DS_2$-VASc Score[a]

| $CHA_2DS_2$-VASc Score = 0 in men or 1 in women | $CHA_2DS_2$-VASc Score = 1 in men or 2 in women | $CHA_2DS_2$-VASc Score ≥ 2 in men or ≥ 3 in women |
|---|---|---|
| Reasonable to omit antithrombotic therapy or consider aspirin | Consider oral anticoagulation, aspirin, or no antithrombotic therapy | Oral anticoagulant therapy is indicated; DOACs are recommended over warfarin in DOAC-eligible patients |

[a]AHA/ACC/Heart Rhythm Society guidelines.

DOAC = direct oral anticoagulant.

**Table 4.** ACCP Guideline Recommendations for Patients with Atrial Fibrillation[a]

| Recommendation | Quality of Evidence |
|---|---|
| Use of a risk factor approach for assessing a patient's stroke risk, instead of a categorical approach of low, moderate, or high risk. Recommend use of the $CHA_2DS_2$-VASc score | Moderate |
| Antithrombotic therapy for patients with ≥ 1 non-sex $CHA_2DS_2$-VASc stroke risk factors (score ≥ 1 in a male or ≥ 2 in a female) | Moderate |
| A bleeding risk assessment at every patient contact and should initially focus on potentially modifiable bleeding risk factors (e.g., BP, medications, treat gastric ulcer, optimize renal function) | Low |
| Recommend use of the HAS-BLED score. Those at high risk of bleeding (HAS-BLED ≥ 3) warrant more frequent and regular reviews of follow-up | Moderate |
| Recommend against antiplatelet therapy (monotherapy or aspirin with clopidogrel) for stroke prevention alone, regardless of stroke risk | Moderate |
| For patients eligible for oral anticoagulation, recommend DOACs over VKA | Moderate |
| Patients taking VKA with a consistently low time in therapeutic range (TTR < 65%), recommend interventions to improve TTR or changing to a DOAC | Moderate |
| Patients with AF > 48 hr or for an unknown duration undergoing elective cardioversion should receive therapeutic anticoagulation with well-managed VKA (INR 2.0–3.0) or a DOAC for at least 3 wk before cardioversion or a transesophageal echocardiography–guided approach with abbreviated anticoagulation before cardioversion rather than no anticoagulation | Moderate |
| Patients with AF > 48 hr or for an unknown duration undergoing elective cardioversion should receive therapeutic anticoagulation with a VKA or a DOAC for at least 4 wk after successful cardioversion rather than no anticoagulation, regardless of their baseline risk of stroke | Moderate |
| Patients with AF and acute ischemic stroke should receive long-term oral anticoagulation unless contraindicated | High |

[a]Recommendations listed only include those considered "Strong" by ACCP. Recommendations considered "Weak" or "Ungraded" are not listed due to the limited quantity and quality of the data.

ACCP = American College of Chest Physicians.

d. HAS-BLED score (Table 5)
   i. 9-point scale to assess risk of major bleeding on warfarin in patients with NVAF
   ii. Few patients have a score of 3 or greater.
   iii. Should not be used to determine who does not get therapy, but more to balance risk of stroke with risk of bleeding
   iv. Predictive value is inconsistent and unreliable with DOACs.

**Table 5.** Components and Bleeding Rates of the HAS-BLED Score

| Risk Factors | Points |
|---|---|
| Hypertension (systolic BP > 160 mm Hg) | 1 |
| Abnormal renal or liver function[a] | 1 or 2 |
| History of stroke | 1 |
| History of bleeding[b] | 1 |
| Labile INRs[c] | 1 |
| Older adults (age > 65) | 1 |
| Drugs or alcohol excess[d] | 1 or 2 |

| Score | % of Patients | Risk of Major Bleeding/Yr |
|---|---|---|
| 0 | 26 | 1.1% |
| 1 | 42 | 1.0% |
| 2 | 24 | 1.9% |
| 3 | 6 | 3.7% |
| 4 | 2 | 8.7% |
| 5 | < 1 | 12.5% |
| > 5 | < 1% | Undetermined |

[a]1 point for renal and 1 point for liver.

Renal = chronic dialysis, renal transplant, or SCr of 2.26 mg/dL or greater

Liver = chronic hepatic disease, bilirubin > 2 times the upper limit of normal, in association with AST/ALT/Alk Phos > 3 times the upper limit of normal

[b]History of bleeding or predisposition to bleeding such as a bleeding diathesis or anemia.

[c]Unstable/high INRs or time in therapeutic range < 60%.

[d]Drugs include antiplatelet or nonsteroidal anti-inflammatory drugs = 1 point; alcohol excess is ≥ 8 alcohol drinks/wk = 1 point.

BP = blood pressure.

E. Anticoagulant Therapy
   1. Warfarin
      a. Vitamin K antagonist
         i. Inhibits vitamin K recycling by inhibition of vitamin K epoxide reductase > vitamin K reductase, preventing γ-carboxylation of clotting factors II, VII, IX, and X, leaving these factors unable to bind to phospholipid membranes and unable to take part in coagulation
         ii. Also inhibits carboxylation and activation of natural anticoagulants protein C and protein S
         iii. *S*-warfarin is about 5 times more potent than *R*-warfarin.
      b. Several trials have shown a 70%–80% risk reduction in stroke and systemic embolism with warfarin therapy compared with placebo.
      c. Dosing for NVAF is based on requirements to achieve an INR goal of 2.0–3.0.
      d. Initial starting dose is typically 5 mg daily, but doses of up to 10 mg daily may be required for some patients. A lower starting dose (2–3 mg daily) should be considered in patients with the following: advanced age, low body weight, drug interactions, malnourishment, heart failure, hyperthyroid state, low albumin or liver disease; selected ethnic groups (e.g., Asians)
         i. Dosing algorithms are available to assist with initiating therapy.
         ii. Using pharmacogenomics data can achieve a faster therapeutic INR and fewer INRs of 4 or greater, but has not reduced thrombotic or bleeding events. Therefore, using pharmacogenomic data is not part of standard of care.

iii. In patients receiving a parenteral direct thrombin inhibitor or in lupus cases when the INR is not reflective of dosing, factor VII or X concentration has been used with some success. A chromogenic factor X assay is likely the most reliable mechanism to measure the anticoagulant activity of warfarin in these patients, especially with INR values greater than 3.0.
iv. Need to consider the half-lives of inhibited clotting factors in order to see the full anticoagulant effects: Factor VII = 6 hours; factor IX = 24 hours; factor X = 36 hours, factor II = 72 hours
v. Functional clotting factors already produced must "run their course" and cannot be inhibited with higher doses, regardless of the INR.

e. Follow-up INR monitoring
i. INR values on a specific day are the result from warfarin doses taken over the previous 3–4 days, and dosing changes made on a specific day are not fully represented in the INR for 3–5 days. It takes 5–7 days to see the full effect of a stable warfarin dose.
ii. If the INR is out of the therapeutic range in the outpatient setting, increase or decrease the cumulative weekly dose by 5%–20%, depending on the INR; if the INR is greater than 4.5, consider holding one or two doses before resuming at the reduced dose.
iii. If the INR is previously stable or therapeutic and a single out-of-range INR is 0.5 or less above or below the therapeutic range, current dosing can be continued; the INR should be rechecked within 1–2 weeks.
iv. In general, no need to adjust dose if INR is within 0.1 of goal, but would monitor more closely (especially if below goal)
v. If the INR decreases to 1.8 or less, the risk of ischemic stroke in NVAF increases by 60%, whereas the risk of bleeding does not significantly increase until the INR is greater than 4.0 (better to be a little high than a little low).
vi. In the setting of continuous enteral feeding, consider holding the feeds 1 hour before and after the dose.

f. Drug interactions
i. Reduced warfarin absorption (e.g., cholestyramine, sucralfate)
ii. Enzyme induction producing a reduced INR and warfarin effect, increased risk of thrombosis (e.g., phenytoin, phenobarbital, carbamazepine, rifampin, St. John's wort); therefore, higher doses of warfarin are often required
iii. Enzyme inhibition producing an increased INR and warfarin effect, increased risk of bleeding
(a) *S*-warfarin mainly metabolized by cytochrome P450 (CYP) 2C9 > CYP3A4 (e.g., metronidazole, trimethoprim/sulfamethoxazole, fluconazole, isoniazid, fluoxetine, sertraline, amiodarone)
(b) *R*-warfarin mainly metabolized by CYP1A2 and CYP3A4 > CYP2C19 (e.g., clarithromycin, erythromycin, azole antifungals, fluoxetine, amiodarone, cyclosporine, sertraline, grapefruit juice, ciprofloxacin, protease inhibitors, diltiazem, verapamil, isoniazid, metronidazole)
iv. Antiplatelet agents through a pharmacodynamic effect (e.g., aspirin, $P2Y_{12}$ inhibitors, nonsteroidal anti-inflammatory drugs, fish oil, gingko, garlic)
v. Agents that affect warfarin clearance (e.g., amiodarone, propafenone, cimetidine)
vi. Agents that reduce vitamin K synthesis in the intestinal flora (e.g., antibiotics)

g. Drug-disease interactions
i. Increased clotting factor consumption (e.g., hyperthyroid state, fever)
ii. Reduced warfarin metabolism (e.g., heart failure, liver disease)
iii. Reduced clotting factor production (e.g., liver disease)

h. Drug-food interactions
i. Recommended dietary intake of vitamin K is 80 mcg/day.
ii. Wide variety of vitamin K in various foods
iii. Goal is to remain consistent with intake of vitamin K–containing foods while on warfarin therapy, which may be challenging for some patients.

2. Dabigatran
    a. Mechanism of action and pharmacologic properties (Table 6)
    b. Dosing recommendations (Table 7). Reduced dose of 75 mg twice daily has not been evaluated in clinical trials. Reduced dose of 110 mg twice daily is not indicated for patients with NVAF in the United States but is used in Canada and Europe.
    c. Evaluated in the RE-LY trial compared with dose-adjusted warfarin (Table 8)
    d. In addition to bleeding, dyspepsia is a common adverse effect, occurring in about 10% of patients and contributing to significantly higher rates of drug discontinuation at 1 year and 2 years in the RE-LY trial.
    e. Stability: Once the bottle is opened, the medication should be used within 4 months to maintain appropriate potency, and capsules cannot be placed in a pillbox.
    f. Drug interactions based on P-glycoprotein (P-gp) (Table 7)
    g. Capsules should not be opened or crushed because this results in a 75% increase in bioavailability.
    h. Converting to and from dabigatran to and from other anticoagulants (Box 1)

**Box 1.** Dabigatran Conversion Strategies to and from Oral and Parenteral Anticoagulants

| **Converting from Dabigatran to Warfarin** | |
|---|---|
| CrCl ≥ 50 mL/min | Start warfarin 3 days before discontinuing dabigatran |
| CrCl 31–50 mL/min | Start warfarin 2 days before discontinuing dabigatran |
| CrCl 15–30 mL/min | Start warfarin 1 day before discontinuing dabigatran |
| CrCl < 15 mL/min | No dosing recommendations are available |
| **Converting from Warfarin to Dabigatran** | |
| Discontinue warfarin and start dabigatran when the INR is < 2.0[a] | |
| **Converting between Dabigatran and Parenteral Anticoagulants** | |
| Start dabigatran 0–2 hr before the next dose of the parenteral drug was to have been administered (e.g., LMWH) or when a continuously administered parenteral drug is discontinued (e.g., intravenous UFH) | |
| For patients currently taking dabigatran, wait 12 hr (CrCl > 30 mL/min/1.73 $m^2$) or 24 hr (CrCl < 30 mL/min/1.73 $m^2$) after the last dose of dabigatran before initiating treatment with a parenteral anticoagulant | |
| Note: High dabigatran concentrations can occur in severe renal impairment, and effects last for several days. A thrombin time can be used to determine when the effects of dabigatran are dissipating. | |

[a]Because dabigatran can contribute to an increased INR, the INR will better reflect warfarin's effect after dabigatran has been discontinued for at least 2 days.

LMWH = low-molecular-weight heparin; UFH = unfractionated heparin.

3. Rivaroxaban
    a. Mechanism of action and pharmacologic properties (Table 6)
    b. Dosing recommendations (Table 7). Reduced dose of 15 mg once daily is available and should be taken with food. Used in around 20% of the patients in the ROCKET-AF trial
    c. Evaluated in the ROCKET-AF trial compared with dose-adjusted warfarin (Table 8)
    d. Drug interactions
        i. Strong CYP3A4 and P-gp inhibitors and inducers (Table 7)
        ii. The rivaroxaban package label has a warning for use of moderate CYP3A4 and P-gp inhibitors (e.g., amiodarone, verapamil, diltiazem, erythromycin, dronedarone, cimetidine) in patients with a CrCl of 15–80 mL/minute/1.73 $m^2$, given increased rivaroxaban concentrations in pharmacokinetic studies. An analysis of patients receiving these agents with rivaroxaban with this level of renal function from the ROCKET-AF trial did not show an increased risk of bleeding.

e. Converting to and from rivaroxaban to and from other anticoagulants (Box 2)

**Box 2.** Rivaroxaban Conversion Strategies to and from Oral and Parenteral Anticoagulants

| **Converting from Rivaroxaban to Warfarin** |
|---|
| Discontinue rivaroxaban, and begin both a parenteral anticoagulant and warfarin at the time the next dose of rivaroxaban would have been taken. Discontinue the parenteral anticoagulant when INR ≥ 2.0 |
| **Converting from Rivaroxaban to Anticoagulants (with rapid onset) Other than Warfarin** |
| Discontinue rivaroxaban, and give the first dose of the other anticoagulant (oral or parenteral; other than warfarin) at the time that the next rivaroxaban dose would have been taken |
| **Converting from Warfarin to Rivaroxaban** |
| Discontinue warfarin and initiate rivaroxaban once INR < 3.0 |
| **Converting from Anticoagulants (with rapid onset) Other than Warfarin to Rivaroxaban** |
| Begin rivaroxaban 0–2 hr before the next scheduled evening administration of the drug (e.g., LMWH or non-warfarin oral anticoagulant), and do not administer the other anticoagulant. For UFH administered by continuous infusion, stop the infusion and start rivaroxaban at the same time |

4. Apixaban
   a. Mechanism of action and pharmacologic properties (Table 6)
   b. Dosing recommendations (Table 7)
      i. Reduced dose of 2.5 mg twice daily is available and was used in about 5% of the patients in the ARISTOTLE trial.
      ii. Data suggest that the reduced dose is being used in many patients (up to 30%), with most not meeting the trial criteria for the reduced dose. One study suggests this is associated with a 20% increased risk of ischemic stroke and with no difference in major bleeding (J Am Coll Cardiol 2017;69:2779-90).
   c. Evaluated in the ARISTOTLE trial compared with dose-adjusted warfarin (Table 8)
   d. Drug interactions are associated with strong CYP3A4 and P-gp inhibitors and inducers (Table 7).
   e. Converting to and from apixaban to and from other anticoagulants (Box 3)

**Box 3.** Apixaban Conversion Strategies to and from Oral and Parenteral Anticoagulants

| **Converting from Apixaban to Warfarin** |
|---|
| Discontinue apixaban, and begin both a parenteral anticoagulant and warfarin at the time the next dose of apixaban would have been taken. Discontinue the parenteral anticoagulant when INR ≥ 2.0 |
| **Converting from Apixaban to Anticoagulants (with rapid onset) Other than Warfarin** |
| Discontinue apixaban, and begin the new anticoagulant (oral or parenteral; other than warfarin) at the usual time of the next dose of apixaban |
| **Converting from Warfarin to Apixaban** |
| Warfarin should be discontinued and apixaban initiated when INR < 2.0 |
| **Converting from Anticoagulants (with rapid onset) Other than Warfarin to Apixaban** |
| Begin apixaban 0–2 hr before the next scheduled administration of the drug (e.g., LMWH or non-warfarin oral anticoagulant), and do not administer the other anticoagulant. For UFH administered by continuous infusion, stop the infusion and start apixaban at the same time |

5. Edoxaban
    a. Mechanism of action and pharmacologic properties (Table 6)
    b. Dosing recommendations (Table 7). Reduced dose of 30 mg once daily is available. Used in around 25% of the patients in the ENGAGE-AF trial
    c. Evaluated in the ENGAGE-AF TIMI 48 trial compared with dose-adjusted warfarin (Table 8)
    d. Drug interactions are associated with P-gp (Table 7).
    e. Converting to and from edoxaban to and from other anticoagulants (Box 4)

**Box 4.** Edoxaban Conversion Strategies to and from Oral and Parenteral Anticoagulants

| **Converting from Edoxaban to Warfarin** |
|---|
| Oral option: For patients taking 60 mg of edoxaban, reduce the dose to 30 mg and begin warfarin concomitantly. For patients receiving 30 mg of edoxaban, reduce the dose to 15 mg and begin warfarin concomitantly. The INR must be measured at least weekly and just before the daily dose of edoxaban to minimize the influence of edoxaban on INR measurements. Once a stable INR ≥ 2.0 is achieved, edoxaban should be discontinued and warfarin continued |
| Parenteral option: Discontinue edoxaban, and administer a parenteral anticoagulant and warfarin at the time of the next scheduled edoxaban dose. Once a stable INR ≥ 2.0 is achieved, the parenteral anticoagulant should be discontinued and warfarin continued |
| **Converting from Edoxaban to Anticoagulants (with rapid onset) Other than Warfarin** |
| Discontinue edoxaban, and begin the new anticoagulant (oral or parenteral; other than warfarin) at the usual time of the next dose of edoxaban |
| **Converting from Warfarin to Edoxaban** |
| Discontinue warfarin and start edoxaban when the INR is ≤ 2.5 |
| **Converting from Anticoagulants (with rapid onset) Other than Warfarin to Edoxaban** |
| Discontinue the other oral anticoagulant (other than warfarin) or LMWH, and begin taking edoxaban at the usual time of the next dose of the other anticoagulant. For UFH administered by continuous infusion, stop the infusion and start edoxaban 4 hr later |

**Table 6.** DOAC Pharmacologic Properties

| | **Dabigatran** | **Rivaroxaban** | **Apixaban** | **Edoxaban** |
|---|---|---|---|---|
| Mechanism of action | Direct IIa inhibitor | Direct Xa inhibitor | Direct Xa inhibitor | Direct Xa inhibitor |
| Bioavailability | 3%–7% | 66% without food, 80%–100% with food | 50% | 62% |
| Onset of anticoagulant activity | 1.5 hr | 2–4 hr | 2–3 hr | 1–2 hr |
| Half-life[a] | 12–17 hr | 9–13 hr | 12 hr | 9–10 hr |
| Renal clearance | 80% | 36% | 27% | 50% |
| Protein binding | 35% | 90% | 87% | 55% |
| Removed by dialysis | Yes | No | No | No |
| P-gp transport | Yes | Yes | Yes | Yes |
| Hepatic metabolism | None | CYP 3A4/5 and 2J2 | CYP3A4/5 | Minimal (4% CYP3A4/5) |
| Antidote for reversal | Yes | Yes | Yes | Yes[b] |

[a]Half-life can be increased in patients with severe illness with renal and/or hepatic failure.

[b]Although andexanet alfa is not approved for reversal of edoxaban, high-dose andexanet alfa has shown reversal in small studies.

**Table 7.** Dosing of DOACs in NVAF

| Agent | Standard Dosing | Dose Adjustment[a] | Avoid Use[a] |
|---|---|---|---|
| Dabigatran | 150 mg twice daily | 75 mg twice daily<br>• CrCl 15–30 mL/min/1.73 $m^2$<br>• CrCl 30–50 mL/min/1.73 $m^2$ with ketoconazole or dronedarone | • CrCl < 15 mL/min /1.73 $m^2$<br>• Dialysis<br>• CrCl 15–30 mL/min/1.73 $m^2$ with amiodarone, verapamil, ketoconazole, dronedarone, diltiazem, and clarithromycin<br>• Rifampin<br>• Chemotherapy agents – Vinblastine, doxorubicin, imatinib, crizotinib, vandetanib, sunitinib, abiraterone, and enzalutamide |
| Rivaroxaban | 20 mg once daily with meals | 15 mg once daily with meals<br>• CrCl 15–50 mL/min/1.73 $m^2$<br>• Dialysis[b] | • Strong CYP3A4 and P-gp inducers (e.g., rifampin, phenytoin, carbamazepine, St. John's wort)<br>• Strong CYP3A4 and P-gp inhibitors (e.g., protease inhibitors, itraconazole, ketoconazole, conivaptan)<br>• Chemotherapy agents – Vinblastine, doxorubicin, imatinib, crizotinib, vandetanib, sunitinib, abiraterone, and enzalutamide |
| Apixaban | 5 mg twice daily | 2.5 mg twice daily<br>• Two of three criteria (age ≥ 80 yr, weight ≤ 60 kg, or SCr ≥ 1.5 mg/dL)<br>• Use with strong CYP3A4 and P-gp inhibitors (e.g., protease inhibitors, itraconazole, ketoconazole, conivaptan)<br>• Dialysis[b,c] | • Strong CYP3A4 and P-gp inducers (e.g., rifampin, phenytoin, carbamazepine, St. John's wort)<br>• If on 2.5 mg twice daily – Strong CYP3A4 and P-gp inhibitors (e.g., protease inhibitors, itraconazole, ketoconazole, conivaptan)<br>• Chemotherapy agents – Vinblastine, doxorubicin, imatinib, crizotinib, vandetanib, sunitinib, abiraterone, and enzalutamide |
| Edoxaban | 60 mg once daily | 30 mg once daily<br>• CrCl 15–50 mL/min/1.73 $m^2$ | • CrCl > 95 mL/min/1.73 $m^2$<br>• CrCl < 15 mL/min/1.73 $m^2$<br>• Dialysis<br>• Rifampin<br>• Chemotherapy agents – Vinblastine, doxorubicin, imatinib, crizotinib, vandetanib, sunitinib, abiraterone, and enzalutamide |

[a]CrCl in the DOAC trials was calculated using Cockcroft-Gault equation with total body weight.

[b]Data in the package label for dosing for rivaroxaban and apixaban in the setting of dialysis are from eight-patient single-dose pharmacokinetic studies. Although no prospective randomized trials support their efficacy or safety in these patients, data from retrospective observational trials suggest safe and effective use in these patients.

[c]The apixaban package label suggests a dose of 5 mg twice daily in patients receiving dialysis who are younger than 80 and weigh more than 60 kg. A study with several days of apixaban administration in patients receiving dialysis showed about a 2-fold increase in Cmax and area under the curve using 5 mg twice daily and suggests that the 2.5-mg twice-daily dose can be considered.

**Table 8.** Comparison of Trial Characteristics of DOACs Compared with Warfarin

| | RE-LY | ROCKET AF | ARISTOTLE | ENGAGE AF-TIMI 48 |
|---|---|---|---|---|
| Study drug | Dabigatran | Rivaroxaban | Apixaban | Edoxaban |
| Study size | 18,113 (3 arms) | 14,264 (2 arms) | 18,201 (2 arms) | 21,105 (3 arms) |
| Double-blind | No | Yes | Yes | Yes |
| Previous VKA use (%) | 50 | 62 | 57 | 59 |
| $CHADS_2$ score<br>Mean<br>0–1 (%)<br>2 (%)<br>3–6 (%) | <br>2.1<br>32<br>36<br>32 | <br>3.5<br>0<br>13<br>87 | <br>2.1<br>34<br>36<br>30 | <br>2.8<br>—<br>77 (≤ 3)<br>23 (4–6) |
| Previous stroke or TIA (%) | 20 | 55 | 19 | 28 |
| Protocol to manage INR | Yes | No | Yes | Yes |
| Mean TTR (%) | 64 | 55 | 62 | 65 |
| Median TTR (%) | NR | 58 | 66 | 68 |
| Median follow-up (yr) | 2.0 | 1.9 | 1.8 | 2.8 |

NR = not reported; TTR = time in therapeutic range; VKA = vitamin K antagonist.

6. Trial results
    a. Primary efficacy end point – Stroke or systemic embolism
        i. All agents noninferior to warfarin – Primary end point of all the trials
        ii. Dabigatran and apixaban were superior to warfarin in the intention-to-treat analysis.
        iii. Rivaroxaban and edoxaban were superior to warfarin in the per-protocol analysis.
    b. Hemorrhagic stroke – All agents significantly better than warfarin. This is the main benefit of a DOAC over warfarin across all trials.
    c. Ischemic stroke – Only dabigatran significantly better than warfarin
    d. Major bleeding
        i. Apixaban and edoxaban significantly safer than warfarin
        ii. Dabigatran and rivaroxaban had safety similar to warfarin.
    e. All-cause mortality
        i. Only apixaban significantly reduced mortality compared with warfarin (p=0.01).
        ii. All agents provided about a 10% relative reduction in mortality.
7. Controversies and considerations
    a. Major differences in the trials (Table 8) prevent concluding that one agent has superior efficacy or safety over any other. The AHA/ACC/Heart Rhythm Society and the European Society of Cardiology guidelines do not prefer one DOAC to another.
    b. Patient risk
        i. The mean $CHADS_2$ score in the ROCKET-AF trial was 3.5 compared with 2.1 in the RE-LY and ARISTOTLE trials. The $CHADS_2$ score in ENGAGE-AF was 2.8.
        ii. Results may have varied because of studying different risks of patients compared with using a different DOAC.
    c. Ischemic stroke
        i. Although dabigatran was the only agent that significantly reduced ischemic stroke, the RE-LY trial was the only unblinded study.
        ii. Previous studies with ximelagatran have shown that blinded warfarin (SPORTIF V) performs better than unblinded warfarin (SPORTIF III) by almost a 1% absolute difference.
        iii. Had the RELY trial been blinded, the outcome might have been different.

d. The difference between the intention-to-treat analysis and the per-protocol analysis is only 28 patients in the ROCKET-AF trial of rivaroxaban (0.2% of the overall trial population) and only 47 patients in the ENGAGE-AF trial of edoxaban (0.3% of the overall trial population). Both agents were superior to warfarin in this analysis.
e. Absolute difference in the primary end point in the intention-to-treat analysis is 0.3% in both the ROCKET-AF trial with rivaroxaban and the ARISTOTLE trial with apixaban. Different statistical findings may be because the ARISTOTLE trial had around 4000 more patients in the overall study.
f. All agents reduce mortality by about 10%, with only apixaban achieving statistical significance. May be because the ARISTOTLE trial has about 2000 more patients per arm than all the other trials
g. Although all of the trials included a drop in hemoglobin of 2 g/dL or more as a major bleed, in the ARISTOTLE trial with apixaban, this was only counted as a major bleed if it occurred within 24 hours. Therefore, slow bleeds such as gastrointestinal bleeds, may not have been counted as major bleeds in this trial, but would have in all of the other trials.
h. Although the time in therapeutic range was lower in the ROCKET-AF trial with rivaroxaban than in other trials, this trial had the highest-risk patients (more difficult to control INR) and was the only trial that did not provide the investigators with a protocol to follow (wanted to evaluate real-world practice). Regardless, analysis has shown that time in therapeutic range with warfarin did not influence the study outcomes for any of the agents other than perhaps dabigatran.

8. General warnings regarding DOACs and special populations
   a. Avoid DOACs in pregnancy.
   b. DOACs are secreted into breast milk; data suggest that dabigatran and rivaroxaban are acceptable, but apixaban concentrations are greater than the acceptable range.
   c. Best to avoid DOACs in patients with moderate to severe hepatic dysfunction (Child-Pugh B or C) due to a lack of data. These patients have been excluded from the Phase III clinical trials.
   d. Avoid DOACs in patients with antiphospholipid syndrome.
      i. Antiphospholipid syndrome is a systemic autoimmune disorder characterized by recurrent arterial and/or venous thrombotic events
      ii. Involves interplay between inflammatory and coagulation pathways leading to activation of vascular and immune cells, down-regulation of protein C and plasminogen, and up-regulation of tissue factor, factor V, and factor VIII
      iii. Antiphospholipid antibodies include lupus anticoagulant, immunoglobulin G or immunoglobulin M anticardiolipin, and anti-β-2 glycoprotein 1. Of these antibodies, lupus anticoagulant is most strongly associated with thrombosis.
      iv. Diagnosis requires a thrombotic event (venous, arterial, or placental) and laboratory confirmation with a second evaluation at least 12 weeks after the first. These patients are at high risk of thrombotic events and typically require indefinite-duration anticoagulation.
      v. A meta-analysis of the four randomized controlled trials (n=472) comparing DOACs to VKA: Three trials used rivaroxaban as the DOAC and one used apixaban. Mean time in therapeutic range for patients on VKA was 60%, and the mean follow up was 19 months. Compared to VKA, DOACs were associated with a significant increase in arterial thrombotic events (10.3% vs. 1.3%; $p<0.001$), mainly driven by an increase in stroke (8.6% vs. 0%; $p<0.001$). There was no difference in other arterial events (MI or major acute limb events), VTE, major bleeding, or clinically relevant nonmajor bleeding (CRNM). Results were consistent for patients who were triple positive antiphospholipid syndrome and those who were only single/double positive, as well as for those with a history of arterial thrombosis and those without.
      vi. These findings do not apply to patients with other, more common, thrombophilias such as Factor V Leiden or thrombin gene mutation 20210A.
   e. Patients with obesity
      i. In 2016 the International Society on Thrombosis and Haemostasis (ISTH) put out a statement that DOACs should be avoided in patients with a BMI $\geq 40$ kg/m$^2$ or $\geq 120$ kg based on a lack of data. Data is now available in these patients.

ii. Pharmacokinetic and pharmacodynamic data assessing rivaroxaban suggest there is no change in the Cmax, area under the curve, or anti-Xa activity in patients with "normal" body weight compared to those weighing >120 kg. Apixaban has a reduction in Cmax of 31%, area under the curve of 23%, and anti-Xa activity of 34% in patients >120 kg. Dabigatran has changes similar to apixaban, and there is sparse data with edoxaban.
iii. An updated 2021 ISTH statement on DOAC use for preventing and treating VTE in patients with obesity states that standard doses of rivaroxaban or apixaban can be used regardless of high BMI or weight and that fewer supportive data exist with apixaban than with rivaroxaban.

f. Bariatric surgery – Although the absorption of rivaroxaban is reduced the most, all agents have an unpredictable reduction in absorption. Therefore, it is prudent to avoid DOACs in patients undergoing bariatric surgery.
g. Patients with low-body weight – Data are limited, but are most supportive of apixaban and rivaroxaban, followed by edoxaban and dabigatran. While no dose adjustment is recommended, these patients do have an increase in concentration that may expose them to a higher risk of bleeding.
h. Patients with advanced renal dysfunction with or without hemodialysis
i. Apixaban 5 mg twice daily and rivaroxaban 15 mg once daily both demonstrate acceptable pharmacokinetic and pharmacodynamic data in these patients, including data in hemodialysis.
ii. Data in patients are most supportive of apixaban and rivaroxaban, followed by edoxaban, and then dabigatran.

9. Perioperative management of anticoagulation
a. Patients receiving oral anticoagulant therapy often have elective surgery/procedures where decisions are made on continuation, holding, and/or bridging of anticoagulant therapy.
b. ACCP has published new guidelines on management of many of these scenarios.
i. Table 9 contains potential thrombosis risk for different clinical scenarios.
ii. Table 10 contains potential bleeding risk of different surgeries/procedures.
iii. Table 11 contains a list of the recommendations
c. In making recommendations, clinicians need to carefully weigh an individual patient's risk of thrombosis and bleeding.

**Table 9.** ACCP Suggested Risk Stratification of Patient-Specific Periprocedural Thromboembolism.

| Risk Category | Mechanical Heart Valve | Atrial Fibrillation | VTE |
|---|---|---|---|
| High: >10% per yr risk of ATE or >10% per mo risk of VTE | Mitral valve with major risk factors for stroke[a]<br>Caged ball or tilting-disc valve mitral or aortic position<br>Recent (<3 mo) stroke or TIA or other high-risk situations[b] | $CHA_2DS_2$-VASC score ≥7 or $CHADS_2$ score of 5 or 6<br>Recent (<3 mo) stroke or TIA<br>Rheumatic valvular heart disease | Recent (<3 mo, <1 mo) VTE<br>Severe thrombophilia[c]<br>Antiphospholipid antibodies<br>Active cancer associated with high-risk VTE[d] |
| Moderate: 4%–10% per yr risk of ATE or 4%–10% per mo risk of VTE | Bileaflet AVR with major risk factors for stroke[a] | $CHA_2DS_2$-VASC score of 5 or 6 or $CHADS_2$ score of 3 or 4 | VTE within past 3–12 mo<br>Recurrent VTE<br>Non-severe thrombophilia[e]<br>Active cancer or recent history of cancer |

**Table 9.** ACCP Suggested Risk Stratification of Patient-Specific Periprocedural Thromboembolism.(*con't*)

| Risk Category | Mechanical Heart Valve | Atrial Fibrillation | VTE |
|---|---|---|---|
| Low: <4% per yr risk of ATE or <2% per mo risk of VTE | Bileaflet AVR without major risk factors for stroke[a] | $CHA_2DS_2$-VASC score of 1–4 or $CHADS_2$ score of 5 or 0–2 (and no prior stroke or TIA) | VTE >12 mo ago |

[a]Atrial fibrillation, prior stroke or transient ischemic attack (TIA), hypertension, diabetes, heart failure, and >75 years of age.

[b]Includes multiple prior strokes, prior perioperative stroke, or prior valve thrombosis.

[c]Deficiency of protein C, protein S, or antithrombin; homozygous factor V Leiden or prothrombin gene G20210A mutation or double heterozygous for each mutation; multiple thrombophilias.

[d]Includes pancreatic cancer, myeloproliferative disorders, primary brain cancer, gastric cancer, and esophageal cancer.

[e]Heterozygous factor V Leiden or prothrombin gene G20210A mutation.

ACCP = American College of Chest Physicians; ATE = arterial thromboembolism; AVR = aortic valve replacement; VTE = venous thromboembolism.

**Table 10.** Suggested Risk Stratification for Procedural Bleed Risk Based on ISTH Guidance Statements

| Bleeding Risk | Surgery/Procedure |
|---|---|
| High bleed risk (30-day risk of major bleed ≥2%) | • Major surgery with extensive tissue injury<br>• Cancer surgery, especially solid tumor resection[a]<br>• Major orthopedic surgery, including shoulder replacement<br>• Reconstructive plastic surgery<br>• Major thoracic surgery<br>• Urologic or GI surgery, especially anastomosis surgery<br>• Transurethral prostate resection, bladder resection, or tumor ablation<br>• Nephrectomy, kidney biopsy<br>• Colonic polyp resection<br>• Bowel resection<br>• Percutaneous endoscopic gastrostomy placement, endoscopic retrograde cholangiopancreatography<br>• Surgery in highly vascular organs[b]<br>• Cardiac, intracranial, or spinal surgery<br>• Any major operation (procedure duration >45 min)<br>• Neuroaxial anesthesia<br>• Epidural injections |
| Low-to-moderate bleed risk (30-day risk of major bleed 0%–2%) | • Arthroscopy<br>• Cutaneous/lymph node biopsies<br>• Foot/hand surgery<br>• Coronary angiography<br>• GI endoscopy with/without biopsy<br>• Colonoscopy with/without biopsy<br>• Abdominal hernia repair<br>• Hemorrhoidal surgery<br>• Bronchoscopy with/without biopsy |
| Minimal bleed risk (30-day risk of major bleeding approximately 0%) | • Minor dermatologic procedures[c]<br>• Ophthalmologic (cataract) procedures<br>• Minor dental procedures,[d] dental cleanings, fillings<br>• Pacemaker or cardioverter-defibrillator implantation |

[a]Lung, esophagus, gastric, colon, hepatobiliary, pancreatic.

[b]Kidneys, liver, or spleen.

[c]Excision of basal and squamous cell skin cancers, actinic keratoses, and premalignant or cancerous skin nevi.

[d]Dental extractions, restorations, prosthetics, endodontics.

GI = gastrointestinal; ISTH = International Society of Thrombosis and Hemostasis.

**Table 11.** ACCP Recommendations for Perioperative Management of Anticoagulation for Elective Surgery/ Procedure

| Recommendation | Classification[a] |
|---|---|
| In patient requiring VKA interruption, stop VKA ≥5 days over an interruption of <5 days | Conditional |
| Resume VKA within 24 hr over a delay of >24 hr | Conditional |
| Resume the first postoperative VKA dose at the patient's usual dose over resuming VKA with double the usual dose | Conditional |
| Avoid routine use of preoperative vitamin K if the INR is elevated (i.e., >1.5) 1–2 days before the procedure | Conditional |
| In patients receiving VKA therapy for a mechanical heart valve and requiring VKA interruption, avoid heparin bridging | Conditional |
| In patients receiving VKA therapy for atrial fibrillation and requiring VKA interruption, avoid heparin bridging | Strong |
| In patients receiving VKA therapy for venous thromboembolism and requiring VKA interruption, avoid heparin bridging | Conditional |
| In patients receiving VKA therapy and at high risk for thromboembolism and requiring VKA interruption, use heparin bridging over no heparin bridging | Conditional |
| In patients receiving VKA therapy and at low-to-moderate risk for thromboembolism and requiring VKA interruption, avoid heparin bridging | Conditional |
| Continue VKA therapy in patients needing a dental procedure over VKA interruption | Conditional |
| In patients receiving VKA who need a dental procedure, use a pro-hemostatic agent with continuation of VKA over alternative options | Conditional |
| In patients receiving VKA therapy who require a minor dermatologic procedure, continue VKA over VKA interruption | Conditional |
| In patients receiving VKA therapy who require a minor ophthalmologic procedure, continue VKA over interruption | Conditional |
| In patients receiving VKA therapy who require a pacemaker or ICD implantation, continue VKA instead of interruption and heparin bridging | Strong |
| In patients receiving VKA therapy requiring VKA interruption for colonoscopy with anticipated polypectomy, avoid heparin bridging | Conditional |
| In patients receiving therapeutic-dose IV UFH bridging, stop UFH ≥4 hr over stopping <4 hr before the surgery/procedure | Conditional |
| In patients receiving therapeutic-dose IV UFH bridging, resume UFH ≥24 hr after over resuming within 24 hr after the surgery/procedure | Conditional |
| In patients receiving LMWH bridging, administer the last preoperative dose at approximately 24 hr over 10 to 12 hr before the surgery/procedure | Conditional |
| In patients receiving LMWH bridging, administer the first postoperative LMWH dose at least 24 hr after over <24 hr after the surgery/procedure | Conditional |
| In patients receiving LMWH bridging, administer half the total dose the day prior to the procedure over full dose | Conditional |
| In patients receiving LMWH bridging, avoid routine measurement of anti-Xa levels to guide perioperative LMWH management | Conditional |
| In patients receiving apixaban, stop apixaban 1–2 days before over continuation[b] | Conditional |
| In patients receiving dabigatran, stop dabigatran for 1–4 days before over continuation[c] | Conditional |
| In patients receiving edoxaban, stop edoxaban for 1–2 days before over continuation[b] | Conditional |

**Table 11.** ACCP Recommendations for Perioperative Management of Anticoagulation for Elective Surgery/ Procedure

| Recommendation | Classification[a] |
|---|---|
| In patients receiving rivaroxaban, stop rivaroxaban 1–2 days before over continuation[b] | Conditional |
| In patients requiring a DOAC interruption, avoid perioperative heparin bridging | Conditional |
| In patients who have had a DOAC interruption, resume the DOAC >24 hr after over within 24 hr after the surgery/procedure | Conditional |
| In patients who have had a DOAC interruption, avoid routine coagulation function testing to guide perioperative DOAC management | Conditional |

[a]Strong means "we recommend" and Conditional means "we suggest".

[b]1 day for low-to-moderate bleed risk procedure and 2 days for high bleed risk procedure.

[c]1 day for low-to-moderate bleed risk procedure and CrCl ≥50 mL/min; 2 days for low-to-moderate bleed risk and CrCl <50 mL/min; 2 days for high bleed risk and CrCl ≥50 mL/min; 4 days for high bleed risk and CrCl <50 mL/min.

ACCP = American College of Chest Physicians; CrCl = creatinine clearance; DOAC = direct oral anticoagulant; ICD = implantable cardio-defibrillator; INR = international normalized ratio; IV = intravenous; LMWH = low molecular weight heparin; UFH = unfractionated heparin; VKA=vitamin K antagonist.

F. Antiplatelet Therapy
   1. Aspirin
      a. Historically used in low or intermediate thrombosis risk of stroke, but also in patients at high risk of bleeding (when anticoagulation therapy is contraindicated)
      b. Meta-analysis of eight trials comparing aspirin with placebo or no therapy in 4876 patients with NVAF
         i. Doses ranged from 25 mg twice daily to 1300 mg once daily.
         ii. Primary prevention aspirin had an absolute reduction of 0.8% for stroke occurrence.
         iii. Secondary prevention aspirin had an absolute reduction of 2.5% for stroke occurrence.
         iv. Benefit of aspirin from one trial drives these results.
      c. Only the SPAF-1 (Stroke Prevention in Atrial Fibrillation) trial has shown a benefit of aspirin in reducing the risk of ischemic stroke in patients with NVAF.
         i. Dose was 325 mg daily.
         ii. Only effective in patients 75 and younger
      d. Apixaban 5 mg twice daily was compared with aspirin in patients who were unsuitable for therapy with a vitamin K antagonist in the AVERROES trial.
         i. Trial was stopped early because of the significantly better efficacy of apixaban compared with aspirin.
         ii. No difference in major bleeding
         iii. 65% of patients received an aspirin dose of 81 mg daily, and only 2% received an aspirin dose of 324 mg.
         iv. Trial shows that apixaban (and likely the other DOACs) can be used safely in patients who are unsuitable for warfarin therapy and should replace aspirin as the traditional alternative to warfarin therapy in these patients.
   2. Aspirin plus clopidogrel – Evaluated in the two ACTIVE trials (Atrial Fibrillation Clopidogrel Trial with Irbesartan for Prevention of Vascular Events). Patients with NVAF and at least one risk factor for stroke
      a. ACTIVE – W (compared with warfarin)
         i. Aspirin 75–100 mg daily plus clopidogrel 75 mg daily compared with dose-adjusted warfarin to an INR of 2.0–3.0
         ii. Trial was stopped early because of the superior efficacy of warfarin.

iii. Aspirin and clopidogrel were inferior to warfarin (5.6% vs. 3.9%; p<0.001) for stroke, systemic embolism, MI, and vascular death.
iv. No difference in major bleeding, but significantly more minor bleeding with aspirin and clopidogrel than with warfarin

b. ACTIVE – A (compared with aspirin)
i. Aspirin 75–100 mg daily plus clopidogrel 75 mg daily compared with aspirin alone if they were not candidates for or refused anticoagulation with warfarin
ii. Aspirin plus clopidogrel was superior to aspirin alone (6.8% vs. 7.6%; p=0.01).
iii. Reduction in the primary end point was driven by reductions in ischemic stroke and MI.
iv. Significant increase in major and minor bleeding with the use of dual antiplatelet therapy
v. Subgroup analysis identified that patients at intermediate risk of stroke ($CHADS_2$ score =1) derived the most benefit from adding clopidogrel to aspirin.

G. Patients with NVAF Who Need Percutaneous Coronary Intervention (require triple antithrombotic therapy)
1. Although the risk of major bleeding with warfarin therapy in patients with AF is around 2% per year, patients receiving warfarin, aspirin, and clopidogrel have a major bleeding rate of around 8% per year.
2. Approaches that have not been prospectively evaluated include the following:
a. A target INR of 2.0–2.5 instead of 2.0–3.0
b. Aspirin 81 mg instead of higher doses
c. Clopidogrel instead of ticagrelor or prasugrel because both newer $P2Y_{12}$ inhibitors have more non-coronary artery bypass grafting major bleeding than clopidogrel
d. Trying to use bare metal stents and/or keeping the duration of dual antiplatelet therapy to a minimum
3. WOEST trial (n=573) compared triple therapy (warfarin, clopidogrel 75 mg daily, and aspirin 80–100 mg daily) with double therapy (same therapy but without the aspirin).
a. The primary end point of any bleeding was significantly reduced by a relative 64% using double therapy compared with triple therapy. Major bleeding was reduced by 44%, but this was not significant.
b. There was a significant 40% relative reduction in major cardiac events with double therapy compared with triple therapy, which was driven by a reduction in noncardiac death. The incidence of MI, stent thrombosis, stroke, and target-vessel revascularization was no different.
c. These data are encouraging, but they are from a small, open-label trial done in the Netherlands and Belgium.
4. PIONEER AF-PCI trial (n=2124) compared three groups for 12 months:
a. Group 1 received rivaroxaban 15 mg once daily (or 10 mg once daily if CrCl was 30–50 mL/minute/1.73 $m^2$) plus clopidogrel 75 mg daily (only 2% received prasugrel and 5% ticagrelor) for 12 months.
b. Group 2 received rivaroxaban 2.5 mg twice daily plus aspirin 75–100 mg daily, plus clopidogrel 75 mg daily (only 2% received prasugrel and 5% ticagrelor) for 1, 6, or 12 months. Patients who received therapy for only 1 or 6 months were then changed rivaroxaban 15 mg once daily (or 10 mg once daily if CrCl 30–50 mL/minute/1.73 $m^2$) plus aspirin 75–100 mg daily for the remainder of the 12 months.
c. Group 3 represented standard care and received adjusted-dose warfarin to an INR of 2.0–3.0 plus aspirin 75–100 mg daily plus clopidogrel 75 mg daily (only 1% received prasugrel and 3% ticagrelor) for 1, 6, or 12 months. Patients who received therapy for only 1 or 6 months continued to receive warfarin and aspirin 75–100 mg daily.
d. The primary outcome of clinically significant bleeding was significantly lower for group 1 (16.8%) and group 2 (18.0%) than for group 3 (26.7%).
e. Although not powered to evaluate ischemic outcomes, there was no difference in the composite of cardiovascular death, MI, and stroke for group 1 (6.5%), group 2 (5.6%), and group 3 (6.0%).

5. RE-DUAL PCI trial (n=2725) compared three groups for 6 months.
    a. Group 1 received dabigatran 110 mg twice daily plus clopidogrel or ticagrelor (12.6%) for at least 12 months.
    b. Group 2 received dabigatran 150 mg twice daily plus clopidogrel or ticagrelor (12.1%) for at least 12 months. Older adult patients (80 and older or 70 and older in Japan) outside the United States were not eligible to be randomized to this group. Therefore, the comparison for this group excluded these patients from group 3. Consequently, findings from this group do not apply to older adult patients.
    c. Group 3 represented standard care and received adjusted-dose warfarin to an INR of 2.0–3.0, plus aspirin at 100 mg or less daily, plus clopidogrel or ticagrelor (7.8%). Aspirin was discontinued after 1 month in patients receiving a bare metal stent and after 3 months in patients receiving a drug-eluting stent.
    d. The primary end point of first major and CRNM bleeding (International Society on Thrombosis and Haemostasis definition) was significantly lower for group 1 (15.4%) than for group 3 (26.9%) and was also lower for group 2 (20.2%) than for the corresponding patients in group 3 (25.7%).
    e. Although not designed to evaluate ischemic outcomes, the 5-point composite outcome of MI, stroke, systemic embolism, death, and unplanned revascularization was noninferior between group 1 (15.2%) and group 3 (13.4%) as well as for group 2 (11.8%) compared with the corresponding patients in group 3 (12.8%).
6. AUGUSTUS trial (n=4614) compared four groups for 6 months:
    a. Group 1 received apixaban 5 mg twice daily (2.5 mg twice daily if they met 2 of the 3 dose reduction criteria) plus a $P2Y_{12}$ inhibitor (over 90% received clopidogrel 75 mg once daily) for 6 months
    b. Group 2 received the same regimen as Group 1, but also received low-dose aspirin for 6 months
    c. Group 3 received adjusted-dose warfarin to an INR of 2.0-3.0 plus a $P2Y_{12}$ inhibitor (over 90% received clopidogrel 75 mg once daily) for 6 months
    d. Group 4 received the same regimen as Group 3, but also received low-dose aspirin for 6 months
    e. The primary endpoint of first major and CRNM bleeding was significantly lower in patients receiving apixaban compared to warfarin and significantly higher in patients receiving aspirin, with the lowest rate in Group 1 (7.3%) and the highest rate in Group 4 (18.7%)
    f. Although not powered to evaluate ischemic outcomes, there was no difference in the composite of death, MI, stroke, stent thrombosis, or urgent revascularization between Group 1 (6.2%), Group 2 (6.2%), Group 3 (7.3%), and Group 4 (5.7%)
7. ENTRUST-AF PCI trial (n=1506) compared two groups for 12 months.
    a. Group 1 received edoxaban 60 mg daily plus clopidogrel. Patients with a CrCl of 15–50 mL/minute/1.73 $m^2$, with a weight of 60 kg or less, or who were taking P-gp inhibitors received edoxaban 30 mg daily.
    b. Group 2 received adjusted-dose warfarin to an INR of 2.0–3.0 plus clopidogrel plus aspirin 100 mg once daily.
    c. The primary end point of major or CRNM bleeding was not significantly different between dual therapy and triple therapy (20.7% vs. 25.6%; p=0.1154).
    d. Although the study was not designed to evaluate ischemic outcomes, the groups did not differ (7% vs. 6%).
8. 2020 ACC Expert Consensus Decision Pathway
    a. Recommends against routine use of triple therapy
    b. Recommends a default strategy of an anticoagulant and a $P2Y_{12}$ inhibitor
        i. DOAC recommended over warfarin
        ii. Clopidogrel recommended over ticagrelor and prasugrel
    c. Durations after PCI
        i. Typically discontinue aspirin at hospital discharge for PCI, but may continue for up to 30 days in patients at high risk of thrombosis and low risk of bleeding
        ii. Patients receiving PCI for stable ischemic heart disease should receive an anticoagulant and a $P2Y_{12}$ inhibitor for 6 months, then an anticoagulant and a $P2Y_{12}$ inhibitor or aspirin for an additional 6 months, then an anticoagulant alone.

iii. Patients receiving PCI for an acute coronary syndrome should receive an anticoagulant and a $P2Y_{12}$ inhibitor for 12 months, then an anticoagulant alone.
iv. Limiting the use of antiplatelet therapy to only 3 months in patients receiving PCI for stable ischemic heart disease, or only 6 months in patients receiving PCI for an acute coronary syndrome, can be considered in patients at high risk of bleeding.

**Patient Cases**

*Questions 1–3 pertain to the following case.*

B.D. is a 73-year-old man (height 69 inches, weight 80 kg) with newly diagnosed NVAF. He also has a history of hypertension, dyslipidemia, stable ischemic heart disease, and heart failure with reduced ejection fraction. His current medications include aspirin 81 mg daily, enalapril 10 mg daily, atorvastatin 80 mg daily, metoprolol succinate 200 mg daily, furosemide 40 mg daily, spironolactone 25 mg daily, and amlodipine 10 mg daily. His current heart rate is 72 beats/minute and blood pressure is 122/72 mm Hg. His laboratory values include potassium 4.9 mEq/L, stable SCr 1.9 mEq/L, and blood glucose 101 mg/dL.

1. Which best depicts B.D.'s $CHA_2DS_2$-VASc score?
   A. 2.
   B. 3.
   C. 4.
   D. 5.

2. Which statement is most accurate regarding DOAC therapy for reducing the risk of stroke in patients with NVAF such as B.D.?
   A. All the DOACs significantly reduced ischemic stroke in the phase III trials compared with warfarin.
   B. All the DOACs significantly reduced hemorrhagic stroke in the phase III trials compared with warfarin.
   C. Apixaban is more effective than rivaroxaban because apixaban was superior to warfarin in the ARISTOTLE trial and rivaroxaban was only noninferior to warfarin in the ROCKET-AF trial.
   D. Dabigatran was studied in the highest-risk patients across the phase III trials and should not be used in patients with a $CHADS_2$ score of less than 3.

3. Which is the most appropriate regimen for reducing B.D.'s risk of stroke?
   A. Dabigatran 75 mg twice daily.
   B. Rivaroxaban 20 mg once daily.
   C. Apixaban 5 mg twice daily.
   D. Edoxaban 60 mg once daily.

4. A 68-year-old man with AF presents with new-onset chest pain. It is determined the patient has a non–ST-segment elevation myocardial infarction, for which undergoes PCI with stent placement. His laboratory values are within normal limits. Which is the best available evidence-based approach to his antithrombotic therapy?
   A. Rivaroxaban 10 mg daily, plus clopidogrel 75 mg daily.
   B. Apixaban 5 mg twice daily, plus clopidogrel 75 mg daily.
   C. Adjusted-dose warfarin to an INR of 2.0–3.0, plus aspirin 81 mg daily, plus clopidogrel 75 mg daily.
   D. Edoxaban 15 mg once daily, plus aspirin 81 mg daily, plus clopidogrel 75 mg daily.

## II. PREVENTION OF VENOUS THROMBOEMBOLISM (VTE)

A. Risk of Developing VTE
   1. VTE consists of deep vein thrombosis (DVT), pulmonary embolism (PE), or both.
   2. Risk factors for developing VTE are listed in Box 5. Risk factors are cumulative.
      a. Not all risk factors carry equal risk; certain risk factors such as orthopedic surgery, trauma, cancer, certain hypercoagulable states, and previous VTE have the highest risk of developing VTE.
      b. Risks of VTE based on different patient groups are listed in Table 12. These event rates have typically been determined by venography in clinical trials and do not reflect the rates of symptomatic DVT or PE.
   3. Risk stratification
      a. Low risk (DVT incidence of less than 10% without thromboprophylaxis)
         i. Minor surgery in patients younger than 40 with no additional risk factors
         ii. Medically ill patients who are fully mobile
      b. Moderate risk (DVT incidence 10%–40% without thromboprophylaxis)
         i. Most general, open gynecologic or urologic surgery patients
         ii. Medically ill patients, bed rest or sick
      c. High risk (DVT incidence 40%–80% without thromboprophylaxis)
         i. Major surgery in patients older than 40 plus a prior VTE
         ii. Cancer
         iii. Hypercoagulable state
         iv. Hip or knee arthroplasty, hip fracture surgery
         v. Major trauma
         vi. Spinal cord injury
   4. Regimens vary depending on patient risk and clinical trial results.
      a. Mechanical prophylaxis
         i. Includes elastic stocking (limited efficacy) and intermittent pneumatic compression
         ii. Intermittent pneumatic compression has to be on the patient for at least 18 hours/day to show efficacy.
         iii. Both types of mechanical prophylaxis are poorly tolerated by patients.
         iv. For patients at high risk of bleeding, such as immediately post-surgery, with intent to start pharmacologic prophylaxis once hemostasis has occurred
         v. Also may be used in the highest-risk patients, such as those with spinal cord injury, in combination with pharmacologic prophylaxis
      b. Pharmacologic prophylaxis (Table 13)
         i. LMWH – Subcutaneous enoxaparin or dalteparin
         ii. UFH – Subcutaneously two or three times daily
         iii. Fondaparinux subcutaneously 2.5 mg daily
         iv. Adjusted-dose warfarin – Only in orthopedic surgery
         v. Dabigatran, rivaroxaban, and apixaban in orthopedic surguery
         vi. Rivaroxaban in medically ill with extended prophylaxis
         vii. Aspirin – Questionable data, but is listed as a possible agent in orthopedic surgery

**Box 5.** Risk Factors for Developing VTE

| |
|---|
| Age ≥ 40 |
| Surgery (e.g., orthopedic, thoracic, abdominal, and genitourinary) |
| Trauma (e.g., fracture of the spine, pelvis, femur, or tibia; spinal cord injuries) |
| Hypercoagulable states (e.g., resistance to activated protein C [factor V Leiden], deficiencies in antithrombin, protein C or protein S deficiency, antiphospholipid antibodies) |
| Central venous catheterization |
| Estrogen use, selective estrogen receptor modulators, or testosterone use |
| Erythropoiesis-stimulating agents |
| Previous VTE |
| Cancer and its treatment (e.g., pancreas, lung, ovary, testes, urinary tract, breast, stomach) |
| Immobility or lower-extremity paresis |
| Certain medical disease states/conditions (e.g., stroke, or paralysis, acute infection, chronic obstructive pulmonary disease, inflammatory bowel disease, nephrotic syndrome, varicose veins, heart failure, acute MI, pregnancy) |
| Smoking |
| Obesity |

VTE = venous thromboembolism.

**Table 12.** VTE Risk in Different Hospitalized Patient Groups

| Patient Group | DVT Prevalence Without Prophylaxis |
|---|---|
| Medically ill patients<br>Heart failure<br>Chronic obstructive pulmonary disease<br>Infection | 10%–20% |
| General surgery | 15%–40% |
| Major gynecologic surgery | 15%–40% |
| Major urologic surgery | 15%–40% |
| Neurosurgery | 15%–20% |
| Stroke | 20%–50% |
| Major orthopedic surgery<br>Total hip replacement surgery<br>Hip fracture surgery<br>Total knee replacement surgery | 40%–60%<br>57%<br>60%<br>84% |
| Major trauma | 40%–80% |
| Patients with spinal cord injury | 60%–80% |
| Critical care patients | 10%–80% |

VTE = venous thromboembolism.

B. Orthopedic Surgery
   1. Typically considered one of the highest-risk settings for developing VTE
      a. More than 50% of patients have a VTE event without prophylaxis.
      b. DVT rates are higher in knee surgery, and PE rates are higher in hip surgery.
   2. Prophylactic regimens are listed in Table 13.
   3. Practical issues
      a. UFH has consistently shown insufficient protection against VTE in patients undergoing orthopedic surgery and should therefore not be considered an acceptable alternative.
      b. Although aspirin has a recommendation from the American College of Chest Physicians (ACCP) and the American Association of Orthopaedic Surgeons guidelines, the recommendation is based on limited data with several limitations.
      c. The recent CRISTAL trial randomized institutions to a crossover design of providing either aspirin 100 mg daily or enoxaparin 40 mg daily in patients undergoing knee replacement surgery (60%) or hip replacement surgery (40%). The trial was stopped early after 62% enrollment because of a significantly lower incidence of symptomatic VTE at 90 days with the use of enoxaparin compared to aspirin (1.8% vs. 3.5%; p=0.0007). There was no difference in major bleeding.
      d. Patients placed on mechanical prophylaxis after surgery because of high risk of bleeding should have their risk of bleeding consistently reassessed, with pharmacologic prophylaxis started as soon as the bleeding risk is decreased.
      e. Patients undergoing knee arthroscopy typically do not need VTE prophylaxis beyond early mobilization unless they have additional VTE risk factors or have a complicated procedure. In those cases, patients should receive VTE prophylaxis with an LMWH.
      f. Dalteparin has not been evaluated in a published prospective trial for VTE prophylaxis in knee replacement surgery.
      g. Dabigatran is available in the United States for VTE prevention in patients undergoing hip replacement surgery, but not knee replacement surgery. Dabigatran was inferior to enoxaparin 30 mg twice daily in patients undergoing knee replacement surgery.
      h. Rivaroxaban has shown a superior reduction in VTE events compared with enoxaparin 40 mg once daily in hip replacement surgery and enoxaparin 40 mg once daily and enoxaparin 30 mg twice daily in knee replacement surgery. Although major bleeding was not significantly increased in these studies, the definition of major bleeding did not include surgical site bleeding (considered nonmajor bleeding).
      i. Apixaban has shown a superior reduction in VTE events compared with enoxaparin 40 mg once daily in hip and knee replacement surgery, with no significant increase in major bleeding. Apixaban was not noninferior to enoxaparin 30 mg twice daily in knee replacement surgery, though the event rates were similar (9.0% apixaban vs. 8.8% enoxaparin). Although major bleeding did not differ, the combination of major and CRNM was significantly reduced with apixaban.
      j. Timing of initiation of VTE prophylaxis after surgery is an important and complicated issue. The risk of thromboembolic events begins immediately after surgery; therefore, VTE prophylaxis is generally more effective when started earlier rather than later. The challenge lies in the fact that early VTE prophylaxis is also associated with increased bleeding compared with VTE prophylaxis started later.
      k. VTE prophylaxis after elective spinal surgery can typically be initiated 12–24 hours postoperatively. Prophylaxis may need to be delayed if the surgical site remains open.

**Table 13.** VTE Prophylaxis in Orthopedic Surgery

| Orthopedic Indication | Enoxaparin | Dalteparin | Fondaparinux | Warfarin | Dabigatran | Rivaroxaban | Apixaban |
|---|---|---|---|---|---|---|---|
| Knee replacement surgery | 30 mg SC q12hr initiated 12–24 hr after surgery | 2500 IU SC given 6–8 hr after surgery; then 5000 IU SC q24hr[a] | 2.5 mg SC q24hr initiated 6–8 hr after surgery | Initiated preoperatively or the evening of the surgical day with adjusted dosing to achieve a target INR of 2.5 ± 0.5 | Insufficient evidence | 10 mg once daily initiated 6–10 hr after surgery | 2.5 mg twice daily, initiated 12–24 hr after surgery |
| Hip replacement surgery | 30 mg SC q12hr initiated 12–24 hr after surgery OR 40 mg SC q24hr initiated 10–12 hr before surgery | 2500 IU SC given 6–8 hr after surgery; then 5000 IU SC q24hr OR 5000 IU SC q24hr initiated the evening before surgery | 2.5 mg SC q24hr initiated 6–8 hr after surgery | Initiated preoperatively or the evening of the surgical day with adjusted dosing to achieve a target INR of 2.5 ± 0.5 | 110 mg initiated 1–4 hr after surgery; then 220 mg once daily | 10 mg once daily initiated 6–10 hr after surgery | 2.5 mg twice daily, initiated 12–24 hr after surgery |
| Hip fracture surgery | 30 mg SC q12hr initiated 12–24 hr after surgery[a] | Insufficient evidence | 2.5 mg SC q24hr initiated 6–8 hr after surgery | Initiated preoperatively or the evening of the surgical day with adjusted dosing to achieve a target INR of 2.5 ± 0.5 | Insufficient evidence | Insufficient evidence | Insufficient evidence |
| Spine surgery | Pharmacologic prophylaxis is generally not recommended unless patients have additional risk factors of advanced age, malignancy, neurologic deficit, previous VTE, or an anterior surgical approach. Because of the lack of clinical trials, pharmacologic prophylaxis recommendations are general and include SC UFH or LMWH | | | | | | |

[a]Not approved by the U.S. Food and Drug Administration (FDA).

q = every; SC = subcutaneous(ly).

C. Non-orthopedic Surgery
   1. Contains a very heterogeneous group of patients and surgical procedures with various risk
   2. Prophylactic regimens are listed in Table 14.
   3. Practical issues
      a. General surgery
         i. Meta-analysis comparisons between UFH and LMWHs show comparative efficacy in preventing DVT, but a greater reduction in the incidence of PE when an LMWH is used.
         ii. Mechanical prophylaxis is sometimes inappropriately selected over pharmacologic prophylaxis because of concerns for bleeding in surgical patients. A meta-analysis of almost 34,000 surgical patients showed that the most common bleeding complications are injection-site bruising (6.9%) and wound hematomas (5.7%). Major bleeding complications occurred in less than 1% of patients.
      b. Neurosurgery
         i. Pharmacologic prophylaxis is typically given with mechanical prophylaxis, and the combination is as safe as, and more effective than, mechanical prophylaxis alone.
         ii. Pharmacologic prophylaxis is typically started 18–24 hours after neurosurgery.
      c. Vascular surgery
         i. Routine prophylaxis is recommended for patients with additional risk factors such as advanced age, limb ischemia, long duration of surgery, and intraoperative local trauma.
         ii. Because of the limited number of trials in patients with vascular surgery, dosing recommendations are based on evidence of pharmacologic agents in general surgery.
      d. Gynecologic surgery
         i. Low-risk gynecologic surgical procedures (laparoscopic procedures or procedures lasting less than 30 minutes) do not require prophylaxis beyond early ambulation.
         ii. Those undergoing major surgery without malignancy should receive UFH or an LMWH.
      e. Gynecologic cancer surgery
         i. UFH three times daily is more effective than twice daily. UFH three times daily and an LMWH seem to have similar efficacy and safety.
         ii. In a subgroup analysis of a general surgery trial, fondaparinux was more effective than dalteparin in patients undergoing surgery for cancer.
      f. Urologic surgery
         i. Patients undergoing a transurethral or laparoscopic urologic procedure do not require prophylaxis beyond early ambulation.
         ii. Because of the limited number of trials of patients undergoing urologic surgery, dosing recommendations are based on evidence of pharmacologic agents in general surgery.
      g. Bariatric surgery – Higher doses of LMWH and UFH are recommended. UFH 7500 units three times daily and enoxaparin 40 mg twice daily have been evaluated. Dalteparin 7500 units daily has been evaluated in a retrospective study using anti-factor Xa (anti-Xa) concentrations.
      h. Thoracic surgery – Because of the limited number of trials of patients undergoing thoracic surgery, dosing recommendations are based on evidence of pharmacologic agents in general surgery.
      i. Coronary bypass surgery
         i. Because of the limited number of trials in patients undergoing coronary artery bypass surgery, dosing recommendations are based on evidence of pharmacologic agents in general surgery.
         ii. Because of concerns about the higher incidence of heparin-induced thrombocytopenia in cardiac surgery patients, an LMWH may be preferred to UFH for prophylaxis.

**Table 14.** VTE Prophylaxis in Non-orthopedic Surgery

| Surgical Indication | UFH | Enoxaparin | Dalteparin | Fondaparinux |
|---|---|---|---|---|
| General surgery | 5000 units SC q8hr or 5000 units SC q12hr | 40 mg SC q24hr | 5000 IU SC q24hr | 2.5 mg SC q24hr |
| Neurosurgery | 5000 units SC q8hr | 40 mg SC q24hr | Insufficient evidence | Insufficient evidence |
| Vascular surgery | 5000 units SC q8r or 5000 units SC q12hr | 40 mg SC q24hr | 5000 IU SC q24hr | 2.5 mg SC q24hr |
| Gynecologic | 5000 units SC q8hr or 5000 units SC q12hr | 40 mg SC q24hr | 5000 IU SC q24hr | 2.5 mg SC q24hr |
| Urologic | 5000 units SC q8hr or 5000 units SC q12hr | 40 mg SC q24hr | 5000 IU SC q24hr | 2.5 mg SC q24hr |
| Laparoscopic | Patients undergoing laparoscopic procedures without additional VTE risk factors do not require prophylaxis beyond early ambulation | | | |
| Bariatric | 5000 units SC q8hr | 40 mg SC q12hr | 7500 IU SC q24hr | 5 mg SC q24hr |
| Thoracic | 5000 units SC q8hr or 5000 units SC q12hr | 40 mg SC q24hr | 5000 IU SC q24hr | 2.5 mg SC q24hr |
| Coronary bypass surgery | 5000 units SC q8hr or 5000 units SC q12hr | 40 mg SC q24hr | 5000 IU SC q24hr | Not discussed in current guidelines |

D. Medically Ill Patients
   1. A heterogeneous group of hospitalized nonsurgical patients
   2. Clinical trials typically include patients with heart failure, acute infection, respiratory insufficiency, inflammatory bowel disease, rheumatoid arthritis, ischemic stroke, and sometimes patients with cancer.
   3. Risk of VTE is typically lower than in surgical patients, but medically ill patients make up around 60% of all VTE cases that occur because of the higher number of medically ill patients.
   4. Prophylactic regimens are listed in Table 15.
   5. The American Society of Hematology (ASH) guidelines recommend the use of a LMWH or fondaparinux over UFH.
   6. Practical issues
      a. Many clinical trials have not shown efficacy with UFH 5000 units every 12 hours; therefore, UFH 5000 units every 8 hours may be the preferred UFH regimen.
      b. Although not evidence based, UFH 5000 units every 12 hours may be considered in individuals with advanced age and low weight (i.e., total body weight less than 50 kg) or elevated baseline activated partial thromboplastin time (aPTT; greater than 1.3–1.4 times baseline).
      c. Enoxaparin 20 mg once daily has been evaluated and is no more effective than placebo.
      d. Enoxaparin 20 mg once daily is equal in efficacy to UFH 5000 units every 12 hours.
      e. In head-to-head trials of UFH 5000 units every 8 hours and enoxaparin 40 mg daily, the regimens have had similar efficacy, except for in higher-risk medically ill patients (heart failure and ischemic stroke), for whom enoxaparin seems to confer greater protection against VTE. In the same trials, enoxaparin has had significantly less hematoma (greater than 5 cm) than UFH. Although some data suggest a lower bleeding rate with LMWH in medically ill patients, these findings are not consistent across trials.

**Table 15.** VTE Prophylaxis in Medically Ill Patients

| UFH | Enoxaparin | Dalteparin | Fondaparinux | Rivaroxaban |
|---|---|---|---|---|
| 5000 units SC q8hr or 5000 units SC q12hr | 40 mg SC q24hr | 5000 IU SC q24hr | 2.5 mg SC q24hr[a] | 10 mg orally q24hr |

[a]Not FDA approved.

7. Extended prophylaxis
    a. Risk of VTE extends beyond discharge, with almost two-thirds of all events occurring within 30 days after hospitalization.
    b. Extended prophylaxis (28 ± 4 days) with enoxaparin has shown a significant reduction in developing VTE, but with significantly more major bleeding than initial treatment with enoxaparin for 10 days followed by placebo.
    c. Extended prophylaxis with apixaban 2.5 mg twice daily did not reduce VTE events compared with enoxaparin for 10 days but did significantly increase major bleeding. The lack of efficacy may be because of the lower-risk patients in this study.
    d. Rivaroxaban is approved for extended VTE prophylaxis (35 ± 4 days) in medically ill patients with moderate to severe restricted morbidity and at least one of the following additional risk factors: age 75 or older, prolonged immobilization, history of cancer, history of VTE, history of heart failure, thrombophilia, acute infectious disease contributing to hospitalization, or BMI greater than 35 $kg/m^2$.
        i. Rivaroxaban 10 mg once daily significantly reduced VTE events without significantly increasing major bleeding compared with enoxaparin for 10 days in a subpopulation of the MAGELLAN trial.
        ii. The original trial (n=8101) showed a significant reduction in VTE events but had significantly more major bleeding.
        iii. Five groups with the highest risk of bleeding were removed from the data. These groups were as follows: treatment of active cancer during admission, use of dual antiplatelet therapy, history of bronchiectasis/pulmonary cavitation, active gastrointestinal bleeding, or any bleeding in the previous 3 months. These patients made up about 20% of the initial study population.
        iv. In the subpopulation (n=6447), VTE events were significantly reduced with rivaroxaban compared with enoxaparin/placebo, and major bleeding was not significantly increased. The safety of rivaroxaban in patients without these five bleeding factors was prospectively confirmed in the MARINER trial of extended prophylaxis in medically ill patients.
    e. Extended VTE prophylaxis in selected medically ill patients is recommended by the Anticoagulation Forum and the North American Thrombosis Forum.

E. Critically Ill Patients
1. A group of patients at very high risk of developing VTE
2. Typically includes patients in general critical care environments, including patients with trauma, acute spinal cord injury, and burns
3. Prophylactic regimens are listed in Table 16.
4. The ASH guidelines recommend the use of a LMWH over UFH.
5. Practical issues
    a. Trauma
        i. A meta-analysis showed UFH to be no more effective than control.
        ii. Enoxaparin 30 mg twice daily has shown better efficacy than UFH 5000 units twice daily.
        iii. Observational analysis in 18,010 trauma patients showed a significant reduction in VTE events and death in patients receiving enoxaparin 30 mg twice daily compared with UFH 5000 units three times daily.
        iv. Evidence for dalteparin is based on observational data.
        v. Pharmacologic prophylaxis can safely be started within 24–36 hours. Pharmacologic prophylaxis for patients with acute spinal cord injury may need to be delayed for 48–72 hours.
        vi. Patients with severe trauma (injury severity score greater than 23) may present with antithrombin deficiency; therefore, subcutaneous prophylaxis may be insufficient. Although not prospectively evaluated, an option may be to use an UFH infusion while the patient is in the

intensive care unit early in the course of therapy. Only a slight increase in the aPTT (35–45 seconds) would be targeted because VTE prevention is the goal.

b. Acute spinal cord injury
   i. UFH three times daily had rates of DVT and bleeding similar to enoxaparin twice daily, but PE was significantly reduced with enoxaparin.
   ii. Although enoxaparin 30 mg twice daily should be used during the acute injury period (about 2–3 weeks), either regimen can be used during the rehabilitation period.
   iii. In a retrospective case-control study, dalteparin 5000 units daily failed to show noninferiority to enoxaparin 30 mg twice daily in preventing VTE (9.7% vs. 1.6%).

c. Burns – The current evidence in burn patients is only from observational studies with UFH, enoxaparin, and dalteparin. The most commonly used regimen is UFH 5000 units subcutaneously every 12 hours.

d. Critical care
   i. In medically ill or postoperative general surgery patients, UFH or an LMWH can be used. In orthopedic surgery or trauma, an LMWH is preferred.
   ii. If mechanical prophylaxis is selected because of a patient's high risk of bleeding, the patient should be reevaluated often and changed to pharmacologic prophylaxis when the bleeding risk decreases.
   iii. Some pharmacodynamic studies suggest that critical care patients with significant edema or critical care patients receiving vasopressors will not achieve detectable anti-Xa concentrations with LMWH.
   iv. In the largest trial of VTE prevention in critical care patients, dalteparin 5000 units subcutaneously once daily provided similar protection against proximal DVT, better protection against PE, similar bleeding, and less heparin-induced thrombocytopenia than UFH 5000 units twice daily.
   v. Dalteparin does not have significant accumulation in critical care patients with renal insufficiency.
   vi. A retrievable inferior vena cava filter may be considered for PE prophylaxis, but this practice has limited evidence and is controversial.

**Table 16.** VTE Prophylaxis in Critically Ill Patients

| Critical Care Setting | UFH | LMWH | Fondaparinux |
|---|---|---|---|
| Trauma | Insufficient evidence | Dalteparin 5000 IU SC q24hr<br>Enoxaparin 30 mg SC q12hr | Insufficient evidence |
| Acute spinal cord injury | 5000 units SC q8hr | Enoxaparin 30 mg SC q12hr or<br>Enoxaparin 40 mg SC q24hr | Insufficient evidence |
| Burns | 5000 units SC q8hr or<br>5000 units SC q12hr | Dalteparin 5000 IU SC q24hr<br>Enoxaparin 40 mg SC q24hr | Insufficient evidence |
| Critical care | 5000 units SC q8hr or<br>5000 units SC q12hr | Dalteparin 5000 IU SC q24hr<br>Enoxaparin 30 mg SC q12hr, or<br>Enoxaparin 40 mg SC q24hr | Insufficient evidence<br>2.5 mg SC daily may be an option in suspected HIT |

HIT = heparin-induced thrombocytopenia.

F. COVID-19

1. Hospitalized patients infected with the SARS-CoV-2 virus have approximately a two-fold increase in thrombotic events compared to other medically ill patients with respiratory distress.

2. Although several infections can increase risk of thrombosis through the vascular damage caused by the inflammatory process, the SARS-CoV-2 virus also creates an antifibrinolysis condition caused by its unique entry into the cell via the angiotensin 2 receptor.
3. ISTH guidelines for antithrombotic treatment in COVID-19 have been updated (Table 17)
   a. In general, hospitalized patients require anticoagulation with standard prophylactic doses of LMWH or UFH.
   b. Rivaroxaban 10 mg daily is recommended in high-risk patients (IMPROVE 2-3 with D-dimer greater than 500 ng/mL or score of 4 or more independent of D-dimer) for 35 days after hospital discharge based on the results of the MICHELLE trial. After hospital discharge for COVID-19, rivaroxaban demonstrated a significant 67% reduction in thrombotic events at 35 days (3% vs. 9%; p=0.029).

**Table 17.** ISTH Guidelines for Antithrombotic Treatment in COVID-19

| Patients | Recommendations |
|---|---|
| Nonhospitalized patients with symptomatic COVID-19 | • Initiation of antiplatelet therapy is not effective to reduce risk of hospitalization, arterial or venous thrombosis, or mortality<br>• Initiation of DOAC therapy is not effective to reduce risk of hospitalization, arterial or venous thrombosis, or mortality<br>• Initiation of oral sulodexide therapy may be considered to reduce risk of hospitalization |
| **Patients** | **Recommendations** |
| Hospitalized, non-critically ill patients | • Prophylactic dose LMWH/UFH is recommended in preference to no LMWH/UFH to reduce risk of thromboembolism and possibly death<br>• Therapeutic dose LMWH/UFH is beneficial in preference to prophylactic or intermediate dose LMWH/UFH in select patients[a] to reduce risk of thromboembolism and end organ failure<br>• Intermediate-dose LMWH/UFH is not recommended in preference to prophylactic-dose LMWH/UFH to reduce risk of thromboembolism and other adverse outcomes.<br>• The addition of an antiplatelet agent to anticoagulant therapy is potentially harmful and should not be used<br>• Therapeutic-dose DOAC is not effective to reduce risk of thromboembolism and other adverse outcomes |
| Hospitalized, critically ill patients[b] | • Intermediate dose LMWH/UFH is not recommended over prophylactic dose LMWH/UFH to reduce risk of adverse events, including mortality and thromboembolism<br>• Therapeutic dose LMWH/UFH is not recommended over usual care or prophylactic dose LMWH/UFH<br>• The addition of an antiplatelet agent to prophylactic dose LMWH/UFH is not well established but might be considered to reduce mortality |
| Discharged from the hospital | • Prophylactic dose rivaroxaban for approximately 30 days may be considered to reduce risk of VTE in select patients[c] |

[a]Patients at low risk of bleeding and with risk factors for thromboembolism or organ failure, such as elevated D-dimer or increased oxygen requirements.

[b]Patients requiring organ support such as invasive or noninvasive positive pressure ventilation, high-flow supplemental oxygen therapy, vasopressor or inotrope support, extracorporeal membrane oxygenation, or continuous renal replacement therapy.

[c]IMPROVE VTE score of 2–3 with D-dimer level more than 500 ng/mL or a score of 4 or more independent of the D-dimer level at discharge (or level closest to discharge).

COVID-19 = coronavirus disease 2019; DOAC = direct oral anticoagulant; IMPROVE = International Medical Prevention Registry on Venous Thromboembolism; ISTH = International Society of Thrombosis and Haemostasis; LMWH = low molecular weight heparin; UFH = unfractionated heparin.

G. Duration of VTE Prophylaxis: Varies on the basis of patient risk and group (Table 18)

**Table 18.** Duration of VTE Prophylaxis

| Indication | Duration |
|---|---|
| General medically ill patients | 6–14 days or as long as immobile during acute illness<br>Rivaroxaban for patients with moderate to severe immobility for a total of 31–39 days |
| Major general surgery | Until hospital discharge |
| Major general surgery in patients with previous VTE | Beyond hospital discharge for up to 28 days |
| Surgery for gastrointestinal, GU, or gynecologic cancer | Beyond hospital discharge for up to 28 days |
| Total knee replacement surgery | At least 10 days |
| Total hip replacement surgery | 4–6 wk |
| Hip fracture surgery | 4–6 wk |
| Critical care patients | For the duration of the intensive care unit stay with reevaluation when the patient is transferred to the general medical ward |
| Major trauma | Until hospital discharge and continued prophylaxis in patients with impaired mobility who undergo inpatient rehabilitation (up to 8 wk) |
| Patients with spinal cord injury | Until hospital discharge in patients with incomplete injuries<br>For 8 wk in patients with uncomplicated complete motor injury<br>For 12 wk or discharge from rehabilitation in patients with complete motor injury and other risk factors |

GU = genitourinary

H. Special Populations – Information on use of VTE prophylaxis in special populations is found in Box 6.

**Box 6.** Use of VTE Prophylaxis in Special Populations

| |
|---|
| Severe Renal Insufficiency<br>• Patients with renal insufficiency are at higher risk of bleeding, regardless of the anticoagulant used<br>• Patients with SCr > 2.5 mg/dL have been excluded from most clinical trials<br>• Enoxaparin should be dosed at 30 mg SC once daily, regardless of the indication for a CrCl < 30 mL/min/1.73 $m^2$<br>• Dalteparin does not seem to significantly accumulate in patients with severe renal insufficiency until the CrCl is < 20 mL/min/1.73 $m^2$ when prophylactic doses are used<br>• Fondaparinux and dabigatran are contraindicated in patients with a CrCl < 30 mL/min/1.73 $m^2$.<br>• Rivaroxaban and apixaban should be avoided in patients with a CrCl < 15 mL/min/1.73 $m^2$<br>• Patients on hemodialysis (renal failure) should receive SC UFH |
| Obesity<br>• The ACCP guidelines recommend possible weight-adjusted dosing in patients with obesity, but the guidelines provide no insight on at what weight this should be considered or what the "adjusted" dosing should be. Patients with obesity are at considerable risk of PE, but data from clinical trials on drug dosing are limited<br>• Several studies suggest that the typical dose of an LMWH has to be higher in patients with a body mass index ≥ 40 kg/$m^2$<br>• Enoxaparin 40 mg SC twice daily has been more efficacious than 30 mg SC twice daily in patients undergoing bariatric surgery<br>• It is reasonable to use enoxaparin 40 mg twice daily or UFH 7500 units three times daily in patients with a BMI > 40 kg/$m^2$ or weight > 120 kg.<br>• Injections of enoxaparin into the thigh in patients with obesity have a lower bioavailability than injections into the abdomen |
| Pregnancy<br>• Warfarin has been associated with congenital abnormalities when used during the first trimester and is therefore contraindicated. Although warfarin could be used during the second trimester, it is typically avoided throughout pregnancy<br>• An LMWH or UFH can be used throughout pregnancy<br>• LMWHs (or fondaparinux) are not contraindicated in the third trimester of pregnancy and can be used in the early third trimester. During the peripartum period, many prefer to use UFH because of its shorter half-life and lower risk of bleeding during delivery<br>• DOACs currently have no role in pregnancy |
| Cirrhosis<br>• Patients with cirrhosis have an approximately 2-fold increased risk of VTE compared to medically ill patients without cirrhosis.<br>• Patients commonly have thrombocytopenia and a prolonged PT and aPTT, which can be interpreted by clinicians as predisposing to bleeding. These patients actually have a rebalanced hemostasis with hypercoagulable features.<br>• Although variceal bleeding is a concern, this is secondary to portal hypertension with little evidence that hemostatic alterations or the use of anticoagulant therapy modulates the risk or severity of variceal bleeding.<br>• ISTH guidance document recommend against the use of thrombocytopenia and/or prolonged PT/INR as an absolute contraindication for VTE prophylaxis.<br>• ISTH guidance document recommends the use of LMWH or fondaparinux over UFH for VTE prophylaxis, at usual doses. |

DOAC = direct-acting oral anticoagulant; PE = pulmonary embolism; SC = subcutaneous(ly).

**Patient Case**

5. B.G. is a 62-year-old man (height 69 inches, weight 110 kg) hospitalized for a heart failure exacerbation. He has symptoms when doing only limited exertion and has been out of bed only to use the bathroom for the past 3 days. His medical history also includes stable ischemic heart disease, hypertension, type 2 diabetes, and a PE 2 years ago. He currently smokes 2 packs/day and drinks 1 glass of wine with dinner most evenings. His current medications include bisoprolol 5 mg daily, lisinopril 10 mg daily, aspirin 81 mg daily, ranolazine 1000 mg twice daily, furosemide 40 mg daily, spironolactone 25 mg daily, and metformin 850 mg twice daily. His blood pressure today is 110/70 mm Hg and heart rate is 58 beats/minute. His laboratory values are normal except for a b-type natriuretic peptide of 1498 ng/mL. Which is the most appropriate VTE prevention strategy for B.G.?
   A. Give fondaparinux 5 mg subcutaneously daily.
   B. Give apixaban 2.5 mg orally twice daily.
   C. Give enoxaparin 40 mg subcutaneously daily.
   D. B.G.'s risk does not warrant prophylactic therapy.

## III. TREATMENT OF VENOUS THROMBOEMBOLISM

A. Introduction
   1. Around 2 million symptomatic and asymptomatic cases of VTE occur in the United States each year.
      a. Around 600,000 cases of PE each year
      b. More than 100,000 deaths occur from PE each year in the United States.
   2. Consequences of VTE
      a. 30%–50% will develop a recurrent VTE event in the following 5–10 years.
      b. Around 30% develop postthrombotic syndrome.
      c. After a DVT event, 20% of patients die within the following year.
      d. After a PE event, 40% of patients die within the following year.

B. Pathophysiology
   1. Venous thrombosis forms from the components of Virchow's triad, which are venous stasis, vascular damage, and/or an inherited or acquired hypercoagulable state.
   2. Virchow's triad components are broken down into a list of risk factors (Box 5). Risk factors are cumulative, and some carry a higher risk than others (e.g., previous VTE, cancer, orthopedic surgery).
   3. Thrombus typically begins in the cusps of venous valves where blood flow is more static. Vascular injury because of trauma or hypoxia initiates the clotting cascade with interaction between endothelial tissue factor and factor VII.
   4. An embolism from a DVT will lodge itself in the next available capillary bed, which is in the pulmonary vasculature leading to PE.
   5. Despite therapy, areas of vascular damage may never fully recover, which leads to a continued risk of recurrent DVT events.
   6. Thrombosis often forms in and around venous valves, causing them to curl. Despite therapy, these valves may not recover their initial shape and function, which leads to continued venous stasis and a continued risk of recurrent DVT and postthrombotic syndrome.
   7. Most upper-extremity DVTs are related to the use of central venous catheters.

C. Presentation and Assessment
   1. DVT
      a. Although many cases are asymptomatic, these acute asymptomatic DVTs can still produce long-term complications.
      b. Most thrombi begin in the lower extremities.
      c. Superficial vein thromboses typically do not embolize unless they extend into a deep vein, are at least 5 cm long, or are within 10 cm of the saphenofemoral junction.
      d. Proximal DVTs are more likely to embolize than are isolated calf DVTs.
      e. Signs and symptoms are nonspecific (Box 7) and need to be confirmed with the appropriate diagnostic test.
         i. D-dimer is a breakdown product of fibrin and fibrinogen and is typically elevated in the setting of VTE. Unfortunately, D-dimer is nonspecific and can also be elevated from conditions such as inflammation and infection. Therefore, a positive test does not tell the clinician whether it is a VTE, but it also could be something else. A negative test helps rule out thrombosis.
         ii. Venography is the gold standard diagnostic tool, but it is invasive (injecting dye into a vein in the heel/ankle), may be painful, and is rarely done in clinical practice.
         iii. Duplex ultrasonography is typically used in clinical practice. Although older Doppler ultrasonography could miss as many as 50% of small DVTs, the diagnostic methods available today are much improved because they include both visual and sound technology.
      f. DVT diagnosis
         i. The Wells model can be used to determine the pretest probability of the patient's having DVT (Table 19).
         ii. Patients with a low pretest probability who are younger than 65 and have a negative D-dimer can have DVT ruled out of their differential diagnosis.
         iii. Other patients should proceed to duplex ultrasonography or other imaging studies to confirm the diagnosis.

**Table 19.** Wells Clinical Model for Evaluating the Pretest Probability of DVT[a,b]

| Clinical Characteristics | Score |
|---|---|
| Active cancer (cancer treatment within previous 6 mo or currently receiving palliative treatment) | 1 |
| Paralysis, paresis, or recent plaster immobilization of the lower extremities | 1 |
| Recently bedridden for ≥ 3 days or major surgery within the previous 12 wk requiring general or regional anesthesia | 1 |
| Localized tenderness along the distribution of the deep venous system | 1 |
| Entire leg swollen | 1 |
| Calf swelling at least 3 cm larger than that on the asymptomatic side (measured 10 cm below tibial tuberosity) | 1 |
| Pitting edema confined to the symptomatic leg | 1 |
| Collateral superficial veins (non-varicose) | 1 |
| Previously documented DVT | 1 |
| Alternative diagnosis at least as likely as DVT | -2 |

[a]Clinical probability of DVT: low < 0; moderate 1–2; high > 3. In patients with symptoms in both legs, the more symptomatic leg is used.
[b]Calculator available at www.mdcalc.com/wells-criteria-for-dvt/.

**Box 7.** Clinical Presentation of DVT and PE

| Deep Venous Thrombosis |
|---|
| Edema |
| Leg pain |
| Calf tenderness |
| Swelling |
| Discoloration (redness) |
| Increased leg warmth |
| **Pulmonary Embolism** |
| Tachycardia |
| Tachypnea |
| Hemoptysis |
| Dyspnea |
| Cough |
| Chest pain |

2. PE (patients with hemodynamic stability [i.e., nonmassive])
    a. Similar to DVT cases, many PE cases are asymptomatic. Most thrombi begin in the lower extremities and embolize.
    b. Onset can be acute, with sudden death occurring in at least 10% of hospitalized cases before a diagnosis is confirmed.
    c. Signs and symptoms are nonspecific (Box 7) and need to be confirmed with the appropriate diagnostic test.
        i. D-dimer is similar to use with DVT. Serum concentrations are typically elevated in patients with PE. A negative test, combined with a low pretest probability score in patients younger than 65 years old, can rule out PE.
        ii. CT is the most commonly used test for diagnosing PE. Unless it is unavailable or a contraindication or concern exists with the use of contrast dye (e.g., renal dysfunction), CT is the preferred diagnostic test for PE. Positive results have good specificity and generally confirm the diagnosis. Both the sensitivity and the specificity of the test are improved with central emboli over those that are more peripheral.
        iii. Ventilation/perfusion scanning measures the distribution of blood flow and air flow in the lungs. When there is a "mismatch" between blood flow and air flow in one area of the lung, the probability of PE is high. Specificity can be impaired in patients with heart failure, chronic obstructive pulmonary disease, or asthma. A scan with a negative finding has good specificity and generally rules out the diagnosis of PE. Findings reported as low or intermediate probability require additional diagnostic testing. This is the preferred diagnostic test for patients with renal dysfunction or with an allergy to contrast dye.
        iv. Pulmonary angiography is the gold standard diagnostic test for PE, but it is invasive, expensive, and associated with significant morbidity from the injection of contrast dye into the pulmonary artery.
    d. PE diagnosis
        i. The Wells model can be used to determine the pretest probability of the patient's having PE (Table 20).
        ii. Patients with low pretest probability, younger than 65 years old, and with a negative D-dimer can have PE ruled out of their differential diagnosis.
        iii. Other patients should proceed to CT or other imaging studies to confirm the diagnosis.

**Table 20.** Wells Criteria Clinical Model for Evaluating the Pretest Probability of PE[a,b]

| Clinical Characteristic | Score |
|---|---|
| Cancer | 1 |
| Hemoptysis | 1 |
| Previous PE or DVT | 1.5 |
| Heart rate > 100 beats/min | 1.5 |
| Recent surgery or immobilization | 1.5 |
| Clinical signs of DVT | 3 |
| Alternative diagnosis less likely than PE | 3 |

[a]Clinical probability of PE: low 0–1; moderate 2–6; high ≥ 7.

[b]Calculator available at www.mdcalc.com/wells-criteria-for-pulmonary-embolism-pe/.

D. Acute Treatment of VTE
   1. Three different approaches to the treatment of VTE (Table 21)
   2. The 2021 ACCP guidelines prefer DOACs to warfarin for the treatment of patients with VTE without cancer because of less bleeding and greater convenience for patients and health care providers.
   3. The 2020 ASH guidelines also prefer DOACs to warfarin for the treatment of VTE.
   4. Initiate therapy until the VTE is ruled out.

**Table 21.** Approaches to the Treatment of VTE

| Treatment Strategy | Anticoagulant Choices |
|---|---|
| Bridging therapy | Injectable anticoagulant (UFH, LMWH, or fondaparinux) initiated with warfarin and overlapped for at least 5 days and until the INR is > 2.0. Then discontinue injectable anticoagulant and continue warfarin for the appropriate duration |
| Switching therapy | Injectable anticoagulant (UFH, LMWH, or fondaparinux) for at least 5 days; then stop injectable anticoagulant therapy and initiate dabigatran or edoxaban for the appropriate duration |
| Monotherapy | Initiate rivaroxaban or apixaban at higher initial dose and then convert patient to lower maintenance dose for the appropriate duration |

   5. Bridging therapy approach to treatment of VTE
      a. Because of the delay in achieving systemic anticoagulation with warfarin therapy and the significant thrombus burden in patients with VTE, an injectable anticoagulant is initiated on the suggestion of a VTE and bridged to warfarin if the diagnosis is confirmed.
      b. Dosing of injectable anticoagulants for the treatment of VTE can be found in Table 22. Achieving therapeutic anticoagulation within the first 24 hours has been associated with reduced rates of recurrent VTE events.
      c. The ACCP guidelines recommend initial injectable anticoagulant therapy with a LMWH or fondaparinux over intravenous or subcutaneous UFH.
      d. Warfarin dosing in the stable outpatient setting is similar to that discussed in the AF section. In the acute situation, dosing may depend on cofactors that drive initial dosing approaches.
      e. Goal INR is 2.0–3.0. Lower INR goals of 1.5–2.0 have not been proven as effective at preventing recurrent VTE and have not shown a meaningful safety benefit.
      f. Bridging to warfarin would likely be the preferred approach in the following:
         i. When patients cannot afford DOAC therapy
         ii. The transition to outpatient therapy makes acquiring a DOAC difficult. Pharmacists play a crucial role in assisting with confirming insurance coverage and other transition issues in these patients.

**Table 22.** Dosing of Injectable Anticoagulants for the Treatment of VTE

| Agent and Route | Dosing |
|---|---|
| **Unfractionated Heparin** | |
| Intravenous UFH[a] | Weight adjusted with an initial bolus of 80 units/kg, followed by an initial infusion of 18 units/kg/hr. Subsequent doses should be adjusted to maintain the goal aPTT for the institution |
| SC UFH | 17,500 units (250 units/kg) given q12hr.[b] Subsequent doses should be adjusted to maintain the goal aPTT for the institution |
| SC UFH | 333 units/kg, followed by 250 units/kg given q12hr without aPTT monitoring[c] |
| **Low-Molecular-Weight Heparin (SC)** | |
| Enoxaparin | 1 mg/kg q12hr or 1.5 mg/kg q24hr[d]<br>If CrCl < 30 mL/min/1.73 $m^2$, give 1 mg/kg q24hr |
| Dalteparin[e,f] | 100 units/kg q12hr or 200 units/kg q24hr |
| **Pentasaccharide (SC)** | |
| Fondaparinux | Weight < 50 kg: 5 mg q24hr<br>Weight 50–100 kg: 7.5 mg q24hr<br>Weight > 100 kg: 10 mg q24hr<br>CrCl < 30 mL/min/1.73 $m^2$ – Contraindicated |

[a]Intravenous administration is preferred because of improved dosing precision.

[b]An initial 5000-unit intravenous bolus is recommended to achieve rapid anticoagulation.

[c]Good regimen for outpatient treatment for patients who cannot afford LMWH. Not practical for patients weighing > 80 kg because of issues with injection volume.

[d]1.5 mg/kg q24hr should be avoided in patients with a history of or current malignancy, weight > 120 kg, DVT with iliac vein involvement, pregnancy, or antiphospholipid syndromes.

[e]No dosing recommendations for patients with severe renal insufficiency. Standard dosing likely not an issue until CrCl is < 20 mL/min/1.73 $m^2$.

[f]Not FDA approved for the treatment of VTE in patients without cancer, which may create insurance coverage issues.

aPTT = activated partial thromboplastin time.

6. Switching therapy approach in VTE treatment
    a. Dabigatran was evaluated in the RE-COVER I (n=2539) and II (n=2568) trials. Both trials had the same design, and both enrolled patients with DVT (68%), PE (23%), or both (9%).
        i. All patients received a median of 9 days of injectable anticoagulation. Patients randomized to dabigatran started the drug after discontinuing the injectable (Table 23; Box 1). Patients randomized to warfarin started the drug at the same time as the injectable anticoagulant and were bridged to an INR of 2.0–3.0 for at least 5 days. Patients were treated for 6 months.
        ii. In the combined trials (n=5107), the primary end point of symptomatic VTE events was similar between dabigatran and warfarin (2.4% vs. 2.2%; p=NS). Noninferiority was achieved (p<0.001).
        iii. Major bleeding was not significantly reduced with dabigatran (1.4% vs. 2.0%). When evaluating major bleeding only after starting oral anticoagulant therapy, there was a relative 40% significant reduction with dabigatran.
        iv. Major and CRNM bleeding combined were significantly reduced with dabigatran compared with warfarin.
        v. There was significantly more dyspepsia with dabigatran than with warfarin.

b. Edoxaban was evaluated in the Hokusai-VTE trial (n=8240), which included patients with DVT (60%), PE (30%), or both (10%).
   i. All patients received a median of 7 days of injectable anticoagulant. Patients randomized to edoxaban started the drug after discontinuing the injectable (Table 23; Box 4). Patients randomized to warfarin started the drug at the same time as the injectable anticoagulant and were bridged to INR of 2.0–3.0 for at least 5 days. Patients were followed for 12 months. The reduced edoxaban dose was used in 18% of patients with maintained efficacy and safety.
   ii. The primary end point of symptomatic VTE events was similar between edoxaban and warfarin (3.2% vs. 3.5%; p=NS). Noninferiority was achieved (p<0.001).
   iii. The subgroup of patients enrolled with severe PE, defined as producing right ventricular dysfunction (n=939), had a significant 48% reduction in the primary end point compared with warfarin.
   iv. Major bleeding was not significantly reduced with edoxaban (1.4% vs. 1.6%).
   v. Major and CRNM bleeding combined was significantly reduced with edoxaban compared with warfarin.

7. Monotherapy approach in VTE treatment
   a. Rivaroxaban was evaluated in the EINSTEIN DVT (n=3449) and EINSTEIN PE (n=4832) trials. The trial designs were the same; however, they included different patient populations.
      i. Rivaroxaban was started without injectable therapy (Table 23) and was compared with enoxaparin 1 mg/kg every 12 hours bridged to dose-adjusted warfarin therapy (INR 2.0–3.0). Median duration of injectable anticoagulant was 8 days. Investigators determined whether patients would be treated for 3, 6, or 12 months. Only 12% and 5% of patients were treated for 3 months in the EINSTEIN DVT and EINSTEIN PE trials, respectively.
      ii. Many patients in the rivaroxaban arms of EINSTEIN DVT (73%) and EINSTEIN PE (93%) still received injectable anticoagulation before entering the study. These patients were transitioned to rivaroxaban upon entering the trial (Box 2). Efficacy and safety outcomes did not differ if patients did or did not receive initial doses of injectable anticoagulation before receiving rivaroxaban.
      iii. In the combined trials (n=8282), the primary end point of symptomatic VTE events was similar between rivaroxaban and standard care (2.1% vs. 2.3%; p=0.41). Noninferiority was achieved (p<0.001).
      iv. Major bleeding was reduced by a relative 46% with rivaroxaban compared with standard care (1.0% vs. 1.7%; p=0.002).
      v. Fragile patients (age older than 75, CrCl less than 50 mL/minute/1.73 $m^2$, or weight less than 50 kg) had a greater than 70% significant relative reduction in major bleeding, with each component of fragility reaching statistical significance independently.
      vi. Major and CRNM bleeding was not different between the groups.
   b. Apixaban was evaluated in the AMPLIFY (n=5395) trial, which included patients with DVT (65%) or PE (35%).
      i. Apixaban was started without injectable therapy (Table 23) and was compared with enoxaparin 1 mg/kg every 12 hours bridged to dose-adjusted warfarin therapy (INR 2.0–3.0). Median duration of injectable anticoagulant was 6.5 days. Patients were treated for 6 months.
      ii. 86% of patients in the apixaban arm initially received at least one dose of injectable anticoagulant before entering the study. These patients were transitioned to apixaban upon entering the trial (Box 3). Efficacy and safety outcomes did not differ regardless of whether patients received initial doses of injectable anticoagulation before receiving apixaban.
      iii. The primary end point of symptomatic VTE events was similar between apixaban and standard care (2.3% vs. 2.7%; p=NS). Noninferiority was achieved (p<0.001).

iv. Major bleeding was reduced by a relative 70% with apixaban compared with standard care (0.6% vs. 1.8%; p<0.001).
v. CRNM bleeding was also reduced with apixaban.

**Table 23.** Dosing of DOACs in the treatment of VTE

| Agent | Standard Dosing | Dose Adjustment[a] | Avoid Use[a] |
|---|---|---|---|
| Dabigatran | 150 mg twice daily after 5–10 days of injectable anticoagulation | None | • CrCl ≤ 30 mL/min/1.73 $m^2$<br>• Avoid use with CrCl 30–50 mL/min and concomitant use of P-gp inhibitors<br>• Chemotherapy agents – Vinblastine, doxorubicin, imatinib, crizotinib, vandetanib, sunitinib, abiraterone, and, enzalutamide |
| Rivaroxaban | 15 mg twice daily with food for 21 days, followed by 20 mg daily with food. After 6 mo, dose can be reduced to 10 mg daily. The 10-mg dose need not be given with food | None | • CrCl < 15 mL/min/1.73 $m^2$<br>• Strong CYP3A4 and P-gp inducers (e.g., rifampin, phenytoin, carbamazepine, St. John's wort)<br>• Strong CYP3A4 and P-gp inhibitors (e.g., protease inhibitors, itraconazole, ketoconazole, conivaptan)<br>• Chemotherapy agents – Vinblastine, doxorubicin, imatinib, crizotinib, vandetanib, sunitinib, abiraterone, and, enzalutamide |
| Apixaban | 10 mg twice daily for 7 days, followed by 5 mg twice daily. After 6 months, dose can be reduced to 2.5 mg twice daily | 50% dose reduction if receiving 5 or 10 mg twice daily with strong CYP3A4 and P-gp inhibitors (e.g., protease inhibitors, itraconazole, ketoconazole, conivaptan) | • CrCl < 15 mL/min/1.73 $m^2$<br>• Strong CYP3A4 and P-gp inducers (e.g., rifampin, phenytoin, carbamazepine, St. John's wort)<br>• If on 2.5 mg twice daily – Strong CYP3A4 and P-gp inhibitors (e.g., protease inhibitors, itraconazole, ketoconazole, conivaptan)<br>• Chemotherapy agents – Vinblastine, doxorubicin, imatinib, crizotinib, vandetanib, sunitinib, abiraterone, and, enzalutamide |
| Edoxaban | 60 mg once daily after 5–10 days of injectable anticoagulation | 30 mg once daily<br>• CrCl 15–50 mL/min/1.73 $m^2$<br>• Potent P-gp inhibitor (verapamil, dronedarone, or quinidine)<br>• Weight ≤ 60 kg | • CrCl < 15 mL/min/1.73 $m^2$<br>• Rifampin<br>• Chemotherapy agents – Vinblastine, doxorubicin, imatinib, crizotinib, vandetanib, sunitinib, abiraterone, and, enzalutamide |

[a]CrCl in the DOAC trials was calculated using the Cockcroft-Gault equation with total body weight.

8. Outpatient therapy
    a. Around 80% of patients with DVT can be treated on an outpatient basis.
    b. Most patients with low risk PE can also be treated at home (Table 24). Use of outpatient treatment for PE may vary depending on geographic practices. Increased education is needed to promote this practice. Availability of using DOACs without injectable medication offers an attractive option and easier transition of care.
    c. Rivaroxaban has been shown to be safe and effective using this approach in a small trial (HoT-PE) and significantly reduced resource use (MERCURY PE). Data with other DOACs are still developing.
    d. The 2020 ASH guidelines recommend the use of outpatient treatment of low-risk PEs.

**Table 24.** PESI and Simplified PESI Scores Predict 30-Day Mortality

| Variable | PESI Score | Simplified PESI Score |
|---|---|---|
| Age > 80 | Age in years | 1 |
| Male sex | 10 | 0 |
| History of cancer | 30 | 1 |
| History of heart failure | 10 | 1[a] |
| History of chronic lung disease | 10 | |
| Heart rate ≥ 110 beats/min | 20 | 1 |
| Systolic BP < 100 mm Hg | 30 | 1 |
| Respiratory rate ≥ 30 breaths/min | 20 | 0 |
| Temperature > 36°C | 20 | 0 |
| Altered mental status[b] | 60 | 0 |
| Oxygen saturation < 90%[c] | 20 | 1 |
| **Classification of Risk by Total Score** | | |
| | ≤ 65 points – Class I | Low risk = 0 points |
| | 66–85 points – Class II | |
| | 86–105 points – Class III | High risk ≥ 1 point |
| | 106–125 points – Class IV | |
| | > 125 points – Class V | |

[a]Heart failure and chronic lung disease are combined into a single category of chronic cardiopulmonary disease.

[b]Disorientation, lethargy, stupor, or coma.

[c]With or without supplemental oxygen.

PESI = Pulmonary Embolism Severity Index.

E. Secondary Prevention of VTE
    1. All patients with VTE should be treated for at least 3 months (Table 25).
    2. Patients without a transient or reversible cause should be considered for long-term, potentially indefinite, oral anticoagulant therapy. Data consistently show significant reductions in VTE with continued therapy for 12–24 additional months. Once therapy is discontinued, VTE rates catch up with those who did not receive extended therapy.
    3. The ACCP guidelines state that there is no need to change the oral anticoagulant if therapy is continued beyond 3 months.

4. Options
    a. Adjusted-dose warfarin to an INR of 2.0–3.0
    b. Dabigatran 150 mg twice daily has shown noninferiority to warfarin for efficacy with similar major bleeding, but less major and CRNM bleeding (RE-MEDY trial). Dabigatran was superior to placebo for efficacy, with similar major bleeding but more major and CRNM bleeding (RE-SONATE trial).
    c. Rivaroxaban 20 mg daily had shown superiority to placebo for efficacy, with similar major bleeding, and more major and CRNM bleeding (EINSTEIN Ext trial). Both rivaroxaban 20 mg and rivaroxaban 10 mg once daily were superior to aspirin, with similar safety (EINSTEIN CHOICE) in patients who had already completed 6 months of therapy (Table 23).
    d. Apixaban 5 mg and 2.5 mg twice daily were superior to placebo for efficacy, with similar safety (AMPLIFY Ext) in patients who had already completed 6 months of therapy (Table 23).
    e. Edoxaban has not completed a long-term trial beyond the Hokusai-VTE trial.
    f. Aspirin (100 mg daily) has shown a 32% relative reduction in recurrent VTE events compared with placebo in two trials after patients completed at least 6 months of oral anticoagulant therapy. Relative reductions in patients receiving a DOAC compared with placebo are typically 70%–80%. The only study comparing a DOAC with aspirin is the EINSTEIN CHOICE trial, in which both rivaroxaban doses were superior to aspirin for efficacy, with similar low rates of bleeding.

**Table 25.** Duration of Anticoagulation Therapy in Patients with VTE

| Indication | Therapy Duration | Comments |
|---|---|---|
| First episode of VTE secondary to a transient or reversible risk factor | 3 mo | Recommendation applies to both proximal DVT and PE |
| First episode of unprovoked VTE | At least 3 mo | Continue oral anticoagulant therapy if patient is not at high risk of bleeding and is adherent to therapy<br>The risk-benefit of indefinite therapy should be reassessed at periodic intervals |
| First episode of VTE with inherited or acquired thrombophilia[a] | At least 3 mo | Continue oral anticoagulant therapy if patient is not at high risk of bleeding and is adherent to therapy<br>Several abnormalities or homozygous traits have at least additive risk<br>The risk-benefit of indefinite therapy should be reassessed at periodic intervals |
| First episode of cancer-associated VTE | At least 3–6 mo and consider extended duration until cancer resolves | LMWH, rivaroxaban, apixaban, or edoxaban is recommended over other anticoagulants |
| Second VTE (provoked or unprovoked) | Indefinite | Applies to patient not at high risk of bleeding |

[a]Factor V Leiden; prothrombin G20210A; antiphospholipid antibody syndrome; excess factor VIII; deficiency in protein C, protein S, antithrombin deficiency.

F. Treatment of Cancer-Associated VTE
    1. Cancer is a significant risk factor for developing thrombosis.
        a. 15% of patients with cancer develop venous or arterial thrombosis.
        b. Cancer increases the risk by up to 4-fold.
        c. Chemotherapy can increase the risk by up to 6.5-fold.
        d. VTE is the second leading cause of death in most cancers.
        e. Risk differs by cancer type.

2. LMWH is preferred as monotherapy for 3–6 months compared with warfarin therapy because of significantly improved efficacy without an increase in major bleeding.
    a. All LMWHs have evidence in these patients. Only dalteparin has specific FDA approval.
    b. The CLOT trial (n=676) used dalteparin 200 units/kg for the first 30 days, followed by 150 units/kg/day for the next 5 months, or warfarin for 6 months.
    c. Despite the evidence, many patients are not treated with LMWH because of cost or unwillingness to use injections for several months.
3. The VTE treatment trials with DOACs enrolled 2.5%–6.0% of patients with active cancer. Compared with warfarin therapy, none of the DOACs had a significant or numerical increase in recurrent VTE events and had similar bleeding. Despite the low percentage of patients with active cancer enrolled in these trials, more than 1000 patients had active cancer. If patients will not receive an LMWH, the ACCP guidelines do not recommend warfarin over a DOAC in patients with cancer.
4. Edoxaban and rivaroxaban have been compared with dalteparin in trials of patients with cancer-induced thrombosis. Collectively, these DOACs better reduced recurrent VTE, but with more major bleeding. Most of the excess bleeding occurs in patients with upper gastrointestinal cancers.
5. Apixaban provided similar efficacy to dalteparin with similar major bleeding. The similar major bleeding in the overall trial is likely because of the lower enrollment of patients with upper gastrointestinal cancers.
6. Although the ISTH and American Society of Clinical Oncology guidelines currently only recommend edoxaban and rivaroxaban for the treatment of cancer-associated VTE (apixaban data not available yet), the National Comprehensive Cancer Network (NCCN) and ACCP also include apixaban. Although NCCN and ACCP suggest the use of apixaban in patients with upper GI cancers (esophageal or gastroesophageal), it would seem prudent to avoid DOACs in these patients.
7. Patients with cancer-associated VTE should be treated with these agents for 6 months and/or while receiving cancer treatment.

G. Massive PE
    1. Clinical presentation
        a. Patients can have tachycardia, hypotension, tachypnea, hypoxia, and signs of right ventricular dysfunction (e.g., distended jugular veins, tricuspid regurgitation).
        b. Electrocardiogram changes (e.g., right bundle branch block, T-wave inversion in leads $V_1$–$V_4$)
        c. Other findings of severe PE
            i. Right ventricular enlargement with a diameter of 90% or more of the left ventricle
            ii. Elevated troponin
            iii. Elevated b-type natriuretic peptide
    2. Prognosis
        a. Presenting hypotensive requiring inotropic support = mortality of around 30%
        b. Presenting in cardiopulmonary arrest = mortality of around 70%
    3. Fibrinolytic therapy
        a. Patients with PE who present with hypotension (systolic blood pressure less than 90 mm Hg or a documented decrease in systolic blood pressure of greater than 40 mm Hg with evidence of poor perfusion), and not at high risk of bleeding, are candidates for systemic fibrinolytic therapy.
        b. Patients with PE whose condition deteriorates after starting anticoagulation therapy but who have not developed hypotension and are at low risk of bleeding should receive fibrinolytic therapy.
        c. Patients without hypotension but with significant right ventricular strain (elevated troponin and/or b-type natriuretic peptide) and dilation are also candidates for fibrinolytic therapy.

   d. Typically, tissue plasminogen activator (t-PA) 100 mg is given for 2 hours or less into a peripheral vein. Tenecteplase 30–50 mg (based on weight) as a single intravenous bolus was also evaluated in a single study, with questionable net benefit.
      i. Bolus administration of t-PA (e.g., 50 mg in 15 minutes or less) is preferred in patients with imminent or actual cardiac arrest. This must be followed by a heparin bolus and infusion.
      ii. t-PA infusions of longer than 2 hours have slower clot resolution.
      iii. Catheter-directed administration does not accelerate fibrinolysis compared with peripheral administration, but it does have more bleeding at the catheter insertion site.
      iv. In the United States, intravenous UFH is stopped during the t-PA infusion and restarted after t-PA infusion as long as the aPTT is 80 seconds or less. It is started without a bolus at the same infusion rate as before t-PA. In many other countries, UFH is continued during the t-PA infusion. These strategies have never been compared.
4. Catheter-based thrombus removal is reserved for the treatment of PE in patients with hypotension who have contraindications to fibrinolysis, failed fibrinolysis, or shock that is likely to cause death within hours, before systemic fibrinolysis can take effect.
5. Surgical pulmonary embolectomy is reserved for the treatment of PE in patients with hypotension who have contraindications to fibrinolysis, failed fibrinolysis or catheter-assisted embolectomy, or shock that is likely to cause death within hours, before systemic fibrinolysis can take effect.

**Patient Case**

*Questions 6 and 7 pertain to the following case.*

R.S. is a 48-year-old man (height 70 inches, weight 90 kg) who presents to the emergency department with pain and swelling in his left leg. On examination, his leg is warm to the touch and tender and has +3 pitting edema below the knee. His D-dimer is positive, and his duplex ultrasonography identified a femoral-popliteal DVT. He understands that he will need to receive anticoagulant therapy but wants to avoid any injections, if possible. He has good insurance coverage. His other medical conditions consist of hypertension and dyslipidemia. His medications include benazepril 20 mg daily and atorvastatin 10 mg daily. His vital signs are stable, and his CrCl is 78 mL/minute/1.73 $m^2$.

6. Which is the most appropriate anticoagulant regimen to initiate for R.S.?
   A. Rivaroxaban 15 mg twice daily for 21 days, followed by 20 mg daily.
   B. Edoxaban 60 mg daily.
   C. Warfarin 2.5 mg daily.
   D. Apixaban 5 mg twice daily for 7 days, followed by 2.5 mg twice daily.

7. Six months later, R.S. presents to the emergency department with significant shortness of breath, substernal chest pain, dizziness, and confusion. His vital signs are heart rate 104 beats/minute, blood pressure 88/60 mm Hg, and respiratory rate 24 breaths/minute. Initial laboratory results show an elevated troponin, with other values within normal ranges. Echocardiogram reveals the right ventricular diameter to be a 1:1 ratio with the left ventricle. Which is the most appropriate therapy for R.S.?
   A. Dabigatran 150 mg twice daily.
   B. t-PA 100 mg over 2 hours.
   C. Enoxaparin 90 mg every 12 hours.
   D. Rivaroxaban 20 mg once daily.

## IV. LEFT VENTRICULAR THROMBUS

A. Left ventricular thrombus forms in the setting of significant myocardial dysfunction with low left ventricular ejection fraction.
   1. Anterior ST-elevated myocardial infarction
      a. After anterior wall MI most thrombi occur in the area of apical wall motion abnormalities in hypokinetic, akinetic, or dyskinetic (aneurysm) segments.
      b. Incidence in patients after an anterior ST-elevated myocardial infarction ranges from 4% to 39%.
      c. Risk is greatest in the first 2 weeks post-MI.
      d. Associated with a 5.5-fold increase in embolic events compared to those without left ventricular thrombus
   2. Nonischemic dilated cardiomyopathy
      a. Lower left ventricular ejection fraction and the presence of scar are risk factors
      b. Accounts for 20%–25% of all left ventricular thrombus.

B. AHA Scientific Statement management suggestions for left ventricular thrombus are in Table 26.

**Table 26.** AHA Suggested Strategies for Management of Left Ventricular Thrombus[a]

| | | |
|---|---|---|
| Prevention | Acute MI with anteroapical akinesis/ dyskinesis | • Shared decision making of weighing risk of thrombus formation and bleeding risk of adding OAC to antiplatelet therapy<br>• If decision for OAC, treat for 1–3 mo |
| | Non-ischemic DCM | • Nonspecific DCM without high-risk factors – no routine preventative OAC<br>• Specific DCM with high risk factors[b] – consider indefinite OAC unless LVEF improves or bleeding contraindications occur |
| Treatment | Acute MI with anteroapical akinesis/ dyskinesis | • 3 mo OAC with repeat imaging afterward |
| | Non-ischemic DCM | • ≥3–6 mo OAC with repeat imaging afterward<br>• Discontinue OAC if thrombus resolution or major bleeding<br>• Consider indefinite OAC if LVEF does not improve, persistent apical akinesis or proinflammatory, or hypercoagulable state |
| Persistent LV thrombosis | | • Trial of alternative OAC or LMWH not unreasonable, particularly if protruding or mobile thrombus<br>• If persistent mural thrombus, particularly if organized or calcified, discontinuation of OAC not unreasonable |

[a]Oral anticoagulation may be with a direct oral anticoagulant or warfarin.

[b]Takotsubo syndrome with LVEF ≤30% and/or apical ballooning, LV noncompliance with history of stroke or TIA and/or LV dysfunction, peripartum cardiomyopathy with administration of bromocriptine and/or LVEF ≤35%, hypertrophic cardiomyopathy with apical aneurysm, chemotherapy-related cardiomyopathy with an LV restrictive filling pattern and/or LVEF ≤30%, cardiac amyloidosis with AL type and/or restrictive filling pattern, cardiomyopathy attributable to Chagas disease with apical aneurysm, eosinophilic myocarditis with prior embolic episode.

AHA = American Heart Association; DCM = dilated cardiomyopathy; LMWH = low molecular weight heparin; LV = left ventricular; LVEF, left ventricular ejection fraction; MI = myocardial infarction; OAC = oral anticoagulation; TIA=transient ischemic attack

## V. TRANSITIONS OF CARE

A. Appropriate transitions of care are critical to optimizing the efficacy and safety of anticoagulation.

B. Transitions of care with the use anticoagulants would include patients with AF, VTE prophylaxis after discharge (i.e., orthopedic surgery, medically ill), and treatment of VTE.

C. There are several components to transitions of care with anticoagulant therapy.
   1. Ensuring patient access to anticoagulant therapy immediately after discharge to prevent a break in therapy: Meds-to-beds programs can greatly improve this issue.
   2. Determine cost of agents (especially for DOACs) and accessibility of INR testing (warfarin) before discharge.
   3. Thorough patient education
      a. General
         i. Signs and symptoms of bleeding
         ii. Signs and symptoms of failed efficacy
         iii. Importance of preventing missed doses
         iv. Expected therapy duration
         v. Avoidance of NSAIDs and use of acetaminophen for general pain
         vi. Seeking medical attention for head trauma or uncontrolled bleeding
         vii. Consider medical alert bracelet for patients receiving long-term anticoagulation.
      b. Warfarin-specific
         i. Use of vitamin K–containing foods
         ii. Importance and frequency of INR monitoring
         iii. Dosing may change, and doses may not be the same every day.
      c. DOAC-specific
         i. Dyspepsia with dabigatran and importance of not stopping therapy until discussion with a health care professional
         ii. Rivaroxaban doses of 15 or 20 mg need to be taken with food.
         iii. Ability to be adherent to twice-daily dosing with dabigatran or apixaban
   4. Consider a "hand-off" call to the patient's community pharmacy to discuss the patient's anticoagulation plan.
   5. Transitions of care for conditions in which anticoagulation is used will likely involve additional elements not related to the patient's anticoagulation therapy.

## VI. REVERSAL OF ANTICOAGULATION

A. Blood Products
   1. In the reversal of anticoagulant therapy, blood products are often part of the management of major bleeding.
   2. Whole blood is spun into red cells and platelet-rich plasma. The platelet-rich plasma is spun again to create platelets and plasma, and the plasma is frozen (FFP).
   3. Packed red blood cells (PRBCs)
      a. Not used for reversal, but used for management of bleeding to provide oxygen delivery to tissues
      b. 1 unit (around 250 mL) has a hematocrit of 70%–80% (twice whole blood) and can raise a patient's hemoglobin by 1–2 g/dL.
      c. Risks include transfusion reactions (e.g., chills, fever, urticaria, tachycardia), infection, and transfusion-related lung injury.

4. Platelets
    a. May be used for reversal of antiplatelet therapy, but data are inconsistent
    b. Each unit (200–300 mL) contains 300,000–600,000 platelets per cubic millimeter.
    c. Same risk as with PRBCs
    d. Commonly part of a massive transfusion protocol
5. FFP
    a. Cells have been spun out of blood, and the plasma contains the proteins in blood, mainly clotting factors.
    b. Must be frozen within 8 hours of blood collection and good for 12 months
    c. Commonly underdosed for reversing warfarin therapy – Takes several units (around 250 mL)
        i. Typical dose = 15–20 mL/kg (around 1.2–1.6 L)
        ii. Critically ill patients: 30 mL/kg (around 2.4 L)
    d. Requires type-and-crossing
    e. Takes 30–45 minutes to thaw
    f. Risk similar to risk with PRBCs and platelets
6. Prothrombin complex concentrate (PCC)
    a. Clotting factor proteins are taken from plasma sample.
    b. About 25-fold more concentrated in clotting factors than FFP
    c. Types (what each contain)
        i. 3-factor: Clotting factors II, IX, and X
        ii. 4-factor: Clotting factors II, IX, X, and VII (4PCC)
        iii. Activated PCC: II, IX, X, and VIIa
        iv. Certain products contain various concentrations of protein C, protein S, and UFH.
    d. Undergoes viral inactivation, reduces adverse effects, and does not require type-and-crossing
7. Cryoprecipitate
    a. Derived by thawing a unit of FFP in the cold (cryo) (4°C) and then collecting the precipitated globulins, which are then resuspended in 20–40 mL of plasma
    b. Contains concentrations of factor VIII, XIII, von Willebrand factor, fibronectin, and fibrinogen
    c. May be used for bleeding from fibrinolytics to provide more fibrinogen to the patient. May be part of a massive transfusion protocol
    d. Dosing of cryoprecipitate can be calculated using the following formula: Number of bags to increase serum fibrinogen 1 g/dL = 0.2 bags/kg
    e. Fibrinogen concentrate is also available (RiaSTAP).
8. Recombinant activated factor VII
    a. Not technically a blood product because made through recombinant technology
    b. Has been used to treat bleeding in patients receiving UFH, LMWH, and DOACs. Most trials are small and observational.
    c. Risk of thrombosis by giving an activated clotting factor
    d. Standard dose is 90 mcg/kg, but lower doses (e.g., 18–30 mcg/kg) have been documented to be effective and are significantly less expensive.
9. Massive transfusion protocols
    a. Indications – When to activate the protocol:
        i. 30%–40% blood volume loss with hypotension
        ii. 10 units of PRBCs in 24 hours
        iii. Transfuse entire blood volume in 24 hours
        iv. 50% blood volume replacement in 3 hours
        v. 4 units of PRBCs in 4 hours, knowing the need to give more

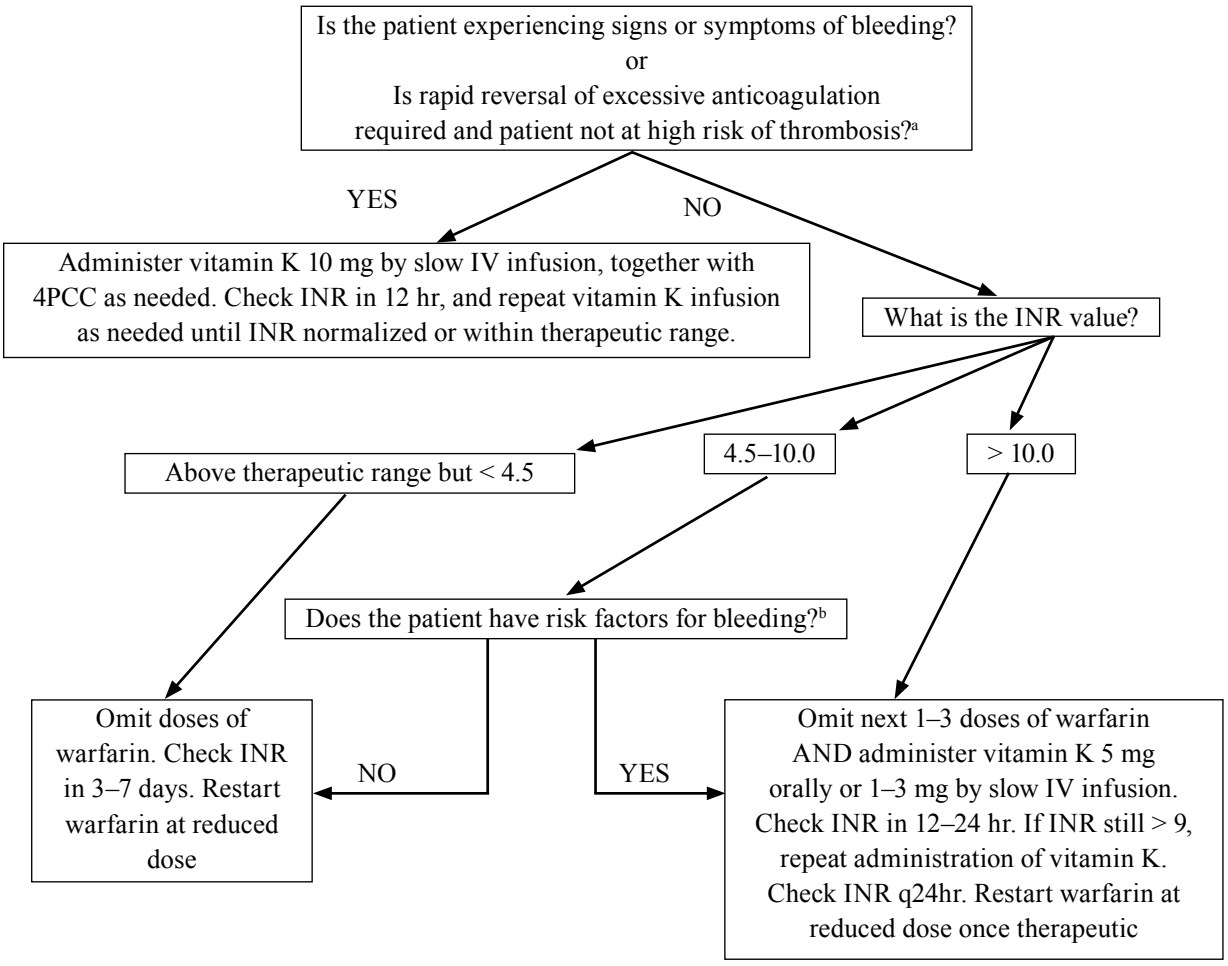
b. Components – Typically, 1:1:1 of PRBCs, platelets, and FFP by volume
    i. Provides a hematocrit of 29%
    ii. Provides a platelet count of 88,000/$mm^3$
    iii. Provides clotting factor activity of 62% normal
    iv. May need to provide periodic units of cryoprecipitate
c. Issues to monitor
    i. Dilution-induced thrombocytopenia
    ii. Citrate-induced hypocalcemia
    iii. Hyperkalemia
    iv. Acidosis

B. Unfractionated Heparin
1. Protamine is an effective and rapid antidote for reversal of UFH.
    a. Basic protein derived from fish sperm that binds to heparin to form a stable salt
    b. Used for the management of significant bleeding, reversal before surgery, or reversal of UFH given during surgery (e.g., coronary artery bypass grafting surgery)
    c. Dosing
        i. 1 mg of protamine neutralizes about 100 units of heparin.
        ii. In patients receiving an intravenous infusion of UFH, need to calculate the amount given in the past 3 hours. The total of the past hour, one-half the previous hour, and one-fourth for the hour before that. This assumes no bolus was given within the previous 8–12 hours.
        iii. Never administer more than 50 mg in a single dose outside going off cardiopulmonary bypass.
    d. aPTT can be used to assess the effectiveness of UFH neutralization.
    e. Adverse effects
        i. Hypotension, bradycardia
        ii. Minimized by giving over slow intravenous infusion instead of intravenous push
        iii. Patients previously receiving protamine sulfate–containing insulin (i.e., neutral protein Hagedorn), having undergone a vasectomy, or having a known sensitivity to fish are at an increased risk of having protamine antibodies and are more likely to have allergic reactions.
        iv. If there is concern about the risk of allergic reaction, corticosteroids and/or antihistamines can be given before protamine.
2. Blood products may be needed in patients with significant bleeding.

C. Low-Molecular-Weight Heparin
1. No specific antidote is available for LMWH.
2. Protamine
    a. Reverses about 50%–60% of the anticoagulant activity of LMWH
    b. Dosing
        i. If dose of LMWH was given within 8 hours of need for reversal, give the following dose. One-half the initial dose can be repeated, if needed.
        ii. 1 mg of protamine neutralizes about 100 anti-Xa units of LMWH (dalteparin).
        iii. 1 mg of protamine neutralizes about 1 mg of enoxaparin (1 mg enoxaparin = 100 anti-Xa units).
        iv. If dose of LMWH was given more than 8 hours before the need for reversal, give 0.5 mg of protamine for every 100 anti-Xa units.
        v. As with UFH, never administer more than 50 mg in a single dose.
3. Recombinant factor VIIa has been evaluated in small observational studies and found effective; it may be considered for significant bleeding when protamine fails.

D. Warfarin
   1. Vitamin K (phytonadione or vitamin $K_1$) – Effective at reversing the anticoagulant effect of warfarin. Vitamin K comes into the vitamin K reduction cycle after vitamin K epoxide reductase converts vitamin K epoxide to vitamin $K_1$. Vitamin $K_1$ is then reduced to vitamin $KH_2$ by vitamin K reductase. Because the anticoagulant effect of warfarin is mainly because of the inhibition of vitamin K epoxide reductase, exogenous vitamin K can continue to be reduced and produce functional carboxylated clotting factors II, VII, IX, and X.
      a. Vitamin K reversal onset is delayed because several new clotting factors must be created to neutralize the effect of warfarin therapy.
         i. Oral vitamin K can take 24–48 hours to normalize the INR. This is the preferred route for managing INRs above the therapeutic range that is not associated with bleeding (Figure 1).
         ii. Intravenous vitamin K can take 8–12 hours to normalize the INR, with full effects not seen until 24 hours. Should be given as slow infusion instead of intravenous "push" because of concerns for allergic reactions
         iii. Subcutaneous vitamin K should be avoided because of delayed and erratic absorption in administering a fat-soluble vitamin into subcutaneous fat tissue.
      b. Vitamin K helps in the reversal of high INRs (Figure 1)
      c. Management of warfarin before and after planned surgical procedures (Tables 9–11).
      d. It is important not to overdose vitamin K because this can lead to overaggressive reversal and difficulty in reinitiating warfarin therapy (warfarin resistance).
   2. FFP vs. 4PCC – Historically, FFP has commonly been used for reversal of warfarin therapy in patients needing urgent surgery or when bleeding.
      a. 4PCC provides much faster reversal of the INR than does FFP.
         i. 4PCC typically only requires one dose (around 200 mL) compared with 4–12 units of FFP – Less time and less volume
         ii. 4PCC need not be thawed and has fewer adverse effects than a blood product.
      b. A study (n=202) of patients with acute major bleeding on warfarin compared FFP (INR 3.6) with 4PCC (INR 3.9).
         i. Patients receiving 4PCC had their INR reversed to baseline within 30 minutes; FFP took about 8 hours to achieve the same INR.
         ii. Patients receiving FFP had more fluid overload because of the volume administered than did patients receiving 4PCC (5.8% vs. 12.8%).
         iii. More posttreatment thrombotic events occurred with 4PCC than with FFP (8.7% vs. 5.5%).
      c. Dosing – Only one 4PCC available in the United States. Dosing is based on actual body weight.
         i. INR 2 to less than 4: 25 units/kg with maximum dose of 2500 units
         ii. INR 4–6: 35 units/kg with maximum dose of 3500 units
         iii. INR greater than 6: 50 units/kg with maximum dose of 5000 units
         iv. Patients with an INR greater than 1.4 but less than 2.0 with cerebral bleeding may still receive 4PCC at a lower dose of 12.5–25 units/kg, but this approach was not part of the prospective study.
         v. Fixed doses of 4PCCs (1000–1500 units) have also been investigated, but not as extensively as weight-based dosing.
         vi. Administer vitamin K concurrently to patients receiving 4PCC to maintain factor concentrations once the effects of 4PCC have dissipated.
      d. The ACCP guidelines recommend a 4PCC over FFP for the rapid reversal of warfarin therapy.

**Figure 1.** Management of bleeding and/or elevated INRs with warfarin therapy




[a]History of hypercoagulability disorders, arterial or venous thrombosis within previous month, thromboembolism associated with malignancy, and high-risk mitral valve (with atrial fibrillation, poor ventricular function, or coexisting aortic valve).

[b]Age > 65, concurrent antiplatelet therapy, concurrent nonsteroidal anti-inflammatory drug use, history of gastrointestinal bleeding, recent surgery or trauma, high risk of fall or trauma, excessive alcohol use, renal failure, cerebrovascular disease, malignancy.

4PCC = 4-factor prothrombin complex concentrate; IV = intravenous(ly); q = every.

E. Dabigatran
   1. Reversal before most procedures is not necessary as long as the drug is held for the appropriate number of days (Tables 9–11).
   2. Vitamin K and protamine are not effective. FFP cannot provide enough clotting factor replacement.
   3. Activated PCC at doses of 25–50 units/kg can normalize the aPTT, ecarin clotting time, and diluted thrombin time within 30 minutes. Lower doses may be effective but require further study.
   4. Recombinant factor VIIa and 4PCC have had mixed results and are typically reserved for when other agents fail to control bleeding in life-threatening settings.
   5. Idarucizumab – Specific antidote for dabigatran
      a. Fully humanized antibody Fab portion with a 350-fold affinity for dabigatran compared with thrombin. Can pull dabigatran out of circulation and off of thrombin and render it inactive

b. REVERSE-AD trial (n=503) evaluated patients receiving dabigatran with uncontrolled bleeding (group A; n=301) or requiring urgent surgery (group B; n=202) receiving 5 g of idarucizumab.
   i. The primary outcome of the trial was the maximum percentage reversal of the anticoagulant effect of dabigatran within 4 hours of administering idarucizumab, as evaluated by the dilute thrombin time and the ecarin clotting time. The reversal was 100% in both groups for both assays. Full reversal occurred within 15 minutes and remained for 12–24 hours.
   ii. Group A most common sites of bleeding were gastrointestinal (46%), intracranial hemorrhage (33%), and trauma (26%). Cessation of bleeding in patients without intracranial hemorrhage was a median of 2.5 hours, with 68% having cessation within 24 hours.
   iii. Group B most common types of surgery were abdominal or infection (24%), fracture or septic arthritis (20%), and cardiovascular (18%). Periprocedural hemostasis was assessed by the investigators as normal in 93% of patients, mildly abnormal in 5%, and moderately abnormal in 2%, with no reports of severely abnormal hemostasis.
   iv. Thrombotic events were noted in 4.8% of patients within 30 days and 6.8% of patients within 90 days. This is most likely because patients were not reinitiated on anticoagulant therapy in a timely fashion.

F. Direct Xa Inhibitors
   1. Reversal before most procedures is not necessary as long as the drug is held for 1–2 days (Tables 9–11). Holding for 4–5 days, as with warfarin, leaves the patient without anticoagulation and may increase the risk of thrombosis.
   2. Vitamin K and protamine are not effective. FFP cannot provide enough clotting factor replacement.
   3. Activated PCC at doses of 25–50 units/kg can normalize the prothrombin time (PT) within 30 minutes. Data are limited to animal models and spiked blood samples.
   4. PCC – Has been used as an option for reversal of a direct Xa inhibitor. Doses are typically 50 units/kg, though some will give 25 units/kg and then re-dose, if needed.
      a. Three small studies of healthy volunteers show a correction in the PT/INR, but none show a correction in the anti-Xa activity.
      b. One prospective study (n=66) showed a 24-hour hemostatic efficacy of 85%. These patients were, on average, 18 hours from their last dose of a factor Xa inhibitor. Anti-Xa function was not assessed in these patients.
      c. Another prospective study (n=77) showed a 24-hour hemostatic efficacy of 69%. Although the average time from the last dose was 12 hours, anti-Xa function was not evaluated.
      d. Not enough patients have been evaluated to determine the thrombotic potential. Administration of supratherapeutic concentrations of clotting factors in patients who already require anticoagulant therapy suggests a risk exists.
   5. Andexanet alfa
      a. Decoy factor Xa protein with a high affinity for Xa inhibitors (also LMWH and fondaparinux)
         i. Change in serine to alanine prevents catalytic activity and prevents the ability to convert prothrombin to thrombin.
         ii. GLA domain is also removed. This prevents the ability to bind to a phospholipid membrane (platelets) and incorporation of the decoy protein into the prothrombinase complex.
      b. Given as bolus and continuous 2-hour infusion. Within minutes of the bolus, Xa concentrations return to baseline, where they remain throughout the rest of the infusion. Once the infusion is stopped, Xa concentrations return to placebo concentrations within the next 2 hours but endogenous thrombin generation stays active. The concept is to provide a time window in which the location of the bleed can be located and treated.

c. Studied in the ANNEXA-4 trial. Full-study data suggest that at the end of the infusion, the Xa concentration is reduced by 90% in patients receiving rivaroxaban and by 92% in patients taking apixaban.
d. In ANNEXA-4, the thrombotic event rate was 10% in 30 days. Only 2% of patients receiving any anticoagulation developed a thrombotic event, and no patients receiving oral anticoagulation developed a thrombotic event. It has not been determined whether this is directly related to the reversal agent or to the delay in initiation of anticoagulant therapy after a bleeding event.
e. Standard dose is a 400-mg intravenous bolus followed by 4 mg/minute for 2 hours. Indicated for patients with last dose of apixaban of 5 mg or less, rivaroxaban dose of 10 mg or less, or any dose of apixaban or rivaroxaban taken more than 8 hours earlier.
f. High dose is an 800-mg intravenous bolus followed by 8 mg/minute for 2 hours. Indicated for patients with last dose of apixaban of 10 mg or rivaroxaban doses of 15 or 20 mg taken within the past 8 hours or if the time of the last dose is unknown
g. Not currently indicated for reversal of edoxaban, enoxaparin, or fondaparinux. In addition, only indicated for the treatment of life-threatening bleeding, and not for patients requiring urgent surgery

**Patient Case**

8. K.D. is a 49-year-old man (height 68 inches, weight 100 kg) who was given a diagnosis of an idiopathic DVT 3 weeks ago. He currently takes warfarin 8 mg daily. He missed his INR readings last week when he went on a short vacation. Today, his INR is 10.4. He is not currently bleeding and has no risk factors for bleeding. In addition to holding his warfarin dose, which is the best initial strategy for managing K.D.'s high INR?

   A. Give vitamin K 2.5 mg orally.
   B. Give 4PCC 50 units/kg.
   C. Give vitamin K 5 mg orally.
   D. Give vitamin K 10 mg intravenously.

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## ANSWERS AND EXPLANATIONS TO PATIENT CASES

**1. Answer: B**

This patient's $CHA_2DS_2$-VASc score is 3. He gets 1 point for his age of 65–74 years (73 years), 1 point for hypertension, and 1 point for heart failure (Answer B). A score of 2 (Answer A) would be correct when using the $CHADS_2$ score instead of the $CHA_2DS_2$-VASc score because his age would not give him any points in the $CHADS_2$ score. The patient's history of stable ischemic heart disease may be assumed to be 1 point for vascular disease, but this is only 1 point in patients with a prior MI, peripheral arterial disease, or aortic disease, making Answer C incorrect. Given his score of 3, Answer D would also be incorrect.

**2. Answer: B**

Critical evaluation of the DOAC phase III trials is necessary to dispel any misconceptions clinicians may have concerning the conclusions of these data. Only dabigatran significantly reduced ischemic stroke in the RE-LY trial, but this may be questioned by the lack of blinding in the trial, making Answer A incorrect. The benefit of the DOACs in each of their respective trials was a significant reduction in hemorrhagic stroke. This drove the overall benefit and safety for all the agents (hemorrhagic stroke is counted as an efficacy and safety end point in all the trials), making Answer B correct. Although clinicians may reach the conclusions in Answer C, evidence is insufficient to make this claim. Cross-trial comparisons are inappropriate because of the different risks of patients studied and the different sample sizes of the trials. The 0.3% absolute difference in the ARISTOTLE and ROCKET-AF trials makes it difficult to conclude that one agent has better efficacy than the other without a head-to-head randomized controlled trial. Answer D is also incorrect because bleeding was similar to warfarin in the RE-LY trial with dabigatran and lower with edoxaban in the ENGAGE trial. Despite these data, the bleeding rates in the trials cannot be compared because of the different times in which bleeding events were accrued in the trials.

**3. Answer: C**

Given the patient's $CHA_2DS_2$-VASc score of 3, he at high risk of ischemic stroke and should receive anticoagulation. The patient's CrCl is about 40 mL/minute/1.73 $m^2$ using the Cockcroft-Gault equation with total body weight. Although any of these agents would be acceptable in this patient, not all the dosing regimens are correct. The dabigatran dose should not be reduced from 150 mg twice daily to 75 mg twice daily until the CrCl is less than 30 mL/minute/1.73 $m^2$, making Answer A incorrect. Both rivaroxaban and edoxaban should be dose reduced when the CrCl is less than 50 mL/minute/1.73 $m^2$ in patients with NVAF. Rivaroxaban goes from 20 mg daily to 15 mg daily, and edoxaban goes from 60 mg daily to 30 mg daily, making Answers B and D incorrect. Apixaban is listed at the typical dose and is not reduced to 2.5 mg daily unless the patient has two of three criteria (age 80 or older, weight 60 kg or less, or SCr 1.5 mg/dL or greater). This patient has the elevated SCr, but his age and weight do not meet these criteria. Therefore, full-dose apixaban is correct (Answer C) for this patient.

**4. Answer: B**

Although dual therapy with rivaroxaban and clopidogrel has been shown to significantly reduce bleeding and hospitalizations compared with warfarin-based triple therapy, the dose of 10 mg of rivaroxaban was only used in patients with a CrCl of 30–50 mL/minute/1.73 $m^2$ in the PIONEER AF-PCI trial (Answer A is incorrect). Answer D is incorrect because triple therapy with edoxaban has not been evaluated in a clinical trial, and the edoxaban dose is too low. Answer B (apixaban plus clopidogrel) and Answer C (warfarin-based triple therapy) were compared in the AUGUSTUS trial. Apixaban 5 mg twice daily plus clopidogrel significantly reduced bleeding and hospitalizations (Answer B is correct; Answer C is incorrect).

**5. Answer: C**

This patient has several risk factors for VTE and requires prophylaxis, making Answer D incorrect. Although fondaparinux is effective and safe for VTE prophylaxis in medically ill patients, the appropriate dose is 2.5 mg subcutaneously daily, not 5 mg daily (Answer A). Although apixaban has been studied for VTE prophylaxis, when evaluated for extended prophylaxis, it did not have efficacy and safety, making Answer B incorrect. Several studies have shown the efficacy and safety of enoxaparin 40 mg subcutaneously once daily for VTE prophylaxis in medically ill patients, making Answer C correct.

**6. Answer: A**

This patient can be treated for his DVT event without receiving injectable anticoagulation. Both rivaroxaban and apixaban provide this ability. Because edoxaban requires at least 5 days of injectable therapy before initiation and warfarin must be bridged with injectable anticoagulation for at least 5 days, both Answers B and C are incorrect. Because the apixaban dose should be 10 mg twice daily for 7 days, followed by 5 mg twice daily, Answer D is incorrect. This apixaban dose could be used in patients receiving P-gp and CYP3A4 inhibitors. The suggested dose of rivaroxaban in Answer A is correct and can be given without use of injectable therapy (Answer A is correct).

**7. Answer: B**

This patient is having a massive PE with hemodynamic compromise (hypotension), elevated troponin, and a significantly dilated right ventricle. These patients were not included in the DOAC VTE treatment trials, and DOACs should not be used, especially in the acute setting, making Answers A and D incorrect. The patient requires fibrinolytic therapy in this setting to open the occluded pulmonary arteries to prevent cardiopulmonary arrest and death. Intravenous t-PA 100 mg over 2 hours is the most commonly used fibrinolytic regimen, making Answer B correct. Patients can also receive anticoagulation with intravenous UFH, but not LMWH because of the longer duration of activity if a fibrinolytic is given, making Answer C incorrect.

**8. Answer: C**

Because this patient is not bleeding and rapid reversal is unnecessary, 4PCC in not needed, making Answer B incorrect. The lack of bleeding in this patient also makes high-dose (10 mg) intravenous vitamin K unnecessary and Answer D incorrect. For an INR over 10 with no bleeding, the dose of oral vitamin K is 5 mg, making Answer C correct and Answer A incorrect.

## ANSWERS AND EXPLANATIONS TO SELF-ASSESSMENT QUESTIONS

**1. Answer: D**

This patient with NVAF has four risk factors for stroke, according to the $CHA_2DS_2$-VASc score. She gets 1 point for being age 65–74 years (68 years), 1 point for having hypertension, 1 point for having diabetes mellitus, and 1 point for being female. Answer A is incorrect because she would have a score of 2 using the $CHADS_2$ score. Those would be hypertension and diabetes mellitus, but that scoring system does not give a point for age unless the patient is 75 or older and gives no point for being female. Her HAS-BLED score is 1 for a point for age older than 65. Although Answer B has the correct $CHA_2DS_2$-VASc score, the HAS-BLED score is incorrect. Even though the patient has hypertension for HAS-BLED, the systolic blood pressure needs to be greater than 160 mm Hg for it to get a point. Therefore, her score is only 1, not 2 as in Answer B. Answer C is also incorrect because it over-calculates both the $CHA_2DS_2$-VASc score and the HAS-BLED score. Because the patient's $CHA_2DS_2$-VASc score is 4 and her HAS-BLED score is 1, Answer D is correct. This patient is a candidate for anticoagulant therapy on the basis of stroke risk and has an acceptable bleeding risk from warfarin therapy.

**2. Answer: B**

Given the patient's $CHA_2DS_2$-VASc score of 4 and no contraindications to anticoagulant therapy, she is at high risk of ischemic stroke and needs anticoagulant therapy, making Answer A incorrect. Apixaban would be an acceptable option, but the reduced dose of 2.5 mg twice daily is only for patients with two high-risk bleeding features (age 80 and older, weight 60 kg or less, or SCr 1.5 mg/dL or greater). She has one factor with a weight less than 60 kg (58 kg), but her age (68 years) and SCr (0.8 mg/mL) do not meet the criteria. Therefore, she should receive apixaban 5 mg twice daily, making Answer C the incorrect apixaban dose. Because patients with NVAF and low body weight do not need a dose reduction to 30 mg of edoxaban, as they do with VTE treatment, Answer D is incorrect. Rivaroxaban is only dose reduced when the CrCl is less than 50 mL/minute/1.73 $m^2$. Because this patient's renal function is above that level, Answer B is correct for using the correct dose of anticoagulant.

**3. Answer: C**

Answer A is incorrect; although protamine is an antidote for UFH and a partial antidote for LMWH, it would not be expected to be effective in reversing dabigatran. Answer B is incorrect because FFP does not provide enough clotting factors to reverse any of the direct oral anticoagulants. Idarucizumab is a fully humanized monoclonal antibody specific to dabigatran. The REVERSE-AD trial demonstrated the ability of idarucizumab to fully reduce the anticoagulant effect of dabigtran within minutes, making Answer C correct. Andexanet alfa is a factor Xa decoy protein used to effectively reverse the anticoagulant activity of factor Xa inhibitors, but is not effective against dabigatran. Therefore, Answer D is incorrect.

**4. Answer: C**

This patient has five risk factors for developing VTE, making Answer C correct and Answers A, B, and D incorrect. She is 40 or older (51 years), has obesity (body mass index 33 $kg/m^2$), recently had surgery, has immobility, and smokes.

**5. Answer: A**

A positive D-dimer is interpreted as possible thrombosis in the patient, but it does not correlate with the amount of thrombus or severity of disease, making Answer B incorrect. Not all patients with PE have a high risk of mortality. This patient's simplified Pulmonary Embolism Severity Index score is 0. She has none of the following: age older than 80, cardiopulmonary disease, heart rate 110 beats/minute or more, systolic blood pressure less than 100 mm Hg, or $O_2$ saturation less than 90%, making Answer C incorrect and Answer A correct. Answer D is incorrect because a negative troponin only helps determine whether the patient may be having a sub massive PE and is not an indicator of outpatient therapy.

**6. Answer: C**

Answer B is incorrect because the duration of higher-intensity rivaroxaban should be 21 days, not 7 days. Apixaban's duration of higher-intensity therapy is 7 days. Answer D is incorrect because the UFH dosing is insufficient. This is the dosing in patients with an acute coronary syndrome. Patients receiving dabigatran or

edoxaban must first receive at least 5 days of injectable therapy. The dosing of enoxaparin and the DOAC is correct in both Answers A and C, but the DOAC should not be overlapped with the injectable anticoagulant, making Answer A incorrect and Answer C correct.

**7. Answer: C**

Protamine 31.5 mg is the correct dose for this patient. To calculate the dose, add the amount of UFH given in the past hour (1800 units) plus one-half given in the previous hour (900 units) plus one-fourth of what was given the hour before that (450 units). This gives a total of 3150 units of UFH in the past 3 hours. A dose of 1 mg of protamine for every 100 units of UFH equals a protamine dose of 31.5 mg (Answer C). Because the bolus dose was given more than 3 hours ago, it is not part of the calculation. Although 80 units would be the calculated dose according to the bolus, the bolus was given too long ago to be considered (Answer A), and no more than 50 mg is given at one time, making Answers A and B incorrect. The dose of 18 mg in Answer D is incorrect because this dose considered only the amount of UFH received in the past hour, not the past 3 hours.

**8. Answer: D**

This patient being hospitalized for acute medical illness (heart failure), severe immobility, and being over 75 years old or with a history of VTE (this patient has both) would have been a patient in the MAGELLAN trial with rivaroxaban 10 mg daily for 31–39 days compared to enoxaparin 40 mg daily for 6–14 days. Patients receiving rivaroxaban in hospital and extended post discharge demonstrated a significant 32% relative risk reduction in VTE, and no increased risk of major bleeding compared to enoxaparin/placebo. The key to preventing major bleeding in these patients is to avoid rivaroxaban in patients with a history of bronchiectasis, hospitalization for active cancer treatment, gastroduodenal ulcer in the last 3 months, any bleeding in the last 3 months, and those receiving DAPT. This regimen is FDA approved, making Answer D correct and Answer A incorrect. Answer C (UFH 5000 units twice daily) would also be incorrect because the duration is shorter, and the efficacy of UFH 5000 twice daily is questionable, especially in higher-risk medically ill patients such as those with heart failure or stroke. Although apixaban 2.5 mg twice daily has been evaluated for extended prophylaxis in medically ill patients, the regimen did not significantly reduce VTE events compared with enoxaparin/placebo but did significantly increase major bleeding, making Answer B incorrect.

# Arrhythmias

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**Learning Objectives**

1. Describe the principles of basic electrocardiogram (ECG) interpretation.
2. Distinguish risk factors and etiologies, clinical features, signs and symptoms, and goals of therapy of sinus bradycardia, atrial fibrillation (AF), supraventricular tachycardia (SVT) (including Wolff-Parkinson-White syndrome [WPW]), premature ventricular complexes (PVCs), and ventricular tachycardia (VT).
3. Compare and contrast appropriate pharmacologic and nonpharmacologic treatment options for the management of sinus bradycardia, AF, SVT, PVCs, and VT.
4. Compare and contrast the mechanisms of action of drugs used for ventricular rate control and conversion to and maintenance of sinus rhythm in patients with AF.
5. Recommend strategies to improve transitions of care between inpatient and outpatient settings for patients on antiarrhythmic drugs.
6. Develop evidence-based patient-specific pharmacotherapy plans for patients with symptomatic sinus bradycardia, AF, SVT (including WPW), PVCs, and VT.
7. Assess common and important drug-drug interactions and adverse effects associated with drugs used for the management of arrhythmias and their complications.

**Abbreviations in This Chapter**

| | |
|---|---|
| ACS | Acute coronary syndrome |
| AF | Atrial fibrillation |
| AV | Atrioventricular |
| AVNRT | Atrioventricular nodal reentrant tachycardia |
| AVRT | Atrioventricular reentrant tachycardia |
| CABG | Coronary artery bypass grafting |
| CAD | Coronary artery disease |
| COPD | Chronic obstructive pulmonary disease |
| CV | Cardiovascular |
| DCC | Direct current cardioversion |
| ED | Emergency department |
| HF | Heart failure |
| HFrEF | Heart failure with reduced ejection fraction |
| HIE | Hyperinsulinemia-euglycemia |
| ICD | Implantable cardioverter-defibrillator |
| LV | Left ventricular |
| LVEF | Left ventricular ejection fraction |
| MI | Myocardial infarction |
| NOAC | Non–vitamin K oral anticoagulant |
| NYHA | New York Heart Association |
| PSVT | Paroxysmal supraventricular tachycardia |
| PVC | Premature ventricular complex |
| SCD | Sudden cardiac death |
| SVT | Supraventricular tachycardia |
| TEE | Transesophageal echocardiogram |
| VF | Ventricular fibrillation |
| VKORC1 | Vitamin K epoxide reductase complex-1 |
| VT | Ventricular tachycardia |
| WPW | Wolff-Parkinson-White syndrome |

**Self-Assessment Questions**

*Answers and explanations to these questions may be found at the end of this chapter.*

1. M.A. is a 57-year-old woman who presents to the emergency department (ED) with complaints of dizziness and syncope. She has no pertinent medical history and currently takes no medications. In the ED, her vital signs are blood pressure 98/68 mm Hg, heart rate 39 beats/minute, respiratory rate 16 breaths/minute, and temperature 37°C (98.6°F). Her electrocardiogram (ECG) reveals a regular rhythm. Which is the best treatment?
   A. Administer atropine 0.5 mg intravenously.
   B. Administer epinephrine 2–10 mcg/minute intravenously.
   C. Administer transcutaneous pacing.
   D. Treatment is not necessary.

2. A.S. is a 75-year-old man who presents to the ED with palpitations, dizziness, and lightheadedness. His medical history is significant for moderate mitral valve stenosis for 12 years. He currently takes furosemide 20 mg orally once daily and aspirin 81 mg orally once daily. His ECG reveals atrial fibrillation (AF). His blood pressure in the ED is 110/72 mm Hg and heart rate is 140 beats/minute. Which is the most appropriate treatment?
   A. Immediate direct current cardioversion (DCC).
   B. Amiodarone 300 mg intravenously over 1 hour.

C. Digoxin 0.25 mg intravenously.

D. Diltiazem 0.25 mg/kg intravenously over 2 minutes.

3. D.R. is a 76-year-old man who is hospitalized in the intensive care unit (ICU) and undergoing intravenous antibiotic treatment for sepsis. During his ICU stay, his blood pressure suddenly decreases, and his ECG reveals AF. D.R. has a medical history of hypertension and heart failure with reduced ejection fraction (HFrEF) (left ventricular ejection fraction [LVEF] 35%). His home medications are lisinopril 20 mg orally once daily, carvedilol 12.5 mg orally twice daily, and spironolactone 12.5 mg orally once daily; he is not receiving these medications while in the ICU. His blood pressure during AF is 91/59 mm Hg and heart rate is 147 beats/minute. Which is the most appropriate treatment?

   A. Amiodarone 300 mg intravenously over 1 hour.

   B. Digoxin 0.25 mg intravenously every 4 hours to a maximum dose of 1.5 mg.

   C. Diltiazem 0.25 mg/kg intravenously, followed by a 5-mg/hour continuous intravenous infusion.

   D. Esmolol 500 mcg/kg intravenously over 1 minute, followed by a 50-mcg/kg/minute continuous intravenous infusion.

*Questions 4 and 5 pertain to the following case.*

G.M. is a 59-year-old woman (weight 75 kg) with a history of hypertension who presents to the ED with palpitations, dizziness, and lightheadedness that began within the past 12 hours. A recent echocardiogram revealed an LVEF of 55%. Her current medications include lisinopril 20 mg orally once daily and hydrochlorothiazide 25 mg orally once daily. Her ECG reveals AF with a QRS duration of 80 milliseconds and a QTc interval of 420 milliseconds. Her blood pressure in the ED is 95/65 mm Hg and heart rate is 144 beats/minute. She has eaten two meals today.

4. Which is the most appropriate treatment for conversion of her AF to sinus rhythm?

   A. Sedate for immediate DCC.

   B. Administer dronedarone 400 mg orally twice daily.

   C. Administer ibutilide 1 mg intravenously over 10 minutes.

   D. Administer sotalol 80 mg orally twice daily.

5. After a follow-up with ambulatory ECG monitoring and a symptom diary, G.M. has fatigue, dizziness, and palpitations two or three times per week that correspond with episodes of AF, and she is given a diagnosis of paroxysmal AF. In addition to appropriate anticoagulation therapy, which long-term oral drug therapy strategy is most appropriate for minimizing/alleviating G.M.'s symptoms?

   A. Amiodarone 200 mg once daily.

   B. Digoxin 0.25 mg once daily.

   C. Diltiazem 240 mg extended release once daily.

   D. Metoprolol tartrate 50 mg twice daily combined with digoxin 0.25 mg once daily.

6. D.W. is a 43-year-old woman with no history of cardiovascular disease who presents to the ED with palpitations, dizziness, and lightheadedness. She takes no medications except for occasional acetaminophen for headaches. Her ECG reveals supraventricular tachycardia (SVT) (no evidence of preexcitation). Her blood pressure in the ED is 96/75 mm Hg and heart rate is 132 beats/minute. Coughing, carotid sinus massage, and Valsalva maneuver have not effectively terminated her arrhythmia. Which is the most appropriate treatment?

   A. Immediate DCC.

   B. Adenosine 6 mg by rapid intravenous infusion.

   C. Ibutilide 1 mg intravenously over 10 minutes.

   D. Procainamide 25 mg/minute continuous intravenous infusion up to 17-mg/kg loading dose.

7. J.P. is a 72-year-old woman with a history of hypertension, HFrEF (LVEF 20%), and paroxysmal AF. Her estimated creatinine clearance (CrCl) is 80 mL/minute/1.73 $m^2$. She currently takes metoprolol succinate 200 mg orally once daily, furosemide 40 mg orally once daily, sacubitril/valsartan 97/103 mg orally twice daily, and spironolactone 25 mg orally once daily. She continues to have episodes of palpitations and dizziness once or twice weekly, which last for about 4–6 hours. During these

episodes, she measures her heart rate, recording heart rates of 95–100 beats/minute. Which is the most appropriate therapy at this time?

A. Amiodarone 200 mg orally twice daily for 4 weeks, followed by 200 mg orally once daily.
B. Dronedarone 400 mg orally every 12 hours.
C. Flecainide 100 mg orally every 12 hours.
D. Sotalol 80 mg orally twice daily.

8. C.B. is 69-year-old woman admitted to the hospital for initiation of dofetilide for persistent AF. Her medications before admission included amlodipine 10 mg orally once daily, apixaban 5 mg orally twice daily, atorvastatin 80 mg orally once daily, hydrochlorothiazide 25 mg orally once daily, metoprolol tartrate 25 mg orally twice daily, and sertraline 100 mg orally once daily. Which is most appropriate to communicate to C.B.'s outpatient pharmacy on discharge?

A. Refills of hydrochlorothiazide should be discontinued.
B. Refills of sertraline should be discontinued.
C. Refills of atorvastatin should be discontinued.
D. Refills of metoprolol tartrate should be discontinued.

# I. ELECTROCARDIOGRAM

## A. ECG Basics

1. The ECG is a noninvasive method for assessing the heart's electrical activity.
2. ECGs are recorded using 12 leads, as single-lead rhythm strips, or as combinations of two or three leads. The 12-lead ECG is recorded using 10 electrodes placed at specific positions on the chest and limbs (Figure 1).
3. The six chest (also known as "precordial") electrodes generate the "V" leads. $V_1$ is placed on the right side of the sternum at the fourth intercostal space, whereas the remainder of the precordial leads are placed to the left of the sternum: $V_2$, at the fourth intercostal space; $V_3$, between $V_2$ and $V_4$; $V_4$, at the fifth intercostal rib at the midclavicular line; $V_5$, between $V_4$ and $V_6$; and $V_6$, at the fifth intercostal space at the midaxillary line.
4. The non-precordial leads, or limb leads, are generated by four electrodes on the limbs, one on each arm and leg. The limb leads form the points of "Einthoven's triangle." Lead I is the voltage between the left arm electrode and the right arm electrode; lead II is the voltage between the left leg electrode and the right arm electrode; and lead III is the voltage between the left leg electrode and the left arm electrode. The other limb leads are known as "augmented vector" (aV) leads: aVR (augmented vector right), aVL (augmented vector left), and aVF (augmented vector foot).
5. 12-lead ECGs are usually recorded at a paper speed of 25 mm/second. At this speed, standard-sized ECG paper used in commercially available 12-lead ECG machines sequentially presents four 2.5-second columns during a continuous 10-second ECG recording. Each column presents a distinct lead, each of which is clearly designated on the recorded ECG (Figure 1).
6. In typical 12-lead ECGs, the first column shows simultaneous leads I, II, and III; the second column shows simultaneous leads aVR, aVL, and aVF; the third column shows simultaneous leads $V_1$, $V_2$, and $V_3$; and the fourth column shows simultaneous leads $V_4$, $V_5$, and $V_6$. Additional rows generally have 10-second continuous recordings of specific leads, generally $V_1$, II, and $V_5$ (Figure 1).
7. ECG paper consists of a series of small and large boxes. Each small box is 1 mm x 1 mm. Vertically, the boxes measure the voltage or amplitude of the signal, and horizontally, the boxes measure time. At a paper speed of 25 mm/s, one small box is 0.04 seconds, or 40 milliseconds. There are five small boxes in one large box; horizontally, therefore, one large box equals 0.2 seconds, or 200 milliseconds. Vertically, each box represents 0.1 mV; therefore, 10 small vertical boxes represent 1.0 mV (Figure 1).

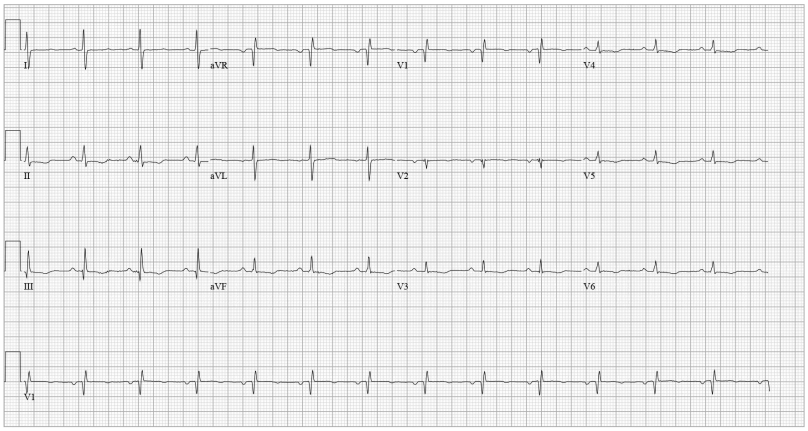


**Figure 1.** 12-lead ECG.

B. ECG Waves and Intervals
   1. P wave represents atrial depolarization.
   2. QRS complex represents ventricular depolarization/conduction time; normal QRS duration in adults is 80–120 milliseconds (0.08–0.12 seconds).
   3. T wave represents phase 3 (terminal phase) of ventricular repolarization.
   4. The period from the beginning of the Q wave to the end of the T wave, known as the QT interval, represents total time of ventricular repolarization.
   5. Atrial repolarization is not represented on the ECG because it occurs during ventricular depolarization and is obscured by the QRS complex.
   6. The PR interval represents the time of impulse conduction from the atria to the ventricles through the atrioventricular (AV) node; the normal PR interval in adults is 120–200 milliseconds (0.12–0.20 seconds).
   7. The QT interval varies with heart rate—the faster the heart rate, the shorter the QT interval, and vice versa. Therefore, the QT interval is corrected for heart rate. Many formulae for heart rate correction of the QT interval have been published, and several are used in research studies. In clinical practice, QT intervals are corrected for heart rate using Bazett's formula, which is:

$$QT_c = \frac{QT}{\sqrt{RR}}$$

      where QTc is the QT interval corrected for heart rate, and RR is the interval from the onset of one QRS complex to the onset of the next QRS complex in seconds (i.e., the heart rate). This formula is programmed into commercially available 12-lead ECG machines. Although Bazett's heart rate correction formula has limitations, such as overcorrecting the QT interval at high heart rates and undercorrecting the QT interval at low heart rates, it remains the heart rate correction formula most widely used in clinical practice.
   8. Normal QTc interval in adults is 360–480 milliseconds (0.36–0.48 seconds) in women and 360–470 milliseconds (0.36–0.47 seconds) in men.
   9. To calculate a QTc interval:
      a. Measure the QT interval from the Q wave to the end of the T wave.
      b. The "tangent" method can be used to determine the end of the T wave (Figure 2).
      c. Once the QT interval has been determined, determine the RR interval in seconds.
      d. Use Bazett's formula to calculate the QTc interval in seconds.
      e. To correctly calculate the QTc interval using the Bazett method, the QT and RR intervals must be calculated in seconds (not milliseconds).

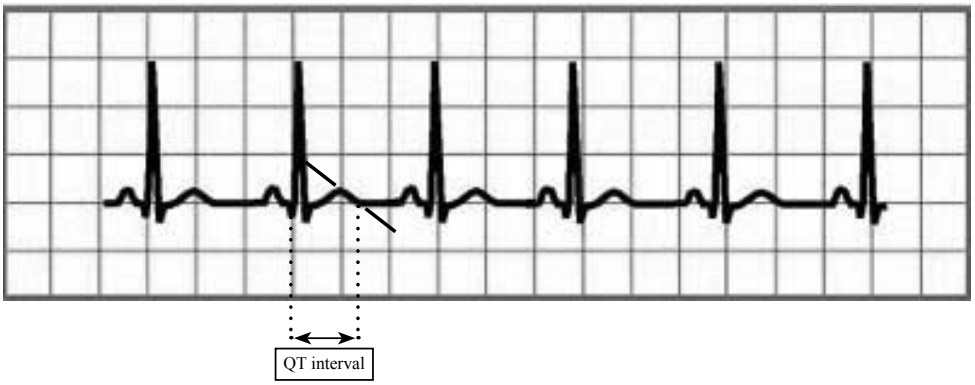


**Figure 2.** Tangent method for measuring QT interval. Draw a tangent to the steepest slope of the last limb of the T wave. The intersection of the tangent with the baseline defines the end of the QT interval.

C. Basic ECG Interpretation: Several methods can be used to calculate the heart rate:
   1. Identify an R wave that falls on a thick line on the ECG (i.e., on a "big box"). Count the number of thick lines until the arrival of the next QRS complex and divide that number into 300. For example, in Figure 3, the R wave falls on around the fourth thick line; 300 divided by 4 gives a heart rate of around 75 beats/minute (this method works only for regular rhythms; if the rhythm is irregular, this method will be inaccurate).
   2. Count the number of QRS complexes in a 3- or 6-second sequence and multiply it by 20 or 10, respectively. Each large box is 0.20 seconds; therefore, five large boxes equals 1 second, 15 large boxes equals 3 seconds, and 30 large boxes equals 6 seconds. This method works for irregular rhythms if a long enough strip is used – at least 6 seconds and, ideally, 10 seconds (multiply the number of complexes by 6).
   3. The most accurate method of determining the heart rate is to measure the RR interval using calipers and divide the RR interval into 60: heart rate = 60/RR interval. In Figure 3, the RR interval is 0.76, making the heart rate ~80 beats/minute. For irregular heart rates, the RR interval can be averaged over 5–10 beats to obtain the heart rate.

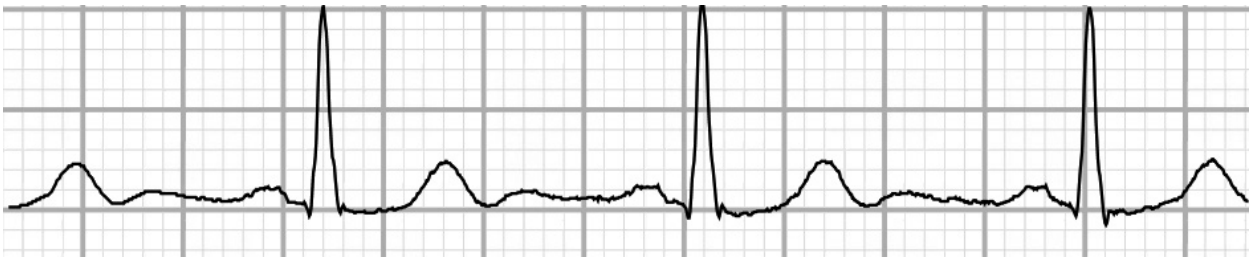

**Figure 3.** Sinus rhythm at a rate of ~80 beats/minute.

   4. Evaluate the intervals:
      a. PR interval: Measured from the beginning of the P wave to the beginning of the R wave (Figure 4)
      b. QRS complex: Measured from the Q wave to the end of the S wave (Figure 4)
      c. QT and QTc intervals: As described earlier

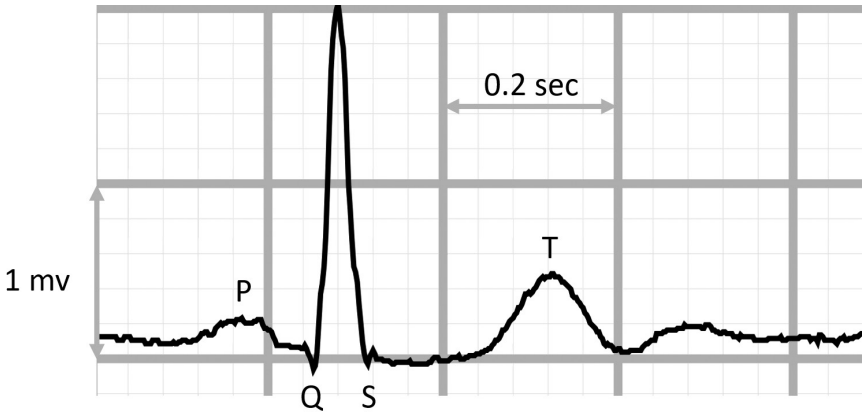


**Figure 4.** Intervals and durations on an ECG.

D. Assessing Whether the Rhythm Is Normal or Abnormal
   1. Simple questions can be asked to determine whether an ECG rhythm is normal:
      a. "Is there a P wave in front of every QRS complex?" If P waves are missing, the rhythm is not normal sinus rhythm. The rhythm could be a junctional rhythm, junctional tachycardia, AF, or other arrhythmia.
      b. "Is there a QRS complex after each P wave?" If P waves are not followed by QRS complexes, the rhythm is not normal and could be an AV block.
      c. "Is the rhythm regular?" Are the intervals between the R waves consistent from beat to beat? This can be evaluated with calipers. If the interval between the R waves is variable, the rhythm is irregular and could be an AV block, AF, or other arrhythmia.
      d. "Is the heart rate in the normal range?" A heart rate of 60–100 beats/minute is considered normal. A heart rate less than 60 beats/minute is defined as bradycardia, and a heart rate greater than 100 beats/minute is a tachycardia.

## II. SINUS BRADYCARDIA

A. Background
   1. Sinus bradycardia is defined as sinus rhythm, but with a heart rate of less than 50 beats/minute (Figure 5). Sick sinus syndrome, also known as sinus node dysfunction, describes age-dependent, progressive degenerative fibrosis of the sinus node tissue and surrounding atrial myocardium, resulting in sinus bradycardia.
   2. Overall prevalence of sinus node dysfunction is 403–666 per million.
   3. Overall incidence of sinus node dysfunction requiring pacemaker therapy is 63 per million per year.
   4. Sinus node dysfunction is present in 1 of every 600 cardiac patients older than 65.
   5. Sinus node dysfunction accounts for around 48% of pacemaker implantations in the United States.
   6. Incidence of sick sinus syndrome: 0.8 per 1000 person-years of follow-up

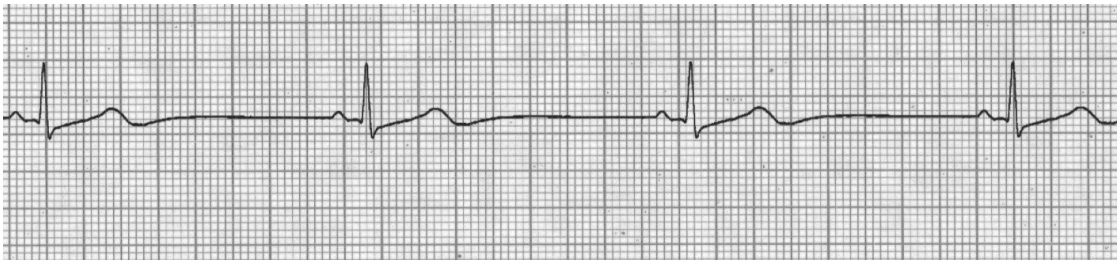

**Figure 5.** Sinus bradycardia. Sinus rhythm with a rate < 60 beats/min.

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B. Etiologies/Risk Factors
   1. Intrinsic
      a. Pathologic conditions involving the sinus node
      b. Idiopathic degenerative disease likely the most common cause. Sinus node dysfunction is called "sick sinus syndrome" and is caused by idiopathic degeneration associated with aging.
      c. Inferior myocardial ischemia
      d. Infiltrative diseases:
         i. Sarcoidosis
         ii. Amyloidosis
         iii. Hemochromatosis

e. Collagen vascular diseases
    i. Systemic lupus erythematosus
    ii. Rheumatoid arthritis
    iii. Scleroderma
f. Surgical trauma (valve replacement, correction of congenital heart disease, heart transplantation)
g. Risk factors for sick sinus syndrome:
    i. Advancing age
    ii. White race
    iii. Higher body mass index
    iv. Hypertension
    v. Right bundle branch block
    vi. Higher N-terminal B-type natriuretic peptide
    vii. History of major cardiovascular (CV) event

2. Extrinsic
    a. Autonomic syndromes:
        i. Carotid sinus hypersensitivity
        ii. Abnormal sympathetic/parasympathetic tone
        iii. Neurocardiac syncope
    b. Electrolyte abnormalities (hyperkalemia, hypokalemia, hypermagnesemia)
    c. Situational perturbations secondary to vagal stimulation:
        i. Coughing
        ii. Defecation
        iii. Micturition
        iv. Vomiting
        v. Sleep (with or without apnea)
    d. Hypothyroidism
    e. Hypothermia
    f. Neurologic disorders
    g. Drugs:
        i. Antiarrhythmic agents (e.g., amiodarone, dronedarone, flecainide, propafenone, sotalol)
        ii. β-Blockers (including opthalmic)
        iii. Bupivacaine
        iv. Calcium channel blockers (CCBs; diltiazem, verapamil)
        v. Cancer chemotherapy drugs (e.g., cisplatin, fluorouracil, paclitaxel)
        vi. Citalopram
        vii. Clonidine
        viii. Dexmedetomidine
        ix. Digoxin
        x. Donepezil
        xi. Fingolimod
        xii. Halothane
        xiii. Ivabradine
        xiv. Ondansetron
        xv. Phenytoin
        xvi. Propofol
        xvii. Thalidomide

C. Signs/Symptoms
   1. Often asymptomatic
   2. Hypotension
   3. Fatigue
   4. Weakness
   5. Dizziness/lightheadedness
   6. Syncope
   7. Symptoms associated with heart failure (HF)
   8. Exercise intolerance

D. Treatment
   1. Only necessary if the patient is symptomatic (many patients have a heart rate less than 60 beats/minute as a normal physiologic variant)
   2. Discontinue medications that may be causing sinus bradycardia (exceptions: in patients post-myocardial infarction [MI] and/or with HFrEF, β-blockers may need to be continued, despite sinus bradycardia, for their mortality-lowering effects. In these patients, a permanent pacemaker may be implanted to allow continuation of life-prolonging β-blocker therapy).
   3. Atropine 0.5–1 mg intravenously, repeated as required every 3–5 minutes up to a maximum dose of 3 mg
      a. Atropine is a parasympatholytic drug that blocks muscarinic acetylcholine receptors. Atropine has bimodal activity at the sinoatrial node; at low doses (i.e., less than 0.5 mg), it is associated with slower rates, and at higher doses (i.e., greater than 0.5 mg), it is associated with faster rates.
      b. The efficacy of atropine for bradycardia (sinus bradycardia and AV block) is supported only by small nonrandomized studies (Table 1).

**Table 1.** Selected Studies Supporting the Efficacy of Atropine for Bradycardia Caused by Sinus Bradycardia or AV Block

| Study/Year | Population | Primary Results |
|---|---|---|
| Chadda et al., 1975 | Bradycardia associated with MI<br>n=32 sinus bradycardia<br>n=29 AV block or junctional rhythm | Heart rate before atropine: 46 ± 14 beats/min<br>Heart rate after atropine: 79 ± 12 beats/min ($p<0.001$) |
| Smith et al., 1994 | n=15 patients with intraoperative bradycardia | Heart rate before atropine: < 60 beats/min<br>After atropine, heart rate ↑ to ≥ 70 beats/min in a mean time of 270 s (range 30–490 s) |
| Brady et al., 1999 | n=131 patients with bradycardia<br>(n=45 AV block)<br>(n=35 sinus bradycardia)<br>(n=38 junctional bradycardia)<br>(n=13 idioventricular bradycardia) | Complete response to atropine (defined as heart rate > 60 beats/min and systolic blood pressure > 90 mm Hg) achieved in 27.5%<br>Partial response achieved in 19.8%<br>Overall, ~47% achieved complete or partial response |

AV = atrioventricular; MI = myocardial infarction.

      c. Atropine adverse effects:
         i. Tachycardia
         ii. Urinary retention
         iii. Blurred vision

   iv. Mydriasis
   v. Dry mouth
   vi. Atropine should not be administered to patients who have undergone a heart transplant and for whom there is no evidence of autonomic reinnervation because of the risk of paradoxical AV block or, less commonly, sinus arrest.
4. If bradycardia is unresponsive to atropine
   a. Transcutaneous pacing may be initiated, OR
   b. Dopamine 5–20 mcg/kg/minute, starting at 5 mcg/kg/minute and increasing by 5 mcg/kg/minute every 2 minutes, OR
   c. Epinephrine 2–10 mcg/minute intravenously or 0.1–0.5 mcg/kg/minute intravenously titrated to desired effect, OR
   d. Isoproterenol 20- to 60-mcg intravenous bolus, followed by doses of 10–20 mcg, or infusion of 1–20 mcg/minute depending on heart rate response
5. In refractory cases, transvenous pacing may also be considered.
6. If symptomatic or hemodynamically unstable sinus bradycardia is caused by a β-blocker overdose, treatment options are:
   a. Glucagon intravenous bolus 3–10 mg intravenously followed by a continuous infusion of 3–5 mg/hour titrated to achieve adequate hemodynamic response. Evidence supporting the efficacy of glucagon for managing β-blocker overdose is from case reports only.
   b. Hyperinsulinemia-euglycemia (HIE) therapy, administered as a regular insulin 1-unit/kg intravenous bolus followed by a continuous infusion of 0.5–1 units/kg/hour. Infusion rate may be titrated every 30 minutes to achieve the desired response. To maintain euglycemia, intravenous dextrose 25 g may be administered with the initial insulin bolus, followed by a continuous dextrose infusion of 0.5 g/kg/hour. Potassium should be monitored closely and repleted as needed.
7. If symptomatic or hemodynamically unstable bradycardia is caused by a CCB overdose, treatment options are as follows:
   a. Calcium chloride 10%, 1–2 g intravenously every 10–20 minutes or a continuous infusion of 0.2–0.4 mL/kg/hour
   b. Calcium gluconate 10%, 3–6 g intravenously every 10–20 minutes or a continuous infusion of 0.6–1.2 mL/kg/hour
   c. Glucagon as described earlier
   d. HIE as described earlier
8. If symptomatic or hemodynamically unstable sinus bradycardia is caused by a digoxin overdose: Digoxin antibody fragments, administered on the basis of the amount ingested or the known serum digoxin concentration. One vial binds around 0.5 mg of digoxin; the dose should be administered over 30 minutes.
9. If symptomatic or hemodynamically unstable bradycardia occurs after a heart transplant, treatment options are as follows:
   a. Aminophylline 6 mg/kg in 100–200 mL of intravenous fluid, administered over 20–30 minutes
   b. Theophylline 300 mg intravenously, followed by an oral dose of 5–10 mg/kg/day titrated to effect
10. If symptomatic or hemodynamically unstable bradycardia occurs after a spinal cord injury, treatment options are as follows:
   a. Aminophylline 6 mg/kg in 100–200 mL of intravenous fluid, administered over 20–30 minutes
   b. Theophylline oral dose of 5–10 mg/kg/day titrated to effect (usual concentration range 10–20 mcg/mL)
11. Sick sinus syndrome usually requires implantation of a permanent pacemaker.
12. Oral theophylline may be considered for the management of chronic sinus node dysfunction for patients who are unwilling to undergo permanent pacemaker implantation.

E. Outcome Evaluation
   1. Monitor heart rate, blood pressure, ECG, and symptoms.
   2. Monitor for adverse effects of antidotes.
   3. Monitor for symptom resolution after discontinuing drugs that may be causing or contributing to sinus bradycardia.

**Patient Case**

1. E.B. is a 60-year-old man with a history of psychosis who is admitted to the ED 6 hours after taking 25 tablets of extended-release diltiazem 240 mg. His medical history is significant for hypertension, for which he was receiving metoprolol 100 mg orally twice daily, diltiazem 240 mg once daily, and hydrochlorothiazide 25 mg orally once daily. In the ED, his blood pressure is 68/58 mm Hg and heart rate is 48 beats/minute. His ECG reveals sinus bradycardia. His blood glucose concentration is 160 mg/dL and serum potassium concentration is 3.5 mEq/L. Which is the optimal treatment strategy for E.B.?
   A. Aminophylline 6 mg/kg administered over 20–30 minutes
   B. Atropine 0.5 mg intravenously; repeat every 5 minutes to a maximum dose of 3 mg.
   C. Insulin 1-international unit/kg intravenous bolus followed by 1 international unit/kg/hour, and intravenous dextrose 25 g followed by 0.5 g/kg/hour.
   D. Placement of a temporary transvenous pacemaker.

## III. ATRIOVENTRICULAR BLOCK

A. Types of AV Block
   1. First-degree AV block
      a. Defined as sinus rhythm with a PR interval greater than 200 milliseconds (0.2 seconds) and 1:1 AV conduction (Figure 6)
      b. Conduction delay occurs in AV node.

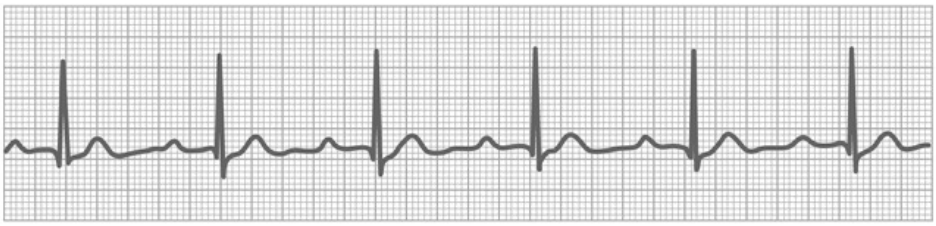

**Figure 6.** First-degree atrioventricular block – PR interval > 0.2 s.

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   2. Second-degree AV block, Mobitz type I (Wenckebach; Figure 7)
      a. Characterized by progressive prolongation of the PR interval until a depolarization generated by the sinus node is not conducted through the AV node, resulting in a P wave that is not followed by a QRS complex
      b. Conduction delay occurs in the AV node or bundle of His.

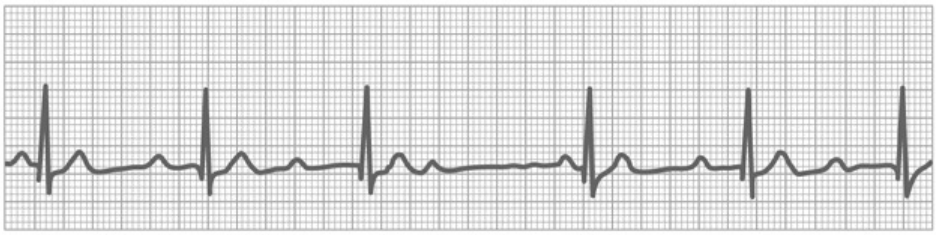

**Figure 7.** Second-degree atrioventricular block Mobitz type I (Wenckebach) – progressive prolongation of PR interval until an impulse is not conducted by the atrioventricular node, resulting in a missing QRS complex.

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3. Second-degree AV block, Mobitz type II (Figure 8)
    a. In this type of AV block, some depolarizations initiated by the sinus node are not conducted through the AV node, resulting in periodic absent ventricular depolarizations. This may occur in a regular pattern (e.g., there may be absence of AV node conduction of every second, third, or fourth depolarization generated by the sinus node). PR intervals are consistent until the QRS complex is absent; then, the pattern repeats.
    b. Conduction delay occurs in the AV node or bundle of His.

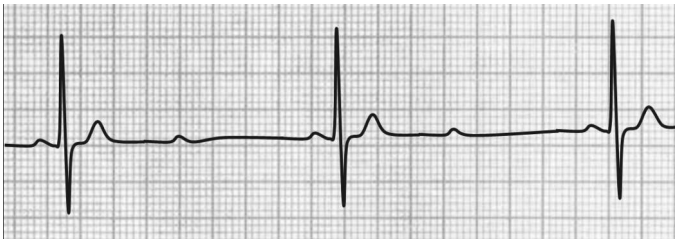

**Figure 8.** Second-degree atrioventricular block Mobitz type II – every second impulse is not conducted by the atrioventricular node, resulting in a missing QRS complex. PR intervals are constant.

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4. Third-degree AV block ("complete heart block") (Figure 9)
    a. Also known as AV dissociation. No depolarizations generated by the sinus node are conducted through the AV node, resulting in the ventricles generating their own idioventricular, or escape, rhythm. P-P and R-R intervals are constant, but there is no association between P waves and R waves. The ventricular escape rate is typically 20–40 breaths/minute.
    b. Conduction block occurs in the AV node or bundle of His.

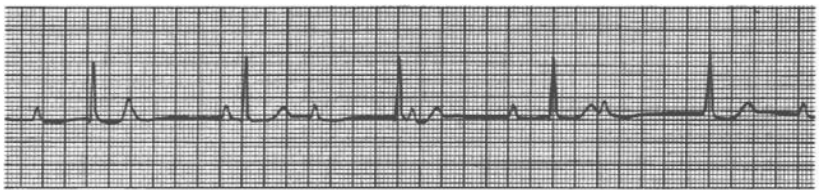

**Figure 9.** Third-degree atrioventricular block (complete heart block, atrioventricular dissociation) – no depolarizations are conducted through the atrioventricular node. Ventricles generate their own depolarizations, resulting in no relationship between atrial repolarization (P waves) and ventricular repolarization (QRS complexes).

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B. Background
   1. Prevalence of first-degree AV block:
      a. 7.8% of black males; 2.1% of white males
      b. 3.0% of black females; 1.3% of white females
   2. Prevalence of second-degree AV block Mobitz type I (Wenckebach): 1%–2%
   3. Prevalence of second-degree AV block Mobitz type II: 0.003%
   4. Prevalence of third-degree AV block:
      a. 0.04% in general adult population
      b. 1.1% of Veterans Administration patients with diabetes mellitus
      c. 0.6% of Veterans Administration patients with hypertension

C. Etiologies/Risk Factors
   1. Older age
   2. Male sex
   3. Black race
   4. Structural heart disease (second-degree Mobitz type II and third degree)
   5. Sleep apnea
   6. Surgical trauma
   7. Chagas disease, Lyme carditis
   8. Endocarditis
   9. All etiologies/risk factors listed for sinus bradycardia, except some different drugs
   10. Drugs:
      a. Antiepileptic drugs (e.g., phenytoin, lacosamide)
      b. Antiarrhythmic agents (e.g., amiodarone, dronedarone, flecainide, propafenone, sotalol)
      c. β-Blockers (including opthalmic)
      d. Bupivacaine
      e. CCBs (diltiazem, verapamil)
      f. Clonidine
      g. Digoxin
      h. Fingolimod
      i. Paclitaxel
      j. Propofol

D. Signs/Symptoms
   1. First-degree AV block usually asymptomatic; rarely, symptoms may occur because of loss of AV synchrony
   2. Second-degree AV block types I and II may be asymptomatic or symptomatic, depending on the heart rate.
   3. Third-degree AV block generally results in heart rates of 40–60 beats/minute, but the rate can be slower. Symptoms depend on the heart rate and can include:
      a. Hypotension
      b. Fatigue
      c. Weakness
      d. Dizziness/lightheadedness
      e. Syncope
      f. Symptoms associated with HF
      g. Exercise intolerance

E. Treatment: Similar to that of sinus bradycardia, as described in the previous section

## IV. ATRIAL FIBRILLATION

A. Background
   1. AF is the most common arrhythmia encountered in clinical practice.
   2. Approximately 2.7–6.1 million Americans have AF.
   3. Prevalence is projected to increase to 12.1 million in 2030.
   4. Prevalence of AF increases with age, rising from 0.5% in patients age 50–59 to greater than 33% in individuals older than 80.

B. Features (Figure 10)
   1. Chaotic and disorganized atrial activity – No organized atrial depolarization
   2. Ventricular rate: 100–180 beats/minute
   3. Rhythm: Irregularly irregular (i.e., irregular rhythm with no distinct pattern to the irregularity)
   4. P waves: Absent, replaced by undulating baseline representing chaotic atrial electrical activity

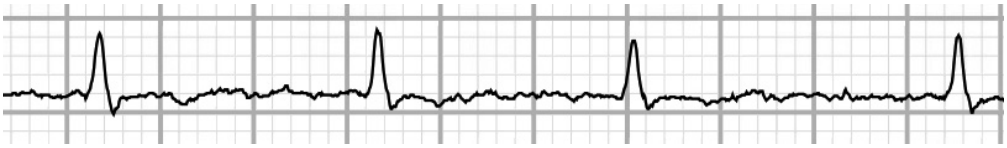

**Figure 10.** Atrial fibrillation.

**Patient Case**

2. A.S. is a 75-year-old woman who presents to the ED with palpitations, dizziness, and lightheadedness that began about 4 hours ago. Her medical history is significant for hypertension and diabetes. Medications before admission include lisinopril 20 mg daily, hydrochlorothiazide 25 mg daily, and metformin 1000 mg once daily in the evening. Her blood pressure in the ED is 78/52 mm Hg, heart rate is 170 beats/minute, and respiratory rate is 24 breaths/minute. On arrival at the ED, she begins to lose consciousness. Her ECG reveals AF. Which is the most appropriate treatment?
   A. Amiodarone 300 mg intravenously administered over 1 hour.
   B. Immediate DCC.
   C. Digoxin 0.25-mg intravenous loading dose every 4 hours up to 1.5 mg total dose.
   D. Diltiazem 0.25 mg/kg intravenously administered over 2 minutes.

C. Definitions
   1. Paroxysmal AF
      a. Terminates spontaneously or with intervention within 7 days of onset
      b. Episodes may recur; frequency of recurrence varies.
   2. Persistent AF: Continuous AF for more than 7 days
   3. Longstanding, persistent AF: Continuous AF for more than 12 months

4. Permanent AF
    a. This terminology is used when the patient and clinician have decided jointly that further efforts to restore and/or maintain sinus rhythm will be abandoned.
    b. Not strictly an inherent pathophysiologic feature of AF; instead, an attitude of acceptance by patient and clinician
    c. Attitude may change depending on symptoms, efficacy of therapy, and evolution of patient and clinician preference.
5. Nonvalvular AF: AF in the absence of moderate-severe mitral stenosis or a mechanical heart valve
6. "Lone" AF – A historical classification referring to patients with AF who have none of the known risk factors. This term is potentially confusing and should no longer be used to assist with therapeutic decision-making.

D. Mechanisms
1. AF occurs when electrophysiologic and/or structural abnormalities modify atrial tissue such that abnormal impulse formation or propagation is provoked.
2. Atrial structural abnormalities
    a. Fibrosis
    b. Dilation
    c. Ischemia
    d. Infiltration
    e. Hypertrophy
3. Inflammation/oxidative stress
4. Atrial tachycardia, atrial remodeling
5. Activation of the renin-angiotensin-aldosterone system
6. Autonomic nervous system activation
    a. Sympathetic nervous system activation
    b. Parasympathetic nervous system activation
7. Atrial electrical abnormalities
    a. Increased heterogeneity of repolarization
    b. Decreased conduction
    c. Shortened action potential duration/refractory period
    d. Increased automaticity
    e. Abnormal intracellular calcium handling
8. Genetic variants
    a. Channelopathy
    b. Cardiomyopathy

E. Initiation and Maintenance of AF
1. AF triggers
    a. AF is triggered by rapidly firing ectopic focal discharges.
    b. Abnormal impulses that trigger AF are most common from left atrial myocardial sleeves extending into the pulmonary veins; this is why pulmonary vein isolation has evolved as the primary strategy for radiofrequency catheter ablation.
    c. Abnormal calcium handling may also trigger AF because of delayed afterdepolarizations caused by diastolic leak of calcium from the sarcoplasmic reticulum.
2. Many theories have been advanced regarding the maintenance of AF once it has been triggered:
    a. Many independent reentrant wavelets as a result of heterogeneous conduction and refractoriness
    b. Many rapidly firing foci, in response to cardiac ganglionic plexi activity

c. Many rotors, or spiral wave reentrant circuits
d. With these mechanisms, wave fronts encounter refractory tissue and are disrupted during propagation, leading to irregular conduction.

3. Autonomic nervous system activity
   a. Activation of the parasympathetic and/or sympathetic nervous system can provoke AF.
   b. Acetylcholine activates the potassium current known as $I_{K,Ach}$, which shortens action potential duration and atrial repolarization and increases dispersion of atrial refractoriness, which promotes atrial reentry.
   c. Sympathetic nervous system activation increases intracellular calcium, leading to increased automaticity and triggering AF.

**Patient Case**

3. L.S. is a 63-year-old man with a new diagnosis of persistent AF. He has a history of gout, dyslipidemia, and chronic obstructive pulmonary disease (COPD). His home medications include allopurinol 100 mg once daily, simvastatin 80 mg once daily, and tiotropium 18 mcg 1 inhalation once daily. His blood pressures and heart rates are 110–120/75–80 mm Hg and 110–130 beats/minute, respectively. Which is the most appropriate rate-control therapy at this time?

   A. Digoxin 250 mcg once daily.
   B. Metoprolol tartrate 25 mg twice daily.
   C. Diltiazem extended release 240 mg once daily.
   D. Amiodarone 200 mg once daily.

F. Etiologies/Risk Factors
   1. Hypertension
   2. Coronary artery disease (CAD)/MI
   3. HFrEF
   4. Older age
   5. Diabetes mellitus
   6. Valvular heart disease
   7. Obesity
   8. Obstructive sleep apnea
   9. Cardiothoracic surgery
   10. Hyperthyroidism
   11. Alcohol use, particularly binge drinking
   12. Family history
   13. Exercise
   14. Increased pulse pressure
   15. Genetic variants
   16. European ancestry
   17. Smoking
   18. Left ventricular (LV) hypertrophy
   19. Left atrial enlargement
   20. Increased C-reactive protein
   21. Increased B-type natriuretic peptide concentrations
   22. Medications (e.g., cardiac stimulants)

G. Signs/Symptoms
   1. May be asymptomatic
   2. Fatigue
   3. Palpitations
   4. Dizziness/lightheadedness
   5. Shortness of breath
   6. Hypotension
   7. Near-syncope/syncope
   8. Angina (in patients with underlying CAD)
   9. HF symptoms (in patients with underlying HF)

H. Morbidity/Mortality
   1. Stroke/systemic embolism
      a. 2-7-fold increase in risk (depending on presence of other risk factors)
      b. Risk increases with age.
      c. AF-associated stroke is often more severe than non–AF-associated stroke.
   2. HF
      a. 3-fold increase in risk
      b. Tachycardia-induced cardiomyopathy
   3. Dementia
      a. 2-fold increase in risk
      b. Etiology unclear, possibly microemboli
   4. Hospitalization
      a. 2-fold increase in risk
      b. Almost 500,000 hospitalizations annually with AF as the primary diagnosis
      c. Patients with AF are 3 times more likely to have several hospital admissions.
   5. Mortality
      a. 2-fold increase in risk
      b. AF contributes to more than 99,000 deaths annually.

I. Cost to Patients/Health Care System
   1. Patients with AF have around $8700 added cost of care per year compared with patients without AF.
   2. Cost of AF to health care system: $27 billion annually in the United States

J. Goals of Therapy
   1. Prevention of stroke and systemic embolism. See the Anticoagulation chapter for the management of stroke prevention in AF.
   2. Control of symptoms and improvement in quality of life by:
      a. Ventricular rate control
      b. Conversion to sinus rhythm
      c. Maintaining sinus rhythm/reducing frequency of paroxysmal episodes

K. Ventricular Rate Control
   1. Control ventricular rate with a β-blocker or a non-dihydropyridine CCB in patients with paroxysmal, persistent, or permanent AF (Tables 2–4; Figure 11).
   2. For managing acute AF with intravenous drug therapy, either diltiazem or verapamil is acceptable. However, in patients with labile or low blood pressure, intravenous diltiazem is preferred to intravenous verapamil because intravenous diltiazem is less likely to profoundly decrease blood pressure.

3. Digoxin is not recommended as first-line therapy for ventricular rate control. The onset of action of intravenous digoxin is more than 1 hour, and up to 6 hours are required for maximum effects. During chronic oral therapy, digoxin slows the resting heart rate but does not slow ventricular rate during exercise. Digoxin may be particularly useful in patients with AF and HFrEF, given its salutary effects in HFrEF.
4. Concerns have emerged regarding the potentially harmful effect of digoxin in patients with AF, including increased mortality (Table 4). However, it is prudent to acknowledge the limitations of these studies, including the retrospective design and lack of routine serum digoxin monitoring. For a more complete review of digoxin and its effect on mortality in AF, see Pharmacotherapy 2021;41:394-404.
5. Amiodarone can be administered intravenously for acute ventricular rate control but is reserved for patients who do not respond to β-blockers or non-dihydropyridine CCBs or for acute administration to critically ill patients with AF (Figure 11).
6. In the acute setting in patients with AF without preexcitation, use an intravenous β-blocker or a non-dihydropyridine CCB for rapid ventricular rate control.
7. A lenient rate control strategy (heart rate less than 110 beats/minute) for long-term rate control is reasonable in asymptomatic patients and those with preserved LV systolic function.
8. A stricter heart rate control strategy (heart rate less than 80 beats/minute) is reasonable for patients with AF symptoms or HFrEF.
9. Dronedarone should not be used in patients with permanent AF or HFrEF. with New York Heart Association (NYHA) class III or IV symptoms.
10. If AF is hemodynamically unstable – Immediate synchronized DCC is necessary. Indicators of hemodynamic instability can include:
    a. Systolic blood pressure less than 90 mm Hg
    b. Heart rate greater than 150 beats/minute
    c. Ischemic chest pain
    d. Altered mental status and/or loss of consciousness

**Table 2.** Drugs for Ventricular Rate Control

| Drug | Loading Dose | Maintenance Dose | Adverse Effects | Important Drug Interactions |
|---|---|---|---|---|
| ß-Blockers | Esmolol: 500 mcg/kg IV over 1 min<br><br>Propranolol: 1 mg IV over 1 min; may repeat 1 mg IV at 2-min intervals, up to three doses<br><br>Metoprolol: 2.5–5 mg IV over 2 min; may repeat 2.5–5 mg IV every 10 min, up to three doses | Esmolol: 50–300 mcg/kg/min continuous IV infusion (administer repeat bolus doses between each dose increase)<br><br>Propranolol (oral): 30–160 mg/day in divided doses<br><br>Metoprolol tartrate (oral): 25–100 mg twice daily<br>Metoprolol succinate (oral): 50–400 mg once daily | AV block<br>Bradycardia<br>HF exacerbation (if dose too high or dose ↑ too aggressively)<br>Hypotension | CYP2D6 inhibitors may ↑ concentrations<br><br>May ↑ lidocaine concentrations |

**Table 2.** Drugs for Ventricular Rate Control *(Cont'd)*

| Drug | Loading Dose | Maintenance Dose | Adverse Effects | Important Drug Interactions |
|---|---|---|---|---|
| Diltiazem | 0.25 mg/kg IV over 2 min | IV: 5–15 mg/hr continuous infusion<br>Oral: 120–360 mg once daily extended release | AV block<br>Bradycardia<br>HF exacerbation<br>Hypotension | CYP3A4 inhibitors may ↑ concentrations<br><br>Inhibits CYP3A4: ↑ cyclosporine and statin (some) concentrations |
| Verapamil | 0.075–0.15 mg/kg IV over at least 2 min; if necessary, an additional dose of 10 mg IV may be administered 30 min later | IV: 0.005 mg/kg/min continuous infusion (rarely used)<br>Oral: 180–480 mg once daily extended release | AV block<br>Bradycardia<br>Constipation (oral)<br>HF exacerbation<br>Hypotension | CYP3A4 inhibitors may ↑ concentrations<br><br>Inhibits P-gp: ↑ digoxin concentrations<br><br>Inhibits CYP3A4: ↑ cyclosporine and statin (some) concentrations<br><br>↑ dofetilide concentrations by competition for renal tubular secretion |
| Digoxin | Varies depending on weight, renal function, concomitant medications, and comorbidities (e.g., HF)<br><br>General dosing: 0.25 mg IV every 6 hr up to a maximum, cumulative dose of 1.5 mg over 24 hr (50%) reduction in loading dose for severe renal dysfunction | Oral: 0.125–0.25 mg once daily (goal < 1.5 ng/mL in patients without HFrEF; goal < 1 ng/mL in patients with HFrEF) | Altered mental status<br>Anorexia<br>Nausea<br>Ventricular arrhythmias (e.g., bidirectional VT)<br>Vomiting | P-gp substrate:<br>Amiodarone, dronedarone, and verapamil ↑ concentrations |
| Amiodarone | 300 mg IV over 1 hr | IV: 10–50 mg/hr continuous infusion over 24 hr<br>Oral: 100–200 mg once daily | AV block<br>Bradycardia<br>Blue-gray skin discoloration<br>Corneal microdeposits<br>Hepatotoxicity<br>Hyperthyroidism<br>Hypotension (IV)<br>Hypothyroidism<br>Peripheral neuropathy<br>Photosensitivity<br>Pulmonary fibrosis | CYP3A4 inhibitors may ↑ concentrations<br><br>Inhibits CYP1A2, CYP2C9, CYP2D6, and CYP3A4: ↑ warfarin and statin (some) concentrations<br><br>Inhibits P-gp: ↑ digoxin concentrations |

HF = heart failure; IV = intravenous(ly).

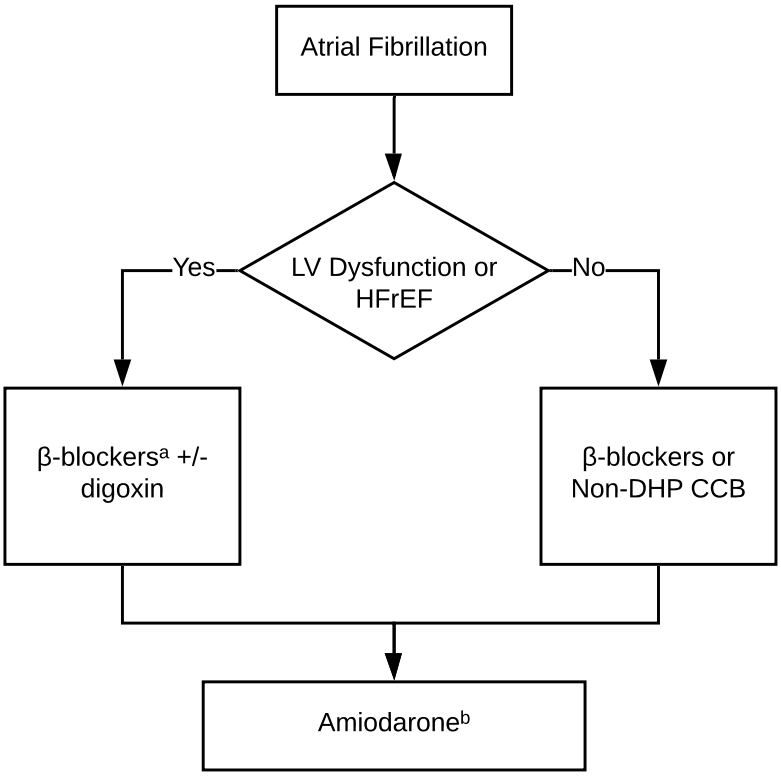


**Figure 11.** Ventricular Rate Control in Atrial Fibrillation

[a]Guideline directed β-blockers should be initiated in hemodynamically stable patients with HFrEF

[b]Due to adverse effect profile amiodarone should be reserved for patients intolerant to first-line therapies

HFrEF = heart failure with reduced ejection fraction; LV = left ventricle; Non-DHP CCB = non-dihydropyridine calcium channel blocker

**Table 3.** Selected Studies of Strategies for Ventricular Rate Control in AF

| Study/Year | Design | Treatment Arms | Population/Follow-Up | Outcomes/Results |
|---|---|---|---|---|
| Abrams et al., 1985 | Prospective, randomized, multicenter, double-blind | Esmolol<br>IV propranolol | n=127 patients with supraventricular tachyarrhythmias (74% AF) | Therapeutic response: ≥ 20% reduction from baseline heart rate after 4 hr, heart rate < 100 beats/min, or sinus rhythm<br>Esmolol: 72%<br>Propranolol 69% (p=NS) |
| Steinberg et al., 1987 | Prospective, unblinded | Oral diltiazem | n=16 patients with AF who did not achieve adequate ventricular rate control on low-level exercise testing on digoxin | Ventricular response at rest and during exercise:<br>Mean ± standard deviation heart rate (beats/min) before and during diltiazem at rest:<br>96 ± 17 vs. 69 ± 10 (p<0.001)<br>Mean ± standard deviation heart rate (beats/min) before and during diltiazem during maximal exercise:<br>163 ± 14 vs. 133 ± 26 (p<0.001) |

**Table 3.** Selected Studies of Strategies for Ventricular Rate Control in AF *(Cont'd)*

| Study/Year | Design | Treatment Arms | Population/Follow-Up | Outcomes/Results |
|---|---|---|---|---|
| Ellenbogen et al., 1991 | Prospective, randomized double-blind placebo-controlled | IV diltiazem continuous infusion<br>Placebo | n=44 patients with AF or atrial flutter who first responded to 20 mg or 20 mg followed by ≥ 1 bolus(es) of diltiazem 25 mg IV | Maintenance of therapeutic response for 24 hr: Decrease in heart rate to < 100 beats/min, ≥ 20% ↓ in heart rate from baseline, or conversion to sinus rhythm within 15 min<br>Diltiazem: 74%<br>Placebo: 0% (p<0.001) |
| Farshi et al., 1999 | Prospective, open-label crossover of five oral drugs | Digoxin 0.25 mg daily<br>Diltiazem CD 240 mg daily<br>Atenolol 50 mg daily<br>Digoxin 0.25 mg daily + diltiazem CD 240 mg daily<br>Digoxin 0.25 mg daily + atenolol 50 mg daily | n=12 patients with "chronic" AF<br>2-wk treatment; then 24-hr Holter monitor | 24-hr mean (± SD) ventricular rate (beats/min):<br>Digoxin: 78.9 ± 16.3<br>Diltiazem: 80.0 ± 15.5<br>Atenolol: 75.9 ± 11.7<br>Digoxin + diltiazem: 67.3 ± 14.1<br>Digoxin + atenolol: 65.0 ± 9.4<br>p-values:<br>Digoxin + atenolol vs. digoxin (p<0.0001)<br>Digoxin + atenolol vs. diltiazem (p<0.002)<br>Digoxin + atenolol vs. atenolol (p<0.001)<br>During exercise, digoxin was associated with the highest ventricular rate; digoxin + atenolol was associated with the lowest ventricular rate |
| Delle Karth et al., 2001 | Prospective, randomized | IV diltiazem 25-mg bolus; then continuous infusion 20 mg/hr<br>IV amiodarone 300-mg bolus<br>IV amiodarone 300-mg bolus, then continuous infusion 45 mg/hr | n=60 patients with AF (n=57), atrial flutter (n=2), or atrial tachycardia (n=1) | Primary end point: > 30% rate reduction within 4 hr<br>Diltiazem: 70%<br>Amiodarone bolus: 55%<br>Amiodarone bolus + infusion: 75% (p=NS)<br>Premature discontinuation because of hypotension:<br>Diltiazem: 30%<br>Amiodarone bolus: 0%<br>Amiodarone bolus + infusion: 5%<br>(p=0.01) |

**Table 3.** Selected Studies of Strategies for Ventricular Rate Control in AF *(Cont'd)*

| Study/Year | Design | Treatment Arms | Population/Follow-Up | Outcomes/Results |
|---|---|---|---|---|
| Siu et al., 2009 | Prospective, randomized, unblinded | IV diltiazem<br>IV amiodarone<br>IV digoxin | n=150 patients admitted to ED with AF and rapid ventricular response (> 120 beats/min) | Primary end point: Sustained ventricular rate control (< 90 beats/min) within 24 hr<br>Diltiazem: 90%<br>Amiodarone: 74%<br>Digoxin: 74%<br>p<0.05<br>Diltiazem vs. digoxin and diltiazem vs. amiodarone<br>Median time to ventricular rate control:<br>Diltiazem: 3 hr<br>Amiodarone: 7 hr<br>Digoxin: 6 hr<br>(p<0.05)<br>Diltiazem vs. amiodarone and diltiazem vs. digoxin |
| Van Gelder et al. (RACE II), 2010 | Prospective, randomized, multicenter, unblended, noninferiority | Lenient rate control (resting heart rate < 110 beats/min)<br>Strict rate control (resting heart rate < 80 beats/min; heart rate during moderate exercise < 110 beats/min) | n=614 patients with permanent AF<br>Maximum follow-up: 3 yr | Primary end point: Composite of cardiovascular death, hospitalization for HF, stroke, systemic embolism, bleeding, and life-threatening arrhythmic events<br>Lenient: 12.9%<br>Strict: 14.9%<br>(p<0.001 for noninferiority)<br>Patients meeting heart rate targets:<br>Lenient: 97.7%<br>Strict: 67.0% (p<0.001) |

**Table 4.** Studies Evaluating Impact of Digoxin on Mortality in AF

| Study/Year | Design | Patient Population | Outcomes/Results |
|---|---|---|---|
| Turakhia et al., 2014 | Retrospective, propensity-matched, cohort study of data from the Retrospective Evaluation and Assessment of Therapies in AF (TREAT-AF) study from the U.S. Department of Veterans Affairs | n=122,465 patients with newly diagnosed nonvalvular AF; 28,679 patients received digoxin | Cumulative mortality:<br>Digoxin 95 per 1000 person-yr<br>No digoxin: 67 per 1000 person-yr (p<0.001)<br>Propensity-matched HR 1.21; 95% CI, 1.17–1.25; p<0.001 |
| Freeman et al., 2015 | Retrospective, cohort study of large health system database | n=14,787 age, sex, and high-dimensional propensity score-matched patients with AF and no previous HF<br>Median follow-up = 1.17 yr | Incident digoxin use associated with ↑ risk of:<br>Death (HR 1.71; 95% CI, 1.52–1.93)<br>Hospitalization: (HR 1.63; 95% CI, 1.56–1.93) |

**Table 4.** Studies Evaluating Impact of Digoxin on Mortality in AF *(Cont'd)*

| Study/Year | Design | Patient Population | Outcomes/Results |
|---|---|---|---|
| Allen et al., 2015 | Prospective, longitudinal registry study | n=2948 patients with AF who received digoxin (46% with HF)<br>n=6671 patients with AF who never received digoxin (37% with HF) | Prevalent digoxin use at registry enrollment not associated with ↑ risk of mortality in patients with HF (HR 1.04; 95% CI, 0.86–1.27) or without HF (HR 1.22; 95% CI, 0.95–1.58)<br>Incident digoxin use not associated with ↑ risk of mortality in patients with HF (HR 1.05; 95% CI, 0.66–1.65)<br>Incident digoxin use associated with ↑ risk of mortality in patients without HF (HR 1.99; 95% CI, 1.12–3.56) |
| Chamaria et al., 2015 | Meta-analysis | n=12 studies of patients with AF taking digoxin<br>n=321,944 patients with AF | Digoxin associated with ↑ risk of all-cause mortality (HR 1.23; 95% CI, 1.16–1.31)<br>In patients with HF, digoxin not associated with ↑ risk of mortality (HR 1.08; 95% CI, 0.99–1.18)<br>In patients without HF, digoxin associated with ↑ risk of mortality (HR 1.38; 95% CI, 1.12–1.71) |
| Qureshi et al., 2016 | Systematic review and meta-analysis | n=16 studies reporting risk of mortality associated with digoxin use in patients with AF (six post hoc analyses of randomized controlled trials)<br>n=111,978 digoxin users<br>n=389,643 non-digoxin users | Digoxin associated with ↑ risk of all-cause mortality (HR 1.27; 95% CI, 1.19–1.36)<br>Digoxin associated with ↑ risk of CV mortality (HR 1.21; 95% CI, 1.07–1.36)<br>Association with ↑ risk of mortality stronger for patients without HF (HR 1.47; 95% CI, 1.25–1.73) than for patients with HF (HR 1.21; 95% CI, 1.07–1.36), interaction; p=0.06 |
| Adedinsewo et al., 2017 | Retrospective, cohort analysis of claims data for Medicare beneficiaries | n=11,297 patients with incident AF | Digoxin associated with ↑ risk of mortality (HR 1.50; 95% CI, 1.05–2.13)<br>Digoxin associated with ↑ risk of hospitalization (HR 1.54; 95% CI, 1.39–1.70) |
| Al-Khateeb et al., 2017 | Cohort study | n=2298 patients in a HF clinic<br>n=325 digoxin users<br>n=750 matched non-digoxin users<br>Median follow-up 4 yr | Digoxin use associated with ↑ risk of all-cause mortality (HR 1.74; 95% CI, 1.20–2.38) |

SCD = sudden cardiac death.

**Table 4.** Studies Evaluating Impact of Digoxin on Mortality in AF *(Cont'd)*

| Study/Year | Design | Patient Population | Outcomes/Results |
|---|---|---|---|
| Eisen et al., 2017 | Post hoc analysis of ENGAGE AF-TIMI 48 (randomized double-blind comparison of two dosing regimens of edoxaban and warfarin in 21,105 patients with AF) | n=21,105 patients with AF in randomized study<br>n=6237 patients treated with digoxin at baseline | Digoxin associated with ↑ risk of SCD (adjusted HR 1.51; 95% CI, 1.10–2.08)<br>Following propensity score-matching, digoxin was associated with ↑ risk of SCD (adjusted HR 1.90; 95% CI, 1.36–2.65)<br>Among patients with HF, digoxin was associated with ↑ risk of:<br>All-cause mortality (HR 1.31 [95% CI, 1.19–1.43])<br>CV death (HR 1.34 [95% CI, 1.20–1.48])<br>SCD (HR 1.58 [1.36–1.85])<br>Death caused by HF/cardiogenic shock (HR 1.49 [95% CI, 1.21–1.84]) |

SCD = sudden cardiac death.

L. Conversion to Sinus Rhythm (Tables 5 and 6; Figure 12)
   1. For patients with AF who are hemodynamically unstable, immediate synchronized DCC should be administered.
   2. If hemodynamically stable AF has been present for less than 48 hours, conversion to sinus rhythm without the need for anticoagulation before cardioversion (except for high-risk patients) is considered safe.
   3. If hemodynamically stable AF has been present for 48 hours or more or if the duration of episode of AF is unknown, conversion to sinus rhythm may be unsafe because a thrombus may be present in the left atrium. The process of conversion to sinus rhythm, whether by synchronized DCC or drugs, can mobilize the thrombus, resulting in stroke or transient ischemic attack. Therefore, conversion to sinus rhythm should not be attempted until the patient has been anticoagulated for at least 3 weeks, or unless a transesophageal echocardiogram (TEE) has eliminated the possibility of a left atrial thrombus.

**Table 5.** Therapies for Conversion to Sinus Rhythm

| Treatment (mechanism of action) | Loading Dose | Maintenance Dose | Adverse Effects | Important Drug Interactions |
|---|---|---|---|---|
| Synchronized DCC (may be elective or emergency) | Sedate, when possible<br>120–200 J biphasic;<br>200 J monophasic | None | Risks of general anesthesia: Allergic reactions<br>Aspiration<br>Transient bradycardia | Not applicable |
| Amiodarone (has antiarrhythmic properties from class I–IV) | IV: 150 mg over 10 min<br>Oral: 600–800 mg/day in two or three divided doses to a total loading dose of 10 g | IV: 1 mg/min for 6 hr; then 0.5 mg/min for 18 hr or change to oral dosing<br>Oral: 200 mg once daily<br>Conversion may take > 6 hr | AV block<br>Bradycardia<br>Hypotension (IV)<br>Phlebitis (IV)<br>QT interval prolongation<br>TdP | CYP3A4 inhibitors may ↑ concentrations<br>Inhibits CYP1A2, CYP2C9, CYP2D6, and CYP3A4: ↑ warfarin and statin (some) concentrations<br>Inhibits P-gp: ↑ digoxin concentrations |

**Table 5.** Therapies for Conversion to Sinus Rhythm *(Cont'd)*

| Treatment (mechanism of action) | Loading Dose | Maintenance Dose | Adverse Effects | Important Drug Interactions |
|---|---|---|---|---|
| Dofetilide (class III antiarrhythmic; pure inhibitor of the delayed rectifier potassium current, $I_{Kr}$, during phase 3 of the myocyte action potential) | Oral[a]: CrCl > 60 mL/min: 500 mcg twice daily<br>CrCl 40–60 mL/min: 250 mcg twice daily<br>CrCl 20–39 mL/min: 125 mcg twice daily<br>CrCl < 20 mL/min: Contraindicated<br>Patients must be hospitalized for at least 3 days during initiation of therapy | Dose at which patients are discharged from hospital – Usually the same as the loading dose<br>Conversion takes place within first several days of therapy | QT interval prolongation<br>TdP | Dofetilide concentrations are increased with concomitant administration of cimetidine, dolutegravir, hydrochlorothiazide, ketoconazole, megestrol, prochlorperazine, trimethoprim, and verapamil concentrations (concomitant use contraindicated)<br>Dofetilide may contribute additive effect with other drugs that prolong the QT interval |
| Ibutilide (class III antiarrhythmic; inhibits delayed rectifier potassium current, $I_{Kr}$, during phase III of the myocyte action potential; activates slow inward sodium channels) | IV: 1 mg over 10 min, followed by a second 1-mg dose, if necessary<br>If weight < 60 kg, use 0.01 mg/kg | None | QT interval prolongation<br>TdP | None known |
| Propafenone (class IC antiarrhythmic with β-blocking activity; inhibits fast inward sodium channels during phase 0 of the myocyte action potential) | Oral (immediate release):<br>Weight < 70 kg: 450 mg once[b]<br>Weight ≥ 70 kg: 600 mg once[b] | None (for conversion to sinus rhythm) | AV block<br>Bradycardia<br>HF exacerbation<br>QRS interval prolongation<br>Ventricular arrhythmias | CYP2D6, 1A2, or 3A4 inhibitors may ↑ concentrations<br>Orlistat may ↓ concentrations<br>Inhibits P-gp: ↑ digoxin concentrations<br>Inhibits CYP2C9: ↑ warfarin concentrations |
| Flecainide (class IC antiarrhythmic; inhibits fast inward sodium channels during phase 0 of the myocyte action potential) | Oral:<br>Weight < 70 kg: 200 mg once[b]<br>Weight ≥ 70 kg: 300 mg once[b] | None (for conversion to sinus rhythm) | Blurred vision<br>Dizziness<br>HF exacerbation<br>QRS interval prolongation<br>Ventricular arrhythmias | CYP2D6 inhibitors may ↑ concentrations |

[a]CrCl should be estimated using the Cockcroft-Gault equation with actual body weight.

[b]Coadministered with a β-blocker.

DCC = direct current cardioversion; J = joules; TdP = torsades de pointes.

**Table 6.** Selected Studies of Strategies for Conversion of AF to Sinus Rhythm

| Study/Year | Design | Treatment Arms | Population/Follow-Up | Outcomes/Results |
|---|---|---|---|---|
| Stambler et al., 1996 | Prospective, randomized, double-blind, placebo-controlled | IV ibutilide 1 mg, followed in 10 min by 0.5 mg<br>IV ibutilide 1 mg, followed in 10 min by 1 mg<br>IV placebo, followed in 10 min by placebo | n=266 patients with sustained AF (n=133) or atrial flutter (n=133)<br>Arrhythmia duration 3 hr – 45 days | Conversion to sinus rhythm:<br>Combined ibutilide dosing groups: 47%<br>Placebo: 2% (p<0.001)<br>No difference in efficacy between the two ibutilide dosing regimens<br>Efficacy higher in atrial flutter than in AF (63% vs. 31%, p<0.001)<br>Ibutilide-induced TdP: 8.3% |
| Digitalis in Atrial Fibrillation Trial Group, 1997 | Prospective, randomized, double-blind, placebo-controlled, multicenter | IV digoxin (mean dose 0.88 ± 0.35 mg)<br>IV placebo | n=239 patients with AF ≤ 7 days | Conversion to sinus rhythm at 16 hr:<br>Digoxin 51%<br>Placebo 46% (p=NS) |
| Boriani et al., 1997 | Prospective, randomized, single-blind placebo-controlled, multicenter | Oral propafenone 600-mg single dose<br>Oral placebo single dose | n=240 hospitalized patients with recent-onset AF | Conversion to sinus rhythm at 3 hr:<br>Propafenone: 45%<br>Placebo: 18% (p<0.001)<br>Conversion to sinus rhythm at 8 hr:<br>Propafenone: 76%<br>Placebo: 37% (p<0.001) |
| Oral et al., 1999 | Prospective, randomized, controlled, unblinded | DCC with ibutilide 1 mg IV pretreatment<br>DCC without ibutilide pretreatment | n=100 patients with AF (mean duration 117 ± 201 days) referred for DCC | DCC rates:<br>Ibutilide pretreatment: 100%<br>No ibutilide pretreatment: 72% (p<0.0001)<br>Incidence of TdP in ibutilide group: 3% (both patients had LVEF < 20%) |
| Vardas et al., 2000 | Prospective, randomized, double-blind, placebo-controlled | IV amiodarone 300 mg for 1 hr; then 20 mg/kg for 24 hr<br>Then: Oral amiodarone 600 mg daily (divided into three doses) for 1 wk, followed by 400 mg daily for 3 wk<br>IV placebo for 24 hr, followed by oral placebo for 4 wk | n=108 patients with symptomatic AF | Conversion to sinus rhythm within 1 hr:<br>Amiodarone: 38%<br>Placebo: 25% (p<0.05)<br>Conversion to sinus rhythm within 24 hr:<br>Amiodarone: 61%<br>Placebo: 40% (p<0.001)<br>Conversion to sinus rhythm at 30 days:<br>Amiodarone: 80.5%<br>Placebo: 40% (p<0.0001) |

**Table 6.** Selected Studies of Strategies for Conversion of AF to Sinus Rhythm *(Cont'd)*

| Study/Year | Design | Treatment Arms | Population/Follow-Up | Outcomes/Results |
|---|---|---|---|---|
| Singh et al. (SAFIRE-D), 2000 | Prospective, randomized, double-blind, placebo-controlled, multicenter | Dofetilide 125, 250, or 500 mcg twice daily<br>Placebo twice daily | n=325 patients with AF or atrial flutter of duration 2–26 wk<br>Follow-up: In-hospital conversion phase 3–5 days | Conversion to sinus rhythm:<br>Dofetilide 125 mcg: 6.1%<br>Dofetilide 250 mcg: 9.8%<br>Dofetilide 500 mcg: 29.9%<br>Placebo: 1.2%<br>250 mcg vs. placebo (p=0.015)<br>500 mcg vs. placebo (p=0.001) |
| Galperin et al., 2001 | Prospective, randomized, double-blind, placebo-controlled | Oral amiodarone 600 mg daily<br>Oral placebo | n=95 patients with chronic AF, average duration 35.6 mo | Conversion to sinus rhythm within 27.3 ± 8.9 days:<br>Amiodarone 34.4%<br>Placebo 0% (p<0.000009)<br>Conversion to sinus rhythm within 27.3 ± 8.9 days among patients with AF duration ≤ 12 mo:<br>Amiodarone 51.7%<br>Placebo 5.6% (p=0.001) |
| Alboni et al., 2004 | Prospective, nonrandomized, noncontrolled feasibility study | Flecainide 200–300 mg single dose<br>or<br>Propafenone 450–600 mg single dose (i.e., "pill-in-the-pocket" approach)<br>Study was not designed to compare flecainide with propafenone | n=268 patients presenting to ED with hemodynamically stable AF of recent onset<br>Final sample size n=210 after excluding patients because of in-hospital treatment failure or adverse effects<br>Patients were discharged with "pill-in-the-pocket"<br>Mean follow-up = 15 ± 5 mo | 92% of patients treated themselves within 36 ± 93 min after symptom onset<br>Successful conversion to sinus rhythm: 94%<br>Time to resolution of symptoms: 113 ± 84 min |
| Singh et al. (SAFE-T), 2005 | Prospective, randomized, double-blind, multicenter | Amiodarone 800 mg daily x 14 days, 600 mg daily x 14 days, 300 mg daily x 1 yr; then 200 mg daily<br>vs.<br>Sotalol 80 mg twice daily x 1 wk; then 160 mg twice daily<br>Placebo | n=665 patients with persistent AF<br>Follow-up 28 days (for conversion to sinus rhythm end point) | Conversion to sinus rhythm within 28 days:<br>Amiodarone 27.1%<br>Sotalol 24.2%<br>Placebo 0.8%<br>Amiodarone vs. sotalol (p=NS)<br>Amiodarone vs. placebo (p<0.001)<br>Sotalol vs. placebo (p<0.001) |

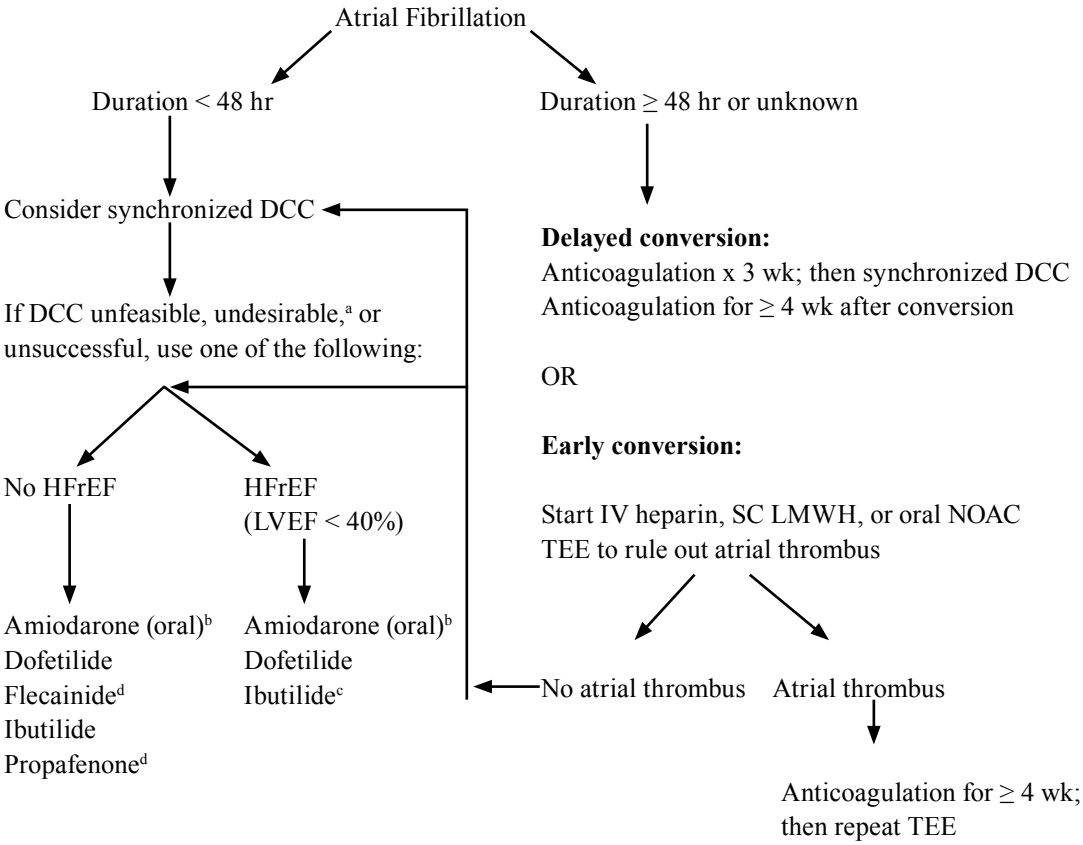


**Figure 12.** Treatment algorithm for conversion of hemodynamically stable atrial fibrillation to sinus rhythm.

DCC = direct current cardioversion; HFrEF = heart failure with reduced ejection fraction; LMWH = low-molecular-weight heparin; LVEF = left ventricular ejection fraction; NOAC = non–vitamin K oral anticoagulant; SC = subcutaneous; TEE = transesophageal echocardiogram.

[a]Patients should not be sedated for synchronized DCC if they have eaten a meal within 12 hr because of the risk of aspiration.

[b]Drugs are listed in alphabetical order, not in order of preference.

[c]Ibutilide can be administered to patients with LVEF 30%–40%, but it should be avoided in patients with LVEF < 30% because of the risk of ventricular proarrhythmia.

[d]Should not be used in patients with a history of structural heart disease.

**Patient Case**

4. K.R. is a 62-year-old man with a history of hypertension, an MI 3 years ago, and paroxysmal AF. His LVEF is 55%. He currently takes hydrochlorothiazide 25 mg once daily, metoprolol tartrate 100 mg twice daily, lisinopril 20 mg once daily, aspirin 81 mg once daily, atorvastatin 20 mg once daily, and warfarin 5 mg once daily (INR 2.2). He continues to have palpitation and dizziness episodes once or twice weekly, which last about 4–6 hours. Which is the most appropriate therapy at this time?

   A. Amiodarone 400 mg twice daily for 4 weeks; then 200 mg once daily.

   B. Dronedarone 400 mg every 12 hours.

   C. Flecainide 100 mg every 12 hours.

   D. Propafenone extended release 225 mg every 12 hours.

M. Maintenance of Sinus Rhythm (Tables 7–9; Figure 13)
   1. Before initiating antiarrhythmic drug therapy, consider whether there are precipitating or reversible causes of AF that may be eliminated or treated.
   2. Antiarrhythmic drug therapy for maintenance of sinus rhythm should only be initiated for patients with paroxysmal AF in whom optimal therapy with ventricular rate control drugs is insufficient to control AF symptoms or the ventricular rate. This recommendation is based on several studies comparing ventricular rate control and rhythm control as strategies for AF management (Table 8), in which symptom control and mortality outcomes associated with rate control therapy were generally similar to those associated with rhythm control therapy; however, rhythm control therapy is associated with a higher incidence of hospitalization and drug-associated adverse effects.
   3. Antiarrhythmic drug therapy for maintenance of sinus rhythm should be discontinued for patients in whom paroxysmal AF has progressed to permanent AF.
   4. Therapy with dofetilide or sotalol must be initiated in an institutionalized setting for at least 3 days, where continuous ECG monitoring and CrCl calculations can be performed (Figures 14 and 15). Intravenous sotalol is also approved for 24-hour initiation in institutional settings.
   5. There are important drug interactions with antiarrhythmic drugs, particularly dofetilide (Table 10) and amiodarone (Table 11).

**Table 7.** Drugs for Maintaining Sinus Rhythm in Patients with AF

| Drug | Dose | Adverse Effects | Recommended Monitoring | Important Drug Interactions |
|---|---|---|---|---|
| Amiodarone | Loading dose: 400–600 mg/day orally in two or three divided doses for 2–4 wk<br>Maintenance dose: 100–200 mg orally once daily | AV block<br>Blue-gray skin discoloration<br>Bradycardia<br>Corneal microdeposits<br>Hepatotoxicity<br>Hyperthyroidism<br>Hypothyroidism<br>Photosensitivity<br>Pulmonary fibrosis | LFTs – Baseline and every 6 mo<br>TFTs ($T_4$ and thyroid-stimulating hormone)– Baseline and every 6 mo<br>Chest radiography – Baseline and annually<br>ECG – Baseline and at least every 6 mo<br>Ophthalmologic evaluation – At baseline if visual impairment or for symptoms<br>PFTs – Baseline and for unexplained dyspnea, especially if underlying lung disease and if chest radiography abnormalities are suggested | CYP3A4 inhibitors may ↑ concentrations<br>Inhibits CYP1A2, CYP2C9, CYP2D6, and CYP3A4: ↑ warfarin and statin (some) concentrations<br>Inhibits P-gp: ↑ digoxin concentrations |

**Table 7.** Drugs for Maintaining Sinus Rhythm in Patients with AF *(Cont'd)*

| Drug | Dose | Adverse Effects | Recommended Monitoring | Important Drug Interactions |
|---|---|---|---|---|
| Dofetilide | CrCl[a] > 60 mL/min: 500 mcg twice daily<br>CrCl 40–60 mL/min: 250 mcg twice daily<br>CrCl 20–39 mL/min: 125 mcg twice daily<br>CrCl < 20 mL/min: Contraindicated | QT interval prolongation<br>TdP | Continuous ECG monitoring during the first 3 days of dosing while hospitalized<br>ECG every 3–6 mo<br>SCr every 3–6 mo | Dofetilide concentrations are increased when coadministered with cimetidine, dolutegravir, hydrochlorothiazide, ketoconazole, megestrol, prochlorperazine, trimethoprim, and verapamil concentrations (concomitant use contraindicated)<br>Dofetilide may contribute additive effects with other drugs that prolong the QT interval |
| Dronedarone | 400 mg orally every 12 hr | Bradycardia<br>Diarrhea<br>Hepatotoxicity<br>Nausea<br>Pulmonary fibrosis<br>Worsening HF | LFTs – Baseline and every 6 mo<br>ECG – Every 3 mo<br>SCr every 3–6 mo | CYP3A inhibitors of may ↑ concentrations (concomitant use of strong CYP3A inhibitors contraindicated)<br>Inhibits CYP3A: ↑ statin (some), verapamil, and diltiazem concentrations<br>Inhibits CYP2D6 ↑ β-blockers and other CYP2D6 substrate concentrations<br>Inhibits P-gp: ↑ dabigatran and digoxin concentrations |
| Sotalol | Initial oral dose:<br>CrCl > 60 mL/min: 80 mg twice daily<br>CrCl 40–60 mL/min: 80 mg once daily<br>CrCl < 40 mL/min: Contraindicated<br>Maintenance dose: If 80-mg doses are tolerated and QTc interval remains < 500 ms after 3 days, patient can be discharged. Alternatively, dose can be increased to 120 mg once or twice daily, as appropriate, during hospitalization and patient followed for 3 days on this dose<br>Intravenous dose: Bolus dose over 1 hr with QTc monitoring every 15 min during infusion. If QTc remains < 500 ms, the first oral doses are administered 5 and 17 hr after the initial infusion | AV block<br>Bradycardia<br>HF exacerbation<br>QT interval prolongation<br>TdP | Continuous ECG monitoring during the first 3 days of dosing while hospitalized<br>ECG every 3–6 mo<br>SCr every 3–6 mo | May contribute additive effects with other drugs that prolong the QT interval or cause sinus bradycardia or AV block |

**Table 7.** Drugs for Maintaining Sinus Rhythm in Patients with AF *(Cont'd)*

| Drug | Dose | Adverse Effects | Recommended Monitoring | Important Drug Interactions |
|---|---|---|---|---|
| Propafenone | Immediate release: 150–300 mg orally every 8 hr<br>Extended release: 225–425 mg orally every 12 hr | AV block<br>Bradycardia<br>HF exacerbation<br>QRS interval prolongation<br>Ventricular arrhythmias | ECG as needed, at least every 6 mo | CYP 2D6, 1A2, or 3A4 inhibitors may ↑ concentrations<br>Orlistat may ↓ concentrations<br>Inhibits P-gp: ↑ digoxin concentrations<br>Inhibits CYP2C9: ↑ warfarin concentrations |
| Flecainide | 50–200 mg orally every 12 hr | Blurred vision<br>Dizziness<br>HF exacerbation<br>QRS interval prolongation<br>Ventricular arrhythmias | ECG as needed, at least every 6 mo | CYP2D6 inhibitors may ↑ concentrations |

LFT = liver function test; ms = millisecond(s); PFT = pulmonary function test; $T_4$ = thyroxine; TFT = thyroid function test.

[a]Throughout the table, renal function estimations should be calculated using the Cockcroft-Gault equation with actual body weight.

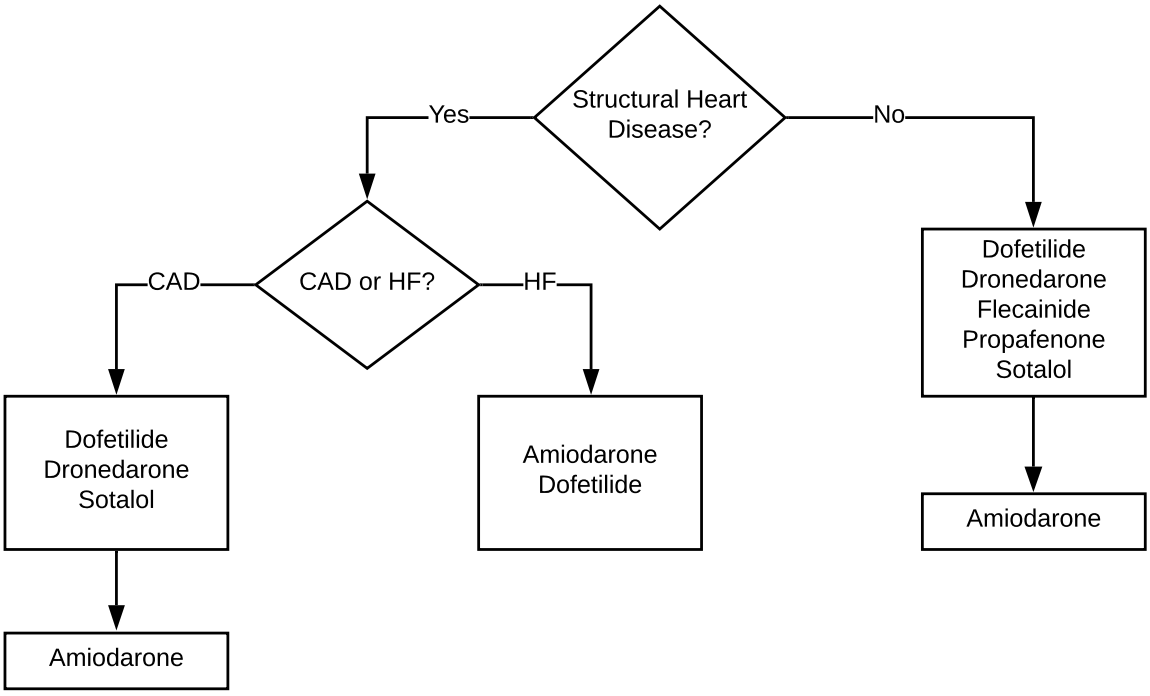


**Figure 13.** Antiarrhythmic Drugs for Maintaining Sinus Rhythm in Atrial Fibrillation

[a]Drugs listed alphabetically within each box. Individual drug-selection should be based on patient preference and patient-specific risk factors for adverse effects

CAD = coronary artery disease; HF = heart failure

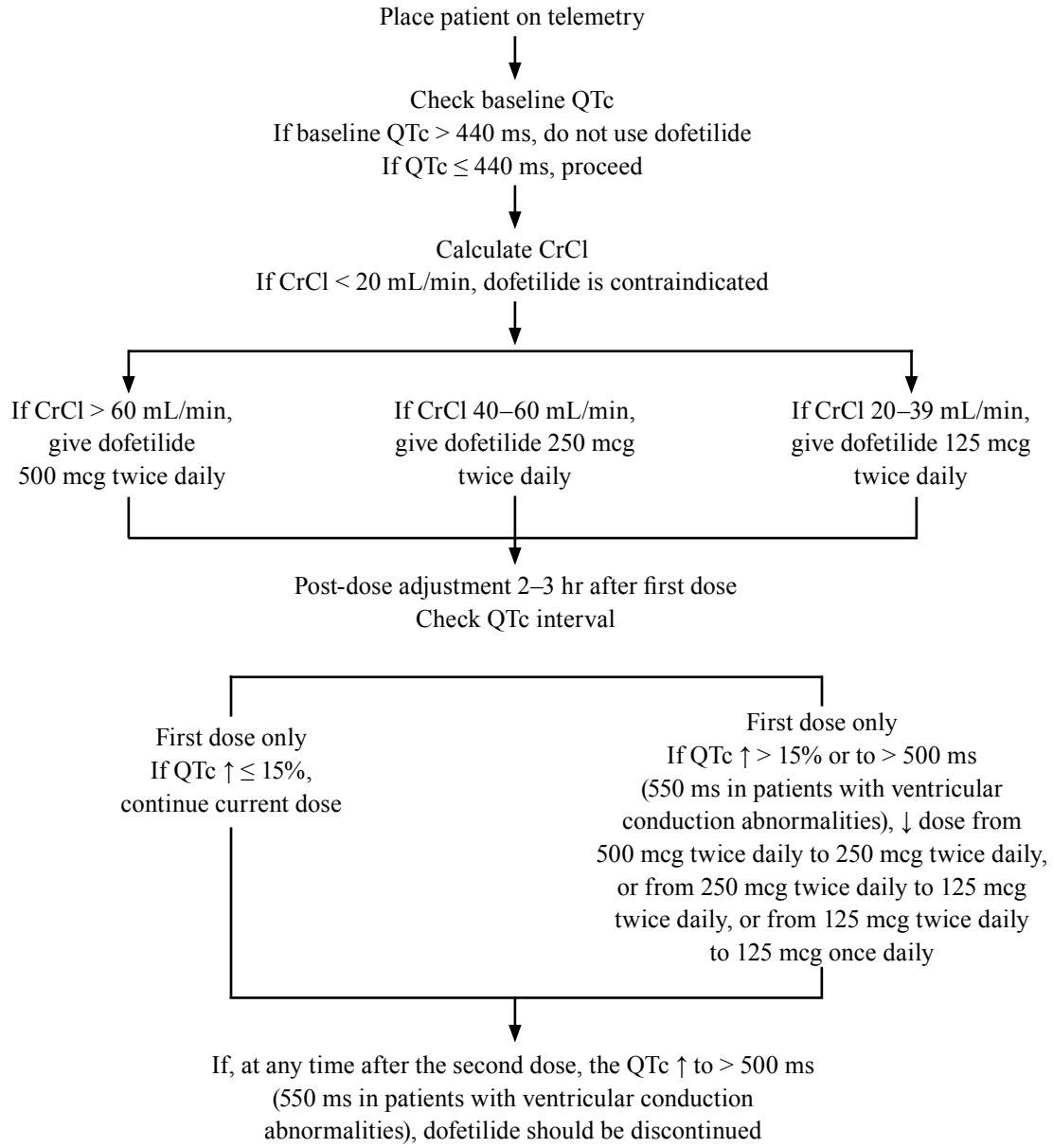


**Figure 14.** Individualized dofetilide initiation algorithm.
ms = millisecond(s).

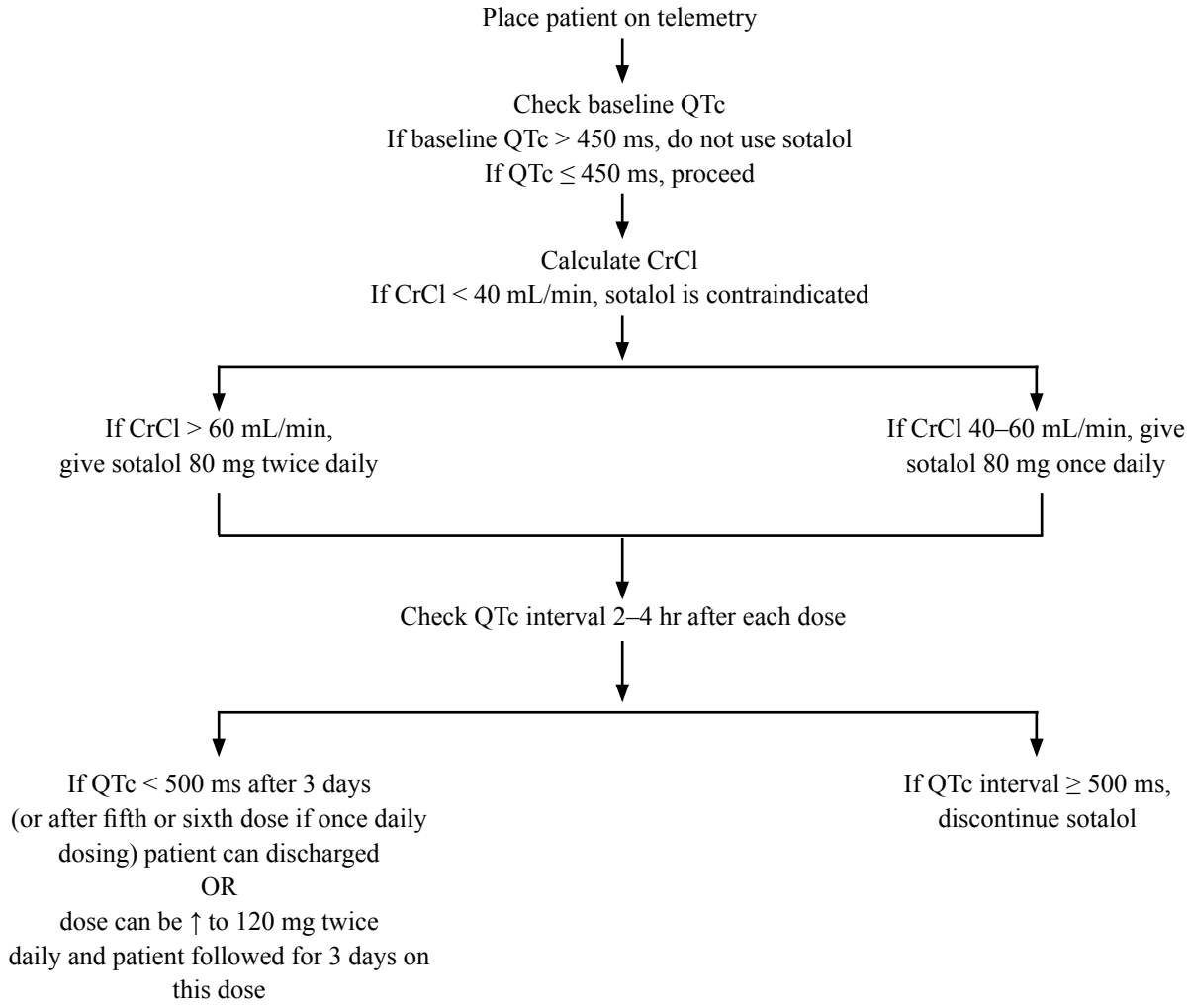


**Figure 15.** Individualized oral sotalol initiation algorithm.

**Table 8.** Selected Studies of Antiarrhythmic Drug Therapy for Maintaining Sinus Rhythm in Patients with AF

| Study/Year | Design | Treatment Arms | Population/Follow-Up | Outcomes/Results |
|---|---|---|---|---|
| Roy et al. (CTAF), 2000 | Prospective, randomized multicenter, unblinded | Amiodarone<br>Sotalol<br>Propafenone<br>Those randomized to sotalol or propafenone group underwent a second randomization to determine whether they received sotalol or propafenone first; if first drug was unsuccessful, second drug was then prescribed | n=403 patients with ≥ 1 episode of AF in previous 6 mo<br>Loading doses of drugs were administered, and DCC was performed within 21 days of randomization<br>Mean follow-up = 16 mo | Primary end point: Length of time to first AF recurrence<br>Amiodarone: Primary end point could not be determined because > 50% of patients remained free of recurrence<br>Sotalol/propafenone: Median time to recurrence = 98 days<br>Proportion of patients who had AF recurrence:<br>Amiodarone: 35%<br>Sotalol/propafenone: 63% (p<0.001)<br>Adverse events requiring discontinuation:<br>Amiodarone 18%<br>Sotalol/propafenone: 11% (p=0.06) |
| Singh et al. (SAFIRE-D), 2000 | Prospective, randomized, double-blind, placebo-controlled, multicenter | Dofetilide 125, 250, or 500 mcg twice daily<br>Placebo twice daily | n=325 patients with AF or atrial flutter of duration 2–26 wk<br>After in-hospital conversion phase: 12 mo | Probability of remaining in sinus rhythm at 1 yr:<br>Dofetilide 125 mcg: 0.40<br>Dofetilide 250 mcg: 0.37<br>Dofetilide 500 mcg: 0.58<br>Placebo: 0.25<br>500 mcg vs. placebo (p=0.001) |
| Pedersen et al., 2001 | Prospective, randomized, double-blind, placebo-controlled | Dofetilide<br>Placebo | n=506 patients with HF and AF or atrial flutter<br>Follow-up = 12 mo | Conversion to sinus rhythm:<br>Dofetilide: 44%<br>Placebo: 14% (p<0.001)<br>Probability of maintaining sinus rhythm for 1 yr:<br>Dofetilide: 79%<br>Placebo: 42% (p<0.001) |
| Pritchett et al. (RAFT), 2003 | Prospective, randomized, double-blind, placebo-controlled | Propafenone sustained release 425, 325, or 225 mg (all twice daily) vs. placebo | n=523 patients with AF | Time to first AF recurrence:<br>Propafenone 425 mg: > 300 days<br>Propafenone 325 mg: 291 days<br>Propafenone 225 mg: 112 days Placebo: 41 days (p<0.05 for all propafenone doses vs. placebo) |

**Table 8.** Selected Studies of Antiarrhythmic Drug Therapy for Maintaining Sinus Rhythm in Patients with AF *(Cont'd)*

| Study/Year | Design | Treatment Arms | Population/Follow-Up | Outcomes/Results |
|---|---|---|---|---|
| Singh et al. (SAFE-T), 2005 | Prospective, randomized, double-blind, multicenter | Amiodarone 800 mg daily x 14 days, 600 mg daily x 14 days, 300 mg daily x 1 yr; then 200 mg daily<br>Sotalol 80 mg twice daily x 1 wk; then 160 mg twice daily<br>Placebo | n=665 patients with persistent AF<br>Follow-up = 1–4.5 yr | Median time to AF recurrence after conversion to sinus rhythm:<br>Amiodarone: 487 days<br>Sotalol: 74 days<br>Placebo: 6 days<br>Amiodarone vs. placebo (p<0.001)<br>Amiodarone vs. sotalol (p<0.001)<br>Sotalol vs. placebo (p<0.001) |
| Singh et al. (EURIDIS/ ADONIS), 2007 | Two identical prospective, randomized, multicenter, placebo-controlled trials | Dronedarone<br>Placebo | n=1237 patients with AF<br>Follow-up = 12 mo | Primary end point: Median time to AF recurrence<br>EURIDIS:<br>Dronedarone: 96 days<br>Placebo: 41 days (p=0.01)<br>ADONIS:<br>Dronedarone: 158 days<br>Placebo: 59 days (p=0.002) |
| Kober et al. (ANDROMEDA), 2008 | Prospective, randomized, multicenter, placebo-controlled | Dronedarone<br>Placebo | n=627 patients with AF and symptomatic HF with severe LV systolic dysfunction | Primary end point: Composite of death from any cause or hospitalization for HF<br>Study terminated prematurely because of excess mortality in the dronedarone group:<br>Dronedarone 8.1%<br>Placebo 3.8% (HR 2.13; 95% CI, 1.07–4.25, p=0.03) |
| Le Heuzey (DIONYSOS), 2010 | Prospective, randomized, double-blind | Amiodarone<br>Dronedarone | n=504 patients with persistent AF<br>Median treatment duration = 7 mo<br>Median follow-up = 12 mo | Primary end point: Composite of AF recurrence or premature study discontinuation<br>Amiodarone: 58.8%<br>Dronedarone: 75.1%<br>(HR 1.59; 95% CI, 1.28–1.98; p<0.0001)<br>Main safety end point (thyroid, hepatic, pulmonary, neurologic, skin, eye, or gastrointestinal events):<br>Amiodarone: 44.5%<br>Dronedarone: 39.3%<br>(HR 0.80; 95% CI, 0.60–1.07; p=NS) |
| Connolly et al. (PALLAS), 2011 | Prospective, randomized, double-blind, multicenter, placebo-controlled | Dronedarone<br>Placebo | n=3236 patients with permanent AF and risk factors for major vascular events | Study discontinued prematurely because of excess deaths in dronedarone group (HR 2.11; 95% CI, 1.00–4.49; p=0.046) |

**Table 9.** Studies of Rate Control vs. Rhythm Control for AF

| Study/Year | Design | Treatment Arms | Population | Outcomes/Results |
|---|---|---|---|---|
| Hohnloser et al. (PIAF), 2000 | Prospective, randomized, open-label pilot | Rate control (diltiazem first-line; if inadequate response, additional rate control therapy left to discretion of physician)<br><br>Rhythm control (amiodarone first-line, then electrical cardioversion, then amiodarone again for maintenance of sinus rhythm) | n=252 patients with AF<br><br>Follow-up: 1 yr | Primary end point: Improvement in AF symptoms<br><br>Rate control: 60.8%<br>Rhythm control: 55.1%<br>(p=NS)<br><br>Adverse effects leading to change in therapy:<br><br>Rate control: 14%<br>Rhythm control: 25%<br>(p=0.036) |
| Van Gelder et al. (RACE), 2002 | Prospective, randomized, multicenter, unblinded | Rate control (digitalis, non-dihydropyridine CCBs, and β-blockers, alone or in combination)<br><br>Rhythm control (electrical cardioversion followed by sotalol. If recurrence within 6 months, repeat electrical cardioversion, then flecainide or propafenone. If recurrence within 6 months, repeat electrical cardioversion, then amiodarone | n=522 patients with persistent AF<br><br>Mean ± standard deviation follow-up = 2.3 ± 0.6 yr | Primary end point: Composite of CV death, HF, thromboembolic complications, bleeding, implantation of a permanent pacemaker, and severe adverse drug effects<br><br>Rate control: 17.2%<br>Rhythm control: 22.6%<br><br>Absolute difference = -5.4% (95% CI, -11.0% to 0.4%); met the criteria for noninferiority |
| Wyse et al. (AFFIRM), 2002 | Prospective, randomized, multicenter, open-label | Rate control (β-blockers, diltiazem or verapamil, digoxin, and combinations of these drugs)<br><br>Rhythm control (Antiarrhythmic drug chosen by treating physician; drugs included amiodarone, disopyramide, flecainide, moricizine, procainamide, propafenone, quinidine, sotalol, dofetilide) | n=4060 patients with AF and high risk of stroke or death<br><br>Follow-up = 5 yr | Primary end point: Death<br><br>Rate control: 21.3%<br><br>Rhythm control: 23.8% (HR 1.15; 95% CI, 0.99–1.34; p=0.08)<br><br>Hospitalizations:<br><br>Rate control: 73.0%<br>Rhythm control: 80.1%<br>(p<0.001)<br><br>Incidence of TdP, pulmonary events, gastrointestinal events, bradycardia, and QT interval prolongation all significantly higher in the rhythm control group |

**Table 9.** Studies of Rate Control vs. Rhythm Control for AF *(Cont'd)*

| Study/Year | Design | Treatment Arms | Population | Outcomes/Results |
|---|---|---|---|---|
| Carlsson et al. (STAF), 2003 | Prospective, randomized, multicenter, open-label pilot | Rate control (β-blockers, CCBs, or AV node ablation/modification)<br><br>Rhythm control (electrical cardioversion, followed by class I antiarrhythmic agents or sotalol) | n=200 patients with persistent AF<br><br>Mean ± standard deviation follow-up = 19.6 ± 8.9 mo | Primary end point: Composite of death, cardiopulmonary resuscitation, cerebrovascular event, and systemic embolism<br><br>Rate control: 6.09%/yr<br>Rhythm control: 5.54%/yr (p=NS) |
| Opolski et al. (HOT-CAFÉ), 2004 | Prospective, randomized, multicenter, open-label | Rate control (β-blockers, CCBs, digoxin, or a combination of those drugs)<br><br>Rhythm control (Electrical cardioversion, followed by antiarrhythmic drug therapy, initially propafenone, disopyramide or sotalol; amiodarone was also used if necessary) | n=205 patients with AF<br><br>Follow-up = 12 mo | Mortality:<br>Rate control: 1.0%<br>Rhythm control: 2.9% (p=NS)<br><br>Hospitalization:<br>Rate control: 12%<br>Rhythm control: 74% (p<0.001) |
| Roy et al. (AF-CHF), 2008 | Prospective, randomized, multicenter, open-label | Rate control (β-blockers with digitalis, followed by AV node ablation, if necessary)<br><br>Rhythm control (electrical cardioversion followed by amiodarone (drug of choice]). Sotalol or dofetilide could also be used, if required | n=1376 patients with AF and symptomatic HF with ejection fraction < 35%<br><br>Mean follow-up = 37 mo | Death from CV causes:<br><br>Rate control: 25%<br>Rhythm control: 27% (HR 1.06; 95% CI, 0.86–1.30; p=NS) |
| Kirchhof et al. (EAST-AFNET 4), 2020 | Prospective, randomized, multicenter, open-label | Usual care (rate control with rhythm control only if needed to control symptoms)<br><br>Early rhythm control (antiarrhythmic drugs or ablation) | n=2789 patients with early AF (defined as diagnosis within 12 mo of enrollment) and risk factors for stroke<br><br>Median follow-up = 5.1 yr | Primary end point: Composite death from cardiovascular causes, stroke, or hospitalization for worsening HF or acute coronary syndrome<br><br>Usual care: 5.0 events/ 100 person-yr<br><br>Early rhythm control: 3.9 events/100 person-yr<br>(HR 0.79; 95% CI, 0.66–0.94; p=0.005) |

**Table 10.** Important Pharmacokinetic Drug Interactions Associated with Dofetilide

| Precipitant Drug | Mechanism | Drug Combination Contraindicated? | Recommendation |
|---|---|---|---|
| Amiloride | Competition for secretion through renal cation transport | No | Use combination with care; monitor QTc interval |
| Cimetidine | Inhibition of renal cation transport | Yes | Avoid concomitant use |
| Dolutegravir | Inhibition of renal cation transport | Yes | Avoid concomitant use |
| Hydrochlorothiazide | Stimulates organic cation–mediated uptake of dofetilide | Yes | Avoid concomitant use |
| Ketoconazole | Inhibition of renal cation transport | Yes | Avoid concomitant use |
| Megestrol | Inhibition of renal cation transport | Yes | Avoid concomitant use |
| Metformin | Competition for secretion through renal cation transport | No | Use combination with care; monitor QTc intervals |
| Prochlorperazine | Inhibition of renal cation transport | Yes | Avoid concomitant use |
| Trimethoprim | Inhibition of renal cation transport | Yes | Avoid concomitant use |
| Verapamil | Unknown | Yes | Avoid concomitant use |

**Table 11.** Important Pharmacokinetic Drug Interactions Associated with Amiodarone

| Precipitant Drug | Object Drug | Mechanism | Drug Combination Contraindicated? | Recommendation |
|---|---|---|---|---|
| Amiodarone | Cyclosporine | Inhibition of CYP3A | No | Monitor blood cyclosporine concentrations and renal function |
| Amiodarone | Dabigatran | Inhibition of P-gp | No | Monitor for bleeding |
| Amiodarone | Dextromethorphan | Inhibition of CYP2D6 | No | Monitor for toxicity |
| Amiodarone | Digoxin | Inhibition of P-gp | No | Review need for digoxin – if possible, discontinue digoxin. If digoxin therapy deemed necessary, ↓ digoxin dose by 50%; monitor serum digoxin concentrations |
| Amiodarone | Edoxaban | Inhibition of P-gp | No | Monitor for bleeding |
| Amiodarone | Fentanyl | Inhibition of CYP3A | No | Monitor blood pressure, heart rate, respiratory rate |
| Amiodarone | Lidocaine | Inhibition of CYP3A | No | Monitor serum lidocaine concentrations |
| Amiodarone | Lovastatin | Inhibition of CYP3A | No | Limit lovastatin dose to 40 mg daily |
| Amiodarone | Phenytoin | Inhibition of CYP2C9 | No | Monitor serum phenytoin concentrations |
| Amiodarone | Procainamide | Inhibition of renal cation transport | Relative | Reduce procainamide dose; monitor serum procainamide and NAPA concentrations and ECG (QTc interval) |
| Amiodarone | Simvastatin | Inhibition of CYP3A | No | Limit simvastatin dose to 20 mg daily |
| Amiodarone | Warfarin | Inhibition of CYP2C9 | No | ↓ warfarin dose by 30%–50%; monitor INR |
| Cimetidine | Amiodarone | Inhibition of CYP3A | No | Consider measuring serum amiodarone concentrations |
| Clarithromycin | Amiodarone | Inhibition of CYP3A | No | Consider measuring serum amiodarone concentrations |

**Table 11.** Important Pharmacokinetic Drug Interactions Associated with Amiodarone *(Cont'd)*

| Precipitant Drug | Object Drug | Mechanism | Drug Combination Contraindicated? | Recommendation |
|---|---|---|---|---|
| Cholestyramine | Amiodarone | Reduces enterohepatic circulation | No | Consider measuring serum amiodarone concentrations |
| Erythromycin | Amiodarone | Inhibition of CYP3A | No | Consider measuring serum amiodarone concentrations |
| Fluconazole | Amiodarone | Inhibition of CYP3A | No | Consider measuring serum amiodarone concentrations |
| Grapefruit juice | Amiodarone | Inhibition of CYP3A | Yes | Avoid concomitant use |
| Ketoconazole | Amiodarone | Inhibition of CYP3A | No | Consider measuring serum amiodarone concentrations |
| Indinavir | Amiodarone | Inhibition of CYP3A | Yes | Avoid concomitant use |
| Nelfinavir | Amiodarone | Inhibition of CYP3A | Yes | Avoid concomitant use |
| Phenytoin | Amiodarone | Induction of CYP3A | No | Consider measuring serum amiodarone concentrations |
| Rifampin | Amiodarone | Induction of CYP3A | No | Consider measuring serum amiodarone concentrations |
| Ritonavir | Amiodarone | Inhibition of CYP3A | Yes | Avoid concomitant use |
| Saquinavir | Amiodarone | Inhibition of CYP3A | Yes | Avoid concomitant use |
| Sofosbuvir | Amiodarone | Risk of bradycardia requiring pacemaker when these drugs are administered together with another HCV direct-acting antiviral agent | No, but recommended not to use in combination unless there are no alternatives | Monitor for bradycardia |
| St. John's wort | Amiodarone | Induction of CYP3A | No | Consider measuring serum amiodarone concentrations |
| Telithromycin | Amiodarone | Inhibition of CYP3A | No | Consider measuring serum amiodarone concentrations |

HCV = hepatitis C virus; NAPA = *N*-acetylprocainamide.

**Table 12.** Selected Studies Comparing Catheter Ablation with Antiarrhythmic Drug Therapy for Maintaining Sinus Rhythm in Patients with AF

| Study/Year | Design | Treatment Arms | Population/Follow-Up | Outcomes/Results |
|---|---|---|---|---|
| Jaïs et al. (A4), 2008 | Prospective, randomized, multicenter, unblinded | Catheter ablation<br>Antiarrhythmic drugs alone or in combination | n=112 patients with paroxysmal AF resistant to at least one antiarrhythmic drug<br>Follow-up = 1 yr | Primary end point: Proportion of patients free of AF recurrence at months 3–12<br>Catheter ablation: 89%<br>Antiarrhythmic drugs: 23% (p<0.0001) |
| Wilber et al. (ThermoCool-AF), 2010 | Prospective, randomized, multicenter, unblinded | Catheter ablation<br>Antiarrhythmic drugs | n=167 patients with ≥ 3 AF episodes in previous 6 mo and who did not respond to ≥ 1 antiarrhythmic drug<br>Follow-up = 9 mo | Primary end point: Freedom from protocol-defined treatment failure, which included documented symptomatic paroxysmal AF<br>Catheter ablation: 66%<br>Antiarrhythmic drugs: 19% (HR 0.30; 95% CI, 0.19–0.47; p<0.01)<br>Major 30-day treatment-related adverse events:<br>Catheter ablation: 4.9%<br>Antiarrhythmic drugs: 8.8% (p value not reported) |
| Mont et al. (SARA), 2014 | Prospective, randomized, multicenter, unblinded | Catheter ablation<br>Antiarrhythmic drugs | n=146 patients with persistent AF<br>Follow-up = 12 mo | Primary end point: Any episode of AF or atrial flutter lasting > 24 hr after a 3-mo blanking period<br>Catheter ablation: 70.4%<br>Antiarrhythmic drugs: 43.7%<br>(p=0.002) |
| Di Biase et al. (AATAC), 2016 | Prospective, randomized, multicenter, unblinded | Catheter ablation<br>Amiodarone | n=203 patients with persistent AF, HFrEF, and ICD or CRT pacemaker<br>Follow-up: Minimum of 24 mo | Primary end point: Proportion of patients free of AF recurrence<br>Catheter ablation: 70%<br>Amiodarone: 35% (p<0.0001)<br>Secondary end points:<br>Mortality:<br>Catheter ablation: 8%<br>Amiodarone: 18% (p=0.037)<br>Unplanned hospitalization:<br>Catheter ablation: 31%<br>Amiodarone: 57% (p<0.001) |

**Table 12.** Selected Studies Comparing Catheter Ablation with Antiarrhythmic Drug Therapy for Maintaining Sinus Rhythm in Patients with AF *(Cont'd)*

| Study/Year | Design | Treatment Arms | Population/Follow-Up | Outcomes/Results |
|---|---|---|---|---|
| Nielsen et al. (MANTRA-PAF), 2017 | Prospective, randomized, multicenter, unblinded | Catheter ablation<br>Antiarrhythmic drugs | n=245 patients with paroxysmal AF<br>Follow-up = 5 yr | Primary end point: Burden of any AF<br>Catheter ablation: 85th and 95th percentiles, 0% and 7%<br>Antiarrhythmic drugs: 85th and 95th percentiles, 7% and 97% (p=0.02)<br>Free of any AF:<br>Catheter ablation: 86%<br>Antiarrhythmic drugs: 71% (RR 0.82; 95% CI, 0.73–0.93; p=0.001) |
| Marrouche et al. (CASTLE-AF), 2018 | Prospective, randomized, multicenter, unblinded | Catheter ablation<br>Medical therapy (rate or rhythm control) | n=363 patients with symptomatic paroxysmal or persistent AF who did not respond to antiarrhythmic drugs, had unacceptable adverse effects, or were unwilling to take these drugs<br>All patients had HFrEF and ICD<br>Mean follow-up = 37.8 mo | Primary end point: Composite of death from any cause or hospitalization for HF<br>Catheter ablation: 28.5%<br>Medical therapy: 44.6% (HR 0.62; 95% CI, 0.43–0.87; p=0.007)<br>Secondary end points:<br>Death from any cause:<br>Catheter ablation: 13.4%<br>Medical therapy: 25.0% (HR 0.53; 95% CI, 0.32–0.86; p=0.01)<br>Hospitalization for worsening HFrEF:<br>Catheter ablation: 20.7%<br>Medical therapy: 35.9% (HR 0.56; 95% CI, 0.37–0.83; p=0.004) |

CRT = cardiac resynchronization therapy; ICD = implantable cardioverter-defibrillator.

**Table 12.** Selected Studies Comparing Catheter Ablation with Antiarrhythmic Drug Therapy for Maintaining Sinus Rhythm in Patients with AF *(Cont'd)*

| Study/Year | Design | Treatment Arms | Population/Follow-Up | Outcomes/Results |
|---|---|---|---|---|
| Packer et al. (CABANA), 2019 | Prospective, randomized, multicenter, unblinded | Catheter ablation<br>Medical therapy (rate or rhythm control) | n=2204 patients with symptomatic paroxysmal or persistent AF and additional risk factors for stroke<br>Median follow-up = 48.5 mo | Primary end point: Composite of death, disabling stroke, serious bleed, or cardiac arrest<br>Catheter ablation: 8.0%<br>Medical therapy: 9.2%<br>(HR 0.86; 95% CI, 0.65–1.15; p=0.30)<br><br>Secondary end points:<br>Death from any cause:<br>Catheter ablation 5.2%<br>Medical therapy: 6.1%<br>(HR 0.85; 95% CI, 0.60–1.21; p=0.38)<br><br>Composite death or CV hospitalization:<br>Catheter ablation: 51.7%<br>Medical therapy: 58.1%<br>(HR 0.83; 95% CI, 0.74–0.93; p=0.001) |
| Andrade et al. (EARLY-AF), 2021 | Prospective, randomized, multicenter, unblinded | Cryoballoon catheter ablation<br><br>Antiarrhythmic drug therapy | n=303 patients with symptomatic AF who had not previously received antiarrhythmic drug therapy<br><br>Follow-up = 1 yr | Primary end point: First occurrence of atrial tachyarrhythmias<br><br>Catheter ablation: 42.9%<br>Antiarrhythmic therapy: 67.8%<br>(HR 0.48; 95% CI, 0.35–0.66; p<0.001) |

CRT = cardiac resynchronization therapy; ICD = implantable cardioverter-defibrillator.

N. Transitions of Care for Antiarrhythmic Drugs in AF
   1. Patients newly initiated on an antiarrhythmic drug should have a thorough medication history performed to assess for drug-drug interactions.
   2. Patients being discharged on dofetilide or sotalol should be educated on the importance of drug-drug interactions with other QT-prolonging medications (e.g., common antibiotics or other serious drug-drug interactions).
   3. Patients discharged on dofetilide who were previously prescribed a contraindicated medication (e.g., hydrochlorothiazide) should have the refills canceled. The patient's providers should be made aware of the interaction.
   4. Barriers to accessing dofetilide should be proactively addressed before discharge (e.g., prior authorizations, ensuring the medication is in stock at the pharmacy).
   5. Patients discharged on amiodarone should have baseline liver, thyroid, and pulmonary function testing.
   6. Patients discharged on amiodarone should be counseled on the potential for drug-drug interactions and toxicities and the importance of follow-up monitoring, as well as schedules for discontinuing loading doses/starting maintenance doses.

O. Upstream Therapy for AF
   1. An angiotensin-converting enzyme (ACE) inhibitor or an angiotensin receptor blocker (ARB) may be effective for primary prevention of new-onset AF in patients with HFrEF and/or hypertension.
   2. ACE inhibitors, ARBs, and statins are not effective for the primary prevention of AF in patients without CV disease.

P. AF in Special Populations
   1. Hypertrophic cardiomyopathy
      a. Patients with hypertrophic cardiomyopathy and AF should be anticoagulated, regardless of $CHA_2DS_2$-VASc score.
      b. Amiodarone and disopyramide are commonly used antiarrhythmic agents in patients with hypertrophic cardiomyopathy and are commonly combined with a β-blocker or a non-dihydropyridine CCB.
   2. AF complicating acute coronary syndrome (ACS)
      a. Urgent cardioversion of new-onset AF is recommended for patients with ACS with hemodynamic compromise, ongoing ischemia, or inadequate rate control.
      b. In patients with ACS and no HFrEF, bronchospasm, or hemodynamic instability, intravenous β-blockers are recommended for ventricular rate control.
      c. In patients with ACS and AF whose $CHA_2DS_2$-VASc score is 2 or more, anticoagulation is recommended unless the bleeding risk outweighs the anticipated benefit.
      d. Administration of amiodarone or digoxin may be considered to slow a rapid response in patients with ACS and AF associated with severe HFrEF or hemodynamic instability.
      e. Administration of non-dihydropyridine CCBs may be considered to slow a rapid ventricular response in patients with ACS and AF only in the absence of significant HFrEF or hemodynamic instability.
   3. Hyperthyroidism
      a. β-Blockers should be used for ventricular rate control in patients with AF associated with thyrotoxicosis.
      b. If β-blockers are contraindicated, non-dihydropyridine CCBs are recommended.
   4. Lung disease: Non-dihydropyridine CCBs are preferred for ventricular rate control in patients with AF and COPD.
   5. Wolff-Parkinson-White syndrome (WPW) and other preexcitation syndromes
      a. Intravenous procainamide or ibutilide is preferred for conversion to sinus rhythm in patients with hemodynamically stable AF.
      b. Use of intravenous amiodarone, adenosine, digoxin, diltiazem, or verapamil in patients with WPW and preexcited AF is potentially harmful. These drugs can accelerate the ventricular rate and lead to hemodynamic instability and ventricular fibrillation (VF) in high-risk patients.
   6. HFrEF: See treatment algorithms for managing AF in patients with HFrEF.
   7. Obesity/overweight: For overweight patients and patients with obesity with AF, weight loss combined with risk factor modification is recommended.
   8. AF after cardiac or noncardiac thoracic surgery
      a. Treatment of postoperative AF:
         i. β-Blockers are preferred for the treatment of hemodynamically stable postoperative AF.
         ii. If treatment with a β-blocker is insufficient to control ventricular rate in patients with postoperative AF, a non-dihydropyridine CCB is recommended.
         iii. It is reasonable to restore sinus rhythm with DCC or ibutilide.
         iv. Antithrombotic therapy is reasonable in patients with postoperative AF – Follow recommendations for nonsurgical patients.
         v. If postoperative AF does not convert spontaneously to sinus rhythm during follow-up, ventricular rate control therapy with anticoagulation and conversion to sinus rhythm are recommended.

b. Prophylaxis of postoperative AF (Table 13)
   i. Prophylaxis of postoperative AF should be considered for patients at high risk: patients undergoing valve replacement surgery with or without coronary artery bypass grafting (CABG) surgery; patients undergoing isolated CABG (i.e., CABG without valve surgery) with any of the following risk factors: age older than 65; LV dysfunction and HF; obesity; hypertension; COPD
   ii. Amiodarone administered preoperatively may reduce the risk of postoperative AF in high-risk patients; amiodarone is preferred to sotalol or colchicine.
   iii. Sotalol administered prophylactically may reduce the risk of postoperative AF in high-risk patients. Oral sotalol may be used for AF prophylaxis in patients at high risk of postoperative AF if amiodarone is contraindicated or not desired.
   iv. Colchicine administered postoperatively may reduce the risk of postoperative AF in high-risk patients; the AF guidelines provide no specific recommendations regarding when to use colchicine versus sotalol.

**Table 13.** Selected Studies of Drug Therapy for Prophylaxis of Postoperative AF

| Study/Year | Design | Treatment Arms | Population/Follow-Up | Outcomes/Results |
|---|---|---|---|---|
| Lamb et al., 1988 | Prospective, randomized, controlled, unblinded | Atenolol 50 mg orally daily beginning 72 hr before surgery and continued after surgery<br>Controls untreated with atenolol | n=60 patients undergoing CABG | Incidence of postoperative AF:<br>Atenolol: 3%<br>Control: 37% (p=0.001) |
| Daoud et al., 1997 | Prospective, randomized, double-blind, placebo-controlled | Amiodarone 200 mg orally three times daily for 7 days before surgery<br>Placebo administered orally three times daily for 7 days before surgery | n=124 patients undergoing CABG, valve replacement/repair, or both | Incidence of postoperative AF:<br>Amiodarone: 25%<br>Placebo: 53% (p=0.003)<br>Length of hospital stay:<br>Amiodarone: 6.5 ± 2.6 days<br>Placebo: 7.9 ± 4.3 days (p=0.04)<br>Adverse effects similar in the two groups |
| Gomes et al., 1999 | Prospective, randomized, double-blind, placebo-controlled | Sotalol (mean oral dose 193 ± 43 mg daily) initiated 24–48 hr before surgery<br>Placebo initiated orally 24–48 hr before surgery | n=85 patients undergoing isolated CABG (n=73) or CABG + valve replacement (n=12) | Incidence of postoperative AF:<br>Sotalol: 12.5%<br>Placebo: 38%<br>(p=0.008)<br>No patients had TdP |
| Giri et al. (AFIST), 2001 | Prospective, randomized, double-blind, placebo-controlled | Amiodarone 6–7 g orally over 6–10 days, initiated 1–5 days preoperatively<br>Placebo administered orally same as amiodarone | n=220 patients undergoing CABG, valve replacement/repair, or both | Incidence of postoperative AF:<br>Amiodarone: 22.5%<br>Placebo: 38.0% (p=0.01)<br>Incidence of cerebrovascular accident:<br>Amiodarone: 1.7%<br>Placebo: 7.0% (p=0.04)<br>Adverse effects similar in the two groups |

**Table 13.** Selected Studies of Drug Therapy for Prophylaxis of Postoperative AF *(Cont'd)*

| Study/Year | Design | Treatment Arms | Population/Follow-Up | Outcomes/Results |
|---|---|---|---|---|
| Mitchell et al. (PAPA BEAR), 2005 | Prospective, randomized, double-blind, placebo-controlled | Amiodarone 10 mg/kg orally daily administered 6 days before surgery through 6 days after surgery<br>Placebo administered orally same as amiodarone | n=601 patients undergoing CABG and/or valve replacement/repair | Incidence of postoperative AF:<br>Amiodarone: 16.1%<br>Placebo: 29.5% (p<0.001)<br>Adverse effects requiring discontinuation:<br>Amiodarone: 11.4%<br>Placebo: 5.3% (p=0.008) |
| Tisdale et al., 2009 | Prospective, randomized, unblinded, controlled | IV amiodarone 1050 mg over 24 hr, followed by 400 mg orally twice daily for 6 days or until discharge, whichever was first<br>Controls untreated with amiodarone | n=130 patients undergoing pulmonary resection | Incidence of postoperative AF:<br>Amiodarone: 13.8%<br>Control: 32.3% (p=0.02)<br>Median length of ICU stay:<br>Amiodarone: 46 hr<br>Control: 84 hr (p=0.03)<br>Adverse effects similar in the two groups |
| Imazio et al. (COPPS), 2011 | Prospective, randomized, double-blind, placebo-controlled, multicenter | Colchicine 1 mg orally twice daily on postoperative day 3, followed by maintenance dose of 0.5 mg orally twice daily (patients ≥ 70 kg) or 0.25 mg orally twice daily (patients < 70 kg)<br>Placebo administered orally – Same as colchicine | n=336 patients undergoing cardiac surgery | Incidence of postoperative AF:<br>Colchicine: 12.0%<br>Placebo: 22.0% (p=0.02)<br>Length of hospital stay:<br>Colchicine: 9.4 ± 3.7 days<br>Placebo: 10.3 ± 4.3 days (p=0.04)<br>Adverse effects similar in the two groups |
| Riber et al., 2012 | Prospective, randomized, double-blind, placebo-controlled | IV amiodarone 300 mg over 20 min immediately after surgery, followed by 600 mg orally twice daily for 5 days postoperatively<br>Placebo administered orally same as amiodarone | n=254 patients undergoing pulmonary resection | Incidence of postoperative AF:<br>Amiodarone: 9%<br>Placebo: 32% (p=0.001)<br>Adverse effects similar in the two groups |
| Imazio et al. (COPPS-2), 2014 | Prospective, randomized, double-blind, placebo-controlled, multicenter | Colchicine 0.5 mg orally twice daily (patients ≥ 70 kg) or 0.5 mg once daily (patients < 70 kg) starting 48–72 hr after surgery and continued for 1 mo postoperatively<br>Placebo administered orally same as colchicine | n=360 patients undergoing cardiac surgery | Primary end point: Postpericardiotomy syndrome<br>Colchicine 19.4%<br>Placebo 29.4%<br>Absolute difference 10.0% (95% CI, 1.1%–18.7%)<br>Secondary end point: Incidence of postoperative AF:<br>Colchicine 33.9%<br>Placebo: 41.9%<br>Absolute difference 7.8% (95% CI, -2.2% to 17.6%) |
| Zheng et al. (STICS), 2016 | Prospective, double-blind, randomized, placebo-controlled trial | Rosuvastatin 20 mg once daily or matching placebo administered up to 8 days before surgery and for 5 days thereafter | n=1922 patients undergoing cardiac surgery | Primary end point:<br>Postoperative AF:<br>Rosuvastatin 21%<br>Placebo: 20%<br>(OR 1.04; 95% CI, 0.84–1.30) |

CABG = coronary artery bypass grafting; ICU = intensive care unit; OR = odds ratio.

## V. SUPRAVENTRICULAR TACHYCARDIA

A. Background
   1. Incidence: 35 cases per 100,000 individuals per year
   2. Prevalence: 225 per 100,000 individuals
   3. Around 89,000 new cases annually
   4. Around 570,000 people have SVT in the United States.

B. Definitions
   1. *SVT* is an umbrella term, describing tachyarrhythmias originating above the ventricles, including:
      a. Inappropriate sinus tachycardia
      b. Atrial tachycardia
      c. Junctional tachycardia
      d. AV nodal reentrant tachycardia (AVNRT)
      e. WPW and other accessory pathway–mediated tachyarrhythmias (often called atrioventricular reentrant tachycardia [AVRT])
      f. AF is NOT included under the term *SVT.*
   2. AVNRT makes up about 56% of SVT; AVRT makes up 27%, and atrial tachycardia makes up 17%.
   3. SVT that occurs intermittently with abrupt onset and termination is called paroxysmal SVT.
   4. When SVT occurs, the underlying mechanism is usually not known. Therefore, for acute termination of SVT with intravenous drugs, the current treatment guidelines refer to treatment of SVT of unknown mechanism.

C. Features of AVNRT (Figure 16)
   1. Regular rhythm
   2. P waves visible
   3. Narrow QRS complexes
   4. Heart rate greater than 100 beats/minute at rest
   5. Mechanism of AVNRT: Reentry within AV node, with one slow pathway and one fast pathway

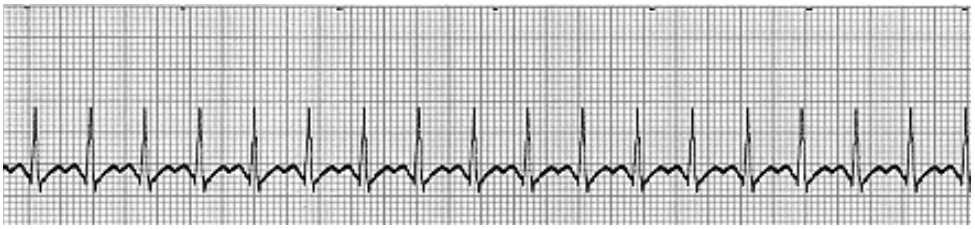

**Figure 16.** Supraventricular tachycardia caused by atrioventricular nodal reentrant tachycardia.



D. Risk Factors for AVNRT
   1. Women have a 2 times higher risk than men.
   2. Individuals older than 65 have a 5 times greater risk than younger individuals.
   3. Often occurs in individuals with no underlying CV disease
   4. In patients with no underlying CV disease, those with SVT are younger (mean age 37 years vs. 69 years) than are patients with CV disease.
   5. In patients with no underlying CV disease, SVT is faster (186 beats/minute vs. 155 beats/minute) than in patients with CV disease.

E. Signs/Symptoms
   1. "Neck-pounding"
   2. Palpitations
   3. Dizziness/lightheadedness
   4. Weakness
   5. Near-syncope
   6. Syncope
   7. Polyuria

F. Goals of SVT Therapy
   1. Terminate SVT; restore sinus rhythm (Tables 14 and 15; Figure 17).
   2. Prevent recurrences (Figure 18).

**Table 14.** Intravenous Drugs Used for Acute Management of SVT of Unknown Mechanism

| Drug | Dose | Adverse Effects | Important Drug Interactions |
|---|---|---|---|
| Adenosine | 6-mg IV rapid bolus, injected into IV as proximal or as close to the heart as possible over 1–2 s, followed by rapid saline flush<br><br>If no response in 1–2 min, 12-mg IV rapid bolus, followed by rapid saline flush<br><br>Can repeat the 12-mg IV dose once | Transient AV block<br>Chest pain<br>Flushing<br>Dyspnea<br>Sinus pauses<br>Bronchospasm (rare)<br>AF can be provoked or can cause decompensation in the presence of preexcitation<br><br>Adverse effects are usually of very short duration because of adenosine's short half-life of ~10 s | Dipyridamole and carbamazepine accentuate response to adenosine: ↓ adenosine dose by 50% |
| Diltiazem[a] | 0.25-mg/kg IV bolus over 2 min, followed by continuous infusion of 5–10 mg/hr, up to maximum of 15 mg/hr | See Table 2 | See Table 2 |
| Verapamil[a] | 5–10 mg (0.075–0.15 mg/kg) IV bolus over 2 min<br><br>If no response, an additional dose of 10 mg (0.15 mg/kg) IV may be administered 30 min later; may then administer 0.005-mg/kg/min continuous infusion | See Table 2 | See Table 2 |
| ß-Blockers | Esmolol: See Table 2<br><br>Propranolol: See Table 2<br><br>Metoprolol: See Table 2 | See Table 2 | See Table 2 |
| Amiodarone | 150 mg IV over 10 min; then 1-mg/min continuous infusion for 6 hr, followed by 0.5-mg/min continuous infusion over remaining 18 hr | See Table 2 | See Table 2 |

[a]Neither diltiazem nor verapamil should be administered to patients with HFrEF.

SVT = supraventricular tachycardia.

**Patient Case**

5. J.M. is a 64-year-old man with no history of CV disease who presents to the ED with palpitations, dizziness, and lightheadedness. His ECG reveals SVT with no evidence of preexcitation. His blood pressure in the ED is 102/80 mm Hg and heart rate is 131 beats/minute. Neither cough nor carotid sinus massage terminate his arrhythmia. In addition, J.M.'s SVT is not responsive to adenosine 6 mg intravenously, followed by two doses of adenosine 12 mg intravenously. Which is the most appropriate treatment?

   A. Digoxin 0.5-mg intravenous bolus; may follow with 0.25 mg intravenously every 6–8 hours up to a maximum cumulative dose of 1 mg over 24 hours.

   B. Diltiazem 0.25-mg/kg intravenous loading dose, followed by a 10-mg/hour continuous intravenous infusion.

   C. Ibutilide 1 mg intravenously, administered over 10 minutes, followed 10 minutes later by a second 1-mg intravenous dose, if necessary.

   D. Procainamide 50 mg/minute intravenous continuous infusion to a total dose of 17 mg/kg, followed by a continuous infusion of 3 mg/minute.

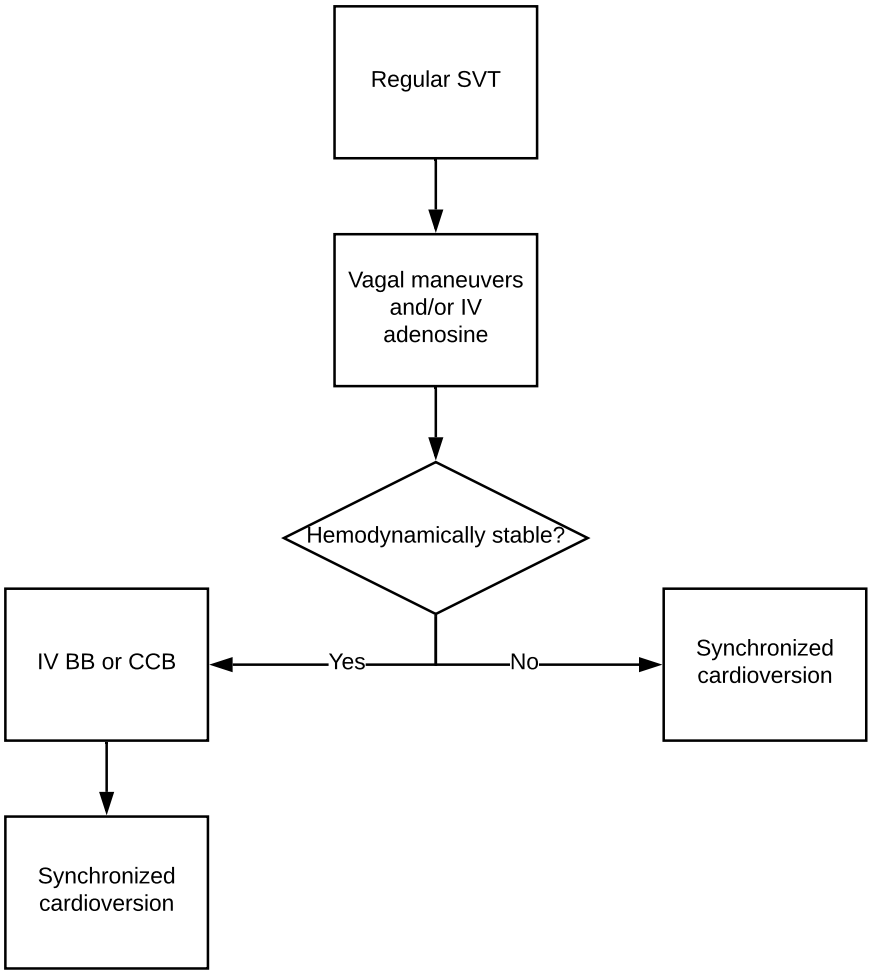


**Figure 17.** Algorithm for acute treatment of supraventricular tachycardia.

BB = beta-blocker; CCB = calcium channel blocker (diltiazem or verapamil); IV = intravenous(ly); SVT = supraventricular tachycardia.

**Patient Case**

6. M.D. is a 75-year-old man with a history of hypertension and HFrEF (LVEF 25%) who had an episode of SVT caused by AVNRT that was terminated with intravenous drug therapy. His current medications include carvedilol 25 mg twice daily, furosemide 40 mg once daily, lisinopril 40 mg once daily, and spironolactone 25 mg once daily. After consultation with his medical team, he has decided not to undergo catheter ablation and prefers to take oral drug therapy to reduce the likelihood of SVT recurrence. His SCr is 1.0 mg/dL. Which is the most appropriate therapy at this time?
   A. Diltiazem CD 240 mg orally once daily.
   B. Dofetilide 500 mcg orally twice daily.
   C. Flecainide 50 mg orally every 12 hours.
   D. Propafenone 150 mg orally every 8 hours.

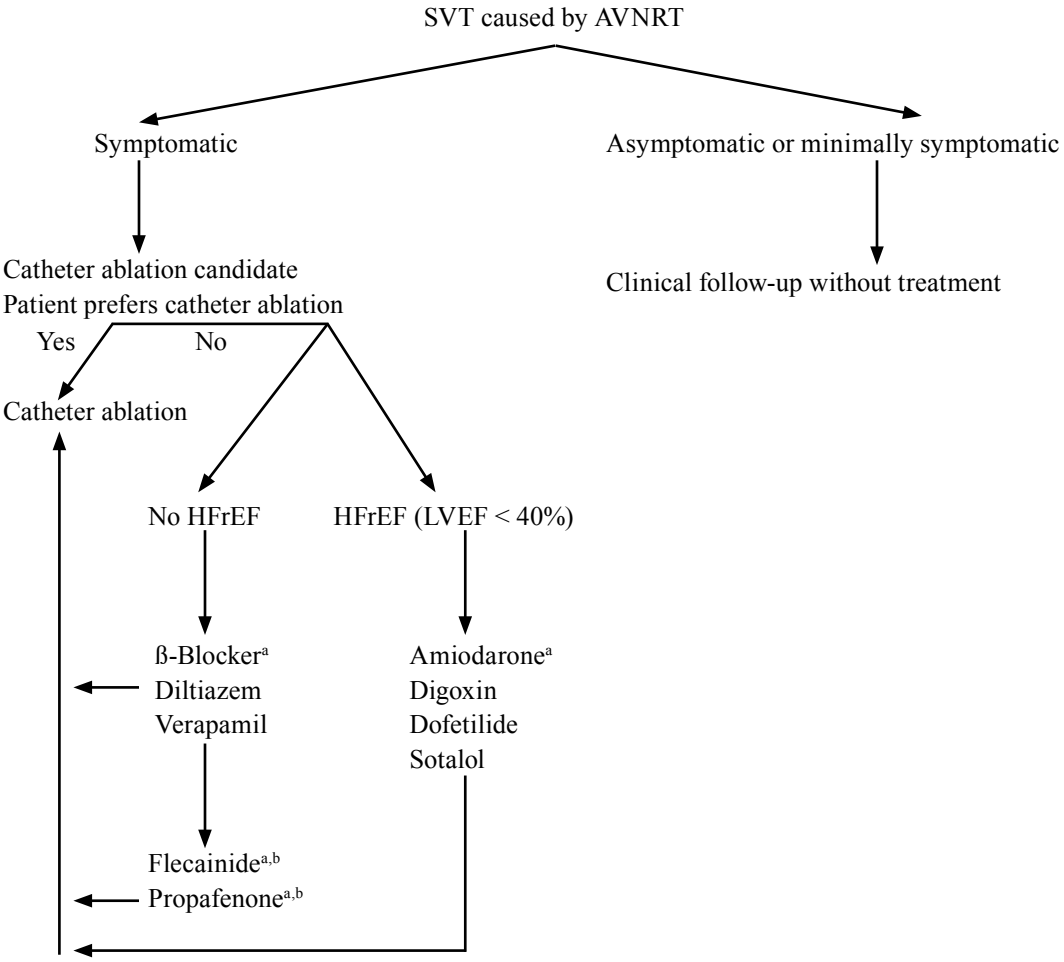


**Figure 18.** Algorithm for preventing recurrence of SVT caused by AVNRT – oral drug therapy.

[a]Drugs are listed in alphabetical order, not order of preference.

[b]Neither flecainide nor propafenone should be used in patients with known CAD or any other form of structural heart disease.

AVNRT = atrioventricular nodal reentrant tachycardia.

**Table 15.** Selected Studies of Drug Therapy for Supraventricular Tachycardia

| Study/Year | Design | Treatment Arms | Population/Follow-Up | Outcomes/Results |
|---|---|---|---|---|
| Cairns et al., 1991 | Prospective, observational | Adenosine IV | n=23 patients admitted to ED with PSVT<br>Two patients excluded after adenosine, found to have other non-SVT arrhythmias | 96% of 24 episodes of SVT in 21 patients converted to sinus rhythm<br>SVT recurred in 57%, managed with other drugs |
| Henthorn et al., 1991 | Prospective, randomized, double-blind, placebo-controlled, crossover | Flecainide dose-ranging phase x 4 wk<br>Then:<br>Flecainide at maximally tolerated dose (maximum 200 mg orally twice daily)<br>Placebo orally twice daily | n=34 patients with PSVT<br>Follow-up = 8 wk | Freedom from symptomatic PSVT events at 60 days:<br>Flecainide: 79%<br>Placebo: 15%<br>(p<0.001)<br>Median time to first symptomatic PSVT event:<br>Flecainide: > 55 days<br>Placebo: 11 days (p<0.001)<br>Median interval between symptomatic PSVT episodes:<br>Flecainide: > 55 days<br>Placebo: 12 days<br>(p<0.001) |
| Gausche et al., 1994 | Prospective case series | Adenosine 12 mg IV, dose repeated if necessary, administered in prehospital setting by paramedic personnel | n=129 patients with PSVT<br>PSVT subsequently confirmed in 79%<br>(AF 12%, sinus tachycardia 5%, atrial flutter 2%) | 85% of patients with PSVT converted to sinus rhythm |
| Wanless et al., 1997 | Prospective, randomized, double-blind, placebo-controlled, multicenter | Sotalol 80 mg orally twice daily<br>Sotalol 160 mg orally twice daily<br>Placebo twice daily | n=126 patients with PSVT<br>n=95 met requirements for primary efficacy analysis | PSVT recurrence:<br>Sotalol 80 mg vs. placebo (RR 0.47; p=0.04)<br>Sotalol 160 mg vs. placebo (RR 0.28; p=0.0009)<br>Sotalol 80 mg vs. 160 mg (RR 0.58; p=0.21) |
| Tendera et al., 2001 | Prospective, randomized, double-blind, placebo-controlled, multicenter | Dofetilide 500 mcg orally twice daily<br>Propafenone 150 mg orally three times daily<br>Placebo | n=122 patients with symptomatic PSVT<br>Treatment period = 6 mo | Probability of remaining free of PSVT episodes at 6 mo:<br>Dofetilide: 50%<br>Propafenone: 54%<br>Placebo: 6%<br>(p<0.01 for dofetilide and propafenone vs. placebo)<br>No proarrhythmias reported with dofetilide<br>n=3 patients discontinued propafenone because of adverse effects |

**Table 15.** Selected Studies of Drug Therapy for Supraventricular Tachycardia *(Cont'd)*

| Study/Year | Design | Treatment Arms | Population/Follow-Up | Outcomes/Results |
|---|---|---|---|---|
| Lim et al., 2009 | Prospective, randomized, controlled, unblinded | Adenosine 6 mg IV, followed, if necessary, by 12 mg IV<br>Slow IV infusion of CCBs (verapamil 1mg/min up to maximum dose of 20 mg or diltiazem 2.5 mg/min to maximum dose of 50 mg) | n=206 patients with SVT | Conversion to sinus rhythm:<br>Adenosine: 86.5%<br>CCBs: 98% (p=0.002) |

CCBs = Calcium channel blockers; IV = Intravenous; PSVT = paroxysmal supraventricular tachycardia; RR = Relative risk.

E. Wolff-Parkinson-White Syndrome
   2. Background
      a. A type of SVT that results in AVRT (not to be confused with AVNRT)
      b. Prevalence: 0.11% of males and 0.04% of females
      c. Prevalence of preexcitation on ECGs in the general population: 0.1%–0.3%
      d. 10-year risk of rapid accessory pathway conduction during AF resulting in sudden cardiac death (SCD): 0.15%–0.24%
      e. Risk of SCD caused by WPW is greatest during the first 2 decades of life.
   3. Definitions
      a. WPW is characterized by documented SVT in a patient with ventricular preexcitation during sinus rhythm.
      b. Preexcitation: An ECG pattern representing the existence of an accessory conduction pathway connecting the atrium to the ventricle. Preexcitation over the accessory pathway competes with conduction through the AV node.
      c. Characteristic ECG pattern of preexcitation
         i. Short PR interval
         ii. Delta wave (slurring of the upstroke of the QRS complex) (Figure 19)
         iii. Not all patients with preexcitation on the ECG develop WPW.
      d. Orthodromic versus antidromic
         (see http://christem.com/acmcem-conf-notes/2016/12/26/conference-notes-12-14-2016-12-21-2016):
         i. Orthodromic: Reentrant impulse travels antegrade (atrium to ventricle) down the AV node and retrograde (ventricle to atrium) up the accessory pathway.
         ii. Antidromic: Reentrant impulse travels antegrade (atrium to ventricle) down the accessory pathway and retrograde (ventricle to atrium) up the AV node.
         iii. Orthodromic AVRT represents 90%–95% of AVRT in patients with accessory pathways, whereas antidromic AVRT represents 5%–10%.

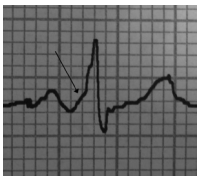

**Figure 19.** Delta wave – slurring of the upstroke of the QRS complex, representing ventricular preexcitation.

Information from: Heilman J. Willscrlt/commons/Credits/Citations. Wikimedia Commons. November 27, 2009. Available at https://commons.wikimedia.org/wiki/File:DeltaWave09.JPG.

4. Features of WPW
    a. AF is common in patients with WPW.
    b. Patients may develop rapid conduction over the accessory pathway and life-threatening ventricular arrhythmias during AF, which can result in SCD.
5. Risk assessment in patients with WPW:
    a. Many asymptomatic patients with preexcitation on the ECG undergo observation, without further evaluation or treatment.
    b. Noninvasive testing, including exercise testing in sinus rhythm and ambulatory ECG monitoring, is useful in risk stratification of some asymptomatic patients with delta waves on ECG.
    c. Noninvasive testing, including exercise testing in sinus rhythm and ambulatory ECG monitoring, is useful in risk stratification and is recommended in patients who have had symptoms associated with WPW.
    d. Electrophysiology studies are sometimes used in asymptomatic patients with preexcitation on the ECG to assess the inducibility of life-threatening arrhythmias.
    e. Electrophysiology studies are recommended in symptomatic patients with preexcitation on the ECG to assess the inducibility of life-threatening arrhythmias.
6. Caution regarding use of specific antiarrhythmic drugs in patients with WPW
    a. In patients with WPW with antidromic AVRT, or in those for whom orthodromic versus antidromic has not been established (which is quite common), many drugs can accelerate antegrade conduction down the accessory pathway and accelerate ventricular rate in patients. The following drugs can be dangerous and should be avoided in these patients:
        i. Adenosine
        ii. β-Blockers
        iii. Diltiazem
        iv. Verapamil
        v. Digoxin
        vi. Amiodarone
    b. Drugs safe to use in patients with WPW:
        i. Ibutilide
        ii. Procainamide
7. Management of WPW
    a. Catheter ablation of the accessory pathway is the recommended strategy.
    b. For patients with preexcitation who develop rapid AF or AVNRT requiring treatment: Ibutilide or procainamide is preferred.

## VI. PREMATURE VENTRICULAR COMPLEXES (PVCs)

A. Background
    1. In a Holter monitor (ambulatory ECG) study of individuals without HF, 0.011% of all heartbeats were PVCs.
    2. Prevalence of PVCs in healthy population: 0.8%
    3. Prevalence of PVCs according to age:
        a. Younger than 20 years: 0.6%
        b. Older than 50: 2.7%
    4. In middle-aged men with and without heart diseases, 62% had at least one PVC on a 6-hour cardiac recording.
    5. PVCs occur in about 50% of all people during long-term monitoring.

B. Features
   1. Wide QRS complexes
   2. Types:
      a. Simple – Isolated single PVCs
      b. Frequent/repetitive forms:
         i. Pairs of PVCs, known as couplets
         ii. PVC occurring every second beat: Bigeminy
         iii. PVC occurring every third beat: Trigeminy
         iv. PVC occurring every fourth beat: Quadrigeminy
         v. Frequent: At least one PVC on a 12-lead ECG or more than 30 PVCs per hour

C. Etiologies/Risk Factors
   1. CAD (including MI)
   2. Anemia
   3. Hypoxia
   4. Cardiac surgery

D. Symptoms
   1. Usually asymptomatic
   2. Frequent/repetitive PVCs can result in:
      a. Palpitations
      b. Dizziness/lightheadedness

E. Prognostic Implications
   1. 30 or younger: PVCs carry no prognostic significance.
   2. Older than 30: PVCs influence long-term risk.
   3. PVCs occurring during exercise may be associated with an increased long-term risk of mortality, but data are conflicting.
   4. In the general population, frequent PVCs are associated with an increased risk of CV disease and mortality.
   5. Very frequent PVCs (more than 10,000–20,000 per day) are associated with PVC-induced cardiomyopathy.
   6. In patients with established CAD, PVCs are associated with an increased risk of mortality.
   7. In survivors of MI, frequent/repetitive forms of PVCs are associated with an increased risk of SCD, which is increased further in patients who also have HF.

F. Treatment
   1. Asymptomatic PVCs should not be treated.
      a. No evidence that suppression of asymptomatic PVCs reduces the risk of mortality or SCD
      b. Antiarrhythmic drug therapy is not recommended for the management of asymptomatic PVCs. Evidence shows that suppression of asymptomatic PVCs with sodium channel blocking antiarrhythmic drugs actually increases mortality (Table 16).
   2. In patients with symptomatic PVCs who do not have structural heart disease, β-blockers or non-dihydropyridine CCBs reduce recurrent arrhythmias and improve symptoms.
   3. In patients with symptomatic PVCs who do not have structural heart disease, an antiarrhythmic medication is reasonable to reduce recurrent symptomatic PVCs and improve symptoms if β-blockers or non-dihydropyridine CCBs are ineffective or poorly tolerated.
   4. Patients with frequent symptomatic PVCs (generally greater than 15% of beats and predominantly of one morphology) that are unresponsive to antiarrhythmic medications (including β-blockers and non-dihydropyridine CCBs), who are intolerant of antiarrhythmic drug therapy, or who do not desire long-term drug therapy can be treated with catheter ablation.

5. For patients with PVC-induced cardiomyopathy, drug therapy (β-blockers, amiodarone) is reasonable to reduce recurrent arrhythmias and improve symptoms and LV function.

**Table 16.** Studies of Antiarrhythmic Drug Therapy for Suppression of Asymptomatic PVCs – Effect on Patient Outcomes

| Study/Year | Design | Treatment Arms | Population/Follow-Up | Outcomes/Results |
|---|---|---|---|---|
| Echt et al. (CAST), 1991 | Initial open-label titration period to identify patients who responded to one of the study drugs with ≥ 80% suppression of PVCs or 90% suppression of runs of VT<br>Then:<br>Patients in whom arrhythmias were suppressed were enrolled in the main study:<br>Prospective, randomized, double-blind, placebo-controlled, multicenter | Encainide 35–50 mg twice daily<br>Flecainide 100–150 mg twice daily<br>Moricizine (used only as a second drug in patients with LVEF ≥ 30%) 200–250 mg three times daily<br>Placebo matched to antiarrhythmic drug selected | n=1498 patients who were 6 days to 2 yr post-MI, had ≥ 6 PVCs/hr on Holter monitor, no runs of VT ≥ 15 beats at a rate of ≥ 120 beats/min, and LVEF ≤ 55%<br>Mean follow-up = 10 mo | Study discontinued prematurely because of excess deaths in the drug treatment groups<br>Mortality:<br>Encainide or flecainide: 8.3%<br>Placebo: 3.5% (p=0.001)<br>Moricizine results not reported in this paper, but were reported in CAST II (see next entry in table) |
| Cardiac Arrhythmia Suppression Trial II Investigators (CAST II), 1992 | 2-wk controlled trial of early effects of low-dose moricizine<br>Then:<br>Prospective, randomized, double-blind, placebo-controlled, multicenter | 2-wk phase:<br>Moricizine 200 mg three times daily<br>Placebo<br>Long-term phase:<br>Moricizine 200–300 mg three times daily<br>Placebo | 14-day exposure phase: 1325 patients<br>Long-term phase: 1155 patients<br>All patients were 4 days to 90 days post-MI, had ≥ 6 PVCs/hr on Holter monitor, no runs of VT ≥ 30 s at a rate of ≥ 120 beats/min, and LVEF ≤ 40%<br>Long-term phase follow-up = 18 mo | Study discontinued prematurely because of excess mortality in moricizine group during first 14 days<br>Mortality during first 14 days:<br>Moricizine: 2.6%<br>Placebo: 0.45%<br>(p<0.02)<br>Mortality during long-term phase:<br>Moricizine: 8.4%<br>Placebo: 7.3%<br>(p=NS) |

**Table 16.** Studies of Antiarrhythmic Drug Therapy for Suppression of Asymptomatic PVCs – Effect on Patient Outcomes *(Cont'd)*

| Study/Year | Design | Treatment Arms | Population/Follow-Up | Outcomes/Results |
|---|---|---|---|---|
| Teo et al., 1993 | Meta-analysis of all completed, published or unpublished randomized parallel trials that evaluated the effects of prophylactic therapy with antiarrhythmic agents on mortality after acute MI | Class I antiarrhythmic agents, β-blockers, CCBs, and amiodarone<br><br>Control | n=98,000 patients from 138 trials | Mortality:<br><br>Class I antiarrhythmic agents: 5.6%<br>Control: 5.0%<br>(OR 1.14; 95% CI, 1.01–1.28; p=0.03)<br><br>β-Blockers: 5.4%<br>Control: 6.5%<br>(OR 0.81; 95% CI, 0.75–0.87; p<0.00001)<br><br>CCBs: 9.7%<br>Control: 9.3%<br>(OR 1.04; 95% CI, 0.95–1.14; p=NS)<br><br>Amiodarone: 9.9%<br>Control: 13.0%<br>(OR 0.71; 95% CI, 0.51–0.97; p=0.03) |

PVC = premature ventricular complex.

## VII. VENTRICULAR TACHYCARDIA

A. Background
   1. This section addresses ventricular tachycardia (VT) with a pulse. Pulseless VT will be addressed in the "Cardiovascular Emergencies" chapter.
   2. The prevalence of monomorphic VT in the United States is unknown.
   3. Up to 20% of patients with an acute MI have ventricular arrhythmias.
   4. 2%–4% of patients with an acute MI develop VT during hospitalization.

B. Features (Figure 20)
   1. Defined as three or more consecutive ventricular complexes at a rate of greater than 100 beats/minute
   2. Nonsustained VT: 3 beats or more and terminates spontaneously
   3. Sustained VT lasts more than 30 seconds or requires termination because of hemodynamic instability in less than 30 seconds.
   4. Morphology:
      a. Monomorphic: Single, consistent QRS morphology
      b. Polymorphic: Changing or multiform QRS morphology (e.g., torsades de pointes, covered in another chapter)
   5. Sustained monomorphic VT in patients with no structural heart disease is called idiopathic VT.
   6. Idiopathic VT sometimes responds to verapamil (known as "verapamil-sensitive VT") and has a characteristic ECG presentation.
   7. Idiopathic VT may also occur in the right ventricular or LV outflow tracts (known as "outflow tract VT").

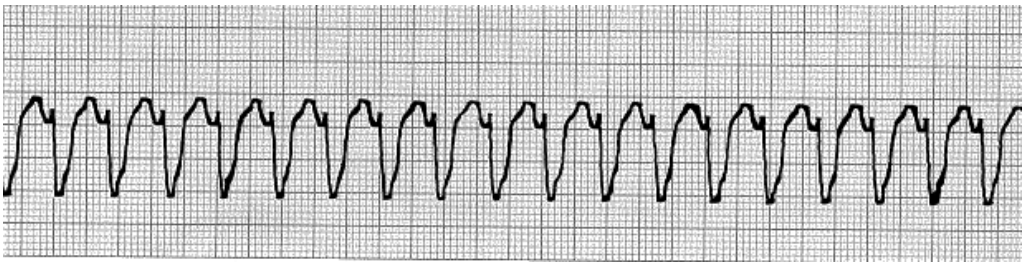

**Figure 20.** Monomorphic ventricular tachycardia.

Reprinted with permission from: Tisdale JE. Review of cardiac arrhythmias and rhythm interpretation. In: Wiggins BS, Sanoski CA, eds. Emergency Cardiovascular Pharmacotherapy. A Point-of-Care Guide. Bethesda, MD: ASHP, 2012:13-48. Copyright© 2012.

C. Etiologies/Risk Factors
   1. CAD (including MI)
   2. HFrEF
   3. Electrolyte abnormalities (hypokalemia, hypomagnesemia)
   4. Drugs (flecainide, propafenone, digoxin)

D. Signs/Symptoms
   1. May be asymptomatic (nonsustained VT)
   2. Palpitations
   3. Dizziness/lightheadedness
   4. Hypotension
   5. Syncope
   6. Angina
   7. Syndrome of SCD: Sustained VT may degenerate into VF, leading to SCD.

E. Goals of Treatment
   1. Terminate VT; restore sinus rhythm (Tables 17 and 18; Figure 21).
   2. Prevent VT recurrence.
   3. Reduce the risk of SCD.

**Patient Case**

*Questions 7 and 8 pertain to the following case.*

7. A.B. is a 65-year-old woman who was admitted to the cardiac ICU today with palpitations and lightheadedness. Her echocardiogram reveals an LVEF of 30%. A.B. also has a history of myocardial infarction, hypertension, and dyslipidemia. Her SCr is 1.0 mg/dL, and she weighs 57 kg. While in the cardiac ICU, she has dizziness and palpitations, and her blood pressure is 95/68 mm Hg. Her ECG reveals monomorphic VT at a rate of 125 beats/minute, which lasts longer than 30 seconds and does not terminate on its own. Which is the most appropriate treatment?

   A. Intravenous amiodarone 150 mg over 10 minutes, followed by 1 mg/minute x 6 hours; then 0.5 mg/minute for 18 hours.

   B. Intravenous lidocaine 1.0-mg/kg intravenous bolus, followed by 0.50- to 0.75-mg/kg intravenous boluses, to a total loading dose of 3 mg/kg; then a continuous intravenous infusion of 2 mg/minute.

   C. Procainamide 50-mg/minute intravenous continuous infusion to a total dose of 17 mg/kg, followed by a continuous infusion of 3 mg/minute.

   D. Sotalol 75 mg intravenously every 12 hours

**Table 17.** Drugs for Acute Termination of Hemodynamically Stable VT

| Drug | Loading Dose | Maintenance Dose | Adverse Effects | Important Drug Interactions |
|---|---|---|---|---|
| Procainamide | IV: 20- to 50-mg/min continuous infusion until one of the following:<br>hypotension occurs; arrhythmia is suppressed; QRS duration ↑ 50% beyond pretreatment value; or total dose of 17 mg/kg administered | IV: 1- to 4-mg/min continuous infusion | Hypotension<br>QT interval prolongation<br>TdP | Cimetidine, ranitidine, and trimethoprim may ↑ concentrations by inhibiting renal organic cationic transport |
| Amiodarone | IV: 150 mg over 10 min | IV: 1-mg/min continuous infusion for 6 hr, then 0.5 mg/min for 18 hr | AV block<br>Bradycardia<br>Hypotension<br>Phlebitis | CYP3A4 inhibitors may ↑ concentrations<br>Inhibits CYP1A2, CYP2C9, CYP2D6, and CYP3A4: ↑ warfarin and statin (some) concentrations<br>Inhibits P-gp: ↑ digoxin concentrations |
| Sotalol | IV: 75 mg every 12 hours | | Hypotension<br>Bradycardia<br>QT interval prolongation<br>TdP | May contribute additive effect with other drugs that prolong the QT interval or cause sinus bradycardia or AV block |
| Lidocaine | IV: 1–1.5 mg/kg<br>If VT persists, additional doses of 0.5–0.75 mg/kg IV may be administered every 5–10 min up to a maximum cumulative dose of 3 mg/kg | 1- to 4-mg/min continuous IV infusion<br>Dose in patients with HFrEF should be ↓ to 1–2 mg/min | Slurred speech<br>Diminished consciousness<br>Seizures<br>Bradycardia | β-Blockers ↓ lidocaine clearance by reduced hepatic blood flow<br>Rifampin ↑ lidocaine clearance by induction of CYP1A2 |

VT = ventricular tachycardia.

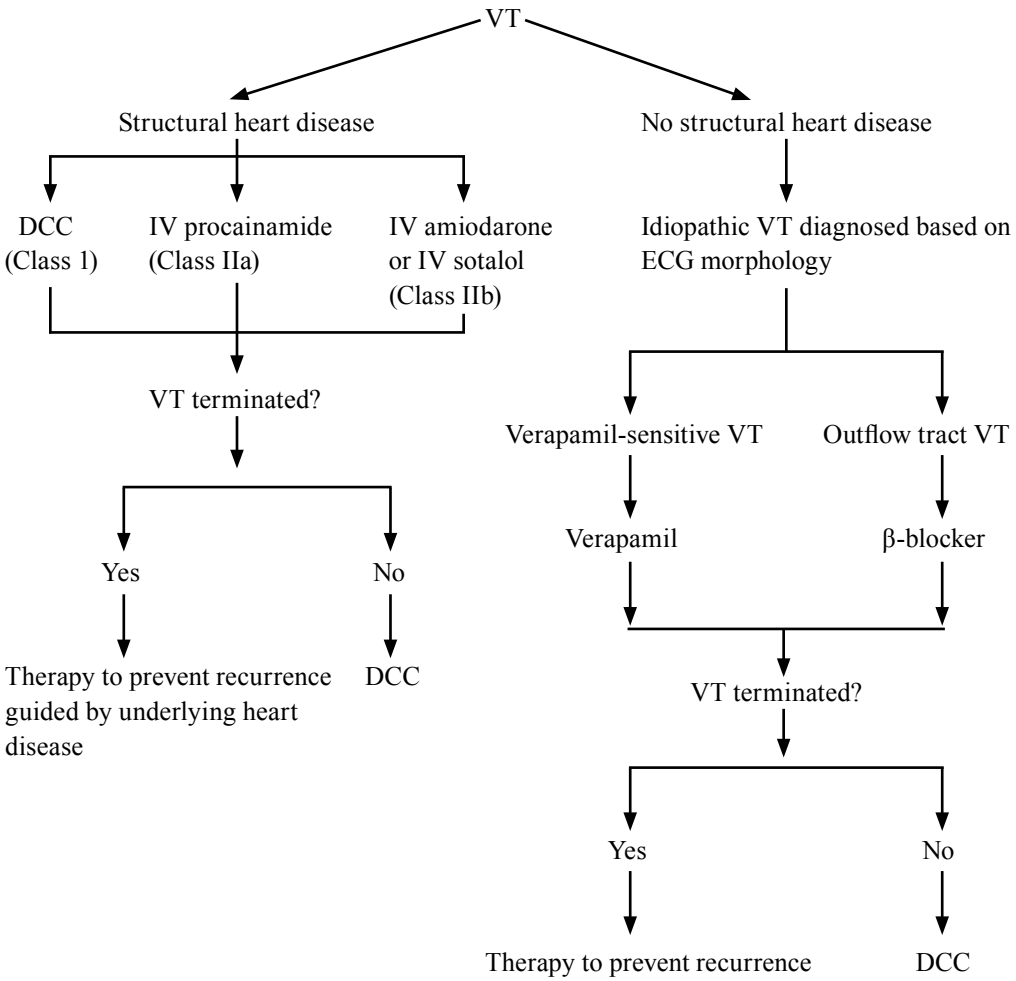


**Figure 21.** Treatment algorithm for acute termination of hemodynamically stable monomorphic ventricular tachycardia.

VT = ventricular tachycardia.

Reference: Al-Khatib SM, Stevenson WG, Ackerman MJ, et al. 2017 AHA/ACC/HRS guideline for management of patients with ventricular arrhythmias and the prevention of sudden cardiac death. Circulation 2018;138:e272-e391.

**Table 18.** Selected Studies of Drug Therapy for Terminating VT

| Study/Year | Design | Treatment Arms | Population/Follow-Up | Outcomes/Results |
|---|---|---|---|---|
| Ho et al., 1994 | Prospective, randomized, double-blind, controlled | Sotalol 100 mg IV administered over 5 min<br>Lidocaine 100 mg IV administered over 5 min<br>Unresponsive patients after 15 min could be crossed over to the alternative therapy | n=33 patients with spontaneous VT not causing cardiac arrest | Termination of VT (intention-to-treat):<br>Sotalol: 69%<br>Lidocaine: 18% (p=0.03)<br>Termination of VT by analysis of n=31 patients with subsequent electrophysiologically proven VT:<br>Sotalol: 69%<br>Lidocaine: 20% (p=0.006) |
| Scheinman et al., 1995 | Prospective, randomized, double-blind, multicenter | Amiodarone 125 mg IV over 24 hr<br>Amiodarone 500 mg IV over 24 hr<br>Amiodarone 1000 mg IV over 24 hr<br>Supplemental dose of amiodarone 150 mg IV could be administered for breakthrough arrhythmias | n=342 patients with refractory, hemodynamically destabilizing VT or VF | Median number of VT events/hr over 24 hr:<br>125 mg: 1.68<br>500 mg: 0.96<br>1000 mg: 0.48<br>(p=NS)<br>Median time to first VT event:<br>125 mg: 9.8 hr<br>500 mg: Not reported<br>1000 mg: 13.7 hr<br>(p=0.02)<br>Hypotension:<br>125 mg: 24%<br>500 mg: 27%<br>1000 mg: 26% |
| Gorgels et al., 1996 | Prospective, randomized, unblinded, controlled | Procainamide 10 mg/kg IV at 100 mg/min<br>Lidocaine 1.5 mg/kg IV administered over 2 min<br>Unresponsive patients (within 15 min) could be crossed over to the alternative therapy | n=29 patients with spontaneous monomorphic VT | Termination of VT within 15 min:<br>Procainamide: 80.0%<br>Lidocaine: 21.4%<br>(p<0.01)<br>Accounting for patients crossed over to alternative therapy, proportion of total VT episodes terminated by drugs:<br>Procainamide: 79.2%<br>Lidocaine: 19.4%<br>(p<0.001) |
| Somberg et al., 2002 | Prospective, randomized, double-blind, controlled | Amiodarone (aqueous) up to two IV boluses of 150 mg, followed by 600 mg by continuous IV infusion over 24 hr<br>Lidocaine up to two IV boluses of 100 mg, followed by a 2-mg/min continuous IV infusion over 24 hr | n=29 patients with VT at a rate ≥120 beats/min and refractory to DCC | Immediate termination of VT:<br>Amiodarone: 78%<br>Lidocaine: 27%<br>(p<0.05)<br>Free of VT at 1 hr:<br>Amiodarone: 67%<br>Lidocaine: 9%<br>(p<0.01)<br>Hypotension:<br>Amiodarone: 7%<br>Lidocaine: 28%<br>(p=0.06) |

**Table 18.** Selected Studies of Drug Therapy for Terminating VT *(Cont'd)*

| Study/Year | Design | Treatment Arms | Population/Follow-Up | Outcomes/Results |
|---|---|---|---|---|
| Ortiz et al., 2016 | Prospective, randomized, open-label | Procainamide 5 mg/kg over 20 min or amiodarone 10 mg/kg over 20 min | n=62 patients with regular wide-complex VT > 120 beats/min and systolic blood pressure > 90 mm Hg | Primary end point:<br>Major cardiac adverse events:<br>Procainamide: 9%<br>Amiodarone: 41%<br>(p=0.006)<br><br>Termination of tachyarrhythmia:<br>Procainamide: 67%<br>Amiodarone: 38%<br>(p=0.026) |

VF = ventricular fibrillation.

**Patient Case**

8. A.B. has her VT terminated by drug therapy. Her medical team ascertains that she is at an increased risk of recurrent VT and SCD. Which treatment option is best to reduce her risk of SCD?
   A. Amiodarone 400 mg orally once daily.
   B. Sotalol 80 mg orally twice daily.
   C. Implantation of an ICD.
   D. Implantation of a permanent pacemaker.

**Table 19.** Therapeutic Options for Prevention of Recurrence of VT and/or Prevention of SCD

| Therapy | Mechanism | Maintenance Dose | Adverse Effects | Drug Interactions |
|---|---|---|---|---|
| ICD | Inserted percutaneously like a pacemaker<br><br>Leads implanted directly onto heart (exception: subcutaneous ICD)<br><br>Delivers electric shock to heart if VT develops | — | Discomfort with shock | — |
| Amiodarone | Sometimes used in patients with ICD to reduce the frequency of shocks and prolong battery life | 400 mg orally daily | As described previously | As described previously |
| Mexiletine | Sometimes used in conjunction with amiodarone to reduce the risk of ICD shocks | 150–200 mg every 8–12 hr | Tremors, nausea, vomiting, ataxia | CYP1A2 and CYP2D6 inhibitors can increase mexiletine concentrations |

**Table 19.** Therapeutic Options for Prevention of Recurrence of VT and/or Prevention of SCD *(Cont'd)*

| Therapy | Mechanism | Maintenance Dose | Adverse Effects | Drug Interactions |
|---|---|---|---|---|
| Sotalol | Sometimes used in patients with ICDs to reduce the frequency of shocks and prolong battery life | 80 mg orally twice daily. May be increased in increments of 80 mg/day every 3 days provided the QTc < 500 ms. Most patients have satisfactory response at 120 mg twice daily.<br>Recommended dosing intervals for patients with kidney disease:<br>CrCl > 60 mL/min, every 12 hr<br>CrCl 30–59 mL/min, every 24 hr<br>CrCl 10–29 mL/min, every 36–48 hr<br>CrCl < 10 mL/min, contraindicated | As described previously | — |
| Catheter ablation | Recommended for patients with prior MI and recurrent episodes of VT who present with VT or VF storm who are intolerant of amiodarone or other antiarrhythmic medication or for whom amiodarone or other antiarrhythmic therapy has failed | — | Tamponade | — |

F. Reducing the Risk of SCD in Patients with Recurrent VT:
   1. Many studies have shown that implantable cardioverter-defibrillators (ICDs) are more effective than antiarrhythmic therapy with amiodarone or sotalol for reducing the risk of SCD.
   2. ICD is the treatment of choice for reducing the risk of SCD caused by recurrent VT.
   3. In patients with ischemic heart disease and recurrent ventricular arrhythmias with significant symptoms or ICD shocks despite optimal device programming and ongoing treatment with a β-blocker, amiodarone or sotalol is useful to suppress recurrent ventricular arrhythmias. In the OPTIC trial (see Table 20), amiodarone combined with a β-blocker was more effective than a β-blocker alone and sotalol alone.

**Table 20.** Selected Studies of Strategies to Reduce the Risk of SCD and Decrease the Recurrence of VT

| Study/Year | Design | Treatment Arms | Population/Follow-Up | Outcomes/Results |
|---|---|---|---|---|
| Moss et al. (MADIT), 1996 | Prospective, randomized, unblinded, controlled, multicenter | ICD implantation<br>Conventional medical therapy (choice of therapy, including whether to use antiarrhythmic drugs, was left to each patient's attending physician) | n=196 patients with NYHA class I–III HF, a documented episode of nonsustained VT, and nonsuppressible VT during electrophysiologic study<br>Average follow-up = 27 mo | Mortality:<br>ICD: 15.8%<br>Conventional medical therapy: 38.6%<br>(p=0.009) |

**Table 20.** Selected Studies of Strategies to Reduce the Risk of SCD and Decrease the Recurrence of VT *(Cont'd)*

| Study/Year | Design | Treatment Arms | Population/Follow-Up | Outcomes/Results |
|---|---|---|---|---|
| Antiarrhythmics vs. Implantable Defibrillators (AVID) Investigators, 1997 | Prospective, randomized, unblinded, controlled, multicenter | ICD implantation<br>Antiarrhythmic drug therapy (primarily amiodarone) | n=1016 patients who presented with VT or VF<br>Follow-up = 3 yr | Overall survival at 3 yr:<br>ICD: 75.4%<br>Antiarrhythmic drugs: 64.1% (p<0.02) |
| Connolly et al. (CIDS), 2000 | Prospective, randomized, unblinded, controlled, multicenter | ICD implantation<br>Amiodarone ≥ 1200 mg/day x 1 wk; then ≥ 400 mg/day x 10 wk; then ≥ 300 mg/day | n=659 patients with resuscitated VT or VF<br>Mean follow-up = 2.9 yr (amiodarone); 3 yr (ICD) | Annual risk of SCD:<br>ICD: 8.3%/yr<br>Amiodarone: 10.2%/yr (p=0.14)<br>Annual risk of arrhythmic death:<br>ICD: 3.0%/yr<br>Amiodarone: 4.5%/yr (p=NS) |
| Buxton et al. (MUSTT), 1999 | Prospective, randomized, unblinded, controlled, multicenter | Electrophysiology study-guided ICD implantation<br>Electrophysiology study-guided antiarrhythmic drug therapy (class I drugs 58%, amiodarone 22%, sotalol 20%)<br>No ICD or antiarrhythmic drug therapy | n=704 patients with CAD, asymptomatic nonsustained VT, LVEF ≤ 40%, and inducible sustained ventricular tachyarrhythmias during electrophysiology study<br>Median follow-up = 39 mo | 5-yr Kaplan-Meier estimates of incidence of cardiac arrest or death from arrhythmia:<br>Electrophysiology study-guided ICD or antiarrhythmic drug therapy: 25%<br>No ICD or antiarrhythmic drugs therapy: 35%<br>(RR 0.73; 95% CI, 0.53–0.99)<br>ICD vs. antiarrhythmic drug therapy (RR 0.24; 95% CI, 0.13–0.45; p<0.001) |
| Moss et al. (MADIT-II), 2002 | Prospective, randomized, unblinded, controlled, multicenter | ICD implantation<br>Conventional medical therapy | n=1232 patients with prior MI and LVEF ≤ 30%<br>Average follow-up = 20 mo | Death from any cause:<br>ICD: 14.2%<br>Conventional medical therapy: 19.8%<br>(p=0.016) |
| Bardy et al. (SCD-HeFT), 2005 | Prospective, randomized, controlled, double-blind (amiodarone vs. placebo groups), multicenter | Conventional therapy for HF plus:<br>ICD implantation<br>Amiodarone 800 mg daily x 1 wk; then 400 mg daily for 3 wk; then 200–400 mg daily (dose selected according to weight)<br>Placebo administered same as amiodarone | n=2521 patients with NYHA class II and III HF and LVEF ≤ 35%<br>Median follow-up = 45.5 mo | Total mortality:<br>ICD: 22%<br>Amiodarone: 28%<br>Placebo: 29%<br>ICD vs. placebo (p=0.007)<br>Amiodarone vs. placebo (p=NS) |

**Table 20.** Selected Studies of Strategies to Reduce the Risk of SCD and Decrease the Recurrence of VT *(Cont'd)*

| Study/Year | Design | Treatment Arms | Population/Follow-Up | Outcomes/Results |
|---|---|---|---|---|
| Connolly et al. (OPTIC), 2006 | Prospective, randomized, unblinded, controlled, multicenter | β-Blocker (metoprolol 100 mg/day, carvedilol 50 mg/day or bisoprolol 10 mg/day)<br><br>Amiodarone (400 mg twice daily x 2 wk, then 400 mg once daily x 4 wk; then 200 mg daily) + β-blocker<br><br>Sotalol 240 mg daily in two or three divided doses (160 mg daily if CrCl 30–60 mL/min/1.73 $m^2$) | n=412 patients who had received an ICD within 21 days for inducible or spontaneously occurring VT or VF<br><br>Median follow-up = 359 days | ICD shock for any reason:<br>β-Blocker: 38.5%<br>Amiodarone + β-blocker: 10.3%<br>Sotalol: 24.3%<br><br>Amiodarone + β-blocker vs. β-blocker alone (p<0.001)<br><br>Amiodarone + β-blocker vs. sotalol (p=0.02)<br><br>Sotalol vs. β-blocker: (p=NS)<br><br>Rates of study drug discontinuation at 1 yr:<br>Amiodarone: 18.2%<br>Sotalol: 23.5%<br>β-Blocker alone: 5.3%<br>(p value not provided) |
| Sapp et al. (VANISH), 2016 | Prospective, randomized, unblinded, controlled, multicenter | Catheter ablation with continuation of baseline antiarrhythmic therapy<br><br>Escalation of antiarrhythmic therapy (amiodarone or amiodarone + mexiletine, depending on baseline therapy) | 259 patients who had a history of myocardial infarction, had an ICD, and had an episode of VT during treatment with amiodarone or another class I or class III antiarrhythmic drug within the previous 6 mo<br><br>Median follow-up: 23 mo | Primary outcome: Composite of death or VT storm (three or more documented episodes of VT within 24 hr) or appropriate ICD shock after a 30-day treatment:<br><br>Catheter ablation: 59.1%<br>Drug escalation: 68.5%<br>(HR 0.72; 95% CI, 0.53–0.98; p=0.04)<br><br>Primary outcome according to receipt of amiodarone at baseline:<br>Receiving amiodarone:<br>Catheter ablation: 61.2%<br>Drug escalation: 77.4%<br>(HR 0.55; 95% CI, 0.38–0.80; p=0.001)<br><br>Not receiving amiodarone:<br>Catheter ablation: 55.3%<br>Drug escalation: 51.2%<br>(HR 1.14; 95% CI, 0.65–2.02; p=0.64) |

CAD = coronary artery disease; NYHA = New York Heart Association.

G. Current Recommendations for ICD Therapy
   1. Class I recommendations
      a. Patients with CAD who either survive sudden cardiac arrest caused by VT/VF or have hemodynamically unstable VT or stable VT not the result of reversible causes, and in whom meaningful survival of greater than 1 year is expected
      b. Patients with CAD and unexplained syncope who have inducible sustained monomorphic VT on electrophysiology study, and in whom meaningful survival of greater than 1 year is expected

c. Patients with an LVEF of 35% or less because of CAD who are at least 40 days post-MI and at least 90 days post-revascularization and have NYHA class II or III HF despite guideline-directed medical therapy, and in whom meaningful survival of greater than 1 year is expected
d. Patients with an LVEF of 30% or less because of CAD who are at least 40 days post-MI and at least 90 days post-revascularization, and have NYHA class I HF despite guideline-directed medical therapy, and in whom meaningful survival of greater than 1 year is expected
e. Patients with nonsustained VT because of a prior MI, an LVEF of 40% or less, and inducible sustained VT or VF at electrophysiology study
f. Patients with nonischemic cardiomyopathy who either survive sudden cardiac arrest caused by VT/VF or have hemodynamically unstable VT or stable VT not attributable to reversible causes, and in whom meaningful survival of greater than 1 year is expected
g. Patients with nonischemic cardiomyopathy, HF with NYHA class II or III symptoms, and an LVEF of 35% or less in whom meaningful survival of greater than 1 year is expected
h. Patients with arrhythmogenic right ventricular cardiomyopathy and an additional marker of increased risk of SCD (resuscitated sudden cardiac arrest, sustained VT, significant ventricular dysfunction with right ventricular EF or LVEF 35% or less), in whom meaningful survival of greater than 1 year is expected
i. Patients with hypertrophic cardiomyopathy who have survived a sudden cardiac arrest caused by VT or VF, or have spontaneous sustained VT causing syncope or hemodynamic compromise, and in whom meaningful survival of greater than 1 year is expected
j. Patients with cardiac sarcoidosis who have sustained VT or are survivors of sudden cardiac arrest or have an LVEF of 35% or less, and in whom meaningful survival of greater than 1 year is expected
k. In patients with neuromuscular disorders, primary and secondary prevention ICDs are recommended for the same indications as for patients with nonischemic cardiomyopathy if meaningful survival of greater than 1 year is expected.
l. Patients with a cardiac channelopathy and sudden cardiac arrest, and in whom meaningful survival of greater than 1 year is expected
m. In patients with symptomatic congenital long QT syndrome in whom a β-blocker is ineffective or poorly tolerated, an ICD is recommended and/or intensification of therapy with additional medications (guided by the specific type of long QT syndrome) and/or left cardiac sympathetic denervation
n. In patients with catecholaminergic polymorphic VT and recurrent sustained VT or syncope while receiving an adequate or maximally tolerated β-blocker, an ICD may be considered, and/or treatment intensification with either combination medication therapy (β-blockers, flecainide) or left cardiac sympathetic denervation
o. Patients with Brugada syndrome with spontaneous type I Brugada ECG pattern and cardiac arrest, sustained ventricular arrhythmias or a recent history of syncope presumed because of a ventricular arrhythmia, if meaningful survival of greater than 1 year is expected
p. Patients with early repolarization pattern on ECG and cardiac arrest or sustained ventricular arrhythmias
q. Patients with short QT syndrome who have a cardiac arrest or sustained ventricular arrhythmias, if meaningful survival of greater than 1 year is expected
r. Patients who have been resuscitated from sudden cardiac arrest because of idiopathic polymorphic VT or VF, if meaningful survival of greater than 1 year is expected
s. Patients with adult congenital heart disease and hemodynamically unstable VT after evaluation and appropriate treatment for residual lesions/ventricular dysfunction has been performed, and if meaningful survival of greater than 1 year is expected
t. Patients with adult congenital heart disease with sudden cardiac arrest because of VT or VF in the absence of reversible causes, if meaningful survival of greater than 1 year is expected

2. Class IIa recommendations
    a. Patients resuscitated from sudden cardiac arrest because of coronary artery spasm in whom medical therapy is ineffective or not tolerated, and in whom meaningful survival of greater than 1 year is expected
    b. In patients with nonischemic cardiomyopathy who have syncope presumed to be caused by ventricular arrhythmias and who do not meet the indications for a primary prevention ICD, an ICD or an electrophysiology study for risk stratification for SCD can be beneficial if meaningful survival of greater than 1 year is expected.
    c. Patients with nonischemic cardiomyopathy because of a Lamin A/C mutation, who have two or more risk factors (nonsustained VT, LVEF less than 45%, non-missense mutation and male sex), in whom meaningful survival of greater than 1 year is expected
    d. Patients with arrhythmogenic right ventricular cardiomyopathy and syncope presumed to be because of ventricular arrhythmias, in whom meaningful survival of greater than 1 year is expected
    e. Patients with hypertrophic cardiomyopathy in whom meaningful survival of greater than 1 year is expected, and who have one or more of the following risk factors:
        i. Maximum LV wall thickness of 30 mm or greater
        ii. SCD in one or more first-degree relatives presumably caused by hypertrophic cardiomyopathy
        iii. One or more episodes of unexplained syncope within the preceding 6 months
    f. Nonhospitalized patients with NYHA class IV symptoms who are candidates for cardiac transplantation or an LV assist device, and in whom meaningful survival of greater than 1 year is expected
    g. Patients with hypertrophic cardiomyopathy who have spontaneous nonsustained VT or an abnormal blood pressure response with exercise, who have additional SCD risk modifiers or high-risk features, in whom meaningful survival of greater than 1 year is expected
    h. Patients with cardiac sarcoidosis and an LVEF greater than 35% who have syncope and/or evidence of myocardial scar by cardiac magnetic resonance imaging or positron emission tomography scan, and/or have an indication for permanent pacing, and in whom meaningful survival of greater than 1 year is expected
    i. In patients with cardiac sarcoidosis and an LVEF greater than 35%, it is reasonable to perform an electrophysiologic study and to implant an ICD if sustained ventricular arrhythmias are inducible, if meaningful survival of greater than 1 year is expected.
    j. Patients with cardiac sarcosis who have an indication for permanent pacing
    k. Patients with HFrEF who are awaiting a heart transplant and who otherwise would not qualify for an ICD (e.g., NYHA class IV and/or use of inotropes) with a plan to discharge to home
    l. Patients with an LV assist device and sustained ventricular arrhythmia
    m. Patients with Emery-Dreifuss and limb-girdle type IB muscular dystrophies with progressive cardiac involvement, if meaningful survival of greater than 1 year is expected
    n. Adult patients with repaired tetralogy of Fallot physiology and inducible VT/VF or spontaneous sustained VT
    o. In patients with repaired moderate or severe complexity adult congenital heart disease with unexplained syncope and at least moderate ventricular dysfunction or marked hypertrophy, either ICD implantation or an electrophysiologic study with ICD implantation for inducible ventricular arrhythmias is reasonable if meaningful survival of greater than 1 year is expected.
3. Class IIb recommendations
    a. Patients resuscitated from sudden cardiac arrest caused by coronary artery spasm, and in whom meaningful survival of greater than 1 year is expected
    b. Patients with nonischemic cardiomyopathy, HF with NYHA class I symptoms, and an LVEF of 35% or less, despite guideline-directed medical therapy, in whom meaningful survival of greater than 1 year is expected

   c. Patients with hypertrophic cardiomyopathy who have spontaneous nonsustained VT or an abnormal blood pressure response with exercise, but no additional SCD risk modifiers
   d. In patients with giant cell myocarditis with VF or hemodynamically unstable VT treated according to guideline-directed medical therapy, an ICD and/or antiarrhythmic drug therapy may be considered if meaningful survival of greater than 1 year is expected.
   e. Patients with a heart transplant and severe allograft vasculopathy with LV dysfunction, and in whom meaningful survival of greater than 1 year is expected
   f. Patients with myotonic dystrophy type 2 with an indication for a permanent pacemaker, if meaningful survival of greater than 1 year is expected
   g. Asymptomatic patients with congenital long QT syndrome and a resting QTc interval greater than 500 milliseconds while receiving a β-blocker
   h. Patients with adult congenital heart disease and severe LV dysfunction (LVEF less than 35%) and symptoms of HF despite guideline-directed medical therapy or additional risk factors, and if meaningful survival of greater than 1 year is expected
4. Class III recommendations (no benefit)
   a. ICD is not indicated for patients with NYHA class IV medication-refractory HF who are also not candidates for cardiac transplantation, an LV assist device, or a cardiac resynchronization therapy defibrillator that incorporates both pacing and defibrillation capacities.
   b. Patients with an unidentified hypertrophic cardiomyopathy genotype in the absence of SCD risk factors
5. Class III recommendation (harm): In patients with incessant VT or VF, an ICD should not be implanted until sufficient control of the arrhythmia is achieved to prevent repeated ICD shocks.

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## ANSWERS AND EXPLANATIONS TO PATIENT CASES

**1. Answer: C**

Aminophylline is recommended only for patients with sinus bradycardia or AV block after a heart transplant or spinal cord injury, scenarios that do not apply to this patient (Answer A is incorrect). Atropine is not recommended for managing bradycardia associated with a CCB overdose because it is unlikely to be effective (Answer B is incorrect). Although placing a transcutaneous pacemaker is reasonable, inserting a temporary transvenous pacemaker is an invasive procedure that should be reserved for patients who do not respond to initial treatment (Answer D is incorrect). Evidence supports HIE for managing bradycardia associated with CCB overdose (Answer C is correct).

**2. Answer: B**

Amiodarone is effective for acute ventricular rate control in patients with AF and for conversion of AF to sinus rhythm, but its onset of action is 4–24 hours, which is too long for a hemodynamically unstable patient (Answer A is incorrect). Intravenous digoxin is no longer guideline recommended as a preferred drug for acute ventricular rate control, and its onset of action (1 hour) and time to peak effect (6 hours) are too long for a hemodynamically unstable patient (Answer C is incorrect). Intravenous diltiazem is rapidly effective for ventricular rate control but is not preferred therapy for hemodynamically unstable patients because it can lower blood pressure even further (Answer D is incorrect). Because this patient is hemodynamically unstable (systolic blood pressure less than 90 mm Hg, heart rate greater than 150 beats/minute, losing consciousness), immediate DCC is indicated (Answer B is correct).

**3. Answer: B**

Digoxin is a potential add-on (not first line) agent to achieve ventricular rate control in AF (Answer A is incorrect). Metoprolol tartrate or diltiazem is a reasonable first-line rate-controlling medication (Answer B is correct). Diltiazem and simvastatin are both substrates for CYP3A4, and coadministration should generally be avoided (Answer C is incorrect). Amiodarone is a last-line rate-controlling medication that is most useful in patients with HFrEF, which this patient does not have (Answer D is incorrect).

**4. Answer: B**

Amiodarone is a second-line drug, not a preferred drug, for maintaining sinus rhythm in patients with paroxysmal AF and CAD (Answer A is incorrect). Flecainide and propafenone are contraindicated in patients with structural heart disease, including CAD, because of an increased risk of proarrhythmia leading to death in this population (Answers C and D are incorrect). Dronedarone is recommended as one of the first-line drug therapy options for patients with paroxysmal AF and concomitant CAD (Answer B is correct).

**5. Answer: B**

Intravenous digoxin is not a preferred drug for terminating SVT caused by AVNRT because of its delayed onset of action and relatively poor efficacy rates (Answer A is incorrect). Ibutilide and procainamide are recommended for the acute management of SVT in patients with evidence of preexcitation, but not for patients without evidence of preexcitation (Answers C and D are incorrect). Intravenous diltiazem, verapamil, or β-blockers are recommended for patients with SVT caused by AVNRT who are unresponsive to adenosine (Answer B is correct).

**6. Answer: B**

Diltiazem is not a preferred drug for the long-term prevention of recurrence of SVT caused by AVNRT in patients with HFrEF because of its negative inotropic effects and propensity to worsen HFrEF (Answer A is incorrect). Flecainide and propafenone are both contraindicated in patients with structural heart disease, including HFrEF, because they also have negative inotropic activity and can worsen HFrEF (Answers C and D are incorrect). Dofetilide is one of the recommended drugs for preventing the recurrence of SVT caused by AVNRT in patients with HFrEF because it has no negative inotropic effects and does not worsen HFrEF (Answer B is correct).

**7. Answer: C**

Intravenous amiodarone has a class IIb recommendation for termination of acute VT, which is a lower recommendation that that for procainamide, and therefore is not the preferred first-line therapy for termination of acute VT (Answer A is incorrect). Intravenous lidocaine is no longer recommended as a preferred therapy for terminating acute VT because study data show amiodarone and procainamide to be more effective (Answer B is incorrect). Like intravenous amiodarone, intravenous sotalol has a class IIb recommendation for termination of acute VT, which is a lower recommendation that that for procainamide, and therefore is not the preferred first-line therapy for termination of acute VT (Answer D is incorrect). Intravenous procainamide has a class IIa recommendation for termination of acute VT, and is therefore the preferred agent for acute termination of VT (Answer C is correct).

**8. Answer: C**

Implanting an ICD is more effective than administering oral amiodarone alone or oral sotalol alone for reducing the risk of SCD (Answer C is correct; Answers A and B are incorrect). Implanting a permanent pacemaker is incorrect because permanent pacemakers (in the absence of coupling with an ICD) do not provide antitachycardia pacing. Antitachycardia pacing is available as a component of ICDs – often, the ICD will generate antitachycardia pacing before delivering a shock. In addition, antitachycardia pacing not coupled with an ICD does not reduce mortality in patients with ventricular arrhythmias (Answer D is incorrect).

## ANSWERS AND EXPLANATIONS TO SELF-ASSESSMENT QUESTIONS

**1. Answer: A**

Atropine is the treatment of choice for symptomatic sinus bradycardia (Answer A is correct). Epinephrine infusion should be reserved for patients who are unresponsive to atropine administered to a total dose of 3 mg (or 0.04 mg/kg) (Answer B is incorrect). Similarly, transcutaneous pacing is reserved for patients who do not respond to drug therapy (Answer C is incorrect). Treatment is definitely necessary because of the patient's low heart rate, low blood pressure, and resulting symptoms (Answer D is incorrect).

**2. Answer: D**

Immediate DCC is not necessary, because, although symptomatic, this patient is not hemodynamically unstable (Answer A is incorrect). Intravenous amiodarone is not indicated because it is recommended for ventricular rate control in patients with AF that has not responded to other drug therapy (Answer B is incorrect). Intravenous digoxin is no longer guideline- recommended as first-line therapy for acute ventricular rate control because of its long onset of action (more than 1 hour) and long time to peak effect (around 6 hours), though it may have some efficacy in patients with HFrEF (Answer C is incorrect). Drugs of choice for acute ventricular rate control for patients with AF are intravenous β-blockers or non-dihydropyridine CCBs (though CCBs are contraindicated in patients with HFrEF) (Answer D is correct).

**3. Answer: A**

Intravenous amiodarone is recommended for acute ventricular rate control in critically patients with AF who have no evidence of preexcitation (Answer A is correct). Intravenous digoxin is no longer guideline recommended as first-line therapy for acute ventricular rate control because of its long onset of action (more than 1 hour) and long time to peak effect (around 6 hours) (Answer B is incorrect). Intravenous diltiazem is contraindicated because the patient has HFrEF, and diltiazem is a negative inotrope that may worsen HFrEF (Answer C is incorrect). Although β-blockers can be administered for ventricular rate control in patients with HFrEF, intravenous amiodarone is preferred for critically ill patients (Answer D is incorrect).

**4. Answer: C**

The patient cannot be sedated for immediate DCC because she has eaten two meals and is therefore at risk of aspiration pneumonitis (Answer A is incorrect). Neither dronedarone nor oral sotalol is recommended for conversion of AF to sinus rhythm because data are lacking to support their efficacy for this indication (Answers B and D are incorrect). Ibutilide is recommended for conversion of AF to sinus rhythm in patients with normal LV function as well as those with HFrEF with an LVEF of 30%–40% (but it should be avoided in patients with an LVEF of less than 30% because of the risk of proarrhythmia) (Answer C is correct).

**5. Answer: C**

Amiodarone is not recommended as the first choice for long-term ventricular rate control in patients with AF because of its adverse effect profile (Answer A is incorrect). Digoxin administered alone is not recommended for ventricular rate control for AF because of its lack of efficacy for ventricular rate control when patients are not at rest (Answer B is incorrect). The combination of β-blockers and digoxin is effective for ventricular rate control because metoprolol diminishes the sympathetic nervous system effects of exercise, allowing the effects of digoxin on the parasympathetic nervous system to be more prominent. However, this combination is recommended for patients who do not respond to initial therapy with a β-blocker alone or for those with HFrEF (Answer D is incorrect). Non-dihydropyridine CCBs or β-blockers are recommended as initial therapy for ventricular rate control, and CCBs are safe for use in patients with normal LV function (Answer C is correct).

**6. Answer: B**

Immediate direct cardioversion is not necessary because this patient is not hemodynamically unstable (Answer A is incorrect). Ibutilide and procainamide are both recommended for SVT associated with WPW, but this patient has no evidence of preexcitation; ibutilide and procainamide are not recommended for SVT that is not the result of WPW (Answers C and D are incorrect). Adenosine is the drug of choice for termination of SVT in patients without preexcitation/WPW (Answer B is correct).

**7. Answer: A**

Dronedarone is contraindicated in patients with HFrEF because data analyses show that it may increase the risk of death in that population (Answer B is incorrect). Flecainide is contraindicated in patients with HFrEF because of its negative inotropic activity (Answer C is incorrect). Sotalol is not recommended for use in patients with HFrEF because these patients are usually already taking a β-blocker, and additional β-blockade is generally poorly tolerated (Answer D is incorrect). Amiodarone is recommended for maintaining sinus rhythm in patients with AF and HFrEF because amiodarone has no negative inotropic activity and is associated with neutral mortality effects in that population (Answer A is correct).

**8. Answer: A**

A thorough medication history and reconciliation is important for patients being initiated on dofetilide. Hydrochlorothiazide interferes with renal elimination of dofetilide, and the two medications should not be coadministered. Calling the pharmacy to cancel refills of hydrochlorothiazide, as well as educating the patient, is an important step to reduce the likelihood of a medication error (Answer A is correct; Answers B, C, and D are incorrect).

# Drug-Induced Cardiovascular Disease and Drugs to Avoid in Cardiovascular Disease

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**Learning Objectives**

1. Identify potential drug-induced cardiovascular diseases.
2. Analyze a medication list to determine causative agents for common drug-induced cardiovascular diseases.
3. Evaluate potential medications that can contribute to the development of torsades de pointes.
4. Review anticancer therapies that cause cardiovascular toxicities.
5. Evaluate patient characteristics and laboratory values to assess the risk of heparin-induced thrombocytopenia and develop an appropriate treatment plan.

**Abbreviations in This Chapter**

| | |
|---|---|
| ACS | Acute coronary syndrome |
| AV | Atrioventricular |
| BB | β-Blocker |
| CCB | Calcium channel blocker |
| COPD | Chronic obstructive pulmonary disease |
| CV | Cardiovascular |
| CYP | Cytochrome P450 |
| ECG | Electrocardiogram |
| ELISA | Enzyme-linked immunosorbent assay |
| HF | Heart failure |
| HIT | Heparin-induced thrombocytopenia |
| NSAID | Nonsteroidal anti-inflammatory drug |
| SA | Sinoatrial |
| SRA | Serotonin release assay |
| TdP | Torsades de pointes |
| TTE | Transthoracic echocardiography |
| VEGF | Vascular endothelial growth factor |

**Self-Assessment Questions**

*Answers and explanations to these questions can be found at the end of this chapter.*

1. A 72-year-old man presents to the emergency department with near-syncope. On presentation, his heart rate is 48 beats/minute. At home, the patient was taking clonidine 0.1 mg twice daily, atenolol 50 mg/day, furosemide 20 mg/daily, albuterol inhaler 1 or 2 puffs as needed for shortness of breath, and aspirin 81 mg/daily. On rounds, the attending physician asks you if any of his home medications could be causing bradycardia. Which is the most appropriate response?
   A. Albuterol.
   B. Atenolol.
   C. Both atenolol and clonidine.
   D. Furosemide.

2. After a motor vehicle accident, a 65-year-old man presents to the hospital, where he is found to have a right femoral shaft fracture. His medical history includes hypertension and benign prostatic hyperplasia. His medications include amlodipine 5 mg/day, doxazosin 4 mg/day, lisinopril 20 mg/day, and clonidine 0.1 mg twice daily. In preparation for surgery, all of his home medications are held. Postoperatively, his blood pressure is 200/97 mm Hg. Which of his home medications is most likely contributing?
   A. Amlodipine.
   B. Doxazosin.
   C. Lisinopril.
   D. Metoprolol tartrate.

*Questions 3–5 pertain to the following case.*

A 46-year-old woman presents to her primary care physician's office for a routine physical examination. Her medical history includes nonischemic cardiomyopathy (left ventricular ejection fraction [LVEF] 30%) and type 2 diabetes. Her current medication regimen includes metformin 1000 mg twice daily, benazepril 10 mg/day, spironolactone 25 mg/day, and furosemide 40 mg twice daily. She has had no heart failure (HF) exacerbations in the past 2 years. Vital signs include blood pressure 125/70 mm Hg and heart rate 68 beats/minute. Fasting laboratory tests at the visit include serum glucose 160 mg/dL, hemoglobin A1C (A1C) 7.8%, serum creatinine (SCr) 1.1 mg/dL, and serum potassium 4.2 mEq/L.

3. Given the patient's suboptimal glucose control, the primary care physician wishes to add a second oral agent. Which agent would be most appropriate for this patient?
   A. Empagliflozin 10 mg/day.
   B. Alogliptin 2.5 mg/day.
   C. Semaglutide 3 mg/day.
   D. Saxagliptin 5 mg/day.

4. Several months later, the patient presents to the hospital with heart palpitations and is found to have new-onset atrial fibrillation with rapid ventricular response (heart rate 144 beats/minute). After initial stabilization, the team would like a recommendation for the most appropriate agent to maintain heart rate control. Which is the most appropriate selection?
   A. Diltiazem.
   B. Verapamil.
   C. Metoprolol succinate.
   D. Metoprolol tartrate.

5. The electrophysiology service has elected to try antiarrhythmic therapy to maintain rhythm control after spontaneous cardioversion. Which is the most appropriate agent for this patient?
   A. Sotalol.
   B. Amiodarone.
   C. Flecainide.
   D. Propafenone.

6. A 53-year-old woman with a history of hypertension and several coronary stents presents to her cardiologist's office for an annual visit. During check-in, her list of home medications is reviewed and documented as aspirin 81 mg/day, prasugrel 10 mg/day, metoprolol tartrate 50 mg twice daily, and atorvastatin 40 mg/day. She also reports recently starting garlic tablets after seeing a television program promoting garlic's cardiovascular (CV) benefits. You are asked to discuss garlic therapy with the patient. Which best describes the potential harmful effect garlic therapy might have in a patient with CV disease?
   A. QT prolongation.
   B. Increased blood pressure.
   C. Increased risk of bleeding.
   D. Tachycardia.

7. A 62-year-old man presents for an outpatient visit with his cardiologist. His medical history includes a kidney transplant 3 months ago, coronary artery disease with coronary artery bypass graft surgery, diabetes, and hypertension. His medication regimen includes tacrolimus 5 mg twice daily, prednisone 5 mg/day, mycophenolate mofetil 1000 mg twice daily, metformin 1000 mg twice daily, aspirin 81 mg/day, atorvastatin 80 mg/day, metoprolol tartrate 100 mg twice daily, and lisinopril 40 mg/day. The patient reports doing well other than high blood pressure when checking his blood pressure at home. His primary care physician recently doubled both his metoprolol and his lisinopril doses. Physical examination is notable for blood pressure 172/92 mm Hg and heart rate 64 beats/minute. After confirming your plan with the transplant nephrologist, which recommendation is most appropriate?
   A. Change tacrolimus to cyclosporine 150 mg twice daily.
   B. Add amlodipine 10 mg/day.
   C. Add chlorthalidone 25 mg/day.
   D. Discontinue tacrolimus.

8. A 25-year-old woman presents to a psychiatry clinic for newly diagnosed generalized anxiety disorder. She has congenital long QT syndrome but is otherwise healthy. Her medications include an oral contraceptive and St. John's wort. The psychiatrist has heard of no reports of QT prolongation associated with buspirone but asks for your opinion on this selection. Which would provide the most updated information on the occurrence of QT prolongation with buspirone?
   A. Search patient safety organizations.
   B. Review the prescribing information on the company website.
   C. Call the manufacturer directly.
   D. Search the primary literature for randomized studies.

## I. DRUG-INDUCED BRADYARRHYTHMIAS

A. Sinus Bradycardia and Atrioventricular (AV) Node Block
   1. Definitions
      a. Sinus bradycardia is defined as a heart rate less than 60 beats/minute originating in the sinoatrial (SA) node..
      b. AV block represents a delay or disturbance in the transmission of an impulse from the atria to the ventricles..
         i. First degree – P waves always precede the QRS; however, delayed conduction from the AV node results in a widened PR interval without any dropped beats (greater than 0.2 seconds)
         ii. Second degree – P waves are sometimes related to the QRS complex as a result of intermittent atrial to ventricular conduction (some impulses between the atria and the ventricle are not conducted). Further classified into second-degree type 1 (Mobitz type 1), in which there is progressive prolongation of PR interval that culminates in a non-conducted P wave, and second-degree type 2 (Mobitz type 2), in which there are intermittent non-conducted P waves.
         iii. Third degree – Also known as complete heart block; there is a complete absence of AV nodal conduction and therefore no relationship between atrial and ventricular depolarizations
   2. Drug-induced causes
      a. Inherent properties of certain pharmacologic agents, particularly in patients with underlying sinus or AV nodal disease
      b. Drug overdose
      c. Impaired drug elimination resulting in drug accumulation (or as a result of drug-drug interactions)
      d. Synergistic or additive effect from more than one agent used in combination
   3. Medications that inhibit sinus node function can cause sinus bradycardia, AV nodal blockade, or both (Table 1).

**Table 1.** Medications/Classes of Medications Commonly Associated with Drug-Induced Sinus Bradycardia and AV Block

| Medication or Medication Class | Sinus Bradycardia | AV Nodal Blockade |
|---|---|---|
| Acetylcholinesterase inhibitors | ✓ | ✓ |
| Adenosine | ✓ | ✓ |
| Amiodarone | ✓ | ✓ |
| Anesthetics | ✓ | ✓ |
| BBs | ✓ | ✓ |
| Citalopram | ✓ | ✓ |
| Class Ia and Ic antiarrhythmics | ✓ | ✓ |
| Clonidine | ✓ | ✓ |
| Dexmedetomidine | ✓ | ✓ |
| Digoxin | ✓ | ✓ |
| Dipyridamole | ✓ | ✓ |
| Dronedarone | ✓ | ✓ |
| Escitalopram | ✓ | ✓ |
| Fingolimod | ✓ | ✓ |

**Table 1.** Medications/Classes of Medications Commonly Associated with Drug-Induced Sinus Bradycardia and AV Block *(Cont'd)*

| Medication or Medication Class | Sinus Bradycardia | AV Nodal Blockade |
|---|---|---|
| Fluoxetine | ✓ | ✓ |
| Ivabradine | ✓ | |
| Non-DHP CCBs | ✓ | ✓ |
| Sotalol | ✓ | ✓ |
| Thalidomide | ✓ | ✓ |

BB = β-blocker; DHP CCB = dihydropyridine calcium channel blocker.

4. Mechanisms by which agents cause sinus bradycardia and AV nodal blockade vary by agent, but most involve inhibition of sinus node automaticity, slowing of conduction, or repolarization and/or AV node conduction and/or prolonging repolarization (Table 2).

**Table 2.** Mechanisms for Sinus Bradycardia and AV Nodal Blockade

| Mechanism(s) | Medications/Classes of Medications |
|---|---|
| Inhibition of sinus nodal automaticity, conduction or delayed repolarization, inhibited conduction through the AV node | Adenosine, BBs, amiodarone, anesthetics, citalopram, escitalopram, fluoxetine, Class Ia and Ic antiarrhythmics, digoxin, dipyridamole, dronedarone, ivabradine, non-DHP CCBs, sotalol |
| Reduction in norepinephrine from central $\alpha_2$ stimulation, decreased sinus nodal automaticity and conduction | Clonidine, dexmedetomidine |
| Acetylcholinesterase inhibition exerting vagotonic effects on the sinus node and AV node | Acetylcholinesterase inhibitors |

5. Risk factors
    a. PR interval greater than 0.2 seconds
    b. Underlying sinus node dysfunction (advanced age)
    c. Female sex
    d. Electrolyte abnormalities
    e. Infection
6. Prevention
    a. Avoid associated agents in patients with preexisting sinus node dysfunction without a pacemaker.
    b. Monitor heart rate closely in patients with first-degree heart block.
    c. Limit use of combinations of agents known to inhibit the SA or AV nodes, ensuring to adhere to maximum daily dose limits (i.e., a β-blocker [BB] plus a non-dihydropyridine calcium channel blocker [non-DHP CCB]).
    d. Dosage adjustment as appropriate in organ dysfunction
        i. Hepatic elimination – Dronedarone, ivabradine, propafenone
        ii. Renal elimination – Atenolol, dexmedetomidine, digoxin, nadolol, sotalol
    e. Monitor closely for drug interactions.
        i. 3A4 inhibitors – Can increase the concentrations of amiodarone, diltiazem, dronedarone, ivabradine, verapamil
        ii. P-glycoprotein (P-gp) inhibitors – Can increase the concentration of digoxin

7. Management
    a. Dose reduce or discontinue offending agent (unless the medication is absolutely necessary without available substitute).
    b. Address other precipitating factors such as electrolyte abnormalities, underlying infection, or thyroid dysfunction.
    c. Atropine 0.5 mg intravenously every 3–5 minutes to a maximum dose of 3 mg
    d. Consider epinephrine 2- to 10-mcg/kg/minute infusion or dopamine 2- to 10-mcg/kg/minute infusion if disease is resistant to atropine.
    e. Temporary/permanent pacemaker
    f. Drug-specific treatment (Table 3)

**Table 3.** Drug-Specific Management of Severe Bradycardia/AV Nodal Blockade

| Medication(s) | Specific Treatment |
|---|---|
| BB/non-DHP CCB | Gastric decontamination – Lavage, activated charcoal<br>Combination of the following:<br>• Calcium chloride/gluconate (up to 3 g total)<br>• Glucagon 1- to 5-mg IV bolus followed by a continuous infusion of 2-5 mg/hr is reasonable for patients with symptomatic or hemodynamically unstable bradycardia<br>• Hyperinsulinemia/euglycemia (HIE)- insulin 1 unit/kg IV bolus; then 0.5- to 1-unit/kg/hr infusion + PRN dextrose 50% 50 mL<br>Symptomatic hypoglycemia – Dextrose 50% (25 g) 50 mL<br>Vasopressor therapy PRN<br>Resistant cases – Consider lipid emulsion 20% 1.5 mL/kg IV bolus over 1–2 min; then 0.25 mL/kg/min infusion |
| Digoxin | Digoxin-specific antibody fragments (DigiFab/Digibind) – Quantity based on acute/chronic ingestion<br>Number of vials for acute toxicity[a] = (digoxin amount ingested in mg)/0.5<br>Number of vials for chronic toxicity = (digoxin level x weight in kg)/100 |

[a]If digoxin tablet is ingested, multiply digoxin amount by 0.8 to account for bioavailability.

IV = intravenous(ly); PRN = as needed.

**Patient Case**

1. A 77-year-old woman (weight 62 kg) presents to the outpatient surgery center for arthroscopic knee surgery. Her medical history includes hypertension, osteoarthritis, diabetes, and hypothyroidism. During check-in, the patient reports feeling tired, with blood pressure 63/36 mm Hg and heart rate 44 beats/minute. At home, the patient was taking levothyroxine 175 mcg/daily, linagliptin 5 mg/daily, metformin 1000 mg twice daily, atenolol 25 mg/daily, quinapril 20 mg/daily, and naproxen 500 mg twice daily. The procedure is canceled, and she is directly admitted to the ICU for monitoring and treatment. Her laboratory values include potassium 5.7 mEq/L, SCr 2.43 mg/dL, glucose 240 mg/dL, magnesium 1.9 mEq/L, and calcium 8.4 mg/dL. Initial treatment includes 2 L of normal saline and atropine 1 mg intravenously x 3 doses. Repeat vital signs are blood pressure 74/42 mm Hg and heart rate 43 beats/minute. An electrocardiogram (ECG) reveals bradycardia without heart block. The patient can maintain her airway, but she has become intermittently responsive. Which is the most appropriate additional treatment for this patient?
   A. Calcium gluconate 1 g intravenous bolus.
   B. Glucagon 5 mg intravenous bolus, followed by continuous infusion at 3 mg/hour.
   C. Calcium gluconate 1 g intravenous bolus, glucagon 5 mg intravenous bolus followed by continuous infusion at 3 mg/hour, insulin 60 units intravenous push, glucose 25 g intravenous push.
   D. Calcium gluconate 1 g intravenous bolus, glucagon 5 mg intravenous bolus followed by continuous infusion at 3 mg/hour, insulin 60 units intravenous push, glucose 25 g intravenous push, lipid emulsion 20% 0.25 mL/kg/minute infusion.

## II. DRUG-INDUCED SUPRAVENTRICULAR ARRHYTHMIAS

A. Atrial Fibrillation/Atrial Flutter
   1. Definitions
      a. Atrial fibrillation – "Irregularly, irregular" pattern on ECG without identifiable p waves
      b. Atrial flutter – Regular pattern with an irregular rhythm on ECG composed of narrow QRS complexes and p waves in a "sawtooth appearance"
   2. Drug-induced atrial fibrillation/flutter is relatively uncommon.
   3. Associated agents typically affect the atrial refractory period/atrial wavelength, slow atrial conduction, or stimulate the sympathetic nervous system (Table 4).
   4. Flecainide and propafenone slow atrial conduction and can result in 1:1 AV conduction; therefore, AV nodal blocking drugs should be prescribed concomitantly.
   5. Antipsychotics, namely chlorpromazine, clozapine, prochlorperazine, olanzapine, risperidone, and quetiapine, may increase cardiac muscarinic blockade, resulting in atrial conduction abnormalities.
   6. Tyrosine kinase inhibitors, anthracyclines, alkylating agents, human epidermal growth factor receptor 2 (HER2)/neu receptor blockers, antimetabolites, microtubule agents, and histone deacetylase inhibitors are anticancer agents that have an increased risk of promoting supraventricular arrhythmias.

**Table 4.** Medications Associated with Atrial Fibrillation/Atrial Flutter and Proposed Mechanisms

| Medication | Mechanism | | | |
|---|---|---|---|---|
| | Slows Atrial Conduction | Shortens Atrial Refractory Period | Sympathetic Nervous System Stimulant | Other |
| Adenosine, alendronate, zoledronic acid | | ✓ | | |
| Albuterol, alcohol, caffeine, dobutamine, dopamine, epinephrine, isoproterenol, milrinone, theophylline | | | ✓ | |
| Amiodarone, levothyroxine, liothyronine, thyroid (porcine) | | | | Hyperthyroidism |
| Ivabradine | | | | Exact mechanism not known; believed to be related to inhibition of the $I_f$ current found in the pulmonary venous myocardium |
| Flecainide, propafenone | ✓ | | | |

7. Management
    a. Discontinue offending agent.
    b. Heart rate control with standard agents (BBs, non-DHP CCBs, digoxin)
    c. Assess the need for cardioversion after an appropriate drug washout period (4 or 5 half-lives) (if duration of atrial fibrillation or flutter is more than 48 hours, must evaluate for thrombus with transthoracic echocardiography [TEE] or initiate anticoagulation for 3 or more weeks before cardioversion).
    d. Direct current cardioversion, if hemodynamically unstable; see arrhythmias chapter for therapeutic management
    e. For drug-induced hyperthyroidism, treat underlying hyperthyroidism.
    f. For theophylline or other oral drug overdose, consider activated charcoal.

B. Atrial Tachycardia
1. Atrial tachycardia is represented by heart rates of 100–250 beats/minute and discrete P waves and may be focal (arising from a single atrial site with uniform P-wave morphology) or multifocal (arising from multiple atrial sites with varying P-wave morphologies).
2. Drug-induced atrial tachycardia is a result of enhanced atrial automaticity, triggered activity, or micro-reentry.
3. Almost all of the associated agents have "stimulant" properties.
    a. Stimulation of β-receptors – Albuterol, dobutamine, epinephrine, isoproterenol, phenylpropanolamine, terbutaline
    b. Phosphodiesterase inhibition – Caffeine, milrinone, theophylline
    c. Digoxin toxicity causing high myocyte calcium concentrations
4. Management
    a. Discontinue offending agent
    b. Specific drug toxicities
        i. Theophylline - Activated charcoal

ii. Digoxin - Digoxin-specific antibody fragment
c. Adenosine 6 mg intravenous push; then 12 mg intravenous push (up to two doses)
d. Administration of rate-controlling medications (BB, non-DHP CCB for normal LVEF, BB for impaired LVEF) or antiarrhythmic drugs (e.g., flecainide, propafenone, sotalol, amiodarone, ibutilide for normal LVEF, amiodarone for impaired LVEF)
e. Direct current cardioversion, if hemodynamically unstable

C. Atrioventricular Nodal Reentrant Tachycardia (AVNRT)
1. AVNRT is characterized by a regular, narrow-complex QRS with either no visible P waves or P waves that appear to be part of the QRS complex.
2. The overall prevalence of drug-induced AVNRT is unknown.
3. AVNRT is the result of a reentrant circuit within two pathways of the AV node, with most cases resulting from anterograde conduction over the slow AV node pathway followed by retrograde conduction through the fast pathway; therefore, drugs that enhance AV nodal conduction or cause premature extrastimuli may stimulate the development of AVNRT.
4. Management
a. Discontinue offending agent.
b. Vagal maneuvers and intravenous adenosine
c. If vagal maneuvers and intravenous adenosine unsuccessful, may consider intravenous non-DHP CCB or BB

## III. DRUG-INDUCED VENTRICULAR ARRHYTHMIAS

A. Monomorphic Ventricular Tachycardia (VT)
1. Properties
a. Manifests wide, uniform QRS complexes (greater than120 milliseconds) in a regular pattern on an ECG with ventricular rates greater than 100 beats/minute
b. May be sustained (lasting more than 30 seconds, requiring termination with either drugs or electricity) or nonsustained (less than 30 seconds and terminates on its own)
c. Symptoms vary from palpitations to sudden cardiac death.
d. An unstable rhythm that has a high risk of degeneration into VT
2. Diagnosis
a. New or worsening VT after medication initiation
b. No other obvious cause for VT (electrolyte depletion, HF, coronary artery disease)
c. Differs from previous VT events – Faster rate, different morphology, more difficult to control, sustained (when previously nonsustained)
3. Risk factors
a. Underlying structural heart disease such as coronary artery disease, cardiomyopathy (infiltrative, dilated), sarcoidosis, congenital defects
b. High drug concentrations
i. Digoxin concentration above 2 ng/mL
ii. Theophylline concentration above 20 mcg/mL
c. Electrolyte depletion (hypomagnesemia, hypokalemia, hypocalcemia)
4. Antiarrhythmic medications are a common cause because of inhibition of sodium channels, reducing ventricular conduction velocity (Table 5).

**Table 5.** Medications/Classes of Medications Associated with Ventricular Tachycardia and Proposed Mechanisms

| Mechanism | Medications |
|---|---|
| Inhibition of sodium-potassium ATPase pump causing increased intracellular calcium and ventricular ectopic activity | Digoxin |
| PDE inhibition preventing breakdown of cAMP, causing increased intracellular calcium and ventricular ectopic activity | Milrinone, theophylline |
| Sodium channel inhibition | Amiodarone, anesthetics, chlorpromazine, desipramine, disopyramide, flecainide, imipramine, lithium, procainamide, propafenone, quinidine |
| Sympathetic nervous system stimulation | Amphetamines, cocaine, dobutamine, dopamine, epinephrine, terbutaline |
| Sympathetic nervous system stimulation, ischemia from "coronary steal" | Adenosine, dipyridamole, regadenoson |

ATPase= adenosine triphosphatase; cAMP= cyclic adenosine monophosphate; PDE = phosphodiesterase.

5. Prevention
    a. Avoid class Ia and Ic antiarrhythmic agents in coronary artery disease or left ventricular dysfunction..
    b. Perform close therapeutic monitoring of medications with narrow therapeutic indices (digoxin and theophylline), and ensure dose adjustments are made if needed for renal impairment (digoxin).
    c. Closely review medication regimen for potential drug interactions that can result in elevated drug concentrations.
    d. Maintain normal magnesium and potassium concentrations.
    e. Maintain digoxin concentrations less than 2 ng/mL (consider less than 1 ng/mL if concomitant HFrEF) and theophylline concentrations less than 20 mcg/mL).
6. Management
    a. Discontinue offending agent.
    b. If hemodynamically unstable: Synchronized cardioversion
    c. If hemodynamically stable: Antiarrhythmic medications (procainamide as long as not causative agent, amiodarone, or lidocaine) and synchronized cardioversion, if necessary
    d. If VT induced by bupivacaine and local anesthetics, consider lipid emulsion.

B. Torsades de Pointes (TdP)
1. Polymorphic ventricular arrhythmia associated with heart rate-corrected QT (QTc) prolongation
2. TdP is often transient and self-limited and terminates spontaneously; however, it can degenerate into VF and sudden cardiac death.
3. Common reason for drug removal from the market (i.e., astemizole, cisapride, gatifloxacin, grepafloxacin, levomethadyl, terfenadine)
4. Normal QTc interval
    a. Men: 360–470 milliseconds
    b. Women: 360–480 milliseconds
5. QTc interval prolongation may be genetic (congenital long QT syndrome) or acquired (most common cause of which is medications)..
6. Risk factors
    a. QTc greater than 500 milliseconds

b. Increase in QTc of 60 milliseconds or more from baseline
c. Female sex
d. Advanced age (older than 65)
e. Electrolyte changes: Hypomagnesemia, hypokalemia, hypocalcemia
f. Combination therapy with more than one agent that prolongs the QT interval (e.g., hydroxychloroquine with azithromycin)
g. Heart failure with reduced ejection fraction
h. Elevated drug concentrations through drug interaction, impaired excretion, or rapid infusion of intravenous formulation
i. Bradycardia

7. Mechanism - Inhibition of the outward rapid delayed rectifier $K^+$ current and/or activation of late sodium current resulting in prolongation of ventricular action potential duration and increased susceptibility to early afterdepolarizations, which can trigger TdP
8. Many medications can prolong QTc and provoke TdP; Table 6 lists commonly associated medications.
9. The Arizona Center for Education and Research on Therapeutics maintains a regularly updated list of medications that prolong QTc and can provoke TdP (https://crediblemeds.org/).

**Table 6.** Medication Classes with **Known** Risk of Drug-Induced Torsades de Pointes[a]

| Drug Class | Medications |
|---|---|
| Anesthetic | Propofol, sevoflurane |
| Antianginal | Bepridil |
| Antiarrhythmic | Amiodarone, disopyramide, dofetilide, dronedarone, flecainide, ibutilide, propafenone, procainamide, quinidine, sotalol |
| Antidepressant | Citalopram, escitalopram |
| Antiemetic | Chlorpromazine, droperidol, ondansetron |
| Antimalarial | Chloroquine, hydroxychloroquine |
| Antimicrobial | Azithromycin, clarithromycin, ciprofloxacin, erythromycin, fluconazole, levofloxacin, moxifloxacin, pentamidine |
| Antipsychotic | Haloperidol, pimozide, thioridazine |
| Cholinesterase inhibitor | Donepezil |
| Illicit substances | Cocaine |
| Opioid agonist | Methadone |
| PDE type 3 inhibitor | Anagrelide, cilostazol |

[a]According to www.crediblemeds.org, other categories include possible and conditional risk.

10. Prevention
    a. Obtain baseline ECG, when possible, and repeat ECG once the drug has reached steady state.
    b. Avoid use, if possible, when baseline QTc is greater than 450 milliseconds; if unavoidable, monitor closely.
    c. Discontinue medication if QTc prolongs to greater than 500 milliseconds.
    d. Reduce dose or discontinue offending agent if QTc increases more than 60 milliseconds from baseline.
    e. Closely review medication regimen for potential drug interactions that can result in elevated drug concentrations.
    f. Maintain normal magnesium (1.7–2.2 mg/dL), potassium (greater than 4 mEq/L), and calcium (8.6–10.3 mg/dL) concentrations.

g. Dosage adjustment as needed for hepatic or renal impairment
    i. Renal adjustment – Ciprofloxacin, disopyramide, dofetilide, flecainide, fluconazole, levofloxacin, procainamide, sotalol
    ii. Hepatic adjustment – Dronedarone, escitalopram, ondansetron, quinidine
h. Avoid rapid intravenous administration, when possible.
i. Avoid use of multiple agents with known risk.
j. Avoid use in patients with congenital long QT syndrome.

11. Agent-specific prevention
    a. Maximum recommended dose
        i. Citalopram 40 mg (20 mg if older than 60, hepatic impairment, poor cytochrome P450 [CYP] 2C19 metabolizers or concurrent CYP2C19 inhibitors) according to U.S. Food and Drug Administration (FDA) recommendations
        ii. Ondansetron 16 mg (32-mg dose removed from market)
        iii. Methadone
            (a) If risk factors are present, ECG should be performed at baseline and within 1 month.
            (b) ECG should be performed annually or if dose exceeds 120 mg daily.
    b. ECG monitoring
        i. Dofetilide
            (a) Specific recommendations in labeling require initiation in facility with continuous ECG monitoring and SCr monitoring for three consecutive days.
            (b) Baseline QTc must be 440 milliseconds or less (500 milliseconds or less in ventricular conduction abnormalities).
            (c) ECG monitoring is required 2-3 hours after administration of doses 1-5.
                (1) Reduce dose in half if QTc is more than 15% from baseline or greater than 500 milliseconds (greater than 550 milliseconds with ventricular conduction abnormalities) after first dose.
                (2) Discontinue therapy if QTc is greater than 500 milliseconds (greater than 550 milliseconds with ventricular conduction abnormalities) after doses 2-5.
        ii. Sotalol
            (a) Specific recommendations in labeling require initiation in facility with continuous ECG monitoring and SCr monitoring for three consecutive days.
            (b) Baseline QTc must be 450 milliseconds or less.
            (c) ECG monitoring required 2-4 hours after administration of doses 1-5. Discontinue therapy or reduce dose if QTc is greater than 500 milliseconds.

12. Management
    a. Discontinue offending agent, and hypokalemia, hypomagnesemia, and/or hypocalcemia should be corrected.
    b. Hemodynamically unstable – Defibrillation
    c. Hemodynamically stable – Intravenous magnesium 1–2 g (regardless of serum magnesium) for all patients, isoproterenol infusion at 2–10 mcg/minute or temporary overdrive pacing for recurrent TdP with bradycardia refractory to intravenous magnesium, and defibrillation in refractory cases
    d. For those without long QT syndrome, oral mexiletine 200–450 mg daily may prevent the recurrence of TdP refractory to discontinuation of QT-prolonging drugs.

**Patient Case**

2. A 48-year-old woman presents to the hospital with fever, chills, dyspnea, and sputum production. Community-acquired pneumonia is diagnosed, and the patient is initiated on azithromycin 500 mg intravenously and ceftriaxone 2 g intravenously. The next morning, her ECG reveals a QTc of 502 milliseconds (baseline 428 milliseconds). You receive a call from a hospitalist asking how to change her antibiotic regimen to reduce her risk of developing TdP. Which is the most appropriate response?
   A. Discontinue both azithromycin and ceftriaxone, and add moxifloxacin 400 mg intravenously daily.
   B. Discontinue only azithromycin, and add doxycycline 100 mg intravenously twice daily.
   C. Discontinue both azithromycin and ceftriaxone, and initiate a health care–associated pneumonia regimen (piperacillin/tazobactam 4.5 g intravenously every 6 hours, ciprofloxacin 500 mg intravenously every 8 hours, and vancomycin 1500 mg intravenously every 12 hours).
   D. Discontinue only azithromycin.

## IV. DRUG-INDUCED VALVULAR DISEASE

A. Uncommon Drug-Induced Disease: Manifests as aortic regurgitation, mitral regurgitation, tricuspid regurgitation, and mitral stenosis
   1. Involves changes to the morphology and functionality of the valvular leaflets as a result of exposure to certain medications
   2. All associated agents are structurally similar to serotonin and agonists of the serotonin-2B receptor.
      a. Receptors are located in the aortic and mitral leaflets as well as in the pulmonary arteries.
      b. Activation of serotonin-2B receptor causes collagen synthesis and fibroblast proliferation, resulting in valvulopathy (similar to valvular effects from carcinoid heart disease)

B. Associated Medications
   1. Bromocriptine
   2. Cabergoline
   3. Ergotamine
   4. Phentermine
   5. 3,4-methylenedioxy-methamphetamine (MDMA)

C. Risk Factors
   1. Prolonged exposure
   2. High dose (ergotamine greater than 6 mg/day; cabergoline cumulative dose greater than 1000 mg)

D. Prevention
   1. Reserve ergotamine use for migraine treatment when no other therapeutic options exist.
   2. Reserve bromocriptine for Parkinson's disease management behind other non-ergot dopamine agonists (ropinirole, pramipexole).
   3. Baseline echocardiogram when cabergoline used for prolactinemia
   4. If a high-risk agent is administered, conduct a thorough cardiac examination, and educate the patient on potential signs of adverse effects.

E. Management
   1. Discontinue offending agent.
   2. Perform echocardiogram to assess valve function.
   3. Treat HF symptoms.
   4. Valve replacement in severe cases

## V. DRUG-INDUCED PERICARDIAL DISEASE

A. Uncommon Drug-Induced Diseases, including pericarditis, pericardial effusions, and hemopericardium
   1. Pericarditis
      a. Most commonly from medications associated with drug-induced lupus
      b. Hydralazine, isoniazid, methyldopa, phenytoin, procainamide
      c. Hypersensitivity pericarditis with eosinophilia to penicillins is uncommon.
      d. Anticancer agents associated with cardiomyopathy may induce pericardiopathy.
   2. Pericardial effusions
      a. Most common agent is minoxidil, particularly in renal impairment.
      b. Mechanism not fully understood and usually deemed idiosyncratic in nature, but possibly related to uremia and vasodilation, causing sodium and fluid retention
   3. Hemopericardium: Occurrence largely described in case reports related to probable underlying pericarditis together with antithrombotic drug effect
      a. Thrombolytic therapy in ST-segment elevation myocardial infarction
      b. Anticoagulant therapy after CV surgery
      c. Monitor for cardiac tamponade.
   4. Management
      a. Pericarditis
         i. Discontinue offending agent.
         ii. NSAIDs or aspirin PLUS colchicine for acute pericarditis; may consider corticosteroids in cases of recurrent pericarditis
         iii. Pericardectomy
      b. Pericardial effusion/hemopericardium
         i. Discontinue offending agent.
         ii. Pericardiocentesis, pericardial window

## VI. DRUG-INDUCED HYPERTENSION

A. Defined as high blood pressure caused by using or withdrawing a medication

B. Several systems in the body are responsible for blood pressure regulation, including the renin-angiotensin-aldosterone system, adrenergic nervous system, hormonal regulation, and vascular endothelium.
   1. Hormonal regulation – Thyroid hormones, vasopressin, insulin, adrenal cortical hormones
   2. Vascular endothelium – Nitric oxide, bradykinin, endothelin, prostacyclin

C. Drug-Induced Hypertension – Occurs through several mechanisms related to interference with these the regulatory systems
   1. Volume retention
   2. Sympathomimetic activation
   3. Direct vasoconstriction
   4. Abrupt withdrawal of BBs or centrally acting α-agonists

D. Typically associated with an exacerbation rather than new-onset hypertension

E. Commonly associated medications and mechanisms (Table 7)

**Table 7.** Medications/Medication Classes Associated with Hypertension and Proposed Mechanisms

| Mechanism | Medications/Classes of Medications |
|---|---|
| Sympathetic nervous system stimulation | Amphetamine/amphetamine derivatives, caffeine, carfilzomib, cocaine, ephedrine, ergot alkaloids, MDMA, phenylephrine, pseudoephedrine, SNRIs, sorafenib, triptans, tricyclic antidepressants, tyrosine kinase inhibitors, vascular endothelial growth factor inhibitors, venlafaxine |
| Abrupt withdrawal | BBs, centrally acting α-agonists |
| Several mechanisms, including sympathetic simulation, vascular smooth muscle contraction, and sodium/water retention | Calcineurin inhibitors (cyclosporine, tacrolimus) |
| Mineralocorticoid receptor stimulation resulting in fluid-volume expansion | Corticosteroids (particularly fludrocortisone, hydrocortisone) |
| Fluid-volume expansion by increased RBC production | Erythropoiesis-stimulating agents |
| Increased production of angiotensinogen stimulating the RAAS | Estrogen-containing oral contraceptives, estrogen replacement therapy/hormone replacement therapy |
| Hypertensive emergency when tyramine-rich foods consumed | MAO inhibitors |
| Prostaglandin inhibition resulting in sodium/water retention | NSAIDs/COX2 inhibitors |
| Stimulation of the sympathetic nervous system and fluid-volume expansion | Testosterone |

RAAS = renin-angiotensin-aldosterone system; RBC = red blood cell; SNRI = serotonin-norepinephrine reuptake inhibitor..

F. Prevention
   1. Avoid associated agents in patients with established hypertension or risk of developing hypertension.
   2. Counsel patients taking monoamine oxidase (MAO) inhibitors about tyramine-containing foods (i.e., cheese, smoked or pickled meats/fish, red wine, chocolate, caffeine, beer). Consider changing to an alternative agent, if possible.
   3. Limit use of systemic corticosteroids, and change to inhaled or topical formulations, if possible.
   4. Consider changing from a serotonin-norepinephrine reuptake inhibitor to a selective serotonin reuptake inhibitor.
   5. Minimize exposure to NSAID therapy.
   6. Lifestyle modifications
   7. Assess for prescription and nonprescription agents, herbal products, food substances, and illicit drugs during patient interviews. Herbal and illicit substances include alcohol, amphetamines, cocaine, ma huang, ginseng, licorice, St. John's wort, and yohimbe.
   8. Counsel patients on importance of adhering to BBs or centrally acting α-agonists and avoiding discontinuing therapy abruptly.

G. Management
   1. Discontinue offending agent.
   2. In case of abrupt discontinuation of BBs or centrally acting α-agonists, reintroduce withdrawn agent and gradually taper off.
   3. Specific agent management
      a. Calcineurin inhibitors

i. Reduce dose, if possible.
ii. Consider changing from cyclosporine to tacrolimus.
iii. Dihydropyridine CCBs are preferred.

b. Erythropoiesis-stimulating agents
i. Discontinue when hemoglobin increases above 13 g/dL.
ii. Reduce dose when hemoglobin concentrations approach 12 g/dL.

c. MAO inhibitors (hypertensive crisis): Treat with a short-acting intravenous agent (esmolol, nitroprusside).

## VII. DRUG-INDUCED HYPOTENSION

A. Commonly related to orthostatic hypotension, defined as a decrease of at least 20 mm Hg or 10 mm Hg in systolic or diastolic blood pressure, respectively, within 3 minutes, and is usually from autonomic failure

B. Causes
1. Intended drug activity (i.e., antihypertensive agents)
2. Unintended drug activity/adverse effect in the setting of autonomic failure or other scenarios

C. Associated Medications and Mechanisms (Table 8)

**Table 8.** Medications/Classes of Medications Associated with Hypotension and Proposed Mechanisms

| Mechanism | Medications/Classes of Medications |
|---|---|
| Antihypertensive effect | α-Blockers, ACE inhibitors, aliskiren, ARBs, BBs, CCBs, centrally acting α-agonists, dexmedetomidine, diuretics, fenoldopam, nitrates, nitroprusside, peripherally acting arterial vasodilators, sacubitril/valsartan |
| Arteriolar vasodilation | Amifostine, epoprostenol, iloprost, treprostinil |
| Central and/or peripheral α inhibition | Alfuzosin, atypical and typical antipsychotics, sedative hypnotics, selective serontonin reuptake inhibitors, tamsulosin, tricyclic antidepressants, trazodone |
| Central and peripheral muscarinic stimulation, resulting in a vagotonic effect on the heart | Donepezil, galantamine |
| Dopamine agonist/increased dopamine concentration | Bromocriptine, carbidopa/levodopa, entacapone, fenoldopam, pramipexole, rasagiline, ropinirole, selegiline, tolcapone |
| Endothelin-1 inhibition | Ambrisentan, bosentan, macitentan |
| Histamine release | Atracurium, codeine, hydrocodone, hydromorphone, fentanyl, morphine, succinylcholine, vancomycin |
| Intravascular volume depletion | Diuretics, mannitol, sodium-glucose cotransporter 2 inhibitors |
| Peripheral vasodilation | Dobutamine |
| PDE inhibition | Milrinone (PDE-3)<br>Avanafil, sildenafil, tadalafil, vardenafil (PDE-5) |
| Solvent in intravenous formulation | Amiodarone, phenytoin |

**Table 8.** Medications/Classes of Medications Associated with Hypotension and Proposed Mechanisms

| Mechanism | Medications/Classes of Medications |
|---|---|
| Soluble guanylate cyclase stimulation resulting in cyclic GMP production and vasodilation | Riociguat |
| Vascular smooth muscle relaxation | Chlorpromazine, prochlorperazine, promethazine |
| Venous smooth muscle vasodilation | Propofol |

ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; GMP = guanosine monophosphate.

D. Prevention
   1. Start antihypertensive therapy with low doses, and titrate slowly.
   2. Counsel patients to rise slowly from sitting position.
   3. Provide antihistamine treatment as needed to prevent histamine-induced hypotension.
   4. Avoid concomitant phosphodiesterase type 5 inhibitors and either nitrates or riociguat.
   5. Limit alcohol and large, carbohydrate-rich meals.
   6. Stay hydrated with at least 2–2.5 L of fluid daily.
   7. Abdominal binders, compression stockings, or physical maneuvers such as legs crossed, squatting, isometric exercises, toe raises or thigh, buttock, and calf muscle contractions, and bending over at the waist to control symptoms

E. Management
   1. Dose reduction of offending agent or administration of slow rate of intravenous fluids as initial therapy
   2. In severe cases, fluid bolus with or without additional vasopressor therapy
   3. Chronic hypotension can be treated with droxidopa, fludrocortisone, or midodrine.
   4. Discontinue offending medication, change to a different agent within the same drug class with a lower incidence of hypotension, or move administration of medication(s) to bedtime.
   5. Cautiously add salt to diet (6–10 g of sodium chloride).

**Patient Case**

3. A 75-year-old man is admitted to the hospital after his home health nurse notes hypotension during a weekly home visit. On presentation, his vital signs include blood pressure 72/48 mm Hg and heart rate 70 beats/minute. His medical history includes depression and dementia. His medication regimen includes donepezil 5 mg/day, venlafaxine extended release 75 mg/day, ginseng 200 mg/day, memantine 5 mg twice daily, and a multivitamin 1 tablet/day. Which medication is most likely contributing to his presentation?
   A. Donepezil.
   B. Venlafaxine.
   C. Ginseng.
   D. Memantine.

## VIII. DRUG-INDUCED HEART FAILURE

A. Medications – Can cause new-onset heart failure (HF), but most commonly HF exacerbations

B. Several Mechanisms for Drug-Induced HF (Box 1)

**Box 1.** Mechanisms for Drug-Induced HF

- Direct cardiotoxicity
- Negative inotropic or chronotropic effects
- Fluid/water or sodium retention
- Interference with beneficial HF medications
- Unknown

HF = heart failure.

C. More than 70 medications associated with Drug-Induced HF or HF exacerbation

D. Agents with high risk and evidence (Table 9)

**Table 9.** Medications/Classes of Medications Associated with High Risk of HF and Proposed Mechanisms

| Mechanism | Medications |
|---|---|
| Arrhythmogenic | Cilostazol, citalopram |
| Direct cardiotoxicity | Amphotericin B, anagrelide, anesthetics, anthracyclines, bevacizumab, chloroquine, clozapine, cyclophosphamide, hydroxychloroquine, ifosfamide, interferon-α, interleukin-2, lapatinib, lithium, stimulants, sunitinib, TNFα inhibitors, trastuzumab |
| Fluid/water retention | Corticosteroids, COX-2 inhibitors NSAIDs, thiazolidinediones |
| Hypertension | NSAIDs |
| Interference with HF medications | NSAIDs |
| Negative inotropic/chronotropic effects | Amitriptyline, diltiazem, disopyramide, dronedarone, flecainide, ibutilide, imipramine, itraconazole, ketamine, nortriptyline, propafenone, sotalol, verapamil |
| Valvular damage | Appetite suppressants, bromocriptine, cabergoline, ergotamine |
| Unknown | Alcohol, alogliptin, amphotericin B, antimetabolites, bosentan, cocaine, epoprostenol, methamphetamines, pramipexole, ropinirole, saxagliptin, sitagliptin |

COX-2 = cyclooxygenase 2; TNFα = tumor necrosis factor alpha.

E. Risk Factors
   1. Preexisting left ventricular dysfunction or hypertrophy
   2. History of coronary artery disease
   3. Risk factors for coronary artery disease or left ventricular dysfunction
   4. Advanced age

F. Prevention
   1. Avoid medications associated with HF or HF exacerbation as much as possible in patients with known HF.
   2. Counsel patients to report signs and symptoms of HF exacerbation.
   3. BBs: "Start low and go slow" with initiation and titration.
   4. Routinely screen patients' medication lists to evaluate for potential offending agents.

G. Treatment
   1. Discontinue offending agent.
   2. Aggressive diuresis

3. General supportive care
4. Standard HF management
5. Promote transitions of care (TOC) programs, which can help with medication education and screening/evaluating medication regimens for potential medications that may exacerbate or cause HF.
    a. HF is a top diagnosis for inpatient stays.
    b. Hospital Readmissions Reduction Program focuses on readmissions within 30 days of six conditions.
        i. Acute myocardial infarction, chronic obstructive pulmonary disease (COPD), HF, pneumonia, coronary artery bypass graft (CABG) surgery, and elective primary total hip arthroplasty and/or total knee arthroplasty
    c. Estimated that one in four patients with HF will be readmitted within 30 days and one in two within 90 days
    d. Readmissions are multifactorial, primarily driven by medication mismanagement and lack of collaboration from inpatient to outpatient care.
    e. Patients should receive medication reconciliation before hospital discharge, followed by a telephonic follow-up within 48–72 hours with or without a second call within 30 days.
    f. TOC education is recommended to consist of:
        i. Basic principles of HF, including signs and symptoms
        ii. Diet (sodium and fluid limits)
        iii. Self-care expectations (e.g., keep a log of home weight)
        iv. Medication education and counseling such as exacerbating agents and non-prescription substances

**Patient Case**

4. A 56-year-old man with obesity discharged from the hospital last month presents to the clinic to establish care with a new primary care physician. The patient initially presented to the hospital with tachycardia, where he was found to have new-onset atrial fibrillation with rapid ventricular response. A new diagnosis of type 2 diabetes was also made during the admission. His discharge regimen included amiodarone 200 mg/day, diltiazem 240 mg/daily, pioglitazone 30 mg/day, and insulin glargine 15 units daily. The patient reports feeling short of breath, with lower-extremity swelling that started about 2 weeks after discharge. Which discharge medication is most likely contributing to these symptoms?

    A. Amiodarone.

    B. Diltiazem.

    C. Pioglitazone.

    D. Insulin glargine.

## IX. DRUG-INDUCED MYOCARDIAL ISCHEMIA/CARDIOVASCULAR RISK

A. Myocardial Ischemia
    1. Classically because of mismatch of oxygen supply and oxygen demand
    2. Can manifest as stable angina or myocardial infarction/acute coronary syndrome
    3. Drug-induced myocardial ischemia most commonly occurs in patients with underlying atherosclerotic disease, except for coronary vasospasm.
    4. Varying mechanisms for drug-induced ischemia
        a. Drug withdrawal
        b. Increased oxygen demand (tachycardia, hypertension)
        c. Decreased oxygen supply (vasoconstriction, vasospasm, abrupt drop in blood pressure)
    5. Medications associated with myocardial ischemia (Table 10)

**Table 10.** Medications/Classes of Medications Associated with Myocardial Ischemia and Proposed Mechanisms

| Medications/ Classes of Medications | Mechanism | | |
|---|---|---|---|
| | Drug Withdrawal | Increased Oxygen Demand | Decreased Oxygen Supply |
| Adenosine, dipyridamole, nitroprusside, regadenoson | | | ✓ coronary steal |
| Amphetamines/ methamphetamines | | ✓ hypertension, tachycardia | ✓ vasospasm |
| BBs | ✓ | | |

**Table 10.** Medications/Classes of Medications Associated with Myocardial Ischemia and Proposed Mechanisms *(Cont'd)*

| Medications/ Classes of Medications | Mechanism | | |
|---|---|---|---|
| | Drug Withdrawal | Increased Oxygen Demand | Decreased Oxygen Supply |
| CCBs | | ✓ reflex tachycardia | |
| Centrally acting α-agonists | ✓ | | |
| Cocaine | | ✓ hypertension, increased contractility, tachycardia | ✓ platelet aggregation, vasospasm, vasoconstriction |
| Dobutamine | | ✓ tachycardia | |
| Ergot alkaloids | | ✓ hypertension | ✓ vasospasm, vasoconstriction |
| Inhaled β-agonists | | ✓ increased contractility, tachycardia | |
| Milrinone | | ✓ tachycardia | |
| Nifedipine (immediate release) | | | ✓ acute hypotension |
| $P2Y_{12}$ inhibitors | ✓ | | |
| Phenylephrine | | ✓ hypertension | ✓ vasoconstriction |
| PDE-5 inhibitors + nitrate use | | | ✓ acute hypotension |
| PDE-5 inhibitors + riociguat | | | ✓ acute hypotension |
| Triptans | | ✓ hypertension | ✓ vasoconstriction, vasospasm |
| Vasodilators (hydralazine, minoxidil) | | ✓ reflex tachycardia | |

6. Prevention
    a. Avoid medications associated with myocardial ischemia in patients with known atherosclerotic disease.
    b. Counsel patients taking BBs, centrally acting α-agonists, and $P2Y_{12}$ inhibitors about the importance of adherence to medications and the danger of missed doses.
    c. Counsel patients taking PDE-5 inhibitors to avoid nitrates and riociguat; if patients are presenting to the emergency department with anginal symptoms, disclose use to providers.
    d. Consider alternative testing to adenosine/dipyridamole/regadenoson for active chest pain.
    e. Use ergot alkaloids only for migraine therapy when there are no other therapeutic options.
    f. Triptans: Contraindicated in patients with known coronary disease
7. Treatment
    a. Discontinue offending agent.
    b. If unable to discontinue, maximize antianginal therapy.
    c. Resume medication in the setting of ischemia from drug withdrawal.

d. Standard guideline-directed medical therapy as usual
    i. Acute coronary syndrome (ACS) is a top diagnosis for inpatient stays.
    ii. ACS and CABG surgical procedures are within the Hospital Readmissions Reduction Program.

8. Cocaine-induced myocardial ischemia/acute coronary syndrome treatment (Figure 1; Box 2)

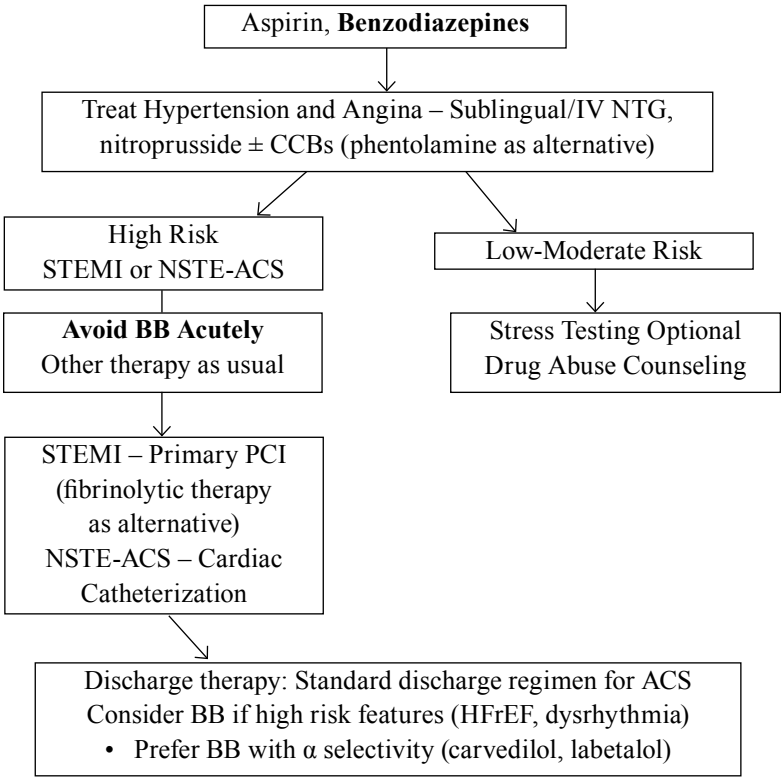



**Figure 1.** Management of cocaine-induced myocardial ischemia/acute coronary syndrome.
Adapted from: American Heart Association, Inc. McCord J, Jneid H, Hollander JE, et al. Management of cocaine-associated chest pain and myocardial infarction: a scientific statement from the American Heart Association Acute Cardiac Care Committee of the Council on Clinical Cardiology. Circulation 2008;117:1897-907.

ACS = acute coronary syndrome; BB = β-blocker; CCB = calcium channel blocker; HFrEF = heart failure with reduced ejection fraction; IV = intravenous(ly); NSTE = non–ST-segment elevation; NTG = nitroglycerin; PCI = percutaneous coronary intervention; STEMI = ST-segment elevation myocardial infarction.

**Box 2.** AHA/ACCF Guideline Recommendations for Cocaine-Induced NSTE-ACS

| |
|---|
| **Class I:** Patients with NSTE-ACS and a recent history of cocaine use should be treated the same as other patients with NSTE-ACS. Exception: In those with signs of acute intoxication (e.g., euphoria, tachycardia, and/or hypertension) and BB use (LOE C) |
| **Class IIa:** Benzodiazepines alone or in combination with nitroglycerin are reasonable for the management of hypertension and tachycardia in acute intoxication. (LOE C) |
| **Class III:** BBs should not be used in patients with ACS and a recent history of cocaine use who have signs of acute intoxication because of the risk of coronary spasm. (LOE C) |

ACS = acute coronary syndrome; AHA/ACCF = American Heart Association/American College of Cardiology Foundation; BB = β-blocker; LOE = level of evidence; NSTE-ACS = non–ST-segment elevation acute coronary syndrome.

9. Methamphetamine-induced myocardial ischemia/acute coronary syndrome should be managed the same as cocaine induced (Figure 1; Box 2).

**Patient Case**

5. A 52-year-old man presents to the cardio-oncology clinic for difficult-to-control blood pressure. He has a diagnosis of metastatic colorectal cancer and is receiving a regimen of bevacizumab plus FOLFOX (fluorouracil, leucovorin, oxaliplatin). Which agent in this regimen is most associated with the development of hypertension?
   A. Bevacizumab.
   B. Fluorouracil.
   C. Leucovorin.
   D. Oxaliplatin.

B. CV Risk
   1. Several classes of medications have been associated with increased CV risk from chronic use.
   2. Commonly, these associated agents alter the risk factors known to contribute to CV disease (e.g., hypertension, diabetes, elevated LDL, obesity).
   3. These patients tend to present with acute coronary syndrome and no identifiable risk factors.
   4. Medications associated with increased CV risk
      a. Illicit drugs (cocaine, amphetamine/methamphetamine, MDMA, nicotine, heroin, anabolic steroids)
      b. Medications associated with hypertension (see section V – minus agents associated with drug withdrawal)
      c. Other medications (Table 11)

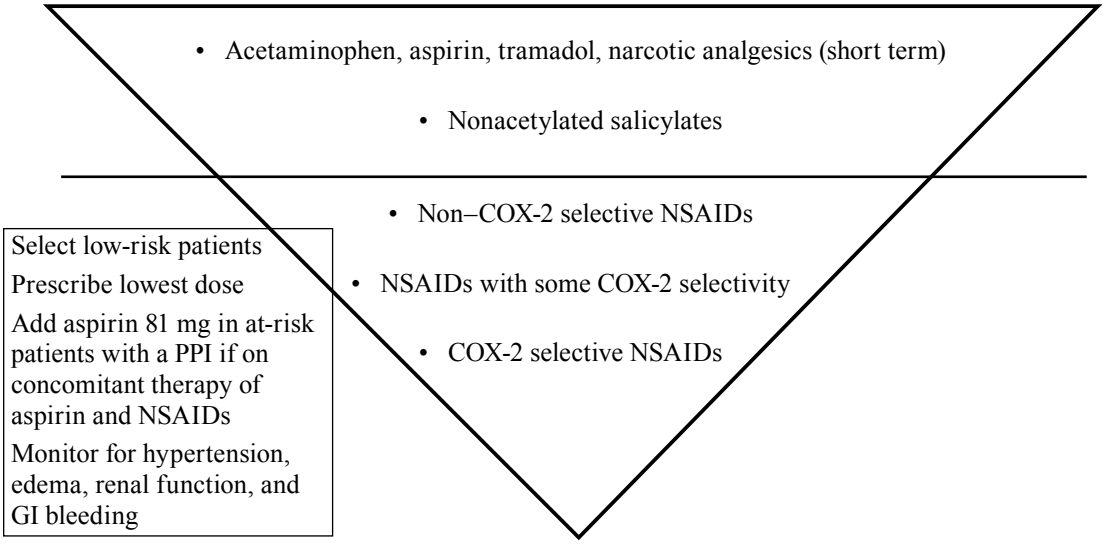
**Table 11.** Medications/Classes of Medications Associated with Increased CV Risk

| | |
|---|---|
| Antiretroviral therapy (ART) – Select agents | • Older-generation protease inhibitors – Indinavir, lopinavir/ritonavir<br>• Nucleoside reverse transcriptase inhibitor – Abacavir, didanosine<br>• Hyperlipidemia, diabetes, insulin resistance, and visceral fat accumulation<br>• HIV itself is an established risk factor for CV disease |
| Atypical antipsychotics | • Weight gain, glucose abnormalities, hyperlipidemia<br>• Schizophrenia associated with higher rates of smoking, hypertension, diabetes, and obesity |
| Calcineurin inhibitors (cyclosporine, tacrolimus) | • Endothelial dysfunction, hypertension, left ventricular dysfunction, hyperlipidemia<br>• CV disease is the most common cause of death after organ transplantation |
| Corticosteroids | • Hyperlipidemia, diabetes, endothelial dysfunction, hypertension |
| Erythropoiesis-stimulating agents | • CHOIR study (epoetin) – Increased risk of CV events in group with a targeted hemoglobin of 13.5 g/dL<br>• TARGET study (darbepoetin) – Increased risk of stroke with target hemoglobin concentration of 13 g/dL<br>• Black box warning |
| Febuxostat | • Significant increased risk of death from any cause and heart-related death compared with allopurinol<br>• Black box warning |

**Table 11.** Medications/Classes of Medications Associated with Increased CV Risk *(Cont'd)*

| | |
|---|---|
| Gonadotropin-releasing hormone agonists | • Goserelin, histrelin, leuprolide, nafarelin, triptorelin<br>• Reduced insulin sensitivity, weight gain, hypertriglyceridemia<br>• Significant increases in diabetes and CV events in prostate cancer trials |
| Hormone replacement therapy (HRT)<br>Estrogen + progesterone | • Women's Health Initiative (primary prevention) found a significant increase in CV events (acute myocardial infarction, silent myocardial infarction, CV death) in the HRT arm vs. placebo<br>• HERS trial (secondary prevention) found no advantage of HRT in reducing nonfatal myocardial infarctions or CV death vs. placebo |
| NSAIDs/COX-2 inhibitors | • Proposed mechanism: Imbalance of COX-1 and COX-2 inhibition leading to platelet aggregation from thromboxane $A_2$ production<br>• An event can occur within the first week of use<br>• Risk of CV toxicity associated with degree of COX-2 inhibition (rofecoxib > diclofenac > meloxicam > celecoxib (low dose) = ibuprofen = naproxen)<br>• Findings from the PRECISION trial indicate similar CV risk between celecoxib (100–200 mg twice daily), ibuprofen (600–800 mg three times daily), and naproxen (375–500 mg daily)<br>• All agents in this class carry a black box warning for CV risk<br>• Comments: Rofecoxib and valdecoxib (both COX-2 inhibitors) were removed from the market because of increased CV risk |

5. Risk minimization
    a. Public health initiative warning of the dangers surrounding CV disease associated with illicit drugs
    b. Counsel patients on the CV risk when starting associated medications and discuss symptoms.
    c. Avoid these medications in patients with established CV risk.
    d. Selected agents
        i. Antiretroviral therapy – Choose alternative agents, when possible.
        ii. Atypical antipsychotics – Consensus recommendations available for initiating and providing ongoing monitoring – Personal/family history, weight (body mass index), waist circumference, blood pressure, fasting blood glucose, fasting lipid profile
        iii. Erythropoiesis-stimulating agents – Maintain hemoglobin concentrations at 10–11.5 g/dL. Begin therapy when hemoglobin is less than 10 g/dL and decrease the dose when hemoglobin rises above 11 g/dL.
        iv. Gonadotropin-releasing hormone agonists – FDA alert (2010) to check A1C periodically and monitor for signs/symptoms of CV disease
        v. Hormone replacement therapy – Use the lowest effective dose for the shortest period.
        vi. NSAIDs/cyclooxygenase-2 (COX-2) inhibitors: American Heart Association stepwise approach (Figure 2; Box 3)




COX = cyclooxygenase; GI = gastrointestinal; NSAID = nonsteroidal anti-inflammatory drug; PPI = proton pump inhibitor.

**Figure 2.** Stepwise approach to musculoskeletal pain management in patients with known cardiovascular disease or risk of cardiovascular disease.

Adapted from: American Heart Association, Inc. Antman EM, Bennett JS, Daugherty A, et al. Use of nonsteroidal antiinflammatory drugs: an update for clinicians: a scientific statement from the American Heart Association. Circulation 2007;115:1634-42.

**Box 3.** NSAID Recommendations from AHA/ACCF 2014 NSTE-ACS Guidelines

| |
|---|
| **Class I:** Before discharge, the need for treatment of chronic musculoskeletal discomfort should be assessed. Pain treatment should begin with acetaminophen, nonacetylated salicylates, tramadol, and small-dose narcotics, which should be used before NSAIDs. (LOE C) |
| **Class IIa:** It is reasonable to use nonselective NSAIDs such as naproxen when initial therapy is insufficient. (LOE C) |
| **Class IIb:** NSAIDs with increasing relative COX-2 selectivity may be considered when intolerable discomfort persists despite attempts at alternative therapy and nonselective NSAID therapy. If considered, use the lowest effective dose for the shortest duration. (LOE C) |
| **Class III:** NSAIDs with increasing COX-2 selectivity should not be used when alternative agents provide adequate pain relief. NSAIDs (except for aspirin) should not be initiated or continued during hospitalization for ACS because of an increased risk of MACE. (LOE B) |

COX-2 = cyclooxygenase-2; MACE = major adverse cardiovascular events; NSAID = nonsteroidal anti-inflammatory.

**Patient Case**

6. A 79-year-old woman (ideal body weight 56 kg) presents to the hospital with new-onset atrial fibrillation. She is initiated on unfractionated heparin during day 1 of her hospitalization. Her platelet count on day 1 is 185,000/mm$^3$. Her hospital course is complicated by pneumonia, necessitating a prolonged heparin infusion. On day 7 of heparin therapy, her platelet count has decreased to 75,000/mm$^3$. Heparin-induced thrombocytopenia is suspected, and a 4Ts score of 7 is calculated (thrombocytopenia 2 points; timing 2 points; thrombosis 0 points; other 1 point). Additional laboratory values on day 7 include SCr 1.5 mg/dL with normal AST, ALT, and total bilirubin values. Which alternative anticoagulant would be most appropriate in this patient?
   A. Enoxaparin 60 mg subcutaneously every 12 hours.
   B. Fondaparinux 7.5 mg subcutaneously daily.
   C. Argatroban 1 mcg/kg/minute.
   D. Bivalirudin 0.1 mcg/kg/hour infusion.

## X. DRUGS TO AVOID IN CARDIOVASCULAR DISEASE

A. Second- and Third-Degree Heart Block – Medications listed in Table 1

B. Congenital Long QT Syndrome – Medications listed in Table 6

C. Hypertension – Medications listed in Table 7

D. Heart Failure – Medications listed in Table 9

E. Coronary Artery Disease – Cocaine, nicotine, class 1A and IC antiarrhythmics, hormone replacement therapy, COX-2 selective NSAIDs (unless no other option exists), NSAIDs

F. Clarithromycin - FDA warning related to increased risk of all-cause mortality in patients with established cardiovascular disease. Avoid use and consider alternative antibiotic.

G. Febuxostat - Increased risk of all-cause mortality and CV mortality compared with allopurinol

H. Herbal/Alternative Medications
   1. Bitter orange – Contains synephrine, which may cause tachycardia, QT prolongation, angina, and myocardial infarction
   2. European elder – Additive diuretic effect
   3. Garlic – Use with caution in combination with antiplatelet/anticoagulant therapy because of bleeding risk from additional antiplatelet activity.
   4. Gingko – Use with caution in combination with antiplatelet/anticoagulant therapy because of bleeding risk from additional antiplatelet activity.
   5. Ginseng – May increase blood pressure
   6. Goldenseal – Inhibits CYP2D6 and CYP3A4, resulting in potential drug interactions
   7. Hawthorn – Potential drug interaction with digoxin, resulting in enhanced digoxin activity
   8. Licorice root – Stimulates mineralocorticoid receptor, which results in increased fluid volume and increased risk of edema and hypertension. Caution in patients with hypertension and heart failure. Hypokalemia risk may be additive.
   9. St. John's wort – Strong CYP3A4 inducer (may decrease statin effectiveness)
   10. Ma Huang – contains ephedra, which may cause arrhythmias, hypertension, HF, MI, stroke

## XI. CARDIO-ONCOLOGY

A. Overview
   1. Recognized subspecialty in cardiology focused on the CV care of patients with cancer
   2. Intersection of cancer and CV disease
      a. Result of targeted oncology therapies that can cause CV, thrombotic, or metabolic complications
      b. Cardiotoxicities of chemotherapeutic agents include arrhythmias, hypertension, hypotension, HF, and myocardial ischemia.
         i. Direct effects include myocardial cell injury resulting in dysfunction.
         ii. Indirect effects include endothelial dysfunction, ischemia caused by thrombosis, and hemodynamic alterations.
      c. Unanswered questions remain related to CV risk from radiation and prevalence of anticancer drug–induced CV disease.
      d. In general, a key consideration is aiming to minimize the use of cardiotoxic drugs, when possible.
      e. ACE inhibitors, ARBs, BBs, and statin therapy are commonly considered for management.
      f. Dexrazoxane/liposomal anthracyclines should be considered for patients treated with anthracyclines.
   3. Patients at higher risk of CV toxicity
      a. Receiving a high-dose anthracycline
      b. Receiving high-dose radiotherapy for heart
      c. Receiving low-dose anthracycline, Bcr-Abl kinase inhibitors, HER2 inhibitors, proteasome inhibitors, or vascular endothelial growth factor (VEGF) inhibitors plus any of the following factors:
         i. Age older than 60
         ii. Lower-dose radiotherapy for heart
         iii. Two or more of the following risk factors: smoking, hypertension, diabetes, dyslipidemia, chronic renal insufficiency, and obesity
      d. Previous heart disease
      e. Elevated N-terminal proB-type natriuretic peptide (NT-pro-BNP) or BNP, TTE, and/or troponin before initiation of anticancer treatment
   4. An ECG and physical examination are recommended for all patients starting cancer therapy as part of their baseline CV risk assessment.

B. Management of anticancer therapy–induced arrhythmias (Table 12)
   1. Atrial fibrillation
      a. Consider alternative therapies, if possible.
      b. Management as usual (see Arrhythmia chapter for details)
         i. Consider drug-drug interaction with rate and rhythm control therapy (i.e., digoxin, non-DHP CCBs are typically avoided).
         ii. Non-vitamin K oral anticoagulants or low-molecular-weight heparins (LMWHs) for stroke prevention
   2. Bradycardia/AV block
      a. Consider alternative therapies, if possible.
      b. Symptomatic – Consider isoproterenol, temporary pacemaker
      c. Thalidomide – Incidence (around 25%–50%); if no alternative agent available, consider permanent pacemaker to allow continued treatment with thalidomide
   3. TdP
      a. Prevention
         i. Maintain normal magnesium, potassium, and calcium concentrations.
         ii. Renal adjustment – Arsenic trioxide, oxaliplatin, vandetanib

   b. Consider treatment alternative if QTc is greater than 500 milliseconds, QT prolongation is greater than 60 milliseconds, or arrhythmias occur.
   c. Management as usual (see TdP section in this chapter)
4. Ventricular arrhythmias
   a. Consider alternative therapies, if possible.
   b. Management as usual (see Arrhythmia chapter for details)
5. Bcr-Abl inhibitors and VEGF inhibitors have an increased risk of QT prolongation.

**Table 12.** Anticancer Therapies Associated with Arrhythmias

| Arrhythmia | Medications/Classes of Medications |
|---|---|
| Atrial fibrillation | Anthracyclines, capecitabine, cisplatin, cyclophosphamide, fluorouracil, ibrutinib, interleukin-2, paclitaxel, ponatinib, rituximab, sorafenib |
| AV block | Anthracyclines, arsenic trioxide, bortezomib, cyclophosphamide, fluorouracil |
| Bradycardia | Anthracyclines, capecitabine, cisplatin, fluorouracil, paclitaxel, thalidomide |
| Torsades de pointes | Arsenic trioxide, glasdegib, mobocertinib, nilotinib, oxaliplatin, pazopanib, ribociclib, sunitinib, toremifene, vandetanib |
| Ventricular tachycardia | Anthracyclines, arsenic trioxide, cisplatin, cyclophosphamide, fluorouracil, ibrutinib, interleukin-2 |

C. Anticancer Therapy–Induced Hypertension (Table 13)
   1. Commonly associated agents cause VEGF inhibition.
      a. Monoclonal antibody–based tyrosine kinase inhibitors – Bevacizumab, ziv-aflibercept
      b. Small-molecule tyrosine kinase inhibitors – Axitinib, cabozantinib, lenvatinib, mobocertinib, pazopanib, regorafenib, sorafenib, sunitinib, trametinib, vandetanib
   2. Management
      a. Initiate antihypertensive therapy if blood pressure is greater than 140/90 mm Hg or diastolic blood pressure increases by 20 mm Hg.
      b. Hold anticancer therapy if systolic blood pressure rises above 160 mm Hg or diastolic blood pressure rises above 100 mm Hg.
      c. Consider discontinuing anticancer therapy if systolic blood pressure rises above 180 mm Hg, diastolic blood pressure rises above 110 mm Hg, or patient has hypertensive crisis.
      d. Antihypertensive drugs of choice – ACE inhibitors, ARBs, DHP CCBs
         i. Non-DHP CCBs should be avoided because of drug-drug interactions.
   3. Surveillance
      a. Anthracycline therapy – Echocardiogram, natriuretic peptides, troponin
         i. If the cumulative dose is greater than 250 mg/m$^2$ of doxorubicin or equivalent and then before each additional dose of 50 mg/m$^2$
         ii. At the end of therapy and 3 months later in those with a cumulative dose greater than 250 mg/m$^2$ of doxorubicin or equivalent
      b. HER2-targeted therapy (lapatinib, pertuzumab, trastuzumab) – Echocardiogram:
         i. Every 3 months during treatment
         ii. No routine testing if asymptomatic after therapy completed
         iii. Echocardiogram 6 months after therapy completed if history of anthracycline use
      c. Radiation therapy
         i. Yearly: ECG, echocardiogram if indicated
         ii. 5 years after radiation: ECG, echocardiogram
         iii. 10 years after radiation: ECG, echocardiogram, stress test, or coronary computed tomography (CT)

4. Prevention
    a. General prevention
        i. Consider cardioprotection (ACE inhibitors, BBs) in select cases.
        ii. Ejection fraction decrease of greater than 10% to a value less than 50% or an ejection fraction decrease of greater than 20% from preexposure
        iii. Absolute global longitudinal strain decrease of 5% or greater or a relative decrease of 12% or greater from preexposure
        iv. Myocardial damage assessed by troponin elevation
        v. Statins should be considered for primary prevention.
    b. Agent-specific prevention
        i. Anthracyclines
            (a) Maximum cumulative dose (450–550 mg/m$^2$)
            (b) Prolonged infusion times or liposomal formulations
            (c) Dexrazoxane
            (d) Withhold if ejection fraction less than 40%
            (e) ACE inhibitors, ARBs, and/or BBs recommended for HF are suggested in most cases for CV protection
            (f) HF therapy for those with symptomatic disease or signs of structural damage who are asymptomatic
        ii. HER2-targeted therapy
            (a) Avoid concomitant anthracycline use.
            (b) Withhold if ejection fraction less than 40%
            (c) ACE inhibitors, ARBs, and/or BBs recommended for HF are suggested in most cases for CV protection
            (d) HF therapy for those with symptomatic disease or signs of structural damage that are asymptomatic
        iii. VEGF inhibitors – ACE inhibitors, ARBs, and DHP CCBs are preferred antihypertensive agents.

**Table 13.** Anticancer Therapies with High Risk of HF and Proposed Mechanisms

| Mechanism | Medications |
|---|---|
| Direct cardiotoxicity or indirectly because of myocarditis, ischemia, hypertension, arrhythmias, or valvular disease | Abiraterone, anthracyclines, atezolizumab, avelumab, axicabtagene ciloleucel, bevacizumab, bicalutamide, bosutinib, capecitabine, cyclophosphamide, dasatinib, decitabine, docetaxel, durvalumab, fludarabine, fluorouracil, flutamide, goserelin, ifosfamide, ipilimumab, lapatinib, lenalidomide, leuprorelin, melphalan, neratinib, nilotinib, nilutamide, nivolumab, pembrolizumab, pertuzumab, pomalidomide, ponatinib, proteasome inhibitors, radiation therapy, RAF + MEK inhibitors, ramucirumab, rituximab, tisagenlecleucel, trastuzumab, tucatinib, tyrosine kinase inhibitors |
| Hypertension | Axitinib, bevacizumab, cabozantinib, lenvatinib, pazopanib, regorafenib, sorafenib, sunitinib, trametinib, vandetanib, ziv-aflibercept |

MEK = mitogen-activated protein kinase; RAF = rapidly accelerated fibrosarcoma.

D. Anticancer Therapy–Induced Myocardial Ischemia
    1. Related to vasospasm and arterial thrombosis
    2. Features – ECG changes, cardiac biomarker elevations possible, patient-reported chest pain
    3. Therapies – Bcr-Abl inhibitors, capecitabine, cisplatin, fluorouracil, lenalidomide, proteasome inhibitors, radiation therapy, VEGF inhibitors

4. Monitoring and management
    a. Concomitant fluorouracil and capecitabine – Consider regular ECG and hold chemotherapy if ischemia occurs.
    b. Drug rechallenge after coronary spasm if no alternative exists
        i. Consider hospital admission for close observation.
        ii. Pretreat with nitrates and/or CCBs.

E. Anticancer Therapy-Induced Myocarditis
1. High mortality rate of 50%
2. Immune checkpoint inhibitors
    a. Atezolizumab, avelumab, cemiplimab, durvalumab, ipilimumab, nivolumab, pembrolizumab, tremelimumab
3. Monitoring and management
    a. Check ECG, troponin, and new CV symptoms before therapy begins.
    b. If myocarditis is suspected, hold chemotherapy and initiate high-dose corticosteroids.
    c. Intensification of immunosuppressive therapy in those refractory to steroids

F. Anticancer Therapy–Induced Pericarditis
1. Immune checkpoint inhibitors
2. Management
    a. Prednisolone and/or colchicine
    b. Hold anticancer therapy if moderate to severe pericardial effusion is present.

## XII. HEPARIN-INDUCED THROMBOCYTOPENIA

A. Overview
1. Overall incidence of heparin-induced thrombocytopenia (HIT) is 0.1%–5%.
    a. 25%–50% of patients with HIT develop thrombosis (HITT).
    b. Strong risk factors for development of HIT
        i. Duration of heparin therapy (more than 5 days)
        ii. Type (unfractionated heparin [UFH] >LMWH >fondaparinux; UFH has 10-fold higher incidence than LMWH) and dosage of heparin (higher dose = higher risk)
        iii. The indication for treatment (surgical, CV, and orthopedic) and trauma patients with higher risk
        iv. Patient's sex (female > male)
    c. Any type of exposure can cause the formation of HIT antibodies (e.g., heparin flushes, heparin-coated catheters).
    d. Patients with HIT present with thrombocytopenia (usually with a 50% or greater decrease in Plt [to below 150,000/mm3 in most]) occurring either immediately or up to 3 weeks after heparin exposure.
    e. HIT results in a paradoxical prothrombotic state, with 50%–89% of patients developing thrombosis if not treated.
    f. Definitions
        i. HIT type 1: Non–immune-mediated mild thrombocytopenia that occurs in 10%–20% of patients within 48–72 hours of UFH use (usually resolves despite continued heparin therapy and is not associated with thrombosis)

ii. HIT type 2: Immune-mediated thrombocytopenia that occurs 4–10 days after exposure to heparin and has associated thrombosis (clinically, when referring to HIT, typically referring to type 2 HIT)

g. Differs from non–immune-mediated mild thrombocytopenia that occurs in 10%–20% of patients within 48–72 hours of unfractionated heparin use (HIT type I)
   i. Usually resolves despite continued therapy and is not associated with thrombosis

2. Pathophysiology
   a. Formation of heparin/platelet factor-4 complex and binding of IgG antibodies causing platelet activation and increased risk of thrombosis
   b. Platelet activation results in thrombin generation in addition to other factors responsible for thrombus formation. Thrombocytopenia occurs because of the removal of immunoglobulin G–coated platelets by macrophages, consumption of platelets at the site of thrombosis or within thrombi, and platelet destruction from the development of consumptive coagulopathy.
3. Typical clinical features
   a. Thrombocytopenia – More than a 50% decrease from baseline (platelet count not below 20,000/mm$^3$)
   b. Timing
      i. Typical onset – Day 5–10 after heparin exposure
      ii. Rapid onset – Before Day 5 (usually within 24 hours) in the setting of recent heparin exposure (previous 100 days)
      iii. Delayed onset – After Day 10 of exposure
   c. Thrombosis
      i. Occurs in up to one-half of HIT cases and may be a limb- or life-threatening condition
      ii. Arterial – Myocardial infarction, stroke, ischemic limb necrosis
      iii. Venous – Deep venous thrombosis, pulmonary embolism, left ventricular thrombosis

B. Diagnosis
   1. Risk of overdiagnosis
      a. Result of the frequency of unfractionated heparin use and the insensitivity of enzyme-linked immunosorbent assay (ELISA) testing
      b. Diagnosis improved using combination of clinical suspicion, 4Ts scoring, and confirmatory platelet activation testing (serotonin release assay [SRA])
   2. 4Ts – Scoring system to predict the likelihood of HIT by clinical characteristics (Table 14)

**Table 14.** 4Ts Scoring System

| Category | 2 points | 1 point | 0 points |
|---|---|---|---|
| **T**hrombocytopenia | Plt falls > 50% and platelet nadir ≥ 20,000/mm$^3$ and no surgery within preceding 3 days | Plt falls 30%–50% or platelet nadir 10,000–19,000/mm$^3$ | Plt falls < 30% or platelet nadir < 10,000/mm$^3$ |
| **T**iming of Plt decrease | Clear onset 5–10 days or ≤ 1 day (prior exposure within 30 days) | Consistent within 5–10 days, but missing Plt, or onset > 10 days, or ≤ 1 day (if exposure within past 3– 100 days) | Onset ≤ 4 days without exposure within past 100 days |
| **T**hrombosis | New confirmed thrombosis, or skin necrosis at heparin injection sites, or acute systemic reaction after IV heparin bolus | Progressive or recurrent thrombosis, or non-necrotizing skin lesions, or suspected thrombosis (not proven) | None |
| O**t**her causes | No other causes identified | Possible | Definite |

Plt = platelet count.

a. 4Ts score result
   i. Low probability: 0-3 points
   ii. Intermediate probability: 4 or 5 points
   iii. High probability: 6-8 points
b. 4Ts score interpretation (based on clinical suspicion without laboratory testing, pending laboratory confirmation)
   i. Low probability result: Can continue heparin
   ii. Intermediate or high probability result: Discontinue heparin, discontinue any recently initiated warfarin (and reverse with vitamin K to replete protein C and S stores to prevent venous limb gangrene), initiate alternative anticoagulant (direct thrombin inhibitor – argatroban or bivalirudin), and order both ELISA and SRA testing to confirm diagnosis.

3. Laboratory testing (Table 15) – Test interpretation

**Table 15.** Common Laboratory Testing for HIT Diagnosis

| Test | Description | Sensitivity/Specificity | Interpretation |
|---|---|---|---|
| **Immunologic (Antigenic)**<br>Detects initial immune response by identifying presence of heparin/platelet factor-4 antibody | | | |
| Enzyme-linked immunosorbent assay (ELISA) | • Readily available in hospital laboratories<br>• Useful to rule out HIT | Sensitivity 99%<br>Specificity 80%–85%<br><br>High negative predictive value (higher incidence of false-positive results than functional test) | • Results reported as positive/negative with an optical density, which can help determine "degree" of immune response<br>• Increased sensitivity by raising positive optical density cutoff value to 1.0 (from ~0.4) |
| **Functional (Platelet Activation)**<br>Detects platelet activation leading to thrombosis by assessing the ability of heparin/platelet factor-4 antibody to bind and activate platelets | | | |
| Serotonin release assay (SRA) | • Send out test: Turnaround time 4–7 days<br>• Gold standard for diagnosis | Sensitivity > 95%<br>Specificity > 95%<br><br>High positive predictive value | • Result reported as % (negative: < 20%) |

HIT = heparin-induced thrombocytopenia.

a. HIT confirmed: ELISA plus SRA positive; ELISA negative/SRA positive
b. HIT negative: ELISA positive/SRA negative; ELISA plus SRA negative
c. Ticagrelor use may interfere with functional tests, resulting in false-negative results.
   i. Diagnosis is based on 4Ts score and ELISA results.

C. Treatment of confirmed HIT or intermediate to high probability of HIT while awaiting confirmatory testing
   1. In patients with an intermediate to high probability of HIT on the basis of a 4Ts score or a positive ELISA (pending confirmation with SRA), recommend:
      a. Discontinue heparin (or LMWH), including flushes, coated catheters, etc.
      b. If the patient is receiving warfarin at the time of diagnosis or there is intermediate-high clinical suspicion, discontinue warfarin and administer vitamin K for reversal to reduce the risk of venous limb gangrene.

c. Initiate an alternative (non-heparin) therapeutic anticoagulant.
   i. Agents are selected on the basis of organ function and need for invasive procedures (see Table 16).

**Table 16.** Alternative Anticoagulants for HIT Treatment

| Drug | Pharmacology | Dose | Notes |
|---|---|---|---|
| Argatroban | • Direct thrombin inhibitor<br>• Hepatic metabolism<br>• Half-life: 40–50 min (normal hepatic function) | • Standard dose: 1–2 mcg/kg/min<br>• Moderate-severe hepatic impairment dose: 0.5 mcg/kg/min<br>• Critical illness dose: 0.2 mcg/kg/min | • Preferred agent in setting of renal impairment<br>• Titrate to aPTT 1.5–3 times control<br>• Maximum dose 10 mcg/kg/min<br>• Falsely elevates INR |
| Bivalirudin | • Direct thrombin inhibitor<br>• Renal elimination (20%)<br>• Half-life: 25–30 min (normal renal function) | Dosing not well established<br>• Standard dose: 0.15–0.2 mg/kg/hr<br>• Moderate renal impairment dose: 0.08–1.2 mg/kg/hr<br>• Severe renal impairment dose: 0.02–0.07 mg/kg/hr | • Consider in setting of hepatic impairment<br>• Titrate to aPTT 1.5–2.5 times control<br>• Falsely elevates INR |
| Fondaparinux | • Half-life: 15–20 hr<br>• Role exploratory but generally favorable in the literature | • Contraindicated if CrCl < 30 mL/min<br>• < 50 kg: 5 mg SC daily<br>• 50–100 kg: 7.5 mg SC daily<br>• > 100 kg: 10 mg SC daily | • No coagulation testing needed<br>• SC administration<br>• Avoid in patients with pending surgical procedures<br>• Can be used long-term in patients who cannot take oral therapy |

CrCl = creatinine clearance; SC = subcutaneous(ly).

d. Direct-acting oral anticoagulants
   i. Recent meta-analyses have found similar efficacy in reducing thrombosis and rate of bleeding among parenteral agents and direct-acting oral anticoagulants.
   ii. Considered a treatment option according the 2018 ASH VTE HIT guidelines (conditional recommendation)
   iii. Dosing is similar to VTE regimen and based on timing of platelet recovery.

5. Warfarin (goal INR 2–3) for all patients with confirmed HIT diagnosis once the platelet count is above 150,000/mm$^3$
   a. Duration depends on the presence of thrombus.
      i. No detected thrombus – 30 days
      ii. Thrombus – Continue for appropriate duration depending on thrombus type (typically 3–6 months).
   b. Start with doses of 5 mg/day or less, and overlap with injectable anticoagulant for at least 5 days.
   c. Will need to account for elevation in INR caused by both argatroban and bivalirudin during transition
6. Avoid platelet transfusions, which may exacerbate the problem.

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## ANSWERS AND EXPLANATIONS TO PATIENT CASES

**1. Answer: C**

Management of acute BB toxicity starts with discontinuing the offending agent and administering atropine at doses of 0.5–1 mg every 3–5 minutes. After that, additional therapies are warranted. Given the patient's symptoms, a combination of glucagon, calcium salts, and hyperinsulinemia/euglycemia (insulin/dextrose) is warranted (Answer C is correct). Glucagon and calcium alone are insufficient for management (Answers A and B are incorrect). Lipid emulsion therapy would be effective but is typically reserved for patients who lack response to more traditional therapy (Answer D is incorrect). At this point, the patient's traditional therapy has not failed.

**2. Answer: B**

Azithromycin, which carries a high risk of TdP, should be discontinued if the QTc increases by 60 milliseconds or more. Discontinuing the current regimen and changing to moxifloxacin alone, though recommended for community-acquired pneumonia, can also prolong the QTc and should be avoided in this patient (Answer A is incorrect). No information is provided to indicate the patient has risk factors for health care–acquired pneumonia; therefore, this regimen is inappropriate (Answer C is incorrect). Treatment of community-acquired pneumonia with ceftriaxone alone would not cover atypical organisms and is not recommended (Answer D). The only regimen that would reduce the risk of further QTc prolongation with appropriate community-acquired pneumonia coverage is doxycycline and ceftriaxone (Answer B is correct).

**3. Answer: A**

Donepezil causes hypotension through central and peripheral muscarinic stimulation, resulting in a vagotonic effect on the heart (Answer A is correct). Both venlafaxine and ginseng can cause hypertension (Answers B and C are incorrect). Memantine has no known effect on blood pressure (Answer D is incorrect).

**4. Answer: C**

Because the patient was recently discharged from the hospital with no reported history of HF, he should be assumed to have new-onset HF. Amiodarone does not cause HF and would be an appropriate antiarrhythmic medication to use in this population (Answer A is incorrect). Although diltiazem should be avoided in patients with HF, it does not cause new-onset HF (Answer B is incorrect). All formulations of insulin can safely be used in patients with HF because insulin does not cause new-onset or worsening HF (Answer D is incorrect). The thiazolidinedione class, which includes pioglitazone, has been implicated in causing both new-onset HF and HF exacerbations (Answer C is correct).

**5. Answer: A**

The anti-VEGF agents (e.g., bevacizumab, sorafenib, sunitinib) cause hypertension (Answer A is correct). The other choices are not associated with the development of hypertension (Answers B–D are incorrect).

**6. Answer: C**

With a 4Ts score in the high probability range, it is appropriate to initiate alternative anticoagulation. Because of the high risk of cross-reactivity, low-molecular-weight heparins should not be used for the treatment of HIT (Answer A is incorrect). The other three agents are all plausible; therefore, agent selection should be based on patient-specific factors. In this case, the patient has normal hepatic function but a calculated CrCl of less than 30 mL/minute. Fondaparinux is contraindicated in patients with a CrCl of less than 30 mL/minute, so it cannot be used in this case (Answer B is incorrect). Bivalirudin can be used in patients with impaired renal function, but the dose should be 0.02–0.05 mcg/kg/minute; therefore, the dose is too high for this patient's degree of renal function (Answer D is incorrect). Argatroban is the preferred agent in this setting, given the patient's degree of renal impairment (Answer C is correct).

## ANSWERS AND EXPLANATIONS TO SELF-ASSESSMENT QUESTIONS

**1. Answer: C**

Albuterol, a β-agonist, can cause tachycardia, not bradycardia (Answer A is incorrect). Dehydration from diuretic use can be associated with near-syncopal events from orthostatic hypotension, but not bradycardia (Answer D is incorrect). β-Blockers cause bradycardia by reducing AV nodal conduction because of their inherent drug activity, but clonidine can also cause bradycardia (Answer B is incorrect). Clonidine stimulates the parasympathetic system, resulting in decreased sinus nodal automaticity and AV nodal conduction. Two of the patient's home medications, atenolol and clonidine, are potential causes of bradycardia (Answer C is correct).

**2. Answer: D**

Although this patient's hypertension could be related to not receiving any antihypertensive therapy before surgery, abrupt BB withdrawal can cause tachycardia, hypertension, or myocardial ischemia (Answer D is correct). Although several mechanisms can explain this phenomenon, it is most likely related to increased β-adrenergic receptor responsiveness. Calcium channel blockers (amlodipine), α-blockers (doxazosin), and ACE inhibitors (lisinopril) can all be abruptly discontinued without concerns for rebound hypertension (Answers A–C are incorrect). The other class of medications associated with rebound hypertension are the centrally acting α-agonists.

**3. Answer: A**

In this case, the patient's history of HFrEF must be considered when choosing the most appropriate add-on therapy. Both alogliptin and saxagliptin carry warnings for increased risk of HF hospitalizations and should be avoided in this population (Answers B and D are incorrect). Although CV benefits have been shown with GLP-1 receptor agonists, semaglutide has no significant impact in HFrEF (Answer C is incorrect). Empagliflozin is the safest option listed and has no concerns for use in a patient with both type 2 diabetes and HF (Answer A is correct). In the EMPEROR-Reduced trial, the risk of CV death or hospitalization rate for HF was significantly lower with empagliflozin than with placebo regardless of the presence or absence of diabetes, suggesting the benefit of empagliflozin in this population (N Engl J Med 2020;383:1413-24.)

**4. Answer: C**

Heart rate control selection in a patient with atrial fibrillation largely depends on the patient's comorbidities. For patients with HF, the non-dihydropyridine CCBs (diltiazem and verapamil) should be avoided because of their negative inotropic properties (Answers A and B are incorrect). Although metoprolol is an acceptable rate control strategy in HF, the preferred product is metoprolol succinate (Answer C is correct), not metoprolol tartrate (Answer D is incorrect). Digoxin is also appropriate for rate control in a patient with HF.

**5. Answer: B**

The class IC antiarrhythmic agents (flecainide and propafenone) and sotalol should be avoided in patients with HF because of the agents' negative inotropic/chronotropic effects (Answers A, C, and D are incorrect). The only two antiarrhythmic agents recommended in patients with HF are amiodarone (Answer B is correct) and dofetilide.

**6. Answer: C**

Patients often take herbal products in combination with prescription medications and should be warned about the potential risk of doing so. Garlic can increase the risk of bleeding, which is of special concern in this patient taking dual antiplatelet therapy after stenting (Answer C is correct). One of the proposed benefits of garlic is lowering blood pressure (Answer B is incorrect) and hyperlipidemia. QT prolongation and tachycardia have been identified as a risk with other substances such as bitter orange (Answers A and D are incorrect).

**7. Answer: B**

Calcineurin inhibitor–induced hypertension should be managed with the patient's transplant team. The risk of hypertension is higher with cyclosporine; thus, changing from tacrolimus to cyclosporine is unlikely to be of benefit (Answer A is incorrect). Although chlorthalidone is a reasonable antihypertensive medication to consider in patients with poorly controlled blood pressure, it is not the recommended agent in this situation (Answer C is incorrect). Discontinuing tacrolimus is incorrect because this agent is needed to prevent organ rejection (Answer D is incorrect). Dihydropyridine CCBs are the recommended antihypertensive agents for managing calcineurin inhibitor–induced hypertension (Answer B is correct).

**8. Answer: A**

The most accurate adverse event information for marketed medications is available from patient safety organizations (Answer A is correct). Often, safety events identified by these organizations form the basis for FDA safety announcements and further investigation. The package labeling is often outdated, including only safety information from clinical trials conducted before drug approval (Answer B is incorrect). Although the manufacturer may be able to provide safety information, the manufacturer's information is limited compared with the comprehensive databases available through patient safety organizations (Answer C is incorrect). The primary literature is outdated and unlikely to identify events that may be occurring in a broad population (Answer D is incorrect).

# Chronic Heart Failure

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**Learning Objectives**

1. Given a patient with heart failure (HF), describe the classifications, staging, clinical presentation, etiologies, and diagnostic considerations.
2. Describe the pathophysiology of HF, focusing on the role that neurohormonal and other vasoactive agents play in HF progression.
3. Given a patient with chronic HF, devise an appropriate pharmacologic and nonpharmacologic therapeutic plan, with an emphasis on guideline-directed therapy and management.
4. Given a patient with chronic HF and several comorbidities, devise an appropriate evidence-based pharmacotherapy plan addressing specific comorbidities related to HF.

**Abbreviations in This Chapter**

| | |
|---|---|
| ACC | American College of Cardiology |
| ACE | Angiotensin-converting enzyme |
| AF | Atrial fibrillation |
| AHA | American Heart Association |
| ARB | Angiotensin receptor blocker |
| ARNI | Angiotensin receptor-neprilysin inhibitor |
| AT I | Angiotensin I |
| AT II | Angiotensin II |
| BNP | B-type natriuretic peptide |
| CAD | Coronary artery disease |
| CO | Cardiac output |
| CRT | Cardiac resynchronization therapy |
| CV | Cardiovascular |
| DM | Diabetes mellitus |
| ECHO | Echocardiogram |
| eGFR | Estimated glomerular filtration rate |
| GDMT | Guideline-directed medical therapy |
| HF | Heart failure |
| HFpEF | Heart failure with preserved ejection fraction |
| HFrEF | Heart failure with reduced ejection fraction |
| HFSA | Heart Failure Society of America |
| HTN | Hypertension |
| ICD | Implantable cardioverter-defibrillator |
| JVP | Jugular venous pulsation |
| LV | Left ventricle/ventricular |
| LVEF | Left ventricular ejection fraction |
| MACE | Major adverse cardiovascular events |
| MI | Myocardial infarction |
| NSR | Normal sinus rhythm |
| NYHA | New York Heart Association |
| PUFA | Polyunsaturated fatty acid |
| QoL | Quality of life |
| RAAS | Renin-angiotensin-aldosterone system |
| SGLT2 | Sodium-glucose cotransporter-2 |
| SOB | Shortness of breath |
| SVR | Systemic vascular resistance |
| UHF | Universal definition and classification of heart failure |

**Self-Assessment Questions**

*Answers and explanations to these questions can be found at the end of this chapter.*

*Questions 1 and 2 pertain to the following case.*

J.S. is a 55-year-old woman with trastuzumab-induced cardiomyopathy resulting in valvular damage. Her most recent left ventricular ejection fraction (LVEF) is 35%. She continues to have dyspnea and fatigue on exertion (New York Heart Association [NYHA] functional class III). Her medications include lisinopril 20 mg/day, furosemide 40 mg twice daily, carvedilol 12.5 mg twice daily, spironolactone 25 mg/day, and digoxin 0.125 mg/day. She has been stable on these doses for the past month. Her most recent laboratory results include sodium (Na) 140 mEq/L, potassium (K) 4.0 mEq/L, chloride (Cl) 105 mEq/L, bicarbonate 26 mEq/L, blood urea nitrogen (BUN) 12 mg/dL, serum creatinine (SCr) 0.8 mg/dL, glucose 98 mg/dL, calcium 9.0 mg/dL, phosphorus 2.8 mg/dL, magnesium 2.0 mEq/L, and digoxin 0.9 ng/mL. Her vital signs today include blood pressure 112/70 mm Hg and heart rate 68 beats/minute. Her lung examination is clear.

1. Which best depicts J.S.'s heart failure (HF) stage?
   A. A.
   B. B.
   C. C.
   D. D.

2. Which would best maximize the management of her HF with reduced ejection fraction (HFrEF)?
   A. Increase digoxin to 0.25 mg daily.
   B. Increase lisinopril to 40 mg daily.

C. Increase spironolactone to 50 mg daily.

D. Increase carvedilol to 25 mg twice daily.

3. In the Cooperative North Scandinavian Enalapril Survival (CONSENSUS) trial, the original planned sample size was 400 patients with HFrEF who were randomized to receive enalapril or placebo. The population was followed for 6 months and evaluated for time to death. This sample size provided a power of 90% for superiority to reject the null hypothesis. Which β value would best correspond to 90% power?

   A. 0.01

   B. 0.05

   C. 0.1

   D. 0.2

4. In the Evaluation of Losartan in the Elderly (ELITE) I study, the investigators found a statistically significant difference in the end point of all-cause mortality in older adults with HFrEF receiving losartan versus captopril. However, the ELITE II study, which had the same study design as ELITE I but with a larger patient population, found no difference in all-cause mortality between those receiving losartan and those receiving captopril. Which best depicts the statistical error made by the ELITE I investigators?

   A. Type I.

   B. Type II.

   C. Selection bias.

   D. Reporting bias.

5. A 78-year-old man with diabetes mellitus (DM) and hypertension (HTN) presents to your clinic with progressive dyspnea (NYHA functional class III) and lower-extremity swelling. In addition to ordering an echocardiogram (ECHO) for assessing left ventricular (LV) systolic function, which is the most appropriate next test to assess his diastolic function?

   A. Cardiac magnetic resonance imaging (MRI).

   B. ECHO-Doppler imaging.

   C. Computed tomography (CT).

   D. Left heart catheterization.

6. You are discussing medical management with a 52-year-old man with HF with preserved ejection fraction (HFpEF) (LVEF of 55%) who was recently discharged from the hospital. He has NYHA functional class III symptoms, which are currently being managed with maximal doses of lisinopril, carvedilol, and furosemide. He asks you about starting digoxin. Which information is most appropriate to give this patient, considering his NYHA functional class and LVEF?

   A. Digoxin will not be of benefit.

   B. Digoxin will decrease your risk of all-cause mortality.

   C. Digoxin will decrease your risk of HF-related hospitalization.

   D. Digoxin will decrease your risk of HF-related mortality and hospitalization.

7. A patient presents to your community pharmacy for refills of lisinopril, furosemide, metoprolol succinate, and digoxin. When you ask how he is feeling, he says that he has been taking his medications as directed and has been eating a low-sodium diet. However, over the past week, he has had shortness of breath (SOB) and has gained about 3 kg (6 lb). He now has to sleep on four pillows so that he does not get SOB. Which would be most appropriate to recommend for this patient?

   A. Continue to weigh yourself every day and adhere to the low-sodium diet.

   B. Consider calling your physician this week because your physician may need to adjust your furosemide dose.

   C. Go to the emergency department for immediate assistance.

   D. Your HF symptoms seem to be controlled—good job.

8. A patient with NYHA functional class IV HF (LVEF less than 40%) currently receives the following medications: lisinopril, bisoprolol, furosemide, digoxin, amlodipine, spironolactone, pregabalin, sertraline, glipizide, and colchicine (as needed). Which medication would most likely exacerbate this patient's HF?

   A. Sertraline.

   B. Amlodipine.

C. Pregabalin.

D. Colchicine.

9. A patient with NYHA functional class III HF (LVEF less than 35%) presents to your family medicine clinic with new-onset gout pain. Which would be the safest recommendation to relieve the patient's pain and swelling?

   A. Prednisone.

   B. Oxycodone.

   C. Indomethacin.

   D. Ibuprofen.

10. A patient presents with stable NYHA functional class III HF (LVEF less than 30%) and newly diagnosed type 2 DM with an estimated glomerular filtration rate (eGFR) of 46 mL/minute/1.73 $m^2$. Which of the following medications could increase this patient's risk for a major cardiac event?

    A. Metformin.

    B. Alogliptin.

    C. Empagliflozin.

    D. Liraglutide.

11. Which patient is the best candidate for initiation of ivabradine?

    A. 55-year-old man with NYHA functional class I HF (LVEF of 60%) and heart rate 75 beats/minute taking lisinopril 20 mg daily for HTN.

    B. 45-year-old man with NYHA functional class II HF (LVEF of 35%) and heart rate 62 beats/minute taking lisinopril 40 mg daily, metoprolol succinate 150 mg daily, and spironolactone 25 mg daily.

    C. 65-year-old woman with NYHA functional class III HF (LVEF of 20%) with heart rate 78 beats/minute taking lisinopril 20 mg daily, eplerenone 50 mg daily, and carvedilol 25 mg twice daily.

    D. 85-year-old man with NYHA function class IV HF (LVEF of 10%) with heart rate 110 beats/minute receiving outpatient dobutamine therapy and awaiting transplantation.

## I. INTRODUCTION CHRONIC HEART FAILURE

**Patient Case**

*Questions 1–5 pertain to the following case.*

K.S. is a 76-year-old woman with obesity who presents with mild exertional dyspnea, which she noticed recently while walking around her neighborhood. She becomes SOB when walking fast or on hills but still walks about ¼ mile per day. She also admits having 1 pillow orthopnea and paroxysmal nocturnal dyspnea. She has had mild edema in the evenings for many years. She denies angina, palpitations, or syncope. She is a nonsmoker. She has a history of HTN, myocardial infarction (MI) 2 years ago, depression, gastroesophageal reflex disease, and hyperlipidemia. Her medications consist of metoprolol succinate 150 mg daily, lisinopril 10 mg daily, furosemide 20 mg daily, aspirin 81 mg daily, sertraline 50 mg daily, omeprazole 20 mg daily, and simvastatin 20 mg at bedtime. Her vital signs today include blood pressure 178/85 mm Hg and heart rate 62 beats/minute. Her physical examination is positive for jugular venous pulsation (JVP), S3 present; trace edema in both extremities; and lungs with slight crackles. Laboratory findings show SCr 2.5 mg/dL and K 4.5 mEq/L. Her electrocardiogram (ECG) reveals normal sinus rhythm (NSR).

1. Given K.S.'s clinical presentation, which symptom has the greatest sensitivity to detect HF?
   A. Shortness of breath.
   B. Paroxysmal nocturnal dyspnea.
   C. Orthopnea.
   D. Edema.

2. Which best describes K.S.'s stage of HF?
   A. A.
   B. B.
   C. C.
   D. D.

3. A B-type natriuretic peptide (BNP) is obtained. Which best depicts what could lead to a lower-than-expected BNP value in K.S.?
   A. Advanced age of 75 years.
   B. Obesity.
   C. Renal insufficiency.
   D. HTN.

4. During this clinic visit, sacubitril/valsartan is initiated. Which vasoactive substance would most likely be increased in K.S. after therapy initiation?
   A. N-terminal proBNP (NT-proBNP).
   B. BNP.
   C. Angiotensin II (AT II).
   D. Aldosterone.

A. Background
   1. HF is a complex clinical syndrome that results from any structural or functional impairment of ventricular filling or ejection of blood. The cardinal manifestations of HF are dyspnea and fatigue, which may limit exercise tolerance, and fluid retention, which may lead to pulmonary and/or splanchnic congestion and/or peripheral edema.
   2. The 2021 universal definition and classification of heart failure (UHF) scientific statement aimed to streamline the continuum of HF, recognizing those without HF who are at risk.
      a. The UHF formally defined HF as the presence of elevated natriuretic peptides or objective evidence of cardiogenic, pulmonary, or systemic congestion together with signs and/or symptoms of HF caused by a structural and/or functional cardiac abnormality (Figure 1).

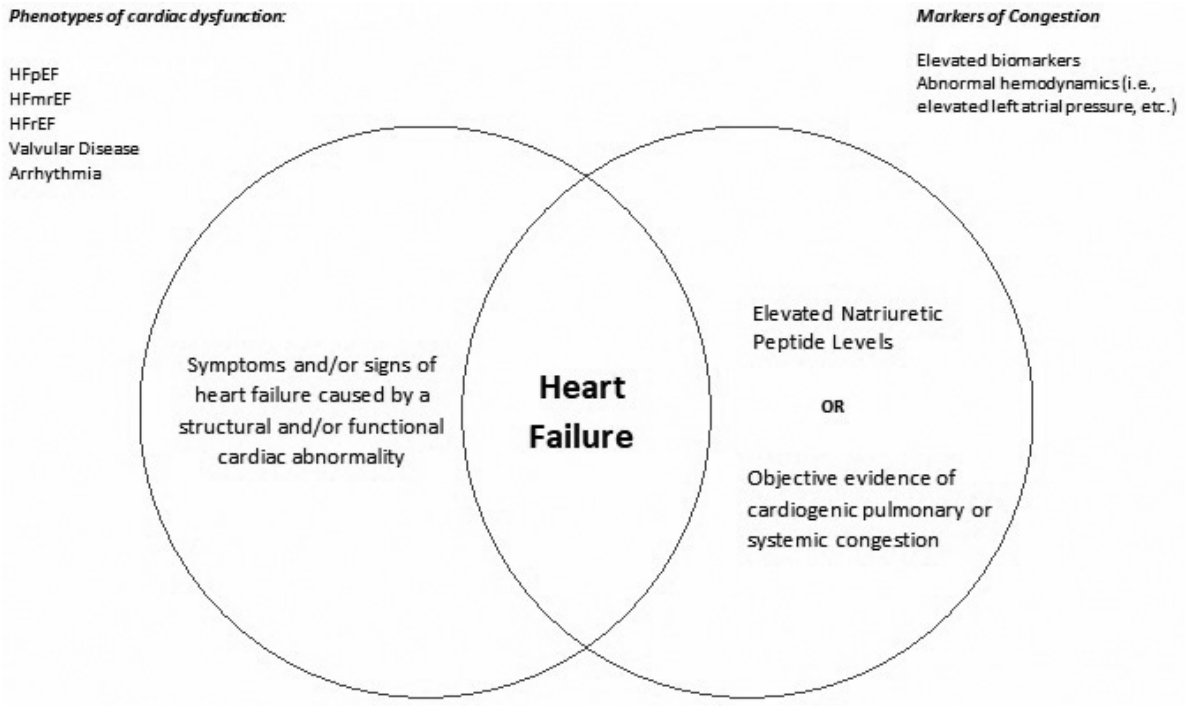


**Figure 1.** Pictorial representation of the new universal definition of heart failure.

Information from: Bozkurt B, Coats AJ, Tsutsui H, et al. Universal definition and classification of heart failure: a report of the Heart Failure Society of America, Heart Failure Association of the European Society of Cardiology, Japanese Heart Failure Society and Writing Committee of the Universal Definition of Heart Failure. Eur J Card Fail 2021;23:352-80.

      b. Staging (does not replace NYHA or ACC/AHA criteria)
         i. At risk (stage A): Patients with no current or prior signs/symptoms of HF but with high-risk comorbidities (e.g., HTN, atherosclerotic cardiovascular [CV] disease) or a family history of heart disease
         ii. Pre-HF (stage B): Patients with no current or prior signs/symptoms of HF, but with evidence of structural heart disease, abnormal cardiac function, or elevated natriuretic peptide concentrations
         iii. HF (stage C): Patients with current or prior symptoms and/or signs of HF caused by a structural and/or functional cardiac abnormality
         iv. Advanced HF (stage D): Patients with severe signs and/or symptoms at rest, recurrent hospitalizations, requiring advanced therapies/mechanical support, or palliative care

c. Classification of HF depends on EF (see Table 1).
d. Recognizing clinical trajectory in HF
    i. Recommendation against the use of "stable HF" because patients should either improve or continue to worsen with guideline-directed medical therapy (GDMT)
    ii. Persistent vs. remission
        (a) Persistent: Replaces "stable"
        (b) Remission: Replaces the use of "recovered" HF, recognizing that, even in those who have flourished with GDMT and may be asymptomatic, the risk of HF recurrence exists

3. Despite advances in pharmacotherapy, HF remains a leading cause of morbidity and mortality in both the United States and worldwide. Mortality is 50% at 5 years.

B. Classifications of HF
1. HF can be classified as predominantly LV, right ventricular, or biventricular, depending on the location of the deficit.
2. Clinically, HF is classified into two major types on the basis of the functional status of heart: HFrEF and heart failure with preserved ejection fraction (HFpEF).
3. Patients with HFpEF are mainly females and older adults, LVEF is usually more than 50%. The volume of the LV cavity is typically normal, but the LV wall is thickened and stiff; hence, the ratio of LV mass/end-diastolic volume is high.
4. HFpEF is further categorized as mildly reduced HF if the LVEF stays at 41%–49%.
5. In contrast, in patients with HFrEF, the LV cavity is typically dilated, and the ratio of LV mass/end-diastolic volume is either normal or reduced. HFrEF can occur at all ages.
6. Patients formerly with a reduced LVEF (less than 40%) who now have an improvement of 10% or more from their baseline EF to above 40% are clinically distinct from the HFpEF population.

**Table 1.** Definitions of HFrEF and HFpEF

| Classifications | LVEF (%) | Description |
|---|---|---|
| HFrEF | ≤ 40 | Also called systolic HF. Randomized controlled trials have mainly enrolled patients with HFrEF, and only in these patients have therapies been shown efficacious to date |
| HFpEF | ≥ 50 | Also called diastolic HF. Several different criteria have been used to further define HFpEF. The diagnosis of HFpEF is challenging because it is largely one of excluding other potential noncardiac causes of symptoms suggestive of HF<br>To date, efficacious therapies have not been identified |
| HFmrEF | 41–49 | These patients fall into a borderline or intermediate group. Their characteristics, treatment patterns, and outcomes appear similar to those of patients with HFpEF |
| HFimpEF | > 40 | It has been recognized that a subset of patients who formerly had a reduced EF now have an improved EF. These patients with improvement or recovery in EF may be clinically distinct from those with persistently preserved or reduced EF. Further research is needed to better characterize these patients |

EF = ejection fraction; HFimpEF = heart failure with improved ejection fraction; HFmrEF = heart failure with mildly reduced ejection fraction; HFpEF = heart failure with preserved ejection fraction; HFrecEF = heart failure with recovered ejection fraction; HFrEF = heart failure with reduced ejection fraction; LVEF = left ventricular ejection fraction.

Information from: Bozkurt B, Coats AJ, Tsutsui H, et al. Universal definition and classification of heart failure: a report of the Heart Failure Society of America, Heart Failure Association of the European Society of Cardiology, Japanese Heart Failure Society and Writing Committee of the Universal Definition of Heart Failure. Eur J Card Fail 2021;23:352-80.

C. Stages and Functional Classifications
   1. The NYHA functional classification defines four levels of function, depending on activity (Table 2).
   2. The American College of Cardiology/American Heart Association (ACC/AHA) staging system is defined by four stages (Table 2).

**Table 2.** Comparison of ACCF/AHA HF Stages and NYHA Functional Classifications

| ACCF/AHA Stages of HF | | NYHA Functional Classification | |
|---|---|---|---|
| A | At high risk of HF but without structural heart disease or symptoms of HF | None | |
| B | Structural heart disease without signs or symptoms of HF | I | No limitation in physical activity. Ordinary physical activity does not cause symptoms of HF |
| C | Structural heart disease with prior or current symptoms of HF | I | No limitation in physical activity. Ordinary physical activity does not cause symptoms of HF |
| | | II | Slight limitation in physical activity. Comfortable at rest, but ordinary physical activity results in symptoms of HF |
| | | III | Marked limitation in physical activity. Comfortable at rest, but less-than-ordinary activity causes symptoms of HF |
| | | IV | Cannot carry out any physical activity without symptoms of HF, or symptoms of HF at rest |
| D | Refractory HF requiring specialized interventions | IV | Cannot carry out any physical activity without symptoms of HF, or symptoms of HF at rest |

ACCF = American College of Cardiology Foundation; HF = heart failure; NYHA = New York Heart Association.

Information from: Yancy CW, Jessup M, Bozkurt B, et al. 2013 ACCF/AHA guideline for the management of heart failure. A report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. Circulation 2013;128:e240-e327.

D. Clinical Presentation/Physical Examination
   1. The clinical presentation of HF consists of symptoms of SOB/dyspnea (sensitivity of 84%–100%, but a specificity of 17%–34%); orthopnea/SOB on lying down (sensitivity of 22%–50% and a specificity of 74%–77%); paroxysmal nocturnal dyspnea (sensitivity 39%–41%, specificity from 80%–84%); fatigue/weakness/lethargy (because of HF-induced circulation-related abnormalities in skeletal muscles); and edema; abdominal distention; and right hypochondrial pain (most likely because of right-sided HF with a sensitivity and specificity of 23% and 80%, respectively).
   2. Because of compensatory mechanisms, early stages of HF lack specific signs; however, late stages of HF have the following signs: tachycardia (99% specificity and 7% sensitivity); pedal edema (93% specificity and 10% sensitivity); increased JVP (usually greater than 6 cm; specificity of 92% and sensitivity of 39%); abnormal lung sounds (crackles) (specificity of 78% and sensitivity of 60%); and S3 gallop (specificity of 99% and sensitivity of 13%). Other signs, such as hepatojugular reflux (HJR) and ascites, though uncommon in HF, have a specificity of 96% and 97%, with a sensitivity of 24% and 1%, respectively.

3. Table 3 describes pertinent physical examination findings in the diagnosis of HF.

**Table 3.** Pertinent Physical Examination Findings in the Diagnosis of HF

| System | Finding | Interpretation |
|---|---|---|
| Vital signs | ↓↓ BP | • Demand ischemia vs. cardiogenic shock |
| | ↑↑ Heart rate | • Poor perfusion |
| | ↓ Oxygen saturation | • Tissue oxygenation |
| | ↓ Respiratory rate | • Hemodynamic stability |
| | ↓↓ Temperature | • Infectious causes or other exacerbating factor |
| CNS | Altered mental status | • Hypoperfusion to vital organs including the brain |
| HEENT | JVP | • Elevated right atrial/central venous pressure |
| | Carotid bruits | • Presence of atherosclerotic disease |
| CV | Rhythm | • Presence of arrhythmias/clinical stability |
| | Heart sounds (S1, S2) | • Abnormal/absent requires further evaluation |
| | Murmurs | • Valvular disease |
| | Gallops (S3, S4) | • S3 – Fluid overload/increase LV filling pressure |
| | | • S4 – Noncompliant LV |
| | Rubs | • Presence of pericarditis |
| | PMI | • Displacement suggestive of ventricular enlargement |
| | RV heave | • RV dysfunction/elevated RV pressure, pulmonary HTN |
| Pulmonary | Crackles/rales/rhonchi | • Pulmonary edema, pneumonia (rales can be absent in chronic HF despite pulmonary congestion) |
| | Breath sounds | • Diminished breath sounds from pleural effusion |
| GI tract | Ascites | • Abdominal congestion |
| | Hepatomegaly | • Hepatic enlargement |
| | HJR | • Hepatic congestion |
| Extremities | Color | • Cyanotic |
| | Temperature | • Cool or cold if perfusion diminished |
| | Pulses | • Diminished pulses |
| | Clubbing | • Clubbing from chronic hypoxia |
| | Edema | • Fluid overload, degree of pitting edema +1 to +4 |

BP = blood pressure; CNS = central nervous system; CV = cardiovascular; GI = gastrointestinal; HEENT = head, eyes, ears, nose, and throat; HJR = hepatojugular reflux; PMI = point of maximal impulse; RV = right ventricle/ventricular.

Information from: Ng TMH, Ackerbauer K. Heart failure. In: Dong BJ, Elliott DP, eds. Ambulatory Care Self-Assessment Program, 2014 Book 3. Cardiology Care. Lenexa, KS: American College of Clinical Pharmacy, 2014:202-20.

E. Diagnosis of HF
   1. HF is evaluated using various parameters: Physical examination to determine the presence of clinical symptoms and signs; blood tests, including complete blood cell count (CBC); urinalysis; complete metabolic profile for concentrations of serum electrolytes (including calcium and magnesium), BUN, SCr, glucose, fasting lipid profile, liver function tests, and thyroid-stimulating hormone
   2. Other diagnostic tests for HF include chest radiography to assess heart size and pulmonary congestion and to detect alternative cardiopulmonary diseases; 2-dimensional ECHO with Doppler for initially evaluating LVEF and filling patterns (considered the "gold-standard" test); transthoracic echocardiography to evaluate ventricular function, size, wall thickness, LVEF, wall motion, and valve function; CT scans to accurately assess cardiac structure and function, including the coronary arteries; and MRI to assess LV volume and LVEF measurements, which are more definitive than ECHO, as well as myocardial perfusion, viability, and fibrosis.
   3. Other HF-specific laboratory tests (especially in patients with a high possibility of an HF diagnosis) include BNP and NT-proBNP.
   4. BNP is a neurohormone, which is an activated form of proBNP, the 108-amino acid polypeptide precursor, stored as secretory granules in both ventricles and, to a lesser extent, in the atria.
   5. In response to volume expansion and pressure overload, proBNP is secreted into ventricles and breaks down into its two cleaved forms, the 76-peptide, biologically inert N-terminal fragment, NT-proBNP, and the 32-peptide, biologically active hormone BNP.
   6. BNP and NT-proBNP have clinical significance both as diagnostic and prognostic markers in HF management (Table 4).
   7. In the Breathing Not Properly study, BNP was accurate in diagnosing HF in patients presenting to the emergency department with dyspnea, with a sensitivity of 90% and specificity of 76% at a cutoff of 100 pg/mL (Table 4).
   8. The sensitivity and specificity of NT-proBNP were identical to those of BNP if an NT-proBNP threshold of 900 pg/L was used, but to improve positive predictive value, age-related cutoffs should be considered (Table 4).

**Table 4.** BNP and NT-proBNP Predictive Values

| | Rule-in Values | PPV (%) | NPV (%) |
|---|---|---|---|
| **NT-proBNP** | | | |
| Age | | | |
| < 50 yr | 450 pg/mL | 76 | 99 |
| 50–75 yr | 900 pg/mL | 83 | 88 |
| > 75 yr | 1800 pg/mL | 92 | 55 |
| **BNP** | | | |
| | 100 pg/mL | 79 | 83 |
| | 150 pg/mL | 83 | 84 |

BNP = B-type natriuretic peptide; NPV = negative predictive value; NT-proBNP = N-terminal pro-BNP; PPV = positive predictive value.

Information from: Januzzi JL, Kimmenade R, Lainchbury J, et al. NT-proBNP testing for diagnosis and short-term prognosis in acute destabilized heart failure: an international pooled analysis of 1256 patients. The International Collaborative of NT-proBNP Study. Eur Heart J 2006;27:330-7.

   9. The ACC/AHA/Heart Failure Society of America (HFSA) 2017 focused update provides recommendations for biomarkers in the prevention, diagnosis, and prognosis of HF. BNP and NT-proBNP can be used in the ambulatory setting to diagnose or exclude HF, evaluate the prognosis of HF, and achieve GDMT.
   10. Biomarkers of myocardial fibrosis (e.g., soluble ST2 receptor, galectin-3, high-sensitivity cardiac troponin) are predictive of hospitalization and death in patients with HF and are additive to natriuretic peptide biomarker concentrations in their prognostic value.

**Patient Case** (*Cont'd*)

5. During an educational session, K.S. asks how long she has to live. Which instrument would be best to predict K.S.'s mortality, given her HF?
   A. Seattle Heart Failure Model.
   B. Minnesota Living with Heart Failure Questionnaire.
   C. Kansas City Cardiomyopathy Questionnaire.
   D. Chronic Heart Failure Assessment Tool.

F. Evaluation of Mortality/Risk Stratification
   1. Several risk scores have been validated to evaluate survival in patients with chronic HF. The two most common are the Heart Failure Survival Score and the Seattle Heart Failure Model (Table 5). Both are used in patients with HFrEF and HFpEF.
   2. Both scores can help determine advanced HF therapies (e.g., heart transplantation or LV assist device placement).
   3. Evaluation of mortality is an essential part of the concept of shared decision-making.

**Table 5.** HFSS and SHFM Risk Scores to Predict Outcomes in Chronic HF

| | **Heart Failure Survival Score** | **Seattle Heart Failure Model** |
|---|---|---|
| **Clinical Variables** | | |
| URL | www.mortalityscore.org/heart_failure.php | http://depts.washington.edu/shfm/ |
| Characteristics of HF | NYHA class<br>Ischemic etiology<br>LV ejection fraction | NYHA class<br>Ischemic etiology |
| Vital signs | Resting heart rate<br>Resting mean BP | Systolic BP |
| ECG | QRS ≥ 0.12 s | |
| Laboratory findings | Serum sodium | Serum sodium<br>Hgb<br>Lymphocytes<br>Uric acid<br>Total cholesterol |
| Medications | | Diuretic dose |
| Stress test | Peak $Vo_2$ | |
| Invasive hemodynamics | Pulmonary capillary wedge pressure | |

**Table 5.** HFSS and SHFM Risk Scores to Predict Outcomes in Chronic HF (*Cont'd*)

| | Heart Failure Survival Score | Seattle Heart Failure Model |
|---|---|---|
| **Interpretation** | | |
| | Scores < 7.2 are classified as high risk, ≥ 8.1 are low risk, and values in between are intermediate risk<br>More recent studies have suggested 89%, 72%, and 60% 1-yr survival rates for the risk groups of low, intermediate, and high<br>Patients in the medium- and high-risk categories are appropriate for consideration of listing for heart transplantation or placement of an LVAD, whereas low-risk patients are appropriately deferred for consideration of these advanced HF therapies | SHFM was developed as a predictor of life expectancy and 1-, 2-, and 5-yr mortality derived from the PRAISE trial<br>Decision points include a 1-yr expected mortality of > 30% in a patient with NYHA class IV HF with an LVEF < 25% as a generally accepted criterion for LVAD placement, whereas 10%–20% annual mortality is considered at the beginning of the appropriate range for consideration of heart transplantation<br>An annual mortality > 20% is the rate at which ICD placement appears to no longer confer a mortality benefit because the predominant mode of death is pump failure rather than sudden cardiac death<br>The value in lower-risk patients is both in providing more knowledge for patients and providers about likely prognosis and in allowing a clearer understanding of the survival changes that can occur with starting new HF medications or placing life-saving devices |

HFSS = Heart Failure Survival Score; Hgb = hemoglobin; ICD = implantable cardioverter-defibrillator; LV = left ventricular; LVAD = left ventricular assist device; PRAISE = Prospective Randomized Amlodipine Survival Evaluation Study; SHFM = Seattle Heart Failure Model; $Vo_2$ = oxygen consumption.

Information from: Allen LA, Stevenson LW, Grady KL, et al. Decision making in advanced heart failure: a scientific statement from the American Heart Association. Circulation 2012;125:1928-52.

G. Evaluation of Quality of Life (QoL)
   1. Several instruments have been validated to evaluate health-related QoL in patients with HF (Table 6).
   2. These have been used clinically and within studies.

**Table 6.** Validated Instruments to Assess Health-Related QoL in HF

| Instrument | Aim: to measure … | Specific Domains | Mode of Administration |
|---|---|---|---|
| Chronic heart failure assessment tool | … health-related QoL in HF from the patient perspective | Symptoms, activity levels, psychosocial, emotions | Self-administered |
| Cardiac Health Profile-congestive HF | … how HF influences subjective perceptions of physical, psychological, and social well-being | None | Self-administered |
| Chronic Heart Failure Questionnaire | … longitudinal change over time within individuals with HF | Dyspnea<br>Fatigue<br>Emotional | Interview-administered |
| Kansas City Cardiomyopathy Questionnaire | … health-related QoL in HF | Physical limitation<br>Symptoms<br>Self-efficacy<br>Social limitation<br>QoL | Self-administered |

**Table 6.** Validated Instruments to Assess Health-Related QoL in HF (*Cont'd*)

| Instrument | Aim: to measure … | Specific Domains | Mode of Administration |
|---|---|---|---|
| Left Ventricular Disease Questionnaire | … impact of LV dysfunction on daily life and well-being | None | Self-administered |
| Minnesota Living with Heart Failure Questionnaire | … the extent to which HF prevents patients from living the way they would want to | Physical<br>Emotional | Self-administered |
| Quality of Life Questionnaire in Severe Heart Failure | … self-assessment of health-related QoL in severe HF | Psychological<br>Physical activity<br>Life dissatisfaction<br>Somatic symptoms | Self-administered |

QoL = quality of life.

Information from: Olatz G, Herdman M, Vilagut G, et al. Assessing health-related quality of life in patients with heart failure: a systematic standardized comparison of available measures. Heart Fail Rev 2014;19:359-67.

## II. PATHOPHYSIOLOGY OF CHRONIC HEART FAILURE

A. Etiologies for HF: Etiological factors for HF can be considered ischemic versus nonischemic. However, a broader view can be considered such as diseased myocardium, abnormal loading conditions, and arrhythmias.

B. Pathophysiology: Role of Neurohormones
   1. With myocardial injury, filling pressures and blood pressure decreases, stimulate baroreceptors in the internal carotid arteries and aortic arch and thus activating the sympathetic nervous system (SNS) and vasopressin. Increases occur in epinephrine and norepinephrine concentrations and increased heart rate, contractility, and afterload occur by peripheral vasoconstriction (Figure 2). In turn, this leads to apoptosis and an increased potential for arrhythmias.

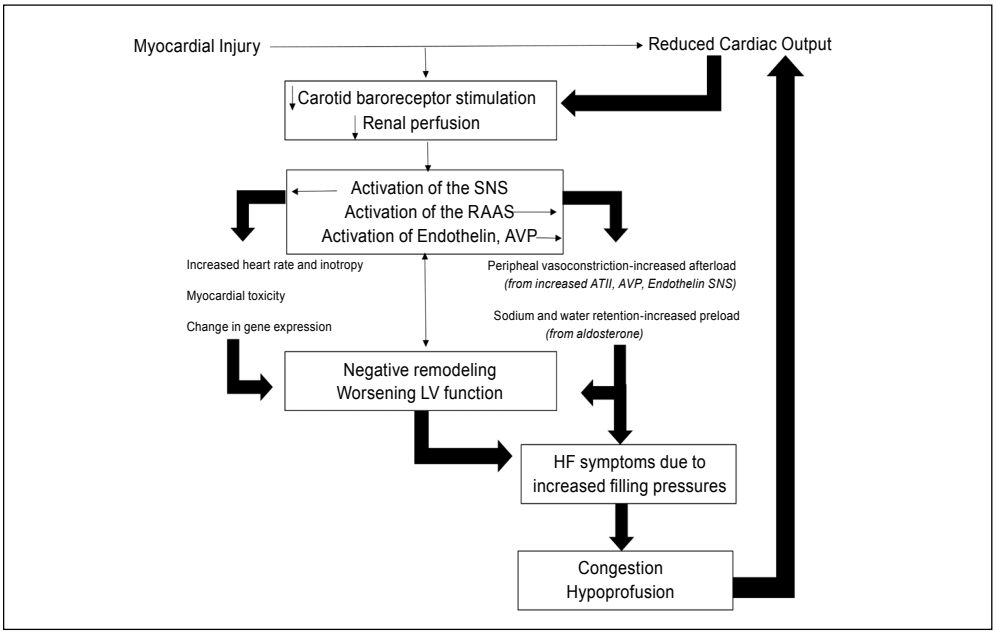


**Figure 2.** Overview of the pathophysiology of heart failure.

AT II = angiotensin 2; AVP = arginine vasopressin; LV = left ventricular; RAAS = renin-angiotensin-aldosterone system; SNS = sympathetic nervous system.

2. Vasopressin is synthesized by neurosecretory cells located predominantly in the supraoptic and paraventricular hypothalamic nuclei. These neurons have axons terminating in the neural lobe of the posterior pituitary (neurohypophysis) that release vasopressin. Vasopressin acts on the $V_2$ renal receptors, increasing free water reabsorption by insertion of protein water channels, aquaporins, in the luminal membranes of the principal cells of the renal-collecting ducts. Vasopressin acts on the $V_{1a}$ receptors in vascular smooth muscle to cause vasoconstriction.
3. Endothelin (ET) is produced from endothelial cells because of shear and mechanical stress, vasopressin, AT II, norepinephrine, and epinephrine.
4. Binding to the ET-A receptor on vascular smooth muscle and myocardium, ET, specifically ET-1, has negative effects on remodeling and vasoconstriction.
5. When the renal perfusion is decreased, the kidney assumes hypovolemia, as low cardiac output (CO) decreases renal perfusion. The inherent compensatory mechanism to retain sodium and water is activation of the renin-angiotensin-aldosterone system (RAAS) (Figure 3).
6. With a decrease in pressure and sodium presentation to the distal tubule, prorenin is released into the circulation. Kallikrein, a protease enzyme, converts prorenin to renin. Renin in turns cleaves angiotensinogen to angiotensin I (AT I). Angiotensin-converting enzyme (ACE), a protease enzyme found circulating in the vasculature, converts AT I to AT II. AT II, in turn, stimulates the adrenal cortex to produce aldosterone and the CNS to secrete antidiuretic hormone. Both bind to receptors in the distal tubule to cause sodium and water retention. Other non-ACE and non-renin pathways exist to produce AT II (Figure 3).
7. Kallikrein also converts bradykininogen to bradykinin, a very potent vasodilator but a powerful pulmonary irritant. ACE in turn degrades bradykinin to inactive fragments (Figure 3).

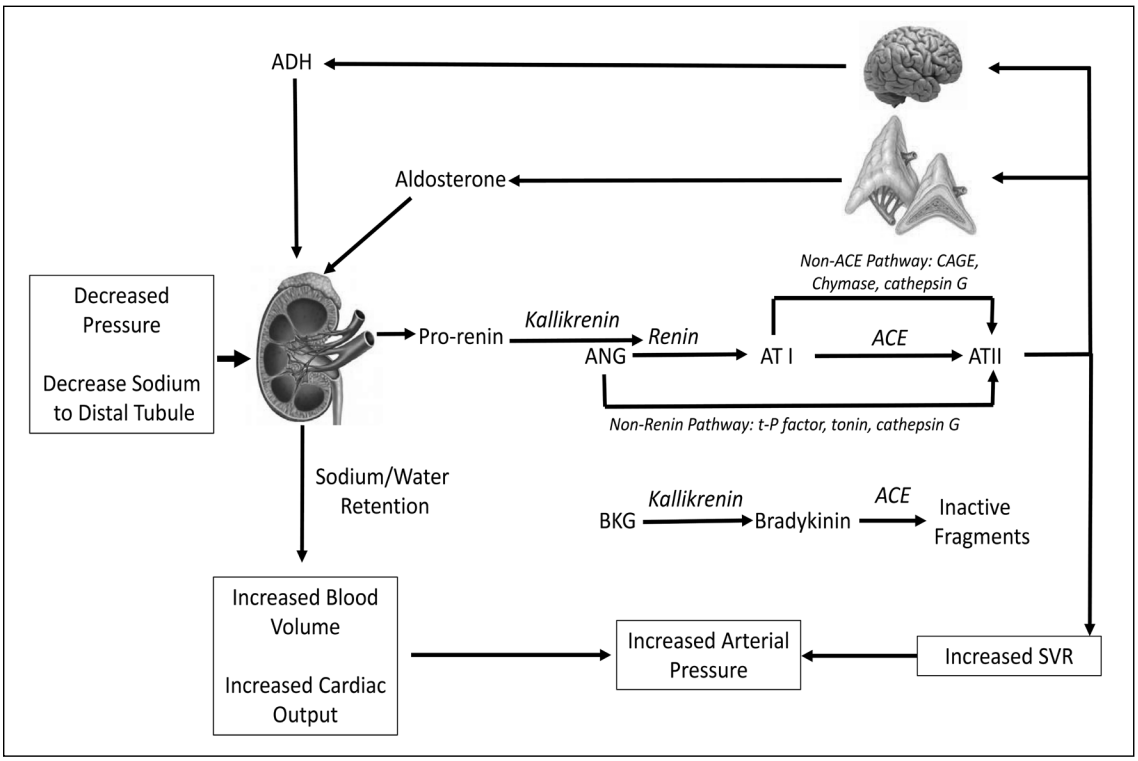


**Figure 3.** Summary of the renin-angiotensin-aldosterone system.

ACE = angiotensin-converting enzyme; ANG = angiotensinogen; AT I = angiotensin I; AT II= angiotensin II; BKG = bradykininogen; SVR = systemic vascular resistance.

8. According to the Frank-Starling principle, with increasing stretch of the myocardium as the result of increased preload (e.g., LV end-diastolic pressure), there is a compensatory increase in CO because of increases in the formation of cross bridges between actin and myosin. However, over time, this is hazardous to the myocardium.
9. With increases in preload, atrial natriuretic peptide (ANP) and BNP are released from the myocardium.
10. ANP is a 28-amino acid peptide that is synthesized, stored, and released by atrial myocytes in response to atrial distension, AT II stimulation, ET, and the SNS (β-adrenoceptor mediated).
11. BNP is 32-amino acid peptide that is synthesized largely by the ventricles (as well as in the brain where it was first identified). BNP is first synthesized as pre-pro-BNP, which is then cleaved to proBNP. Proteolysis of proBNP results in BNP, and the NT-proBNP neutral endopeptidase (also called neprilysin) is a circulating enzyme that degrades BNP (Figure 3).
12. BNP increases eGFR and filtration fraction, which produces natriuresis and diuresis; and decreases renin release, thereby decreasing circulating concentrations of AT II and aldosterone, resulting in further natriuresis and diuresis and increased systemic vasodilation and decreased systemic vascular resistance (SVR). Activation of the natriuretic peptides in turn offsets the harmful effects of SNS RAAS (Figure 4).

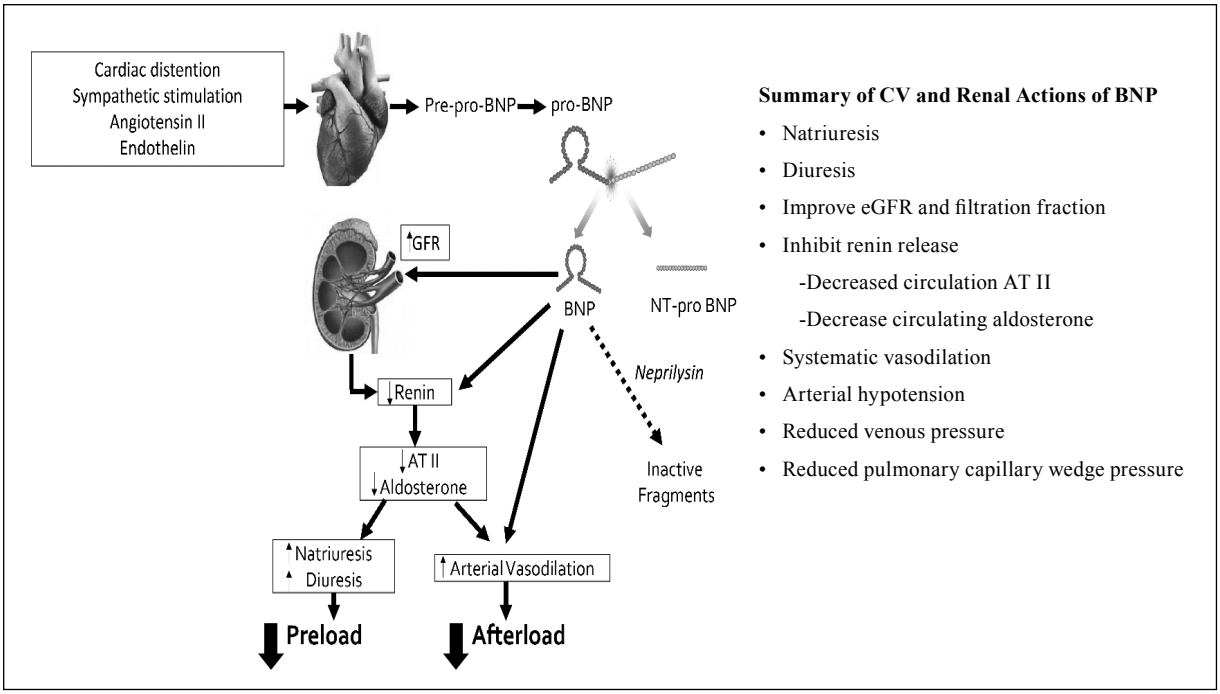


**Figure 4.** Cardiovascular and renal effects of B-type natriuretic peptide.
eGFR = estimated glomerular filtration rate.

13. Nitric oxide is enzymatically formed from L-arginine by three isoforms of nitric oxide synthetase (NOS): neuronal type (nNOS, NOS1), cytokine-inducible type (iNOS, NOS2), and endothelial type (eNOS, NOS3). Nitric oxide is a venodilator and antioxidant that reduces myocardial remodeling. Chronic HF is associated with arterial endothelial dysfunction and impaired endothelium-dependent, flow-mediated dilation; the mechanism is probably a reduction in NOS by eNOS as well as a decrease in endothelial release of and response to nitric oxide.

14. Several neurohormones are elevated in HF. Table 7 describes the pathophysiological effects of the specific organs and tissues that contribute to HF development and progression.

**Table 7.** Pathophysiological Effects of Neurohormones and Vasoactive Agents

| | Site of Action | Pathophysiological Effect |
|---|---|---|
| AT II | Vascular smooth muscle | • Arterial vasoconstriction |
| | Endothelium | • Increased ET secretion |
| | CNS | • Increased SNS activity |
| | | • Increased ADH |
| | | • Increased thirst |
| | | • Increased vasopressin secretion |
| | Adrenal gland | • Increased aldosterone secretion |
| | Kidney | • Efferent arterial vasoconstriction |
| | | • Glomerular and intestinal fibrosis |
| | | • Increased sodium and water retention |
| | | • Cellular hypertrophy |
| | | • Coronary artery vasoconstriction |
| | Heart | • Myocardial fibrosis |
| | Pituitary gland | • Increased vasopressin secretion |
| Aldosterone | Endothelium | • Endothelial dysfunction |
| | | • Vascular remodeling |
| | | • Vascular inflammation |
| | | • Baroreceptor dysfunction |
| | Brain | • Increased SNS activity |
| | | • Increased sodium and water retention |
| | Kidney | • Excretion of potassium and magnesium |
| | | • Increased arrhythmia potential |
| | | • Myocardial fibrosis |
| | | • Ventricular remodeling |
| | Heart | • Ventricular hypertrophy |
| Catecholamines (epinephrine, norepinephrine) | Heart | • Increased myocyte growth |
| | | • Increased inotropic and chronic response |
| | | • Increased myocyte toxicity |
| | | • Increased myocyte apoptosis |
| | | • Increased arrhythmia potential |
| | | • Arterial vasoconstriction |
| | Endothelium | • Increased ET secretion |
| | Kidney | • Increased renal artery vasoconstriction |

**Table 7.** Pathophysiological Effects of Neurohormones and Vasoactive Agents (*Cont'd*)

| | Site of Action | Pathophysiological Effect |
|---|---|---|
| ET | Kidney | • Increased renal artery vasoconstriction<br>• Increased sodium and water retention |
| | Vascular smooth muscle | • Vasoconstriction<br>• Smooth muscle hypertrophy<br>• Smooth muscle proliferation<br>• Increased collagen synthesis |
| | Heart | • Myocyte hypertrophy<br>• Myocyte fibrosis<br>• Increased collagen synthesis |
| Vasopressin | Kidney | • Increased water reabsorption |
| | Vascular smooth muscle | • Vasoconstriction |

ADH = antidiuretic hormone; ET = endothelin.

## III. PHARMACOTHERAPY OF HEART FAILURE WITH REDUCED EJECTION FRACTION

**Patient Case**

*Questions 6, 8, and 9 pertain to the following case.*

J.M. is a 62-year-old white man with an MI 3 years ago, HTN, depression, peripheral arterial disease, osteoarthritis, hypothyroidism, type 2 DM (diet controlled), and HFrEF (LVEF of 25%). His medications include aspirin 81 mg/day, simvastatin 40 mg every night, lisinopril 20 daily, metoprolol succinate 150 mg/day, furosemide 80 mg twice daily, cilostazol 100 mg twice daily, acetaminophen 650 mg four times daily, and levothyroxine 0.1 mg/day. He has no known drug allergies. His vital signs include blood pressure 155/90 mm Hg and heart rate 65 beats/minute. He weighs 100 kg (220 lb). Pertinent laboratory results include K 4.1 mEq/L, SCr 1.6 mg/dL, and thyroid-stimulating hormone 2.6 mIU/L. His HF is stable and considered NYHA functional class III.

6. Which would best maximize the management of J.M.'s HF?
   A. Add digoxin 0.125 mg daily.
   B. Add losartan 25 mg daily.
   C. Add spironolactone 25 mg daily.
   D. Add amlodipine 5 mg daily.

A. Overall Management According to Stages (Table 8)

**Table 8.** Stages in the Development of HF and Recommended Therapy by Stage

| Stage | Patient Population | Goals of Therapy | Pharmacotherapy | Nonpharmacologic |
|---|---|---|---|---|
| A | High risk of developing HF with no structural heart disease<br><br>Risk factors: HTN, atherosclerotic disease, DM, obesity, metabolic syndrome, patients using cardiotoxins or having a family history of cardiomyopathy<br><br>No signs or symptoms of HF | Heart-healthy lifestyle<br><br>Prevent vascular and CAD, prevent LV structural abnormalities<br><br>Treat HTN, DM, and CAD according to current guidelines | Statin therapy for CAD and DM<br><br>ACE inhibitor or ARB for vascular disease or DM | |
| B | Previous MI, LV remodeling including LVH and low LVEF, asymptomatic valvular disease<br><br>No signs or symptoms of HF | Prevent HF symptoms<br><br>Prevent further remodeling | ACE, ARB, or ARNI unless contraindication<br><br>β-Blocker unless contraindication | In selected patients:<br>• ICD<br>• Revascularization or valvular surgery as appropriate |
| C | Known structural heart disease<br><br>Prior or current signs and symptoms of HF | Control HF symptoms<br><br>Improve QoL<br><br>Prevent hospitalization mortality | Drugs for routine use:<br>• Diuretics for fluid retention<br>• β-Blockers<br>• Aldosterone antagonists<br>• ARNIs<br>• SGLT2 inhibitors<br><br>Drugs for use in selected patients:<br>• Hydral-nitrates<br>• Digoxin<br>• Ivabradine | In selected patients:<br>• CRT<br>• ICD<br>• Revascularization or valvular surgery as appropriate |
| D | Refectory HF despite medical management<br><br>Patients with HF symptoms at rest and recurrent hospitalizations | Control symptoms<br><br>Reduce hospital readmissions<br><br>Establish patient's end-of-life goals | Chronic inotropes<br>(See chapter on ADHF) | • Advanced care measures<br>• Heart transplantation<br>• Temporary or permanent MCS<br>• Palliative care and hospice<br>• ICD deactivation |

ARB = angiotensin receptor blocker; ARNI = angiotensin-receptor neprilysin inhibitor; hydral-nitrates = hydralazine combined with isosorbide dinitrate; LVH = left ventricular hypertrophy; MCS = mechanical circulatory support SGLT = sodium-glucose cotransporter-2.

Information from: Yancy CW, Jessup M, Bozkurt B, et al. 2013 ACCF/AHA guideline for the management of heart failure. A report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. Circulation 2013;128:e240-e327.

B. Drugs for Routine Use
   1. Diuretics
      a. Place in therapy: Indicated in patients with evidence of fluid retention
      b. Short-term benefits (days)
         i. Decreased JVP

ii. Decreased pulmonary congestion
iii. Decreased peripheral edema

c. Intermediate-term benefits (weeks to months)
i. Decreased daily symptoms
ii. Increased exercise tolerance

d. Long-term benefits (months to years): No benefit on mortality

e. Mechanism of action: Inhibits sodium reabsorption in the ascending loop of Henle (loop diuretics) or the distal tubule (thiazide diuretics)

f. Dosing and administration considerations (Table 9)

**Table 9.** Diuretics and Recommended Dosing[a]

| Agent | Oral Bioavailability (%) | Initial Daily Dose | Maximal Total Daily Dose (mg) | Duration of Action (hr) |
|---|---|---|---|---|
| **Loop Diuretics (inhibit 20%–25% of sodium reabsorption)** | | | | |
| Furosemide[b] | 10–67 | 20–40 mg daily or BID | 600 | 6–8 |
| Bumetanide[b] | 80–100 | 0.5–1 mg daily or BID | 10 | 4–6 |
| Torsemide | 80–100 | 10–20 mg daily or BID | 200 | 12–16 |
| Ethacrynic acid[b] | 100 | 25–50 mg daily or BID | 200 | 6–8 |
| **Thiazide Diuretics (inhibit 10%–15% of sodium reabsorption)** | | | | |
| Hydrochlorothiazide | 65–75 | 25 mg daily or BID | 100 | 6–12 |
| Metolazone | 40–65 | 2.5-5 mg daily | 20 | 12–24 |
| Chlorthalidone | 64 | 12.5–25 mg daily | 100 | 24–72 |
| Chlorothiazide | 30–50 | 250–500 mg daily or BID | 2000 | 6–12 |

[a]Equivalent doses: Furosemide 40 mg = bumetanide 1 mg = torsemide 10–20 mg = ethacrynic acid 50 mg.

[b]Available in oral and intravenous formulations.

BID = twice daily.

i. Should be combined with an ACE inhibitor or ARB and a β-blocker
ii. Start with low initial dose; may then double the dose and titrate on the basis of the patient's weight and diuresis. Note the difference in bioavailability of oral doses.
iii. If a patient has fluid overload, initiate and adjust therapy for a weight loss of 0.45–0.9 kg (1–2 lb) per day.
iv. May combine loop diuretic with a thiazide diuretic for dual-nephron blockade
v. Loop diuretics are preferred because of their greater diuretic capabilities; loop diuretics also retain efficacy with decreased renal function. Thiazide diuretics may be adequate if only mild volume overload and HTN
vi. No preference on initial loop diuretic
(a) Ethacrynic acid is usually reserved for patients with severe sulfa allergies.
vii. TRANSFORM-HF (Presented at the AHA 2022 Annual Scientific Sessions, official publication planned for 2023)
(a) 2859 patients hospitalized for HF, regardless of EF (64% of patients had an EF below 40%), were randomized to either torsemide or furosemide (around two-thirds of patients were receiving a diuretic before admission).
(b) Background therapy included β-blockers (82%), ACE inhibitors/ARBs/angiotensin receptor-neprilysin inhibitors (ARNIs) (68%), mineralocorticoid receptor antagonists (MRAs) (44%), and sodium-glucose cotransporter 2 (SGLT2) inhibitors (8%).

(c) Median follow-up of 17.4 months
(d) No difference in the primary outcome of rate of all-cause mortality between the torsemide and furosemide groups (26.1% vs. 26.2%; HR 1.02; 95% CI, 0.89–1.18)
(e) No difference between torsemide and furosemide for the composite of all-cause mortality or all-cause hospitalization at 12 months (47.3% vs. 49.3%; HR 0.92; 95% CI, 0.83–1.02) or for total hospitalizations (37.5% vs. 40.4%; rate ratio 0.94; 95% CI, 0.84–1.07)

g. Monitoring: Monitor and replace potassium and magnesium as needed, especially with loop diuretics (goal with CV disease is potassium of 4.0 mEq/L or greater and magnesium of 2.0 mEq/L or greater to minimize the risk of arrhythmias). Monitor every 1–2 weeks after start or dose increase.

2. ARNIs
   a. Place in therapy (according to the 2022 ACC/AHA/HFSA guidelines)
      i. ARNI (recommended over ACE inhibitor or ARB) in conjunction with GDMT β-blockers, aldosterone antagonists, and SGLT-2 inhibitors in selected patients are recommended for patients with chronic Stage C HFrEF to reduce morbidity and mortality.
   b. Benefits
      i. Decreased composite end point of death from CV causes or hospitalization for HF (20% RRR compared with enalapril)
      ii. Decreased all-cause mortality (16% RRR) and CV death (20% RRR) compared with enalapril
   c. Landmark randomized trial with ARNIs (Table 10)

**Table 10.** Landmark Randomized Controlled Trial with ARNIs

| Study | Year | Treatment Arms | Population | Follow-up Time | Primary End Point |
|---|---|---|---|---|---|
| PARADIGM-HF[a] | 2014 | Sacubitril/valsartan (n=4187)<br><br>Enalapril (n=4212) | LVEF ≤ 40%, NYHA II–IV, stabilized on a β-blocker and an ACE inhibitor (or ARB) equivalent to at least 10 mg of enalapril daily, mean age 64 yr | 27 mo (mean) | Compared with enalapril, sacubitril/valsartan had a 20% reduction in CV death or HF hospitalization (HR 0.80; 95% CI, 0.71–0.89; p<0.001), a 20% reduction in CV death (HR 0.80; 95% CI, 0.71–0.89; p<0.001), and a 19% reduction in first HF hospitalization (HR 0.79; 95% CI, 0.71–0.89; p<0.001) |
| PIONEER-HF | 2019 | Sacubitril/valsartan (n=440)<br><br>Enalapril (n=441) | Hospitalized patients with LVEF < 40%, NYHA II–IV, NT-proBNP > 1600 pg/mL or BNP > 400 pg/mL, and a previous diagnosis of AHF | 68 hr (median) | Initiation of sacubitril/valsartan therapy inpatient led to a greater reduction in the NT-proBNP concentration than enalapril therapy (ratio of change with sacubitril/valsartan vs. enalapril 0.71; 95% CI, 0.63–0.81; p<0.001). Rates of worsening renal function, hyperkalemia, symptomatic hypotension, and angioedema did not differ significantly between the two groups. |

[a]Study stopped early.

AHF = acute heart failure; BNP = B-type natriuretic peptide; CI = Confidence interval; CV = cardiovascular; HR = Hazard ratio; NT-pro BNP = N-terminal pro-B-type natriuretic peptide; PARADIGM-HF = Prospective Comparison of ARNI with ACEI to Determine Impact on Global Mortality and Morbidity in Heart Failure; PIONEER-HF = Comparison of Sacubitril–Valsartan versus Enalapril on Effect on NT-proBNP in Patients Stabilized from an Acute Heart Failure Episode.

   d. Mechanism of action
      i. Sacubitril – Prodrug metabolized to an active metabolite that inhibits neprilysin, increasing natriuretic peptide concentrations

ii. Valsartan – ARB; selectively blocks the AT II type 1 receptor and inhibits AT II–dependent aldosterone release

e. Dosing and administration
   i. Dosing from an ACE inhibitor or ARB to an ARNI (Table 11)
   ii. For patients not currently taking an ACE inhibitor or an ARB, or for those with severe renal impairment (eGFR less than 30 mL/minute/1.73 $m^2$) or moderate hepatic impairment, the starting dosage of sacubitril/valsartan is 24/26 mg twice daily.
   iii. The benefit for patients taking lower doses of sacubitril/valsartan relative to those taking lower doses of enalapril was similar to that for patients who remained on target doses of both drugs.

**Table 11.** Dosing of Sacubitril/Valsartan

| Patient Type | Initial Dose | Target Dose |
|---|---|---|
| **Conversion from ACE inhibitor** | | |
| Patient taking ACE inhibitor at total daily dose > 10 mg of enalapril or equivalent (lisinopril > 10 mg or ramipril > 5 mg) | Stop ACE inhibitor for 36 hr before starting sacubitril/valsartan<br>49/51 mg BID | Double the dose after 2–4 wk, as tolerated, to reach the target dose of 97/103 mg BID |
| Patient taking ACE inhibitor at total dose ≤ 10 mg of enalapril or equivalent (lisinopril ≤ 10 mg or ramipril ≤ 5 mg) | Stop ACE inhibitor for 36 hr before starting sacubitril/valsartan<br>24/26 mg BID | |
| **Conversion from ARB** | | |
| Patient taking an ARB at total daily dose > 160 mg of valsartan or equivalent (losartan > 50 mg or olmesartan > 10 mg) | Stop ARB and begin sacubitril/valsartan with next scheduled dosing interval<br>49/51 mg BID | Double the dose after 2–4 wk, as tolerated, to reach the target dose of 97/103 mg BID |
| Patient taking ARB at total daily dose ≤ 160 mg of valsartan or equivalent (losartan ≤ 50 mg or olmesartan ≤ 10 mg) | Stop ARB and begin sacubitril/valsartan with next scheduled dosing interval<br>24/26 mg BID | |

   iv. The bioavailability of valsartan in sacubitril/valsartan is 40% greater than that of valsartan alone (Table 12).

**Table 12.** Equivalent Doses of Valsartan Alone vs. Valsartan in Sacubitril

| Sacubitril/Valsartan | Equivalent Valsartan Dose | Equivalent Daily Valsartan Dose |
|---|---|---|
| 24/26 mg BID | 40 mg of valsartan BID | 80 mg daily |
| 49/51 mg BID | 80 mg of valsartan BID | 160 mg daily |
| 97/103 mg BID | 160 mg of valsartan BID | 320 mg daily |

f. Monitoring
   i. Hypotension and hyperkalemia were the most common adverse effects in the clinical trial. However, hyperkalemia was less common than with an ACE inhibitor.
   ii. Symptomatic hypotension occurred in 14% of patients taking sacubitril/valsartan, even though the study excluded those with baseline hypotension. Hypotension was more common with sacubitril/valsartan than with enalapril.

iii. Cough (11.3%) and elevated SCr (3.3%) occurred in patients treated with the combination, but less commonly than with enalapril.
iv. Because sacubitril will inhibit neprilysin and BNP degradation, BNP will be elevated after initiation of sacubitril/valsartan; therefore a NT-proBNP will be needed for evaluation of HF management and severity.
v. Neprilysin inhibition can cause angioedema, which occurred in 0.5% of patients treated with the combination compared with 0.2% of those treated with enalapril. African American patients appear to be at high risk.
vi. Avoid in pregnancy and patients with any history of angioedema, regardless of ACE inhibitor exposure.

3. ACE inhibitors
   a. Place in therapy: Recommended in all patients with HFrEF with prior or current symptoms to reduce morbidity and mortality
   b. Benefits
      i. Decreased mortality (about a 25%–50% relative risk reduction [RRR] compared with placebo, depending on severity of HF)
      ii. Decreased hospitalizations (about 30% RRR compared with placebo)
      iii. Symptom improvement and improved clinical status
      iv. Improved sense of well-being
   c. Landmark randomized trials with ACE inhibitors (Table 13)

**Table 13.** Landmark Randomized Controlled Trials with ACE Inhibitors

| Study | Year | Treatment Arms | Population | Follow-up Time | Primary Outcomes/Results |
|---|---|---|---|---|---|
| CONSENSUS | 1987 | Enalapril (n=126)<br><br>Placebo (n=127) | NYHA IV, mean age 70 yr | 188 days (mean) | Enalapril was associated with a 40% reduction in all-cause mortality at 6 mo compared with placebo (26% vs. 44%, p=0.002, respectively) and 31% at 1 yr (36% vs. 50%, p=0.001, respectively) |
| SOLVD-Treatment | 1991 | Enalapril (n=1285)<br><br>Placebo (n=1284) | LVEF ≤ 35%, NYHA II and III, mean age 61 yr | 41.4 mo (mean) | Enalapril was associated with a 16% RR in all-cause mortality (39.7% vs. 35.2%, p=0.0036, respectively) and a 26% RRR in the composite of death or hospitalization compared with placebo (47.7% vs. 57.3%, p<0.0001, respectively) |
| SOLVD-Prevention | 1992 | Enalapril (n=2117)<br><br>Placebo (n=2111) | LVEF ≤ 35%, NYHA I and II, mean age 59 yr | 37.4 mo (mean) | Enalapril was associated with an 8% RR in all-cause mortality (95% CI, -8% to 21%, p=0.30); 12% reduction in CV mortality (95% CI, -3% to 26%, p=0.12); 37% reduction in the development of HF (95% CI, 28%–44%, p<0.001); 20% RR in mortality or HF hospitalization (95% CI, 9%–30%, p<0.001); 36% RR in first HF hospitalization (95% CI, 22%–46%, p<0.001); and 29% RR in all-cause mortality or development of HF (95% CI, 21%–36%, p<0.0001) |

**Table 13.** Landmark Randomized Controlled Trials with ACE Inhibitors (*Cont'd*)

| Study | Year | Treatment Arms | Population | Follow-up Time | Primary Outcomes/Results |
|---|---|---|---|---|---|
| SAVE | 1992 | Captopril (n=1116)<br><br>Placebo (n=1115) | LVEF ≤ 40%, post-MI, mean age 59 yr | 42 mo (mean) | Captopril was associated with a 19% RR in all-cause mortality (95% CI, 3%–32%, p=0.019), 21% RRR in CV deaths (95% CI, 5%–35%, p<0.001), 37% RR in development of severe HF (95% CI, 20%–50%, p<0.001), and 22% RR in HF hospitalization (95% CI, 4%–37%, p=0.019) |
| ATLAS | 1999 | Low-dose lisinopril (n=1596)<br><br>High-dose lisinopril (n=1568) | LVEF ≤ 30%, NYHA II–IV, mean age 64 yr | 47.5 mo (median) | High dose was associated with an 8% RR in all-cause mortality (HR 0.92; 95% CI, 0.82–1.03; p=0.128) and a 10% RR in CV mortality (HR 0.90; 95% CI, 0.81–1.01; p=0.073) |

ATLAS = Assessment of the Treatment with Lisinopril and Survival; CI = confidence interval; CONSENSUS = Cooperative North Scandinavian Enalapril Survival Study; HR = hazard ratio; RR = risk reduction; RRR = relative risk reduction; SAVE = Survival and Ventricular Enlargement; SOLVD = Studies of Left Ventricular Dysfunction.

d. Mechanism of action
    i. Blocks production of AT II
        (a) Decreases sympathetic stimulation
        (b) Decreases production of aldosterone and vasopressin
        (c) Decreases vasoconstriction (afterload and preload)
    ii. Increases bradykinins (blocking their metabolism)
        (a) Increases vasodilatory prostaglandins
        (b) Delays and prevents myocardial remodeling
e. Dosing and administration
    i. Start low, and double the dose every 1–4 weeks to target dose (Table 14).
    ii. The ATLAS trial, which compared low-dose lisinopril (2.5–5 mg/day) with high-dose lisinopril (32.5–35 mg/day), found no difference in the primary end point of all-cause mortality or CV mortality but did show a significant 12% lower risk of death or hospitalization for any reason and 24% fewer hospitalizations for HF in the high-dose cohort.
    iii. Avoid use in patients who have had angioedema as the result of previous ACE inhibitor use or those who are pregnant or plan to become pregnant.
    iv. Use caution if systolic blood pressure is less than 80 mm Hg, SCr is greater than 3 mg/dL, Na is less than 130 mEq/L, or K is greater than 5.0 mEq/L or if the patient has bilateral renal artery stenosis.
f. Monitoring
    i. Serum creatinine and potassium every 1–2 weeks after initiating therapy or with increasing the dose, especially in high-risk patients (preexisting hypotension, DM, potassium supplements, azotemia, MRA). Serum creatinine may increase (up to a 30% increase is acceptable) because of renal efferent artery dilation (results in a slightly decreased glomerular filtration rate). Rarely, acute renal failure occurs, especially if the patient is intravascularly depleted (be careful to avoid overdiuresis). For chronic therapy, consider monitoring renal function every 4 months.
    ii. Monitor blood pressure and symptoms of hypotension (e.g., dizziness, lightheadedness).
        (a) Blood pressure may be lower to begin with because of low CO.

(b) Blood pressure = CO × SVR.
(c) As CO increases because of decreased SVR, blood pressure may decrease slightly or remain the same.
(d) Symptoms of hypotension are often not present with small dose increases. Remember to treat the patient, not the number.

g. Adverse effects
   i. Angioedema (less than 1%): May change to angiotensin receptor blocker (ARB) (cross-reactivity is 10%) or hydralazine combined with isosorbide dinitrate
   ii. Cough (20%): May change to ARBs (less than 1%)

**Table 14.** Dosing of ACE Inhibitors

| ACE Inhibitor | Initial Dose(s) | Maximum Dose(s) | Mean Dosages Achieved in HF Trials |
|---|---|---|---|
| Captopril | 6.25 mg TID | 50 mg TID | 122.7 mg/day |
| Enalapril | 2.5 mg BID | 10–20 mg BID | 16.6 mg/day |
| Fosinopril | 5–10 mg daily | 40 mg daily | |
| Lisinopril | 2.5–5 mg daily | 20–40 mg daily | 32.5–35.0 mg/day |
| Perindopril | 2 mg daily | 8–16 mg daily | |
| Quinapril | 5 mg BID | 20 mg BID | |
| Ramipril | 1.25–2.5 mg daily | 10 mg daily | |
| Trandolapril | 1 mg daily | 4 mg daily | |

TID = three times daily.

Information from: Yancy CW, Jessup M, Bozkurt B, et al. 2013 ACCF/AHA guideline for the management of heart failure. A report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. Circulation 2013;128:e240-e327.

4. ARBs
   a. Place in therapy: Recommended in patients with HFrEF with current or prior symptoms
   b. Benefits:
      i. Have not been proven superior to ACE inhibitors at target HF dosages
      ii. Decrease HF-related hospitalization and CV death
      iii. Considered if the patient has had ACE inhibitor–induced angioedema (cross-reactivity 10%)
   c. Landmark randomized trials with ARBs (Table 15)

**Table 15.** Landmark Randomized Controlled Trials with ARBs

| Study | Year | Treatment Arms | Population | Follow-up Time | Primary End Point |
|---|---|---|---|---|---|
| ELITE I | 1997 | Losartan (n=352)<br><br>Captopril (n=370) | LVEF ≤ 40%, ACE inhibitor naive, NYHA II–IV, mean age 74 yr | 48 wk | No difference between losartan and captopril in the frequency of persisting (confirmed) increases in SCr (RR 2.0% (95% CI, -51% to +36%, p=0.63) |
| ELITE II | 2000 | Losartan (n=1578)<br><br>Captopril (n=1574) | LVEF ≤ 40%, ACE inhibitor naive, NYHA II–IV, mean age 72 yr | 555 days (mean) | No difference between losartan and captopril in all-cause mortality (17.7% vs. 15.9%, p=0.16, respectively) or the composite or all-cause mortality or all-cause hospital admission (47.7% vs. 44.9%, p=0.18, respectively) |

**Table 15.** Landmark Randomized Controlled Trials with ARBs (*Cont'd*)

| Study | Year | Treatment Arms | Population | Follow-up Time | Primary End Point |
|---|---|---|---|---|---|
| CHARM-ALTERNATIVE | 2003 | Candesartan (n=1013)<br><br>Placebo (n=1015) | LVEF ≤ 40%, NYHA II–IV, intolerant of ACE inhibitors, mean age 67 yr | 33.7 mo (median) | Compared with placebo, candesartan had a 30% RR in the composite of CV death or HF hospitalization (adjusted HR 0.70; 95% CI, 0.60–0.81; p<0.0001) |
| HEAAL | 2009 | Low-dose losartan (n=1919)<br><br>High-dose losartan (n=1927) | LVEF ≤ 40%, NYHA II–IV, intolerant of ACE inhibitors, mean age 66 yr | 4.7 yr (median) | High-dose losartan had a 10% RR in the composite of all-cause mortality or HF hospitalization (HR 0.90; 95% CI, 0.82–0.99; p=0.027) |

CHARM = Candesartan in Heart Failure Assessment of Reduction in Mortality and Morbidity; ELITE = Evaluation of Losartan in the Elderly; HEAAL = Heart Failure Endpoint Evaluation of Angiotensin II Antagonist Losartan.

d. Mechanism of action
   i. Selectively blocks the binding of AT II to the AT II receptor
   ii. Does not affect ACE or inhibit kinin catabolism
   iii. Same benefits as ACE inhibitors
   iv. Losartan reduces uric acid, which is believed to play a causal role in HF.
e. Dosing and administration (Table 16)
   i. Same as ACE inhibitors for monitoring and titration
   ii. Data from the HEAAL trial suggest that high-dose losartan (150 mg/day) compared with low-dose losartan (50 mg/day) had a 10% reduction in the composite of all-cause mortality or HF hospitalization.
f. Monitoring
   i. Same as for ACE inhibitors
   ii. Expect no cough and rare angioedema.

**Table 16.** Dosing of ARBs

| Angiotensin Receptor Blocker | Initial Dose(s) | Maximum Dose(s) | Mean Dosages Achieved in HF Trials |
|---|---|---|---|
| Candesartan | 4–8 mg daily | 32 mg daily | 24 mg/day |
| Losartan | 25–50 mg daily | 50–150 mg daily | 129 mg/day |
| Valsartan | 20–40 mg BID | 160 mg BID | 254 mg/day |

Information from: Yancy CW, Jessup M, Bozkurt B, et al. 2013 ACCF/AHA guideline for the management of heart failure. A report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. Circulation 2013;128:e240-e327.

5. β-Blockers
   a. Place in therapy: Recommended in all patients with HFrEF, even stage B, with current or prior symptoms of HF unless contraindicated
   b. Benefits (when added to an ACE inhibitor)
      i. Decreased mortality (about 35% RRR compared with placebo)
      ii. Decreased hospitalizations (about 25% RRR compared with placebo)
      iii. Symptom improvement
      iv. Improved clinical status – Increases LVEF

v. Carvedilol is the only β-blocker studied in patients with severe HF (COPERNICUS trial); however, these patients were stable and euvolemic.

c. Landmark randomized trials with β-blockers (Table 17)

**Table 17.** Landmark Randomized Trials with β-Blockers

| Study | Year | Treatment Arms | Population | Follow-up Time | Primary End Point |
|---|---|---|---|---|---|
| MDC | 1993 | Metoprolol tartrate (n=194)<br>Placebo (n=189) | LVEF < 40%, NYHA II–IV, mean age 49 yr | 12 mo | Metoprolol tartrate had a 34% RRR in death or need for transplantation compared with placebo (95% CI, -6% to 62%; p=0.058) |
| CIBIS I | 1994 | Bisoprolol (n=320)<br>Placebo (n=321) | LVEF < 40%, NYHA III and IV, mean age 60 yr | 1.9 yr (mean) | No difference in mortality between bisoprolol and placebo (RR 0.80; 95% CI, 0.56–1.15; p=0.22)<br>Study was underpowered |
| US CARVEDILOL STUDY[a] | 1996 | Carvedilol (n=696)<br>Placebo (n=398) | LVEF < 35%, NYHA II–IV, mean age 58 yr | 6.5 mo (median) | Carvedilol had a 65% reduction in attributable risk of death (95% CI, 39%–80%, p<0.001), a 27% reduction in the risk of hospitalization for CV causes (p<0.036), and a 38% reduction in the combined risk of hospitalization or death (p<0.001) |
| CIBIS II[a] | 1999 | Bisoprolol (n=1327)<br>Placebo (n=1320) | LVEF ≤ 35%, NYHA II–IV, mean age 61 yr | 1.3 yr (mean) | All-cause mortality was significantly lower with bisoprolol than with placebo (HR 0.66; 95% CI, 0.54–0.81; p<0.0001) |
| MERIT-HF[a] | 1999 | Metoprolol CR/XL (n=1990)<br>Placebo (n=2001) | LVEF ≤ 40%, NYHA II–IV, mean age 64 yr | 1 yr (mean) | All-cause mortality was significantly lower with metoprolol CR/XL than with placebo (7.2%, per patient-year of follow-up vs. 11.0%) (RR 0.66; 95% CI, 0.53–0.81; p=0.00009) |
| COPERNICUS[a] | 2001 | Carvedilol (n=1156)<br>Placebo (n=1133) | LVEF < 25%, mean age 63 yr | 10.4 mo (mean) | Carvedilol had a 35% reduction in risk of death compared with placebo (95% CI, 0.19–0.48, p=0.00013 [unadjusted]) |
| BEST[a] | 2001 | Bucindolol (n=1354)<br>Placebo (n=1354) | LVEF < 35%, NYHA III and IV, mean age 60 yr | 2 yr | No significant difference between groups (p=0.16) in all-cause mortality; a survival benefit occurred only in the nonblack patients |

**Table 17.** Landmark Randomized Trials with β-Blockers (*Cont'd*)

| Study | Year | Treatment Arms | Population | Follow-up Time | Primary End Point |
|---|---|---|---|---|---|
| COMET | 2003 | Carvedilol (n=1511)<br><br>Metoprolol tartrate (n=1518) | LVEF ≤ 35%, NYHA II–IV, mean age 62 yr | 58 mo (mean) | All-cause mortality was 34% for carvedilol vs. 40% for metoprolol (HR 0.83; 95% CI, 0.74–0.93; p=0.0017); the composite end point of mortality or all-cause admission occurred in 74% of carvedilol group and 76% of the metoprolol group (HR 0.94; 95% CI, 0.86–1.02; p=0.122) |
| CIBIS III | 2005 | Bisoprolol-first (n=505)<br><br>Enalapril-first (n=505) | LVEF ≤ 35%, NYHA II and III, mean age 73 yr | 1.25 yr (mean) | Bisoprolol-first treatment was noninferior to enalapril-first treatment regarding mortality or all-cause hospitalization (HR 0.94; 95% CI, 0.77–1.16) |

[a]Study stopped early.

BEST = Beta Blocker Evaluation Trial; CIBIS = Cardiac Insufficiency Bisoprolol Study; COMET = Carvedilol or Metoprolol European Trial; COPERNICUS = Carvedilol Prospective Randomized Cumulative Survival Study; MDC = Metoprolol in Dilated Cardiomyopathy; MERIT-HF = Metoprolol CR/XL Randomised Intervention Trial in Congestive Heart Failure.

d. Mechanism of action
   i. Blocks the effect of norepinephrine and other sympathetic neurotransmitters on the heart and vascular system
      (a) Decreases ventricular arrhythmias (sudden cardiac death)
      (b) Decreases cardiac hypertrophy and cardiac cell death
      (c) Decreases vasoconstriction and heart rate
      (d) Decreases cardiac remodeling
   ii. Carvedilol also provides $\alpha_1$-blockade.
      (a) Further decreases SVR (afterload)
      (b) Results in greater reduction in blood pressure than metoprolol succinate
   iii. Of the GDMT β-blockers, bisoprolol is the most cardioselective for the $\beta_1$-receptor; of the β-blockers, nebivolol is the most cardioselective.
   iv. Nebivolol increases nitric oxide and endothelial nitric oxide synthase; however, nebivolol is not a GDMT because it does not have the same extent of mortality reduction as other GDMT β-blockers.

e. Dosing and administration (Table 18)
   i. Only bisoprolol, carvedilol, and metoprolol succinate are recommended in HFrEF.
   ii. Add to existing ACE inhibitor or ARB therapy after trying to reach target ACE inhibitor dosing when HF symptoms are stable and patients are euvolemic.
   iii. However, in the CIBIS III trial, initiating bisoprolol first was noninferior to initiating enalapril first.
   iv. Should not be prescribed without diuretics in patients with a current or recent history of fluid retention
   v. Start low, and increase (double) the dose every 2 weeks (or slower, if needed) to the target dose. Aim to achieve the target dose in 8–12 weeks.
   vi. Avoid abrupt discontinuation; can precipitate clinical deterioration
   vii. May not notice improvement in symptoms for several months
   viii. Should be considered even in patients with reactive airway disease or asymptomatic bradycardia

ix. Higher doses of β-blockers are suggestive of a greater reduction in mortality and improvement in LVEF.

**Table 18.** Dosing of β-Blockers

| β-Blocker | Initial Dose(s) | Maximum Dose(s) | Mean Dosages Achieved in HF Trials |
|---|---|---|---|
| Bisoprolol | 1.25 mg daily | 10 mg daily | 7.5 mg/day |
| Carvedilol | 3.125 mg BID | 50 mg BID | 37 mg/day |
| Carvedilol CR | 10 mg daily | 80 mg daily | |
| Metoprolol succinate CR/XL | 12.5–25 mg daily | 200 mg daily | 159 mg/day |

CR = controlled release; CR/XL= controlled release/extended release.

Information from: Yancy CW, Jessup M, Bozkurt B, et al. 2013 ACCF/AHA guideline for the management of heart failure. A report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. Circulation 2013;128:e240-e327.

f. Monitoring
   i. Blood pressure, heart rate, and symptoms of hypotension (monitor 1–2 weeks)
      (a) Significant hypotension, bradycardia, or dizziness occurs in about 1% of patients when the β-blocker is titrated slowly. If these symptoms appear, lower the dose by 50%.
      (b) Of importance, remember that higher β-blocker doses are associated with greater mortality reduction. Therefore, if hypotension alone is the problem, try reducing the ACE inhibitor (or another antihypertensive) first.
   ii. Increased edema or fluid retention (monitor 1–2 weeks)
      (a) 1%–2% more common than with placebo (in euvolemic, stable patients)
      (b) Responds to diuretic increase
   iii. Fatigue or weakness
      (a) 1%–2% more common than with placebo
      (b) Usually resolves spontaneously in several weeks
      (c) May require dosage decrease or discontinuation

6. Aldosterone antagonists
   a. Place in therapy
      i. Recommended in patients with NYHA class II–IV HF with an LVEF of 35% or less to reduce morbidity and mortality unless a contraindication exists. Patients with NYHA class II HF should have a history of CV hospitalization or elevated BNP concentrations.
      ii. Recommended in patients after an acute MI who have an LVEF of 35% or less with symptoms of HF or history of DM, unless contraindicated
   b. Benefits of spironolactone
      i. Decreased mortality (30% RRR compared with placebo)
      ii. Decreased hospitalizations for HF (35% RRR compared with placebo)
      iii. Improved symptoms
   c. Benefits of eplerenone
      i. Decreased death from CV causes or hospitalization from HF (37% RRR compared with placebo)
      ii. Decreased hospitalizations from HF (42% RRR compared with placebo)
      iii. Decreased mortality (24% RRR compared with placebo)
   d. Benefits of eplerenone in LV dysfunction after MI
      i. Decreased mortality (15% RRR compared with placebo)
      ii. Decreased the composite of death from CV causes or hospitalization for CV events (13% RRR compared with placebo)

e. Landmark randomized trials with aldosterone antagonists (Table 19)

**Table 19.** Landmark Randomized Controlled Trials with Aldosterone Antagonists

| Study | Year | Treatment Arms | Population | Follow-up Time | Primary End Point |
|---|---|---|---|---|---|
| RALES | 1999 | Spironolactone (n=822)<br><br>Placebo (841) | LVEF ≤ 35%, NYHA III and IV, mean age 62 yr | 24 mo (mean) | Spironolactone had a 30% reduction in risk of death compared with placebo (RR 0.70; 95% CI, 0.60–0.82; p<0.001) |
| EPHESUS | 2003 | Eplerenone (n=3319)<br><br>Placebo (n=3313) | LVEF ≤ 40%, post-MI; mean age 64 yr | 16 mo (mean) | Eplerenone had a 15% reduction in risk of death compared with placebo (RR 0.85; 95% CI, 0.75–0.96; p=0.008) |
| EMPHASIS-HF[a] | 2011 | Eplerenone (n=1364)<br><br>Placebo (n=1373) | LVEF ≤ 30%, NYHA II, mean age 69 yr | 21 mo (mean) | Eplerenone had a 34% reduction in risk of death from CV causes or hospitalization for HF compared with placebo (HR 0.66; 95% CI, 0.56–0.78; p<0.001) |

[a]Study stopped early.

EMPHASIS-HF = Eplerenone in Mild Patients Hospitalization and Survival Study in Heart Failure; EPHESUS = Eplerenone Post–Acute Myocardial Infarction Heart Failure Efficacy and Survival Study. RALES=Randomized Aldactone Evaluation Study

f. Mechanism of action: Blocks the effects of aldosterone in the kidneys, heart, and vasculature
   i. Decreases potassium and magnesium loss; decreases ventricular arrhythmias and sudden death
   ii. Decreases sodium and fluid retention
   iii. Eliminates catecholamine potentiation; decreases blood pressure
   iv. Blocks direct fibrotic actions on the myocardium
   v. Compared with spironolactone, eplerenone is more selective for aldosterone receptors in the vasculature, kidney, myocardium, and brain.

g. Dosing and administration (Table 20)
   i. Should be added to ACE inhibitor (or ARB) and β-blocker therapy
   ii. Avoid use if SCr is greater than 2.0 mg/dL for females or 2.5 mg/dL for males, eGFR is less than 30 mL/minute/1.73 $m^2$, or K is greater than 5.0 mEq/L.
   iii. In the absence of hypokalemia (K less than 4.0 mEq/L), supplemental potassium is not recommended when taking an aldosterone antagonist.

**Table 20.** Dosing of Aldosterone Receptor Antagonists

| Values | Eplerenone | Spironolactone |
|---|---|---|
| eGFR > 50 mL/min/1.73 $m^2$ and K ≤ 5 mEq/L | 25 mg daily | 12.5–25 mg daily |
| Maintenance dose after 1 mo if K ≤ 5 mEq/L and eGFR > 50 mL/min/1.73 $m^2$ | 50 mg daily | 25 mg daily or BID |
| eGFR 30–49 mL/min/1.73 $m^2$ and K ≤ 5 mEq/L | 25 mg every other day | 12.5 mg daily or every other day |
| Maintenance dose after 1 mo if K ≤ 5 mEq/L and eGFR 30–49 mL/min/1.73 $m^2$ | 25 mg daily | 12.5–25 mg daily |

eGFR = estimated glomerular filtration rate.

Information from: Heidenreich PA, Bozkurt B, Aguilar D, et al. 2022 AHA/ACC/HFSA guideline for the management of heart failure: a report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. Circulation 2022;145:e895-e1032.

h. Monitoring
    i. K and SCr within 2–3 days and again at 7 days after starting therapy, then monthly for first 3 months, then every 3 months thereafter. If the ACE inhibitor or ARB dose is increased, restart monitoring.
        (a) Hyperkalemia was reported in only 2% of the patients in trials; however, in practice, it occurs in about 20% of patients.
        (b) Decrease dose by 50% or discontinue if K is greater than 5.5 mEq/L.
        (c) See Box 1 for recommendations to avoid hyperkalemia.

**Box 1.** Recommendations to Minimize Hyperkalemia with Aldosterone Antagonists

- Impaired renal function is a risk factor for hyperkalemia during treatment with aldosterone antagonists. The risk of hyperkalemia increases progressively when SCr is > 1.6 mg/dL.[a] In older adult patients or others with low muscle mass in whom SCr does not accurately reflect glomerular filtration rate, determining that eGFR or CrCl is > 30 mL/min/1.73 $m^2$ is recommended
- Aldosterone antagonists would not ordinarily be initiated in patients with a baseline serum potassium > 5.0 mEq/L
- An initial dose of spironolactone of 12.5 mg or eplerenone 25 mg is typical, after which the dose may be increased to spironolactone 25 mg or eplerenone 50 mg, if appropriate
- The risk of hyperkalemia is increased with concomitant use of higher doses of ACE inhibitors (captopril ≥ 75 mg daily; enalapril or lisinopril ≥ 10 mg daily)
- Potassium supplements are usually discontinued or reduced when aldosterone antagonists are initiated
- Close monitoring of serum potassium is required; potassium concentrations and renal function are usually checked in 3 days and at 1 wk after initiating therapy and at least monthly for the first 3 mo
- Avoid salt substitutes and foods high in potassium

[a]Although the entry criteria for the trials of aldosterone antagonists included SCr < 2.5 mg/dL, most patients had a much lower SCr concentration; in one trial, 95% of patients had an SCr ≤ 1.7 mg/dL.

eGFR = estimated glomerular filtration rate.

Information from: Yancy CW, Jessup M, Bozkurt B, et al. 2013 ACCF/AHA guideline for the management of heart failure. A report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. Circulation 2013;128:e240-e327.

ii. Drug-drug interactions
  (a) Spironolactone: Caution with other drugs that increase potassium
  (b) Eplerenone: Substrate of cytochrome P450 (CYP) 3A4. Avoid with strong CYP3A4 inhibitors (e.g., ketoconazole), and consider lower dose with moderate inhibitors (e.g., verapamil, erythromycin, saquinavir, fluconazole); use caution with other drugs that increase potassium.

iii. Gynecomastia
  (a) Spironolactone: Reported at a rate of 10% in clinical trials
  (b) Eplerenone may be considered as an alternative to spironolactone in painful gynecomastia.

7. Sodium-glucose cotransporter-2 (SGLT) inhibitors
  a. Place in therapy
    i. 2022 ACC/AHA/HFSA guidelines: In appropriate patients with HFrEF (NYHA II–IV) with or without DM (type 2), empagliflozin or dapagliflozin is recommended.
  b. Benefits
    i. Decreased composite end point of worsening HF or CV death, etc.
    ii. Dapagliflozin decreased the rate of CV death (HR 0.82; 95% CI, 0.69–0.98); however, empagliflozin did not (HR 0.92; 95% CI, 0.75–1.12).
  c. Landmark randomized trials with SGLT2 inhibitors (Table 21)

**Table 21.** Landmark Randomized Trials with SGLT2 Inhibitors

| Study | Year | Treatment Arms | Population | Follow-up Time | Primary End Point |
|---|---|---|---|---|---|
| DAPA-HF | 2019 | Dapagliflozin (n=2373), placebo (n=2371) | LVEF < 40%, NYHA I–IV, with or without type 2 DM, stabilized on GDMT | 18 mo | Compared with placebo, dapagliflozin had a 23% relative risk reduction in CV death and HF hospitalization (HR 0.74; 95% CI, 0.65–0.85; p<0.001) |
| EMPEROR-Reduced | 2020 | Empagliflozin (n=1863), placebo (n=1867) | LVEF < 40%, NYHA I–IV, with or without type 2 DM, stabilized on GDMT | 16 mo | Compared with placebo, empagliflozin had a 21% relative risk reduction in CV death and HF hospitalization (HR 0.75; 95% CI, 0.65–0.86; p<0.001) |
| SOLOIST-WHF | 2021 | Sotagliflozin (n=608), placebo (n=614) | Hospitalized patients (admission for decompensated HF with intravenous diuretics), any EF (median = 35%), type 2 DM diagnosis | 9 mo | Compared with standard of care, initiation of sotagliflozin before, or within 48 hr after, discharge for acute decompensated HF resulted in a decrease of 25.3 events (total number of deaths from CV causes and hospitalizations and urgent visits for HF) per 100 patient-years (HR 0.67; 95% CI, 0.52–0.85; p<0.001) |

**Table 21.** Landmark Randomized Trials with SGLT2 Inhibitors (*Cont'd*)

| Study | Year | Treatment Arms | Population | Follow-up Time | Primary End Point |
|---|---|---|---|---|---|
| EMPULSE | 2021 | Empagliflozin (n=265), placebo (n=265) | Admission for acute decompensated HF (no EF cutoffs) | 90 days | Compared with placebo, empagliflozin had a clinical benefit (composite of death, number of HF events, time to first HF event, and change in Kansas City Cardiomyopathy Questionnaire-Total Symptom Score [KCCQ-TSS] from baseline to 90 days) at a rate of 53.9% vs. 39.7% in the placebo group (p=0.0054) |

d. Mechanisms of action: Inhibit SGLT2 in the proximal convoluted tubule, reducing glucose reabsorption
e. Dosing and administration
    i. Dapagliflozin
        (a) Initial/target dose: 10 mg
        (b) Renal considerations: eGFR less than 25 mL/minute/1.73 $m^2$, contraindicated
    ii. Empagliflozin
        (a) Initial/target dose: 10 mg
        (b) Renal considerations: eGFR less than 20 mL/minute/1.73 $m^2$, contraindicated
f. Monitoring
    i. No significant difference in adverse events related to volume depletion, hypotension, or renal events
        (a) Diuretic dose may require adjustment within the first week after initiation, though there is no specific recommendation when starting an SGLT2 inhibitor.
    ii. Genital mycotic infections were more common with SGLT2 inhibitors; thus, proper genitourinary hygiene is recommended.
    iii. Euglycemic diabetic ketoacidosis is more common with SGLT2 inhibitors in patients with type 2 DM; patients should be counseled on signs/symptoms.
    iv. Necrotizing fascitis of the perineum is also more common with SGLT2 inhibitors, though it is extremely rare.
g. Special considerations
    i. SGLT2 inhibitors temporarily reduce GFR during the first 8–16 weeks after therapy initiation.
        (a) Long term, both dapagliflozin and empagliflozin reduce the slope of GFR decline more than placebo.

**Patient Case**

7. M.G. is a 43-year-old man who is following up in your HF transitions-of-care clinic 2 weeks after admission for acute decompensated HF. His comorbidities include hypothyroidism and gastroesophageal reflux disease. His physical examination reveals no significant abnormalities. His current medications include metoprolol × l 100 mg once daily, sacubitril/valsartan 97–103 mg twice daily, spironolactone 25 mg once daily, levothyroxine 100 mg once daily, and omeprazole 20 mg once daily. M.G. asks about SGLT2 inhibitors because he recently saw an advertisement on TV for empagliflozin. He would like to know your thoughts on starting this type of medication. Which is most accurate?

   A. SGLT2 inhibitors are only effective in patients with HFrEF and a history of type 2 DM.

   B. SGLT2 inhibitors are effective in patients with HFrEF with or without a history of type 2 DM.

   C. Empagliflozin is contraindicated in patients with an eGFR of 40 mL/minute/1.73 $m^2$ or less.

   D. SGLT2 inhibitors should be avoided in patients requiring a loop diuretic.

C. Drugs for Use in Selected Patients

1. Digoxin

   a. Place in therapy: The 2022 ACC/AHA guidelines recommend that digoxin be considered in patients with HFrEF to decrease hospitalizations, but they do not address when to add digoxin. The 2016 European Society of Cardiology guidelines recommend considering digoxin in symptomatic patients in NSR, despite treatment with an ACE inhibitor (or ARB), a β-blocker, and an aldosterone receptor antagonist, to reduce the risk of hospitalization (both all-cause and HF-hospitalizations). Of note, digoxin was not included in the 2017 ACC/AHA/HFSA guidelines.

   b. Benefits

      i. Improved symptoms
      ii. Improved exercise tolerance
      iii. Decreased hospitalizations
      iv. No effect on mortality
      v. Based on the PROVED and RADIANCE trials, withdrawal of digoxin in patients with HFrEF was associated with a reduction in exercise tolerance; however, these data were published before the use of β-blockers and MRAs.
      vi. Greater effects with low LVEF (less than 25%) or NYHA classes III and IV
      vii. According to a retrospective analysis of the DIG trial, women receiving digoxin had a higher risk of death; however, this was later found to be caused by higher digoxin concentrations in women as the result of potential drug interactions with estrogen replacement therapy.

c. Landmark randomized trials with digoxin (Table 22)

**Table 22.** Landmark Randomized Controlled Trials with Digoxin

| Study | Year | Treatment Arms | Population | Follow-up Time | Primary End Point |
|---|---|---|---|---|---|
| DIG | 1997 | Digoxin (n=3397)<br>Placebo (n=3403) | LVEF ≤ 45%, NYHA II–IV, mean age 62 yr | 37 mo (mean) | No significant differences in mortality (p=0.80); in digoxin group, trend toward a decrease in risk of death caused by HF (RR 0.88; 95% CI, 0.77–1.01; p=0.06); in digoxin group, 6% fewer hospitalizations and fewer patients hospitalized for HF (RR 0.72; 95% CI, 0.66–0.79; p<0.001) |
| DIG (High Risk Sub-Study) – Post hoc analysis of DIG trial | 2013 | NYHA III and IV<br>Digoxin (n=1118)<br>Placebo (n=1105)<br>LVEF < 25%<br>Digoxin (n=1127)<br>Placebo (n=1129)<br>CTR > 55%<br>Digoxin (n=1175)<br>Placebo (n=1170) | LVEF ≤ 45%, NYHA II–IV, mean age 62 yr | 37 mo (mean) | Compared with placebo, those receiving digoxin had a significant reduction in the 2-yr composite end point of HF mortality or HF hospitalization: NYHA III and IV (HR 0.65; 95% CI, 0.57–0.75; p<0.001); LVEF < 25% (HR 0.61; 95% CI, 0.53–0.71; p<0.001); and CTR 55% (HR 0.65; 95% CI, 0.57–0.75; p<0.001) |

CTR = cardiothoracic ratio; DIG = Digitalis Investigation Group.

d. Dosing and administration
   i. For most patients, 0.125 mg/day is adequate to achieve the desired serum concentration.
   ii. Consider dosing 0.125 mg every other day in patients older than 70 years, those with impaired renal function, or those with low lean body mass.
   iii. No indication to load patients with digoxin in the setting of HF
   iv. Digoxin dosing algorithm available at http://clincalc.com/digoxin/
   v. Drug interactions: Digoxin concentrations are increased with concomitant P-glycoprotein inhibitors:
      (a) Clarithromycin, erythromycin
      (b) Amiodarone, dronedarone
      (c) Itraconazole, posaconazole
      (d) Cyclosporine, tacrolimus
      (e) Verapamil
      (f) Quinidine, propafenone

e. Monitoring
   i. Serum concentrations should be less than 1 ng/mL; in general, concentrations of 0.5–0.9 ng/mL are suggested; check concentration within 5–7 days of initiation. Level should be a trough.
      (a) Minimizes the risk of adverse effects and ventricular arrhythmias associated with increased concentrations
      (b) Risk of toxicity increases with age and renal dysfunction.
      (c) Risk of toxicity increases in the presence of hypokalemia, hypomagnesemia, or hypercalcemia.
   ii. Post hoc analysis of DIG trial found that digoxin was not associated with reduced mortality among patients with concentrations of 0.9–1.1 ng/mL (2.6% increase; 95% CI, 3.0%–8.3%), whereas patients with concentrations of 1.2 ng/mL and higher had an 11.8% (95% CI, 5.7%–18.0%) higher absolute mortality rate than patients receiving placebo.
   iii. Serum creatinine, potassium, magnesium, and calcium should be monitored because of renal clearance.

f. Overdose
   i. Signs of digoxin toxicity
      (a) Gastrointestinal (GI): Nausea, vomiting, abdominal pain, anorexia
      (b) Neurological: Weakness, confusion
      (c) Electrolyte: Hyperkalemia (greater than 5.5 mEq/L)
      (d) Cardiac: Bradycardia, heart block, arrhythmias (may be difficult to assess if patient has pacer or ICD)
      (e) Visual: Sensitive to light, blurred vision, yellow halos around lights
   ii. Digoxin immune fab (ovine): Considered for life-threatening or potentially life-threatening overdose, which includes:
      (a) Severe ventricular arrhythmias
      (b) Progressive bradycardia
      (c) Second- or third-degree heart block not responding to atropine
      (d) K greater than 5.5 mEq/L with rapidly progressive signs and symptoms of digoxin toxicity
   iii. Digoxin immune fab (ovine) dosing
      (a) Acute ingestion: Known amounts of digoxin

$$\text{Dose in vials} = \frac{\text{Amount of digoxin ingested (mg)} \times 0.8}{\text{0.5 mg per vial}}$$

      (b) Chronic ingestion: Known digoxin serum concentration

$$\text{Dose in vials} = \frac{\textit{Serum digoxin}\ \text{(ng/mL)} \times \text{weight (kg)}}{100}$$

2. Hydralazine combined with isosorbide dinitrate
   a. Place in therapy
      i. Recommended in addition to ACE inhibitors and β-blockers to reduce morbidity and mortality for patients self-described as African Americans with NYHA functional class III or IV HFrEF
      ii. May be useful in patients with current or prior symptoms of HFrEF who cannot tolerate an ACE inhibitor or an ARB because of hyperkalemia and/or renal dysfunction or if the patient is pregnant and cannot take an ACE inhibitor or ARB
   b. Benefits – Decreased mortality (43% risk reduction [RR] compared with placebo, in A-HEFT trial)

c. Landmark randomized controlled trials (Table 23)

**Table 23.** Landmark Randomized Controlled Trials with Hydral-Nitrates

| Study | Year | Treatment Arms | Population | Follow-up Time | Primary End Point |
|---|---|---|---|---|---|
| V-HeFT I | 1986 | Hydral-nitrates (n=273)<br><br>Prazosin (n=183)<br><br>Placebo (n=273) | LVEF < 30%, mean age 58 yr | 2.3 yr (mean) | Hydral-nitrate therapy was associated with a trend in all-cause mortality compared with placebo (38.7% vs. 44.9%, p=0.09) with a 34% reduction in mortality compared with placebo (p<0.028). However, study was not powered to adequately assess for mortality comparisons between groups |
| V-HeFT II | 1991 | Hydral-nitrates (n=403)<br><br>Enalapril (n=401) | LVEF < 45%, NYHA II–IV, mean age 60.5 yr | 2.5 yr (mean) | Enalapril compared with hydral-nitrates reduced all-cause mortality (38.2% vs. 32.8%, p=0.008) |
| A-HeFT[a] | 2004 | BiDil (n=518)<br><br>Placebo (n=532) | LVEF ≤ 30%, NYHA III and IV, self-declared African American, mean age 57 yr | 12.8 mo (mean) | BiDil had a better composite score made up of weighted values for death from any cause, a first HF hospitalization, and change in the QoL compared with the placebo group (-0.1 ± 1.9 vs. -0.5 ± 2.0, p=0.01; range of possible values, -6 to +2). Compared with placebo, BiDil was associated with a 43% reduction in mortality |

[a]Study stopped early.

A-HeFT = African American Heart Failure Trial; BiDil=isosorbide dinitrate 20 mg/hydralazine 37.5 mg; V-HeFT = Vasodilator Heart Failure Trial.

d. Mechanism of action
   i. Hydralazine
      (a) Arterial vasodilator (reduces afterload)
      (b) Increases effect of nitrates through antioxidant mechanisms
   ii. Isosorbide dinitrate
      (a) Stimulates nitric oxide signaling in the endothelium
      (b) Venous vasodilator (reduces preload)

e. Dosing and administration (Table 24)

**Table 24.** Dosing of Hydralazine Combined with Isosorbide Dinitrate

| Hydral-Nitrates | Initial Dose(s) | Maximum Dose(s) | Mean Dosages Achieved in HF Trials |
|---|---|---|---|
| Fixed-dose combination (BiDil) | 37.5 mg of hydralazine/20 mg of isosorbide dinitrate TID | 75 mg of hydralazine/40 mg of isosorbide dinitrate TID | ~175 mg of hydralazine/ 90 mg of isosorbide dinitrate daily |
| Hydralazine and isosorbide dinitrate | Hydralazine 25–50 mg, TID-QID, and isosorbide dinitrate 20–30 mg, TID-QID | Hydralazine 300 mg daily in divided doses and isosorbide dinitrate 120 mg daily in divided doses | |

QID = four times daily.

Information from: Heidenreich PA, Bozkurt B, Aguilar D, et al. 2022 AHA/ACC/HFSA guideline for the management of heart failure: a report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. Circulation 2022;145:e895-e1032.

f. Monitoring
   i. Headache
   ii. Hypotension
   iii. Drug-induced lupus with hydralazine
      (a) Patient risk factors consist of high dose, female sex, family history of autoimmune disease, therapy duration exceeding 3–6 months, slow acetylator, and *HLA-DRw4* phenotypes.
      (b) A baseline antinuclear antibody (ANA) should be determined before initiating hydralazine therapy.
      (c) Routine follow-up ANA tests are not recommended because a positive test often does not indicate drug-induced lupus; 50% of patients receiving hydralazine therapy have a positive ANA yet do not have lupus.
      (d) Patients who report lupus-like symptoms while receiving hydralazine should discontinue hydralazine and receive close monitoring and subsequent ANA concentrations plus antihistone antibodies to rule out lupus.
      (e) Typical presenting symptoms include fever, weight loss, and musculoskeletal symptoms (e.g., arthritis).

**Patient Case** (*Cont'd*)

8. J.M. has heard about sacubitril/valsartan and wants to try this new drug. Which would best be considered before initiating sacubitril/valsartan?
   A. Decrease the dose of metoprolol succinate to minimize hypotension.
   B. Discontinue lisinopril at least 36 hours before beginning sacubitril/valsartan.
   C. Obtain a baseline BNP before beginning sacubitril/valsartan.
   D. Increase furosemide to 100 mg to minimize fluid retention.

9. Which dose of sacubitril/valsartan would be best for J.M.?
   A. 12/12.5 mg twice daily.
   B. 24/26 mg twice daily.
   C. 49/51 mg twice daily.
   D. 97/103 mg twice daily.

3. Vericiguat
    a. Place in therapy: The 2021 ACC expert decision pathway update does not give a specific recommendation for the use of Vericiguat. It may offer a potential benefit for HF hospitalization reduction in patient's not able to be maximized on GDMT.
    b. Landmark randomized trial (Table 25)

**Table 25.** Landmark Randomized Trial with Vericiguat

| Study | Year | Treatment Arms | Population | Follow-up Time | Primary End Point |
|---|---|---|---|---|---|
| VICTORIA | 2020 | Vericiguat (n=2526), placebo (n=2524) | LVEF < 45%, NYHA II–IV, maintained on GDMT | 11 mo | Vericiguat reduced the relative risk of death from CV causes or first HF hospitalization by 7.8% compared with placebo (HR 0.90; 95% CI, 0.82–0.98; p=0.02) |

    c. Mechanisms of action: Directly stimulates soluble guanylate cyclase, increasing the production of intracellular cyclic GMP resulting in the vasodilation of vascular smooth muscle
    d. Dosing and administration: 2.5 mg once daily titrated to a maximum of 10 mg once daily
    e. Monitoring:
        i. Contraindicated in pregnant patients
        ii. Use with caution in patients taking concomitant nitrates.

4. Ivabradine
    a. Place in therapy (according to 2022 AHA/ACC/HFSA guidelines): Ivabradine can help reduce HF hospitalizations for patients with symptomatic (NYHA functional classes II and III), stable, chronic HFrEF (LVEF of 35% or less) who are receiving GDMT, including a β-blocker at maximum tolerated dose, and who are in NSR with a heart rate of 70 beats/minute or greater at rest.
    b. Benefits/landmark randomized study of ivabradine
        i. SHIFT trial (see Table 26)
        ii. The target of ivabradine is heart rate slowing (the presumed benefit of action), but only 25% of patients studied were receiving optimal doses of β-blocker therapy.

**Table 26.** Landmark Controlled Trial with Ivabradine

| Study | Year | Treatment Arms | Population | Follow-up Time | Primary End Point |
|---|---|---|---|---|---|
| SHIFT | 2010 | Ivabradine (n=3241)<br><br>Placebo (n=3264) | LVEF < 35%, NYHA II–IV, heart rate ≥ 70 beats/min, stabilized on GDMT including a β-blocker, mean age 60 yr | 23 mo (median) | Compared with placebo, ivabradine had an 18% reduction in CV death or HF hospitalization (HR 0.82; 95% CI, 0.75–0.90; p<0.0001) |

GDMT = guideline-directed medical therapy; SHIFT = Systolic Heart Failure Treatment with the I(f) Inhibitor Ivabradine Trial.

    c. Mechanism of action: Selectively inhibits the $I_f$ current in the sinoatrial node, providing heart rate reduction

d. Dosing and administration (Table 27)
   i. Given the well-proven mortality benefits of β-blocker therapy, these agents should be initiated and titrated to target doses, as tolerated, before assessing the resting heart rate for consideration of ivabradine initiation.
   ii. Starting dose is 5 mg twice daily taken with food.
   iii. For patients with conduction defects or in whom bradycardia could lead to hemodynamic compromise, start with 2.5 mg twice daily.
   iv. Table 27 summarizes dosing adjustments on the basis of heart rate.

**Table 27.** Dosing Adjustments on the Basis of Heart Rate for Ivabradine

| Heart Rate | Dose Adjustment |
|---|---|
| > 60 beats/min | Increase dose by 2.5 mg BID to maximum of 7.5 mg PO BID |
| 50–60 beats/min | Maintain current dose |
| < 50 beats/min or signs or symptoms of bradycardia | Decrease dose by 2.5 mg BID if current dose is 2.5 mg PO BID, discontinue therapy |

PO = oral(ly).

e. Monitoring
   i. Assess heart rate 2 weeks after therapy initiation or modification and periodically thereafter.
   ii. Women of childbearing age should use contraception.
   iii. Monitor for new-onset atrial fibrillation (AF).
   iv. Symptomatic bradycardia (5%), asymptomatic bradycardia (6%), new-onset AF (9%), blurred vision (1%), and phosphenes (3%) were statistically higher in the ivabradine cohort.
   v. Contraindicated in acute decompensated HF, blood pressure less than 90/50 mm Hg, sick sinus syndrome, second- or third-degree heart block, heart rate less than 60 beats/minute, severe hepatic impairment, AF, and pacemaker-dependent
   vi. Drug interactions: Ivabradine is a substrate of CYP3A4
      (a) Avoid strong CYP3A4 inhibitors (e.g., azole antifungals [e.g., itraconazole], macrolide antibiotics [e.g., clarithromycin, telithromycin], HIV protease inhibitors [e.g., nelfinavir], and nefazodone.
      (b) Avoid moderate CYP3A4 inhibitors (e.g., diltiazem, verapamil, grapefruit juice).
      (c) Avoid CYP3A4 inducers (e.g., St. John's wort, rifampicin, barbiturates, and phenytoin).
   vii. Drug-device interactions:
      (a) Patients with demand pacemakers set at 60 beats/minute or greater cannot achieve a target heart rate of less than 60 beats/minute.
      (b) These patients were excluded from the SHIFT trial.

D. Other Drugs
   1. Anticoagulation
      a. Recommended in HF with permanent, persistent, or paroxysmal AF with an additional risk factor for stroke (no preference on agent)
      b. Reasonable in patients with HF who have permanent, persistent, or paroxysmal AF with no additional risk factor for stroke
      c. Not recommended in the absence of AF, prior stroke, or a cardioembolic source
   2. Statins
      a. Not recommended solely on the basis of HF diagnosis

b. In all patients with a recent or remote history of MI or acute coronary syndrome, statins should be used to prevent symptomatic HF and CV events.
c. Associated with a reduction in hospitalization – a secondary end point (Table 28)

**Table 28.** Landmark Randomized Controlled Trials with Statins

| Study | Year | Treatment Arms | Population | Follow-up Time | Primary End Point |
|---|---|---|---|---|---|
| CORONA | 2007 | Rosuvastatin (n=2514)<br><br>Placebo (n=2497) | ≥ 60 yr, NYHA II–IV, HF of ischemic cause, LVEF < 40% (≤ 35% for NYHA II) | 32.8 mo (mean) | No significant difference existed between groups in death from CV causes, nonfatal MI, or nonfatal stroke (HR 0.92; 95% CI, 0.83–1.02; p=0.12)<br>In a prespecified secondary analysis, hospitalizations for CV causes were fewer in the rosuvastatin group than in placebo (p<0.001) |

CORONA = Controlled Rosuvastatin Multinational Trial in Heart Failure.

3. Omega-3 fatty acids
   a. Omega-3 polyunsaturated fatty acid (PUFA) supplementation is reasonable as adjunctive therapy in patients with NYHA class II–IV symptoms and HFrEF or HFpEF, unless contraindicated, to reduce mortality and CV hospitalizations.
   b. Table 29 summarizes the landmark controlled trials with omega-3 PUFAs.

**Table 29.** Landmark Randomized Controlled Trials with PUFAs

| Study | Year | Treatment Arms | Population | Follow-up Time | Primary End Point |
|---|---|---|---|---|---|
| GISSI Prevenzione | 1999 | 1 g of omega-3 PUFAs (850–882 mg of eicosapentaenoic acid [EPA] and docosahexaenoic acid [DHA] as ethyl esters in the ratio of 1:1.2, n=2836)<br><br>Vitamin E (300 mg, n=2830)<br><br>Both omega-3 PUFAs and vitamin E (n=2828)<br><br>Placebo (n=2828) | MI within 3 mo | 3.5 yr (mean) | Treatment with omega-3 PUFAs, but not vitamin E, significantly lowered the risk of death, nonfatal MI, and stroke by 10% (95% CI, 1–18) by two-way analysis and 15% (95% CI, 2–26) by four-way analysis<br><br>Benefit was attributable to a decrease in the risk of death (RRR 14%; 95% CI, 3–24; two-way; RRR 20%; 95% CI, 6–33, four-way) and CV death (RRR 17%; 95% CI, 3–29 two-way; RRR 30%; 95% CI, 13–44 four-way)<br><br>Effect of the combined treatment with both vitamin E and omega-3 PUFAs was similar to that for omega-3 PUFAs for the risk of death, nonfatal MI, and stroke (RRR 14%; 95% CI, 1–26) and for fatal events (RRR 20%; 95% CI, 5–33) |

**Table 29.** Landmark Randomized Controlled Trials with PUFAs (*Cont'd*)

| Study | Year | Treatment Arms | Population | Follow-up Time | Primary End Point |
|---|---|---|---|---|---|
| GISSI-HF | 2008 | 1 g daily of omega-3 PUFAs (850–882 mg of EPA/DHA, n=3494)<br><br>Placebo (n=3481) | Evidence of chronic HF, NYHA II–IV, mean age 67 yrs | 3.9 yr (mean) | Death from any cause was reduced from 29% with placebo to 27% in those treated with omega-3 PUFAs (adjusted HR 0.91; 95.5% CI, 0.833–0.998; p=0.041)<br><br>Death or admission to hospital for CV causes was reduced from 59% with placebo to 58% in those treated with omega-3 PUFAs (adjusted HR 0.92; 99% CI, 0.849–0.999; p=0.009) |

GISSI = Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto miocardico; PUFA = polyunsaturated fatty acid.

**Patient Case**

*Questions 10 and 11 pertain to the following case.*

L.S., an 87-year-old woman, is referred for a second opinion after four hospitalizations for HF in the past 6 months. She has a long history of HTN. She denies having angina or CAD. She describes symptoms consistent with NYHA functional class III. Both an implantable cardioverter-defibrillator (ICD) and a dual-chamber pacemaker set at 65 beats/minute were placed in the past 6 months; since then, no ventricular arrhythmia has been noted, and no shocks have been delivered. Her medications are lisinopril 5 mg once daily, digoxin 0.125 mg once daily, carvedilol 6.25 mg twice daily, spironolactone 25 mg once daily, furosemide 20 mg once daily, and potassium chloride 10 mEq once daily. Vital signs include blood pressure 152/84 mm Hg and heart rate 64 beats/minute, regular. Laboratory values are SCr 1.2 mg/dL and K 4.7 mEq/L. Physical examination reveals lungs: clear to auscultation; cardiac: JVP elevated to 12 cm with a large V wave, S3 present; and extremities: 2+ edema to knee bilaterally. An ECHO reveals LV end-diastolic dimension 6.0 cm, LVEF 38%, global hypokinesis, and LV wall thickness 13 mm. An ECG reveals R-R 857 milliseconds, PR interval 176 milliseconds, QRS duration 104 milliseconds, and QT/corrected QT interval 424/438 milliseconds.

10. Which would be the most appropriate recommendation for L.S.?
    A. Add metolazone.
    B. Add ivabradine.
    C. Consider cardiac resynchronization therapy (CRT).
    D. Increase lisinopril and furosemide.

E. Devices
   1. ICD: Recommended for primary prevention of sudden cardiac death in patients with ischemic and non-ischemic symptoms
      a. Recommended for patients 40 days post-MI, LVEF of 35% or less, or NYHA class II and III symptoms on GDMT. Life expectancy should be greater than 1 year.
      b. Recommended for patients 40 days post-MI, LVEF of 30% or less, and NYHA class I symptoms on GDMT. Life expectancy should be greater than 1 year.
      c. Table 30 summarizes landmark controlled trials with ICDs.
   2. CRT

a. Indicated for patients who have LVEF of 35% or less, NSR, left bundle-branch block with a QRS duration of 150 milliseconds or greater, and NYHA class II, III, or ambulatory IV symptoms on GDMT
b. Can be used for patients with an LVEF of 35% or less, NSR, a non–left bundle-branch block pattern with QRS of 150 milliseconds or more, and NYHA class III/ambulatory class IV symptoms on GDMT
c. Can be used for patients who have LVEF of 35% or less, NSR, left bundle-branch block with a QRS 120–149 milliseconds, and NYHA class II, III, or ambulatory IV symptoms on GDMT
d. Can be useful for patients with AF and LVEF of 35% or less on GDMT if (a) the patient requires ventricular pacing or otherwise meets the CRT criteria and (b) atrioventricular nodal ablation or rate control allows almost 100% ventricular pacing with CRT
e. Can be used for patients on GDMT who have an LVEF of 35% or less and are undergoing new or replacement device implantation with anticipated ventricular pacing (LVEF greater than 40%)
f. Table 30 summarizes landmark controlled trials with CRT.

**Patient Case** (*Cont'd*)

11. Because of L.S.'s many hospitalizations, she is enrolled in the CardioMEMS program. Which would be best to recommend regarding anticoagulation for this patient?
    A. Add warfarin 5 mg daily (titrate to an INR of 2–3).
    B. Add aspirin 81 mg/day.
    C. Add both clopidogrel 75 mg/day and aspirin 81 mg/day.
    D. Add clopidogrel 75 mg/day.

3. Implantable sensors (CardioMEMS)
    a. Indicated for wirelessly measuring and monitoring pulmonary artery (PA) pressure and heart rate in patients with NYHA functional class III HF who have been hospitalized for HF in the previous year
    b. Captures the following data: PA pressure waveform; systolic, diastolic, and mean PA pressures and HF
    c. The first and only U.S. Food and Drug Administration (FDA)-approved HF monitor proven to significantly reduce HF hospital admissions and improve QoL (Table 30)
    d. After insertion of device, patients must take aspirin 81–325 mg/day with clopidogrel 75 mg/day for 1 month. After 1 month, clopidogrel is discontinued and aspirin is continued indefinitely.
    e. Reports need to be reviewed and responded to by staff. Findings may be because of increased medication titrations and lower PA pressures.

**Table 30.** Landmark Randomized Controlled Trials with Devices

| Study | Year | Treatment Arms | Population | Follow-up Time | Primary End Point |
|---|---|---|---|---|---|
| SCD-HeFT | 2005 | ICD (n=829)<br>Amiodarone (n=845)<br>Placebo (n=847) | NYHA II and III, LVEF ≤ 35%, median age 60 yrs | 46.5 mo (median) | Amiodarone was associated with a risk of death similar to placebo (HR 1.06; 97.5% CI, 0.86–1.30; p=0.53), and ICD therapy was associated with a decreased risk of death (HR 0.77; 97.5% CI, 0.62–0.96; p=0.007) and an absolute decrease in mortality of 7.2 percentage points after 5 yr in the overall population |
| MADIT-CRT[a] | 2009 | ICD only (n=731)<br>CRT-ICD (n=1089) | NYHA I and II, EF ≤ 30%; QRS ≥ 130 ms), mean age 65 yrs | 2.4 yr (mean) | CRT (added to ICD) slowed the progression of HF in high-risk (QRS ≥130 ms, LVEF ≤ 30%), mildly symptomatic patients (NYHA I and II) |
| CHAMPION trial | 2011 | CardioMEMS (n=270)<br>Standard of care (n=280) | NYHA III, previous HF admission within 12 mo, mean age 62 yrs | 15 mo (mean) | During the entire follow-up, CardioMEMS had a 37% reduction in HF hospitalization compared with standard of care (HR 0.63; 95% CI, 0.52–0.77; p<0.0001) |

[a]Stopped early.

CHAMPION = CardioMEMS Heart Sensor Allows Monitoring of Pressure to Improve Outcomes in NYHA Class III Heart Failure Patients; MADIT-CRT = Multicenter Automatic Defibrillator Implantation Trial with Cardiac Resynchronization Therapy; ms = millisecond(s); SCD-HeFT: Sudden Cardiac Death in Heart Failure Trial.

## IV. PHARMACOTHERAPY OF HEART FAILURE WITH PRESERVED EJECTION FRACTION

**Patient Case**

12. D.F. is an 84-year-old woman with a medical history significant for type 2 DM (diet controlled), osteoporosis, hypercholesterolemia, and HTN who presents to the clinic with a 1-year history of dyspnea on exertion, which has worsened over the past month. Her medications are lisinopril 20 mg daily, alendronate 70 mg once weekly, calcium/vitamin D 500 ng/125 international units three times daily, simvastatin 20 mg daily, and aspirin 81 mg daily. Vital signs include blood pressure 120/80 mm Hg and heart rate 80 beats/minute. Physical examination reveals lungs: + rales/rhonchi; cardiac: JVP elevated to 7 cm with a large V wave, S3 present; and extremities: 2+ edema to knee bilaterally. Laboratory values are as follows: SCr 1.2 mg/dL, K 4.7 mEq/L, and BNP 856 pg/mL. An ECHO reveals an LVEF of 66%, mild tricuspid regurgitation, mild mitral regurgitation, and LV hypertrophy. Which is the most appropriate therapeutic recommendation for D.F.'s HF at this time?
    A. Add furosemide.
    B. Add hydrochlorothiazide.
    C. Add spironolactone.
    D. Add isosorbide mononitrate.

A. Overall Management
    1. Clinical evidence for efficacious agents for HFpEF has generally been disappointing. Therapies for symptoms, comorbidities, and risk factors that may worsen CV disease are recommended.

2. Class I recommendations:
    a. Systolic and diastolic blood pressure should be controlled in patients with HFpEF, according to published clinical practice guidelines, to prevent morbidity.
    b. Diuretics should be used for relief of symptoms caused by volume overload in patients with HFpEF.
3. Class II recommendations:
    a. Management of AF according to published clinical practice guidelines in patients with HFpEF is reasonable to improve symptomatic HF.
    b. Use of ARNIs, SGLT2 inhibitors, ACE inhibitors, and ARBs in patients with HTN is reasonable to control blood pressure.
    c. In appropriately selected patients with HFpEF (with LVEF of 45% or more, elevated BNP concentrations or HF admission within 1 year, eGFR greater than 30 mL/minute, SCr less than 2.5 mg/dL, K less than 5.0 mEq/L), aldosterone receptor antagonists may be considered to decrease hospitalizations.

B. Specific Drugs Studied in HFpEF
1. ARNIs
    a. No significant difference in rate of CV deaths or hospitalizations; however, women (HR 0.73; 95 CI, 0.59-0.90) and those 65 and older (HR 0.85; 95 CI, 0.73 -0.99) receiving sacubitril/valsartan had improved primary outcomes
    b. FDA approved to reduce the risk of CV death and hospitalization for HF in adult patients with chronic HF. Benefits are most evident in patients with LVEF below normal.
2. SGLT2 inhibitors
    a. Empagliflozin 10 mg daily is FDA approved to reduce the risk of CV death or hospitalization in patients with or without type 2 DM and an EF greater than 40%.
    b. Dapagliflozin 10 mg may also be considered to reduce the risk of CV death or hospitalization, though it has not been formally FDA approved for HFpEF (off-label indication).
3. Aldosterone antagonists
    a. Mechanistic studies have suggested that aldosterone antagonists can improve diastolic function in patients with HFpEF, possibly by a similar effect on remodeling.
    b. In appropriately selected patients with HFpEF (with an ejection fraction of 45% or greater, elevated BNP concentrations or HF admission within 1 year, eGFR greater than 30 mL/minute, SCr less than 2.5 mg/dL, K less than 5.0 mEq/L), aldosterone receptor antagonists may be considered to decrease hospitalizations (Table 31).
4. ACE inhibitors
    a. ACE inhibitors have not been shown to reduce mortality in HFpEF.
    b. Improve exercise tolerance and reduce hospitalizations (Table 31)
5. ARBs
    a. ARBs have not been shown to reduce mortality in HFpEF.
    b. May reduce HF hospitalizations (Table 31)
6. Digoxin
    a. In the 2013 ACC/AHA guidelines, digoxin can be considered for rate control in AF and HFpEF, but non-dihydropyridine calcium channel blockers may be more effective.
    b. In those with NSR and HFpEF, digoxin is not mentioned in the 2016, 2017, or 2021 ACC/AHA/HFSA guidelines.
    c. In the ancillary digitalis investigation group trial, digoxin did not affect all-cause or cause-specific mortality or all-cause or CV hospitalization compared with placebo (Table 31).
7. Nitrates
    a. Routine nitrate use in patients with HFpEF is not recommended (Table 31).
    b. This recommendation does not apply to patients with HFpEF and symptomatic CAD for whom nitrates may provide symptomatic relief.

8. Phosphodiesterase type 5 inhibitors
    a. Phosphodiesterase type 5 inhibition augments the nitric oxide system by up-regulating cGMP activity.
    b. Routine use of phosphodiesterase type 5 inhibitors in patients with HFpEF is not recommended (Table 31).

**Table 31.** Landmark Controlled Trials of HFpEF

| Study | Year | Treatment Arms | Population | Follow-up Time | Primary End Point |
|---|---|---|---|---|---|
| **ACE Inhibitors** | | | | | |
| PEP-CHF | 2006 | Perindopril (n=426)<br><br>Placebo (n=424) | ≥ 70 yr of age, HFpEF dx | 26.2 mo (mean) | By 1 yr, perindopril had no effect on all-cause mortality or HF hospitalization (HR 0.69; 95% CI, 0.47–1.01, p=0.055) but did reduce HF hospitalizations alone (HR 0.63; 95% CI, 0.41–0.97, p=0.033)<br>Perindopril was associated with improvement in NYHA class (p=0.030), and 6-min walk distance (p=0.011) |
| **ARBs** | | | | | |
| CHARM-PRESERVED | 2003 | Candesartan (n=1514)<br><br>Placebo (n=1509) | NYHA II–IV, LVEF > 40%, mean age 67 years | 36.3 mo (mean) | Compared with placebo, candesartan did not affect CV mortality or HF hospitalization (adjusted HR 0.86; 95% CI, 0.74–1.0; p=0.051)<br>Compared with placebo, candesartan reduced HF hospitalization (adjusted HR 0.84; 95% CI, 0.7–1.00, p=0.047) |
| I-PRESERVE | 2008 | Irbesartan (n=2067)<br><br>Placebo (n=2061) | > 60 yr of age, LVEF ≥ 45, NYHA II–IV | 49.5 mo (mean) | Compared with placebo, irbesartan had no effect on all-cause mortality or hospitalization for a CV cause (HR 0.95; 95% CI, 0.86–1.05; p=0.35) |
| **Digoxin** | | | | | |
| DIG-ANCILLARY | 2006 | Digoxin (n=492)<br><br>Placebo (n=496) | LVEF > 45% in NSR, NYHA I–IV, mean age 67 yrs | 37 mo (mean) | Digoxin had no effect on all-cause or cause-specific mortality or on all-cause or CV hospitalization. Digoxin was associated with a trend toward a reduction in hospitalizations caused by worsening HF (HR 0.79; 95% CI, 0.59–1.04; p=0.094) but also a trend toward an increase in hospitalizations for unstable angina (HR 1.37; 95% CI, 0.99–1.91; p=0.061) |

**Table 31.** Landmark Controlled Trials of HFpEF (*Cont'd*)

| Study | Year | Treatment Arms | Population | Follow-up Time | Primary End Point |
|---|---|---|---|---|---|
| **Aldosterone Antagonists** | | | | | |
| TOP-CAT | 2014 | Spironolactone (n=1722)<br><br>Placebo (n=1723) | > 50 yr of age, LVEF ≥ 45%, K < 5 mEq/L, previous HF hospitalization in past year or BNP ≥ 100 pg/mL or NT-proBNP ≥ 360 pg/mL, NYHA I-IV | 3.3 yr (mean) | No difference existed between groups in death from CV causes, aborted cardiac arrest, or HF hospitalization (HR 0.89; 95% CI, 0.77–1.04, p=0.14)<br>Compared with placebo, spironolactone had a lower incidence of HF hospitalizations (HR 0.83; 95% CI, 0.69–0.99, p=0.04)<br>Treatment with spironolactone was associated with increased SCr and a doubling of the rate of hyperkalemia (18.7% vs. 9.1% in the placebo group)<br>An unusual amount of regional variation occurred in this trial, prompting a post hoc analysis of TOPCAT, which showed that rates of the primary end point were 4-fold lower in Russia/Georgia than in North America and South America (the Americas)<br>The post hoc analysis showed efficacy in the Americas (HR 0.83) but not in Russia/Georgia (HR 1.10)<br>These post hoc analyses suggest that patients with symptomatic HFpEF with certain characteristics (LVEF ≥ 45%, elevated BNP concentration or HF admission within 1 yr, eGFR > 30 mL/min, SCr < 2.5 mg/dL, and K < 5.0 mEq/L), particularly those with elevated BNP concentrations, have clinical benefit with spironolactone |
| **Nitrates** | | | | | |
| NEAT-HFpEF | 2015 | Isosorbide mononitrate (n=51)<br><br>Placebo (n=59) | > 50 yr of age, LVEF ≥ 50%, NYHA II and III | 1.8 yr (median) | With all dose regimens, physical activity in the isosorbide mononitrate group was lower than in the placebo group (-439 accelerometer units, 95% CI, -792 to -86, p=0.02)<br>Activity levels decreased progressively and significantly with increased doses of isosorbide mononitrate (but not placebo)<br>No significant between-group differences in the 6-min walk distance, QoL, or NT-proBNP concentrations |

**Table 31.** Landmark Controlled Trials of HFpEF (*Cont'd*)

| Study | Year | Treatment Arms | Population | Follow-up Time | Primary End Point |
|---|---|---|---|---|---|
| **Phosphodiesterase-5 Inhibitors** | | | | | |
| RELAX | 2013 | Sildenafil (n=113)<br><br>Placebo (n=103) | NYHA II–IV, LVEF ≥ 50%, mean age 69 yrs | 24 wk | No significant difference between groups in peak oxygen consumption, clinical status rank score, or exercise tolerance |
| **ARNI** | | | | | |
| PARAGON-HF | 2019 | Sacubitril/ valsartan (n=2419)<br><br>Valsartan (n=2403) | NYHA II–IV, LVEF ≥ 45%, elevated natriuretic peptides, evidence of structural heart disease, mean age 73 yr | 35 mo (median) | No significant difference in rate of CV deaths or hospitalizations<br>NYHA class improved in 15.0% of patients in the sacubitril/valsartan group and in 12.6% of patients in the valsartan group (OR 1.45; 95% CI: 1.13–1.86); renal function worsened in 1.4% and 2.7%, respectively (HR 0.50; 95% CI: 0.33–0.77) |
| **SGLT2 Inhibitors** | | | | | |
| EMPEROR-PRESERVED | 2021 | Empagliflozin (n=2997 patients), placebo (n=2991 patients) | LVEF > 40% (40%–50% = 33%, 50%–60% = 34%, > 60% = 33%), NYHA II–IV (99.5% II–III), mean age 72 | 26 mo | Empagliflozin reduced the primary composite end point (death from CV causes or hospitalization for HF) vs. placebo (HR 0.79; 95% CI, 0.69–0.90; p<0.001) |
| DAPA-HF | 2022 | Dapagliflozin (n=3131), placebo (3132) | LVEF > 40%, NYHA II–IV (II = 75%, III = 24%), mean age 71 yr | 2.3 yr | Dapagliflozin reduced the primary composite end point (death from CV causes or hospitalization for HF) vs. placebo (HR 0.82; 95% CI, 0.73–0.92; p<0.001) |

ARNI = angiotensin receptor neprilysin inhibitor; DELIVER = Dapagliflozin in Heart Failure with Mildly Reduced or Preserved Ejection Fraction; dx = diagnosis; HFpEF = heart failure with preserved ejection fraction; I-PRESERVE = Irbesartan in Heart Failure with Preserved Ejection Fraction Study; NEAT HFpEF = Nitrate's Effect on Activity Tolerance in Heart Failure with Preserved Ejection Fraction; OR = odds ratio; PARAGON-HF = Prospective Comparison of ARNI with ARB Global Outcomes in HF With Preserved Ejection Fraction; PEP-CHF = perindopril in elderly people with chronic heart failure; RELAX = Phosphodiesterase-5 Inhibition to Improve Clinical Status and Exercise Capacity in Heart Failure with Preserved Ejection Fraction; TOPCAT = Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist.

## V. IMPORTANT CONSIDERATIONS IN HEART FAILURE

**Patient Case**

*Questions 13–15 pertain to the following case.*

C.A. is a 75-year-old woman (height 56 inches, weight 71 kg [156 lb]) who resides in an assisted living. She is referred to your cardiology clinic for medication therapy management. She is ambulatory, generally alert, and oriented, with no cognitive impairment. Her medical history is significant for NYHA functional class III HFpEF (LVEF of 55%), HTN, chronic obstructive pulmonary disease, and osteoarthritis. She takes the following medications: amlodipine 20 mg daily, furosemide 20 mg daily, fluticasone/salmeterol 45/21 mcg 2 puffs twice daily, albuterol metered dose inhaler as needed, and acetaminophen 500 mg three times daily as needed. On physical examination, C.A. appears well nourished and groomed. She is mildly SOB on exertion but in no apparent pain or distress. Evaluation of her lungs reveals diminished breath sounds in the bases with no adventitious sounds. Abdomen palpation is soft and nontender, with active bowel sounds and no signs of hepatosplenomegaly. She has 1+ nonpitting chronic edema and vascular changes to lower extremities. Her vital signs indicate blood pressure 155/85 mm Hg, heart rate 100 beats/minute, and oxygen saturation 94% on 2 L/minute. Her physical examination is positive for JVP, S3 present; trace edema in both extremities, and lungs with slight crackles. Laboratory tests show SCr 1.3 mg/dL, K 4.0 mEq/L, and BNP 875 pg/mL. Her CBC is significant for hemoglobin 12 g/dL, hematocrit 23%, and mean corpuscular volume 80 fL/cell. Her iron studies completed before clinic show ferritin 50 ng/mL and transferrin saturation (TSAT) 15%. Her vitamin $B_{12}$ concentration is 310 pg/mL. Her ECG reveals NSR.

13. Given C.A.'s clinical presentation and laboratory findings, which would be the best recommendation to improve her QoL?
    A. Ferrous sulfate 325 mg orally three times daily with ascorbic acid.
    B. Cyanocobalamin 1000 mcg intramuscularly weekly for 4 weeks.
    C. Outpatient intravenous iron therapy weekly for 4 weeks.
    D. Darbepoetin alfa 0.75 mcg/kg once every 2 weeks.

14. Which best depicts C.A.'s blood pressure goal?
    A. Less than 130/80 mm Hg.
    B. Less than 140/90 mm Hg.
    C. Less than 150/90 mm Hg.
    D. Less than 140/80 mm Hg.

15. C.A.'s furosemide dose is increased; however, she needs better control of her blood pressure. Which would be most appropriate to add to amlodipine?
    A. Carvedilol.
    B. Bisoprolol.
    C. Spironolactone.
    D. Metolazone.

A. Iron Deficiency

1. Background: Anemia is independently associated with HF disease severity, and iron deficiency appears to be uniquely associated with reduced exercise capacity. Figure 5 describes the evaluation of iron-deficiency anemia in HF.

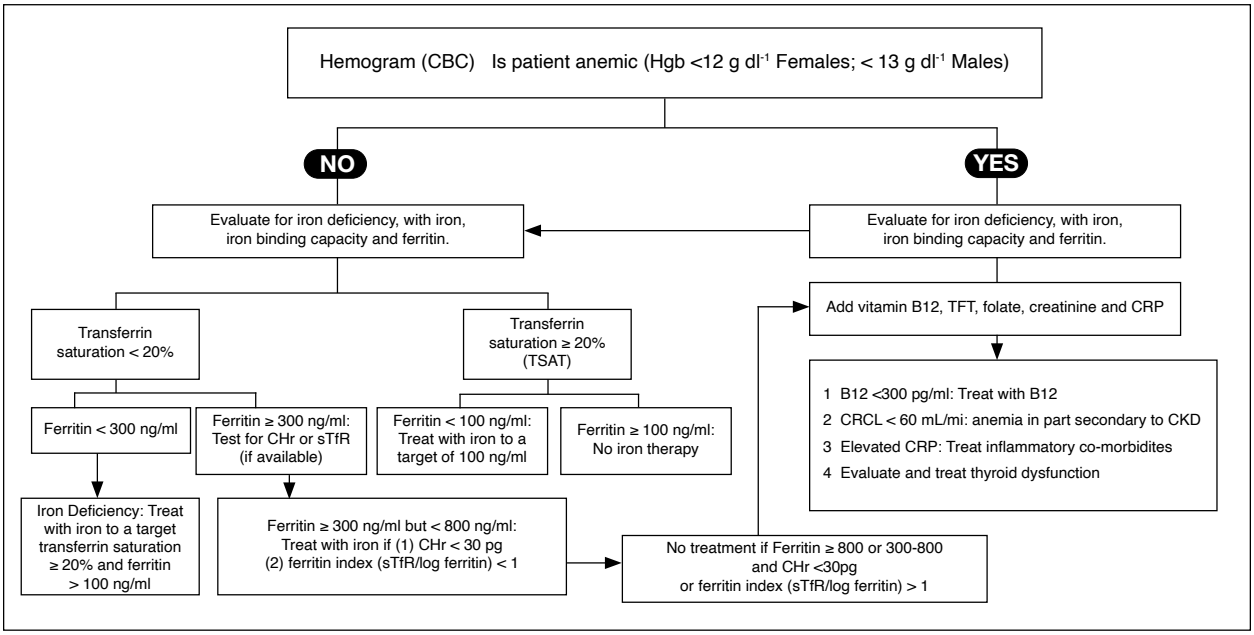


**Figure 5.** Evaluating iron-deficiency anemia in patients with heart failure

CHr = reticulocyte hemoglobin concentration; CRP = C-reactive protein; sTfR = soluble transferrin receptor; TFT = thyroid function test; TSAT = transferrin saturation.

Information from: Goodnough LT, Comin-Colet J, Leal-Noval S, et al. Management of anemia in patients with congestive heart failure. Am J Hematol 2017;92:88-93.

2. Intravenous iron replacement
   a. In patients with NYHA class II and III HF and iron deficiency (ferritin less than 100 ng/mL or 100–300 ng/mL if TSAT is less than 20%), intravenous iron replacement may be reasonable to improve functional status and QoL.
   b. Studies examining correction of iron deficiency in HF have shown improvement in surrogate end points such as QoL, NT-proBNP, LVEF, and, more recently, HF hospitalization (Table 32).
   c. Oral iron repletion is not effective, according to the IRONOUT-HF trial.

**Table 32.** Landmark Controlled Trials with Intravenous Iron

| Study | Year | Treatment Arms | Population | Follow-up Time | Primary End Point |
|---|---|---|---|---|---|
| FERRIC-HF | 2008 | Iron sucrose (n=11)<br><br>Placebo (n=24) | NYHA II and III, LVEF ≤ 45%, exercise limited, anemic: Hgb < 12.5 g/dL (anemic group) or 12.5–14.5 g/dL non-anemic group); ferritin < 100 mcg/L or between 100 g/L and 300 mcg/L with TSAT < 20% | 18 wk | Iron sucrose was associated with a statistically significant improvement in mean ferritin concentrations (p<0.0001), NYHA functional class (p=0.007), and patient global assessment (p=0.002) |
| FAIR-HF | 2009 | Ferric carboxymaltose (n=304)<br><br>Placebo (n=155) | NYHA II and III, LVEF ≤ 45%, baseline Hgb 9.5–13.5 g/dL, iron deficiency, defined as either ferritin < 100 mcg/L or ferritin 100–299 mcg/L with TSAT < 20% | 24 wk | Ferric carboxymaltose was associated with a statistically significant improvement in patient global assessment (p<0.001), NYHA functional class (p<0.001), exercise tolerance (p<0.001), and QoL (p<0.001) but only a trend in reduced hospitalizations for CV causes |
| CONFIRM-HF | 2015 | Ferric carboxymaltose (n=150)<br><br>Placebo (n=151) | NYHA II and III, LVEF ≤ 45%, BNP > 100 pg/mL and/or N-proBNP > 400 pg/mL); iron deficiency: defined as either ferritin < 100 mcg/L or ferritin 100–300 mcg/L with TSAT < 20% | 52 wk | Ferric carboxymaltose treatment was associated with improvement in functional capacity, symptoms, and QoL and may be associated with an RR for HF hospitalization (HR 0.39; 95% CI, 0.19–0.82; p=0.009) |
| IRONOUT-HF | 2017 | Oral polysaccharide iron complex 150 mg (n=111)<br><br>Placebo (n=114) | NYHA II-IV, LVEF < 40%; iron deficiency: defined as ferritin 15-100 ng/mL or between 100-299 ng/mL with a TSATl < 20% and hemoglobin levels between 9-15 g/dL (men) or 9-13.5 g/dL (women) | 16 wk | High-dose oral iron did not improve exercise capacity over 16 weeks. These results do not support use of oral iron supplementation in patients with HFrEF |
| AFFIRM-AHF | 2020 | Ferric carboxymaltose | NYHA II–IV, LVEF < 50%, hospitalized for HF, iron deficiency (defined as ferritin < 100 mcg/L, or 100–299 mcg/L with TSAT < 20%) | 24 wk | Ferric carboxymaltose was associated with a reduced risk of HF hospitalization (p=0.05), but not CV death (p=0.81) |

**Table 32.** Landmark Controlled Trials with Intravenous Iron (*Cont'd*)

| Study | Year | Treatment Arms | Population | Follow-up Time | Primary End Point |
|---|---|---|---|---|---|
| IRONMAN | 2022 | Ferric derisomaltose (n=569), placebo (n=568) | Average age 73 yr, average LVEF 34%, NYHA II–IV, TSAT < 20% or ferritin < 100 mcg/L, NT-proBNP (ng/L) > 250 if sinus rhythm/> 1000 if atrial fibrillation, increased risk of CV events, with either current or recent (< 6 mo) HF hospitalization | 2.7 yr | Ferric derisomaltose did not decrease the risk of CV death or HF hospitalization vs. usual care (22.4 vs. 27.5 events/100 patient-years (p=0.07) |

CONFIRM-HF = Ferric Carboxymaltose Evaluation on Performance in Patients with Iron Deficiency in Combination with Chronic Heart Failure; FAIR-HF = Ferinject Assessment in Patients with Iron Deficiency and Chronic Heart Failure; FERRIC-HF = Ferric Iron Sucrose in Heart Failure; IRONOUT-HF = Iron Repletion Effects on Oxygen Uptake in Heart Failure; TSAT = transferrin saturation.

3. Erythropoiesis-stimulating agents
    a. A meta-analysis of 11 randomized controlled trials (n=794) comparing erythropoiesis-stimulating agents with control in patients with HF showed significant improvements in 6-minute walk distance, exercise duration, peak oxygen consumption, NYHA functional class, LVEF, BNP, HF-related hospitalizations, and QoL.
    b. In the RED-HOT trial, correction of anemia with darbepoetin alfa did not result in benefit but caused a significant increase in the risk of thromboembolic events and a nonsignificant increase in fatal and nonfatal strokes, supporting findings from other trials.
    c. In patients with HF and anemia, erythropoiesis-stimulating agents should not be used to improve morbidity and mortality.

B. HTN
1. Overall recommendation: In patients at increased risk (Stage A), the optimal blood pressure in those with HTN should be less than 130/80 mm Hg.
2. Specific to HFrEF: Patients with HFrEF and HTN should be prescribed GDMT titrated to attain a systolic blood pressure less than 130 mm Hg.
3. Specific to HFpEF: Patients with HFpEF and persistent HTN after management of volume overload should be prescribed GDMT titrated to attain a systolic blood pressure less than 130 mm Hg.

C. Sleep Disorders
1. In patients with NYHA class II–IV HF and suspected sleep-disordered breathing or excessive daytime sleepiness, a formal sleep assessment is reasonable.
2. Obstructive sleep apnea
    a. In patients with CV disease and obstructive sleep apnea, continuous positive airway pressure (CPAP) may be reasonable to improve sleep quality and daytime sleepiness.
    b. In randomized controlled trials, CPAP improved quality of sleep but did not reduce CV events, possibly because CPAP was used only about 3 hours per night.
    c. In patients with HF, obstructive sleep apnea, and AF, CPAP use delayed progression to more permanent forms of AF.
3. Central sleep apnea
    a. In patients with NYHA class II–IV HFrEF and central sleep apnea, adaptive servo-ventilation causes harm.

b. Mortality rates (all-cause and CV) were higher with adaptive servo-ventilation plus GDMT than with GDMT alone in a single randomized controlled trial to test the addition of adaptive servo-ventilation (5 hours or more per night, 7 nights/week) to GDMT in patients with HFrEF and central sleep apnea.

D. DM
   1. Background:
      a. DM is a risk factor for developing HF independently of age, HTN, obesity, hypercholesterolemia, or CAD.
      b. The association between mortality and hemoglobin A1C (A1C) in patients with DM and HF appears U-shaped, with the lowest risk of death in patients with modest glucose control (A1C between 7.2 to 7.8) and with increased risk with extremely high or low A1C concentrations.
   2. Treatment considerations
      a. Table 33 summarizes the major adverse cardiac events with DM medications.

**Table 33.** Summary of MACE According to Clinical Trials with DM Medications

| | MACE Outcome | HF Outcome | Use in HF |
|---|---|---|---|
| Insulin | Neutral | Neutral | Yes |
| Metformin | Neutral | Neutral | Yes |
| Sulfonylureas | Neutral, questionable | Neutral, questionable | Yes |
| Thiazolidinediones | | | |
| Rosiglitazone | Neutral | Increased | Avoid |
| Pioglitazone | Decreased | Increased | Avoid |
| GLP-1 A | | | |
| Lixisenatide | Neutral | Neutral | Yes |
| Liraglutide | Decreased | Neutral | |
| DPP4-I | | | |
| Saxagliptin | Neutral | Increased | Caution |
| Alogliptin | Neutral | Increased (NS) | Caution |
| Sitagliptin | Neutral | Neutral | Yes |
| SGLT2-I | Decreased | Decreased | Yes |

DPP4-I = dipeptidyl peptidase 4 inhibitor; GLP-1 A = glucagon-like peptide agonist; MACE = major adverse cardiac events; NS = not significant; SGLT2-I = sodium glucose cotransporter 2 inhibitor.

Information from: Fitchett DH, Udell JA, Inzucchi SE. Heart failure outcomes in clinical trials of glucose-lowering agents in patients with diabetes. Eur J Heart Fail 2017;19:43-53.

   b. Metformin: In patients with type 2 DM and stable HF, metformin may be used if the eGFR is greater than 30 mL/minute/1.73 $m^2$, but it should be avoided in unstable or hospitalized patients with HF, according to FDA recommendations.
   c. Thiazolidinediones: American Diabetes Association recommends against use in patients with symptomatic HF.
   d. Glucagon-like peptide agonist 1 A
      i. ELIXA trial: In patients with type 2 DM with a recent MI or hospitalized for unstable angina, HF hospitalization did not differ between lixisenatide and placebo (HR 0.96; 95% CI, 0.75–1.23).

ii. LEADER trial: In patients with type 2 DM and high risk of a CV event, HF hospitalizations did not differ between liraglutide and placebo (HR 0.87; 95% CI, 0.73–1.05).
iii. FIGHT study: In patients recently hospitalized with HFrEF, liraglutide did not lead to greater post-hospitalization clinical stability.
iv. EXSCEL trial: In patients with type 2 DM with or without previous CV disease, the incidence of MACE did not differ between exenatide and placebo.

e. Dipeptidyl peptidase 4 inhibitor
i. EXAMINE trial: Alogliptin was associated with a nonsignificant increase in hospitalization for HF (HR 1.19; 95% CI, 0.9–1.58). Patients with higher NT-proBNP concentrations at baseline and a history of HF had no higher incidence of hospitalization for HF associated with alogliptin treatment. However, for patients with no history of HF, alogliptin significantly increased hospitalization for HF (HR 1.76; 95% CI, 1.07–2.90).
ii. SAVOR-TIMI 53: Hospitalization for HF was increased by 27% with saxagliptin (HR 1.27; 95% CI, 1.07–1.51, p=0.007). Patients at greatest risk were those with prior HF, an elevated baseline NT-proBNP, or chronic kidney disease.
iii. TECOS-HF: Sitagliptin did not increase HF hospitalizations in patients with HF and DM.

E. Transthyretin Amyloidosis (ATTR amyloidosis)
1. Typically a late-onset disease characterized by the deposition of amyloid fibrils composed of misfolded proteins in the myocardium
2. Reported prevalence was 13% among those with HFpEF, 16% among those undergoing transcatheter aortic valve replacement, and 5% among those with hypertrophic cardiomyopathy.
3. Median survival: 2.6–3.5 years after diagnosis
4. Tafamidis (Vyndamax)
a. Mechanism of action: Binds transthyretin, preventing tetramer dissociation and pathogenic protein misfolding that leads to fibrotic deposition in the myocardium and other visceral organs
b. FDA approved for hereditary and wild-type ATTR cardiomyopathy
c. Dosing: Tafamidis (Vyndamax) (80 mg once daily), tafamidis meglumine (Vyndaqel) (61 mg once daily)
5. ATTR-ACT (2018)
a. Enrolled patients with HFrEF and HFpEF with no specific LVEF requirement; required biopsy-confirmed ATTR amyloidosis
b. Over 30 months, tafamidis compared with placebo was associated with lower all-cause mortality (HR 0.70; 95% CI, 0.51–0.96; p<0.001) and risk of HF hospitalization (RR 0.68; 95% CI, 0.56–0.81; p<0.001).

F. Potassium-Binding Agents
1. Many patients cannot tolerate the initiation or titration of RAAS inhibitor therapies, given clinically significant hyperkalemia.
2. Potassium-binding options can play an important role in ensuring appropriate GDMT.
3. Available agents
a. Patiromer: 8.4, 16.8, or 25.2 g orally once daily
b. Sodium zirconium cyclosilicate (Lokelma): Loading dose 10 g three times daily for 48 hours, followed by maintenance dose 5–15 g daily
i. Sodium content: 400 mg per 5 g of sodium zirconium cyclosilicate
c. Sodium polystyrene sulfate: Avoid chronic use because of the risk of intestinal and bowel necrosis.
4. Considerations
a. Patiromer: Oral medications should administered either 3 hours before or 3 hours after patiromer.

b. Sodium zirconium cyclosilicate: Oral medications with pH-dependent solubility should be administered at least 2 hours before or 2 hours after sodium zirconium cyclosilicate. Spacing is not needed if it has been determined the concomitant medication does not have pH-dependent solubility.

G. Influenza
1. Individuals with HFrEF have a higher risk of significant morbidity and mortality if they have a diagnosis of influenza.
a. Danish registry study and post hoc analysis of PARADIGM-HF both showed reduced mortality with annual influenza vaccination.
2. INVESTED trial determined that high-dose trivalent influenza vaccine, compared with standard-dose quadrivalent vaccine, did not significantly reduce all-cause mortality or hospitalizations for cardiac or pulmonary causes (HR 1.06; 95% CI, 0.97–1.17; p=0.21).
3. Influenza vaccination is still recommended in this population.

## VI. TRANSITIONS OF CARE

A. Background
1. Transitions of care is an essential component of any therapeutic plan to ensure safe transitions from one health care setting to another (e.g., hospital to home, nursing facility to home).
2. Effective transitions are a byproduct of planning and early intervention to find solutions to resource access issues, medication costs, and other logistical considerations such as dialysis and outpatient infusions.
3. For patients hospitalized with heart failure, the Centers for Medicare & Medicaid Services tracks 30-day readmission rates, penalizing institutions with excessively high rates.
a. Registry data would suggest an average readmission/30-day mortality rate of 15%–25% after hospital discharge.
b. EVOLUTION-HF (Utilization of Dapagliflozin and Other Guideline Directed Medical Therapies in Heart Failure Patients: A Multinational Observational Study Based on Secondary Data)
i. Assessed 266,589 patients from Japan, Sweden, and the United States who started any GDMT within 12 months of discharge for an HF-related hospitalization
ii. Delayed initiation of novel GDMT if not started during hospitalization (ARNIs and SGLT2 inhibitors) in all three countries relative to β-blockers, MRAs, and ACE inhibitors/ARBs
iii. Low rates of conversion from ACE inhibitor/ARB to ARNI (less than 5% in the United States)
iv. ARNI target dose achievement at 12 months in the United States was 12.6% with a 40.3% discontinuation rate.
v. Dapagliflozin discontinuation rate was 53.5% in the United States with target dose achievement of 46.5%, likely because most patients are started on the target dose initially.
c. Means of intervention
i. Patient education
(a) Maximizing time during admission for education related to medications, diet, exercise, and HF basics (weight monitoring, fluid assessment)
ii. Telehealth
(a) Has grown significantly with the constraints of in-person visits secondary to the COVID-19 pandemic
(1) Single-center experience with more than 14,000 clinic encounters for patients with HF found no difference with respect to 30- or 90-day mortality for those seen digitally compared with in-person.

(b) Many patients prefer given distance from tertiary care facilities.
(c) Does not replace the need for in-person visits, when necessary

iii. GDMT clinics
(a) Non-physician providers, including pharmacists, are increasingly effective at achieving goal GDMT in patients with HF when
(1) Can be achieved through telehealth visits, telephonic encounters, or in-person visits using delegation protocols and/or titration algorithms

## VII. NONPHARMACOLOGIC CONSIDERATIONS

A. Essential Goals of Patient and Caregiver Education
1. Recognize the signs and symptoms of early decompensation (which is often individualized), as well as the symptoms of drug toxicity, and understand when to seek care (Table 34).
2. Check and record blood pressure and heart rate.
3. Check accurate daily weights (e.g., taken at the same time while wearing the same thing every day on an accurate scale).
4. Demonstrate an understanding of how to take all prescribed medications and the importance of not missing doses and of obtaining refills on time. The provider should assess for rationing of medications and help the patient troubleshoot difficulty with adhering to a medication routine.
5. Participate safely in regular physical activity or a structured exercise training program.
6. Impart skills that will allow patients to eat a low-sodium diet (e.g., ensure they can interpret food labels and have a plan to avoid convenient but high-sodium foods like fast food).
7. Influenza vaccine annually and pneumococcal vaccine every 5 years. Patients with HF who received their influenza vaccination had an 18% reduced risk of death (all-cause: HR 0.82; 95% CI, 0.81–0.84; $p<0.001$; CV causes: HF 0.82; 95% CI, 0.81–0.84; $p<0.001$).

B. Diet
1. Although experts and major society guidelines agree that a low-sodium diet is important for most patients with HF, controversy exists regarding exactly how much sodium constitutes a "low-sodium" diet.
2. The AHA specifically recommends sodium restriction to less than 1.5 g/day in stages A and B to help prevent the development of HF symptoms.
3. Although the current evidence is limited, AHA/ACC recommends a low-sodium diet, less than 3 g/day for all symptomatic patients and those with frequent HF exacerbations (stages C and D).
4. Fluid restriction, though not routinely recommended, is important in certain patients. Many patients have excessive thirst because of up-regulation of the RAAS and antidiuretic hormone.
5. A careful history will help a provider determine whether intensification of hormonal blockade will benefit an individual patient in addition to limiting fluid intake to 1.5–2 L per day. Reasonable in stage D if serum sodium is low

C. Exercise
1. The ACC/AHA 2013 HF management guidelines recommend exercise training (or regular physical activity) for patients with HF who can participate to improve functional status.
2. HF-ACTION showed that patients with HFrEF who were receiving GDMT and a supervised home-based aerobic program had lower rates of hospitalization and all-cause mortality and better QoL than patients receiving GDMT alone.

**Table 34.** Patient Education Provided by AHRQ Addressing HF Symptoms

| | |
|---|---|
| **Green Zone: All Clear**<br>No SOB<br>• No swelling<br>• No weight gain<br>• No chest pain<br>• No decrease in your ability to maintain your activity level | **Green Zone Means:**<br>• Your symptoms are under control<br>• Continue taking your medications as ordered<br>• Continue daily weights<br>• Follow low-sodium diet<br>• Keep all physician appointments |
| **Yellow Zone: Caution**<br>If you have any of the following signs and symptoms:<br>• Weight gain ≥ 1.4 kg (3 lb) in 2 days<br>• Increased cough<br>• Increased swelling<br>• Increase in SOB with activity<br>• Increase in the number of pillows needed<br>• Anything else unusual that bothers you<br>**Call your physician if you are going into the YELLOW zone** | **Yellow Zone Means:**<br>• Your symptoms may indicate that you need an adjustment of your medications<br>• **Call your physician, nurse coordinator, or home health nurse**<br>Name:_____<br>Number:_____<br>Instructions: _____<br>_____ |
| **Red Zone: Medical Alert**<br>• Unrelieved SOB: SOB at rest<br>• Unrelieved chest pain<br>• Wheezing or chest tightness at rest<br>• Need to sit in chair to sleep<br>• Weight gain or loss of more than 2.3 kg (5 lb) in 2 days<br>• Confusion<br>**Call your physician immediately or go to ED if you are going into the RED zone** | **Red Zone Means:**<br>This indicates that you need to be evaluated by a physician right away<br>• **Call your physician right away**<br>Physician_____<br>Number_____ |

AHRQ = Agency for Healthcare Research and Quality; ED = emergency department.

Information from: Agency for Healthcare Research and Quality (AHRQ). Red-Yellow-Green Congestive Heart Failure (CHF) Tool. April 2008. Available at https://innovations.ahrq.gov/qualitytools/red-yellow-green-congestive-heart-failure-chf-tool.

D. Drugs to Avoid or Use with Caution
   1. NSAIDs, including selective cyclooxygenase-2 inhibitors
      a. Promote sodium and water retention
      b. Blunt diuretic response
      c. Increase morbidity and mortality
   2. Class I and III antiarrhythmic agents (except for amiodarone and dofetilide)
      a. Negative inotropic activity
      b. Proarrhythmic effects
      c. Amiodarone and dofetilide have been proven safe in patients with HF.
      d. Avoid dronedarone. Contraindicated in patients with symptomatic HF with recent decompensation necessitating hospitalization or NYHA class IV HF
   3. Non-dihydropyridine calcium channel blockers in HFrEF

   a. Negative inotropic activity
   b. Promote neurohormonal activation
   c. Amlodipine and felodipine have been proven safe in patients with HF and can be added when additional blood pressure reduction is needed, according to PRAISE I and II (amlodipine) as well as Val-HeFT III (felodipine).
4. Minoxidil
   a. Promotes sodium and water retention
   b. Stimulates the RAAS
5. Thiazolidinediones: Promote sodium and water retention
6. Amphetamines (e.g., methylphenidate)
   a. α- and β-agonist activity
   b. Cause tachycardia
   c. Proarrhythmic effects
7. Nutritional supplements
8. Cilostazol: Inhibits phosphodiesterase type 3
9. Itraconazole: Negative inotropic activity.
10. Pregabalin and gabapentin (greater than 1600 mg/day)
    a. Inhibit calcium channels
    b. Cause lower-extremity edema, HF exacerbation (Circulation 2016:134:e261)

Information from: Page RL, Cheng D, Dow T, et al. Drugs that may cause or exacerbate heart failure: a scientific statement from the American Heart Association; on behalf of the American Heart Association Clinical Pharmacology and Heart Failure and Transplantation Committees of the Council on Clinical Cardiology, Council on Cardiovascular Surgery and Anesthesia, Council on Cardiovascular and Stroke Nursing, and Council on Quality of Care and Outcomes Research. Circulation 2016;134:e261.

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## ANSWERS AND EXPLANATIONS TO PATIENT CASES

**1. Answer: A**
Understanding the signs and symptoms specific to HF is extremely important, especially within a clinic setting. The pharmacist should be able to delineate which symptoms are suggestive of HF. For this patient, she presents with SOB and dyspnea on exertion, which has a sensitivity of 84%–100%, making Answer A correct. Although she does have paroxysmal nocturnal dyspnea (Answer B) and orthopnea (Answer C), these symptoms have a sensitivity of only 23% and 39%, respectively, making them incorrect. Edema (Answer D) has a sensitivity of only 23%.

**2. Answer: C**
This patient has a medical history of structural heart disease because of her previous MI, and her symptoms are consistent with HFrEF (e.g., dyspnea and fatigue on exertion), which is consistent with stage C (Answer C). Answer A would be correct if the patient had no risk factors for HF and no structural heart disease or symptoms of HF. Answer B would be correct if this patient currently had no signs or symptoms of HF. Answer D would be correct if her HF have deteriorated such that she had symptoms at rest despite maximally tolerated GDMT.

**3. Answer: B**
The next step in evaluating the patient's HF would be to obtain a BNP or NT-proBNP. It is important to understand which patient-specific factors can influence these values because either BNP or NT-proBNP can be used to evaluate disease severity and HF management. Advanced age (Answer A) and renal insufficiency (Answer C) can cause higher-than-expected natriuretic peptide concentrations. Obesity (Answer B) can lower natriuretic peptides more than expected, making Answer B correct. Hypertension (Answer D) does not influence natriuretic peptide concentrations.

**4. Answer: B**
Sacubitril is a neprilysin inhibitor, which prevents the degradation of BNP through neprilysin inhibition (Answer B). Thus, BNP concentrations would probably be increased, making Answer B correct. In addition, increases in BNP would reduce circulating concentrations of both AT II (Answer C) and aldosterone (Answer D). Neprilysin does not influence NT-proBNP (Answer A), which would be expected to decrease as the patient's HF symptoms improve.

**5. Answer: A**
Shared decision-making between patient and provider is important in GDMT. One part of shared decision-making is the evaluation and discussion of a patient's mortality as related to the patient's HF. Pharmacists need to understand the tools that can accomplish this. Answer A, the Seattle Heart Failure Module, is a validated scoring system that can help provide a patient's risk of mortality. The Minnesota Living with Heart Failure Questionnaire (Answer B), Kansas City Cardiomyopathy Questionnaire (Answer C), and chronic heart failure assessment tool (Answer D) evaluate QoL rather than mortality.

**6. Answer: C**
On evaluating this patient's GDMT, he is receiving an ACE inhibitor, a β-blocker, and a diuretic, which are at target doses. According to the 2017 ACC/AHA/HFSA HF management update, the only GDMT he is not receiving is an aldosterone antagonist. The patient meets the criteria for either spironolactone or eplerenone because he has NYHA class II–IV, LVEF 35% or less, SCr 2.5 mg/dL or less, and K 5.0 mEq/L or less. According to the RALES trial, this patient could expect benefits such as a reduced mortality and hospitalization if spironolactone is added to his current regimen (Answer C). In addition, spironolactone could assist with blood pressure reduction. Although digoxin (Answer A) is a possible choice, according to the DIG trial, this drug would only reduce hospitalizations, not mortality. Answer B, add losartan, would only be recommended if the patient were not an ideal candidate for an aldosterone antagonist. Adding an ARB to an ACE inhibitor does not provide a mortality reduction benefit, according to both the CHARM-Added and Val-HeFT trials. Answer D is incorrect because adding amlodipine to GDMT has a neutral effect on mortality, according to the PRAISE I and II trials. Amlodipine or felodipine can be added to a drug regimen for additional blood pressure reduction; however, the patient should already be receiving maximized GDMT, which would include an aldosterone antagonist.

**7. Answer: B**

According to the results of both the DAPA-HF and the EMPEROR-Reduced clinical trials, both dapagliflozin and empagliflozin reduce a composite of CV death and HF hospitalization in patients with HFrEF regardless of type 2 DM status (Answer A is incorrect; Answer B is correct). In EMPEROR-REDUCED, patients with an eGFR > 20 were enrolled (Answer C is incorrect). There is no data to support not initiating SGLT-2 inhibitors in patients already maintained on loop diuretic therapy (Answer D is incorrect). Loop diuretic dose, however, may need to be adjusted by 15-25% percent to account for the diuretic effects of the SGLT-2 inhibitors.

**8. Answer: B**

When transitioning from an ACE inhibitor to an ARNI, package labeling recommends discontinuing the ACE inhibitor within 36 hours of beginning the ARNI (Answer B). Discontinuing the ACE inhibitor in a timely fashion reduces the risk of angioedema. Answer A, lowering the dose of metoprolol succinate, is incorrect because the patient is not at his goal blood pressure, and reducing the metoprolol dose could reduce the mortality benefits of the β-blocker. Answer C is incorrect; an ARNI will increase BNP because of inhibition of neprilysin by sacubitril. Monitoring the effects of an ARNI on natriuretic peptides should be done through the NT-proBNP that is not affected by sacubitril. Answer D, increasing the furosemide dose, is incorrect because the patient has no signs of volume overload at this time. In addition, some increase in diuresis would be expected when adding an ARNI.

**9. Answer: C**

Dose conversion is an integral part of therapeutic drug management, whether in the inpatient or the outpatient setting. Because of the risk of hypotension and angioedema, appropriate dosing of ARNIs is critical to minimize adverse effects. Answer C, 49/51 mg, is correct because the patient is currently receiving an ACE inhibitor at a total daily dose of greater than 10 mg of enalapril or equivalent (e.g., lisinopril greater than 10 mg or ramipril greater than 5 mg). Answer B, 24/26 mg, is incorrect because the patient would need to be receiving an ACE inhibitor at a total dose of 10 mg of enalapril or less or equivalent (e.g., lisinopril at 10 mg or less or ramipril at 5 mg or less). Answer D, 97/103 mg, is incorrect because this is the maximal dose of sacubitril/valsartan and not a recommended starting dose. Answer A, 12/12.5 mg, is incorrect because this would require splitting the dose, and sacubitril/valsartan should not be split, according to package labeling.

**10. Answer: D**

Repeated hospitalizations are common in patients with HF, especially older adults. Thus, it is critical to ensure that the medical regimen is optimized. This patient needs much higher doses of ACE inhibitors and diuretics, and indeed, she has no apparent contraindications to this therapy (i.e., hypotension, hyperkalemia, or renal insufficiency). If titration of the ACE inhibitor results in significant renal insufficiency, treatment can be changed to hydralazine combined with isosorbide dinitrate. Underdosage of the ACE inhibitor and failure to titrate diuretics are some of the most common errors in managing HF and may be responsible for repeated hospitalizations. Thus, Answer D is correct. Because the patient has marked fluid overload, a simultaneous increase in diuretics is appropriate, though caution should be used while titrating the ACE inhibitor. Answer A, add metolazone, is incorrect because this patient is only receiving a low dose of loop diuretic, and dual-nephron blockade would be warranted if she did not initially respond to higher doses of a loop diuretic. Answer B is incorrect because the patient has placement of a pacemaker set greater than 60 beats/minute and cannot achieve a target heart rate of 60 beats/minute or less. In addition, she is not currently receiving maximally tolerated doses of the β-blocker. Cardiac resynchronization therapy is unnecessary because she is not receiving maximal GDMT and has no ECG evidence of dyssynchrony (i.e., QRS prolongation) (Answer C is incorrect).

**11. Answer: C**

With implantation of the CardioMEMS device, antiplatelet therapy is warranted, according to the CHAMPION trial. Patients should be initiated on dual antiplatelet therapy with clopidogrel 75 mg/day together with aspirin 81–325 mg/day for 1 month, followed by aspirin 81 mg/day indefinitely, making Answer C correct. Answer A, add warfarin, is incorrect according to the WASH, WATCH, and WARCEF studies, which state that warfarin is not recommended in the absence of AF, prior stroke, or cardioembolic source in patients with HF. Answer B, aspirin alone, and Answer D, clopidogrel alone, are incorrect because dual antiplatelet therapy is needed.

**12. Answer: A**

This patient has a diagnosis of HFpEF, given her LVEF of 66%. She presents with symptoms of fluid overload (e.g., elevated JVP, +2 edema, + rales/rhonchi, and an elevated BNP). This is a classic example of a patient with HFpEF. According to the ACC/AHA/HFSA 2017 guidelines, diuretics should be used for relief of symptoms caused by volume overload in patients with HFpEF. Because the patient is not currently receiving a diuretic, Answer A, begin furosemide, is correct. Answer B, add hydrochlorothiazide, is incorrect because her blood pressure is controlled, and she needs a loop diuretic rather than a thiazide, which would not provide the level of diuresis needed. Answer C is also a potential choice, given that this patient meets the criteria for spironolactone, according to TOPCAT. However, spironolactone would not provide the appropriate level of diuresis needed at this time, and the patient's blood pressure is well controlled with lisinopril. Answer D, add isosorbide mononitrate, is incorrect; routine use of nitrates in HFpEF is not recommended, according to NEAT-HFpEF, unless the patient has ischemic symptoms.

**13. Answer: C**

Given this patient's CBC, she does not have iron-deficiency anemia; however, her iron studies show that she is iron deficient. The ACC/AHA/HFSA 2017 guidelines recommend intravenous iron for patients with NYHA class II and III HF and iron deficiency (ferritin less than 100 ng/mL or 100–300 ng/mL if TSAT is less than 20%); intravenous iron replacement might be reasonable to improve functional status and QoL. Because this patient meets these criteria, she would be a good candidate for outpatient intravenous iron, making Answer C correct. Although oral iron is inexpensive, it is not well tolerated, needs to be taken in an acidic environment, and is not well absorbed in patients with HF. The ACC/AHA/HFSA 2017 guidelines state that data are insufficient to recommend oral iron replacement in patients like the patient in this case, making Answer A incorrect. Given that the patient's vitamin $B_{12}$ serum concentrations are above 300 ng/mL, she does not need replacement at this time, making Answer B incorrect. Routine use of erythropoiesis-stimulating agents is not recommended to improve morbidity and mortality in patients with anemia and HF (Answer D is incorrect). In RED-HOT, correction of anemia with darbepoetin alfa did not result in benefit but caused a significant increase in the risk of thromboembolic events and a nonsignificant increase in fatal and nonfatal strokes.

**14. Answer: A**

This patient's blood pressure is not well controlled on amlodipine. According to the ACC/AHA/HFSA 2017 guidelines, patients with HFpEF and persistent HTN after management of volume overload should be prescribed GDMT titrated to attain a systolic blood pressure less than 130 mm Hg. With this in mind, Answer A, less than 130/80 mm Hg, would be best. Answer B, less than 140/90 mm Hg, is the blood pressure goal recommended by the Eighth Joint National Committee (JNC8) for patients with chronic kidney disease. It is also the blood pressure goal recommended by the American Society of Hypertension and International Society of Hypertension for patients with underlying CV disease or those with chronic kidney disease or DM. Answer C, less than 150/90 mm Hg, is the blood pressure goal recommended by the JNC8 for adults 60 and older. Answer D, less than 140/80 mm Hg, is the blood pressure goal recommended by the American Diabetes Association for patients with DM.

**15. Answer: C**

For many common antihypertensive agents, including α-blockers, β-blockers, and calcium channel blockers, data are limited to guide the choice of antihypertensive therapy in the setting of HFpEF. Nevertheless, according to the ACC/AHA/HFSA 2017 guidelines, RAAS inhibition with an ACE inhibitor, ARB, and aldosterone antagonist is preferred. This patient has a history of bronchospastic disease; therefore, carvedilol (Answer A) and bisoprolol (Answer B) would be inappropriate. Of note, if a β-blocker were warranted, bisoprolol would be the better of the two because it is the most selective for the β-receptor. Answer D is incorrect; although dual-nephron blockade with metolazone could assist with the patient's diuresis, it might not help control her blood pressure. Answer C would be best, according to the TOPCAT trial. In the ACC/AHA/HFSA 2017 guidelines, spironolactone is recommended in some patients with HFpEF (with ejection fraction 45% or more, elevated BNP concentrations or HF admission within 1 year, eGFR greater than 30 mL/minute, SCr less than 2.5 mg/dL, K less than 5.0 mEq/L), to decrease hospitalizations. This patient meets these criteria and would benefit from the potassium-raising effects of an aldosterone antagonist. Finally, spironolactone is recommended as a hypertensive agent in patients with resistant HTN.

## ANSWERS AND EXPLANATIONS TO SELF-ASSESSMENT QUESTIONS

**1. Answer: C**

This patient has a medical history of structural heart disease related to trastuzumab exposure and has symptoms consistent with HFrEF (e.g., dyspnea and fatigue on exertion), which is consistent with stage C (Answer C). Answer A would be correct if the patient had risk factors for HF and no structural heart disease or symptoms of HF. Answer B would be correct if the patient had no signs or symptoms of HF. Answer D would be correct if the patient's HF had deteriorated such that she was having symptoms at rest, despite maximally tolerated GDMT.

**2. Answer: D**

The patient is receiving the following GDMT: an ACE inhibitor, a β-blocker, digoxin, and an aldosterone antagonist, yet she continues to have HF-related symptoms. Answer A is incorrect because the patient's digoxin concentration is 0.9 ng/mL, which is within the desired therapeutic range; thus, a dose increase is unwarranted at this time. Answer B (increase the lisinopril dose to 40 mg/day) is not the best choice because ATLAS showed no difference in all-cause or CV mortality between high and low lisinopril doses. In addition, the patient has a low blood pressure of 112/70 mm Hg, and a higher lisinopril dose could lead to hypotension without a mortality benefit. The patient already receives spironolactone at a target dose with a K of 4.0 mEq/L, which is within goal CV range (Answer C is incorrect). No trial to date has shown a difference in mortality between high and low doses of aldosterone antagonists. Answer D is correct because this patient is not at her target dose of β-blocker. Higher doses of carvedilol have caused a greater improvement in LVEF and a greater reduction in mortality.

**3. Answer: C**

Power is calculated as $1 - \beta$. If a trial were powered at 90% to reject the null hypothesis and show superiority, β would be calculated as 0.10, making Answer C correct. Answer B would equate to a power of 95% and Answer D to an 80% power level, making these answers incorrect. Answer A would be equated to a power of 99%, which would also be incorrect.

**4. Answer: A**

Answer A is correct because a type I error is the reporting of a false-positive result, meaning the investigators rejected the null hypothesis when, in fact, they should have accepted it. Answer B is incorrect because a type II error is reporting a false-negative result, meaning the investigators accepted the null hypothesis when, in fact, they should have rejected it. Answer C, selection bias, and Answer D, reporting bias, are types of biases. Answer C is incorrect because this bias involves individuals being more likely than others to be selected for the study, which was not true with this study. Answer D is incorrect because this type of bias involves a skew in the availability of data such that observations of a certain type are more likely to be reported. This is incorrect because the sample size of each treatment arm is large enough that data should be more equality distributed than skewed.

**5. Answer: B**

Current assessment of LV diastolic function focuses on the analysis of ventricular filling patterns that can easily be determined by Doppler imaging techniques, making Answer B correct. This technique is readily available, is relatively easy to perform, lacks ionizing radiation, and can provide important information regarding LV function, cardiac anatomy, and estimated filling pressures. The gold-standard test remains left heart catheterization. However, because it is invasive, time-consuming, expensive, and not readily available, it is infrequently performed for these indications, making Answer D incorrect. Other techniques such as cardiac MRI (Answer A) and CT imaging (Answer C) are time-intensive, expensive tests. Computed tomography imaging assesses cardiac structure and function, including the coronary arteries, whereas cardiac MRI provides information on myocardial perfusion, viability, and fibrosis.

**6. Answer: A**

The DIG trial showed that digoxin use in patients with HFrEF in NSR does not reduce all-cause mortality but does reduce the risk of HF-related hospitalization In patients with a more severe HFrEF (e.g., LVEF less than 25% or NYHA functional class III or IV), a 40% or more reduction in HF-related mortality and hospitalization can be expected. However, this patient

has HFpEF, given his LVEF of 55%. In the Ancillary Digitalis Investigation Group trial, digoxin was not associated with any clinical benefit in patients with HFpEF. (Answer A is correct; Answers B, C, and D are incorrect)

**7. Answer: C**
Using the AHRQ Red, Yellow, and Green Zones tool, this patient, given his presenting signs and symptoms, is in the Red Zone, which suggests that he needs immediate assistance such as going to the emergency department or a physician's office (Answer C is correct; Answers A, B, and D are incorrect). The Red Zone is defined as a medical alert according to the following signs and symptoms: weight gain or loss of more than 2.3 kg (5 lb) in 1 week; severe swelling in feet ankles, legs, or abdomen; unrelieved SOB or severe breathing trouble; unrelieved chest pain; and need to sleep sitting straight up.

**8. Answer: C**
Pregabalin use in patients with HF has been associated with increased development of both peripheral edema and pulmonary edema, which is resistant to loop diuretics. The mechanism of the edema associated with pregabalin is believed to be similar to that of a dihydropyridine calcium channel blocker, which affects the microvascular system, leading to lower-extremity edema, making Answer C correct. In SADHART, sertraline was safe in patients with HFrEF for the treatment of depression (Answer A is incorrect). In PRAISE I and II, amlodipine had a neutral effect on mortality when added to GDMT (Answer B is incorrect). Although digoxin could potentially interact with colchicine, increasing the risk of myopathy, colchicine is being used as needed (Answer D is incorrect).

**9. Answer: A**
Indomethacin (Answer C) and ibuprofen (Answer D), which will relieve both pain and inflammation associated with gout, have been associated with an increase in HF exacerbations as the result of inhibition of renal-protective prostaglandins, leading to fluid retention. Oxycodone (Answer B) will relieve only the pain. However, because of the recent Centers for Disease Control and Prevention recommendations surrounding the use of opiates for long-term pain, an opiate would not be the best choice because of the potential for addiction. Prednisone (Answer A) is in fact the safest medication and will relieve both pain and inflammation without affecting protective prostaglandins. Data analyses for patients with HF and gout have even suggested an improvement in diuresis in patients who receive steroid bursts.

**10. Answer: B**
An FDA safety review found that type 2 DM medications containing saxagliptin and alogliptin may increase the risk of HF hospitalizations, particularly in patients who already have heart or kidney disease (Answer B is correct). As a result, the FDA has added new warnings to the drug labels regarding this safety issue. The FDA recently changed the package labeling for metformin to include its use in patients with stable HF with an eGFR greater than 30 mL/minute/1.73 $m^2$. Because this patient's eGFR is 46 mL/minute/1.73 $m^2$, metformin could be used safely (Answer A is incorrect). In EMPA-REG, empagliflozin reduced HF admission or CV death by 34% and HF admission by 35% in patients with type 2 DM and underlying CV disease; thus, this agent would be a good choice in this patient (Answer C is incorrect). Finally, liraglutide has not shown any major adverse cardiac events in large randomized controlled trials of patients with type 2 DM; hence, this drug could also be used safely (Answer D is incorrect).

**11. Answer: C**
According to data from the SHIFT trial, the ideal candidate for ivabradine would be a patient with HFrEF with NYHA functional classes II and III and a heart rate greater than 70 beats/minute who is taking maximally tolerated dose of a β-blocker and is in NSR. Answer C is correct because this patient matches each of these criteria. Answer A is incorrect because this patient has NYHA class I HF and HFpEF. Answer B is incorrect because the patient has a heart rate of 62 beats/minute on maximal doses of metoprolol succinate. Answer D is incorrect because the patient is NYHA class IV, and the patient's heart rate of 110 beats/minute was most likely caused by dobutamine.

# Decompensated Heart Failure

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**Learning Objectives**

1. Classify a patient with decompensated heart failure (HF) into a hemodynamic subset based on signs/symptoms, laboratory values, and hemodynamic measures obtained via pulmonary artery catheter (PAC) monitoring.
2. Design an initial pharmacotherapeutic treatment and monitoring plan for a patient with decompensated HF based on hemodynamic subset.
3. Devise a modified treatment and monitoring plan in a patient with decompensated HF and diuretic resistance.
4. Compare and contrast the use of intravenous (IV) vasodilators and positive inotropes in the treatment of decompensated HF, and among the agents within each drug class.
5. List strategies for reducing the risk of HF readmission among patients recovering from decompensated HF.

**Abbreviations in This Chapter**

| | |
|---|---|
| BNP | B-type natriuretic peptide |
| CO | Cardiac output |
| CI | Cardiac index |
| GDMT | Guideline-directed medical therapy |
| HF | Heart failure |
| HFrEF | Heart failure with reduced ejection fraction |
| HFpEF | Heart failure with preserved ejection fraction |
| NT-proBNP | N-terminal pro-B-type natriuretic peptide |
| PAC | Pulmonary artery catheter |
| PCWP | Pulmonary capillary wedge pressure |
| SGLT2 | Sodium-glucose cotransporter 2 |
| SV | Stroke volume |
| SVR | Systemic vascular resistance |
| UF | Ultrafiltration |
| WRF | Worsening renal function |

**Self-Assessment Questions**

*Answers to these questions can be found at the end of this chapter.*

*Questions 1-3 pertain to the following case.*

A 76-year-old man with a past medical history significant for ischemic cardiomyopathy (ejection fraction [EF 25%]), hypertension, and chronic kidney disease, presents to the cardiac intensive care unit with worsening dyspnea and 8-kg (17.6-lb) weight gain in the past 2 weeks after running out of his home medications. Previously he was taking aspirin 81 mg once daily, atorvastatin 40 mg once daily, lisinopril 20 mg once daily, metoprolol succinate 100 mg once daily, spironolactone 25 mg once daily, and furosemide 40 mg twice daily. His vital signs include a blood pressure of 118/68 mmHg and heart rate of 76 bpm. Laboratory values include sodium 136 mEq/L, potassium 4.8 mEq/L, SCr 1.9 mg/dL (baseline 1.5 mg/dL), N-terminal pro-B-type natriuretic peptide (NT-proBNP) 9600 pg/mL, AST 28 units/L, and ALT 32 units/L. Other pertinent findings include jugular venous pressure (JVP) of 12 cm. In the emergency department, he received a single bolus dose of intravenous furosemide 80 mg.

1. Which of the following is the most appropriate strategy for rapidly improving his congestive symptoms with furosemide?
   A. 40 mg intravenous twice daily.
   B. 80 mg intravenous twice daily.
   C. 2.5 mg/hour intravenous infusion.
   D. 12.5 mg/hour intravenous infusion.

2. Despite initial attempts at diuresis, the patient is only net negative 1 L over the next 24 hours. Which of the following would most effectively augment his diuresis?
   A. Metolazone 5 mg by mouth once daily.
   B. Hydrochlorothiazide 50 mg by mouth once daily.
   C. Spironolactone 100 mg by mouth once daily.
   D. Dopamine 2 mcg/kg/min intravenous infusion.

3. Because of the patient's poor response, the team places a pulmonary artery catheter (PAC), which reveals the following: pulmonary capillary wedge pressure (PCWP) 30 mmHg, cardiac index (CI) 1.8

L/min/$m^2$, and systemic vascular resistance (SVR) 2000 dyne·s/$cm^5$. His blood pressure is 102/60 mmHg. Which of the following is the most appropriate therapy to add?

A. Milrinone 0.5 mcg/kg/min intravenous infusion.
B. Dobutamine 3 mcg/kg/min intravenous infusion.
C. Sodium nitroprusside 0.2 mcg/kg/min.
D. Nitroglycerin 25 mcg/min infusion.

4. In the DOSE trial comparing diuretic strategies in patients with decompensated HF, patients received the treatment to which they were randomized for the first 48 hours. From 48 to 72 hours, clinicians were permitted to make adjustments (e.g., changing dose, adding thiazide-type diuretics) before measurement of end points at 72 hours. Some statistically significant differences emerged between the treatment arms; for example, patients in the intravenous bolus arm were twice as likely to receive a dose-increase compared with those in the continuous infusion arm. Which best describes the methodological problem these adjustments introduced to the study design?

A. Decreased external validity.
B. Decreased internal validity.
C. Publication bias.
D. Sampling bias.

*Questions 5-6 pertain to the following case.*
A 62-year-old man with ischemic cardiomyopathy (EF 30%) and hypertension presents with dyspnea and lower extremity edema. He admits to a 10-lb weight gain in the past 2 weeks since his primary care physician increased his carvedilol dose from 6.25 mg twice daily to 12.5 mg twice daily to improve blood pressure. Other medications include sacubitril/valsartan 49/51 mg twice daily, eplerenone 50 mg once daily, and furosemide 80 mg orally twice daily. On admission, blood pressure is 118/82 mmHg and heart rate is 88 bpm. Laboratory values include sodium 138 mEq/L, NT-proBNP 4400 pg/mL, and SCr 1.3 mg/dL (baseline). Other pertinent findings include crackles bilaterally at the bases, and 2+ bilateral lower extremity edema.

5. Which of the following is optimal for managing carvedilol at this time?

A. Increase dose to 25 mg twice daily.
B. Decrease dose to 6.25 mg twice daily.
C. Discontinue carvedilol.
D. Change carvedilol to metoprolol succinate 100 mg once daily.

6. Despite intravenous loop diuretics for several days, the patient's condition continues to deteriorate, and neurohormonal antagonists had to be discontinued. His most recent blood pressure was 92/56 mmHg and his heart rate was 86 bpm. The team decides to place a PAC, which reveals the following: PCWP 22 mmHg, CI 1.6 L/min/$m^2$, and SVR 920 dyne·s/$cm^5$. Which of the following is best to add at this time?

A. Dobutamine 2.5 mcg/kg/min infusion.
B. Sodium nitroprusside 0.2 mcg/kg/min infusion.
C. Dopamine 2 mcg/kg/min infusion.
D. Norepinephrine 0.05 mcg/kg/min infusion.

7. In the TACTICS-HF trial, a total of 257 patients with decompensated HF, were randomized within 24 hours to tolvaptan 30 mg/day (n=129) or placebo (n=128). At 72 hours, renal dysfunction was observed in 39 patients randomized to tolvaptan and 27 randomized to placebo (p=0.037). Which of the following best depicts how many patients on average needed to be exposed to tolvaptan to produce one case of renal dysfunction?

A. 1.
B. 9.
C. 11.
D. 14.

8. Which of the following best describes a metric used by the American Heart Association's Get with the Guidelines–Heart Failure program to recognize the quality of care provided to patients with heart failure with reduced ejection fraction?

A. Receiving an oral diuretic and rescue plan instructions at discharge.
B. Having a documented right heart catheterization during hospitalization.
C. Receiving an evidence-based β-blocker at discharge.
D. Enrollment in an interprofessional disease state management program.

## I. INTRODUCTION

A. Definitions and Terminology
   1. No precise definition exists for heart failure (HF) syndromes that warrant escalation of care (e.g., emergency department visit, hospitalization), and HF terminology has varied.
   2. Decompensated HF versus acute decompensated heart failure (ADHF)
      a. Historically, *ADHF* emerged as the predominant terminology for acute worsening of HF. However, this terminology has fallen out of favor because many patients have had chronic progressive worsening of HF rather than an acute inciting event. The 2021 Universal Definition and Classification of Heart Failure recommends referring to these patients as having "decompensated HF" to include patients with either acute or chronic progressive etiologies of deterioration. Even though *ADHF* is still prevalent/used interchangeably (including in the 2022 HF guidelines), the term *decompensated HF* is used throughout this chapter.
      b. Neither definition distinguishes between *de novo* HF and exacerbation of chronic HF.
      c. Characterized by clinically evident worsening of HF signs and symptoms
      d. Presents most commonly as congestion (vs. low output)
   3. Cardiogenic shock is a subset of decompensated HF characterized by acute reduction in cardiac output (CO) resulting in tissue hypoperfusion.

B. Epidemiology
   1. Second most common cause of hospitalization in the United States, after sepsis
   2. Mortality
      a. Hospitalization increases risk of mortality by 3-fold.
      b. Mortality rates at 30 days and 1 year after discharge are 10.4% and 22%, respectively.
      c. Mortality predictors include low systolic blood pressure and (SBP) renal dysfunction (i.e., elevated SCr and BUN), according to the Acute Decompensated Heart Failure National Registry (ADHERE).
   3. Costs of HF care
      a. Expected to increase to $69.8 billion ($244 per every U.S. adult) by 2030
      b. Hospitalization-related costs are the major driver of these cost increases.

C. Etiology and Pathophysiology
   1. A minority of hospitalizations for decompensated HF are caused by *de novo* HF or progression of left ventricular dysfunction to end-stage HF.
   2. Most admissions are an acute worsening of chronic HF (see the Chronic Heart Failure chapter for a comprehensive discussion of HF etiology).
   3. Exacerbations of HF with reduced EF (HFrEF) and HF with preserved EF (HFpEF) occur in about equal proportions.
   4. Pathophysiology is usually multifactorial, and may include one or more of the following:
      a. Volume accumulation
         i. As a result of compensatory neurohormonal activation in response to tissue hypoperfusion.
         ii. Increases in circulating blood volume normally increase preload and thus stroke volume (SV); however, because of the flattened Frank-Starling curve in HFrEF (Figure 1A) or decreased ventricular compliance in HFpEF (i.e., increased stiffness), increases in preload do not considerably improve SV.
      b. Decreased CO caused by decreased SV (↓CO = HR x ↓SV)
         i. Decreased contractility may result from injury to the myocardium, thereby decreasing SV.
         ii. Increased afterload may impair ventricular performance, thereby decreasing SV (Figure 1B). The primary driver of afterload is systemic vascular resistance (SVR).
         iii. Decreased SV resulting from low preload is rare in decompensated HF but can occur in the setting of over-diuresis.

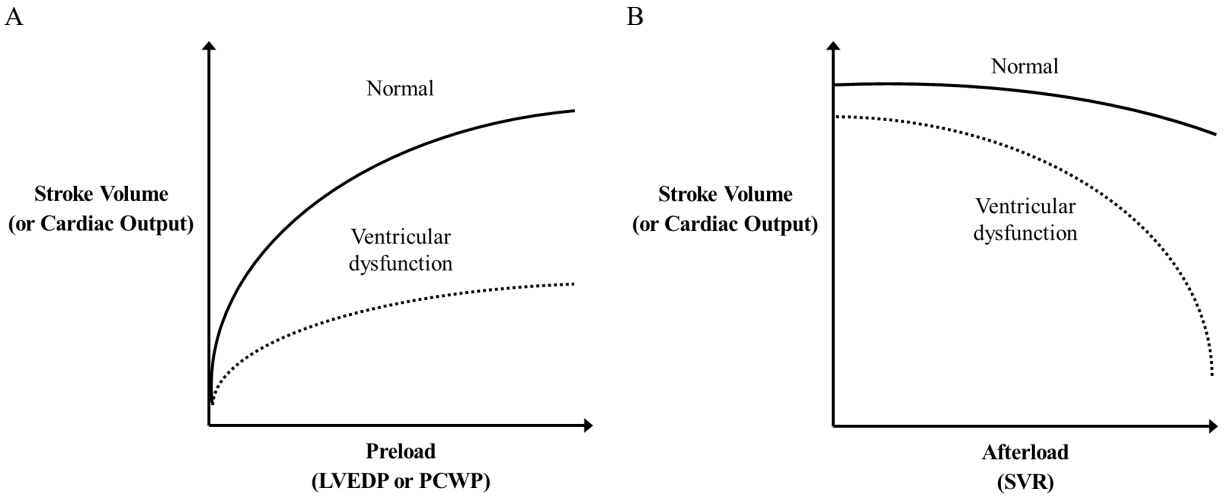


**Figure 1.** Differences in the relationship between stroke volume and preload (A) and afterload (B).
LVEDP = left ventricular end-diastolic pressure; PCWP = pulmonary capillary wedge pressure; SVR = systemic vascular resistance.

c. Decreased CO caused by decreased ventricular rate (↓CO = ↓HR x SV)
   i. May occur with bradyarrhythmias
   ii. *Rapid* ventricular rates (e.g., atrial fibrillation with rapid ventricular response, ventricular tachycardia) may also decrease CO but are caused by decreased diastolic filling time, which reduces SV.

5. Effects outlined in 4 a–c are often caused by one or more precipitating factors listed in Table 1.

**Table 1**. Precipitating Factors for Decompensated Heart Failure

| Factors | Examples |
|---|---|
| Nonadherence to medications or dietary restrictions | Diuretics, guideline-directed medical therapy, salt restriction |
| Acute cardiovascular events | Myocardial infarction, arrhythmias, pulmonary embolism |
| Negatively inotropic drugs | Diltiazem, verapamil; rapid β-blocker dose increase |
| Drugs that promote salt and water retention | Nonsteroidal anti-inflammatory drugs, corticosteroids |
| Endocrine abnormalities | Hyper- or hypothyroidism, diabetes mellitus |
| Alcohol or illicit drug use | Cocaine, amphetamines |

## II. CLINICAL EVALUATION

A. Hemodynamic Subsets
   1. Because decompensated HF management is directed at the suspected cause of decompensation, patients can be categorized into one of four hemodynamic subsets (Figure 2).
   2. Hemodynamic classification can often be made based on clinical presentation alone.
   3. Hemodynamic classification may require invasive hemodynamic monitoring with a pulmonary artery catheter (PAC, often called a *Swan-Ganz catheter*). Although no large randomized controlled trials have shown that PAC monitoring improves outcomes in decompensated HF, it may be considered in certain scenarios, such as in patients with:
      a. Hemodynamic status that cannot be ascertained based on initial evaluation
      b. Refractory symptoms despite initial therapy
      c. New or worsening end-organ dysfunction

d. Initiation/titration of intravenous vasodilator or inotropic therapy
e. Mixed shock syndromes (e.g., septic plus cardiogenic shock)
f. Evaluation for pulmonary arterial hypertension or advanced therapies, such as durable mechanical circulatory support (MCS) or heart transplantation

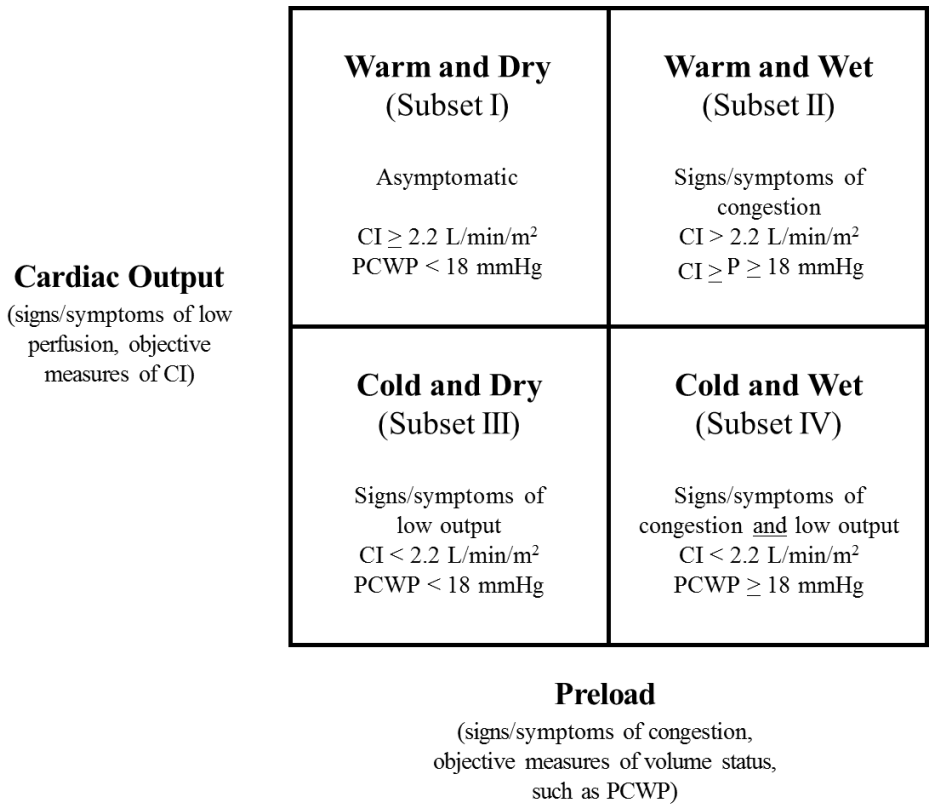


**Figure 2.** Classification of decompensated heart failure into hemodynamic subsets.
CI = cardiac index; PCWP = pulmonary capillary wedge pressure.

B. Signs and symptoms of decompensated HF are shown in Table 2.

**Table 2.** Signs and Symptoms of Decompensated Heart Failure: Congestion and Low Output

| Congestion | Low Output |
|---|---|
| Dyspnea on exertion or at rest | Altered mental status, somnolence |
| Orthopnea, bendopnea | Fatigue, poor exercise tolerance |
| Paroxysmal nocturnal dyspnea | Malaise |
| Crackles or rales on lung auscultation | Nausea/anorexia, cachexia |
| S3 gallop on chest auscultation | Narrow pulse pressure |
| Jugular venous distention, hepatojugular reflux | Cool extremities |
| Ascites, early satiety, hepatomegaly | Reduced urine output |
| Lower extremity edema | |

C. Laboratory Markers (key points are noted here; please see Chronic Heart Failure chapter for additional details)
   1. B-type natriuretic peptide (BNP) or N-terminal pro-B-type natriuretic peptide (NT-proBNP)
      a. Released by cardiac myocytes in response to stretch-related injury
      b. Primarily useful for excluding decompensated HF in the differential diagnosis of dyspnea when normal (less than 100 pg/mL and less than 300 pg/mL for BNP and NT-proBNP, respectively)
      c. Pre-discharge concentrations may be helpful for establishing post-discharge prognosis.
      d. May be elevated with older age, female sex, renal dysfunction, and other cardiopulmonary disorders (e.g., pulmonary embolism, pulmonary arterial hypertension)
      e. In patients receiving angiotensin receptor neprilysin inhibitor therapy, NT-proBNP may be easier to interpret than BNP.
   2. Additional laboratory evidence of congestion: hyponatremia, hemodilution (e.g., Hgb, Hct), impaired organ synthetic function (e.g., elevated INR, elevated SCr) caused by venous congestion (i.e., congestive hepatopathy or nephropathy)
   3. Evidence of impaired tissue perfusion: markers of end-organ function (e.g., elevated SCr, liver transaminases), elevated lactate, low mixed venous oxygen concentration.
   4. Laboratory tests to evaluate etiology and/or precipitating factors (e.g., troponin, thyroid function)

D. Imaging
   1. Echocardiogram: diagnosis of *de novo* HF or evaluation for the progression of chronic HF
   2. Chest radiograph: differential diagnosis of dyspnea and serially to monitor the course of decongestion
   3. Other imaging to assess HF etiology or evaluate precipitating factors (e.g., electrocardiogram, angiography, cardiac magnetic resonance imaging)

E. Invasive Hemodynamic Monitoring by PAC
   1. Hemodynamic values obtained by or used in conjunction with a PAC are shown in Table 3.
   2. Pulmonary capillary wedge pressure (PCWP)
      a. Represents left ventricular end-diastolic pressure in diastole, or preload (i.e., volume)
      b. Obtained by "wedging" the PAC in a small pulmonary vessel; if the PAC cannot be wedged, then a PA diastolic pressure is sometimes used as a substitute if it previously correlated with PCWP.
      c. Normal PCWP is 6–12 mmHg, but higher values (less than 18 mmHg) are permitted in HF because of the higher intraventricular pressures necessary to maximize CO (see Figure 1A).
   3. Cardiac output (usually normalized for body surface area as cardiac index [CI])
      a. Often represents contractility, but must be interpreted in context of PCWP (preload) and SVR (afterload) (see Figure 1)
      b. Measured by Fick or thermodilution methods.
         i. Fick method: calculated based on estimates of oxygen consumption and differences in arteriovenous oxygen concentrations
         ii. Thermodilution method: saline injection at a known temperature from a proximal port to determine temperature change at a distal port
         iii. Both methods have advantages and disadvantages; preferences often differ by clinician.
      c. A low CO does not necessarily indicate the presence of cardiogenic shock because end-organ function may be preserved at rest despite poor systolic function.
   4. Systemic vascular resistance (SVR)
      a. Represents the resistance to flow imparted by the systemic vasculature, or afterload.
      b. The equation for SVR is based on CO; errors in CO will result in an inaccurate SVR.

**Table 3.** Common Reference Ranges for Hemodynamic Values in Decompensated Heart Failure

| Parameter | Range |
|---|---|
| Central venous pressure (CVP, or right atrial pressure) | 2–6 mmHg |
| Pulmonary arterial pressure (PAP, systolic [PAS]/diastolic [PAD]) | 15–30 mmHg/5–15 mmHg |
| Mean pulmonary arterial pressure (mPAP) | 10–20 mmHg |
| Pulmonary vascular resistance (PVR) | 150–250 dyne · s/cm$^5$ |
| Pulmonary capillary wedge pressure (PCWP) | 6–12 mmHg |
| Cardiac output (CO) | 4–6 L/min |
| Cardiac index (CI) | 2.8–4.2 L/min/m$^2$ |
| Heart rate (HR) | 60–110 beats per minute |
| Mean arterial pressure (MAP) | 70–100 mmHg |
| Systemic arterial or blood pressure (systolic [SBP] / diastolic [DBP]) | 100–120 / 60–80 mmHg |
| Systemic vascular resistance (SVR) | 800–1200 dyne·s/cm$^5$ |

**Patient Cases**

*Questions 1 and 2 pertain to the following case.*

A 70-year-old woman with a history of nonischemic cardiomyopathy (EF 20%) presents with worsening dyspnea over the past several days. About 1 week ago, she was discharged from another facility after being newly diagnosed with atrial fibrillation. To control her heart rate, she was started on digoxin 125 mcg once daily and her metoprolol succinate was increased from 50 mg to 150 mg once daily. Her other medications include lisinopril 10 mg once daily, spironolactone 25 mg once daily, torsemide 40 mg once daily, and apixaban 5 mg twice daily. Vital signs include a blood pressure of 118/78 mmHg and a heart rate of 66 bpm. Laboratory values include sodium 138 mEq/L, potassium 4.2 mEq/L, SCr 1.4 mg/dL (baseline), AST 36 units/L, ALT 28 units/L, lactate 1.6 mmol/L, NT-proBNP 4200 pg/mL, and serum digoxin concentration of 0.9 ng/mL. Other findings include an S3 heart sound and crackles bilaterally to one-third the height of the lung fields.

1. Which of the following is the most likely precipitating factor for decompensated HF in this patient?
   A. Uncontrolled atrial fibrillation.
   B. Increased β-blocker dose.
   C. Nonadherence to diuretic therapy.
   D. Digoxin toxicity.

2. In which of the following hemodynamic subsets would this patient's illness best be classified?
   A. Subset I (warm and dry).
   B. Subset II (warm and wet).
   C. Subset III (cold and dry).
   D. Subset IV (cold and wet).

**Patient Cases** *(Cont'd)*

3. A 62-year-old man with a history of ischemic cardiomyopathy (EF 25%) presents to the cardiac intensive care unit with decompensated HF, and initial efforts to improve his symptoms are ineffective. The team decides to place a PAC and the following values are obtained: PCWP 28 mmHg, CI 1.8 L/min/$m^2$, and SVR 1800 dyne·s/$cm^5$. Based on these findings, which of the following is most likely to improve tissue perfusion?
   A. Decreasing preload.
   B. Increasing preload.
   C. Decreasing afterload.
   D. Increasing afterload.

## III. THERAPEUTIC GOALS

A. Address Precipitating Factor(s) for Decompensated HF (if able to be identified)

B. Relieve Signs and Symptoms of Congestion and/or Tissue Hypoperfusion

C. Restore Hemodynamic Stability

D. Reduce In-Hospital Morbidity (e.g., end-organ damage) and Mortality (Note: No decompensated HF pharmacologic therapies have individually been proven to improve survival.)

E. Minimize Risk for Rehospitalization.

F. Optimize Guideline-Directed Medical Therapy (GDMT) and Establish a Transition Care Plan.

## IV. SUMMARY OF TREATMENT APPROACHES

A. Address Precipitating Factors (see relevant chapters for the management of Acute Coronary Syndromes, Arrhythmias, and other conditions that may cause decompensated HF)

B. Evaluate GDMT Taken Before Admission (Table 4)
   1. Discontinuation of GDMT worsens outcomes, so GDMT should be continued during decompensated HF treatment if possible (e.g., B-CONVINCED trial).
   2. Considerations for GDMT discontinuation during decompensated HF treatment are listed in Table 5.
   3. Adherence to GDMT before hospitalization should be ascertained based on medication history and reconciliation because re-initiation (especially at high doses) during decompensated HF could compromise recovery.

**Table 4**. Recommendations for the Management of GDMT During Hospitalization

| Recommendation | Class | LOE |
|---|---|---|
| Continue GDMT during hospitalization (unless contraindicated) | 1 | B |
| Continue GDMT in hospitalized patients experiencing mild renal dysfunction and/or asymptomatic blood pressure reduction | 1 | B |

GDMT = guideline-directed medical therapy.

**Table 5**. Considerations for Holding or Discontinuing Guideline-Directed Medical Therapy During Decompensated HF

| Drug or Drug Class | Scenarios in Which Discontinuation May be Considered |
|---|---|
| ACE inhibitors, ARBs, ARNIs | Worsening renal function after recent drug initiation or increase, symptomatic hypotension, severe hyperkalemia ($K^+$ >5.5 mEq/L) |
| β-blockers | Decompensated HF caused by recent drug initiation or increase, evidence of new or worsening low output or cardiogenic shock, symptomatic hypotension or bradycardia |
| Aldosterone antagonists | Worsening renal function, severe hyperkalemia ($K^+$ >5.5 mEq/L) |
| SGLT2 inhibitors | Symptomatic hypotension, hypovolemia, or evidence of euglycemic ketoacidosis |
| Nitrates/hydralazine | Symptomatic hypotension |
| Ivabradine | Contraindicated in decompensated HF (per FDA label), other scenarios include blood pressure <90/50 mmHg, heart rate <60 bpm, atrial fibrillation, or anticipated use of strong CYP3A4 inhibitors |
| Digoxin | Symptomatic bradycardia, life-threatening arrhythmias, elevated serum concentrations (>1.0 ng/mL), or signs/symptoms of digoxin toxicity |
| Vericiguat | Symptomatic hypotension, planned nitrate initiation, or pregnancy |

ACE = angiotensin-converting enzyme; ARB = angiotensin II receptor blocker; ARNI = angiotensin receptor neprilysin inhibitor; HF = heart failure; SGLT2 = sodium glucose co-transporter 2.

C. Table 6 shows ACC/AHA recommendations for managing decompensated HF according to volume and perfusion status, with corresponding strengths for each recommendation and levels of evidence.

**Table 6**. Recommendations for Managing Decompensated HF Based on Hemodynamic Goal

| Hemodynamic Goal | Recommendation | Class | LOE |
|---|---|---|---|
| Decongestion | Administer intravenous loop diuretics | 1 | B |
| | Refractory symptoms: increase loop diuretic dose or add second diuretic (e.g., thiazide) | 2a | B |
| | Intravenous vasodilator (nitroglycerin or sodium nitroprusside) in absence of hypotension | 2b | B |
| | Ultrafiltration received a class IIb recommendation for decongestion in the 2013 guidelines, but because of variable efficacy and increased adverse events, it is no longer included in the 2022 recommendations | N/A | N/A |

**Table 6**. Recommendations for Managing Decompensated HF Based on Hemodynamic Goal *(Cont'd)*

| Hemodynamic Goal | Recommendation | Class | LOE |
|---|---|---|---|
| Perfusion | Intravenous vasodilators for low CO not addressed in guidelines but may be used over inotropes if low output and normal or elevated blood pressure; PAC monitoring to establish evidence of elevated SVR and guide therapy initiation/titration | N/A | N/A |
| | Cardiogenic shock: intravenous inotropes to maintain tissue perfusion as a temporizing measure | 1 | B |
| | Nondurable MCS may be used in patients with disease refractory to medical therapy[a] | 2a | B |
| | For cardiogenic shock, management by a multidisciplinary team is reasonable | 2a | B |
| | PAC monitoring may be considered to define hemodynamic subsets and management strategies | 2b | B |
| | Previous guidelines gave a class III harm recommendation for intravenous inotropes in absence of cardiogenic shock or low blood pressure and low CO caused by systolic dysfunction. While this is not specifically addressed in 2022 guidelines, inotropes are still not recommended in the absence of cardiogenic shock | N/A | N/A |

[a]See the chapter on Cardiac Transplantation and Mechanical Circulatory Support for more information.

CO = cardiac output; GDMT = guideline-directed medical therapy; HF = heart failure; LOE = level of evidence; MCS = mechanical circulatory support; N/A = not applicable; PAC = pulmonary artery catheter; SVR = systemic vascular resistance.

Information from: Heidenreich PA, Bozkurt B, Aguilar D, et al. 2022 AHA/ACC/HFSA guideline for the management of heart failure: a report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. Circulation 2022;145:e895-e1032.

## V. DIURETICS

A. Loop Diuretics
   1. Available agents (Table 7)
      a. Preference for intravenous furosemide versus bumetanide is institution-specific; differences between the two are usually of limited clinical significance when used at equipotent doses.
      b. Torsemide is not available as an intravenous formulation in the United States.
   2. Mechanism of benefit
      a. Facilitates diuresis by inhibiting sodium reabsorption in the ascending loop of Henle, with an onset of action of around 20–30 minutes after intravenous administration.
      b. Intracardiac pressures decrease within 5–15 minutes of intravenous administration, suggesting extra-renal mechanisms (i.e., functional venodilation) are involved.
   3. Dosing and administration
      a. Preferred route is intravenous administration because of more rapid onset of action and impaired absorption of oral therapy caused by abdominal edema and decreased GI perfusion.
      b. Initial doses of up to 2.5-fold the prior-to-admission dose may be considered (DOSE trial). Considerations for converting between diuretics and from oral to intravenous are provided in Table 7.
         i. Higher doses improve congestive symptoms sooner.
         ii. Higher doses increase the risk of transient WRF, but outcomes after transient WRF are no different than patients without WRF.

c. Because of a steep dose-response, an insufficient diuretic response should be treated by doubling the dose (to overcome the diuretic threshold) before increasing frequency.
d. Merits of intravenous bolus vs. continuous infusion administration remain controversial.
    i. No differences observed between the two methods compared in the DOSE trial, but the intravenous bolus group was twice as likely to receive a dose increase or addition of a thiazide-type diuretic.
    ii. Continuous infusions have been associated with improved diuresis end points (e.g., weight, urine output) in smaller studies and meta-analyses.
    iii. Increased WRF rates were observed with continuous infusion administration in patients with HFpEF (ROPA-DOP trial), but the study was underpowered and dosing details were not described.

4. Monitoring
    a. Efficacy: signs/symptoms of congestion, urine output, daily weights
    b. Toxicity: blood pressure, serum electrolytes (potassium, magnesium), SCr/BUN, ototoxicity (higher risk with furosemide than with bumetanide), musculoskeletal effects (higher risk with bumetanide than with furosemide)

**Table 7.** Diuretics Commonly Used in the Management of Decompensated Heart Failure[a]

| Characteristic | Furosemide | Bumetanide | Metolazone | Hydrochlorothiazide | Chlorothiazide |
|---|---|---|---|---|---|
| **Class** | Loop diuretic | Loop diuretic | Thiazide-type diuretic | Thiazide-type diuretic | Thiazide-type diuretic |
| **PO to IV Conversion** | 2:1 | 1:1 | N/A | N/A | Oral form not used in decompensated HF |
| **Dose Equivalence (IV)** | 20–40 mg | 1 mg | N/A | N/A | N/A |
| **Usual Intermittent Dose (Maximum)[b]** | 40–160 mg IV once to three times daily (200 mg/dose) | 0.5–4 mg IV once to three times daily (5 mg/dose) | 2.5–5 mg PO once daily (20 mg/day) | 25–50 mg PO once or twice daily (100 mg/day) | 0.5–1 g IV once or twice daily (2 g/day) |
| **Usual Continuous IV Infusion Dose (Maximum)[b]** | 5–20 mg/hr (40 mg/hr) | 0.5–2 mg/hr (4 mg/hr) | N/A | N/A | N/A |
| **Onset (Peak)** | 5–15 minutes IV (1–2 hr) | 2–3 minutes IV (1–2 hr) | 2–3 hr PO (6–8 hr) | 2 hr PO (4 hr) | 15 minutes IV (30 minutes) |
| **Duration of Action** | 4–6 hr | 4–6 hr | 12–24 hr | 5–15 hr | 6–12 hr |

[a]Torsemide is no longer available as an intravenous formulation. For reference, dose equivalency is torsemide 20 mg PO: furosemide 20–40 mg IV: furosemide 40–80 mg PO, and the duration of the torsemide effects is 18–24 hr. See the chapter on Chronic Heart Failure for additional information.

[b]Traditional loop diuretic maximums are increasingly being challenged by new literature. Small studies suggest that increasing doses beyond these maximums is both safe and effective. Further studies are needed.

IV = intravenous; N/A = not applicable; PO = per mouth.

Some information from: Rodgers JE, Reed BN. Acute decompensated heart failure. In: DiPiro JT, Talbert RL, Yee G, et al., eds. *Pharmacotherapy: A Pathophysiologic Approach*, 10th ed. New York: McGraw-Hill.

B. Diuretic Resistance
    1. Common in decompensated HF; no precise estimates of prevalence because of the lack of a consensus definition
    2. Mechanisms are often multifactorial; however, the etiology of diuretic resistance is most often intrarenal and should be managed as such (i.e., increasing loop doses, adding combination diuretic blockade).

The term *braking phenomenon* refers to the need to administer progressively higher doses of loop diuretic and not any one etiology in particular.

3. A useful framework for overcoming diuretic resistance can be derived from the stepped pharmacologic arm of the CARRESS-HF trial.
    a. Increase loop diuretic dose, change to continuous infusion, or add a thiazide-type diuretic.
    b. Place a PAC to guide therapy; consider ultrafiltration (UF) or temporary mechanical circulatory support.
    c. Vasopressin antagonists were not included in the CARRESS-HF trial, but therapy could be considered if severe hyponatremia limits escalation of diuretic therapy.
4. Thiazide-type diuretics
    a. Available agents are shown in Table 7.
        i. A recent randomized controlled trial in decompensated HF suggested oral metolazone was as effective and safe as intravenous chlorothiazide at a significantly lower cost.
        ii. Chlorothiazide appears to be superior to hydrochlorothiazide.
    b. Mechanism of benefit is to inhibit compensatory sodium reabsorption in the distal convoluted tubule (i.e., sequential nephron blockade).
    c. Monitoring is similar to loop diuretics except that the addition of a thiazide-type diuretic increases the risk of WRF and electrolyte abnormalities versus loop diuretic alone.
5. Carbonic anhydrase inhibitors
    a. Recent randomized controlled trial ADVOR showed improved decongestion and shorter length of stay when acetazolamide 500 mg intravenously daily was added to loop diuretics during admission for decompensated HF.
    b. Mechanism of benefit is inhibition of proximal tubular sodium reabsorption.
    c. Note that the population included was not indicative of patients with diuretic resistance (intravenous furosemide-equivalent doses greater than 80 mg/day excluded), and use of sodium-glucose cotransporter 2 (SGLT2) inhibitors was excluded.
    d. Use of acetazolamide appeared to be safe with no significant increase in adverse events.
6. Although high-dose aldosterone antagonists (e.g., spironolactone ≥100 mg/day) exert diuretic effects, their use has not been shown to improve outcomes in decompensated HF (ATHENA-HF).
7. Several additional strategies to overcome diuretic resistance, including SGLT2 inhibitors, hypertonic saline, chloride supplementation, and use of urine sodium as a measure of diuretic efficiency, are also being evaluated.

**Patient Case**

*Questions 4 and 5 pertain to the following case.*

A 58-year-old woman with a medical history of HFpEF (EF 55%) and hypertension presents to the emergency department with worsening dyspnea and lower extremity edema over the past several months. At home she takes amlodipine 10 mg once daily, candesartan 16 mg once daily, and furosemide 40 mg twice daily. On admission her vital signs include a blood pressure of 132/84 mmHg and a heart rate of 78 bpm. Laboratory values include sodium 142 mEq/L, potassium 4.4 mEq/L, SCr 1.2 mg/dL (baseline), and BNP 550 pg/mL. Other pertinent findings include crackles on auscultation and 2+ pitting edema bilaterally. Before being transferred from the emergency department, she received bumetanide 1 mg intravenous once.

4. Which of the following is the most appropriate initial management plan for this patient's decompensated HF?
    A. Nitroglycerin 50 mcg/min intravenous infusion.
    B. Torsemide 100 mg by mouth once daily.
    C. Bumetanide 4 mg/hour intravenous infusion.
    D. Furosemide 5 mg/hour intravenous infusion.

**Patient Case *(Cont'd)***

5. Despite being net-negative 2 L over the next 12 hours, her symptoms do not improve, and the team is considering adding a thiazide-type diuretic. Which of the following is the greatest advantage of oral metolazone over intravenous chlorothiazide in this setting?
   A. Greater efficacy.
   B. Greater safety.
   C. Longer duration of action.
   D. Faster onset of action.

## VI. VASODILATORS

A. Available Agents
   1. Nitroglycerin and sodium nitroprusside are the intravenous vasodilators used in decompensated HF (Table 8).

B. Mechanism of Benefit
   1. Vasodilators act as nitric oxide donors, increasing the synthesis of cyclic guanosine monophosphate in vascular smooth muscle; tolerance occurs sooner with nitroglycerin.
   2. Venous vasodilation (both nitroglycerin and sodium nitroprusside)
      a. Reduces preload by increasing venous capacitance
      b. Does not typically compromise SV/CO in HFrEF because of the flatter Frank-Starling curve (Figure 1A)
      c. Use with caution in HFpEF or restrictive physiologies (i.e., amyloid) given greater preload dependence
   3. Arterial vasodilation (primarily sodium nitroprusside)
      a. Reduces afterload by decreasing SVR, thereby improving left ventricular performance and increasing SV/CO
      b. Use with caution in HFpEF because reductions in afterload are not met with improved ventricular contraction as they are in HFrEF
   4. Support for intravenous vasodilators
      a. Vasodilators are safer than inotropes based on large retrospective registry data (ADHERE).
      b. Only nitroglycerin has been studied prospectively for decompensated HF, improving some but not all measures of congestion in the VMAC trial.
      c. Hemodynamic improvements for decompensated HF observed with sodium nitroprusside in retrospective study
      d. Several recent studies of nesiritide, ularitide, and serelaxin failed to demonstrate clinical benefit, although patient heterogeneity may have obscured effects (e.g., 20%–45% of trial patients had HFpEF).

C. Dosing and Administration (see Table 8)

D. Monitoring
   1. Both agents require the monitoring of blood pressure and heart rate; monitoring invasive hemodynamics by PAC should also be considered (especially for sodium nitroprusside).
   2. Initiation of sodium nitroprusside often requires admission to the intensive care unit and/or the placement of an arterial line for monitoring.

3. Although rare at the doses and durations typically used in decompensated HF (less than 3 mcg/kg/min for fewer than 3 days), patients receiving sodium nitroprusside should be monitored for cyanide and thiocyanate toxicity (e.g., altered mental status, metabolic acidosis, nausea/vomiting).
4. Monitoring of serum thiocyanate concentrations is commonly suggested but not routinely available, hepatic and renal function should be monitored to assess the risk of toxicity with sodium nitroprusside.

**Table 8.** Vasodilators in the Management of Decompensated Heart Failure

| Characteristic | Nitroglycerin | Sodium Nitroprusside |
|---|---|---|
| **Clinical effects** | ↓ PCWP because of venous vasodilation; systemic arterial vasodilation at higher doses (>100 mcg/min) resulting in ↓ SVR | ↓ PCWP and ↓ SVR because of venous and arterial vasodilation, respectively; ↑ SV/CO because of improved ventricular performance |
| **Dosing and titration (Maximum dose)** | 10–25 mcg/min titrated by 10–25 mcg/min every 10–20 minutes (200 mcg/min); tachyphylaxis occurs with prolonged use | 0.1–0.2 mcg/kg/min titrated by 0.1–0.2 mcg/kg/min every 10–20 minutes (3 mcg/kg/min); tachyphylaxis is less common but may occur with prolonged use |
| **Onset** | Immediate | Immediate |
| **Half-life** | 3 minutes | 2 minutes |
| **Metabolism and elimination** | Metabolized hepatically to inactive components, which are then eliminated renally | Conjugated with Hgb to release cyanide, which is hepatically metabolized to thiocyanate, which is then renally eliminated |

CO = cardiac output; PCWP = pulmonary capillary wedge pressure; SV = stroke volume; SVR = systemic vascular resistance.

Some information from: Rodgers JE, Reed BN. Acute decompensated heart failure. In: DiPiro JT, Talbert RL, Yee G, et al., eds. *Pharmacotherapy: A Pathophysiologic Approach*, 10th ed. New York: McGraw-Hill.

## VII. INOTROPES

A. Available Agents
   1. Dobutamine and milrinone are the two inotropes most commonly used in decompensated HF (Table 9).
   2. Alternatives in patients with mixed shock syndromes (e.g., elements of both cardiogenic and vasodilatory shock) include the combination of dobutamine and norepinephrine, or dopamine alone. α-Mediated vasoconstriction by norepinephrine or dopamine can prevent the worsening hypotension that may occur with inotropic therapy.
   3. Although digoxin exerts inotropic effects at higher serum concentrations, these effects do not predominate at the concentrations targeted since the late 1990s (less than 1 ng/mL).

B. Mechanism of Benefit
   1. Dobutamine and milrinone act by increasing intracellular concentrations of cyclic adenosine monophosphate in myocardial cells, which in turn increases the availability of calcium for contractility (i.e., enhanced SV/CO).
   2. Differences in the mechanisms of action of dobutamine and milrinone are described in Table 9.
   3. Of the two agents, only milrinone has been studied prospectively (OPTIME-CHF trial); it did not improve outcomes among a broad population of patients with decompensated HF (patients with cardiogenic shock were excluded) and increased the rate of tachycardia and hypotension.
   4. Compared with intravenous vasodilators, both agents increase the risk of arrhythmias and mortality.

5. A recent study randomizing dobutamine versus milrinone in patients with cardiogenic shock showed no difference in cardiovascular or renal outcomes between agents (DOREMI trial).
6. Preference for either agent often differs by clinician, with the exception of a few scenarios:
    a. Dobutamine is generally preferred in patients with hypotension given fewer vasodilatory effects compared with milrinone.
    b. Milrinone may be preferred when reductions in pulmonary vascular resistance are desired.
    c. The proposed advantage of milrinone over dobutamine in patients taking β-blockers before admission is overstated and may depend on the β-blocker being taken and the time since the last dose.
    d. Milrinone is not contraindicated in patients with renal dysfunction, but therapy should be initiated at lower doses and titrated more slowly to avoid the risk of accumulation (i.e., increased risk of hypotension and arrhythmias).
    e. Although some clinicians assert that a difference exists between the types of arrhythmias caused by dobutamine and milrinone (e.g., ventricular vs. atrial), this difference is not supported by evidence from the literature.

C. Dosing and Administration (see Table 9)

D. Monitoring
1. Blood pressure, heart rate, and ECG; invasive hemodynamics by PAC may also be considered.
2. Markers of end-organ function should be monitored to assess improvements in tissue perfusion.
3. Renal function should be monitored closely with milrinone because of the risk of accumulation.
4. Rarer adverse effects include thrombocytopenia with milrinone (less common than with its predecessor inamrinone) and eosinophilic reactions with dobutamine.

**Table 9.** Dobutamine and Milrinone in the Management of Decompensated Heart Failure

| Characteristic | Dobutamine | Milrinone |
|---|---|---|
| **Mechanism of action** | Acts as an agonist at β-1 adrenergic receptors in myocardial tissue;<br>at lower doses, acts as an agonist at β-2;<br>α-1 adrenergic activity at higher doses | Inhibits PDE-3 in myocardial and vascular smooth muscle cells, preventing degradation of intracellular cAMP[a] |
| **Clinical effects** | ↑ HR and ↑ CO because of β-1 effects<br>↓ SVR may occur as a reflexive response to ↑ CO or peripheral β-2 effects;<br>usually offset by peripheral α-1 effects<br>↓ PCWP and PVR (minor) | ↑ CO and ↓ SVR because of PDE-3 inhibition in myocardial and vascular smooth muscle cells, respectively<br>↑ HR (reflexive response to vasodilation)<br>↓ PCWP and PVR because of pulmonary artery vasodilation (more than dobutamine) |
| **Usual doses (Maximum dose)** | 2–10 mcg/kg/min (20 mcg/kg/min) | 0.125–0.5 mcg/kg/min (0.75 mcg/kg/min);<br>bolus avoided because of risk of hypotension |
| **Onset** | <10 minutes | 5–15 minutes |
| **Half–life** | 2 minutes | 2–4 hr; significantly longer with renal dysfunction |
| **Metabolism and elimination** | Metabolized by tissues/liver to inactive components, which are then eliminated renally | Primarily eliminated renally |

[a]Sometimes referred to as an *inodilator*.

cAMP = cyclic adenosine monophosphate; CO = cardiac output; HR = heart rate; PCWP = pulmonary capillary wedge pressure; PDE-3 = phosphodiesterase type 3; PVR = pulmonary vascular resistance; SV = stroke volume; SVR = systemic vascular resistance.

Some information from: Rodgers JE, Reed BN. Acute decompensated heart failure. In: DiPiro JT, Talbert RL, Yee G, et al., eds. *Pharmacotherapy: A Pathophysiologic Approach*, 10th ed. New York: McGraw-Hill.

## VIII. OTHER MODALITIES

A. Tolvaptan (vasopressin antagonists)
   1. No longer specifically addressed in any recommendations from the 2022 guideline update. May be considered in patients with severe or symptomatic hyponatremia, particularly if disease is refractory to reversal of potential causes and free water restriction
   2. Inhibits vasopressin-2 receptors, preventing reabsorption of free water in the cortical collecting ducts, which promotes aquaresis and increases serum sodium concentrations
   3. Only associated with improvements in serum sodium concentrations and some markers of congestion in decompensated HF (TACTICS-HF, EVEREST)
   4. Tolvaptan's effects on weight loss and urine output are similar to those of metolazone and chlorothiazide (3T trial). However, the high cost of tolvaptan combined with its lack of effect on other end points (e.g., length of stay, readmissions) has resulted in therapy being reserved primarily for severe or symptomatic hypervolemic hyponatremia.
   5. Should only be initiated in a hospital setting, where serum sodium can be monitored closely to avoid overly rapid correction of hyponatremia (less than 12 mEq within 24 hours recommended) and risk of osmotic demyelination syndrome (i.e., severe neurologic effects and death)
   6. Unlikely to be helpful in WRF and implicated in increased rates of WRF
   7. Dosing: 15 mg/day; after 24 hours or more, therapy may be increased to 30 mg/day (maximum 60 mg/day)
   8. Adverse effects: thirst, polyuria, fatigue, and transaminitis; risk of hepatotoxicity precludes its use beyond 30 days
   9. Avoid with strong CYP3A inhibitors or inducers

B. Ultrafiltration
   1. No longer specifically addressed in any recommendations from the 2022 guideline update, noting that many aspects require further investigation
   2. Method by which fluid is removed by hydrostatic pressure across a semipermeable membrane; electrolytes and toxins are not removed, in contrast to hemodialysis
   3. Proposed advantages over diuretic therapy are continuous and controlled fluid removal without affecting electrolytes
   4. Practical disadvantages include the need for peripheral vascular access, anticoagulation (usually with heparin) to avoid line thrombosis, and cost.
   5. Safe and efficacious alternative to diuretic therapy in the UNLOAD-HF trial; however, increased rates of renal failure and other complications were observed when UF was compared with stepped pharmacologic therapy in patients with decompensated HF and baseline renal dysfunction (CARRESS-HF trial)
   6. Studies to identify an ideal patient population for UF are ongoing
   7. Administration: up to 500 mL/hour of continuous fluid removal

C. SGLT2 Inhibitors
   1. Although most data for the use of SGLT2 inhibitors in HF are in the outpatient setting, data increasingly support the role of SGLT2 inhibitors during decompensation, and several studies remain under way.
   2. Initiation of SGLT2 inhibitors during hospitalization for decompensated HF appears safe and is associated with improvements in a composite of mortality, HF events, and symptoms at 90 days (EMPULSE, SOLOIST-WHF).
      a. EMPULSE randomized stabilized patients (defined as SBP of 100 mm Hg or greater and no symptoms of hypotension in the preceding 6 hours; no increase in intravenous diuretic dose or

vasodilators for 6 hours and no intravenous inotropes for 24 hours), regardless of EF, to empagliflozin or placebo on hospital days 2–5.

b. SOLOIST-WHF randomized clinically stable patients (defined as SBP of 100 mm Hg or greater without the need for oxygen, intravenous inotrope, or vasodilator therapy [excluding nitrates], and already transitioned to oral diuretics) to sotagliflozin or placebo during the peri-discharge period.

c. SGLT2 inhibitors did not increase the risk of serious adverse events, including ketoacidosis and acute renal failure.

3. The role of SGLT2 inhibitors in overcoming diuretic resistance has shown promise in several small trials. Further studies are underway.
4. Doses used in inpatient studies are similar to those used in chronic stable HF. See the Chronic Heart Failure chapter for more information on dosing, adverse effects, and monitoring.

**Patient Case**

A 62-year-old man is transferred to the cardiac intensive care unit at your facility after presenting to an outside hospital with decompensated HF. Despite receiving furosemide 120 mg intravenous once, followed by an infusion at 10 mg/hour, his symptoms persisted, and his blood pressure began to decrease. Vital signs now include a blood pressure of 92/58 mmHg and heart rate of 88 bpm. Before his arrival on the unit, a PAC was placed, revealing the following: PCWP 26 mmHg, CI 1.6 L/min/$m^2$, and SVR 880 dyne·s/$cm^5$. Laboratory values include sodium 132 mEq/L, potassium 5.2 mEq/L, SCr 2.0 mg/dL (up from 1.0 mg/dL at baseline), AST 67 units/mL, ALT 92 units/mL, and serum lactate 3.2 mmol/L. The patient's extremities are cool, but his mental status is appropriate.

6. Which of the following therapies is best to restore tissue perfusion in this patient?
   A. Dobutamine 3 mcg/kg/min intravenous infusion.
   B. Milrinone 0.375 mcg/kg/min intravenous infusion.
   C. Nitroglycerin 50 mcg/min intravenous infusion.
   D. Sodium nitroprusside 0.3 mcg/kg/min intravenous infusion.

7. Which of the following interventions is best to address this patient's volume status?
   A. Add tolvaptan 15 mg once daily, titrated to 60 mg/day.
   B. Administer bolus furosemide and increase infusion to 20 mg/hour.
   C. Initiate UF at 250 mL/hour of fluid removal.
   D. Hold diuretics and administer intravenous fluids.

## IX. TRANSITIONS OF CARE AND OTHER CONSIDERATIONS

A. As patients recover from decompensated HF, therapeutic goals shift to improving long-term morbidity and mortality and to reducing the risk of hospital readmission.

B. Strategies to Reduce HF Readmission (Table 10)

**Table 10**. Recommendations for the Optimization of GDMT During Hospitalization

| Recommendation | Class | LOE |
|---|---|---|
| Initiate GDMT in the hospital once clinical stability is achieved | 1 | B |
| If GDMT discontinuation is necessary, reinitiate and optimize as soon as possible | 1 | B |

GDMT = guideline-directed medical therapy.

1. Hospitalization is an ideal time to optimize GDMT, including reinitiation of previously held therapies if appropriate. Initiation of β-blocker before discharge increases the likelihood that patients will receive therapy later on.
2. The PIONEER-HF trial showed that angiotensin receptor-neprilysin inhibitor therapy is safe in patients with decompensated HF who are hemodynamically stable (defined as SBP of at least 100 mm Hg without increase in intravenous diuretic dose, no use of intravenous vasodilators during the preceding 6 hours, and no use of intravenous inotropes during the preceding 24 hours); however, patient access should be ensured before discharge.
3. Initiation of empagliflozin during hospitalization for decompensated HF appears safe and is associated with improved outcomes (EMPULSE, SOLOIST-WHF). In studies of patients with chronic heart failure, only a minority required adjustments to diuretic therapy following initiation of an SGLT2 inhibitor. However, volume status should still be assessed and monitored closely given the potential for natriuretic effects.
4. Intensive GDMT optimization starting before discharge and continued during follow-up has been associated with decreased readmissions and all-cause death with no increase in serious adverse events (STRONG-HF).
5. Data is conflicting on whether a trial of oral diuretic therapy prior to discharge decreases the risk of readmission. The largest study to date suggests this practice does not correlate with outpatient diuretic response and does not decrease readmissions.
6. Wireless pulmonary artery monitor to guide titration of outpatient therapy in high-risk patients
7. Pharmacist-provided patient education (with emphasis on adherence) before discharge and/or by telephone follow-up and other interprofessional interventions
8. Follow-up within 7-14 days of discharge

C. Measures to Evaluate Quality of Care
   1. Rates of 30-day HF readmissions are used by the Centers for Medicare & Medicaid Services (and many private health insurers) to determine reimbursement rates.
   2. The Joint Commission retired HF-related measures, but the American Heart Association (AHA) Get with the Guidelines Recognition Program retained them. Criteria are the percentage of patients:
      a. With documented assessment of left ventricular function before, during, or planned after discharge
      b. With documentation of left ventricular systolic dysfunction, defined as an EF less than 40%, who are prescribed an angiotensin-converting enzyme inhibitor or angiotensin II receptor blocker at discharge
      c. Who are prescribed an evidence-based β-blocker (bisoprolol, carvedilol, metoprolol succinate) at discharge
      d. For whom a follow-up appointment was scheduled
   3. Use of 30-day readmissions as a quality measure has been criticized, with recent data suggesting it could paradoxically increase mortality risk in some cases.

**Patient Case**

8. A 57-year-old man is hospitalized for decompensated HF (EF 30%). After several days of treatment with dobutamine and intravenous furosemide, he is now stabilized off inotropes and nearing discharge. Vital signs today include blood pressure 112/64 mm Hg and heart rate 88 beats/minute. Allergies include lisinopril (angioedema). Laboratory values include Na 135 mEq/L, K 4.2 mEq/L, and SCr 1.1 mg/dL (1.0 mg/dL baseline). On examination, the patient appears warm and well-perfused with trace edema. Which of the following interventions would be most appropriate before discharge to reduce the risk of readmission for HF?

   A. Continue intravenous diuresis until discharge.

   B. Initiate metoprolol succinate at target dose.

   C. Initiate empagliflozin 10 mg daily.

   D. Initiate sacubitril/valsartan 24/26 mg twice daily.

D. Table 11 summarizes landmark trials in decompensated HF.

**Table 11**. Summary of Select Landmark Trials in Decompensated HF

| Trial | Population | Key Findings |
|---|---|---|
| ADHERE - Vasoactive Medications (Abraham 2005) | Decompensated HF | Lower mortality with intravenous vasodilators (nesiritide[a], nitroglycerin) vs. intravenous inotropes (dobutamine, milrinone) |
| ADVOR (Mullens 2022) | Decompensated HF | Acetazolamide was associated with greater decongestion at discharge and shorter length of stay without increasing adverse events |
| ATHENA-HF (Butler 2017) | Decompensated HF | High-dose spironolactone (100 mg) in patients on spironolactone before admission did not improve NT-proBNP or congestion vs. usual care |
| CARRESS-HF (Bart 2012) | Decompensated HF with renal dysfunction | Ultrafiltration increased WRF rates and adverse events vs. stepped pharmacologic therapy (diuretics, vasodilators, inotropes) |
| DAD-HF II (Triposkiadis 2014) | Decompensated HF | Addition of dopamine (5 mcg/kg/min) to low-dose furosemide not associated with any benefits vs. high-dose or low-dose furosemide alone |
| DOREMI (Mathew 2021) | Cardiogenic shock | No difference in cardiovascular or renal outcomes between dobutamine and milrinone. Similar incidence of arrhythmias between agents |
| DOSE (Felker 2011) | Decompensated HF | High-dose furosemide (2.5-times home dose) improved signs/symptoms of congestion vs. low-dose furosemide (arithmetically equivalent to the oral home dose) but with slight increase in risk of WRF; no differences between intravenous bolus and continuous infusion administration. |
| EMPULSE (Voors 2022) | Decompensated HF (once stabilized) | Initiation of empagliflozin during hospitalization for decompensated HF improves outcomes without increasing adverse events |
| OPTIME-CHF (Felker 2003) | Decompensated HF without cardiac shock | Addition of milrinone: did not improve outcomes; increased rate of adverse events (hypotension, tachycardia) |
| ROSE (Chen 2013) | Decompensated HF with renal dysfunction | Neither low-dose dopamine (2 mcg/kg/min) nor low-dose nesiritide[a] (0.05 mcg/kg/min) improved signs/symptoms of congestion or renal function vs. placebo |

**Table 11**. Summary of Select Landmark Trials in Decompensated HF *(Cont'd)*

| Trial | Population | Key Findings |
|---|---|---|
| TACTICS-HF (Felker 2017) | Decompensated HF | Tolvaptan increased weight loss and fluid loss vs. usual care but did not improve dyspnea; rates of WRF also higher with tolvaptan |
| VMAC (Publication Committee for the VMAC Investigators 2002) | Decompensated HF | Nesiritide[a] and nitroglycerin improved dyspnea vs. placebo; nesiritide[a] associated with greater hemodynamic benefits vs. nitroglycerin |

[a]Nesiritide was discontinued by the manufacturer in February 2018.

HF = heart failure; NT-proBNP = n-terminal-B-type natriuretic peptide; WRF = worsening renal function.

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## ANSWERS AND EXPLANATIONS TO PATIENT CASES

**1. Answer: B**

In patients with HFrEF, β-blocker therapy should not be doubled sooner than every 2 weeks, even in those with concomitant conditions (e.g., arrhythmias, angina). Because this patient's metoprolol succinate was tripled in a very short time span, the increased dose is the most likely precipitating factor for her decompensated HF (Answer B). Given the patient's heart rate (much lower than the lenient rate control goal in atrial fibrillation of resting HR lower than 110 bpm and also lower than the strict goal of less than 80 bpm), it is unlikely that this presentation is a worsening of atrial fibrillation (making Answer A incorrect). Although nonadherence to diuretic therapy is a common precipitating factor for decompensated HF, this patient shows no evidence of nonadherence (making Answer C incorrect). Answer D is incorrect because the patient's serum digoxin concentration is less than 1 ng/mL and she does not have any classic symptoms of digoxin toxicity.

**2. Answer: B**

The patient's presenting concern is dyspnea and she has several other findings suggestive of volume overload, including an elevated NT-proBNP, S3 heart sound, and crackles bilaterally, making Answers A and C incorrect. Although rapidly increasing β-blocker therapy could provoke a low output state, multiple data points, including an adequate blood pressure and end-organ function (normal SCr, AST, ALT) and a normal serum lactate, suggest normal output for this patient (also making Answer D incorrect). Because she has evidence of volume overload but not low output, Answer B is the correct answer.

**3. Answer: C**

Although this patient's preload is elevated (as evidenced by a high PCWP), decreasing preload would improve signs and symptoms of congestion but not tissue perfusion, making Answer A incorrect. Answer B is incorrect because of the flatness of the Frank-Starling curve in HFrEF (i.e., increases in preload at the higher ends of left ventricular end-diastolic pressure do not appreciably improve CI). Answer D is incorrect because the patient's afterload is already high, and increasing it further would lead to further decrements in CI. Answer C is correct because reducing afterload will reduce the force against which the left ventricle must work, thereby improving CI.

**4. Answer: D**

Loop diuretics are the drugs of choice for congestive symptoms in ADHF, making Answer A incorrect. Although nitroglycerin could be considered as adjunct therapy for refractory congestive symptoms in HFrEF, it should be used with caution in patients with HFpEF because of greater preload-dependence. Answer B is incorrect because intravenous diuretics are preferred for initial therapy because of impaired GI absorption (likely gut edema in this patient because she does not have HFrEF). Although intravenous bumetanide would be an appropriate choice, a continuous infusion at 4 mg/hour would far exceed the increases in dose from prior-to-admission diuretics that were shown to be safe in the DOSE trial (Answer C is incorrect). Furosemide 5 mg/hour is an appropriate increase from her prior-to-admission dose, and either intravenous bolus or continuous infusion administration are acceptable, making Answer D correct.

**5. Answer: C**

Small studies in decompensated HF have demonstrated comparable efficacy and safety between oral metolazone and intravenous chlorothiazide, but no studies exist to show that metolazone is superior in either regard (Answers A and B are incorrect). Metolazone has a duration of action of up to 24 hours or longer in patients with decompensated HF, whereas the effects of chlorothiazide generally only last 6–12 hours, making Answer C the correct answer. Because metolazone is administered orally and undergoes erratic absorption in decompensated HF, it has a slower onset of action compared with intravenous chlorothiazide, making Answer D incorrect.

**6. Answer: A**

This patient has evidence of low CO, in addition to a low-normal SVR (also a low systemic blood pressure), suggesting that vasodilators would not be helpful (Answers C and D incorrect). Although nitroglycerin may have negligible effects on arterial blood pressure at lower doses, it will not improve CO. Between the two inotropes, dobutamine is the best choice (Answer A) because it improves contractility without exerting a significant effect on blood pressure. Milrinone is not absolutely contraindicated; however, the high initial dose and the risk of accumulation given the patient's WRF makes Answer B a less safe choice because milrinone could further lower blood pressure.

**7. Answer: B**

Because the patient has only mild asymptomatic hyponatremia and WRF, initiating tolvaptan is not appropriate (Answer A is incorrect). Although the patient has WRF, the PCWP is elevated and the CI is low, indicating that renal dysfunction is likely caused by low output rather than hypovolemia (Answer D is incorrect). Higher doses of furosemide will be necessary to achieve the diuretic threshold, and several trials have shown that transient WRF with high-dose diuretics does not confer poor long-term outcomes (Answer B is correct). Answer C is incorrect based on the CARRESS trial, which showed that UF can worsen pre-existing renal dysfunction in decompensated HF, especially in patients requiring vasoactive therapies.

**8. Answer: C**

Several strategies can be implemented before discharge to reduce the risk of HF readmissions, and the consensus guidelines emphasize hospitalization as an ideal time to optimize guideline-directed medical therapy. While data is conflicting on whether observing patients for 24 hours on oral diuretics prior to discharge is associated with decreased readmissions, continuing IV diuretics up until discharge has not been associated with improved outcomes. Regardless, a diuretic regimen that includes a plan for adjustments should be established prior to discharge (Answer A is incorrect). Although initiating β-blockers before discharge is associated with greater long-term β-blocker use, these agents should be reinitiated at a low dose and titrated carefully to avoid decompensation (Answer B is incorrect). Initiation of SGLT2 inhibitors before discharge has been associated with decreased hospitalizations (Answer C is correct). Although the PIONEER study showed safety with inpatient initiation of sacubitril/valsartan, it is contraindicated in this patient because of his angioedema with lisinopril (Answer D is incorrect).

## ANSWERS AND EXPLANATIONS TO SELF-ASSESSMENT QUESTIONS

**1. Answer: B**

The DOSE trial demonstrated that intravenous loop diuretic doses of up to 2.5 times the oral dose being taken before admission improve symptoms sooner than lower doses. In addition, it showed that administration as an intravenous bolus or continuous infusion was equally efficacious. Because the patient was taking furosemide 40 mg twice daily at home, up to 100 mg intravenous twice daily or up to an 8 mg/hour infusion would be an appropriate initial strategy (Answer B is correct). Although the regimens in Answers A and C are safe to administer based on the DOSE trial, symptom resolution would be less rapid. Answer D is incorrect because the total daily dose (12.5 mg/hour or 300 mg/day) is 3.75 times the patient's home dose, thereby exceeding the dose-increases shown to be safe in the DOSE trial.

**2. Answer: A**

Although both Answers A and B are thiazide-type diuretics, the patient is less likely to respond to hydrochlorothiazide given his worsening renal function (Answer B incorrect). Metolazone is less dependent on renal function and would likely retain its diuretic effects (Answer A correct). In a recent trial, high-dose spironolactone failed to improve congestion in patients with decompensated HF, making Answer C incorrect. Finally, Answer D is incorrect based on the failure of low-dose dopamine to improve outcomes in several clinical trials (DAD II, ROSE, ROPA-DOP trials).

**3. Answer: C**

Although the patient's CI is low, this decrease in ventricular performance is likely a result of high SVR. Consequently, the most appropriate strategy in this case is to reduce afterload with the use of an intravenous vasodilator rather than place the patient at an increased risk of arrhythmias and in-hospital mortality with an intravenous inotrope (Answers A and B incorrect). Of the two vasodilator options, sodium nitroprusside is the better choice because it is a venous and arterial vasodilator even at low doses, whereas nitroglycerin only causes venous vasodilation at the dose listed (making Answer D incorrect).

**4. Answer: B**

Answer B is correct because *internal validity* refers to how well a trial minimizes confounding. Because clinicians were permitted to make changes to therapy, this approach may have confounded differences in the safety and efficacy of the treatment arms and thus decreased internal validity. Answer A is incorrect because making adjustments to diuretic therapy based on a patient's response resembles clinical practice; although this approach may have impacted the ability to demonstrate a difference between treatment arms, it is more generalizable and thus represents increased external validity. Even though the results in the DOSE trial were mostly equivocal, it was still published in a prominent journal, thus Answer C is incorrect. Finally, Answer D is incorrect because the ability for clinicians to alter treatment at 48 hours did not affect which patients were enrolled in the study.

**5. Answer: B**

Because the recent increase in carvedilol is likely to have precipitated this patient's decompensated HF, the dose should be decreased (Answer B is correct). Even though the patient's heart rate is elevated, increasing the dose of carvedilol would likely worsen this patient's decompensated HF, making Answer A incorrect. Answer C is incorrect because there is no evidence of cardiogenic shock or other contraindications to β-blocker therapy, and discontinuation during a hospitalization is associated with worse outcomes. Answer D is incorrect because metoprolol succinate 100 mg is comparable to his current therapy and is unlikely to ameliorate his symptoms.

**6. Answer: A**

Because the patient's CI is low, and SVR is within normal range, a positive inotrope (dobutamine; Answer A is correct) should be selected rather than an intravenous vasodilator (Answer B is incorrect). Although dopamine has positive inotropic effects, these effects are minimal at a dose of 2 mcg/kg/min, making Answer C incorrect. Norepinephrine also exerts some positive inotropic effects but these are counterbalanced by increases in afterload, which may worsen left ventricular performance (Answer D is incorrect).

**7. Answer: C**

The answer to this question requires calculation of the number needed to harm (NNH). The absolute risk of renal dysfunction was 39/129 or 0.302 in the tolvaptan arm and 27/128 or 0.211 in the placebo arm, resulting in an absolute risk increase of 0.302–0.211=0.091. The NNH is 1/absolute risk increase, or 1/0.091=10.989, which rounds up to 11 patients, making Answer C correct and all the other options incorrect.

**8. Answer: C**

Although the Joint Commission retired its HF-related measures, several of these measures are still used by the American Heart Association's Get with the Guidelines program. One such measure is a prescription for an evidence-based β-blocker (bisoprolol, carvedilol, or metoprolol succinate) at discharge in patients with HFrEF. Although providing patients with rescue plan instructions is described in practice guidelines, these instructions are not formally recognized by the program (Answer A is incorrect). A right heart catheterization during admission is not a recognized quality measure (Answer B is incorrect). Finally, despite growing data that interprofessional disease state management can improve outcomes, it is not yet recognized as a quality measure, making Answer D incorrect.

# Heart Transplant and Mechanical Circulatory Support

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**Learning Objectives**

1. Evaluate levels of risk in the heart transplant candidate.
2. Derive rational peri- and postoperative rejection mitigation strategies in heart transplant recipients.
3. Devise effective thromboprophylactic strategies for patients receiving percutaneous ventricular assist device support.
4. Construct safe and effective drug therapy regimens for patients receiving extracorporeal membrane oxygenation support.
5. Design effective treatment plans for patients with complications of durable left ventricular assist device therapy.

**Abbreviations in This Chapter**

| | |
|---|---|
| ACR | Acute cellular rejection |
| ACT | Activated clotting time |
| AMR | Antibody-mediated rejection |
| aPTT | Activated partial thromboplastin time |
| CAV | Cardiac allograft vasculopathy |
| CF-LVAD | Continuous-flow left ventricular assist device |
| CMV | Cytomegalovirus |
| CNI | Calcineurin inhibitor |
| cPRA | Calculated panel reactive antibody |
| DSA | Donor-specific antibody |
| ECMO | Extracorporeal membrane oxygenation |
| EMB | Endomyocardial biopsy |
| GIB | Gastrointestinal bleeding |
| HF | Heart failure |
| HT | Heart transplantation |
| IABP | Intra-aortic balloon pump |
| IVIg | Intravenous immunoglobulin |
| LV | Left ventricle/ventricular |
| LVAD | Left ventricular assist device |
| MCS | Mechanical circulatory support |
| mTOR | Mammalian target of rapamycin |
| PCWP | Pulmonary capillary wedge pressure |
| rATG | Rabbit antithymocyte globulin |
| RV | Right ventricle/ventricular |
| TTE | Transthoracic echocardiography |
| UFH | Unfractionated heparin |

**Self-Assessment Questions**

*Answers and explanations to these questions can be found at the end of this chapter.*

*Questions 1 and 2 pertain to the following case.*

A.S. is a 64-year-old woman who presents for her annual follow-up 4 years after heart transplantation (HT). She feels well and has no complaints. She has developed posttransplant diabetes, hypertension, and chronic kidney disease from cyclosporine. Other than an elevated baseline serum creatinine (SCr) (1.6 mg/dL), her laboratory test results are within normal limits. Her surveillance biopsy reveals moderate-rejection (2R) acute cellular rejection (ACR). An echocardiogram reveals a normal ejection fraction (55%), and she has no signs of heart failure (HF) or graft dysfunction. Her pertinent medications are cyclosporine 125 mg twice daily (goal trough 50–100 ng/mL), pravastatin 10 mg/day, mycophenolate mofetil 500 mg twice daily, aspirin 81 mg/day, insulin glargine 32 units/day, and amlodipine 2.5 mg/day.

1. Which recommendation is most appropriate for managing this patient's cellular rejection?
   A. Prednisone 50 mg by mouth twice daily for 5 days as outpatient therapy.
   B. Admit to hospital; methylprednisolone 1000 mg intravenously per day for 3 days.
   C. Admit to hospital; antithymocyte globulin 1.5 mg/kg intravenously per day for 5 days.
   D. Admit to hospital; intravenous immunoglobulin (IVIg) 500 mg/kg intravenously per day for 4 days.

2. Which change to the patient's background immunosuppression would be most appropriate, given the acute episode of cellular rejection?
   A. Change cyclosporine to tacrolimus.
   B. Change cyclosporine to everolimus.
   C. Change mycophenolate mofetil to everolimus.
   D. Resume chronic steroid therapy and continue current regimen.

3. A 32-year-old man who underwent HT 6 months ago presents with increasing shortness of breath and fatigue over the past few weeks. On echocardiography, his ejection fraction has decreased to 30%

from a previous baseline of 55%. His biopsy results show 3R ACR. Which treatment regimen would be best for this patient?

A. Prednisone 50 mg by mouth twice daily for 5 days as outpatient therapy.

B. Admit to hospital; methylprednisolone 1000 mg intravenously/day for 3 days.

C. Admit to hospital; antithymocyte globulin 1.5 mg/kg intravenously/day for 5 days.

D. Admit to hospital; IVIg 500 mg/kg intravenously/day for 4 days.

4. A 65-year-old man with a history of ischemic dilated cardiomyopathy is now postoperative day 5 from a HeartMate 3 implantation. Surgical hemostasis has been achieved, and the patient is therapeutically anticoagulated with intravenous heparin. Which is the most appropriate thromboprophylactic strategy to recommend for this patient?

A. Aspirin 325 mg/day, warfarin with international normalized ratio (INR) goal 2.0–3.0.

B. Aspirin 325 mg/day, warfarin with INR goal 2.0–2.5.

C. Aspirin 81 mg/day, warfarin with INR goal 2.0–2.5.

D. Aspirin 81 mg/day, warfarin with INR goal 2.0–3.0.

5. A 24-year-old woman with a history of peripartum cardiomyopathy after HeartMate 3 left ventricular assist device (LVAD) implantation 4 months ago is readmitted to the hospital with pulmonary edema and severe fatigue. Her laboratory studies are notable for an elevated SCr (1.6 mg/dL, previously 0.8 mg/dL), an INR of 2.8, and a serum lactate dehydrogenase of 4285 IU/L (normal less than 250 IU/L). Her blood pressure is stable; however, her flow and power readings on the device are elevated. A CT reveals an outflow graft obstruction/thrombosis. Which suggested treatment plan would be most appropriate for this patient?

A. Surgical device exchange.

B. Intravenous alteplase.

C. Intravenous heparin.

D. Intravenous milrinone.

*Questions 6 and 7 pertain to the following case.*

M.M. is a 66-year-old woman who presents for her 6-month posttransplant clinic visit and endomyocardial biopsy (EMB). She feels tired, and her exercise tolerance is decreasing. She has posttransplant hypertension and chronic kidney disease (SCr 1.8 mg/dL). Her two children are her caregivers. Calculated panel reactive antibody (cPRA) at transplantation was 43%. Transthoracic echocardiography (TTE) at the time of EMB reveals a left ventricular ejection fraction (LVEF) of 40%. She has never had rejection that required treatment posttransplantation, and she is adherent to her medication. Her pertinent medications are tacrolimus 6 mg twice daily (goal trough 10–12 ng/mL), pravastatin 20 mg at bedtime, mycophenolate mofetil 500 mg twice daily, ramipril 5 mg twice daily, prednisone 5 mg/day, valganciclovir 450 mg day, clotrimazole troche 1 lozenge three times daily, and sulfamethoxazole/trimethoprim 1 single-strength tablet/day.

6. Which type of rejection is most likely on the differential?

A. ACR.

B. Antibody-mediated rejection (AMR).

C. Cardiac allograft vasculopathy (CAV).

D. ACR, AMR, and CAV.

7. Which diagnostic test would be best to request next to further delineate this rejection event?

A. AlloMap.

B. Luminex donor-specific antibody (DSA).

C. Intravascular ultrasound.

D. Cardiac magnetic resonance imaging.

8. A 34-year-old African American man presents with hereditary nonischemic dilated cardiomyopathy with TITIN-mutation. He was successfully bridged to transplantation with a HeartMate 3 LVAD in place for 1.2 years. He is sensitized with a cPRA of 45% but has an HLA-compatible deceased donor. His donor was procured in standard fashion for bicaval transplantation using UW-based cold preservation. Which is the most appropriate induction

immunosuppression approach for this patient?

A. No induction.
B. Basiliximab.
C. Antithymocyte globulin.
D. Alemtuzumab.

## I. INTRODUCTION TO ADVANCED HEART FAILURE

A. Criteria for Advanced HF
   1. Despite advances in pharmacotherapy, HF remains a leading cause of morbidity and mortality in the United States and around the world.
   2. Advanced HF (i.e., stage D) has about a 90% 1-year mortality rate without HT or continuous-flow left ventricular assist device (CF-LVAD) implantation.
   3. No single test or laboratory value can identify patients with advanced HF.
   4. The European Society of Cardiology has created a list of objective criteria to recognize patients with advanced HF (Box 1).

**Box 1.** European Society of Cardiology Definition of Advanced HF

All of the following criteria must be present despite optimal guideline-directed treatment:
1. Severe and persistent symptoms of HF (NYHA class III or IV)
2. Severe cardiac dysfunction as defined by a reduced LVEF < 30%, isolated RV failure, non-operable severe valve abnormalities, congenital abnormalities, persistently high (or increasing) BNP or NT-proBNP values, or data of severe diastolic dysfunction or LV structural abnormalities
3. Episodes of pulmonary or systemic congestion requiring high-dose intravenous diuretics, episodes of low output requiring inotropes or vasoactive drugs, or malignant arrhythmias causing > 1 unplanned visit or hospitalization in 12 mo
4. Severe impairment of exercise capacity with inability to exercise or low 6-min walking distance test (< 300 m) or $Pvo_2$ (< 12–14 mL/kg/min) estimated to be of cardiac origin

BNP = B-type natriuretic peptide; HF = heart failure; LV = left ventricle/ventricular; LVEF = left ventricular ejection fraction; NT-proBNP = N-terminal pro-B-type natriuretic peptide; NYHA = New York Heart Association; $Pvo_2$ = peak oxygen consumption; RV = right ventricle/ventricular.

Information from: Crespo-Leiro MG, Metra M, Lund LH, et al. Advanced heart failure: a position statement of the Heart Failure Association of the European Society of Cardiology. Eur J Heart Fail 2018;20:1505-35.

B. Candidacy for Advanced Therapies
   1. Evaluation process is complex and incorporates an assessment of other organ function, patient adherence to therapies to date, caregiver support, and financial stability, among other considerations.
   2. Various guidelines suggest criteria for selecting candidates for HT and CF-LVAD implantation (Table 1).
   3. Ultimately, individual centers construct their own selection criteria according to factors like patient volume and tolerance for higher-risk patients.
   4. Table 1 contains examples of common inclusion and exclusion criteria for both HT and durable LVAD.
      a. Prohibiting conditions common to both options:
         i. Limited life expectancy (for reasons other than HF)
         ii. Severe pulmonary disease
         iii. Cerebrovascular accident with deficit
      b. Others are uniquely exclusive:
         i. Severe right ventricular (RV) failure would preclude CF-LVAD but not HT.
         ii. Fixed pulmonary artery hypertension would prevent HT but not CF-LVAD implantation.
   5. Candidacy is dynamic, depending on the progression or resolution of comorbid conditions.
      a. Patients listed for HT can decompensate while awaiting a donor, which may necessitate:
         i. Use of mechanical support as a bridge-to-transplantation
         ii. Removal from the waiting list
      b. Patients initially under mechanical circulatory support (MCS) as destination therapy may later become candidates for HT.
      c. All patients with advanced HF should be referred to palliative care.

**Table 1.** Indications and Contraindications for HT and Durable LVAD Therapy

| | Heart Transplantation | Durable LVAD |
|---|---|---|
| Indications | • Cardiogenic shock requiring continuous inotropic support or temporary MCS<br>• Persistent NYHA class IV HF symptoms refractory to maximal medical therapy (LVEF < 20%; peak oxygen consumption < 12 mL/kg/min)<br>• Intractable angina not amenable to revascularization<br>• Intractable arrhythmias | • NYHA class IV HF symptoms<br>• LVEF < 25%<br>• Failure to respond to optimal medical management<br>• Inability to wean from temporary mechanical circulatory support or inotrope therapy |
| Contraindications | • Systemic illness with life expectancy < 2 yr (malignancy, AIDS, lupus)<br>• COPD with $FEV_1$ < 1 L/min<br>• Clinically severe cerebrovascular disease<br>• Fixed pulmonary artery hypertension (e.g., PVR > 3 Wood units)<br>• Renal dysfunction with eGFR < 30 mL/min/1.73 $m^2$[a]<br>• Age > 70[a]<br>• Active infection (not LVAD related)[a]<br>• Peptic ulcer disease[a]<br>• Diabetes with end-organ damage (e.g., neuropathy) or poor glycemic control (hemoglobin A1C [A1C] > 7.5%)[a]<br>• Peripheral vascular disease[a]<br>• Morbid obesity (BMI > 35 kg/$m^2$)[a]<br>• Active mental illness or dementia[a]<br>• Inadequate social support[a]<br>• Drug or tobacco use within 6 mo<br>• HIT within 100 days[a]<br>• Poor adherence to drug regimen or lifestyle changes<br>• Financial constraints<br>• Severe extracardiac amyloid organ dysfunction | • Morbid obesity[a]<br>• Small body habitus (BSA < 1.5 $m^2$)[a]<br>• CKD[a]<br>• Mild-moderate hepatic dysfunction[a]<br>• Malnutrition[a]<br>• Sepsis or active infection<br>• Severe right HF<br>• Severe carotid artery disease<br>• Severe COPD<br>• Severe CVA with deficit<br>• Hemodialysis<br>• Persistent coagulopathy<br>• Non-cardiac illness with limited life expectancy<br>• HF expected to recover without durable LVAD |

[a]Denotes a relative contraindication.

BMI = body mass index; BSA = body surface area; CKD = chronic kidney disease; COPD = chronic obstructive pulmonary disease; CVA = cerebrovascular accident; eGFR = estimated glomerular filtration rate; $FEV_1$ = forced expiratory volume in 1 second; HF = heart failure; HIT = heparin-induced thrombocytopenia; HT = heart transplantation; IABP = intra-aortic balloon pump; LVAD = left ventricular assist device; LVEF = left ventricular ejection fraction; MCS = mechanical circulatory support; NYHA = New York Heart Association; PVR = pulmonary vascular resistance.

Adapted from: Owens AT, Jessup M. Should left ventricular assist device be standard of care for patients with refractory heart failure who are not transplantation candidates? Left ventricular assist devices should not be standard of care for transplantation-ineligible patients. Circulation 2012;126:3088-94.

## II. HEART TRANSPLANTATION

A. Pretransplant Sensitization Management
   1. See the antibody-mediated rejection (AMR) section for antibody testing options.
   2. Patients should be screened for anti-HLA when they are evaluated for transplantation. If anti-HLA antibodies are present, the patient is sensitized to non–self-antigens.
   3. Parous females should be considered sensitized regardless of whether anti-HLA antibodies are detectable at the time of evaluation.
   4. Patients who are sensitized should undergo solid phase antibody (i.e., Luminex) testing to identify the specific binding epitopes for crossmatching.
   5. Sensitization may be represented by the % cPRA.
      a. cPRA is inversely proportional to the likelihood of finding a suitable donor in the donor pool (e.g., a patient with a cPRA of 72% would have around 28% of the donor pool available).
      b. cPRA may be calculated many ways. In general, centers use cPRA to manage their tolerance of risk and either include all known anti-HLA antibodies the recipient has or only the antibodies that the center is unwilling to accept at the time of transplantation. These thresholds are unique to every center and every program.
      c. cPRA calculator: https://optn.transplant.hrsa.gov/resources/allocation-calculators/cpra-calculator/
   6. If the patient has a very high cPRA and several unacceptable antigens, select experienced centers may try antibody desensitization using therapies that would be typical of treatment for AMR (see AMR section). Desensitization is associated with shorter wait times in sensitized patients without a decrement in 1-year survival after HT at experienced centers.

Information from: Kobashigawa J, Colvin M, Potena L, et al. The management of antibodies in heart transplantation: an ISHLT consensus document. J Heart Lung Transplant 2018;37:537-47.

B. Perioperative Care of the Donor and Recipient
   1. HT donor management
      a. Full donor management guidelines are beyond the scope of this chapter.
      b. HT donors should receive intravenous thyroxine resuscitation to minimize RV failure if the cause of death is in the central nervous system.
      c. HT donors should be managed by experienced personnel at the organ procurement organization to minimize toxic exposure to high-dose catecholamines.
      d. Donor hearts should be preserved using one of three preservation solutions: UW, Celsior, or HTK.
         i. Outcomes are superior when preserved with UW over Celsior solution in large database analyses. HTK also is associated with improved outcomes over Celsior solution.
         ii. UW is a high-potassium formula that may result in increased atrioventricular nodal dysfunction and prolonged need for intracardiac pacing or chronotropic support.
   2. Antimicrobial prophylaxis for sternal infections in the HT recipient
      a. *Staphylococcus* spp. are the major pathogens of concern.
         i. In the absence of trials of antimicrobial prophylaxis specifically in HT recipients, agents used should be similar to those used for other general cardiac procedures.
         ii. Cefazolin 2 g intravenously once 30 minutes before median sternotomy and 2 g intravenously every 8 hours (or renally adjusted equivalent) for 24–48 hours post-closure of the mediastinum
         iii. Vancomycin 15 mg/kg intravenously once 30 minutes before median sternotomy and 15 mg/kg intravenously as renally adjusted continuing for 24–48 hours post-closure of the mediastinum should be used if methicillin-resistant *Staphylococcus aureus* represents several infections in the operating room and/or intensive care unit (ICU) where the HT recipient will be cared for.

b. Additional coverage is not necessary for gram-negative, anaerobic, or fungal infections in routine patient care.
    i. Individualization may be necessary at specific centers according to local antibiograms.
    ii. Caution should be used against unnecessarily broad or long-duration antimicrobial prophylaxis regimens. Increasing antimicrobial pressure in specific environments increases the resistance patterns of pathogens.
c. Patients with infected MCS devices should be covered for the known pathogens growing on the driveline and/or pump pocket for a full course once the device is explanted. The explanted device should be sent for full microbiological examination, including the driveline.

3. Anticoagulation reversal and hemostasis
    a. Warfarin/other anticoagulants should be fully reversed before transplantation.
        i. Warfarin: Vitamin K 5–10 mg intravenously plus prothrombin complex concentrates (PCCs; 4 factor: Kcentra) are preferred for rapid and sustained reversal. Fresh frozen plasma can be considered as an alternative when PCCs are not available.
        ii. Others:
            (a) Limited data suggest that dabigatran can safely be reversed with idarucizumab at the time of transplantation. However, continue with caution with this strategy, given the limited data.
            (b) No data exist for the reversal of anti–factor Xa (anti-Xa) inhibitor therapy with andexanet alfa at the time of HT. Recommend to transition listed patients from an anti-Xa inhibitor to either warfarin (preferred) or dabigatran (alternative) when transplantation is approaching.
4. Vasoactive support in the HT recipient
    a. Euvolemia should be maintained posttransplantation. Hypervolemia can cause stress to the RV free wall.
    b. Inotropic support should be used to maintain adequate heart rate and contractility, particularly if the donor heart was preserved with a high-potassium formula such as UW solution. Options include:
        i. Dobutamine 5–10 mcg/kg/minute
        ii. Dopamine 5–15 mcg/kg/minute
        iii. Epinephrine 0.01–0.1 mcg/kg/minute
        iv. Milrinone 0.375–0.75 mcg/kg/minute
    c. α-Agonists may be used to maintain adequate mean arterial pressure. Options include:
        i. Norepinephrine 0.01–0.1 mcg/kg/minute
        ii. Dopamine 5–15 mcg/kg/minute
        iii. Epinephrine 0.01–0.1 mcg/kg/minute
    d. Vasopressin or methylene blue may be added to α-agonists in the setting of postoperative vasoplegia. The 2023 guidelines recommend that when used, patients should only receive a single dose of methylene blue as salvage therapy.
    e. Angiotensin II has not been studied in heart transplant recipients, but based on the safety and efficacy data in nontransplant patients, it could be considered rescue therapy for those with refractory posttransplant vasoplegia according to the 2023 guidelines.

C. Rejection Surveillance
1. TTE
    a. TTE should be performed routinely to assess alterations in left ventricular (LV) function.
    b. At minimum, TTE should be performed with each biopsy or Non-invasive surveillance during the first posttransplant year; perhaps more commonly at programs that use biopsy infrequently.
    c. TTE should be performed every 3–6 months after the first year to evaluate allograft function and if the patient presents with new-onset HF symptoms.

2. EMB
    a. Protocol EMB should be performed for at least 1 year posttransplantation (Box 2); many programs continue to perform EMB past the first year at every 4–6 months for up to 5 years. However, a growing number of programs are reducing the number of post-transplant biopsies in favor of non-invasive strategies for rejection surveillance (see numbers 3 and 4 below).
    b. Loss of allograft function on TTE or new-onset HF symptoms should prompt for-cause EMB to evaluate for the presence of rejection.
    c. Minimum of three fragments of myocardium fixed in paraffin are required for adequate evaluation; ideally, one frozen fragment with myocardium.
    d. Routine hematoxylin and eosin (H&E) stain on the paraffin-fixed sections, together with one frozen piece for immunofluorescence.

**Box 2.** Example EMB Schedule for the First Posttransplant Year

| | |
|---|---|
| Biopsy 1, 2, 3, 4, and 5: | Weekly |
| Biopsy 6, 7, and 8: | Every 14 days |
| Biopsy 9 and 10: | Every 3 wk |
| Biopsy 11, 12, and 13: | Every 4 wk |
| Subsequent biopsies during first year after HT: | Every 5–6 wk |

EMB = endomyocardial biopsy; HT = heart transplantation.

Information from: Velleca A, Shullo MA, Dhital K, et al. The International Society for Heart and Lung Transplantation (ISHLT) guidelines for the care of heart transplant recipients.J Heart Lung Transplant 2023. In press. doi: 10.1016/j.healun.2022.09.023

3. Gene expression profiling (AlloMap)
    a. Evaluates expression levels of 11 genes to distinguish the absence of cellular rejection
    b. Excellent negative predictive value (99.6%) but poor positive predictive value for cellular rejection
    c. Reasonable replacement for EMB in most patients during the 6-month to 5-year period. AlloMap should not be the sole method of ACR surveillance during the first 6 posttransplant months.
    d. If AlloMap is 34 or less, high confidence that 2R or greater ACR would be absent on EMB
    e. If AlloMap is greater than 34, unclear confidence that ACR would or would not be absent on EMB; thus, EMB should be performed to rule out ACR
    f. GEP can only be used after day 55 post-transplant.
4. Donor-derived cell-free DNA (AlloSure)
    a. Donor DNA can be detected and quantified in the recipient serum in the setting of allograft injury (i.e., rejection).
    b. Measured as a percent donor-derived cell-free DNA (%ddcfDNA)
    c. Can detect both cellular and humoral rejection
    d. A 0.25% ddcfDNA threshold has a negative predictive value for acute rejection of 99% and has been shown to safely eliminate 81% of routine protocol biopsies after HT (Circulation 2021;143:1184-97).

Information from: Pham MX, Moayedi Y, Foroutan F, Miller RJH, et al. Risk evaluation using gene expression screening to monitor for acute cellular rejection in heart transplant recipients. J Heart Lung Transplant 2019;38:51-8.

D. Classification of Rejection
    1. Acute cellular rejection (ACR)
        a. Posttransplant surveillance for ACR – Histological evidence: Routine H&E for perivascular lymphocytes and myocyte damage/dropout: Perform on every protocol or for-cause EMB.
        b. Diagnosis and nomenclature (Table 2)

**Table 2.** ISHLT Classification of ACR

| Current Classification (2004) | Previous Classification (1990) | Criteria |
|---|---|---|
| Grade 0 | Grade 0 | No rejection |
| Grade 1R | Grade 1A, 1B, and 2 | Mild – Interstitial and/or perivascular infiltrate with up to one focus of myocyte damage |
| Grade 2R | Grade 3A | Moderate – Two or more foci of infiltrate with associated myocardial damage |
| Grade 3R | Grade 3B and 4 | Severe – Diffuse infiltrate with multifocal myocyte damage, with or without edema, hemorrhage, or vasculitis |

ACR = acute cellular rejection; ISHLT = International Society for Heart & Lung Transplantation.

Information from: Stewart S, Winters GL, Fishbein MC, et al. Revision of the 1990 working formulation for the standardization of nomenclature in the diagnosis of heart rejection. J Heart Lung Transplant 2005;24:1710-20.

2. Antibody-mediated rejection (AMR)
    a. Posttransplant surveillance for AMR
        i. Histological evidence: Immunofluorescence on frozen tissue is preferred to immunoperoxidase on paraffin-fixed tissue.
            (a) Perform on for-cause EMB when rejection is suspected.
            (b) Suggested minimum schedule: 2 weeks; 1, 3, 6, and 12 months
        ii. Donor-specific antibody (DSA): Solid-phase, single-antigen bead assay (e.g., Luminex) methods preferred for detecting circulating antibody. Suggested minimum schedule: 2 weeks, 1, 3, 6, and 12 months; then annually and for-cause
    b. Diagnosis is multifactorial (Table 3).

**Table 3.** AHA and ISHLT AMR Diagnostic Criteria

| Required Findings (1–4) | | Optional Findings |
|---|---|---|
| 1. Clinical evidence of acute graft dysfunction | | |
| 2. Histological evidence of acute capillary injury (a and b) | a. Capillary endothelial changes<br>b. Capillary macrophages | c. Capillary neutrophilia<br>d. Interstitial edema |
| 3. Immunopathological evidence for antibody-mediated injury (a or b or c) | a. IgG/IgM/IgA C3d or C4d or C1q by immunofluorescence<br>b. CD68 plus C4d by immunohistochemistry<br>c. Fibrin in vessels | |
| 4. Serological evidence of DSA | | Anti-HLA class I or class II antibodies at the time of biopsy |

AHA = American Heart Association; AMR = antibody-mediated rejection; anti-HLA = anti-human leukocyte antibody; CD68 = cluster of differentiation 68; C1q = complement component 1q; DSA = donor-specific antibody; Ig = immunoglobulin.

Information from: Colvin MM, Cook JL, Chang P, et al. Antibody-mediated rejection in cardiac transplantation: emerging knowledge in diagnosis and management: a scientific statement from the American Heart Association. Circulation 2015;131:1608-39.

c. Nomenclature (Table 4)

**Table 4.** ISHLT Pathological AMR Classification

| Category | Description |
|---|---|
| pAMR 0 | Negative histological and immunopathological studies |
| pAMR 1 (H+) | Histological AMR alone: Histological findings present but immunopathological findings absent |
| pAMR 1 (I+) | Immunopathological AMR alone: Immunopathological findings present but histological findings absent |
| pAMR 2 | Pathological AMR: Both histology and immunopathology positive |
| pAMR 3 | Severe pathological AMR: Severe AMR with histology positive for interstitial hemorrhage, capillary fragmentation, mixed inflammatory infiltrates, endothelial cell pyknosis and/or karyorrhexis, marked edema |

pAMR = pathologic antibody-mediated rejection.

Information from: Berry GJ, Angelini A, Burke MM, et al. The ISHLT working formulation for pathologic diagnosis of antibody-mediated rejection in heart transplantation: evolution and current status. J Heart Lung Transplant 2011;30:601-11; Colvin MM, Cook JL, Chang P, et al. Antibody-mediated rejection in cardiac transplantation: emerging knowledge in diagnosis and management: a scientific statement from the American Heart Association. Circulation 2015;131:1608-39..

d. Clinical manifestations occur in four stages (Table 5).

**Table 5.** Clinical Stages of AMR

| Category | Description |
|---|---|
| Subclinical | DSA present, no pathological evidence of graft injury or dysfunction |
| Preclinical | DSA present, pathological evidence of graft injury, no evidence of graft dysfunction, no symptoms |
| Acute clinical | DSA present, pathological evidence of graft injury, graft dysfunction, may or may not have symptoms |
| Chronic disease | CAV, chronic graft dysfunction, restrictive cardiac physiology |

CAV = cardiac allograft vasculopathy.

Information from: Colvin MM, Cook JL, Chang P, et al. Antibody-mediated rejection in cardiac transplantation: emerging knowledge in diagnosis and management: a scientific statement from the American Heart Association. Circulation 2015;131:1608-39; Berry GJ, Angelini A, Burke MM, et al. The ISHLT working formulation for pathologic diagnosis of antibody-mediated rejection in heart transplantation: evolution and current status. J Heart Lung Transplant 2011;30:601-11.

3. Cardiac allograft vasculopathy (CAV)
   a. 50% of cardiac transplant recipients have clinically significant CAV by 10 years posttransplantation.
   b. Associated with significant reductions in allograft function and poor survival
   c. Typically irreversible, but stability is possible
   d. Diagnostic criteria are based on coronary angiography (Table 6).
   e. Intravascular ultrasound is more sensitive and specific for early lesion detection by assessing the relative increase in the coronary artery neointima from "baseline," which typically is assessed 1–3 months posttransplantation.
   f. CAV characterized by:
      i. Type A lesion: Discrete, tubular, or multiple stenoses (atypical for CAV)
      ii. Type B1 lesion: Abrupt onset with distal diffuse concentric narrowing and obliterated vessels (typical for CAV)

iii. Type B2 lesion: Gradual, concentric tapering with distal portion having some residual lumen
iv. Type C lesion: Narrowed irregular distal branches with terminations that are often non-tapered and squared off, ending abruptly

**Table 6.** ISHLT CAV Nomenclature

| CAV Grade | Description |
|---|---|
| CAV 0 (not significant): | No detectable angiographic lesion |
| CAV 1 (mild): | Angiographic LM < 50%, or primary vessel with maximum lesion of < 70%, or any branch stenosis < 70% (including diffuse narrowing) without allograft dysfunction |
| CAV 2 (moderate): | Angiographic LM ≥ 50%; a single primary vessel ≥ 70%, or isolated branch stenosis ≥ 70% in branches of two systems, without allograft dysfunction |
| CAV 3 (severe): | Angiographic LM ≥ 50%, or two or more primary vessels ≥ 70% stenosis, or isolated branch stenosis ≥ 70% in all three systems; or CAV 1 or CAV 2 with allograft dysfunction (defined as LVEF ≤ 45% usually in the presence of regional wall motion abnormalities) or evidence of significant restrictive physiology |

LM = left main.

Information from: Velleca A, Shullo MA, Dhital K, et al. The International Society for Heart and Lung Transplantation (ISHLT) guidelines for the care of heart transplant recipients.J Heart Lung Transplant 2023. In press. doi: 10.1016/j.healun.2022.09.023.

g. Primary vessel denotes the proximal and middle 33% of the left anterior descending artery, the left circumflex, and the ramus and the dominant or codominant right coronary artery with the posterior descending and posterolateral branches.
h. Secondary branch vessel includes the distal 33% of the primary vessels or any segment within a large septal perforator, diagonals and obtuse marginal branches, or any portion of a non-dominant right coronary artery.
i. Restrictive cardiac allograft physiology is defined as symptomatic HF with echocardiographic E to A velocity ratio greater than 2, shortened isovolumetric relaxation time (less than 60 milliseconds), shortened deceleration time (less than 150 milliseconds), or restrictive hemodynamic values (right atrial pressure greater than 12 mm Hg, pulmonary capillary wedge pressure greater than 25 mm Hg, cardiac index less than 2 L/minute/$m^2$).

Information from: Velleca A, Shullo MA, Dhital K, et al. The International Society for Heart and Lung Transplantation (ISHLT) guidelines for the care of heart transplant recipients.J Heart Lung Transplant 2023. In press. doi: 10.1016/j.healun.2022.09.023

E. Immunomodulation/Rejection Prophylaxis
1. Induction immunotherapy
a. More than 50% of transplant centers use induction agents at the time of transplantation. (Figure 1)
b. Two types in the United States:
i. Lymphodepleting (antithymocyte globulin, alemtuzumab): Product most commonly used in the United States: Rabbit antithymocyte globulin (Thymoglobulin, rATG)
(a) Significant adverse drug reactions
(1) Common: Leukopenia, thrombocytopenia, infusion-site reaction
(2) Uncommon: Serum sickness – Can be fatal if missed, opportunistic infections, anaphylaxis
ii. Nondepleting interleukin-2 receptor antagonist (basiliximab): Minimal adverse drug reactions
c. Goals:
i. Decrease ACR events over the first 6 posttransplant months
ii. Delay calcineurin inhibitor (CNI) initiation in patients at high risk of perioperative acute kidney injury

iii. Induction provides no survival advantage over lack of induction. May improve 1-year survival in high-risk patients with preformed DSAs

d. Induction immunotherapy is usually reserved for patients with high immunologic risk features, such those with pretransplant donor-specific antibodies, sensitization, and multiparous females.

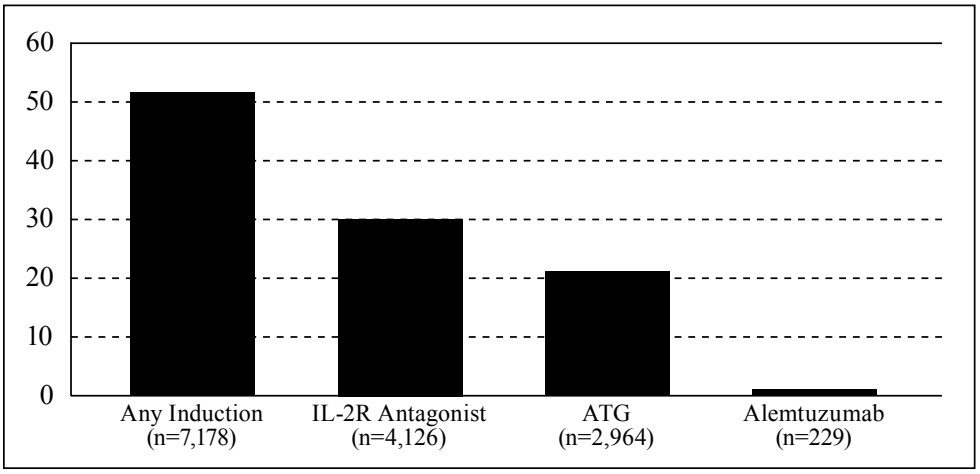


**Figure 1.** Percent induction immunosuppression use, January 2009 – June 2015.

ATG = antithymocyte globulin; IL-2R = interleukin-2 receptor.

Information from: Lund LH, Edwards LB, Kucheryavaya AY, et al. The Registry of the International Society of Heart and Lung Transplantation: Thirty-third Official Adult Heart Transplantation Report – 2016; Focus Theme: Primary Diagnostic Indications for Transplant. J Heart Lung Transplant 2016;35:1158-69; Velleca A, Shullo MA, Dhital K, et al. The International Society for Heart and Lung Transplantation (ISHLT) guidelines for the care of heart transplant recipients.J Heart Lung Transplant 2023. In press. doi: 10.1016/j.healun.2022.09.023. Printed with permission from ISHLT.

2. Maintenance immunotherapy
   a. Most transplant centers use CNI-based triple immunosuppression for the first year post-HT (Figure 2).
   b. Over 90% of patients will receive tacrolimus and either mycophenolate mofetil or mycophenolate acid (Table 7).
      i. Cyclosporine use is now infrequent (higher risk of cellular rejection than tacrolimus).
      ii. Azathioprine use is also rare (associated with more adverse effects and cellular rejection than mycophenolate mofetil/mycophenolate acid).
   c. Steroid use remains common during the first year after HT.
   d. Immunotherapy shifts after the first year.
      i. Less frequent use of steroids:
         (a) Aim is to minimize long-term toxicities associated with these medications.
         (b) Most HT recipients can be weaned off steroids by 1 year if no rejection episodes occur. However, patients with low immunologic risk profiles can be weaned off steroids sooner (e.g., within 3 months).
      ii. Incorporation of mammalian target of rapamycin (mTOR) inhibitors
         (a) Can be used to reduce or eliminate CNI exposure in the setting of declining renal function
         (b) Also used to slow progression of CAV, either de novo (i.e., early after transplant) or as salvage therapy once CAV has already manifested
   e. HT recipients are usually maintained long term on one of three regimens:
      i. CNI plus mycophenolate mofetil/mycophenolate acid (around 67%)
      ii. CNI plus mTOR (around 8%)
      iii. mTOR plus mycophenolate mofetil/mycophenolate acid (around 5%)

f. Patient-specific factors generally dictate the choice of long-term regimen (Table 8).
g. Patients undergoing HT should be screened for contraindications to mTOR inhibitors before starting these therapies.
    i. Unhealed wounds or recent surgery
    ii. Uncontrolled hypertriglyceridemia
    iii. Proteinuria (e.g., greater than 800 mg/day)
    iv. Recent rejection (either cellular or humoral in past 6 months)
    v. Anemia or leukopenia
h. Various strategies for changing agents have been described (Table 9).
i. Goal trough regimens for CNI and mTOR inhibitors should be individualized according to the patient's condition.
    i. Higher trough goals for CNI early after transplantation and after an episode of rejection
    ii. Lower trough goals after the first year to reduce toxicity (e.g., renal injury) (Table 7)
    iii. Lower both CNI and mTOR inhibitor trough goals when using these drugs classes in combination (Table 8)
    iv. Higher mTOR trough goals when used with mycophenolate mofetil/mycophenolate acid (e.g., CNI-sparing regimen – Table 8)

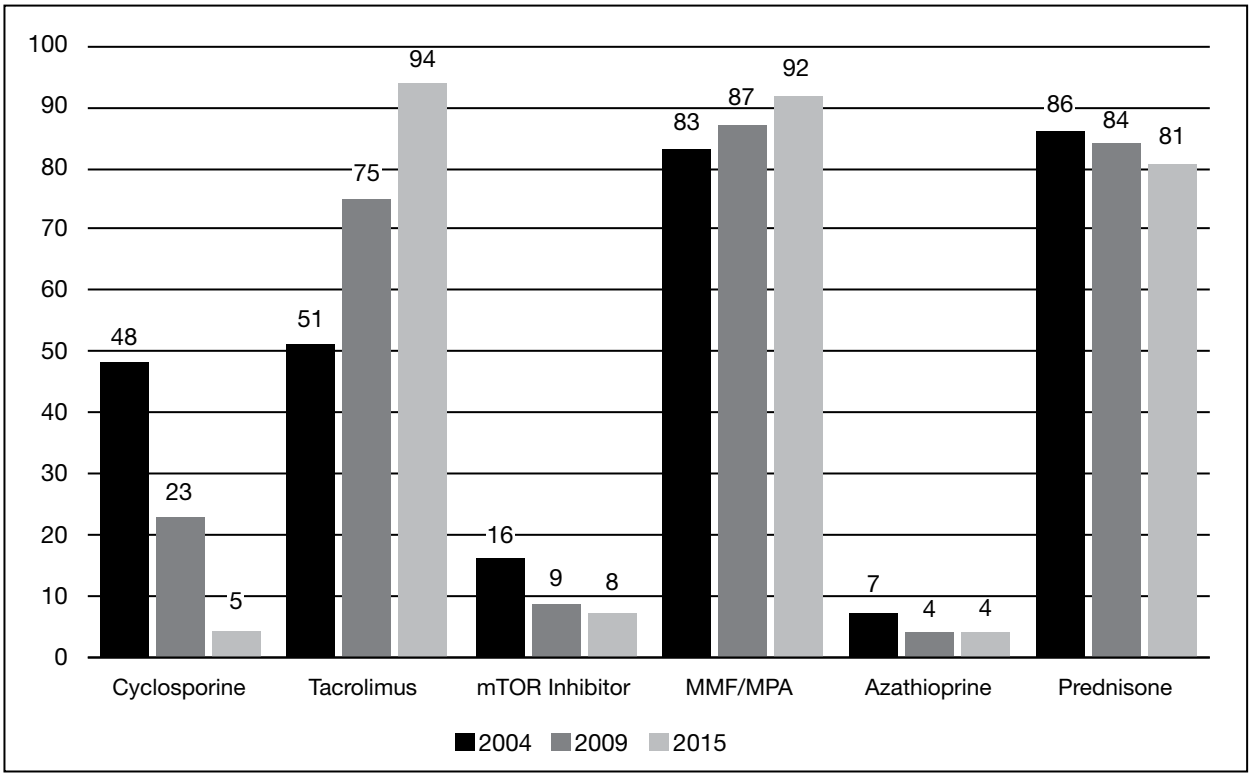


**Figure 2.** Use of maintenance immunosuppressive agents during the first posttransplant year. Agents are categorized according to the percentage of HT recipients taking each therapy at time of 1-year follow-up from three distinct time intervals.

HT = heart transplantation; MMF = mycophenolate mofetil; MPA = mycophenolate acid; mTOR = mammalian target of rapamycin.

Information from: Lund LH, Edwards LB, Kucheryavaya AY, et al. The Registry of the International Society of Heart and Lung Transplantation: Thirty-third Official Adult Heart Transplantation Report – 2016; Focus Theme: Primary Diagnostic Indications for Transplant. J Heart Lung Transplant 2016;35:1158-69.

**Table 7.** Example Maintenance Immunosuppression Regimen Immediately After HT

| Tacrolimus | Mycophenolate Mofetil | Prednisone |
|---|---|---|
| Start 0.05 mg/kg PO BID or 0.01 mg/kg/day as a continuous IV infusion (if NPO) Titrate to target trough | 1000–1500 mg PO BID | POD1: 50mg PO BID |
| | | POD2: 40 mg PO BID |
| | | POD3: 30 mg PO BID |
| Target trough: | | POD4: 20 mg PO BID |
| 1–3 mo: 12–15 ng/mL | | POD5: 10 mg PO BID |
| 3–6 mo: 10–12 ng/mL | | Stop taper at 10 mg PO BID |
| 6–12 mo: 8–10 ng/mL | | Wean according to biopsy results |
| > 12 mo: 6–8 ng/mL | | |

BID = twice daily; IV = intravenous(ly); NPO = nothing by mouth; PO = oral(ly); POD = postoperative day.

**Table 8.** Comparison of Various Long-term Immunosuppression Regimens

| Regimen | Advantages | Disadvantages |
|---|---|---|
| **CNI + MMF/MPA** | • Standard regimen<br>• Robust immunosuppression<br>• Avoids mTOR toxicities[a] | • Chronic renal injury from CNI exposure<br>• Other CNI toxicities[b]<br>• Higher rates of CMV disease and CAV |
| **CNI + mTOR** | • Robust immunosuppression<br>• Avoids MMF/MPA toxicities[c]<br>• Can slow CAV progression | • High rate of renal injury because of additive effect from both classes<br>• mTOR toxicities[a] |
| **mTOR + MMF/MPA** | • Can slow CAV progression<br>• Lower risk of renal injury<br>• Lower risk of CMV disease<br>• Lower risk of PTLD | • Higher risk of cellular rejection<br>• mTOR toxicities[a]<br>• MMF/MPA toxicities[c] |

[a]mTOR inhibitors are poorly tolerated, with discontinue rates as high as 20% within the first year of starting therapy. Common toxicities include nausea/vomiting/diarrhea, peripheral edema, poor wound healing, proteinuria, mouth sores, anemia/leukopenia, hypertriglyceridemia, and pneumonitis.

[b]CNI toxicities are many; common adverse effects include hypertension, hyperlipidemia, electrolyte disturbances, cosmetic issues (e.g., alopecia and hirsutism), renal injury, new-onset diabetes, and neurological sequelae (e.g., headache, tremors, seizure).

[c]Common MMF/MPA adverse effects include diarrhea/nausea and leukopenia/thrombocytopenia. These medications are also teratogenic, and a U.S. Food and Drug Administration (FDA) Risk Evaluation and Mitigation Strategies (REMS) program is required for females of childbearing age.

CAV = cardiac allograft vasculopathy; CMV = cytomegalovirus; CNI = calcineurin inhibitor; MMF = mycophenolate mofetil; MPA = mycophenolate acid; mTOR = mammalian target of rapamycin; PTLD = posttransplant lymphoproliferative disorder.

**Table 9.** Example of Strategies for Converting to mTOR Immunosuppression Regimens

| | Strategy 1: Change to CNI-Sparing | Strategy 2: Change to CNI-Minimizing |
|---|---|---|
| **Starting Regimen** | CNI + MMF/MPA | CNI + MMF/MPA |
| Step 1 | • Start everolimus 0.75–1.0 mg PO BID<br>• Decrease CNI dose by 50%<br>• Continue MMF/MPA | • Start everolimus 0.5–0.75 mg PO BID<br>• Decrease CNI dose by 50%<br>• Continue MMF/MPA |
| Step 2 | • Discontinue CNI once everolimus serum trough is 6–10 ng/mL<br>• Continue MMF/MPA | • Discontinue MMF/MPA once everolimus serum trough is 3–8 ng/mL<br>• Continue lower CNI through goal |
| | • Monitor closely for signs of rejection during the first weeks after conversion with echocardiography and/or biopsy<br>• Monitor for adverse events related to mTOR therapy | |

Information from: Velleca A, Shullo MA, Dhital K, et al. The International Society for Heart and Lung Transplantation (ISHLT) guidelines for the care of heart transplant recipients. J Heart Lung Transplant 2023. In press. doi: 10.1016/j.healun.2022.09.023

F. Immunomodulation/Rejection Treatment
   1. Cellular
      a. Patients with clinical evidence of graft dysfunction should still be treated as having presumed ACR.
         i. Echocardiographic evidence of myocardial dysfunction (e.g., decreased ejection fraction, new wall motion abnormalities)
         ii. Poor hemodynamic parameters on right heart catheterization (e.g., low cardiac output)
         iii. New-onset arrhythmia (e.g., atrial fibrillation or heart block)
         iv. Signs and symptoms of decompensated HF
      b. Patients with lower-grade rejection (0 or 1R) and without clinical evidence of ACR are generally not treated. Those with grade 1R findings with clinical evidence of rejection should receive intravenous pulse steroids (see regimen that follows).
      c. Patients with lower-grade rejection (2R or less) and without clinical evidence of ACR are generally treated with a steroid pulse.
         i. Methylprednisolone 500–1000 mg intravenously for 3 days, followed by oral taper (preferred if less than 60 days post-HT)
         ii. Prednisone (100 mg/day) by mouth for 3–5 days (preferred if greater than 60 days post-HT)
         iii. Response rates for steroid therapy are 75%–85%.
      d. Patients with evidence of severe graft dysfunction or any patient with grade 3R rejection should be treated with rATG.
         i. Usual dose is 1.0–1.5 mg/kg/day (using ideal body weight) for 3–14 days.
         ii. Infusion-related reactions (e.g., hypotension, fever) require premedication with a steroid, acetaminophen, and diphenhydramine or a decrease in the infusion rate.
         iii. Leukopenia and thrombocytopenia may also necessitate dose reduction (Table 10).
      e. Patients who do not respond to steroids should be transitioned to rATG therapy.
      f. Those with persistent clinical evidence of rejection despite rATG should be evaluated for alternative diagnoses (e.g., AMR).
      g. Episodes of ACR should prompt reassessment and augmentation of background immunosuppression.
         i. Temporary resumption of chronic steroid therapy if this was previously discontinued
         ii. Transition from cyclosporine to tacrolimus
         iii. Transition from azathioprine to mycophenolate mofetil/mycophenolate acid

h. Patients who receive treatment with either rATG or a steroid burst should resume opportunistic infection prophylaxis for 3–6 months.

**Table 10.** Dose Reduction for rATG Based on Laboratory Values

| Laboratory Value | Dose Adjustment |
|---|---|
| WBC > 3000 x $10^3$ cells/$mm^3$ **OR** ANC ≥ 1500 **OR** platelets > 75,000/$mm^3$ | No change |
| WBC 2–3000 x $10^3$ cells/$mm^3$ **OR** ANC 1–1400 **OR** platelets 50,000–70,000/$mm^3$ | Decrease by 50% |
| WBC < 2000 x $10^3$ cells/$mm^3$ **OR** ANC < 1000 **OR** platelets < 50,000/$mm^3$ | Hold next dose |

ANC = absolute neutrophil count; rATG = rabbit antithymocyte globulin; WBC = white blood cell count.

2. Antibody-mediated rejection (AMR) (Box 3)
   a. Treatment (Table 11)
      i. Antibody removal using plasma exchange (plasmapheresis), plus
      ii. Blunting of IgG DSA rebound using total IVIg, plus
      iii. Anti–B cell/plasma cell–directed therapies
         (a) CD20 antagonists: Rituximab
         (b) Proteasome inhibitors: Bortezomib/carfilzomib
      iv. With or without anticomplement therapies – C5-convertase inhibitor: Eculizumab
      v. With or without T cell–directed therapies (see ACR)
   b. Monitor for resolution of graft dysfunction and depletion of circulating DSA using solid-phase single-antigen bead assays.
   c. Maintenance immunosuppression should be augmented, as tolerated, to include tacrolimus plus high-dose mycophenolate plus mTOR inhibitor to minimize chronic changes to the coronary vasculature (CAV) after AMR.

**Table 11.** Treatment Based on AMR Category

| Category | DSA | Graft Dysfunction | Treatment |
|---|---|---|---|
| pAMR 0 | - | - | No treatment needed |
| | + | - | Increased surveillance |
| pAMR 1 | + | - | Increased surveillance |
| | ± | + | Consider treatment for AMR |
| pAMR 2 | ± | + | Consider treatment for AMR |
| pAMR 3 | ± | + | Treat for AMR |

Information from: Colvin MM, Cook JL, Chang P, et al.; American Heart Association Heart Failure and Transplantation Committee of the Council on Clinical Cardiology; American Heart Association Heart Failure and Transplantation Committee of the Council on Cardiopulmonary Critical Care, Perioperative and Resuscitation; American Heart Association Heart Failure and Transplantation Committee of the Council on Cardiovascular Disease in the Young; American Heart Association Heart Failure and Transplantation Committee of the Council on Clinical Cardiology, Council on Cardiovascular and Stroke Nursing; American Heart Association Heart Failure and Transplantation Committee of the Council on Cardiovascular Radiology and Intervention; American Heart Association Heart Failure and Transplantation Committee of the Council on Cardiovascular Surgery and Anesthesia. Antibody-mediated rejection in cardiac transplantation: emerging knowledge in diagnosis and management: a scientific statement from the American Heart Association. Circulation 2015;131:1608-39; Velleca A, Shullo MA, Dhital K, et al. The International Society for Heart and Lung Transplantation (ISHLT) guidelines for the care of heart transplant recipients. J Heart Lung Transplant 2023. In press. doi: 10.1016/j.healun.2022.09.023

**Box 3.** Example Antibody-Mediated Rejection Regimen

| |
|---|
| Plasma exchange 1.5 volumes per session x 8 sessions every other day<br>Intravenous immunoglobulin 1 gm/kg/day of ideal body weight for 2 days after session 8<br>Bortezomib 1.3 mg/m$^2$ on days 1, 4, 8, 11 |

**Patient Cases**

*Questions 1 and 2 pertain to the following case.*

P.D., a 52-year-old white man (weight 82 kg) who underwent HT 2 years ago for nonischemic dilated cardiomyopathy, now presents to the emergency department with a 2-day history of shortness of breath and decreasing exercise tolerance. His post-HT course has been complicated by medication nonadherence and four episodes of treated 2R cellular rejection with preserved LVEF. A TTE performed in the emergency department revealed an LVEF of 40%, intraventricular septal flattening, enlarged RV, and dilated bilateral atria (consistent with HT). He was taken to the cardiac catheterization laboratory for measurement of intracardiac pressures and EMB. His pulmonary artery catheterization revealed a right atrial pressure of 12 mm Hg, pulmonary artery wedge pressure of 24 mm Hg, pulmonary artery mean pressure of 35 mm Hg, and cardiac index of 2.1 L/minute/m$^2$. Five EMB fragments were sent in formalin for paraffin fixation and one frozen piece for immunofluorescence, and DSA sampling was sent to the HLA laboratory. His pertinent medications are as follows: tacrolimus 4 mg twice daily (goal trough 6–8 ng/mL), mycophenolate mofetil 1500 mg twice daily, rosuvastatin 20 mg at bedtime, ramipril 5 mg twice daily, amlodipine 5 mg/day, calcium plus vitamin D supplement twice daily, and sulfamethoxazole/trimethoprim 1 single-strength tablet/day. You decide to empirically treat this patient for ACR with intravenous methylprednisolone 1 g daily x 3 days. On the second day of therapy, your team is alerted to the pathological findings on EMB consistent with mixed 2R ACR and pAMR 2. The HLA laboratory alerts your team on the same day that complement fixing DSA directed at DQB05:01*DQA03:02 was detected.

1. Which treatment approach is most appropriate for this patient at this time?
   A. Finish methylprednisolone; add high-dose IVIg alone.
   B. Stop methylprednisolone; add plasma exchange plus IVIg.
   C. Stop methylprednisolone; add bortezomib plus IVIg plus thymoglobulin.
   D. Finish methylprednisolone; add bortezomib plus plasma exchange plus IVIg.

2. Which therapy would best be added to this patient's maintenance immunosuppression regimen?
   A. Prednisone.
   B. Methotrexate.
   C. Everolimus.
   D. Cyclophosphamide.

G. Infection Prophylaxis
   1. Cytomegalovirus (CMV) prophylaxis
      a. Decision for use of antiviral prophylaxis is based on risk (Table 12).
      b. Universal prophylaxis decreases the risk of early CMV disease and is easy to coordinate but exposes patients to drug costs and toxicity (e.g., leukopenia).
      c. Preemptive therapy (i.e., routine surveillance of serum CMV viral load with initiation of prophylaxis, once positive) spares drug costs and adverse effects but can be difficult to coordinate in the outpatient setting.

2. *Pneumocystis jirovecii* pneumonia prophylaxis
    a. Sulfamethoxazole/trimethoprim is the gold standard agent. Common regimens range from 1 single-strength tablet thrice weekly to daily administration. *Pneumocystis jiroveci* penumonia prophylaxis is typically continued for 6–12 months after the transplant and 3–6 months after antithymocyte globulin or thymocyte-depleting agent.
    b. Patients with contraindications to sulfamethoxazole/trimethoprim (e.g., renal insufficiency, hyperkalemia, leukopenia, sulfa allergy) can receive alternative agents.
        i. Dapsone is inexpensive but requires glucose-6-phosphate dehydrogenase deficiency screening before use and can also cause photosensitivity reactions and leukopenia.
        ii. Atovaquone is more expensive and can cause liver injury; however, it does not cause leukopenia or thrombocytopenia.
3. *Toxoplasmosis* sp. prophylaxis
    a. Sulfamethoxazole/trimethoprim covers *Toxoplasmosis* sp., so additional prophylaxis is usually not required.
    b. Patients with *Toxoplasmosis* serology mismatch (i.e., donor positive, recipient negative) have the highest risk of infection. These patients should remain on an agent with activity against *Toxoplasmosis* for at least 12 months post-HT. New guidelines suggest these patients can be considered for lifelong prophylaxis.
4. Fungal prophylaxis
    a. Oral candidiasis prophylaxis is required for the first 6–12 posttransplant months.
    b. Nystatin 5 mL swish and swallow 3 or 4 times daily is a preferred regimen.
    c. Clotrimazole lozenges are an acceptable alternative; however, this agent inhibits cytochrome P450 (CYP) 3A4 and therefore interacts with CNIs.
    d. Routine prophylaxis against molds is not required. However, patients with high-risk features for Aspergillus infection, such as those on ECMO or renal-replacement therapy post-operatively, could be considered for extended fungal prophylaxis regimens.

**Table 12.** Example Protocol for CMV Prophylaxis After HT

| Serology | Risk | Recommended Strategy | Regimen | Duration |
|---|---|---|---|---|
| **D+, R-** | High | Prophylaxis | Valganciclovir 900 mg daily[a] | 6 mo[b] |
| **R+** | Intermediate | Either prophylaxis or preemptive therapy | Valganciclovir 900 mg daily[a] | 3 mo[b] |
| **D-, R-** | Low | No CMV therapy; initiate prophylaxis against HSV | Acyclovir 400 mg PO BID[a] | 3 mo |

[a]Adjusted for renal function.

[b]After completion of therapy in new transplants, check CMV DNA polymerase chain reaction monthly for 3 mo. CMV viremia warrants initiation of valganciclovir.

D = donor; HSV = herpes simplex virus; R = recipient.

Information from: Razonable R, Humar A. Cytomegalovirus in solid organ transplant recipients-guidelines of the American Society of Transplantation Infectious Diseases Community of Practice. Clin Transplant 2019;33:e13512.

H. Management of Comorbid Conditions
    1. CAV prophylaxis
        a. An extensive review was recently published (Pharmacotherapy 2015;35:489-501).
        b. General strategies involve use of mTOR inhibitor regimens (as described earlier) and statins.
            i. Many randomized clinical trials have shown that statins reduce the incidence of CAV as well

as attenuate disease progression.
   ii. Benefits related both to reductions in cholesterol and immunomodulating effects
   iii. Pravastatin is often used because of the lack of drug-drug interactions with CNIs.
c. Diltiazem has been shown to attenuate CAV progression in some small studies. This benefit may be related to "boosting" of immunosuppression by increasing CNI exposure by inhibition of CYP3A4.
d. Limited evidence also exists for angiotensin-converting enzyme (ACE) inhibitors; however, this class of medication must be used very carefully in combination with CNIs because of overlapping adverse effects (i.e., hyperkalemia and renal injury).
e. Antiplatelet therapies have been studied; however, the available evidence has shown limited benefit for these medications. Aspirin remains the preferred antiplatelet agent based on very limited evidence.
f. CMV titer monitoring/prophylaxis reduces CMV burden and CAV.

2. Hypertension
   a. Hypertension is a common drug-induced adverse event after HT that generally develops within the first few weeks of immunosuppression therapy. In general, HT recipients should have a blood pressure target of less than 130/80 mm Hg.
   b. CNIs cause renal artery and systemic vasoconstriction, whereas steroids expand the extracellular volume through sodium retention.
   c. Dihydropyridine calcium channel blockers (e.g., amlodipine) are generally considered first-line agents for treating hypertension in the early post-HT period.
      i. Limited drug interactions with CNI therapy
      ii. Counteract vasoconstriction at the afferent arteriole, which may mitigate the risk of renal injury from CNI therapy
      iii. Lack negative chronotropic or inotropic effects
   d. Recent evidence in an animal model suggests that the renal sodium chloride cotransporter is central to the pathogenesis of CNI-induced hypertension.
      i. Thiazide diuretics were very effective at treating CNI-induced hypertension in this same model.
      ii. In addition to being inexpensive and easy to take, thiazide agents can treat CNI-induced hyperkalemia.
   e. β-Blockers should generally be avoided early after transplant.

3. Hyperkalemia
   a. Both CNIs cause hyperkalemia (cyclosporine more so than tacrolimus) through impairment of renal potassium excretion.
   b. CNIs can also induce a renal tubular acidosis (usually type 4 – hyperkalemic, hyperchloremic) by aldosterone resistance (i.e., pseudohypoaldosteronism).
   c. Most problematic early after transplantation when CNI concentrations are highest
   d. Patients with concomitant hypertension and hyperkalemia should be treated with thiazide diuretics as first line.
   e. Patients with normal or low blood pressure require alternative agents for potassium management.
      i. Novel therapies for hyperkalemia should be considered first line for most patients. Sodium zirconium cylosilicate (Lokelma) provides control of both acute and chronic hyperkalemia, and should be considered first line. Of note it can be given at the same time as transplant medications (i.e., does not require spacing). When sodium zirconium cylosilicate is not available, alternative binders like patiromer can be considered; however, these agents must be separated from transplant medications.
      ii. Those with concomitant acidosis (i.e., low serum bicarbonate) can be treated with oral sodium bicarbonate tablets (usual dose is 650–1300 mg by mouth twice daily).
      iii. When laboratory studies suggest pseudohypoaldosteronism (i.e., low serum sodium and hyperkalemia), fludrocortisone therapy can be effective.

4. Drug-drug interactions
    a. CNIs are substrates of both the CYP3A4 enzyme system and P-glycoprotein.
    b. These agents are subject to many drug interactions.
    c. The extent/significance and management of these interactions vary significantly and need to be considered on a case-by-case basis.
    d. Table 13 lists several of the most common drug-drug interactions, together with suggested management strategies for CNIs.

**Table 13.** Common CNI Drug-Drug Interactions and Suggested Management Strategy

| Drug | Mechanism of Interaction | Effect on CNI Concentrations | Management |
|---|---|---|---|
| **CCBs:** | Inhibit CYP3A | | |
| Diltiazem, verapamil | | ↑ | Decrease CNI dose by 50% |
| Nifedipine, amlodipine | | ↑/no change | Monitor concentrations |
| **Other cardiovascular agents:** | Inhibit CYP3A and | | |
| Amiodarone | P-gp/ABCB1 transporter | ↑ | Cut CNI dose by 50% |
| Dronedarone | | ↑ | Use alternative/monitor |
| **Azole antifungals:** | Inhibit CYP3A4 ± P-gp | | |
| Clotrimazole | | ↑ | Cut CNI dose by 50% |
| Fluconazole | | ↑ | Cut CNI dose by 50% |
| Itraconazole | | ↑ | Cut CNI dose by 50% |
| Ketoconazole | | ↑ | Cut CNI dose by 50% |
| Posaconazole | | ↑ | Cut CNI dose by 25%–70% |
| Voriconazole | | ↑ | Cut CNI dose by 50%–70% |
| **Other antifungals:** | Unknown | | |
| Caspofungin | | ↓/no change | Monitor concentrations |
| **Macrolides:** | Inhibit CYP3A | | |
| Erythromycin | | ↑ | Cut CNI dose by 50%–75% |
| Clarithromycin | | ↑ | Cut CNI dose by 50%–75% |
| **Antiepileptics:** | Induce CYP3A4 | | |
| Carbamazepine | | ↓ | Monitor concentrations |
| Phenobarbital | | ↓ | Monitor concentrations |
| Phenytoin | | ↓ | Double CNI dose |
| **Other anti-infectives:** | Various | | |
| Metronidazole | Inhibit CYP3A4 ± P-gp | ↑ | Monitor concentrations/consider dose decrease |
| Nafcillin | Induce CYP3A4 | ↓ | Monitor/consider dose increase |
| Rifampin | Induce CYP3A4 | ↓ | Increase does by 200% |
| Rifabutin | Induce CYP3A4 ± P-gp | ↓ | Double CNI dose |
| St John's wort | Induces CYP3A4 + P-gp | ↓ | Avoid use |
| Cimetidine | Inhibit CYP3A4 | ↑ | Consider famotidine instead |
| Metoclopramide | Increased absorption | ↑ | Monitor/consider dose decrease |
| Nefazodone | Inhibit CYP3A4 | ↑ | Use alternative SNRI |

CCB = calcium channel blocker; CYP = cytochrome P450; P-gp = P-glycoprotein; SNRI = serotonin-norepinephrine reuptake inhibitor.

**Patient Case**

*Questions 3 and 4 pertain to the following case.*

A.S., a 68-year-old man (weight 77 kg) with a history of hypertension, diabetes, and end-stage ischemic cardiomyopathy, presents for his routine follow-up 8 months after successful HT (CMV +/+, toxoplasmosis -/-). His diabetes has worsened posttransplantation, and his most recent A1C value was 8.3%. His post-HT course has otherwise been unremarkable, with no episodes of cellular or humoral rejection and no opportunistic infections. Other than an elevated A1C and blood glucose, his SCr has risen slowly to 2.1 mg/dL from a pretransplant baseline of 1.4 mg/dL. In working up his worsening renal function, he is found to have proteinuria (1.2 g/day). His pertinent medications are as follows: tacrolimus 3 mg orally twice daily (goal trough 8–10 ng/mL), valganciclovir 450 mg/day, mycophenolate mofetil 1000 mg twice daily, dapsone 100 mg/day, prednisone 10 mg/day, nystatin 5 mL four times daily, pravastatin 20 mg/day, aspirin 81 mg/day, insulin glargine 20 units/day, and amlodipine 5 mg/day. Given his worsening renal function, the team is considering an mTOR inhibitor to reduce CNI exposure.

3. Which recommendation is most appropriate regarding this patient's immunotherapy at this time?
   A. Change tacrolimus to everolimus.
   B. Change mycophenolate mofetil to everolimus.
   C. Add everolimus to his current regimen.
   D. Taper off prednisone; continue tacrolimus and mycophenolate mofetil.

4. Which change to the patient's infection prophylaxis regimen is most appropriate at this time?
   A. Change nystatin to clotrimazole lozenges.
   B. Discontinue valganciclovir.
   C. Change dapsone to sulfamethoxazole/trimethoprim.
   D. Decrease valganciclovir to 450 mg every other day.

## III. PERCUTANEOUS VENTRICULAR ASSIST DEVICES

A. Intra-aortic Balloon Pump (IABP)
   1. Placed by femoral arterial catheter and advanced up the aorta
   2. Inflation enables diastolic augmentation to improve coronary perfusion pressure.
   3. Deflation facilitates afterload during systole to ease cardiac output (Table 14).
   4. Tachyarrhythmias and aortic regurgitation/insufficiency interfere with this type of MCS.
   5. Level of support coincides with timing of inflation/deflation per related heartbeat; for example: 1:1 = one inflation/deflation per every heartbeat (maximal support), and 1:3 one inflation/deflation for every third heartbeat (less support)
   6. Heparin-based anticoagulation is commonly used; however, limited evidence suggests that it is unnecessary.

**Table 14.** Comparison of Available Temporary Support Devices

| | IABP | Impella | TandemHeart | VA ECMO |
|---|---|---|---|---|
| Maximum support | 0.5–1 L/min | 2.5–6.2 L/min | Up to 5 L/min | > 5 L/min |
| LV unloading | + | ++,+++,++++ | +++ | ++ |
| Coronary perfusion | + | + | – | – |
| Bleeding risk | + | ++ | +++ | ++++ |
| Management complexity | + | ++ | ++++ | +++ |
| Maximum implant time[a] | Weeks | 14 days | 14 days | Days to weeks |

[a]According to manufacturer recommendations. Experienced centers may exceed these suggested durations.

LV = left ventricle/ventricular; VA ECMO = venoarterial extracorporeal membrane oxygenation.

Information from: Reference: Atkinson TM, Ohman EM, O'Neill WW; et al.; Interventional Scientific Council of the American College of Cardiology. A practical approach to mechanical circulatory support in patients undergoing percutaneous coronary intervention: an interventional perspective. JACC Cardiovasc Interv 2016;9:871-83.

B. Impella Devices
   1. Indicated for temporary MCS during high-risk percutaneous coronary intervention or for refractory cardiogenic shock
   2. Operates with five distinct platforms (Impella 2.5, Impella CP, Impella 5.0, Impella LD, Impella 5.5) for LV support (Table 14)
   3. Contains catheter-mounted microaxial pump on a French catheter shaft (various sizes), which houses the motor driveline and the purge line system
   4. Insertion is usually done through a femoral approach, and the device is positioned across the aortic valve into the LV.
      a. Inflow cannula positioned in the LV
      b. Outflow cannula sits immediately superior to the aortic valve.
   5. Impella RP version now available for support during RV failure
   6. Superior hemodynamic improvement over IABP (Table 14) in refractory cardiogenic shock
      a. Greater LV unloading and improvements in cardiac output
      b. No proven mortality improvements
      c. Recent analyses suggest higher costs and rates of adverse events (e.g., bleeding) with Impella than with IABP when used for cardiogenic shock.
   7. Requires therapeutic anticoagulation
      a. The manufacturer recommends routine anticoagulation with a targeted activated clotting time (ACT) of 160–180 seconds, which most clinicians interpret as equivalent to an aPTT of 60–80 seconds. However, recent evidence suggests that a lower-intensity anticoagulation target (anti-Xa concentration 0.2–0.4 IU/mL) can reduce bleeding risk.
      b. Complicated by need for a heparin-based purge solution
         i. Used to lubricate the motor and maintain a pressure within the device at 300–1100 mm Hg. Heparin also has a unique ionic charge that prevents protein deposition within the purge gaps in the motor.
         ii. Standard concentration is 25,000 units of unfractionated heparin (UFH) in 500 mL of 5% dextrose solution (50 units/mL).
         iii. Device console automatically adjusts the flow rate of the purge to 2–30 mL/hour to maintain purge pressure.
            (a) Can result in significant fluctuations in heparin exposure
            (b) May overdose low-body-weight patients
      c. Heparin-based purge must be balanced with intravenous heparin to provide safe and effective anticoagulation (Patient Case Scenario 5-6).

d. Adverse events include:
   i. Hemolysis
   ii. Limb ischemia and vascular injury
   iii. Bleeding
   iv. Damage to LV and chordae tendineae/papillary muscles
e. Alternative purge solutions
   i. When bleeding, coagulopathy, or HIT develops on Impella support, the heparin-based purge solution should be changed to a bicarbonate-based purge solution (25 mEq in 1000 mL of dextrose 5% in water).
   ii. Alternative anticoagulants like direct thrombin inhibitors should not be used in the purge solution, even in the setting of active HIT.
f. Should not be used in patients with mechanical aortic valve, aortic valve disease, or LV thrombus
g. Severe peripheral vascular disease is a contraindication to Impella use.
h. Monitoring for device flow and lactate dehydrogenase can prevent clot burden and provide early intervention for increased systemic anticoagulation or device exchange. Purge flow pressures should also be monitored.

**Patient Case**

*Questions 5 and 6 pertain to the following case.*

J.T. is a 56-year-old man (weight 65 kg) who is admitted with acute anterior ST-segment elevation myocardial infarction with severe refractory cardiogenic shock requiring Impella CP support. He arrives in the ICU with a purge solution containing 25,000 units of heparin in a 500 mL solution of 5% dextrose. The purge is flowing at 16 mL/hour. J.T.'s current aPTT value is 78 seconds (goal 60–80 seconds).

5. Which is most appropriate regarding J.T.'s anticoagulation therapy?
   A. Discontinue heparin from the purge solution, and place the patient on intravenous heparin 800 units/hour.
   B. Add intravenous heparin at 300 units/hour to the patient's current regimen.
   C. Continue the current regimen, and recheck an aPTT value in 6 hours.
   D. Discontinue heparin from the purge solution, and initiate argatroban therapy.

Two hours after J.T.'s arrival to the ICU, the nurse inspects the controller for the Impella CP, and the purge rate has decreased to 10 mL/hour.

6. Which change to the anticoagulation regimen would be best for J.T.?
   A. Discontinue heparin from the purge solution and place the patient on intravenous heparin 800 units/hour.
   B. Add intravenous heparin at 300 units/hour to the patient's current regimen.
   C. Continue the current regimen and recheck an aPTT value in 4 hours.
   D. Discontinue heparin from the purge solution and initiate argatroban therapy.

C. TandemHeart Device
   1. A low-speed centrifugal continuous-flow pump that can be introduced percutaneously in the cardiac catheterization laboratory
      a. Inserted by a venous trans-septal puncture through the femoral vein; a left atrial cannula channels blood into the pump

   b. A femoral artery cannula carries the blood to the systemic arterial circulation.
2. Redirection of blood from the left atrium reduces LV preload, LV workload, filling pressures, wall stress, and myocardial oxygen demand.
   a. Can provide full cardiac support (Table 14**)** in refractory cardiogenic shock
   b. LV unloading superior to IABP
3. Anticoagulation with the TandemHeart is complicated by the need for a heparinized infusate of 1000 mL of normal saline with 90,000 units of UFH.
   a. Infusate runs at a fixed rate of 10 mL/hour, which, unlike the Impella devices, does not fluctuate UFH exposure.
   b. Infusate must be saline because dextrose-containing products can damage the motor and lead to catastrophic failure of the device.
4. Manufacturer recommends an aPTT of 65–80 seconds or an ACT value of 180–220 seconds during device support.
5. Additional UFH can be administered intravenously as needed to achieve therapeutic anticoagulation (Table 15).
6. Potential complications include tamponade, hemolysis, thrombosis, bleeding, air embolism, device dislodgement, infection, and stroke.
7. Potential option for aortic valve pathology because it does not pass through aorta
8. Should not be used in those with severe peripheral arterial disease, intracardiac thrombus, septal defects, or aortic insufficiency

**Table 15.** Example Anticoagulation Protocol for the TandemHeart Device

| aPTT (seconds) | Instructions |
|---|---|
| < 55 | Continue current infusate (heparin 45,000 units/500 mL of saline) at 10 mL/hr, and initiate intravenous heparin at 2 units/kg/hr |
| 55–75 | Therapeutic – No changes |
| 76–90 | Change infusate to heparin 25,000 units/500 mL of saline at 10 mL/hr, and initiate intravenous heparin at 2 units/kg/hr |
| 91–110 | Change infusate to heparin 25,000 units/500 mL of saline at 10 mL/hr; do not initiate intravenous heparin |
| > 110 | Change infusate to saline (no heparin) at 10 mL/hr |

aPTT = activated partial thromboplastin time.

Adapted from: Lee Y, Weeks PA. Effectiveness of protocol-guided heparin anticoagulation in patients with the TandemHeart percutaneous ventricular assist device. ASAIO J 2015;61:207-8.

## IV. EXTRACORPOREAL MEMBRANE OXYGENATION

A. Extracorporeal Membrane Oxygenation (ECMO): A form of acute temporary MCS capable of fully replacing cardiopulmonary circulation in patients with severe cardiac and/or pulmonary dysfunction
   1. A typical ECMO circuit is composed of a pump, a semipermeable membrane oxygenator, and a heat exchanger (Figure 3).

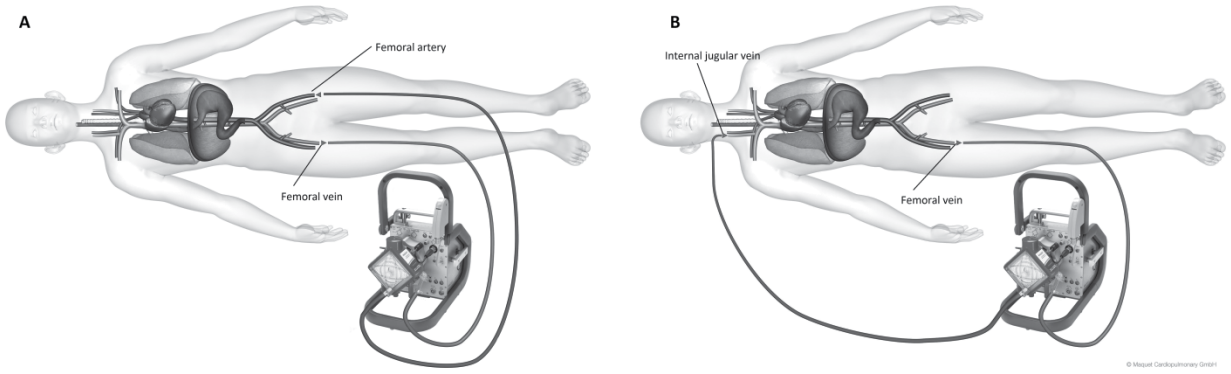


**Figure 3. A.** Peripheral venoarterial ECMO configuration indicated in refractory cardiogenic shock or cardiopulmonary arrest. **B.** Peripheral venovenous ECMO configuration indicated in refractory respiratory failure without circulatory compromise.

ECMO = extracorporeal membrane oxygenation.

2. The oxygenator is the interface between blood and ambient gases and facilitates ventilation and oxygenation of the patient's blood.
    a. This can be manipulated by adjusting the oxygen concentration for oxygenation, which is used when pulmonary dysfunction is present.
    b. Flow of gas through the system (commonly called "sweep"), which is used to facilitate ventilation of carbon dioxide
3. The heat exchanger can facilitate therapeutic hypothermia after cardiac arrest and can also be used to control the rate of rewarming after surgery.

B. Many Different Configurations of ECMO (Figure 3)
    1. Venovenous used for isolated pulmonary dysfunction
    2. Venoarterial used for cardiopulmonary support
    3. Cannulation can be central (i.e., directly into the heart) or peripheral (e.g., using the femoral veins and/or arteries).
        a. Peripheral cannulation is less invasive and can often be done at the bedside rather than in the operating room.
        b. Cannulation position affects complications and determines the need for supplementary drug therapy (see the text that follows).

C. ECMO: Provides full cardiac support (Table 14)
    1. Can provide supraphysiological cardiac output support
    2. Central cannulation usually obviates the need for inotropic support.
    3. Peripheral cannulation can <u>increase</u> systemic vascular resistance (SVR), unlike IABP, which can decrease SVR.
        a. Can result in aortic valve closure and subsequent risk of thrombosis on the valve or in the aortic root
        b. Can also decrease native LV contraction, resulting in elevations in pulmonary capillary wedge pressure (PCWP), eventually leading to pulmonary edema
        c. Positive inotropes (e.g., dobutamine) may therefore be used to enhance native LV function, which can reduce the risk of aortic valve thrombosis and prevent/treat pulmonary edema.

D. Effective Anticoagulation: Remains the cornerstone of successful ECMO support
   1. Patients have superimposed risks of bleeding and thrombosis.
   2. UFH is the most commonly used anticoagulant.
      a. Usual bolus of 50–100 units/kg of body weight at the time of cannulation
      b. Infusion rates are typically 20–50 units/kg/hour.
      c. Emerging evidence continues to grow supporting the use of bivalirudin as an alternative to heparin. A recent meta-analysis of six studies suggests that bivalirudin may reduce the incidence of circuit thrombosis compared with heparin (J Pharm Pract 2022;8971900221143406).
   3. ACT, aPTT, and heparin anti-Xa concentrations are all used to monitor UFH.
      a. Suggested anticoagulation targets vary depending on the type of assay (Table 16).
      b. No clear evidence of superiority for one assay over another
      c. All goals should be individualized on the basis of patient-specific factors (e.g., decrease anti-Xa goal to 0.2–0.4 IU/mL in the presence of minor bleeding or oozing from cannula sites).
      d. Each assay has limitations; thus, the Extracorporeal Life Support Organization guidelines often suggest using more than one test to monitor anticoagulation (Table 16).
   4. Select centers may use thromboelastography.
      a. Includes assessment of platelet function and fibrinolysis
      b. Limited by technical difficulty, training required, delayed turnaround time, and interpretation challenges
   5. Antithrombin III (AT III) monitoring and supplementation in deficient patients can be considered.
      a. Goal is to overcome heparin resistance and ensure adequate anticoagulation.
      b. Available evidence is limited and has failed to show improved outcomes.
      c. Extracorporeal Life Support Organization guidelines suggest to consider AT III replacement when:
         i. Excessive heparin dosing (greater than 35 units/kg/hour)
         ii. AT III activity level less than 30%
   6. Serum fibrinogen concentrations should be monitored regularly.
      a. Fibrinogen depletion can increase bleeding risk while the patient is receiving UFH.
      b. If fibrinogen is less than 100–150 mg/dL, cryoprecipitate supplementation may reduce the risk of spontaneous life-threatening hemorrhage.
   7. For suspected heparin-induced thrombocytopenia, alternative anticoagulants can be used while the patient is receiving ECMO support.
      a. Argatroban infusion can be initiated at 0.5–1 mcg/kg/minute and adjusted to maintain aPTT 1.5–2.5 times baseline values.
      b. Bivalirudin infusion can be initiated at 0.03–0.1 mg/kg/hour and adjusted to maintain aPTT at 1.5–2.5 times baseline.

**Table 16.** Comparison of Various Anticoagulation Monitoring Assays Used During ECMO Support

| | ACT | aPTT | Anti-Xa Concentrations |
|---|---|---|---|
| **Classification** | Functional assay | Functional assay | Kinetic assay |
| **Source** | Whole blood | Plasma | Whole blood |
| **Processing** | Bedside test | Lab (in house) | Lab (may be sent out) |
| **Target range** | 180–220 s | 1.5–2.5 x control | 0.3–0.7 IU/mL |
| **Limitations and comparisons** | Sensitive to platelet/ clotting factor levels | Sensitive to platelet/ clotting factor levels | Less sensitive to blood components |

ACT = activated clotting time; anti-Xa = anti-factor Xa.

Information from: Mulder MMG, Fawzy I, Lancé MD. ECMO and anticoagulation: a comprehensive review. Neth J Crit Care 2018;26:6-13.

**Patient Case**

*Questions 7 and 8 pertain to the following case.*

A.J. is a 65-year-old man (weight 73 kg) with a medical history of chronic systolic heart failure. He presents with an acute heart failure exacerbation and is initiated on diuretic therapy. Two days later, he has a ventricular fibrillation arrest. He is defibrillated successfully but is placed on VA ECMO by peripheral cannulation for ongoing cardiogenic shock. A.J. is then brought to the ICU for further management. His ECMO flow is 2.8 L/minute at 3500 rpm. A.J. receives heparin 10,000 units intravenously at the time of cannulation.

7. Which is best to recommend regarding anticoagulant therapy?
   A. Immediately initiate fixed-dose heparin of 400 units/hour, and send ACT, aPTT, and anti-Xa.
   B. Send aPTT, anti-Xa, and ACT immediately as "STAT" to assess the degree of anticoagulation remaining from 10,000 units given previously.
   C. Initiate venous thromboembolism prophylaxis with heparin 5000 units subcutaneously every 8 hours; patient has no indication for therapeutic anticoagulation.
   D. Initiate enoxaparin 70 mg every 12 hours for therapeutic anticoagulation.

Two days into ECMO support, A.J.'s heparin requirements continue to increase, and he is now receiving a dose of 45 units/kg/hour (dose yesterday was 35 units/kg/hour). His hemoglobin remains stable, and his coagulation studies reveal the following: aPTT 48 seconds, anti-Xa 0.15 IU/mL, and ACT 155 seconds.

8. Which best explains A.J.'s escalating dose requirements of heparin?
   A. Excessive endogenous production of thrombin; change heparin to argatroban.
   B. Acquired antithrombin deficiency; assess AT activity level and consider replacement with recombinant AT III.
   C. There are no major problems with A.J.'s anticoagulation; continue to titrate heparin to target aPTT 1.5–2.5 times normal.
   D. Anticoagulation currently appears to be within the therapeutic range; continue current regimen.

E. ECMO Support: Can alter the pharmacokinetics of many medications
   1. Results from sequestration within the circuit from priming fluid used, material of cannulas, and total time use on the oxygenator. The first 48–72 hours may require higher dosing to account for system saturation/sequestration and upon cannula or oxygenator exchange.
      a. Example: β-Lactam antibiotics
      b. Lipophilic drugs are more susceptible.
      c. Examples: Fentanyl, midazolam, propofol, heparin, and voriconazole
   2. Alterations in volume of distribution and clearance because of critical illness
   3. Increase in patient's circulating volume during priming of circuit
   4. Extensive review recently published (Pharmacotherapy 2017;37:221-35)

F. Potential Complications of ECMO: Include thrombosis, bleeding, infection, stroke, and vascular injury

G. ECMO should generally not be used in those with severe peripheral arterial disease , aortic insufficiency, or terminal illness..

## V. DURABLE CONTINUOUS-FLOW LEFT VENTRICULAR ASSIST DEVICES

A. One durable, fully implantable CF-LVAD is commercially available for long-term support as bridge-to-transplantation or destination therapy. Note that while the HeartMate 2 is no longer being implanted, it will still be discussed as there are still patients alive on device support. Similarly, in 2021, the HeartWare HVAD was decommissioned after signals surfaced for elevated stroke risk. However, because there are still patients alive on HVAD support, this device will also still be mentioned in this chapter.
   1. HeartMate 2 (Thoratec, Pleasanton, CA), HeartWare HVAD (HeartWare International, Framingham, MA), and the HeartMate 3 (Thoratec, Pleasanton, CA)
   2. All devices require cannulation of the apex of the LV to provide direct mechanical cardiac unloading.
   3. Each propels blood forward through an outflow graft that is anastomosed to the ascending aorta.
   4. The HeartMate 2 and HeartMate 3 devices provide a snapshot of four device parameters (flow, speed, pulsatility index, and power) on the device console (Table 17).
   5. The HeartWare HVAD monitor provides continuous waveform analysis of flow and power.

B. All three devices drastically improve survival, with a 1-year mortality rate of around 10% (vs. 90% for medical therapy).
   1. Significant improvements in quality of life and organ perfusion
   2. Unfortunately, complications are common, and over 50% of CF-LVAD recipients are readmitted to the hospital during the first year of support.

C. Bleeding
   1. Remains the most common complication, with most bleeds occurring within the gastrointestinal tract
   2. Incidence of gastrointestinal bleeding (GIB) is around 15% within the first 6 months of device support.
      a. Arteriovenous malformations are the most commonly identified source when patients present with GIB (19%–61%).
      b. Ulcerative lesions are the most common secondary source (8.7%–28.2%).

**Table 17.** Device Parameters for CF-LVAD

| Parameter | Normal Values | Can Be Elevated by: | Can Be Decreased by: | Pharmacotherapy Considerations |
|---|---|---|---|---|
| **Flow** | 4–6 L/min[a] | • Sepsis<br>• Device thrombosis<br>• Aortic insufficiency | • RV failure<br>• Dehydration<br>• Hemorrhage<br>• Hypertension<br>• Arrhythmias | • Monitor for decreases in flow when titrating β-blockers or diuretics<br>• Titrate afterload-reducing agents to avoid hypertension and optimize flow<br>• Monitor for evidence of blood loss or device thrombosis |
| **Speed** | 8800–9800 rpm[b]<br>2800–3400 rpm[c]<br>5000–6000 rpm[d] | None – Adjusted by health care team | • Blood loss<br>• Dehydration | Sudden drops in speed (i.e., suction event) may represent dehydration and should prompt assessment of diuretic regimen, fluid status, and potential hemorrhage |

**Table 17.** Device Parameters for CF-LVAD *(Cont'd)*

| Parameter | Normal Values | Can Be Elevated by: | Can Be Decreased by: | Pharmacotherapy Considerations |
|---|---|---|---|---|
| **Pulsatility index** | 4–7[e] (HeartMate 2)<br>3–5 (HeartMate 3)[e] | Hypertension | • Hypotension<br>• Dehydration<br>• RV failure | Sudden drops in pulsatility index (i.e., suction event) in HeartMate 2 may represent dehydration and should prompt assessment of diuretic regimen and fluid status |
| **Power** | 5–7 W | • Device thrombosis<br>• Hypertension | • Hypotension<br>• Sepsis | Sustained power elevation should prompt evaluation for device thrombosis |

[a]Normal value depends on the patient's body mass index.

[b]Typical range for HeartMate 2 device.

[c]Typical range for HeartWare HVAD.

[d]Typical range for HeartMate 3 device.

[e]Calculated only by HeartMate 2 and HeartMate 3 device; when the left ventricle contracts, the increase in ventricular pressure causes an increase in pump flow during cardiac systole. The magnitude of these flow pulses are measured and averaged over 15-second intervals to produce a "Pulsatility Index." The magnitude of the PI value is related to the amount of assistance provided by the pump. Higher values indicate more ventricular filling and higher pulsatility (i.e., the pump is providing less support to the left ventricle). Lower values indicate less ventricular filling and lower pulsatility (i.e., the pump is providing greater support and further unloading the ventricle).

CF-LVAD = continuous-flow left ventricular assist device; RV = right ventricle; rpm = revolutions per minute; W = watts.

Information from: Jennings DL, Schillig J, Chambers R. The pharmacotherapy of the HeartMate 2, a continuous flow left-ventricular assist device, in patients with advanced heart failure: integration of disease, device and drug. Ann Pharmacother 2010;44:1647-50.

3. Etiology is multifaceted but directly related to the continuous-flow nature of contemporary devices.
    a. Alterations in angiogenesis because of excessive thrombin generation and loss of pulsatility
    b. Acquired von Willebrand syndrome secondary to sheer forces from the device and destruction of high-molecular-weight multimers
    c. Ongoing need for antithrombotic therapy (aspirin and warfarin)
    d. Patient-specific factors (e.g., advanced age, history of bleeding)
4. Diagnosis can involve esophagogastroduodenoscopy, colonoscopy, double balloon enteroscopy capsule endoscopy, and tagged red blood scan or angiography.
5. Endoscopic intervention (i.e., cryoprecipitate, banding, laser therapy) can be implemented if a lesion is identified; however, the recurrence rate is high.
6. Study of Reduced Anti-coagulation/Anti-platelet Therapy in Patients with the HeartMate 2 LVAD (TRACE) trial was recently published.
    a. Observational study of 100 HeartMate 2 recipients who were followed for 1 year after an index bleeding event (primarily GIB)
    b. Evaluated various strategies for reduced antithrombotic therapy
    c. Rebleeding rates were high, regardless of reduced therapy.
        i. 17 of 38 (45%) in warfarin only
        ii. 12 of 28 (43%) in aspirin only
        iii. 14 of 34 (41%) in no antithrombotic therapy
    d. Rates of device thrombosis and stroke were infrequent (0.08 and 0.07 events per patient-year, respectively) but still occurred more commonly than in recent registry reports.
    e. Results suggest that reducing antithrombotic therapy is ineffective in treating GIB and may increase thrombotic complications.
    f. These findings are only applicable to HeartMate 2 recipients.

7. Octreotide produces vasoconstriction of the splanchnic artery, causing a decrease in duodenal and splanchnic blood flow by blocking the release of glucagon (vasodilator) and inhibiting the production of nitric oxide.
    a. May also enhance platelet aggregation
    b. Several case reports and case series have suggested a benefit in patients with recurrent GIB.
        i. Subcutaneous doses of 50–100 mcg, either twice or three times daily
        ii. Long-acting intramuscular depot form at 20–30 mg every month
    c. Common adverse drug events reported include injection-site pain, nausea, abdominal cramping, diarrhea, malabsorption of fat, and flatulence.
    d. Main limitations are parenteral administration and high cost of long-acting product.
8. Thalidomide has antiangiogenic properties and has been described in case reports in patients with recurrent GIB.
    a. Initial dose of 50 mg twice daily
    b. Significant adverse effects noted, including symptomatic autonomic and peripheral neuropathy
    c. Also has an FDA boxed warning for thromboembolism
        i. Should not be used in patients with a history of device thrombosis
        ii. Antithrombotic therapy should not be discontinued in patients receiving thalidomide.
    d. Prescribers and pharmacies are required to be enrolled through the THALOMID REMS program to prescribe thalidomide.
    e. Should be reserved for refractory bleeding (Figure 4)
9. Recent retrospective analysis of 131 CF-LVAD recipients suggests benefit of ACE inhibitor or angiotensin receptor blocker (ARB) therapy.
    a. Both drug classes have antiangiogenic properties.
    b. Logistic regression showed a significant reduction in all-cause GIB (odds ratio 0.29; 95% confidence interval, 0.12–0.72) when patients were maintained on these therapies.
    c. Given the low cost, ease of administration, and acceptable adverse effect profile, an ACE inhibitor or ARB should be considered first line for CF-LVAD recipients who develop GIB unless a contraindication to such therapy is present (Figure 4).
10. Recent evidence also suggests that omega-3 products and digoxin can reduce rates of GIB in LVAD patient cohorts (Circ Heart Fail 2018;11:e005082; Circ Heart Fail 2018;11:e004899).
    a. Both agents are supported by a single retrospective cohort study.
    b. Omega-3 at a dose of 4 g daily was associated with no adverse events; however, omega-3 products can be expensive.
    c. Digoxin is inexpensive; however, significant adverse effects are associated with its use, and the need for judicious monitoring hinders its use.
    d. Both agents can be considered as alternatives in patients with disease refractory to initial therapy with an ACE inhibitor or ARB (Figure 4).

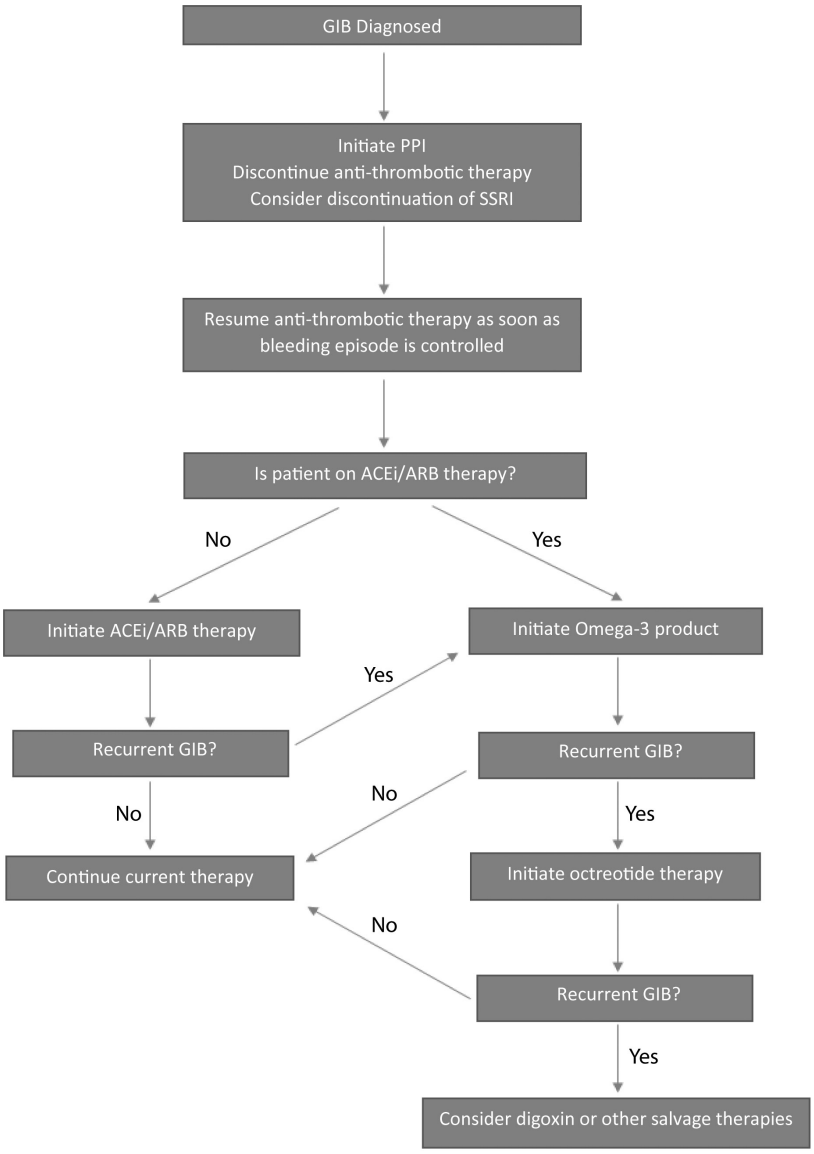


**Figure 4.** Suggested algorithm for managing gastrointestinal bleeding in the CF-LVAD recipient.
ACEi = ACE inhibitor; ARB = angiotensin receptor blocker; CF-LVAD = continuous-flow left ventricular assist device; GIB = gastrointestinal bleed.

D. Prevention of Device-Related Thrombosis for CF-LVADs
   1. Pump thrombosis and stroke are relatively uncommon complications, but both can be fatal.
   2. Reported incidence varies according to device type and population characteristics.
   3. Thromboprophylaxis involves initiation of intravenous UFH soon after device implantation, with early transition to warfarin and aspirin therapy.
   4. The Prevention of HeartMate 2 Pump Thrombosis Through Clinical Management (PREVENT) trial recently evaluated a multimodal approach aimed at reducing the rate of device thrombosis in 300 HeartMate 2 recipients (Box 4).

5. Centers having strict compliance with the PREVENT protocol had significantly lower rates of pump thrombosis within 6 months of implantation (1.9 vs. 8.9%; p<0.01). While these data are derived from a HeartMate 2 cohort, these practices are still largely followed in the HeartMate 3 patient populations.

**Box 4.** Anticoagulation and Antiplatelet Management Protocol from PREVENT Study

- In patients without persistent bleeding, begin bridging with UFH or low-molecular-weight heparin within 48 hr of device implantation
- Target aPTT values of 40–45 s in the first 48 hr, followed by titration toward an aPTT goal of 50–60 s by 96 hr
- If UFH is contraindicated, consider an alternative agent such as bivalirudin, argatroban, or intravenous warfarin
- Initiate warfarin within 48 hr to obtain a goal INR of 2.0–2.5 by postoperative day 5–7, at which time UFH can be discontinued
- When surgical hemostasis is achieved, initiate aspirin (81–325 mg daily) 2–5 days postoperatively
- Maintain the patient throughout device support on aspirin and warfarin with a goal INR of 2.0–2.5

aPTT = activated partial thromboplastin time; UFH = unfractionated heparin.

Information from: Maltais S, Kilic A, Nathan S, et al.; PREVENT Study Investigators. PREVENtion of HeartMate 2 Pump Thrombosis Through Clinical Management: the PREVENT multi-center study. J Heart Lung Transplant 2017;36:1-12.

6. With respect to long-term anticoagulation, a recent analysis including over 10,000 INR values in 249 HeartMate 2 recipients was published.
    a. Identified that the optimal INR on the basis of weighted mortality of thrombotic and bleeding events was 2.6
    b. Lowest rates of combined adverse events with INR values between 2.0–3.2
    c. Significant increase in stroke and pump thrombosis with INR values under 2.0
    d. Higher rates of GIB and intracerebral hemorrhage with INR values over 3.0
7. Taken together, HeartMate 2 recipients should be maintained on warfarin with a target INR of 2.0–3.0, together with aspirin 81–100 mg daily.
8. According to data from the bridge-to-transplant trial of the HeartWare HVAD, a similar INR target of 2.0–3.0 should be used for this device, together with aspirin 100–325 mg daily.
9. UFH should be initiated early after surgery for both devices (once hemostasis has been achieved); a regimen similar to that used in the PREVENT study is appropriate.
10. The HeartMate 3 device was approved in August of 2017
    a. Designed with specific features to enhance hemocompatability and reduce the risk of thrombosis (wider blood flow passages, intrinsic pulse to wash motor)
    b. Rates of pump thrombosis at 2-years was reduced to 1.1% with HeartMate 3 compared to 15.7% in HeartMate 2 (p<0.001)
    c. Standard anticoagulation regimen is still warfarin with target INR goal of 2.0–3.0 along with aspirin 81–100 mg daily.
    d. MAGENTUM 1 is a small pilot study recently published that suggested a lower INR target of 1.5–1.9 is feasible with this device; additional data are needed before this regimen can be deployed in clinical practice.
11. Direct acting oral anticoagulants (DOAC) in CF-LVADs
    a. Majority of data comes from a single-center, open label trial of 16 HVAD patients
    b. Randomized to either phenprocoumon or dabigatran at a dose of 110 and 75 mg twice daily in patients with normal or impaired renal function (glomerular filtration rate greater than 80 mL/min or between 80 and 30 mL/min, respectively)

c. The study was stopped prematurely when 4 of the 8 HVAD patients in the dabigatran group experienced a thromboembolic event
d. Study limited by small sample size and underdosing of dabigatran
e. Warfarin should remain the preferred oral anticoagulant prescribed to CF-LVAD patients. A recent series of 15 patients with HeartMate 3 implantation suggested that apixaban protects against thrombotic complications while reducing bleeding risk compared with warfarin. Although these preliminary data are encouraging, pending publication of larger patient cohorts, DOACs can be considered only as salvage therapy for patients who definitively fail warfarin (ASAIO J 2022;68:318-22).

E. Treatment of Device-Related Thrombosis for CF-LVADs (Pharmacotherapy 2015;35:79-98)
1. Pathophysiology is complex and multifaceted.
a. Inherent lack of hemocompatibility of the blood-contacting surfaces within the device
b. Thrombus formation begins when activated platelets and the titanium alloy interface.
c. As activated platelets continue to aggregate, local concentrations of tissue factor spike and form complexes with factor VIIa, stimulating the extrinsic pathway.
d. Eventually, a stabilized clot forms within the device, which increases sheer stress on erythrocytes.
e. The ensuing hemolysis perpetuates this vicious cycle by carbon monoxide release, which is itself a procoagulant molecule.
f. As the clot expands, either within the pump motor itself or in the cannula, device function eventually becomes compromised.
2. Diagnosis of pump thrombosis is difficult, given the radio-opaque nature of CF-LVAD.
a. Patients may present with signs and symptoms of worsening HF.
b. Altered device parameters (Table 17)
c. Elevated serum lactate dehydrogenase values
d. Other clinical evidence of hemolysis (e.g., tea-colored urine, anemia)
e. Pump speed change test (i.e., "Ramp" test) using echocardiography can help establish diagnosis.
3. Drug therapy (e.g., UFH, glycoprotein IIb/IIIa inhibitors, thrombolytics) has largely proven ineffective in the treatment of suspected thrombosis in HeartMate 2 recipients.
a. Evidence limited to case reports and case series
b. Extensive review published (Pharmacotherapy 2015;35:79-98)
c. Medical therapy should be reserved as salvage treatment for those who are not candidates for surgery.
4. Surgical therapy (either device exchange or HT) is preferred for HeartMate 2 recipients with suspected pump thrombosis.
a. Superior survival rates compared with drug therapy
b. Can often be accomplished with minimally invasive surgery (i.e., subcostal approach to spare sternal reentry)
5. Device exchange is a more extensive surgery with the HeartWare HVAD, given the intrapericardial location of this pump.
a. Limited evidence still suggests that surgery is superior to drug therapy for suspected device thrombosis.
b. A recent case series (n=15) suggests that thrombolytic therapy is useful in selected patients (JACC Heart Fail 2015;3:849-56).
i. Using log files of power readings stored in the device may identify early signals of thrombosis.
ii. Facilitates intervention before thrombi become too extensive to be treated pharmacologically
iii. Unfortunately, details regarding the thrombolytic dose and regimen were not provided.
iv. Still should be viewed as hypothesis-generating until prospectively confirmed
6. Given the very low rate of device thrombosis with the HeartMate 3, data regarding optimal management do not exist. Given the experience with the HeartMate 2, surgical device exchange is likely the preferred treatment; however, this recommendation is completely empiric.

F. Treatment of Device-Related Infections
   1. Major complication associated with CF-LVAD therapy
      a. Reported rates are 25%–80%.
      b. Can be associated with the device itself
         i. Percutaneous driveline most common
         ii. Intraperitoneal pocket (HeartMate 2 device only)
         iii. Pump motor and/or cannulas
      c. Other infection sites also common (e.g., pneumonia and urinary tract infections)
   2. Epidemiological studies have shown that CF-LVAD recipients are susceptible to gram-positive, gram-negative (including *Pseudomonas* sp.), and fungal (e.g., *Candida* sp.) infections.
      a. Consider broad-spectrum empiric coverage, especially if the patient has severe sepsis or septic shock.
      b. Tailor antimicrobial therapy as soon as culture data are available.
   3. Once the device/driveline is seeded and becomes the source of infection, surgery is the only definitive therapy.
      a. Chronic suppressive antimicrobial therapy is commonly used as a temporizing measure.
      b. Debridement of tissue at the driveline exit site is a common strategy.
      c. Complete device exchange with relocation of the driveline is curative.
      d. Patients with bridge-to-transplantation with device-related infection can escalate on the HT wait list and gain status (i.e., status 3 by exception).
      e. Patients with preexisting device-related infection who undergo HT may require extended courses of postoperative antimicrobial treatment as well as modification or omission of induction immunotherapy.

G. Treatment of RV Failure After CF-LVAD Implantation
   1. The anatomy and physiology of the RV are very distinct from the LV.
      a. Whereas the LV exerts powerful torsional and rotational forces, the RV operates using peristaltic contractions (similar to the gastrointestinal smooth muscles).
      b. The RV largely depends on the low hydraulic impedance characteristics of the pulmonary vascular bed.
      c. The RV can achieve comparable output with a myocardial energy cost of about one-fifth that of the LV.
   2. Unanticipated RV failure occurs in up to 40% of durable CF-LVAD recipients.
   3. No uniform definition for severe RV failure exists.
      a. Commonly manifests as hypotension, low device flow and low pulsatility indices, and echocardiographic evidence of RV dysfunction (Figure 5)
      b. Distinguishing RV failure from other causes of hypotension and low flow (e.g., inadequate device speed or hypovolemia) may require a pulmonary artery catheter.
   4. Typical first-line treatment for RV failure includes decongestive therapy (e.g., diuretics), device speed optimization, and inotropes (e.g., dobutamine).
   5. If the pulmonary vascular resistance is elevated (greater than 250 dynes/second/cm$^5$ or 3 Wood units) or the patient has other evidence of a high RV afterload (e.g., a transpulmonary gradient greater than 12 mm Hg [mPAP-PCWP]), a selective pulmonary artery vasodilator is the preferred initial pharmacologic agent (Figure 5).
   6. No clear evidence to guide selection of one pulmonary vasodilator over another (Table 18)
   7. Patients who respond to inhaled pulmonary vasodilator therapy may need to be transitioned to an oral pulmonary vasodilator (e.g., sildenafil).
   8. Those whose medical therapy fails or who have severe RV failure should receive mechanical right heart support.

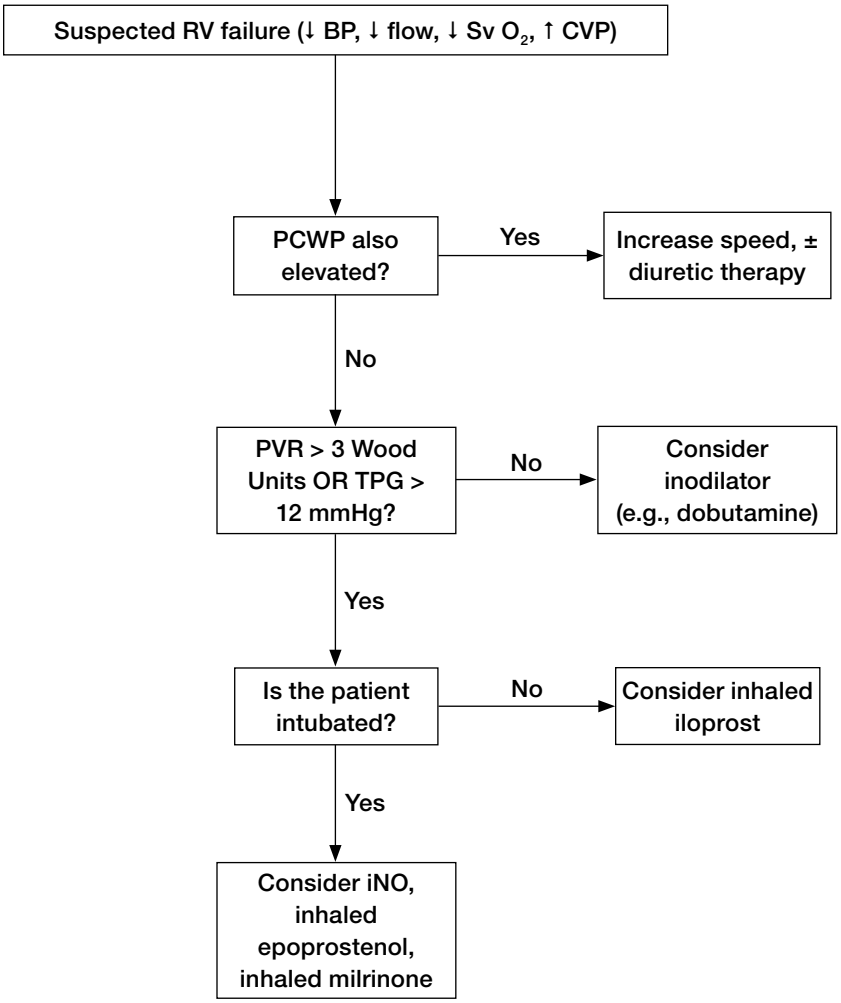


**Figure 5.** Flowchart for pharmacologic management of right ventricular (RV) failure.

BP = blood pressure; CVP = central venous pressure; iNO = inhaled nitric oxide; PCWP = pulmonary capillary wedge pressure; PVR = pulmonary vascular resistance; $Svo_2$ = mixed venous oxygen saturation; TPG = transpulmonary gradient.

Information from: Sabato LA, Salerno DM, Moretz JD, et al. Inhaled pulmonary vasodilator therapy for management of right ventricular dysfunction after left ventricular assist device placement and cardiac transplantation. Pharmacotherapy 2017;37:944-55.

**Table 18.** Comparison of Commonly Used Selective Pulmonary Artery Vasodilators in the ICU

| Agent | Mechanism of Action | Common Doses | Notes |
|---|---|---|---|
| **Inhaled nitric oxide** | Activates intracellular guanylyl cyclase, which increases concentrations of cyclic guanosine 3'5'-monophosphate | 1–20 ppm by continuous inhalation | • Very short half-life<br>• Can cause methemoglobinemia<br>• Very expensive<br>• Limited systemic exposure |
| **Inhaled epoprostenol** | Activates intracellular adenylate cyclase, which increases concentrations of cyclic adenosine monophosphate | 25–50 ng/kg/min | • Complicated administration<br>• Patient must be intubated<br>• Less expensive<br>• Some systemic exposure<br>◦ Potential for platelet inhibition and bleeding<br>◦ Potential hypotension |
| **Inhaled iloprost** | Activates intracellular adenylate cyclase, which increases concentrations of cyclic adenosine monophosphate | 2.5–5 mcg inhaled 6–9 times daily | • Ease of administration<br>• Patient can be extubated<br>• Very expensive<br>• Some systemic exposure<br>◦ Potential for platelet inhibition and bleeding<br>◦ Potential hypotension |
| **Inhaled milrinone** | Inhibits phosphodiesterase III, which increases concentrations of cyclic adenosine monophosphate | 6 mg/hr continuous inhalation | • Complicated administration<br>• Patient must be intubated<br>• Less expensive<br>• Systemic exposure<br>◦ Potential hypotension<br>◦ Arrhythmia |

Information from: Sabato LA, Salerno DM, Moretz JD, et al. Inhaled pulmonary vasodilator therapy for management of right ventricular dysfunction after left ventricular assist device placement and cardiac transplantation. Pharmacotherapy 2017;37:944-55.

H. Treatment of Hypertension After CF-LVAD Implantation
   1. All durable CF-LVADs are sensitive to increases in afterload.
      a. Elevations in systemic arterial pressure can impede device function and reduce forward flow (Table 17)
      b. Hypertension linked to increased stroke risk, especially in HeartWare HVAD recipients
   2. Systemic blood pressure is measured using a Doppler probe, given the lack of pulsatility.
      a. Goal mean arterial pressure is generally considered 70–80 mm Hg.
      b. Antihypertensive therapy should be initiated once mean arterial pressure is greater than 90 mm Hg.
   3. ACE inhibitors or ARBs should be first-line agents.
      a. Heart failure guideline-directed medical therapy should be prioritized as antihypertensive therapy to improve myocardial function.
      b. May reduce the risk of GIB (as described earlier)
   4. Dihydropyridine calcium channel blockers (e.g., amlodipine) are also acceptable options.
   5. β-Blockers can be used, assuming that RV function is acceptable.
   6. Most CF-LVAD recipients require one or two antihypertensive medications to maintain an optimal mean arterial pressure.

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## ANSWERS AND EXPLANATIONS TO PATIENT CASES

**1. Answer: D**

This case highlights a routine HT recipient with routine posttransplant problems that have complicated his course. He clearly is experiencing a rejection event at the time of presentation and has a significant history of rejection events. Given his biopsy results and clinical presentation, this patient clearly has mixed cellular and antibody-mediated rejection and must be treated for both problems simultaneously. Thus, Answers B and C are incorrect because they interrupt full treatment for cellular rejection. Answer A is incorrect because the AMR treatment strategy is insufficient to remove circulating antibodies and produce a durable response. Thus, Answer D represents the most reasonable treatment option that finishes cellular rejection therapy and provides full AMR treatment.

**2. Answer: C**

This patient is at high risk of developing early CAV. Thus, Answer C is most reasonable to down-regulate the development of fibrotic neointimal thickening of the allograft coronary arteries, and Answers A, B, and D are incorrect. In addition, mTOR antagonists may slow the rapid turnover of plasma cells, thereby decreasing DSA production.

**3. Answer: D**

This patient is experiencing worsening renal function, and the team is concerned regarding the potential for CNI-related renal injury. Although this adverse effect is possible, the patient has uncontrolled diabetes, which is also contributing to the patient's progressive kidney disease. Although changing to everolimus (Answer A) would theoretically reduce CNI exposure, this therapy is contraindicated because of the patient's proteinuria. Answer B is also not recommended because combining tacrolimus and everolimus could actually worsen this patient's renal function. Answer C is incorrect for the same reason. Answer D is correct because weaning the steroid may improve the patient's control of his diabetes, which may in turn slow the decline in his renal function. Answer D is also preferred because this patient has not had any rejection episodes, and weaning of steroids may prevent other adverse effects such as osteoporosis and opportunistic infections.

**4. Answer: B**

This patient is at intermediate risk of CMV (+/+), and as such, 3 months of prophylactic therapy is sufficient. Because the patient has completed this period and is 8 months posttransplantation, discontinuing valganciclovir (Answer B) would be most appropriate. Answer A is incorrect because there would be no therapeutic advantage to changing nystatin to clotrimazole, and clotrimazole would interact with the patient's tacrolimus and potentially lead to higher trough concentrations without empiric dose reduction. Changing from dapsone to trimethoprim/sulfamethoxazole (Answer C) would not be appropriate, given this patient's worsening renal function. Answer D is not the best answer because this patient no longer requires therapy with valganciclovir.

**5. Answer: C**

This patient is receiving 800 units/hour of heparin from the purge solution, and the aPTT value is therapeutic. Therefore, no changes are necessary, and his current regimen can be continued (Answer C). Answer A is incorrect because the Impella device requires heparin in the purge solution. Answer B is incorrect because adding intravenous heparin to this patient's regimen would result in a supratherapeutic aPTT. Answer D is incorrect because this patient has no signs of heparin-induced thrombocytopenia and therefore has no indication for argatroban.

**6. Answer: B**

Two hours later, the Impella controller has reduced the purge solution from 16 mL/hour to 10 mL/hour, reducing the patient's overall heparin exposure from 800 units/hour to 500 units/hour. To replace the heparin that has been lost from the purge solution, intravenous heparin at 300 units/hour should be initiated (Answer B). Answer A is still incorrect because heparin cannot be removed from the purge solution. Answer C is incorrect; waiting for 6 hours without supplementing the heparin in the purge solution with intravenous heparin would likely result in the patient's not receiving therapeutic anticoagulation. Answer D is still incorrect because the patient has no signs or symptoms of heparin-induced thrombocytopenia.

**7. Answer: B**

Heparin is the gold standard anticoagulant for patients receiving ECMO support. However, Answer A is incorrect because initiating a fixed dose of heparin without first assessing the patient's status would be unwise. This dose of heparin (400 units) is also likely much too low, given this patient's weight and the normal heparin requirements for patients receiving ECMO support. Answer B is correct because this patient received a large bolus of heparin in the catheterization laboratory, and his coagulation status should be assessed before initiating heparin. Answer C is incorrect because this patient requires therapeutic levels of anticoagulation, not deep venous thrombosis prophylactic dosing. Answer D is incorrect because heparin is preferred to enoxaparin in patients receiving ECMO.

**8. Answer: B**

Acquired antithrombin deficiency is common in critically ill patients receiving ECMO support, and although there is no clear evidence supporting antithrombin replacement in patients who are deficient, evidence of escalating heparin doses poses the added concern of suboptimal anticoagulation. This patient's anti-Xa, aPTT, and ACT data further show subtherapeutic anticoagulation, despite such a high dose of heparin (Answer B is correct). Answer A is unlikely because patients in a critically ill state would not commonly have the synthetic liver function to produce excessive thrombin; also, changing to direct thrombin inhibitor therapy without evidence of heparin-induced thrombocytopenia would be inappropriate. Answer C is incorrect because it implies that continuing to escalate the heparin dose would be the solution in this case. Answer D is incorrect because there appears to be subtherapeutic anticoagulation by several methods assessed.

## ANSWERS AND EXPLANATIONS TO SELF-ASSESSMENT QUESTIONS

**1. Answer: A**
This case highlights a patient many years post-HT who presents with an asymptomatic moderate cellular rejection. Given the age of the graft and the absence of symptoms, an oral steroid burst is the most appropriate treatment (Answer A). Admission to the hospital for either intravenous steroids (Answer B) or thymoglobulin (Answer C) would be inappropriate, given the lack of evidence of graft dysfunction. Answer B would be appropriate if the patient were closer to initial transplantation (i.e., within 60 days). Answer D would be inappropriate because this patient is not experiencing AMR.

**2. Answer: A**
Given the episode of cellular rejection, changing cyclosporine to tacrolimus would be best (Answer A). Tacrolimus is more potent than cyclosporine and decreases episodes of cellular rejection. Answer B is incorrect because changing cyclosporine to everolimus would actually reduce the intensity of this patient's immunosuppression, which would not be desired, given the recent rejection. Answer C is incorrect because combining cyclosporine with everolimus carries the risk of synergistic nephrotoxicity, which would not be desirable, given this patient's baseline SCr concentration. The patient also does not have CAV; thus, adding everolimus to cyclosporine would not provide its intended benefit. Answer D is undesirable, given the many potential toxicities associated with chronic steroid administration; this patient, in particular, already has diabetes, which could be worsened by steroid administration.

**3. Answer: C**
This case highlights a patient with a high-grade ACR in the setting of graft dysfunction. In this scenario, the most appropriate agent would be thymoglobulin (Answer C). Steroids (Answers A and B), either intravenously or by mouth, would not be preferred, given the severe nature of this type of rejection. Answer D (IVIg) is used for AMR and is therefore inappropriate for this case.

**4. Answer: D**
This case highlights a patient after HeartMate 3 implantation. The reader is asked to select the optimal pharmacotherapeutic regimen for preventing thrombosis in this patient. Answer D is correct, according to the most current evidence with this device. Higher aspirin doses are not required for the HeartMate 3, and use of non-standard INR ranges (i.e., 2.0–2.5) is not recommended in general (Answers A–C are incorrect).

**5. Answer: A**
The patient in this case has many of the classic manifestations of pump thrombus. As explained in the chapter, data do not support drug therapy for this condition, and surgical device exchange (Answer A) is the preferred treatment modality. Answers B–D involve drug therapy and are therefore incorrect.

**6. Answer: B**
This case highlights a routine HT recipient with routine posttransplant problems that have complicated her course. Given her presentation symptomatology, she is likely experiencing a rejection event with depressed LVEF. Given the rapidity of decline in LVEF, short time out from transplantation, and absence of other rejection events, CAV is probably not the source of this acute problem. Of importance, this patient has had two full-term pregnancies and anti-HLA antibodies before transplantation; thus, in addition to cellular rejection, AMR may be contributing to her allograft dysfunction, making Answer B correct and Answers C and D incorrect. Although ACR may be the only source of her current problem, AMR must be on the differential, given pretransplant detectable antibodies, making Answer A incorrect.

**7. Answer: B**
To determine whether AMR is also playing a role in this patient's allograft dysfunction, she must be screened for circulating DSA. The only test on the list that can identify DSAs is Answer B, making Answer B correct and Answers A, C, and D incorrect.

**8. Answer: C**
This case vignette identifies a patient with substantial risk factors for ACR: African American race, MCS bridge to transplantation, and pretransplant anti-HLA antibodies. Lymphodepleting induction should be used to reduce the risk of ACR, making Answers A and B incorrect. Direct evidence exists that antithymocyte globulin may decrease CAV when used as induction, which is not true for alemtuzumab, making Answer C correct and Answer D incorrect.

# Acute Coronary Syndrome

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**Learning Objectives**

1. Distinguish between reperfusion strategies for acute coronary syndrome (ACS): ST-segment elevation myocardial infarction (STEMI) and non–ST-segment elevation (NSTE) ACS.
2. Devise a pharmacotherapeutic treatment plan for a patient with STEMI undergoing primary percutaneous coronary intervention (PCI) and for a patient with NSTE-ACS undergoing an invasive or conservative approach.
3. Differentiate between the best possible pharmacologic options for preventing thrombotic events in the acute management of ACS.
4. Analyze differences in evidence, pharmacology, pharmacokinetics, drug-drug interactions, monitoring, and adverse events between the $P2Y_{12}$ inhibitors and anticoagulants used in ACS management.
5. Devise an individualized evidence-based treatment plan for patients in need of secondary prevention post-ACS, including mortality-reducing therapies.

**Abbreviations in This Chapter**

| | |
|---|---|
| ACS | Acute coronary syndrome |
| CABG | Coronary artery bypass grafting |
| CAD | Coronary artery disease |
| CV | Cardiovascular |
| cTn | Cardiac troponin |
| DAPT | Dual antiplatelet therapy |
| DES | Drug-eluting stent |
| DM | Diabetes mellitus |
| ECG | Electrocardiogram |
| ED | Emergency department |
| GP | Glycoprotein |
| HIT | Heparin-induced thrombocytopenia |
| hs-cTn | High-sensitivity cardiac troponin |
| HTN | Hypertension |
| LDL | Low-density lipoprotein cholesterol |
| LVEF | Left ventricular ejection fraction |
| MI | Myocardial infarction |
| NSTE-ACS | Non–ST-segment elevation acute coronary syndrome |
| NSTEMI | Non–ST-segment elevation myocardial infarction |
| PCI | Percutaneous coronary intervention |
| Plt | Platelet count |
| STEMI | ST-segment elevation myocardial infarction |
| TIA | Transient ischemic attack |
| TIMI | Thrombolysis in myocardial infarction |
| UA | Unstable angina |

**Self-Assessment Questions**

*Answers and explanations to these questions can be found at the end of this chapter.*

*Questions 1–3 pertain to the following case.*

A 62-year-old man (weight 70 kg) with an unknown medical history presents to the emergency department (ED) with the chief concern of chest pain that woke him from sleep and radiates to his jaw. An electrocardiogram (ECG) reveals ST-segment elevation in leads V4–V6. His blood pressure is 142/62 mm Hg, and heart rate is 64 beats/minute. His oxygen saturation ($Sao_2$) is 95% on room air. Cardiac markers have been obtained, and the first troponin result was positive. Preparations are under way to take the patient to the cardiac catheterization laboratory. One hour has elapsed since his first medical contact with triage. He reports taking only amlodipine 10 mg at home for blood pressure.

1. Which treatment strategy is most appropriate for this patient at this time?
   A. Primary percutaneous coronary intervention (PCI) within 90 minutes.
   B. PCI within 120 minutes.
   C. Early invasive approach with reteplase 10 units intravenous push x 2.
   D. Tenecteplase 40 mg intravenous push.

2. Which will best address this patient's ischemic pain while minimizing the risk of complications periprocedurally?
   A. Intravenous metoprolol 5 mg x 3.
   B. Nitroglycerin 10 mcg/minute intravenously.
   C. Morphine 2 mg intravenously as needed.
   D. Enalaprilat intravenously.

3. Which is the best evidence-based treatment strategy for this patient if stenting occurs in the catheterization laboratory?
   A. Aspirin 325 mg, clopidogrel 600-mg loading dose, and unfractionated heparin infusion 80-unit/kg bolus.

B. Aspirin 81 mg, prasugrel 60-mg loading dose, and unfractionated heparin infusion 80-unit/kg bolus.

C. Aspirin 325 mg, ticagrelor 180-mg loading dose, and unfractionated heparin infusion 70-unit/kg bolus.

D. Aspirin 81 mg, prasugrel 60-mg loading dose, and bivalirudin 0.75-mg/kg bolus.

4. A 75-year-old African American woman (weight 86 kg) presents to the ED with chest pressure (10/10). Her ECG reveals ST-segment depression in inferior leads. Her medical history is significant for hypertension (HTN) and chronic kidney disease. Pertinent laboratory results are troponin 4.8 ng/L, serum creatinine (SCr) 2.7 mg/dL, and estimated creatinine clearance (CrCl) 24 mL/minute/1.73 $m^2$. She has been given aspirin 325 mg single dose; a nitroglycerin drip, initiated at 5 mcg/minute, will be titrated to chest pain relief and blood pressure. She consents for cardiac catheterization after adequate hydration. Which anticoagulation strategy is most appropriate to initiate in this patient?

   A. Intravenous heparin 4000-unit intravenous bolus, followed by a 1000-unit/hour continuous infusion.

   B. Enoxaparin 90 mg subcutaneously every 12 hours.

   C. Fondaparinux 2.5 mg subcutaneously daily.

   D. Bivalirudin 64.5-mg bolus, followed by a 151-mg/hour infusion.

5. A 55-year-old man (weight 75 kg) presents to the hospital with the chief concern of chest pain that was unrelieved at home with nitroglycerin. His ECG reveals ST-segment depression and T-wave inversion. Cardiac markers show an elevated troponin I. His medical history is significant for coronary artery disease (CAD), HTN, and diabetes mellitus (DM). His thrombolysis in myocardial infarction (TIMI) score is 4, and his SCr is 1.0 mg/dL. The patient had a recent admission for acute coronary syndrome (ACS) about 6 months ago. During his previous hospitalization, the patient was thought to have developed heparin-induced thrombocytopenia (HIT) because his platelet count (Plt) dropped to 40,000/$mm^3$ after his previous catheterization. Given this patient's diagnosis and history, and if he is taken to the catheterization laboratory for an early invasive strategy, which treatment regimen would be most appropriate to replace unfractionated heparin during his treatment?

   A. Bivalirudin 56.2-mg intravenous bolus, followed by a 131-mg/hour infusion.

   B. Enoxaparin 80 mg subcutaneously every 12 hours.

   C. Eptifibatide 13,500-mcg intravenous bolus × 2, followed by a 150-mcg/minute infusion.

   D. Fondaparinux 2.5 mg subcutaneously daily.

6. A 75-year-old man with chest pain, which resolved soon after admission, and positive troponins undergoes coronary angiography, which shows three-vessel disease. He is scheduled for elective coronary artery bypass grafting (CABG) surgery. He had received a drug-eluting stent (DES) 6 months earlier and was receiving clopidogrel 75 mg daily together with aspirin 81 mg daily. Which is the best antiplatelet management strategy before surgery?

   A. Discontinue clopidogrel; go ahead with surgery after 5 days; continue aspirin.

   B. Recommend that surgery be postponed for 7 days; discontinue clopidogrel and aspirin.

   C. Recommend that surgery be postponed for 5 days; discontinue clopidogrel and aspirin.

   D. Go ahead with surgery, and continue both clopidogrel 75 mg daily and aspirin.

7. A 65-year-old white man with a recent discharge diagnosis of myocardial infarction (MI) presents for a 1-month checkup. He also has HTN. He was discharged home on aspirin 81 mg daily, clopidogrel 75 mg daily, lisinopril 10 mg daily, metoprolol 25 mg twice daily, and atorvastatin 80 mg daily. He reports adherence to his medications, yet he has no medical insurance and prefers generic medications, when possible. Today, his fasting laboratory results include glucose 90 mg/dL, total cholesterol 270 mg/dL, high-density lipoprotein cholesterol (HDL) 31 mg/dL, low-density lipoprotein cholesterol (LDL) 189 mg/dL, and triglycerides (TG)

250 mg/dL. His blood pressure is 166/90 mm Hg. Which is the most appropriate addition in medication therapy for this Patient?

A. Non-statin therapy is not recommended.

B. Give ezetimibe 10 mg daily.

C. Give fenofibrate 145 mg daily.

D. Give evolocumab 420 subcutaneously, monthly.

8. A physician on your team asks you to report an adverse drug reaction (ADR) experienced by a patient taking ticagrelor. The patient had severe dyspnea after he was given a 180-mg loading dose. The dyspnea did not resolve within 48 hours and required drug discontinuation. Clopidogrel was initiated as a replacement because the patient received a DES. Which statement best describes The Joint Commission requirements for institutional ADR reporting?

A. A MedWatch report must be completed that explains the situation in which the ADR occurred.

B. Institutions must create their own definition of ADRs that practitioners will know when and how to complete reporting.

C. Because dyspnea is a known adverse event of ticagrelor, no reporting is required.

D. Only severe or life-threatening ADRs need to be reported.

# I. INTRODUCTION

A. Definitions and Pathophysiology
   1. ACS is a spectrum of conditions compatible with acute myocardial ischemia or infarction caused by an abrupt reduction in coronary blood flow because of an acute thrombus.
   2. Atherogenic plaque rupture is the typical underlying pathophysiology for ACS, causing several prothrombotic substances to be released, which results in platelet activation and aggregation and eventual thrombus formation, leading to partial or total occlusion of the coronary artery.
   3. ACS can be divided into ST-segment elevation myocardial infarction (STEMI) and non–ST-segment elevation acute coronary syndrome (NSTE-ACS).
      a. STEMI
         i. Defined by characteristic symptoms of myocardial ischemia in association with persistent ST-segment elevation on ECG with positive troponins
         ii. Represents a total occlusion of the coronary artery, usually involving platelets and thrombin
         iii. STEMI is an indication for an immediate coronary angiography to determine whether reperfusion can be performed.
      b. NSTE-ACS
         i. Suggested by the absence of persistent ST-segment elevation
         ii. Represents partial (platelet rich) occlusion of the coronary artery
         iii. NSTE-ACS can be divided into unstable angina (UA) and non-STEMI (NSTEMI) according to whether cardiac biomarkers of necrosis are present. UA and NSTEMI are closely related conditions whose pathogenesis and clinical presentation are similar but vary in severity.
         iv. ECG abnormalities and elevated troponins in isolation are insufficient to make the diagnosis and must be interpreted in the appropriate clinical context (Table 1).
   4. Universal definition of MI
      a. Because myocardial ischemia can occur outside the setting of plaque rupture, and transient elevations in cardiac biomarkers can confuse diagnosis and cause harm from misapplied therapies, a universal definition of MI has been developed worldwide (now in its fourth iteration: Circulation 2018;138:e618-51).
      b. Delineates specific causes of myocardial ischemia
         i. Type 1 MI: Infarction caused by atherothrombotic coronary artery disease (CAD) and usually precipitated by atherosclerotic plaque disruption (most common)
         ii. Type 2 MI: Infarction occurring secondary to an ischemia imbalance not related to a coronary thrombosis (i.e., oxygen supply and demand mismatch)
         iii. Type 3 MI: MI that results in death, with the inability to measure troponins
         iv. Type 4 MI: Procedural infarction with cardiac troponin values more than five times the 99th percentile upper reference limit occurring < 48 hours after the index procedure (type 4a) and stent thrombosis (type 4b) , and restenosis associated with percutaneous coronary intervention (type 4c)
         v. Type 5 MI: Cardiac surgery infarction, occurring during CABG revascularization
      c. Identifying source of myocardial ischemia before applying treatment is vital to achieving successful outcomes.
   5. Optimal inhibition of thrombosis is paramount in ACS management (specifically type 1 MI).

**Table 1.** ACS Subclassifications and Clinical Findings

| | Subjective Findings | Objective Findings | Extent of Injury |
|---|---|---|---|
| NSTE-ACS UA | Usually presents as a pressure-type chest pain that typically occurs at rest or with minimal exertion<br>Pain usually starts in the retrosternal area and can radiate to either or both arms, neck, or jaw<br>Pain may also present with diaphoresis, dyspnea, nausea, abdominal pain, or syncope<br>Unexplained new-onset or increased exertional dyspnea is the most common angina equivalent<br>Less common accompanying symptoms[a] (without chest pain) include epigastric pain, indigestion, nausea, vomiting, diaphoresis, unexplained fatigue, and syncope | ST-segment depression, T-wave inversion, or transient or nonspecific ECG changes may occur<br>No positive biomarkers for cardiac necrosis | No myocardial necrosis; partial occlusion of coronary artery |
| NSTEMI | | ST-segment depression, T-wave inversion, or transient or nonspecific ECG changes may occur<br>Positive biomarkers (cTn or hs-cTn elevation) | Myocardial injury; partial occlusion of coronary artery |
| STEMI | Classic symptoms include worsening of pain or pressure in chest, characterized as viselike, suffocating, squeezing, aching, gripping, and excruciating, that may be accompanied by radiation<br>Can present with less common accompanying symptoms[a] as well; diagnosis cannot be made by symptoms alone without accompanying ECG and biomarker assessment | ST-segment elevation<br>> 1 mm above baseline on ECG in two or more contiguous leads<br>Positive biomarkers (cTn or hs-cTn elevation) | Myocardial necrosis; total occlusion of coronary artery |

[a]Up to one-half of all MIs are silent or unrecognized, and one-third present with symptoms other than chest discomfort. Women, older adults, and those with diabetes tend to present more often with accompanying symptoms.

ACS = acute coronary syndrome; cTn= cardiac troponin; hs-cTn = high-sensitivity cardiac troponin; MI = myocardial infarction; NSTE-ACS = non–ST-segment elevation acute coronary syndrome; NSTEMI = non–ST-segment elevation myocardial infarction; STEMI = ST-segment elevation myocardial infarction; UA = unstable angina.

B. Initial Evaluation and Risk Stratification (Figure 1)
   1. A 12-lead ECG should be performed and interpreted within 10 minutes of presentation.
      a. Persistent ST-segment elevation should be treated according to the STEMI guidelines.
      b. Serial ECGs may be performed if the initial ECG is nondiagnostic.
   2. Serial cardiac troponins (cTn) should be obtained at presentation and 3–6 hours after symptom onset.
      a. Diagnosis is confirmed with the detection of a rise and/or fall of troponin, with at least one value above the 99th percentile of upper limit of normal and accompanying signs or symptoms of MI (i.e., chest pain, new ST changes, or new left bundle branch block).
      b. Subsequent troponin concentrations should be obtained as confirmation, especially when the initial concentration was not positive.
      c. Troponins appear in the blood within 6 hours of infarction and can remain elevated for up to 10 days.
   3. High-sensitivity cardiac troponin (hs-cTn) is the preferred biomarker over conventional cTn assays for detecting myocardial injury.
      a. hs-cTn assays measure cTn concentrations from 10- to 100-fold lower than conventional assays and can detect troponin in most healthy people.

b. There is greater sensitivity and negative predictive values with the use of hs-cTn, and the time interval to detectable concentrations at patient presentation is shorter with hs-cTn, allowing for faster detection.
c. hs-cTn assays can be repeated 1–3 hours from arrival with the pattern of rise or fall (i.e., delta) and the repeat value itself to inform risk stratification.

4. At initial presentation of NSTE-ACS, the clinical history, angina symptoms and equivalents, physical estimation, ECG, renal function, and cardiac troponin measurements can be integrated into an estimation of the risk of death and nonfatal cardiac ischemic events, which is useful for selecting the site of care, antithrombotic therapies, and invasive management. Risk calculators include the following:
   a. TIMI risk score (available at www.timi.org) is useful in predicting 30-day and 1-year mortality in patients with NSTE-ACS.
      i. Composed of seven 1-point indicators rated on presentation; 1 point is given for each of the following: 65 or older, three or more risk factors for CAD, prior coronary stenosis 50% or greater, ST-segment deviation on ECG, two or more anginal events in previous 24 hours, use of aspirin in previous 7 days, and elevated cardiac biomarkers (Table 2)
      ii. Risk of mortality, new or recurrent MI, or severe recurrent ischemia through 14 days; 0–2 is low risk, 3 is intermediate risk, and 4 or more is high risk
      iii. Among patients with higher risk scores (e.g., TIMI score of 3 or more), there is a greater benefit from early invasive strategies.
   b. The GRACE risk model (www.outcomes-umassmed.org/grace/acs_risk2/index.html) predicts in-hospital and post-discharge mortality or MI. Patients with high GRACE risk model scores (i.e., GRACE score greater than 140) can be identified for early invasive strategies.
      i. The GRACE model uses the following eight variables from history, physical examination, ECG, and laboratory values to estimate risk: age, systolic blood pressure, heart rate, SCr, cardiac arrest at admission, elevated cardiac biomarkers, ST-segment deviation on ECG, and Killip class at presentation.
      ii. The GRACE score 2.0 (https://www.outcomes-umassmed.org/grace/acs_risk2/index.html) is an updated model that allows for a mortality calculation for each score, rather than score ranges in the original GRACE score, and allows substituting renal failure and use of diuretics if the Killip class or SCr values are unavailable.

**Table 2.** TIMI Risk Score for Unstable Angina/NSTEMI[a,b]

| **Historical** | **Points** |
|---|---|
| Age > 65 | 1 |
| Three cardiac risk factors (HTN, diabetes, hyperlipidemia, smoking, family history) | 1 |
| Known CAD ≥ 50% stenosis | 1 |
| **Presentation** | |
| Severe angina (≥ 2 episodes within 24 hr) | 1 |
| ASA within 7 days | 1 |
| Elevated markers | 1 |
| ST-segment deviation ≥ 0.5 mm | 1 |

[a]Risk of mortality, new or recurrent MI, or severe recurrent ischemia through 14 days. Low is 0–2, intermediate is 3, and > 4 is high risk. TIMI score: score = 0–1, mortality 7%; score = 2, mortality 8%; score = 3, mortality 13%; score = 4, mortality 20%; score = 5, mortality 26%; and score = 6–7, mortality 41%.

[b]Risk score = total points (0–7).

ASA = aspirin; CAD = coronary artery disease; HTN = hypertension; NSTEMI = non–ST-segment elevation myocardial infarction; TIMI = thrombolysis in myocardial infarction.

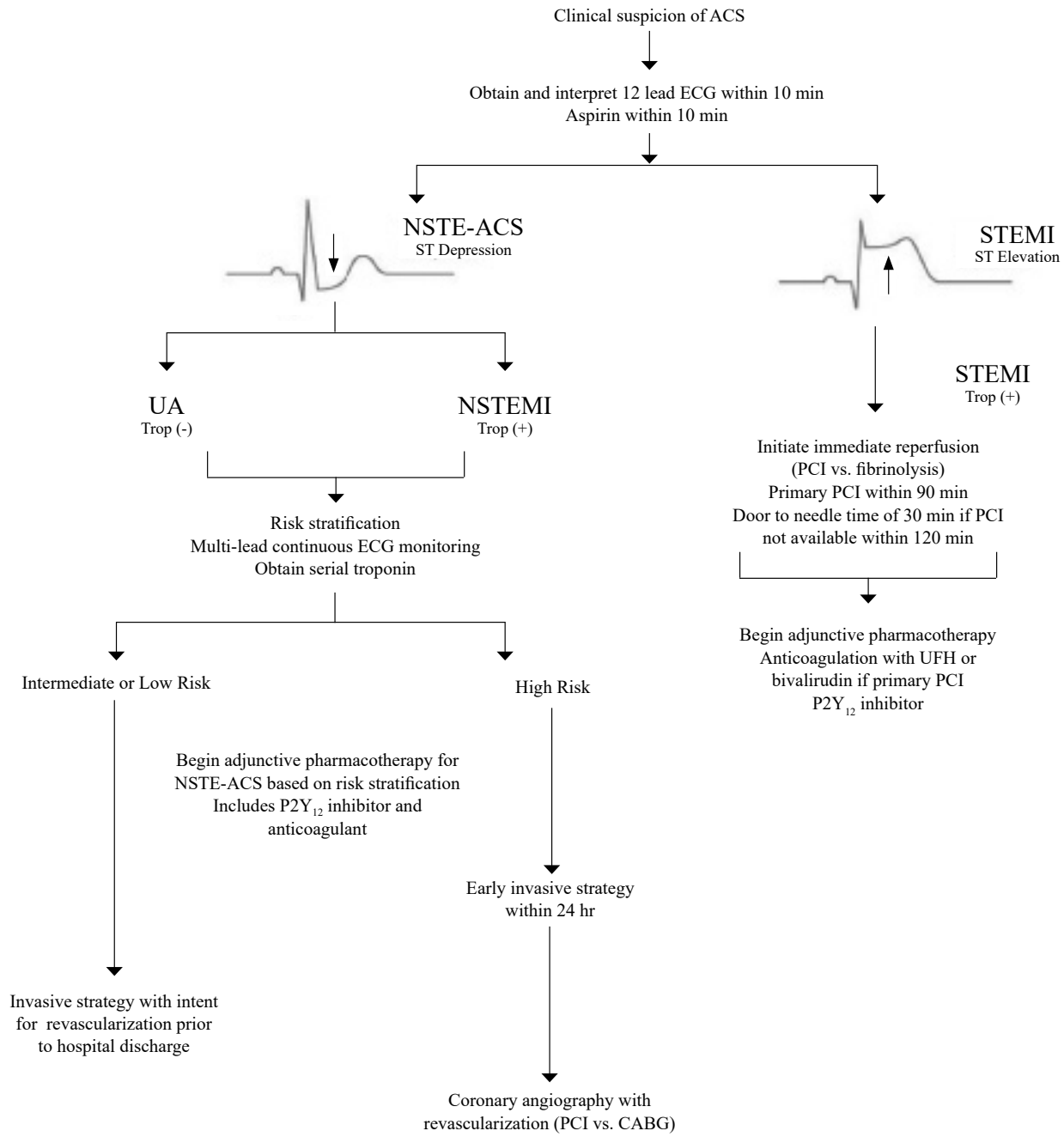


**Figure 1.** Acute coronary syndrome diagnosis and risk stratification.

ACS = acute coronary syndrome; CABG = coronary artery bypass grafting; NSTE = non–ST-segment elevation; NSTEMI = non–ST-segment elevation myocardial infarction; PCI = percutaneous coronary intervention; STEMI = ST-segment elevation myocardial infarction; UA = unstable angina; UFH = unfractionated heparin.

C. Decision for Invasive Management (Circulation 2014;130:e344-426; Circulation 2013;127:e362-425)
   1. STEMI
      a. Goal of therapy is to restore the patency of the infarct-related artery and minimize infarct size. Secondary goals include preventing complications such as arrhythmias or death and controlling chest pain and associated symptoms.
      b. Requires urgent revascularization either by mechanical intervention (catheterization laboratory) or with drug therapy
      c. Primary PCI is preferred to fibrinolytic (drug) therapy.
         i. Greater than 90% achievement of good blood flow with primary PCI in STEMI
         ii. Only 50%–60% achievement of good blood flow with fibrinolytic therapy
      d. Performance measure includes goal of primary PCI within 90 minutes of first medical contact.
      e. Fibrinolytic therapy is indicated for patients with STEMI in whom PCI cannot be performed within 120 minutes (discussed later in chapter).
      f. Surgical revascularization may be indicated, depending on the severity of CAD, complexity of anatomy, or development of other complications.
   2. NSTE-ACS
      a. Goals of therapy are to prevent total occlusion of the related artery and to control chest pain and associated symptoms.
      b. Patients with NSTE-ACS are treated according to risk (TIMI, GRACE) (Figure 2).

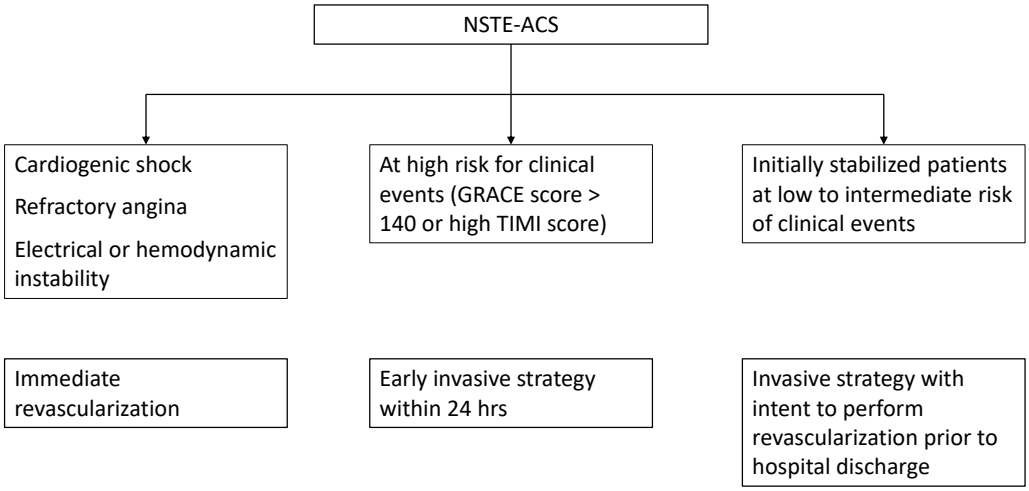


**Figure 2.** Timing of invasive strategy in patients with NSTE-ACS.

GRACE = Global Registry of Acute Coronary Events; NSTE-ACS = non–ST-segment elevation acute coronary syndrome; TIMI = thrombolysis in myocardial infarction.

      c. An immediate invasive strategy (emergent coronary angiography and revascularization) is recommended in patients with cardiogenic shock as well as patients with refractory angina or hemodynamic or electrical instability (i.e., ventricular arrhythmias).
      d. An early invasive strategy refers to diagnostic angiography and intent to perform revascularization within 24 hours.
         i. Indicated in those with NSTE-ACS who are at high risk according to clinical findings
         ii. An early invasive strategy in high-risk patients is associated with a lower incidence of recurrent ischemia or need for urgent revascularization and a shorter length of stay.

iii. Not for those with serious comorbidities or contraindications to such procedures (hepatic, renal, and pulmonary failure; cancer) for whom the risks of the procedure might outweigh the benefits of revascularization

e. An invasive strategy with intent for revascularization prior to hospital discharge is recommended in initially stabilized patients at intermediate or low risk of clinical events.

f. A conservative strategy refers to the use of medications alone (i.e., antiplatelets, anticoagulants, and anti-anginal medications) as the initial treatment.
   i. May be considered after shared-decision making in low-risk patients or in patients who are not good candidates for an invasive strategy (e.g., chronic kidney disease, frailty, limited life expectancy).

g. Surgical revascularization may be indicated, depending on the severity of CAD, complexity of anatomy, or development of other complications.

## II. ANTI-ISCHEMIC INTERVENTIONS

A. Early hospital care includes anti-ischemic and analgesic medications.

B. "MONA" plus β-Blocker (Table 3)

**Table 3.** Initial Anti-ischemic Therapies in ACS Management

| | |
|---|---|
| M = morphine, or other narcotic analgesic | • Provides analgesia and decreases pain-induced sympathetic/adrenergic tone<br>• Commonly used because it may also induce vasodilation and mediate some degree of afterload reduction<br>• Morphine 1–5 mg IV every 5–30 min is reasonable if symptoms are not relieved despite maximally tolerated anti-ischemic medications[a]<br>• Carries a class 2b recommendation and may not be favored more than other narcotic analgesics, given that at least two large trials have identified an association between morphine administration and risk of death (N Engl J Med 2014;371:1016-27; Am Heart J 2005;149:1043-9)<br>• Slows the absorption of antiplatelet therapy, reduces time to peak antiplatelet activity, and may decrease AUC |
| O = oxygen | • Can help attenuate anginal pain secondary to tissue hypoxia<br>• Consider supplemental oxygen if $Sao_2$ < 90%, respiratory distress, or high-risk features of hypoxemia[b] |
| N = nitroglycerin | • Facilitates coronary vasodilation and may also help in severe cardiogenic pulmonary edema caused by venous capacitance<br>• NTG spray or sublingual tablet (0.3–0.4 mg) every 5 min for up to three doses to relieve acute chest pain (if pain is unrelieved after one dose, call 911); afterward, assess need for IV<br>• IV used in first 48 hr for treatment of persistent ischemic chest pain, HF, and HTN<br>• IV NTG 5–10 mcg/min; titrate to chest pain relief or max 200 mcg/min<br>• Use should not preclude other mortality-reducing therapies (β-blocker, ACE inhibitor)<br>• **CIs:** Sildenafil or vardenafil (use within 24 hr) or tadalafil (use within 48 hr); SBP < 90 mm Hg or ≥ 30 mm Hg below baseline, heart rate < 50 beats/min, heart rate > 100 beats/min in absence of symptomatic HF, or suspected right ventricular infarction |
| A = aspirin | • Inhibits platelet activation<br>• Chew and swallow non–enteric-coated 162–325 mg x 1 dose[b]<br>• Clopidogrel if aspirin allergy<br>• Performance measure |
| β-Blocker | • Decrease myocardial ischemia, reinfarction, and frequency of dysrhythmias, and increase long-term survival<br>• Oral β-blocker[b] should be initiated within 24 hours in patients who do not have signs of HF, evidence of low-output state, increased risk of cardiogenic shock, or other CIs to β-blockade (e.g., PR interval > 0.24 s, second- or third-degree heart block, active asthma, or reactive airway disease)<br>• Reasonable to continue in patients with NSTE-ACS with normal LV function[b]<br>• Use metoprolol succinate, carvedilol, or bisoprolol in concomitant stabilized HFrEF[b]; add cautiously in decompensated HF<br>• Avoid agents with intrinsic sympathomimetic activity (acebutolol, pindolol, penbutolol)<br>• IV β-blocker[c] is potentially harmful in patients who have risk factors for shock (age > 70 yr, heart rate > 110 beats/min, SBP < 120 mm Hg, and late presentation) |

[a]Class 2b, may be considered.

[b]Class 1, should be performed or administered; class 2a, reasonable to be performed or administered.

[c]Class 3, not to be administered or harmful.

ACE = angiotensin-converting enzyme; ACS = acute coronary syndrome; AUC = area under the curve; CI = contraindication; HF = heart failure; HFrEF = heart failure with reduced ejection fraction; HTN = hypertension; IV = intravenous(ly); LV = left ventricular; NSTE = non–ST-segment elevation; NTG = nitrogylcerin; SBP = systolic blood pressure; STEMI = ST-segment elevation myocardial infarction.

**Patient Cases**

*Questions 1 and 2 pertain to the following case.*

A 55-year-old African American woman with obesity (weight 120 kg) and a history of ischemic coronary artery disease and diabetes presents to the ED after developing severe back pain accompanied by nausea and vomiting. She describes a similar event earlier in the morning that awoke her from sleep. Electrocardiographic evaluation reveals ST-segment depression in leads V2–V4. A chest radiograph demonstrates pulmonary edema. Laboratory values include sodium 144 mEq/L, potassium 3.8 mEq/L, SCr 3.2 mg/dL, and glucose 182 mg/dL. Estimated CrCl is 38 mL/minute. Cardiac troponin is 3.4 ng/mL. Blood pressure is 138/90 mm Hg with a heart rate of 80 beats/minute. She takes hydrochlorothiazide 25 mg/day, metformin 850 mg twice daily, and aspirin 81 mg/day.

1. Which best represents this patient's TIMI risk score?
   A. 2.
   B. 3.
   C. 4.
   D. 5.

2. Which addresses the most appropriate reperfusion for this woman?
   A. Fibrinolytic therapy.
   B. An early invasive strategy.
   C. A conservative treatment approach.
   D. An antithrombotic strategy.

3. Which patient would be the best candidate for a conservative management approach?
   A. 68-year-old man with HTN, DM, and hyperlipidemia with chest pain, T-wave inversion, and daily aspirin use.
   B. 45-year-old man with ST-segment depression and positive troponins.
   C. 65-year-old woman with resolved chest pain and negative troponins.
   D. 59-year-old woman with recent stent placement and ST-segment elevation.

## III. ANTIPLATELET THERAPY

A. Patients with STEMI and NSTE-ACS should be treated with antiplatelet therapy (Tables 4–6).
   1. Platelets are activated by several different mechanisms, only some of which can be inhibited by medications.
   2. Combination therapy with dual antiplatelet therapy plus a concomitant anticoagulant is the mainstay of acute ACS management, which targets the underlying pathophysiology of thrombus formation in ACS.
   3. The roles and combinations of antiplatelet therapies continue to be refined through clinical trials in varying subsets of ACS presentation (Table 4).
   4. In general, all patients receive aspirin and a $P2Y_{12}$ receptor antagonist, and some patients derive benefit from adding GP IIb/IIIa inhibition in the acute management of ACS.

**Table 4.** Antiplatelet Management Strategies According to ACS Presentation

| Antiplatelet | NSTE-ACS Conservative | NSTE-ACS Invasive | STEMI PPCI | STEMI + Fibrinolytic |
|---|---|---|---|---|
| Aspirin | Aspirin | Aspirin | Aspirin | Aspirin |
| $P2Y_{12}$ receptor antagonist | Clopidogrel<br>Ticagrelor | Clopidogrel<br>Prasugrel[a]<br>Ticagrelor[a]<br>Cangrelor[b] | Clopidogrel<br>Prasugrel[a]<br>Ticagrelor[a]<br>Cangrelor[b] | Clopidogrel[c]<br>Ticagrelor[d] |
| GP IIb/IIIa inhibitor | Reserved for patients undergoing PCI with large thrombus burden, no-reflow, or slow flow | | | |

[a]In patients with ACS undergoing PCI, it is reasonable to use ticagrelor or prasugrel in preference to clopidogrel to reduce ischemic events, including stent thrombosis (class 2a, 2021 Guideline for Coronary Artery Revascularization).

[b]Cangrelor may be considered in patients undergoing PCI who are P2Y12 inhibitor naïve (Class 2b, 2021 Guideline for Coronary Artery Revascularization).

[c]Pre-PCI after fibrinolytic therapy: 300-mg LD if within 24 hr of event; clopidogrel 600-mg LD if more than 24 hr after event.

[d]Ticagrelor may be used as an alternative to clopidogrel in patients less than 75 years of age who undergo PCI within 24 hr of fibrinolytic administration (Class 2b, 2021 Guideline for Coronary Artery Revascularization).

ACS = acute coronary syndrome; LD = loading dose; NSTE = non–ST-segment elevation; PCI = percutaneous coronary intervention; PPCI = primary percutaneous coronary intervention; STEMI = ST-segment elevation myocardial infarction.

Information from: Amsterdam EA, Wenger NK, Brindis RG, et al. 2014 ACC/AHA guideline for the management of patients with non–ST-elevation acute coronary syndromes: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Circulation 2014;130:e344-e426; Lawton JS, Tamis-Holland JE, Bangalore S, et al. 2021 ACC/AHA/SCAI guideline for coronary artery revascularization: a report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. Circulation 2022;145:e18-114. O'Gara PT, Kushner FG, Ascheim DD, et al. 2013 ACCF/AHA guideline for the management of ST-elevation myocardial infarction: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol 2013;61:e78-140.

B. Antiplatelet Therapy Recommendations
   1. Aspirin
      a. An irreversible cyclooxygenase (COX)-1 inhibitor blocking the formation of thromboxane $A_2$– and thromboxane $A_2$–mediated platelet activation
      b. Given to all patients (class 1)
      c. Established first-line therapy in ACS; reduces the incidence of recurrent MI and death
      d. Loading dose is necessary for aspirin-naive patients; avoid enteric-coated aspirin initially because of its delayed and reduced absorption.
         i. Dosing is 162–325 mg for patients at initial presentation of ACS.
         ii. Dosing is 81–325 mg for those who are undergoing PCI, depending on chronic aspirin therapy regimen.
      e. Aspirin is given indefinitely at a preferred dose of 81 mg post-ACS with or without PCI (class 1).
         i. Higher doses (greater than 160 mg) are associated with more bleeding than lower doses (less than 160 mg).
         ii. Higher doses (greater than 160 mg) do not improve outcomes post-ACS more effectively than lower doses (less than 160 mg).
      f. Dual antiplatelet therapy (DAPT) with aspirin plus a $P2Y_{12}$ receptor inhibitor is ideally indicated for all patients post-ACS for at least 12 months (discussed later in chapter). The optimal aspirin dose in patients treated with DAPT appears to be 75–100 mg daily.
   2. Oral $P2Y_{12}$ inhibitors
      a. Inhibit the effect of adenosine diphosphate on the platelet, a key mediator resulting in amplification of platelet activation
      b. $P2Y_{12}$ inhibitor therapy is given to all patients (class 1).

c. Choice of oral $P2Y_{12}$ inhibitor depends on the treatment strategy and pharmacokinetic differences (Tables 5–6).
   i. Agents
      (a) Clopidogrel
         (1) An inactive thienopyridine prodrug that requires oxidation by isoenzymes of cytochrome 450 (CYP; mainly 2C19) by a two-step process to generate an active metabolite
            (A) Genetic polymorphisms of CYP2C19 (i.e., poor metabolizers) may form less active metabolite and have reduced antiplatelet activity.
            (B) Avoiding drug interactions with potent CYP2C19 inhibitors (omeprazole and esomeprazole) is cited in the package insert.
         (2) Given once daily (300- to 600-mg loading dose and 75-mg maintenance dose)
            (A) A 600 mg loading dose is preferred in patients undergoing PCI because of a faster onset of action.
         (3) Risks include bleeding, pruritus
         (4) No routine monitoring recommended
      (b) Prasugrel
         (1) A thienopyridine prodrug that irreversibly blocks $P2Y_{12}$ receptors with a faster onset and more profound inhibitory effect than clopidogrel
         (2) Given once daily (60-mg loading dose and 10-mg/day maintenance dose in most patients)
            (A) Maintenance dose of 5 mg daily is recommended in patients with body weight less than 60 kg and can be used if deemed necessary in patients 75 years of age or more.
         (3) Risks include significant and fatal bleeding, rash
         (4) No routine monitoring required
      (c) Ticagrelor
         (1) A cyclopentyl-triazolo-pyrimidine that reversibly binds $P2Y_{12}$ with a more rapid onset of action and higher potency than clopidogrel; more rapid offset of action and platelet function recovery
         (2) Additional inhibition of adenosine reuptake by equilibrative nucleoside transporter 1
         (3) Given twice daily (180-mg loading and 90-mg twice-daily maintenance dose)
         (4) Risks include bleeding, dyspnea, and ventricular pauses (non-bleeding adverse effects because of inhibition of adenosine reuptake).
         (5) Monitor for drug interactions because ticagrelor is a substrate and a weak inhibitor of CYP3A4 and P-glycoprotein.
   ii. Efficacy data and guideline recommendations:
      (a) Clopidogrel and ticagrelor are preferred for a conservative (medical) treatment strategy (Table 5).
         (1) Clopidogrel (300- to 600-mg loading dose and 75-mg daily maintenance dose) has positive efficacy data for NSTE-ACS in patients who are not taken for invasive revascularization, according to the CURE trial, in which, regardless of stenting, clopidogrel added to aspirin (for 1 month or more out to 9 months) provided a significant relative risk reduction (around 20%) in cardiovascular (CV) death, MI, or stroke with an absolute 1% increase in bleeding risk.
         (2) Ticagrelor (180 mg loading and 90 mg twice daily) was superior to clopidogrel in the PLATO trial (n=18,624 patients with ACS); at 12 months, the primary composite efficacy end point (death from CV causes, MI, or stroke) was significantly reduced with ticagrelor (9.8% vs. 11.7%; hazard ratio [HR] 0.84; 95% confidence interval [CI], 0.77–0.92; $p<0.001$) (number needed to treat 53). Similar reductions in CV death and

all-cause mortality (4.3% vs. 5.8%; HR 0.76; 95% CI, 0.64–0.90; p=0.002) occurred, as did reductions in stent thrombosis (1.3% vs. 1.9%; HR 0.67; 85% CI, 0.50–0.91; p=0.009). Non-CABG major bleeding was significantly increased with ticagrelor, but overall, TIMI major and fatal bleeding was similar between groups.

(3) Prasugrel is not recommended in medically treated patients with ACS. Medically treated patients were excluded in the TRITON-TIMI 38 trial. In the TRILOGY-ACS study, prasugrel failed to show a significant benefit in CV events compared with clopidogrel.

(b) Clopidogrel, ticagrelor, and prasugrel are options for an early invasive strategy (Table 5).

(1) In the PCI-CURE study, 2658 patients undergoing PCI from the CURE trial who received clopidogrel in addition to aspirin had significantly lower events at 30 days and a 31% reduction at 9 months in CV death or MI compared with those receiving only aspirin (p=0.002).

(2) In the TRITON-TIMI 38 trial, prasugrel (loading dose 60 mg and maintenance dose of 10 mg daily) was compared with clopidogrel in 13,608 patients with ACS scheduled for PCI; rates of CV death, nonfatal MI, and stroke were significantly reduced in those receiving prasugrel (9.9% vs. 12.2%; HR 0.82; 95% CI, 0.73–0.90; p<0.001) (number needed to treat 43). Rates of TIMI major hemorrhage, including both fatal and nonfatal bleeds, increased in the prasugrel group.

(A) It is reasonable to choose prasugrel over clopidogrel for $P2Y_{12}$ inhibitor treatment in patients with NSTE-ACS or STEMI who undergo PCI who are not at a high risk of bleeding complications and who have no history of transient ischemic attack (TIA) or stroke (class 2a).

(B) Identified that subgroups of patients that benefited the most from prasugrel were those presenting with STEMI and stent thrombosis and those with diabetes

(3) In the PLATO trial (as described earlier), ticagrelor reduced major ischemic events in patients for STEMI and NSTE-ACS, including patients intended for revascularization at time of randomization. Ticagrelor should be chosen over clopidogrel for $P2Y_{12}$ inhibitor treatment in patients with NSTE-ACS or STEMI treated with an early invasive strategy or coronary stenting (class 2a).

(c) Two randomized clinical trials have directly compared ticagrelor and prasugrel.

(1) The PRAGUE-18 randomized 1230 patients with STEMI or high-risk NSTEMI treated with PCI to receive prasugrel or ticagrelor. The trial was underpowered because of premature discontinuation of enrollment for futility. There were no significant differences in the primary composite end point or bleeding event rates between prasugrel and ticagrelor.

(2) The ISAR-REACT 5 was an open-label superiority trial that randomized 4018 patients with ACS and a planned invasive approach to receive ticagrelor or prasugrel. A ticagrelor loading dose was administered as soon as possible after randomization, whereas a prasugrel loading dose was delayed in patients without ST-segment elevation until after coronary angiography. The primary end point of death, MI, or stroke at 1 year was higher in patients treated with ticagrelor (9.3%) than in those treated with prasugrel (6.9%; HR 1.36; 95% CI, 1.09–1.70; p=0.006). There was no significant difference between treatment groups in major bleeding event rates.

iii. Safety considerations:

(a) Prasugrel should not be administered to patients with a history of stroke or TIA (class 3).

(1) In TRITON-TIMI 38 trial, net harm occurred from prasugrel in patients with a history of cerebrovascular events (N Engl J Med 2007;357:2001-15).

(2) In addition, there was no clinical benefit in patients older than 75 (HR 0.99; 95% CI, 0.81–1.21; p=0.92) or those weighing less than 60 kg (HR 1.03; 95% CI, 0.69–1.53; p=0.89) in TRITON, and prasugrel should be given to these groups cautiously.

(b) Boxed warning: The efficacy of ticagrelor is decreased in patients treated with higher aspirin doses (greater than 300 mg daily) versus lower doses (less than 100 mg daily). In PLATO, patients treated with daily aspirin doses of greater than 300 mg had better clinical outcomes with clopidogrel (HR 1.45; 95% CI, 1.01–2.09), and those treated with doses of 100 mg or less had better outcomes with ticagrelor (HR 0.77; 95% CI, 0.69–0.86).
(c) Dyspnea with ticagrelor can occur in up to 15% of patients within the first week of therapy.
(d) Ticagrelor should be held for at least 3 days before surgery, clopidogrel should be held for at least 5 days, and prasugrel should be held for 7 days before major surgery.

**Table 5.** Guideline Recommendations for $P2Y_{12}$ Inhibitor Therapy in ACS with or without PCI[a]

| Guideline Recommendation | Class/Grade |
|---|---|
| An LD of $P2Y_{12}$ receptor inhibitor should be given in patients with ACS who undergo PCI. Options include: | 1 |
| a. Clopidogrel[b] 600 mg, followed by 75 mg daily | LOE B |
| b. Prasugrel 60 mg, followed by 10 mg daily[c]; or | LOE B |
| c. Ticagrelor 180 mg, followed by 90 mg BID | LOE B |
| • 2021 ACC/AHA guideline for coronary artery revascularization | |
| For patients with NSTE-ACS treated with PCI or patients with NSTE-ACS treated with medical therapy alone: | 1 |
| a. Clopidogrel 600 mg, followed by 75 mg daily | |
| b. Ticagrelor 180 mg, followed by 90 mg BID | LOE B |
| • 2014 NSTE-ACS guideline | LOE B |
| For patients with ACS treated with an early invasive or conservative strategy:<br>It is reasonable to use **ticagrelor** in preference to clopidogrel | 2a |
| • 2021 ACC/AHA guideline for coronary artery revascularization | LOE B |
| • 2016 ACC/AHA focused update on duration of DAPT | |
| For patients with ACS treated with PCI:<br>It is reasonable to choose **prasugrel** over clopidogrel | 2a |
| • 2021 ACC/AHA guideline for coronary artery revascularization | LOE B |
| Prasugrel should not be administered to patients with a history of TIA or stroke | Class 3 |
| • 2021 ACC/AHA guideline for coronary artery revascularization | |
| For patients who are $P2Y_{12}$ inhibitor naive and undergoing PCI, cangrelor may be reasonable | Class 2b |
| • 2021 ACC/AHA guideline for coronary artery revascularization | LOE B |

[a]Class 1, should be performed or administered; class 2a, reasonable to be performed or administered; class 2b, may be considered; class 3, not to be administered or harmful.

[b]Pre-PCI after fibrinolytic therapy: 300 mg LD if within 24 hr of event; clopidogrel 600 mg LD if > 24 hr after event.

[c]Maintenance dose of 5 mg daily is recommended in patients with body weight < 60 kg and can be used if deemed necessary in patients ≥ 75 yr.

ACC/AHA = American College of Cardiology/American Heart Association; ACS = acute coronary syndrome; BID = twice daily; DAPT = dual antiplatelet therapy; LD = loading dose; NSTE = non–ST-segment elevation; PCI = percutaneous coronary intervention; TIA = transient ischemic attack.

Information from: Lawton JS, Tamis-Holland JE, Bangalore S, et al. 2021 ACC/AHA/SCAI guideline for coronary artery revascularization: a report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. Circulation 2022;145:e18-e114; Levine GN, Bates ER, Bittl JA, et al. 2016 ACC/AHA guideline focused update on duration of antiplatelet therapy in patients with coronary artery disease: a report of the American College of Cardiology/American Heart Association Task Force on clinical practice guidelines. J Am Coll Cardiol 2016;68:1082-115; Amsterdam EA, Wenger NK, Brindis RG, et al. 2014 ACC/AHA guideline for the management of patients with non–ST-elevation acute coronary syndromes: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Circulation 2014;130:e344-e426.

**Table 6.** Comparison of Oral $P2Y_{12}$ Receptor Inhibitors

| Parameter | Clopidogrel (Plavix)[a] | Prasugrel (Effient)[b] | Ticagrelor (Brilinta)[c] |
|---|---|---|---|
| Mechanism of action | Thienopyridine; inhibits ADP-mediated platelet activation at the $P2Y_{12}$ receptor | Thienopyridine; inhibits ADP-mediated platelet activation at the $P2Y_{12}$ receptor | Inhibits ADP-mediated platelet activation at the $P2Y_{12}$ receptor via a distinct site |
| Peak platelet inhibition | 300 mg load ~6 hr<br>600 mg load ~2 hr | 60 mg load ~30 min[d] | 180 mg load ~30 min[d] |
| % platelet inhibition | 30%–40% | 60%–70% | 60%–70% |
| LD | 300–600 mg[e] | 60 mg | 180 mg |
| Maintenance dose | 75 mg daily | 10 mg daily; 5 mg if weight < 60 kg or age ≥ 75 | 90 mg BID[f] |
| Metabolism | Prodrug; converted by two-step process to active metabolite involving 2C19 in addition to other CYP enzymes | Prodrug; converted by 1 step to active metabolite by several CYP pathways | Not prodrug; reversible, noncompetitive binding; 3A4 (primary), 3A5, P-gp inhibitor |
| Reversible platelet binding | No | No | Yes |
| Half-life | 8 hr (metabolite) | 3.7 hr (metabolite, range 2–15 hr) | 7 hr (parent), 9 hr (active metabolite) |
| Nonresponders | Exposure to active drug affected by *CYP2C19* genetic polymorphisms | No known issues | No known issues |
| Drug-drug/drug-diesease interactions and common non–bleeding-related adverse events | PPIs inhibit CYP2C19 (concomitant use with esomeprazole/omeprazole is discouraged on package labeling); increased bleeding with NSAIDs, OACs, O3FAs | No clinically significant drug interactions; more bleeding with NSAIDs, OACs | Careful with asthma, bradycardia; use not recommended in severe hepatic impairment; More bleeding with NSAIDs, OACs; strong 3A4 inducers ↓ ticagrelor concentrations; strong 3A4 inhibitors ↑ ticagrelor concentrations; do not exceed 40 mg of simvastatin or lovastatin<br>Limit aspirin to < 100 mg. Monitor digoxin concentrations |
| Surgery hold time[g] | 5 days | 7 days | 3 days |
| Bleeding risk | Less than prasugrel and ticagrelor with standard dosing | Risk of non-CABG, spontaneous, and fatal bleeds higher than with standard-dose clopidogrel | Risk of non-CABG bleeds higher than with standard-dose clopidogrel |
| Box warning | *CYP2C19* polymorphisms | Age-related bleeding, CVA | Aspirin dosing > 100 mg |
| CIs | | TIA, CVA | ICH, severe hepatic disease |
| Supporting trials | CREDO, CURE, PCI-CURE, CLARITY, COMMIT | TRITON-TIMI 38, TRILOGY, ACCOAST, ISAR-REACT 5 | PLATO, PEGASUS |
| FDA indication | ACS managed medically or with PCI | ACS with PCI | ACS managed medically or with PCI |

[a]Administer clopidogrel indefinitely if aspirin allergy. Avoid LD if patient is ≥ 75 yr in STEMI when fibrinolysis is given.

[b]Avoid prasugrel in patients with active pathologic bleeding or a history of TIA or CVA and in patients ≥ 75 yr unless the patient has diabetes mellitus (DM) or a history of MI.

[c]Avoid ticagrelor in patients with active pathologic bleeding or a history of ICH. Avoid aspirin doses > 100 mg daily (exception: first dose of 325 mg).

[d]A significant antiplatelet effect has been observed at 30 min. Onset of effect is quicker, and extent of platelet inhibition is greater than with clopidogrel.

[e]A 600-mg LD results in greater, more rapid, and more reliable platelet inhibition than a 300-mg LD.

[f]Maintenance dosing of 60 mg BID FDA approved for reduction of thrombotic events after initial 12 mo of therapy.

[g]In emergency CABG, clopidogrel and ticagrelor should be held for at least 24 hr to minimize the risk of CABG-related bleeding.

ACS = acute coronary syndrome; ADP = adenosine diphosphate; BID = twice daily; CABG = coronary artery bypass graft; CI = contraindication; CVA = cerebrovascular accident; CYP = cytochrome P450; ICH = intracranial hemorrhage; LD = loading dose; MI = myocardial infarction; NSAID = nonsteroidal anti-inflammatory drug; O3FA = omega-3 fatty acid; OAC = oral anticoagulant; PCI = percutaneous coronary intervention; P-gp = P-glycoprotein; PPI = proton pump inhibitor; STEMI = ST-segment elevation myocardial infarction; TIA = transient ischemic attack.

Information from: Lawton JS, Tamis-Holland JE, Bangalore S, et al. 2021 ACC/AHA/SCAI guideline for coronary artery revascularization: a report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. Circulation 2022;145:e18-e114; Amsterdam EA, Wenger NK, Brindis RG, et al. 2014 ACC/AHA guideline for the management of patients with non–ST-elevation acute coronary syndromes: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Circulation 2014;130:e344-e426.

3. Intravenous $P2Y_{12}$ inhibitors
    a. Cangrelor, a direct-acting, rapidly reversible, intravenous $P2Y_{12}$ inhibitor, achieves a high level of platelet inhibition (greater than 90% with a 30-mcg/kg intravenous bolus, followed by a 4-mcg/kg/minute infusion) within 5 minutes and reaches steady state within 15–30 minutes of administration.
    b. Cangrelor's rapid onset and offset (half-life less than 5 minutes) allows a quick, high degree of platelet inhibition with resolution of normal platelet function within 1 hour of ending treatment.
    c. Cangrelor has been primarily studied in the setting of PCI and may be considered in patients who are $P2Y_{12}$ inhibitor naive (Class 2b).
    d. Cangrelor use may also be considered in patients undergoing PCI who are unable to take oral medications (e.g., significant nausea, altered mental status)
    e. Trials comparing cangrelor with clopidogrel in ACS did not show the superiority of cangrelor.
    f. Both the CHAMPION PCI and the CHAMPION PLATFORM trials were discontinued prematurely.
    g. Cangrelor demonstrated superior efficacy to post-PCI clopidogrel with increases in minor (not major) bleeding (CHAMPION PHOENIX).
    h. A meta-analysis of the three CHAMPION trials reported a significant reduction in the primary CV composite end point (death, MI, ischemia-driven revascularization, or stent thrombosis at 48 hours) with cangrelor and an increase in mild, but not major, bleeding events (Lancet 2013;382:1981-92).
    i. Cangrelor treatment was associated with increased risk for dyspnea.
    j. Cangrelor has not been studied in settings with preloaded clopidogrel or compared with prasugrel or ticagrelor.
    k. Cangrelor has a potential use as a bridge therapy after discontinuation of oral $P2Y_{12}$ inhibitors in high-risk patients undergoing CABG (JAMA 2012;307:265-74).
    l. The onset of action of both clopidogrel and prasugrel is delayed when coadministered with cangrelor, suggesting that cangrelor preferentially binds to the $P2Y_{12}$ and prevents irreversible inhibition with prasugrel and clopidogrel's active metabolite. Therefore, clopidogrel and prasugrel should not be initiated until termination of the cangrelor infusion. No such drug interaction exists with ticagrelor. A ticagrelor loading dose can be administered any time during a cangrelor infusion or immediately after discontinuation. A prasugrel or clopidogrel loading dose should be administered immediately after cangrelor discontinuation.
    m. Expense and lack of evidence showing superiority to other $P2Y_{12}$ inhibitors limit the use of cangrelor.
4. Intravenous GP IIb/IIIa receptor inhibitors
    a. Block the final common pathway of platelet aggregation; achieve 80% inhibition of ex vivo platelet aggregation
    b. Double-bolus eptifibatide and high-dose bolus tirofiban are options in patients with ACS and treated with PCI (Table 7).
        i. Abciximab is included in the clinical practice guidelines; however, it is no longer manufactured.

c. GP IIb/IIIa inhibitors reduce the incidence of composite ischemic events, primarily through a decrease in documented MI, but they increase the risk of bleeding.
d. Most, but not all, data were gathered in the era before routine $P2Y_{12}$ inhibitor use.
e. Most studies have combined GP IIb/IIIa inhibitors with unfractionated heparin as the anticoagulant.
f. Upstream administration (given before PCI) is not superior to delayed administration (given at the time of PCI).
    i. Upstream administration is noninferior to delayed timing in reducing ischemic events.
    ii. Those receiving upstream GP IIb/IIIa inhibitors have significantly higher rates of bleeding than those receiving delayed administration.
    iii. Bolus-only GP IIb/IIIa inhibitor administration has been adopted in clinical practice.
g. In modern clinical practice, GP IIb/IIIa inhibitors are typically used in the catheterization laboratory for adjunctive or bailout use in cases of high thrombus burden, no-reflow, or slow flow during the procedure (class 2a).
h. Common adverse events of GP IIb/IIIa inhibitors:
    i. The most common adverse effect is bleeding, with rates as low as 1.4% and as high as 10.6%, depending on length of therapy and how bleeding rates were accrued in the individual studies.
    ii. Of note, the smaller molecule agents eptifibatide and tirofiban depend on renal clearance; adjustment of the infusion is recommended to decrease the risk of bleeding; monitor SCr (CrCl)
    iii. All GP IIb/IIIa inhibitors can cause thrombocytopenia; monitor hemoglobin (Hgb), hematocrit (Hct), and Plt.
    iv. Secondary to their short half-life, eptifibatide and tirofiban can be reversed within a few hours by discontinuing the infusion.

**Table 7.** GP IIb/IIIa Inhibitor Dosing

| | **Dosing for Patients Undergoing PCI** | **Renal Adjustments** |
|---|---|---|
| Eptifibatide (Integrilin) | 180 mcg/kg IV bolus × 2 (10 min apart); 2 mcg/kg/min initiated after first bolus for up to 18 hr | If CrCl < 50 mL/min/1.73 $m^2$, reduce infusion 50%; avoid in patients on hemodialysis; not studied in patients with SCr > 4 mg/dL |
| Tirofiban (Aggrastat) | 25 mcg/kg IV bolus over 3 min; then 0.15 mcg/kg/min for up to 18 hr | If CrCl ≤ 60 mL/min/1.73 $m^2$, reduce infusion 50% |

CrCl = creatinine clearance; IV, intravenous; SCr = serum creatinine.

5. Platelet function and genetic testing
    a. Currently, routine use of platelet function and genetic testing is not recommended in clinical practice guidelines.
    b. Genetic testing
        i. Genetic polymorphisms within the *CYP2C19* gene affect the antiplatelet action of clopidogrel.
        ii. Loss-of-function (LOF) alleles for the *CYP2C19* gene are associated with lower concentrations of the active metabolite for clopidogrel, lower platelet inhibition, and higher CV event rates in patients treated with clopidogrel.
        iii. Prospective randomized trials using genetic testing:
            (a) In the Popular Genetics trial, 2488 patients with a STEMI who underwent PCI were randomized to a genotype-guided treatment (ticagrelor or prasugrel with LOF alleles or clopidogrel for non-LOF alleles) or standard treatment with prasugrel or ticagrelor (N Engl J Med 2019;381:1621-31). The genotype-guided group was noninferior to the standard group for net adverse clinical events of all-cause death, MI, definite ST, stroke, or major bleeding (5.1% vs. 5.9%; p=0.001 for noninferiority). Bleeding events were significantly lower in the genotype-guided group (9.8% vs. 12.5%; HR 0.78; 95% CI, 0.61–0.98; p=0.04).

(b) In the TAILOR-PCI trial (n=5302), a genotype-guided treatment (ticagrelor for LOF carriers or clopidogrel for non-LOF carriers) did not significantly reduce a composite end point of CV death, MI, stroke, severe recurrent ischemia, or ST compared with conventional therapy with clopidogrel (4% vs. 5.9%; HR 0.66; 95% CI, 0.43–1.02; p=0.06). There were no significant differences between treatment groups for major or minor bleeding events (JAMA 2020;324:761-71).

c. Platelet function testing (PFT)
   i. PFT has prognostic value for ischemic and bleeding events after PCI.
   ii. Early clinical trials failed to show an improvement in clinical outcomes using PFT but were limited by variable definitions of high platelet reactivity (HPR), options for $P2Y_{12}$ inhibitor therapy, and low-risk patient populations.
   iii. Many PFT assays are available; however, point-of-care tests are preferred (i.e., VerifyNow, Multiplate, thromboelastography with platelet mapping).
   iv. In the TROPICAL-ACS trial (n=2610 patients with ACS), a PFT-guided de-escalation strategy (prasugrel in patients with HPR or clopidogrel in patients without HPR) showed noninferiority with a composite end point of CV death, MI, stroke, or BARC 2 or higher bleeding to standard treatment with prasugrel (7.3% vs. 9%; HR 0.81; 95% CI, 0.62–1.06; p=0.0004 for noninferiority). Bleeding event rates were similar and not significantly different between treatment groups (Lancet 2017;390:1747-57).

d. Selective use of PFT or genetic testing may be considered in certain patients with ACS.
   i. Clinical characteristics, including bleeding risk and thrombotic risk, and angiographic, procedural, and socioeconomic considerations should be accounted for in addition to PFT or genetic testing.
   ii. PFT or genetic testing can be used to support an antiplatelet de-escalation strategy in patients with ACS.
   iii. PFT can be used to aid in the timing of cardiac or non-cardiac surgery instead of arbitrarily waiting 5–7 days after antiplatelet discontinuation.

**Patient Cases**

4. Which best depicts the preferred treatment strategy for prasugrel given in addition to aspirin for the prevention of thrombotic events in a patient post-PCI?
   A. 10 mg for a 70-year-old man (weight 55 kg) with a history of stent thrombosis.
   B. 10 mg for a 62-year-old woman (weight 80 kg) with a history of chronic kidney disease and a CrCl of 50 mL/minute/1.73 $m^2$.
   C. 5 mg for a 74-year-old man (weight 70 kg) with a history of DM and TIA.
   D. 5 mg for a 45-year-old woman (weight 65 kg) with a history of stroke after a motor vehicle accident.

5. A 55-year-old white man (weight 98 kg) is in the ED with substernal chest pain that radiates to his left jaw. On physical examination, he is in moderate distress. His vital signs include blood pressure 156/90 mm Hg and heart rate 82 beats/minute. His ECG reveals normal sinus rhythm with ST-segment segment depression in leads II, III, and aVF. His medical history is significant for CAD, diabetes, and gastroesophageal reflux disease on omeprazole 20 mg twice daily. He is given aspirin 325 mg orally x 1, and troponin concentrations are obtained, the first measuring 7.8 ng/mL. His SCr is normal. The interventional cardiologist finds a 90% lesion in the right coronary artery and places a DES. Which is the preferred antiplatelet therapy to be added to aspirin 81 mg daily at this time?
   A. Cangrelor 30-mcg/kg intravenous bolus, followed by a 4-mcg/kg/minute infusion.
   B. Prasugrel 60-mg loading dose, followed by 5 mg once daily.
   C. Ticagrelor 180-mg loading dose, followed by 90 mg twice daily.
   D. Clopidogrel 600-mg loading dose, followed by 75 mg daily.

6. Which best describes a therapeutic benefit of ticagrelor compared with prasugrel?
   A. Once-daily administration.
   B. Shorter discontinuation time before elective CABG.
   C. May be administered with strong inhibitors of 3A4.
   D. Lower incidence of bleeding.

## IV. ANTICOAGULANT THERAPY

A. Patients with STEMI and NSTE-ACS should be treated with anticoagulant therapy (Tables 8 and 9).
   1. Use of anticoagulants is mainly in the procedural setting, though use may continue for a finite period post-procedure.
   2. Selection and use among agents may depend on ACS presentation, timing/dose of preprocedural antiplatelet medication, clot burden during procedure, and estimated risk of bleeding periprocedurally.
   3. All anticoagulants increase the risk of bleeding and require some type of monitoring for agent-specific risks.

**Table 8.** Anticoagulant Management Strategies in ACS[a]

| | **Class 1 Recommendations** |
|---|---|
| STEMI (PPCI) | UFH, bivalirudin[c] |
| STEMI, with fibrinolytic[b] therapy | UFH, enoxaparin, fondaparinux |
| NSTE-ACS, early invasive strategy | Bivalirudin[c],UFH |
| NSTE-ACS, conservative (medical) strategy | Enoxaparin, fondaparinux[d],UFH |

[a]Class 1, should be performed or administered; class 2a, reasonable to be performed or administered; class 2b, may be considered; class 3, not to be administered or harmful.

[b]Fibrinolytics preferred when PCI cannot be performed within 120 min of first medical contact (class 1). Door-to-needle time < 30 min. Those who receive fibrinolytic therapy should receive anticoagulation after fibrinolysis for at least 48 hr with intravenous UFH or IV/SC enoxaparin during hospitalization, up to 8 days (preferred, selected patients), or IV/SC fondaparinux during hospitalization, up to 8 days.

[c]Bivalirudin should be used in patients with heparin-induced thrombocytopenia (class 1); reasonable alternative to UFH to reduce bleeding (class 2b).

[d]Fondaparinux should not be used as the sole anticoagulant to support PCI. Give additional anticoagulant during revascularization if fondaparinux was initially chosen as the anticoagulant strategy. Fondaparinux is given a class 1 recommendation in the 2014 NSTE-ACS guidelines (for a conservative strategy) and a class 3 or harmful recommendation in the 2022 coronary artery revascularization guidelines when PCI is indicated.

ACS = acute coronary syndrome; IV = intravenous(ly); NSTE = non–ST-segment elevation; PCI = percutaneous coronary intervention; PPCI = primary percutaneous coronary intervention; SC = subcutaneous(ly); STEMI = ST-segement elevation myocardial infarction; UFH = unfractionated heparin.

Information from: Lawton JS, Tamis-Holland JE, Bangalore S, et al. 2021 ACC/AHA/SCAI guideline for coronary artery revascularization: a report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. Circulation 2022;145:e18-e114; Amsterdam EA, Wenger NK, Brindis RG, et al. 2014 ACC/AHA guideline for the management of patients with non–ST-elevation acute coronary syndromes: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Circulation 2014;130:e344-e426.

B. Anticoagulant Agents (see Table 9 for dosing and contraindications)
   1. Unfractionated heparin
      a. Exerts its effects as an indirect thrombin inhibitor by binding to antithrombin III, rapidly accelerating the body's antithrombin effect
      b. Given as intravenous bolus with or without infusion and adjusted according to activated partial thromboplastin time or activated clotting time to maintain therapeutic anticoagulation according to specific hospital protocol; usually continued for 48 hours or until PCI is performed
         i. Intravenous UFH: initial bolus of 60 units/kg (maximum 4000 units)
         ii. Initial infusion of 12 units/kg/hour (maximum 1000 units/hour) adjusted on the basis of aPTT to maintain therapeutic anticoagulation according to specific hospital protocol, continued for 48 hours or until PCI is performed
      c. Risks include bleeding, thrombocytopenia, and HIT with or without thrombosis.
      d. Monitoring includes activated partial thromboplastin time or activated clotting time, Hgb/Hct, and Plt.
      e. Unlike other anticoagulants, unfractionated heparin is not renally cleared and can safely be used in those with renal impairment.
   2. Enoxaparin
      a. Molecular weight is one-third that of unfractionated heparin with balanced anti-factor Xa (anti-Xa) and anti-IIa activity.
      b. Given as a subcutaneous injection at least 2 inches on either side of the belly button at a 90-degree angle into 1 inch of pinched skin (avoid injection into muscle); alternative dosing sites. Risks include bleeding, injection-site hematomas, spinal or epidural hematomas, retroperitoneal hematoma/bleeding, thrombocytopenia including HIT, and mechanical prosthetic valve thrombosis (in pregnancy).
         i. Dosing varies based on reperfusion strategy and time from last dose to procedure (Table 9)
         ii. 30 mg IV bolus given in STEMI (if age <75) and in select patients with NSTE-ACS

iii. Specific peri-procedural dosing for PCI in relation to time of last subcutaneous dose (see 3b. Invasive strategy)
iv. Decrease dosing interval to once daily when CrCl < 30 ml/min/1.73 $m^2$

c. Does not require routine anti-Xa monitoring; obtain SCr to calculate CrCl for dosing; monitor Hgb, Hct, Plt, SCr

3. Fondaparinux
   a. Selective inhibitor of activated factor X
   b. Longest half-life of anticoagulants (17 hours)
   c. Given as a subcutaneous injection into fatty tissue at a 90-degree angle into a pinched skinfold; alternative dosing sites between the left and right anterolateral and posterolateral abdominal wall.
      i. Dosing NSTE-ACS: 2.5 mg subcutaneously daily, continued for the duration of hospitalization or until PCI is performed
      ii. Not to be used as the sole anticoagulant during PCI (class 3)
      iii. Contraindicated if CrCl <30 ml/min/1.73 $m^2$
   d. Risks include bleeding and thrombocytopenia, spinal or epidural hematomas
   e. No increased risk of HIT
   f. Does not require routine anti-Xa monitoring; requires SCr to calculate CrCl to assess for contraindications; monitor Hgb, Hct, Plt, SCr
4. Bivalirudin
   a. A direct thrombin inhibitor; directly inhibits thrombin in both circulating and bound clots and also inhibits thrombin-mediated platelet aggregation
   b. Given as an intravenous bolus with or without infusion fixed rate and usually continued until end of PCI (with or without extended post-infusion in some high-risk patients)
      i. Early invasive strategy dosing: 0.1 mg/kg loading dose followed by 0.25 mg/kg per hour (only in patients with planned PCI), continued until diagnostic angiography or PCI
      ii. PCI dosing: 0.75 mg/kg IVB, 1.75 mg/kg/hr IV continued throughout the procedure
      iii. Adjust rate of infusion to 1 mg/kg/hr when CrCl < 30 ml/min/1.73 $m^2$ or to 0.25 mg/kg/hr in patients receiving hemodialysis
      iv. Can extend duration of infusion for up to 4 hours after procedure for prolonged anticoagulation
   c. Risks include bleeding.
   d. Does not require monitoring for adjustment; monitor SCr (adjustment required for infusion in those impaired CrCl), Hgb, Hct, Plt
   e. Can be given to a patient with a history of or suspected HIT undergoing PCI

C. Anticoagulant Therapy Guideline Recommendations
   1. An anticoagulant should be administered to all patients with ACS in addition to antiplatelet therapy to reduce the risk of intracoronary and catheter thrombus formation (Tables 8 and 9), irrespective of initial treatment strategy (early invasive vs. conservative).
      a. Enoxaparin: 30-mg intravenous bolus; then 1 mg/kg subcutaneously every 12 hours (or 1 mg/kg subcutaneously once daily for CrCl less than 30 mL/minute/1.73 $m^2$); continued for the duration of hospitalization or until PCI is performed
      b. Bivalirudin: 0.1-mg/kg loading dose, followed by 0.25 mg/kg per hour (only in patients with early invasive strategy); continued until diagnostic angiography or PCI, with only provisional use of a GP IIb/IIIa inhibitor
      c. Fondaparinux: 2.5 mg subcutaneously daily; continued for the duration of hospitalization or until PCI is performed

   d. Intravenous unfractionated heparin: Initial bolus of 60 units/kg (maximum 4000 units) with initial infusion of 12 units/kg/hour (maximum 1000 units/hour) adjusted according to activated partial thromboplastin time to maintain therapeutic anticoagulation according to specific hospital protocol; continued for 48 hours or until PCI is performed
2. For a conservative (medical) strategy, unfractionated heparin, enoxaparin, and fondaparinux are class 1–recommended options.
3. For an invasive strategy, unfractionated heparin, and bivalirudin are class 1–recommended options, although bivalirudin is recommended to replace unfractionated heparin only in patients with HIT to avoid thrombotic complications.
   a. Fondaparinux should not be the sole anticoagulant to support PCI (class 3). Give an additional 85 units/kg of intravenous unfractionated heparin immediately before PCI revascularization to reduce the risk of catheter thrombosis if fondaparinux was initially chosen as the anticoagulant strategy if no GP IIb/IIIa inhibitor is used and 60 units/kg intravenously if a GP IIb/IIIa inhibitor is used, with unfractionated heparin dosing according to target activated clotting time.
   b. Use of enoxaparin during PCI may be reasonable in patients with NSTE-ACS treated with upstream subcutaneous enoxaparin.
      i. An additional dose of 0.3 mg/kg of intravenous enoxaparin should be administered at the time of PCI to patients who have received fewer than two therapeutic subcutaneous doses or received their last subcutaneous dose 8–12 hours before PCI.
      ii. Patients who have received enoxaparin within 8 hours of the last subcutaneous dose usually have adequate anticoagulation to undergo PCI without a supplemental bolus.
      iii. In patients on therapeutic subcutaneous enoxaparin, to whom the last dose was administered within 12 hours of PCI, unfractionated heparin should not be used for PCI and may increase bleeding (class 3).
      iv. Patients who undergo PCI more than 12 hours after the last subcutaneous dose are usually treated with full-dose de novo anticoagulation with an established regimen (e.g., full-dose unfractionated heparin or bivalirudin).
      v. In patients who have not received anticoagulant therapy, a 0.5- to 0.75-mg/kg intravenous loading dose is needed.
   c. In those who are at high risk of bleeding, it is reasonable to use bivalirudin in preference to unfractionated heparin (class 2b).
      i. For patients who have received unfractionated heparin, wait 30 minutes; then give a 0.75-mg/kg intravenous loading dose, followed by a 1.75-mg/kg/hour intravenous infusion.
      ii. For patients already receiving a bivalirudin infusion, give an additional 0.5-mg/kg loading dose and increase the infusion to 1.75 mg/kg/hour during PCI.
   d. Anticoagulant therapy is usually discontinued post-PCI unless there is a compelling reason to continue it.
4. In patients undergoing primary PCI, either unfractionated heparin or bivalirudin may be used.
   a. Bivalirudin has been favored for its predictable pharmacokinetics, effects on thrombin-mediated platelet inhibition, and favorable outcomes with respect to adverse bleeding profile, whereas unfractionated heparin is the gold standard anticoagulant during primary PCI.
   b. Direct comparisons between bivalirudin and unfractionated heparin in this setting are complicated by variances in the use of GP IIb/IIIa inhibitors, $P2Y_{12}$ inhibitors, access sites, and anticoagulant dosing strategies.
5. When a fibrinolytic agent is given as a reperfusion strategy, unfractionated heparin, enoxaparin, and fondaparinux are recommended.
   a. Those given fibrinolytic therapy should receive anticoagulation after fibrinolysis for at least 48 hours with intravenous unfractionated heparin or intravenous/subcutaneous enoxaparin during hospitalization, up to 8 days (preferred, selected patients), or intravenous/subcutaneous fondaparinux during hospitalization, up to 8 days.
   b. Bivalirudin is not recommended in this population.

**Table 9.** Antithrombotic Dosing in ACS with or without PCI

| | UFH | Enoxaparin (Lovenox) | Fondaparinux (Arixtra) | Bivalirudin (Angiomax) |
|---|---|---|---|---|
| Classification | Indirect thrombin inhibitor | LMWH | Factor Xa inhibitor | Direct thrombin inhibitor |
| NSTE-ACS | 60 units/kg IVB (max 4000 units), 12 units/kg/hr IV (max 1000 units/hr) for 48 hr or until PCI performed; goal aPTT/anti-Xa according to hospital-specific protocol | 1 mg/kg SC every 12 hr for 24–48 hr or until PCI performed or throughout hospitalization (up to 8 days); 30 mg IVB | 2.5 mg SC daily | 0.1 mg/kg IVB; then 0.25 mg/kg/hr IV (only for planned invasive strategy) |
| PCI | Supplemental doses to target ACT[a]<br>If GP IIb/IIIa inhibitors, UFH 50–70 units/kg IVB<br>If no GP IIb/IIIa inhibitors, UFH 70–100 units/kg IVB | If last dose < 8 hr, nothing additional needed<br>If last dose was 8–12 hrs earlier or only 1 SQ dose was administered before PCI, 0.3 mg/kg IVB | Fondaparinux should not be used as a sole anticoagulant for PCI | 0.75 mg/kg IVB, 1.75 mg/kg/hr IV<br>Discontinue at end of PCI, or continue for up to 4 hr after procedure if needed<br>Hold UFH 30 min before administration |
| STEMI ± PPCI | Supplemental doses to target ACT[a]<br>If GP IIb/IIIa, UFH 50–70 units/kg IVB<br>If no GP IIb/IIIa, UFH 70–100 units/kg IVB | 30 mg IVB, followed immediately by 1 mg/kg SC every 12 hr; do not exceed 100 mg on first two doses<br>If > 75 yr, omit bolus; 0.75 mg/kg SC every 12 hr; do not exceed 75 mg on first two doses | 2.5 mg IVB; then 2.5 mg SC daily | 0.75 mg/kg IVB, 1.75 mg/kg/hr IV |
| Dose adjustments and CIs | Avoid if history of HIT | If CrCl < 30 mL/min/1.73 $m^2$, 1 mg/kg SC daily<br>Avoid if history of HIT | CI if CrCl < 30 mL/min/1.73 $m^2$ | Adjust infusion dose in severe renal dysfunction<br>If CrCl < 30 mL/min/1.73 $m^2$, reduce infusion to 1 mg/kg/hr; if on hemodialysis, reduce infusion to 0.25 mg/kg/hr |

[a]Target ACT is 250–300 s for HemoTec and I-Stat and 300–350 s for Hemochron without GP IIb/IIIa inhibitors and is 200–250 s in patients given concomitant GP IIb/IIIa inhibitors.

ACT = activated clotting time; aPTT = activated partial thromboplastin time; CI = contraindication; CrCl = creatinine clearance; HIT = heparin-induced thrombocytopenia; IV = intravenous(ly); IVB = intravenous bolus; LMWH = low-molecular-weight heparin; NSTE-ACS = non–ST-segment elevation acute coronary syndrome; PCI = percutaneous coronary intervention; PPCI = primary percutaneous coronary intervention; SC = subcutaneous(ly); STEMI = ST-segment elevation myocardial infarction; UFH = unfractionated heparin.

**Patient Cases**

7. A 50-year-old woman (weight 85 kg) with a history of HTN and DM presents with backache, fatigue, and unusual shortness of breath. Her ECG reveals ST-segment depression in the anterior leads. Troponin is negative x 2. Her CrCl is estimated by Cockroft-Gault as 80 mL/minute/1.73 $m^2$. She is initiated on aspirin and ticagrelor, with a plan for a conservative (medical therapy) approach. Which is the best anticoagulant strategy for this patient, in addition to aspirin and ticagrelor?
   A. Bivalirudin 0.75-mg/kg bolus, followed by a 1.75-mg/kg/hour infusion.
   B. Unfractionated heparin 60-unit/kg intravenous bolus, followed by a 12-unit/kg/hour infusion.
   C. Fondaparinux 2.5-mg intravenous bolus, followed by 2.5 mg subcutaneously daily.
   D. Enoxaparin 30-mg intravenous bolus, followed by 40 mg subcutaneously twice daily.

8. Which best describes a therapeutic benefit of bivalirudin over unfractionated heparin?
   A. Less bleeding than with unfractionated heparin alone.
   B. Can be given without oral antiplatelet.
   C. Can be given in renal failure.
   D. No risk of HIT.

## V. OTHER ANTITHROMBOTIC THERAPIES

A. Fibrinolytic Therapy
   1. Indicated for patients with STEMI in whom PCI cannot be performed (Table 10)
   2. In the absence of contraindications (Table 11), fibrinolytic therapy should be given to patients with STEMI (class 1 when onset of ischemic symptoms is within the previous 12 hours) when it is anticipated that primary PCI cannot be performed within 120 minutes of first medical contact, with an ideal door-to-needle time of less than 30 minutes.
   3. Patients undergoing reperfusion with fibrinolytics should receive anticoagulant therapy (UFH, enoxaparin, and fondaparinux are recommended) for at least 48 hours and preferably for the duration of the index hospitalization, for up to 8 days, or until revascularization is performed.
   4. Recommended regimens include the following:
      a. Administer unfractionated heparin at a 60-unit/kg bolus (maximum 4000 units) and at 12 units/kg/hour (maximum 1000 units/hour) to obtain an activated partial thromboplastin time of 1.5–2.0 times control (about 50–70 seconds).
      b. Enoxaparin 30 mg intravenously (if 75 or older, omit bolus), followed in 15 minutes by a 1-mg/kg subcutaneous injection (if 75 or older, 0.75 mg/kg) every 12 hours for the duration of index hospitalization, for up to 8 days, or until revascularization. Maximum 100 mg for the first two doses. If 75 or older, maximum 75 mg for the first two doses. If CrCl is less than 30 mL/minute/1.73 $m^2$, extend dosing interval to daily administration.
      c. Fondaparinux administered with initial 2.5-mg intravenous dose, followed in 24 hours by 2.5-mg/day subcutaneous injections (contraindicated if CrCl is less than 30 mL/minute/1.73 $m^2$) for the duration of the index hospitalization, for up to 8 days, or until revascularization

B. Fibrinolytic therapy is not recommended in patients with NSTE-ACS (class 3: harm).

**Table 10.** Fibrinolytic Therapy

| Agent | Dosing |
|---|---|
| Alteplase (t-PA, Activase) | ≤ 67 kg: 15 mg IVP over 1–2 min; then 0.75 mg/kg IV over 30 min (max 50 mg); then 0.5 mg/kg (max 35 mg) over 60 min<br>> 67 kg: 15 mg IVP over 1–2 min; then 50 mg over 30 min; then 35 mg over 1 hr (max total dose 100 mg) |
| Reteplase (r-PA, Retavase) | 10 units IVP; repeat 10 units IV in 30 min |
| Tenecteplase (TNK-t-PA, TNKase) | < 60 kg: 30 mg IVP; 60–69 kg: 35 mg IVP; 70–79 kg: 40 mg IVP; 80–89 kg: 45 mg IVP; > 90 kg: 50 mg IVP (~0.5 mg/kg) |

IV = intravenous(ly); IVP = intravenous push; r-PA = recombinant plasminogen activator; t-PA = tissue plasminogen activator.

**Table 11.** CIs to Fibrinolytic Therapy

| Relative CIs | Absolute CIs |
|---|---|
| BP > 180/110 mm Hg on presentation or history of chronic poorly controlled HTN<br>History of ischemic stroke > 3 mo before<br>Recent major surgery (< 3 wk before)<br>Traumatic or prolonged CPR (> 10 min)<br>Recent internal bleeding (within 2–4 wk)<br>Active peptic ulcer<br>Noncompressible vascular punctures<br>Pregnancy<br>Known intracranial pathology (dementia)<br>Oral anticoagulant therapy | Any prior hemorrhagic stroke<br>Ischemic stroke within 3 mo (except in past 4½ hr)<br>Intracranial neoplasm or arteriovenous malformation<br>Active internal bleeding<br>Aortic dissection<br>Considerable facial trauma or closed-head trauma in past 3 mo<br>Intracranial or intraspinal surgery within 2 mo<br>Severe uncontrolled HTN (unresponsive to emergency therapy)<br>For streptokinase,[a] treatment within previous 6 mo (if considering streptokinase again) |

[a]Streptokinase is no longer marketed in the United States but is available in other countries.

BP = blood pressure; CI = contraindication; CPR = cardiopulmonary resuscitation; HTN = hypertension.

C. Factor Xa Inhibitors
   1. Rivaroxaban
      a. A direct oral anticoagulant that inhibits factor Xa
      b. Studied in this setting of ACS in addition to aspirin with and without thienopyridine (ATLAS ACS trials)
         i. Randomized to rivaroxaban 2.5 mg or 5 mg twice daily or placebo was added to standard therapy within 7 days post-ACS
         ii. Only studied with aspirin plus clopidogrel or ticlopidine (98% aspirin and 92% clopidogrel), not with other $P2Y_{12}$ inhibitors
         iii. Both rivaroxaban doses reduced the primary end point of death from CV causes, MI, or stroke.
            (a) 2.5-mg dose, 9.1% versus 10.7%; HR 0.84; 95% CI, 0.72–0.97; p=0.02
            (b) 5-mg dose, 8.8% versus 10.7%; HR 0.85; 95% CI, 0.73–0.98; p=0.03
         iv. Clinically significant bleeding occurred with both doses.
            (a) Major bleeding unrelated to CABG: 5-mg dose 2.1% versus 0.6%, p<0.0001
            (b) Intracranial hemorrhage 5-mg dose: 2.1% versus 0.6%, p<0.0001
            (c) Lower dose had less TIMI minor bleeding, TIMI bleeding requiring medical attention, and intracranial hemorrhage than the 5-mg dose, but rates of TIMI major bleeding unrelated to CABG were no different.

(d) No specific subgroups benefited more than others from rivaroxaban therapy, but the patient subgroup with previous TIA/stroke had a nonstatistically significant greater bleeding risk.
(e) Because of concerns for missing data and lack of complete follow-up, the FDA rejected the new drug application for rivaroxaban's ACS indication.

c. Safety with a $P2Y_{12}$ inhibitor without aspirin was studied in the phase II GEMINI ACS-1 trial (Lancet 2017;389:1799-808).
i. Within 10 days post-ACS event (49% STEMI), in which patients were already receiving aspirin 100 mg daily and either ticagrelor 90 mg twice daily or clopidogrel 75 mg daily, randomized to either continuing aspirin (n=1518) or rivaroxaban 2.5 mg twice daily (n=1519)
ii. Primary end point: TIMI non-CABG clinically significant bleeding for rivaroxaban versus aspirin: 5.3% versus 4.9%, p=0.58
iii. Ischemic end points were similar, but study was not powered to detect differences in efficacy outcomes.
iv. Suggests that dropping aspirin and adding low-dose rivaroxaban to $P2Y_{12}$ inhibitors has a bleeding profile similar to DAPT

d. In the COMPASS trial, rivaroxaban 2.5 mg twice daily in addition to aspirin reduced a composite CV end point in patients with stable CVD (discussed in further detail in the Stable Atherosclerotic Disease chapter).

2. Apixaban
a. A direct oral anticoagulant that inhibits factor Xa
b. Studied in the setting of ACS in the APPRAISE-2 trial
i. Discontinued prematurely secondary to safety signal (N Engl J Med 2011;365:699-708)
ii. Randomized apixaban 5 mg twice daily or placebo in stable patients post-ACS who were receiving DAPT (with aspirin plus any $P2Y_{12}$ inhibitor) with two or more high-risk features
(a) Initiated therapy after a median of 6 days post-index event and 2 days after discontinuing parenteral anticoagulant
(b) About a 2-year follow-up
iii. Adding 5 mg twice daily to DAPT in high-risk patients post-ACS increased bleeding without significantly reducing recurrent ischemic events.
(a) Primary outcome of CV death, MI, or ischemic stroke not affected by adding apixaban (7.5% vs. 7.9%; 95% CI, 0.8–1.1; p=0.51)
(b) TIMI major bleeding was greater in those receiving apixaban (1.3% vs. 0.5%; HR 2.59; 95% CI, 1.50–4.46; p=0.001).
iv. More intracranial and fatal bleeding events occurred with apixaban than with placebo.

D. Thrombin Receptor Antagonists
1. Thrombin-mediated platelet activation occurs through protease-activated receptor (PAR)-1 and PAR-4, with PAR-1 being the principal thrombin receptor on human platelets.
2. Inhibition of PAR-1 inhibits several cellular effects on platelets, including platelet shape change, increased thromboxane $A_2$ production, release of adenosine diphosphate, and stimulation of platelet procoagulant activity.
3. Vorapaxar is the first oral, potent, competitive PAR-1 antagonist that blocks thrombin-mediated platelet activation and reduces stent thrombosis.
a. Rapid GI absorption with high bioavailability
b. Peak concentration 1–2 hours after oral loading
c. Significant inhibition of platelet function up to 4 weeks after discontinuation (half-life 159–310 hours)
d. Adverse drug events include bleeding, depression, anemia, rash
i. Bleeding, including intracranial hemorrhage and fatal bleeding
ii. Older age, lower body weight, and renal/hepatic dysfunction are risk factors for bleeding events.

e. Drug interactions; avoid the concurrent use of strong CYP3A inhibitors/inducers
f. Contraindicated in patients with a history of stroke, TIA, or intracranial hemorrhage
g. No reversal agent

4. Vorapaxar has been studied in addition to standard therapy (mainly aspirin plus clopidogrel) post-ACS:
   a. TRACER: The Thrombin Receptor Antagonist for Clinical Event Reduction in Acute Coronary Syndrome study was terminated early secondary to safety concerns and lack of treatment benefit:
      i. Randomized to placebo or vorapaxar (40-mg loading dose and 2.5 mg daily), initiated at initial NSTE ACS presentation before revascularization
      ii. Vorapaxar did not reduce the primary end point of death from CV causes, MI, stroke, recurrent ischemia with rehospitalization, or urgent coronary revascularization compared with placebo but partly reduced future MI events in a subgroup analysis.
      iii. Major bleeding (3.2% vs. 2.1%; HR 1.85; 95% CI, 1.39–2.747; p<0.001) and intracranial hemorrhage (1.1% vs. 0.2%; HR 3.39; 95% CI, 1.78–6.45; p<0.001) were significantly higher in the vorapaxar arm than in placebo.
      iv. No difference in fatal bleeding between vorapaxar and placebo
      v. Further analysis of the TRACER data found that vorapaxar significantly reduced the occurrence of type 1 MI by 17% compared with placebo (HR 0.83; 95% CI, 0.73–0.95; p=0.007).
      vi. TRACER: Does not support early initiation during acute hospitalization
   b. The TRA 2°P-TIMI 50 trial assessed vorapaxar in the secondary prevention of atherothrombotic events among patients with recent MI, peripheral arterial disease, or stroke.
      i. Randomized to vorapaxar 2.5 mg once daily (without loading dose) or placebo in addition to standard of care (aspirin plus clopidogrel in most patients)
      ii. Drug was initiated at least 2 weeks after the ACS and preferably within 12 months.
      iii. Vorapaxar significantly reduced the occurrence of the primary end point, CV death, MI, or stroke (9.3% vs. 10.5% at 3 years; HR 0.87; 95% CI, 0.80–0.94; p<0.001); reduced the secondary end point of stent thrombosis (1.1% vs. 1.4%; HR 0.71; 95% CI, 0.52–0.98; p<0.04)
      iv. Bleeding was higher in the vorapaxar group (4.2% vs. 2.5%; HR 1.66; 95% CI, 1.43–1.93; p<0.0001).
      v. Greatest benefit from vorapaxar was in patients who qualified with MI (17,779 patients) in whom vorapaxar decreased the primary end point by 20% at 3 years (8.1% vs. 9.7%; HR 0.80; 95% CI, 0.72–0.89; p<0.0001).
      vi. Trial was terminated early in patients with a history of stroke because of increased intracranial hemorrhage (2.4% vs. 0.9%, p<0.001) and no benefit on primary end point (NOTE: CONTRAINDICATION IF TIA/STROKE).
      vii. According to the TRA 2°P-TIMI 50 trial, vorapaxar has been FDA approved for reducing thrombotic CV events among patients with a history of MI or peripheral arterial disease and no history of a TIA or stroke.
      viii. Secondary analysis of the 20,170 patients who met FDA label indication estimates a 20% reduction in risk of CV death, MI, or stroke at the expense of increased GUSTO moderate or severe bleeding. For every 1000 patients treated, vorapaxar prevented 16 CV deaths, MIs, or strokes at the expense of 3 GUSTO severe and 13 GUSTO moderate or severe bleeding outcomes.
   c. No efficacy or safety data are available on adding vorapaxar to more potent $P2Y_{12}$ inhibitors.

**Patient Case**

*Questions 9 and 10 pertain to the following case.*

A 76-year-old male smoker (weight 62 kg) has a history of HTN, benign prostatic hypertrophy, and lower back pain. Three weeks ago, he began to have substernal chest pain with exertion (together with dyspnea), which radiated to both arms and was associated with nausea and diaphoresis. Episodes have increased to four or five times daily; they are relieved with rest. He has never had an ECG. Today, he awoke with 7/10 chest pain and went to the ED of a rural community hospital 2 hours later. He was acutely dyspneic and had ongoing pain. Home medications are aspirin 81 mg/day for 2 months, doxazosin 2 mg/day, and ibuprofen 800 mg three times daily. Vital signs include heart rate 42 beats/minute (sinus bradycardia) and blood pressure 104/48 mm Hg. Laboratory results include blood urea nitrogen 45 mg/dL, SCr 2.5 mg/dL, and troponin 1.5 ng/mL (normal value less than 0.1 ng/mL). His ECG reveals a 3-mm ST-segment elevation. Aspirin, ticagrelor, and sublingual nitroglycerin were given in the ED. The nearest hospital with a catheterization laboratory facility is 2½ hours away.

9. Which regimen is best to recommend?
   A. Give alteplase 15 units intravenously plus enoxaparin 30-mg intravenous bolus.
   B. Use a conservative treatment strategy with unfractionated heparin 4000-unit intravenous bolus, followed by 750 units intravenously per hour.
   C. Give tenecteplase 35 mg intravenously plus unfractionated heparin 4000-unit intravenous bolus, followed by 800 units intravenously per hour.
   D. Transfer the patient to a facility for primary PCI.

10. Which medication most likely contributed to this man's current presentation of ACS?
   A. Doxazosin may cause rebound chest pain.
   B. Ibuprofen increases the risk of ACS and stroke.
   C. Aspirin resistance contributes to subsequent ACS.
   D. Nitroglycerin, given in the ED, can decrease the effectiveness of ticagrelor.

## VI. POST-PERCUTANEOUS INTERVENTION COMPLICATIONS

A. Bleeding
   1. Use of concomitant antiplatelet and anticoagulant agents increases the risk of bleeding, especially in those whose doses are not adjusted appropriately.
      a. Renal adjustments should be considered for GP IIb/IIIa receptor antagonists, bivalirudin, fondaparinux, and enoxaparin.
      b. SCr with estimated CrCl should be assessed in every patient.
   2. Catheterization access site has been identified as a major contributor to post-PCI bleeding complications. A radial approach has less bleeding risk than a femoral approach.

B. Dissection/Rupture of Free Wall, Coronary Artery, or Aorta

C. Stent Thrombosis
   1. A catastrophic event, resulting in life-threatening complications
   2. Premature discontinuation of DAPT is the most important predictor of stent thrombosis.
      a. When antiplatelet therapy is discontinued early, related thrombosis events increase exponentially (JAMA 2005;293:2126-30).
      b. Almost 1 in 7 patients may discontinue $P2Y_{12}$ inhibitors within 30 days post-PCI, thus increasing mortality risk (adjusted HR 9.0; 95% CI, 1.3–60.6) (JAMA 2013;310:189-98).

c. Mortality rates associated with stent thrombosis can be as high as 45%.
d. Counseling on therapy duration and avoiding premature discontinuation is of paramount importance.

3. Duration of DAPT
   a. 12 months
      i. Aspirin should be continued indefinitely at a maintenance dose of 81 mg daily in all patients post-ACS (class 1).
      ii. In patients with NSTE-ACS who were treated with a conservative approach, aspirin plus either clopidogrel 75 mg daily or ticagrelor 90 mg twice daily should be continued for up to 12 months.
      iii. Post-PCI (bare metal stent or DES), aspirin plus clopidogrel 75 mg daily, prasugrel 10 mg daily, or ticagrelor 90 mg twice daily should be continued for at least 12 months.
   b. Early discontinuation of DAPT
      i. Early discontinuation after 6 months of $P2Y_{12}$ inhibitor may be considered if high bleeding risk or significant overt bleeding develops (class 2b).
         (a) DAPT should be continued post-ACS (with or without stent) for at least 12 months (class 1).
         (b) Shorter-duration DAPT can be considered for patients with stable ischemic heart disease who have undergone PCI with elective DES placement (class 1, 6 months for elective DES placement; class 1, 1 month for elective BMS placement).
            (1) It is reasonable to discontinue $P2Y_{12}$ inhibitor at 3 months after elective DES placement if high bleeding risk or significant overt bleeding develops (class 2b).
      ii. Early aspirin discontinuation after 1–3 months with transition to $P2Y_{12}$ inhibitor monotherapy may be reasonable in selected patients undergoing PCI to reduce the risk of bleeding events (class 2a).
      iii. In general, shorter durations of DAPT are appropriate for those with a lower ischemic risk and a high bleeding risk, whereas longer-duration DAPT may be reasonable for patients with a higher ischemic risk and a lower bleeding risk.
         (a) Prior recommendations for DAPT duration for patients treated with DESs were based on data from "first-generation" stents.
         (b) Trials comparing shorter durations of DAPT have evaluated newer-generation stents in patients undergoing PCI (including elective cases).
         (c) Compared with first-generation stents, newer-generation stents have an improved safety profile and a lower risk of stent thrombosis.
         (d) Proton pump inhibitors can reduce the risk of bleeding from DAPT
   c. Long-term DAPT
      i. In general, longer-duration DAPT may be reasonable for patients at higher ischemic risk with a lower bleeding risk.
      ii. Trials evaluating the need for an extended duration of DAPT post-PCI in patients with and without ACS undergoing PCI (greater than 12 months) show reduced stent thrombosis and ischemia end points with increased bleeding for patients continued on DAPT beyond 12 months (Eur Heart J 2015;36:1219-22; BMJ 2015;350:h1618; Lancet 2015;385:792-8).
      iii. The risk of stent thrombosis is greater on DAPT cessation (N Engl J Med 2014;371:2155-66); however, continued DAPT beyond 1 year is not associated with reduced CV or total mortality.
      iv. A longer duration of $P2Y_{12}$ inhibitor therapy is an individualized approach, given the patient's risk of ischemic events and bleeding.
         (a) It is reasonable to consider DAPT beyond 12 months if the patient is tolerating therapy and not at high risk of bleeding (class 2b).
         (b) Durations of DAPT may be reasonable beyond 12 months if the patient is at high risk for CV events and has no significant history of bleeding on DAPT (class 2b)
         (c) A DAPT score derived from the dual antiplatelet study may help the clinician decide whether to prolong or extend DAPT in patients treated with coronary stent implantation (Table 12).

(1) For those with a high DAPT score (2 or higher), prolonged DAPT reduces net (ischemic plus bleeding) events.
(2) For those with a low DAPT score (less than 2), the benefit-risk for prolonged DAPT is unfavorable (increased bleeding without a reduction in ischemic events).
(3) Derived from the DAPT study, which included 11,648 patients with mainly clopidogrel as the $P2Y_{12}$ inhibitor

v. DAPT duration more or less than 12 months should be made jointly by the clinician and the patient, balancing the risks of stent thrombosis and ischemic complications with the risk of bleeding.
vi. Escalation or de-escalation of $P2Y_{12}$ therapy
(a) Data on switching antiplatelet therapies are primarily based on studies that were not powered to assess the clinical impact of switching.
(b) Common reasons for de-escalation of therapy include bleeding and cost
(c) Common reasons for escalation of therapy (from clopidogrel to ticagrelor or prasugrel) include high risk of coronary stent thrombosis or intolerance to clopidogrel
(d) An international white paper gives consensus on switching strategies (Angiolillo DJ et al. Circulation 2017;136:1955-75) based on time of switch (within the first 30 days or after during maintenance therapy) and reason for switching $P2Y_{12}$ inhibitor (escalation vs. de-escalation)
(1) If escalating, loading doses are recommended regardless of time of last dose of $P2Y_{12}$ inhibitor; can start new $P2Y_{12}$ inhibitor 24 hours after last dose of previous $P2Y_{12}$ inhibitor
(2) If de-escalating, loading doses are not generally necessary, especially when switching because of bleeding; start new $P2Y_{12}$ 24 hours after last dose of previous $P2Y_{12}$ inhibitor
(3) Loading doses are recommended if switching during the acute or early phase (i.e., ≤ 30 days post stenting)
(4) Loading doses are not generally necessary if $P2Y_{12}$ is being switched after first 30 days of therapy except when switching from ticagrelor to either clopidogrel or prasugrel.

**Table 12.** DAPT Score to Determine Favorability of Prolonged DAPT[a]

| Factors Used to Calculate DAPT Score | Add Points for Total Score |
|---|---|
| Age ≥ 75 | -2 |
| Age 65–74 | -1 |
| Current tobacco user | 1 |
| DM | |
| NSTEMI or STEMI at presentation | |
| Prior MI or PCI | |
| Stent diameter < 3 mm | |
| Paclitaxel-eluting stent | |
| CHF or LVEF < 30% | 2 |
| Saphenous vein graft PCI | 2 |

[a]A score ≥ 2 favors prolonged DAPT; a score < 2 is of unfavorable risk-benefit.

CHF = congestive heart failure; DAPT = dual antiplatelet therapy; DM = diabetes mellitus; LVEF = left ventricle ejection fraction; MI = myocardial infarction; NSTEMI = non–ST-segment elevation myocardial infarction; PCI = percutaneous coronary intervention; STEMI = ST-segment elevation myocardial infarction.

Information from: Levine GN, Bates ER, Bittl JA, et al. 2016 ACC/AHA guideline focused update on duration of antiplatelet therapy in patients with coronary artery disease: a report of the American College of Cardiology/American Heart Association Task Force on clinical practice guidelines. JACC 2016;68:1082-115; Yeh RW, Secemsky EA, Kereiaskes DJ, et al. Development and validation of a prediction rule for benefit and harm of dual antiplatelet therapy beyond 1 year after percutaneous coronary intervention JAMA 2016;315:1735-49.

D. Mechanical Complications (papillary muscle rupture and mitral regurgitation)

E. Arrhythmias (particularly after reperfusion)

F. Contrast-Induced Nephropathy
   1. Adequate hydration and minimization of the volume of contrast media remain the core prevention strategies for contrast-induced nephropathy.
   2. The PRESERVE trial (NEJM 2018;378:603-18) demonstrated no added benefit of bicarbonate or acetylcysteine over isotonic saline in patients undergoing angiography with decreased eGFR +/- diabetes
   3. Patients with ACS undergoing urgent procedures who may be at higher risk for contrast induced acute kidney injury were not included, however.

**Patient Cases**

11. A 75-year-old African American patient develops a GI bleed while on prasugrel and aspirin. The patient's DAPT is held until he is considered stable. The patient had a DES placed 45 days ago after he was hospitalized for an ACS. Which of the following is the best strategy for DAPT in this patient?
    A. Switch to ticagrelor 60 mg twice daily without load 24 hours after last prasugrel dose.
    B. Switch to ticagrelor 90 mg twice daily after a 180-mg load 24 hours after last prasugrel dose.
    C. Switch to clopidogrel 75 mg per day after a 300-mg load 24 hours after last prasugrel dose.
    D. Switch to clopidogrel 75 mg daily without load 24 hours after last prasugrel dose..

12. A 67-year-old man had an NSTEMI and received a DES to his right coronary artery. He is in the cardiology clinic for a follow-up about 12 months post-discharge without complaint. He has diabetes and HTN, both controlled at the current visit. He takes aspirin 81 mg daily, ticagrelor 90 mg twice daily, metoprolol 50 mg twice daily, lisinopril 10 mg daily, and atorvastatin 80 mg. The physician is considering longer-term DAPT. Which best describes the most evidence-based approach to prolonging the duration of DAPT in this man?
    A. Risk greater than benefit; discontinue DAPT at this visit.
    B. Risk greater than benefit; discontinue ticagrelor but continue aspirin indefinitely.
    C. Benefit greater than risk; continue DAPT at current dosing.
    D. Benefit greater than risk; decrease ticagrelor to 60 mg and continue aspirin.

## VII. LIPID-LOWERING THERAPIES IN ACUTE CORONARY SYNDROME

A. Statins
   1. Post-MI, statins reduce total mortality, CV mortality, and stroke.
   2. All patients should receive high-intensity statins post-ACS, preferably before revascularization (class 1).
      a. Landmark clinical trials have unequivocally shown the value of statins in secondary prevention post-MI.
      b. A meta-analysis of randomized controlled clinical trials of almost 18,000 patients with recent ACS (less than 14 days) found that statin therapy reduces mortality by 19%, with benefits observed after around 4 months of treatment.
      c. Acute benefit includes reduced the frequency of periprocedural MI during PCI, and statins should be initiated as early as possible.
      d. Chronic benefit includes reduced secondary MI and other CV outcomes.

3. The amount of atherosclerotic CV disease risk reduction with statins is directly related to the amount of LDL reduction achieved as a percentage of baseline.
    a. Current evidence shows that higher-dose statin therapy, such as atorvastatin 40–80 mg daily and rosuvastatin 20–40 mg daily, produces greater reduction in CV events such as MI, ischemic stroke, and revascularization than less-intensive statin regimens (e.g., simvastatin 20–40 mg daily).
    b. Atorvastatin 40–80 mg and rosuvastatin 20–40 mg are considered high-intensity statins.
2. After an ACS event, patients should be considered for the addition of non-statin therapies with ezetimibe or proprotein convertase subtilisin/kexin type 9 enzyme (PSCK9) inhibitor if either of the circumstances listed below are met:
    a. Patients at very high risk on maximally tolerated statin with less than 50% LDL-C reduction or if LDL-C is 55 mg/dL or greater.
    b. Patients on maximally tolerated statin with less than 50% LDL-C reduction or if LDL-C is 70 mg/dL or greater.

B. Ezetimibe
1. Ezetimibe added to a moderate-dose simvastatin in patients with a recent (within 10 days) ACS and an LDL concentration of 50–100 mg/dL modestly reduced the frequency of a composite end point of CV events or stroke over a median follow-up of 6 years compared with simvastatin alone in the IMPROVE-IT study.
2. Showed safety with 10 mg daily added to moderate-intensity statin therapy with about a 10% reduction in primary outcome of composite of CV death, MI, hospital admission for UA, revascularization, or stroke (HR 0.94; 95% CI, 0.8–0.97; p=0.003)
3. Ezetimibe 10 mg daily is recommended by clinical guidelines as first-line add-on therapy when additional LDL lowering is desired post-ACS for clinically modest reductions in outcome (lowers LDL by about 20% in addition to statin therapy).

C. PCSK9 Inhibitors
1. New class of drugs that inhibit the PCSK9 enzyme, which plays a major role in the breakdown of hepatic LDL receptors; inhibition of this enzyme enables more efficient hepatic uptake of LDL, decreasing serum LDL concentrations by more than 50% in most cases
2. Both evolocumab (Repatha) and alirocumab (Praluent) are FDA approved for dyslipidemia (see the Dyslipidemia chapter), and both have evidence in cardiovascular disease event reduction, although studied in slightly different populations.
    a. Evolocumab
        i. Evolocumab (either 140 mg every 2 weeks or 420 mg every month, depending on patient preference) added to statin therapy in patients with atherosclerotic disease (more than 80% had previous MI) achieved an LDL reduction of 59% and a 15% relative risk reduction in composite CV end point of MI, stroke, hospitalization for angina, or revascularization compared with the statin alone arm, without an increase in adverse events (FOURIER study; N Engl J Med 2017;376:1713-22).
        ii. Of importance, patients who had ACS within the previous 4 weeks were excluded from enrollment.
    b. Alirocumab
        i. The ODYSSEY OUTCOMES trial demonstrated alirocumab (75 to 150 mg taken every other week), significantly reduced ishchemic events (15% relative risk reduction), including all cause mortality and MI compared with placebo among patients with an ACS event within the preceding 1-12 months who were also receiving intensive or maximally tolerated statin therapy.
        ii. The ODYSSEY population differed from FOURIER in that FOURIER had a post-ACS population of 20%.

D. Omega-3 Fatty Acids
   1. Hypertriglyceridemia is associated with an increased risk of CV events.
   2. Prior studies with other TG-lowering therapies (fibrates, niacin) have not shown improved CV outcomes.
   3. In the REDUCE-IT trial (n=8179), icosapent ethyl (Vascepa) 2 g twice daily reduced a composite end point of CV death, nonfatal MI, nonfatal stroke, coronary revascularization, or UA compared with placebo (17.2% vs. 22%; HR 0.75; 95% CI, 0.68–0.83; p<0.001). CV death was also significantly reduced with icosapent ethyl (4.3% vs. 5.2% with placebo; p=0.03). Rates of atrial fibrillation or flutter were higher with icosapent ethyl than with placebo (N Engl J Med 2019;380:11-22).
   4. Clinical trials with other forms of omega-3 fatty acids have not shown improved CV outcomes (N Engl J Med 2018;379:1540-50; Eur Heart J 2020;41:3925-32; JAMA 2020;324:2268-80).
   5. Clinical practice guidelines recommend icosapent ethyl in patients with established atherosclerotic CV disease or high-risk patients with TG of 150–499 mg/dL despite statin treatment.

## VIII. CORONARY ARTERY BYPASS GRAFTING REVASCULARIZATION

A. The decision to perform CABG over PCI is outside the scope of this chapter. In general, CABG is performed in patients with left main disease, in patients with complex multivessel disease, in some patients with high SYNTAX scores (a score combining anatomic and clinical prognostic variables; www.syntaxscore.com), and when PCI cannot be performed.

B. Antiplatelet hold time recommendations in patients going on to CABG are outlined in Table 13.

C. Post-CABG antiplatelet recommendations
   1. ASA therapy remains the gold standard antiplatelet therapy post-operatively and is crucial for graft patency after CABG
   2. Clopidogrel is used as an alternative to aspirin
   3. DAPT may be considered for certain patients after CABG surgery.
      a. DAPT may be considered for at least 12 months post-operatively in patients who present with ACS who go on to receive revascularization with CABG
         i. Data on DAPT after CABG in patients with ACS are primarily limited to post hoc analyses of clinical trials.
         ii. Clopidogrel, prasugrel, and ticagrelor may be used depending on clinical characteristics and bleeding risk.
      b. Patients who receive DAPT after stent implantation and undergo CABG should resume DAPT until the recommended therapy duration is completed.
      c. DAPT with clopidogrel or ticagrelor after CABG in patients with stable CAD remains controversial, with conflicting data on specific benefits.
         i. American clinical guidelines provide a weak recommendation on the use of DAPT with clopidogrel or ticagrelor for 12 months to improve vein graft patency in patients with stable CAD who undergo CABG surgery (class 2b/LOE B).

**Table 13.** Recommendations for Holding Antiplatelets and Anticoagulants Before CABG Surgery

| Medication | Recommendation for Holding Duration | Other Considerations |
|---|---|---|
| Aspirin | Do not hold (class 1; LOE B) | |
| Clopidogrel | 5 days | In patients referred for urgent CABG, clopidogrel should be discontinued for at least 24 hr to reduce major bleeding (class 1; LOE B) |
| Ticagrelor | 3 days | In patients referred for urgent CABG, ticagrelor should be discontinued for at least 24 hr to reduce major bleeding (class 1; LOE B) |
| Prasugrel | 7 days | |
| Cangrelor[a] | 1–6 hr before surgery | |
| GP IIb/IIIa inhibitors | Discontinue eptifibatide/tirofiban for 4 hr before CABG (class 1; LOE B) | |
| UFH | 1–4 hr[b] | According to pharmacokinetics, increased risk of exposure to UFH will be minimized after a few hours because of short half-life |
| Enoxaparin | Minimum 12 hr[b] | LMWH given < 12 hr increased the transfusion rate and number of PRBCs transfused per patient Enoxaparin administration within 48 hr of surgery increases the risk of reoperative bleeding |
| Fondaparinux | 3–5 days[b] | If CrCl > 50 mL/min/1.73 $m^2$, stop 3 days before surgery; if CrCl < 50 mL/min/1.73 $m^2$, stop 5 days prior |
| Bivalirudin | 1–3 hr, depending on CrCl[b] | If CrCl > 30 mL/min/1.73 $m^2$, stop bivalirudin 1½ hours before surgery |

[a]Angiolillo DJ, Firstenberg MS, Price MJ, et al. Bridging antiplatelet therapy with cangrelor in patients undergoing cardiac surgery. JAMA 2012;307:265-74.

[b]May vary, depending on institution-specific policy and surgeon; CABG guideline recommendations included, when applicable.

CABG = coronary artery bypass graft; CrCl = creatinine clearance; LMWH = low molecular weight heparin; PRBC = packed red blood cell; UFH = unfractionated heparin.

## IX. SPECIAL POPULATIONS

A. Combined Oral Anticoagulant Therapy and Antiplatelet Therapy in ACS (triple therapy)
   1. Combined oral anticoagulant therapy and antiplatelet therapy in patients with atrial fibrillation undergoing PCI
      a. Triple therapy with an oral anticoagulant, low-dose aspirin and a $P2Y_{12}$ inhibitor should be minimized because it substantially increases the risk for bleeding
      b. New consensus recommendations based on clinical trial data (WOEST, PIONEER AF, RE-DUAL PCI, AUGUSTUS, ENTRUST-AF PCI) represent a paradigm shift from older management with triple therapy:
         i. Double antithrombotic therapy (anticoagulant plus $P2Y_{12}$ inhibitor without aspirin) reduces bleeding events as compared to triple therapy without increasing ischemic events
            (a) Use aspirin in the peri-procedure phase continued throughout the hospitalization
            (b) Most patients should receive double therapy at time of hospital discharge
            (c) Triple therapy should only be extended beyond hospital discharge for select patients at the highest risk for ischemic events and lowest bleeding risks for a limited time period (i.e., 1 month)
         ii. Direct acting oral anticoagulants are preferred over vitamin K antagonists because of reduced bleeding risk

(a) Continue the anticoagulant life-long
(b) Warfarin remains the drug of choice in patients with mechanical heart valves
(c) Warfarin can be considered if preferred by the patient provided well controlled INR without bleeding complications
(d) If warfarin is chosen, maintain INR at the lower end of the therapeutic range (i.e., 2-2.5)

iii. Clopidogrel is the preferred $P2Y_{12}$ inhibitor although ticagrelor may be reasonable in patients at high ischemic/thrombotic and low bleeding risks (i.e., avoid prasugrel)
(a) Discontinue $P2Y_{12}$ inhibitor therapy at 1 year in most patients, although same considerations apply for shortening the duration (i.e., 6 months in those with high bleeding risk) and extending the duration (i.e., >12 months in those at high thrombotic risk with low bleeding risk)

2. Proton pump inhibitors should be prescribed to those with a history of GI bleeding (and are reasonable in those with no known history of GI bleeding) who need triple antithrombotic therapy.

B. Older Patients (i.e., 75 and older)
1. Doses should be individualized by weight or CrCl to reduce adverse events caused by age-related changes in pharmacokinetics and dynamics, volume of distribution, comorbidities, drug interactions, and increased drug sensitivity.
2. CABG may be preferred to PCI in older patients, particularly those with DM or complex three-vessel disease (e.g., SYNTAX score greater than 22), with or without involvement of the proximal left anterior descending artery.

C. Chronic Kidney Disease
1. CrCl should be estimated in patients with ACS, and doses of renally cleared medications should be adjusted accordingly.
2. Patients with chronic kidney disease undergoing coronary and LV angiography should receive adequate hydration and reduced contrast volume.
3. In patients with a CrCl less than 60 mL/minute/1.73 $m^2$, ticagrelor was associated with a 4% absolute risk reduction in all-cause mortality compared with clopidogrel in a prespecified analysis from PLATO with no increased risk of bleeding.
4. In TRITON-TIMI 38, prasugrel was superior to clopidogrel in patients with and without CKD (creatinine clearance < or > 60 mL/minute/1.73 $m^2$)

D. Women
1. Women of all ages have higher rates of in-hospital and long-term complications from ACS than men.
2. Women derive the same benefit from aspirin, $P2Y_{12}$ inhibitors, anticoagulants, β-blockers, angiotensin-converting enzyme (ACE) inhibitors, and statins as men, but women may be at a higher risk of adverse events.
a. Women have a higher rate of bleeding complications, renal failure, and vascular complications.
b. For women, careful monitoring of antithrombotic therapy has been shown to decrease bleeding.
3. Women with NSTE-ACS and high-risk features (e.g., troponin positive) should undergo an early invasive strategy.
a. A 43% higher bleeding risk during hospitalization was found in women compared with men in the GRACE registry, which appears to be related to inappropriate dosing of antithrombotic therapy.
b. Utilizing bleeding avoidance strategies (vascular closure devices, bivalirudin, radial access, and combined approach) has demonstrated benefit in women undergoing PCI (CathPCI registry).
4. Hormone therapy with estrogen plus progestin, or estrogen alone, should not be given as new drugs for secondary prevention and should not be continued in previous users unless the benefits outweigh the estimated risks (class 3: harm).

a. Hormone therapy increases the risk of thrombotic events, especially in the first year of therapy, and does not provide CV protection.
b. Women who are more than 1 year past the initiation of hormone therapy who want to continue such therapy for another compelling indication should weigh risk-benefit, recognizing the greater risk of CV events and breast cancer (combination therapy) or stroke (estrogen).

## X. SECONDARY PREVENTION AND TRANSITIONS OF CARE

A. Long-term Management Post-ACS
1. Goals include controlling CAD risk factors and preventing the development of systolic heart failure, recurrent MIs and stroke, and death.
2. Pharmacotherapy that reduces mortality, heart failure, reinfarction or stroke, and stent thrombosis should be initiated before hospital discharge (Table 14).
a. DAPT (previously covered in the Stent Thrombosis section)
i. Reduces the risk of stent thrombosis and in patients post-stenting but also reduces subsequent CV events post-ACS with or without stenting
ii. Continued for at least 12 months in patients post-ACS
(a) If ticagrelor is chosen as the $P2Y_{12}$ inhibitor, dosing can be continued at a reduced dose of 60 mg twice daily after 12 months of therapy with 90 mg twice daily.
(1) Efficacy and safety was confirmed in the PEGASUS-TIMI 54 trial (N Engl J Med 2015;372:1791-800).
(2) 21,162 patients with a history of MI within the previous 1–3 years were randomized to a high dose (90 mg twice daily) or a lower dose (60 mg twice daily) in addition to low-dose aspirin over 33 months.
(3) Both ticagrelor doses reduced the risk of the primary efficacy end point, a composite of CV death, MI, or stroke, compared with placebo (ticagrelor 90 mg: 7.85%; ticagrelor 60 mg: 7.77%. placebo: 9.04%; $p<0.01$ for each ticagrelor dose vs. placebo).
(4) Risk of bleeding was lower with the 60-mg dose than with the 90-mg dose (ticagrelor 90 mg: 2.60%; ticagrelor 60 mg: 2.30%; placebo: 1.06%; $p<0.001$ for each dose vs. placebo).
(5) FDA-approved dosing for ticagrelor beyond 12 months is 60 mg twice daily.
b. β-Blockers
i. Indicated for all patients unless contraindicated
ii. If they are not initiated orally within the first 24 hours, reevaluate for possible initiation before discharge.
iii. Continue for at least 3 years (when ejection fraction is greater than 40%).
iv. If moderate or severe LV failure, initiate carvedilol, bisoprolol, or metoprolol succinate with gradual titration. Continue indefinitely in patients with an ejection fraction less than 40%.
c. ACE inhibitors/angiotensin receptor blockers (ARBs)
i. ACE inhibitors should be initiated and continued indefinitely for all patients with an LVEF of 40% or less and in those with HTN, DM, or stable chronic kidney disease unless contraindicated.
(a) Those with clinically detectable heart failure, and hence at highest risk, will benefit most (AIRE [*Lancet* 1993;342:821-8], ISIS-4 [Lancet 1995;345:669-85]).
(b) Patients at lower risk will still have some benefit, theoretically through protection from ventricular remodeling.
(c) Intravenous ACE inhibition within the first 24 hours of infarct gave no benefit but increased the risk of hypotension and possibly increased the risk of mortality (CONSENSUS-II [N

Engl J Med 1992;327:678-84]); therefore, an intravenous ACE inhibitor should be avoided during early ACS management.

ii. Oral ACE inhibitors may be acceptable in all other patients with cardiac or other vascular disease.

iii. ARBs can be used as an alternative to ACE inhibitors in patients intolerant of ACE inhibitors.

iv. Contraindications include hypotension, pregnancy, and bilateral renal artery stenosis.

d. Angiotensin receptor-neprilysin inhibitor

i. Use is not recommended in all patients after an ACS event but can be considered in patients with chronic heart failure with reduced ejection fraction.

ii. The PARADISE-MI trial compared sacubitril/valsartan to rampril in 5661 patients after an acute MI with LV dysfunction, pulmonary congestion, or both and found no difference in a composite of death from cardiovascular causes or incident heart failure between treatment groups (N Engl J Med 2021;385:1845-55).

e. Aldosterone receptor blockers

i. Indicated in patients post-MI already receiving ACE inhibitor and β-blocker who have an LVEF of 40% or less and either symptomatic heart failure or diabetes, unless contraindicated

ii. Contraindications include hyperkalemia ($K^+$ 5.0 or greater), CrCl less than 30 mL/minute/1.73 $m^2$, and SCr greater than 2.5 mg/dL in men and greater than 2.0 mg/dL in women.

f. Lipid management: High-intensity statins are indicated in all patients post-ACS without contraindications. (Previously discussed in Section VII. Lipid Lowering therapies after ACS)

B. Other considerations

1. Pain control

a. Nonsteroidal anti-inflammatory drugs (NSAIDs) and select COX-2 inhibitors (class 3) should be discontinued at the time of presentation because they have been associated with an increased risk of major adverse cardiac events.

b. Before discharge, the patient's musculoskeletal discomfort should be addressed, and a stepped-care approach should be used to select therapy.

c. Pain should be treated with acetaminophen, nonacetylated salicylates, tramadol, or narcotics at the lowest dose to control symptoms.

d. It is reasonable to use nonselective NSAIDs such as naproxen if initial therapy is insufficient.

i. Monitor regularly for sustained HTN, edema, worsening renal function, or GI bleeding.

ii. If these occur, consider dose reduction or discontinuation.

2. Vaccination

a. Pneumococcal vaccination is recommended for patients 65 and older and in high-risk patients (including smokers with asthma) with CV disease.

b. An annual influenza vaccination is recommended for all patients after an ACS event.

i. In the IAMI trial, influenza vaccination early after an MI resulted in a lower risk of a composite of all-cause death, MI, or stent thrombosis, including a lower risk of all-cause death and CV death compared to placebo (Circulation 2021;144:1476-84).

c. Vaccination against COVID-19 is recommended in all patients with CV disease because these patients are at high risk for severe symptoms.

3. Patient education

a. Patients should be educated about appropriate cholesterol management, blood pressure control, smoking cessation, and lifestyle management.

b. Risk factor modification should be addressed in all patients post-ACS.

4. Cardiac rehabilitation: All eligible patients should be referred to a comprehensive CV rehabilitation program.

**Table 14.** Discharge Medication Reconciliation After Hospitalization for ACS[a]

| | |
|---|---|
| **Mortality-reducing therapies to be initiated before discharge post-ACS** | |
| DAPT | Prescription of aspirin plus an oral $P2Y_{12}$ inhibitor should be confirmed before discharge with at least 12 mo of therapy post-ACS<br>Counseling on the importance of adherence to DAPT should be stressed |
| β-Blockers | Indicated for all patients without CIs<br>Reevaluate for possible initiation before discharge in those not initiated on oral therapy within first 24 hr of admission<br>Continued for 3 yr in those with normal LVEF; indefinitely in those with HFrEF (carvedilol, bisoprolol, metoprolol succinate)<br>**CIs:** PR interval > 0.24 s, second- or third-degree heart block, active asthma, or reactive airway disease |
| ACE inhibitors | Should be initiated and continued indefinitely for all patients with LVEF ≤ 40% and in those with HTN, DM, or stable chronic kidney disease unless CI<br>Benefit likely comes from prevention of cardiac remodeling<br>ACE inhibitors may be acceptable in all other patients with cardiac or other vascular disease<br>Angiotensin receptor blocker indicated if CI to or intolerant of ACE inhibitor<br>**CIs:** Hypotension, pregnancy, bilateral renal artery stenosis |
| Aldosterone antagonist | Indicated within the first 7 days in patients post-MI already receiving an ACE inhibitor and β-blocker and who have LVEF ≤ 40% and either symptomatic HF or DM, unless CIs<br>Inhibits the effects of aldosterone, which promotes vascular and myocardial fibrosis, endothelial dysfunction, HTN, LV hypertrophy, sodium retention, K and magnesium loss, and arrhythmias<br>**CIs:** Hyperkalemia ($K^+ \geq 5.0$), CrCl < 30 mL/min/1.73 $m^2$, SCr > 2.5 mg/dL in men and > 2.0 mg/dL in women |
| Statins | High-intensity statin therapy (atorvastatin 40–80 mg/day, rosuvastatin 20–40 mg/day) should be initiated or continued in all patients without CIs<br>Post-MI, statins reduce total mortality, CV mortality, and stroke<br>**CIs:** Pregnancy; note dosing restrictions on CYP3A4-interacting medications, caution with fibrates<br>Other additional lipid-lowering therapies may include ezetimibe or inhibitors of PCSK9 |
| **Additional anti-ischemic therapies for select patients (non–mortality reducing)** | |
| Nitrates | Patients should be given sublingual or spray NTG with verbal instructions for its use unless CI<br>For patients with angina lasting ≥ 1 min, give NTG (one dose and immediately call 911 to access to emergency medical services if angina does not subside within 3–5 min<br>Long-term nitrates should be continued post-discharge in patients requiring nitrates in the hospital who did not undergo revascularization or with incomplete or unsuccessful revascularization<br>**CIs:** Sildenafil or vardenafil use within 24 hr or tadalafil use within 48 hr; SBP < 90 mm Hg or ≥ 30 mm Hg below baseline, heart rate < 50 beats/min, heart rate > 100 beats/min in absence of symptomatic HF or right ventricular infarction |
| CCBs | CCBs are recommended for ischemic symptoms when β-blockers are not successful, are CI, or cause unacceptable adverse effects<br>Nondihydropyridine CCBs: Verapamil, diltiazem recommended if continuing or commonly recurring ischemia and CI to β-blocker therapy or recurrent ischemia after β-blockers and nitrates fully used<br>No real benefit or detriment to mortality; primarily for symptom relief<br>Immediate-release nifedipine should be avoided<br>Long-acting CCBs and nitrates are recommended for patients with coronary vasospasm<br>CCBs alone or in combination are useful in treating vasospastic angina<br>**CIs:** Clinically significant LV dysfunction, increased risk of cardiogenic shock, PR interval > 0.24 s, or second or third-degree heart block without a pacemaker |

[a]Class 1, should be performed or administered; class 2a, reasonable to be performed or administered; class 2b, may be considered; class 3, not to be administered or harmful.

ACE = angiotensin-converting enzyme; ACS = acute coronary syndrome; CCB = calcium channel blocker; CI = contraindication;

CrCl = creatinine clearance; CV = cardiovascular; DAPT = dual antiplatelet therapy; DM = diabetes mellitus; HF = heart failure; HFrEF = heart failure with reduced ejection fraction; HTN = hypertension; LV = left ventricle; LVEF = left ventricle ejection fraction; MI = myocardial infarction; NTG = nitroglycerin; SBP = systolic blood pressure; SCr = serum creatinine.

## XI. QUALITY MEASURES IN ACUTE CORONARY SYNDROME

A. Ongoing Care – Quality Measures for NSTEMI or STEMI Independent of Revascularization or Medical Management
   1. Medications that should be initiated before discharge or contraindications that should be documented in the medical record:
      a. Aspirin
      b. Statin
      c. $P2Y_{12}$ inhibitor
      d. β-Blocker
      e. If LVEF is 40% or less, ACE inhibitor or angiotensin receptor blocker and aldosterone antagonist (if also evidence of heart failure and/or DM)
   2. Interventions and/or referrals
      a. STEMI
         i. Time to PCI in a patient with STEMI
         ii. Time from ED arrival to ED discharge when transferring for STEMI PCI to another hospital
      b. LV function assessment (by imaging or during catheterization)
      c. Cardiac rehabilitation
      d. Smoking cessation counseling
      e. A lipid profile, including the LDL, should preferably be measured within 24 hours of admission. Any lipid profile measured between 6 months before first medical contact and hospital discharge qualifies for this quality measure.

B. For more information on cardiology-related quality measures and registries, see www.ncdr.com/.

**Patient Case**

13. For which patient would eplerenone 25 mg best be part of the drug treatment regimen for ACS at discharge?
    A. 48-year-old woman with K 4.8 mg/dL and SCr 2.1 mg/dL already receiving lisinopril and metoprolol and unknown ejection fraction.
    B. 62-year-old man with diabetes and blood pressure 100/70 mm Hg who cannot tolerate lisinopril with ejection fraction of 45%.
    C. Patient with ejection fraction of 25% and symptomatic diabetes; tolerating lisinopril and metoprolol with blood pressure 125/85 mm Hg.
    D. Patient with ejection fraction of 40% not taking metoprolol or lisinopril; blood pressure 140/85 mm Hg.

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## ANSWERS AND EXPLANATIONS TO PATIENT CASES

**1. Answer: D**
This patient's TIMI risk score is 5 (Answer D is correct; Answers A, B, and C are incorrect), with 1 point given for each of her risk factors: known ischemic heart disease, two or more angina events in the previous 24 hours, use of aspirin in the previous 7 days, elevated cardiac biomarkers (troponin), and ST segment changes. With a TIMI risk score of 5, her risk of mortality, new or recurrent MI, or severe recurrent ischemia through 14 days would be estimated at 26%.

**2. Answer: B**
This patient's TIMI risk score is 5, and her GRACE 2.0 score is 142, which places this patient at high risk of clinical events. (Answer B is correct). Fibrinolysis would be inappropriate in this patient because fibrinolytic therapy is contraindicated in NSTE-ACS (Answer A is incorrect). A conservative treatment approach is reserved for patients at low risk of clinical events with shared decision-making or in patients who are not good candidates for revascularization. Answer C is incorrect, given that this patient is at high risk of clinical events and no contraindications or known objections to PCI. Answer D is incorrect; this patient should receive both antiplatelet and antithrombotic agents, and given her high-risk features, she would best be taken to the catheterization laboratory for an early invasive strategy.

**3. Answer: C**
Of the patients described, the patient with the lowest risk is the one with negative troponins (Answer C is correct) and with resolved symptoms with a low TIMI score. Answer A is incorrect because the TIMI score would be at least 3, given the details provided. The patients in Answers B and D would need invasive therapy, not a more conservative approach, because of their positive troponins (Answer B is incorrect) and ST-segment elevation (Answer D is incorrect).

**4. Answer: B**
Answer A is incorrect because dosing for patients weighing less than 60 kg should be 5 mg daily. Answer B is correct because the patient has no contraindications to prasugrel, and the dosing is correct, given this patient's weight and age. Answers C and D are incorrect because prasugrel is contraindicated in patients with a history of stroke or TIA, regardless of time or origin of stroke. Patients who received prasugrel in the TRITON-TIMI study who had a history of stroke had worse outcomes than those given clopidogrel and had an increased risk of hemorrhagic stroke.

**5. Answer: C**
Intravenous cangrelor (Answer A) is not best at this time because the patient is tolerating oral medications and because of the expense of the drug. Prasugrel is preferred to clopidogrel; however, the maintenance dose should be 10 mg daily, not 5 mg daily. (Answer B is incorrect). Ticagrelor is preferred to clopidogrel in patients with ACS who undergo PCI, and the dosing is appropriate (Answer C is correct). Answer D is incorrect because ticagrelor is preferred to clopidogrel in patients with ACS.

**6. Answer: B**
Ticagrelor is administered twice daily, which can be a disadvantage for patients with adherence issues (Answer A is incorrect). Ideally, ticagrelor should be held 3 days before elective CABG surgery, whereas prasugrel should be held 7 days (Answer B is correct). Ticagrelor and its metabolite are metabolized by CYP3A4, and they inhibit the P-glycoprotein system; thus, there is a potential for drug interactions with ticagrelor. Concomitant use of strong 3A4 inhibitors and inducers should be avoided (Answer C is incorrect). In head-to-head clinical studies to date, bleeding rates between prasugrel and ticagrelor have been similar (Answer D is incorrect).

**7. Answer: B**
If a conservative approach is selected, bivalirudin is not an option because it has not been studied in this conservative setting (Answer A is incorrect). Answer B is correct because this is the correct dosing for unfractionated heparin, and the patient has no known contraindications. Answers C and D are dosing strategies for STEMI, in which an intravenous bolus is given, followed by subcutaneous dosing. Because this patient has NSTE-ACS, this dosing is not necessary. Answer D is further incorrect because it is a prophylactic maintenance dose, whereas higher dosing would be indicated in NSTE-ACS.

**8. Answer: D**
The advantage of less bleeding with bivalirudin over

unfractionated heparin has mainly been studied when heparin has been given with concomitant GP IIb/IIIa inhibitors. The superiority of either unfractionated heparin or bivalirudin in primary PCI has been the subject of recent trials, which have had conflicting results (Answer A is incorrect). Answer B is incorrect because an antiplatelet should be given with both bivalirudin and unfractionated heparin. Bivalirudin is cleared renally; therefore, Answer C is not an advantage of bivalirudin over unfractionated heparin. Bivalirudin is a direct thrombin inhibitor and does not have a risk of HIT. Bivalirudin is the preferred treatment during PCI in patients with a risk of HIT and would be better than unfractionated heparin in this setting.

**9. Answer: C**

Fibrinolytic therapy would be best for this patient with STEMI when PCI cannot be performed within 120 minutes (preferably with a door-to-needle time of 30 minutes). Answer C has the most appropriate dosing strategy, with weight-based tenecteplase given concomitantly with heparin (60-unit/kg intravenous bolus and 12-unit/kg/hour infusion). Answer A is incorrect because alteplase requires an intravenous infusion after an initial bolus. Answer B is incorrect because a conservative approach is inappropriate in STEMI. Although Answer D is preferred when a catheterization laboratory facility is nearby, it is incorrect because of the distance and time required to transfer the patient.

**10. Answer: B**

Both NSAIDs and select COX-2 inhibitors should be discontinued at the time of ACS presentation because they have been associated with an increased risk of major adverse cardiac events (Answer B is correct). Answer A is incorrect because doxazosin is not known to cause ischemia-type pain. Although aspirin resistance could contribute to the lack of effect from aspirin, aspirin is usually protective of ACS, not causative (Answer C is incorrect). Answer D is incorrect because nitroglycerin has no drug interaction with ticagrelor. Morphine can slow the absorption of $P2Y_{12}$ inhibitors; thus, it has been downgraded to a class 2b recommendation. Moreover, higher aspirin doses (more than 100 mg daily) decrease the effectiveness of ticagrelor.

**11. Answer: D**

This patient has experienced a bleed on prasugrel and needs a de-escalation of $P2Y_{12}$ inhibition. Answer D is appropriate because loading doses are not necessary when after 30 days from index event or stent placement, and loading doses are also not generally recommended after a bleeding event (Answer C is incorrect). Answers A and B are incorrect because clopidogrel is the preferred $P2Y_{12}$ inhibitor after a bleeding event.

**12. Answer: B**

Given this man's DAPT risk score of less than 2 (-1 for age 67; +1 for previous NSTEMI, +1 for DM), the risk of bleeding with prolonged use of DAPT outweighs the benefit after 12 months. Ticagrelor can be discontinued at 12 months (Answer B is correct). Answer A is incorrect because aspirin should be continued indefinitely for secondary prevention. Answers C and D are incorrect because benefit is greater than risk when the DAPT score exceeds 2.

**13. Answer: C**

To reduce mortality, administration of a mineralocorticoid receptor antagonist, either eplerenone or spironolactone, should be considered within the first 7 days post-MI in patients who are already receiving an ACE inhibitor (or angiotensin receptor blocker) and a β-blocker and have an LVEF of 40% (0.40) or less and either heart failure symptoms or DM. The patient in Answer C meets these criteria, whereas Answers A and B are incorrect because of the patients' ejection fractions, and Answer D is incorrect because the patient is not receiving a β-blocker. In addition, Answer A would not be the best choice given that she is a woman with a SCr >2.0 mg/dL.

## ANSWERS AND EXPLANATIONS TO SELF-ASSESSMENT QUESTIONS

**1. Answer: A**

This patient presents with chest pain symptoms, positive troponin, and ECG changes that indicate STEMI. Because he presents to a hospital with catheterization laboratory facilities, he should be taken for immediate reperfusion with PCI. Answer A is correct because the goal "first medical contact to device" time for primary PCI is 90 minutes, which is likely to be met with quick transport to the laboratory. Answer B is incorrect because the time is longer than the current performance measure goal. Answer C (reteplase) and Answer D (tenecteplase) are incorrect because primary PCI is preferred to fibrinolytic therapy, especially when PCI can be performed within 120 minutes.

**2. Answer: B**

Answer A is incorrect because intravenous β-blockade is not preferred and could place this patient at risk of cardiogenic shock, given his relatively low heart rate. Low-dose oral β-blockade initiated within the first 24 hours would be appropriate as long as blood pressure remained stable and heart rate could tolerate. Answer B is appropriate and would facilitate coronary vasodilation, relieving ischemic discomfort temporarily as he is prepared for PCI. Of importance, nitroglycerin (Answer B is correct) would not interfere with the anticipated administration of a $P2Y_{12}$ inhibitor during the intervention, unlike morphine (Answer C) potentially would. The recommendation for morphine has been downgraded to class 2b because it may slow the absorption of the antiplatelet therapy. At least two large trials have identified an association between morphine administration and risk of death. Answer D is incorrect, given that intravenous use of ACE inhibitors is contraindicated because of the risk of hypotension.

**3. Answer: C**

Aspirin, together with a $P2Y_{12}$ inhibitor, and an anticoagulant are indicated in this patient with STEMI undergoing primary PCI. Both unfractionated heparin and bivalirudin are options for anticoagulation in this setting, whereas clopidogrel, ticagrelor, and prasugrel are appropriate if stenting occurs. However, prasugrel and ticagrelor would be preferred over clopidogrel (Answer A is incorrect). Answer B outlines the correct dosing strategy for unfractionated heparin and the correct loading dose for prasugrel; however, Answer B is incorrect because at least 162 mg of aspirin should be administered on presentation, preferably within 10 minutes of arriving at the ED. Answer C contains the correct aspirin and ticagrelor loading doses, as well as the appropriate heparin dosing strategy. Answer D is incorrect because of the lack of aspirin loading dose.

**4. Answer: A**

The NSTE-ACS guidelines recommend an anticoagulant during an acute event. Because this patient is going for cardiac catheterization, class 1–recommended options include enoxaparin, unfractionated heparin, and bivalirudin. Answer C is incorrect because fondaparinux is contraindicated when the CrCl less than 30 mL/minute/1.73 $m^2$. Furthermore, fondaparinux is not optimal because it is associated with increased risk of catheter-related thrombosis during intervention, and it carries a class 3, or harmful recommendation. Of the remaining three options, unfractionated heparin (Answer A) is preferred because of its rapid clearance. Unfractionated heparin is dosed appropriately as a maximum of 4000-unit bolus, and 1000 units/hour is recommended. Both enoxaparin (Answer B) and bivalirudin (Answer D) are appropriate but would have to be dose adjusted, given this patient's CrCl of less than 30 mL/minute/1.73 $m^2$. However, the dosages in Answers B and D would be appropriate for patients with a normal CrCl.

**5. Answer: A**

Bivalirudin, a direct thrombin inhibitor, is appropriate in patients undergoing PCI when HIT is involved (Answer A is correct). Although low-molecular-weight heparins do not carry the same risk of HIT as unfractionated heparin, cross-reactivity can occur, and low-molecular-weight heparins should be avoided in confirmed or suspected cases of HIT (Answer B is incorrect). Eptifibatide, a GP IIb/IIIa inhibitor, is an antiplatelet agent and would not be an appropriate replacement for unfractionated heparin during PCI (Answer C is incorrect). Fondaparinux should not be used as a sole anticoagulant during PCI, making Answer D incorrect.

**6. Answer: A**

The U.S. guidelines for treating patients undergoing CABG surgery recommend discontinuing clopidogrel for at least 5 days in the setting of elective CABG. This patient had a DES placed 6 months ago, making the patient at high risk of ischemic events. Clinical practice guidelines recommend continuing aspirin in the perioperative setting (Answer A is correct). Answers B and C are incorrect because aspirin should be continued. Answer D is incorrect because the $P2Y_{12}$ inhibitor should be discontinued for at least 5 days to minimize the risk of bleeding from CABG.

**7. Answer: B**

This patient had a recent MI and additionally has other high risk features (age, hypertension) and would be classified as very high risk based upon recent clinical practice guidelines. The addition of non-statin therapy would be recommended in patients already on maximally tolerated statin therapy who do not achieve at least a 50% reduction in LDL-C or an LDL-C less than 55 mg/dL in very high risk patients (Answer A is incorrect). According to the results of the IMPROVE-IT trial, ezetimibe had a statistical benefit in CV events when added to statin therapy who had ACS and is available in a generic formulation, making Answer B correct. Fenofibrate has not been shown in clinical trials to improve outcomes from either its TG-lowering effects or its HDL-raising effects; its use is limited to TG greater than 500 mg/dL (Answer C is incorrect). Evolocumab has had overall CV mortality-lowering outcomes (20%), but the patient's lack of medical insurance would be a barrier for evolocumab therapy (Answer D is incorrect).

**8. Answer: B**

MedWatch is the FDA Safety Information and Adverse Event Reporting Program for health care professionals to report the adverse events that occur after a drug is approved. Although it is commonly used only for reporting serious reactions to the FDA and would not be mandatory in this case (Answer A is incorrect), it can be used to report any adverse event. Information recorded is submitted to the manufacturer and used to determine whether black box warnings are necessary or whether new adverse effects occur with a drug. The Joint Commission requires that all institutions have a definition of an ADR for the institution that can be understood and remembered by all health care professionals (Answer B is correct). In addition, The Joint Commission requires that each drug dose administered be monitored for adverse effects, that each institution have a system in place for reporting ADRs, and that the institution ensure that the reporting mechanism identifies all key ADRs. Even adverse effects that are well known can be submitted to the FDA, especially if the adverse event requires drug discontinuation (Answer C is incorrect). Answer D is incorrect because serious ADEs are reportable to the FDA, as are severe and life-threatening events.

# Cardiovascular Emergencies

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**Learning Objectives**

1. Choose appropriate management pathways/treatment for a patient with cardiac arrest according to patient presentation.
2. Differentiate between the various categories of shock.
3. Select the optimal management strategies for the various types of shock.
4. Construct a pharmacotherapy regimen for the various hypertensive crises.
5. Select an appropriate management plan for a patient presenting with acute aortic syndrome.
6. Design a pharmacotherapy plan for the management of acute ischemic stroke.

**Abbreviations in This Chapter**

| | |
|---|---|
| AAS | Acute aortic syndrome |
| AD | Aortic dissection |
| AED | Automated external defibrillator |
| CO | Cardiac output |
| CPR | Cardiopulmonary resuscitation |
| CVP | Central venous pressure |
| DBP | Diastolic blood pressure |
| ED | Emergency department |
| HTN | Hypertension |
| ICU | Intensive care unit |
| IVF | Intravenous fluid |
| LV | Left ventricle/ventricular |
| MAP | Mean arterial pressure |
| PCWP | Pulmonary capillary wedge pressure |
| ROSC | Return of spontaneous circulation |
| RV | Right ventricle/ventricular |
| SBP | Systolic blood pressure |
| SCA | Sudden cardiac arrest |
| SV | Stroke volume |
| SVR | Systemic vascular resistance |
| VF | Ventricular fibrillation |
| VT | Ventricular tachycardia |

**Self-Assessment Questions**

*Answers and explanations to these questions can be found at the end of this chapter.*

*Questions 1 and 2 pertain to the following case.*

A 69-year-old woman with a medical history of coronary artery disease and heart failure with reduced ejection fraction is admitted to a monitored bed for suspected heart failure exacerbation. Her laboratory values include serum creatinine (SCr) 1.5 mg/dL (baseline 1.0 mg/dL), potassium (K) 4.1 mEq/L, magnesium 1.8 mEq/L, aspartate aminotransferase (AST) 100 IU/L, and white blood cell count (WBC) 13 x $10^3$ cells/$mm^3$. All other laboratory values are unremarkable. While obtaining a medication history, you notice what appears to be monomorphic ventricular tachycardia (VT) on the monitor with a heart rate ranging between 120 and 130 beats per minute and a systolic blood pressure (SBP) of 88/60 mm Hg. You alert the emergency response team, and a biphasic defibrillator is brought to the bedside. A synchronized cardioversion is performed with mild sedation. The patient becomes unresponsive after cardioversion and has no pulse. The monitor continues to show monomorphic ventricular tachycardia. Cardiopulmonary resuscitation (CPR) is initiated immediately with high-quality chest compressions. A peripheral line is in place, and she is immediately ventilated by bag-valve mask.

1. Which of the following is the most appropriate course of action at this time?
   A. Administer epinephrine 1 mg intravenously x 1.
   B. Obtain an advanced airway.
   C. Deliver an unsynchronized shock at 120 J.
   D. Administer a dose of amiodarone 300 mg intravenously x 1.

2. After 10 minutes of resuscitative efforts, the rhythm changes from pulseless VT to asystole. Which is the most appropriate action to manage this patient's rhythm disturbance?
   A. Deliver an unsynchronized shock/defibrillation at 120 J.
   B. Resume high-quality chest compressions.
   C. Administer atropine 1 mg intravenously.
   D. Administer 1 g of magnesium.

*Questions 3 and 4 pertain to the following case.*
A 59-year-old man is day 1 following a coronary artery bypass grafting procedure. He is in the coronary care unit and has a pulmonary artery catheter in place. His morning laboratory values reveal a 3-point drop in hemoglobin (Hgb) from 10.1 g/dL to 7.1 g/dL since surgery. He has a consistent blood pressure of around 82/36 mm Hg this morning. His pulmonary artery catheter values are as follows: central venous pressure (CVP) 2 mm Hg, pulmonary capillary wedge pressure (PCWP) 8 mm Hg, cardiac output (CO) 3 L/minute, and systemic vascular resistance (SVR) 1300 dynes × seconds × $cm^{-5}$. Bedside echocardiogram reveals collapse of the left ventricular (LV) wall, no right ventricular (RV) strain, ejection fraction 40%–45%, and no tamponade. The patient does not have a fever.

3. Which shock state does this patient's hemodynamic and clinical picture most consistently represent?
   A. Hypovolemic.
   B. Obstructive.
   C. Vasodilatory.
   D. Cardiogenic.

4. Which is the most appropriate initial management strategy for this patient's shock?
   A. Initiate a norepinephrine drip.
   B. Administer hydroxyethyl starch.
   C. Initiate dobutamine.
   D. Administer lactated Ringer solution.

*Questions 5 and 6 pertain to the following case.*
A 29-year-old woman at 36 weeks' gestation presents to the emergency department (ED) with acute chest pain, blurred vision, headache, and shortness of breath. Her husband denies any illicit drug, alcohol, or cigarette use. Urine toxicology is negative. Initial vital signs are as follows: blood pressure 202/140 mm Hg, heart rate 88 beats/minute, respiratory rate 22 breaths/minute, and pain 9/10 (chest pain). Initial laboratory values are as follows: SCr 2 mg/dL (baseline 0.9 mg/dL), AST 608 U/L, alanine aminotransferase 458 U/L, lipase 20 U/L, total bilirubin 1 mg/dL, direct bilirubin 0.4 mg/dL, WBC 6 x $10^3$ cells/$mm^3$, Hgb 9 mg/dL, troponin T 1 ng/mL, and D-dimer less than 0.5 mcg/mL. Chest radiography reveals moderate bilateral pleural effusions and no focal consolidations. She takes only folic acid, omeprazole, and a prenatal vitamin. She has a soy allergy.

5. Which criteria best indicate that she is having a hypertensive emergency and describes the optimal initial treatment targets?
   A. Blood pressure greater than 180/120 mm Hg and reduce to less than 110/80 mm Hg over 4 hours.
   B. Blood pressure greater than 200/120 mm Hg and reduce by 30% within 2 hours.
   C. Blood pressure greater than 180/120 mm Hg and reduce by 25% within minutes to hours.
   D. Blood pressure greater than 180/120 mm Hg and reduce to 140/80 mm Hg during the first hour.

6. Which is the most appropriate initial treatment strategy for her blood pressure?
   A. Enalaprilat 1.25 mg intravenously every 6 hours.
   B. Clevidipine intravenously at 1 mg/hour.
   C. Hydralazine 10 mg intravenous bolus every 30 minutes as needed.
   D. Phentolamine 20 mg intravenously as needed.

7. A 33-year-old African American man is transferred to your hospital with acute chest pain (9/10) radiating to his back. He has no family history of cardiovascular disease; however, his medical history is notable for severe uncontrolled hypertension (HTN) associated with nonadherence to medication and appointments. He has no history of smoking or illicit drug use. On physical examination, temperature and oxygen saturation were normal. Heart rate was 80 beats/minute and respiratory rate was 18 breaths/minute. His blood pressure was 188/85 mm Hg. Laboratory results show normal cardiac enzymes, stable SCr at 1.0 mg/dL, negative D-dimer, and no ST changes on electrocardiogram (ECG). Computed tomography (CT) reveals a type A dissection. Which would be the optimal blood pressure and heart rate target for this patient in the acute phase of management?
   A. Reduce mean arterial pressure (MAP) by 25% in the first 60 minutes and heart rate to less than 60 beats/minute.

B. Reduce SBP to less than 185 mm Hg in 30 minutes and heart rate to less than 80 beats/minute.

C. Reduce SBP to less than 120 mm Hg over 20 minutes and heart rate to less than 60 beats/minute.

D. Reduce SBP to less than 140 mm Hg over 60 minutes and heart rate to less than 80 beats/minute.

*Questions 8 and 9 pertain to the following case*

A 72-year-old man (height 67 inches [170 cm], weight 65 kg) is brought by emergency medical services to the ED with stroke symptoms that presented 2 hours prior to arrival. Door-to-CT completion time was 30 minutes. The CT results, interpreted at the time of the test, revealed a right frontal lobe infarction. His medical history includes diabetes, myocardial infarction, atrial fibrillation, and HTN. His home medications include glyburide, sotalol, and warfarin. He took aspirin 325 mg at symptom onset. His international normalized ratio (INR) is 1.4, platelet count (Plt) is 174,000/mm$^3$, prothrombin time is 20 seconds, partial thromboplastin time is 32 seconds, and blood pressure is 168/74 mm Hg; ECG reveals a heart rate of 120 beats/minute with atrial fibrillation. Other pertinent laboratory results include glucose 97 mg/dL, sodium (Na) 137 mEq/L, K 3.6 mEq/L, blood urea nitrogen (BUN) 15 mg/dL, and SCr 0.5 mg/dL. His National Institutes of Health Stroke Scale (NIHSS) score is 22. Urine drug and tobacco screen were negative.

8. Which best represents the role of aspirin in acute stroke?

   A. Aspirin at an initial dose of 325 mg should be administered within 24–48 hours from symptom onset.

   B. Aspirin should be administered on hospital arrival, irrespective of the treatment strategy chosen.

   C. Aspirin should only be administered if fibrinolytic therapy is not given.

   D. Aspirin at the initial dose should be administered within 72 hours of symptom onset.

9. Which statement best describes the role of intravenous alteplase for this patient?

   A. He is not a candidate for alteplase because of aspirin therapy.

   B. He is not a candidate for alteplase because he is taking warfarin.

   C. He is a candidate for alteplase because of a lack of contraindications.

   D. He is a candidate for alteplase because he is younger than 75 years.

## I. ADVANCED CARDIAC LIFE SUPPORT

This chapter focuses on treatment of the general population. Please see the chapter on mechanical circulatory support regarding arrest events in these patients.

A. Background
   1. Sudden cardiac arrest (SCA) is defined as termination of the heart to contract, resulting in hemodynamic collapse, and ultimately, to unresponsiveness.
   2. If corrective measures are not taken in a timely manner, SCA can progress to sudden cardiac death.
   3. SCA is one of the leading causes of death in many parts of the world, with an annualized incidence of out-of-hospital arrest in the United States of more than 347,000 adults.
   4. SCA most often occurs in patients with some form of structural heart disease, with coronary heart disease as the leading cause.
   5. SCA can vary in etiology (noncardiac vs. cardiac), circumstances (unwitnessed vs. witnessed), and setting (in-hospital vs. out-of-hospital).
   6. Most risk factors for coronary heart disease are also risk factors for SCA.

B. Management of SCA
   1. The American Heart Association's "chain of survival" outlines the critical actions necessary to treat life-threatening emergencies..
   2. The construct of the "chain of survival" is as follows:
      a. Immediate recognition of SCA and activation of the emergency response system
         i. Ensure scene is safe.
         ii. Check responsiveness of the patient and assess breathing.
         iii. If no response, abnormal or absent breathing, activate emergency response resources.
         iv. If the patient has a pulse but the patient's breathing is not normal or is absent, provide rescue breaths at a rate of 1 breath every 6 seconds (10 breaths/minute), and recheck pulse every 2 minutes.
            (a) If possible opioid overdose, administer naloxone if available, per protocol.
      b. Start CPR following the compressions-airway-breathing (C-A-B) sequence if the patient is not breathing and has no pulse detected definitively within 10 seconds:
         i. C – Chest compressions
            (a) Increased intrathoracic pressure and compressions of the heart lead to increased perfusion and oxygen delivery ($DO_2$) to the brain and myocardium.
            (b) All patients with SCA should receive chest compressions.
            (c) Patients should be placed on a hard and flat surface to provide optimal compressions.
            (d) Compressions should be performed at a rate of 100–120 compressions per minute at a depth of at least 2 inches (5 cm), with adequate chest recoil following each compression to optimize coronary perfusion and blood flow during CPR.
            (e) It is critical to limit interruption of chest compressions; increasing the number of compressions given per minute can increase survival rates from cardiac arrest, improve the rate of return of spontaneous circulation (ROSC), and increase neurologically intact survival.
            (f) To prevent fatigue during compressions, it is recommended that individuals providing compressions change every 2 minutes (or after five cycles of compressions at a rate of 30:2 compressions/ventilation), with a maximum of 5 seconds for this change to occur.
            (g) End-tidal carbon dioxide ($EtCO_2$), coronary perfusion pressure (aortic diastolic pressure, right atrial diastolic pressure), arterial relaxation pressure, regional cerebral oxygenation, and central venous oxygen saturation ($ScvO_2$) correlate with CO and myocardial blood flow during CPR; inability to achieve target threshold of these parameters increases the likelihood of not achieving ROSC (Table 1). Of note, many of these aspects cannot routinely be measured during CPR. $EtCO_2$ may be measured with continuous waveform capnography, if available.

**Table 1.** Parameters Associated with ROSC

| Variable | ROSC Rarely Achieved |
|---|---|
| $EtCO_2$ | < 10 mm Hg |
| Coronary perfusion pressure | < 15–20 mm Hg |
| Arterial relaxation (diastolic) pressure | < 20–40 mm Hg |
| Regional cerebral oxygenation | < 25% |
| $ScvO_2$ | < 30% |

$EtCO_2$ = End-tidal carbon dioxide ROSC = return of spontaneous circulation.

ii. A – Airway
   (a) Physiologically, the need for assisted ventilation has a lower priority over chest compressions because oxygen content should be adequate at the time of arrest, and compression and gasp should provide some passive $DO_2$. Passive oxygen content is 21%, whereas rescue breathing is 17%.
   (b) During chest compressions, air is expelled from the chest, and oxygen is drawn into the chest by passive recoil.
   (c) Health care providers can use the head-tilt/chin-lift maneuver to open the airway and/or place an artificial airway if the patient has no evidence of head or neck trauma.

iii. B – Rescue breaths
   (a) Primary function is oxygenation, with secondary function to remove carbon dioxide
   (b) As noted earlier, compressions should supersede airway or rescue breaths because arterial oxygen content of the blood remains unchanged until CPR is begun.
   (c) During CPR, without an advanced airway, health care providers should follow a compression/ventilation ratio of 30:2 to avoid excessive ventilation. Excessive ventilation can increase intrathoracic pressure, decrease venous return, and lead to gastric inflation and aspiration.
   (d) It is acceptable to deliver each breath over 1 second by mouth-to-mouth, mouth-to-barrier, mouth-to-stoma, or mouth-to-nose. Alternatively, breaths may be delivered via a bag valve mask (BVM) at the same ratio, if available, and at least two rescuers are present.
   (e) Give only enough tidal volume to witness chest rise.

c. Early defibrillation using a manual or automated external defibrillator (AED)
   i. Defibrillation shock is the same as unsynchronized shock.
   ii. Successful defibrillation is defined as 5 seconds or greater of termination of the arrhythmia after a shock is delivered.
   iii. Early defibrillation for ventricular fibrillation (VF) or pulseless ventricular tachycardia (VT), (the most common rhythm in witnessed out-of-hospital arrest) is crucial because delays in defibrillation can lead to asystole and decreased survival over time.
      (a) Survival rates are highest for VF when CPR and defibrillation occur within 3–5 minutes of the event; CPR prolongs VF and delays the progression to asystole.
      (b) For every minute that passes after collapse, survival decreases by 7%–10%.
   iv. Chest compressions *should only be halted while a shock is being delivered or when prompted by the AED;* they should continue while the AED and/or manual defibrillator is charging, and should resume immediately following shock delivery.
   v. Most AEDs are biphasic, and the dosage of energy should be delivered according to the manufacturer (typically, 120 or 200 J)

**Patient Case**

*Questions 1 and 2 pertain to the following case.*

A 60-year-old man in front of you at your local coffee shop suddenly collapses. You ask a bystander to call 911 because the man does not respond on initial assessment. He is not breathing, there is no chest movement, and you cannot feel a pulse.

1. Which best describes the most appropriate initial response?
   A. Open the airway, deliver two rescue breaths, and await emergency medical services arrival.
   B. Deliver two rescue breaths, followed by 30 chest compressions.
   C. Ensure the environment is save, and await emergency medical services arrival.
   D. Start chest compressions at 100–120 beats/minute.

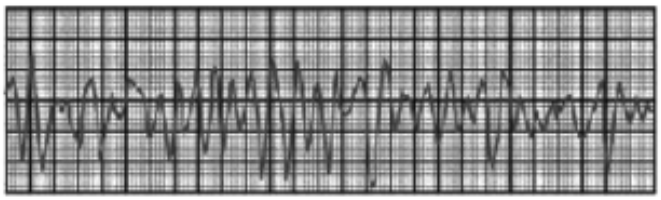
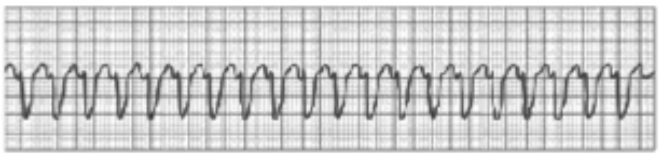
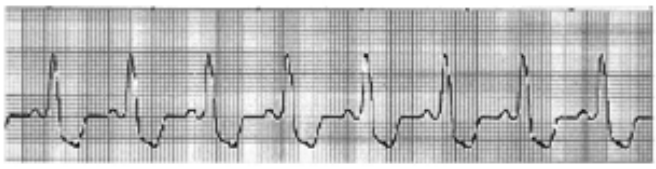
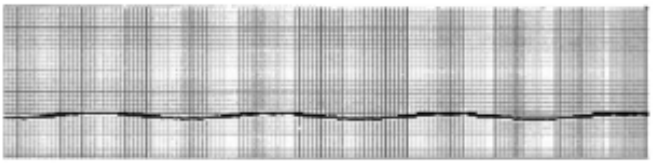
2. You have been doing chest compressions for about 2 minutes by the time someone arrives with an AED. Which is the most appropriate next step?
   A. Change providers and continue chest compressions for another 2 minutes.
   B. Stop compressions to remove clothing, and place AED pads.
   C. Provide two rescue breaths; then defibrillate the patient.
   D. Continue CPR, turn on the AED, attach pads, and wait for AED to begin analyzing the rhythm.

vi. Electrode pad placement:
   (a) Various pad positions can be used for effective termination of ventricular arrhythmias, including anterolateral, anteroposterior, anterior-left infrascapular, and anterior-right infrascapular.
   (b) Lateral pads should be placed under the breast tissue, and hair on the chest should be shaved, if present.
   (c) Pads or paddles should not be placed on top of implantable cardioverter-defibrillators or pacemakers.
   (d) Do not place pads on top of medication patches; patches should be removed.

d. Early advanced care - Effective ACLS
   i. Advanced airways
      (a) The two main classes of advanced airways are endotracheal (ET) intubation and supraglottic airways.
         (1) ET intubation is more difficult because of the need to visualize the glottis. However, this approach maintains airway patency, allowing for suctioning, ensuring high $DO_2$, providing medication administration, allowing for specific tidal volume delivery, and providing protection from aspiration.
         (2) A supraglottic airway does not require visualization of the glottis, allowing for continuous chest compressions, and provides ventilations as effectively as a bag-mask. Options consist of laryngeal mask airways, Combitube, and laryngeal tube.
      (b) Proper placement of an advanced airway should be confirmed by visual inspection of chest rise during ventilations, auscultation of lungs, measurement of exhaled carbon dioxide, chest radiograph, and waveform capnography.
      (c) After placement of an advanced airway, chest compressions should be given at a rate of 100–120 compressions per minute with a breath delivered every 6 seconds (10 breaths/minute) to avoid overventilation. Compressions and ventilations are no longer synchronized.

ii. The four primary arrest rhythms (Table 2) are divided into two groups: the shockable rhythms (VF and pulseless VT) and the nonshockable rhythms (pulseless electrical activity and asystole).
iii. The foundation of advanced cardiac life support is basic life support.
iv. Medications and advanced airways do NOT improve overall survival but do increase rates of ROSC or survival to hospital admission; chest compressions should not be compromised to establish intravenous access or to administer medications.
    (a) Administration of medications by central line is ideal, if possible, because of the ability to obtain higher peak concentrations and shorter drug circulation times; however, CPR should not be stopped to dedicate time for a central line placement. For this reason, many emergency providers have transitioned to obtainment of intraosseous access for medication delivery, which can be achieved rapidly and without interruption of compressions.
    (b) Medications administered peripherally should be followed by a 20-mL bolus of intravenous fluid (IFV), usually normal saline, to facilitate drug distribution.
    (c) If intraosseous access is used, administration and drug delivery are similar to those for central venous access. Sites that may be used for intraosseous administration include the proximal humerus, proximal tibia, distal tibia, and iliac crest.
    (d) ET administration may also be used. However, intravenous/intraosseous administration is preferred. Medications that may be given by ET tube include naloxone, atropine, vasopressin, epinephrine, and lidocaine (NAVEL). When given by the ET route, the recommended dose to administer is 2–2.5 times higher than the intravenous/intraosseous dose and should be diluted with 5–10 mL of normal saline.
    (e) Peak effect of intravenous/intraosseous-administered medications will be delayed by 1–2 minutes during CPR secondary to poor perfusion.
v. During cardiac arrest, evaluation of reversible causes should be continual, and treatment should begin immediately once a cause is isolated. These causes have been classified by the mnemonic "H's and T's" to enable a rapid differential assessment by providers.
    (a) Hs: Hypoxia, hypovolemia, hydrogen ions (acidosis), hypo/hyperkalemia, hypothermia
    (b) Ts: Toxins, tamponade (cardiac), thrombosis (pulmonary embolism or coronary thrombosis), tension pneumothorax
vi. Post-cardiac care should occur immediately after ROSC.
vii. Management of VF/pulseless VT (Figure 1; Table 3). Early evidence in prehospital arrest suggested amiodarone increased survival to hospital admission compared with placebo and lidocaine; however, recent randomized, double-blind data analyses suggest no benefit compared with lidocaine or placebo after one-shock-refractory VF/pulseless VT.

**Table 2.** Arrest Rhythms

| | | |
|---|---|---|
| Ventricular fibrillation | VF features:<br>a) Wide complex<br>b) Polymorphic<br>c) Disorganized<br>d) Coarse or fine<br>e) No/minimal forward blood flow |  |
| Pulseless VT | Pulseless VT features:<br>a) Wide complex<br>b) Monomorphic or polymorphic<br>c) Generally organized<br>d) No/minimal forward flow |  |
| Pulseless electrical activity | Pulseless electrical activity features:<br>a) Not a rhythm itself but defined as an organized rhythm that would be expected to produce mechanical activity but does not<br>b) Negligible mechanical ventricular activity<br>c) Absence of a palpable pulse |  |
| Asystole | Asystole features:<br>a) Absence of detectable ventricular electrical activity<br>b) Accompanied by absence of mechanical ventricular activity |  |

VT = ventricular tachycardia.

Information from: Coons JC, Abel EE. Cardiovascular critical care. In: Updates in Therapeutics®: Critical Care Pharmacy Review and Recertification Course, 2017 ed. Lenexa, KS: American College of Clinical Pharmacy, 2017:113-4.

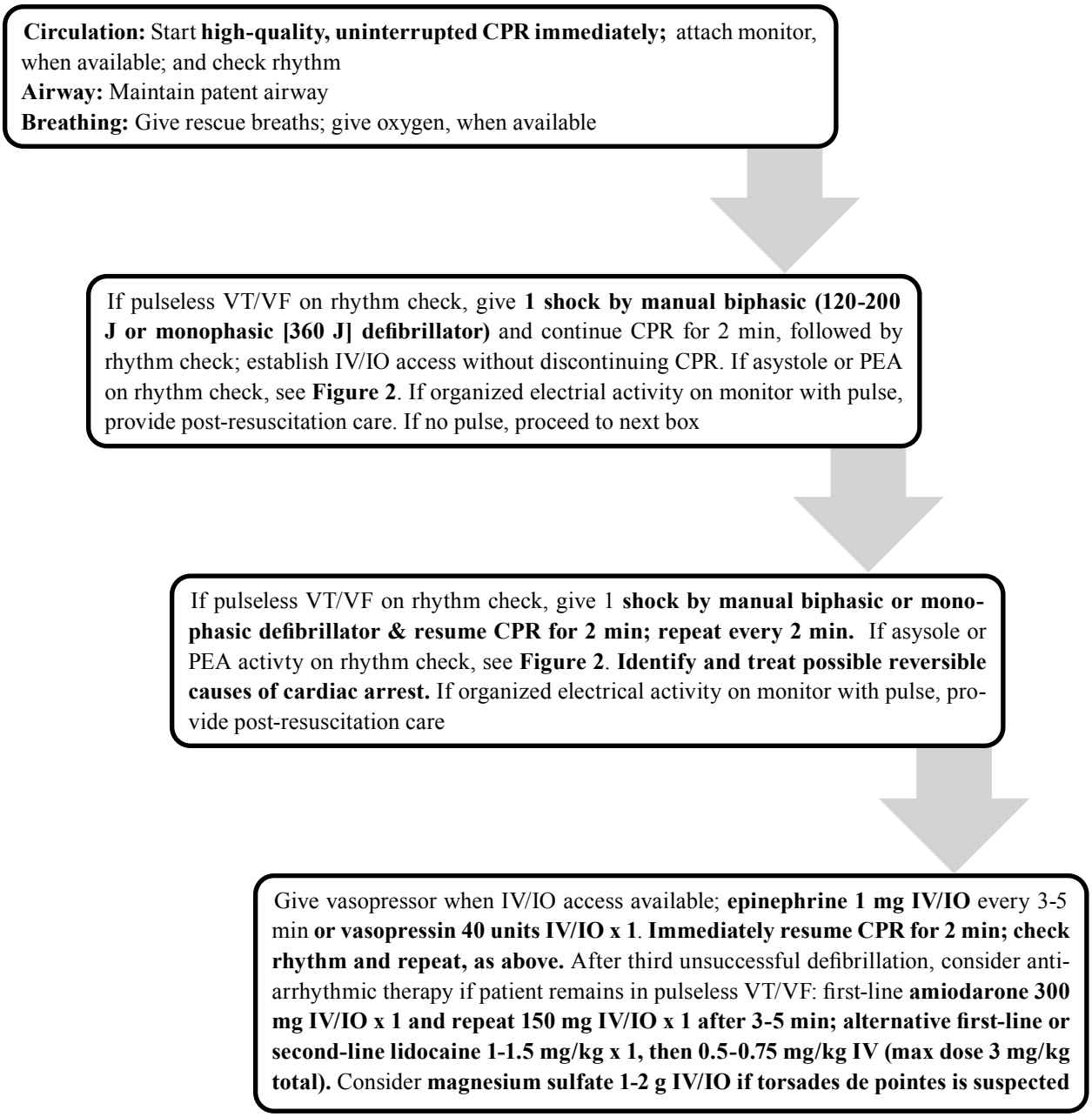



**Figure 1.** Ventricular fibrillation/pulseless ventricular tachycardia algorithm.

CPR = cardiopulmonary resuscitation; IO = intraosseous(ly); IV = intravenous(ly); PEA = pulseless electrical activity; VF = ventricular fibrillation; VT = ventricular tachycardia.

**Table 3.** Medications Used During Sudden Cardiac Arrest

| Medication | Primary Mechanism of Action in Cardiac Arrest | Dosage, Route, Frequency | Clinical Benefits |
|---|---|---|---|
| Epinephrine | Adrenergic agonist effects leading to vasoconstriction | 1 mg IV/IO q3–5 min<br>2–2.5 mg ET q3–5 min | • Increases coronary and cerebral perfusion pressure during CPR<br>• Increases ROSC<br>• Increase survival to hospital admission |
| Amiodarone | Na+/K+/Ca2+ channel and beta receptor antagonist (class III antiarrhythmic) | First dose: 300 mg IV/IO x 1<br>Second dose: 150 mg IV/IO x 1 | • Conflicting data on clinical outcomes compared with lidocaine or placebo for out-of-hospital arrests |
| Lidocaine | Na+ channel antagonist (class IB antiarrhythmic) | First dose: 1–1.5 mg/kg IV/IO x 1<br>Subsequent dosing: 0.5–0.75 mg/kg q5–10 min<br>Max 3 mg/kg cumulative dose | • Conflicting data on clinical outcomes for out-of-hospital cardiac arrest; no improvement in overall or discharge survival |
| Magnesium sulfate | Stops EAD in torsades de pointes by inhibiting Ca2+ channel influx | 1–2 g diluted in 10 mL of 5% dextrose or sterile water IV/IO × 1 | • Can help terminate torsades de pointes in patients with prolonged QT interval<br>• No benefit for routine use in cardiac arrest |

EAD = early after depolarization; ET = endotracheal; q = every.

viii. Management of pulseless electrical activity/asystole (Figure 2)

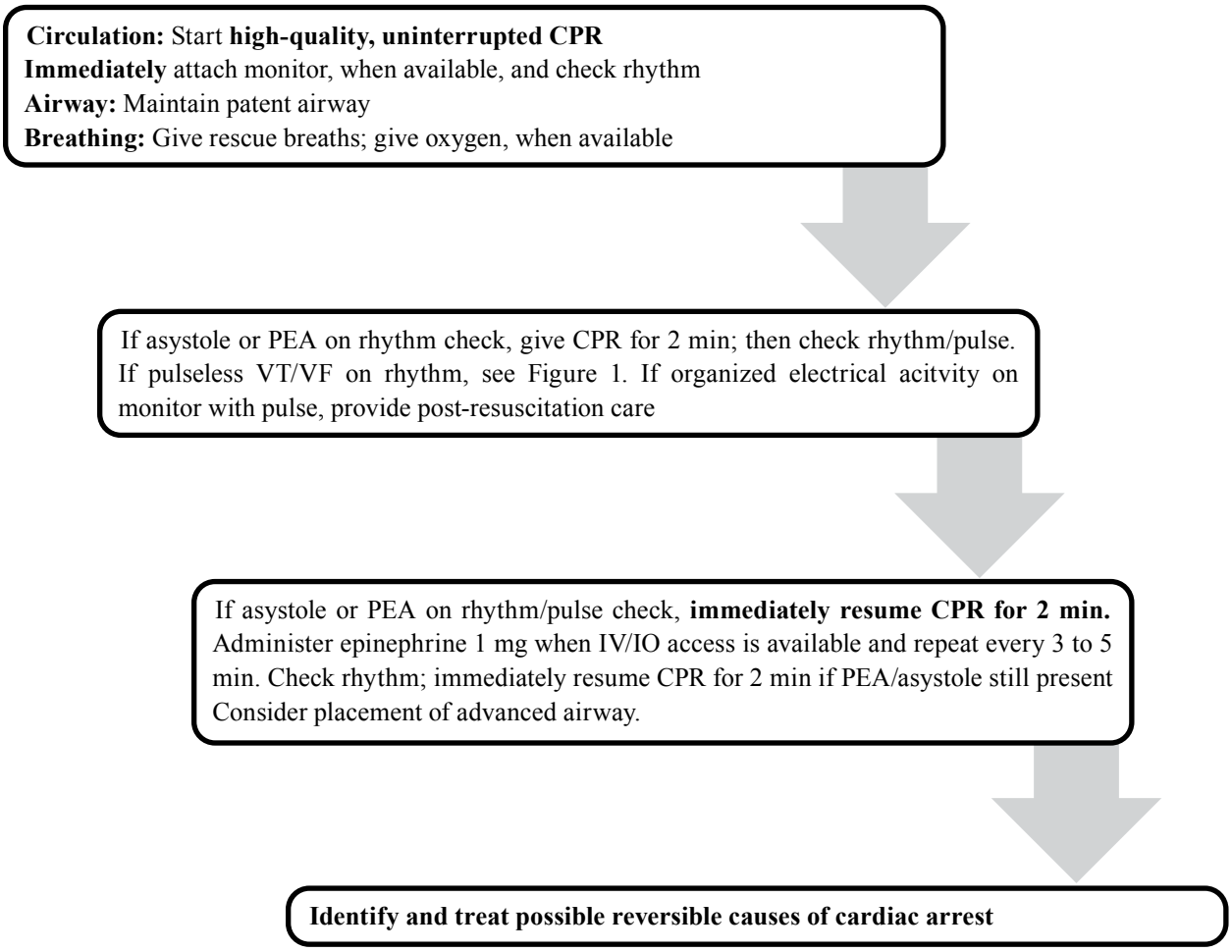



**Figure 2.** Pulseless electrical activity/asystole algorithm.

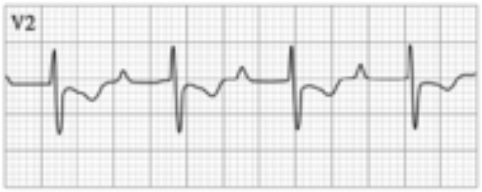
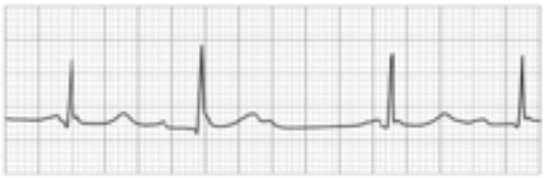
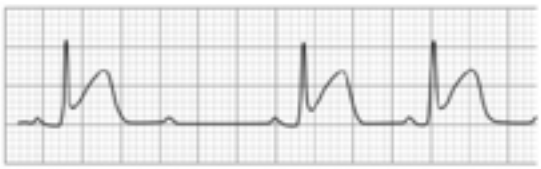
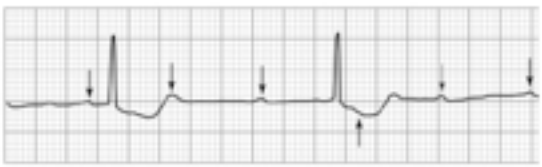
**Patient Case**

3. A 55-year-old man with an unknown medical history comes to your ED with altered mental status. He is placed in a bed when he suddenly becomes unconscious and pulseless. The nursing staff starts CPR. Which statement best describes the most appropriate treatment?
   - A. Survival from cardiac arrest solely depends on medications and advanced airways; CPR should be halted so that airway and line placement can occur.
   - B. The treatable, reversible causes of cardiac arrest should be reviewed and addressed while CPR and laboratory/diagnostic tests are being performed.
   - C. If the patient is in PEA or asystole, pads should be placed, the patient cleared, and the shock delivered.
   - D. All patients should be given sodium bicarbonate to prevent acidosis.

ix. The following medications are currently not recommended for routine use during cardiac arrest (VF and pulseless VT), given the lack of data, lack of proven benefit, or potential increased harm: magnesium, sodium bicarbonate, calcium, atropine, IVFs, vasopressin, dextrose. However, these medications may specifically be indicated if an underlying cause is identified (e.g., calcium for hyperkalemia or IVFs for hypovolemia).

x. Symptomatic bradycardia
   (a) Primary causes of bradycardia: Coronary artery disease, conduction diseases, select medications (e.g., beta blockers, calcium channel blockers, digoxin, etc.), electrolyte abnormalities, endocarditis, myocarditis, surgery (more common with cardiac), hypothyroidism, tumors, and vagus nerve–mediated heart block
   (b) Basics of bradycardia ECGs: Narrow QRS complexes commonly indicate SA node dysfunction, whereas wide complexes indicate either AV node or His-Purkinje dysfunction.
   (c) Table 4 highlights the various bradyarrhythmias.

**Table 4.** Bradyarrhythmias

| Type | ECG Example | Description |
|---|---|---|
| First-degree block |  | Delayed conduction from the sinoatrial (SA) node to the atrioventricular (AV) node defined by a P-R interval > 0.2 s<br>Relatively benign; however, underlying contributors should be evaluated and minimized (i.e., β-blockers and other agents) |
| Second-degree Mobitz type 1 (Wenckebach) |  | Consistent P-P interval with progressive prolongation of the P-R (indicating impaired SA to AV node conduction), eventually resulting in the absence of a QRS complex because of the lack of AV node conduction of atrial impulse<br>Of most concern in older adult patients for whom this may indicate progressive conduction disease; may be more benign in younger patients<br>"Longer, longer, longer, drop … must be Wenckebach" |
| Second-degree Mobitz type 2 |  | Consistent P-P interval and consistent P-R interval duration with spontaneous absence of a QRS complex because of the lack of AV node conduction of atrial impulse<br>Usually indicative of more significant conduction disease and associated with syncope, HF, and increased mortality rates |
| Third-degree (complete heart block) |  | Characterized by consistent P-P intervals, consistent R-R intervals, and variable/random P-R interval representing independent, uncoordinated atrial and ventricular conduction (A-V dissociation) |

HF = heart failure.

Information from: Coons JC, Abel EE. Cardiovascular critical care. In: Updates in Therapeutics®: Critical Care Pharmacy Review and Recertification Course, 2017 ed. Lenexa, KS: American College of Clinical Pharmacy, 2017:113-4.

(d) If a patient presents with a heart rate less than 50 beats/minute, and is unstable (hypotension, altered mental status, signs of shock, ischemic chest discomfort, or acute heart failure), emergency treatment is warranted. The medication of choice for symptomatic bradycardia is atropine 1 mg administered intravenously every 3–5 minutes (maximum of 3 mg intravenously). Of note, administering doses of atropine less than 0.5 mg can result in a paradoxical decrease in heart rate and potentially worsen bradycardia. Second-line agents to atropine include intravenous dopamine at 5–20 mcg/kg/minute, or epinephrine at 0.1–0.5 mcg/kg/minute

(e) Search for reversible causes (Hs/Ts).

(f) Nonpharmacologic measures such as transcutaneous or transvenous pacing are likely warranted for ongoing symptomatic bradycardia or emergently indicated if first-line therapy fails. Of note, transcutaneous pacing is able to be performed with most monitor/defibrillator units but may be very uncomfortable for patients because of skeletal muscle contraction synchronous with heart rate pacing; sedation and/or analgesic relief should strongly be considered when using this pacing method.

xi. Tachycardia

(a) Tachyarrhythmias are caused by any of the following abnormalities: enhanced automaticity, reentry, or triggered activity. These are often the result of ischemic heart disease or heart failure.

(b) ECG basics of tachyarrhythmias: Review for the presence of P waves, and measure the width of the QRS complex.

xii. Integrated post-cardiac arrest care

(a) Immediately post-ROSC, the goal is to optimize hemodynamics with a target MAP of greater than 65 mmHg and SBP greater than 90 mmHg, urinary output greater than 1 mL/kg/hour, and normal serum lactate. Use intravenous crystalloids, vasopressor and inotrope infusions (Table 5), transfusions, and renal replacement as indicated to achieve these goals.

**Table 5.** Common Vasoactive Agents Used After Cardiac Arrest or in Shock Syndromes

| Medication | Typical Dosing Range | Clinical Pearls |
|---|---|---|
| Epinephrine | 0.01–0.5 mcg/kg/min | Mixed β and α activity, with α1 activity > β2 activity at higher concentrations<br>Used to treat severe hypotension (e.g., SBP < 70 mm Hg, MAP < 65 mm Hg)<br>Used for symptomatic bradycardia<br>Used for hemodynamically unstable anaphylactic reactions<br>Higher doses associated with increased α1 activity |
| Norepinephrine | 0.01–0.5 mcg/kg/min | α1 > β1 receptor activity<br>Used to treat severe hypotension (e.g., SBP < 70 mm Hg, MAP < 65 mm Hg)<br>Should be used in volume-resuscitated patients<br>Currently first-line vasopressor for septic shock<br>Higher doses associated with increased α1 activity |
| Phenylephrine | 0.1-10 mcg/kg/min | Pure α1-agonist<br>Used to treat severe hypotension (e.g., SBP < 70 mm Hg, MAP < 65 mm Hg)<br>Should be used in volume-resuscitated patients<br>Avoid in patients with low CO without augmentation. |

**Table 5.** Common Vasoactive Agents Used After Cardiac Arrest or in Shock Syndromes *(Cont'd)*

| Medication | Typical Dosing Range | Clinical Pearls |
|---|---|---|
| Dopamine | 5–20 mcg/kg/min | Dose-related receptor activity:<br>2–5 mcg/kg/min dopamine receptor,<br>5–10 mcg/kg/min β1-receptor,<br>> 10 mcg/kg/min α1-receptor<br>Does not provide exclusive receptor activity across dosing ranges and can thus be arrhythmogenic at any dose<br>Use cautiously in patients with a history of heart disease or arrhythmias<br>Useful for patients with bradycardia and hypotension |
| Dobutamine | 2–20 mcg/kg/min | Predominance of inotropic properties but with activity on β1 > β2 > α1-receptor<br>Used to treat low CO<br>α1-agonist and β2-agonist counterbalance, leading to little change in SVR<br>Can lead to vasodilation at higher doses<br>Less systemic or pulmonary vasodilation than milrinone<br>More tachycardia than milrinone but similar risk of ventricular arrhythmias<br>Use cautiously in patients with a history of arrhythmias |
| Milrinone | 0.125–0.75 mcg/kg/min | Phosphodiesterase type 3 inhibitor leading to increased intracellular cAMP leading to influx of calcium and subsequently increased inotropy and chronotropy<br>Used to treat low CO<br>Do not use loading dose, given the risk of risk of significant systemic hypotension<br>Longer duration of activity than dobutamine<br>Accumulates in renal dysfunction (should consider lower doses, if present)<br>More systemic and pulmonary vasodilation than dobutamine<br>Less tachycardia than dobutamine but similar risk of ventricular arrhythmias<br>Use cautiously in patients with a history of arrhythmias |
| Synthetic angiotensin II | Initial: 20–80 ng/kg/min<br>Maintenance: 1.25-40 ng/kg/min | Indicated in vasodilatory shock refractory to initial vasopressor therapy<br>Avoid in cardiogenic shock<br>Initial infusion rates were used in the first 3 hours of initiation |

CO = cardiac output; SBP = systolic blood pressure; SVR = systemic vascular resistance.

(b) Consider initiating an amiodarone infusion if the patient had successful ROSC with amiodarone boluses (1 mg/minute x 6 hours; then 0.5 mg/minute x 18 hours. Infusion of 0.5 mg/min may be continued in unstable patients).
(c) Patients should be transferred to the appropriate level of care to ensure proper monitoring and ability to receive these therapies.
(d) Continue to identify and treat any potential causes for the arrest (e.g., acute coronary syndrome). Consider emergent cardiac intervention if acute ST-elevation mayocardial infarction is present and/or the patient has suspected cardiogenic shock and may be a candidate for mechanical circulatory support.

(e) Optimize mechanical ventilation with a goal oxygen saturation of 92%–98%.
(f) Once ROSC is obtained, consider initiating targeted temperature management if not following commands.
    (1) Evidence indicates only marginal benefit in survival and improved neurological outcomes.
    (2) Target body temperature is 32°C–36°C (89.6°F–96.8°F) for 24 hours after achieving target temperature; however, new evidence suggests an equivocal benefit at 34–36°C or maintenance of normothermia versus lowering of body temperature to 32°C.
    (3) Can use surface-cooling devices, ice packs, cooling blankets, or intravascular cooling devices to achieve cooling. Intravascular cooling generally allows greater control over temperature management with less shivering.
    (4) Rewarming should be a passive process over 8 hours, generally at a rate of 0.5 degrees per hour and no faster because of the risk of cerebral edema.
    (5) Major complications/considerations of hypothermia are highlighted in Table 6.
    (6) Hypothermia can affect the pharmacodynamic and pharmacokinetic properties of several adjunctive agents, including fentanyl, morphine, propofol, midazolam, rocuronium, vecuronium, cisatracurium, and phenytoin.

**Table 6.** Major Organ-Specific Complications of TTM

| | |
|---|---|
| Musculoskeletal | **Shivering:**<br>Body's natural response to hypothermia, preceded by arteriovenous vasoconstriction; most common complication of hypothermia; can increase metabolic heat production by 600%, thereby slowing the induction of hypothermia. Typically slows or stops at core temperatures < 33.5°C<br>1. Agents that decrease the shivering threshold (i.e., decreases the temperature at which shivering will occur):<br>a) Scheduled acetaminophen 650 mg q4–6 hr or buspirone 30 mg q12 hr confer modest (0.2°C–0.4°C) reductions in shivering threshold<br>b) Magnesium sulfate and buspirone reduce the shivering threshold (by up to 2°C); can be considered during the induction phase of hypothermia<br>c) Meperidine decreases the shivering threshold (up to 2°C). However, use caution in the setting of decreased glomerular filtration rate (GFR) because of the potentially increased risk of seizures. In this setting, lower doses as well as increased frequency should be adopted or alternative agents chosen<br>d) Dexmedetomidine and clonidine also decrease the shivering threshold (~0.8°C); caution should be exercised when using these agents, given the potential for hypotension and bradycardia<br>e) Propofol decreases the shivering threshold by ~0.6°C and has a linear relationship between serum concentrations and reduction in body temperature; use caution, given the hypotensive and bradycardic effects<br>f) Ketamine 0.25–0.75 mg/kg reduces perioperative shivering and may be considered in patients experiencing hypothermia. Higher doses are significantly more likely to produce cognitive adverse effects and should be avoided during active neurologic examination.<br>2. Options to stop shivering include:<br>a) Continuous or as-needed paralytics can be used for prevention and treatment of shivering (see the chapter on management of paralytics for appropriate selection and dosing of agent[s])<br>—Hypothermia decreases clearance and prolongs the duration of neuromuscular blockade (see Table 5 for examples)<br>—Train-of-four is not a reliable method of monitoring during hypothermia; clinical monitoring or continuous EEG (electroencephalography) may be warranted<br>b) Surface warming if using internal cooling devices |

**Table 6.** Major Organ-Specific Complications of TTM *(Cont'd)*

| | |
|---|---|
| Neurological | **Sedation and Analgesia:**<br>Use adequate pain control and sedation<br>Target Richmond Agitation-Sedation Scale score of -3 to -4 during hypothermia<br>Accumulation of parent and active metabolites can be expected for each analgesic and sedative, which leads to prolonged sedation and potentially untoward adverse effects<br>Bispectral index monitoring may also be used to monitor sedation depth (goal 40–60)<br>**Seizures:**<br>Possible complication of cardiac arrest and therapeutic hypothermia<br>Consider benzodiazepines as first line therapy to abort seizure<br>Phenytoin, fosphenytoin, barbiturates, valproic acid, levetiracetam, and propofol can all be used, with vigilant monitoring of adverse effects because of decreased clearance<br>**ICP:**<br>Risk increases post-cardiac arrest, probably because of ischemic injury and cytotoxic edema that is partly attenuated by TTM<br>Major increase appears to occur during rewarming phase |
| Cardiac | **Arrhythmias:**<br>Include VT, VF, and AF<br>If life threatening, consider discontinuing TTM and active rewarming<br>Sinus bradycardia is common and, in isolation, should not be treated unless it leads to hemodynamic instability (hypotension or organ dysfunction)<br>**ECG observations:**<br>Prolonged PR, QRS, and QT intervals<br>Use caution when using medications that prolong the QT interval<br>Sinus bradycardia<br>**Hemodynamics:**<br>Decreased CO<br>Fluid shifts away from central compartment |
| Hepatobiliary | Elevated transaminases<br>Reduced activity of non-cytochrome and cytochrome P450–mediated metabolism<br>See Table 5 for examples of metabolic changes in selected medications during hypothermia |
| Endocrinological | Hyperglycemia caused by a decreased insulin production and effect in periphery, increased gluconeogenesis, and glycogenolysis<br>Continuous insulin infusions may be necessary for glucose control. Goal glucose concentrations should be < 180 mg/dL without inducing hypoglycemia |
| Renal | Decreased effective glomerular filtration (urinary output may increase because of cold diuresis, but not effective in improving GFR)<br>Electrolyte shifts into the cell (K+, PO 3-, Na+, Ca2+) during cooling phase; reverse during rewarming<br>-Therefore, on rewarming, use caution with electrolyte replacement and monitor levels accordingly |
| Hematological | Coagulopathy caused by thrombocytopenia, impaired activation and activity of clotting factors, impaired platelet function<br>Actively bleeding patients should not be cooled |

ICP = intracranial pressure; TTM = targeted temperature management.

(g) Other considerations for arrest:
   (1) Seizures, myoclonus, or both occur in 5%–15% of patients who achieve ROSC because of hypoxic cerebral injury. Standard agents for treating myoclonus are clonazepam, levetiracetam, and valproic acid. For seizure, benzodiazepines, levetiracetam, phenytoin, valproic acid, propofol, and barbiturates can be used for seizure management.
   (2) Patients may have acute renal dysfunction or require renal replacement therapy; adjust or avoid medications accordingly.
   (3) Control blood glucose and avoid hypoglycemia. Insulin infusions provide the best option for adequate control.
   (4) Monitor for signs or symptoms of infection and treat appropriately.
   (5) Continually assess patient prognosis.

## II. CARDIAC TAMPONADE

A. General Features
   1. A life-threatening, slow or rapid compression of the chambers of the heart because of increased pericardial pressure leading to progressively reduced filling pressures and decreased systemic perfusion
   2. In tamponade, an accumulation of fluid in the pericardium leads to an increase in pericardial pressure. This results in an increase and equalization of diastolic pressures between the left and right heart (equalization of CVP, pulmonary artery diastolic pressure, and PCWP) and impaired ventricular filling. CVP and PCWP elevations should not be mistaken as representing an increase in ventricular volume (preload).
   3. Usually caused by neoplastic disease, renal failure, blunt chest trauma, iatrogenic causes, or idiopathic or viral pericarditis; however, can also be caused by bacterial infection, tuberculosis, collagen vascular disease, aortic dissection (AD), pneumopericardium, or post-myocardial infraction rupture
   4. Acute tamponade signs and symptoms include chest pain, tachypnea, tachycardia, dyspnea, cool extremities, and peripheral cyanosis.
      a. Beck triad: (1) hypotension, (2) jugular venous distension caused by elevated jugular venous pressure, (3) muted or distant heart sounds
      b. Low or narrow pulse pressure, defined as a pulse pressure less than 30 mm Hg
      c. Pulsus paradoxus – A decline of 10 mm Hg or more in SBP on inspiration
      d. Pericardial friction rub may be heard if inflammation is the key driver.
   5. Subacute tamponade is often less dramatic, and patients may have hypotension with a narrow pulse pressure but otherwise be asymptomatic initially. However, as intrapericardial pressures reach a critical number, the more common signs of acute tamponade become apparent.

B. Diagnosis
   1. Echocardiogram: Pericardial effusion, chamber collapse, a dilated inferior vena cava, or respiratory variations in cardiac blood volumes and flow rates
   2. ECG features: Sinus tachycardia, diffuse low voltage features, and alternating amplitude of QRS complexes
   3. Chest radiography features:
      a. Subacute – Cardiomegaly and lungs clear
      b. Acute – Cardiomegaly absent because of the quick nature of the tamponade

C. Treatment
   1. See the sections on obstructive shock in the text that follows for temporizing management considerations.
   2. The definitive treatment is removal of pericardial fluid by drainage. Three methods to remove fluid:
      a. Pericardiocentesis – Can be performed rapidly and is often the procedure of choice initially for acute management
      b. Pericardial window – May be necessary in patients who have recurrent episodes or as a palliative therapy in patients with metastatic cancer
      c. Pericardiectomy – May be necessary in patients who have recurrent episodes
   3. For hemodynamic instability, fluid removal should occur emergently.
   4. Patients who are stable or who have minimal symptoms can be treated conservatively with serial echocardiograms, hemodynamic monitoring, avoidance of volume depletion, and treatment of the underlying etiology for the tamponade (see the section on pericarditis for managing this disease state).
   5. In patients who are stable but who have recurrent tamponade, pericardial drainage may be required.
   6. Removal of medications associated with pericardial effusion (e.g., minoxidil, hydralazine, isoniazid, phenytoin, etc.)

## III. SHOCK SYNDROMES

A. Shock
   1. Shock is a state of cellular and tissue hypoxia caused by reduced $DO_2$ and/or increased oxygen consumption or use – "Acute circulatory failure"
   2. Shock is initially reversible, but it must be recognized and treated promptly.
   3. Recognition of shock requires interpretation of hemodynamics, clinical presentation, and biochemical markers.
   4. Four major classifications for shock: (1) hypovolemic, (2) obstructive, (3) distributive and vasodilatory, and (4) cardiogenic. However, these are not exclusive, and patients can have concurrent forms of the various shock types.
   5. Arterial hypotension is often the earliest signal of shock. Typically, an SBP of less than 90 mm Hg or a MAP of less than 65 mm Hg indicates shock. Of note, blood pressure limits are arbitrary and may not be patient-specific (e.g., a patient with HTN at baseline).
   6. Other signs of shock include poor mentation (compared with baseline); cold, clammy skin (because of decreased capillary refill); reduced urinary output; and impaired kidney function. Biochemical markers include hyperlactatemia (greater than 2 mmol/L) and reduced $SVO_2$ (less than 70%).

B. Hemodynamics and Metabolic Demand
   1. Table 7 outlines the various hemodynamic parameters, measured and/or calculated, used to assess for various shock states, and Table 8 outlines various hemodynamic monitoring devices.

**Table 7.** Hemodynamic Parameters

| Value | Equation (as applicable) | Normal Value |
|---|---|---|
| SBP | | 90–140 mm Hg |
| DBP | | 60–90 mm Hg |
| Mean arterial blood pressure (MAP) | [SBP + (2 × DBP)]/3 | 70–100 mm Hg |
| Pulse pressure (PP) | [SBP − DBP] | 40–60 mm Hg |
| Heart rate (HR) | | 60–100 beats/min |
| Cardiac output (CO) | HR x SV/1000 | 4–7 L/min |
| Cardiac index (CI) | CO/BSA | 2.5–4.2 L/min/$m^2$ |
| Stroke volume (SV) | CO/HR x 1000 | 60–130 mL/beat |
| Stroke volume index (SVI) | SV/BSA | 235-55 mL/$m^2$ |
| Pulmonary artery systolic pressure (PASP) | | 20–30 mm Hg |
| Pulmonary artery diastolic pressure (PADP) | | 8–12 mm Hg |
| Mean pulmonary artery pressure (mPAP) | [PASP + (2 × PADP)]/3 | 12–15 mm Hg |
| Pulmonary capillary wedge pressure (PCWP) or pulmonary arterial occlusion pressure (PAOP) | | 5–12 mm Hg |
| Central venous pressure (CVP) or right atrial pressure (RAP) | | 2–6 mm Hg |
| Pulmonary vascular resistance (PVR) (divide by 80 for Wood units) | 80 × [(mPAP − PCWP)/CO] | 20–120 dynes•s•$cm^{-5}$ (< 2 Wood units) |
| SVR | 80 × [(MAP − CVP)/CO] | 800–1200 dynes•s•$cm^{-5}$ |
| Oxygen delivery ($DO_2$) | 10 × CO (L/min) × $CaO_2$ | 520–570 mL/min/$m^2$ |
| Arterial oxygen content ($CaO_2$) | (1.34 × Hgb[a] × $SaO_2$) + (0.003 × $PaO_2$) | 20 mL/dL |
| Venous oxygen content ($CVO_2$) | (1.34 × Hgb[a] × $Svo_2$) × (0.003 × $PVO_2$) | 15 mL/dL |
| Resting oxygen consumption ($VO_2$) | 10 × CO (L/min) × ($CaO_2$ − $CvO_2$) | 110–160 mL/min/$m^2$ |
| Oxygen extraction ratio (O2ER) | $VO_2/DO_2$ × 100 | 20%–30% |

[a]Hgb units are in grams per deciliter.

DBP = diastolic blood pressure; $SaO_2$ = oxygen saturation.

2. The main physiological determinants of tissue perfusion and oxygenation by blood pressure are CO and SVR: Blood pressure = CO x SVR
   a. Oxygen is inspired and delivered to alveoli, where it reversibly binds to hemoglobin.
   b. By the heart's CO acting as a pump, hemoglobin with oxygen is transported to the tissues. The rate of delivery can be estimated as $DO_2$; see Table 7.
   c. Once at the tissues, the oxygen dissociates from hemoglobin and is taken up by mitochondria for metabolic processes.
3. CO is heart rate multiplied by SV. It also can be estimated using the Fick equation: $CO = VO_2/(CaO_2 - CvO_2)$.
4. The drivers of SV, the amount of blood ejected from the ventricle per beat, are predominantly preload, myocardial contractility, and afterload.
   a. Preload is the volume or pressure of blood returned to the LV from the venous circulation, denoted by LV end-diastolic volume and proportionally related to CV. The PCWP is the best obtainable estimate of preload.
   b. Myocardial contractility is an inherent property of the myocardium and allows the heart to increase the extent or force of contraction.
   c. Afterload is the wall stress across the ventricular myocardium during systole. It is the force the ventricle must overcome to eject its volume and is inversely related to SV.
5. SVR, also known as total peripheral resistance, is the resistance to flow that must be overcome by LV.
   a. SVR is the driver of afterload.
   b. Vasoconstriction increases SVR, and vasodilation decreases SVR.
   c. Skin temperature can provide a generalized approximation of SVR, where warmer skin indicates vasodilation and perfusion.
6. MAP is the average arterial pressure throughout the cardiac cycle and is the driving pressure for peripheral blood flow.
7. Given these factors, the early aims of shock treatment are to limit tissue hypoxia, interrupt the metabolic processes, and, ultimately, prevent end-organ damage.
8. In the early stages of shock, blood pressure is preserved through stimulation of the sympathetic system, release of endogenous vasopressin, and vasoconstriction through formation of angiotensin II. Blood flow is prioritized to vital organs like the brain and heart.
9. Without correction, endogenous response becomes inadequate, and blood pressure declines, progressing to a worsened state of shock.

**Table 8.** Hemodynamic Monitoring Devices

| Device or Category | Obtainable Parameters | Advantages | Limitations |
|---|---|---|---|
| Noninvasive BP monitoring[a] | SBP, DBP, MAP | • Noninvasive<br>• Bedside practitioner familiarity | • Limited accuracy in shock<br>• Does not provide continuous monitoring<br>• Less sensitive in predicting end-organ dysfunction |
| Arterial BP catheter | SBP, DBP, MAP | • More accurate BP measurement in shock than noninvasive methods<br>• Ready access for arterial blood gas sampling Continuous monitoring | • Invasive<br>• Inaccurate damping influences SBP and DBP measurements (MAP still accurate)<br>• Catheter-related infection<br>• Brachial site lacks collateral circulation (may result in decreased arterial perfusion) |
| Left atrial catheter | Measured left atrial pressures | • More accurate measurement of LV preload | • Risk of air embolus<br>• Requires arterial (i.e., left heart) catheterization; may be obtained in the workup of suspected cardiogenic shock |
| Central venous catheter (CVC) | CVP/RAP, $ScvO_2$ | • Easier and safer to insert than a PAC<br>• $ScvO_2$ may be available as a continuous measurement<br>• Access for administration of highly osmotic and caustic agents | • CVP/RAP not a true estimate of LV end-diastolic pressure<br>• CVP/RAP does not accurately predict fluid responsiveness<br>• $ScvO_2$ not equivalent to $SVO_2$ (see later in the chapter) |
| Pulmonary artery catheter (PAC; Swan-Ganz catheter) | PASP, PADP, PCWP, CO, CI, mixed venous $O_2$ saturation ($mVO_2$) CPO, PAPI | • Placement at bedside; one-time measurement versus continuous monitoring to guide therapy<br>• Potentially can provide a complete hemodynamic picture to distinguish shock syndromes<br>• PCWP more accessible than left heart catheterization to determine preload<br>• Ability to determine cardiac output both via thermodilution and oxygen consumption (Fick CO) | • Invasive<br>• Risk of pulmonary artery rupture<br>• Risk of central line infection<br>• Thermodilution CO may be inaccurate with tricuspid regurgitation |
| Echocardiography | Cardiac chamber size and function, pericardial appearance (and presence of fluid), inferior vena cava (IVC) collapsibility, ejection fraction, RVSP (an estimate of PASP), LVOT VTI (to calculate CO/CI) | • Noninvasive (transthoracic)<br>• Visualization of ventricular function instead of presumed function according to CO<br>• IVC collapsibility can predict fluid responsiveness | • Subjectivity of user assessment<br>• Not done continuously; therefore, cannot detect acute changes or must be repeated when the patient's status changes |

**Table 8.** Hemodynamic Monitoring Devices *(Cont'd)*

| Device or Category | Obtainable Parameters | Advantages | Limitations |
|---|---|---|---|
| Esophageal Doppler (ODM II, CardioQ, HemoSonic 100) | CO and CI | • Ease of use<br>• Bedside practitioner familiarity | • Assumptions used by the device may not be valid in the setting of hemodynamic instability (fixed partition of blood flow to cephalic vessels and descending aorta, constant aortic cross-sectional area)<br>• Accuracy depends on position (need for frequent repositioning) |
| Bioimpedance/ bioreactance (NICOM, BioZ, ECOM) | Continuous CO and CI, SV, SVR<br>SVV (NICOM) | • Noninvasive<br>• NICOM CO correlates well with CO values from thermodilution and pulse pressure waveform analysis | • Conflicting validation results with BioZ and ECOM, particularly in patients with septic shock<br>• ECOM requires ET intubation |

[a]Includes manual sphygmomanometry and automated oscillometric (cuff) techniques.

BP = blood pressure; CI = cardiac index; CPO = cardiac power output; LV = left ventricular; LVOT VTI = left ventricular outflow tract velocity time integral; PAC = pulmonary artery catheter; PADP = pulmonary artery diastolic pressure; PAPI = pulmonary artery pulsatility index; PASP = pulmonary artery systolic pressure; PCWP = pulmonary capillary wedge pressure; RAP = right atrial pressure; RVSP = right ventricular systolic pressure; SVV = stroke volume variation.

Information from: Alhashemi JA, Cecconi M, Hofer CK. Cardiac output monitoring: an integrative perspective. Crit Care 2011;15:214.

C. Markers of Perfusion
   1. Global perfusion
      a. End-organ perfusion (altered mental status, low urinary output, mottled skin)
      b. Elevated blood lactate concentration (above 2 mmol/L)
         i. Lactate is the end product for anaerobic metabolism.
         ii. Because lactate is cleared by the liver, a liver impaired by shock may decrease clearance.
      c. Central venous oxygen saturation ($ScvO_2$) and $SVO_2$
         i. Both are the oxyhemoglobin saturation, expressed in percentage of venous blood obtained from the central vein and pulmonary artery.
         ii. $ScvO_2$ is obtained from the subclavian or internal jugular central venous catheter.
         iii. $SVO_2$ from a pulmonary artery catheter better represents systemic oxygen extraction because it represents the mixing of venous blood from the superior vena cava, inferior vena cava, and coronary sinus.
         iv. Although the two measures are not equivalent in value, they have good correlation.
         v. An $SVO_2$ value above 70% is considered adequate, whereas values less than 40% are considered critically low. Values above 80% indicate poor tissue oxygen extraction capacity or hyperdynamic cardiac states.

D. Diagnosis of Shock on the Basis of Hemodynamic Parameters: Table 9 provides an overview of the various shock states and associated hemodynamic profiles.

**Table 9.** Hemodynamic Profiles of Shock States

| Shock State | CVP | PCWP | CO | SVR |
|---|---|---|---|---|
| Hypovolemic | ↓[a] | ↓[a] | ↓ | ↑ |
| Cardiogenic | ↑ | ↑ | ↓[a] | ↑ |
| Obstructive | | | | |
| Impaired diastolic filling (e.g., cardiac tamponade) | ↑ | ↑ | ↓[a] | ↑ |
| Impaired systolic contraction (e.g., massive PE) | ↑ | ↓ or ↔ | ↓[a] | ↑ |
| Vasodilatory/distributive | | | | |
| Pre-resuscitation | ↓ | ↓ | ↓ | ↓[a] |
| Post-resuscitation | ↑ | ↑ | ↑ | ↓[a] |

[a]Pathophysiological hallmark of shock state.

PE = pulmonary embolism.

Information from: Vincent JL, De Backer D. Circulatory shock. N Engl J Med 2013;369:1726-34; Dellinger RP. Cardiovascular management of septic shock. Crit Care Med 2003;31:946-55; and Weil MH, Shubin H. Proposed reclassification of shock states with special reference to distributive defects. Adv Exp Med Biol 1971;23:13-23.

E. Resuscitation/Treatment of Shock in General
   1. The approach to treating a patient with circulatory shock can be divided into four phases, each having different (and sometimes overlapping) treatment goals and therapeutic strategies.
      a. The first phase focuses on salvage, in which a minimum perfusion pressure and CO must be achieved to maintain the patient's survival. Optimization of volume replacement and vasopressor therapy is the primary focus of therapy in this stage. (Treatment of the underlying cause of the patient's shock should be evaluated [e.g., antimicrobials for sepsis, revascularization for myocardial infarction].)
      b. Optimization to ensure adequate $DO_2$ is the second phase. Important targets: (1) MAP greater than 65 mm Hg or SBP greater than 90 mm Hg, (2) adequate end-organ perfusion, (3) adequate $DO_2$, (4) lactate clearance
      c. The third phase is patient stabilization with efforts to further limit end-organ damage.
      d. The fourth phase is de-escalation, where the insult is clear and the patient can be removed from vasoactive drips, need for fluids, or other life-support measures.
   2. The following agents are used to treat shock:
      a. IVFs
         i. IVFs are first line in the treatment of patients with undifferentiated hypotension and shock.
         ii. IVFs are given to increase preload and subsequently increase SV, CO, and $DO_2$.
         iii. IVFs should be administered in bolus doses of 500–1000 mL and repeated until blood pressure and tissue perfusion are acceptable, until pulmonary edema occurs, or until there is no clear response.
            (a) Fluid responsiveness is defined as at least a 10%–15% increase in CO after administration.
            (b) Dynamic markers, better for measuring the success of fluid responsiveness, include stroke volume variation, systolic pressure variation, pulse pressure variation, and inferior vena cava variation. For example, in a systemic review, thresholds to predict fluid responsiveness were pulse pressure variation greater than 12.5% and stroke volume variation greater than 11.6%.
            (c) Static markers include CVP and PCWP.
            (d) Discussion of the pros and cons of each type of marker is beyond the scope of this chapter.

iv. In general, crystalloids such as lactated Ringer or 0.9% sodium chloride are the agents of choice because of data and cost.
   (a) The Saline versus Albumin Fluid Evaluation (SAFE) study enrolled almost 7000 patients with varied types of shock requiring fluid resuscitation, with 90% power; found no difference in 28-day mortality between treatment with 0.9% sodium chloride and treatment with 4% albumin (20.9% vs. 21.1%, p=0.87). However, this was not a study of strictly fluid resuscitation because all of the allocated study fluid was for fluid resuscitation in the intensive care unit (ICU) until death, discharge, or 28 days after randomization.
   (b) A pragmatic open-label randomized study of crystalloids compared with colloids for resuscitation showed no difference between groups in 28-day mortality (27.0% vs. 25.4%, p=0.26) but did find a difference in 90-day mortality, with worse outcomes in the colloid group (34.2% vs. 30.2%, p=0.03).

v. The type of crystalloid fluid used for resuscitation, whether chloride rich (i.e., 0.9% sodium chloride) or chloride poor (i.e., lactated Ringer solution), is an area of increasing interest. Administration of chloride-rich fluids may lead to afferent renal arteriole vasoconstriction (leading to a decrease in renal perfusion and kidney injury) and may cause a metabolic acidosis by lowering the strong ion difference. As such, crystalloids that better approximate the electrolyte composition of plasma ("chloride-poor," "balanced salt," or "balanced crystalloid" solutions) have been evaluated (Table 10).

**Table 10.** Sodium and Chloride Content of Commonly Used Resuscitation Fluids

| Fluid | Sodium (mmol/L) | Chloride (mmol/L) |
|---|---|---|
| "Chloride rich"[a] | | |
| 0.9% sodium chloride | 154 | 154 |
| 5% albumin | 130–160[b] | 0–128[b] |
| Hydroxyethyl starch 6% (130/0.4) | 154 | 154 |
| Hydroxyethyl starch 6% (670/0.75) | 143 | 124 |
| "Chloride poor"[a] | | |
| 25% albumin | 130–160[b] | 0–19[b] |
| Lactated Ringer solution | 131 | 111 |
| Plasma-Lyte 148 | 140 | 98 |
| Normosol-R | 140 | 98 |

[a]The distinction between "chloride rich" and "chloride poor" is based on chloride content above or below 120 mmol/L.

[b]Differs according to manufacturer because of differences in buffer type (e.g., sodium bicarbonate or sodium chloride) and amount used. Reported chloride content of 4% Albumex (CSL Bioplasma) is 128 mmol/L, and that of 20% Albumex (CSL Bioplasma) is 19 mmol/L (products used in Australia/New Zealand), which led to the distinction of "chloride rich" and "chloride poor" for 4%–5% albumin and 20%–25% albumin, respectively. However, neither 5% Flexbumin (Baxter, Westlake Village, CA) nor 25% Flexbumin (Baxter; products available in the United States) contains chloride.

Information from: Guidet B, Soni N, Della Roca G, et al. A balanced view of balanced solutions. Crit Care 2010;14:325; Frazee EN, Leedahl DD, Kashani KB. Key controversies in colloid and crystalloid fluid utilization. Hosp Pharm 2015;50:446-53; and Yunos NM, Bellomo R, Hegarty C, et al. Association between a chloride-liberal vs chloride-restrictive intravenous fluid administration strategy and kidney injury in critically ill adults. JAMA 2012;308:1566-72.

vi. Hydroxyethyl starch solution should be avoided for fluid resuscitation in the ICU.
   (a) A study of 7000 critically ill patients requiring fluid resuscitation compared a low-molecular-weight, low-molar-substitution (130/0.4) hydroxyethyl starch solution with 0.9% sodium chloride. There was no difference in 90-day mortality between the hydroxyethyl starch and 0.9% sodium chloride groups (18.0% vs. 17.0%, p=0.26), but patients allocated to hydroxyethyl starch had a greater need for renal replacement therapy (7.0% vs. 5.8%, p=0.04) and a higher incidence of adverse events (5.3% vs. 2.8%, p<0.001).

(b) A systematic review and meta-analysis that analyzed only unbiased trials found an association between hydroxyethyl starch use and increased patient mortality (RR 1.09; 95% confidence interval [CI], 1.02–1.17; p=0.02) and need for renal replacement therapy (RR 1.32; 95% CI, 1.15–1.50; p<0.001).

b. Vasoactive agents
   i. Vasoactive agents can be broadly differentiated into three groups: (1) vasopressors, (2) inotropes, and (3) vasodilators.
   ii. Vasopressors are indicated if hypotension is refractory to fluid administration or in the setting of severe hypotension while fluids are administered.
   iii. Vasopressors are primarily pharmacologically beneficial by augmenting SVR, and some increase CO. Table 5 highlights various pharmacologic aspects of these agents.
      (a) Once the decision to initiate a vasoactive agent is made, the agent is chosen according to which best achieves the desired pharmacodynamics effects(s). In most shock syndromes, limited literature exists to guide optimal vasoactive agent selection.
      (b) Ideally, vasoactive agents should be given by central line to minimize the risk of extravasation and tissue necrosis.
   iv. Vasopressor clinical data
      (a) A multicenter randomized trial included patients requiring vasopressors for shock of any type and excluded those requiring vasopressors for more than 4 hours before enrollment. Enrolled patients were allocated to either blinded norepinephrine or dopamine. There was no difference in 28-day mortality between patients receiving dopamine and those receiving norepinephrine (52.5% vs. 48.5%, p=0.10), but patients receiving dopamine more commonly developed an arrhythmia (24.1% vs. 12.4%, p<0.001), required open-label norepinephrine (26% vs. 20%, p<0.001), and required more days with vasopressor support.
         (1) A predefined subgroup analysis evaluated the influence of shock type on the outcome. Patients with cardiogenic shock allocated to dopamine had a higher mortality rate than those allocated to norepinephrine (log-rank p=0.03). However, the overall effect of treatment did not differ among the shock subgroups (interaction p=0.87), suggesting that the reported differences in mortality according to subgroup are false.
         (2) These data suggest that although norepinephrine does not improve mortality compared with dopamine, it is safer and more effective in increasing a patient's blood pressure. Given these data, a case could be made for norepinephrine as the first-line vasoactive agent in all shock types.
      (b) A multicenter randomized trial comparing norepinephrine with epinephrine for patients with undifferentiated shock found no difference between agents in the time to achieving a goal MAP (median 40 hours vs. 35.1 hours, p=0.26) or median number of vasopressor-free days at day 28 (25.4 days vs. 26.0 days, p=0.31). Patients allocated to epinephrine had higher heart rates and lactic acid concentrations on the first study day (but not on subsequent days) and were more often withdrawn from the study by the treating clinician (12.9% vs. 2.8%, p=0.002). These data suggest that epinephrine has no efficacy benefit over norepinephrine and is associated with an increased incidence of adverse effects.
      (c) A multicenter randomized trial of synthetic angiotensin II versus placebo was conducted in patients with vasodilatory shock refractory to at least one vasopressor agent and fluid resuscitation. The primary end point (increase in MAP by at least 10 mm Hg or >75) was significantly greater in patients randomized to angiotensin II versus placebo (69.9% vs. 23.4%; OR 7.95; 95% CI, 4.76-13.3). All-cause mortality at 28-days was numerically lower in patients randomized to angiotensin II but was not statistically significant (46% vs. 54%, p=0.12).
   v. Inotropes, listed in Table 5, exert a pharmacodynamic effect that increases CO after adequate fluid administration.

F. Cardiogenic Shock
   1. Characterized by three hallmarks:
      a. Sustained hypotension unresponsive to fluids alone
      b. Evidence of myocardial dysfunction with reduced cardiac index (less than 2.2 L/minute/$m^2$)
      c. Signs and symptoms of hypoperfusion in the setting of elevated cardiac filling pressures (e.g., PCWP greater than 18 mm Hg)
   2. Patients will have signs and symptoms of heart failure (see Acute Heart Failure chapter).
   3. Usually caused by LV failure secondary to myocardial infarction, but can occur because of acute valvular disease, myocarditis, HTN, congenital birth defects, RV failure (e.g., pulmonary embolism)
   4. Resuscitation/treatment
      a. Treatment largely depends on managing the underlying chronic or acute cardiovascular disease states.
      b. Means of managing these disease states are included in various other chapters (see Acute Coronary Syndrome, Heart Failure, Valvular Heart Disease, Arrhythmias, etc.).
      c. Hemodynamic management of cardiogenic shock is shown in Figure 3, and more detail can be found in the chapter on heart failure.
      d. Temporary mechanical circulatory support is increasingly utilized in clinical practice to stabilize and support patients.
      e. Cardiac power index (CPO) and pulmonary artery pulsatility index (PAPI) are increasingly used to isolate cardiac failure from other shock pathophysiologies and, more specifically, left ventricular, right ventricular, or biventricular failure. This approach may aid in the decision to use temporary mechanical support and to determine the type of support offered.

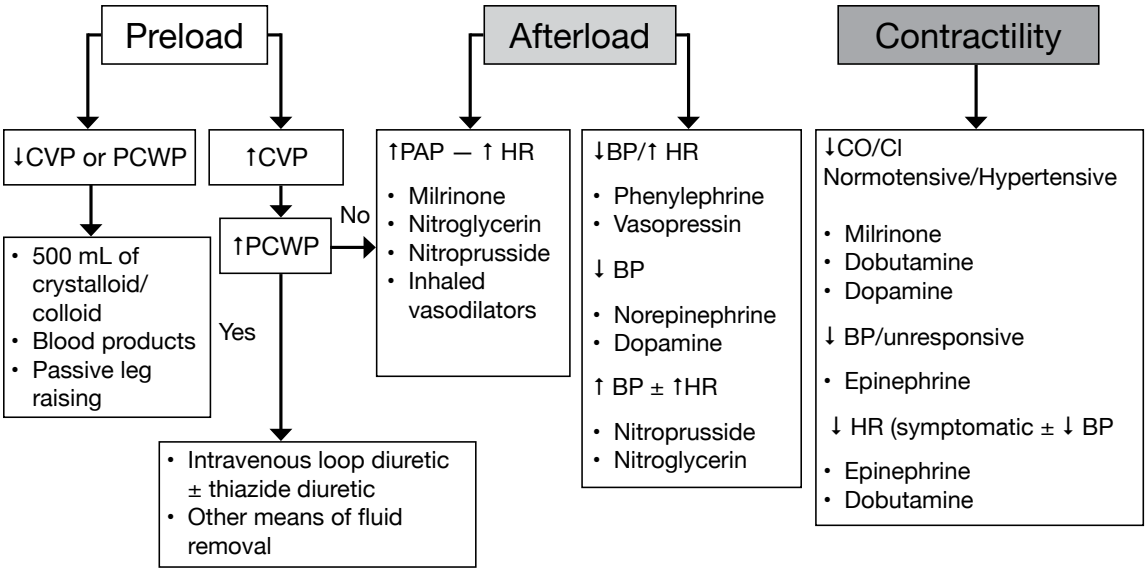



**Figure 3.** Shock management and treatment considerations based on hemodynamic parameters.

BP = blood pressure; CI = cardiac index; CO = cardiac output; CVP = central venous pressure; HR = heart rate; PAP = pulmonary artery pressure; PCWP = pulmonary capillary wedge pressure.

Adapted from: Blais DM. Managing Cardiovascular Surgery Intensive Care Unit Patients. In: Pharmacotherapy Self-Assessment Program, 2010. Critical and Urgent Care. Lenexa, KS: American College of Clinical Pharmacy, 2010 37-51.

G. Hypovolemic Shock
   1. Trauma is one of the most common causes of hypovolemic shock.
   2. Hemorrhagic shock occurs when intravascular volume loss impairs $DO_2$.
   3. The estimated blood volume for a patient weighing 70 kg is 5 L.
   4. A reduction in intravascular volume leads to reduced tissue perfusion.
   5. Can be categorized as:
      a. Whole blood loss: Whole blood loss from an open wound or into a body compartment
      b. Plasma loss: Loss of extracellular fluid (e.g., burns, pancreatitis, peritonitis, vomiting, and diarrhea)
   6. Clinical features of hypovolemic shock: Hypotension, tachycardia, diaphoresis, altered mental status, and decreased urinary output
   7. Because of the response of the sympathetic nervous system and reduced parasympathetic system activity, these patients often present with tachycardia at onset, though heart rate can be suppressed through the use of AV nodal blocking agents (e.g., beta blockers).
   8. Intrinsic response compensates for acute blood loss within hours.
      a. Reduced capillary pressures lead to fluid redistribution from the interstitium to the vascular compartments as albumin shifts into the plasma from the interstitium.
      b. The transcapillary refill can recruit up to 1 L into intravascular compartments.
   9. Humoral response is delayed, developing over hours to several days. After decreased renal perfusion, secretion of antidiuretic hormone, aldosterone, and renin increase sodium and volume retention to restore the interstitial deficit from transcapillary refill.
   10. These patients may also have acute traumatic coagulopathy.
   11. Resuscitation and treatment
      a. Rapid identification and correction of the source of bleeding
      b. Recommended general goal of therapy is to ensure patient has permissive hypotension, defined as SBP 80–90 mm Hg and urinary output greater than 30 mL/hour.
      c. Fluids, like in most shock states, are the primary starting therapy.
         i. Indicated when diminished mental status or absent radial pulse (SBP less than 90 mm Hg)
         ii. Benefits: Fluids restore intravascular volume, reverse tissue hypoperfusion, and correct oxygen debt.
         iii. Risk: Fluids do not increase oxygen-carrying capacity; they can precipitate dilutional coagulopathy and lead to tissue edema.
         iv. Crystalloids are the preferred choice in therapy. Lactated Ringer solution may produce less hyperchloremia, but the impact on mortality or morbidity is unknown.
         v. Colloids were associated with increased mortality in a subgroup analysis of the SAFE trial, and synthetic colloids may contribute to coagulopathy.
      d. Packed red blood cells and blood products
         i. Indicated when estimated blood loss is greater than 30% of total blood volume
         ii. The amount of blood products to transfuse is based on clinical examination, given that initial Hgb or hematocrit (Hct) readings may not reflect blood loss because of compensatory mechanisms.
         iii. Although there are no randomized controlled trials in trauma, European guidelines recommend maintaining an Hgb of 7–9 g/dL after initial resuscitation.
         iv. For acute upper gastrointestinal bleeding, a restrictive transfusion threshold (Hgb less than 7 g/dL) compared with a liberal transfusion threshold (Hgb less than 9 g/dL) was associated with a higher 6-week survival rate (95% vs. 91%, hazard ratio 0.55 [95% CI, 0.33–0.92; p=0.02]) and lower rates of further bleeding (10% vs. 16%, p=0.01) and adverse effects (40% vs. 48%, p=0.02).

v. Some evidence exists for higher transfusion requirements in patients with coronary artery disease. The REALITY trial was a randomized study of transfusion thresholds (hemoglobin <10 g/dL vs. <8 g/dL) in patients with anemia and acute myocardial infarction. Although the primary endpoint (major adverse cardiovascular events [MACE]) was noninferior between groups, numeric but not statistically significant increases in clinically important secondary endpoints such as death, recurrent MI, and emergent revascularization were noted in the transfusion <8 g/dL group.

vi. A randomized controlled trial of cardiac surgery patients compared a restrictive transfusion threshold (less than 7.5 g/dL) with a liberal transfusion threshold (less than 9 g/dL). Groups did not differ with respect to the composite primary end point of serious infection or ischemic event at 3 months (35.1% vs. 33.0%; odds ratio 1.11; 95% CI, 0.91–1.34; p=0.30). However, there were more deaths in the restrictive group (4.2% vs. 2.6%; HR 1.64; 95% CI, 1.00–2.67; p=0.045). However, the exploration of an outcome at 3 months and the fact this is a secondary end point make interpreting this result challenging.

e. Vasopressors

i. Attractive adjunct to hemorrhagic shock to minimize the amount of fluid required to reverse tissue hypoperfusion. Can increase cardiac afterload and are independently associated with increased mortality in trauma

ii. May be used as a temporizing measure in the setting of profound hypoperfusion despite ongoing volume resuscitation

iii. In life-threatening hypotension, vasopressors may be recommended only after hypovolemia has been corrected or when cardiac arrest is imminent.

H. Obstructive Shock

1. Obstructive shock occurs as a result of extracardiac obstruction to flow in the cardiovascular system. The sources of extracardiac obstruction may be either impaired diastolic filling (e.g., cardiac tamponade, tension pneumothorax, or constrictive pericarditis) or impaired systolic contraction (e.g., massive pulmonary embolism, acute or chronic pulmonary hypertension or AD). Rarely, obstructive shock may also be a result of left ventricular outflow tract (LVOT) obstruction in patients with hypertrophic cardiomyopathy.
2. Obstructive shock is relatively rare, with only about 2% of patients with shock requiring vasoactive medications in this category.
3. The hallmark of this form of shock is reduced CO.
   a. For impaired diastolic filling, RV preload is significantly decreased because of impaired venous return (see the earlier section on cardiac tamponade).
   b. For impaired systolic function, ventricular afterload is acutely increased, leading to ventricular failure. This typically occurs in the setting of acute RV afterload increase (measured by pulmonary vascular resistance) caused by massive pulmonary embolism or acute pulmonary hypertension. An acute increase in LV afterload does not typically lead to shock. An acute rise in RV afterload leads to reduced RV CO and a subsequent decrease in LV CO→systemic hypotension→reduced RV tissues perfusion (decreased right coronary artery perfusion)→RV free wall ischemia→reduced RV free wall contractility and further impairment of RV CO (a viscous cycle). In addition, acute RV pressure overload leads to a shift of intraventricular septum to the LV→impaired LV diastolic filling (because of intraventricular dependence)→further decrease in LV CO.
4. Resuscitation and treatment
   a. Fluid administration and vasoactive medications may be used as a temporizing measure to increase tissue perfusion. IVFs are usually recommended but may not improve CO.
      i. Cardiac tamponade: Patients with preexisting hypovolemia may respond to fluids, but in general, hemodynamics may not improve with fluids alone. Despite this, fluid administration is usually recommended in tamponade.

ii. Massive pulmonary embolism: Initial fluid administration improves CO, but care should be taken because excessive fluid administration can lead to further RV dilation and impaired LV CO from worsened septal shifting and decreased LV filling (because of intraventricular dependence).
iii. Optimizing fluids in patients with acute or chronic pulmonary hypertension is challenging. Some patients (those with signs of intravascular volume depletion) may require fluids, whereas others may require diuretics to reduce RV dilation and improve LV filling (even in vasoactive medication administration).

b. Vasopressors should be initiated to increase MAP and maintain an adequate perfusion pressure. This is critical in massive pulmonary embolism because adequate right coronary artery perfusion is important to prevent/reduce RV free wall ischemia. Of note, caution must be used because catecholamine vasopressors may increase pulmonary vascular resistance.
i. Inotropes may increase RV CO in the setting of massive pulmonary embolism or acute or chronic pulmonary hypertension but are likely ineffective in tamponade. Inotropes are also not helpful and are likely harmful in hypertrophic cardiomyopathy because of the potential to increase outflow tract obstruction.
ii. Inhaled nitric oxide or aerosolized prostacyclin therapy may be effective in decreasing RV afterload in the setting of acute or chronic pulmonary hypertension but is not helpful for pulmonary embolism or tamponade. Milrinone may be uniquely indicated in pulmonary hypertension because of the potential to increase RV inotropy and pulmonary vasodilation.
iii. Definitive treatment of the extracardiac obstruction is key.
(a) Impaired diastolic filling states:
a. Cardiac tamponade: See the earlier section on this topic.
b. Tension pneumothorax: Needle decompression or potential chest tube thoracostomy
(b) Impaired systolic function during massive pulmonary embolism: See the chapter on managing pulmonary embolism.

I. Vasodilatory and Distributive Shock
1. Vasodilatory shock: Shock caused by a decrease in SVR leading to hypoperfusion. Distributive shock – Subset of vasodilatory shock that describes misdistribution of blood flow at the level of the microcirculation (shunting) or at the organ level
2. The three most common causes of vasodilatory shock are septic shock (the most common vasodilatory shock encompassing 94% of cases), immune-mediated (anaphylactic) shock, and neurogenic shock.
3. Vasodilatory shock is the most common type of shock, with 66% of patients requiring vasoactive therapy.
4. Pathophysiology
a. Vasodilatory shock occurs secondary to failure of the vascular smooth muscles cells to constrict, whether from failure of vasoconstriction methods or inappropriate activation of vasodilatory mechanisms. In most cases (except for neurogenic shock), this failure occurs despite high plasma concentrations of endogenous vasoconstrictors.
b. Potential mechanisms
i. Activation of cellular adenosine triphosphate–dependent potassium channels leading to hyperpolarization of the vascular smooth muscle cells (through potassium efflux), which prevents extracellular calcium influx by voltage-gated calcium channels. As a result, cellular depolarization is prevented, the high cytosolic calcium concentrations needed for vasoconstriction are not achieved, and vasodilation occurs.
ii. Increased expression of inducible nitric oxide synthase leads to increased intracellular nitric oxide concentration and vasodilation.

iii. Inappropriately low plasma vasopressin concentrations despite the degree of shock
iv. Pathogenesis depends on cause of shock – Different shocks release different cytokines and substances that lead to the effects described earlier, the intricate details of which are beyond the scope of this chapter.

5. Resuscitation and treatment
   a. The underlying causes of the shock states must be addressed quickly when resuscitation is initiated.
      i. Septic shock requires rapid (within 1 hour of recognition) administration of antimicrobials with activity against all likely pathogens.
      ii. In anaphylactic shock, the offending agents should be removed.
   b. Epinephrine is emergently indicated in anaphylaxis beginning with intramuscular injection (0.3-0.5 mg repeating at 5-15 minute intervals). Epinephrine is first-line therapy for anaphylactic shock because of its ability to not only increase vascular and cardiac tone but also reversal of beta-2 mediated bronchospasm.
   c. Treatment goal and end points are similar to those in other variations of shock. One of the only exceptions is with acute spinal cord injury; a higher MAP goal of at least of 85 mm Hg has been associated with improved outcomes in uncontrolled studies.
   d. As in other shock cases, IVFs with crystalloids are typically the initial resuscitation measure of choice or as adjunctive therapy to epinephrine for anaphylactic shock. These should be given until the patient is no longer fluid responsive (no further change in MAP).
   e. Vasopressors should be initiated for hypotension not responsive to fluid resuscitation.
      i. According to the SOAP II and VASST trials, norepinephrine is usually considered the first-line vasopressor in septic shock because of its ability to increase SVR without decreasing CO.
      ii. Epinephrine infusions are indicated in anaphylactic shock not responsive to repeated intramuscular injections and IVFs.
      iii. For neurogenic shock, agents with vasoconstrictive and inotropic properties are preferred.
      iv. For refractory vasodilatory shock on multiple high-dose vasopressors, consider the addition of intravenous angiotensin II.
   f. Adjunctive therapy for anaphylactic shock include concomitant histamine-1 and histamine-2 receptor antagonists and corticosteroids.
   g. Routine use of corticosteroids for septic shock is no longer indicated but may be considered for patients with concomitant adrenal insufficiency.
   h. Patients with vasodilatory shock secondary to adrenal insufficiency should receive intravenous corticosteroids.

**Patient Case**

4. A 35-year-old man who presents after right and left coronary angiogram is admitted to your unit because of suspected anaphylaxis to contrast. He was given intramuscular epinephrine in the catheterization laboratory before transfer. On arrival at the unit, his blood pressure is 78/42 mm Hg; he was given 1 L of 0.9% sodium chloride, diphenhydramine, famotidine, and methylprednisolone. The patient remained hypotensive and was given an additional 1 L of 0.9% sodium chloride with some response. His MAP is 62 mm Hg. A central venous catheter shows CVP 3 mm Hg, venous oxygen saturation 61%, and lactate concentration 4.2 mmol/L. Post-catheterization Hgb was 10.5 g/dL (pre-catheterization 12.6 mg/dL). Together with fluid resuscitation, which agent would be best to initiate in this patient?

   A. Packed red blood cells.
   B. Vasopressin infusion 0.04 units/minute.
   C. Fresh frozen plasma.
   D. Norepinephrine 0.03 mcg/kg/minute.

## IV. HYPERTENSIVE CRISIS

A. Background
   1. Hypertensive urgency: Accelerated, malignant, or perioperative HTN, defined as an SBP of 180 mm Hg or greater and/or a diastolic blood pressure (DBP) of 120 mm Hg or greater, in the absence of symptoms or new or progressive target-organ damage. In general, blood pressure reduction can occur over several days.
   2. Hypertensive emergency: Severe elevations in blood pressure, typically defined as an SBP of 180 mm Hg or greater and/or a DBP of 120 mm Hg or greater, with the presence of acute or ongoing target-organ damage such as acute kidney injury, heart failure, mental status changes, hypertensive encephalopahty, intracerebral hemorrhage (ICH), acute ischemic stroke, acute MI, acute LV failure with pulmonary edema, or unstable angina. Table 11 provides a list of example conditions that, when accompanied by high blood pressure, define hypertensive emergency.
   3. Common causes of these conditions include substance abuse (e.g., cocaine/stimulant abuse), nonadherence, withdrawal, drug-drug/food interactions, pheochromocytoma, and pregnancy.

**Table 11.** Examples of Acute Target-Organ Damage

| | |
|---|---|
| Eclampsia, preeclampsia | Hypertensive encephalopathy |
| Acute kidney injury | Acute shortness of breath, flash PE, or acute LV dysfunction |
| Acute AD (type A or B) | Acute intracranial bleeding (nontraumatic) |
| Seizures | Acute myocardial ischemia/infarction |
| Retinopathy | Cerebral infarction |

AD = aortic dissection. LV = left ventricular; PE = pulmonary edema

B. Management: Goals of Care
   1. Hypertensive urgency: Lower blood pressure slowly during the first 24–48 hours using oral medications (typically, resumption of home medications).
   2. Hypertensive crisis without compelling indications: Lower SBP by no more than 25% in the first 60 minutes. Given the tenuous nature of hypertensive crisis and the need for intravenous medications and monitoring, an ICU admission is typically required.
      a. During the next 2–6 hours: Aim for an SBP of 160 mm Hg and/or a DBP of 100 mm Hg.
      b. Over the next 24–48 hours, cautiously reduce blood pressure to normal.
   3. Compelling conditions exist regarding these goals for acute AD, severe preeclampsia or eclampsia, ischemic stroke, or pheochromocytoma crisis. Please see the sections on acute aortic syndrome (AAS) and ischemic stroke in the text that follows for these recommendations. Hemorrhagic stroke also has exceptions, depending on individual factors and whether intracranial pressure is known. See the chapter on managing bleeding reversal.
   4. For patients with severe pre-eclampsia or eclampsia or pheocromocytomia shoud have SBP reduced to less than 140 mm Hg during the first hour. In patients with AD, target an SBP of less than 120 mm Hg in the first hour; this is addressed in greater detail later in the chapter.

C. Treatment Options

1. Choice of agent varies depending on patient scenario; there is no one drug of choice (Tables 12 and 13).

**Table 12.** Commonly Used Intravenous Drugs for Hypertensive Emergencies

| Drug (onset, duration) | Intravenous Dose | Adverse Effects |
|---|---|---|
| **Vasodilators** | | |
| Sodium nitroprusside (immediate, 2–3 min) | **Initial:** 0.3–0.5 mcg/kg/min, titrate in increments of 0.5 mcg/kg/min, max dose: 10 mcg/kg/min | Cyanide or thiocyanate toxicity, nausea, vomiting, methemoglobinemia<br>Contraindications (CIs): Renal, hepatic failure (use lowest possible rate and monitor thiocyanate concentrations)<br>**Caution:** May elevate ICP |
| Nitroglycerin (2–5 min, 5–10 min) | **Initial:** 5–10 mcg/min, titrated by 5 mcg/min q2-5 min, max dose: 200 mcg/min | Headache, nausea, vomiting, tachyphylaxis, methemoglobinemia<br>**Caution:** May elevate ICP (Note: Higher doses may be required [> 100 mcg/min] to achieve greater arterial vasodilation) |
| Hydralazine (10 min, 1–4 hr) | **Initial:** 10–20 mg q4–6 hr (max dose not to exceed 40 mg/dose) | Reflex tachycardia, headache, flushing<br>**Caution:** Use with caution in angina or MI, elevated ICP, AD |
| Enalaprilat (within 30 min, 12–24 hr) | **Initial:** 1.25 mg administered over 5 min, may increase dose q6 hr up to a maximum of 5 mg q6 hr | Acute kidney injury, hyperkalemia<br>**CIs:** Avoid use in pregnancy, renal artery stenosis, angioedema<br>(**Note:** Long half-life) |
| Fenoldopam (< 5 min, 30 min) | **Initial:** 0.1–0.3 mcg/kg/min, may titrate in increments of 0.05–0.1 mcg/kg/min q15 min, max dose: 1.6 mcg/kg/min | Headache, flushing, tachycardia, cerebral ischemia<br>**Caution:** Use with caution in patients with glaucoma |
| Nicardipine (1–5 min, 15–30 min; up to 4 hr if prolonged infusion) | **Initial:** 5 mg/hr, may increase q5 min by 2.5 mg/hr up to a maximum of 15 mg/hr | Reflex tachycardia, nausea, vomiting, headache, flushing<br>**Caution:** Use with caution in patients with angina or MI, acute HF |
| Clevidipine (2–4 min, 5–15 min) | **Initial:** 1–2 mg/hr, may double the dose q90 seconds until target BP achieved, max dose: 32 mg/hr | Patients with renal failure and hepatic failure and older adults not specifically studied<br>**CIs:** Soy or egg product allergy, severe aortic stenosis, defective lipid metabolism (e.g., pathologic hyperlipidemia, lipoid nephrosis, or acute pancreatitis if accompanied by hyperlipidemia)<br>**Caution:** Use with caution in HF, concomitant β-blocker use, reflex tachycardia, rebound HTN |
| Phentolamine (not routinely used; see Table 13) | **IV bolus: Initial:** 5 mg, repeated as needed every 10 min; max dose 15 mg | Bradycardia, mouth pain, headache, post-injection site pain<br>**Caution:** Use with caution in patients with a history of cardiovascular disease |
| **Adrenergic Inhibitors** | | |
| Esmolol (1–2 min, 10–30 min) | **Initial:** 500–1000 mcg/kg bolus over 1 min then 50 mcg/kg/min infusion, max dose: 300 mcg/kg/min | Bronchospasm, HF exacerbation, bradycardia or AV block<br>**Caution:** Use with caution in acute HF, asthma, heart block |
| Labetalol (Normodyne, Trandate) (5–10 min, 3–6 hr) | **Initial:** 10–20 mg IV push over 2 min, may increase dose at 10-min intervals to a maximum single dose of 80 mg, max dose: 300 mg/24 hr<br>Continuous infusion: Initial rate of 0.4-1 mg/kg/hr titrated to a maximum of 3 mg/kg/hr | Same as esmolol |

MI = myocardial infarction.

**Table 13.** Indications and Special Considerations for Medications Used for Hypertensive Emergencies

| Medication | Indications | Special Considerations |
|---|---|---|
| Nitroprusside | Most indications (exclusions: ICP elevation, coronary infarction/ischemia) | Liver failure – cyanide accumulation<br>Renal failure – thiocyanate accumulation<br>Can obtain serum cyanide and thiocyanate concentrations to monitor<br>Toxicity associated with prolonged infusions (> 72 hr) or high doses (> 3 mcg/kg/min)<br>May result in coronary steal<br>Increases ICP |
| Hydralazine | Pregnancy | Can result in prolonged hypotension (less predictable dose response)<br>Risk of reflex tachycardia<br>Headaches, lupus-like syndrome (with long-term use) |
| Nicardipine | Acute ischemic or hemorrhagic stroke<br>Acute renal failure<br>Perioperative hypertension<br>Pheochromocytoma<br>Pregnancy | Risk of reflex tachycardia<br>Infusion can lead to large fluid volumes administered |
| Clevidipine | Acute ischemic or hemorrhagic stroke<br>Acute renal failure<br>Perioperative hypertension<br>Pheochromocytoma<br>Pulmonary edema | Formulated in oil-in-water formulation providing 2 kcal/mL of lipid calories<br>Caution for patients allergic to soy or eggs |
| Nitroglycerin | Coronary ischemia/infarction<br>Acute LV<br>Pulmonary edema | Tachyphylaxis occurs rapidly, requiring dose titrations<br>Adverse effects: Flushing, headache, erythema; often dose-limiting adverse effects<br>Venous dilatation > arterial vasodilator |
| Esmolol | AD<br>Coronary ischemia/ infarction | Contraindicated in acute decompensated HF<br>Should be used in conjunction with an arterial vasodilator for BP management in AD (initiate esmolol first because of the delayed onset relative to vasodilators such as nitroprusside)<br>Metabolism is organ-independent (hydrolyzed by esterases in blood)<br>Useful in tachyarrhythmias |
| Labetalol | Acute ischemic or hemorrhagic stroke<br>AD<br>Coronary ischemia/ infarction<br>Pregnancy | May be used as monotherapy in acute AD<br>Contraindicated in acute decompensated HF<br>Prolonged hypotension and/or bradycardia may occur with overtreatment; dose cautiously |
| Enalaprilat | Acute LV failure | Contraindicated in pregnancy<br>Caution in dose adjustments, given prolonged duration of action |
| Phentolamine | Catecholamine excess (e.g., pheochromocytoma) | Use in catecholamine-induced hypertensive emergency |
| Fenoldopam | Most indications | Risk of reflex tachycardia<br>Caution with glaucoma<br>Can cause hypokalemia, flushing<br>May increase ICP |

2. Benzodiazepines and nitrates are the first-line agents used for cocaine-induced hypertensive emergency, followed by phentolamine. NTG and NTP may also be used but may get reflex tachy and then also have labetalol
3. All intravenous medications should be transitioned to oral medications as soon as possible. Goal = within the first 24 hours

**Patient Case**

*Questions 5 and 6 pertain to the following case.*

A 40-year-old man presents to the ED with blood pressure 200/100 mm Hg, signs of shortness of breath, and encephalopathy. His urine drug screen is positive for methamphetamine.

5. Which is the most appropriate goal for his blood pressure reduction?
   A. Goal SBP reduction by 25% during the first 60 minutes.
   B. Goal SBP reduction by 50% during the first 60 minutes.
   C. Goal SBP reduction by 25% during the first 24 hours.
   D. Goal SBP reduction by 50% during the first 24 hours.

6. Which agent would be best for initial blood pressure management?
   A. Fenoldopam 0.1 mcg/kg/minute intravenous infusion.
   B. Esmolol 50 mcg/kg/minute intravenous infusion.
   C. Hydralazine 20 mg intravenous bolus x 1.
   D. Nitroprusside 0.5-mcg/kg/minute intravenous infusion.

## V. ACUTE AORTIC SYNDROME

A. AAS embodies a group of severe, life-threatening disorders of the aorta and includes AD, intramural hematoma, and penetrating aortic ulcer.
   1. Acute denotation describes a disease process that has occurred within the past 1–14 days or is occurring. Anything occurring 14–90 days is considered subacute and, beyond 90 days, is considered chronic.
   2. AD
      a. AD is defined as a separation of the layers of the aortic wall caused by intimal tear.
         i. This tear can occur in the ascending aorta, descending aorta, or abdominal aorta.
         ii. Various factors like atherosclerotic disease and HTN disrupt the architecture and integrity of the aortic wall, and blood passing creates shear force tears. Once torn, the blood passes through the tear and separates the intima from the media and/or adventitia, creating a true and false lumen. Another hypothesis for the occurrence of ADs is primary rupture of the vasa vasorum leading to hemorrhage in the aortic wall creating the intimal disruption.
         iii. As blood pools, it can propagate the dissection further and create other symptoms or issues.
      b. AD occurs in 90% of AAS cases.
      c. Incidence of AD is estimated at two to four cases per 100,000 individuals, though exact incidence is difficult to categorize because many people die before it is recognized.
      d. Risk factors include HTN, atherosclerosis, prior cardiac surgery, history of known aneurysm, connective tissue disorders (e.g., Marfan), bicuspid aortic valve, trauma, and inflammatory disorders. HTN is common in 75% of cases.

e. AD is twice as common in men as in women.
f. Ascending AD typically occurs at age 50–60, whereas descending disease typically occurs at age 60–70.
g. Two major classifications for AD exist, according to the location of the dissection.
    i. The DeBakey classification divides ADs into types I, II, and III:
        (a) Type I: Has origins in the ascending aorta and extends at least to the aortic arch and often to the descending aorta, often to the iliac arteries
        (b) Type II: Centralized on the ascending aorta alone
        (c) Type III: Has origins at the descending aorta and goes above or below the diaphragm
    ii. The Stanford classification divides AD into type A or B:
        (a) Type A is an AD with ascending aorta involvement.
        (b) Type B is any location excluding the ascending aorta.
    iii. Symptoms of AD can be variable and include sudden-onset sharp, stabbing chest or back pain (around 90%–96%), syncope, and ischemic peripheral neuropathy.
    iv. Other physical findings include pulse deficits, aortic regurgitation, and neurological manifestations.
    v. Patients often present with acute HTN, more so in type B dissections. Depending on location, may affect complications to other organ systems (e.g., renal failure if descending dissection affects renal artery)
    vi. CT angiography or magnetic resonance imaging is the imaging modality of choice in hemodynamically stable patients, whereas transthoracic echocardiography or transesophageal echocardiography is the imaging modality of choice in unstable patients.

3. Intramural hematoma
    a. Intramural hematoma is a hematoma confined to the medial layer of the aorta without a detectable intimal tear. The mechanism has not been explained, but theories suggest spontaneous rupture of the vasa vasorum or rupture of a penetrating atherosclerotic ulcer.
    b. Incidence of 6% in one Western registry
    c. Symptoms and diagnosis similar to ADs
4. Penetrating aortic ulcer
    a. Penetrating aortic ulcer is a focal atherosclerotic plaque that corrodes a variable depth through the internal elastic lamina into the media.
    b. Incidence of 2.3%–11%
    c. Tends to occur in older men
    d. These often occur in the descending aorta.
    e. Symptoms and diagnosis similar to ADs

B. Treatment/Management of AAS
1. Patients with suspected AAS should be admitted to an ICU as soon as possible. Patients generally require intensive blood pressure and heart rate monitoring.
2. Patients should receive pain control with opioid therapy.
3. Aggressive blood pressure and heart rate control to reduce ventricular force should be achieved to reduce stress on the aorta. See the agents and dosing in the section on hypertensive emergency.
    a. General goal of SBP of 100–120 mm Hg and heart rate of 60 beats/minute or lower within the first 60 minutes.
    b. Initial treatment typically consists of IV esmolol because of its short half-life and ability to titrate. Labetalol can also be considered. The calcium channel blockers diltiazem and verapamil can be used if the patient cannot tolerate β-blockers.
    c. Nitroprusside can be added if blood pressure control cannot be achieved with these agents; however, heart rate must be controlled first.

4. Around 8%–31% of patients with type A dissections will have cardiac tamponade. Please see the section on managing tamponade.
5. For type A AAS, surgery is the definitive treatment and is emergently indicated.
6. For type B AAS, patients may respond over time to medical therapy, endovascular management, or ultimately surgical intervention. Degree of intervention is dictated by complications of AAS, location, and medical history.

**Patient Case**

7. A 56-year-old white woman with a long-standing history of hypertension presents with a blood pressure of 210/120 mm Hg and sharp stabbing chest and back pain. A CT done immediately reveals a type A dissection. She is initiated on an esmolol drip to achieve heart rate and blood pressure goals. Vital signs improved to a blood pressure of 100 mm Hg/80 mm Hg and heart rate 59 beats/minute with esmolol. Which other pharmacologic intervention would be most critical in her treatment at this time?

   A. Initiate 1 L of 0.9% normal saline.

   B. Initiate a diltiazem 5-mg/hour intravenous infusion.

   C. Initiate hydromorphone by patient-controlled analgesia 0.1 mg intravenously with a 5-minute lockout.

   D. No further intervention is needed.

## VI. ACUTE ISCHEMIC STROKE

A. This section will discuss the acute phase management of ischemic stroke. See the chapter on secondary prevention for chronic management.

B. Epidemiology
   1. Updated definitions
      a. Central nervous system infarction: Brain, spinal cord, or retinal cell death caused by ischemia, given pathological evidence, imaging, or other objective evidence of cerebral, spinal cord, or retinal focal ischemic injury in a defined vascular distribution, or clinical evidence of cerebral, spinal cord, or retinal focal ischemic injury, if symptoms persist for 24 hours or more or until death, and other etiologies excluded
      b. Ischemic stroke: An episode of neurological dysfunction caused by focal cerebral, spinal, or retinal infarction
   2. Third or fourth most common cause of death in all developed countries
   3. More than 795,000 cases per year in the United States (128,842 deaths)
   4. Most common cause of adult disability
   5. Risk factors
      a. Nonmodifiable
         i. Age: Stroke risk doubles each decade after 55 years.
         ii. Race: Risk for Native Americans is greater than for African Americans, whose risk is greater than for whites.
         iii. Sex: Risks are greater for men than for women; however, about half of all strokes occur in women.
         iv. Low birth weight: Odds of stroke for those with birth weights less than 2500 g are twice has high as for those weighing more than 4000 g.

v. Family history: Parental history increases risk; some coagulopathies (e.g., protein C and S deficiencies, factor V Leiden mutations) are inherited.
vi. Somewhat modifiable: Diabetes mellitus increases risk 1.8–6 times; risk reduction has not been shown with good glycemic control.

b. Modifiable
i. HTN increases risk 1.4–8 times; 32% risk reduction with control
ii. Smoking increases risk 1.9 times; 50% risk reduction in 1 year, baseline risk at 5 years with smoking cessation; exposure to environmental cigarette smoke also increases risk
iii. Oral contraceptives with less than 50 mcg of estrogen double the risk of stroke; those with more than 50 mcg of estrogen have 4.5 times increased risk; risk increases with age; adding smoking to oral contraceptive use increases risk of stroke 7.2 times; obesity and HTN also increase the risk with oral contraceptives
iv. Postmenopausal hormone therapy increases risk 1.4 times.
v. Atrial fibrillation increases risk 2.6–4.5 times; 68% risk reduction with warfarin or other anticoagulants.
vi. Coronary heart disease increases risk 1.55 times (women) to 1.73 times (men).
vii. Asymptomatic carotid stenosis increases risk 2 times; about a 50% risk reduction with endarterectomy
viii. Dyslipidemia: High total cholesterol increases risk 1.5 times; low high-density lipoprotein cholesterol (less than 35 mg/dL) increases risk 2 times; 27%–32% risk reduction with statins in patients with coronary heart disease, HTN, or diabetes. Twenty-five percent risk reduction with high-dose statins compared with low-dose statins
ix. Obesity (especially abdominal body fat) increases risk 1.75–2.37 times; risk reduction with weight loss is unknown.
x. Physical inactivity increases risk 2.7 times; risk reduction with increased activity is unknown.
xi. Sickle cell disease increases risk 200–400 times; 91% risk reduction with transfusion therapy
xii. Peripheral artery disease increases risk 3 times; the impact of risk reduction strategies is unknown.
xiii. Pregnancy increases risk 2.4 times over nonpregnant women; the risk remains elevated for the first 6 weeks postpartum.
xiv. Patent foramen ovale increases the risk of stroke in young patients (younger than 55 years).
xv. Depression increases the risk of stroke 1.35 times compared with nondepressed people.

c. Less well documented: Alcohol abuse (5 or more drinks a day), hyperhomocystinemia, drug abuse (cocaine, amphetamines, and heroin), hypercoagulability, periodontal disease, inflammation and infection, sleep-disordered breathing (sleep apnea and snoring), metabolic syndrome, and migraine with aura

C. Primary Prevention
1. Reduction in risk factors (e.g., control of HTN, smoking cessation, control of diabetes, cholesterol reduction)
2. Patient education: Patients should be educated about stroke warning signs and instructed to seek emergency care if they have any of them. Warning signs: Sudden numbness or weakness of the face, arm, or leg, especially on one side of the body; sudden confusion; trouble speaking or understanding; sudden trouble seeing in one or both eyes; sudden trouble walking; dizziness, loss of balance or coordination; sudden, severe headache with no known cause
3. Treatment of atrial fibrillation: Up to 70% of cases are inappropriately treated. Please see atrial fibrillation and anticoagulation chapters.

D. Treatment
   1. Treatment goals in the acute phase include ensuring medical stability, with an immediate focus on clinical stability acquiring recent medical history and chief concern; obtaining proper and timely laboratory tests and imaging; and determining whether the patient is a candidate for tissue plasminogen activator (alteplase) or other therapies.
      a. Time is of critical importance.
         i. Immediate general assessment by the stroke team, ED physician, or another expert within 10 minutes of arrival at a facility for suspected stroke. Obtain laboratory measures, including complete blood cell count, complete metabolic panel, coagulation panel, blood glucose, and coagulation laboratory values.
         ii. Neurological assessment by stroke team or designee and non-contrast CT performed within 25 minutes of arrival. Typically, the NIHSS is used.
         iii. Interpretation of CT scan within 45 minutes of arrival
         iv. Initiation of fibrinolytic therapy in appropriate patients within 1 hour of arrival and 3 hours of symptom onset or in select patients up to 4.5 hours (see Table 14), ideally.
      b. Provide IVFs as indicated.
   2. Desired outcomes include reducing ongoing neurological injury and decreasing mortality and long-term disability.
   3. Heparin
      a. Lack of good outcomes data; generally not recommended for stroke treatment at therapeutic doses; increases risk of hemorrhagic transformation; heparin and low-molecular-weight heparin are often used for deep venous thrombosis prevention, at normal doses, after event
      b. Avoid in hemorrhagic stroke.
   4. Fibrinolytic agents
      a. Within 4½ hours of symptom onset
      b. 3-month outcome significantly improved (decreased disability)
      c. Intracerebral hemorrhage increased but no increase in mortality
      d. Alteplase (tPA): Dose 0.9 mg/kg intravenously (maximum is 90 mg), with 10% as a bolus given over 1 minute and the remainder over 1 hour. The bolus should be administered within 60 minutes of hospital arrival. Goal door to needle (DTN) time
      e. Antiplatelet agents should be held for 24 hours after administration.
      f. Tenecteplase (0.4 mg/kg intravenously as a single dose) may be considered as an alternative to alteplase in patients with minor neurological impairment and no major occlusion.

5. Table 14 provides the patient selection criteria for fibrinolysis.

**Table 14.** Typical Inclusion/Exclusion Criteria for Fibinolytic Therapy in Ischemic Stroke

| Inclusion | Exclusion |
|---|---|
| • Onset of symptoms < 4½ hr from drug administration<br>• Baseline head CT excludes intracerebral hemorrhage or other risk factors<br>• Age > 18 yr<br><br>*Vital signs and laboratory values:*<br>• INR ≤ 1.7<br>• Plt ≥ 100,000/mm$^3$<br>• Note: Recommendations now are not to delay thrombolysis when INR and Plt are unknown and there is no discernible reason to suspect an abnormal test<br>• Blood glucose > 50 mg/dL<br>• Blood pressure control (SBP < 185 mm Hg, DBP < 110 mm Hg) before alteplase administration | • Recent intracranial or intraspinal surgery head trauma or stroke < 3 mo<br>• Active internal bleeding<br>• Symptoms suggest subarachnoid hemorrhage<br>• Any history of intracranial hemorrhage<br>• Intracranial neoplasm, arteriovenous malformation, or aneurysm<br>• Arterial puncture at noncompressible site < 1 wk<br>• Acute bleeding diathesis<br>• Current use (< 48 hr) of non-vitamin K oral anticoagulant agents with evidence of elevated sensitive laboratory tests or LMWH use within 24 hours<br><br>*Additional exclusion criteria for 3- to 4½-hr window:*<br>• History of both prior stroke and diabetes<br>• NIHSS score > 25<br>• Current treatment with oral anticoagulants (unless INR ≤ 1.7) For patients taking warfarin and with an INR ≤1.7 who present in the 3- to 4.5-hr window, IV alteplase appears safe and may be beneficial<br>• Evidence of ischemic injury > 1/3 of middle cerebral artery territory |

LMWH = low molecular weight heparin

6. HTN in ischemic stroke
   a. HTN in this setting is an adaptive response to maintain cerebral perfusion pressure to the brain.
   b. Cerebral perfusion pressure equals MAP minus the intracranial pressures.
   c. Treatment of HTN in this setting should occur only if alteplase is required, with the goal SBP less than 185 mm Hg and DBP less than 110 mm Hg to decrease the risk of hemorrhagic stroke conversion.
   d. Otherwise, the goal is to cautiously avoid hypotension or under perfusion to the infarcted areas – no more than 15% blood pressure reduction
7. Initiate aspirin (160- to 325-mg initial dose with 50- to 100-mg maintenance dose) within 48 hours of stroke onset in patients not eligible for alteplase.
8. Use of a stent retriever or catheter aspiration device within 6 hours may be beneficial in select patients (typically large-vessel occlusions) who have received alteplase (Table 15).
   a. Tenecteplase (0.25 mg/kg intravenously x1, maximum dose: 25 mg) may be superior to alteplase in patients that are candidates for thrombectomy and is increasingly being used in the U.S. due to cost-effectiveness and ease of dosing.

**Table 15.** Overview of Mechanical Thrombectomy Studies in Patients with Ischemic Stroke

| Study | Groups Compared | Efficacy |
|---|---|---|
| MR CLEAN | Alteplase ± stent retriever or intra-arterial thrombolytic (within 6 hr of symptom onset) | Increased likelihood of favorable outcome at day 90 (OR 1.67; 95% CI, 1.2–2.3) |
| EXTEND-IA | Alteplase ± stent retriever (within 6 hr of symptom onset) | Increased likelihood of independence at day 90 (adjusted OR 4.2; 95% CI, 1.2–12) |
| SWIFT PRIME | Alteplase ± stent retriever (within 6 hr of symptom onset) | Increased likelihood of independence at day 90 (RR 1.7; 95% CI, 1.2–2.3) |
| ESCAPE | Alteplase ± stent retriever (within 12 hr of symptom onset) | Increased likelihood of mRS improvement by 1 point (OR 2.6; 95% CI, 1.7–3.8) and lower mortality (OR 0.5; 95% CI, 0.3–0.8) |
| DAWN | Thrombectomy or usual care (within 6–24 hr of symptom onset and mismatch of severity of clinical defect and infarct volume) | Increased likelihood of functional independence at day 90 (49% vs. 13%, posterior probability for superiority > 0.99) |
| DEFUSE 3 | Thrombectomy vs. usual care (6–12 hr after symptom onset with non-infarcted brain tissue) | Increased likelihood of independence at day 90 (45% vs. 17%, p<0.001) |

mRS = modified Rankin scale.

9. Seizure prophylaxis is not indicated after ischemic stroke.
10. Fever is common after stroke, but outcomes data are lacking regarding whether it would be of benefit to treat. However, experts recommend trying to keep normothermic with proper source control and antipyretic agents (e.g., acetaminophen).
11. Hyper- and hypoglycemia should be avoided, and strict blood glucose management (140–180 mg/dL) should occur with monitoring and insulin infusion.
12. Start or resume high-potency statin therapy as soon as oral medications can be administered. Although the data have limitations, this may be of benefit in the acute phase.

**Patient Case**

8. A 55-year-old man (weight 100 kg [220 lb]) with a history of HTN began having stroke-like symptoms 90 minutes ago. His wife gave him 324 mg aspirin and brought him to the ED. His blood pressure on arrival is 175/92 mm Hg. An urgent head CT confirms the diagnosis of acute ischemic stroke. Which is the most appropriate treatment for the patient at time?
   A. Give only conservative management because he was given aspirin.
   B. Administer alteplase 22 mg as an intravenous bolus over 10 minutes, followed by a 68-mg infusion over 60 minutes.
   C. Give conservative management because of his elevated blood pressure and aspirin administration.
   D. Administer an alteplase 9-mg intravenous bolus, followed by 81 mg over 60 minutes.

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## ANSWERS AND EXPLANATIONS TO PATIENT CASES

**1. Answer: D**

The recommendations for cardiac arrest are to call for help and check for responsiveness. If the patient has no response, proper chest compressions should be performed at a rate of 100–120 compressions per minute and at a depth of at least 2 inches, with adequate chest recoil after each compression (Answer D is correct). Delivery of rescue breaths as initial therapy is no longer recommended because chest compressions should be performed first (Answer A is incorrect). Although ensuring the environment is safe is appropriate, delaying CPR while waiting for emergency medical services is incorrect (Answer C). Delivery of two rescue breaths followed by 30 chest compressions is the correct ratio; however, chest compressions should be initiated before rescue breaths (Answer B is incorrect).

**2. Answer: D**

Continuing CPR while the AED is being turned on and attached is the most appropriate step to minimize interruptions in chest compressions (Answer D is correct). Although changing providers is recommended, the AED has now arrived, and changing can occur once the AED has determined whether a shock is indicated. Changing now would cause another interruption once the AED begins rhythm analysis (Answer A is incorrect). Discontinuing chest compressions while turning on the AED and attaching pads may be necessary if you are the only bystander, but because another person brought the AED, that individual should assist with preparing the AED to minimize interruptions in chest compression (Answer B is incorrect). Rescue breathing is inappropriate at this time (Answer C is incorrect).

**3. Answer: B**

In all cardiac arrests, the treatable causes (Hs and Ts) should be reviewed and addressed, if possible (Answer B is correct). In patients for whom laboratory and diagnostic data are known, the information should be reviewed while CPR is being provided. In patients for whom the information is unknown, clinical evaluation and attainment of information should occur, if possible. The retrieval of information, administration of medications, or placement of advanced airway should never delay or halt CPR or defibrillation when it is indicated (Answer A is incorrect). Pulseless electrical activity and asystole are not wide complex rhythms and do not respond to defibrillation (Answer C is incorrect). Sodium bicarbonate is not routinely indicated in any arrest (Answer D is incorrect).

**4. Answer: D**

The patient has features of vasodilatory shock secondary to contrast anaphylaxis. He should, and has, received aggressive fluid resuscitation and should be initiated on a vasoactive agent such as norepinephrine with the primary effects of augmenting afterload (Answer D is correct). Although the patient has poor $DO_2$ because of poor preload, this should be corrected with fluids. His Hgb is adequate; therefore, blood products are not indicated (Answers A and C are incorrect). Other agents should be used if the previous measures fail to achieve desired goals or if other causes are suspected (Answer B is incorrect).

**5. Answer: A**

The initial goal reduction in this patient's blood pressure, given that he is having a hypertensive emergency, is a 25% reduction in SBP within the first 60 minutes (Answer A is correct). More rapid blood pressure reductions may result in a lack of cerebral perfusion; therefore, they are not recommended (Answer B is incorrect). The patient is not having any of the specific hypertensive emergencies (e.g., AD or stroke) that would call for a more rapid or slower blood pressure reduction (Answers C and D are incorrect).

**6. Answer: D**

The patient is probably having a hypertensive crisis because of his substance use disorder with methamphetamine. Agents with β-blockade effects should be avoided in these patients (Answer B is incorrect). It is important to use an agent that can provide control but also be short acting. Thus, hydralazine is not an ideal choice (Answer C is incorrect). Fenoldopam would not be an ideal choice, given its mechanism of action as a dopamine receptor agonist (Answer A is incorrect). The treatment of choice for this crisis is nitroprusside (Answer D is correct).

**7. Answer: C**

In addition to lowering blood pressure to an SBP of 100–120 mm Hg and heart rate to less than 60 beats/minute, the patient must be given pain management to assist in reaching these goals. Because pain can increase the heart rate, opioid agents are preferred (Answer C is correct; Answer D is incorrect). The patient currently has no indication for fluid resuscitation (Answer A is incorrect). Calcium channel blockers (such as diltiazem) are recommended for patients who cannot tolerate β-blockade (Answer B is incorrect).

**8. Answer: D**

The recommended alteplase dose for acute ischemic stroke is 0.9 mg/kg (maximal total dose of 90 mg), with 10% (9 mg) given as a bolus over 1 minute. This patient's weight is 100 kg (220/2.2), thus the maximum maintenance infusion dose should be 81 mg (Answer D is correct). His weight should be converted to kilograms to determine the correct dose. A bolus dose of 22 mg would indicate a weight of 220 kg instead of 220 lb (Answer B is incorrect). Aspirin administration alone is not a contraindication to fibrinolytic therapy (Answer A is incorrect). His blood pressure is not above the threshold; thus, he would still be candidate for fibrinolytics, and aspirin therapy would not eliminate his candidacy (Answer C is incorrect).

## ANSWERS AND EXPLANATIONS TO SELF-ASSESSMENT QUESTIONS

**1. Answer: C**

The most appropriate treatment of a patient at this point with pulseless VT cardiac arrest is to provide rapid defibrillation (Answer C is correct). The recommended voltage for a biphasic defibrillator is 120–200 J (according to the manufacturer's recommendations). The first dose of epinephrine should occur after the first shock if there is no ROSC (Answer A is incorrect). The foundation of cardiac arrest is chest compressions and minimal interruptions. Given that the patient is receiving appropriate ventilation by the bag-valve mask, it is not necessary to interrupt chest compressions for intubation (Answer B is incorrect). Although amiodarone at a dose of 300 mg is correct, amiodarone is recommended for refractory VF/pulseless VT and is therefore not indicated at this time (Answer D is incorrect).

**2. Answer: B**

The rhythm is now asystole; therefore, the pulseless electrical activity/asystole algorithm should be followed. The primary goal is to provide high-quality chest compressions and search for any reversible underlying cause of the cardiac arrest Hs and Ts (Answer B is correct). Defibrillation is inappropriate for asystole because there is an absence of electrical activity in the heart and would therefore be ineffective (Answer A is incorrect). Although atropine was previously recommended for pulseless electrical activity/asystole, it was removed from the 2010 advanced cardiac life support guidelines because of the lack of data supporting any beneficial outcome (Answer C is incorrect). Finally, magnesium only has evidence for and is only recommended for the treatment of torsades de pointes (Answer D is incorrect).

**3. Answer: A**

Given the patient's low CVP, PCWP, and CO and elevated SVR, he appears to have hypovolemic shock. The dramatic decrease in Hgb supports this as well (Answer A is correct). The lack of a high CVP, together with the echocardiographic findings and the absence of RV strain and tamponade, does not support an obstructive cause (Answer B is incorrect). The high SVR and the absence of a fever make the suggestion of vasodilatory shock less likely (Answer C is incorrect). Finally, the low CVP and PCWP do not support cardiogenic shock (Answer D is incorrect).

**4. Answer: D**

In patients with hypovolemic shock, rapid identification and correction of the source of bleeding are key. However, fluids and blood products can be used as temporizing measures. Fluids restore intravascular volume and reverse tissue hypoperfusion. Vasopressor agents can increase cardiac afterload alone and should be used only after an adequate attempt at fluid and blood product replacement (Answer A is incorrect). Similarly, inotropes will increase demand of the heart while not increasing perfusion, given limited volume (Answer C is incorrect). Of the two fluid choices, lactated Ringer appears to have more favorable effects with respect to kidney injury and is more cost-effective than hydroxyethyl starches (Answer B is incorrect; Answer D is correct).

**5. Answer: D**

By definition, this patient is having a hypertensive emergency because she has an abrupt, severe increase in blood pressure (SBP greater than 180 mm Hg and/or DBP greater than 120 mm Hg) with the presence of target-organ damage, as noted by this patient's troponin elevations, mental status changes, eclampsia with pregnancy, and acute kidney injury. The initial goal for hypertensive emergencies with preclampsia is to reduce systolic blood pressure to less than 140 mm HG over the first hour (Answer D is correct). A reduction in blood pressure to less than 110/80 mm Hg is too aggressive (Answer A is incorrect). An SBP greater than 200 mm Hg is also above the level defined for a hypertensive emergency, but the treatment goal of a 30% reduction exceeds the recommendation to reduce blood pressure by no more than 25% (Answer B is incorrect). A blood pressure reduction by 25% is not aggressive enough since it should be SBP less than 140 mm Hg in the first hour given her eclampsia (Answer C is incorrect).

**6. Answer: C**

The patient should be initiated on hydralazine for blood pressure management, given her current pregnancy (Answer C is correct). Hydralazine is one of the agents of choice for pregnant patients with hypertensive emergencies. The patient has a contraindication to enalaprilat, given her pregnancy history (Answer A is incorrect). In addition, the patient has an allergy to soy, which eliminates the use of clevidipine (Answer B is incorrect). Finally, phentolamine is not a preferred agent

in pregnancy. Moreover, this agent is typically reserved for those having a catecholamine crisis, and the doses typically used are 1–5 mg intravenously with a maximum bolus dose of 15 mg (Answer D is incorrect).

**7. Answer: C**

In a patient with an acute AD, the goal is to achieve an SBP below 100–120 mm Hg, ideally less than 100 mm Hg, within 20 minutes, and a heart rate goal of less than 60 beats/minute (Answer C is correct). The goal of a 25% reduction is the general recommendation for hypertensive emergencies; however, acute ADs are considered an exception to this rule in favor of the more aggressive cutoffs (Answer A is incorrect). The cutoff of less than 185 mm Hg is more directed toward patients with ischemic stroke who need permissive HTN, and the heart rate goal should be less than 60 beats/minute (Answer B is incorrect). The cutoff of less than 140 mm Hg is not aggressive enough for a patient with AD, and the heart rate goal should be less than 60 beats/minute (Answer D is incorrect).

**8. Answer: A**

Current guidelines recommend that aspirin be administered within 24–48 hours of symptom onset (Answer A is correct). Although aspirin is recommended for stroke, giving it immediately on arrival without first determining the treatment strategy is not recommended. Furthermore, aspirin should not be used as a substitute for other acute interventions, such as fibrinolytic therapy (Answer B is incorrect). Aspirin therapy should be administered to patients with stroke irrespective of the administration of fibrinolytic therapy. However, in general, in patients who receive fibrinolytic therapy, aspirin administration should be delayed for at least 24 hours (Answer C is incorrect). The 72-hour window for aspirin administration for a stroke is outside the 24- to 48-hour window that is recommended (Answer D is incorrect).

**9. Answer: C**

This patient presented to the ED about 2 hours after symptom onset, and the door-to-imaging interpretation time was 30 minutes. This places the patient in the 3-hour window after his stroke, making him a candidate for alteplase (Answer C is correct). Use of warfarin is not a contraindication for alteplase administration unless the INR is greater than 1.7 (Answer B is incorrect). Ideally, if fibrinolytic therapy is administered, aspirin therapy should be withheld for at least 24 hours. However, the American Heart Association/American Stroke Association guidelines do not preclude the use of alteplase in patients who have recently consumed aspirin (Answer A is incorrect). Age alone does not qualify a patient for fibrinolytic therapy because the patient is required to meet all the criteria before administration. However, exceptions are sometimes made, depending on risk-benefit evaluation (Answer D is incorrect).

# Pulmonary Arterial Hypertension

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**Learning Objectives**

1. Describe the classification of pulmonary hypertension and implications for treatment.
2. Discuss the importance of pulmonary arterial hypertension (PAH) pathobiology and the role of various pathways as treatment targets in the development of PAH-specific treatment.
3. Define treatment goals for the management of PAH.
4. Outline targeted medications for PAH, including indications, dosing, monitoring, and their place within current treatment algorithms.
5. Identify common adverse effects and drug interactions associated with PAH medications.
6. Highlight appropriate treatment approaches for the management of decompensated PAH.
7. Design a treatment plan for a patient with PAH.

**Abbreviations in This Chapter**

| | |
|---|---|
| BNP | Brain natriuretic peptide |
| CCB | Calcium channel blocker |
| CTEPH | Chronic thromboembolic pulmonary hypertension |
| ERA | Endothelin receptor antagonist |
| ET-1 | Endothelin-1 |
| FC | Functional class |
| LV | Left ventricle/ventricular |
| mPAP | Mean pulmonary artery pressure |
| PAH | Pulmonary arterial hypertension |
| PCWP | Pulmonary capillary wedge pressure |
| PDE5i | Phosphodiesterase type 5 inhibitor |
| PH | Pulmonary hypertension |
| PVR | Pulmonary vascular resistance |
| RAP | Right atrial pressure |
| REMS | Risk Evaluation and Mitigation Strategies |
| RHC | Right heart catheterization |
| RV | Right ventricle/ventricular |
| sGC | Soluble guanylate cyclase |
| 6MWD | 6-minute walk distance |
| TTE | Transthoracic echocardiogram |
| WHO | World Health Organization |

**Self-Assessment Questions**

*Answers and explanations to these questions can be found at the end of this chapter.*

*Questions 1–10 pertain to the following case.*

A 36-year-old woman (weight 71 kg) was transferred to the intensive care unit (ICU) from an outlying hospital after having 2–3 weeks of progressively worsening dyspnea and intermittent episodes of chest pressure. She recently developed difficulty breathing, even when at rest. She arrives on 6 L of oxygen by high-flow nasal cannula and dopamine 7 mcg/kg/minute. Notes show that she was relatively hypotensive (88/49–102/55 mm Hg) and tachycardic (heart rate 110–118 beats/minute) on presentation to the outlying hospital. A 12-lead electrocardiogram revealed sinus tachycardia.

Her medical history is significant for asthma and hypothyroidism. The patient reports that she currently takes an albuterol inhaler 2 puffs every 6 hours as needed and levothyroxine 112 mcg/day orally.

Relevant family history includes that of her mother, who was given a diagnosis of pulmonary arterial hypertension (PAH) in her 30s and died in her early 40s because of complications from the disease. The patient denies smoking and using illicit substances. She drinks 1 or 2 alcoholic beverages a few times per week.

- Vital signs on transfer: Blood pressure 112/60 mm Hg, heart rate 122 beats/minute, respiratory rate 19 breaths/minute, arterial oxygen saturation ($Sao_2$) 90%, temperature 99.7°F (37.6°C)
- The team's physical assessment reveals ongoing distress, difficulty breathing, and the presence of a right radial arterial line.
- A transthoracic echocardiogram (TTE) reveals a left ventricular (LV) ejection fraction of 60%, a flattened septum consistent with right ventricular (RV) pressure and volume overload, and moderate to severely reduced RV function.
- A right heart catheterization (RHC) performed at the receiving hospital reveals right atrial pressure (RAP) 14 mm Hg, RV pressure 76/11 mm Hg, pulmonary artery (PA) pressure 73/55 mm Hg with a mean pulmonary artery pressure (mPAP) 55 mm Hg, pulmonary capillary wedge pressure (PCWP) 8 mm Hg, cardiac output 2.2 L/minute, cardiac index 1.4 L/minute/$m^2$, and pulmonary vascular resistance (PVR) 21 Wood units.

- Vasoreactivity testing with inhaled nitric oxide was performed and showed no change in her mPAP. A computed tomography (CT) scan of her chest was unremarkable, and a ventilation-perfusion scan was low probability for chronic thromboembolic pulmonary hypertension (CTEPH).
- Her serum chemistry panel results are as follows: sodium 136 mEq/L, potassium 4.2 mEq/L, chloride 102 mEq/L, carbon dioxide 20 mEq/L, blood urea nitrogen (BUN) 17 mg/dL, serum creatinine (SCr) 0.9 mg/dL, and glucose 122 mg/dL.
- Results of the complete blood cell count are as follows: white blood cell count $7.3 \times 10^3$ cells/mm$^3$, hemoglobin (Hgb) 12.5 g/dL, hematocrit 36.1%, and platelet count 383,000/mm$^3$.
- Additional laboratory values include aspartate aminotransferase (AST) 34 IU/L, alanine aminotransferase (ALT) 22 IU/L, hemoglobin A1C 6.3%, and brain natriuretic peptide (BNP) 1423 pg/mL.
- As part of her PAH evaluation, she was determined to be HIV negative. A workup for both connective tissue diseases and hypercoagulable conditions was unremarkable. Genetic screening was positive for a bone morphogenetic protein receptor type II (*BMPR2*) mutation.

1. Which is the most likely cause of this patient's admission and transfer?
   A. Cardiogenic shock caused by a heart failure exacerbation.
   B. Acute RV failure caused by PAH.
   C. Acute LV failure caused by PAH.
   D. Uncomplicated PAH now requiring combination therapy.

2. Which group best depicts this patient's World Health Organization (WHO) clinical classification of pulmonary hypertension (PH)?
   A. 1.
   B. 2.
   C. 3.
   D. 4.

3. Given this patient's clinical presentation, which best reflects her WHO functional class (FC)?
   A. I.
   B. II.
   C. III.
   D. IV.

4. Which is the most likely etiology of this patient's PAH?
   A. Idiopathic.
   B. Associated with heart failure.
   C. Heritable.
   D. Drug induced.

5. After the RHC, the patient is transferred to the cardiac ICU for further care. Which changes/interventions in this patient's hemodynamic support would be best to recommend?
   A. Increase dopamine to achieve a mean arterial pressure greater than 65 mm Hg.
   B. Change to vasopressin 0.04 unit/minute.
   C. Change to sildenafil 10 mg intravenously three times daily.
   D. Change to milrinone 0.25 mcg/kg/minute.

6. Which intervention would be best to recommend next to treat RV failure?
   A. Treprostinil 3 breaths inhaled four times daily.
   B. Epoprostenol 2 ng/kg/minute intravenous infusion.
   C. Treprostinil 2 ng/kg/minute intravenous infusion.
   D. Bosentan 62.5 mg orally twice daily.

7. Over the next several days, the patient becomes more clinically stable and is transferred to the step-down unit. The team is discussing her disposition, and the attending physician asks you to counsel the patient on some of the PAH therapies that are being considered. With respect to prostacyclin use, which adverse effect would be most anticipated with treatment initiation?
   A. Jaw pain.
   B. Transaminitis.
   C. Teratogenicity.
   D. Changes in vision.

8. The team ultimately decided to discharge the patient to home on epoprostenol (Flolan; also Veletri) after titrating the agent to a target dose of 10 ng/kg/minute intravenous infusion, together with sildenafil 20 mg orally three times daily. She tolerated the medication with only mild gastrointestinal (GI) adverse effects. After about 1 month of treatment, she is seen in the outpatient PH clinic. At this visit, she reports significantly improved symptoms with few limitations in her activities of daily living. A 6-minute walk distance (6MWD) is reported as 400 m. In addition, a follow-up TTE reveals a decrease in RV size with mildly reduced RV function. She is scheduled for a follow-up RHC at the next visit. Despite the patient's overall improved clinical course, she expresses a strong desire to use an alternative treatment that will not require an intravenous catheter because she has concerns about infection. Which would be the most reasonable alternative and reason for changing from epoprostenol in this patient?
   A. Give iloprost inhaled so that infusion therapy can be avoided.
   B. Give riociguat so that infusion therapy can be avoided.
   C. Change to treprostinil (Remodulin) subcutaneously so that an indwelling central venous catheter will no longer be required.
   D. Give treprostinil diolamine extended release to provide an oral prostacyclin in place of infusion therapy.

9. During the current outpatient PH clinic visit, the patient also asks about possible drug-drug interactions with treprostinil. Which would be most likely to interact?
   A. Warfarin.
   B. Glyburide.
   C. Cyclosporine.
   D. Albuterol.

10. As part of a treat-to-target strategy approach to PAH care for this patient, which best describes one of the recommended treatment goals?
   A. 6MWD greater than 440 m.
   B. Normal or near-normal LV size and function by echocardiography.
   C. 6MWD greater than 300 m.
   D. WHO FC II or III symptoms.

## I. DEFINITIONS AND CLASSIFICATION

A. Definition
1. PAH is a progressive disease characterized by PVR increases that ultimately lead to RV failure and death (N Engl J Med 2004;351:1655-65).
2. PH is defined as an mPAP above 20 mm Hg by RHC.
3. PAH is described hemodynamically by the presence of precapillary PH (PCWP of 15 mm Hg or less and PVR equal to or greater than 3 Wood units) in the absence of other causes of precapillary PH (i.e., lung diseases, CTEPH) (Eur Respir J 2019;53:1801913).
4. PH may either be precapillary, caused by pulmonary vascular remodeling leading to increased PVR, or postcapillary, as the result of an increase in pulmonary venous pressure in left-sided heart diseases.

B. Epidemiology
1. PAH is a rare disease state with an overall incidence of 15 per 1 million people, according to the French registry (Am J Respir Crit Care Med 2006;173:1023-30).
2. Predominantly affects young female patients. Mean age of 50 ± 14 years; 80% female (Chest 2010; 137:376-87).
3. Median survival is 7 years, according to U.S. registry data (Chest 2010;137:376-87). Significant improvement compared with median survival of 2.8 years according to National Institutes of Health registry in the 1980s (Ann Intern Med 1991;115:343-9).

C. WHO Clinical Classification of PH
1. Updated during the Sixth World Symposium on Pulmonary Hypertension (WSPH) in 2018 (Eur Respir J 2019;53:1801913).
2. PH groups are based on shared pathological features, similarities in hemodynamics, and management strategies.
    a. WHO Group 1 – PAH (many different underlying etiologies)
        i. Idiopathic
        ii. Heritable
        iii. Drug and toxin-induced
        iv. Associated conditions: connective tissue disease, HIV infection, portal hypertension, congenital heart diseases, schistosomiasis
        v. Long-term responders to calcium channel blockers (CCBs)
        vi. Overt features of venous/capillaries (pulmonary veno-occlusive disease/pulmonary capillary hemangiomatosis)
        vii. Persistent PH of the newborn
    b. WHO Group 2 – PH caused by left heart disease
        i. Heart failure with preserved ejection fraction
        ii. Heart failure with reduced ejection fraction
        iii. Valvular heart disease
        iv. Congenital/acquired cardiovascular conditions leading to postcapillary PH
    c. WHO Group 3 - PH caused by lung diseases and/or hypoxia
        i. Obstructive lung disease
        ii. Restrictive lung disease
        iii. Other lung disease with mixed restrictive/obstructive pattern
        iv. Hypoxia without lung disease
        v. Developmental lung disorders

   d. WHO Group 4 – PH caused by pulmonary artery obstructions
      i. Chronic thromboembolic PH (CTEPH)
      ii. Other pulmonary artery obstructions
   e. WHO Group 5 - PH with unclear and/or multifactorial mechanisms
      i. Hematologic disorders (chronic hemolytic anemia, myeloproliferative disorders)
      ii. Systemic (sarcoidosis, pulmonary histiocytosis) and metabolic disorders (glycogen storage disease, Gaucher disease)
      iii. Others (fibrosing mediastinitis, chronic renal failure)
      iv. Complex congenital heart disease
3. In the contemporary U.S. Registry to Evaluate Early and Long-term PAH disease management (REVEAL) (Circulation 2010;122:164-72), the proportions of patients who met different subcategories were as follows:
   a. Associated PAH (50.7%). Associated conditions included connective tissue disease (49.9%), congenital heart disease (19.5%), portal hypertension (10.6%), drug/toxin induced (10.5%), HIV associated (4%), and other (5.5%).
   b. Idiopathic PAH (46.2%), formerly known as primary PH
   c. Familial PAH (2.7%)

D. Risk Factors
1. Connective tissue disorders are the most common cause of PAH.
   a. About 50% are caused by scleroderma (systemic sclerosis or formerly called CREST syndrome: calcinosis, Raynaud phenomenon, esophageal dysmotility, sclerodactyly, and telangiectasias) (N Engl J Med 2009;360:1989-2003).
   b. Prevalence of PAH among patients with scleroderma is 7%–12% (J Am Coll Cardiol 2013;62:D34-41).
   c. Other types of connective tissue disorders associated with PAH include systemic lupus erythematosus, Sjögren syndrome, rheumatoid arthritis, and mixed connective tissue disease (J Am Coll Cardiol 2013;62:D34-41; Rheumatology 2009;48:304-8).
2. In familial PAH, genetic mutations are detectable in 80% of families with several cases of the disease (J Am Coll Cardiol 2013;62:D34-41). The most common mutation is *BMPR2*, part of the tumor growth factor β superfamily. 10%-20% of idiopathic PAH cases are caused by mutations in *BMPR2* (Eur Respir J 2019;53:1801899).
3. Drug- and toxin-induced causes (Eur Respir J 2019;53:1801913).
   a. Definite: aminorex, benfluorex, dexfenfluramine, fenfluramine, methamphetamines, dasatinib, toxic rapeseed oil. Historically, anorexigens such as fenfluramine and dexfenfluramine were associated with PAH according to their serotonergic properties (J Am Coll Cardiol 2009;53:1573-619).
   b. Possible: cocaine, phenylpropanolamine, L-tryptophan, St. John's wort, amphetamines, interferon-α and-β, alkylating agents, bosutinib, direct-acting antiviral agents against hepatitis C virus, leflunomide, indirubin (Chinese herb Qing-Dai), ponatinib, selective proteasome inhibitors (carfilzomib). Caution is warranted with amphetamine-related derivatives (e.g., phentermine, methylphenidate, topiramate, ropinirole) (J Am Coll Cardiol 2013;62:D34-41).

**Patient Cases**

*Questions 1–8 pertain to the following case.*

H.L. is a 53-year-old woman with a medical history significant for scleroderma, Raynaud phenomenon, Sjögren syndrome, gastroesophageal reflux disease, coronary artery disease, dyslipidemia, and chronic kidney disease who presents for her initial visit to the advanced heart failure/PH clinic. She reports a 4-month history of dyspnea on exertion and fatigue with ordinary household activities. She was referred by her general cardiologist, who had the patient complete both a TTE and an RHC. The TTE was interpreted as follows: LV ejection fraction of 65% with normal LV and RV size and function, mild tricuspid regurgitation, and estimated pulmonary artery systolic pressure of 40 mm Hg. The RHC showed the following: RAP 12 mm Hg, pulmonary artery pressure 56/25 mm Hg with an mPAP of 35 mm Hg, PCWP 13 mm Hg, PVR 5 Wood units, and cardiac index 3.4 L/minute/$m^2$.

At today's cardiology visit, the patient's vital signs are stable with blood pressure 122/72 mm Hg, heart rate 88 beats/minute, temperature 97.3°F (36.3°C), $Sao_2$ 97% on room air, and respiratory rate 17 breaths/minute. Cardiovascular assessment reveals regular rate and rhythm without any murmurs. Other recently completed tests showed an unremarkable chest CT, normal spirometry, and low probability ventilation-perfusion scan. Relevant laboratory tests include SCr 1.7 mg/dL, AST 22 IU/L, ALT 19 IU/L, Hgb 10.5 g/dL, BNP 85 pg/mL, and positive antinuclear antibody. Finally, a baseline 6MWD at today's visit was 460 m. The patient's home medications include aspirin 81 mg daily, simvastatin 20 mg at bedtime, carvedilol 12.5 mg twice daily, calcitriol 0.25 mcg daily, pantoprazole 40 mg twice daily, hydroxychloroquine 200 mg daily, and prednisone 5 mg daily.

1. Given H.L.'s comorbidities and clinical presentation, which is the most likely cause of PH?
   A. Coronary artery disease
   B. Idiopathic
   C. Connective tissue disease
   D. Chronic kidney disease

## II. PATHOPHYSIOLOGY

A. Central Features of PAH
   1. The pathophysiology is complex and multifactorial.
   2. Vasoconstriction, vascular wall remodeling, and in situ thrombosis (N Engl J Med 2004;351:1655-65)
      a. Net effect is an increase in PVR.
      b. Vasculopathy affects primarily distal pulmonary arteries through intimal hyperplasia, medial hypertrophy, adventitial proliferation, inflammation, thrombosis, and development of plexiform lesions (J Am Coll Cardiol 2009;53:1573-619).

B. Dysregulation and imbalance of vasodilators (i.e., nitric oxide, prostacyclins) and vasoconstrictors (i.e., thromboxane $A_2$, endothelin-1 [ET-1]) within vascular endothelium and smooth muscle (N Engl J Med 2004;351:1655-65). These are the primary pathways and therapeutic targets for PAH.
   1. Nitric oxide
      a. Potent vasodilator, inhibits platelet activation and vascular smooth muscle cell proliferation (J Am Coll Cardiol 2009;53:1573-619)
      b. Deficiency is a result of impaired synthesis and signaling by the nitric oxide–soluble guanylate cyclase (sGC)–cyclic guanosine monophosphate (cGMP) pathway (J Am Coll Cardiol 2013;62:D60-72).
         i. Nitric oxide activates its molecular target, sGC, which leads to increases in cGMP.
         ii. Degradation of cGMP is regulated by the enzyme phosphodiesterase type 5 (PDE5) (J Am Coll Cardiol 2009;53:1573-619).

2. ET-1
    a. Potent vasoconstrictor and mitogen that exerts its effects on pulmonary vascular smooth muscle by ET type A ($ET_A$) and ET type B ($ET_B$) receptors (J Am Coll Cardiol 2013;62:D60-72). $ET_B$ receptors also mediate nitric oxide release and clearance of ET-1.
    b. ET-1 concentrations are increased and its clearance is impaired.
3. Prostacyclin (prostaglandin $I_2$ or PGI2) is a major metabolite of arachidonic acid metabolism and has significant effects on pulmonary vascular smooth muscle. Potent vasodilator, inhibitor of platelet activation, and antiproliferative (J Am Coll Cardiol 2009;53:1573-619)

## III. CLINICAL PRESENTATION

A. Onset may be insidious, and symptoms are very nonspecific.
    1. Dyspnea, fatigue, exercise intolerance, chest pain, fluid retention, and syncope (less common) (J Am Coll Cardiol 2009;53:1573-619)
    2. RV function is a major determinant of exercise capacity and outcome in patients with PAH (Eur Heart J 2016;37:67-119); signs and symptoms of RV dysfunction may signal advanced disease (i.e., increased jugular venous pressure, lower-extremity edema, hepatomegaly, tricuspid regurgitation).

B. Symptom severity is categorized according to WHO FC (J Am Coll Cardiol 2009;53:1573-619)
    1. WHO FC I: No limitations of physical activity
    2. WHO FC II: Symptoms on ordinary exertion
    3. WHO FC III: Symptoms on less-than-ordinary exertion
    4. WHO FC IV: Symptoms at rest

C. 56% of patients with PAH in the U.S. REVEAL registry had WHO FC III or IV symptoms (Chest 2010;137:376-87).

## IV. DIAGNOSIS

A. Careful patient assessment and comprehensive testing are warranted to exclude secondary causes of PH – Echocardiography, pulmonary function testing, sleep studies, serologies, ventilation-perfusion scanning, and chest CT scans.

B. An RHC is required to confirm the diagnosis of PAH. Normal left-side filling pressures (PCWPs) are necessary to exclude passive increases in pulmonary pressures because of left-sided heart disease (group 2 PH), or postcapillary PH.

C. Precapillary PH concerns patients from groups 1, 3, 4, some from group 5, and rarely those from group 2 with combined pre- and postcapillary PH (Eur Respir J 2019;53:1801913).

D. Delay from symptom onset to diagnosis – 27 months (J Am Coll Cardiol 2015;6 5:1976-97).

Box 1. PH vs. PAH based on hemodynamics (Eur Respir J 2019;53:1801913).

| PH | PAH |
|---|---|
| mPAP > 20 mm Hg | mPAP > 20 mm Hg<br>PCWP ≤ 15 mm Hg<br>PVR ≥ 3 Wood units |

## V. RISK ASSESSMENT

A. A constellation of clinical variables can be assessed for both prognosis and treatment approach (Box 2).

Box 2. Comparative Risk Assessment (Eur Respir J 2019;53:1801913; Eur Heart J 2022;43:3618-731).

| Determinants of Prognosis[a] | Low Risk < 5% | Intermediate Risk 5%-20% | High Risk > 20% |
|---|---|---|---|
| Right heart failure | Absent | Absent | Present |
| Symptom progression | No | Slow | Rapid |
| Syncope | No | Occasional | Repeated |
| WHO FC | I, II | III | IV |
| 6MWD | > 440 m | 165-440 m | < 165 m |
| CPET | Peak $VO_2$ > 15 mL/min/kg | Peak $VO_2$ 11-15 mL/min/kg | Peak $VO_2$ < 11 mL/min/kg |
| Biomarkers: BNP or NT-proBNP | BNP: < 50 ng/L<br>NT-proBNP: < 300 ng/L | BNP: 50–800 ng/L<br>NT-proBNP: 300–1100 ng/L | BNP: > 800 ng/L<br>NT-proBNP: > 1100 ng/L |
| Echocardiography | RA area < 18 $cm^2$<br>No pericardial effusion | RA area 18-26 $cm^2$<br>Minimal pericardial effusion | RA area > 26 $cm^2$<br>Moderate or large pericardial effusion |
| Cardiac MRI | RVEF > 54% | RVEF 37%–54% | RVEF < 37% |
| Hemodynamics | RAP < 8 mm Hg<br>CI ≥ 2.5 L/min/$m^2$<br>$SvO_2$ > 65% | RAP 8-14 mm Hg<br>CI 2-2.4 L/min/$m^2$<br>$SvO_2$ 60-65% | RAP > 14 mm Hg<br>CI < 2 L/min/$m^2$<br>$SvO_2$ < 60% |

[a]Estimated 1-year mortality

BNP = brain natriuretic peptide; CI = cardiac index; CPET = cardiopulmonary exercise testing; FC = functional class; NT-proBNP = N-terminal pro-brain natriuretic peptide; RA = right atrial; RAP = right atrial pressure; RVEF = right ventricular ejection fraction; 6MWD = 6-minute walk distance; $SvO_2$ = mixed venous oxygen saturation; $VO_2$ = oxygen consumption; WHO = World Health Organization.

B. RV function is a major predictor of functional capacity and outcome (J Am Coll Cardiol 2009;53:1573-619).

C. The REVEAL registry identified several factors associated with mortality (Circulation 2010;122:164-72).
   1. Factors associated with increased risk of mortality: Portal hypertension, connective tissue disease associated with PAH, family history of PAH, renal insufficiency, men older than 60, WHO FC III–IV symptoms, resting systolic blood pressure less than 110 mm Hg, heart rate greater than 92 beats/minute at rest, 6MWD less than 165 m, BNP greater than 180 pg/mL, PVR greater than 32 Wood units, mean RAP greater than 20 mm Hg, pericardial effusion, percent predicted diffusion capacity of carbon dioxide ($D_{LCO}$) of 32% or less
   2. Factors associated with decreased risk of mortality: WHO FC I symptoms, 6MWD of 440 m or greater, BNP less than 50 pg/mL, $D_{LCO}$ of 80% or more

D. A contemporary prognostic equation based on these clinical variables can be used to estimate 1-year survival at any point in the care of a patient with PAH (Chest 2012;141:354-62).

E. The REVEAL 2.0 risk score calculator includes all-cause hospitalizations within the previous 6 months and estimated glomerular filtration rate (eGFR), each of which has been shown to impact mortality (J Heart Lung Transplant 2018;37:696-705; Chest 2019;156:323-37).
F. An abridged version, REVEAL Lite 2, provides a simplified approach to risk assessment using fewer vari ables in the clinic setting (Chest 2021;159:337-46).

## VI. TREATMENT GOALS

A. The aforementioned risk prediction variables (Box 2) can be combined to form a goal-oriented approach to therapy.

B. This treat-to-target strategy uses predetermined treatment goals and refinement of therapeutic strategy if these goals are not met (Eur Respir J 2005;26:858-63).

C. Regular comprehensive and multiparametric assessment is recommended to achieve low-risk status as defined by the following: WHO FC I or II, 6MWD greater than 440 m, normalization of RV function by hemodynamics (RAP less than 8 mm Hg and cardiac index of 2.5 or greater L/minute/$m^2$; mixed venous oxygen saturation greater than 65%), normalization of biomarkers (BNP less than 50 pg/mL, N-terminal pro-brain natriuretic peptide [NT-proBNP] less than 300 pg/mL) (Eur Heart J 2016;37:67-119; Eur Heart J 2018;39:4175-81; Eur Respir J 2017;50:1700740; Eur Respir J 2017;50;1700889). Note that these treatment goals may not be achievable in patients with advanced disease.
    1. 6MWD has been used as the primary end point in most clinical trials of PAH therapies. Noninvasive, simple, reproducible, and correlates with hemodynamics and survival, despite known limitations (J Am Coll Cardiol 2013;62:D73-81)
    2. More contemporary clinical trials have included a primary composite outcome of time to clinical failure (i.e., death, hospitalization because of worsening PAH, disease progression, unsatisfactory clinical response).

D. Follow-up should occur every 3–6 months after baseline assessment and after changes in therapy (medical assessment, FC, 6MWD).
E. Current treatment approach aims to achieve low-risk status by emphasizing upfront combination therapy for most treatment-naive patients. Treatment escalation with sequential combination therapy during follow-up is warranted for patients who have not achieved low-risk status (Eur Respir J 2019;53:1801889).

## VII. PHARMACOTHERAPY

A. Significant improvements in PAH outcomes have been realized through advances in pharmacotherapy. See Figure 1.
    1. Initial monotherapy in treatment-naive patients improves exercise capacity, hemodynamics, and outcome versus no treatment.
    2. Initial combination therapy in treatment-naive and newly diagnosed (incident) patients improves exercise capacity, hemodynamics, and outcome versus initial monotherapy.
    3. Sequential combination therapy in already-treated (prevalent) patients improves exercise capacity, hemodynamics, and outcome versus continuing background therapy only (Eur Respir J 2019;53: 1801889).

B. 16 unique medication formulations are currently U.S. Food and Drug Administration (FDA) approved.
   1. Most are approved for group 1 disease (PAH).
   2. Riociguat is approved for both group 1 and group 4 disease (CTEPH).
   3. Inhaled treprostinil is approved for both group 1 and group 3 disease (N Engl J Med 2021;384:325-44).
   4. Off-label use of PAH-targeted therapies for other PH groups has either limited data or evidence of harm (J Am Coll Cardiol 2009;53:1573-619), thereby underscoring the need for expert referral.
   5. Current guidelines strongly recommend against the use of PAH therapies in group 2 PH (Eur Respir J 2019;53:1801897). For example, PAH therapies can further increase pulmonary venous pressure, leading to volume overload in patients with postcapillary PH.

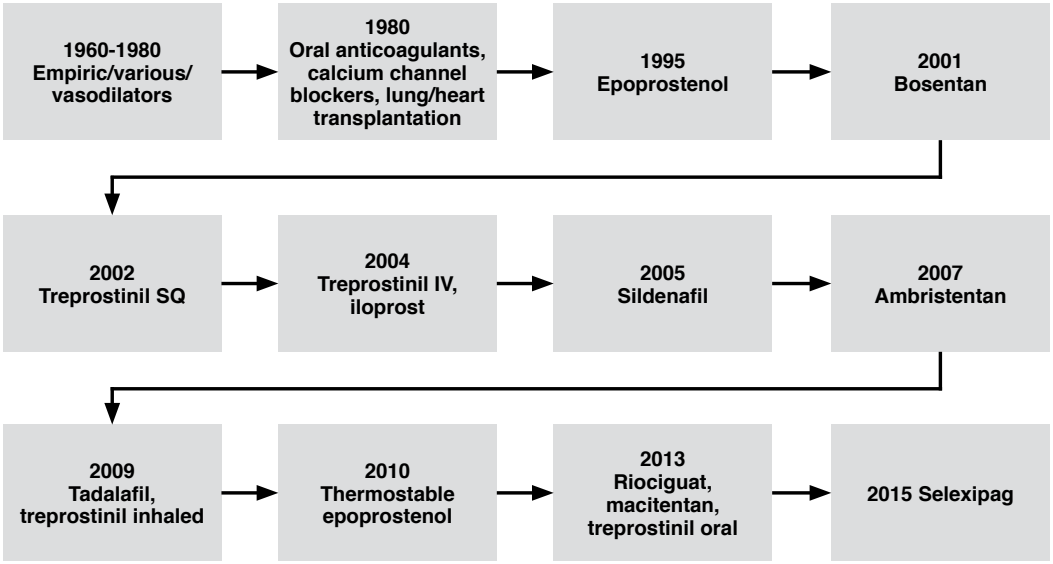


**Figure 1.** Pharmacotherapy timeline.
IV = intravenous(ly); SQ = subcutaneous(ly).

C. Supportive Care and Background Therapies (J Am Coll Cardiol 2009;53:1573-619; Eur Heart J 2016;37:67-119)
   1. General measures
   2. Avoidance of pregnancy (*backup contraception methods particularly with concomitant endothelin receptor antagonist [ERA] therapy because of decreased effectiveness of oral contraceptives and teratogenicity of ERAs*), immunization against SARS-CoV-2, influenza and pneumococcal infections, psychosocial support, physical activity within symptom limits. Note that each ERA and riociguat therapy has its own REMS program with specific requirements
   3. Supportive therapy:
      a. Oxygen: Improves hypoxia and prevents vasoconstriction; target is $Sao_2$ greater than 90%
      b. Diuretics – Manage RV volume overload (i.e., increased jugular venous pressure, lower-extremity edema, abdominal distention).
      c. Digoxin
         i. Consider for RV failure, low cardiac output, and/or atrial arrhythmias, although data are limited for PAH.
         ii. Caution with impaired kidney function, low body weight, older adults
      d. Warfarin
         i. Anticoagulation is not generally recommended but may be considered on an individual basis.
         ii. May be used in patients with idiopathic PAH because of historical studies that showed improvement in mortality (before modern era with availability of PAH-specific therapies);

however, registry data are mixed and inconclusive (Circulation 2015;132:2403-11; Circulation 2014;129:57-65)

iii. A meta-analysis suggests tailoring anticoagulation to PAH subtype (mortality benefit found with idiopathic PAH, whereas mortality increase seen with scleroderma-associated PAH) (Circ Cardiovasc Qual Outcomes 2018;11:e004757).

iv. Additional rationales for use include (1) risk of catheter-associated thrombosis related to long-term prostacyclin therapy and (2) risk of stasis-associated deep venous thrombosis in patients with severe right heart failure.

v. Target international normalized ratio range of 1.5–2.5.

D. Acute Pulmonary Vasoreactivity Testing

1. Typically used to identify patients with idiopathic, heritable, or drug-induced PAH who may favorably respond to high doses of CCBs
2. Inhaled nitric oxide is often used; however, alternatives may include inhaled iloprost or intravenous epoprostenol.
3. Positive response = Reduction in mean PAP of 10 mm Hg or greater to reach a mean PAP of 40 mm Hg or less with no change or increase in cardiac output
4. Most patients tested are not vasoreactive, and of those with a positive response, less than 10% have a long-term response to CCBs (Circulation 2005;111:3105-11).
   a. Patients with a long-term response to CCBs, defined as: New York Heart Association FC I/II with sustained hemodynamic improvement (same or better than with acute testing) after ≥ 1 year on CCB therapy only
   b. These patients are now recognized as a unique entity and recognized as such in the updated clinical classification (Eur Respir J 2019;53:1801913).
   c. CCB use in vasoreactive patients associated with improved survival (N Engl J Med 1992;327:76-81)
   d. If CCBs can be used, agents other than verapamil are recommended to avoid potent negative inotropic effects.
   e. CCB dosing is often supraphysiologic in this setting; therefore, higher incidence of adverse effects (Eur Heart J 2016;37:67-119)
      i. Diltiazem preferred for relative tachycardia at baseline
      ii. Nifedipine or amlodipine preferred for relative bradycardia at baseline

E. Targeted Therapies (J Am Coll Cardiol 2013;62:D60-72)

1. PAH-approved therapies need to be initiated for patients who are either non-vasoreactive or who were vasoreactive but no longer respond to CCBs.
2. A summary of the pharmacotherapy for PAH, including pharmacology, indications, dosing, and special considerations, is in Table 1. In addition, commonly encountered adverse effects and drug-drug interactions with these medications are highlighted in Table 2 and Table 3.
3. PDE5 inhibitor (PDE5i)
   a. Two oral agents have been approved: sildenafil and tadalafil; note that sildenafil is also available intravenously.
   b. Tadalafil has a longer half-life and needs to be dose-adjusted in kidney impairment.
   c. These agents are often used first line in lower-risk patients because of their favorable tolerability, lower costs, and ease of access.
4. sGC stimulator
   a. Riociguat is the first in-class oral agent approved for both PAH and CTEPH.
   b. Acts in synergy with endogenous nitric oxide and directly stimulates sGC, independent of nitric oxide availability

c. Contraindicated with PDE5i
d. Risk Evaluation and Mitigation Strategies (REMS) program requirements before initiation: Procurement by specialty pharmacy
e. Patients with PAH who are not at treatment goal on PDE5i therapy may benefit from changing to riociguat vs. continuing on PDE5i treatment (Lancet Respir Med 2021;9:573-84).

5. ERAs
   a. Three oral agents are approved: bosentan, ambrisentan, and macitentan.
   b. Receptor selectivity differs among agents (ambrisentan is an $ET_A$ antagonist, whereas bosentan and macitentan are nonselective $ET_A$ and $ET_B$ blockers), although clinical significance is unknown.
   c. All ERAs have REMS program requirements before initiation: Procurement by specialty pharmacy
   d. Bosentan is associated with a higher risk of transaminitis (around 10%) than other agents.
   e. Ambrisentan is associated with a higher incidence of peripheral edema.
   f. Macitentan has sustained receptor binding and enhanced tissue penetration; evaluated in a large event-driven trial, it showed significant improvement in a composite of morbidity/mortality (N Engl J Med 2013;369:809-18).
6. Prostacyclins
   a. Infusion therapies
      i. Epoprostenol
         (a) Cornerstone of therapy for advanced disease and high-risk patients
         (b) Epoprostenol had mortality benefit among patients with severe disease (N Engl J Med 1996;334:296-301).
         (c) Most potent prostacyclin
         (d) Intravenous infusion by CADD-Legacy pump and central venous catheter
         (e) Dose titrated depending on patient tolerability
         (f) Flolan and Veletri formulations differ in temperature and light exposure stability, type of diluent required, and frequency of admixture.
            (1) Veletri is considered "thermostable."
            (2) Flolan has alternative pH 12 sterile diluent, which allows for "thermostability."
      ii. Treprostinil
         (a) Analog of epoprostenol with improved stability and longer half-life
         (b) Given subcutaneously or by intravenous infusion
         (c) Subcutaneously by microinfusion pump and small catheter
         (d) Intravenous infusion by CADD-Legacy pump and central venous catheter (similar to epoprostenol)
         (e) Remunity uses a novel SC pump and prefilled cartridges of treprostinil.
         (f) Dose titrated based on patient tolerability
         (g) Preemptive site management (i.e., topical analgesics, anesthetics, anti-inflammatory, and/or antihistamines) may be required with SC therapy because of site pain
         (h) Intravenous infusion associated with a higher risk of gram-negative bloodstream infections than epoprostenol. Consider use of higher pH diluent to reduce this risk (Chest 2012; 141:36-42).
   b. Inhaled therapies
      i. Iloprost and treprostinil
      ii. Iloprost requires administration frequency of six to nine times/day with an average treatment time of 6–12 minutes for each dose.
      iii. Treprostinil is dosed four times daily via Tyvaso Inhalation System.
      iv. Recent FDA approval of new dry-powder inhaled formulation of treprostinil (Tyvaso DPI) and tentative approval of a similar formulation (Yutrepia)

v. Each medication requires a specialized patient-specific delivery device that must be obtained from a specialty pharmacy or the patient.
vi. Maximum doses of inhaled treprostinil about equivalent to lower doses of infusion treprostinil (around 15 ng/kg/minute) on the basis of mean maximum concentrations achieved (J Clin Pharmacol 2004;44:83-8; Pulm Circ 2013;3:116-20)
vii. Stable patients taking lower doses of infusion treprostinil may be transitioned to inhaled therapy if adverse effects (i.e., bloodstream infections, difficulty with parenteral access) are encountered (Pulm Circ 2013;3:116-20).

c. Oral therapies
i. Treprostinil diolamine extended release is the first oral prostacyclin approved for PAH.
ii. Dosing three times daily associated with better tolerability and higher doses than twice daily.
iii. Approved to delay disease progression and to improve exercise capacity (Am J Respir Crit Care Med 2020;201:707-17; Circulation 2013;127:624-33; Chest 2013;144:952-8).
iv. Carefully selected, lower-risk patients may be considered for transition to oral treprostinil or selexipag from infusion or inhaled prostacyclins (J Heart Lung Transplant 2017;36:193-201; J Heart Lung Transplant 2019;38:43-50).

d. All prostacyclin formulations require procurement by specialty pharmacy.

7. Selective prostacyclin receptor (IP) agonist
a. Selexipag is the first in-class oral agent approved for PAH.
b. Mode of action similar to prostacyclin, but a non-prostanoid. IP is a prostanoid receptor in the lungs that regulates vascular tone, platelet activity, and so forth.
c. Evaluated in a large event-driven trial that showed significant improvement in a composite of morbidity/mortality (N Engl J Med 2015;373:2522-33)
d. Procurement by specialty pharmacy

F. Evidence-Based Treatment Algorithm (Eur Respir J 2019;53:1801889).
1. Treatment recommendations based on evidence from randomized controlled trials and classified according to the classes of recommendations and level of evidence
a. The primary efficacy end point for most PAH trials was the 6MWD; other end points commonly evaluated included symptoms, FC, hemodynamics, and time to clinical worsening.
b. Most treatments evaluated in randomized controlled trials were compared with placebo.
c. Sixth WSPH treatment algorithm (Eur Respir J 2019;53:1801889). See Figure 2.
d. Treatment regimen and intensity based on initial risk stratification

G. Combination Therapy
1. Rationale is to target different pathological processes to maximize efficacy and minimize toxicity.
a. Many signaling pathways in PAH (N Engl J Med 2004;351:1425-36)
b. Significant mortality is associated with PAH (Chest 2012;142:448-56).
c. Monotherapy is associated with poor long-term clinical outcomes for most patients (Circulation 2010;122:156-63).

2. Approaches include sequential (stepwise) or up-front combination therapy.
a. Studies with sequential approach are mixed, although trial designs and treatment combinations studied were heterogeneous.
i. Modest increase in exercise capacity (Am J Cardiol 2011;108:1177-82)
ii. Reduction in clinical worsening (Lancet Respir Med 2016;4:291-305)

b. Up-front combination therapy: The Ambrisentan and Tadalafil in Patients with Pulmonary Arterial Hypertension (AMBITION) trial (N Engl J Med 2015;373:834-44) (Table 6)
i. Up-front combination versus pooled monotherapy: Hazard ratio 0.50 (95% confidence interval, 0.35–0.72), $p<0.001$. See Table 6 for dosing information.
ii. Mean treatment duration – 517 days

iii. Adverse effects such as peripheral edema, headache, nasal congestion, and anemia were more common in the combination group than in the pooled monotherapy group. No differences in hypotension, rates of discontinuation, or serious adverse effects
iv. Debate exists regarding whether results can be extrapolated to other in-class medications ("class effect") (Eur Respir J 2016;47:1727-36; Br J Pharmacol 2005;60:107-12).

c. Up-front triple versus dual combination therapy: The Efficacy and Safety of Initial Triple Versus Initial Dual Oral Combination Therapy in Patients With Newly Diagnosed Pulmonary Arterial Hypertension trial (J Am Coll Cardiol 2021;78:1393-403)
i. Up-front triple therapy (macitentan, tadalafil, selexipag) versus up-front dual therapy (macitentan, tadalafil) in patients with newly diagnosed PAH showed no between-group difference in PVR at 26 weeks.

3. Guidelines (Eur Respir J 2019;53:1801889).
a. Sixth WSPH guidelines (Refer to Figure 2, Table 4 and Table 5) for non-vasoreactive patients recommend initial combination therapy for most treatment-naive patients.
i. Low or intermediate risk (initial oral combination therapy). Tables 4 and 5.
ii. High risk (initial combination including IV prostacyclin analogue). Note that epoprostenol has the highest recommendation based on mortality benefit. Tables 4 and 5.

b. Residual role for initial monotherapy (efficacy/safety ratio of initial combination therapy not established):
i. Responders to acute vasoreactivity tests and with WHO FC I/II and sustained hemodynamic improvement after ≥ 1 year on CCB only
ii. Long-term-treated patients with monotherapy (> 5-10 years) who are stable with low-risk profile
iii. Idiopathic PAH patients > 75 years old with multiple risk factors for heart failure with preserved ejection fraction (hypertension, diabetes mellitus, coronary artery disease, atrial fibrillation, obesity)
iv. Patients with suspicion or high probability of pulmonary veno-occlusive disease or pulmonary capillary hemangiomatosis
v. Patients with PAH associated with HIV or portal hypertension or uncorrected congenital heart disease
vi. Patients with very mild disease (e.g., WHO FC I, PVR 3-4 Wood units, mPAP < 30 mm Hg, normal RV by echocardiography)
vii. Combination therapy unavailable or contraindicated (e.g., severe liver disease)
viii. Note that evidence-based first-line monotherapy is not proposed since head-to-head comparisons are lacking. The choice of medication is often based on a variety of factors (i.e., route of administration, adverse effects, drug interaction potential, patient preferences, comorbidities, prescriber experience, and cost).

c. Follow-up therapy after 3-6 months:
i. Continue treatment if low-risk status achieved
ii. For intermediate-risk status, escalate triple combination therapy (or dual therapy if initial monotherapy chosen). Note that the following combinations have the highest recommendation and evidence for sequential treatment: macitentan and sildenafil; riociguat and bosentan; selexipag and ERA and/or PDE5i.
iii. For high-risk status, maximal medical therapy is recommended (triple combination therapy including a SC or IV prostacyclin analogue) and referral for lung transplantation.

d. Transitions to alternative therapy may be considered for a number of reasons, including: to improve adverse effect profile, convenience, or adherence with therapy. In patients not meeting treatment goals, escalation (i.e., oral to infusion therapy) may be necessary to improve patient status. Conversely, de-escalation to less invasive therapy (i.e., infusion to oral therapy) is not recommended except in rare situations and under close expert care because of relative lack of robust evidence.

e. Balloon atrial septostomy for palliation

4. Transitions of care
    a. Complex medication access steps including prior authorization requirements for PAH medications that require a multidisciplinary team
    b. Coordination between critical care and ambulatory care pharmacist can improve TOC related to PAH medication access for patients (Am J Health-Syst Pharm. 2020;77:958-65).
5. Future Directions:
    a. Sotatercept, a novel fusion protein, binds activins and growth differentiation factors to help restore balance between growth-promoting and growth-inhibiting signaling pathways. It was shown to significantly reduce PVR vs. placebo at 24 weeks (N Engl J Med 2021;384:1204-15).

**Patient Cases** *(continued)*

2. According to the current treatment guideline recommendations, which PAH-targeted medication(s) would be most appropriate for the initial management of PAH for H.L.?
    A. Epoprostenol
    B. Sildenafil and macitentan
    C. Riociguat and tadalafil
    D. Sildenafil

3. According to the AMBITION trial, which treatment approach for initial therapy of PAH was associated with improved clinical outcomes?
    A. Up-front combination therapy: tadalafil and ambrisentan
    B. Sequential therapy: tadalafil, followed by addition of ambrisentan
    C. Up-front combination therapy: tadalafil, macitentan, and selexipag
    D. Sequential therapy: epoprostenol, followed by addition of sildenafil

4. When considering the PDE5i class of medications for this patient, which clinical factor is most important in agent selection (sildenafil vs. tadalafil)?
    A. Concurrent nitrate use
    B. Baseline $SaO_2$
    C. Etiology of PAH
    D. Kidney function

Within the first 3 months after the initial clinic visit, H.L. responded well to your initial therapy recommendations. She had an overall improvement in her symptoms and did not require any hospitalizations. She also denied adverse effects with treatment. She is now being seen at the 6-month clinic visit, during which a repeat 6MWD has decreased to 390 m from baseline (460 m). Her symptoms remain relatively stable, but a repeat TTE reveals moderate tricuspid regurgitation with mild to moderately reduced RV function. The physician is now considering escalation of her treatment regimen.

5. Which statement is most accurate with respect to prostacyclin analogues and selective IP receptor agonists?
    A. Iloprost is an inhaled prostacyclin that is administered four times daily.
    B. Treprostinil is available as parenteral, inhaled, and oral formulations.
    C. Treprostinil diolamine extended release is a suitable replacement for infusion prostacyclin therapy for most patients.
    D. Selexipag is expected to be better tolerated than prostacyclins.

**Patient Cases** *(continued)*

6. Which medication poses the most significant drug interaction potential with treprostinil?
   A. Terazosin
   B. Bosentan
   C. Gemfibrozil
   D. Simvastatin

H. Treatment of the Acutely Decompensated Patient with PAH
   1. Acute RV failure (Figure 3)
      a. Definition – Clinical syndrome of right-sided heart failure usually accompanied by hemodynamic findings of low cardiac output and high RV filling pressures (Nat Rev Cardiol 2013;10:204-18)
      b. Treatment should focus on reducing PVR (RV afterload) and supporting RV function.
      c. Consider early use of inotropes if impaired kidney function, central venous pressure 15 mm Hg or greater, cardiac index less than 2 L/minute/$m^2$
      d. Positive inotropes for low cardiac output and to support RV function (Anesth Analg 2003;96:1603-16)
         i. Inotropic vasodilators preferred if blood pressure is stable
            (a) Dobutamine or milrinone
            (b) Milrinone offers potential advantages compared with dobutamine because of milrinone's greater vasodilatory properties; however, caution with accumulation in kidney impairment
            (c) Titration according to cardiac index or pulmonary artery mixed venous oxygen saturation ($SvO_2$).
         ii. Vasopressors may be needed if blood pressure is low.
            (a) Norepinephrine or vasopressin preferred
            (b) Norepinephrine provides mixed α and β effects.
            (c) Vasopressin associated with pulmonary vasodilator effects
            (d) Epinephrine may be required if cardiac output is severely reduced.
            (e) Titration according to blood pressure (e.g., mean arterial pressure greater than 65 mm Hg)
      e. Central venous pressure (RV preload) should be optimized so that volume overload and septal shifting leading to impaired LV filling are avoided (Nat Rev Cardiol 2013;10:204-18). Use caution with diuresis if LV filling pressure is low (i.e., PCWP less than 10 mm Hg, renal hypoperfusion, or systemic hypotension).
      f. Treat atrial arrhythmias. Loss of atrioventricular synchrony has harmful effects on RV function.
      g. Pulmonary vasodilators to unload the RV
         i. Parenteral prostacyclin – Intravenous epoprostenol is recommended over treprostinil because of more rapid response, ability to titrate with shorter intervals, and higher potency.
         ii. Inhaled nitric oxide (N Engl J Med 2005;353:2683-95)
            (a) Advantages include pulmonary selectivity, fewer systemic effects such as hypotension
            (b) Disadvantages are costs and delivery system needed
         iii. Inhaled epoprostenol may be a less costly alternative for patients with PH, refractory hypoxemia, or right heart dysfunction (J Thorac Cardiovasc Surg 2004;127:1058-67).
         iv. Initial triple therapy with IV epoprostenol, PDE5i, and ERA in newly diagnosed patients with RV failure has favorable results (Eur Respir J 2014;43:1691-97).
      h. Mechanical RV support (Nat Rev Cardiol 2013;10:204-18)
         i. Venoarterial extracorporeal membrane oxygenation (VA ECMO) may be required.
         ii. Balloon atrial septostomy
         iii. More permanent devices, such as RV assist device or total artificial heart
         iv. Definitive therapy is heart, lung, or combined transplantation.

2. Sepsis/septic shock
    a. Maintain mean arterial pressure greater than mPAP.
    b. Keep central venous pressure at around 10–15 mm Hg.
    c. Consider a Swan-Ganz catheter.
    d. Broad-spectrum antibiotics.
    e. Removal of infected Hickman or peripherally inserted central catheter line.
    f. Avoid intubation, if possible, and consider early VA or venovenous ECMO.
    g. Early initiation of vasopressor support: Maintain greater than 10 mm Hg pressure gradient between systolic blood pressure and pulmonary artery systolic pressure or systemic vascular resistance/PVR ratio greater than 1.
    h. Vasopressin (Anesth Analg 2001;93:7-13) or norepinephrine may be considered for vasopressor support.

**Patient Cases** *(continued)*
H.L is now being seen at her 12-month follow-up clinic visit. She was initiated on inhaled treprostinil at the 6-month visit (titrated to 9 breaths four times daily over several weeks) and has been adherent to this regimen since then. However, her symptoms have deteriorated such that she becomes short of breath even at rest. Her 6MWD is also further reduced to 240 m, her TTE reveals moderate to severely reduced RV function, and a repeat RHC now reveals the following: right atrial artery pressure 14 mm Hg, pulmonary artery pressure 76/35 mm Hg with mPAP of 49 mm Hg, PCWP 12 mm Hg, PVR 10 Wood units, and cardiac index 1.8 L/minute/$m^2$. Her blood pressure at today's visit is 96/55 mm Hg with a heart rate of 115 beats/minute and an $Sao_2$ of 90% on 3 L.

7. Which would be the next most appropriate step to treat this patient?
    A. Discontinue inhaled treprostinil and initiate treprostinil intravenously.
    B. Discontinue inhaled treprostinil and initiate epoprostenol intravenously.
    C. Discontinue inhaled treprostinil and initiate selexipag.
    D. Increase inhaled treprostinil to 12 breaths four times daily.

8. Which additional intervention would be most appropriate to support her RV function in the hospital setting?
    A. Milrinone 0.25 mcg/kg/minute intravenous infusion with increases according to cardiac index
    B. Dobutamine 2.5 mcg/kg/minute intravenous infusion titrated to blood pressure
    C. Epinephrine 0.05 mcg/kg/minute intravenous infusion titrated to blood pressure
    D. Vasopressin 0.04 units/min intravenous infusion titrated to blood pressure

**Table 1.** Overview of Pharmacotherapy for PAH

| Medication | Class | Indication | Dosing | Pharmacologic Properties and Other Special Considerations |
|---|---|---|---|---|
| Sildenafil (Revatio) | PDE5i | Improve exercise ability and delay clinical worsening | 20 mg PO TID<br>10 mg IV TID (short-term use in patients unable to take PO) | N /A |
| Tadalafil (Adcirca) | PDE5i | Improve exercise ability | 40 mg/day PO<br>-Initiate 20 mg if renal/hepatic impairment or concurrent ritonavir<br>-Avoid if CrCl < 30 mL/min/1.73 $m^2$ | N/A |

**Table 1.** Overview of Pharmacotherapy for PAH (*continued*)

| Medication | Class | Indication | Dosing | Pharmacologic Properties and Other Special Considerations |
|---|---|---|---|---|
| Bosentan (Tracleer) | ERA | Improve exercise ability and decrease clinical worsening | 62.5 mg PO BID; then 125 mg PO BID after 4 wk (< 40 kg: Initial and maintenance: 62.5 mg PO BID) | -Dual antagonist of ET-$1_A$ and ET-$1_B$ receptors<br>-Tracleer and bosentan REMS programs: Baseline and monthly pregnancy testing and liver function testing required<br>-Specialty pharmacy for procurement |
| Ambrisentan (Letairis) | ERA | Improve exercise ability and delay clinical worsening; in combination with tadalafil to reduce the risks of disease progression and hospitalization for worsening PAH and to improve exercise ability | 10 mg/day PO | -Selective ET-$1_A$ antagonist<br>-Letairis and ambrisentan REMS programs: Baseline and monthly pregnancy testing required<br>-Specialty pharmacy for procurement |
| Macitentan (Opsumit) | ERA | Delay progression of PAH | 10 mg/day PO | -Tissue selective<br>-Lipophilic<br>-Dual antagonist of ET-$1_A$ and ET-$1_B$ receptors<br>-Opsumit REMS: Baseline and monthly pregnancy testing required<br>-Specialty pharmacy for procurement |
| | | | | |
| Iloprost (Ventavis) | Prostacyclin | Improve a composite end point consisting of exercise tolerance, symptoms, and lack of deterioration | -Initiate 2.5 mcg; then titrate to 5 mcg inhaled as tolerated and administer six to nine times daily (minimum of 2 hr between doses during waking hours) (maximum 45 mcg/day) | -Only administered by I-neb AAD (adaptive aerosol delivery) system<br>-Use higher-concentration ampule (20 mcg/mL) for patients with extended treatment time or at 5-mcg dose<br>-Specialty pharmacy for procurement |
| Treprostinil (Tyvaso) | Prostacyclin | Improve exercise ability | Tyvaso-specific:<br>-3 breaths four times daily<br>-Titrate by 3 breaths every 1–2 wk to 9 breaths four times daily<br>Tyvaso DPI-specific:<br>-One 16-mcg cartridge per treatment four times daily<br>-Titrate by 16 mcg every 1–2 wk to 48–64 mcg four times daily | -Administered by Tyvaso Inhalation System or Tyvaso DPI<br>-Specialty pharmacy for procurement |

**Table 1.** Overview of Pharmacotherapy for PAH (*continued*)

| Medication | Class | Indication | Dosing | Pharmacologic Properties and Other Special Considerations |
|---|---|---|---|---|
| Treprostinil (Remodulin) | Prostacyclin | Diminish symptoms associated with exercise and reduce the rate of clinical deterioration for patients who require transition from epoprostenol (Flolan) | 1.25 ng/kg/min SC or IV titrated to dose-limiting adverse effects (usual range 40–80 ng/kg/min, but depends on many factors such as risk status, tolerability, disease etiology)<br>-Decrease initial dose to 0.625 ng/kg/min for patients with mild to moderate hepatic insufficiency<br>-Suggested dosing titration of 1.25 ng/kg/min per week for the first 4 wk of treatment; then 2.5 ng/kg/min per week<br>(*Note: Significant inter- and intrapatient variability in response*) | -Half-life 4 hr<br>-Backup pump to avoid abrupt withdrawal of therapy<br>-Stable at room temperature<br>-Specialty pharmacy for procurement<br>-SC: Undiluted, every 48- to 72-hr syringe change; administer by SC pump (CADD-MS3)<br>-SC (treprostinil): Can be prepared by patient or caregiver or sent as prefilled cartridges by specialty pharmacy<br>-IV: Requires further dilution, every 48-hr cassette change; administer by CADD-Legacy pump through tunneled central venous catheter |
| Epoprostenol IV (Flolan, Veletri) | Prostacyclin | Improve exercise capacity | -2 ng/kg/min titrated to dose-limiting adverse effects (usual range 20–40 ng/kg/min, but depends on many factors such as risk status, tolerability, disease etiology)<br>-Suggested dosing titration of 1- to 2-ng/kg/min increments at intervals of ≥ 15 min depending on clinical response (*Note: Significant inter- and intrapatient variability in response*) | -Half-life 4–6 min<br>-Backup cassette and pump to avoid abrupt withdrawal of therapy<br>-Protect from light<br>-Administer by CADD-Legacy pump through tunneled central venous catheter<br>-Specialty pharmacy for procurement<br>-Flolan-specific: (1) ice packs needed unless newer pH 12 sterile diluent for Flolan is used; (2) reconstitution/dilution with either sterile diluent for Flolan or newer pH 12 sterile diluent for Flolan; (3) cassette changes typically occur every 24 hr (exceptions include 8-hr stability at room temperature when using sterile diluent for Flolan and extended stability with newer pH 12 sterile diluent for Flolan); (4) newer pH 12 sterile diluent for Flolan also allows for preparation of cassettes in advance as needed<br>Veletri-specific: (1) no ice packs needed (thermostable); (2) reconstitution/dilution with either 0.9% sodium chloride or sterile water; (3) extended stability allows for extended administration times and preparation of cassettes in advance as needed |

**Table 1.** Overview of Pharmacotherapy for PAH (*continued*)

| Medication | Class | Indication | Dosing | Pharmacologic Properties and Other Special Considerations |
|---|---|---|---|---|
| Treprostinil diolamine extended release (Orenitram) | Prostacyclin | Delay disease progression and improve exercise capacity | 0.125 mg PO TID or 0.25 mg PO BID; titrate by 0.125 mg TID or by 0.25 mg BID, every 3–4 days or longer | Administer with food to improve bioavailability (high-calorie, high-fat meal)<br>-If ≥ 2 doses missed, may need to start at a lower dose and re-titrate<br>-Specialty pharmacy for procurement |
| | | | | |
| Riociguat (Adempas) | sGC stimulator | Improve exercise capacity and WHO FC in patients with persistent/ recurrent CTEPH (after surgery or for inoperable disease) and improve exercise capacity and WHO FC and delay clinical worsening in patients with PAH | 1 mg PO TID; then titrate by 0.5 mg every 2 wk up to 2.5 mg PO TID<br>-Start at 0.5 mg PO TID if risk of hypotension or with concomitant strong cytochrome P450 [CYP] and P-gp inhibitors<br>-Avoid if CrCl < 15 mL/ min/1.73 $m^2$ or on dialysis | -Adempas REMS (pregnancy test at baseline and monthly)<br>-If dose interruption for ≥ 3 days, re-titrate<br>-Specialty pharmacy for procurement |
| | | | | |
| Selexipag (Uptravi) | Selective IP receptor agonist | Delay disease progression and reduce risk of hospitalization for PAH | 200 mcg PO BID, titrated weekly as tolerated to maximum of 1600 mcg PO BID<br>-Start at 200 mcg daily, then increase by 200 mcg daily at weekly intervals for moderate hepatic impairment | Mode of action similar to prostacyclin, but a non-prostanoid<br>-If dose interruption for ≥ 3 days, reinitiate at lower dose and then re-titrate<br>-Specialty pharmacy for procurement |

BID = twice daily; CrCl = creatinine clearance; ERA = endothelin receptor antagonist; ET-1 = endothelin-1; IV = intravenous(ly); LFT = liver function test; PDE5i = phosphodiesterase type 5 inhibitor; P-gp = P-glycoprotein; PO = oral(ly); SC = subcutaneous(ly); sGC = soluble guanylate cyclase; TID = three times daily.

**Table 2.** Adverse Reactions Associated with PAH Pharmacotherapy (Eur Heart J 2016;37:67-119)

| Medication/Class | Adverse Effects |
|---|---|
| ERAs | Headache, flushing, peripheral edema, nasal congestion, sinusitis, transaminitis, liver injury, anemia, teratogenicity |
| PDE5i | Headache, dyspepsia, flushing, epistaxis, insomnia, hypotension, visual changes, hearing impairment |
| Prostacyclins | Nausea, vomiting, diarrhea, flushing, jaw pain, headache, rash, erythema, hypotension, leg pain<br>– Inhaled: Cough, throat irritation |
| Riociguat | Headache, dizziness, dyspepsia, gastroesophageal reflux, nausea, diarrhea, vomiting, hypotension, anemia, constipation, teratogenicity |
| Selexipag | Headache, diarrhea, jaw pain, nausea, myalgia, vomiting, extremity pain, flushing |

ERAs = endothelin receptor antagonists; PDE5i = phosphodiesterase type 5 inhibitors.

**Table 3.** Drug Interactions with PAH Pharmacotherapy (Eur Heart J 2016;37:67-119)

| Medication/Class | Interactions |
|---|---|
| ERAs | Bosentan: Cyclosporine, glyburide, sildenafil, simvastatin/lovastatin/atorvastatin, warfarin, hormonal contraceptives (dual methods of contraception advised), ketoconazole, ritonavir, rifampin<br>Ambrisentan: Cyclosporine<br>Macitentan: Ketoconazole, ritonavir, rifampin |
| PDE5i | Strong CYP3A4 inhibitors/inducers, nitrates, α-blockers, alcohol, riociguat |
| Prostacyclins | Vasodilators, antiplatelets, anticoagulants<br>– Treprostinil: Gemfibrozil, rifampin |
| Riociguat | Strong CYP and P-gp inhibitors/inducers, PDE5i, nonspecific PDEi medications (i.e., theophylline, dipyridamole), nitrates, antacids, smoking |
| Selexipag | CYP2C8 inhibitors (e.g., clopidogrel, deferasirox, teriflunomide) and inducers (e.g., rifampin) |

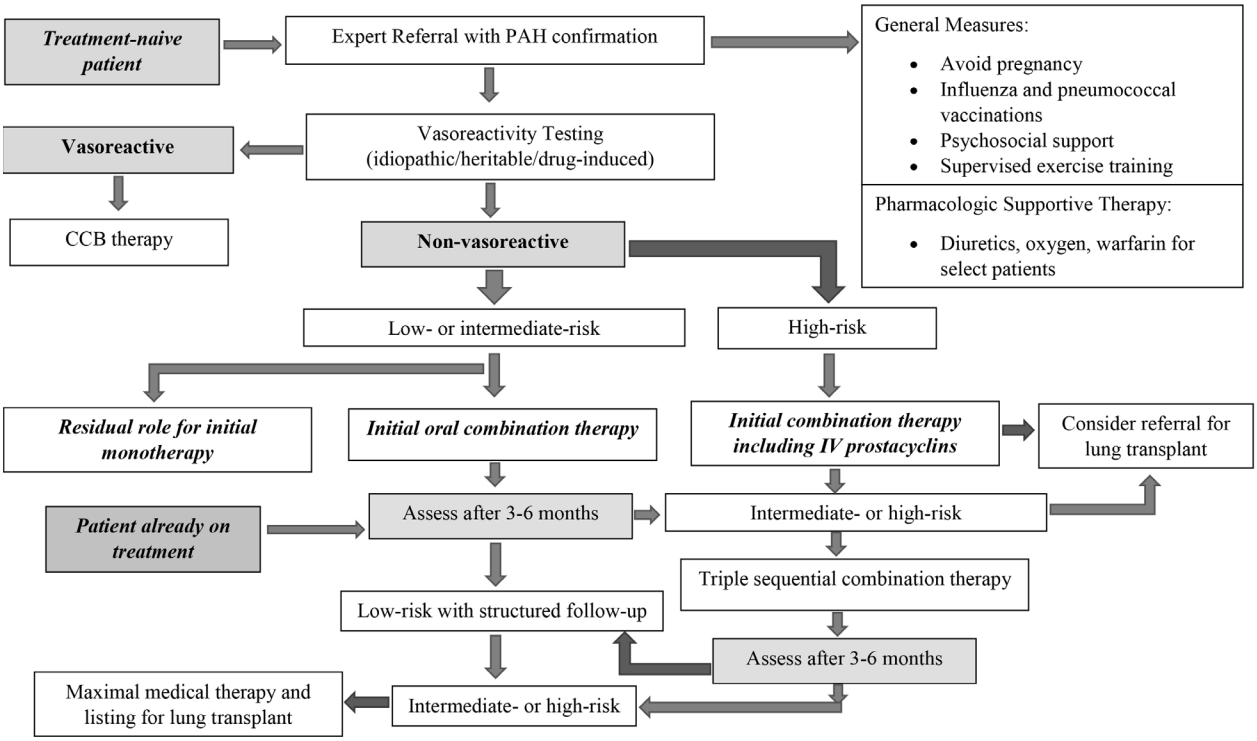


**Figure 2.** Sixth World Symposium Pulmonary Arterial Hypertension Treatment Algorithm (Eur Respir J 2019; 53:1801889).

**Table 4.** Treatment Guidelines – Initial Combination Therapy for PAH (Eur Heart J 2016;37:67-119)

| Treatment | Class and Level of Recommendation | | | | | |
|---|---|---|---|---|---|---|
| | WHO FC II | | WHO FC III | | WHO FC IV | |
| Ambrisentan + tadalafil | I | B | I | B | IIb | C |
| Other ERA + PDE5i | IIa | C | IIa | C | IIb | C |
| Bosentan + sildenafil + IV epoprostenol | | | IIa | C | IIa | C |
| Bosentan + IV epoprostenol | | | IIa | C | IIa | C |
| Other ERA or PDE5i + SC treprostinil | | | IIb | C | IIb | C |
| Other ERA or PDE5i + other IV prostacyclin analogues | | | IIb | C | IIb | C |

ERA = endothelin receptor antagonist; IV = intravenous(ly); PDE5i = phosphodiesterase type 5 inhibitors; SC = subcutaneous(ly).

**Table 5.** Classes of Recommendations and Level of Evidence (Eur Heart J 2016;37:67-119)

| Class of Recommendations | Level of Evidence |
|---|---|
| I Evidence and/or general agreement that a given treatment or procedure is beneficial, useful, effective | A Data derived from multiple randomized clinical trials or meta-analyses |
| II Conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of the given treatment or procedure | B Data derived from a single randomized clinical trial or large nonrandomized studies |
| IIa Weight of evidence/opinion is in favor of usefulness/efficacy | C Consensus of opinion of the experts and/or small studies, retrospective studies, registries |
| IIb Usefulness/efficacy is less well established by evidence/opinion | |
| III Evidence of general agreement that the given treatment or procedure is not useful/effective and, in some cases, may be harmful | |

**Table 6.** AMBITION Trial

| Design | Patients (n=500) | Groups | Primary End Point |
|---|---|---|---|
| Randomized, double-blind, multicenter, multinational trial | Incident PAH<br>WHO FC II–III<br>Idiopathic, heritable, associated with: connective tissue diseases, drugs, HIV, and congenital heart diseases | Tadalafil + ambrisentan vs. monotherapy with either<br>Dosing scheme:<br>Ambrisentan 5 mg daily x 8 wk; then 10 mg daily<br>Tadalafil 20 mg daily x 4 wk; then 40 mg daily | Time to clinical failure: Death from any cause, hospitalization because of worsening PAH, disease progression, unsatisfactory long-term clinical response |

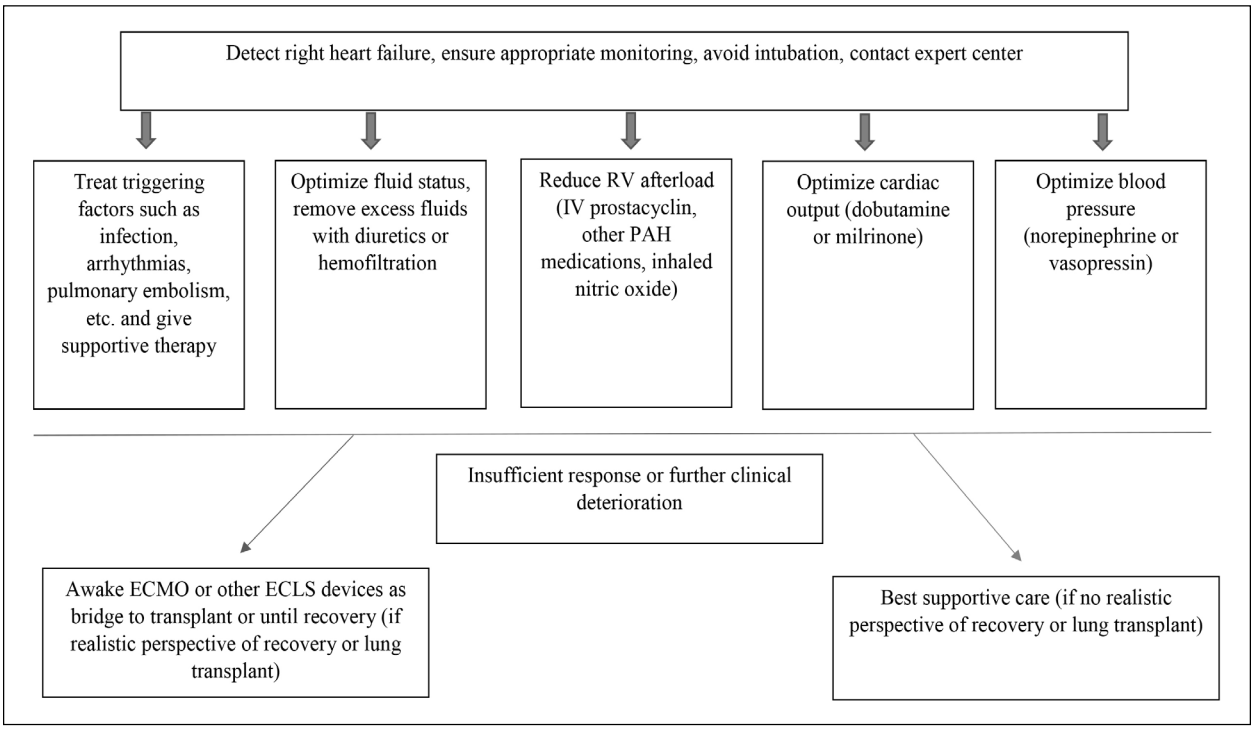


**Figure 3.** Treatment Algorithm for Patients with Severe Right-Sided Heart Failure (Eur Respir J 2019;53:1801906).
ECLS = extracorporeal lung support; ECMO = extracorporeal membrane oxygenation.

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## ANSWERS AND EXPLANATIONS TO PATIENT CASES

**1. Answer: C**

Answer C is correct. The most likely cause of the patient's PAH is connective tissue disease, which in her case may include contributions from scleroderma, Raynaud phenomenon, and Sjögren syndrome. Connective tissue disorders are the most common cause of PAH. These diseases are associated with PAH and categorized as WHO group 1. The patient cannot have idiopathic disease when a likely etiology is identified (Answer B is incorrect). Coronary artery disease could lead to WHO group 2 PH, but this would not be a cause of PAH (Answer A is incorrect). Chronic kidney disease is not associated with PAH, but it could be a potential contributor to WHO group 5 PH (Answer D is incorrect).

**2. Answer: B**

The patient has WHO FC II symptoms (dyspnea on exertion and fatigue with ordinary activities). According to the Sixth World Symposium guidelines, initial combination therapy is appropriate for most patients. Because she exhibits low-to-intermediate risk features of PAH, initial oral combination therapy is recommended. Therefore, Answer B, sildenafil and macitentan, is the best answer. Answers C is not appropriate because riociguat and tadalafil should not be used together (hypotensive risk as they both target the NO pathway). Answer A would be appropriate if the patient presented with high-risk features, but should also include background oral therapy. Finally, Answer D is incorrect because the patient does not meet any of the suggested criteria for initial monotherapy.

**3. Answer: A**

Answer A is correct. The AMBITION trial showed that up-front combination therapy with tadalafil and ambrisentan unequivocally improved clinical outcomes compared with monotherapy with either agent. This study did not evaluate stepwise therapy (Answers B and D are incorrect). Up-front triple combination therapy was not studied in the AMBITION trial (Answer C is incorrect).

**4. Answer: D**

Answer D is correct. Kidney function is partly responsible for the elimination of tadalafil; therefore, CrCl is an important determinant of dose adjustment (CrCl 31–80 mL/minute/1.73 $m^2$) and contraindication (CrCl less than 30 mL/minute/1.73 $m^2$). Conversely, the pharmacokinetics of sildenafil are not significantly affected in the presence of kidney impairment. Concurrent nitrate use is a contraindication to the use of either agent (Answer A is incorrect). Baseline $Sa_{O_2}$ is not relevant to PDE5i agent selection (Answer B is incorrect). Finally, the underlying etiology of PAH would not help distinguish the use of either agent. They have both been studied for various subsets of PAH, including idiopathic and associated conditions such as connective tissue diseases (Answer C is incorrect).

**5. Answer: B**

Answer B is correct. Treprostinil is available in many formulations, including inhaled and oral. Iloprost is an inhaled prostacyclin analog, but it is dosed six to nine times per day (Answer A is incorrect). Treprostinil diolamine extended release is indicated to improve exercise capacity in patients with WHO class II or III symptoms. Although small studies have shown the feasibility of changing from treprostinil infusion in carefully selected patients, it has not been shown to be a suitable alternative to prostacyclin infusion for most patients (Answer C is incorrect). Selexipag is a selective IP receptor agonist that targets the same receptors as prostacyclins (even though it is chemically unique from prostacyclins). Head-to-head studies of selexipag and prostacyclins have not yet been conducted; therefore, the relative safety of these agents is currently unknown. Despite the selectivity, clinical studies of selexipag have yielded types of adverse effects similar to what would be expected with prostacyclins (Answer D is incorrect).

**6. Answer: C**

Answer C is correct. Treprostinil is a substrate of the CYP 2C8 and 2C9 isoenzymes. Gemfibrozil is a strong inhibitor of this isoenzyme, which increases the exposure of treprostinil. The other medications listed (terazosin, bosentan, and simvastatin) are not expected to interact with treprostinil (Answers A, B, and D are incorrect).

**7. Answer: B**

Answer B is correct. The patient now has WHO FC IV symptoms and has had clinical deterioration, as evidenced by worsening 6MWD performance, echocardiographic features of RV dysfunction, and hemodynamics. The most appropriate recommendation according to the Sixth World Symposium on PAH guidelines is to initiate intravenous epoprostenol, which has survival benefits in patients with advanced disease. Treprostinil intravenously could be considered as an alternative, but it is less potent and cannot be titrated as quickly as epoprostenol. In addition, treprostinil has not been extensively studied in patients with WHO FC IV symptoms (Answer A is incorrect). Selexipag has not been studied in patients with advanced disease and should not be viewed as an alternative to infusion therapy at this time (Answer C is incorrect). An increase in treprostinil inhaled to a supratherapeutic dose regimen is not evidence based and would not be expected to offer any benefit in the context of advanced disease (Answer D is incorrect).

**8. Answer: A**

Answer A is correct. Milrinone offers the advantages of positive inotropy to support the RV, together with vasodilatation of the pulmonary arteries. Milrinone should be used on the basis of cardiac index or pulmonary $Svo_2$ as opposed to blood pressure. Dobutamine would also be reasonable for inotropic support; however, like milrinone, dobutamine should be titrated according to cardiac index rather than blood pressure (Answer B is incorrect). Epinephrine could be considered if the cardiac index were sufficiently low or if the blood pressure were too low to tolerate milrinone or dobutamine. In this case, however, epinephrine would not be the best choice (Answer C is incorrect). Finally, vasopressin is a pure vasopressor and therefore would not be useful for providing inotropic support of the RV (Answer D is incorrect).

## ANSWERS AND EXPLANATIONS TO SELF-ASSESSMENT QUESTIONS

**1. Answer: B**

Answer B is correct. The patient's clinical presentation is most consistent with acute RV failure (echocardiogram revealed RV pressures and volume overload and moderate to severely reduced RV function) secondary to severe PAH. The diagnosis of PAH is confirmed by RHC (mPAP of 55 mm Hg with a PCWP of 8 mm Hg; also noted PVR of 21 Wood units). The RHC also revealed an elevated RV preload (RA pressure of 14 mm Hg and reduced cardiac index of 1.4 L/minute/$m^2$). Although the patient is in cardiogenic shock with evidence of RV failure, the underlying cause is PAH, not left-sided heart failure (Answer A is incorrect). The patient is not in LV failure, as evidenced by a normal PCWP, and PAH is causing RV failure (Answer C is incorrect). In this case, the patient's clinical presentation of PAH is not uncomplicated because she is in shock and requiring an inotrope. Although she may require more than one agent to support her RV and treat PAH, the role of combination (oral) therapy is reserved for either sequential or up-front therapy in more stable patients (WHO FC II–III symptoms), making Answer D incorrect.

**2. Answer: A**

Answer A is correct. The patient's WHO group is 1, referring to PAH. This diagnosis was confirmed by the RHC. The normal left-sided filling pressures (PCWPs) make Answer B incorrect. The patient has no history of underlying lung disease other than asthma, and the chest CT scan was unremarkable, making group 3 disease unlikely (Answer C is incorrect). Finally, her ventilation-perfusion scan revealed low probability for CTEPH (Answer D is incorrect).

**3. Answer: D**

Answer D is correct. The patient's clinical presentation is most consistent with WHO FC IV symptoms, given her complaints of difficulty breathing when at rest. Answers A–C are incorrect because they refer to symptoms that occur with greater levels of activity or exertion.

**4. Answer: C**

Answer C is correct. Because of the patient's strong family history of PAH (mother with diagnosis) and confirmation of the presence of the *BMPR2* mutation in this patient, the most likely etiology is heritable. Idiopathic disease implies the lack of another identifiable cause (Answer A is incorrect). Heart failure is not an associated disease in the context of conditions linked to PAH. Rather, heart failure as a cause would be categorized as WHO group 2 (Answer B is incorrect). Finally, the patient has no history of drug- or toxin-induced PAH (Answer D is incorrect).

**5. Answer: D**

Answer D is correct. The patient's RHC reveals a low cardiac index and very high pulmonary artery pressures and PVR; therefore, an inotrope with vasodilatory effects would be most appropriate. The patient is already receiving dopamine, which has moderate inotropic effects with a greater potential for tachyarrhythmias than other agents (and the patient's current heart rate is 122 beats/minute). Therefore, Answer A is incorrect. Vasopressin could be considered to increase the systemic vascular resistance/PVR ratio for blood pressure support; however, this would not provide inotropic support for the RV (Answer B is incorrect). Sildenafil is a pulmonary vasodilator that would help lower pulmonary artery pressures and unload the RV; however, sildenafil should only be used as a short-term alternative to oral sildenafil and not in lieu of a positive inotrope (Answer C is incorrect).

**6. Answer: B**

Answer B is correct. Epoprostenol is the preferred treatment for WHO FC IV symptoms and for treatment of the decompensated patient with RV failure caused by PAH. Epoprostenol is the most potent prostacyclin, has a rapid onset, and is recommended in the PAH guidelines for this situation, according to prior studies. Inhaled treprostinil is not sufficiently potent relative to parenteral therapy and is thus not recommended for severe PAH with RV failure (Answer A is incorrect). Treprostinil could be considered, but it is less preferred in the acute setting because of its longer duration of action and inability to be rapidly titrated compared with epoprostenol. (Answer C is incorrect). Bosentan is also not recommended for acute RV failure in patients with WHO FC IV symptoms (Answer D is incorrect).

**7. Answer: A**

Answer A is correct. Jaw pain is a classic adverse effect that occurs with the prostacyclin class. Both transaminitis and teratogenicity are class effects related to ERAs (Answers B and C are incorrect), whereas changes in vision may occur with the PDE5i class (Answer D is incorrect).

**8. Answer: C**

Answer C is correct. The only reasonable alternative in this setting would be treprostinil. This prostacyclin is a derivative of epoprostenol that can be administered by the continuous subcutaneous route. This formulation does not require an indwelling central venous catheter for administration, unlike epoprostenol, thereby mitigating the patient's concerns with bloodstream infection. Of note, treprostinil may need to be gradually titrated because it is not as potent as epoprostenol and because of the severity of the patient's disease. Avoiding infusion therapy using inhaled iloprost or oral riociguat would not be appropriate because these agents do not offer the same degree of benefit and have not been proven effective in advanced PAH or as an alternative to epoprostenol therapy (Answers A and B are incorrect). Similarly, oral therapy with treprostinil is inappropriate in this setting (Answer D is incorrect). Using oral therapy as an alternative to epoprostenol infusion therapy has not been studied and would not be expected to provide equivalent clinical effects.

**9. Answer: A**

Answer A is correct. All prostacyclins, including treprostinil, exert antiplatelet effects. Therefore, warfarin may interact through additive effects on bleeding risk. Both cyclosporine and glyburide are contraindicated with bosentan because of the risk of hepatotoxicity, but they do not interact with treprostinil (Answers B and C are incorrect). There is no basis or evidence for an interaction between albuterol and treprostinil (Answer D is incorrect).

**10. Answer: A**

Answer A is correct. A 6MWD target greater than 440 m is recommended as part of a treat-to-target approach for PAH management. The RV size and function, rather than the LV markers, are important determinants of outcome and provide additional treatment goals (Answer B is incorrect). The threshold for 6MWD is not high enough (greater than 300 m) to be a treatment goal, as identified earlier (Answer C is incorrect). Finally, the goal for WHO FC symptoms should be I or II as opposed to II or III (Answer D is incorrect).

# Specialized Topics in Cardiovascular Disease

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# Specialized Topics in Cardiovascular Disease

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**Learning Objectives**

1. Recommend empiric antibiotic therapy for patients with suspected infective endocarditis (IE).
2. Develop a therapeutic plan regarding medication therapy for patients with IE or patients requiring prophylactic therapy for IE prevention.
3. Identify patients who require IE prophylactic therapy.
4. Develop a treatment plan for patients with pericarditis.
5. Recommend appropriate therapy for patients with myocarditis.
6. Plan a medication therapy regimen for patients with valvular heart disease.

**Abbreviations in This Chapter**

| | |
|---|---|
| ACE | Angiotensin-converting enzyme |
| AF | Atrial fibrillation |
| AR | Aortic regurgitation |
| ARB | Angiotensin II receptor blocker |
| AS | Aortic stenosis |
| AVR | Aortic valve replacement |
| DOAC | Direct oral anticoagulant |
| ECG | Electrocardiography |
| ECMO | Extracorporeal membrane oxygenation |
| HACEK | *Haemophilus* spp., *Aggregatibacter* spp., *Cardiobacterium hominis*, *Eikenella corrodens*, and *Kingella* spp. |
| IE | Infective endocarditis |
| LV | Left ventricle/ventricular |
| MR | Mitral regurgitation |
| MRSA | Methicillin-resistant *Staphylococcus aureus* |
| MS | Mitral stenosis |
| NSAID | Nonsteroidal anti-inflammatory drug |
| PWID | Person/People who inject drugs |
| TAVI | Transcatheter aortic valve implantation |
| TTE | Transthoracic echocardiography |
| VHD | Valvular heart disease |
| VGS | Viridans group streptococci |
| VKA | Vitamin K antagonist |

**Self-Assessment Questions**

*Answers and explanations to these questions can be found at the end of this chapter.*

1. J.T. is a 68-year-old man who presents with fever, chills, and acute decompensated heart failure. He is given a diagnosis of infective endocarditis (IE) involving a mechanical mitral valve. Current laboratory values are as follows: sodium 138 mEq/L, potassium 3.8 mEq/L, chloride 108 mEq/L, carbon dioxide 27 mmol/L, blood urea nitrogen (BUN) 24 mg/dL, serum creatinine (SCr) 1.4 mg/dL, glucose 123 mg/dL, and white blood cell count (WBC) 16.8 x $10^3$ cells/$mm^3$ with 82% neutrophils and 5% bands. He has a history of anaphylaxis to penicillin. Three of four blood cultures are positive for methicillin-resistant *Staphylococcus aureus* (MRSA). Which is the best antibiotic regimen for J.T.'s IE?
   A. Nafcillin plus rifampin plus gentamicin.
   B. Ampicillin plus ceftriaxone.
   C. Vancomycin plus rifampin plus gentamicin.
   D. Vancomycin plus gentamicin.

2. F.G. is a 46-year-old woman who has completed 1 week of penicillin G plus gentamicin in the hospital for uncomplicated native valve IE caused by penicillin-resistant viridans group streptococci (minimum inhibitory concentration [MIC] of 0.5 mcg/mL or greater). She is hemodynamically stable and has no acute or chronic organ dysfunction. She gets a rash from fluoroquinolones. She works from home and has good support from her husband and children. Which best depicts what F.G. is a candidate for regarding IE therapy?
   A. Give a 2-week course of current therapy.
   B. Give outpatient parenteral antimicrobial therapy.
   C. Change to ceftriaxone alone.
   D. Give outpatient oral antimicrobial therapy.

3. For which procedure would a patient with a mechanical mitral valve most require IE prophylaxis?
   A. Routine dental cleaning.
   B. Elective plastic surgery.
   C. Screening colonoscopy.
   D. Infected renal calculus removal.

4. O.F. is a 23-year-old man from India who presents with 3 days of worsening chest pain. He is found to have a pericardial friction rub, widespread PR-segment depressions on electrocardiography (ECG), elevated C-reactive protein and erythrocyte sedimentation rate, and mildly elevated troponin I and the MB form of creatinine kinase. He has no fever, and his WBC is normal. His chest radiography is normal, a transthoracic echocardiography (TTE) reveals no pericardial effusion, and his HIV screening is negative. He is admitted for acute pericarditis and to rule out myocardial infarction. Which would be best to use in O.F.'s treatment regimen for acute pericarditis?
   A. Aspirin.
   B. Colchicine.
   C. Intrapericardial tissue plasminogen activator.
   D. Azathioprine.

5. J.K. is a 16-year-old female adolescent with acute fulminant viral myocarditis. On initial presentation 1 week ago, she rapidly decompensated and progressed to hemodynamically unstable dilated cardiomyopathy. Extracorporeal membrane oxygenation (ECMO) was initiated on hospital day 2, together with vasopressor support to maintain cardiac output and hemodynamics. Which therapy would most likely benefit J.K.'s myocarditis?
   A. Antiviral.
   B. Corticosteroids.
   C. Intravenous immunoglobulin.
   D. Cyclosporine.

6. I.W. is a 63-year-old African American woman with stage B calcific aortic stenosis (AS) and reduced left ventricular (LV) end diastolic volume. Her medical history is significant for depression and hyperlipidemia. Her current medications include sertraline 50 mg orally daily, rosuvastatin 10 mg orally daily, and ibuprofen 200 mg orally three times daily as needed for headache. She has no known medication allergies. At the last two visits with her primary care provider, her blood pressure readings were 145/89 mm Hg and 151/92 mm Hg. Which is the best medication for I.W.'s hypertension, given her history of AS?
   A. Ramipril.
   B. Hydrochlorothiazide.
   C. Amlodipine.
   D. Aliskiren.

7. M.W. is a 74-year-old man who underwent an elective surgical mitral valve replacement with a bioprosthetic valve. He has no additional risk factors for bleeding. Which anticoagulation regimen is best to add to daily low-dose aspirin for M.W.?
   A. Vitamin K antagonist (VKA) with a goal international normalized ratio (INR) of 3 for up to 6 months.
   B. Clopidogrel 75 mg daily.
   C. Dabigatran 150 mg twice daily.
   D. VKA with a goal INR of 2.5 for at least 3 months.

8. M.S. is a 32-year-old woman with a mechanical mitral valve who was 1 week late with her usual menses. Her two home pregnancy tests were positive. Her only medications include aspirin 81 mg by mouth daily and warfarin 7.5 mg by mouth on Sunday, Tuesday, Thursday, and Saturday and 10 mg on Monday, Wednesday, and Friday. Her INR readings in the past 6 months have been 2.7, 2.9, 2.8, 3.2, 3.0, and 2.7. Which is the best recommendation regarding anticoagulation therapy in M.S. at this time?
   A. Continue warfarin at the current dose.
   B. Reduce the warfarin dose to target an INR of 2.5.
   C. Discontinue warfarin and initiate anti-factor Xa (anti-Xa)-guided low-molecular-weight heparin.
   D. Discontinue warfarin and initiate unfractionated heparin.

## I. INFECTIVE ENDOCARDITIS

A. Introduction
1. Infection of the endocardium generally involving one of more heart valves
2. Common risk factors include mitral valve prolapse, prosthetic valves and other cardiac devices, and people who inject drugs (PWID). Other risk factors include increased age, chronic hemodialysis, previous IE, poor oral hygiene, and poor control of other infections, especially bacteremia.
3. Incidence is about 15 cases per 100,000 in the United States.
4. Fourth most common life-threatening infection syndrome after sepsis, pneumonia, and intra-abdominal abscess
5. Complications include heart failure, valvular insufficiency, metastatic infection, periannular abscess, mycotic aneurysm, acute kidney injury, musculoskeletal disorders, and systemic embolization with possible infarction (e.g., myocardial infarction, cerebral infarction, splenic infarction, pulmonary embolism [with right-sided IE]).

B. Presentation
1. Signs and symptoms: Temperature higher than 100.4°F (38°C), chills, conjunctival hemorrhages, Janeway lesions, Osler nodes, Roth spots, weight loss (including anorexia), night sweats, malaise, fatigue, new cardiac murmur, clubbing, splenomegaly, arthralgias, myalgias
2. Laboratory findings: Leukocytosis, elevated erythrocyte sedimentation rate, elevated C-reactive protein; all are very nonspecific for IE
3. Many or most of these may not be present (especially with right-sided IE); thus, clinical suspicion for IE should guide diagnostic evaluation.

C. Etiology (Table 1)

**Table 1.** Etiology of IE and Associated Risk Factor(s)

| Risk Factor | Pathogen(s) |
|---|---|
| PWID | *S. aureus*, coagulase-negative staphylococci, β-hemolytic streptococci, fungi, aerobic gram-negative bacilli |
| Prosthetic or indwelling cardiac device[a] | *S. aureus*, coagulase-negative staphylococci, fungi, aerobic gram-negative bacilli |
| Genitourinary or gynecologic disorder including pregnancy and birth | Enterococci, group B streptococci, *Listeria monocytogenes*, aerobic gram-negative bacilli, *Neisseria gonorrhoeae* |
| Poor dental hygiene; dental procedures | VGS, HACEK microorganisms (rare) |
| Chronic skin disorder/infection | *S. aureus*, β-hemolytic streptococci |
| Pneumonia, meningitis | *Streptococcus pneumoniae* |
| GI complications | *Streptococcus gallolyticus*, enterococci |

[a]Includes prosthetic valves, pacemakers, and other devices implanted in the myocardium.

GI = gastrointestinal; HACEK = *Haemophilus* spp., *Aggregatibacter* spp., *Cardiobacterium hominis*, *Eikenella corrodens*, and *Kingella* spp.; PWID = people who inject drugs; VGS = viridans group streptococci.

D. Diagnosis
   1. Laboratory assessment - Blood cultures: At least three sets; obtained by venipuncture from separate sites; first and last sample should be separated by at least 1 hour
   2. Imaging assessment - Expeditious echocardiography (less than 12 hours after initial evaluation) to assess for oscillating intracardiac mass or vegetation, annular abscess, prosthetic valve dehiscence, new valve regurgitation; may be falsely negative if vegetations are small or already embolized
      a. TTE - used early in diagnostic assessment.
         i. Initial imaging strategy because noninvasive, less costly, and does not require preprocedural period of fasting
         ii. May be less useful for patients with chronic obstructive pulmonary disease, previous thoracic or cardiovascular surgery, morbid obesity, prosthetic valves, or other conditions that obstruct windows
         iii. Can be used to serially monitor treatment response
         iv. May reveal high-risk findings (i.e., large or mobile vegetations, valvular insufficiency, perivalvular extension, secondary ventricular dysfunction)
      b. Transesophageal echocardiography - gold standard imaging assessment modality; used to rule out IE from a negative TTE.
         i. More sensitive than TTE for detecting vegetations and abscesses
         ii. Used intraoperatively and to confirm high-risk TTE findings if initial TTE negative but IE suspected, if windows were poor on TTE, or in all high-risk patients (i.e., prosthetic heart valves, many congenital heart diseases, previous endocarditis, new murmur, heart failure, or other stigmata of endocarditis), moderate-high clinical suspicion, or difficult imaging candidate (i.e., patient with obesity)
         iii. May be less sensitive if initial TTE positive for high-risk echocardiographic features (i.e., large or mobile vegetations or abnormalities, valvular insufficiency, suggestion of right ventricular outflow tract obstruction, perivalvular extension, or quantification of hemodynamic alterations caused by valve regurgitation or secondary ventricular dysfunction)
   3. Clinical assessment - Modified Duke criteria (Table 2)
      a. Used to guide diagnosis, but not meant to be definitive

**Table 2.** Classification of IE According to Modified Duke Criteria

| Diagnostic Classification | Definition |
|---|---|
| Definite IE | |
| *Either pathological criteria* | Microorganisms revealed by culture or histological examination of a vegetation, a vegetation that has embolized, or an intracardiac abscess specimen; or pathological lesions; vegetation or intracardiac abscess confirmed by histological examination revealing active endocarditis |
| *OR clinical criteria* | Two major criteria; one major criterion and three minor criteria; or five minor criteria |
| Possible IE | Either: One major criterion and one minor criterion or three minor criteria |
| Rejected | Firm alternative diagnosis explaining evidence of IE; or resolution of IE syndrome with antibiotic therapy for ≤ 4 days; or no pathological evidence of IE at surgery or autopsy with antibiotic therapy for ≤ 4 days; or does not meet the criteria for possible IE, as earlier |

b. "Definite" and "possible" diagnostic classifications rely on major and minor diagnostic criteria (Table 3).

**Table 3.** Definitions of Major and Minor Duke Diagnostic Criteria

| Criterion | Definition |
|---|---|
| Major | • Blood culture positive for IE<br>• Typical microorganisms consistent with IE from two separate blood cultures: VGS, *S. gallolyticus* (*bovis*), HACEK group, *S. aureus*; or community-acquired enterococci in the absence of a primary focus, or microorganisms consistent with IE from persistently positive blood cultures defined as follows: at least two positive cultures of blood samples obtained > 12 hr apart or all 3 or most of ≥ 4 separate cultures of blood (with first and last sample obtained at least 1 hr apart)<br>• Single positive blood culture for *Coxiella burnetii* or anti–phase 1 IgG antibody titer ≥ 1:800<br>• Evidence of endocardial involvement<br>• Echocardiogram positive for IE defined as follows: oscillating intracardiac mass on valve or supporting structures, in the path of regurgitant jets, or on implanted material in the absence of an alternative anatomic explanation; abscess; or new partial dehiscence of prosthetic valve or new valvular regurgitation (worsening or changing or preexisting murmur not sufficient) |
| Minor | • Predisposition, predisposing heart condition, or PWID<br>• Fever, temperature > 100.4°F (38°C)<br>• Vascular phenomena, major arterial emboli, septic pulmonary infarcts, mycotic aneurysm, intracranial hemorrhage, conjunctival hemorrhages, and Janeway lesions<br>• Immunological phenomena: Glomerulonephritis, Osler nodes, Roth spots, and rheumatoid factor<br>• Microbiological evidence: Positive blood culture but does not meet a major criterion as noted earlier (excludes single positive cultures for coagulase negative staphylococci and organisms that do not cause endocarditis) or serological evidence of active infection with organism consistent with IE |

IgG = immunoglobulin G.

E. Treatment
   1. Antimicrobial therapy: Duration
      a. It is reasonable to obtain two sets of blood cultures every 24–48 hours until bacteremia has cleared.
      b. The counting of antibiotic therapy days should begin with the first day in which blood cultures are negative if they were initially positive.
      c. If valve replacement is performed and tissue cultures are positive, antibiotic therapy duration should begin after surgery.
      d. Patients with satisfactory clinical response to intravenous antimicrobial therapy (at least 10 days; 7 days post-operative if surgical valve replacement) with positive blood cultures for streptococcus, Enterococcus faecalis, Staphylococcus aureus, or coagulase-negative staphylococci could be considered for a change to oral antimicrobial therapy if TTE before change reveals no paravalvular infection, if frequent and appropriate follow-up is ensured, and if a TTE can be performed 1–3 days before antibiotic completion.
   2. Empiric antimicrobial therapy (Table 4): Local community resistance patterns and institutional antibiograms may help guide empiric therapy selection.
   3. Surgery
      a. Early valve replacement surgery (i.e., during initial hospitalization and before completion of antibiotic therapy)
         i. Indicated for all patients with IE and valve dysfunction and signs or symptoms of heart failure
         ii. Consider for patients with left-sided IE caused by fungi or highly resistant organisms (e.g., vancomycin-resistant enterococci, multidrug-resistant gram-negative bacilli)

iii. Also consider for native valve endocarditis in whom mobile vegetations greater than 10 mm are present.
iv. Indicated for patients with the following complications: Heart block, annular or aortic abscess, or destructive penetrating lesion
v. Indicated for patients with recurrent prosthetic valve endocarditis or persistent infection (i.e., bacteremia or fever for more than 5–7 days) after the start of appropriate therapy

b. Late valve replacement surgery (i.e., after antibiotics): May be considered if patients are not candidates for early intervention or for patients with major embolic cerebrovascular accident or intracranial hemorrhage within the previous 4 weeks if hemodynamically stable

**Table 4.** Recommended Empiric Therapy Awaiting Cultures

| Antibiotic Regimen | Dose[a] and Route | Comments |
|---|---|---|
| **Native valve or late prosthetic valve (≥ 12 mo post-surgery) endocarditis; no PWID** | | |
| (Penicillin G *OR* ampicillin)<br>+<br>(nafcillin *OR* oxacillin)<br>+<br>gentamicin[b] | PCN: 20 million units/day IV continuously or in four divided doses<br>Ampicillin: 2 g IV every 4 hr<br>Nafcillin/oxacillin: 2 g IV every 4 hr<br>Gentamicin: 3 mg/kg/day IV or IM in three divided doses | |
| **Severe (type I hypersensitivity reaction) or unknown β-lactam allergy** | | |
| Vancomycin[c]<br>+<br>gentamicin[b] | Vancomycin: 30 mg/kg/day IV in two equally divided doses<br>Gentamicin 3 mg/kg/day IV or IM in three divided doses | |
| **Native valve and positive PWID or evidence of right-sided endocarditis** | | |
| Vancomycin[c]<br>*OR*<br>daptomycin | Vancomycin: 30 mg/kg/day IV in two equally divided doses<br>Daptomycin: 10 mg/kg IV daily | Daptomycin 6-mg/kg daily doses can be used for right-sided endocarditis |
| **Early (< 12 mo post-surgery) PVE** | | |
| Vancomycin[c]<br>+<br>gentamicin[b]<br>+<br>rifampin | Vancomycin: 30 mg/kg/day IV in two equally divided doses<br>Gentamicin: 3 mg/kg/day IV or IM in three divided doses<br>Rifampin: 900 mg/day IV or PO in three divided doses | |

[a]Doses are for patients with normal renal and hepatic function.

[b]Target steady-state gentamicin peaks of < 4 mcg/mL and troughs of < 1 mcg/mL.

[c]Adjust vancomycin dose to achieve steady-state serum trough concentrations of 10–20 mcg/mL.

IM = intramuscular(ly); IV = intravenous(ly); PCN = penicillin; PO = oral(ly); PVE = prosthetic valve endocarditis.

**Patient Case**

*Questions 1–3 pertain to the following case.*

J.S. is a 32-year-old woman who presents to the emergency department with complaints of a fever, chills, and night sweats. She states that her symptoms began 3 days ago and have progressively worsened. She has been too ill to eat and has lost about 5 lb since her symptoms began. Her medical history is only significant for seasonal allergies, for which she takes loratadine 10 mg as needed. She has no medication allergies. Her social history is positive for intravenous heroin use, and her family history is noncontributory. Physical examination reveals temperature 102.4°F (39.1°C), heart rate 91 beats/minute, respiratory rate 18 breaths/minute, and blood pressure 128/78 mm Hg. She has a tricuspid valve murmur and several needle tracks on her arms. The rest of her physical examination is unremarkable. Laboratory analyses show normal serum electrolytes with SCr 1.2 mg/dL, BUN 23 mg/dL, WBC 19 x $10^3$ cells/$mm^3$ with 88% neutrophils and 7% bands, hemoglobin 11.8 g/dL, hematocrit 35.2%, and platelet count 132,000/$mm^3$. A 12-lead ECG reveals normal sinus rhythm with no heart blocks or ST-T changes. A TTE reveals a 5-mm mobile mass on the anterior tricuspid leaflet.

1. Which is the best empiric therapy to treat suspected IE in J.S.?
   A. Ampicillin plus oxacillin plus gentamicin.
   B. Vancomycin plus gentamicin plus rifampin.
   C. Vancomycin alone.
   D. Vancomycin plus gentamicin.

4. Pathogen-specific therapy (Tables 5-7)

**Table 5.** Native and Prosthetic Valve IE Caused by VGS and *S. gallolyticus*

| Antibiotic Regimen | Dose[a] and Route | Duration (wk) | Comments |
|---|---|---|---|
| **For strains with PCN MICs ≤ 0.12 mcg/mL (highly PCN susceptible)** | | | |
| *Recommended 4-wk treatment* | | | |
| Penicillin G[b]<br><br>*OR*<br><br>ceftriaxone | PCN: 12–18 million units/day (24 million units in PVE) IV continuously or in four or six divided doses<br>Ceftriaxone: 2 g/day IV or IM in one dose | 4 | • Preferred in patients > 65 yr or those with impaired eighth cranial nerve or kidney dysfunction<br>• 6-wk therapy in patients with PVE with or without gentamicin for 2 wk[c]; CrCl should be ≥ 20 mL/min/1.73 $m^2$ |
| *Recommended 2-wk treatment (only for patients with uncomplicated NVE)* | | | |
| (Penicillin G[b] *OR* ceftriaxone)<br>+<br>gentamicin | PCN: 12–18 million units/day IV continuously or in six divided doses<br>Ceftriaxone: 2 g/day IV or IM in one dose<br>Gentamicin: 3 mg/kg/day IV or IM in one dose | 2 | Gentamicin doses should be adjusted to obtain steady-state serum peak concentrations of 3–4 mcg/mL and trough concentrations < 1 mcg/mL when divided into several daily doses |

**Table 5.** Native and Prosthetic Valve IE Caused by VGS and *S. gallolyticus (Cont'd)*

| Antibiotic Regimen | Dose[a] and Route | Duration (wk) | Comments |
|---|---|---|---|
| **For strains with PCN MICs ≤ 0.12 mcg/mL (highly PCN susceptible)** | | | |
| *Severe (type I hypersensitivity reaction) or unknown β-lactam allergy* | | | |
| Vancomycin | 30 mg/kg/day IV in two equally divided doses | 4 | • Adjust doses to a serum trough concentration of 10–15 mcg/mL; some experts recommend 15–20 mcg/mL<br>• 6-wk therapy in patients with PVE |
| **For strains with PCN MICs of > 0.12 to < 0.5 mcg/mL (relatively PCN-resistant strains)** | | | |
| *Standard therapy* | | | |
| (Penicillin G[b] + gentamicin)<br>*OR*<br>(Ceftriaxone ± gentamicin[d]) | PCN: 12–18 million units/day (24 million units in PVE) IV continuously or in four to six divided doses<br>Gentamicin: 3 mg/kg/day IV or IM in one dose<br>Ceftriaxone: 2 g/day IV or IM in one dose | PCN: 4<br>Gentamicin: 2<br>Ceftriaxone: 4 | • 6-wk therapy in patients with PVE with or without gentamicin for 2 wk<br>• Gentamicin doses should be adjusted to obtain steady-state serum peak concentrations of 3–4 mcg/mL and trough concentrations < 1 mcg/mL when divided into several daily doses; reasonable to extend gentamicin to 6 wk if MIC > 0.12 mcg/mL |
| *Severe (type I hypersensitivity reaction) or unknown β-lactam allergy* | | | |
| Vancomycin | 30 mg/kg/day IV in two equally divided doses | 4 | • Adjust doses to a serum trough concentration of 10–15 mcg/mL; some experts recommend 15–20 mcg/mL<br>• 6-wk therapy in patients with PVE |
| **For strains with PCN MICs ≥ 0.5 mcg/mL** | | | |
| *Standard therapy* | | | |
| (Penicillin G[b] *OR* ceftriaxone) + gentamicin | PCN: 24 million units/day IV continuously or four to six divided doses<br>Ceftriaxone: 2 g/day IV or IM in one dose<br>Gentamicin: 3 mg/kg/day IV or IM in one dose | PCN: 4<br>Ceftriaxone: 4<br>Gentamicin: 2 | • 6-wk therapy in patients with PVE<br>• Gentamicin doses should be adjusted to obtain steady-state serum peak concentrations of 3–4 mcg/mL and trough concentrations < 1 mcg/mL when divided into several daily doses |
| *Severe (type I hypersensitivity reaction) or unknown β-lactam allergy* | | | |
| Vancomycin | 30 mg/kg/day IV in two equally divided doses | 4 | • Adjust doses to a serum trough concentration of 10–15 mcg/mL; some experts recommend 15–20 mcg/mL<br>• 6-wk therapy in patients with PVE |

[a]Doses are for patients with normal renal and hepatic function.

[b]Ampicillin 2 g IV every 4 hr for 4 wk is a reasonable alternative to PCN.

[c]The gentamicin dose is the same used throughout Table 4.

[d]Ceftriaxone may be used alone according to the American Heart Association guidelines; for PVE, combination therapy for relatively resistant VGS was no better than monotherapy with ceftriaxone.

NVE = native valve endocarditis.

a. Therapy for *S. pneumoniae*, *Streptococcus pyogenes*, and group B, C, F, and G β-hemolytic streptococci
   i. Four weeks of penicillin, cefazolin, or ceftriaxone for *S. pneumoniae*; 6 weeks for prosthetic valve endocarditis
   ii. High-dose penicillin or a third-generation cephalosporin for penicillin-resistant *S. pneumoniae* without meningitis; use cefotaxime or ceftriaxone if meningitis is present or suspected
      (a) Vancomycin and rifampin may be added for strains resistant to cefotaxime (i.e., MIC of 2 mcg/mL or greater).
      (b) Infectious disease consultation is recommended.
   iii. Penicillin G or ceftriaxone for 4–6 weeks for *S. pyogenes*
   iv. Penicillin G or ceftriaxone for 4–6 weeks plus gentamicin for 2 weeks for group B, C, or G streptococci
   v. Vancomycin is recommended for patients with a severe (type I hypersensitivity reaction) or unknown penicillin allergy.

**Table 6.** Staphylococci

| Antibiotic Regimen | Dose[a] and Route | Duration (wk) | Comments |
|---|---|---|---|
| **Native valve** | | | |
| *Methicillin-susceptible staphylococci* | | | |
| Nafcillin *OR* oxacillin | 12 g/day IV in four to six equally divided doses | 6 | • 2 wk for uncomplicated right-sided IE<br>• Nafcillin preferred with associated brain abscess; vancomycin if PCN allergic<br>• Cefazolin 6 g/day in three divided doses recommended for patients with MSSA and non-anaphylactoid PCN allergy |
| *Methicillin-resistant staphylococci or anaphylactoid PCN allergy*[b] | | | |
| Vancomycin | 30 mg/kg/day IV in two equally divided doses | 6 | Adjust vancomycin dose to achieve steady-state serum trough concentrations of 10–20 mcg/mL |
| Daptomycin | ≥ 8 mg/kg/dose | 6 | The addition of IV fosfomycin may reduce microbiological failure and complicated bacteremia but increase adverse events. |
| **Prosthetic valve** | | | |
| *Methicillin-susceptible staphylococci* | | | |
| (Nafcillin *OR* oxacillin)<br>+<br>Rifampin<br>+<br>gentamicin[c] | Nafcillin/ oxacillin: 12 g/day IV in six equally divided doses<br>Rifampin: 900 mg/day IV or PO in three divided doses<br>Gentamicin: 3 mg/kg/day IV or IM in two or three divided doses | Nafcillin/ oxacillin: ≥ 6<br>Rifampin: ≥ 6<br>Gentamicin: 2 | • Can use alternative aminoglycoside for strains resistant to gentamicin<br>• Fluoroquinolones may be considered for strains resistant to all aminoglycosides<br>• Cefazolin 6 g/day in three divided doses recommended for patients with MSSA and non-anaphylactoid PCN allergy |

**Table 6.** Staphylococci *(Cont'd)*

| Antibiotic Regimen | Dose[a] and Route | Duration (wk) | Comments |
|---|---|---|---|
| **Prosthetic valve** | | | |
| *Methicillin-resistant staphylococci or anaphylactoid PCN allergy*[b] | | | |
| Vancomycin<br>+<br>rifampin<br>+<br>gentamicin[c] | Vancomycin:<br>30 mg/kg/day IV in two equally divided doses<br>Rifampin: 900 mg/day IV or PO in three divided doses<br>Gentamicin:<br>3 mg/kg/day IV or IM in two or three divided doses | Vancomycin: ≥ 6<br>Rifampin: ≥ 6<br>Gentamicin: 2 | • Adjust vancomycin dose to achieve steady-state serum trough concentrations of 10–20 mcg/mL<br>• Can use alternative aminoglycoside for strains resistant to gentamicin<br>• Fluoroquinolones may be considered for strains resistant to all aminoglycosides |

[a]Doses are for patients with normal renal and hepatic function.

[b]Consider PCN skin testing and desensitization in stable patients.

[c]Administer close to β-lactam antibiotic or vancomycin.

IE = infective endocarditis; MSSA = methicillin-susceptible *S. aureus*.

**Table 7.** Enterococci

| Antibiotic Regimen | Dose[a] and Route | Duration (wk) | Comments |
|---|---|---|---|
| **Strains susceptible to PCN and gentamicin** | | | |
| (Ampicillin *OR* penicillin G)<br>+<br>gentamicin[b] | Ampicillin: 2 g IV every 4 hr<br>PCN: 18–30 million units/day IV continuously or in six divided doses<br>Gentamicin: 3 mg/kg/day IBW IV in two or three divided doses | 4–6 | 6-wk therapy for symptoms > 3 mo or PVE |
| Ampicillin<br>+<br>ceftriaxone | Ampicillin: 2 g IV every 4 hr<br>Ceftriaxone: 2 g IV every 12 hr | 6 | Recommended for patients with CrCl < 50 mL/min/1.73 $m^2$ |
| **Strains resistant to aminoglycosides or gentamicin** | | | |
| Ampicillin<br>+<br>ceftriaxone | Ampicillin: 2 g IV every 4 hr<br>Ceftriaxone: 2 g IV every 12 hr | 6 | Could use 4-wk regimen in native valve infection and symptoms < 3 mo |
| (Ampicillin *OR* penicillin G)<br>+<br>streptomycin[c] | Ampicillin: 2 g IV every 4 hr<br>PCN: 18–30 million units/day IV continuously<br>or in six divided doses<br>Streptomycin: 15 mg/kg/day IBW IV or IM in two divided doses | 4–6 | Avoid when rapid serum streptomycin serum concentrations unavailable or patients with CrCl < 50 mL/min/1.73 $m^2$ or eighth cranial nerve dysfunction |

**Table 7.** Enterococci *(Cont'd)*

| Antibiotic Regimen | Dose[a] and Route | Duration (wk) | Comments |
|---|---|---|---|
| **Strains resistant to PCN or severe (type I hypersensitivity reaction) PCN allergy** | | | |
| Vancomycin + gentamicin[b] | Vancomycin: 30 mg/kg/day IV in two equally divided doses<br>Gentamicin: 3 mg/kg/day IBW IV or IM in three divided doses | 6 | • Adjust vancomycin dose to achieve steady-state serum trough concentrations of 10–20 mcg/mL<br>• In non–PCN-allergic patients with β-lactamase–producing strain, ampicillin/sulbactam[d] may replace vancomycin |
| **Strains resistant to PCN, aminoglycosides, and vancomycin** | | | |
| Linezolid *OR* daptomycin | Linezolid: 600 mg IV or PO every 12 hr<br>Daptomycin: 10–12 mg/kg/dose | > 6 | Consider daptomycin combined with ampicillin or ceftaroline with persistent bacteremia or high daptomycin MIC (i.e., 3 mcg/mL) |

[a]Doses are for patients with normal renal and hepatic function.

[b]Adjust dose to achieve peak serum concentrations of 3–4 mcg/mL and trough concentrations < 1 mcg/mL.

[c]Adjust dose to achieve peak serum concentrations of 20–35 mcg/mL and trough concentrations < 10 mcg/mL.

[d]Ampicillin/sulbactam dose is 3 g IV every 6 hr.

CrCl = creatinine clearance; IBW = ideal body weight.

**Table 8.** HACEK Microorganisms

| Antibiotic Regimen[a] | Dose[b] and Route | Comments |
|---|---|---|
| Ceftriaxone | 2 g/day IV or IM in one dose | May substitute cefotaxime or other third- or fourth-generation cephalosporin |
| Ampicillin | 2 g IV every 4 hr | • Option for susceptible isolated organisms<br>• May also consider ampicillin/sulbactam if susceptible |
| Ciprofloxacin | 400 mg IV every 12 hr or 500 mg PO every 12 hr | • Recommended for those who cannot tolerate cephalosporins or ampicillin<br>• Levofloxacin or moxifloxacin may also be used |

[a]For NVE, provide 4 wk of therapy; 6 wk for PVE.

[b]Doses are for patients with normal renal and hepatic function.

b. Non–*Haemophilus* spp., *Aggregatibacter* spp., *Cardiobacterium hominis*, *Eikenella corrodens*, and *Kingella* spp. (HACEK) gram-negative bacilli (Table 8)
   i. β-Lactam antibiotic combined with either an aminoglycoside or a fluoroquinolone for 6 weeks
   ii. Consultation with an infectious disease specialist is recommended.

c. Culture-negative endocarditis
   i. Consultation with an infectious disease specialist is recommended.
   ii. Therapy for acute (i.e., within days) clinical presentations of native valve infection should include coverage for *S. aureus*, β-hemolytic streptococci, and aerobic gram-negative bacilli.
   iii. Therapy for subacute (i.e., within weeks) presentation of native valve infection should include coverage for *S. aureus*, viridans group streptococci, HACEK, and enterococci.
   iv. Therapy for early (less than 12 months since valve placed) prosthetic valve infection should include coverage for staphylococci, enterococci, and aerobic gram-negative bacilli.
   v. Therapy for late (12 months or more since valve placed) prosthetic valve infection should include coverage for staphylococci, viridans group streptococci, and enterococci.

   d. Fungi
      i. Consultation with an infectious disease specialist is recommended.
      ii. Valve surgery is usually required for treatment.
      iii. Treatment usually includes amphotericin B with or without flucytosine, or a high-dose echinocandin; voriconazole is the treatment of choice for *Aspergillus*; treatment duration is usually more than 6 weeks.
      iv. If treatment is successful, lifelong suppression therapy with an oral azole is recommended.
5. Right-sided IE
   a. Five to 10% of IE cases
   b. Most common with PWID
   c. Usually affects the tricuspid valve, with *S. aureus* being the predominant infecting organism
   d. Empiric therapy should include coverage for *S. aureus* (with nafcillin, oxacillin, or daptomycin), with empiric coverage for MRSA depending on local prevalence; growing evidence suggests no need to add an aminoglycoside.
   e. Treatment duration of 2 weeks is usually adequate for uncomplicated IE (no evidence of renal failure, extrapulmonary metastatic infections, aortic or mitral valve involvement, meningitis, infection with MRSA), but treatment should be extended to 4–6 weeks with the use of vancomycin or other glycopeptides, complications, or slow response (greater than 96 hours).
6. Patients with infected implantable electronic devices
   a. Local device infection (i.e., infection limited to the device pocket) is more common than device-related IE.
   b. Cardiac-device related IE is defined by infection on the electrode leads, cardiac valve leaflets, or endocardial surface.
   c. Staphylococci account for 60%–80% of cases, with up to 50% of cases being methicillin resistant.
   d. Except for superficial or incisional infection at the pocket site that does not involve the device, treatment requires complete hardware removal.
   e. Empiric therapy should include vancomycin to cover MRSA and be initiated before hardware removal.
   f. Duration of antimicrobial therapy should be at least 2 weeks after hardware removal for bloodstream infections. Courses of at least 4–6 weeks are needed for complicated infections (endocarditis, osteomyelitis, persistent bacteremia). Shorter courses (10–14 days) after device removal are reasonable for pocket site infections.

**Patient Case**

2. On day 3 of hospitalization, four of four of J.S.'s blood culture bottles return positive for methicillin-susceptible *S. aureus*. Which therapeutic plan is best for completing treatment of IE in J.S.?

   A. Oxacillin 12 g/day for 2 weeks.

   B. Vancomycin 30 mg/kg/day for 6 weeks.

   C. Daptomycin 10 mg/kg daily for 2 weeks.

   D. Nafcillin 12 g/day for 6 weeks.

7. Outpatient parenteral antimicrobial therapy (Table 9)
   a. A plan for OAPT for patients who qualify should be established prior to hospital discharge.
   b. Transition of care for the patient to the outpatient setting should involve a collaborative effort between the following members of the health care team: infectious disease provider, cardiologist (and cardiac surgeon if applicable), patient care manager, pharmacist, specialty and/or infusion pharmacy, home health services and/or infusion center.

**Table 9.** Considerations in OPAT

| Phase of Therapy | Recommendations |
|---|---|
| Critical phase (weeks 0–2) | • OPAT not recommended<br>• Highest chance of complications during this phase<br>• Consider OPAT if: VGS, *S. gallolyticus*, native valve, patient stable, no complications |
| Continuation phase (after 2 wk) | • Consider OPAT if medically stable<br>• Do not consider OPAT if: Heart failure, echocardiographic features of concern, persistent fever or positive cultures, neurological signs, or renal impairment |
| Essential criteria for effective OPAT | • Proper education of patient, family, and staff<br>• Reliable home support system with easy hospital access<br>• Regular home infusion nurse visits<br>• Appropriate storage for antibiotics<br>• Regular clinician visits |

OPAT = outpatient parenteral antimicrobial therapy.

F. Antithrombotic Therapy in IE
   1. Antiplatelet therapy
      a. Adjunctive therapy for endocarditis with antiplatelet agents is not recommended.
      b. Long-term antiplatelet therapy may be continued at the time of the IE development in the absence of bleeding complications.
   2. Anticoagulation
      a. It is reasonable to discontinue anticoagulation for 2 weeks in patients who have had a central nervous system embolic event (e.g., stroke, retinal hemorrhage [Roth spots]).
      b. Cautious reinitiation of anticoagulation should be done with unfractionated or low-molecular-weight heparin that is a bridge to warfarin.

G. Prevention
   1. Cardiac conditions with the highest risk of IE for which prophylaxis is recommended
      a. Prosthetic cardiac valve (either surgically implanted or transcatheter implanted) or valve material such as annuloplasty rings and chords
      b. Previous IE
      c. Congenital heart disease
         i. Unrepaired cyanotic congenital heart disease
         ii. Repaired congenital heart disease with residual shunts or valvular regurgitation at the site of or near the prosthetic patch or device
      d. Cardiac transplant recipients with valvulopathy; recommended by the American Heart Association/American College of Cardiology (AHA/ACC), but not supported by the European Society of Cardiology (ESC)
   2. Prophylaxis for IE is only recommended for patients with the conditions listed previously undergoing the following procedures:
      a. Dental procedures involving manipulation of gingival tissue, the periapical region of teeth, or perforation of the oral mucosa
      b. Invasive respiratory tract procedure involving incision or biopsy of the respiratory mucosa
      c. Patients undergoing a gastrointestinal (GI) or genitourinary tract procedure with established GI or genitourinary infection
      d. Patients undergoing a surgical procedure that involves infected skin, skin structure, or musculoskeletal tissue
      e. Patients undergoing cardiac surgery

3. Procedures in which antibiotic prophylaxis is not recommended
    a. The following dental procedures: Local anesthetic injections in noninfected tissues, treatment of superficial caries, removal of sutures, dental radiographs, placement or adjustment of removable prosthodontic or orthodontic appliances or braces, the shedding of deciduous teeth, or trauma to the lips and oral mucosa
    b. Bronchoscopy, laryngoscopy, or intubation of the respiratory tract
    c. Gastroscopy, colonoscopy, cystoscopy, vaginal or caesarean delivery, or transesophageal echocardiography
    d. Procedures on noninfected skin and soft tissue
4. Prophylactic regimens (Table 10)

**Table 10.** Recommended Regimens for Dental Procedures

| Agent | Single Dose Regimen 30–60 Min Before Procedure | |
|---|---|---|
| | **Adults** | **Children** |
| **Not allergic to PCN** | | |
| Amoxicillin | 2 g PO | 50 mg/kg PO |
| Ampicillin[a] | 2 g IM or IV | 50 mg/kg IM or IV |
| Cefazolin[b] or ceftriaxone[a,b] | 1 g IM or IV | 50 mg/kg IM or IV |
| **Allergic to PCN** | | |
| Cephalexin[b,c] | 2 g PO | 50 mg/kg PO |
| Clindamycin | 600 mg PO, IM, or IV | 20 mg/kg PO, IM, or IV |
| Azithromycin or clarithromycin | 500 mg PO | 15 mg/kg PO |
| Cefazolin[b] or ceftriaxone[a,b] | 1 g IM or IV | 50 mg/kg IM or IV |

[a]Use if patient cannot take PO medication.
[b]Avoid cephalosporins in patients with type I hypersensitivity reactions.
[c]May use an equivalent dose of another first- or second-generation PO cephalosporin.

**Patient Case**

3. Three months after successful treatment of her IE, J.S. is scheduled to undergo incision, drainage, and debridement of a 3-cm infected subcutaneous abscess on her left forearm. Which best depicts J.S.'s qualifying indication for receiving IE prophylaxis before the procedure?
    A. She had a previous *S. aureus* infection.
    B. She has a history of PWID.
    C. Only dental procedures require prophylaxis.
    D. She is undergoing surgery on an infected skin structure.

## II. PERICARDITIS

A. Introduction
    1. Epidemiology
        a. Incidence of acute pericarditis is reported to be 27.7 per 100,000 patient-years.
        b. Accounts for 0.1% of hospital admissions and 5% of emergency department admissions for chest pain
        c. Men 16–65 years of age were at higher risk than women, with young adults at highest risk.
        d. In-hospital mortality for acute pericarditis is reported as 1.1%.
        e. The recurrence rate is 30% within the first 18 months of acute pericarditis.

2. Etiology
   a. Viral pericarditis causes most cases of acute pericarditis in developed countries, whereas tuberculosis is the primary cause in developing countries and worldwide. Definitive diagnosis requires a comprehensive workup of pericardial fluid and pericardioscopy/epicardial biopsy.
      i. Markers of inflammation/immune reaction and infection are often negative in serum.
      ii. HIV and hepatitis C virus are commonly detected.
   b. Other etiologies (Table 11)

**Table 11.** Infectious and Noninfectious Causes of Pericardial Disease

| Infectious | Noninfectious |
|---|---|
| Common<br>Viral<br><br>*Uncommon/rare*<br>Bacterial<br>Fungal<br>Parasitic | Common<br>Autoimmune (e.g., lupus, rheumatoid arthritis)<br>Neoplastic (especially lung and breast cancer)<br>Metabolic (e.g., uremia, myxedema)<br>Traumatic and iatrogenic<br>• Early onset (rare): Such as from radiation injury<br>• Delayed onset (more common): Such as with post-myocardial infarction syndrome, radiofrequency ablation<br>Amyloidosis<br>Aortic dissection<br>Pulmonary arterial hypertension<br>Chronic heart failure<br><br>*Uncommon/rare*<br>Drug related (e.g., phenytoin, hydralazine, doxorubicin, mesalamine, penicillin, methyldopa, minoxidil, COVID-19 mRNA vaccines)<br>Congenital absence of the pericardium |

B. Classifications and Diagnosis of Pericarditis (Table 12)

**Table 12.** Classification and Diagnostic Criteria for Pericarditis

| Classification | Definition and Diagnostic Criteria |
|---|---|
| Acute | Inflammatory pericardial syndrome diagnosed with ≥ 2 of the following:<br>• Pericarditic chest pain: Sharp and pleuritic; improves with sitting up or leaning forward; radiates to trapezius ridges<br>• Pericardial friction rub<br>• New widespread ST-segment elevation or PR depression on ECG<br>• Pericardial effusion (new or worsening)<br>Additional supportive findings:<br>• Elevation of markers of inflammation (i.e., CRP, ESR, and WBC);<br>• Evidence of pericardial inflammation on imaging (e.g., CT, CMR) |
| Incessant | Pericarditis lasting > 4–6 wk but < 3 mo without remission |
| Recurrent | Recurrence of pericarditis after a first acute episode with a symptom-free interval ≥ 4–6 wk |
| Chronic | Pericarditis lasting > 3 mo |

CMR = cardiac magnetic resonance; CRP = C-reactive protein; CT = computed tomography; ECG = electrocardiography; ESR = erythrocyte sedimentation rate; WBC = white blood cell count.

C. Predictors of Poor Prognosis
   1. Major predictors: Temperature higher than 100.4°F (38°C), subacute onset, female sex, large pericardial effusion, cardiac tamponade, lack of response to nonsteroidal anti-inflammatory drug (NSAID) therapy after 1 week
   2. Minor predictors: Myopericarditis, immunosuppression, trauma, anticoagulant therapy, cardiac troponin elevation

D. Therapy
   1. The most robust evidence for the use of pharmacotherapy in acute or recurrent pericarditis is from patients with viral or idiopathic pericarditis; thus, little research supports recommended therapies for other causes.
   2. Expected response to therapy
      a. Symptom resolution within 72 hours
      b. Remission within 7 days
      c. Window of recurrence is within 18 months.
   3. Acute pericarditis
      a. Exercise restriction
         i. Until symptom resolution and normalization of C-reactive protein, ECG, and echocardiogram
         ii. At least 3 months recommended for athletes, even with clinical resolution because of risk of sudden cardiac death
      b. Aspirin or NSAIDs are first line; aspirin preferred in post-myocardial infarction to treat symptoms of pericarditis.
      c. Omeprazole was used in all landmark trials to reduce NSAID-related GI adverse effects, but acid suppressants have not been specifically studied for this purpose in this population.
      d. Colchicine is the first-line adjuvant therapy to aspirin or NSAIDs.
         i. Improves therapy response; quicker symptom resolution
         ii. Reduces recurrence more than aspirin or NSAIDs alone
      e. Corticosteroids are not recommended as first-line therapy for acute pericarditis of viral or idiopathic etiology because they significantly increase the risk of recurrence and should be avoided in post-myocardial infarction pericarditis. Low-dose corticosteroids may be added to aspirin/NSAID and colchicine therapy if incomplete response, contraindications, or intolerance of first-line therapy, and infection has been ruled out.
      f. Recommended dosing (see Table 13)
   4. Recurrent pericarditis
      a. Use restrictions as with acute pericarditis.
      b. Aspirin or NSAIDs are first line with a duration of several weeks or months; duration depends on high-sensitivity C-reactive protein response and alleviation of symptoms.
      c. Colchicine is first-line adjuvant therapy with aspirin or NSAID therapy for at least 6 months to improve response and decrease recurrence.
      d. Low- to moderate-dose corticosteroids may be added to aspirin/NSAID and colchicine therapy if incomplete response, contraindications, or intolerance of first-line therapy
         i. See Table 14 for recommended steroid therapy taper.
         ii. Try to maintain current steroid dose, or withhold steroids if already discontinued, in instances of recurrence.
      e. See Table 13 for recommended drug doses.
      f. Azathioprine, intravenous immunoglobulin, or anakinra may be added if intolerance of or inability to wean corticosteroid therapy
         i. Only use in infection-negative cases
         ii. Should consult with a rheumatologist or immunologist

g. Rilonacept, an interleukin (IL)-1α and IL-1β cytokine trap, showed rapid improvement in pain with minimal disease recurrence in a phase III trial of adult and adolescent patients with noninfectious related pericarditis. Most study participants were taking NSAIDs and colchicine and had at least two previous episodes of recurrence. Rilonacept is indicated for treatment of recurrent pericarditis and reduction in risk in patients 12 years of age and older. It may also be considered in weaning patients from standard therapy.

h. Pericardiectomy may be used in refractory cases.

5. Transitions of care
   a. Establishment of outpatient continuation of therapy should begin several days prior to discharge from the acute care setting.
   b. Transitions of care for therapy may involve several other providers and ancillary services depending on the patient's specific needs and therapy (e.g., specialty pharmacy).

**Table 13.** Recommended Dosing of Anti-inflammatory Agents for Pericarditis

| Drug | Usual Dose | Duration | Tapering |
|---|---|---|---|
| Aspirin | 750–1000 mg every 8 hr | Up to 54 wk | Decrease doses by 250–500 mg every 1–2 wk[a] |
| Ibuprofen[b] | 600 mg every 8 hr | Up to 54 wk | Decrease doses by 200–400 mg every 1–2 wk[a] |
| Colchicine | 0.5 mg daily (< 70 kg) or 0.5 mg BID (≥ 70 kg)[c] | 3 mo (6 mo for recurrent pericarditis) | Not mandatory; alternatively 0.5 mg every other day (< 70 kg) or 0.5 mg daily (≥ 70 kg) in the last weeks[d] |
| Prednisone[b] | 0.25–0.5 mg/kg/day | Until symptom resolution and normalization of CRP | Slow tapering recommended (see Table 14) |
| Anakinra[e] | 2 mg/kg/day (up to 100 mg) | 3–6 mo | Taper over 3 mo for best chance of recurrence prevention |
| Azathioprine | 150 mg orally once daily | 2 - 3 mo | Taper to 100 mg daily to suppress clinical symptoms |
| Rilonacept | Children (12–17 yr): 4.4 mg/kg SQ (max. dose 320 mg), then 2.2 mg/kg SQ (max. dose 160 mg) weekly; adults: 320 mg SQ then 160 mg SQ weekly | 9 mo median duration in Phase III trial | None |

[a]Monitor CRP and continue same dose if CRP does not decrease after 1 wk.

[b]May use equipotent dose of another agent from the medication class.

[c]The 0.5-mg tablets are not available in the United States, and the 0.6-mg tablets are used empirically in their place.

[d]Can use same taper schedule with 0.6-mg tablets.

[e]Shown to be beneficial in small trials and one moderate-size registry study of patients with recurrent pericarditis unresponsive to colchicine who were steroid-dependent.

BID = twice daily; SC = subcutaneously.

**Table 14.** Tapering of Corticosteroid Therapy in Pericarditis[a]

| Starting Daily Dose | Taper[b] |
|---|---|
| > 50 mg | 10 mg/day every 1–2 wk |
| 25–50 mg | 5–10 mg/day every 1–2 wk |
| 15–25 mg | 2.5 mg/day every 2–4 wk |
| < 15 mg | 1.25–2.5 mg/day every 2–6 wk |

[a]Information included is for prednisone.

[b]Only continue with taper if patient is asymptomatic and CRP is normal.

E. Pericarditis Involving the Myocardium (myopericarditis)
   1. Common etiologies include viral and other infectious causes, depending on geographic region.
   2. Classic presentation is chest pain associated with other signs/symptoms of pericarditis (see Table 12), together with elevated markers of myocardial damage (e.g., troponins).
   3. Coronary angiography is recommended to rule out acute coronary syndrome.
   4. Therapy
      a. Rest and avoidance of physical exercise for all patients; at least 6 months for athletes
      b. Aspirin and NSAIDs are used first line to control chest pain; aspirin is preferred in patients with coronary artery disease because NSAIDs are associated with myocardial scar thinning.
      c. Corticosteroids are used second line.
      d. Colchicine has no established role in myopericarditis.
      e. See Table 13 for recommended drug doses; use the lowest effective dose.

F. Constrictive Pericarditis
   1. Mainly caused by impaired diastolic filling
   2. Classic presentation includes signs/symptoms of right-sided heart failure with preserved left and right ejection fraction (e.g., fatigue, peripheral edema, shortness of breath, ascites, hepatomegaly, pleural effusion).
   3. Treatment
      a. Pericardiectomy is the main therapeutic intervention.
      b. Anti-inflammatory agents may be used to prevent progression to constriction, to resolve transient constriction, or as a supportive therapy in advanced cases or when surgery is contraindicated.

**Patient Case**

*Questions 4 and 5 pertain to the following case.*

S.V. is a 47-year-old man who presents to the emergency department with new-onset chest pain. The pain began early in the day and was mild at first, but it has gradually worsened and is now 7/10. The pain worsens during inhalation and improves when sitting up. His medical history is significant for hypertension, hyperlipidemia, and pericarditis. His last episode of pericarditis was 8 months ago. He has no medication allergies, and his home medications include lisinopril 10 mg orally daily, atorvastatin 10 mg orally daily, aspirin 81 mg orally daily, and a multivitamin daily. His family history is significant for early coronary artery disease in his father and hypertension and stroke in his mother. He smokes about 10 cigarettes per day and occasionally drinks alcohol on the weekend. He has a positive pericardial rub on auscultation. An ECG reveals sinus rhythm with widespread ST-segment elevations. Cardiac troponin I and MB form of creatinine kinase are normal. A TTE reveals moderate pericardial effusion. S.V. is given a diagnosis of recurrent pericarditis.

**Patient Case** *(Cont'd)*

4. Which is the best initial therapy for recurrent pericarditis in S.V.?
   A. Aspirin.
   B. Prednisone.
   C. Colchicine.
   D. Diclofenac.

5. Which therapy would best be added to initial therapy for S.V. to reduce the chance of another recurrence of pericarditis?
   A. Prednisone.
   B. Colchicine.
   C. Azathioprine.
   D. Anakinra.

G. Special Pericardial Syndromes
   1. Bacterial pericarditis
      a. Rare in developed countries
      b. Tuberculous pericarditis is the most common form; most common cause of pericardial disease in developing countries
      c. Tuberculous pericarditis
         i. Clinical presentation includes signs/symptoms of congestive heart failure.
         ii. Definitive diagnosis made by detection of tubercle bacilli in pericardial fluid or during pericardial histology
         iii. Therapy
            (a) Antituberculosis therapy is recommended in endemic areas or in proven tuberculosis infection.
            (b) Rifampin/rifampicin-containing regimens reduce progression to constrictive pericarditis by up to 40%.
            (c) Intrapericardial urokinase and adjunctive high-dose prednisone/prednisolone may also reduce the incidence of constrictive pericarditis from tuberculous pericarditis; avoid steroids in patients with HIV infection because of association with higher incidence of HIV-associated malignancy.
      d. Purulent pericarditis
         i. Caused by various bacterial pathogens
         ii. Urgent pericardiocentesis is indicated in suspected cases.
            (a) Used for diagnosis
            (b) Distinctions from tuberculous and neoplastic pericarditis include low pericardial/serum glucose ratio and elevated WBC.
         iii. Therapy
            (a) Therapeutic pericardiocentesis
            (b) Early initiation of empiric therapy and then targeted antimicrobial therapy
            (c) Intrapericardial thrombolytics may be used for loculated pericardial effusions.
            (d) Subxiphoid pericardiostomy or pericardiectomy may be considered.

2. Pericarditis in kidney disease
    a. May occur before initiation of renal replacement therapy for chronic kidney disease or once stable on therapy
    b. Adequate dialysis is the main treatment modality in patients with uremic pericarditis.
    c. Pericardial aspiration or drainage may be considered.
    d. NSAIDs and corticosteroids may also be considered when dialysis is ineffective.
    e. Colchicine should be avoided in renal impairment.
3. Pericarditis in systemic autoimmune and inflammatory disorders
    a. May be asymptomatic, depending on the activity of the underlying disease
    b. Common with the following: Systemic lupus erythematosus, Sjögren syndrome, rheumatoid arthritis, scleroderma
    c. May occur with the following: Systemic vascularities, Behçet syndrome, sarcoidosis, inflammatory bowel disease
    d. Treatment targeting the underlying disorder in consultation with a specialist is warranted; discontinue any possible causitive agent(s).
4. Post-cardiac injury syndromes
    a. Any of a group of syndromes triggered by initial direct damage to the pericardial or pleural tissues (e.g., post-myocardial infarction pericarditis, post-pericardiotomy syndrome, and posttraumatic pericarditis)
    b. Therapy
        i. Aspirin or NSAIDs should be used as initial therapy; aspirin is preferred in patients with coronary artery disease because NSAIDs are associated with myocardial scar thinning.
        ii. Colchicine may be added as in acute idiopathic (viral) pericarditis.
    c. Colchicine may be used postoperatively in cardiac surgery patients for 1 month to prevent pericarditis.

H. Pericarditis in Pediatric Patients
1. High-dose NSAIDs are first line.
2. Aspirin should be avoided because of the risk of Reye syndrome.
3. Colchicine may be added to NSAIDs.
4. Corticosteroids should be avoided because of their harmful adverse effects in growing children.
5. Studies investigating anakinra have included pediatric patients.
6. Rilonacept is approved for pediatric patients 12–17 years of age.

## III. MYOCARDITIS

A. Introduction
1. Myocarditis includes any of several clinical presentations that result from inflammation of the myocardium; up to one-third of cases lead to dilated cardiomyopathy.
2. Definitions from the World Health Organization (WHO)
    a. Myocarditis: Inflammatory disease of the myocardium diagnosed by established histological, immunological, and histo-immunochemical criteria
    b. Inflammatory cardiomyopathy: Myocarditis in association with cardiac dysfunction
    c. Dilated cardiomyopathy (ESC and WHO definitions): Clinical diagnosis characterized by dilation and impaired contraction of the left or both ventricles that is not explained by abnormal loading conditions or coronary artery disease
3. Myocarditis, inflammatory cardiomyopathy, and dilated cardiomyopathy are not mutually exclusive.
4. Affects all ages, but is predominant in young individuals (median age is early 40s); with COVID-19 mRNA vaccines it is most common in males between 12 and 29 years of age and in those who have received a second dose.

5. About 50% of the cases resolve within the first 2–4 weeks.
    a. About 25% of patients develop persistent cardiac dysfunction.
    b. About 12%–25% of patients will acutely deteriorate and die or progress to end-stage dilated cardiomyopathy with need for heart transplantation.

B. Myocarditis is classified according to etiology, cell type, and clinical type (Table 15).

**Table 15.** Classification of Myocarditis

| Etiology | Cell Type | Clinical Type |
|---|---|---|
| Virus (e.g., SARS-Cov-2)<br>Bacteria<br>Fungi<br>Rickettsia<br>Spirochetes<br>Parasites, protozoa<br>Other infectious organisms<br>Medications (e.g., COVID-19 mRNA vaccines), chemical substances<br>Autoimmune<br>Collagen, Kawasaki disease<br>Sarcoidosis<br>Radiation<br>Heat stroke<br>Unknown | Lymphocytic<br>Giant cell<br>Eosinophilic<br>Granulomatous | Acute<br>Fulminant<br>Chronic |

C. Presentation
    1. Usually begins with flu-like symptoms and/or GI symptoms (e.g., nausea, vomiting, diarrhea, decreased appetite); may present as sudden cardiac death.
    2. Cardiac symptoms occur hours to days later.
        a. Heart failure: Dyspnea, peripheral edema, jugular venous distension, rales, possible left and/or right ventricular dysfunction with or without dilated cardiomyopathy
        b. Chest pain: ST/T wave changes, elevated troponin (may be sustained over weeks to months), MB form of creatinine kinase, aspartate aminotransferase, and/or lactate dehydrogenase
        c. Arrhythmias: Bundle branch block, atrioventricular (AV) node block, and/or ventricular arrhythmias
    3. Patients may have elevated markers of inflammation: C-reactive protein, erythrocyte sedimentation rate
    4. Patients with fulminate presentation or rapid progression can present with cardiogenic shock, life-threatening arrhythmias, and severe LV dysfunction.

D. Diagnosis
    1. Endomyocardial biopsy is the gold standard (based on the Dallas criteria).
        a. Not routine in clinical practice and not available at all institutions; risk of false negative because of sampling factors
        b. Identifies the etiology and cell type of inflammation
        c. Allows for better selection of therapy
        d. Usually reserved for life-threatening presentations or certain suspected causes (e.g., fulminant, giant cell)
        e. Tissue should be analyzed using histology, immunohistochemistry, and viral polymerase chain reaction.
    2. Abnormal ECG findings may initiate a further diagnostic workup.

3. Coronary angiography may be performed to rule out acute coronary syndrome.
4. Echocardiography is useful in ruling out other causes (e.g., valve abnormality) and for monitoring ventricular size and function.
5. Cardiac magnetic resonance imaging (MRI) can provide noninvasive myocardial tissue characterization to support a diagnosis.
    a. Only used in clinically stable patients; can be used to guide endomyocardial biopsy
    b. Its use should not delay endomyocardial biopsy in patients with life-threatening presentation.
6. Assessment of serum cardiac autoantibodies may be performed in the absence of viral or other causes.
    a. Indicates an autoimmune cause
    b. May help guide therapy (e.g., immunosuppression)

E. Management
1. The main principles are treatment of heart failure and arrhythmias.
2. Physical activity should be restricted in patients with asymptomatic or mild symptoms; at least 6 months is recommended.
3. Patients presenting with hemodynamically stable heart failure should be treated with guideline-directed medical therapy, including diuretics, angiotensin-converting enzyme inhibitors (ACE) or angiotensin II receptor blockers (ARBs), β-blockers, and aldosterone receptor antagonists.
4. In patients with hemodynamic instability, acute/fulminant myocarditis, cardiogenic shock, or severe LV dysfunction, support with a ventricular assist device or ECMO may be necessary.
    a. Used as a bridge to recovery or transplantation
    b. ECMO is beneficial in myocarditis recovery in both adult and pediatric patients.
5. Arrhythmias
    a. Should be managed according to current guidelines
    b. Common arrhythmias include sinus bradycardia and prolonged QRS duration.
    c. Temporary pacing may be needed for complete AV block.
    d. Use of implanted cardioverter-defibrillators is not recommended because patients may recover.
    e. A wearable external defibrillator may be used temporarily.
6. Corticosteroids
    a. Used first-line in most noninfectious cases.
    b. May be used alone or in combination with immunosuppressants
    c. Infection-related myocarditis must be ruled out.
    d. Limited evidence shows they may be beneficial in the treatment of autoimmune, giant cell, and eosinophilic myocarditis and cardiac sarcoidosis.
7. Immunosuppressants
    a. Used second-line after corticosteroids.
    b. Usually azathioprine and/or cyclosporine combined with corticosteroids; mycophenolate mofetil improved LV ejection fraction in one small observational study
    c. Infection-related myocarditis must be ruled out by endomyocardial biopsy.
    d. Limited evidence shows they may be beneficial in the treatment of autoimmune and giant cell myocarditis and cardiac sarcoidosis.
8. Intravenous immunoglobulin
    a. May be beneficial in refractory viral and autoimmune-related myocarditis
    b. May reduce mortality and improve LV ejection fraction
    c. Results in trials involving adults and children with viral myocarditis have been inconsistent.
9. Antiviral therapy has no proven role in the treatment of myocarditis.

**Patient Case**

6. A.N. is a 13-year-old male adolescent with a diagnosis of acute viral myocarditis. He is hemodynamically stable but has signs of heart failure, including jugular venous distension, ascites, shortness of breath, and reduced LV ejection fraction on TTE. Which therapy would best be initiated for A.N.'s myocarditis?
   A. ECMO.
   B. Furosemide.
   C. Methylprednisolone.
   D. Intravenous immunoglobulin.

## IV. VALVULAR DISORDERS

A. Introduction
   1. Can present acutely (e.g., IE) or progress slowly over time (e.g., calcific AS)
   2. Causes of valvular heart disease (VHD) are multifactorial but have predominant etiologies.
      a. Valvular calcification is the most common etiology of AS in adults.
      b. The leading cause of aortic regurgitation (AR), also called aortic insufficiency, is abnormal valve leaflets (e.g., IE, congenital bicuspid valve) or aortic root disease (e.g., Marfan aortic dissection).
      c. Rheumatic fever is a primary cause of mitral stenosis (MS) in nonindustrialized countries, whereas calcification of the valve leaflets occurs with increasing frequency in older adult North American patients.
      d. Acute mitral regurgitation (MR) can result from chordae tendineae or papillary muscle rupture (e.g., from acute myocardial infarction); chronic MR often results secondarily from LV dilation and remodeling.

B. Diagnosis
   1. Physical examination should be performed in all patients.
   2. Initially, ECG and chest radiography should be performed in patients with suspected VHD to assess rhythm and pulmonary congestion or other lung pathology.
   3. Echocardiography (using TTE) is the gold standard for confirming a diagnosis of VHD and in assessing severity and prognosis.
   4. Cardiac catheterization may be used to assess pressures in the cardiac chambers.
   5. Exercise stress testing may be used to resolve discrepancies between clinical signs/symptoms and other objective testing.
      a. Avoid in symptomatic patients with AS with high valve velocity or pressure gradients.
      b. May use invasive hemodynamic assessment
   6. Cardiac MRI may be useful with inadequate echocardiographic results or testing discrepancies.
   7. Computed tomography may also be used to assess the severity of VHD.

C. Staging and Progression of VHD (Table 16)

**Table 16.** General Staging and Progression of VHD

| Stage | Definition | Description |
|---|---|---|
| A | At risk | Risk factors for VHD |
| B | Progression | Progressive VHD of mild to moderate severity without symptoms |
| C | Asymptomatic severe | Asymptomatic with criteria for severe VHD:<br>C1: Compensated left or right ventricle in asymptomatic severe VHD<br>C2: Decompensated left or right ventricle in asymptomatic severe VHD |
| D | Symptomatic severe | Symptomatic VHD |

VHD = valvular heart disease.

D. Signs and Symptoms (Table 17)

**Table 17.** Signs and Symptoms with VHD

| Valve Disorder | Definition | Stage D Symptoms |
|---|---|---|
| AS | Narrowing of the aortic valve with reduced flow through the valve | DOE, exercise intolerance, angina, syncope or presyncope, HF |
| AR | Valvular dysfunction that allows flow of blood back into the LV | DOE, angina, or severe HF symptoms |
| MS | Narrowing of the mitral valve with reduced flow through the valve | Decreased exercise tolerance, DOE |
| Acute MR | Acute valvular dysfunction that allows flow of blood back into the left atrium and pulmonary veins during systole | Decreased exercise tolerance, DOE |
| Chronic MR | Gradual valvular dysfunction that allows flow of blood back into the left atrium and pulmonary veins during systole | HF symptoms that persist with revascularization and medical therapy, decreased exercise tolerance, DOE |
| TR | Valvular dysfunction that allows flow of blood back into the right atrium during systole | Fatigue, palpitations, dyspnea, abdominal bloating, anorexia, edema |

AR = aortic regurgitation; AS = aortic stenosis; DOE = dyspnea on exertion; HF = heart failure; LV = left ventricle/ventricular; MR = mitral regurgitation; MS = mitral stenosis; TR = tricuspid regurgitation.

E. Therapy
   1. Prompt recognition and initiation of antimicrobial therapy is recommended for primary prevention of rheumatic fever in patients with suspected streptococcal pharyngitis.
   2. Secondary prevention of rheumatic heart disease
      a. Patients with prior documented rheumatic fever or rheumatic heart disease (especially MS) should receive long-term antistreptococcal group (group A) prophylaxis.
      b. Recommended therapy (Table 18) should be given for at least 10 years or until the patient is 40 years of age, whichever is longer.

**Table 18.** Secondary Prevention Therapy for Rheumatic Heart Disease in Adults

| Agent | Regimen |
|---|---|
| Benzathine penicillin G | 1.2 million units IM every 4 wk[a] |
| Penicillin V potassium | 200 mg PO BID |
| Sulfadiazine | 1 g PO once daily |
| Macrolide or azalide antibiotic[b] | Erythromycin 250 mg PO BID |

[a]Recommendation is to administer every 3 wk in certain high-risk situations.

[b]For patients with PCN or sulfa allergy.

3. Symptom-based guideline-directed medical therapy
    a. Aortic Stenosis (AS)
        i. Treat hypertension and heart failure according to guideline-directed medical therapy (i.e., diuretics, β-blockers, ACEs/ARBs, aldosterone receptor antagonists, and/or sacubitril/valsartan, sodium-glucose cotransporter 2 inhibitors, and ivabradine), beginning with low medication doses and slow titration.
        ii. ACE inhibitors or ARBs and β-blockers (especially with concurrent coronary artery disease) are appropriate.
        iii. Avoid diuretics in patients with a small LV because of the possible decrease in cardiac output.
        iv. Vasodilators (e.g., sodium nitroprusside, nitroglycerin) may be used with invasive monitoring in acute decompensated AS to reduce afterload and improve cardiac output in patients with New York Heart Association class IV heart failure symptoms.
        v. Statin therapy is indicated for all patients with calcific AS for primary and secondary prevention of atherosclerosis; however, it is not indicated to prevent hemodynamic progression of AS.
    b. Aortic Regurgitation (AR)
        i. β-Blockers are useful in acute AR caused by aortic dissection because they reduce shear stress and propagation of the lesion. They should be avoided in other causes of acute AR because they decrease compensatory tachycardia and precipitously reduce blood pressure in acute AR.
        ii. Chronic
            (a) In treating hypertension in patients with chronic AR, systolic blood pressure less than 140 mm Hg is the target.
            (b) Dihydropyridine calcium channel blockers or ACE inhibitors/ARBs are first line for managing hypertension and ACE inhibitors or ARBs are first line for heart failure in patients with chronic AR.
            (c) β-Blockers are less effective because the reduction in heart rate they produce increases stroke volume, thus increasing systolic blood pressure.
            (d) ACE inhibitors/ARBs and/or sacubitril/valsartan is recommended in patients with symptomatic severe AR and/or LV dysfunction when surgery is contraindicated.
    c. Mitral Stenosis (MS)
        i. Symptoms can be improved with diuretics, beta-blockers, nondihydropyridine calcium channel blockers, and ivabradine.
        ii. Patients with MS and concurrent atrial fibrillation (AF) should have heart rate controlled with an appropriate agent (e.g., β-blocker, non-dihydropyridine calcium channel blocker).
        iii. β-Blockers can be beneficial in patients with MS and resting or exercise-induced tachycardia who are in normal sinus rhythm.

d. Mitral Regurgitation (MR)
   i. Vasodilators (e.g., sodium nitroprusside, nicardipine) can improve hemodynamic compensation in acute MR by reducing afterload, thus reducing LV output by the regurgitant pathway.
   ii. Nitrates and diuretics are used in acute MR to reduce filling pressures.
   iii. Patients with chronic severe secondary MR and LV dysfunction should be treated with guideline-directed medical therapy for heart failure (i.e., diuretics, β-blockers, ACEs/ARBs, aldosterone receptor antagonists, and/or sacubitril/valsartan, sodium-glucose cotransporter 2 inhibitors, and ivabradine).
   iv. Vasodilators are not recommended in asymptomatic normotensive patients with chronic MR and normal LV function.

e. Tricuspid regurgitation
   i. Diuretics (usually loop diuretics) are useful in severe tricuspid regurgitation with signs of right-sided heart failure.
   ii. Aldosterone antagonists may be considered for hepatic congestion associated with increased renin activity.
   iii. Targeted pulmonary vasodilators may be considered to reduce elevated pulmonary arterial pressures in severe functional tricuspid regurgitation.

**Patient Case**

*Questions 7 and 8 pertain to the following case.*

B.G. is a 72-year-old woman who presents to her cardiologist with complaints of worsening shortness of breath over the past 2 weeks and inability to complete normal activities of daily living without assistance. She has a history of AS and coronary artery bypass grafting 5 years ago. Her medical history is significant for coronary artery disease, chronic obstructive pulmonary disease, type 2 diabetes, hypertension, heart failure with reduced ejection fraction, and AF. Her social history is significant for smoking 1 pack/day, but she quit 5 years ago; she denies alcohol and illicit drug use. Her home medications include metformin 1000 mg orally twice daily, aspirin 81 mg orally daily, atorvastatin 80 mg orally daily, tiotropium Respimat 2 inhalations daily, lisinopril 10 mg orally daily, metoprolol succinate 50 mg orally daily, furosemide 40 mg orally daily, insulin glargine 20 units subcutaneously at bedtime, rivaroxaban 20 mg orally daily, and albuterol metered dose inhaler 2 puffs every 4 hours as needed for shortness of breath. She has no known drug allergies. On physical examination, her heart rate is 81 beats/minute, respiratory rate is 20 breaths/minute, and blood pressure is 125/89 mm Hg, and she has no signs of volume overload. A TTE done 1 week earlier reveals LV ejection fraction 35%, reduced LV volume, reduced AV area (0.9 $cm^2$), and increased AV pressure gradient of 50 mm Hg.

7. Which medication therapy changes would most likely benefit B.G. while she awaits elective AVR?
   A. Add spironolactone.
   B. Replace metoprolol with diltiazem.
   C. Add isosorbide mononitrate.
   D. Reduce furosemide to 20 mg daily.

4. Surgery
   a. Most patients with VHD require surgical valvular repair or replacement; those with some types of acute or symptomatic VHD usually require urgent or emergency surgery.
   b. Operative mortality risk can be determined with a validated scoring tool.
      i. EuroSCORE (European System for Cardiac Operative Risk Evaluation): www.euroscore.org/
      ii. Society of Thoracic Surgeons score: http://riskcalc.sts.org/stswebriskcalc/#/

5. Transcatheter edge-to-edge repair
    a. Catheter-based intervention used for both mitral (MitraClip™) and tricuspid (TriClip™) valve repair
    b. Recommended in patients with primary MR and severe symptoms and high or prohibitive surgical risk if life expectancy is at least 1 year
    c. Recommended in patients with secondary MR related to LV systolic dysfunction who have persistent severe symptoms while receiving guideline-directed medical therapy for heart failure
    d. Recommended for primary or secondary severe symptomatic tricuspid regurgitation in inoperable patients at a center with expertise in the procedure
6. Prosthetic valves: Choice of valve type should be a shared decision-making process, considering the risk-benefit of anticoagulation and need for reintervention in the future (Table 19). Valve types are shown in Table 20.

**Table 19.** Shared Decision Considerations with Valve Prosthesis

| Factor | Favors Mechanical | Favors Bioprosthetic |
|---|---|---|
| Age | Less than 50 | Greater than 65 |
| Anticoagulation complications | Low risk | High risk |
| Valve sounds | Tolerant of sounds | Intolerant of sounds |
| Adherence | Adherent to medications and monitoring | Nonadherent to medications and monitoring |
| Anticoagulation need | Additional need (e.g., AF) | None |
| Reintervention risk | High | Low |
| Aortic root size (for AVR) | Small | Large |

AF = atrial fibrillation; AVR = aortic valve replacement.

**Table 20.** Available Prosthetic Valves

| Mechanical | Bioprosthetic |
|---|---|
| Caged ball: Starr-Edwards | Porcine: Hancock I and II, Carpentier-Edwards, Medtronic Freestyle, Bicor |
| Tilting disc: Björk-Shiley, Medtronic-Hall, Ultracor, Omniscience | Bovine: Carpentier-Edwards Perimount, Mitroflow, Ionescu-Shiley |
| Bileaflet: St. Jude, On-X, Carbomedics, Edwards–Duromedics, Edwards Tekna | |

7. Transcatheter aortic valve implantation (TAVI)
    a. Recommended in patients who meet the requirements for aortic valve replacement (AVR) but have prohibitive surgical risk and are predicted to have a post-TAVI survival greater than 12 months
    b. Is a recommended alternative to surgical AVR in older patients (>75 years of age) or with a high surgical risk (i.e., greater than 8% expected mortality)
    c. Reasonable alternative to surgical AVR in patients with an intermediate surgical risk
    d. Also FDA approved as an alternative to surgical AVR in patients with severe AR and low risk of death or complications from surgical valve replacement
    e. Four valves currently approved in the United States: Edwards Sapien 3 and Sapien XT, Medtronic CoreValve, and Evolut R
    f. The Sapien 3 and XT valve has been studied in transcatheter pulmonary valve replacement. Transcatheter pulmonary valve replacement at an experienced center is recommended by the ESC/EACTS guidelines for inoperable patients.

g. Unfractionated heparin is typically used during the procedure to target an activated partial thromboplastin time of 50–300 seconds; bivalirudin may be an alternative for patients with contraindications to heparin.

F. Antithrombotic Therapy in Patients with VHD
   1. Patients with AF and VHD
      a. Anticoagulation with a VKA is indicated in patients with rheumatic MS and AF; direct oral anticoagulants (DOACs) are contraindicated in rheumatic MS.
      b. Anticoagulation is indicated in patients with AF who have native aortic or tricuspid valve disease or MR; a DOAC may be used as an alternative to a VKA in these patients (2021 ESC/EACTS guidelines recommend DOACs over VKAs).
   2. Patients with valve repair
      a. Consider VKA for the first 3 months after mitral and tricuspid valve repair.
      b. Consider ASA 75–100 mg daily for the first 3 months after aortic valve-sparing surgery if no other need for oral anticoagulation therapy.
   3. Patients with valve replacement(s) (Table 21)

**Table 21.** Antithrombotic Therapy in Patients with Valve Replacement(s)

| Antithrombotic Therapy | Surgical Bioprosthetic Valves | Surgical Mechanical Valves | TAVI |
|---|---|---|---|
| Antiplatelet agents | • Reasonable for AVR or MVR: ASA 75–100 mg daily<br>• ASA 75–100 mg daily alone may be considered for 3 months following AVR in patients with no baseline indication for oral anticoagulation. | ASA 75–100 mg daily can be considered in patients with concomitant atherosclerotic disease when bleeding risk is low | - ASA 75–100 mg daily as the only antithrombitic therapy is recommended for life if no other indications for anticoagulation<br>- 2020 ACC/AHA Guidelines state that ASA 75–100 mg daily ± clopidogrel 75 mg daily for 3–6 mo is reasonable in patients at low risk of bleeding; this regimen has been shown in recent meta-analyses to increase bleeding without reducing thrombotic events. |

(*Continued on next page*)

**Table 21.** Antithrombotic Therapy in Patients with Valve Replacement(s) (*Continued*)

| Antithrombotic Therapy | Surgical Bioprosthetic Valves | Surgical Mechanical Valves | TAVI |
|---|---|---|---|
| Oral anticoagulants | • VKA with an INR goal of 2.5 is reasonable for at least 3 mo and up to 6 mo with MVR or AVR in patients with low bleeding risk<br>• Consider DOACs over VKAs 3 months after bioprosthetic valve replacement in patients with AF.<br>• Consider DOACs over VKAs within 3 months following MVR in patients with AF. | • All patients with mechanical heart valves require life-long anticoagulation therapy.<br>• VKA with an INR goal of 2.5 for bileaflet or current-generation single-tilting disc AVR and no additional thromboembolic risk factors[b]<br>• VKA with an INR goal of 3 for MVR, or AVR with older-generation prosthesis (e.g., caged ball) or additional thromboembolic risk factors[b]<br>• VKA with an INR of 1.5–2 is reasonable after the first 3 mo with On-X AVR if no additional thromboembolic risk factors and given with ASA 75-100 mg daily[b] | • VKA as the only antithrombotic agent with an INR goal of 2.5 is recommended for patients with another indication for anticoagulation.<br>• DOACs are not recommended as oral anticoagulation therapy in patients with TAVI. |

[a]Single antiplatelet therapy with aspirin is preferred to dual antiplatelet therapy for patients who receive an anticoagulant, or are a high bleeding risk.

[b]Includes AF, previous thromboembolism, LV dysfunction, or hypercoagulable conditions.

ASA = aspirin; AVR = aortic valve replacement; DOAC = direct oral anticoagulant; INR = international normalized ratio; MVR = mitral valve replacement; TAVI = transcatheter aortic valve implantation; VKA = vitamin K antagonist.

**Patient Case**

8. One month after the visit with her cardiologist, B.G. undergoes TAVI. Which is the best antithrombotic regimen for B.G. after her TAVI procedure?
   A. Low-dose aspirin plus clopidogrel.
   B. Rivaroxaban plus clopidogrel.
   C. Warfarin alone.
   D. Low-dose aspirin plus warfarin.

4. Transitions of care after valve replacement
   a. Management of antithrombotic therapy following valve replacement should be a collaborative approach involving the surgical team and outpatient providers (e.g., primary care provider, anticoagulation clinic).
   b. Ideally, outpatient antithrombotic therapy management should be established for the patient prior to surgery if the procedure is elective.
5. Bridging therapy
   a. Unfractionated or low-molecular-weight heparin initiated when the INR falls below the therapeutic threshold in the pre- or postoperative period; heparin is discontinued 4–6 hours (for unfractionated heparin) or 12 hours (for low-molecular-weight heparin) before surgery
   b. Anticoagulation is generally resumed 12–24 hours postoperatively once surgical bleeding risk has stabilized.
   c. It is recommended that VKA therapy be continued in patients with mechanical heart valves who

are undergoing minor procedures (e.g., dental extractions, cataract removal) in which bleeding can be easily controlled.

d. Bridging unnecessary in patients with a bileaflet mechanical AVR who are undergoing invasive or surgical procedures and have no other risk factors for thrombosis

e. Individual consideration to bridging anticoagulation therapy while the INR is subtherapeutic is reasonable in patients undergoing invasive or surgical procedures with the following:
   i. Mechanical prosthetic heart valve.
   ii. AF with significant mitral stenosis.
   iii. AF with CHA2DS2-VASc score 3 or greater for women or 2 for men.
   iv. Acute thrombotic event within the previous 4 weeks.
   v. High acute thromboembolic risk.

f. 2021 ESC/EACTS guidelines recommend restarting P2Y12 inhibitors postoperatively after valve surgery (once there is no concern for bleeding) in patients receiving dual-antiplatelet therapy for recent PCI (within 1 month) prior to surgery.

6. Failure of initial therapy
   a. Some patients may have an embolic event while receiving anticoagulant therapy.
   b. Mechanical valves
      i. Adequacy of anticoagulation should be investigated.
      ii. If the INR was subtherapeutic, efforts should be made to improve the time in therapeutic range.
      iii. If the INR was therapeutic, the INR goal should be increased or daily low-dose aspirin (i.e., 75–100 mg) should be added:
         (a) 3 (range 2.5–3.5) for AVR
         (b) 4 (range 3.5–4) for mitral valve replacement
   c. For patients with bioprosthetic valves who have an embolic event while only taking antiplatelet therapy, changing to a VKA may be considered.

G. Prosthetic Valve Thrombosis
   1. For patients with symptomatic thrombosis of a left-sided mechanical valve, either emergency surgery or a low-dose slowly infused fibrinolytic is recommended; tissue plasminogen activator 10 mg intravenous bolus followed by 90 mg over 90 minutes with UFH is recommended in the 2021 ESC/EACTS guidelines.
   2. A VKA is reasonable to use initially in patients with a suspected or confirmed bioprosthetic valve thrombosis if the patient's condition is hemodynamically stable and the patient has no contraindications to anticoagulation.
   3. Considerations in deciding between surgery and fibrinolytic therapy are provided in Box 1.

**Box 1.** Factors Favoring Fibrinolytic Therapy

| | |
|---|---|
| • Lack of institutional surgical expertise | • No left atrial thrombus |
| • High surgical risk | • No need for coronary revascularization |
| • No fibrinolytic contraindications | • No other valve disease |
| • First episode of valve thrombosis | • Thrombus visualized on echocardiogram |
| • NYHA class I–III HF | • Patient choice |
| • Small clot ($\leq 0.8$ cm$^2$) | |

HF = heart failure; NYHA = New York Heart Association.

H. Considerations with VHD in Pregnancy
   1. Native VHD
      a. Valvular stenosis
         i. Pregnant patients with MS and AF should receive anticoagulation; warfarin is preferred in

the second and third trimesters, with a conversion to a continuous infusion of unfractionated heparin before planned delivery.
   ii. β-Blockers are reasonable for rate control in pregnant patients with MS.
   iii. Diuretics may be used for pregnant patients with MS and heart failure symptoms.
b. Valvular regurgitation
   i. There are few options other than appropriate guideline-directed medical therapy for pregnant patients with regurgitant VHD.
   ii. Surgery should be avoided during pregnancy unless the patient has refractory New York Heart Association class IV heart failure symptoms.
c. ACE inhibitors and ARBs are contraindicated in pregnancy.

2. Prosthetic valves
   a. Ideally, valve interventions should be done before a planned pregnancy.
   b. Asymptomatic patients with valve stenosis should not have valve surgery during pregnancy.
   c. Bioprosthetic valves are preferred to mechanical valves in women of childbearing age who require valve replacement because of the increased risk posed with the anticoagulation needed with mechanical valves.
   d. Antithrombotic therapy in the first trimester for patients with mechanical valves
      i. Warfarin is recommended if the daily dose required to maintain a therapeutic INR is 5 mg or less.
      ii. Low-molecular-weight heparin (given at least twice daily) is preferred to unfractionated heparin when the daily warfarin dose needed to maintain a therapeutic INR is greater than 5 mg, or the decision is made not to use warfarin.
         (a) Dosing must be guided by anti-Xa concentrations (goal 0.8–1.2 units/mL, 4–6 hours post-dose for aortic valve prosthesis; 1–1.2 units/mL, 4–6 hours post-dose for mitral and right-sided valve prosthesis).
         (b) Continuously infused intravenous unfractionated heparin may be used as an alternative, but the risk of thrombosis is greater.
   e. Antithrombotic therapy in the second and third trimesters in patients with mechanical prosthetic valves
      i. Warfarin is recommended.
      ii. Changing from VKA to low-molecular-weight heparin or intravenous unfractionated heparin is recommended at least 1 week before planned delivery.
      iii. A change to continuous intravenous unfractionated heparin to target an activated partial thromboplastin time greater than 2 times control should be initiated at least 36 hours before planned delivery; therapy should be discontinued at least 6 hours before planned vaginal delivery.
      iv. If urgent delivery is required for a patient therapeutically anticoagulated on a VKA, reversal of anticoagulation should be initiated.
   f. Low-dose (75–100 mg) daily aspirin can be considered in addition to anticoagulation during all trimesters of pregnancy for patients with mechanical valves if it is needed for other indications.

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## ANSWERS AND EXPLANATIONS TO PATIENT CASES

**1. Answer: C**

With the currently available clinical data, this patient has one major criterion and two minor criteria for IE. Thus, she has possible IE, according to the modified Duke criteria. Her major risk factor for IE is that she is a PWID, which is currently active, given the needle track marks found during physical examination. She also probably has right-sided IE, as evidenced by the tricuspid murmur heard during cardiac auscultation, the mobile mass found on the tricuspid valve during the TTE, and the lack of any other signs or symptoms of left-sided IE. Given these factors, the most likely pathogen is *S. aureus*, and guideline-recommended empiric therapy for patients with suspected native valve right-sided IE, or a positive PWID history, is either vancomycin (Answer C) or daptomycin. Ampicillin plus oxacillin plus gentamicin (Answer A) would be used for patients with suspected left-sided native valve or late prosthetic valve IE. Vancomycin plus gentamicin plus rifampin (Answer B) is recommended for early prosthetic valve endocarditis, and vancomycin plus gentamicin (Answer D) is for patients with left-sided native valve IE and severe penicillin allergy.

**2. Answer: A**

Because blood cultures confirm that this patient has IE caused by methicillin-susceptible *S. aureus*, the best therapeutic regimen would be a penicillinase-resistant penicillin such as nafcillin or oxacillin. This regimen is also recommended for patients with uncomplicated right-sided IE being treated with penicillin therapy, and 2 weeks of therapy is adequate. Thus, oxacillin 12 g/day for 2 weeks (Answer A) is correct, and nafcillin 12 g/day for 6 weeks (Answer D) is incorrect because of the unnecessarily long treatment duration. The treatment duration for the vancomycin regimen (Answer B) is correct, but this therapy is only recommended for native valve IE caused by MRSA or in patients with a severe penicillin allergy. Similarly, daptomycin (Answer C) is also only recommended for native valve IE caused by MRSA or patients with a severe penicillin allergy, and the duration should be 6 weeks.

**3. Answer: D**

To receive IE prophylaxis before procedures, patients must first have a condition that places them at risk of IE. A history of IE places this patient at risk; thus, she should receive prophylaxis for qualifying procedures. In this particular scenario, the fact that the patient will be undergoing a surgical procedure on infected skin/skin structure (Answer D) qualifies her for IE prophylaxis. That she had a previous *S. aureus* infection (Answer A) (other than that the infection was IE) does not qualify her for IE prophylaxis. Although her history places her at risk of IE, patients with a PWID history, but no history of IE, do not need IE prophylaxis (Answer B). Finally, IE prophylaxis is recommended for patients with qualifying conditions for IE prophylaxis who are undergoing certain dental procedures, but dental procedures are not the only procedures requiring IE prophylaxis (Answer C).

**4. Answer: A**

Aspirin or NSAIDs are first-line therapy for acute or recurrent pericarditis. Because this patient already takes low-dose aspirin for primary prevention of cardiovascular disease, increasing the aspirin dose (Answer A) would be best for treating pericarditis. Diclofenac (Answer D) would not be a good choice because it has the highest association among NSAIDs with cardiovascular events. Prednisone (Answer B) or another low-dose corticosteroid would only be used in recurrent pericarditis if there was an incomplete response or contraindication to initial therapy with aspirin/NSAID and colchicine. Colchicine (Answer C) is not required initial therapy for pericarditis, but it may be added to aspirin/NSAID therapy to improve response and decrease recurrence.

**5. Answer: B**

Adding colchicine (Answer B) to aspirin/NSAID therapy for recurrent pericarditis reduces the chance of recurrence and improves response to anti-inflammatory therapy. Corticosteroids such as prednisone (Answer A) are only added to the initial therapy of an anti-inflammatory plus colchicine when there is an incomplete response, intolerance, or contraindications to initial therapy. Both azathioprine (Answer C) and anakinra (Answer D) are only used when the patient is intolerant of, or refractory to, other therapies or when corticosteroids cannot be weaned.

**6. Answer: B**

Because this patient has hemodynamically stable myocarditis, ECMO (Answer A) is not indicated; ECMO is only used in hemodynamically unstable myocarditis. However, the patient does have symptoms of heart failure with volume overload, as evidenced by jugular venous distension, ascites, shortness of breath, and reduced LV ejection fraction. Furosemide (Answer B) or another loop diuretic would be indicated to reduce intravascular volume and relieve symptoms (i.e., shortness of breath). Corticosteroids such as methylprednisolone (Answer C) are only recommended in certain autoimmune causes of myocarditis and are contraindicated in infectious causes. Intravenous immunoglobulin (Answer D) may be used in viral myocarditis, but it is only recommended in refractory disease.

**7. Answer: D**

This patient has stage D VHD and needs surgical valve replacement. Because she is hemodynamically stable, her surgery can be scheduled electively, but she needs to be kept medically stable so that she does not acutely decompensate. For patients with severe AS and small LV, diuretic therapy should be avoided in order to increase LV end diastolic volume and maintain adequate cardiac output. Therefore, the best therapeutic intervention at this time is to reduce this patient's furosemide dose (Answer D). This is appropriate because she currently has no signs of volume overload. Spironolactone is recommended as part of guideline-directed medical therapy in patients with chronic MR and LV dysfunction (Answer A is incorrect). Non-dihydropyridine calcium channel blockers such as diltiazem (Answer B) are only used for patients with MS who need rate control for AF and should be avoided in patients with reduced ejection fraction heart failure, like this patient. A nitrate (Answer C) should only be added in patients with severe AS who have New York Heart Association class IV symptoms, which this patient does not.

**8. Answer: C**

This patient will require continued anticoagulation because of her AF, as well as antithrombotic therapy for her AVR. Clinical trial data do not support the use of DOACs in patients with TAVI, and show a higher incidence of bleeding and adverse thrombotic events with DOACs.. Therefore, Answer B (rivaroxaban plus clopidogrel) is incorrect. Answer A (low-dose aspirin plus clopidogrel) is incorrect because it does not include a VKA, and the use of dual-antiplatelet therapy in patients with TAVI without a clear indication (e.g., PCI) increases bleeding without reducing thrombotic events. Answer D (low-dose aspirin plus warfarin) is incorrect because the combination has been shown to increase bleeding risk without conferring additional benefit to prevent thrombotic events. Answer C (warfarin alone) is the best regimen for this patient sbecause it confers a lower risk of bleeding than warfarin plus aspirin. This patient has a high bleeding risk, given her need for chronic anticoagulation and her many comorbidities.

## ANSWERS AND EXPLANATION TO SELF-ASSESSMENT QUESTIONS

**1. Answer: C**
Vancomycin plus rifampin plus gentamicin (Answer C) is the regimen recommended by the ACC/AHA IE guidelines. The patient has a type I hypersensitivity reaction to penicillin; thus, any penicillin-containing regimen (Answers A and B) would be incorrect. Moreover, Answers A (nafcillin plus rifampin plus gentamicin) and B (ampicillin plus ceftriaxone) are incorrect because neither provides adequate coverage for MRSA IE; Answer B is recommended for enterococcal IE. Answer D (vancomycin plus gentamicin) is incorrect because rifampin would need to be added for prosthetic valve IE.

**2. Answer: B**
This patient is a good candidate for outpatient parenteral antimicrobial therapy (Answer B), according to both the ACC/AHA and the ESC IE guidelines. The full course of antimicrobial therapy for IE should always be given parenterally, making Answer D (outpatient oral antimicrobial therapy) incorrect. Moreover, only penicillin-susceptible *Streptococcus* strains can be treated with a 2-week regimen, making Answer A incorrect. Finally, ceftriaxone as a single agent (Answer C) is only recommended for treating native valve IE caused by streptococcal strains with penicillin MICs less than 0.5 mcg/mL.

**3. Answer: D**
Removal of an infected renal calculus (Answer D) is the AHA/ACC and ESC-recommended IE prophylaxis for genitourinary procedures with an established genitourinary infection. Dental procedures involving gingival tissue manipulation, the periapical region, or perforation of the oral mucosa require IE prophylaxis, but cleanings (Answer A) do not. Only procedures on infected skin require IE prophylaxis, making Answer B (elective plastic surgery) incorrect. Invasive GI procedures in the absence of an established GI infection do not require IE prophylaxis, making Answer C (screening colonoscopy) incorrect.

**4. Answer: A**
Aspirin (Answer A) is correct. Because of the patient's positive cardiac enzymes, he likely has myopericarditis, and aspirin or NSAIDs are preferred first-line agents for myopericarditis. Moreover, aspirin would be preferred to NSAIDs because the patient is also being ruled out for an acute myocardial infarction. Colchicine has not been studied in myopericarditis or as monotherapy without aspirin or an NSAID, making Answer B incorrect. Moreover, the patient had no evidence of pericardial effusion on TTE, infection was ruled out with clear chest radiography, and he had negative HIV screening and a normal WBC; thus, use of intrapericardial tissue plasminogen activator (Answer C) to clear loculated pericardial effusions is unwarranted. Finally, azathioprine (Answer D) is only useful in recurrent pericarditis or certain autoimmune-related causes.

**5. Answer: C**
Intravenous immunoglobulin (Answer C) is correct because the ESC myocarditis guidelines state that it may reduce mortality and improve LV function in refractory viral myocarditis. Corticosteroids (Answer B) and immunosuppressants such as cyclosporine (Answer D) should not be used in infection-related myocarditis. Finally, antivirals (Answer A) have no proven benefit in myocarditis.

**6. Answer: A**
Ramipril (Answer A) is best because the AHA/ACC and ESC guidelines recommend that hypertension be initially managed with ACE inhibitors/ARBs or β-blockers in patients with AS. Hydrochlorothiazide (Answer B) is incorrect because diuretics should generally be avoided in patients with AS and reduced ventricular size. Amlodipine (Answer C) is incorrect because dihydropyridine calcium channel blockers are preferred in AR not AS. Finally, aliskiren (Answer D) is not recommended because it has not been studied in AS.

**7. Answer: D**
A VKA for at least the first 3 months targeting a goal INR of 2.5 (Answer D) is correct. The ACC/AHA and ESC guidelines for VHD recommend adding a VKA to low-dose aspirin therapy in patients with a low risk of bleeding after bioprosthetic valve replacement. Clopidogrel (Answer B) added to low-dose aspirin is incorrect because this dual-antiplatelet regimen has not been studied in patients with surgical bioprosthetic valve replacements. Dabigatran 150 mg twice daily

(Answer C) is incorrect because DOACs are only recommended in patients with bioprosthetic heart valves with concomitant AF. Answer A (VKA with a goal INR of 3 for up to 6 months) is incorrect because the recommended goal INR of 3 is higher than recommended for bioprosthetic heart valves.

**8. Answer: C**

A low-molecular-weight heparin guided by anti-Xa monitoring (Answer C) is the recommended anticoagulant in the first trimester of pregnancy for patients with a prosthetic heart valve who require more than 5 mg/day of warfarin to maintain a therapeutic INR. The ACC/AHA guidelines for VHD recommend avoiding warfarin during the first trimester in pregnant patients with prosthetic heart valves when the dose required to maintain a therapeutic INR is greater than 5 mg daily, making Answer A incorrect. Reducing the warfarin dose to target an INR of 2.5 (Answer B) is incorrect because a higher target INR is needed with a prosthetic mitral valve replacement to significantly reduce the risk of thromboembolism. Unfractionated heparin (Answer D) is incorrect because unfractionated heparin is not as effective as low-molecular-weight heparin.

# Translation of Evidence into Practice

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and

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**Learning Objectives**

1. Identify different types of data (nominal, ordinal, continuous) to determine the appropriate type of statistical test (parametric vs. nonparametric).
2. Select appropriate statistical tests based on the anticipated sample distribution, data type, and study design.
3 Identify the most appropriate study design to answer a given research question.
4. Describe the key tenets of internal and external validity of cardiovascular-related trials.
5. Describe the advantages and disadvantages of surrogate and composite outcomes in cardiovascular studies.

**Abbreviations in This Chapter**

| | |
|---|---|
| ANOVA | Analysis of variance |
| CI | Confidence interval |
| HR | Hazard ratio |
| RCT | Randomized controlled trial |
| SD | Standard deviation |

**Self-Assessment Questions**

*Answers and explanations to these questions can be found at the end of the chapter.*

1. Researchers conducted a 12-week randomized controlled trial comparing two doses of a new cholesterol-lowering medication with placebo. The primary end point of the trial was the change in low-density lipoprotein cholesterol (LDL) from baseline between the three groups. Which statistical test would be most appropriate for comparing this end point?
   A. Analysis of variance (ANOVA).
   B. Chi-square.
   C. Mann-Whitney *U* test.
   D. t-test.

*Questions 2 and 3 pertain to the following case.*

A multicenter, double-blind, active-controlled trial randomized 8442 patients with New York Heart Association class II–IV heart failure and an ejection fraction of 40% or less to receive either sacubitril/valsartan or enalapril. The primary combined outcome was death from cardiovascular causes or hospitalization for heart failure. Data were analyzed according to intention-to-treat analysis using a Cox proportional hazards model. The hazard ratio (HR) and 95% confidence interval (CI) between groups for sacubitril/valsartan was 0.80 and 0.73–0.87, respectively, compared with enalapril. In a prespecified subgroup of patients 75 and older, sacubitril/valsartan was associated with an HR of 0.86 (95% CI, 0.72–1.04).

2. Which statement is most appropriate to describe the findings of this study?
   A. Sacubitril/valsartan statistically significantly reduced the combined end point versus enalapril ($p<0.05$).
   B. Sacubitril/valsartan statistically significantly reduced the combined end point versus enalapril ($p<0.0001$).
   C. Sacubitril/valsartan did not significantly reduce the combined end point versus enalapril ($p>0.05$).
   D. Without a p-value, it is not possible to determine whether sacubitril/valsartan affected the combined end point.

3. When the study was being designed, the outcome for which the study was most likely to have been powered was the difference in the rate of one factor. Which best describes that factor?
   A. Heart failure hospitalization.
   B. Combined end point.
   C. Combined end point in patients 75 and older.
   D. Combined end point in patients younger than 75.

4. The 2022 ACC/AHA/HFSA guideline for the management of heart failure is best considered which type of literature?
   A. Primary.
   B. Secondary.
   C. Tertiary.
   D. Guidelines.

5. You want to conduct a study that will include patients hospitalized for acute decompensated heart failure (ADHF), looking at whether they received milrinone or dobutamine during any point of their

hospitalization and evaluating all-cause mortality. Which design is most appropriate for this study?

A. Cross-sectional.
B. Case-control.
C. Cohort.
D. Case series.

6. While evaluating a clinical trial to present during a journal club, you discover that the authors used a Mann-Whitney *U* test to conduct their statistical analysis. Which type of data would this test most likely be used to compare?

A. Nominal.
B. Survival.
C. Parametric.
D. Nonparametric.

7. A multicenter clinical trial enrolled 7020 patients with type 2 diabetes at high cardiovascular risk and randomized them to receive either empagliflozin or placebo. The objective was to determine whether the rate of a composite outcome of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke occurred no more often with empagliflozin than with placebo. Which most accurately describes this study design?

A. Equivalence.
B. Noninferiority.
C. Superiority.
D. Pragmatic.

8. You are precepting a resident's research project that is aimed at identifying predictors of corrected QT (QTc) interval prolongation in patients admitted to the cardiac intensive care unit. Which technique would be most useful in completing such an analysis?

A. Correlation.
B. Kaplan-Meier curve.
C. Regression.
D. Chi-square.

9. A single-center retrospective cohort study compared statins and control in patients who underwent cardiac valve surgery. The primary outcome was the occurrence of postoperative atrial fibrillation (POAF). The rate of POAF was 34.3% in the statin group and 27.5% in the control group with an odds ratio of 1.38 and a 95% CI of 0.80–2.40. Which conclusion is most appropriate?

A. Statins are superior to control.
B. Superiority of statins to control was not established.
C. Statins are inferior to control.
D. No conclusion can be drawn because p-values are unavailable.

## I. INTRODUCTION

A. Cardiovascular Specialty Examination content outline, Domain 2: Translation of Evidence into Practice (20%)
   1. Apply knowledge of the appropriate design and conduct of clinical trials involving patients with or at risk of cardiovascular disease.
   2. Evaluate and critique cardiovascular literature, including study design and methodology, statistical analysis, significance of reported data, and conclusions, and applicability of results to patients with or at risk of cardiovascular disease.
   3. Identify and evaluate landmark clinical trials and apply the results to patients with or at risk of cardiovascular disease.
   4. Interpret and apply pertinent cardiovascular guideline recommendations to patients with or at risk of cardiovascular disease. (not covered here)

## II. PRIMARY, SECONDARY, AND TERTIARY SOURCES OF CARDIOVASCULAR-RELATED INFORMATION

A. Primary Literature
   1. Original Research, either published or unpublished
      a. Forms the foundation of the literature hierarchy
      b. Is the source of information for the development of secondary and tertiary sources
   2. Information is presented in its original form
   3. Could include journal articles, conference papers, technical reports, and theses and dissertations
   4. Examples: Research studies, case reports, editorials, letters to the editor
   5. Advantages
      a. Ability to obtain current, original, complete, detailed information on a topic
      b. Information has most often been peer reviewed (except for sources such as editorials and letters to the editor).
   6. Disadvantages
      a. Requires in-depth knowledge of study design and biostatistics to properly interpret
      b. Conducting thorough searches to find the primary literature can be challenging and time-consuming.
   7. Top 10 Cardiovascular Journals (by impact factor [IF], 2021)
      a. *Nature Reviews Cardiology* (IF = 49.4)
      b. *Circulation* (IF = 39.9)
      c. *European Heart Journal* (IF = 35.9)
      d. *JAMA Cardiology* (IF = 30.2)
      e. *JACC* (IF = 27.2)
      f. *Circulation Research* (IF = 23.2)
      g. *European Journal of Heart Failure* (IF = 18.2)
      h. *Current Problems in Cardiology* (IF = 16.5)
      i. *JACC Cardiovascular Imaging* (IF = 16.1)
      j. *Cardiovascular Research* (IF = 14.2)

B. Secondary Literature
   1. Includes indexing and abstracting systems that organize and provide easy retrieval of the abstract for a primary source
   2. Examples include PubMed (MEDLINE), Embase, National Library of Medicine Gateway, Scopus, Web of Science, International Pharmaceutical Abstracts, and Cochrane Library.
   3. Each database has its own scope or focus (or foci, if plural).
      a. MEDLINE = biomedical sciences
      b. PsycINFO = behavioral and social science research
      c. CINAHL = nursing and allied health literature
   4. MeSH (Medical Subject Headings) are used to organize the literature and can be used to identify relevant citations. Apply for PubMed and MEDLINE only. Other databases use key words.
   5. Advantages
      a. Quick access to primary literature
      b. Provides broad scope or concise information on topics, depending on preference
      c. Citations are peer reviewed (mostly) and routinely updated.
   6. Disadvantages
      a. May be time lag between publication and indexing in the database
      b. Can easily get lost in the weeds without experience or guidance
      c. Some require subscriptions, which can be costly if not covered by the institution.
      d. May still have to pay to get access to the full paper, even in publicly free databases such as PubMed

C. Tertiary Literature
   1. General sources of information derived from primary and secondary sources
   2. Can include guidelines, textbooks, reference texts, review articles, and websites
   3. Advantages
      a. Convenient and more accessible than other sources
      b. Easy-to-find topic-specific sources
      c. Usually written by experts in the given field
   4. Disadvantages
      a. Can be an appreciable lag time between time of writing and publication (especially for textbooks)
      b. Print sources may have space limitations.
      c. May not be complete reviews of a topic, but rather a select discussion of literature based on the author's opinions or biases
   5. General Drug Information Resources
      a. AHFS (American Hospital Formulary Service)
      b. Clinical Pharmacology
      c. Drug Facts & Comparisons
      d. *Drug Information Handbook*
      e. *Handbook on Injectable Drugs*
      f. Lexi-Comp
      g. *Martindale: The Complete Drug Reference*
      h. Micromedex
      i. *Physicians' Desk Reference*
   6. Cardiology Textbooks/Resources
      a. *Braunwald's Heart Disease: A Textbook of Cardiovascular Medicine*
      b. *Current Diagnosis and Treatment Cardiology*
      c. *ESC Textbook of Cardiovascular Medicine*
      d. *Hurst's The Heart*
      e. UpToDate (general medicine resource that includes cardiology information)

## III. BIOSTATISTICAL METHODS USED IN CARDIOVASCULAR TRIALS

A. Clinician and trainee understanding of biostatistics and literature evaluation is generally poor.

B. Survey of 214 PGY1 residents showed an overall mean biostatistics knowledge score of 47.3% (range 0–90) (Ann Pharmacother 2012;46:991-9).
   1. Identify analytic method for a nominal variable = 69.4% correct
   2. Identify analytic method for continuous variable = 52.5% correct
   3. Identify analytic method for ordinal variable = 41.9% correct
   4. Interpret p>0.05 = 59.6% correct
   5. Identify proportional hazard regression = 24.8% correct
   6. Calculate number needed to treat = 49.0% correct
   7. Interpret standard deviation (SD) = 44.9% correct
   8. Interpret relative risk = 75.8% correct

C. Common Types of Variables and Data
   1. Discrete variables (e.g., dichotomous, categorical)
      a. Nominal: Classified into groups in an unordered manner and with no indication of relative severity
         i. Sex (male or female), mortality (dead or alive), development of atrial fibrillation (yes or no), race (white, African American, Asian American, Hispanic)
         ii. Dichotomous are variables that have only two possible outcomes (e.g., yes/no, male/female).
      b. Ordinal: Ranked in a specific order, but with no consistent level of magnitude between ranks. New York Heart Association functional classes I–IV
   2. Continuous variables
      a. Can be any value within a given range
      b. Interval: Ranked in a specific order with a consistent level of magnitude between units and an arbitrary zero point: Degrees Fahrenheit
      c. Ratio: Similar to "Interval" but with an absolute zero: Blood pressure, heart rate, cholesterol

D. Descriptive Statistics
   1. Measures of Central Tendency
      a. Mean (a.k.a. average)
         i. Sum of all the values divided by the total number of values
         ii. Used for continuous data that are normally distributed
         iii. Most commonly reported and understood measure of central tendency
         iv. Strongly affected by extreme values in the data (outliers)
      b. Median (a.k.a. middle or 50th percentile)
         i. Is the middle value (when placed from highest to lowest), with half of the values above it and half below it
         ii. Can be applied to ordinal or continuous data
         iii. More appropriate measure of central tendency when the data are skewed or asymmetric
         iv. Unlike the mean, the median is insensitive to extreme values.
      c. Mode
         i. Is the most commonly reported value in a distribution
         ii. Rarely used in biomedical literature
         iii. Can be used for nominal, ordinal, or continuous data
         iv. Sometimes, there may be more than one mode (e.g., bimodal, trimodal).

2. Measures of Variability
    a. Standard deviation (SD)
        i. Measure of variability around the mean for continuous data that are normally or near-normally distributed
        ii. Calculated as the square root of the variance. Variance is the average squared difference of each observation from the mean.
        iii. By the empirical rule for normal distributions, 68% of the sample values are found within ± 1 SD, 95% are found within ± 2 SD, and 99% are found within ± 3 SD.
        iv. Be careful to not confuse with standard error of the mean (SEM = SD/√n), which quantifies uncertainty in the estimate of the mean and will always be smaller than the SD. SEM is used for calculating CIs (95% CI is about the mean ± 2 times the SEM).
    b. Range
        i. Represents the difference between the highest and lowest data values
        ii. Easy to compute (simple subtraction) but does not give a tremendous amount of information by itself
    c. Percentiles
        i. The point (value) in a distribution in which a value is larger than some percentage of the other values in the sample. The 75% percentile lies at a point at which 75% of the other values are smaller.
        ii. Does not assume the population has a normal distribution
        iii. The interquartile range (IQR) is an example of the use of percentiles to describe the middle 50% values. The IQR encompasses the 25th–75th percentile. Is most commonly paired with the median, which represents the 50th percentile
3. Data presentation should include not only measure of central tendency (which can be misleading on its own) but also measures of data spread.
    a. Mean ± SD (or SEM)
    b. Median and IQR
4. Discrete Distributions
    a. Binomial distribution
    b. Poisson distribution

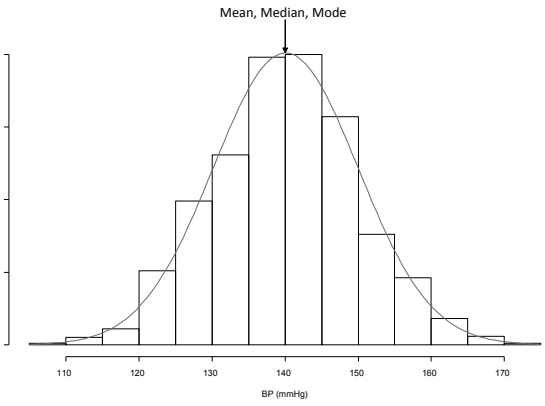


**Figure 1.** Normal distribution

5. Normal (Gaussian) Distribution
    a. Most common model for population distributions
    b. Symmetric or bell-shaped frequency distribution (see Figure 1)

c. A visual check of a distribution can help determine whether it is normally distributed (whether it appears symmetric and bell shaped). Need the data to perform these checks (cannot do from published study)
    i. Frequency distribution and histograms (should always be done)
    ii. Median and mean will be about equal for normally distributed data (most practical and easy to perform).
d. Mean and SD values define a normally distributed population.

E. Hypothesis Testing
1. Null and Alternative Hypotheses
    a. Null hypothesis ($H_0$): Example: No difference between groups being compared (treatment A equals treatment B)
    b. Alternative hypothesis: Example: Opposite of null hypothesis; states that there is a difference (treatment A does not equal treatment B)
    c. The structure or the manner in which the hypothesis is written dictates which statistical test is used. Two-sample t-test: $H_0$: Mean 1 = Mean 2
    d. Used to assist in determining whether any observed differences between groups can be explained by chance
    e. Tests for statistical significance (hypothesis testing) determine whether the data are consistent with the $H_0$ (e.g., no difference).
    f. The results of the hypothesis testing will indicate whether enough evidence exists for the $H_0$ to be rejected.
        i. If the $H_0$ is rejected: Statistically significant difference between groups (unlikely attributable to chance)
        ii. If the $H_0$ is not rejected: No statistically significant difference between groups (any apparent differences may be attributable to chance). Note that we are not concluding that the treatments are equal.
    g. Types of hypothesis testing: Situations in which two groups are being compared. These procedures can be applied to many other examples of situations.
2. To determine what is sufficient evidence to reject the $H_0$: Set the a priori significance level (α) and generate the decision rule.
    a. Developed after the research question has been stated in hypothesis form
    b. Used to determine the level of acceptable error caused by a false positive (also known as level of significance). Convention: A priori α is usually 0.05.
3. Perform the experiment and estimate the test statistic.
    a. A test statistic is calculated from the observed data in the study, which are compared with the critical value.
    b. Depending on this test statistic's value, the $H_0$ is not rejected (often called fail to reject) or rejected.
    c. In general, the test statistic and critical value are not presented in the literature; instead, p-values are generally reported and compared with a priori α values to assess statistical significance. p-value: Probability of obtaining a test statistic and critical value as extreme as or more extreme than the one actually obtained
    d. Because computers are used in these tests, this step is often transparent; the p-value estimated in the statistical test is compared with the a priori α (usually 0.05), and the decision is made to either accept or reject the $H_0$.

4. p-values (Am Stat 2019;73(Suppl):1-19)
   a. "p" stands for "probability."
   b. Defined as the probability, assuming the null hypothesis is true, of obtaining a result equal to or more extreme than what was actually observed in the investigation
   c. This value is then compared with the predetermined α value, and a decision to accept or reject the $H_0$ is made (statistical significance).
      i. Remember that the conventional α = 0.05 is an arbitrary cutoff and not a magic bullet.
      ii. Does a p=0.052 really mean something different from a p=0.047? Should these results truly be interpreted differently?
   d. Statistical significance should not be confused with, and does not suggest, clinical significance.
   e. It is inappropriate to interpret a smaller p-value (e.g., 0.00001 vs. 0.001) as being more meaningful, particularly if both are deemed statistically significant. Rather, a smaller p-value shows a lower probability that the findings are the result of "chance." p-values do not reflect magnitude or importance of a difference between groups.
5. Confidence Intervals (CIs)
   a. Commonly reported as a way to estimate a population parameter. In the medical literature, 95% CIs are the most commonly reported CIs. In repeated samples, 95% of all CIs include true population value (i.e., the likelihood or confidence [or probability] that the population value is contained within the interval). In some cases, 90% or 99% CIs are reported.
   b. CIs instead of hypothesis testing
      i. Hypothesis testing and calculation of p-values tell us whether a statistically significant difference exists between groups, but they tell us nothing about the magnitude of the difference.
      ii. CIs help us determine the importance of a finding or findings, which we can apply to a situation.
      iii. CIs give us an idea of the range of magnitude of the difference between groups and the statistical significance.
      iv. CIs can also tell us whether results are statistically significant (if it crosses the line of unity [e.g., 1 for a relative risk or odds ratio]).
      v. CIs are a range of data, together with a point estimate of the difference.
      vi. Wide CIs
         (a) Many results are possible, either larger or smaller than the point estimate provided by the study.
         (b) All values contained in the CI are statistically plausible.
      vii. If the estimate is the difference between two continuous variables (for a mean or median): A CI that includes zero (no difference between two variables) can be interpreted as not statistically significant (a p-value of 0.05 or greater). There is no need to show both the 95% CI and the p-value.
      viii. Interpretation of CIs for odds ratios, HRs, and relative risks is somewhat different. In those cases, a value of 1 indicates no difference in risk, and if the CI includes 1, there is no statistical difference.

F. Decision Errors

**Table 1.** Summary of Decision Errors

| | **Underlying Truth or Reality** | |
|---|---|---|
| **Test Result** | $H_0$ is true (no difference) | $H_0$ is false (difference) |
| Accept $H_0$ (no difference) | No error (correct decision) | Type II error (β error) |
| Reject $H_0$ (difference) | Type I error (α error) | No error (correct decision) |

$H_0$ = null hypothesis.

1. Type I Error: Probability of making this error is defined as the significance level α (see Table 1).
    a. Convention is to set the α to 0.05, effectively meaning that, 1 in 20 times, a type I error will occur when the $H_0$ is rejected. Thus, 5.0% of the time, a researcher will conclude that there is a statistically significant difference when one does not actually exist.
    b. The calculated chance that a type I error has occurred is called the p-value.
    c. The p-value tells us the likelihood of obtaining a given (or a more extreme) test result if the $H_0$ is true. When the α level is set a priori, the $H_0$ is rejected when p is less than α. In other words, the p-value tells us the probability of being wrong when we conclude that a true difference exists (false positive).
    d. A lower p-value does not mean the result is more important or more meaningful but only that it is statistically significant and less likely to be attributable to chance.
2. Type II Error: Probability of making this error is called beta.
    a. Concluding that no difference exists when one truly does (not rejecting the $H_0$ when it should be rejected)
    b. It has become a convention to set β at 0.10–0.20 (80%–90% power).
3. Power $(1 - \beta)$
    a. The probability of making a correct decision when the $H_0$ is false; the ability to detect differences between groups if one actually exists
    b. Depends on the following factors:
        i. Predetermined α
        ii. Sample size
        iii. The size of the difference between the outcomes you want to detect. Often not known before conducting the experiment, so to estimate the power of your test, you will have to specify how large a change is worth detecting
        iv. Variability in the outcomes that are being measured
        v. Number of events
    c. Items iii and iv are generally determined from previous data or the literature. Power is decreased by the following (in addition to the earlier criteria):
        i. Poor study design methods
        ii. Incorrect statistical tests (use of nonparametric tests when parametric tests are appropriate)
    d. Statistical power analysis and sample size calculation
        i. Related to the previous discussion of power and sample size
        ii. Sample size estimates should be performed in all studies a priori.
        iii. Necessary components for estimating appropriate sample size
            (a) Acceptable type II error rate (usually 0.10–0.20)
            (b) Observed difference in predicted study outcomes that is clinically significant
            (c) The expected variability in item ii (for continuous variables)
            (d) Acceptable type I error rate (usually 0.05)
            (e) Statistical test that will be used for primary end point
    e. Statistical significance versus clinical significance
        i. As stated earlier, the size of the p-value is not related to the clinical importance of the result. Smaller values mean only that chance is less likely to explain observed differences.
        ii. Statistically significant does not mean clinically significant.
        iii. Lack of statistical significance does not mean that results are not clinically important.
        iv. When considering nonsignificant findings, consider sample size, estimated power, and observed variability.

G. Choosing the Most Appropriate Statistical Test
   1. Choice of Appropriate Statistical Test Depends on the Following:
      a. Type of data (nominal, ordinal, or continuous)
      b. Distribution of data (e.g., normal)
      c. Number of groups
      d. Study design (e.g., parallel, crossover)
      e. Presence of confounding variables
      f. One-tailed versus two-tailed
      g. Parametric versus nonparametric tests
         i. Parametric tests assume the following:
            (a) Data being investigated have an underlying distribution that is normal or close to normal or, more correctly, randomly drawn from a parent population with a normal distribution. Remember how to estimate this (mean ~ median)?
            (b) Data measured are continuous data, measured on either an interval or a ratio scale.
            (c) Parametric tests assume that the data being investigated have variances that are homogeneous between the groups investigated. This is often called homoscedasticity.
         ii. Nonparametric tests could be the default when p-values are needed and there are no covariates to adjust for.
            (a) Do not make assumption about the distribution of the underlying data.
            (b) Can be used for ordinal or interval data.
         iii. Pre-testing for normality to determine parametric vs. nonparametric test is discouraged.
            (a) Many analyses are insufficiently powered
            (b) Alters the type I error and doesn't acknowledge that nonparametric tests are efficient even under normality.
   2. Tests for Nominal Data
      a. Pearson's Chi-squared ($\chi^2$) test: Compares expected and observed proportions between two or more groups
         i. Tests of independence
         ii. Test of goodness of fit
      b. Fisher exact test: Traditionally thought to be preferred when analyzing rare events (cells containing fewer than 5 predicted observations).
         i. More computationally expensive
         ii. Pearson's Chi-square likely sufficient with rare events
      c. McNemar test: Paired samples
      d. Mantel-Haenszel: Controls for the influence of confounders or stratification
   3. Tests for Continuous Data
      a. Parametric tests
         i. t-test: Several different types, assume continuous response from a normal distribution
            (a) One-sample test: Compares the mean of the study sample with the population mean
            (b) Two-sample, independent samples, or unpaired test: Compares the means of two independent samples
            (c) Paired test: Compares the mean difference of paired or matched samples
            (d) Common error: Use of multiple t-tests with more than two groups (increases possibility of committing a type I error); therefore, an analysis of variance (ANOVA) is used instead
         ii. ANOVA: A more generalized version of the t-test that can be applied to more than two groups
            (a) One-way ANOVA: Compares the means of three or more groups in a study (independent samples test)
            (b) Two-way ANOVA: Addition of a grouping factor (e.g., age)

(c) Repeated-measures ANOVA: Compares multiple tests (e.g., at different time intervals) within the same group
(d) Important reminder: An ANOVA can only say whether a difference exists somewhere. It does not tell you which groups are different.
(e) Post hoc tests/adjustments (Bonferroni, Tukey, Scheffé, Newman-Keuls) can be performed to determine which groups actually differed from each other.
(f) ANCOVA (analysis of covariance): Method to examine the influence of a categorical variable (independent variable) on a continuous variable (dependent variable) while statistically controlling for other variables (confounding)

b. Nonparametric tests
   i. These tests can be good default when p values are needed and no covariates are being adjusted for.
      (a) Do not require assumption of a certain distribution of raw data
      (b) Can be used for interval or ordinal data
   ii. Tests for independent samples
      (a) Wilcoxon rank sum test, Mann-Whitney *U* test, or Wilcoxon-Mann-Whitney test: Compare two independent samples (related to a t-test)
      (b) Kruskal-Wallis one-way ANOVA by ranks
         (1) Compares three or more independent groups (related to one-way ANOVA)
         (2) Post hoc testing
   iii. Tests for related or paired samples
      (a) Wilcoxon signed-rank test: Compares two matched or paired samples
      (b) Friedman ANOVA by ranks: Compares three or more matched or paired groups

4. Correlation
   a. Examines the strength of the association between two variables. Does not necessarily assume that one variable is useful in predicting the other
   b. Pearson's correlation
      i. The strength of the relationship between two variables that are normally distributed, ratio or interval scaled, and linearly related is measured with a correlation coefficient.
      ii. Often called the degree of association between the two variables
      iii. Does not necessarily imply that one variable depends on the other (regression analysis will do that)
      iv. Pearson correlation (r) ranges from −1 to +1 and can take any value in between:

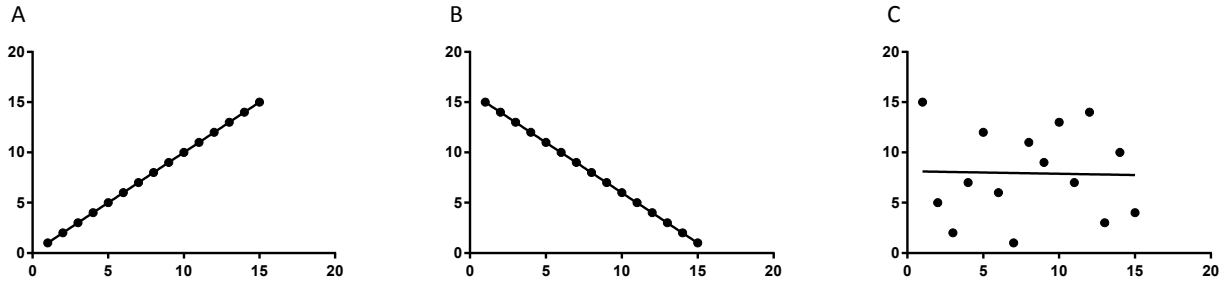


**Figure 2.** Scatterplots illustrating positive correlation (r=1; graph A), negative correlation (r = -1; graph B), and no correlation (r=0, graph C).

      v. The closer the r value is to 1 (either + or -), the more highly correlated the variables. The closer the r value is to 0, the weaker the relationship.

vi. Hypothesis testing determines whether the correlation coefficient is different from zero. This test is highly influenced by sample size.
vii. Important to the proper use of correlation analysis is the interpretation of the graphic representation of the two variables (see graph in Figure 2) to visually examine the relationship.

c. Spearman's rank correlation: Nonparametric test that quantifies the strength of an association between two continuous variables that are not normally distributed. Can also be used for ordinal data

5. Regression
   a. Examines the association between a variable and an outcome while adjusting for other variables.
      i. Example: model the association between treatment and death, adjusting for age, sex, and comorbidities.
   b. Uses of regression: Hypothesis testing, estimation, prediction, confounder adjustment
      i. Prediction model: Making predictions of the dependent variable from the independent variable(s)
      ii. $Y = mx + b$ (dependent variable = slope $X$ independent variable + intercept)
   c. Regression analysis determines the extent of variability in the dependent variable that can be explained by the independent variable.
      i. Coefficient of determination ($r^2$) measured describing this relationship. Values of $r^2$ can range from 0 to 1. An $r^2$ of 0.80 = 80% of the variability in $Y$ is explained by the variability in $X$.
      ii. Like the interpretation of r, the interpretation of $r^2$ depends on the scientific arena (e.g., clinical research, basic research, social science research) to which it is applied.
   d. Types of regression analysis
      i. Simple linear regression: one continuous response variable and one independent variable (descriptor, predictor, covariable)
      ii. Multiple linear regression: one continuous response variable and two or more independent variables
      iii. Simple logistic regression: one categorical response variable and one independent variable
      iv. Multiple logistic regression: one categorical response variable and two or more independent variables
   e. Example of linear regression (Figure 3)
      i. The following data are from a study evaluating intravenous hydralazine for managing hypertensive urgency. The authors wanted to evaluate the relationship between the baseline systolic blood pressure and the change in systolic blood pressure 2 hours after intravenous hydralazine administration in the 94 subjects who were retrospectively studied (J Am Soc Hypertens 2011;5:473-7).

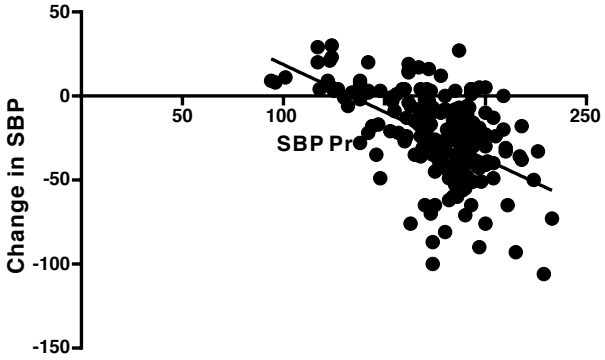


**Figure 3.** Relationship between baseline systolic blood pressure (SBP; *x*-axis) and change in SBP after intravenous hydralazine administration (*y*-axis).

ii. The authors performed regression analysis and reported the following: Slope: -0.563, y-intercept: 75.1, $p<0.0001$, $r^2 = 0.29$
iii. Answer the following questions:
(a) What are the assumptions necessary to use regression analysis?
(b) Provide an interpretation of the coefficient of determination.
(c) Predict the change in systolic blood pressure when the baseline values are 200 and 150 mm Hg.
(d) What does the $p<0.0001$ indicate?

6. Survival Analysis (Chest 2020;158(1S):S39-S48)
a. Studies the time between entry in a study and some event (e.g., death, myocardial infarction [MI])
b. Uses censoring that considers that some subjects leave the study for reasons other than the event (e.g., lost to follow-up, end of study period). Standard statistical methods (e.g., t-tests, logistic regression) may not be appropriate for these data because of censoring.
c. Considers that not all subjects enter the study at the same time and are usually followed for different durations
d. Estimating the survival function
i. Kaplan-Meier method (Figure 4)

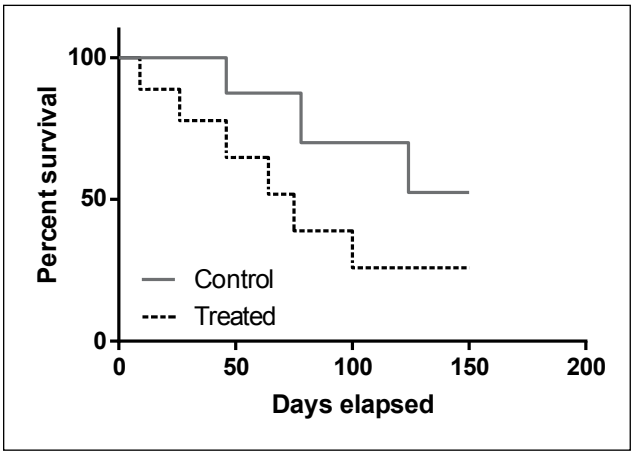


**Figure 4.** Example of a Kaplan-Meier curve.

(a) Uses survival times (or censored survival times) to estimate the proportion of people who would survive a given length of time under the same circumstances
(b) Allows the production of a table (life table) and a graph (survival curve)
(c) We can visually evaluate the curves, but we need a test to evaluate them formally.
ii. Log-rank test
(a) Compares the survival distributions between two or more groups
(b) Precludes an analysis of the effects of several variables or the magnitude of difference between groups or the CI
(c) $H_0$: No difference in survival between the two populations
iii. Cox proportional hazards model
(a) Most popular method to evaluate the impact of covariates
(b) Investigates several variables at a time
(c) Actual method of construction and calculation is complex.
(d) Compares time to survival in two or more groups after adjusting for other variables
(e) Allows calculation of an HR (and CI)
(f) Need to test proportionality assumption (either graphically or statistically)

7. Figure 5 shows a flowchart that can be used to identify the most appropriate statistical test based on data type.

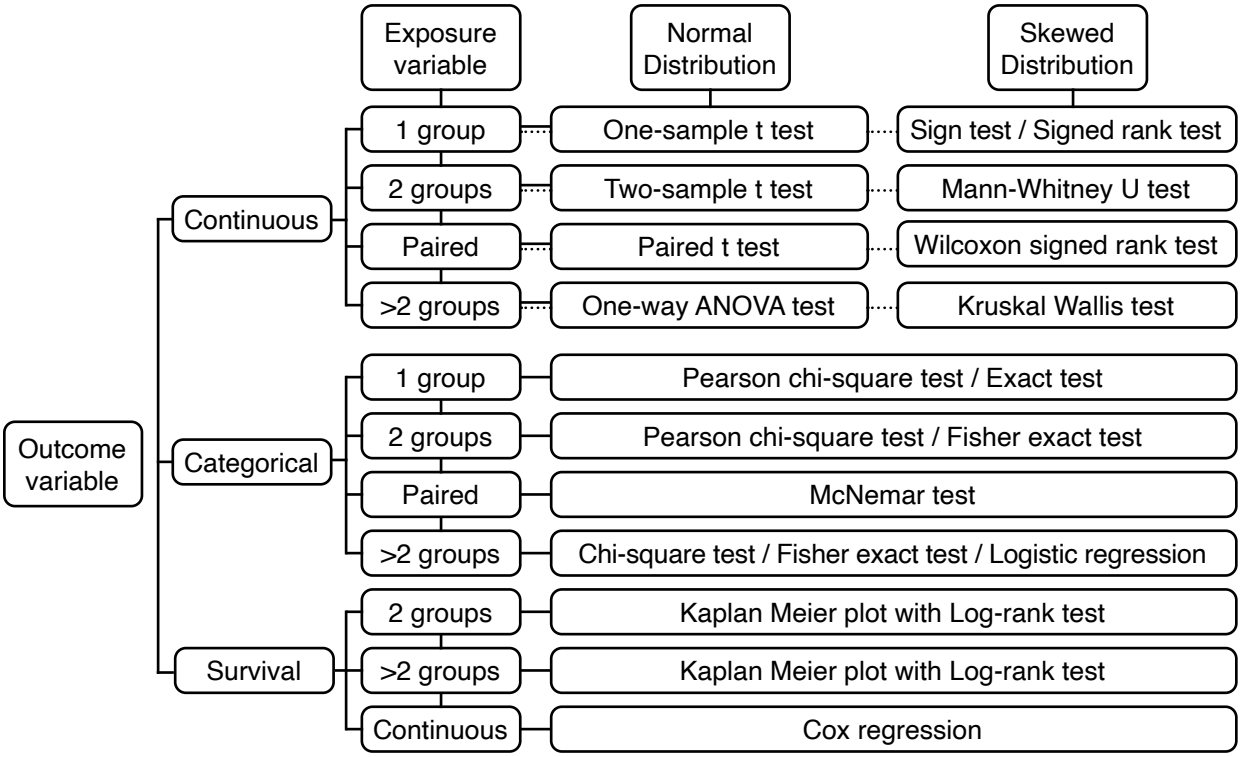


**Figure 5.** Flowchart for identifying the appropriate statistical test.

## IV. RESEARCH DESIGN AND METHODOLOGY OF CARDIOVASCULAR TRIALS

A. Research Design Classification
   1. Study Purpose: Descriptive versus analytic
   2. Time Orientation: Prospective versus retrospective design
      a. Prospective design: Begins in the present and progresses forward, collecting data from subjects whose outcomes lie in the future
      b. Retrospective design: Begins and ends in the present; however, this design involves a major backward look to collect information about exposures and outcomes that occurred in the past
   3. Experimental Setting
      a. Randomized controlled trials (RCTs)
      b. Observational studies

B. Case Reports/Case Series
   1. Document and describe experiences, novel treatments, and unusual events. Allows hypothesis generation that can be tested with other study designs. Note that the title does not say "study."
      a. Possible adverse drug reactions in one or more patients: QTc interval prolongation associated with fluoroquinolone antibiotics
      b. Case report: One patient
      c. Case series: More than one patient with a similar experience or many case reports combined into a descriptive review

d. Reports should provide sufficient detail to allow readers to recognize same/similar cases at their center/practice.

2. Advantages: Hypotheses are formed, which may be the first step in describing an important clinical problem. Easy to perform and inexpensive
3. Disadvantages: Do not provide explanation other than conjecture and do not establish causality or association. Can use Naranjo algorithm (Clin Pharmacol Ther 1981;30:239-45)

C. Observational Study Designs
   1. Important to remember that observational study designs investigate associations, not causation
   2. Cross-Sectional Study (a.k.a. prevalence study) (Chest 2020;158(1S):S65-S71)
      a. Identify the prevalence or characteristics of a condition in a group of individuals (Figure 6)
      b. Advantages
         i. Easy design, all data collected at one time
         ii. "Snapshot in time"
      c. Disadvantages
         i. Does not allow the study of a factor (or factors) in individual subjects over time, just at the time of assessment
         ii. Difficult to study rare conditions

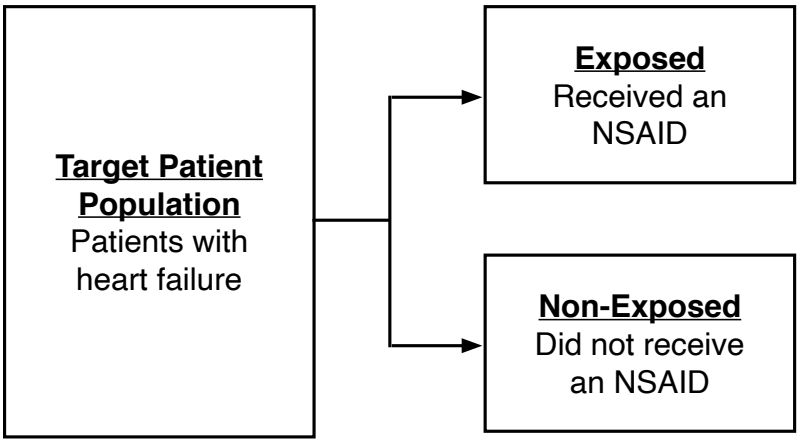


**Figure 6.** Design of a cross-sectional study evaluating the prevalence of NSAID use in patients with heart failure.
NSAID = nonsteroidal anti-inflammatory drug.

3. Case-Control Study (J Am Coll Clin Pharm 2021;4:1485-91)
   a. Aim is to determine the association between exposure/risk and disease/condition (Figure 7).
   b. Begins with cases that have the disease/condition of interest and comparison group without the disease condition. Both groups are investigated for previous exposures of interest.
   c. Nested case-control: Incorporates the case-control approach whereby both the cases and the controls are from an established cohort
   d. Useful method (and perhaps the only practical way) to study exposures in rare diseases or diseases that take long periods to develop or rare adverse drug events
   e. Critical assumptions to minimize bias
      i. Cases are selected to be representative of those who have the disease.
      ii. Controls are representative of the general population that does not have the disease and are as identical as possible to the cases, minus the presence of the disease.

f. Information is collected from cases and controls in the same way.
g. Advantages
    i. Inexpensive and can be conducted quickly
    ii. Allows investigation of several possible exposures or associations
h. Disadvantages
    i. Confounding must be controlled for.
    ii. Uncertainty of the temporal relationship between the exposure and the outcome
    iii. Observational and recall bias: Looking back to recall exposures and their possible levels of exposure
    iv. Cannot measure disease incidence
    v. Selection bias: Case selection and control matching can be difficult.
    vi. Not suitable if the exposure is rare.
i. Measurement of association. Odds ratio: Odds of exposure in those with the condition/disease (cases) compared with those without the condition/disease (controls).

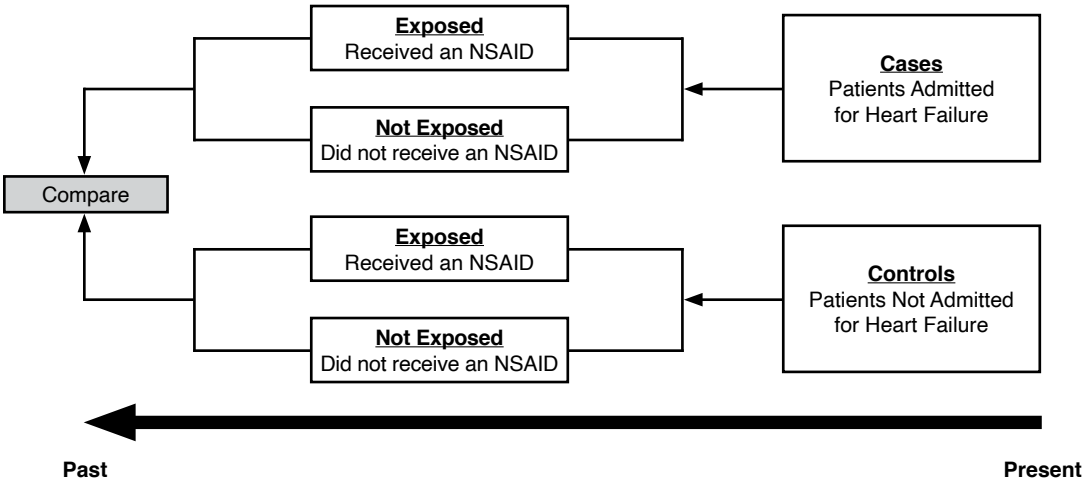


**Figure 7.** Design of a case-control study evaluating the association between NSAID use and hospitalization for heart failure.

4. Cohort Study (Chest 2020;158(1S):S72-S78)
    a. Determines the association between exposures/factors and disease/condition development (Figure 8)
    b. Describes the incidence or natural history of a disease/condition and measures it in time sequence
    c. Retrospective (historical): Begins and ends in the present but involves a major backward look to collect information about events that occurred in the past
        i. Advantages
            (a) Less expensive and time-consuming
            (b) No loss to follow-up (depending on the data source), ability to investigate issues not amenable to a clinical trial or ethical or safety issues
            (c) Can standardize exposure and outcome criteria at the start of the study
        ii. Disadvantages
            (a) Only as good as the data available
            (b) Changing exposure over time
            (c) Little control of confounding variables through nonstatistical approaches, recall bias

d. Prospective/longitudinal: Begins in the present and progresses forward, collecting data from subjects whose outcomes lie in the future
    i. Advantages
        (a) Can control for confounding factors to a greater extent
        (b) Easier to plan for data collection
    ii. Disadvantages
        (a) More expensive and time-intensive
        (b) Loss of subject follow-up
        (c) Difficult to study rare diseases/conditions at a reasonable cost
e. Measurement of association. Relative risk: The risk of an event or development of a condition relative to the exposure; the risk of someone developing a condition when exposed compared with someone who has not been exposed

5. Confounder Adjustment–Propensity Scores (J Am Coll Clin Pharm 2022;5:467-75; Stat Med 2021;40:1718-35)
    a. Because observational studies cannot randomize who did and did not receive an intervention, confounder imbalance arises
        i. Imbalance can result in biased estimates of the treatment effect
    b. Propensity scores
        i. A method of using data to reduce confounding in treatment effect estimates
        ii. Definition: the conditional probability of assignment to a particular treatment given a vector of observed covariates
        iii. Scores (probabilities) range from 0– 1
        iv. Estimated using traditional logistic regression models and available confounding covariates
    c. Methods for using propensity scores for covariate adjustment
        i. Covariate adjustment
            (a) Run multiple regression model with propensity score as a covariate
            (b) Allows for fewer variables in the regression model
            (c) Assessing covariate balance between treated and comparator groups is difficult
        ii. Stratification
            (a) Estimate treatment effect within strata of the propensity score, such as based on quintiles
            (b) Compare outcomes between groups within each stratum, then pool to obtain an overall treatment effect estimate
            (c) Assumes relatively similar numbers of individuals between treatment and comparator groups
        iii. Matching
            (a) Assign propensity scores to each group
            (b) "Match" individuals from treatment and comparison groups with a similar score within an established distance
            (c) Can match in different ratios of treatment to comparison, such as 1:1, 2:1
            (d) After matching, compare outcomes between groups
            (e) Limitations: Results in a smaller population; does not use all available data; matching does not "simulate" a RCT
        iv. Weighting
            (a) Create a weight for each individual in the dataset based on the individual's propensity score
            (b) Inverse probability of treatment weighting (IPTW): Weight is assigned based on the propensity score and the inverse probability of receiving the treatment that the individual actually received.

(c) Overlap weighting: Weight is assigned based on the propensity score and the probability of the individual belonging to the opposite treatment group.
(d) Benefit: Uses all individuals in the database
(e) Limitations: Methods to address extreme weights are needed.

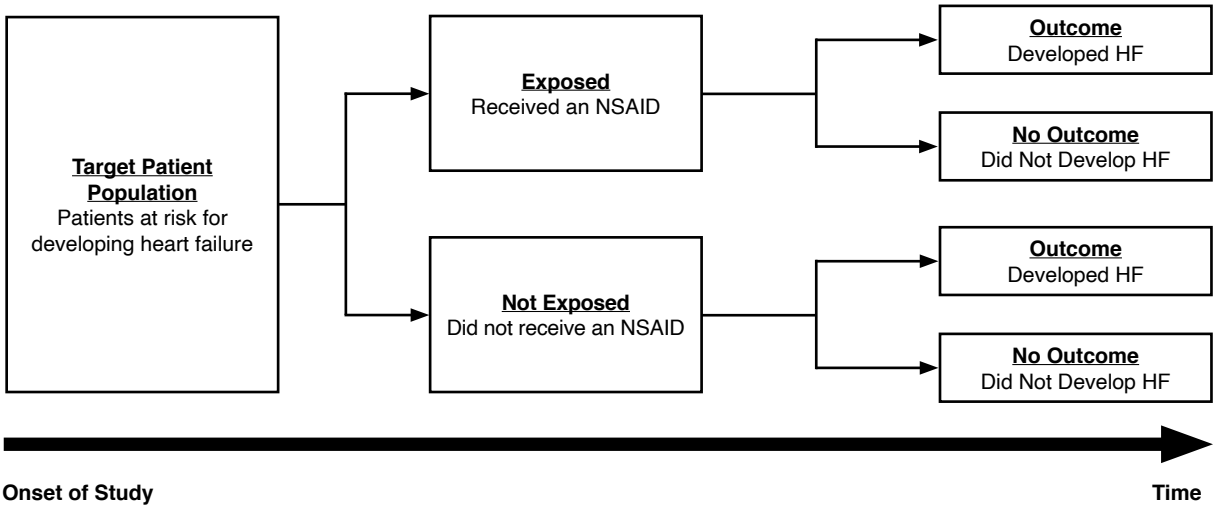


**Figure 8.** Design of a cohort study estimating the risk of developing heart failure (HF) with the use of NSAIDs.

D. Randomized Controlled Trials (Chest 2020;158(1S):S79-S87)
   1. Characteristics
      a. Experimental or interventional, investigator makes intervention and evaluates cause and effect
      b. Some previous background information or studies should exist to suggest that the intervention used will likely be beneficial.
      c. Design allows for assessment of causality.
         i. Sufficient cause
         ii. Necessary cause
         iii. Risk factor
      d. Minimized bias through randomization and/or stratification
         i. Randomization
         ii. Block randomization
         iii. Stratification
         iv. Cluster randomization
      e. Treatment controls
         i. Placebo-controlled
         ii. Active-controlled
         iii. Historical control
      f. Blinding methods
         i. Definition: Keeping trial participants, investigators, or assessors (those collecting outcomes data) unaware of an assigned intervention so that they are not influenced by that knowledge
         ii. Non-blind (open-label): Everyone involved knows who has received which interventions throughout the trial.
         iii. Single-blind: Either subjects or investigators are unaware of subject assignment to active/control.
         iv. Double-blind: Subjects and investigators all remain unaware of subject assignment.

v. Triple-blind: Double-blind trial that also maintains blind data analysis
vi. Double-dummy: Two placebo groups are necessary to match active and control therapies.

g. Allocation concealment
i. Refers to the technique used to implement, not generate, the sequence
ii. Secures strict implementation of a random allocation sequence without foreknowledge of treatment assignments

2. RCT: Parallel Design (Figure 9)

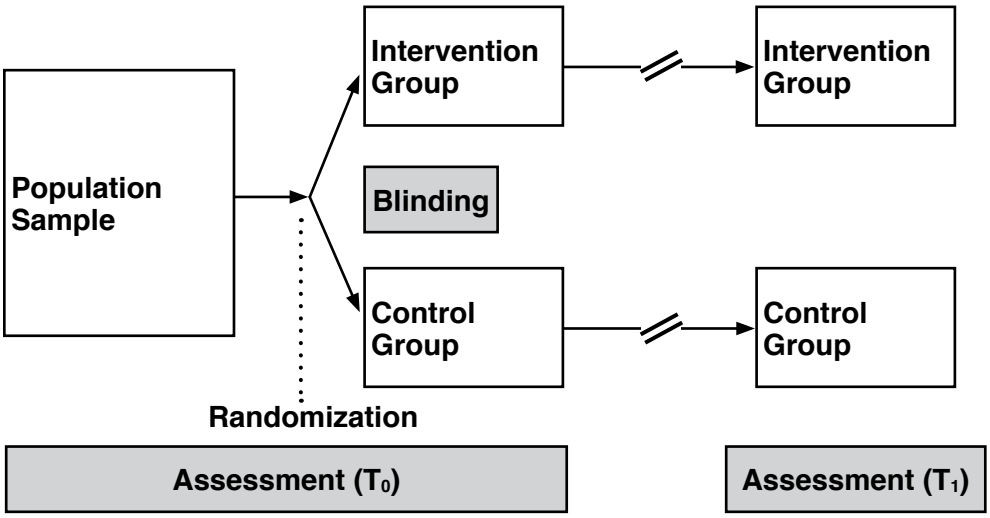


**Figure 9.** Randomized controlled trial: parallel design.

$T_o$ = time zero (baseline); $T_1$ = time one (first follow-up assessment)

3. RCT: Crossover Design (Figure 10)

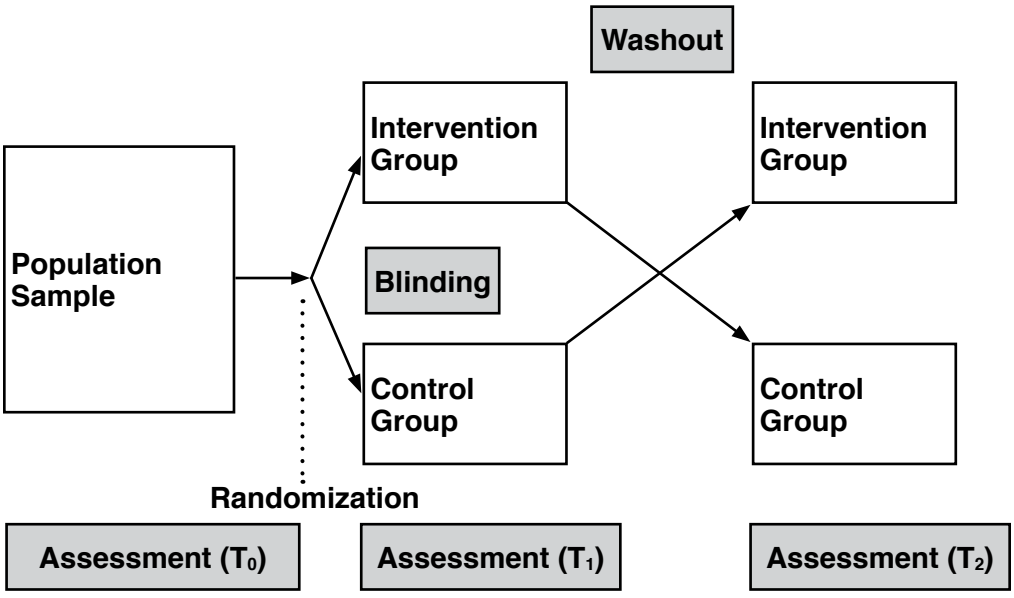


**Figure 10.** Randomized controlled trial: crossover design.

Assessments can be done at the end of phase 1 ($T_1$) or at the end of phase 2 ($T_2$).

4. RCT: Factorial Design (Figure 11)

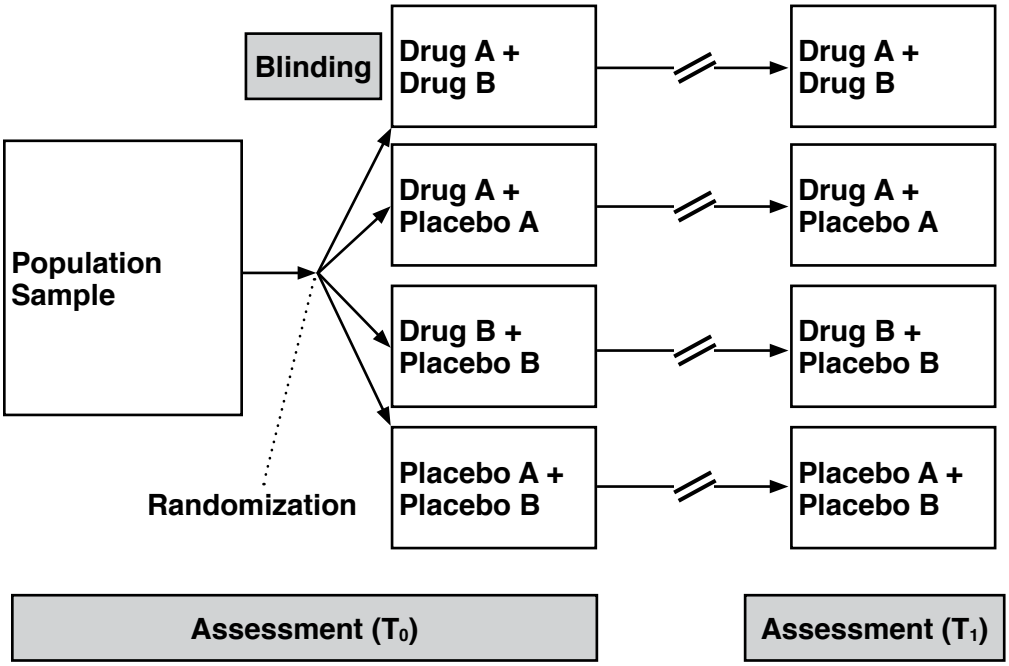


**Figure 11.** Randomized controlled trial: factorial design.

5. Superiority vs. Equivalence vs. Noninferiority (JAMA 2012;308:2605-11)
   a. A superiority trial is designed to detect a difference between experimental treatments. This is the typical design in a clinical trial.
   b. An equivalence trial is designed to confirm the absence of a meaningful difference between treatments, neither better nor worse (both directions). The key is the definition of the specified margins. What difference is important? One example is a bioequivalence trial.
   c. A noninferiority trial is designed to investigate whether a treatment is not clinically worse (not less effective than stated margin, or inferior) than an existing treatment (Figure 12).
      i. Useful when placebo administration is not possible for ethical reasons or when trying to demonstrate cardiovascular safety (although this remains controversial)
      ii. EXAMINE (Examination of Cardiovascular Outcomes with Alogliptin versus Standard of Care)
         (a) Designed to determine whether alogliptin was noninferior to placebo for major cardiovascular events in patients with type 2 diabetes at very high cardiovascular risk
         (b) Noninferior difference was defined as an upper bounds of the 95% CI for the HR of the primary composite outcome of less than 1.8 (allows an 80% excess events or excess risk).
      iii. Essentials of noninferiority (efficacy) design
         (a) Control group must be effective.
         (b) Current study similar to previous study with control and with equal doses, clinical conditions, and design used
         (c) Adequate power is essential, and usually, larger sample sizes are required.
         (d) Need to have a clinically defined noninferiority margin a priori
         (e) Need to have both an intention-to-treat and a per-protocol done for analysis

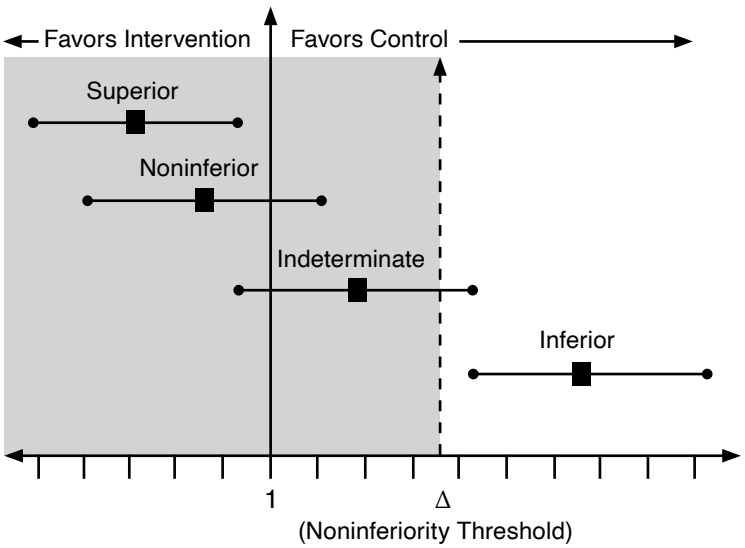


**Figure 12.** Potential outcomes of a noninferiority trial.

Modified from: Jackevicius CA. Beyond randomized placebo controlled trials in cardiology. In: Boucher BA, Haas CE, eds. Critical Care Self-Assessment Program, 2017 Book 1. Cardiology Critical Care. Lenexa, KS: American College of Clinical Pharmacy, 2017:167-92.

6. Explanatory vs. Pragmatic Clinical Trials (J Am Coll Clin Pharm 2022;5:99-106)
    a. Explanatory trials: Determine difference between two groups
    b. Pragmatic trials: Inform a clinical or policy decision using real-world populations
        i. Designed to show the real-world effectiveness of interventions in broad patient populations outside the rigors of a traditional RCT
        ii. Study participants should be similar to those who would receive the intervention if it were to become standard of care.
        iii. Investigators involved with routine clinical practice are preferred to experienced trialists, particularly those who work in a group practice setting.
        iv. Interventions are commonly not masked.
        v. End points focus on those that are important to patients (e.g., hospitalizations, quality of life, symptoms) or that have been underrepresented in RCTs.
        vi. Disadvantage: Generally have lower internal validity

## V. INTERNAL AND EXTERNAL VALIDITY OF CARDIOVASCULAR-RELATED TRIALS

A. Internal Validity
    1. The degree to which the outcome (either efficacy or safety) can be explained by differences in assigned groups
    2. Often related to proper design, conduction, and analysis of the study in order to minimize systematic bias
    3. Some of the more important factors that may affect internal validity include:
        a. Poor study design
        b. Inadequate allocation sequence generation and concealment
        c. Lack of or inappropriate blinding of participants, personnel, and outcome assessors
        d. Use of imprecise or inaccurate measurements
        e. Use of inappropriate statistical methods
        f. Incomplete outcome data or selective outcome reporting
    4. Limitations are magnified with use of nonrandomized/observational study designs.

B. External Validity (Lancet 2005;365:82-93)
   1. The degree to which the findings of a trial can be extrapolated to a population beyond a study
   2. Lack of consideration for external validity is a common criticism of clinical research (regardless of the design).
   3. Could help explain the underuse of clinical trial results in routine clinical practice
   4. Some of the more important factors that may affect external validity include:
      a. Setting of the trial (health care system, country, selection of participating centers/clinicians)
      b. Selection of patients (eligibility and exclusion criteria, placebo/treatment run-in period)
      c. Study patient characteristics (baseline clinical characteristics, racial/ethnic/sex group breakdowns, uniformity of underlying pathology, comorbidities, severity of disease)
      d. Differences between trial protocol and routine practice (intervention timing, appropriateness of control, background therapy and standardization, frequency of monitoring)
      e. Outcome measures and follow-up (relevance and acceptance of surrogate outcomes, reproducibility of findings, use of patient-centered outcomes, frequency/adequacy of follow-up)
      f. Adverse effects of treatment (impact of run-in period, discontinuation rates, completeness of adverse drug event reporting, intensity of safety procedures)
   5. Limitations could be minimized with use of pragmatic design (although internal validity is reduced).

## VI. BENEFITS, LIMITATIONS, AND RATIONALE FOR THE SELECTION OF CARDIOVASCULAR-RELATED STUDY END POINTS

A. Surrogate End Points
   1. Institute of Medicine Definition of Surrogate End Point: Intended to substitute for a clinical end point and expected to predict clinical benefit on epidemiologic, therapeutic, pathophysiologic, or other evidence
   2. Often one of the initial steps in the drug approval process. Show improvements in surrogate (intermediary) end point and then examine clinical end point in larger trial
   3. Studies are often completed faster with fewer participants, shorter duration, and less cost.
   4. Are often measurements (physiologic, laboratory) rather than events
   5. Examples of Surrogate End Points by Disease State (Eur Heart J 2015;36:2212-8)
      a. Hypertension/vascular physiology: Blood pressure, carotid intima-media thickness, microalbuminuria
      b. Lipid disorders/atherosclerosis: LDL, HDL, intravascular ultrasonography
      c. Diabetes: Serum glucose, hemoglobin A1C, microalbuminuria
      d. Acute coronary syndromes: Troponins, brain natriuretic peptide (BNP), infarct size, return of TIMI (thrombolysis in myocardial infarction) flow
      e. Heart failure: Ejection fraction, BNP, exercise capacity, hemodynamics (e.g., cardiac output), remodeling (e.g., left ventricular volume)
   6. Premature Ventricular Contraction (PVC) Example
      a. In patients with an MI, PVCs are a known risk marker for sudden cardiac death.
      b. It was thought that suppression of PVCs with antiarrhythmic drugs would lower mortality risk after an MI.
      c. The CAST trial enrolled 1498 patients after an MI and randomized them to either encainide or its placebo or flecainide or its placebo (N Engl J Med 1991;324:187-8).
         i. After a mean follow-up of 10 months, arrhythmic death was increased with encainide/flecainide compared with placebo (p=0.0004), as was death from nonarrhythmic cardiac causes (p=0.01).

ii. Nonlethal events did not differ between groups.
iii. Commonly quoted example of surrogate end point not being consistent with clinical outcome of the trial

7. HDL Example
   a. Epidemiologic studies have shown an inverse association between HDL concentrations and cardiovascular risk.
   b. Torcetrapib was an inhibitor of cholesteryl ester transfer protein that was shown in early studies to increase HDL by about 60% when added to atorvastatin.
   c. The ILLUMINATE trial enrolled 15,057 patients with high cardiovascular risk and randomized them to torcetrapib plus atorvastatin versus atorvastatin alone (N Engl J Med 2007;357:2109-22).
      i. Combination increased HDL by 28.4 mg/dL and lowered LDL by 19.7 mg/dL more than atorvastatin alone.
      ii. After a median follow-up of 550 days, the trial was stopped because of an increase in the primary major adverse cardiovascular event end point (HR 1.25; 95% CI, 1.09–1.44) with torcetrapib, mainly driven by a 58% increase in mortality (HR 1.58; 95% CI, 1.14–2.19).
      iii. Blood pressure was also increased about 4 mm Hg with torcetrapib.
      iv. The drug development program of torcetrapib was halted.
8. In 1990–2011, 220 surrogate cardiovascular trials were published in three major journals (*New England Journal of Medicine*, *Lancet*, and *JAMA*) (J Am Heart Assoc 2017;6:e005285).
   a. 157 (71.4%) had a positive outcome.
   b. 59 (26.8%) were followed by at least one clinical end point trial published in those same journals.
      i. 24 of 59 (40.7%) showed clinical end point trial results that validated the positive surrogate trial.
      ii. 20 of 59 (33.9%) showed negative results.

B. Composite End Points (Circ Cardiovasc Qual Outcomes 2014;7:170-8)
   1. A composite outcome is one in which an event is considered to have occurred if one of several outcomes is observed.
   2. In cardiovascular trials, major adverse cardiovascular events are commonly used and include:
      a. Cardiovascular death
      b. Nonfatal MI
      c. Nonfatal stroke
      d. May also include target vessel revascularization or hospitalization (although not always as a primary outcome)
   3. Trials often focus on time-to-event analysis using bivariate outcomes.
   4. Components should be clinically relevant and of similar importance to a patient, easily ascertainable, capable of unbiased assessment, sensitive to the hypothesized effects of the treatment, and inexpensive to measure.
   5. Primary rationale for use of a composite outcome = smaller sample size
      a. Single outcome: Estimated 10% event rate in the control group, the required sample size to detect a 50% lower rate (5%) in a group is 1170 patients (585 per group), assuming an $\alpha$ of 0.05 (2-sided) and a power of 0.90
      b. Composite outcome: Estimated 30% event rate in the control group, the required sample size to detect a 50% lower rate (15%) in a group is 330 patients (165 per group), assuming the same $\alpha$ and $\beta$
   6. Use of composite outcomes avoids the problem of competing risks. Example: In a heart failure trial, the end point of heart failure hospitalization does not account for mortality. A patient who is censored for death is not at the same risk of hospitalization as a patient who survived longer.

7. Disadvantages
    a. Assumes equal weighting of outcomes: as an example, the composite of mortality or hospitalization from any cause assigns the same weight from cardiovascular death and a hospitalization for an appendectomy. Patients and clinicians may not consider outcomes equally important.
    b. There could be a loss of power if the treatment effect is not similar for all components of the composite.
    c. Of concern if components of the composite go in opposite directions (decrease in hospitalizations but increase in mortality). Also difficult to interpret when the gradient of importance to patients is substantial or the gradient in the magnitude of the treatment effect also exists
    d. Difficult to compare findings from trials that use different composite outcomes

C. End Point Adjudication in Cardiovascular Trials (Lancet 2020;395:1878-82)
1. Enhance the validation of cardiovascular end points in randomized trials through independent, blinded, and standardized identification, processing, and review of events
2. Recommended in:
    a. Trials conducted by non-cardiovascular clinicians
    b. Trials conducted by cardiovascular clinicians when:
        i. Trial is unblinded
        ii. Evaluation of subcategories of major adverse cardiovascular event end points
        iii. Evaluation of more subjective end points in addition to major adverse cardiovascular event (e.g., revascularization, hospitalization)
3. External adjudication committees only have access to information provided to them.
    a. Presumptions of improved accuracy may not always be true.

## VII. HIERARCHY OF EVIDENCE RELATED TO THE MANAGEMENT OR PREVENTION OF CARDIOVASCULAR DISEASE

A. Relative Strength of Evidence: Hierarchy of Study Designs (Figure 13). This hierarchy holds assuming that all of the study designs are performed using the best possible techniques (e.g., a poorly conducted RCT is not necessarily higher on the hierarchy than a well-done cohort study).

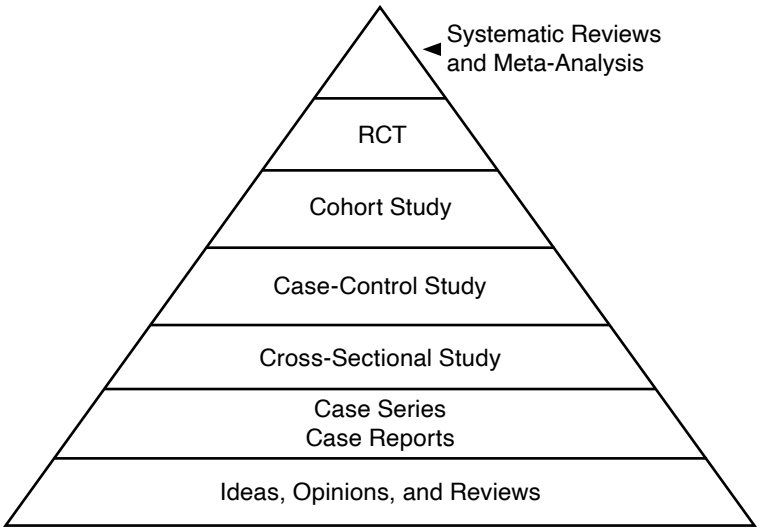


**Figure 13.** Hierarchy of clinical study design.
RCT = randomized controlled trial.

## VIII. ACKNOWLEDGMENTS

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## ANSWERS AND EXPLANATIONS TO SELF-ASSESSMENT QUESTIONS

**1. Answer: A**
When evaluating continuous data, such as the change in LDL from baseline, between three groups, an ANOVA should be used (Answer A is correct). A chi-square test (Answer B is incorrect) and a Mann-Whitney *U* test (Answer C is incorrect) are used for ordinal data. A t-test (Answer D is incorrect) can be used to evaluate continuous data, but only with two groups; thus, it would not be appropriate in this situation.

**2. Answer: A**
Given the HR and 95% CI, a statistically significant difference between groups can be determined with a p-value less than 0.05 (Answer A is correct; Answer C is incorrect). Answer B is incorrect because the level of statistical significance to match a p-value less than 0.0001 from the 95% CI given in the case cannot be determined. When a 95% CI is provided, a p-value is not needed to determine statistical significance (Answer D is incorrect).

**3. Answer: B**
Clinical trials are usually adequately powered to compare primary end points (Answer B is correct). Because Answer A is part of the composite outcome, the study was likely not powered to detect this outcome independently. Similarly, even though the subgroup analysis was determined a priori, the study is not typically designed to have sufficient power to make this comparison (Answers C and D are incorrect).

**4. Answer: C**
Although this document is a guideline, it does not have its own designated category of literature (Answer D is incorrect). Guidelines are considered a tertiary source of literature (Answer C is correct). The guideline recommendations are based on the primary literature (Answer A is incorrect) and may have been found through a bibliographic search engine such as PubMed (Answer B is incorrect).

**5. Answer: C**
The investigation is most appropriately designed as a cohort study, in which the population of interest (hospitalized patients with ADHF) is included, exposures are determined (milrinone or dobutamine), and an outcome is evaluated (all-cause mortality) (Answer C is correct). A cross-sectional study would look at all patients currently hospitalized on milrinone or dobutamine and whether they died (Answer A is incorrect). A case-control study would take hospitalized patients with ADHF who either died or survived (cases and controls) and look back to determine whether they received milrinone or dobutamine (Answer B is incorrect). A case series would report on more than one patient who was hospitalized for ADHF, had received milrinone or dobutamine, and had subsequently died with no statistical comparisons performed (Answer D is incorrect).

**6. Answer: D**
A Mann-Whitney *U* test is used to analyze continuous data (Answer A is incorrect) that are not normally distributed (Answer C is incorrect; Answer D is correct). This type of test is not appropriate for assessing survival data (Answer B is incorrect).

**7. Answer: B**
This clinical trial describes a noninferiority study (Answer B is correct) whereby investigators are assessing whether empagliflozin is not clinically worse than placebo. An equivalence trial (Answer A is incorrect) would be used if they wanted to confirm the absence of a meaningful difference between treatment arms, neither better nor worse. A superiority trial (Answer C is incorrect) would be used to determine whether empagliflozin reduced the risk of the composite outcome more than placebo. A pragmatic trial (Answer D is incorrect) would be designed to show the real-world effectiveness of interventions in broad patient populations outside the rigors of a traditional RCT and does not describe this study.

**8. Answer: C**
Regression analysis is the most effective way to identify multivariate predictors of an outcome such as QTc interval prolongation (Answer C is correct). There are many different types of regression, but all share the ability to evaluate the impact of multiple variables simultaneously on an outcome variable. Correlation analysis is used to assess the association between two (or more) variables, not to identify predictors (Answer A is incorrect). Kaplan-Meier curves are used to graphically depict survival curves or time to an event (Answer B is incorrect). A chi-square test is used to compare

nominal data, not to identify multivariate predictors (Answer D is incorrect).

**9. Answer: B**

The CI of the difference in the odds of POAF between the statin and control groups included 1; thus, there is no statistically significant difference between the two groups (Answers A and C are incorrect; Answer B is correct). Answer D is incorrect because statistical significant can be determined using the CI without the benefit of reported p-values.

# Principles of Cardiology Pharmacy Practice Administration

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# Principles of Cardiology Pharmacy Practice Administration

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**Learning Objectives**

1. Distinguish between policies, procedures, and clinical protocols related to the medication use process.
2. Identify formulary management activities to improve the prescribing of safe, effective, and affordable treatments in an organization.
3. Describe strategies to plan for and respond safely and efficiently to drug product shortages.
4. List high-risk medications and medication-related processes that are suited for a medication use evaluation (MUE) and recognize the steps in the MUE process.
5. Describe national quality initiatives and regulatory requirements aimed at improving health care delivery and patient health outcomes.
6. Define pharmacoeconomic principles and be able to apply them to patient care.
7. Compare a medication error, adverse drug event (ADE), adverse drug reaction (ADR), and preventable ADE.
8. Analyze an ADE reporting program, including committee structure, committee reporting mechanisms, and methods of detecting, reporting, and managing ADEs.

**Abbreviations in This Chapter**

| | |
|---|---|
| ADE | Adverse drug event |
| ADR | Adverse drug reaction |
| CDTM | Collaborative drug therapy management |
| CMS | Centers for Medicare & Medicaid Services |
| CPA | Collaborative practice agreement |
| CPOE | Computerized prescriber order entry |
| FDA | U.S. Food and Drug Administration |
| MTM | Medication therapy management |
| MUE | Medication use evaluation |
| NPSG | National Patient Safety Goal |
| PHI | Protected health information |
| PI | Performance improvement |
| P&T | Pharmacy and therapeutics (committee) |
| QALY | Quality-adjusted life-year |
| QI | Quality improvement |
| TJC | The Joint Commission |
| VTE | Venous thromboembolism |

**Self-Assessment Questions**

*Answers and explanations to these questions can be found at the end of the chapter.*

1. Which best describes the appropriate process for creating a new policy or procedure?
   a. Review evidence, establish purpose, draft policy, review policy, identify stakeholders.
   b. Establish purpose, identify stakeholders, review evidence, draft policy, review policy.
   c. Identify stakeholders, establish purpose, review evidence, review policy, draft policy.
   d. Establish purpose, review evidence, draft policy, identify stakeholders, review policy.

2. Alirocumab, a proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitor, is being considered for addition to formulary. Which best describes how this drug may be added to the formulary?
   a. Formulary but restricted to the specific populations in which it was proven safe and efficacious.
   b. Nonformulary because it is a new drug, and efficacy and safety have not yet been proven.
   c. Formulary but restricted to use by the physician who requested that it be added to formulary.
   d. Nonformulary because of its cost.

3. The pharmacy buyer at your facility has just alerted you to a new drug shortage for premixed heparin infusion bags. Which of the following is an appropriate action to take to address this shortage?
   a. Purchase all product that remains available within your supply chain
   b. Determine your current supply and estimate days on hand
   c. Switch all patients to an appropriate alternative
   d. Create a plan to respond to the shortage with key pharmacy stakeholders

4. The pharmacy and therapeutics (P&T) committee would like to evaluate the use of pharmacotherapy for venous thromboembolism (VTE) prophylaxis in medical-surgical units. Which is the best

method for conducting this evaluation?

a. Review adverse drug event (ADE) data.
b. Review medication error data.
c. Perform a medication use evaluation (MUE).
d. Administer a performance improvement (PI) initiative.

5. As the cardiology clinical pharmacist in an ambulatory clinic, you are asked to evaluate your clinic's compliance with The Joint Commission's (TJC) National Patient Safety Goal (NPSG) 03.05.01 (Reduce the likelihood of patient harm associated with the use of anticoagulant therapy). Which best reflects compliance with this NPSG?

a. Use programmable heparin pumps to provide consistent dosing.
b. Use approved protocols for perioperative management of patients on oral anticoagulants.
c. Use unit-dose, prefilled, or premixed products, when available.
d. Provide education to patients and families regarding anticoagulant therapy.

6. When quantifying the value of a cardiology pharmacist's services, which economic evaluation method is best to use?

a. Cost-benefit analysis.
b. Cost-effectiveness analysis.
c. Cost-minimization analysis.
d. Cost-of-illness analysis.

7. A patient with nonvalvular atrial fibrillation is prescribed rivaroxaban for stroke prevention. The patient is later initiated on rifampin, which increases rivaroxaban hepatic metabolism through cytochrome P450 3A4 and induction of P-glycoprotein, causing a subtherapeutic serum concentration of rivaroxaban, which in turn causes the patient to develop a stroke. Which best describes this interaction?

a. ADR.
b. Side effect.
c. ADE.
d. Preventable ADE.

8. During morning rounds with the medical team, you discover a patient with a serum potassium concentration of 6.5 mEq/L. You quickly review the patient's medication list and notice the patient has been receiving lisinopril. You determine this is an ADE and submit a voluntary incident report. Which best describes this type of ADE detection?

a. Prospective surveillance.
b. Concurrent surveillance.
c. Direct observation.
d. Retrospective surveillance.

## I. POLICY AND GUIDELINE DEVELOPMENT

A. Policy and Procedures
   1. Policy – A course or plan of action designed to determine decisions and actions; the existence of written policies and procedures establishes standards of practice or quality/compliance measures and protects against error. Statement that clearly and unambiguously describes the organization's guiding principles and views about a particular matter.
      a. Benefits
         i. Keeps the institution efficient
         ii. Provides a training tool during a new employee's orientation
         iii. Provides reference material for consistent practice
         iv. Minimizes practice variations
      b. Development and implementation should involve all team members so that the process works smoothly.
      c. Reduces the organizational risk by mandating compliance (Box 1)

**Box 1.** List of Policies Required by The Joint Commission

| | |
|---|---|
| 1. As-needed medications | 8. Compounded or admixed drugs |
| 2. Standing orders | 9. Medication-related devices |
| 3. Automatic stop | 10. Investigational medications |
| 4. Titrating medications | 11. Herbal/natural products |
| 5. Tapering medications | 12. Discharge and transfermedications |
| 6. Range orders | 13. Anticoagulation-relatedlaboratory monitoring |
| 7. Signed and held orders | 14. Antimicrobial stewardship |

   2. Procedure – A simple course of action intended to achieve a result; describes in detail a logical sequence of a process to be followed to complete the task in a consistent manner.
      a. Benefits
         i. Aids in doing business as a team
         ii. Identifies each team member's responsibility to the respective task of the procedure
         iii. Helps team members work more effectively together because the expected outcome is identified
      b. Allows procedures to be described in the following forms:
         i. Written steps of the process
         ii. Flowcharts
         iii. Checklists
      c. Can be used as a quality improvement (QI) tool or a source of measures

B. Pharmacists should take leadership roles in contributing to the development of policies and procedures affecting each aspect of the medication use process (e.g., prescribing, preparation, administration). These policies and procedures may be specific to the pharmacy department, but they often apply to other parts of the health system. Policies and procedures should reflect an organization's current practice and are usually cyclical; thus, pharmacists should seek opportunities to become involved at any stage in the cycle of development, implementation, and assessment.

C. Framework of a Policy and Procedure
   1. How to write policies
      a. Planning
         i. Identify key stakeholders in the organization.

ii. Appoint a facilitator, especially if there are known differences in opinions or practices among participants.
iii. Define aims, objectives, and strategies.
iv. Determine priorities for policy development.

b. Research and consultative process for developing a particular policy
i. Research the standard of care or best practice.
ii. Obtain other perspectives and viewpoints, which will include identifying organizational or external issues.
(a) Encourages participation and feeling of ownership in the process
(b) Provides new ideas and expertise
iii. An alternative viewpoint identifies inconsistency, ambiguity, and/or duplication.

c. Policy drafting
i. Once the policy content is reviewed and agreed on, a structured format is used to write the policy.
ii. An initial draft should be distributed to relevant stakeholders/experts for comments.
iii. Depending on feedback, more than one draft may be required.

d. Policy review process
i. Formal process that may or may not be required within the institution (i.e., standing policy and procedures committee, which develops and reviews the policy and provides recommendations and decisions)
ii. Involvement and approval from the P&T committee, cardiology committees, or other oversight committees

e. Document the date of ratification of the final draft of the policy and establish and document a review date.
f. Communicate the new policy to all relevant people.

2. A structured format provides consistency across a health system. Standard sections may include:
a. Purpose statement – Includes the audience the policy is intended to address and why the policy and procedure were developed. The purpose statement should be concise yet comprehensive (e.g., "This policy establishes the position of [health system name] regarding herbal product use.").
b. Definitions – Explains terms such as acronyms and technical or legal terms that may be unfamiliar to the reader
c. Policy statement – Succinct statement of the health system's position regarding the subject matter (e.g., "It is the policy of [health system name] that the use of herbal products in the acute care setting is not permitted.")
d. Procedure – Description of the steps taken to accomplish the purpose of the policy statement
e. Documentation – Information on what needs to be documented in the medical record or elsewhere
f. Resources/references
g. Owner
h. Approving committee(s) and date

D. Clinical Protocol/Pathway – A patient care management plan that includes best practices for managing a particular disease or condition. Clinical pathways and guideline-based order sets developed and implemented by multidisciplinary teams (e.g., physicians, pharmacists, nurses) to improve adherence to performance measures, medication safety, and patient outcomes. A clinical protocol is a preapproved plan of care that authorizes designated, qualified, licensed personnel to perform patient assessment and corresponding decision points and provider contact points in order to independently determine and initiate interventions and/or treatments.

1. Supports clinical decision-making by defining best practice
2. Uses evidence-based and standardized treatment options
3. Developed by examining the evidence and gaining consensus among practitioners
4. Should have a physician champion
5. Protocol can be an extension of a clinical policy or practice standard.
6. Clinical protocols are written for specific patient conditions to expedite care and are often kept separate from institutional policies and procedures unless required for regulatory/accreditation purposes (e.g., anticoagulation policies to meet requirements of NPSG).
7. Disease and drug therapy protocols
8. Every clinical protocol or pathway should be regularly reviewed for relevance and appropriateness (e.g., every 1–3 years), depending on organizational structure/standards.

E. Checklist to Follow When Developing Protocols, Policies, and/or Procedures
   1. Scope and purpose
      a. Overall objectives are specifically described.
      b. Health questions covered by the guideline are specifically described.
      c. The patient population to which the guideline applies is specifically described.
   2. Stakeholder involvement
      a. Guideline development group includes individuals relevant to the guideline.
      b. Target population's views and preferences have been identified.
      c. Target users of the guideline are defined.
   3. Development of guideline(s)
      a. Literature search is systematic.
      b. Criteria for selecting evidence are clearly defined.
      c. Strengths and limitations of evidence are described.
      d. Health benefits, adverse effects, and risks are considered when developing recommendations.
      e. Link between recommendations and supporting evidence is provided.
      f. Guideline is externally reviewed by experts.
      g. Defined times for guideline updates are provided.
   4. Clarity of recommendations
      a. Recommendations are clear and unambiguous.
      b. Different options are clearly presented.
   5. Applicability
      a. Guideline describes facilitators and barriers to the application.
      b. Guideline provides tools on how it should be applied to practice.
      c. Guideline presents monitoring and/or auditing criteria.

**Patient Case**

1. As the cardiology pharmacist, you have been asked to develop a policy for initiating and maintaining anticoagulant therapy. Which is the best example of a component that should be involved first in establishing this policy?

   A. Distribute the policy to key stakeholders.

   B. Create the policy to meet the needs of your practice setting.

   C. Develop and communicate the new policy to hospital administration.

   D. Use evidence-based medicine and consensus among stakeholders to support the policy.

## II. FORMULARY DEVELOPMENT/MANAGEMENT

A. Formulary Management – An integrated patient care process that enables physicians, pharmacists, and other health care professionals to work together to methodically evaluate medications on an ongoing basis for inclusion or exclusion, establish guidelines for optimal medication use, and develop policies and procedures for prescribing, dispensing, and administering medications.

B. P&T Committees – Responsible for maintaining the drug formulary and ensuring that new medications that can improve patient care are reviewed for formulary inclusion.
   1. Oversee all aspects of medication management in an institution or organization
   2. The committee provides a forum for professional staff (physicians, pharmacists, nurses, dietitians, information technology, etc.) to collaborate.
   3. Review scientific evidence on clinical and cost-effectiveness in drug selection decisions
   4. ADR and medication error monitoring
   5. Quality assurance
   6. Policy and procedure approval
   7. Education to providers and staff
   8. Traditionally associated with institutional pharmacy, though other organizations have P&T committees (e.g., ambulatory clinics, managed care organizations, insurance companies)
   9. Multihospital systems may also have a system-level P&T if clinical standardization across facilities is a priority.

C. Drug Formularies
   1. Formulary committees deal strictly with determining which drugs are carried within an institution or organization.
   2. A drug formulary can guide prescribing toward:
      a. Safest agents
      b. Most effective agents for treating a particular medical problem
      c. Most reasonable cost
   3. At a minimum, the drug selection criteria should include the following:
      a. Indications for use (U.S. Food and Drug Administration [FDA] label approved and off-label)
      b. Efficacy and effectiveness
      c. Drug interactions
      d. Adverse effects
      e. Sentinel event advisories
      f. Cost acquisition and total cost of care – Pharmacoeconomic analysis
      g. Consideration for continuity of care (e.g., local health plan formularies)
   4. Evaluating drugs for inclusion is typically done using a template or formal monograph.
      a. Safety
      b. Efficacy
      c. Cost-effectiveness
      d. Other considerations
         i. Variety of dosage forms available for the medication
         ii. Estimated volume of use
         iii. Convenience
         iv. Dosing schedule
         v. Adherence
         vi. Abuse potential
         vii. Physician demand

viii. Ease of preparation
ix. Storage requirements

5. A comprehensive literature review should be used to determine a drug's efficacy and toxicity profile, with stronger levels of evidence guiding decisions.
   a. High-quality prospective randomized controlled trials and meta-analyses should have greater weight than retrospective trials and poorly designed prospective trials.
   b. Case reports should be used only when no other evidence is available.
6. If objective data are lacking, a committee may decide to schedule a product for a follow-up review (e.g., MUE).
7. Internal prescribing data may also be used in formulary decisions, such as
   a. Quantity of drug used over a specified time
   b. MUE data
   c. ADR data
   d. Medication error data
8. Usually, only two or three drugs from any class are added to avoid therapeutic redundancy. Including only one agent per class is probably too restrictive to accommodate intolerances and responsiveness to medications.
9. Drugs may be added to the formulary with no restrictions, or they may be added with restrictions. Restrictions may be based on:
   a. Efficacy
   b. Safety
   c. Patient-specific populations (because of limited efficacy or safety evidence)
   d. Cost
10. Drugs are commonly restricted to a prescriber who is a specialist or a clinical pharmacist specialist, a specialty unit such as the intensive care unit, or a population such as pediatric patients or postoperative surgical patients. Example: Dofetilide may be restricted to use in monitored or telemetry units or for use by cardiologists.
11. Barriers to optimal formulary decisions
    a. Physician experience/preference
    b. Pharmaceutical company detailing
    c. Unpublished or anecdotal studies and reports
12. Conflict of interest
    a. Decision-makers for a drug's formulary status may have a conflict of interest by receiving direct or indirect compensation from including a drug on the formulary.
       i. Stock in a company
       ii. Honoraria for speaking
       iii. Consulting fees
       iv. Gifts or grants from a company
    b. P&T committees are responsible for identifying and addressing conflict-of-interest issues in the decision-making process.
    c. Ways to avoid bias
       i. Conflict-of-interest policy, requiring regular disclosure of any possible conflicts
       ii. Regular voting P&T committee members may have to abstain from the vote if they disclose a possible conflict of interest.
       iii. Committee may vote to decide whether a conflict is significant enough to prevent voting by the individual.
    d. Once a drug is accepted for formulary approval, periodic assessments in the form of an MUE or reviews of use, cost, safety, and efficacy should be made, preferably within 3–6 months and again in 1 year. The goal is to determine the drug's effectiveness (different from efficacy). Effectiveness is the use of a drug in the real-world setting outside a randomized controlled trial.

e. An assessment of all drugs that are on formulary within a class should be made annually or more often when there is an important change in prescribing information, when a landmark trial or publication affects the drug's use, or when new FDA label–approved agents are available within the drug class. Medication assessments typically prompt updates and modifications to the drug's current use.

D. Drug Shortages
   1. Contributing factors
      a. Unique market
         i. Choice of agent is not price sensitive.
         ii. Consumers have little or no control over product selection.
         iii. Lack of transparency regarding manufacturing makes purchasing decisions on basis of quality difficult.
      b. Manufacturing:
         i. Majority of shortages are caused by production delays due to quality issues
         ii. Lack of capacity of other manufacturers to make up the shortfall created when one or more manufacturer halts production.
         iii. Business decisions to continue or halt manufacturing a particular product.
      c. Shortage of active pharmaceutical ingredients or other raw materials
      d. Restricted distribution and allocation to certain pharmacies, clinicians, and patients complying with manufacturer agreements
      e. Inventory practices
         i. Just-in-time inventory management reduces cost of inventory but may lead to unexpected shortages.
         ii. Manufacturers and distributors may aim to minimize end-of-quarter or end-of-year inventories to meet quotas.
         iii. Hoarding before impending shortage affects supply for others.
         iv. Pharmacy location
            (a) Rural pharmacies may experience delays from distant distribution center and inability to borrow from nearby facility.
            (b) Multiple pharmacies in close proximity relying on single wholesaler.
   2. Planning for shortages
      a. Guidelines published by ASHP on managing drug product shortages (https://www.ashp.org/-/media/assets/policy-guidelines/docs/guidelines/managing-drug-product-shortages.ashx)
      b. Identify shortage team with leader
         i. Interdisciplinary team who can access information and make decisions.
         ii. Responsible for the following activities:
            (a) Data gathering and monitoring
            (b) Purchasing alternatives
            (c) Changing storage, preparation, and dispensing procedures
            (d) Deciding to conserve vs. ration
            (e) Implementing technology changes
            (f) Communications
         iii. Ad hoc stakeholders to consult for specific shortages (e.g., service line chiefs)
      c. Resource allocation committee
         i. Oversee allocation of scarce resources
         ii. Consider patient characteristics and clinical evidence for prioritization and rationing of shortage drugs.

iii. Standardized ethics framework will help to eliminate difficult bedside decisions.
iv. Consider impact on clinical trials and processes for notifying investigators and amending trial enrollment.

d. Process for approving alternative therapies
i. Representatives from medicine, nursing, pharmacy, and other impacted disciplines as needed (e.g., respiratory, nutrition)
ii. Follow same formulary management process for approving or changing products to ensure automation, technology, and other safety steps are addressed.

3. Responding to shortages
a. Operational assessment
i. Validate details of shortage and estimate duration
ii. Estimate supply on hand and from alternative sources
iii. Evaluate past usage
iv. Estimate time to impact on health-system
v. Estimate supply of alternative therapies
b. Therapeutic assessment
i. Identify patient populations affected
ii. Identify therapeutic alternatives
c. Shortage impact analysis
i. Alternative therapy differences
ii. Prescribing, distribution, administration processes
iii. Financial impact
d. Communicate plan to affected clinicians and administrators
i. Multiple communication methods are preferred over single strategy
ii. EHR alerts can be used to communicate information at the time of medication order
e. Implement system and process changes
i. Information system
ii. Technological changes (e.g., automated dispensing cabinets, barcoding)
iii. Inventory system changes
iv. Medication-related processes

E. Medication Use Evaluation
1. An MUE is a PI effort to measure and describe the medication use process or medication treatment response and identify actual or potential medication-related problems with a goal of optimizing patient outcomes.
2. The scope of an MUE may include a drug or class of drugs, a disease state or condition, and/or the process or processes. MUEs focus on several elements of the medication process/use such as prescribing, pharmacist medication order verification, dispensing, preparing, administering, monitoring, patient education, and outcomes.
3. Objectives of an MUE
a. Evaluate medication effectiveness.
b. Improve safety.
c. Avoid medication errors or ADEs.
d. Standardize therapy or process to reduce variation.
e. Meet regulatory or accreditation standards.
f. Identify educational opportunities for health care professionals.
g. Minimize costs.

4. The type and number of MUEs should be determined by the risk mitigated when using a medication. Medications selected for an MUE may be based on the following:
   a. High risk
   b. High volume
   c. ADEs
   d. Preventable ADEs
   e. Near-miss and harmful medication errors
   f. Nonformulary requests
   g. Pharmacy intervention data
   h. Treatment failures
   i. Physician or nurse identification or request
   j. Patient concerns
   k. Off-label use
   l. High cost
5. Examples of medications and medication use processes in cardiology patients that may be selected for an MUE can be found in Boxes 2 and 3.

**Box 2.** List of Medications Used in Cardiology Patients Suited for an MUE

| | |
|---|---|
| 1. Albumin | 13. Idarucizumab and andexanet alfa |
| 2. Alteplase and tenecteplase | 14. Isoproterenol |
| 3. Argatroban | 15. Ivabradine |
| 4. Bivalirudin | 16. Nesiritide |
| 5. Cangrelor | 17. Nicardipine IV |
| 6. Digoxin immune fab | 18. Recombinant activated factor VIIa |
| 7. Direct oral anticoagulants | 19. Prothrombin complex concentrates |
| 8. Enoxaparin | 20. Sacubitril/valsartan |
| 9. Esmolol | 21. Sodium nitroprusside |
| 10. Ethacrynic acid | 22. Tolvaptan and conivaptan |
| 11. Glycoprotein IIb/IIIa inhibitors | 23. Vasopressin |
| 12. Heparin | 24. Warfarin |

IV = intravenous; MUE = medication use evaluation.

**Box 3.** Examples of Medication-Related Processes Suited for an MUE in Cardiology Patients

1. Management of oral anticoagulant overdose
2. VTE prophylaxis
3. Oral antiplatelet loading regimens for PCI
4. Anticoagulation during PCI
5. Use of β-blockers for myocardial infarction
6. Use of ACE inhibitors for heart failure
7. IV-to-PO switch therapy (e.g., antihypertensives, diuretics)
8. Antihypertensive use for acute stroke
9. Antihypertensive use during CABG surgery
10. Pharmacologic management of hemostasis during CABG surgery
11. Alteplase use for acute stroke
12. Monitoring for dysrhythmias with QTc-prolonging drugs
13. IV push medication guidelines
14. Vasopressor titration

ACE = angiotensin-converting enzyme; CABG = coronary artery bypass grafting; PCI = percutaneous coronary intervention; PO = oral(ly); QTc = corrected QT interval; VTE = venous thromboembolism.

6. An organizational body (e.g., P&T, QI committee) should be responsible for proactively identifying target medications and overseeing the MUE process. An MUE subcommittee should be multidisciplinary and may be composed of the following:
    a. Clinical pharmacists
    b. Physicians
    c. Nurses
    d. Administrators
    e. PI/QA representatives
    f. Risk management representatives
7. MUEs should have specific criteria – These criteria are best determined by a multidisciplinary team of medication or disease experts. Criteria are most often applied retrospectively to determine the extent to which a particular drug is used in accordance with established criteria. Gaps or deviations from established criteria are opportunities to improve the medication use or process.
8. MUE programs should be incorporated into the overall hospital PI process and should follow the model used by the health system (e.g., Model for Improvement).
9. Pharmacist responsibilities
    a. Develop an operational plan consistent with health-system goals and resources.
    b. Collaborate with the multidisciplinary team to establish criteria and design a medication use process.
    c. Apply established criteria to a selected sample of medication orders.
    d. Manage the MUE process.
    e. Interpret and report the MUE results, and recommend improvements to the medication use process to the P&T committee and department chairs.
    f. Develop the necessary medication use system changes in cooperation with the appropriate departments and medical services responsible for providing care.
    g. Provide education or develop policies regarding medication use changes, such as:
        i. In-service lectures
        ii. Newsletter publications
        iii. Drug alerts
        iv. Guideline development
        v. Protocols
        vi. Policy and procedures
        vii. Computerized prescriber order entry (CPOE) pathways, prescribing guides, or information or pop-up warnings
10. After plans of correction are determined and actions taken, a follow-up MUE should be completed to document that improvement has occurred successfully. If any new changes have occurred in the medication use process, the MUE criteria should be reassessed and the new criteria incorporated.

**Patient Cases**

2. Which scenario best represents the most appropriate application of formulary management activities?
   A. Physician justifies a formulary addition because of a case-series report.
   B. P&T committee includes only one drug per therapeutic class to contain costs.
   C. Cangrelor is added to formulary but can only be prescribed by interventional cardiologists.
   D. New drugs added to formulary should be proven effective.

3. Which medication use process is best suited for an MUE?
   A. Review of warfarin dosing and ordering of international normalized ratios (INRs).
   B. Review of accuracy of medication history documentation.
   C. Review of errors caused by pharmacist-bypassed CPOE alerts.
   D. Review of compliance with a clinical protocol.

## III. ACCREDITING ORGANIZATIONS AND QUALITY IMPROVEMENT EFFORTS

A. Accreditation is often necessary for a variety of healthcare organizations to receive payment through programs, including federally funded Medicare and Medicaid programs.

B. Accreditation: The Joint Commission
   1. Independent not-for-profit organization that sets standards for the accreditation of health care facilities through its mission "to continuously improve health care for the public, in collaboration with other stakeholders, by evaluating health care organizations and inspiring them to excel in providing safe and effective care of the highest quality and value"
   2. Accredits and certifies more than 22,000 health care organizations in the United States. Accreditation is reassessed every 3 years on the basis of adherence to hospital standards, as assessed during on-site surveys and quality reporting of performance indicators.
      a. Standards address performance in functional areas of patient rights, patient treatment, medication safety, and infection control. NPSG were established to help accredited organizations address specific areas of concern in patient safety. Goals differ by health care setting and can change on the basis of recommendations from the Patient Safety Advisory Group.
      b. In on-site surveys, which are unannounced, tracer methodology is used to evaluate a patient's medical record as a road map through a health care organization to evaluate its compliance with standards and systems to provide care and services. First-generation tracers follow a patient through care areas, whereas second-generation tracers focus on major organizational areas, such as high-alert medications and medication shortages.
   3. Performance measurement
      a. National Hospital Quality Measures – ORYX
         i. Required chart-abstracted measures: Perinatal care
         ii. Choice of any four of the following additional electronic clinical quality measures:
            (a) Emergency department
            (b) Opioid use
            (c) Perinatal care (five measures)
            (d) Stroke (four measures) (Box 4)
            (e) VTE (two measures)
            (f) Hospital harm (two measures)

**Box 4.** National Hospital Inpatient Quality Measure for Stroke (STK)-6

**Measure:** Discharged on Statin Medication

**Type of Measure:** Process

**Description:** Ischemic stroke patients who are prescribed statin medication at hospital discharge.

**Rationale:** There is an extensive and consistent body of evidence supporting the use of statins for secondary prevention in patients with clinically evident atherosclerotic cardiovascular disease (ASCVD), which includes individuals with ischemic stroke due to large artery atherosclerosis, individuals with ischemic stroke due to intrinsic small vessel disease, and individuals with ischemic stroke not directly due to atherosclerosis but with clinically evident atherosclerotic disease in an uninvolved cerebral or noncerebral bed. Both women and men with clinical ASCVD are at increased risk for recurrent ASCVD and ASCVD death. High-intensity statin therapy should be initiated or continued as first-line therapy in women and men less than or equal to 75 years of age who have clinical ASCVD, unless contraindicated. In patients with clinical ASCVD and a contraindication to high-intensity statin therapy, moderate-intensity therapy should be considered as an alternative if it can be tolerated. In individuals greater than 75 years of age, the potential for ASCVD risk reduction benefits, adverse effects, drug-drug interactions, and patient preferences should be considered, and statin therapy individualized based on these considerations (Stone, 2013).

iii. Small hospitals (average daily census of 10 or fewer patients) and critical access hospitals required to report on a minimum of any of the three measures listed earlier

b. Disease-specific care certification programs – Additional performance measures in addition to standard requirements
   i. Comprehensive cardiac center
   ii. Advanced certification for heart failure – Inpatient and outpatient
   iii. Advanced certification for ventricular assist device
   iv. Stroke and comprehensive stroke
   v. Acute stroke ready
c. 2023 NPSGs
   i. NPSG.03.05.01 – Reduce the likelihood of patient harm associated with the use of anticoagulant therapy
   ii. Hospital and ambulatory elements of performance
      (a) Uses approved protocols and evidence-based practice guidelines for initiating and maintaining anticoagulant therapy that addresses medication selection; dosing, including adjustments for age and renal or liver function; drug-drug and drug-food interactions; and other risk factors as applicable.
      (b) The organization has a written policy addressing the need for baseline and ongoing laboratory tests to monitor and adjust anticoagulant therapy. For patients receiving warfarin therapy, use a current INR to monitor and adjust dosage. For patients on a direct oral anticoagulant (DOAC), follow evidence-based practice guidelines regarding the need for laboratory testing.
      (c) Provide education to patients and families specific to the anticoagulant medication prescribed, including the following:
         (1) Adherence to medication dose and schedule
         (2) Importance of follow-up appointments and laboratory testing (if applicable)
         (3) Potential drug-drug and drug-food interactions
         (4) The potential for adverse drug reactions
      (d) Organization addresses anticoagulation safety practices through the following:
         (1) Establishing a process to identify, respond to, and report adverse drug events, including adverse drug event outcomes.

(2) Evaluating anticoagulation safety practices, taking actions to improve safety practices, and measuring the effectiveness of those actions in a time frame determined by the hospital.

(e) Use approved protocols and evidence-based practice guidelines for reversal of anticoagulation and management of bleeding events related to each anticoagulant medication.

iii. Additional elements of performance for hospital-only

(a) Use unit-dose, prefilled, or premixed products, when available.

(b) Use approved protocols and evidence-based practice guidelines for perioperative management of all patients on oral anticoagulants. Perioperative management may address the use of bridging medications, timing for stopping an anticoagulant, and timing and dosing for restarting an anticoagulant.

(c) When heparin is administered intravenously and continuously, the hospital uses programmable pumps in order to provide consistent and accurate dosing.

C. Accreditation and Certification: The National Committee for Quality Assurance (NCQA)

1. Private, not-for-profit organization with a mission to improve the quality of health care through measurement, transparency, and accountability
2. Responsible for the development and maintenance of the HEDIS
   a. Consists of more than 90 measures across six domains of care that health plans use to measure performance and focus improvement efforts. Domains include effectiveness of care, access to/availability of care, experience of care, use and risk-adjusted use, health plan descriptive information, and measures collected using electronic clinical data systems.
   b. Several measures are included in CMS's Quality Rating System for health plans participating in federally facilitated marketplaces for consumers to view.
   c. Examples of cardiology-related measures:
      i. Controlling high blood pressure
      ii. Persistence of β-blocker treatment after a myocardial infarction
      iii. Statin therapy for patients with cardiovascular disease
3. Voluntary accreditation programs, certification programs, physician recognition programs, and distinctions are directed at health plans (e.g., health maintenance organizations, preferred provider organizations, and consumer-directed health plans), physician networks, medical groups, and individual physicians.
   a. Notably certifies and recognizes PCMHs
   b. Assessments may include on-site clinical and administrative processes, through data collection for the HEDIS, and measuring member satisfaction through the Consumer Assessment of Healthcare Providers and Systems survey.
4. The Quality Compass: A comparison tool that allows users to view measure results and benchmark information. The tool ranks health plans using the HEDIS measures.
5. Public reporting: "The State of Health Care Quality," which is an annual overall assessment of the performance of the American health care system; "America's Best Health Plans," in collaboration with U.S. News & World Report; and the online Health Plan Report Card with a searchable database detailing health plans' accreditation and performance ratings

D. Quality Improvement Efforts

1. Strategies to enhance health care quality
   a. Value-based purchasing: rewarding of high-quality care by such groups as CMS, employer purchasers, health plans and consumers; achieved by measuring and reporting on quality measures. Represents shift from fee-for-service (quantity of care) to pay-for-performance (quality of care).

   b. Outcomes-based performance: payment and reimbursement based on the achievement of a specific outcome rather than a single action or service
   c. Publicly reporting data: to drive systems to benchmark and achieve quality care
2. The National Quality Forum (NQF)
   a. Nonprofit organization comprising stakeholders from consumer organizations, public and private purchasers, physicians, nurses, accrediting and certifying bodies, supporting industries, and health care research and quality improvement organizations
   b. Aimed at improving quality through a three-part mission:
      i. Building consensus on national priorities and goals for performance improvement and working in partnership to achieve them
         (a) As a result of the Medicare Improvements for Patients and Providers Act, the NQF identified priorities for health care performance measurement based on evidence related to 20 high-priority conditions.
         (b) The conditions were identified by CMS to account for more than 95% of their costs.
      ii. Endorsing national consensus standards for measuring and publicly reporting on performance; assessing evidence to support and endorse quality measures proposed by other organizations (NCQA, American Medical Association, etc.) through a transparent, consensus-based practice
      iii. Promoting the attainment of national goals through education and outreach programs
3. The Agency for Healthcare Research and Quality (AHRQ)
   a. The health services research arm of the U.S. Department of Health and Human Services.
   b. Sponsors the National Quality Measures Clearinghouse – A "public repository for evidence-based quality measures and measure sets."
   c. Consumer Assessment of Healthcare Providers and Systems (CAHPS) – Surveys ask consumers and patients to report on and evaluate their experiences with health care. CAHPS hospital survey (HCAHPS) – Administered by Centers for Medicare & Medicaid Services (CMS); includes medication-specific questions such as:
      i. Before giving you any new medicine, how often did hospital staff tell you what the medicine was for?
      ii. Before giving you any new medicine, how often did hospital staff describe possible side effects in a way you could understand?
      iii. When I left the hospital, I clearly understood the purpose for taking each of my medications.
4. The Pharmacy Quality Alliance (PQA)
   a. The mission of the PQA is to improve the quality of medication use across health care settings.
   b. Develops medication-related performance measures—including adherence, medication use in older adults, opioid use, and medication therapy management, among others—through a collaborative process with key stakeholders
5. Centers for Medicare and Medicaid Services (CMS)
   a. Implements quality initiatives to ensure quality health care for Medicare beneficiaries. CMS uses quality measures in its various quality initiatives that include QI, pay for reporting, and public reporting.
   b. National Hospital Inpatient Quality Measures – Measures aligned with TJC
   c. Outcome measures
      i. 30-day risk-standardized mortality measures
      ii. 30-day risk-standardized readmission measures
      iii. Excess days in acute care
      iv. Agency for Healthcare Research and Quality patient safety indicators

d. Process measures
    i. Acute myocardial infarction
        (a) Aspirin at arrival
        (b) Aspirin prescribed at discharge
        (c) ACE inhibitor or Angiotensin receptor blocker for left ventricular systolic dysfunction
        (d) Adult smoking cessation advice/counseling
        (e) β-Blocker prescribed at discharge (f) β-Blocker at arrival
        (f) Thrombolytic agent received within 30 minutes of hospital arrival (non-PCI capable hospitals)
        (g) Primary percutaneous intervention within 120 minutes of hospital arrival
    ii. Heart failure
        (a) Discharge instructions
        (b) Left ventricular function assessment
        (c) ACE inhibitor or angiotensin receptor blocker for left ventricular systolic dysfunction
        (d) Adult smoking cessation advice/counseling
e. Hospital Compare – Consumer-oriented website that reports information on how well hospitals provide recommended care to their patients
    i. Hospital Quality Star Rating
    ii. Surgical complications and health care–associated infections
    iii. Readmissions and deaths by medical condition or surgical procedure
    iv. 30-day hospital-wide readmission
f. Innovation center – Develops new payment and service delivery models
    i. Accountable Care Organizations (ACOs) - Coordinated delivery of high-quality care by groups of clinicians, hospitals, and other health-care providers. Goals include avoiding unnecessary duplication of services and preventing medical errors.
    ii. Episode-based payment initiatives - hospital is financially accountable for the quality and cost of an episode of care, which incentivizes increased coordination of care (Example: Bundled Payments for Care Improvement).
    iii. Initiatives to speed the adoption of best practices
        (a) Million Hearts (collaboration with the Centers for Disease Control and Prevention) –Aims to prevent myocardial infarction and stroke by improving access to effective, quality care; focusing on disease prevention efforts; and improving prescription medications and adherence to appropriate medications
        (b) Million Hearts cardiovascular disease risk reduction model – Targeted incentives for health care practitioners to engage in beneficiary cardiovascular disease risk calculation and population-level risk management

6. The Leapfrog Group is a voluntary program that works with employers to enable and direct purchasing power toward health care decisions focused on safety, quality, and value. It compares hospital performance on the metrics most important to consumers and purchasers of care. A Hospital Safety Grade of A, B, C, D, or F has been applied to more than 2500 hospitals on the basis of prevention of errors, accidents, injuries, and infections.
7. Institute for Safe Medication Practices
    a. Nonprofit organization responsible for targeting medication error prevention and safe medication use; a certified patient safety organization
    b. Based on a nonpunitive approach and system-based solutions
    c. Five key areas of focus: Knowledge, analysis, education, cooperative, and communication
    d. Medication Errors Reporting System – Practitioner self-reporting program

8. Professional Society Quality Initiatives
    a. American Society of Health-System Pharmacists Practice Advancement Initiative – Goal is to significantly advance the health of patients by supporting futuristic practice models that support the most effective use of pharmacists as direct patient care providers. The initiative aims to assist leaders and practitioners in creating a framework, determining services, identifying emerging technology, developing templates, and implementing change.
    b. American College of Cardiology
        i. Anticoagulation initiative
        ii. Appropriate Use Criteria program
        iii. LDL: Address the Risk
        iv. Patient Navigator Program: Focus MI
        v. Reduce the Risk: PCI Bleed Campaign
        vi. Succeed in Managing Cardiovascular Risk in Diabetes
        vii. Succeed in Managing Heart Failure
        viii. Succeed in Managing Heart Valve Disease
        ix. Surviving MI
    c. American Heart Association
        i. Get With the Guidelines (GWTG)
            (a) Stroke
            (b) Heart Failure
            (c) Resuscitation
            (d) Atrial fibrillation
            (e) Coronary artery disease
        ii. Mission: Lifeline
        iii. Target programs (heart failure, stroke, and aortic stenosis)
        iv. Hospital certification programs (stroke, cardiac)
        iv. Post-acute and outpatient certifications (heart failure, hypertension)
        vi. Individual professional certifications (tobacco cessation, telehealth specialist)

E. Identifying Quality Issues – Tools are used to describe data or a process, identify areas for improvement, suggest solutions, assess effects of change, and show process or output variation.
    1. Root-cause analysis
        a. Completed after a sentinel event to determine why the error occurred
        b. Goal is to identify the cause or factors that contributed to the error so that actions can be taken to prevent recurrence.
            i. What happened?
            ii. Why did it happen?
            iii. How to prevent it from happening again?
        c. Steps include:
            i. Identify the underlying reason for an event.
            ii. Identify causes and analyze related processes/systems.
            iii. Identify ways to improve processes/systems to reduce chance of recurrence.
            iv. Create action plan for implementing process/system improvements.
            v. Implement improvements.
            vi. Evaluate the effectiveness of improvements.
        d. Resources
            i. TJC framework for conducting a root-cause analysis and action plan (https://www.jointcommission.org/-/media/tjc/documents/resources/patient-safety-topics/sentinel-event/rca_framework_101017.pdf?db=web&hash=B2B439317A20C3D1982F9FBB94E1724B)

ii. The VA National Center for Patient Safety root-cause analysis tools (https://www.patientsafety.va.gov/professionals/onthejob/rca.asp)

2. Healthcare Failure Mode and Effect Analysis (HFMEA)
   a. Systematic method of identifying and preventing product and process problems before they occur
   b. Steps include:
      i. Define the topic.
      ii. Assemble the team.
      iii. Graphically describe the process.
      iv. Conduct a hazard analysis.
         (a) Hazard scoring matrix
         (b) Decision tree
      v. Describe actions needed to eliminate each hazard identified.
   c. Resource – VA National Center for Patient Safety (https://www.patientsafety.va.gov/professionals/onthejob/hfmea.asp)
3. Gap analysis
   a. Used to compare best practices with processes currently in place in an organization to determine gaps
   b. May focus on pharmacy services, pharmacy technology, or a specific medication or medication process
   c. Steps include:
      i. Identify the existing process or gap analysis questions.
      ii. Identify the existing outcome.
      iii. Identify the desired outcome.
      iv. Identify the process for achieving the desired outcome.
      v. Assess the response to the level of adherence or implementation (e.g., fully, partly, in progress, no activity, or nonadherent).
      vi. Develop an action plan to fill the gap.
      vii. Develop and prioritize the requirements, and develop a timeline for completion to bridge the gap.
   d. Resource: Agency for Healthcare Research and Quality Indicators Toolkit (https://archive.ahrq.gov/professionals/systems/hospital/qitoolkit/d5-gapanalysis.pdf)
4. Benchmarking
   a. Used by health systems to compare performance with other systems or an external standard
   b. Helps determine where performance falls compared with others
   c. Uncovers opportunity for improvement when another institution's performance is better than yours
5. MUE – A PI effort to measure and describe the medication use process or medication treatment response and identify actual or potential medication-related problems with a goal of optimizing patient outcomes. See complete section on MUE.

F. Data Sources
   1. Committee reviews
   2. Medical records
   3. Statistics
   4. Patient concerns or comments
   5. Reports from third party payers and regulatory agencies
   6. Incident reports
   7. Root-cause analysis reports
   8. Accident reports

9. Patient-care conferences
10. PI reports
11. Patient-care evaluation studies
12. Patient-satisfaction survey results
13. External comparative benchmark data

G. Cardiology Pharmacist's Role in QI – Example metrics for evaluating the quality of cardiology pharmacy services
    1. Length of stay
    2. Readmission rate
    3. Evidence-based medication on hospital discharge (myocardial infarction, heart failure)
    4. Process and outcome measures
    5. ADEs
    6. Drug interactions
    7. Medication errors
    8. Medication adherence
    9. Heart failure hospitalizations
    10. Bleeding and thromboembolism rates
    11. Mortality

H. Opportunities for Involvement in QI
    1. Quality management/improvement department
    2. Risk management department
    3. Committees
        a. P&T
        b. Pain management
        c. Education and training
        d. Patient safety
        e. Medication safety
    4. Pharmacy-specific
        a. Discharge counseling
        b. Medication reconciliation
        c. Medication ordering and supply
        d. Throughput, including CPOE, robots, and automated dispensing cabinets
        e. Safety and timeliness of medication administration
        f. Adherence to medication-related accreditation standards

I. Publishing QI Results
    1. Important to publish QI data to promote improved efforts in health care
    2. Reduces the chances of the same mistakes being repeated
    3. Shares your work by spreading important and useful information
    4. Standards for Quality Improvement Reporting Excellence (SQUIRE) – Provides a framework for reporting new knowledge about how to improve health care (http://squire-statement.org/index.cfm?fuseaction=Page.ViewPage&PageID=471)

**Patient Case**

4. During a code blue event, 10 mL of epinephrine was drawn from a 30 mg/30 mL multi-dose vial and administered to the patient resulting in a dose 10 times the recommended ACLS dose for cardiac arrest. The patient ultimately expired. Which quality tool is most appropriate to conduct a review of this incident?
   A. Healthcare failure mode and effect analysis
   B. Root cause analysis
   C. Gap analysis
   D. Medication use evaluation

## IV. PHARMACOECONOMICS

A. Overview
   1. Outcomes research: An attempt to identify, measure, and evaluate the end results (outcomes) of the structure and processes of the health care system and the well-being of patients and populations (economic, clinical, and humanistic outcomes [ECHO model])
   2. Pharmacoeconomics is the description and analysis of the costs of drugs and pharmaceutical services and their effects on individuals, health care systems, and society. Pharmacoeconomics is a type of outcomes research that can be used to quantify the value of pharmaceutical care.
   3. For practitioners, pharmacoeconomics may be thought of as weighing the cost of providing a pharmacy product or service against the consequences (outcomes) of using the product or service to determine which alternative yields the best outcome per dollar spent.
   4. Economic evaluations: Studies that identify, measure, and compare the costs and consequences of a pharmaceutical product or service
      a. Full economic evaluations
         i. Cost-minimization analysis
         ii. Cost-benefit analysis
         iii. Cost-effectiveness analysis
         iv. Cost-utility analysis
      b. Other cost evaluations
         i. Cost of illness
         ii. Budget impact analysis
   5. Humanistic outcomes or patient-reported outcome measures
      a. Quality of life
      b. Health-related quality of life
      c. Health status
      d. Well-being
      e. Symptoms and functional status
      f. Patient preferences/satisfaction

B. Types of Costs
   1. Costs versus charges
      a. Charges are often reported incorrectly in the literature as costs.
      b. Costs are expenses incurred by an organization providing patient care.
      c. Charges are costs plus profit.
      d. Ratio of cost to charge is used to estimate costs from charges.

2. Total cost of care – Extends beyond the acquisition cost of a drug and includes waste cost, preparation cost, distribution cost, administration cost, toxicity cost, and monitoring cost
3. Perspective – Describes whose costs are relevant, given the purpose of the study
    a. Helps determine which costs are important to measure
    b. Perspective can be that of providers, payers, patients, or society.
4. Costs should be adjusted for time if collected more than 1 year before the study or more than 1 year into the future.
    a. Retrospective – Adjust the cost by multiplying the number of doses used by the current cost of medication.
    b. Estimated future dollars spent or saved – Use the discount rate to calculate the present value.
5. Direct costs – Resources consumed in the prevention, detection, or treatment of a disease or illness. These costs can be medical or nonmedical.
    a. Medical – Costs associated with medical care
        i. Fixed costs – Overhead costs; costs remain constant and do not change. Not typically included in a pharmacoeconomic analysis. Examples: Cost of electricity, rent, lighting, building maintenance
        ii. Variable costs – Medications, hospitalization, laboratory testing, procedures – All depend on the volume of use; the more services that are used, the greater the expense.
    b. Nonmedical – Costs as a result of the illness or disease that do not involve the purchase of medical services. Examples: Transportation to health care, child care, specialty diets, clothing
6. Indirect costs – Costs as a result of morbidity or mortality. Relate to the change in productivity ability as a result of the disease or illness. Examples: Income lost because of premature death, inability to work. Sometimes, it is a challenge to assign dollar values.
7. Intangible costs – Costs that represent nonfinancial outcomes of the disease and medical care. It is difficult to measure or assign values to intangible costs. Examples: Costs from pain and suffering, grief, other nonfinancial outcomes of disease
8. Incremental costs – Extra costs needed to purchase an additional benefit or effect of the medical care. Example: Additional medications to control hypertension above standard therapy. Often used in cost-effectiveness analysis

C. Economic Evaluations
    1. Cost-minimization analysis – Costs are expressed in monetary terms, and outcomes are considered equivalent. Results are provided as cost savings (Table 1).
        a. Compares the cost of two or more treatment alternatives, treatments, or services and determined to be equal in efficacy
        b. Costs are compared to determine the least expensive alternative.
        c. Should not be used if no evidence exists to support the efficacy of the treatment alternative. Example: Comparing therapeutic agents in the same therapeutic class; comparing different dosage forms or dosing strategies of the same drug
    2. Cost-benefit analysis – Compares the outcomes of the intervention expressed in monetary terms with the cost of the resources consumed. Results are expressed as either cost-benefit ratio or net cost/ net benefit (Table 1).
        a. Resources consumed by the intervention are measured in dollars.
        b. Benefits of the intervention are translated to dollar values, including direct benefits, indirect benefits, intangible benefits
        c. Assigning monetary value to health outcomes is difficult:
            i. Human capital approach – Health benefits are equal to the economic productivity they permit (i.e., cost of disease = cost of lost productivity).

ii. Willingness-to-pay – Estimate of how much people would pay to reduce their chance of an adverse health outcome

d. Provides the yield of an investment. Example: Justifying and documenting the value of an existing pharmacy service or the potential worth of an existing service—specifically, determining the value of pharmacokinetic service compared with a vaccination program

3. Cost-effectiveness analysis – Compares two or more treatment alternatives or programs in which resources used are measured in monetary terms and outcomes in natural health units (e.g., cures, lives saved, blood pressure) (Table 1)

**Table 1**. Comparison of Pharmacoeconomic Evaluations

| Analysis | Cost Measurement | Outcome Measurement |
|---|---|---|
| Cost-minimization | Monetary | Various but assumed to be equivalent |
| Cost-benefit | Monetary | Monetary |
| Cost-effectiveness | Monetary | Natural health units |
| Cost-utility | Monetary | Patient preferences or quality of life (QALY) |

QALY = quality-adjusted life-year.

a. Goals of cost-effectiveness analysis – To determine which alternative can produce the desired effect or maximization of effect

b. Tries to reveal the optimal alternative, which may not always be the least expensive but provides the desired outcome

c. Results expressed as a ratio:

i. Average cost-effectiveness ratio = total cost of a program or treatment alternative divided by its clinical outcome. Allows for outcomes to be reduced to a single value to allow for comparison

ii. Incremental cost-effectiveness ratio (ICER) = the additional cost and effectiveness gained when a treatment is compared with the next best alternative.

(a) ICER = (cost of treatment A cost of treatment B)/(clinical success of treatment A - clinical success of treatment B) or

(b) ICER = (cost of treatment A - cost of treatment B)/(QALY from treatment A - QALY from treatment B) (Table 2)

**Table 2**. Incremental Cost-Effectiveness Ratio Example

| Treatment | Cost | Outcomes (QALYs[a]) |
|---|---|---|
| A | $2500 | 3.2 |
| B | $1000 | 1 |
| Increment (of A over B) | $1500 | 2.2 |
| Incremental cost/Incremental outcome | $1500 / 2.2 QALYs = $681.82 gained | |

[a]3.2 QALYs = 4 years x 0.8 units of utility; 1 QALY = 2 years x 0.5 units of utility

QALY = Quality-adjusted life-year

4. Cost-utility analysis – Compares two or more treatment alternatives or programs in which resources are measured in monetary terms and outcome is expressed in patient preferences or quality of life or quality-adjusted life-years (QALYs) (Table 1)

a. Form of cost-effectiveness analysis in which values (utilities) are assigned to the outcome

b. Life and death are reference states for the utilities, with perfect health = 1.0 and death = 0.0.

c. Determine the life-years gained and then multiply by the utility of that life-year. For example, if a person has a life expectancy of 20 years but is disabled and functioning at only 70% of his or her capacity, the QALY is 20 years x 0.7 = 14 QALYs.
d. Utilities or a patient's preference for a disease state can be measured by obtaining information from the literature, approaching a convenience sample of experts, decision theory using a direct approach, or employing psychometric methods using indirect approaches. Direct approaches include rating scales, time trade-off, and standard gamble. Indirect approaches include multi-attribute health state scores (e.g., quality-of-life assessment tools).
e. Measures the function and overall well-being of patients using quality-of-life assessment tools
    i. General health-related quality-of-life instruments
        (a) Nottingham Health Profile
        (b) Sickness Impact Profile
        (c) Posttraumatic Stress Disorder Questionnaire
        (d) EuroQol Questionnaire
        (e) Medical Outcome Study Short Form 36 (SF-36) or Short Form 12 (SF-12)
    ii. Disease-specific quality-of-life instruments
        (a) Minnesota Living with Heart Failure Questionnaire
        (b) Seattle Angina Questionnaire
        (c) Cardiac Depression Scale
        (d) Hospital Anxiety and Depression Scale

    Example: Pharmacist management of chronic heart failure medications in an ambulatory clinic. The evaluation could measure the quality of heart failure symptom control according to the patient's perception.

5. Cost of illness
    a. Estimate of the overall cost of a particular disease in a defined population
    b. Considers direct and indirect costs of the disease or illness
    Examples: Cost of hypertension, cost of kidney disease
6. Budget impact analysis or budget impact model
    a. Estimates the financial impact of a new health care intervention within the health care setting and is therefore limited in its perspective
    b. Useful in budget planning
    c. Aids in determining the projected impact of a formulary addition

**Table 3**. Comparison of Pharmacoeconomic Evaluations

| Analysis | Advantages | Disadvantages |
|---|---|---|
| Cost-minimization | Simple | Outcomes must be shown to be equivalent |
| Cost-benefit | Can compare alternatives with different outcomes | Difficult to assign monetary value to health benefits or consequences |
| Cost-effectiveness | Outcomes are readily understood by practitioners and need not be converted to monetary values | Alternatives used in comparison must have outcomes measured in the same units |
| Cost-utility | Different outcomes can be compared using one common unit (QALY) without requiring monetary value | Difficult to determine an accurate QALY – Less precise than natural health units. Not well understood by providers and payers |

D. Application of Pharmacoeconomics
   1. Formulary management
      a. Inclusion or exclusion of newly marketed or other target drugs
      b. Inclusion of drugs with criteria or restriction
      c. Deletion of medications from the formulary
      d. Limiting the use of nonformulary items
      e. Affecting physician or provider prescribing patterns
   2. Clinical guidelines, policies, or protocols – Assists in influencing prescribing, and promoting the most cost-effective and desirable use of drugs
   3. Drug use policy – Policies implemented to promote the most efficient use of health care products and services. Drug use policies can influence providers' prescribing practices to provide high-quality care, given the resources available.
   4. Services or program evaluations – Use of pharmacoeconomics can aid in determining the value of an existing medical or pharmacy service or the potential worth of starting a new service.
   5. Individual patient treatment decisions – Evaluating the impact of drug therapy on a patient's quality of life can be useful when customizing a pharmacotherapy regimen.

**Patient Case**

5. From the patient's perspective, which best describes direct costs?
   A. Copay for medical office visit.
   B. Loss of income from knee replacement recovery.
   C. Pain and suffering experienced during a motor vehicle crash.
   D. Electricity used in medical office.

## V. LEGAL COMPLIANCE

A. Standards of Conduct – Derived from statutes and regulations, professional standards or values, and codes of ethics. Violations can affect pharmacy or pharmacist licensure or accreditation status and may result in litigation or criminal prosecution.
   1. Federal and state statutes and regulations
   2. American Pharmacist Association: Code of Ethics
   3. American College of Clinical Pharmacy (ACCP): Standards of Practice for Clinical Pharmacists
   4. American Society of Health-System Pharmacists: Minimum Standard for Pharmacies in Hospitals

B. Omnibus Budget Reconciliation Act of 1990 (OBRA 1990) – Required states participating in Medicaid program to establish standards for:
   1. Maintaining proper records – Reasonable efforts to obtain, record, and maintain patient information, including name, address, telephone number, age and sex, individual history (disease states, allergies, medications), and pharmacist's comments about the patient's drug therapy
   2. Prospective drug use review – Before dispensing medication, a pharmacist must evaluate a patient's medication record for potential therapy problems such as therapeutic duplication, drug-disease contra-indications, drug-drug interactions, incorrect dosage or treatment duration, drug-allergy interactions, and evidence of clinical abuse/misuse.
   3. Patient counseling – A dispensing pharmacist must offer to counsel on significant drug therapy points, including description of the medication, route of administration, dose, dosage form, and therapy duration. In addition, the standards require the pharmacist to counsel on any special precautions, common side effects or interactions, contraindications, proper storage, self-monitoring, what to do if a dose is missed, and refill information.

C. Health Insurance Portability and Accountability Act of 1996 (HIPAA) – Established federal standards for protecting the privacy and security of patients' protected health information (PHI)
   1. Covered persons/entities
      a. Health plans
      b. Health care providers
      c. Health care clearinghouses
   2. Protected information
      a. Individually identifiable health information or PHI
      b. Relates to:
         i. Individual's past, present, or future physical or mental health or condition
         ii. Provision of health care to the individual, or
         iii. The past, present, or future payment for the provision of health care, and that identifies the individual. Many common identifiers are considered individually identifiable (e.g., name, address, date of birth, social security number)
      c. Requirements of covered entity to protect information
         i. Designate a "privacy officer."
         ii. Ensure that employees are trained.
         iii. Provide patients with "Notice of Privacy Practices."
         iv. Create safeguards in contracts with business associates exposed to PHI.
      d. Covered entities, including pharmacies, must obtain the patient's written authorization to disclose or use PHI that is not for treatment, payment, or health care operations.
      e. Exceptions to releasing PHI without authorization:
         i. Spousal abuse or child neglect
         ii. Law enforcement compliance
         iii. Avoiding threat to health or safety
         iv. Reporting an ADR to the FDA MedWatch program
      f. PHI may also be released if it is "de-identified" by removing all PHI.

**Box 5**. Examples of Protected Health Information

1. Name
2. Social Security number
3. Telephone and/or fax numbers
4. Geographic subdivisions smaller than a state(street, city, precinct, county, and ZIP code)
5. Dates (except year): Birth date, admission date,discharge date, date of death, and all ages > 89
6. Medical record number, health plan number,account number, or prescription number
7. Certification or license numbers
8. Vehicle identifiers (e.g., serial number, license platenumber)
9. Name of relative medical device identifiers (e.g.,serial numbers)
10. Patient's website URL, computer IP address, ande-mail address
11. Biometric identifiers (e.g., DNA, fingerprints, voicerecording, body description, retinal scan)
12. Photographic images (identifiable)
13. Any other unique characteristic or code

D. Prescription Drug Marketing Act of 1987 – Prohibits diversion of prescription drug samples into the retail market

E. State Pharmacy Statutes and Boards of Pharmacy – Establish standards for facilities licensed as pharmacies and standards of conduct for pharmacists and pharmacy employees. Licensing bodies for location of pharmacies and individuals able to practice

F. State Prescription Drug Monitoring Programs – Collect information on controlled substances or other "drugs of concern" to reduce abuse/misuse. Information is available to individuals authorized by state law to receive such information for professional purposes (e.g., pharmacists).

## VI. SAFE MEDICATION USE

A. Definitions
   1. Medication error – A mishap that occurs during prescribing, transcribing, dispensing, administering, or monitoring a drug. Medication errors that are intercepted and stopped before they occur are called "near misses." Some medication errors cause injury (result in an ADE), and some do not.
      a. Harm is physical or psychological injury or damage to a person's health, including both temporary and permanent injuries.
      b. Medication errors are categorized into the following: no error (category A), error and no harm (categories B–D), error and harm (categories E–H), and error and death (category I) (Table 4).

**Table 4**. Categorizing Medication Errors

| Category | Description |
|---|---|
| A | No error – Scenarios that have the capacity to cause error |
| B | An error occurred but did not reach the patient (an "error of omission" does reach the patient) |
| C | An error occurred and reached the patient but did not cause harm |
| D | An error occurred that reached the patient and required monitoring to confirm that it resulted in no harm to the patient or required intervention to prevent harm |
| E | An error occurred that may have contributed to or resulted in temporary harm to the patient and required intervention |
| F | An error occurred that may have contributed to or resulted in temporary harm to the patient and required initial or prolonged hospitalization |
| G | An error occurred that may have contributed to or resulted in permanent patient harm |
| H | An error occurred that required intervention necessary to sustain life |
| I | An error occurred that may have contributed to or resulted in the patient's death |

   2. ADE – An injury resulting from the use of a drug that includes harm caused by the drug (ADRs and overdoses) and harm from using the drug, including dose reductions and discontinuations of drug therapy
   3. ADRs
      a. World Health Organization: "Any response to a drug which is noxious and unintended, and which occurs at doses normally used in man for prophylaxis, diagnosis, or therapy of disease, or for the modification of physiological function"
      b. Karch and Lasagna (JAMA 1975;234:1236-41): "Any response to a drug that is noxious and unintended, and that occurs at doses used in humans for prophylaxis, diagnosis, or therapy, excluding failure to accomplish the intended purpose"
      c. The primary difference is that the World Health Organization definition suggests that therapeutic failures (e.g., clopidogrel failing to prevent ischemic stroke) are an unintended effect and thus an ADR, whereas Karch and Lasagna exclude therapeutic failures.

d. Both definitions refer to doses normally used in humans, which excludes overdoses and medication errors that exceed normal doses (these are still ADEs).
e. In general, side effects and ADRs are used synonymously. The term side effect may minimize or downplay the risk of injury from medications. It has been suggested that the term side effect be avoided in favor of the term ADR.

Example: Diphenhydramine causing sedation when used to treat allergic rhinitis is unintended – This is an ADR; conversely, sedation when diphenhydramine is being used as a sedative hypnotic is an intended effect, not an ADR.

4. Overall, ADE is the broader term that is used to describe any harmful event associated with a medication, including inappropriate use such as an overdose, whereas ADR is used when an adverse response, including harm, occurs with normal use of the medication.
5. Preventable ADE – Occurs when a breach of standard professional behavior, practice, or technique was identified or when necessary precautions were not taken, or when the event was preventable by modification of behavior, practice, technique, or care
   a. Results from any medication error that reaches the patient and causes harm
   b. About 30%–50% of all ADEs are preventable.
   c. Drug interactions account for 3%–5% of all preventable in-hospital ADEs.

   Example: Heparin administration without the use of weight-based dosing, causing an elevated partial thromboplastin time and an intracranial hemorrhage
6. Non-preventable ADEs are ADEs not associated with a medication error. Unintended reactions (ADRs) without known mitigation strategies resulting in patient harm. Example: A patient taking rivaroxaban with appropriate dosing, administration, and monitoring develops gastrointestinal bleeding.
7. Serious ADE (FDA definition) – Serious adverse events related to drugs or devices in which "the patient outcome is death, life threatening (real risk of dying), hospitalization (initial or prolonged), disability (significant, persistent, or permanent), congenital anomaly, or required intervention to prevent permanent impairment or damage." Example: Olanzapine-induced torsades de pointes

B. ADE Monitoring and Reporting Program
   1. TJC medication management standard requires hospitals to respond to actual or potential ADEs, significant ADRs, and medication errors.
   2. American Society of Health-System Pharmacists recommends a comprehensive ADR monitoring and reporting program as part of an organization's overall drug use system.
   3. A comprehensive ADE program should have a policy and procedure, with guidelines for ADE detection, reporting, management, surveillance, and education.
   4. ADE/medication safety committee
      a. Often a subcommittee of the P&T committee
      b. Pharmacists should leverage their expertise with drug-induced diseases to take a leadership role in developing, maintaining, and providing ongoing evaluation of ADE programs.
      c. ADE committees should be multidisciplinary and include:
         i. Physicians
         ii. Pharmacists
         iii. Nurses
         iv. Risk management personnel
         v. Quality assurance and PI personnel
         vi. Other health care providers
   5. ADR and ADE data should be reported as mild, moderate, or severe. Many scales are available in the literature. Definitions for each should be established. An example is provided in Table 5.

**Table 5**. Definitions for the Degree of ADR Severity[a]

| | |
|---|---|
| Mild ADR | Results in heightened need for patient monitoring with or without a change in vital signs, but no ultimate patient harm, or any adverse event that results in the need for increased laboratory monitoring |
| Moderate ADR | Results in the need for aggressive intervention with antidotes or increased length of hospital stay (e.g., severe hypotension [e.g., BP < 90/50 mm Hg], bleeding necessitating transfusions) |
| Severe ADR or ADE | Results in harm to the patient, prolonged hospitalization, transfer to a higher level of care, permanent organ damage (e.g., irreversible hepatotoxicity or renal failure), or death with probable ADE causality nomogram score |

[a]Other ADE severity scales are available.

ADE = adverse drug event; ADR = adverse drug reaction; BP = blood pressure.

6. The ADE subcommittee should designate which ADEs are preventable and should provide explanations regarding why they were preventable.
7. The ADE committee will determine which ADEs are reported externally.
    a. FDA MedWatch
        i. The following may be voluntarily reported with respect to an FDA-regulated medication, biologic, dietary supplement, cosmetic, or medical device:
            (a) Serious ADE
            (b) Product quality problem
            (c) Product use error
            (d) Therapeutic inequivalence/failure
        ii. The FDA Adverse Event Reporting System is a database that contains information on adverse events and medication error reports that have been submitted to the FDA.
    b. Drug manufacturer – Reports from health care professionals are entered in the FDA Adverse Event Reporting System database.
    c. Vaccine Adverse Event Reporting System – National vaccine safety surveillance system cosponsored by the Centers for Disease Control and Prevention and the FDA (vaers.hhs.gov)
    d. Institute for Safe Medication Practices
        i. ISMP Medication Error Reporting Program (MERP)
        ii. ISMP Vaccine Error Reporting Program (VERP)
8. The committee should report the data regarding who is detecting ADEs and who reports, documents, and manages the ADEs.
9. The committee should provide trending data that are based on either drug or drug class and by specialty units.
10. The committee should benchmark the hospital's ADEs against itself in previous years and compare them with the data from other hospitals published in the literature. Total ADE data can be reported according to the following:
    a. Total number of ADEs
    b. ADEs per admission
    c. ADEs per patient
    d. ADEs per patient days
    e. ADEs per doses dispensed
    f. ADEs per doses administered
11. A popular method of reporting ADEs is by the total number of admissions, with an acceptable benchmark of 2.5%–10%. For example, a hospital with 10,000 admissions reporting 1000 ADEs would have a 10% ADE reporting rate.

12. The ADR report information from the committee should be disseminated to medical staff and other health care providers for educational purposes.

C. Detecting ADEs
   1. Incident voluntary reporting is an ethical obligation of all health care professionals, and the success of any surveillance system depends on the willing participation of health care professionals in reporting ADEs.
   2. Voluntary reporting is the primary source of event identification for most institutions; however, events are grossly underreported for reasons that include:
      a. Complex reporting process
      b. Culture of fear
      c. Culture of risk tolerance
      d. Concern of liability
      e. Perception reporting is not a priority.
   3. Three types of surveillance systems used to detect ADEs
      a. Prospective
      b. Concurrent
      c. Retrospective
   4. ADRs are more likely to be detected when a combination of surveillance systems is used.
   5. Prospective surveillance – Occurs before initiating medication therapy and can be accomplished by:
      a. Monitoring patients at high risk of ADEs such as:
         i. Polypharmacy
         ii. Extremes of age (e.g., neonatal, pediatric, geriatric)
         iii. Vulnerable disease states (e.g., renal or hepatic impairment)
         iv. Severity of illness
         v. History of allergy/previous ADE
         vi. Pharmacodynamic/pharmacokinetic changes
      b. Monitoring of patients who are receiving medications known to have a high potential for causing ADEs – Drug classes commonly implicated in ADEs include:
         i. Anticoagulants
         ii. Antimicrobials
         iii. Antineoplastics
         iv. Cardiac agents (e.g., antiarrhythmics, digoxin, antihypertensives)
         v. Central nervous system agents (e.g., analgesics, anticonvulsants, sedatives/hypnotics)
         vi. Diagnostic agents (e.g., contrast media)
         vii. Antidiabetic agents (including insulin)

         Challenge: Labor-intensive and involves continuous monitoring
      c. Direct observation of medication administration by nurses or physicians
      d. Clinical decision support alerts
         i. Prescribing – Prescribers can be notified of high-risk scenarios during the ordering process to prevent medication errors, such as incorrectly dosing enoxaparin in a patient with impaired renal function.
         ii. Order verification – Pharmacists receive preventive alerts during order verification to avoid medication errors and the potential for ADEs. Common alerts pharmacists receive are to prevent drug-drug interactions.
         iii. High-risk scenarios – Pharmacists may receive advanced alerts outside order verification indicating a patient is being initiated on a drug for which the current clinical scenario presents a risk. An alert for a patient receiving an epidural and initiated on an anticoagulant presents an opportunity to prevent an ADE.

6. Concurrent surveillance – Identification of ADEs close to when they occur. Concurrent methods include:
   a. Spontaneous reporting of ADEs by practitioners during their normal work using telephone hotlines or report forms
   b. Monitoring of orders by pharmacy personnel for triggers that an ADE has occurred. Triggers include the following:
      i. Abnormal test results such as serum drug concentrations above therapeutic concentrations and laboratory test results outside a particular range or threshold. Examples of trigger laboratories or conditions are listed in Box 6.
      ii. Alerting order – An order or sequence of orders that suggests an ADE took place
         (a) Sudden discontinuation of one or more medications
         (b) Unexpected reduction in dosage
         (c) Order for medication routinely used to treat ADEs such as antidotes, physiologic antagonists, or agents for gastric decontamination. Examples of trigger drugs are listed in Box 7.
7. Retrospective surveillance – Involves a review of medical records for ADEs. Disadvantages include inadequate documentation of events and inability to intervene in a timely manner. In addition, retrospective surveillance alone does comply with TJC expectations for active monitoring.

**Box 6**. Laboratories or Conditions Used as Triggers or Tracers to Aid in Reporting ADEs

| | |
|---|---|
| 1. PTT > 100 s | 8. Rising serum creatinine |
| 2. INR > 6 | 9. Potassium > 6 mEq/L or < 3 mEq/L |
| 3. Glucose < 50 mg/dL | 10. QTc > 500 msec |
| 4. WBCs < 3 x $10^3$ cells/$mm^3$ | 11. Plt < 50,000/$mm^3$ |
| 5. Rash | 12. Hemoglobin < 7 g/dL |
| 6. Fall | 13. Digoxin concentration > 2 ng/mL |
| 7. Transfer to higher level of care | 14. Oversedation/lethargy |

ADE = adverse drug event; Plt = platelet count; PTT = partial thromboplastin time; WBC = white blood cell.

**Box 7**. Medications Used as Triggers or Tracers to Aid in Reporting ADEs

| | |
|---|---|
| 1. Activated charcoal | 13. Icatibant |
| 2. Antidiarrheal agents | 14. Magnesium IV |
| 3. Atropine IV | 15. Naloxone |
| 4. Benztropine | 16. Phentolamine |
| 5. C1 inhibitor | 17. Potassium IV |
| 6. Dextrose 50% IV push | 18. Prednisone |
| 7. Digoxin immune fab | 19. Protamine |
| 8. Diphenhydramine | 20. Prothrombin complex concentrates |
| 9. Epinephrine IM or IV | 21. Sodium polystyrene sulfonate |
| 10. Fidaxomicin | 22. Topical corticosteroids |
| 11. Flumazenil | 23. Vitamin K |
| 12. Glucagon | |

IM = intramuscular(ly).

D. Determining Causality of ADEs: Identified events must be confirmed for causality. Many instruments are available to aid in the link between drug and event. Structured instruments create a more reliable and valid assessment. The available methods for assessing ADE causality fall into three broad categories:
   1. Expert judgment/global introspection – Individual assessment of the event by a health care practitioner who bases assessment on his or her clinical knowledge and experience without using any standardized tool

2. Algorithm – Use of specific questions to assign a weighted score that helps determine the probability of causality for the event (e.g., the Naranjo Criteria for Causality)
3. Probabilistic – This method uses epidemiologic data to calculate the probability of causality using advanced statistical methods.

E. Causality assessment includes temporal sequence, dechallenge (removal of the suspect drug), rechallenge (reintroducing the suspect drug), evaluation of other causes, objective evidence that is available or obtained, and history of a reaction to a similar drug.

F. Documenting ADRs and ADEs
1. A drug-induced allergy is an ADR or ADE that is routinely documented in the patient's medical record to prevent reexposure and unintended consequences.
2. For the same purpose as documenting drug allergies, all other ADRs or ADEs should also be documented in the electronic medical record and maintained in the record indefinitely.
3. Depending on the severity of the ADR or ADE, the CPOE system can be programmed to prompt further review and recommend appropriate action when the same drug or a drug from the same or similar drug class is ordered.

G. Reducing Risk of Errors
1. Organizations should prospectively perform risk assessment and implement strategies to reduce certain types of errors.
2. Areas of focus
   a. High-risk populations (e.g., elderly, renal dysfunction)
   b. High-risk processes (e.g., chemotherapy compounding)
   c. High-alert medications (e.g., insulin, anticoagulants)
   d. Easily confused drug names (e.g., look-alike/sound-alike medications)

**Box 8.** Examples of Safety Strategies to Reduce Medication Errors

1. Use of oral syringes without capability of IV port connection
2. Use of smart infusion IV pumps
3. Implementing barcode technology
4. Electronic prescribing with clinical decision support
5. Use of evidence-based protocols and ordersets
6. Limiting and standardizing available drug concentrations, diluents, and container sizes
7. Using commercially available products when possible over compounding
8. Dispensing medications in most ready-to-use form to reduce need for nursing manipulation
9. Performing independent double checks on dosing and infusion pump programming when appropriate.
10. Storing high-risk medications in the pharmacy (e.g., concentrated electrolytes, insulin U-500)

3. Risk Evaluation and Mitigation Strategy (REMS): FDA-mandated program to manage the safe use of certain drugs with known or potential serious risk.
   a. Focus on specific serious risks, not all adverse events of a medication (e.g., hepatic toxicity with bosentan; teratogenicity with riociguat)
   b. Requirements of REMS vary by drug
   c. May include a medication guide, patient package insert, communication plan, elements to ensure safe use, and an implementation system

H. Medication Safety and Drug Shortages
   1. Drug shortages often require use of alternative products that may lead to medication safety issues:
      a. Alternate manufacturers with different labeling
      b. Different drug concentration or package size
      c. Alternate dosage form
      d. Use of less familiar alternative drug
   2. Drug shortage action plan must examine potential safety hazards with alternative products.
   3. System changes made to address shortage should be reversed once shortage resolved.

I. Drug Interactions – When the effects of one drug can be changed by the presence of another
   1. Interactions range from benign and insignificant to harmful and life threatening.
   2. Related toxicity (ADR) may be preventable.
      a. Avoid the combination and change to alternative therapy.
      b. Adjust doses to compensate for the interaction.
      c. If the combination cannot be avoided, monitor for efficacy and toxicity.
   3. A documented drug interaction with known outcomes can be considered an ADR, medication error, or preventable ADR.
   4. Drug information databases (e.g., Lexicomp, Micromedex) can provide types of interactions and severity.
   5. Safety measures to avoid drug interactions
      a. Pharmacist review and validation
      b. CPOE and clinical decision support
      c. Education (e.g., pocket drug cards, drug alerts, electronic drug information databases)
   6. Evaluating causation
      a. Assessment of causation of a drug interaction includes a temporal relationship, consideration of the pharmacologic properties of the object and precipitant drug, patient factors and disease states, the possible contribution of other drugs, and, when possible, a positive dechallenge.
      b. The Drug Interaction Probability Scale (DIPS) may be used to determine drug-drug interaction causation, including the adverse outcomes in a specific patient (see Appendix 1).
      c. The DIPS is patterned after the Naranjo ADR Probability Scale. A series of 10 questions related to the drug interaction are assessed with "yes," "no," "unknown," or "not available" answers and are then scored and tabulated. The total score determines the probability of the drug-drug interaction occurring in the patient and is scaled as follows:
         i. Highly probable: More than 8
         ii. Probable: 5–8
         iii. Possible: 2–4
         iv. Doubtful: 2 or fewer
      d. When using the DIPS, the evaluator must have comprehensive knowledge of the pharmacologic properties of both the object drug and the precipitator drug, especially their pharmacokinetic and pharmacodynamic properties and their mechanisms of drug action and interactions.

**Patient Case**

*Questions 6 and 7 pertain to the following case.*

J.S., a 74-year-old woman with atrial fibrillation, takes warfarin 3 mg daily for stroke prevention and has been stable on this regimen for the past 8 months. At her office visit 2 weeks ago, her INR was 2.7, and no changes were made to her regimen. She denied any changes in other medications or diet. She now presents to the emergency department with an intracranial hemorrhage and requires intubation. Her INR today is 2.8. Her husband states she has been taking warfarin as directed.

6. Which best describes the cause of this patient's intracranial hemorrhage?
   A. ADE.
   B. Preventable ADE.
   C. Medication error.
   D. Preventable ADR.

7. Which best classifies the degree of severity of this patient's intracranial hemorrhage?
   A. Mild.
   B. Moderate.
   C. Severe.
   D. Depends on the patient's outcome.

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## ANSWERS AND EXPLANATIONS TO PATIENT CASES

**1. Answer: D**
Using evidence-based practice helps provide support in creating policies with support and consensus among relevant stakeholders (Answer D is correct). Key stakeholders are critical to policy development but should be identified during policy planning (Answer A). Policies should be written in a structured format adopted by the organization to provide consistency across all departments (Answer B). New policies should be communicated to all relevant stakeholders (Answer C).

**2. Answer: C**
Drugs are often added to formulary with restrictions based on efficacy, safety, patient-specific populations, or cost. Cangrelor use is limited to interventional cardiology and may not be safely prescribed by physicians in other specialties (Answer C is correct). Formulary decisions should be guided by strong levels of evidence such as randomized controlled trials (Answer A). Including only one agent per class on a formulary is probably too restrictive to accommodate intolerances and responsiveness to medications (Answer B). Effectiveness refers to the use of a drug in a real-world (post-marketing) setting. Many new drugs will only have clinical trial data that prove efficacy. New drugs added to formulary require periodic assessments to ensure effectiveness and ongoing safety (Answer D).

**3. Answer: A**
An MUE is drug- or disease-specific and is best suited for reviewing warfarin dosing and ordering of INRs (Answer A is correct). Quality improvement activities are best suited for monitoring the medication use process that may not be specific to a drug or disease, such as the review of the accuracy of medication history documentation, review of errors caused by pharmacist-bypassed CPOE alerts, and review of compliance with a clinical protocol (Answers B–D are incorrect).

**4. Answer: B**
A root cause analysis is completed following a sentinel event to determine why the error occurred. The epinephrine overdose in this case may have contributed to the death of the patient which would be considered a sentinel event (Answer B is correct). A healthcare failure mode and effects analysis is a systematic method of identifying and preventing product and process problems before they occur (Answer A is incorrect). A gap analysis is used to compare best practices with processes currently in place to determine gaps (Answer C is incorrect). A medication use evaluation is a process improvement effort used to measure and describe the medication use process. An MUE is applied more broadly than a single error (Answer D is incorrect).

**5. Answer: A**
Direct costs are the resources consumed in the prevention, detection, or treatment of a disease or illness. These can be medical (e.g., physician office visits) or nonmedical (e.g., transportation to the office visit) (Answer A is correct). Loss of income because of knee replacement recovery is an indirect cost because it is related to the morbidity of the surgery (Answer B). Pain and suffering as the result of a motor vehicle crash is an intangible cost because it is a nonfinancial outcome of the crash (Answer C). The electric bill for the medical office is a direct cost from the medical office's perspective (Answer D).

**6. Answer: A**
Because this patient developed an intracranial hemorrhage despite being stable on a warfarin regimen for the past 8 months and an INR within the acceptable range, this ADE was not a preventable error and was not caused by a medication error, making Answer A correct and Answers B–D incorrect.

**7. Answer: C**
A severe ADE is defined as an ADE that results in harm to the patient, prolonged hospitalization, transfer to a higher level of care, permanent organ damage, or death, with the probable ADE causality nomogram score. Because this patient developed a life-threatening intracranial hemorrhage and intubation resulting in patient harm, hospitalization, and transfer to a higher level of care, this case meets the criteria for a "severe" ADE, making Answer C correct and Answers A, B, and D incorrect.

## ANSWERS AND EXPLANATIONS TO SELF-ASSESSMENT QUESTIONS

**1. Answer: B**
When developing a new policy, the scope and purpose should be identified and described. Stakeholders relevant to the policy should then be identified and included in the development and drafting process. Development of the policy should begin with a review of the evidence or best practice, followed by drafting and reviewing the policy (Answer B is correct). Answers A, C, and D all include appropriate steps in the incorrect order.

**2. Answer: A**
Drugs may be added to the formulary with restrictions on prescribing for specific patient populations in which they have been proven safe and efficacious. Alirocumab has been studied in patients who are currently receiving maximally tolerated statins (Answer A is correct). New drugs are FDA approved according to the results of phase III clinical trials that have proven safety and efficacy. New drugs may be added to the formulary with a follow-up assessment within 3–6 months to determine effectiveness, which describes the use of the drug in a real-world setting (Answer B). Formulary drugs may be restricted to use by certain physician specialties or specialty units within the institution, but not to a single physician (Answer C). The cost of a drug may be considered during a formulary evaluation but should not be the sole factor in making a drug nonformulary (Answer D).

**3. Answer: B**
When responding to a drug shortage, an operational assessment should be conducted which includes validating details of the shortage and estimating a duration, estimating supply on hand and available from alternative sources, evaluating past usage, and estimating time to impact on health-system (Answer B is correct). Hoarding remaining supply of a drug expected to become short worsens the shortage for other facilities (Answer A is incorrect). A therapeutic assessment will help determine which patient populations are affected and potential therapeutic alternatives. Patients may then be prioritized to receive any remaining supply but not all patients need to be automatically switched to alternative therapy, especially when some supply remains (Answer C is incorrect). A drug shortage response team should be comprised of individuals who are able to access information and make decisions. This team should include all relevant stakeholders including those outside the pharmacy department (Answer D is incorrect).

**4. Answer: C**
Evaluating the use of pharmacotherapy for VTE prophylaxis is best suited for an MUE (Answer C is correct). The goal of an MUE is to ensure optimal MTM and improve patient safety and outcomes for drug-related processes—in this case, pharmacotherapy in VTE. Although reviewing ADE data and medication error data is helpful in detecting and determining problems associated with the use of pharmacotherapy in VTE prophylaxis, these are isolated events and are reporter-dependent, and a lack of reports does not ensure that the use of pharmacotherapy in VTE prophylaxis is appropriate (Answers A and B are incorrect). Although one component of an MUE is PI, a review of the quality should occur before determining whether a PI project is necessary (Answer D is incorrect). An interventional MUE incorporates a review of quality in the form of making a pharmacotherapeutic intervention—PI. Only an MUE is a robust and comprehensive method of evaluating the use of pharmacotherapy in VTE prophylaxis.

**5. Answer: D**
Providing education regarding anticoagulant therapy to patients and families is required by TJC NPSG 03.05.01 (Answer D is correct). Only 6 of the 8 elements required for hospital accreditation are also required for ambulatory health care. Using programmable pumps for heparin administration, approved protocols for perioperative care, and unit-dose products, prefilled syringes, or premixed infusion bags is not required for ambulatory care. (Answers A, B, and C).

**6. Answer: A**
A cost-benefit analysis is the best economic tool to evaluate the value of a cardiology pharmacist's service. For example, the financial value can be determined in dollars by comparing the cost of implementing a cardiology pharmacist's service (pharmacist salary and benefits) with the benefits gained through the cardiology pharmacist's activities such as reduced length of stay and decreased drug cost (Answer A is correct). A cost-effectiveness analysis estimates costs and outcomes of

treatment (intervention), but the two are measured in different units (Answer B). A cost-minimization analysis compares the cost of two or more treatment alternatives that are equal in efficacy (Answer C). A cost-of-illness analysis is not a cost analysis (Answer D).

**7. Answer: D**

A preventable ADE, by definition, is a medication error that occurs and reaches the patient to cause harm because of a breach of standard professional behavior or practice. The drug interaction between rivaroxaban and rifampin is a known interaction that is described in the prescribing information. This is a medication error, and the stroke is the harm (Answer D is correct). Although this case of rifampin-rivaroxaban drug interaction–induced stroke is an ADE, a preventable ADE best describes this case (Answer C is incorrect). In general, ADRs and side effects are synonymous terms, and a stroke resulting from a rifampin-rivaroxaban drug interaction is an ADR; however, a preventable ADE best describes this case (Answers A and B are incorrect).

**8. Answer: B**

Concurrent surveillance is identifying ADEs close to the time they occur and are spontaneously reported by practitioners during their normal work (Answer B is correct). Prospective surveillance occurs before initiation of medication therapy (Answer A). Direct observation is a type of prospective surveillance that includes observing medication administration by nurses or physicians (Answer C). Retrospective surveillance includes identifying ADEs after they have occurred through a review of medical records (Answer D).

**Appendix 1. Drug Interaction Probability Scale**

The Drug Interaction Probability Scale (DIPS) is designed to assess the probability of a causal relationship between a potential drug interaction and an event. It is patterned after the Naranjo ADR Probability Scale (Naranjo CA, Busto U, Sellers EM, et al. A method for estimating the probability of adverse drug reactions. Clin Pharmacol Ther 1981;30:239-45).

**Directions**
Circle the appropriate answer for each question, and add up the total score.
Object drug = Drug affected by the interaction.
Precipitant drug = Drug that causes the interaction.
Use the Unknown (Unk) or Not Applicable (NA) category if (a) you do not have the information or (b) the question is not applicable (e.g., no dechallenge; dose not changed).

| Questions | Yes | No | NA/ Unk |
|---|---|---|---|
| 1. Are there previous credible reports of this interaction in humans? | +1 | –1 | 0 |
| 2. Is the observed interaction consistent with the known interactive properties of the precipitant drug? | +1 | –1 | 0 |
| 3. Is the observed interaction consistent with the known interactive properties of object drug? | +1 | –1 | 0 |
| 4. Is the event consistent with the known or reasonable time course of the interaction (onset or offset)? | +1 | –1 | 0 |
| 5. Did the interaction remit on dechallenge of the precipitant drug with no change in the object drug? (if no dechallenge, use Unknown or NA and skip Question 6) | +1 | –2 | 0 |
| 6. Did the interaction reappear when the precipitant drug was readministered in the presence of continued use of object drug? | +2 | –1 | 0 |
| 7. Are there reasonable alternative causes for the event?[a] | –1 | +1 | 0 |
| 8. Was the object drug detected in the blood or other fluids in concentrations consistent with the proposed interaction? | +1 | 0 | 0 |
| 9. Was the drug interaction confirmed by any objective evidence consistent with the effects on the object drug (other than drug concentrations from question 8)? | +1 | 0 | 0 |
| 10. Was the interaction greater when the precipitant drug dose was increased or less when the precipitant drug dose was decreased? | +1 | –1 | 0 |

[a]Consider clinical conditions, other interacting drugs, lack of adherence, risk factors (e.g., age, inappropriate doses of object drug). A NO answer presumes that enough information was presented so that one would expect any alternative causes to be mentioned. When in doubt, use Unknown or NA designation.

Total Score _____ Highly Probable: > 8
Probable: 5–8
Possible: 2–4
Doubtful: < 2

# Pharmacogenomics of Cardiovascular Disease

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# Pharmacogenomics of Cardiovascular Disease

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**Learning Objectives**

1. Apply Clinical Pharmacogenetics Implementation Consortium (CPIC) guidance in the clinical setting.
2. Associate clinically actionable genetic polymorphisms with response to cardiovascular pharmacotherapies.
3. For a given patient, estimate therapeutic response to antiplatelet therapy using *CYP2C19* genotype information.
4. For a given patient, analyze the impact of the *SLCO1B1* genotype on the risk of myopathy with statins.
5. For a given patient, estimate the dose of warfarin using *VKORC1* and *CYP2C9* genotype information.

**Abbreviations in This Chapter**

| | |
|---|---|
| CK | Creatine kinase |
| CPIC | Clinical Pharmacogenetics Implementation Consortium |
| OAT | Organic anion transporting |
| PCI | Percutaneous coronary intervention |
| SLCO1B1 | Solute carrier organic anion transporter family, member 1B1 |
| SNP | Single nucleotide polymorphism |
| VKORC1 | Vitamin K epoxide reductase complex 1 |

**Self-Assessment Questions**

*Answers and explanations to these questions can be found at the end of the chapter.*

1. A 50-year-old woman had a deep venous thrombosis, and warfarin was prescribed with use of unfractionated heparin before stable INR. Which genetic polymorphism would most likely affect this patient's warfarin dose requirement?
   A. *CYP2C9* polymorphism.
   B. *SLCO1B1* polymorphism.
   C. *CYP2C19* polymorphism.
   D. No known pharmacogenetic interactions.

2. Which best describes the response to simvastatin in a patient with the **5* variant allele in the *SLCO1B1* gene?
   A. Decreased risk of myopathy.
   B. Standard risk of myopathy.
   C. Increased risk of myopathy.
   D. Increased risk of myopathy and decreased effectiveness in LDL lowering.

3. Which best represents the maximum recommended daily simvastatin dose in a person whose genotype is **5/*5* for the *SLCO1B1* gene?
   A. Contraindicated.
   B. 20 mg.
   C. 40 mg.
   D. 80 mg.

4. A patient with a reported pharmacogenetic test result of *CYP2C19* of **2/*3* is receiving clopidogrel. Which best depicts the patient's risk of an adverse cardiovascular event (e.g., thrombosis) because of treatment failure?
   A. Increased.
   B. Moderate.
   C. Decreased.
   D. No change because of genetic result.

5. Which statement is most accurate about a *CYP2C19 *17/*17* genotype and the current CPIC guidelines?
   A. Patients convert clopidogrel to an inactive metabolite to a greater extent than **1/*1*; therefore, a decrease in clopidogrel dose is recommended.
   B. Patients convert clopidogrel to an active metabolite to a greater extent than **1/*1*, but no change in clopidogrel dose is recommended.
   C. Patients convert clopidogrel to an active metabolite to a lesser extent than **1/*1*; therefore, a decrease in clopidogrel dose is recommended.
   D. Patients convert clopidogrel to an active metabolite to a lesser extent than **1/*1*; therefore, an alternative antiplatelet drug is recommended.

6. With respect to genetic testing, which is most accurate?
   A. CPIC guidelines recommend when a genetic test should be obtained.
   B. CPIC guidelines recommend dosing of all drugs that include pharmacogenetic information in the FDA-approved label.
   C. CPIC guidelines do not consider whether a commercial genetic test is available for a particular genotype.
   D. CPIC guidelines are not designed to provide information on whether a genetic test should be obtained.

## I. INTRODUCTION

A. Definitions
1. Precision medicine
   a. An emerging approach for disease treatment and prevention that considers individual variability in genes, environment, and lifestyle for each person
   b. Allows for the prediction of which treatment or prevention strategy for a specific disease might work best in a particular individual
   c. In contrast to one-size-fits-all approach
   d. Precision Medicine Initiative
      i. In 2015, President Barack Obama announced the Precision Medicine Initiative.
      ii. Focused in cancer care early on; ultimately has the goal of bringing precision medicine to all areas of health and health care on a large scale
      iii. The National Institutes of Health has launched a 1-million-person cohort, recently renamed "All of Us," whereby individuals will provide genetic data, biological samples, and other health information, which will then be used by researchers to develop improved diagnosis and treatment strategies.
2. Personalized medicine
   a. The term *personalized medicine* is sometimes used synonymously with *precision medicine* to identify a form of medicine that uses information about a person's genes, proteins, and environment to prevent, diagnose, and treat disease.
   b. The word "personalized" should not be misinterpreted to imply that treatments and preventions are being developed uniquely for an individual.
3. Pharmacogenomics and pharmacogenetics
   a. *Pharmacogenetics* studies how variation in one single gene influences response to a single drug. Pharmacogenetics has largely been used in relation to the study of inherited genetic differences in drug metabolic pathways.
   b. *Pharmacogenomics* is a broader term that studies how all the genes in the genome can influence drug response.
   c. A combination of pharmacology and genomics can be used to develop effective, safe medications and dosage regimens that are tailored to variations in an individual's genetic makeup.
   d. Although often used interchangeably with pharmacogenomics, pharmacogenetics generally focuses on a single drug-gene interaction.
4. Epigenetics and epigenomics
   a. Epigenetics examines the processes regulating the activity (expression) of certain genes, whereas epigenomics considers the epigenetic changes across many genes in a cell or entire organism.
   b. Epigenetic changes can help determine whether genes are turned on or off and can influence the production of proteins in certain cells, ensuring that only necessary proteins are produced (https://epi.grants.cancer.gov/epigen.html).
5. Single nucleotide polymorphisms (SNPs)
   a. A SNP is a variation in a single nucleotide (adenine [A], thymine [T], cytosine [C], or guanine [G]) that occurs at a specific position in the genome.
   b. An example of a sequence change is the following: AAGCCTA changes to AAGCTTA.
   c. SNPs may fall within coding sequences of a gene.
      i. Synonymous SNPs – Do not affect the protein sequence
      ii. Nonsynonymous SNPs – Do affect the protein sequence
         (a) Missense: A point mutation in which a single nucleotide change results in a codon that codes for a different amino acid

(b) Nonsense: A mutation in which a sense codon that corresponds to one of the 20 amino acids specified by the genetic code is changed to a chain-terminating codon

d. SNPs not in protein-coding regions – Can affect gene splicing, messenger RNA degradation, and RNA coding and transcription factor binding

e. SNPs can also occur in intergenic regions, which is the sequence of DNA located between genes. Intergenic DNA regions are a subset of noncoding DNA.

6. Candidate gene association study
   a. Focuses on *associations* between genetic variation within prespecified genes of interest and phenotypes or disease states
   b. Candidate gene association studies can include SNPs of interest, or they may also include insertion-deletion polymorphisms or copy number variation polymorphisms.
   c. Findings should be replicated in several populations for confirmation of effect.
7. Genome-wide association study
   a. A search across the genome for SNPs (genetic variation) that occur more commonly in a population with a specific disease or drug response (often called cases) than in people without the disease or who have a typical drug response (often called controls)
   b. Allows for investigation of millions of polymorphisms
   c. Findings should be replicated in several populations for confirmation of effect.
8. Allele
   a. An allele is a variant form of a given gene, located on a specific position (or genetic locus) on a specific chromosome.
   b. Humans have 23 pairs of chromosomes. At each genetic locus, there are two alleles, with each inherited from each parent.
   c. Different alleles can result in different phenotypes.
      i. If both alleles at a gene are the same, they are called homozygous with respect to that gene location.
      ii. If alleles are different, they are called heterozygous with respect to that gene location.
9. Genotype: Each pair of alleles makes up the genotype of a specific gene.
10. Phenotype
    a. The phenotype is a composite of an individual's observable characteristics or traits.
    b. Results from the expression of an individual's genetic code, as well as the environment

B. Pharmacogenetic Testing – Can be done preemptively or reactively in response to a drug order
   1. Preemptive genotyping
      a. Usually accomplished using a multigene, chip-based approach such that several genes and genetic polymorphisms are tested at the same time, and the results are then available for whenever they are needed in the future
      b. Advantages include reduced cost and availability of results at the time of future drug prescribing.
      c. Disadvantages include lack of reimbursement for preemptive testing and the testing of genes that may never be needed to guide therapy; however, there is no additional cost and thus ultimately little disadvantage.
      d. Many institutions, primarily in the academic setting, have implemented a preemptive pharmacogenomics program, including St. Jude, Vanderbilt, Indiana University, and the University of Florida, for example.
   2. Reactive genotyping testing
      a. Usually tests a single gene or a few genes and is ordered at the time of need
      b. Advantages include that the test may be reimbursed by third-party payers, testing only the genotype needed at the time.

   c. Disadvantages include increased cost and turnaround time because results may not be available at the time they are needed to make a treatment or dosing decision.
3. Interpretation of results
   a. Understanding how to interpret the results of genetic tests is critical for successful clinical implementation of pharmacogenetics.
   b. In institutions that have implemented pharmacogenetic testing, where the results are run locally and returned by the electronic health record, clinical decision support is usually built into the electronic health record system, triggered by a specific drug-gene pair; this helps guide clinicians in interpreting the genetic test result and recommends drug/dose according to the results.
   c. When genetic tests are sent to external laboratories for analysis, test results are less predictable regarding how the results are reported and usually are not linked to the institution's clinical decision support to help guide clinicians in prescribing a drug/dose according to the test result.

C. Drug Labeling and Pharmacogenetics
1. The U.S. Food and Drug Administration (FDA) has placed increased focus on the impact of pharmacogenetics on drug response, adverse effects, and pharmacokinetics over the past decade.
2. 190 unique FDA-approved drugs currently include pharmacogenomic biomarker information in the drug labeling (https://www.fda.gov/drugs/scienceresearch/researchareas/pharmacogenetics/ucm083378.htm).
   a. Pharmacogenetic biomarkers included in FDA labeling include:
      i. Germline or somatic gene variants (polymorphisms, mutations)
      ii. Functional deficiencies with a genetic etiology
      iii. Gene expression differences
      iv. Chromosomal abnormalities
      v. Selected protein biomarkers that are used to select treatments
   b. The FDA has published a table containing a listing of drugs, the genes within each drug, and a labeling section that includes pharmacogenetic biomarker information (https://www.fda.gov/drugs/science-and-research-drugs/table-pharmacogenomic-biomarkers-drug-labeling). Although the FDA-approved label of more than 190 drugs includes information regarding pharmacogenetic biomarkers, in most of these cases, evidence is insufficient to implement specific pharmacogenetic testing.

D. Clinical Pharmacogenetics Implementation Consortium (CPIC) (https://cpicpgx.org/): CPIC was established to overcome barriers to clinical implementation of pharmacogenetics because of lack of available peer-reviewed, updated, and detailed gene/drug clinical practice guidelines.
1. CPIC guidelines are centered either on genes or on drug-gene combinations with focus on germline variation only.
2. Priority for establishing guidelines is based on the availability of commercially available tests offered in Clinical Laboratory Improvement Amendments–approved clinical settings.
3. CPIC guidelines:
   a. Designed to help clinicians understand how available genetic test results should be used and applied at the individual patient level
   b. Not designed to provide information on whether a genetic test should be ordered or the timing of a specific genetic test
   c. 23 different CPIC guidelines currently exist, each based on an individual drug (https://cpicpgx.org/guidelines/).
4. Most consider the availability of a CPIC guideline, which is developed on the basis of current available evidence supporting a particular drug-gene(s) combination, as the threshold for clinical implementation readiness.

## II. THREE CPIC GUIDELINES FOR PHARMACOTHERAPIES ARE PRESCRIBED IN CARDIOVASCULAR PATIENTS: CLOPIDOGREL, SIMVASTATIN, AND WARFARIN

A. Clopidogrel and cytochrome P450 2C19 (*CYP2C19*)

1. Clopidogrel is a thienopyridine prodrug that requires enzymatic bioactivation, primarily by the hepatic CYP2C19 enzyme, among others (Figure 1).

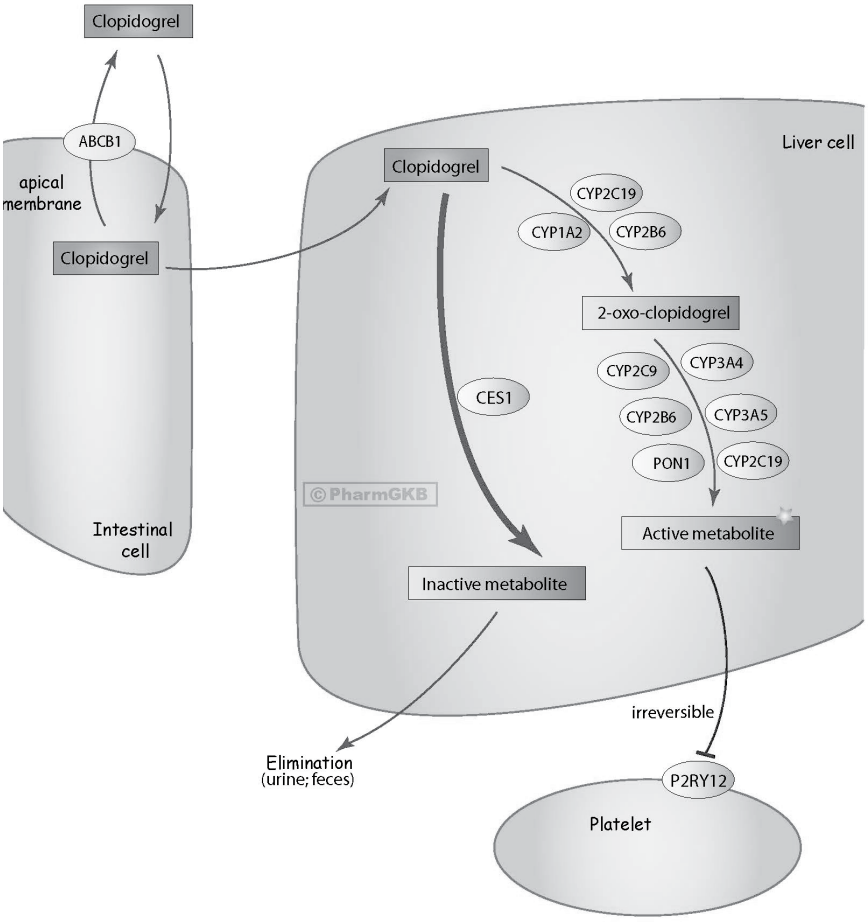


**Figure 1.** Metabolism of clopidogrel.

Reprinted from: Sangkuhl K, Klein TE, Altman RB. Clopidogrel pathway. Pharmacogenet Genomics 2010;20:463-5; with permission by PharmGKB and Stanford University.

2. After bioactivation, the active metabolite binds irreversibly to inhibit the $P2Y_{12}$ adenosine diphosphate receptor on platelets, which prevents aggregation.
3. Clopidogrel prevents thromboembolism-related cardiovascular events.
   a. In patients with acute coronary syndromes
   b. In patients after stent placement during percutaneous coronary interventions (PCIs)
   c. Wide patient variability in response – Around 25% are nonresponsive, meaning residual platelet aggregation exists post-clopidogrel dosing.
   d. Although clopidogrel is also used in secondary stroke prevention and peripheral artery disease, most pharmacogenetic-related studies involving clopidogrel have been done in the context of patients with acute coronary syndromes treated with PCI.

4. Variability in clopidogrel response is largely because of the highly polymorphic nature of *CYP2C19* and is summarized in Table 1.

**Table 1.** *CYP2C19* Phenotype, Genotype, and Effect on Clopidogrel Response, and CPIC Recommendations for Antiplatelet Therapy

| ***CYP2C19* Phenotype** | **Overall Prevalence (approximate)[a]** | **Genotype** | **Example** | **Clinical Effect** | **CPIC Clopidogrel Dose Recommendation (strength of evidence)** |
|---|---|---|---|---|---|
| Ultrarapid metabolizer | 2%–5% | Two increased-function alleles | **17/*17* | Greatest antiplatelet effect, lowest on-treatment platelet reactivity | Label-recommended dosage and administration (strong) |
| Rapid metabolizer | 2%–30% | One normal-function allele and one increased-function allele | **1/*17* | Some increase in antiplatelet effect | Label-recommended dosage and administration (strong) |
| Normal metabolizer (wild type) | 30%–50% | Two normal-function alleles | **1/*1* | Expected antiplatelet effect | Label-recommended dosage and administration (strong) |
| Intermediate metabolizer | 18%–45% | One normal-function allele and one no-function allele or one no-function allele and one increased-function allele | **1/*2, *1/*3, *2/*17* | Some reduction in antiplatelet effect | Alternative antiplatelet therapy if no contraindication (prasugrel or ticagrelor) (moderate) |
| Poor metabolizer | 1%–15% | Two no-function alleles | **2/*2, *2/*3, *3/*3* | Lowest antiplatelet effect (highest on-treatment platelet reactivity), reduced active metabolite | Alternative antiplatelet therapy if no contraindication (prasugrel or ticagrelor) (strong) |

[a]Prevalence varies widely by race. Central, South, and East Asians have the highest prevalence of the **2* allele.

   a. FDA-cleared *CYP2C19* laboratory tests are currently available.
   b. For *CYP2C19* genotyping results to be applied clinically in the United States, the test must be performed in laboratories operating under College of American Pathologists/Clinical Laboratory Improvement Amendments regulations.
   c. More than 30 genetic variants of *CYP2C19* are known, though far fewer have been associated with functional consequences.
   d. *CYP2C19* nomenclature for clinically relevant polymorphisms:
      i. Normal-function allele: *CYP2C19*1*, associated with normal metabolism
      ii. No-function alleles: *CYP2C19*2* rs4244285 (most common) and *CYP2C19*3* rs4986893
      iii. Increased-function allele: *CYP2C19*17* rs12248560
      iv. Individuals can carry one or two variant (either no-function or increased-function) alleles.
      v. The number and type of *CYP2C19* mutant alleles in an individual determine the individual's CYP2C19 metabolizer status (phenotype).
5. The CPIC guideline for clopidogrel (https://cpicpgx.org/guidelines/guideline-for-clopidogrel-and-cyp2c19/) is indication specific, with recommendations for $P2Y_{12}$ inhibitor therapy according to the *CYP2C19* genotype in patients with acute coronary syndromes who have undergone a PCI (Table 1).
   a. Label-recommended doses should be effective in patients with ultrarapid, rapid, or normal metabolizer status.
   b. Patients with intermediate or poor metabolizer status should be treated with alternative antiplatelet therapy, barring any contraindications (prasugrel or ticagrelor).

c. The FDA-approved clopidogrel label warns of reduced clopidogrel effectiveness in patients with poor metabolizer status and recommends consideration of alternative antiplatelet therapy in these patients; however, it is silent regarding risk and recommendations in patients with intermediate metabolizer status.
d. Some studies suggest that **17* allele carriers have enhanced platelet inhibition and clopidogrel response, and perhaps an increased risk of bleeding complications; however, results are discordant, and further studies are required to confirm this finding.

6. Adverse cardiovascular outcomes and *CYP2C19* genotype-guided clopidogrel dosing
   a. Currently, clinical guidelines (American College of Cardiology, American Heart Association) do not include definitive recommendations for genotype-guided clopidogrel use, primarily because of the lack of data from large randomized controlled trials showing improved clinical outcomes with genotype-guided antiplatelet drug selection.
   b. Post hoc analyses from randomized clinical trials and registries show a higher risk of adverse cardiovascular events among patients undergoing a PCI treated with clopidogrel who have a *CYP2C19* no-function allele than among similarly treated patients without a no-function allele.
   c. Outcomes data outside the PCI population are inconsistent.
   d. New data analyses from a real-world evaluation of a pharmacogenetic-guided approach to clopidogrel prescribing indicate that the risk of major adverse cardiovascular outcomes was significantly higher in patients with a *CYP2C19* no-function allele who were prescribed clopidogrel compared with those prescribed an alternative antiplatelet agent.
   e. POPular Genetics is a randomized clinical trial in which patients undergoing PCI with stent implantation were randomly assigned to receive a *CYP2C19* genotype-guided $P2Y_{12}$ inhibitor or standard treatment with either ticagrelor or prasugrel for 12 months. In the genotype-guided group, carriers of *CYP2C19*2* or *3 loss-of-function alleles received ticagrelor or prasugrel and noncarriers received clopidogrel. Among the enrolled patients, the group receiving the *CYP2C19* genotype-guided strategy for selecting oral $P2Y_{12}$ inhibitor therapy was noninferior to the group receiving standard treatment for the overall primary outcome of adverse CV events; however, for the primary bleeding outcome, the genotype-guided strategy was associated with a significantly lower incidence of bleeding.

7. Proton pump inhibitors (PPIs) and clopidogrel
   a. PPIs are often prescribed concurrently with clopidogrel because of the increased risk of bleeding.
   b. Some PPIs inhibit *CYP2C19* activity.
      i. Omeprazole and esomeprazole are the strongest inhibitors of *CYP2C19*.
      ii. Pantoprazole is the weakest inhibitor of *CYP2C19*.
   c. Evidence suggests that PPIs interfere with the activation of clopidogrel and diminish its antiplatelet effect.
   d. The FDA-approved label recommends avoiding concurrent use of omeprazole and esomeprazole with clopidogrel.

**Patient Cases**

1. M.J. is a 66-year-old man who presented for a left heart catheterization secondary to unstable angina. He presents after a percutaneous coronary intervention of his left anterior descending artery with placement of a drug-eluting stent in the setting of an ST-segment elevation myocardial infarction (STEMI). Of note, the patient has a documented history of transient ischemic attack. Before admission, the patient's antiplatelet therapy consisted of aspirin and clopidogrel. The patient has no known drug allergies. His medical history includes a STEMI, hypertension, high cholesterol, and coronary artery disease. His medications include aspirin 81 mg daily, atorvastatin 80 mg daily, clopidogrel 75 mg daily, isosorbide mononitrate 30 mg daily, lisinopril 5 mg daily, metformin 1000 mg twice daily, metoprolol succinate 100 mg daily, and nitroglycerine 0.4 mg sublingually as needed for chest pain. The patient underwent genotyping for *CYP2C19*, which revealed the **1/*2* genotype. Given this information, which is the best recommendation regarding his antiplatelet therapy?
   A. Continue clopidogrel plus aspirin.
   B. Change to prasugrel plus aspirin.
   C. Change to ticagrelor plus aspirin.
   D. Give aspirin alone.

2. M.B. is a 57-year-old man who presents to the emergency department with acute chest pain. He was transported to the catheterization laboratory and now presents after percutaneous coronary intervention, during which he received two drug-eluting stents. His medical history includes a history of coronary artery disease. His current medications include aspirin 81 mg daily, atorvastatin 80 mg daily, carvedilol 6.25 mg twice daily, docusate calcium 4 tablets at bedtime, furosemide 20 g twice daily as needed for swelling/edema, isosorbide mononitrate 30 mg daily, and lisinopril 40 mg daily. The patient has no known drug allergies. The patient underwent genotyping for *CYP2C19*, which revealed the **1/*17* genotype. Which is the best recommendation for antiplatelet therapy (in addition to aspirin) in this patient?
   A. Reduced-dose clopidogrel.
   B. Prasugrel.
   C. Ticagrelor.
   D. Standard-dose clopidogrel.

B. Simvastatin myopathy and solute carrier organic anion transporter family, member 1B1 (*SLCO1B1*)
   1. Statins, including simvastatin, are highly effective for reducing cardiovascular risk in both primary and secondary heart disease.
   2. Myopathy is an adverse effect of statins, especially simvastatin.
      a. Defined as muscle pain or weakness with elevated creatine kinase (CK) concentrations. Symptoms can range from mild myalgia with no CK elevation to life-threatening rhabdomyolysis with substantially elevated CK concentrations and muscle injury.
      b. Although statin-induced myopathy is relatively rare in randomized clinical trials (3%–5%), it is more common in clinical practice (10%–15%).
      c. Exact mechanism is unknown, but risk factors include
         i. Higher statin doses
         ii. Use with drugs that increase statin bioavailability. Cyclosporine, for example, is a strong inhibitor of the organic anion transporting (OAT) polypeptide 1B1 transporter and CYP3A4 enzyme and increases the area under the curve for simvastatin acid by 3- to 8-fold.
         iii. Genetic polymorphisms that affect statin pharmacokinetics

3. *SLCO1B1* encodes for the OAT polypeptide 1B1 transporter. Genetic polymorphisms of *SLCO1B1* rs4149056 contained within *SLCO1B1*5*, **15*, and **17* have been associated with statin myopathies.
   a. No *SLCO1B1* test is currently FDA approved; however, College of American Pathologists/Clinical Laboratory Improvement Amendments–certified laboratories can run the *SLCO1B1* assay and return results.
   b. Relationship between rs4149056 and simvastatin-related muscle toxicity is clearly established.
   c. Relationship between rs4149056 and other statins is less clear.
4. The CPIC guideline regarding simvastatin and *SLCO1B1* is available at https://cpicpgx.org/guidelines/guideline-for-simvastatin-and-slco1b1/ and includes dosing guidelines according to genotype.
5. *SLCO1B1* (Figure 2) encodes for OAT polypeptide C (not pictured in Figure 2) and plays a role in statin pharmacokinetics.

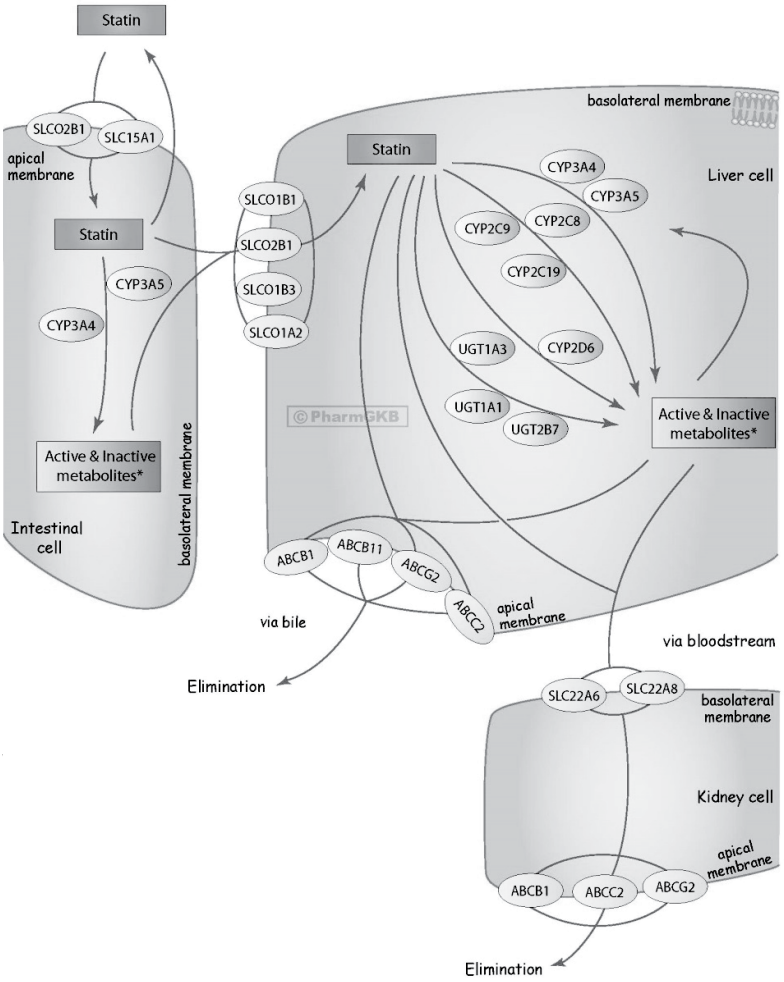


**Figure 2.** Pharmacokinetics of statins.

Reprinted from: Whirl-Carrillo M, McDonagh EM, Hebert JM, et al. Pharmacogenomics knowledge for personalized medicine. Clin Pharmacol Ther 2012;92:414-7; with permission of PharmGKB and Stanford University.

a. OAT polypeptide 1B1 transports all statins into hepatocytes.
   i. Fluvastatin is more lipophilic and is the statin least affected by the *SLCO1B1* polymorphism.
   ii. Although the *SLCO1B1* polymorphism affects several statins, the strength of evidence is highest for simvastatin; thus, the CPIC guidelines on *SLCO1B1* were written for simvastatin-induced myopathy.
b. *SLCO1B1*5*, **15*, and **17* reduce OAT polypeptide 1B1 transport activity and are summarized in Table 2.
   i. Carriers of these decreased-function *SLCO1B1* alleles have increased plasma statin concentrations.
   ii. Increased statin concentrations have been associated with increased risk of statin myopathy.
   iii. Around 16% of whites, 1%–2% of African Americans, and 10%–16% of Asians carry these decreased-function *SLCO1B1* alleles.
c. Relative risk of myopathy with simvastatin 40 mg/day is about 2.5/variant (decreased-function) allele. For patients with one or two decreased-function alleles, the CPIC guideline recommends starting at a lower dose of simvastatin (20 mg/day) or starting an alternative statin (Table 2).

**Table 2.** *SLCO1B1* Phenotype, Genotype, and CPIC Recommendations for Simvastatin Dosing

| SLCO1B1 Phenotype | Overall Prevalence (approximate) | Genotype | Example | Clinical Effect | CPIC Simvastatin Dose Recommendation |
|---|---|---|---|---|---|
| Normal function (wild type) | 55%–88% | Two normal-function alleles | **1a/*1a, *1a/*1b, *1b/*1b* | Expected simvastatin effect and normal myopathy risk | Label- and specific disease recommended simvastatin dosage and administration (strong) |
| Decreased (intermediate) function | 11%–36% | One normal-function allele and one decreased-function allele | **1a/*5, *1a/*15, *1a/*17, *1b/*5, *1b/*15, *1b/*17* | Increased risk of myopathy | Prescribe a lower simvastatin dose (20 mg) or an alternative statin (e.g., pravastatin or rosuvastatin); consider routine CK monitoring (strong) |
| Poor (low) function | 0%–6% | Two decreased-function alleles | **5/*5, *5/*15, *5/*17, *15/*15, *15/*17, *17/*17* | High myopathy risk | Prescribe a lower simvastatin dose (20 mg) or an alternative statin (e.g., pravastatin or rosuvastatin); consider routine CK monitoring (strong) |

**Patient Case**

3. A 62-year-old white man has a medical history of coronary artery disease, diabetes, peripheral neuropathy, and hyperlipidemia. While presenting to the pharmacy to refill his medications, he states that he has achy muscle pain. Medications include simvastatin 40 mg at bedtime, aspirin 81 mg daily, nortriptyline 50 mg at bedtime, metformin 1000 mg twice daily, and glipizide 10 mg daily. The patient underwent genotyping for *SLCO1B1*, which revealed a **5*5* genotype. Which is the best recommendation regarding his lipid therapy?

   A. Continue simvastatin 40 mg daily.

   B. Decrease to simvastatin 20 mg.

   C. Use an alternative statin option.

   D. Use a PCSK9 inhibitor instead of a statin.

C. Warfarin and *CYP2C9,* vitamin K epoxide reductase C1 (*VKORC1*), rs12777823 and *CYP4F2*
   1. Although newer direct oral anticoagulants are available and effective that usually require less monitoring, because of issues of cost and tolerance and limited FDA-approved indications, warfarin remains a commonly prescribed medication.
   2. Warfarin has a narrow therapeutic index with large interpatient variability in the dose required to achieve target anticoagulation.
   3. Complications of warfarin therapy are among the most commonly reported adverse events to the FDA and a common cause for emergency department visits.
   4. Substantial evidence from candidate gene and genome-wide association studies consistently shows that genetic variability affects warfarin dose response.
   5. Although clinical trials evaluating the usefulness of genotype-guided warfarin dosing have resulted in inconsistent evidence, reducing enthusiasm for routinely genotyping individuals undergoing warfarin therapy, the warfarin FDA label includes pharmacogenetic guidance.
      a. The European Pharmacogenetics of Anticoagulant Therapy (EU-PACT) study showed that, in a European population, use of a pharmacogenetic dosing algorithm reduced the time to stable warfarin dose, improved the percent time spent in therapeutic range, and decreased the number of episodes in which the international normalized ratio (INR) was greater than 4, compared with standard dosing.
      b. The Clarification of Optimal Anticoagulation Through Genetics (COAG) study, which was conducted in an ethnically diverse population, showed that use of a pharmacogenetic dosing algorithm caused no difference in time to stable dose, percent time in therapeutic range, reduction in number of episodes of INR greater than 4 or less than 2, or bleeding risk compared with a clinical dosing algorithm. Among African Americans, the percent time in therapeutic range was lower in the pharmacogenetic dosing group than in the clinical dosing group, with a higher incidence of supratherapeutic INRs in the pharmacogenetic group.
      c. Several issues may have contributed to the negative findings from COAG and serve as the basis for the current CPIC guidelines, with differing recommendations by ancestry.
         i. One-third of patients enrolled in COAG were African Americans, yet the CYP2C9 variants (*CYP2C9*5*, **6*, **8*, **11* rs12777823) most common in African Americans were not genotyped.
         ii. Failure to account for CYP2C cluster variants leads to over-estimation of warfarin dose requirements in African Americans.
         iii. Consistent with this, pharmacogenetic versus clinical dosing in African Americans in the COAG trial led to a significantly increased risk of over-anticoagulation.
      d. The Genetics-Informatics Trial (GIFT) was a randomized controlled trial examining the effectiveness and safety of genotype-guided dosing versus clinical algorithm for warfarin dosing in orthopedic patients.
         i. GIFT composite outcome included symptomatic and asymptomatic venous thromboembolism, major hemorrhage, INR of 4 or greater, and death and was the first warfarin pharmacogenetics study powered for clinical outcomes.
         ii. GIFT included genotyping for *CYP2C9*2* and **3*, *CYP4F2*3*, and VKORC1-1639 but did not include the African-specific *CYP2C9* alleles or rs12777823.
         iii. Results of GIFT, presented in early 2017, showed a 27% relative reduction in the composite outcome with genotype-guided versus clinical algorithm dosing, documenting the clinical benefits of a genotype-guided approach to warfarin dosing.
      e. Genes most associated with warfarin response include *CYP2C9*, *VKORC1*, *CYP4F2*, and a SNP rs12777823 in the *CYP2C*.
      f. There are FDA-cleared *CYP2C9* and *VKORC1* laboratory tests; however, there is no currently FDA-cleared test for *CYP4F2* or rs12777823.

g. The CPIC guideline regarding warfarin and genetic variability is available at https://cpicpgx.org/guidelines/guideline-for-warfarin-and-cyp2c9-and-vkorc1/ and includes warfarin dosing guidelines according to genotype.
h. *CYP2C9* and warfarin
    i. *CYP2C9* is a hepatic drug-metabolizing enzyme and is the enzyme primarily responsible for *S*-warfarin, which is 3–5 times more potent than *R*-warfarin (Figure 3).
    ii. *CYP2C9* genetic polymorphisms account for up to 18% of the variability in warfarin dosing.
    iii. *CYP2C9*1* is considered a "normal metabolizer" allele.
        (a) Among individuals of European ancestry, *CYP2C9*2* (rs1799853) and **3* (rs1057910) are the most common decreased-function alleles and impair warfarin metabolism by 30%–40% and 80%–90%, respectively, resulting in a greater risk of bleeding, lower dose requirement, and longer time to reach stable INR.
        (b) *CYP2C9*5, *6*, **8*, and **11* are also associated with decreased enzyme function and are found with the highest frequency among those of African ancestry.

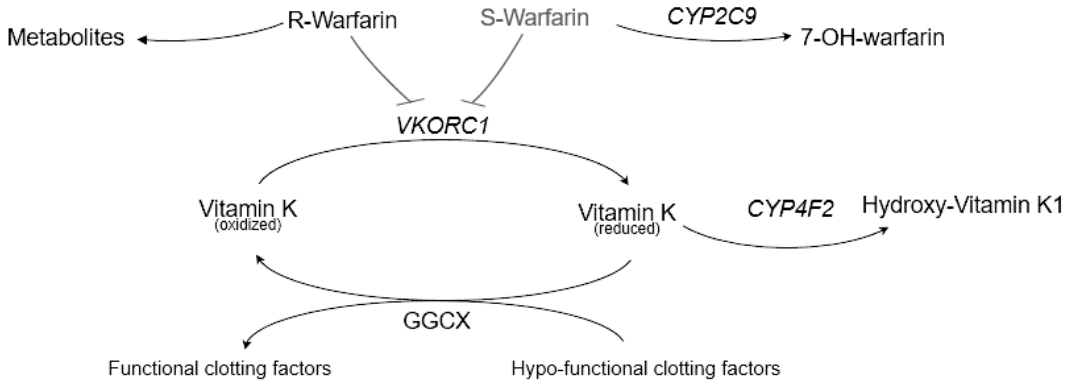


**Figure 3.** Warfarin pharmacokinetic and pharmacodynamic pathway diagram.

i. *VKORC1* and warfarin
    i. *VKORC1* encodes the VKOR protein, which is the target enzyme of warfarin, and the VKORC1 variation accounts for up to 30% of the variance in warfarin dosing.
    ii. Vitamin K epoxide is converted to vitamin K by *VKORC1*.
    iii. A common *VKORC1* variant, rs9923231 (-1639G>A), is associated with a significantly increased response to warfarin (warfarin sensitivity).
    iv. rs9923231 (-1639G>A) frequency varies by race, occurring in about 40% of whites and only 10%–13% of African Americans and Africans.
    v. Patients with one A allele (-1639GA) or two A alleles (-1639AA) at rs9923231 require progressively lower warfarin doses than do patients with one normal-function allele (-1639GG).
j. *CYP4F2* and warfarin
    i. *CYP4F2* catalyzes the metabolism of vitamin K to hydroxyvitamin $K_1$, thus removing vitamin K from the vitamin K cycle.
    ii. *CYP4F2* variants account for up to 11% of the variability in warfarin dosing.
    iii. *CYP4F2* is a counterpart to *VKORC1* by limiting the accumulation of vitamin K.
    iv. A variant in *CYP4F2—CYP4F2*3* rs2108622—decreases enzyme activity and is associated with an increased warfarin dose. *CYP4F2* variants are more common in individuals of European and Asian ancestry than in those of African ancestry.

v. Dosing algorithms that include *CYP4F2*, together with clinical factors (age, sex, race, weight, height, smoking status, warfarin indication, target INR, interacting drugs) that affect warfarin response, as well as *CYP2C9* and *VKORC1* improve the accuracy of warfarin dose prediction.

k. *CYP2C* cluster
   i. rs12777823 is a SNP in the *CYP2C* cluster that is associated with reduced warfarin clearance, independent of *CYP2C9*2* and **3* in African Americans.
   ii. Although rs12777823 is common in several populations, only those of African ancestry who carry one or two variant alleles at this SNP require a warfarin dose reduction of around 7–9 mg/week.
   iii. Dosing algorithms that include the *CYP2C* cluster improve the accuracy of warfarin dose prediction in African ancestry patients.

6. Warfarin pharmacogenetic dosing algorithms: The warfarin CPIC guideline recommends that pharmacogenetic warfarin dosing be accomplished through one of the available pharmacogenetic dosing algorithms.
   a. The Gage algorithm (primary) and the International Warfarin Pharmacogenetics Consortium algorithm (IWPC) (secondary) are available at www.warfarindosing.org/Source/Home.aspx.
   b. Figure 4 includes a summary of the CPIC warfarin dosing algorithms in adults, according to patient ancestry and including strength of the evidence for specific gene-based recommendations.
   c. Use of warfarin dosing algorithms computes the anticipated stable daily warfarin dose, and the clinician then prescribes a regimen that approximates this anticipated dose. Once additional INRs are obtained, the algorithms can be reapplied for refinement of warfarin daily/weekly dose.\

**Patient Case**

4. A 71-year-old white woman (height 68 inches, weight 54.4 kg [120 lb]) was recently given a diagnosis of atrial fibrillation (INR target 2.5), and you are consulted to manage her anticoagulation with warfarin (she cannot afford to take one of the newer oral anticoagulants). She has not yet received any warfarin doses. Her medical history includes diabetes, hyperlipidemia, and hypertension. She smokes 1 pack/day and has a baseline INR of 1.1. Her medications include rosuvastatin, lisinopril, metformin, and carvedilol. As part of a service provided by the anticoagulation clinic, she has undergone *CYP2C9* and *VKORC1* genotyping, and the results revealed *CYP2C9 *2*3* and *VKORC1* G>A. Given her pharmacogenomics profile, which would be best regarding her warfarin therapy?

   A. Her dose requirement is likely to be 5 mg daily.

   B. Her dose requirement is likely to be less than 5 mg daily.

   C. Her dose requirement is likely to be greater than 5 mg daily.

   D. She should not receive warfarin because she is unlikely to achieve a stable INR.

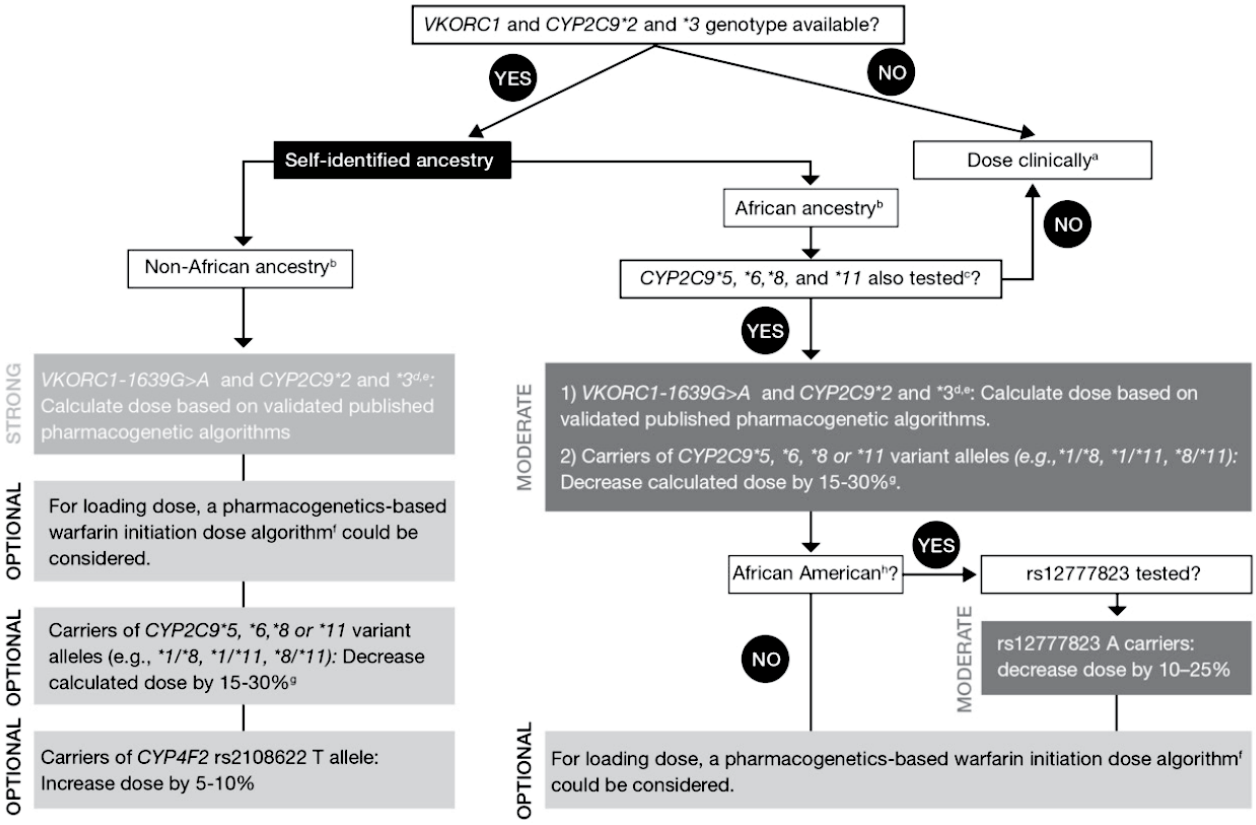


**Figure 4.** Dosing recommendations for warfarin dosing are based on genotype for adult patients.

[a]"Dose clinically" means to dose without genetic information, which may include use of a clinical dosing algorithm or a standard dose approach.

[b]Data are strongest for European and East Asian ancestry populations and are consistent in other populations.

[c]45%–50% of individuals with self-reported African ancestry carry *CYP2C9*5*, **6*, **8*, **11*, or rs12777823. IF *CYP2C9*5*, **6*, **8*, and **11* WERE NOT TESTED, DOSE WARFARIN CLINICALLY. Note: These data derive primarily from African Americans, who are largely from West Africa. It is unknown whether the same associations exist for those from other parts of Africa.

[d]Most algorithms are developed for the target INR 2–3.

[e]Consider an alternative agent in individuals with genotypes associated with CYP2C9 poor metabolism (e.g., *CYP2C9*3/*3*, **2/*3*, **3/*3*) or both increased sensitivity (VKORC1 A/G or A/A) and CYP2C9 poor metabolism.

[f]See the EU-PACT trial for a pharmacogenetics-based warfarin initiation (loading) dose algorithm, with the caveat that the loading dose pharmacogenetics algorithm has not been specifically tested or validated in populations of African ancestry.

[g]Larger dose reductions may be needed in variant homozygotes (i.e., 20%–40%).

[h]African American refers to individuals mainly originating from West Africa.

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## ANSWERS AND EXPLANATIONS TO PATIENT CASES

**1. Answer: C**

This patient needs dual antiplatelet therapy because of his recent drug-eluting stent placement. His genotype makes him an intermediate metabolizer (IM) phenotype because of one no-function allele (**2*), which makes him less likely to be able to adequately metabolize clopidogrel and clopidogrel would have an insufficient antiplatelet effect. In patients with an IM phenotype, the CPIC clopidogrel-*CYP2C19* guideline recommends treatment with an alternative antiplatelet agent, instead of clopidogrel (Answer A is incorrect). With respect to the choice between prasugrel and ticagrelor, because this patient has a history of transient ischemic attack, prasugrel is contraindicated (Answer B is incorrect), and ticagrelor would be best for this patient (Answer C is correct). Aspirin alone in this patient is not the best response because the patient needs dual antiplatelet therapy, given his stent placement, acute coronary syndrome, and STEMI history (Answer D is incorrect).

**2. Answer: D**

This patient presents after two drug-eluting stents; thus, he needs antiplatelet therapy. His *CYP2C19* genotype indicates he has one normal-function allele and one increased-function allele with a rapid metabolizer (RM) phenotype. In patients with an RM phenotype, the CPIC clopidogrel-*CYP2C19* guideline recommends treatment with a label-recommended clopidogrel dose (Answer D is correct). The clopidogrel dose should not be reduced because of a single increased-function allele (Answer A is incorrect). In addition, alternative antiplatelet agents need not be used in patients with the RM phenotype (Answers B and C are incorrect). Data regarding increased risk of bleeding in patients with one increased-function allele (or two) are inconclusive; thus, the current evidence does not warrant a decreased clopidogrel dose or an alternative antiplatelet therapy in the setting of increased function allele(s).

**3. Answer: C**

This patient's *SLCO1B1* genotype indicates he has a poor-function phenotype because he has two no-function alleles, and he is at high risk of myopathy, which he is currently experiencing. In patients with a poor-function phenotype, the *SLCO1B1*-simvastatin CPIC guideline recommends either a decreased simvastatin dose (Answer B) or use of an alternative statin (Answer C). In this patient who already has myopathy, and given that all other statins are available in a generic version, it would be best clinically to try an alternative statin to maintain LDL lowering as well as reduce myopathy symptoms (Answer C). Answer A is incorrect because simvastatin 40 mg should not be continued in a patient with a low-function phenotype. Answer D is incorrect because statin use need not be discontinued altogether. Use of a PCSK9 inhibitor in this patient would substantially increase overall medication costs, which is unnecessary.

**4. Answer: B**

This patient has two *CYP2C9* decreased-function alleles, which is associated with impaired warfarin metabolism, resulting in a lower dose requirement and a greater risk of bleeding (Answer B is correct). In addition, her *VKORC1* genotype indicates that she will have increased response to warfarin (increased warfarin sensitivity). Answer A is incorrect because 5 mg daily is the usual warfarin dose requirement, and the usual warfarin dose in this patient would likely result in excess bleeding risk. Answer C is also incorrect because this patient is very unlikely to require a warfarin dose greater than 5 mg daily. Answer D is incorrect because it is possible to use tools on the basis of clinical factors and genetic information to estimate a starting warfarin dose and determine dosing adjustments that can result in a stable INR. This patient has already indicated that she cannot afford the more expensive anticoagulant agents, and not being treated with any anticoagulation agent would place this patient at increased risk of clot formation and stroke.

## ANSWERS AND EXPLANATIONS TO SELF-ASSESSMENT QUESTIONS

**1. Answer: A**

*CYP2C9* is primarily responsible for the metabolism of the enantiomer *S*-warfarin, which is the more potent form of warfarin (Answer A is correct). The **2* and **3* polymorphisms cause decreased warfarin metabolism, resulting in decreased warfarin dose requirements, increased INR levels, and a higher risk of bleeding during warfarin therapy. The *SLCO1B1* genotype (Answer B) is associated with simvastatin efficacy and toxicity, and *CYP2C19* (Answer C) is associated with clopidogrel metabolism and efficacy. Answer D is incorrect because there are several known pharmacogenetic interactions with warfarin.

**2. Answer: C**

The *SLCO1B1* genotype encodes for a transporter for simvastatin from the gut to the liver. Carriers of the **5* allele have reduced liver uptake of simvastatin from the gut and thus are at a higher risk of developing myopathy because of higher concentrations in the blood (Answer C is correct). This person has a variant and thus is not at standard or decreased risk of toxicity (Answers A and B are incorrect). There is no good evidence associating *SLCO1B1* genotype and LDL lowering (Answer D is incorrect).

**3. Answer: B**

The CPIC guideline for simvastatin and *SLCO1B1*, on the basis of the available data, recommends a maximum daily dose of 20 mg of simvastatin in a person with a **5*5* genotype (Answer B is correct). The current guidelines do not specify that simvastatin would be contraindicated (Answer A). Both 40 mg (Answer C) and 80 mg (Answer D) are too high a dose for individuals with this variant (80 mg is too high for anyone) unless they have already been taking this dose before knowing their genetic information and are tolerating it well; if so, the current dose can be continued.

**4. Answer: A**

The *CYP2C19 *2/*3* genotype is considered a poor metabolizer for clopidogrel; thus, individuals with this genotype will have decreased antiplatelet effect and high platelet activity, making them at an increased risk of an adverse thrombotic event (Answer A is correct). Answers B–D are incorrect for this genotype.

**5. Answer: B**

The *CYP2C19 *17/*17* genotype is considered an ultra-metabolizer status and is associated with the greatest antiplatelet effect and the lowest on-treatment platelet reactivity. However, current data support use of the standard clopidogrel dose (75 mg daily) for this genotype (Answer B is correct). Answer A is incorrect because the **17*17* genotype is not associated with conversion of clopidogrel to an inactive metabolite or with decreased dose. Answer C is incorrect because although the **17*17* genotype is associated with increased conversion to active metabolite, data do not support that this is associated with an increased bleeding risk; thus, a decreased dose is not recommended. Answer D is incorrect because patients with a **17*17* genotype do not require alternative antiplatelet therapy.

**6. Answer: D**

The CPIC guidelines are not designed to provide information on whether a genetic test should be ordered or the timing of a specific genetic test (Answer D is correct; Answer A is incorrect). Currently, only 23 of 190 drugs with pharmacogenetic information in the package label have guideline information available (Answer B is incorrect). The CPIC guidelines do give priority to availability of commercially available pharmacogenetic tests offered in Clinical Laboratory Improvement Amendments–approved clinical settings (Answer C is incorrect).

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