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HEART FAILURE

Roy £. Gardner
Theresa A. McDonagh
Daniel J. Doherty
Niki L. Walker

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Oxford Specialist Handbooks in Cardiology

Heart Failure

Third Edition

Roy S. Gardner

Consultant Cardiologist, Scottish National Advanced Heart Failure Service, Golden Jubilee National Hospital, Clydebank, and Honorary Professor of Cardiology, University of Glasgow, UK

Theresa A. McDonagh

Consultant Cardiologist and Professor of Heart Failure at King's College Hospital NHS Foundation Trust, London and King's College London, London, UK

Daniel J. Doherty

Clinical Research Fellow, Cardiology Speciality Registrar, University of Glasgow, UK

Niki L. Walker

Consultant Cardiologist, Scottish Adult Congenital Cardiac Service, Golden Jubilee National Hospital, Clydebank, UK

OXFORD
UNIVERSITY PRESS

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Great Clarendon Street, Oxford, OX2 6DP,
United Kingdom

Oxford University Press is a department of the University of Oxford.
It furthers the University's objective of excellence in research, scholarship,
and education by publishing worldwide. Oxford is a registered trade mark of
Oxford University Press in the UK and in certain other countries.

First Edition published in 2007
Second Edition published in 2014
Third Edition published in 2025

Published in the United States of America by Oxford University Press
198 Madison Avenue, New York, NY 10016, United States of America.

British Library Cataloguing in Publication Data

Data available

Library of Congress Control Number: 2025938048

ISBN 978–0–19–287077–3

DOI: 10.1093/med/9780192870773.001.0001

Printed and bound by
CPI Group (UK) Ltd., Croydon, CR0 4YY

Contents

Symbols and abbreviations

⚠	warning
►	important
►►	don't dawdle
💣	controversial topic
♂	male
♀	female
↓	decrease
↑	increase
→	leading to cross-reference website
6-MWT	6 minute walk test
ACC	American College of Cardiology
ACE	angiotensin-converting enzyme
ACEi	angiotensin-converting enzyme inhibitor
ACTH	adrenocorticotrophic hormone
ADP	adenosine diphosphate
AF	atrial fibrillation
AHA	American Heart Association
A-HeFT	African-American heart failure trial
AHF	acute heart failure
AHI	apnoea-hypopnoea index
AIRE	acute infarction ramipril efficacy study
AMI	acute myocardial infarction
ANP	atrial natriuretic peptide
AR	aortic regurgitation
ARB	angiotensin II receptor blockers
ARVC	arrhythmogenic right ventricular cardiomyopathy
AS	aortic stenosis
AT1	angiotensin II type-1
ATII	angiotensin II
ATG	antithymocyte globulin
ATLAS	assessment of treatment with lisinopril and survival trial
ATP	anti-tachycardia pacing
AV	atrioventricular
AVNRT	atrioventricular nodal tachycardia
AVRT	atrioventricular re-entry tachycardia
BiPAP	bi-level positive pressure support
BiVAD	biventricular assist device
BK	bradykinin
BNP	B-type natriuretic peptide
BP	blood pressure
BSA	body surface area
BTC	bridge to candidacy
BTD	bridge to decision
BTR	bridge to recovery
BTT	bridge to transplantation
CABG	coronary artery bypass graft
CAD	coronary artery disease
CHARM	candesartan in heart failure: assessment of reduction in mortality and morbidity trial
CHB	complete heart block
CHD	coronary heart disease
CHF	chronic heart failure
CIBIS	cardiac insufficiency bisoprolol study
CMR	cardiac magnetic resonance
CNS	central nervous system
CO	cardiac output
COCPIT	comparative outcome and clinical profiles in transplantation
COMET	carvedilol or metoprolol European trial
COMT	catechol-O-methyl transferase
CONSENSUS	cooperative North Scandinavian enalapril survival study
COPERNICUS	carvedilol prospective randomized cumulative survival study
COX	cyclo-oxygenase
CPAP	continuous positive airways pressure
CPET	cardiopulmonary exercise testing
CRT	cardiac resynchronization therapy

CRT-D	cardiac resynchronization therapy-defibrillator
CRT-P	cardiac resynchronization therapy pacemaker
CSA	central sleep apnoea
CTR	cardiothoracic ratio
CTx	cardiac transplantation
CVP	central venous pressure
DAD	delayed after depolarization
DAVID	dual chamber and VVI implantable defibrillator trial
DCM	dilated cardiomyopathy
DD	diastolic dysfunction
DIC	disseminated intravascular coagulation
DIG	Digitalis Investigation Group
DMD	Duchenne muscular dystrophy
DNA	deoxyribonucleic acid
EAD	early after depolarization
ECMO	extracorporeal membrane oxygenation
ecNOS	endothelial cell NOS
EDTA	ethylene diamine tetraacetic acid
EEG	electroencephalogram
eGFR	estimated glomerular filtration rate
ELITE	evaluation of losartan in the elderly study
EMA	European Medicines Agency
EMF	endomyocardial fibrosis
EMG	electromyography
EPHESUS	epelerenone post-acute myocardial infarction heart failure efficacy and survival study
ESC	European Society of Cardiology
FDA	Food and Drug Administration
FEV_1	forced expiratory volume in 1 second
FVC	forced vital capacity
Gd	gadolinium
GFR	glomerular filtration rate
HCM	hypertrophic cardiomyopathy
HCP	healthcare professional
HDL	high-density lipoprotein
HES	hypereosinophilic syndrome
HF	heart failure
HFSS	heart failure survival score
HIV	human immunodeficiency virus
HLA	human leukocyte antigen
IABP	intra-aortic balloon pump
ICD	implantable cardioverter-defibrillator
IL	interleukin
INTERMACS	Interagency Registry for Mechanically Assisted Circulatory Support
ISDN	isosorbide dinitrate
ISHLT	International Society for Heart and Lung Transplantation
IVD	interventricular delay
IVS	interventricular septum
LA	left atrium
LBBB	left bundle branch block
LDL	low-density lipoprotein
LIDO	levosimendan infusion versus dobutamine trial
LV	left ventricular
LVAD	left ventricular assist device
LVEDP	left ventricular end-diastolic pressure
LVEF	left ventricular ejection fraction
LVH	left ventricular hypertrophy
LVNC	left ventricular non-compaction
LVOT	left ventricular outflow tract
LVSD	left ventricular systolic dysfunction
MAGGIC	meta-analysis global group in chronic heart failure trial
MAO	monoamine oxidase
MAOI	monoamine oxidase inhibitor
MAP	mean arterial pressure
MCS	mechanical circulatory support MDRD modification of diet in renal disease
MERIT-HF	metoprolol CR/XL randomized interventional trial in heart failure
MMF	mycophenolate mofetil
MR	mitral regurgitation
MRA	mineralocorticoid receptor antagonists
MS	mitral stenosis
MTWA	microvolt T-wave alternans
MUGA	multiple-uptake gated acquisition
NEP	neutral endopeptidase
NIPPV	non-invasive positive pressure ventilation

NSAID	non-steroidal anti-inflammatory drug
NT-proBNP	N-terminal Brain Natriuretic Peptide
NYHA	New York Heart Association
OSA	obstructive sleep apnoea
PA	pulmonary artery
PAC	pulmonary artery catheter
PAFC	pulmonary artery flotation catheter
PAP	pulmonary artery pressure
PCI	percutaneous coronary intervention
PCWP	pulmonary capillary wedge pressure
PDEI	phosphodiesterase inhibitors
PEEP	positive end-expiratory pressure
PEF	preserved ejection fraction
PLVEF	preserved LV function
PMBV	percutaneous mitral balloon valvotomy
PND	paroxysmal nocturnal dyspnoea
PPAR	peroxisome proliferator-activated receptor
PPCM	peripartum cardiomyopathy
PPI	proton-pump inhibitor
PR	pulmonary regurgitation
PS	pulmonary stenosis
PVR	pulmonary vascular resistance
RA	right atrium
RhA	rheumatoid arthritis
RAAS	renin–angiotensin–aldosterone system
RALES	randomized aldactone evaluation study
RCT	randomized controlled trials
REF	reduced e: randomisjection fraction
REMATCH	randomized evaluation of mechanical assistance for the treatment of congestive heart failure trial
RER	respiratory exchange ratio
REVIVE	randomized multicentre evaluation of intravenous levosimendan efficacy
RNVG	radionuclide ventriculography
RRR	regular rate and rhythm
RV	right ventricular
RVAD	right ventricular assist device
SAM	systolic anterior motion
SAVE	survival and ventricular enlargement study
SAVER	surgical anterior ventricular endocardial restoration
SBP	systolic blood pressure
SCA	senile cardiac amyloidosis
SCD	sudden cardiac death
SDC	serum digoxin concentrations
SENIORS	study of the effects of nebivolol intervention on outcomes and re-hospitalization in seniors with heart failure trial
SHFM	Seattle heart failure model
SLE	systemic lupus erythematosis
SNP	sodium nitroprusside
SNS	sympathetic nervous system
SOLVD	studies of left ventricular dysfunction
SPECT	single photon emission computed tomography
SPWMD	septal-to-posterior wall motion delay
STICH	surgical treatment for ischaemic heart failure trial
SUPPORT	study to understand prognoses and preferences for outcomes and risks of treatments
SVR	systemic vascular resistance
TAH	total artificial heart
TAPSE	tricuspid annular plane systolic excursion
TDI	tissue Doppler imaging
TM	thrombomodulin
TNF-α	tumour necrosis factor-α
TOE	transoesophageal echocardiography
TPG	transpulmonary gradient
TPMT	thiopurine methyltransferase
TR	tricuspid regurgitation
TRACE	trandolapril cardiac evaluation study
TS	tricuspid stenosis
TTE	transthoracic echocardiogram
TV	tricuspid valve
TZD	thiazolidinedione
UF	ultrafiltration
VAD	ventricular assist device
Val-HeFT	valsartan heart failure trial
Vd	volume of distribution

VE	minute ventilation
VO_2	respiratory oxygen uptake
VMAC	vasodilation in the management of acute CHF
VTI	velocity-time integral
VT	ventilatory threshold

Section I

General Introduction

Chapter 1

Definition of heart failure, basic epidemiology, and pathophysiology

Definition

Physiological—the inability of the heart to pump sufficient oxygenated blood to the metabolizing tissues despite an adequate filling pressure.

Working clinical definition—the clinical syndrome consisting of symptoms such as breathlessness, fatigue, and swelling of the ankles caused by cardiac dysfunction.

Chronic heart failure (HF) can be caused by any type of cardiac dysfunction and is most commonly attributable to left ventricular dysfunction. Only rarely does a patient present with HF as a result of isolated right-ventricular (RV) dysfunction. RV dysfunction is usually secondary to left ventricular (LV) dysfunction and its sequelae.

The most common and best-studied cause of HF is left ventricular systolic dysfunction (LVSD), now known has HFrEF (reduced ejection fraction). HF also occurs in the presence of preserved systolic function. This is referred to as HFpEF (preserved ejection fraction). Left ventricular systolic dysfunction is relatively easy to diagnose by a range of non-invasive methods. The diagnosis of HFpEF is more difficult (➔ Chapter 2). It is often attributed to diastolic dysfunction, although abnormalities of systolic and diastolic function frequently co-exist. To prove diastolic dysfunction, invasive haemodynamics are necessary, but many non-invasive tests can infer its presence.

Classification

Heart failure can present either as a chronic condition or acutely, occurring *de novo* or as a decompensation of chronic HF. Acute HF is covered in ➔ Chapters 25 and 26.

Current US guidelines also classify patients into the following stages (Table 1.1):

This system emphasizes the need for prevention of the development of HF in the first place by aggressive risk factor control. It also highlights the importance of treating asymptomatic LVSD to prevent its progression to symptomatic LVSD, that is, HF.

The latest European Society of Cardiology (ESC) guidelines have significantly enhanced the terminology of HF (Table 1.2):

Heart failure with reduced ejection fraction (**HFrEF**) = LVEF less than or equal to 40%.

Table 1.1 Stages of HF. Adapted from: Heidenreich PA, 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.

Stage A	Those at high risk of developing HF, for example, hypertensives, diabetics.
Stage B	Patients with structural cardiac disease or remodelling who have not yet developed HF, that is, asymptomatic LV dysfunction.
Stage C	Patients with current or prior HF symptoms.
Stage D	Those with end-stage HF.

Table 1.2 Definition of heart failure

Type of HF		HFrEF	HFmrEF	HFpEF
CRITERIA	1	Symptoms ± Signs[a]	Symptoms ± Signs[a]	Symptoms ± Signs[a]
	2	LVEF ≤ 40%	LVEF 41–49%[b]	LVEF ≥ 50%
	3			Objective evidence of cardiac structural and/or functional abnormalities consistent with the presence of LV diastolic dysfunction/raised LV filling pressures, including raised natriuretic peptides[c]

HF = heart failure; HFmrEF = heart failure with mildly reduced ejection fraction; HFpEF = heart failure with preserved ejection fraction; HFrEF = heart failure with reduced ejection fraction; LV = left ventricle; LVEF = left ventricular ejection fraction.

[a] Signs may not be present in the early stages of HF (especially in HFpEF) and in optimally treated patients.

[b] For the diagnosis of HFmrEF, the presence of other evidence of structural heart disease (e.g. increased left atrial size. LV hypertrophy or echocardiography measures of impaired LV filling) makes the diagnosis more likely.

[c] For the diagnosis of HFpEF, the greater the number of abnormalities present, the higher the likelihood of HFpEF.

Heart failure with mildly reduced ejection fraction (**HFmrEF**) = LVEF 41–49%.

Heart failure with preserved ejection fraction (**HFpEF**) = LVEF greater than or equal to 50%.

The original HF trials focused on patients with reduced ejection fraction. The importance of these definitions is that patients with HFmrEF may benefit from therapies in a similar fashion to HFrEF, while those with HFpEF may benefit from specific therapies, but also require careful assessment before attributing symptoms to HFpEF. However, it is likely that HFmrEF will be merged with HFrEF in the future.

In addition to left heart dysfunction causing HF symptoms, right heart dysfunction can also cause HF symptoms. Often RV dysfunction is secondary to LV dysfunction, however other causes should be considered, as covered in Chapter 25.

Key references

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McKee PA, et al. The natural history of congestive heart failure. *N Engl J Med*. 1971;285:1441–1446.

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Epidemiology

Prevalence

- Using clinical criteria, HF prevalence is 1–2% of the population.
- Increased in older people (>10% over the age of 70).
- Approximately 50% of patients with significant left ventricular systolic dysfunction have no symptoms or signs of heart failure (**asymptomatic LVSD**).
- Approximately 50% of those with HF have HFpEF based on studies of hospitalized patients.

Incidence

- The Framingham heart study (US) results show an annual incidence of 0.2–0.3% in those aged 50–59 years, increasing 10-fold in those aged 80–89 (Fig. 1.1).
- European population data is similar, with an annual incidence of 0.5% in all adults.
- HF incidence is increasing due to patient age and median age of presentation is 76 years.
- HFpEF is associated with multimorbidity and occurs more among:
  - Elderly individuals.
  - Women.
  - African Americans.

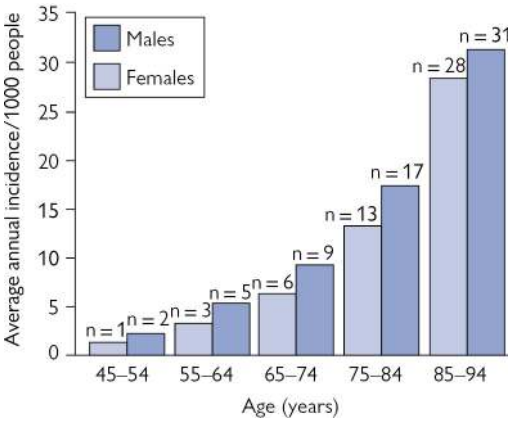

Fig. 1.1 Incidence of heart failure. McKee PA et al. The natural history of congestive heart failure: the Framingham study. *N Engl J Med*. 1971;285:1441–1446 with permission from Massachusetts Medical Society.

Aetiology

See Box 1.1

- There is geographical variation.
- In Westernized societies, two-thirds are secondary to ischaemic heart disease (coronary artery disease) and often resulting in HFrEF.
- Other important contributors are:
  - Hypertension
  - Valve disease
  - Alcohol
- Rheumatic disease is the most common cause in the developing world.
- Chagas disease is an important cause in South America (Chapter 14).
- Hypertension is an important factor in Africans and African Americans. It is proportionately more common in HFpEF.
- There has been a shift in the aetiology over time in long-term population-based studies, such as Framingham.
  - Decreased importance of hypertension.
  - Increased relevance of ischaemic heart disease (Fig. 1.2).

Box 1.1 Causes of chronic heart failure

- Coronary artery disease.
- Hypertension.
- Valve disease.
- Cardiomyopathy.
- Congenital heart disease.
- Infective: for example, viral myocarditis, Chagas, HIV, Lyme disease.
- Alcohol.
- Drug-induced: for example, anthracyclines, trastuzimab, immune-checkpoint inhibitors.
- Deficiencies: for example, selenium, beriberi, thiamine.
- Tachycardia induced.
- Infiltrative states: amyloid, sarcoid, iron overload, Anderson-Fabry.
- High output: for example, A–V fistulae, Paget's disease.

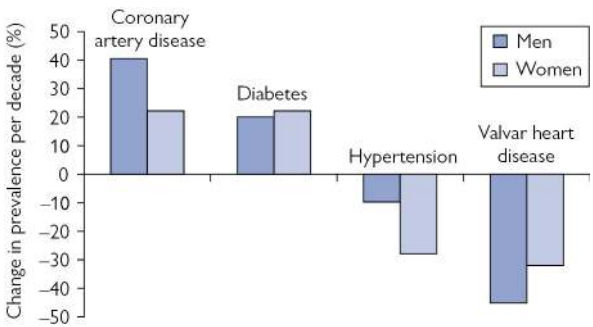

Fig. 1.2 The changing pattern of aetiology of CHF in the Framingham study with time. McMurray JJ & Stewart S. Epidemiology, aetiology, and prognosis of heart failure. *Heart.* 2000;83:596–602 with permission from BMJ Publishing Group Ltd.

Prognosis

The prognosis in HF is poor. Population-based studies report significantly lower survival rates than those seen in HF treatment trials.

- The mortality from HF at 5 years in the Framingham study (32-year follow-up):
  - 62% in men
  - 42% in women.
- UK data:
  - Six-month mortality rate 30%
  - Over 40% do not survive 18 months from the time of diagnosis.
- Mortality rates are in excess of many common solid malignant tumours (breast, prostate, colon, and melanoma).
- Population-based studies: survival of HFpEF is better.
- Hospitalized patients with HFpEF: similar mortality rates to those patients with HFrEF.
- HF is extremely disabling, with frequent and recurrent hospitalizations.
- HF reduces quality of life to a greater extent than other chronic medical disorders including arthritis and stroke.
- HF is an expensive condition, consuming 1–2% of total NHS expenditure in the UK.
- The mortality of acute heart failure is worse than that of chronic HF. Over 30% of patients admitted to hospital with HF are dead at 1 year, with around 11% dying during the admission. Mortality rates vary according to the presentation. They are worst for cardiogenic shock.

Trends in epidemiology

HF is projected to increase in prevalence by 50% in the next 20 years. The prevalence and incidence of HF are rising due to:

- Changing demography of the population, that is, more elderly at risk.
- Improved survival of other cardiovascular diseases, for example, myocardial infarction (MI).
- Improved survival rates for HF.

Key references

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Levy D, et al. Long-term trends in the incidence of and survival with heart failure. *N Engl J Med.* 2002;347:1397–1402.

The National Heart Failure Audit. https://www.nicor.org.uk/national-cardiac-audit-programme/heart-failure-audit-nhfa

Pathophysiology

Sustained cardiac dysfunction leads to haemodynamic, autonomic, neurohumoral, and immunological abnormalities. These drive the pathway to HF. Many of the processes are maladaptive, originally designed to protect the organism from exsanguination and hence to maintain blood pressure and vital organ perfusion.

The best-described mechanisms are the activation of various neurohormonal systems. In addition, there is intense activation of cytokines and inflammatory markers. These processes combine to cause fluid retention and myocardial cell death leading to a vicious cycle of deteriorating left ventricular performance.

Haemodynamics

Decreased cardiac output leads to the following:

- ↑ Left ventricular end-diastolic pressure (LVEDP).
- ↑ Pulmonary capillary wedge pressure (PCWP).
- The development of pulmonary oedema.

PCWP is a poor correlate of symptoms because other factors also contribute.

Initially, increased filling pressures augment ventricular performance early in the disease process (Frank Starling law), but as the increased filling pressures persist, the myocardium fails and cardiac output drops.

The renin–angiotensin–aldosterone system (RAAS)

Decreased cardiac output decreases renal afferent arteriolar blood flow, causing secretion of renin and production of angiotensinogen and angiotensin I. This is converted in the lung by the angiotensin-converting enzyme (ACE) to the octapeptide, angiotensin II (ATII) (Fig. 1.3).

ATII is a major effector hormone of this system, causing the following:

- Vasoconstriction
- Myocyte hypertrophy and fibrosis
- Aldosterone release
- Activation of noradrenaline and endothelin.

Aldosterone causes sodium- and water-retention and hypokalaemia, resulting in the following:

- Pulmonary and peripheral oedema
- Myocardial cell loss via apoptosis
- Myocardial fibrosis
- Increased afterload.

Key reference

Swedberg K. Importance of neuroendocrine activation in chronic heart failure. Impact on treatment strategies. *Eur J Heart Fail.* 2000;2:229–233.

The sympathetic nervous system (SNS)

Decreased cardiac output activates baroreceptors, causing activation of the SNS. The effects of high circulating concentrations of epinephrine and norepinephrine include

- ↑ Heart rate.
- ↑ Blood pressure.

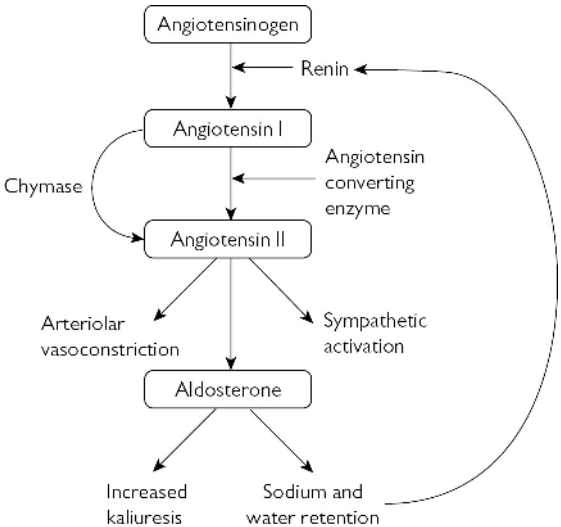

Fig. 1.3 The renin–angiotensin–aldosterone system.

- ↑ Myocardial oxygen demand.
- Toxic effects on the myocardium—cell death.
- Down-regulation of β_1 receptors in the heart.

There is a concomitant decrease in parasympathetic nervous activity.

Other circulating and paracrine effects

Other circulating and paracrine effects include increased production of the following:

- Endothelin: a potent vasoconstrictor peptide.
- Vasopressin: leading to water retention and vasoconstriction.
- Cytokines such as TNF-α, IL-1, and IL-6 cause myocyte apoptosis, which contributes to the development of cardiac cachexia in advanced HF.
- Increased circulating steroid hormones and growth hormone.

Counter-regulatory systems

Not all the hormonal systems activated in HF are deleterious. Various counter-regulatory mechanisms to oppose sodium and water retention are also activated, for example, the natriuretic peptide system.

The natriuretic peptide system

Myocardial pathology and the increased wall stress caused by a raised LVEDP and LA pressure, lead to LV and LA wall stretch and the secretion of the natriuretic peptide hormones (Fig. 1.4). These natriuretic peptides cause

- Natriuresis.
- Vasodilatation.
- Offset the activation of the RAAS and SNS.

Two types of natriuretic peptide circulate in high concentrations in HF:

- Brain natriuretic peptides (Fig. 1.5)
  - BNP, the active peptide.
  - NT-proBNP, the inactive N-terminal cleavage fragment.
- Atrial natriuretic peptide (ANP and NT-ANP).

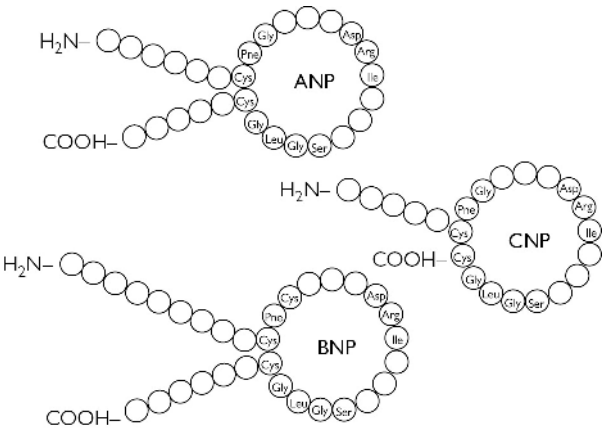

Fig. 1.4 The natriuretic peptides. *Heart Failure in Clinical Practice* (2nd edition) edited by McMurray J & Cleland J. Martin Dunitz Ltd, London, 2000 (Fig. 5.1) with permission from Taylor and Francis.

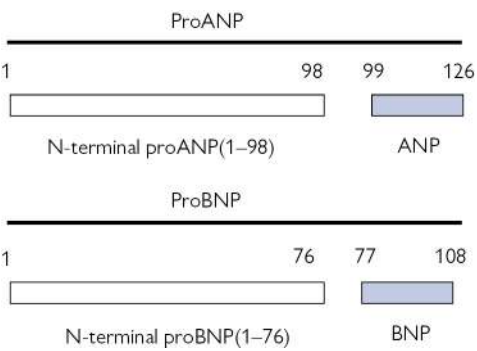

Fig. 1.5 Cleavage of pro-hormones of BNP and ANP into active peptides and inactive N-terminal fragments.

Adrenomedullin, another natriuretic hormone, is also produced and circulates in higher concentration. When HF progresses, the more powerful negative effects of the RAAS and SNS outweigh these beneficial processes.

Key reference

Rademaker MT & Richards AM. Cardiac natriuretic peptides for cardiac health. *Clin Sci (Lond)*. 2005;108:23–36.

Peripheral changes

Abnormalities of skeletal muscle occur in HF, including:

- Wasting.
- Impaired perfusion.
- Increased fatigability.
- Abnormal histology and metabolism.

These correlate with symptoms of fatigue, exercise intolerance, and poor prognosis. These changes may be secondary to

- Physical inactivity, anorexia, and poor intestinal absorption.
- Insulin resistance, TNF-α, and norepinephrine.

Arrhythmias

The HF syndrome is associated with an increased propensity for both atrial and ventricular arrhythmias. In particular, the development of atrial fibrillation (AF) can contribute to the further deterioration of LV function.

There are multiple mechanisms for arrhythmias in HF, including structural changes, ischaemia, and neurohormonal activation (➔ Chapter 11). Additional factors such hypo- and hyperkalaemia, hypo- and hypermagnesaemia, drug interactions, and toxicity may precipitate arrhythmias.

Co-morbidities

HF is frequently associated with co-morbidities that can lead to progression and deterioration. These can occur due to the HF syndrome, the treatment, or due to other diseases, for example, diabetes.

The commonest co-morbidities are

- **Renal dysfunction**: eGFR <50 mL/min/1.73^2 is present in 20–50% of all HF patients. It may be caused by reduced renal perfusion, the effects of drugs or comorbid conditions such as renal artery stenosis, hypertension, and diabetes. The presence of renal dysfunction increases both morbidity and mortality in HF (➔ Chapter 23).
- **Anaemia**: This is present in up to 40% of those with advanced HF. It can be anaemia of chronic disease or due to iron deficiency often associated with aspirin and chronic gastrointestinal (GI) blood loss. Anaemia is also associated with increased morbidity and mortality in HF (➔ Chapter 19).

Intercurrent cardiac events

Progression of HF can also be caused by further myocardial insults, for example, MI, ischaemia (causing hibernation and stunning), hypertension, valvular regurgitation or stenosis, or arrhythmia.

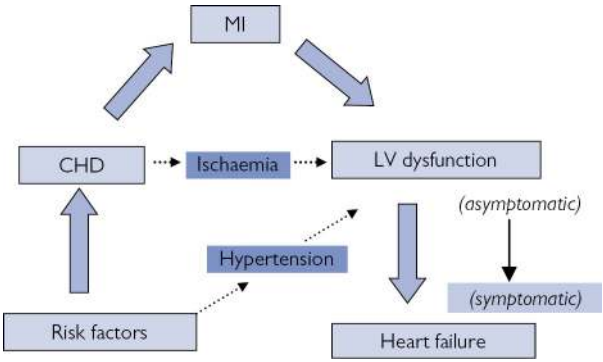

Fig. 1.6 The cardiovascular continuum.

Progressive LV remodelling

These processes cause sodium- and water-retention, and depression of myocardial performance. This ultimately leads to adverse remodelling of the left ventricle: a process involving myocyte hypertrophy, death, and fibrosis.

In HFrEF, this inexorable progression of the syndrome can lead to a dilated, spherical ventricle. The natural history of this so-called 'cardiovascular continuum' (Fig. 1.6), starts early on with risk factors for heart disease, which leads to MI and LV dysfunction. At the syndrome reaches end-stage, death occurs either from progressive pump failure or suddenly, often as a consequence of ventricular arrhythmia.

Key references

Bristow MR. Why does the myocardium fail? Insights from basic science. *Lancet.* 1998;352(Suppl I):SI8–14.

Mann DL & Young JB. Basic mechanisms in congestive heart failure. Recognising the role of pro-inflammatory cytokines. *Chest.* 1994;105:897–904.

Weber KT. Aldosterone in congestive heart failure. *N Engl J Med.* 2001;348:1689–1697.

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Section II

Chronic heart failure

Chapter 2

Diagnosis and investigation

Introduction

Heart failure is a clinical syndrome: a constellation of symptoms and signs that are ultimately due to cardiac dysfunction.

► HF is not a diagnosis, and a cause for the underlying cardiac dysfunction must always be sought and treated, if possible.

There are two aspects to the diagnosis and investigation of HF:

- Confirmation of the presence and type of cardiac dysfunction.
- Ascertainment of the cause of that cardiac dysfunction.

A thorough investigation to search for the co-morbidities that often accompany heart failure should be pursued. These are possible precipitants of decompensation, which may affect its subsequent management.

Diagnosis of heart failure

Clinical symptoms and signs

The cardinal symptoms and signs of HF are:

- Breathlessness.
- Fatigue.
- Peripheral oedema.

Breathlessness is usually exertional, but in more advanced cases appears at rest. Orthopnoea and paroxysmal nocturnal dyspnoea (PND) may occur especially in the presence of pulmonary oedema.

Physical signs can be present and relate either to the presence of fluid retention and/or poor cardiac output. They can include:

- Sinus tachycardia.
- Atrial fibrillation or other arrhythmia.
- Hypotension.
- Increased JVP.
- Ankle and sacral oedema.
- Pulmonary crackles.
- Signs of pleural effusion.
- Displaced apex beat.
- Hepatomegaly.
- Ascites.
- Third and/or fourth heart sounds.
- Murmurs.

The important point about these clinical symptoms and signs is that they raise the suspicion of HF. Clinical acumen alone leads to an inaccurate diagnosis of HF in up to 50% of cases. The symptoms and signs are either both oversensitive and non-specific or, if they are specific, lack sensitivity. Symptoms are used to assign an NHYA class to patients (Tables 2.1 and 2.2).

► The presence of cardiac dysfunction must be proved to make the diagnosis.

Guidelines for the diagnosis of heart failure

Recognized guidelines (ESC, ACC/AHA, NICE, SIGN) all state that to diagnose HF, the following should be present (Fig. 2.1):

- Symptoms and/or signs of HF.
- Cardiac dysfunction at rest.

Table 2.1 New York Heart Association (NYHA) functional classification of heart failure

Class I	No limitation; ordinary exercise does not cause undue dyspnoea, fatigue, or palpitation
Class II	Slight limitation of physical activity; comfortable at rest but ordinary activity results in dyspnoea, fatigue, or palpitation
Class III	Marked limitation of physical activity; comfortable at rest but less than ordinary activity results in dyspnoea, fatigue, or palpitation
Class IV	Unable to carry out any physical activity without discomfort; symptoms of heart failure are present even at rest with increased discomfort with any physical activity

Table 2.2 Sensitivity and specificity of clinical symptoms and signs in heart failure

Clinical features	Sensitivity (%)	Specificity (%)
Breathlessness	66	52
Orthopnoea	21	81
PND	33	76
History of oedema	23	80
Tachycardia	7	99
Pulmonary crackles	13	91
Oedema on examination	10	93
Third heart sound	31	95
Raised JVP	10	97

Reproduced from Sosin M et al. *A Colour Handbook of Heart Failure. Investigation, Diagnosis and Treatment*. Manson Publishing, 2006, with permission from John Wiley & Sons.

Investigation of suspected heart failure

The latest ESC guideline on heart failure has summarized the key investigations for HF as follows (see also Table 2.3):

- **12-lead ECG**: HF is rare in the presence of a normal ECG. The negative predictive value of the ECG is >90%.
- **B-type natriuretic peptide** (BNP or NT-proBNP): a value within the normal range has an extremely high negative predictive value (>98%) for the exclusion of HF (Fig. 2.2).
  - Increased values indicate either a cardiac functional/structural abnormality or renal dysfunction.
  - BNP/NT-proBNP concentrations:
    - ↑ with age in normal individuals.
    - higher in ♂ than ♀.
    - age–sex corrected normal values may aid diagnosis.
  - Increased BNP/NT-proBNP concentrations need further investigation and cardiac assessment.
- **CXR**: A normal chest X-ray does not exclude a diagnosis of HF as the cardiothoracic ratio (CTR) is normal in 50% of cases.
  - Cardiomegaly (CTR >0.50) may be suggestive of a cardiac abnormality, particularly with evidence of pulmonary congestion.
  - Helps to identify and exclude other causes of breathlessness.

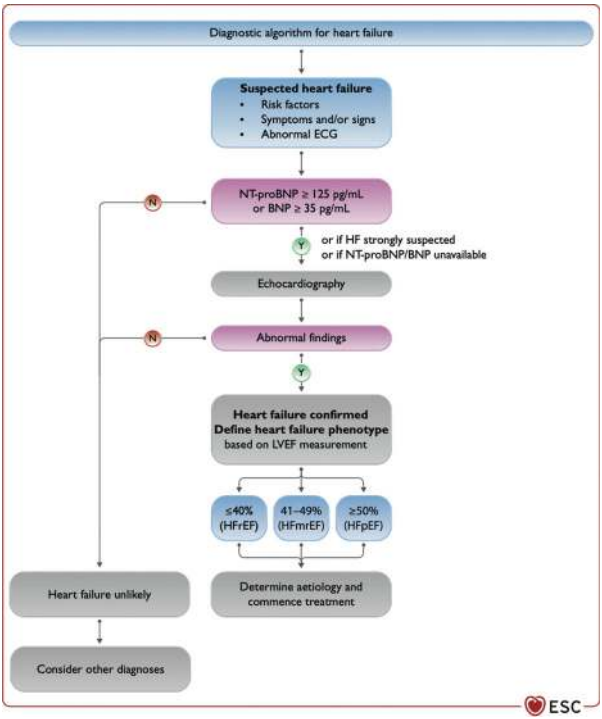

Fig. 2.1 The diagnostic algorithm for heart failure. BNP = B-type natriuretic peptide; ECG = electrocardiogram; HFmrEF = heart failure with mildly reduced ejection fraction; HFpEF = heart failure with preserved ejection fraction; HFrEF = heart failure with reduced ejection fraction; LVEF = left ventricular ejection fraction; NT-proBNP = N-terminal pro-B-type natriuretic peptide. McDonagh TA, et al. Guidelines for the diagnosis and treatment of acute and chronic heart failure 2021. *Eur Heart J.* 2021; 42: 3599–3726.

Table 2.3 Recommended diagnostic tests in all patients with suspected chronic HF. BNP = B-type natriuretic peptide; ECG = electrocardiogram; HBA1c = glycated haemoglobin; NT = proBNP = N-terminal pro-B-type natriuretic peptide; TSAT = transferrin saturaton. [a] Class of recommendation [b] Level of evidence [c] See Figure 2.1 for diagnostic reference ranges. McDonagh TA, et al. Guidelines for the diagnosis and treatment of acute and chronic heart failure 2021. *Eur Heart J.* 2021;42:3599–3726.

Recommendations	Class[a]	Level[b]
BN / NT-proBNP[c]	I	B
12-lead ECG	I	C
Transthoracic echocardiography	I	C
Chest radiography (X-ray)	I	C
Routine blood tests for comorbidities including full blood count, urea, and electrolytes thyroid function, fasting glucose, and HbA1c, lipids, iron status (TSAT and ferritin)	I	C

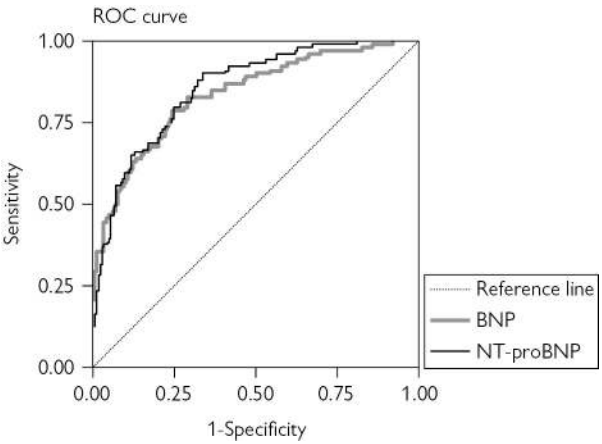

Fig. 2.2 Accuracy of BNP and NT-proBNP in the diagnosis of suspected heart failure. Receiver operating characteristics curves for BNP and NT-proBNP. Area under the curve is 0.84 (95% CI 0.79–0.89) for BNP and 0.85 (0.81– 0.90) for NT-proBNP. Zaphiriou A, et al. *Eur J Heart Fail.* 2005;7:537–541, with permission from Elsevier.

Diagnosis of cardiac dysfunction

LV function is usually assessed non-invasively by **echocardiography**. The types of cardiac dysfunction (i.e. myocardial, valvular, or pericardial) should be identified. Additional information about heart function or valve function can be obtained from stress echocardiography.

For myocardial dysfunction the detection of systolic dysfunction is a crucial preliminary step. The most common way of expressing myocardial performance is by the calculating the LV ejection fraction (LVEF).

$$\text{LVEF}(\%) = \frac{\text{LV diastolic volume} - \text{LV systolic volume}}{\text{LV diastolic volume}} \times 100.$$

Other modalities can be used, for example, cardiac MR or cardiac CT, or invasive contrast ventriculography at cardiac catheterization.

Key references

Heidenreich PA, et al. ACC/AHA/HFSA 2022 guideline update for the diagnosis and management of chronic heart failure: executive summary: a report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. *Circulation*. 2022;145:e876–e894.

McDonagh TA, et al. Guidelines for the diagnosis and treatment of acute and chronic heart failure 2021. Eur Heart J. 2021;42:3599–3726.

Echocardiography

LV function and dimensions are usually determined by echocardiography. An accurate LVEF can be obtained by the biplane Simpson's rule method (Fig. 2.3). Simpler and more common methods include:

- Regional wall motion scores.
- Global subjective assessment (eye ball technique).
- A–V plane displacement.

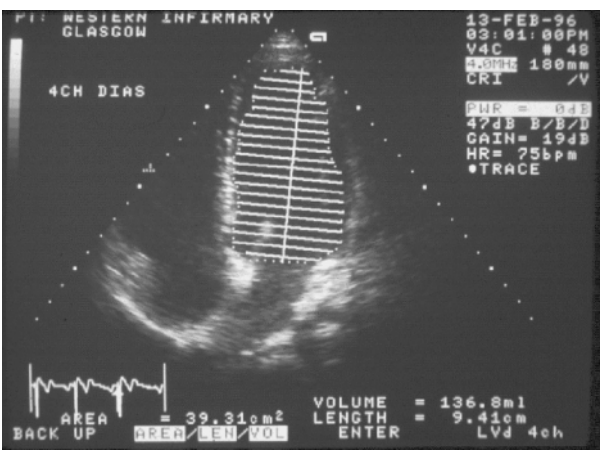

Fig. 2.3 Example of Simpson's rule for the calculation of LVEF.

⚠ M-mode fractional shortening only measures basal function.

In systolic dysfunction, the LV is frequently dilated and valve pathology is often identified. Identifying abnormalities of diastolic function is much more complicated by echocardiography. Simple methods such as the E/A ratios on mitral pulsed-wave Doppler are confounded by age and loading conditions. Newer methods, including pulmonary venous flow modalities and most recently tissue Doppler imaging, provide more accurate results, which compare well with invasive haemodynamic parameters. The findings of left ventricular hypertrophy (LVH) and increased left atrial volume are becoming increasingly important in the diagnosis of HFpEF.

Key reference

Lindow T, et al. Echocardiographic estimation of pulmonary artery wedge pressure: invasive derivation, validation, and prognostic association beyond diastolic dysfunction grading. *Eur Heart J Cardiovasc Imaging*. 2024;25:498–509.

Cardiac magnetic resonance (CMR)

CMR (Fig. 2.4) provides accurate information on LV size, volumes, and LVEF. It is the most reliable non-invasive test for LVH and calculations of LV mass. With permission from Professor Henry J Dargie.

► CMR can be used in patients with coronary artery stents, metallic valves and most modern pacemakers/ICDs, providing they are 'CMR conditional'.

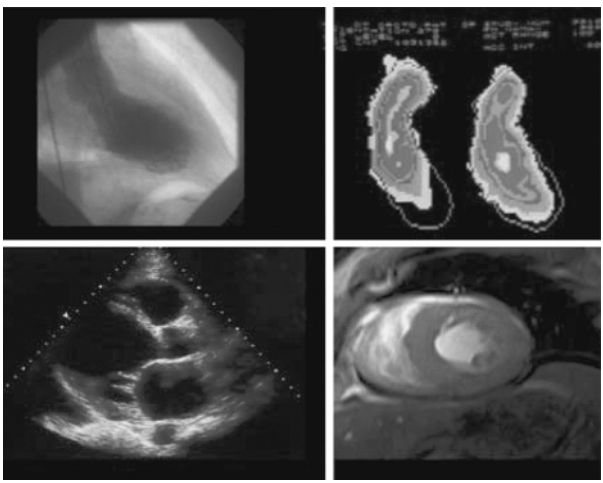

Fig. 2.4 Commonly used methods for assessing cardiac dysfunction. Top left: LV contrast angiogram. Top right: radionuclide ventriculogram/MUGA. Bottom left: 2D echocardiogram. Bottom right: CMR scan.

Nuclear cardiology

Calculation of the LVEF (Fig. 2.4) by multiple-uptake gated acquisition scans with Technetium 99 (MUGA) or radionuclide ventriculography (RNVG) provides a more accurate and reproducible result than echocardiography.

Angiographic LV function

Contrast, biplane LV (Fig. 2.4) angiography provides an accurate measure of LV systolic function. The gold standard of measurement of diastolic dysfunction is the assessment of pressure-volume loops during invasive haemodynamic studies.

Diagnosis of underlying aetiology of cardiac dysfunction, assessment of comorbidities and precipitating factors

Once the cardiac dysfunction is classified, the aetiology should be identified and, if possible, treated appropriately. Many of these tests also characterize the cardiac dysfunction more accurately and give pointers to the feasibility of future therapy. Some of the investigations also provide prognostic information, which helps to target more aggressive/invasive management. Commonly used tests are

- 12-lead ECG:
  - Q waves may indicate previous MI.
  - LVH may point to hypertension.
  - ST-T changes may indicate ischaemia, LVH, or be non-specific.
  - QRS duration may indicate dyssynchrony.
- Exercise test:
  - This is often used to investigate underlying coronary artery disease.
  - Metabolic exercise testing is also used as a prognostic aid and to discriminate between heart and lung pathology—patients with predominant lung pathology desaturate on exercise.
- Routine blood tests (heart failure screen):
  - FBC—anaemia can be a cause or effect of HF.
  - Urea and electrolytes (Na^+, K^+).
  - Creatinine—eGFR should be estimated (➔ Formulae for estimating GFR).
  - TFTs—hypo- and hyperthyroidism can cause HF.
  - Ferritin—haemochromatosis is a reversible cause of HF.
  - Lipids—hypercholesterolaemia is associated with the main cause of HF, ischaemic heart disease.
  - Blood glucose.
- Rarer blood tests, when aetiology is in doubt:
  - Viral titres in suspected myocarditis.
  - HIV.
  - Genetic testing (in consultation with a geneticist).
- Lung function testing:
  - FVC and FEV_1 reduced in HF.
  - Reversibility testing is useful to determine future β-adrenoreceptor antagonist use.
- 24-hour Holter monitor:
  - usually used in patients with symptomatic arrhythmias.

Formulae for estimating GFR

MDRD-1 equation:

GFR (expressed in mL/minute/1.73 m^2) = 170

- × [plasma creatinine]$^{-0.999}$ × [age]$^{-0.176}$ × [0.762 if ♀]
- × [1.180 if patient is black] × [urea]$^{-0.170}$ × [albumin]$^{+0.318}$.

MDRD-2 (abbreviated) equation:

GFR (expressed in mL/minute/1.73 m^2) = 186

- × [plasma creatinine]$^{-1.154}$ × [age]$^{-0.203}$
- × [0.742 if ♀] × [1.212 if patient is black].

$$\text{Body surface area } (m^2) = \sqrt{[\text{weight(kg)} \times \text{height(cm)}/3600]}.$$

Cockcroft–Gault formula for creatinine clearance (mL/minute/1.73 m^2):

♂: 1.23 × Weight (kg) × [140–age]/plasma Cr (μmol/L) × 1.73/BSA.
♀: 1.03 × Weight (kg) × [140–age]/plasma Cr (μmol/L) × 1.73/BSA.

Key reference

O'Meara E, et al. The modification of diet in renal disease (MDRD) equations provide valid estimations of glomerular filtration rates in patients with advanced heart failure. *Eur J Heart Fail.* 2006;8:63–67.

Further echocardiography

Echocardiography can also be used to assess the following:
- Regional wall motion abnormalities suggesting coronary artery disease.
- Valve function.
- Dyssynchrony.
- Estimation of pulmonary artery pressure.

Myocardial perfusion scanning

Planar myocardial scintigraphy or single photon emission computed tomography (SPECT) using a variety of agents (thallium, tetrafosmin, 99m technetium sestamibi) can be used to detect inducible ischaemia and hibernating myocardium.

Stress echocardiography

Echocardiography with exercise or pharmacological stress (usually with a dobutamine infusion) can be used to detect ischaemia or hibernation.

Coronary angiography

Invasive investigation of the coronary anatomy is indicated in patients with HF and:
- Angina despite medical therapy.
- Symptomatic ventricular arrhythmia.

Coronary angiography could be considered in those with significant inducible ischaemia/hibernation on non-invasive tests and suspicion of coronary artery disease. CT coronary angiography (CTCA) can be used as a non-invasive 'rule out' investigation.

Right and left cardiac catheterization (➔ Chapter 28)

Invasive investigation also facilitates:
- Measurement of LVEDP, PCWP, and cardiac output.
- PAP, SVR, and PVR for those where the diagnosis is in doubt, for cardiac transplantation assessment.
- Investigations of shunts with O_2-saturation data.

Cardiac biopsy (➔ Chapter 29)

This is rarely used, usually to diagnose infiltrative or inflammatory diseases such as amyloid, sarcoid, or giant cell myocarditis.

Conclusions

As a result of careful assessment of the type of cardiac dysfunction, investigation of the underlying aetiology, and comorbidities, the stage should be set to:

- Commence, uptitrate, and monitor general pharmacotherapy for HF.
- Identify subgroups of HF patients known to benefit from device therapy.
- Target specific therapies, such as the management of ischaemic heart disease, appropriately.
- Treat comorbidities with increasing focus on novel therapies for comorbidities including type II diabetes and obesity.
- Risk stratify those at highest risk of a poor outcome to a more advanced level of care.

See Leeson P, et al. (2007) *Echocardiography*, pp. 188–195. Oxford University Press.

Chapter 3

Estimating prognosis

Introduction

With advances in medical therapy, the prognosis of HF has improved dramatically for those with HFrEF. However, some patients remain symptomatic and at high risk of death despite maximal medical therapy, and identifying these individuals, who would potentially benefit from a range of novel device therapies or cardiac transplantation, can be challenging.

Overall prognosis is better in HFmrEF compared with HFrEF. Prognosis in HFpEF remains under review with conflicting observational and meta-analysis data.

Advanced HF in patients who have persistent symptoms despite maximal therapies has a worse prognosis with one-year mortality high at 25–75%.

Over 300 parameters have been shown to be predictive of a poor outcome in patients with HF, the most consistent of which will be illustrated in this chapter (Table 3.1). To date, the most effective single marker appears to be the B-type natriuretic peptides (BNP/NT-proBNP).

Table 3.1 Powerful markers of an adverse outcome in patients with heart failure

Category	Prognostic marker	Relationship
Demographics	Age	Direct
Aetiology	Ischaemic heart disease	Direct
Co-morbidity	Chronic renal failure	Direct
	Diabetes mellitus	Direct
	Body mass index	Inverse
Symptoms and signs	Pulse	Direct
	Blood pressure	Inverse
	NYHA class	Direct
	S_3	Direct
Therapy	ACE inhibitors/ARBs	Inverse
	ARNI	Inverse
	β-blocker	Inverse
	Aldosterone antagonist	Inverse
	SGLT2 inhibitor	Inverse
Laboratory tests	Sodium	Inverse
	Troponin	Direct
	Creatinine	Direct
	Haemoglobin	Inverse
Electrocardiography	QRS duration	Direct
	Heart rate variability	Inverse
	Non-sustained VT	Direct
Imaging	LV end-diastolic dimension	Direct

Table 3.1 (*Contd.*)

Category	Prognostic marker	Relationship
	Left atrial volume	Direct
	LV ejection fraction	Inverse
Haemodynamics	Peak VO_2	Inverse
	6 minute walk	Inverse
	Pulmonary capillary wedge pressure	Direct
	Cardiac output	Inverse
Neurohormones	Brain natriuretic peptide/NT-proBNP	Direct
	Atrial natriuretic peptide	Direct
	Norepinephrine (noradrenaline)	Direct
	Adrenomedullin	Direct
	Endothelin-1	Direct
Scoring systems	Heart Failure Survival Score	Inverse
	Seattle Heart Failure Model	Direct
	MAGGIC risk calculator	Direct

Key references

Chioncel O, et al. Epidemiology and one-year outcomes in patients with chronic heart failure and preserved, mid-range and reduced ejection fraction: an analysis of the ESC Heart Failure Long-Term Registry. *Eur J Heart Fail.* 2017;19:1574–1585.

McDonagh TA, et al. 2021 ESC guidelines for the diagnosis and treatment of acute and chronic heart failure. *EHJ.* 2021;42:3599–3726.

Simple clinical parameters

Demographics

Risk is greater in:

- Men.
- The elderly.
- The winter months.
- Social isolation.

Risk may fall in:

- Those with alcoholic cardiomyopathy abstaining from alcohol.

Coexisting disease

Risk is greater in patients with:

- Chronic renal failure.
- Ischaemic heart disease.
- Cachexia.
- Anaemia.
- Diabetes mellitus.
- Depression.
- Atrial fibrillation.

Clinical parameters

Risk is greater with:

- Increasing NYHA class.
- Increasing heart rate.
- Low blood pressure.
- Low body weight (cardiac cachexia).
- Third heart sound.
- Elevated JVP.
- Syncope.
- Clinical profile—wet-cold and wet-warm at the highest risk (see ➔ Chapter 25).
- Angina.
- Ventricular arrhythmias (VT/VF).

Non-invasive markers

Prognostic markers in blood tests include:
- High BNP/NT-proBNP (Fig. 3.1).
- Hyponatraemia.
- Increased troponin T or I.
- Anaemia.
- Increased uric acid.

Prognostic markers on ECG:
- Prolonged QRS duration (in particular LBBB).
- Ventricular arrhythmias.
- T-wave alternans testing—inability to perform the test is the most predictive of an adverse outcome!

Prognostic markers on imaging:
- Reduced LVEF.
- Dilated LV.
- iLA volume.
- Severe mitral or tricuspid regurgitation.

Markers in exercise testing:
- 6-minute walk test.
- Peak VO_2.

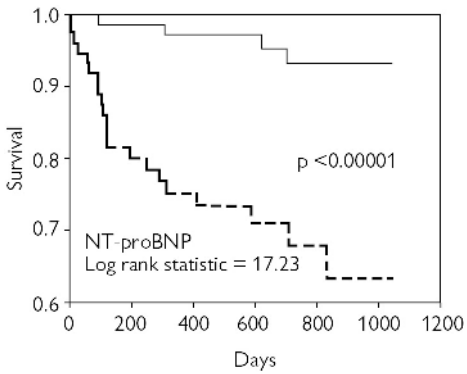

Fig. 3.1 Kaplan–Meier survival curve for NT-proBNP stratified above (broken line) and below (solid line) the median concentration, against all-cause mortality in 150 patients with advanced heart failure. Gardner RS, et al. N-terminal brain natriuretic peptide is a more powerful predictor of mortality than endothelin-1, adrenomedullin, and tumour necrosis factor-alpha in patients referred for consideration of cardiac transplantation. *Eur J Heart Fail.* 2005;7:253–260.

Invasive markers

The prognostic markers in right heart catheterization include:

- Increased pulmonary capillary wedge pressure.
- Pulmonary vascular resistance which has a linear relation to mortality and a pre-transplant PVR >3 Wood units has been shown to increase the risk of death following surgery.

The heart failure survival score (HFSS)

The HFSS is a composite scoring system developed and validated in 1997. It relies on all seven clinical parameters and stratifies patients into three categories of risk: low, medium, and high (Table 3.2). Patients in a high-risk category are thought to benefit from cardiac transplantation, whereas those in lower categories can be safely deferred.

Table 3.2 Heart failure survival score

Coronary artery disease (yes = 1; no = 0)	(..... × 0.6931) =	+
Intraventricular conduction delay (y = 1; n = 0)	(..... × 0.6083) =	+
Left ventricular ejection fraction (%)	(..... × –0.0464) =	+
Heart rate (bpm)	(..... × 0.0216) =	+
Na^+ concentration (mmol/L)	(..... × –0.0470) =	+
Mean arterial pressure (mmHg)	(..... × –0.0255) =	+
Peak VO_2 (mL/minute/kg)	(..... × –0.0546) =	
	HFSS =	.....

- High risk <7.19 35% 1-year survival.
- Medium risk 7.20–8.09 60% 1-year survival.
- Low risk >8.10 88% 1-year survival.

While the HFSS was developed and validated prior to the routine use of our current armamentarium of disease-modifying therapy, it has since been revalidated in more contemporary cohorts. However, NT-proBNP appears to be a better prognostic marker than the HFSS in patients with advanced heart failure.

Key references

Aaronson KD, et al. Development and prospective validation of a clinical index to predict survival in ambulatory patients referred for cardiac transplant evaluation. *Circulation*, 1997;95: 2660–2667.

Ahmad T, et al. Alerting clinicians to 1 year mortality risk in patients with heart failure: the REVEAL-HF randomized clinical trial. *JAMA Cardiol.* 2022;7:905–912.

Gardner RS, et al. N-terminal pro-brain natriuretic peptide. A new gold standard in predicting mortality in patients with advanced heart failure. *Eur Heart J.* 2003;24:1735–1743.

Gardner RS, et al. Who needs a heart transplant? *Eur Heart J* 2006;27:770–772.

Koelling TM, Joseph S, & Aaronson KD. Heart failure survival score continues to predict clinical outcomes in patients with heart failure receiving beta-blockers. *J Heart Lung Transplant.* 2004;23:1414–1422.

The Seattle heart failure model

The Seattle heart failure model (SHFM) was derived in the PRAISE-1 database of 1125 heart failure patients with the use of a multivariable Cox model. It was subsequently prospectively validated in five additional cohorts, ELITE-2, Val-HeFT, UW, RENAISSANCE, and INCHF, involving 9942 heart failure patients and 17, 307 person-years of follow-up (Figs. 3.2 and 3.3).

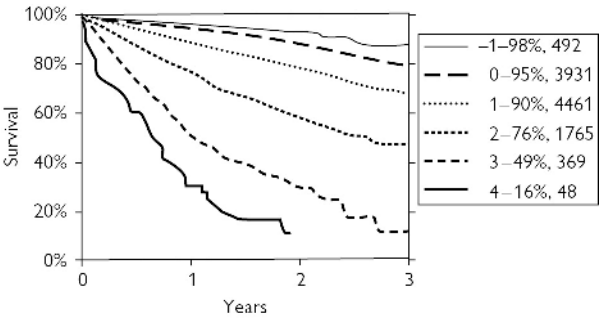

Fig. 3.2 The combined data set of the derivation and five validation cohorts for a Seattle Heart Failure Score rounded to –1 to 4. The score, the predicted 1-year survival for the score, and the number of patients with that score are shown. Levy WC, et al. The Seattle heart failure model: prediction of survival in heart failure. *Circulation*. 2006;113:1424–1433.

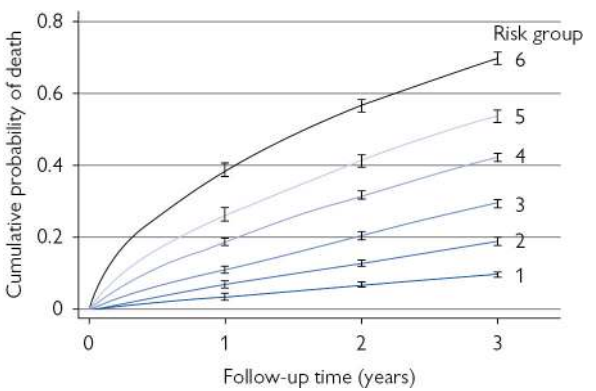

Fig. 3.3 The predicted effects on survival of sequentially adding medications and an ICD for a heart failure patient using the Seattle heart failure model. Levy WC et al. The Seattle heart failure model: prediction of survival in heart failure. *Circulation*. 2006;113:1424–1433.

The model accurately predicts survival of patients with HF with the use of commonly obtained clinical characteristics. Importantly, the validation cohorts included patients with a wide range of ages (14–100 years), EFs (1–75%), and heart failure symptoms (NYHA class I–IV).

The score includes the following variables:

- NYHA class.
- Ischaemic aetiology.
- Diuretic dose.
- LVEF.
- Systolic BP.
- Serum sodium.
- Haemoglobin.
- Percent lymphocytes.
- Uric acid.
- Serum cholesterol.

Renal function was not an independent predictor in this model and VO_2 was not included in the score as <1% of patients in these six data sets had this data available. Also of note is that the B-type natriuretic peptides were not included in the development of the model.

Key references

Levy WC, et al. The Seattle heart failure model: prediction of survival in heart failure. *Circulation.* 2006;113:1424–1433.

Web link: http://www.SeattleHeartFailureModel.org

The MAGGIC heart failure risk calculator

The MAGGIC (Meta-analysis Global Group In Chronic Heart Failure) heart failure risk calculator presents 1- and 3-year all-cause mortality estimates for people with chronic HF. It was constructed with research data for 39,372 patients collected from 30 cohort studies between 1980 and 2006.

Like the Seattle Heart Failure Score, the MAGGIC heart failure cohort included patients with a wide range of age, ejection fraction, and HF symptoms (NYHA class I–IV), but the MAGGIC risk calculator uses perhaps even more readily available variables (Table 3.3 and Fig. 3.4):

- Age
- Gender
- Presence of diabetes or COPD
- HF diagnosis within the last 18 months
- Current smoker
- NYHA class
- BMI
- Systolic blood pressure
- Creatinine
- LV ejection fraction
- Receiving (or not) ACEi/ARB and β-blockers.

Table 3.3 MAGGIC risk calculator chart to calculate the integer risk score for each patient

Risk factor	Addition to risk score								Risk score
Ejection fraction (%)	<20	20–24	25–29	30–34	35–39	40+			
	+7	+6	+5	+3	+2	0			
Extra for age (years)	<55	56–59	60–64	65–69	70–74	75–79	80+		
EF < 30	0	+1	+2	+4	+6	+8	+10		
EF 30–39	0	+2	+4	+6	+8	+10	+13		
EF 40+	0	+3	+5	+7	+9	+12	+15		
Extra for Systolic blood pressure (mm Hg)	<110	110–119	120–129	130–139	140–149	150+			
EF < 30	+5	+4	+3	+2	+1	0			
EF 30–39	+3	+2	+1	+1	0	0			
EF 40+	+2	+1	+1	0	0	0			
BMI (kg/m²)	<15	15–19	20–24	25–29	30+				
	+6	+5	+3	+2	0				
Creatinine (μmol/L)	<90	90–109	110–129	130–149	150–169	170–209	210–249	250+	
	0	+1	+2	+3	+4	+5	+6	+8	
NYHA Class	1	2	3	4					
	0	+2	+6	+8					
Male				+1					
Current smoker				+1					
Diabetic				+3					
Diagnosis of COPD				+2					
First diagnosis of heart failure in the past 18 months				+2					
Not on beta-blocker				+3					
Not on ACEI/ ARB				+1					
							Total risk score =		

Pocock SJ, et al. Predicting survival in heart failure: a risk score based on 39,372 patients from 30 studies. *Eur Heart J*. 2013;34:1404–1413.

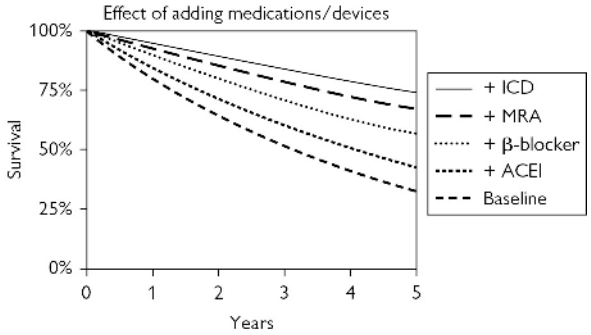

Fig. 3.4 Cumulative mortality risk over 3 years for patients classified into six risk groups from the MAGGIC risk calculator. Risk groups 1–4 represent the first four quintiles of risk (integer scores 0–16, 17–20, 21–24, and 25–28, respectively). Risk groups 5 and 6 represent the top two deciles of risk (integer scores 29–32 and 33 or more, respectively). 95% CIs are plotted at 1, 2, and 3 years' follow-up. Pocock SJ, et al. Predicting survival in heart failure: a risk score based on 39,372 patients from 30 studies. *Eur Heart J*. 2013;34:1404–1413.

Key references

Pocock SJ, et al. Predicting survival in heart failure: a risk score based on 39, 372 patients from 30 studies. *Eur Heart J*. 2013;34:1404–1413.

Web link: http://www.heartfailurerisk.org

Chapter 4

Non-pharmacological management

Education

Heart failure care is becoming increasingly complex, and the patients are usually elderly. Education of patients about their condition and its management is mandatory. Careful explanation of the diagnosis and the role of each of the management choices improves adherence with therapy. Where appropriate, discussion may extend to advance planning about end-of-life issues.

Discussion points should include:

- Diagnosis.
- Prognosis.
- Plan of investigation.
- Role of drug therapy.
- Importance of fluid management.
- Daily weight.
- Exercise training.
- Sexual activity.
- Work.
- Travel.
- Things to avoid—including smoking, vaping, and excess alcohol.

The extensive range of topics to be covered highlights the value of a multidisciplinary team approach (➔ Chapter 42). The different team members can tailor the topics to the individual patient's and their family's needs without haste and avoid information overload at initial consultations.

If a patient is hospitalized with an episode of acute decompensated heart failure, the multidisciplinary team should be involved in the discharge plan and follow-up.

Regular follow-up with the multidisciplinary team offers an opportunity for assessment of the development of depressive illness or stress. If depression develops and requires pharmacological intervention, then the selective serotonin reuptake inhibitors are the preferred therapy.

The involvement of a multidisciplinary team in the care of an individual receives the strongest recommendation within the recent European Society of Cardiology (ESC) heart failure guidelines. This status stresses the importance of this intervention in the successful long-term care, particularly in minimizing heart failure (HF) hospitalizations.

Lifestyle modification

Unusually for cardiology, there is very little prospective, randomized controlled trial evidence to quote when discussing advice about patient lifestyle modification. However, many of the recommendations reflect sensible health advice.

Irrespective of the aetiology of the patient's heart failure, they should be advised to:

- Stop smoking.
- Reduce alcohol consumption (<2 units per day for men and <1 units per day for women), except for alcohol related cardiomyopathy where abstinence from alcohol should be advocated.
- In obese patients, weight loss is advised, particularly if there is sleep-disordered breathing.
- Limit salt intake to <3 g/day.
- Limit fluid intake to <1.5 litres per day if there is evidence of fluid retention. This can be relaxed to <2 litres/day in hot weather.

Patients should be advised to keep a daily weight chart to facilitate early detection of decompensation of their heart failure. This can be combined with advice about patient-titrated diuretic therapy. Patients are normally advised to increase their diuretic therapy by 40 mg of furosemide or equivalent if the weight increases by 1 kg over each of two consecutive days.

Exercise

A vicious cycle is established in chronic HF. Reduced perfusion in skeletal muscle triggers skeletal muscle dysfunction, reducing exercise capacity. The reduced exercise capacity further deconditions the patient, worsening the HF, and so the skeletal muscle hypoperfusion.

There is a convincing body of evidence that exercise training in heart failure improves symptoms and quality of life. There is some evidence from meta-analyses that it may even reduce hospitalization and improve survival, although some uncertainty persists.

Exercise training is recommended, in conjunction with pharmacological therapy, in all patients with HF who are able regardless of LVEF.

Key references

Gottlieb SS et al. Effects of exercise training on peak performance and quality of life in congestive heart failure patients. *J Cardiac Failure*. 1999;5:188–194.

Kitzman DW et al. Physical rehabilitation for older patients hospitalized for heart failure. N Engl J Med. 2021;385:203–216.

Van der Meer S et al. Effect of outpatient exercise training programmes in patients with chronic heart failure: a systematic review. *Eur J Prev Cardiol.* 2012;19:795–803.

Future care planning

Future care planning, or anticipatory care planning as previously called, is an important aspect of the holistic care of people with long-term conditions, including HF. It seeks to empower the individual with information about their likely prognosis and the potential trajectory of their health. This allows them to share their wishes about care with family and caregivers. It also allows them to ensure that their affairs are in order, for example, with plans for their children, property, and assets.

Future care planning was previously seen as the realm of palliative care. However, it is recognized that all the healthcare specialists involved in care should ensure that patient education is part of their role. We should not wait until a person's health has deteriorated towards end stage before mention is made of future care planning. Rather, it should be a thread through all consultations that is sympathetic to the person's wishes and stage of understanding.

Future care planning should be responsive to the stage of the patient's disease. In advanced HF, consideration of cardiac transplantation or mechanical circulatory support may be appropriate, but so may discussions about resuscitation, or deactivating the defibrillator component of devices, or withdrawing therapies that do not benefit symptoms or quality of life. Time should be taken to discuss where end-of-life care is preferred. All of this information should be shared with the care team. Signposting to possible social care support should be available.

Key references

Advance Care Planning. Understanding heart failure guidelines. https://www.hfpolicynetwork.org/wp-content/uploads/Understanding-HF-guidelines-Advance-care-planning.pdf

Nishikawa Y et al. Advance care planning for adults with heart failure. *Cochrane Database Syst Rev.* 2020;2:CD013022.

Sexual activity

Patients may express anxiety about sexual activity after a diagnosis of HF is made. In patients with stable, compensated NYHA I–II HF, sexual activity is considered safe. NYHA III–IV suggests that symptoms of HF may preclude sexual activity.

In coronary artery disease and HF, patients with angina should be advised to avoid sexual activity that induces chest pain and reminded that the use of nitrates absolutely contraindicates the use of sildenafil and other phosphodiesterase-5 inhibitors.

The use of β-blockers may increase the likelihood of impotence. Referral to a specialist impotence clinic may be appropriate, as there are many pharmacological and non-pharmacological aids that may be of benefit.

Hypertrophic cardiomyopathy (HCM) is a specific condition that requires risk stratification before advising the patient about sexual activity. Because of the possibility of syncope or sudden cardiac death related to exertion, an exercise test and echocardiogram are useful in risk stratification. Of note, exercise programmes involving mild to moderate activity have now demonstrated safety, as well as evidence of functional improvement and improved quality of life in symptomatic and asymptomatic HCM.

Patients with an implantable cardioverter defibrillator (ICD) or CRT-D implanted should be aware of the small risk of device activation related to sexual activity. They should be advised that their partner would not receive a painful shock. However, the partner may be aware of the shock or a muscle spasm, which while startling, will not be painful! Normal post-shock advice should then be instituted with emergency services being contacted if the patient remains unstable. If the patient is well, the local cardiology service should be contacted within 24 hours for a device check.

Employment

As part of the assessment of a patient with HF it is important to address their employment status. If their job is predominantly sedentary, then it should be possible to continue despite their diagnosis. Physical jobs may require review and support in considering alternative employment.

If the severity of symptoms precludes full-time employment, then the multidisciplinary team may be able to assist in negotiating reduced hours, retraining, or identifying relevant social security benefits.

Travel advice

Patients with stable, compensated HF may be reassured about their safety to travel. However, they should be advised to ensure that they have adequate medical cover included in their travel insurance and that the insurance company is aware of their diagnosis. General travel advice should include carrying a written medical report and a full supply of medication for the trip in original containers with a list of medications in their hand luggage.

The mode of travel should be considered. Travel by car will allow route planning to facilitate the needs of a diuretic user. They should be encouraged to stop every 2–3 hours and mobilize to reduce the development of dependent oedema and deep venous thrombosis. Rail travel makes these considerations easier to accommodate. Patients should be advised about how to modify their diuretics and fluid intake in hot climates.

Passengers using air travel should be similarly advised. The additional considerations for flights include whether oxygen will be required (British Thoracic Society Guidelines). A further issue for an increasing number of patients with HF is that they may have an implantable device that could trigger airport security systems. They should carry their device card with them at all times and present it to the security staff. A manual search is then performed.

Preparation and planning of travel can reduce the stress for all concerned: for example, would wheelchair assistance around the airport help?

Immunization

Heart failure is associated with pulmonary oedema and pulmonary hypertension. These increase the risk of developing a pulmonary infection that is poorly tolerated because of the cardiac comorbidity. Immunization of HF patients against influenza has been shown to reduce hospitalization for decompensated heart failure by 37%.

It is advised that patients with HF should receive:

- Pneumococcal vaccine.
- Annual influenza and COVID immunization.

Nutrition

As detailed in ➔ Chapter 14, there are specific cardiomyopathies that result from nutritional deficiencies, e.g. beriberi (vitamin B_1/thiamine). Dietary advice is obviously crucial in the management of these patients.

All patients with HF could benefit from nutritional advice in terms of nutritional balance, calorie restriction in the obese and nutritional supplementation in cardiac cachexia.

Oxygen and aviation

Air travel has become a routine feature of life. Most flights are pressurized to cabin altitudes of 8000 ft with a reduction in partial pressure of oxygen to result in an inspired oxygen content of 15.1%. The diagnosis of HF may indicate that the patient is more at risk from this reduced oxygen tension, as found in commercial aircraft.

Careful assessment of patients is required. Patients should be stable and remote from recent hospitalizations with decompensated HF. Patients with severe disease in NYHA functional class IV should not fly unless essential. Patients who require more than 4 L/min of oxygen cannot fly. More information can be found in the referenced articles below.

Key references

Coker RK et al. BTS Clinical Statement on air travel for passengers with respiratory disease. *Thorax*. 2022;77:329–350.

Mortazavi A et al. Altitude-related hypoxia: risk assessment and management for passengers on commercial aircraft. *Aviat Space Environ Med*. 2003;74:922–927.

Chapter 5

Pharmacological management

The key drugs

The medical treatment of heart failure has been revolutionized by large randomized controlled clinical trials studying the effects of antagonists of the renin–angiotensin–aldosterone and sympathetic nervous systems. These drugs now form the cornerstones in the management of the condition.

The individual pharmacology and evidence for use of specific drugs are covered in Chapters 32–40. In heart failure with reduced ejection fraction (HFrEF), the core-4 or 4-pillars: ARNI (or ACEi), beta-blocker, MRA, and SGLT2 inhibitor should be initiated as quickly but as safely as possible. Drugs to avoid in patients with HF are discussed later in the book.

Angiotensin receptor neprilysin inhibitors (ARNI)

(See also Chapter 33.)

- The angiotensin receptor neprilysin inhibitor sacubitril valsartan is one of the first-line agents for patients with HFrEF (Table 5.1).
- Reduced both HF hospitalization and mortality compared to enalapril in the PARADIGM-HF trial.
- Use with caution in patients with significant renal disease.
- Angioedema with previous use is an absolute contraindication.
- Avoid concomitant use of an ACE inhibitor.
- When switching from an ACE inhibitor, ensure at least a 36-hour washout period.

How to use sacubitril valsartan in clinical practice

- ARNIs can usually be safely started in the outpatient or inpatient setting (when haemodynamically stable).
- Start at a medium dose and uptitrate to target after 2 weeks if blood pressure and renal function allow and no symptoms of hypotension.
- It is advisable to stop potassium-sparing diuretics prior to the commencement of an ARNI.
- Often, in elderly or frail patients, reducing the loop diuretic by one increment facilitates the introduction of sacubitril valsartan.
- Check renal function within 1 week.
- Beware of hyperkalaemia.

Angiotensin-converting enzyme inhibitors (ACEi)

(See also Chapter 32.)

- These were first-line agents for all patients with heart failure due to left ventricular systolic dysfunction (LVSD)—this is also true in patients with asymptomatic LVSD. However, their use has largely been replaced by sacubitril valsartan in those with HFrEF due to the results of PARADIGM-HF.

Table 5.1 Titration steps for sacubitril valsartan

Drug	Start dose (mg)	Target dose (mg)
Sacubitril/valsartan	49/51* bd	97/103 bd

*24/26 mg can be used as a starting dose in selected patients (e.g. low blood pressure, RAASi naïve, or CKD)

Table 5.2 ACE inhibitors with an evidence base in LVSD and their suggested dosing

Drug	Start dose (mg)	Target dose (mg)	Frequency
Captopril	6.25	50–100	tds
Enalapril	2.5	10–20	bd
Ramipril	1.25	5	bd
Trandolapril	0.5	4	od
Lisinopril	2.5	30–35	od

- ACEi unequivocally reduce both morbidity and mortality in clinical trials with an average relative risk reduction of 20–25%.
- Use with caution in patients with significant renal disease.
- Angioedema with previous use is an absolute contraindication.
- Drugs with proven efficacy in clinical trials are captopril, enalapril, ramipril, lisinopril, trandolapril (Table 5.2).

How to use ACE inhibitors in clinical practice

- ACE inhibitors can usually be safely started in the outpatient setting.
- Start at a low dose and up-titrate at weekly/fortnightly intervals as blood pressure and renal function allow and no symptoms of hypotension.
- It is advisable to stop potassium-sparing diuretics prior to commencement of ACEi.
- Often, in elderly or frail patients, stopping the loop diuretic facilitates the introduction.
- Check renal function within 1 week.
- Beware of hyperkalaemia.
- Watch for ACEi-induced cough (5–10%).
- Use with caution in aortic stenosis.
- Symptomatic hypotension can be minimized by nocturnal dosing.

Worsening renal function

- Some increase in urea, creatinine, and potassium is to be expected after initiation of an ACE inhibitor; if an increase is small and asymptomatic no action is necessary.
- An increase in creatinine of up to 50% above baseline, or 266 μmol/L (3 mg/dL), whichever is the smaller, is acceptable.
- An increase in potassium to a value <5.5 mmol/L is acceptable.
- If urea, creatinine, or potassium do increase excessively, consider stopping concomitant nephrotoxic drugs (e.g. NSAIDs), other potassium supplements/retaining agents and, if no signs of congestion, reducing the dose of diuretic.
- If greater increases in creatinine or potassium than those outlined previously persist despite adjustment of concomitant medication, the dose of the ACE inhibitor should be halved and blood chemistry rechecked within 1–2 weeks; if there is still an unsatisfactory response, specialist advice should be sought.

- If potassium increases to >5.5 mmol/L or creatinine increases by >100% or to above 310 μmol/L (3.5 mg/dL) the ACE inhibitor should be stopped and specialist advice sought.
- Blood chemistry should be monitored frequently and serially until potassium and creatinine have plateaued.

β-adrenoceptor antagonists

(➔ See also Chapter 35.)

- These are also mandatory drugs for all patients with heart failure due to LVSD (this is also true in patients with asymptomatic LVSD postmyocardial infarction).
- They unequivocally reduce both morbidity and mortality in clinical trials with a 35% relative risk reduction on average.
- They can be used in patients with COPD but are contraindicated in patients with significant reversible airways obstruction (check pulmonary function tests).
- Peripheral vascular disease is not a contraindication to β-adrenoceptor antagonist therapy.
- Drugs with proven efficacy in clinical trials are carvedilol, bisoprolol, metoprolol CR/XL, and nebivolol (Table 5.3).

How to use beta-adrenoceptor antagonists in clinical practice

- Can be initiated safely in the outpatient setting.
- In patients with more advanced disease, or those who are elderly/frail, inpatient commencement should be considered.
- Start at a low dose and uptitrate every 2–4 weeks, provided pulse >50/minute and systolic BP >90 mmHg.
- Use with caution in first-degree heart block.
- Contraindicated in higher degrees of heart block.
- Do not commence in decompensated heart failure (e.g. in patients with pulmonary or peripheral oedema, or in the ITU setting on inotropes).
- Titrate to the maximum tolerated dose (➔ Chapter 35).
- In patients on β-adrenoceptor antagonists admitted with decompensated heart failure, continue the current dose if possible, or

Table 5.3 β-adrenoreceptor antagonists with an evidence base in CHF and their suggested dosing

Drug	Start dose (mg)	Up-titration steps (mg)	Target dose (mg)	Frequency
Carvedilol	3.125	6.25–12.5 to 25–50*	25/50*	bd
Bisoprolol	1.25	2.5–5 to 7.5–10	10	od
Metoprolol	12.5†/25	25–50 to 100–200	200 CR/XL	od
Nebivolol	1.25	2.5–5 to 10	10	od

* In patients over 85 kg.

† In patients in NYHA class III/IV.

reduce one dose decrement. Only stop the β-adrenoceptor antagonist if absolutely necessary.

► Evidence base is only for metoprolol succinate not tartrate, which is the shorter-acting preparation available in the United Kingdom.

Mineralocorticoid receptor antagonists (MRAs)

(See also Chapter 36.)

- These are for NYHA II–IV patients with CHF due to LVSD.
- They reduce both morbidity and mortality in clinical trials by 30%.
- The drugs with proven efficacy in HFrEF are spironolactone and eplerenone. There is now also evidence for finerenone in HFmrEF/HFpEF.

How to use MRAs in clinical practice

- Use with caution if the baseline creatinine is >221 μmol/L.
- Monitor within 1 week after starting for renal dysfunction and hyperkalaemia.
- Use with caution in the elderly.
- Stop MRA temporarily during episodes of diarrhoea and/or vomiting.
- Men may experience painful gynaecomastia with spironolactone; in these cases, eplerenone can be substituted.

SGLT2 inhibitors

(See also Chapter 37.)

- These are one of the core-4 therapies for symptomatic HFrEF patients.
- There is also evidence that SGLT2 inhibitors improve outcomes in patients with HFmrEF and HFpEF.
- The drugs with proven efficacy are dapagliflozin, empagliflozin.
- **How to initiate**
  - Recommended in symptomatic patients with HF across the spectrum of LV ejection fraction (Table 5.4).
  - Monitor blood pressure—aim for systolic BP >90 mmHg.
  - Monitor renal function—a small, reversible reduction in eGFR can be expected on initiation.
  - Monitor glucose in those with type II diabetes on other diabetic drugs, which may predispose to hypoglycaemia.
  - Monitor fluid balance—diuretic effect at initiation, so may require diuretic dose alteration.
  - No dose up-titration is required (dapagliflozin and empagliflozin).
  - Sick day rules—discontinue if unable to maintain fluid intake and resume with normal diet.

Table 5.4 SGLT2 inhibitor dosing in HF and renal impairment

Drug	Dose (mg)	Dose adjustment in renal impairment	Studied lower eGFR threshold
Dapagliflozin	10 mg od	No	25
Empagliflozin	10 mg od	No	20
Sotagliflozin*	200–400 mg	No	25

*Not licensed in the United Kingdom.

Contraindications to initiation

- Pregnancy or breastfeeding.
- Severe CKD (eGFR <15 mL for dapagliflozin or eGFR <20 mL for empagliflozin).
- Symptoms of hypotension or SBP <95 mmHg.

NOTE: SGLT2 inhibitors are not recommended in patients with Type 1 diabetes.

Adverse effects

- Genital mycotic infections (5–15% and more common in females).
- Diabetic ketoacidosis (rare and in trials only in those with diabetes; can be euglycaemic).

Angiotensin receptor antagonists (ARB)

(➔ See also Chapter 34.)

- These can be used in patients with ACEi intolerance due to cough or due to angioedema; they produce similar reductions in cardiovascular endpoints to ACEi.
- They cause similar amounts of renal dysfunction as ACEi.
- Again, start at a low dose and uptitrate, checking renal function and blood pressure.
- Drugs with proven efficacy are: losartan, valsartan, and candesartan.
- ARBs can also be added to ACEi in patients who remain symptomatic but are intolerant to MRAs. However, it is now correct practice to use ARNI (or ACEi), β-blockers, and MRA in the first instance.

Diuretics

(➔ See also Chapter 38.)

- In general, this is loop diuretic therapy, that is, furosemide, bumetanide, or torasemide.
- These are for the relief of symptoms and signs of pulmonary or peripheral congestion.
- Use the minimum dose necessary to render the patient euvolaemic.
- Side effects to look out for are renal dysfunction, hypokalaemia, hyponatraemia, hyperglycaemia, and gout—⚠ monitor U&Es.
- Rather than increasing to industrial doses (i.e. >80 mg bd furosemide or equivalent), add a thiazide diuretic (e.g. bendroflumethazide 2.5 mg) or metolazone (2.5–5 mg) to block differing sites in the nephron and overcome diuretic resistance.
- With this strategy, monitor U&Es carefully.
- Remember to advise patients to adhere to a fluid restriction (➔ Chapter 4).
- Patients should be encouraged to tailor their diuretic therapy according to weight and needs.

General principles for use of key drugs

- Aim to establish patients on the core-4 therapies (ARNI [or ACEi], beta-blocker, MRA, and SGLT2 inhibitor) as quickly but as safely as possible. Remember to seek specialist advice, especially in patients with more advanced heart failure or more complex drug regimens.
- It is better to achieve small doses of ARNI and β-adrenoreceptor, rather than a larger dose of either alone.
- Optimum pharmacological therapy is best achieved within a multidisciplinary management programme, where up-titration and monitoring can be rigorously adhered to (Section VI).
- Particularly with combinations of disease-modifying therapy, careful monitoring of renal function should be undertaken.
- The flow diagram of pharmacotherapy is summarized in Figs. 5.1 (HFrEF), 5.2 (HFmrEF), and 5.3 (HFpEF).

European Society of Cardiology HF Guidelines 2021. McDonagh TA et al. *Eur Heart J* Sep 21;42(36):3599–3726 by permission of Oxford University Press.

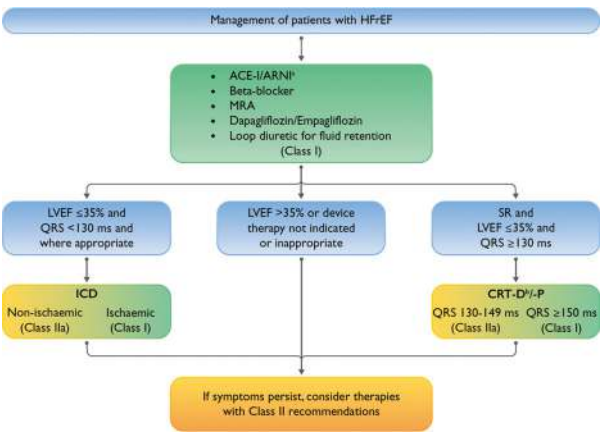

Fig. 5.1 Therapeutic algorithm of Class I therapy indications for a patient with heart failure with reduced ejection fraction. ACE-I = angiotensin-converting enzyme inhibitor; ARNI = angiotensin receptor neprilysin inhibitor; CRT-D = cardiac resynchronization therapy with defibrillator; CRT-P = cardiac resynchronization therapy with pacemaker; ICD = implantable cardioverter-defibrillator; HFrEF = heart failure with reduced ejection fraction; MRA = mineralocorticoid receptor antagonist; [a]As a replacement for ACE-I. [b] Where appropriate. Class I = green. Class IIa = yellow.

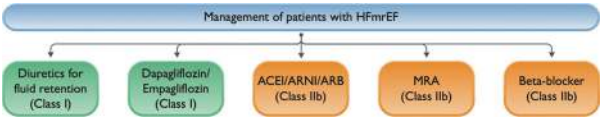

Fig. 5.2 Management of patients with heart failure with mildly reduced ejection fraction. ACE-I = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; ARNI = angiotensin receptor neprilysin inhibitor; HFmrEF = heart failure with mildly reduced ejection fraction; MRA = mineralocorticoid receptor antagonist. McDonagh et al. *Eur Heart J* 2023 Oct 1;44(37):3627–3639.

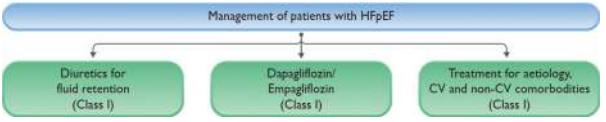

Fig. 5.3 Management of patients with heart failure with preserved ejection fraction. CV, cardiovascular; HFpEF, heart failure with preserved ejection fraction. McDonagh et al. *Eur Heart J* 2023 Oct 1;44(37):3627–3639.

Other drug options

Ivabradine

(See also ➔ Chapter 39.)

- Can be considered for patients in NYHA II–IV heart failure, with a heart rate ≥70/min in sinus rhythm, and LVEF ≤35%, *despite* treatment with evidence-based doses of disease-modifying therapy:
  - ARNI (or ACE inhibitor).
  - Beta-blocker.
  - Mineralocorticoid receptor antagonist.
  - SGLT2 inhibitor.
- May be considered to reduce the risk of HF hospitalization in patients in sinus rhythm with an EF ≤35% and a heart rate ≥70/min who are unable to tolerate a beta-blocker (e.g. true asthmatics). Patients should also receive an ACE inhibitor (or ARB) and an aldosterone antagonist.

Hydralazine and nitrates

(See also ➔ Chapter 41.)

- Consider using this in the case of patients intolerant to ARNI, ACE inhibitors, and angiotensin receptor antagonists.
- Consider this as an additional agent to standard medical therapy for CHF (ACE/ARB plus β-blocker and/or aldosterone antagonists) in African Americans.

Digoxin

(See also ➔ Chapter 39.)

- The role of digoxin appears less clear.
- Introduce digoxin in patients who remain symptomatic, for example, with frequent hospitalizations despite maximal medical therapy, or to provide rate control to patients with atrial fibrillation (AF).
- It should be avoided in those with ventricular arrhythmias.

Vericiguat

(See also ➔ Chapter 40.)

- Vericiguat may be considered in patients in NYHA class II–IV HFrEF who have had worsening HF despite treatment with an ACEi (or ARNI), a beta-blocker, and an MRA to reduce the risk of CV mortality or HF hospitalization, although the effects seen in the VICTORIA trial were modest. The results of the VICTOR trial are awaited.

Antiplatelet and anticoagulants

- The role of antiplatelet agents in heart failure is currently uncertain.
- The role for long-term use of aspirin post-MI is not known, as the benefit of aspirin lessens 6–12 months post-MI.
- Aspirin may actually worsen outcomes in CHF patients due to:
  - Prostaglandin inhibition → adverse hemodynamic and renal effects, leading to more frequent HF hospitalizations.
- The benefits of warfarin therapy in CHF are currently uncertain, except in patients with AF or known LV thrombus.

- The use of novel anti-thrombotics (e.g. dabigatran) has not been formally tested in heart failure patients. However, subgroup analysis from the RE-LY trial in AF suggests equivalence to warfarin.

Statins

- The role of statins in heart failure has been cast in doubt after two large randomized controlled trials (GISSI-HF and CORONA)—which included patients with heart failure of an ischaemic aetiology—did not show an improved prognosis with rosuvastatin.

Drugs to use with caution or avoid

α-adrenoreceptor antagonists (e.g. doxazosin and prazosin) have no role in the treatment of HF and may exacerbate it.

Anti-arrhythmic drugs: The majority of anti-arrhythmic drugs have negatively inotropic effects and can cause a deterioration in HF. Due to their beneficial effects in HF, β-blockers should be considered first line. The pro-arrhythmic nature of HF is exacerbated by some of the anti-arrhythmics, particularly those with class I actions (e.g. flecainide). In supraventricular arrhythmias, sinus rhythm may be maintained using amiodarone or dofetilide (not licensed for use in the UK), but not dronedarone. This was shown to increase mortality in patients with moderate to severe heart failure, when the ANDROMEDA (Antiarrhythmic Trial with Dronedarone in Moderate to Severe CHF Evaluating Morbidity Decrease) study was stopped early on the recommendations of the study's steering committee and independent data safety and monitoring board. Consideration should be made of the possibility of radio-frequency ablation to cure the arrhythmia. If AF is the accepted rhythm, then rate control can usually be achieved by one of the accepted β-blockers and with digoxin if required. Patients with ventricular arrhythmias should be considered for an ICD.

β-blockers: The use of carvedilol, bisoprolol, and metoprolol CR/XL in the management of LVSD is well established. However, β-blockers with intrinsic sympathomimetic activity (e.g. pindolol and acebutolol) should be avoided as they can cause deterioration in heart failure status.

Calcium channel blockers (except amlodipine and felodipine) are negatively inotropic and can be associated with decompensation of heart failure and increased mortality. Amlodipine or felodipine may be used in patients with HF and poorly controlled angina or hypertension. However, patients should be advised of the higher incidence of leg oedema with these agents.

Cilostazol: a phosphodiesterase inhibitor that has arterial vasodilator effects—is licensed for the treatment of intermittent claudication. Based on studies of other phosphodiesterase inhibitors that have demonstrated increased mortality in HF, the FDA have advised that cilostazol should not be prescribed to any patient with a diagnosis of HF.

Corticosteroids should be prescribed with care, as the balance between beneficial effects and detrimental effects in terms of fluid balance needs to be established.

Homeopathic remedies: Caution should be advised in the use of homeopathic remedies, particularly those with catecholamine-like actions (ma huang, ephedra, and ephedrine and its metabolites). Other natural remedies may have significant interactions with anticoagulants (e.g. St John's wort, *Gingko biloba*, ginseng, and homeopathic garlic), digoxin (e.g. hawthorne and St John's wort), β-blockers, vasodilators, and anti-arrhythmics.

Non-steroidal anti-inflammatory drugs (NSAIDs) are associated with deterioration of HF symptoms by systemic vasoconstriction. Although they are not thought to cause HF, they may cause renal dysfunction, or exacerbate renal dysfunction associated with ACE inhibitors, angiotensin receptor blockers, and aldosterone antagonists.

Oral hypoglycaemic agents: Thiazolidinediones (e.g. rosiglitazone and pioglitazone) should not be used in patients with HF.

Phosphodiesterase-5 inhibitors such as sildenafil are established treatments for erectile dysfunction in men. They can cause systemic hypotension and are therefore contraindicated if the patient is taking any nitrate preparation or an α-blocker. A small study of sildenafil in men with NYHA II or III HF suggested that the reduction in blood pressure was small (6mmHg) and asymptomatic.

Recreational drugs: Patients with HF should be advised to abstain from illicit drugs including cocaine and amphetamines which may cause an acute decompensation of their heart failure symptoms.

Chapter 6

Device therapy

Introduction

The majority of patients with HFrEF stabilize or improve with pharmacological therapy. Device therapy in heart failure addresses two potential consequences of left ventricular dysfunction, namely malignant ventricular arrhythmias (or potentially, bradycardia) that can lead to sudden cardiac death (SCD) and ventricular dyssynchrony. These two phenomena can coexist in the CHF patient. Implantable cardiac defibrillators (ICDs) address the issue of malignant ventricular arrhythmias or bradycardia that might cause SCD and cardiac resynchronization therapy (CRT) is aimed at those with dyssynchrony.

Cardiac resynchronization therapy pacing (CRT-P), also known as biventricular pacing, has a clear role in selected patients with heart failure who remain symptomatic despite maximum tolerated pharmacological therapy. Implantable cardiac defibrillators (ICD) have also been shown to reduce arrhythmic deaths in both ischaemic and non-ischaemic cardiomyopathy, although enthusiasm has waned in this latter category due to the effect of contemporary medical therapy on sudden death. CRT-P can be combined with ICD functions (cardiac resynchronization therapy-defibrillator: CRT-D) to achieve the benefits of both devices, although, interestingly, CRT-P has also been shown to reduce SCD, despite the absence of a defibrillator function.

The implantation of any of these devices carries with it the usual risks associated with pacemaker implantation: infection and lead displacement being the most common; and also the need for regular hospital contact, albeit most devices implanted currently can be followed up remotely. While the risk of complications is relatively low, mainly causing minor inconvenience, it does highlight the importance of appropriate patient and device selection.

Dual chamber pacing in heart failure

Standard dual chamber pacing was investigated as a potential therapeutic intervention that might facilitate:

- More aggressive use of beta-blockers.
- Optimization of atrioventricular delay, reducing mitral regurgitation.

The DAVID study compared VVI pacing (lower rate limit of 40 bpm) with DDDR pacing (lower rate limit of 70 bpm) after implantation of an ICD. At the time of data analysis, it was realized that the DDDR group had been paced 60% of the time while the VVI group were only paced 1% of the time. Thus, the study demonstrates the effect of DDDR pacing compared to sinus rhythm. A significantly higher number of patients died or were hospitalized with heart failure in the group who were DDDR paced (27%, versus 16% in the VVI group). Such pacing is thought to induce mechanical dyssynchrony by effectively causing left bundle branch block (LBBB). Therefore, standard dual chamber pacing is not recommended as a therapy for heart failure.

In patients who require pacing for the treatment of bradycardia, the guidelines recommend CRT rather than RV pacing in those with HFrEF. If not, then dual chamber pacing should be used as backup only with pacing algorithms set to minimize unnecessary pacing.

Key reference

Wilkoff BL, et al. Dual-chamber pacing or ventricular backup pacing in patients with an implantable defibrillator: the Dual Chamber and VVI Implantable Defibrillator (DAVID) Trial. *JAMA*. 2002;288:3115–3123.

Dyssynchrony

CRT aims to address the problem of ventricular dyssynchrony in heart failure. Dyssynchrony is a complex phenomenon. It can be thought of as occurring at three interrelated levels:

- *Electrical dyssynchrony* consists of inter- or intraventricular conduction delay.
  - Usually electrical dyssynchrony manifests as a LBBB.
  - LBBB occurs in ~24% of patients with LV systolic dysfunction.
  - It becomes more common as the severity of the LVSD increases (38% of patients with moderate to severe HF).
  - The mortality of HF increases in proportion to the QRS width.
- *Structural dyssynchrony* results from the disruption of the myocardial collagen matrix impairing electrical conduction and mechanical efficiency.
- *Mechanical dyssynchrony* manifests as regional wall motion abnormalities leading to:
  - Increased workload and stress.
  - Paradoxical septal wall motion.
  - Presystolic mitral regurgitation.
  - Reduced diastolic filling times.

These features of dyssynchrony further exacerbate systolic dysfunction. Atrioventricular conduction delay that often occurs in heart failure is also associated with features that adversely affect systolic function:

- Loss of 'top up' from atrial systole at the end of ventricular diastole. In atrial fibrillation this has been shown to reduce cardiac output by 25–40%.
- Atrioventricular delay results in delayed closure of the mitral valve with resultant mitral regurgitation.

The subject is made more complicated by the observation that not all patients with LBBB have evidence of mechanical ventricular dyssynchrony and a small proportion of patients with a normal QRS duration do have echocardiographic evidence of dyssynchrony.

However, the PROSPECT trial demonstrated that echocardiographic parameters of dyssynchrony have striking variability, poor reproducibility, and limited predictive power when applied in clinical practice. Furthermore, EchoCRT has shown us that implanting CRT in patients with echocardiographic evidence of dyssynchrony, but a narrow QRS (<130 ms) can lead to an adverse outcome. As such, patient selection should use the parameter prospectively validated in landmark clinical trials, and meta-analyses: the QRS duration.

LBBB, and potentially other forms of intraventricular conduction delays that result in ventricular dyssynchrony, can be reversed by pacing both ventricles. Cardiac resynchronization therapy (CRT) can also address the atrioventricular conduction delay that often occurs in heart failure.

Cardiac resynchronization therapy

CRT typically uses leads in the right atrium, right-ventricular apex, and the coronary sinus. The coronary sinus lead paces the left ventricular free wall.

CRT has been shown to improve:

- Quality of life.
- Left-ventricular ejection fraction.
- Exercise capacity.
- Contractile function.
- Reverse LV remodelling.

CRT has been shown to reduce:

- Hospital admissions.
- Mortality in NYHA II–IV.
- Pulmonary capillary wedge pressure.

All these changes in haemodynamics result in improved myocardial efficiency and reduced myocardial oxygen demand. After implantation of CRT, cessation of resynchronization for only 72 hours results in marked deterioration of the rate of rise of left-ventricular systolic pressure and mitral regurgitation. For maximal effects to be obtained, biventricular pacing should be achieved as near to 100% of the time as is possible.

Indications

Current ESC guidelines *recommend* (Class I) CRT in the following patients:

- Symptomatic patients with heart failure despite optimal medical therapy (OMT).
  - LVEF ≤35%.
  - Sinus rhythm.
  - LBBB ≥150 ms.
- CRT *should be considered* (class IIa) in symptomatic patients with heart failure on OMT with:
  - LVEF ≤35%.
  - Sinus rhythm.
  - QRS duration 130-149 ms in LBBB, or ≥150 ms in non-LBBB.
- CRT *may be considered* (class IIb) in symptomatic patients with heart failure on OMT with:
  - LVEF ≤35%.
  - Sinus rhythm.
  - QRS duration >130 ms in non-LBBB.

These criteria derive from the landmark clinical trials that established the morbidity and mortality benefits of CRT-P and CRT-D (Table 6.1). However, approximately 30% of patients have been reported not to improve with CRT (non-responders). It is difficult to know what 'non-response' is, as patients may have otherwise been dead, or have symptoms attributable to comorbidities. Genuine reasons for non-response include:

- Incorrect patient selection (i.e. narrow QRS, non-LBBB).
- Poor LV lead position.
- Failure to achieve adequate BiV pacing (e.g. atrial arrhythmias, frequent ventricular ectopy).

Table 6.1 Trials of CRT-P ± D and HF

	No. of patients	LVEF (%)	Follow-up (months)	Key finding
MUSTIC (2001)	67	23	3	CRT-P improved 6 MWT
MIRACLE (2002)	453	24	6	CRT-D improved QoL, NYHA, and 6 MWT
PATH-CHF (2002)	42	21	12	No difference between CRT and LV pacing
CONTAK-CD (2003)	490	21	6	CRT-P improved peak VO_2 and 6 MWT
MIRACLE-ICD (2003)	369	24	6	CRT-D improved QoL, NYHA, and peak VO_2
PATH-CHF II (2003)	101	23	3	CRT-P in QRS duration >150 ms improved peak VO_2, 6 MWT, and QoL
COMPANION (2004)	1520	22	17	CRT-P and CRT-D reduced time to death and CHF hospitalization; CRT-D also reduced ACM
CARE-HF (2005)	813	26	29	CRT-P reduced ACM, improved LVEF, and QoL
MADIT-CRT (2009)	1820	24	29	CRT-D reduced ACM/HF events more than ICDs
RAFT (2010)	1798	23	40	CRT-D reduced ACM and hospitalization more than ICDs

ACM: all-cause mortality; CRT-P(D): cardiac resynchronization therapy pacemaker (defibrillator); LVEF: left ventricular ejection fraction; 6-MWT: 6-minute walk test.

Only a small proportion of patients included in CRT trials had a narrower QRS duration. Subsequent meta-analyses suggest patients with a QRS >150 ms in LBBB are most likely to derive the greatest benefit from CRT.

Clinical trial evidence base

CARE-HF The effect of cardiac resynchronization on morbidity and mortality in heart failure.

Although the criteria for the trials include QRS duration >120 ms, the majority of patients included in the trials had a wide LBBB morphology. The mean QRS direction in CARE-HF was 160 ms. The efficacy of CRT-P in RBBB is not established as patients with this QRS morphology are underrepresented in clinical trials, but the inclusion criteria of most of these are based on QRS duration not morphology.

► It must be stressed that the benefits seen in the large outcome trials of CRT were in addition to optimal pharmacological therapy, that is, ACE inhibition, β-blockade, and mineralocorticoid receptor antagonism.

Nowadays, it is accepted that this list should also include an SGLT2i and ARNI (in lieu of ACEi).

CRT-P in atrial fibrillation

Patients with atrial arrhythmias were excluded from CARE-HF. The MUSTIC-AF trial is a small trial that compared RV pacing with biventricular pacing in patients with heart failure, a wide QRS, and chronic AF who required a pacemaker for bradycardia. Only 37 patients completed the crossover phase, limiting the interpretation of the trial, however, significant improvements were seen in exercise capacity. This is not sufficient evidence to advocate the use of CRT-P in these patients. However, in patients with chronic AF and heart failure who require AV nodal ablation for arrhythmia control, biventricular pacing appears to be better than standard pacing.

Key reference

Leclercq C, et al. Comparative effects of permanent biventricular and right-univentricular pacing in heart failure pacing in chronic atrial fibrillation. *Eur Heart J.* 2002;23:1780–1787.

Optimization of CRT

There are aspects of CRT that must be addressed in order to optimize pacing in an individual. These relate to the positioning of the LV lead and then optimization of the pacing settings: particularly the AV delay.

Ventricular pacing position

The LV lead should be positioned on the free wall of the LV at the point of latest activation. In general, this is on the posterolateral wall of the LV—achieved by positioning the LV lead in a posterolateral cardiac vein. This is not always possible, as it is determined by cardiac venous anatomy. In ischaemic cardiomyopathy, LV lead placement should ideally avoid regions of the infarction scar.

Atrioventricular delay

There are two potential benefits in optimizing AV delay—reduced mitral regurgitation and improved left-ventricular diastolic filling time, with resultant improvement in cardiac output.

Atrioventricular delay optimization protocols use Doppler echocardiography. These can either measure LV diastolic filling time (mitral inflow) or LV systolic function (aortic velocity-time integral). Aortic VTI has been suggested to achieve a greater increase in stroke volume.

Mitral inflow method

Pulsed-wave transmitral velocities are measured at the mitral leaflet tips. Diastolic filling time is the time from the onset of transmitral flow to closure of the mitral valve. The rationale is to maximize the distance between the E and the A waves without the A wave being truncated by mitral valve closure.

The AV delay is determined by the time between ventricular activation and the end of the A wave at an AV delay of 160 ms (*a*). LV electromechanical delay is the time from LV stimulation to closure of the mitral valve (*b*). The optimized AV delay is then set as (160 – (*b*–*a*)) ms (Fig. 6.1).

Aortic VTI method

Continuous-wave Doppler from an apical five-chamber window is used to measure the aortic VTI. While pacing in VDD mode the AV delay is decreased from 200 ms to a minimum of 60 ms in 20 ms increments. After at least 10 paced beats at the pacing interval, a mean of 3 beats is taken to establish the aortic VTI. The AV delay is then fine-tuned in 10 ms increments. The optimized AV delay is the one that results in the maximum aortic VTI (Fig. 6.2).

V–V interval

No long-term data are available to suggest that altering the VV interval improves outcome in CRT-P. However, small studies do suggest that altering the VV pacing interval can affect surrogate measure of cardiac output such as the echocardiographic aortic VTI. The VV interval has to be individually optimized as some patients respond to pacing the RV first, some others to pacing the LV first, and yet others benefit from simultaneous RV and LV pacing.

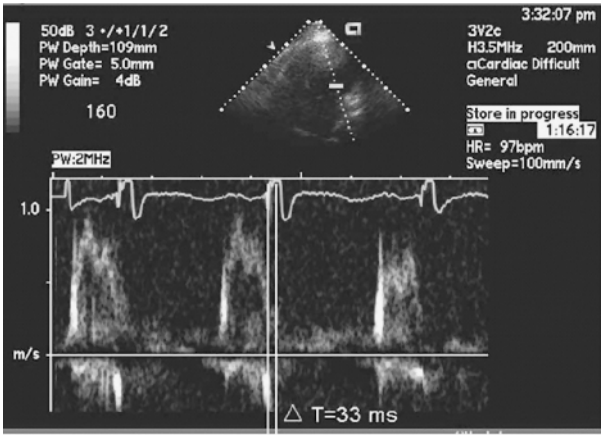

Fig. 6.1 Doppler signals for mitral inflow method.

Reproduced from Kerlan JE et al. Prospective comparison of echocardiographic atrioventricular delay optimisation methods for cardiac resynchronization therapy. *Heart Rhythm* 2006;3:148–154 with permission from Elsevier.

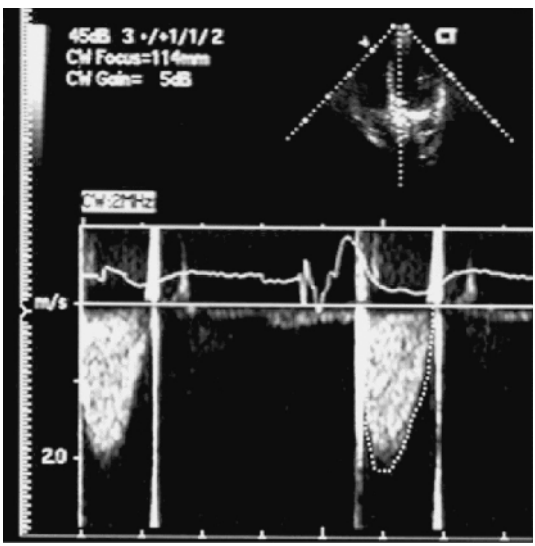

Fig. 6.2 Doppler signals for aortic VTI method.

Reproduced from Kerlan JE et al. Prospective comparison of echocardiographic atrioventricular delay optimisation methods for cardiac resynchronization therapy. *Heart Rhythm* 2006; 3: 148–54 with permission from Elsevier.

Follow-up of the patient post-CRT

It is important to remember that the patient post-CRT still has heart failure. They should be followed up, preferably in a heart failure clinic. Specifically, patients who respond to CRT often have an immediate increase in their cardiac output and blood pressure. This can result in an improvement in renal function. Patients should therefore be seen at 1-week post-CRT to ascertain whether they require a reduction in their diuretic therapy.

Thereafter, due consideration should be given to optimizing their heart failure therapy further. Specifically, this should include up-titration of the β-blocker dose, which may have been previously hampered by bradycardia. In addition, it may be possible to up-titrate doses of ARNI or ACEi if CRT has improved arterial blood pressure and/or renal function. Addition of an MRA may also be feasible in some patients post-CRT, where it proved difficult beforehand. Finally, consideration should also be given to the patient who has undergone generator replacement for battery depletion as they often remain on historical therapy.

To derive maximum benefit, ideally, patients post-CRT should be cared for within a multiprofessional heart failure programme.

Implantable cardioverter defibrillators (ICD)

Heart failure is an arrhythmogenic condition arising from a combination of structural heart disease and electrolyte imbalance. Further pro-arrhythmic stress occurs in ischaemic cardiomyopathy due to ischaemic events. Ventricular arrhythmias, from premature ventricular beats through to ventricular fibrillation, occur in >80% of patients with heart failure and cardiomyopathy. Up to 50% of heart failure deaths are SCD, although not all of which will be arrhythmic. However, the proportion of patients dying suddenly in heart failure decreases with increasing severity of the condition. While trials of specific pharmacological anti-arrhythmic therapy for the prevention of SCD have been disappointing, the risk of sudden death has fallen substantially with the use of the core-4 HF therapies: ACEi/ARNI, BB, MRA, SGLT2i.

Implantable cardiac defibrillators have revolutionized the management of arrhythmias. An ICD is an advanced form of pacemaker that can detect and treat arrhythmias—usually ventricular arrhythmias. Several types of system are available—a single chamber device with a bipolar lead placed in the right-ventricular apex, a dual chamber device with the addition of an atrial lead which may improve distinction of atrial from ventricular arrhythmias, or allow up-titration of beta-blockers; or an ICD can be combined with CRT so-called CRT-D.

Most ICDs use heart rate criteria to determine VT and VF. This can be important, particularly, in young patients who may achieve sinus tachycardia into the arrhythmia detection zone, or patients with fast paroxysmal atrial arrhythmias. ICDs use the following detection qualifiers to distinguish VT and VF:

- Rate detection zone.
- Detection cycles: the number of consecutive beats required to diagnose arrhythmia.
- Rate stability: VT is a relatively stable rhythm, so this feature establishes the maximum interbeat variation that still allows VT to be diagnosed.
- Sudden onset: ventricular arrhythmias usually have a sudden onset compared to sinus tachycardia that gradually ramps up.

ICD therapies may offer shock therapy only or be programmable allowing attempts at overdrive (anti-tachycardia) pacing (ATP) of VT before resorting to defibrillation. Tiered therapy allows increasingly aggressive therapy in the treatment of VT that is likely to be haemodynamically stable, usually defined as a heart rate of 200 bpm or cycle length of 300 ms (Table 6.2). This cut-off may be inappropriate in patients with heart failure who are less likely to tolerate fast arrhythmias. However, an important part of ICD implantation is fine-tuning of the device to meet the individual patient's requirements. In the MADIT-RIT study, 'high-rate therapy' with a single treatment zone >200/min (and a monitor zone >170/min) significantly reduced inappropriate and unnecessary appropriate therapy, and reduced mortality.

▶▶ Magnet mode in ICDs

Placing and keeping a magnet over the ICD deactivates the defibrillator—useful if it is giving recurrent inappropriate shocks.

Table 6.2 Conversion of heart rate in beats/minute into R–R interval (cycle length) in milliseconds

R–R interval = 1000/(HR/60)										
HR (bpm)	300	290	280	270	260	250	240	230	220	210
R–R (ms)	200	207	214	222	231	240	250	261	273	286
HR (bpm)	200	190	180	170	160	150	140	130	120	110
R–R (ms)	300	316	333	353	375	400	429	462	500	545
HR (bpm)	100	90	80	70	60	50	40	30	20	10
R–R (ms)	600	667	750	857	1000	1200	1500	2000	3000	6000

Key reference

Moss AJ, et al. MADIT-RIT: Reduction in inappropriate therapy and mortality through ICD programming. *N Engl J Med.* 2012;367:2275–2283.

Indications for ICD therapy

The indications for ICD therapy in heart failure have emerged from the publication of several large randomized controlled trials (RCTs); see Tables 6.3–6.5. The MADIT II study showed a mortality benefit for ICDs in patients with IHD who had a LVEF <30%. Notably, this was a study conducted with patients with LVSD who did not necessarily have heart failure. Subsequently, the SCD-HeFT study was carried out on patients with HF in NYHA II and III with LVEF <35%, of either ischaemic or non-ischaemic aetiology. The study showed a reduction in all-cause mortality for those treated with ICDs (particularly in NYHA II) compared to those on OMT or optimal medical treatment plus amiodarone, that is, amiodarone did not confer any survival benefit. Most recently, the DANISH trial, using contemporary medical therapy did NOT show a mortality benefit from ICDs in patients with heart failure of a non-ischaemic aetiology, with lack of effect most notable in those >60years of age. As such, the enthusiasm for ICDs in this population has waned of late and reflected in a change in guideline recommendation from Class I to IIa in those with heart failure of a non-ischaemic aetiology.

Table 6.3 Primary prevention trials of ICD and ischaemic cardiomyopathy

				Mortality (%)		
	No. of patients	LVEF (%)	Follow-up (months)	Control	ICD	p value
MADIT (1996)	196	26	27	39	16	0.0009
CABG-Patch (1997)	900	27	32	21	22	0.64
MADIT II (2002)	1232	23	20	20	14	0.007
DINAMIT (2004)	674		30	17	19	0.66
SCD-HeFT (2005)	2521	25	45.5	29	22	0.007

Table 6.4 Secondary prevention trials of ICD and ischaemic cardiomyopathy

				Mortality (%)		
	No. of patients	LVEF (%)	Follow-up (months)	Control	ICD	p value
AVID (1997)	1016	35	18	24	16	0.02
CIDS (2000)	659	34	35	30	25	0.14

Table 6.5 Primary prevention trials of ICD and non-ischaemic cardiomyopathy

				Mortality (%)		
	No. of patients	LVEF (%)	Follow-up (months)	Control	ICD	p value
CAT (2002)	104	24	27	31	26	0.55
AMIOVERT (2003)	103	22	32	13	12	0.80
DEFINITE (2004)	450	21	20	14	8	0.06
SCD-HeFT (2005)	2521	25	45.5	29	22	0.007
DANISH (2016)	1116	25	68	23	22	0.28

Table 6.6 ESC HF Guidelines 2021. Recommendations for the use of ICDs in patients with heart failure

Recommendations	Class	Level
Secondary prevention		
An ICD is recommended to reduce the risk of sudden death and all-cause mortality in patients who have recovered from a ventricular arrhythmia causing haemodynamic instability, and who are expected to survive for >1 year with good functional status, in the absence of reversible causes or unless the ventricular arrhythmia has occurred <48 h after a MI	I	A
Primary prevention		
An ICD is recommended to reduce the risk of sudden death and all-cause mortality in patients with symptomatic HF (NYHA class II–III) of an ischaemic aetiology (unless they have had a MI in the prior 40 days—see next), and an LVEF ≤35% despite ≥3 months of OMT, provided they are expected to survive substantially longer than 1 year with good functional status	I	A
An ICD should be considered to reduce the risk of sudden death and all-cause mortality in patients with symptomatic HF (NYHA class II-III) of a non-ischaemic aetiology, and an LVEF ≤35% despite ≥3 months of OMT, provided they are expected to survive substantially longer than 1 year with good functional status	IIa	A

Class: class of recommendation; Level: level of evidence. McDonagh TA, et al. European Society of Cardiology Heart Failure 2021 Guidelines. *Eur Heart J*. 2021 Sep 21;42(36):3599–3726 by permission of Oxford University Press.

The ESC HF Guidelines suggest that ICDs should not be used in patients with NYHA IV heart failure, except in those who are candidates for cardiac transplantation or ventricular assist devices (VADs)—although ICDs in VAD recipients is contentious. Rather, the ESC HF Guidelines recommend ICDs in HF patients described in table 6.6.

Some guidelines previously advocated the demonstration of inducible VT at electrophysiological testing, although this is no longer felt necessary. Implementation of these guidelines has huge resource implications, and predictive markers of a sudden death have been sought. One of the promising techniques to try to identify patients who do not need an ICD was microvolt T-wave alternans (MTWA). However, a subsequent study showed that the most predictive aspect of MTWA was an inability to perform the test!

Key reference

Jackson CE, et al. Spectral microvolt T-wave alternans testing has no prognostic value in patients recently hospitalized with decompensated heart failure. *Eur J Heart Fail.* 2013;15:1253–1261.

Contraindications for ICD therapy

- Reversible cause for VT or VF.
- Comorbidity limiting prognosis.
- Patient choice.

In the setting of HFrEF and ischaemic heart disease, there is currently no evidence for implantation in the first month post-MI. The DINAMIT study demonstrated no difference in outcome in those treated with an ICD or medical therapy. There was a trend towards harm early on for the ICD group.

ICDs are used in addition to OMT. In order to reduce the frequency of ICD events, β-blocker therapy should be maximized where possible.

Healthcare professionals must be considerate in supporting patients in whom ICDs are to be implanted as many may struggle with the concept. Also, the patient should be advised as to what to do and who to contact if they receive a shock from their device.

Finally, a conversation regarding the possibility of device deactivation is usually appropriate *prior* to implantation, although a recent EHRA survey suggests that this practice is not commonplace.

Device deactivation

ICD therapy before death is undesirable if a patient dies soon after receiving an ICD shock and their life was not meaningfully prolonged by the shock. There are case reports of patients who have received multiple ICD shocks in their last hours or minutes of life, resulting in considerable distress for them and their relatives.

In a position statement on palliative care in heart failure, the European Society of Cardiology suggests that ICD deactivation should be considered 'when it is clinically obvious that a patient is about to die, when a DNR order is in force, and when impairment of quality of life is such that sudden death might be considered a relief'.

All modern ICDs can be deactivated. This can be quickly achieved by placing a magnet over the pulse generator, resulting in suspension of tachyarrhythmia detection. Devices can also be permanently deactivated using the programmer.

Key references

Antiarrhythmics versus Implantable Defibrillators (AVID) Investigators. A comparison of antiarrhythmic-drug therapy with implantable defibrillators in patients resuscitated from near-fatal ventricular arrhythmias. *N Engl J Med.* 1997;337:1576–1583.

Bardy GH, et al. Amiodarone or implantable cardioverter-defibrillator for congestive heart failure (SCD-HeFT). *N Engl J Med.* 2005;352:225–237.

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Kadish A, et al. Prophylactic defibrillator implantation in patients with non-ischaemic dilated cardiomyopathy (DEFINITE). *N Engl J Med.* 2004;350:2151–2158.

Lee DS, et al. Effectiveness of implantable defibrillators for preventing arrhythmic events and death: a meta-analysis. *J Am Coll Cardiol.* 2003;41:1573.

Moss AJ, et al. Prophylactic implantation of a defibrillator in patients with myocardial infarction and reduced ejection fraction (MADIT-II). *N Engl J Med.* 2002;346:877–883.

Kober L, et al. Defibrillator implantation in patients with non-ischemic systolic heart failure. *NEJM.* 2016;375:1221–1230.

Subcutaneous ICD

An alternative approach to a transvenous ICD, is the subcutaneous ICD (S-ICD) (Fig. 6.3). The generator is implanted in the left axilla, with subcutaneous tunnelling of the lead to the xiphoid process then up towards the sternal notch.

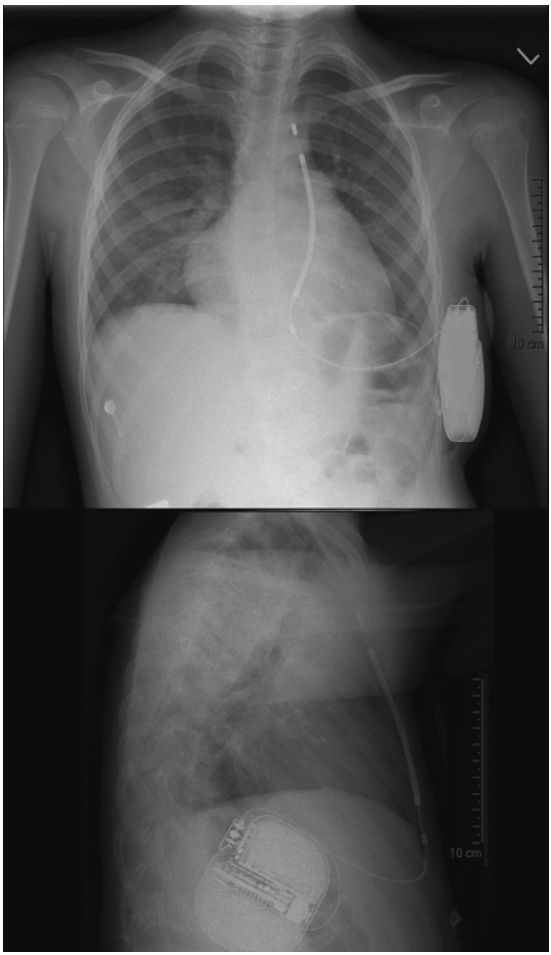

Fig. 6.3 PA and lateral X-ray of a subcutaneous ICD in situ.

Advantages:

- Effective defibrillation therapy without transvenous leads.
- Preserves venous anatomy.
- Implanted using anatomical landmarks—no need for ionizing radiation.
- No risk of pneumothorax.
- No risk of lead displacement.
- No risk of myocardial perforation/vascular injury.
- Lower risk of systemic infection.
- Easier to extract in the event of infection.

Disadvantages:

- Currently unable to offer either bradycardia or anti-tachycardia pacing.
- Larger generator ('can').
- High output—80 Joules (although all shocks hurt!).
- Unable to be 'upgraded' to dual chamber ICD, or CRT-D.

Currently, S-ICDs are worth considering in individuals at high risk of SCD, or as secondary prevention, where the predicted need for pacing is low. However, in the near future, there is the potential to combine an S-ICD with a leadless pacemaker, in order to offer anti-tachycardia pacing. The generator is also expected to be reduced in size with developing battery technology.

Key references

Gardy GH, et al. An entirely subcutaneous implantable cardioverter-defibrillator. *N Engl J Med.* 2010;363:36–44.

Gold MR, et al. Post-approval study of a subcutaneous implantable cardioverster-defibrillator system. *J Am Coll Cardiol.* 2023;82:383–397.

CRT-P or CRT-D?

Deciding whether to implant CRT-P or CRT-D is difficult and requires consideration of both the CRT and ICD evidence, as only one trial has had both CRT-D and CRT-P in the treatment of heart failure.

The COMPANION trial demonstrated that patients with a QRS duration >120 ms (median 160 ms) with NYHA III–IV heart failure, nearly half of whom had non-ischaemic cardiomyopathy, had a survival benefit from CRT-D compared OMT. Patients with CRT-P had a trend towards a reduction in all-cause mortality. The difference between CRT-P and CRT-D in the trial was not statistically significant, nor was the trial powered to look for a difference. Both CRT-D and CRT-P significantly reduced the primary endpoint in this study—that of all-cause mortality or admission to hospital with heart failure. The mortality benefit from CRT-D begins immediately after implantation, but CRT-P seems to require reverse remodelling to take place before the mortality benefit is seen.

In addition, many of the patients included in CARE-HF would now meet the criteria for an ICD based on their LVEF and NYHA class. As sudden cardiac death (SCD) is more common in NYHA II heart failure than in NYHA III (64% versus 33%), theoretically, if CRT-P improves NYHA class for those in class III, it may, in fact, increase the likelihood of sudden cardiac death by moving them into stage II!

In reality, the type of device implanted in patients with heart failure has significant geographical variation. In the US, the vast majority of CRT devices implanted are CRT-D. However, because of financial considerations in socialized healthcare systems, a much greater proportion receive CRT-P. Undeniably, the DANISH trial has modified the thoughts of implanting teams, particularly when considering patients with advancing years, and with excellent doses of contemporary medical therapy, the addition of a defibrillator component to a device may not add significantly to its overall benefit.

ICD or CRT-D?

Two studies (RAFT and MADIT-CRT) have been published, which look at whether CRT-D or ICDs should be implanted in patients with mild–moderate heart failure and wide QRS. The addition of CRT to an ICD reduced the rate of death, or hospitalization, or heart failure events. However, those receiving CRT-D had a higher risk of adverse events—principally driven by a higher rate of lead dislodgement, or coronary sinus dissection.

Conversely, EchoCRT has shown us that CRT-D in patients with a QRS <130 ms and echocardiographic evidence of dyssynchrony, are at greater risk of mortality than those receiving an ICD.

Clinical trial evidence base

COMPANION Cardiac resynchronization therapy with or without an implantable defibrillation in advanced heart failure

RAFT Cardiac resynchronization therapy for mild-moderate heart failure

MADIT-CRT Cardiac resynchronization therapy for the prevention of heart failure events in those with minimal symptoms

EchoCRT Cardiac resynchronization therapy in heart failure with a narrow QRS complex

Which device in whom?

Symptomatic HF with LVSD

On the basis of current trial evidence, the following device management is suggested for the patient in sinus rhythm (Tables 6.7 and 6.8). The benefits of CRT in patients with atrial fibrillation remains uncertain.

Asymptomatic LVSD

The device management of asymptomatic LVSD is more difficult. By definition, these patients are in NYHA class I. Trial evidence that is available is from the post-myocardial infarction populations studied in MADIT I, MADIT II, and MUSTT. Furthermore, MADIT-CRT also recruited NYHA I patients with HF of an ischaemic aetiology.

In the post-myocardial infarction population with an LVEF <30%, MADIT II data suggests survival benefit with the implantation of an ICD in those with minimally symptomatic HF. However, those with a broad QRS (particularly LBBB), *may* also benefit from the addition of CRT, by way of reduced HF events. Although, in the prespecified sub-group analysis NYHA I patients in MADIT-CRT did not have obvious benefits from CRT-D over ICD.

This has to be assessed at a local level and often on an individual patient basis as the cost ramifications of such a policy is significant.

Table 6.7 ESC HF Guidelines 2021. Recommendations for CRT in patients with symptomatic heart failure, in sinus rhythm and on OMT*

Recommendations symptomatic HF on optimal medical therapy	Class	Level
LBBB QRS morphology		
CRT is recommended for symptomatic patients with HF in SR with a QRS duration ≥150 ms and LBBB QRS morphology and with LVEF ≤35% despite OMT in order to improve symptoms and reduce morbidity and mortality	I	A
CRT should be considered for symptomatic patients with HF in SR with a QRS duration of 130-149 ms and LBBB QRS morphology and with LVEF ≤35% despite OMT in order to improve symptoms and reduce morbidity and mortality	IIa	B
Non-LBBB QRS morphology		
CRT should be considered for symptomatic patients with HF in SR with a QRS duration ≥150 ms and non-LBBB QRS morphology and with LVEF ≤35% despite OMT in order to improve symptoms and reduce morbidity and mortality	IIa	B
CRT may be considered for symptomatic patients with HF in SR with a QRS duration of 130-149 ms and non-LBBB QRS morphology and with LVEF ≤35% despite OMT in order to improve symptoms and reduce morbidity and mortality	IIb	B
QRS<130 ms		
CRT is not recommended in patients with a QRS duration <130 ms who do not have an indication for pacing due to high degree AV block	III	A

Table 6.8 ESC 2021 Guidelines. Other recommendations for CRT*

Recommendations NYHA II on optimal medical therapy	Class	Level
CRT rather than RV pacing is recommended for patients with HFrEF regardless of NYHA class or QRS width who have an indication for ventricular pacing for high degree AV block in order to reduce morbidity. This includes patients with AF.	I	A
Patients with an LVEF ≤35% who have received a conventional pacemaker or an ICD and subsequently develop worsening HF despite OMT and who have a significant proportion of RV pacing should be considered for 'upgrade' to CRT.	IIa	B

*McDonagh et al. European Society of Cardiology Guidelines 2021. *European Heart Journal* 2021;42(36):3599–3726.

Class: class of recommendation; Level: level of evidence.

Conduction system pacing

There is growing enthusiasm for conduction system pacing (CSP) in the device implanting community, in pursuit of avoiding the detrimental effects of right ventricular pacing and overcoming potential challenges of coronary sinus lead placement. However, data supporting its use in HF patients are scarce. CSP includes techniques such as His bundle pacing (HBP) and left bundle branch pacing (LBBP) (Fig. 6.4).

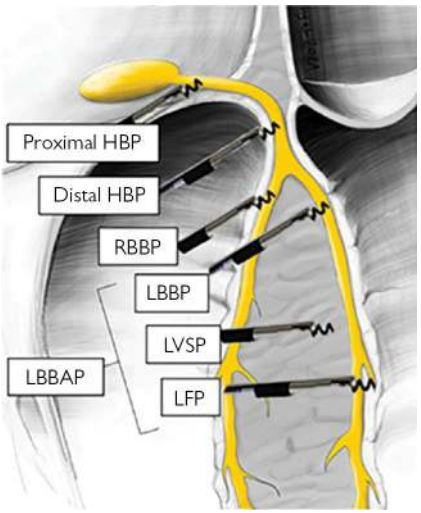

Fig. 6.4 Outline of capture types obtainable at various levels of the conduction system. HBP = His bundle pacing; LBBAP = left bundle branch area pacing; LBPP = left bundle branch pacing; LFP = left fascicular pacing; LVSP = left ventricular septal pacing; RBBP = right bundle branch pacing; LAFP = left anterior fascicle pacing; LPFP = left posterior fascicle pacing; LSFP = lest septal fascicle pacing. Adapted from Burri H, *Europace* 2023;15:1208–1236 (figure 1).

Key reference

Jastrzebski, et al. Conduction system pacing: overview, definitions, and nomenclature. *Eur Heart J*. 2023;25(SG):G4–G14.

Implantable haemodynamic monitoring devices

Device therapy, including CRT and ICD, is becoming an important component of the heart failure treatment armamentarium for an increasing proportion of patients with HF. These devices can be combined with haemodynamic monitoring sensors, which measure the following parameters:

- Pulmonary artery pressure—sensor in the pulmonary artery.
- Inferior vena cava (IVC) sensor to measure congestion.
- Right ventricular pressure—sensor in RV.
- Left atrial pressure.
- SVO_2—oxygen saturation sensor in the RV.
- Electrogram—distal tip electrode in RV lead.
- Intrathoracic impedance—from RV tip to device, or multiple vectors.
- Tidal volume and respiratory rate.
- First and third heart sounds (S1 and S_3).
- Posture.

From the data collected, it is possible to estimate RV dP/dt_{max}. This is derived from the observation that the right-ventricular dP/dt_{max} occurs as the pulmonary valve opens and the RV and PA pressures equilibrate. The RV dP/dt_{max} estimates the PA diastolic pressure.

The electrogram allows for determination of rhythm (for example, to calculate the burden of atrial fibrillation), heart rate, and heart rate variability. These data, combined with a trace of activity level, can identify deterioration in the patient's cardiac status which is likely to result in hospitalization: the heart rate rises as the heart rate variability and activity level fall. Intrathoracic impedance is inversely correlated with PCWP. It is sensitive to the fluid content of the lung parenchyma. Thus, if fluid begins to accumulate in the lungs the intrathoracic impedance falls. This change happens before patient symptoms develop. However, the recent study with Optivol led to an increase in hospitalization! Newer systems with multiple parameters are currently under investigation.

Of the invasive monitoring devices, the most commonly used is currently CardioMEMS—a nitinol-winged, wireless, battery-less pulmonary artery sensor. Once deployed into the pulmonary artery, this has been shown to accurately assess pulmonary artery pressure (Figs. 6.5 and 6.6). In the CHAMPION study, patients with this device had a lower rate of heart failure hospitalization, although in the more recent GUIDE-HF study haemodynamic-guided management of heart failure did not result in a lower composite endpoint rate of mortality and total heart failure events compared with the control group.

The stage beyond isolated information from invasive monitors is the integration of these data with non-invasive measures, such as weight, blood pressure, BNP/NT-proBNP, and correlation with patient symptoms. Technology is now available that achieves all of this and can relay this information to the patient's physician via the telephone or internet. Thus, without leaving their home the patient can benefit from regular follow-up. Such technology challenges clinicians to ensure robust arrangements are in place so that all of the information is logged, and action taken where necessary.

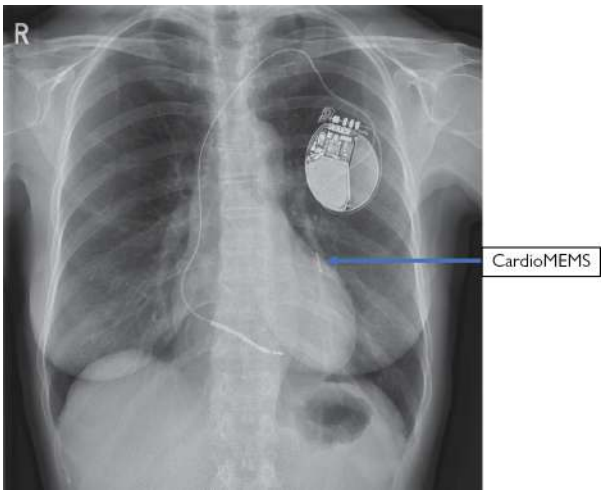

Fig. 6.5 PA chest X-ray of a single chamber ICD, and a CardioMEMS device (arrow).

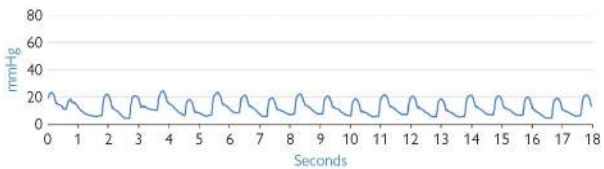

Fig. 6.6 Pulmonary artery pressure trace from a CardioMEMS device.

Chapter 7

Coronary revascularization in heart failure with reduced ejection fraction

Introduction

Ischaemic heart disease (IHD), or coronary artery disease (CAD), is the most common cause of HF in westernized countries, and the survival of patients with HF caused by IHD is poorer than those with non-ischaemic aetiology.

IHD and HF involves two distinct pathological processes; myocardial infarction (MI) with irreversible damage, and myocardial ischaemia. The latter can have an impact on LV dysfunction in three ways:

- *Inducible ischaemia* can lead to a transitory reduction in LV performance.
- *Hibernating myocardium* that can have contractility restored with revascularization.
- *Stunned myocardium* describing a more transient contractile dysfunction secondary to an ischaemic insult.

Patients with angina and HF are considered in ➔ Chapter 10. This chapter will consider the wider remit of assessment for revascularization in HF caused by IHD.

Ischaemic heart disease and heart failure

As described in ➔ Chapter 2, HF is not a diagnosis and the aetiology should be identified. The rigour with which the diagnosis of IHD is sought varies from centre to centre, with some still performing diagnostic coronary angiography in all HF subjects.

Cardiologists previously restricted invasive coronary angiography to those with chest pain or evidence of ischaemia on non-invasive testing (exercise testing or myocardial perfusion imaging). However, with the reduced risk of CT coronary angiography and recognition of the non-anginal presentations of coronary ischaemia there is acceptance that coronary artery assessment may be considered if an ischaemic aetiology is suggested.

The management of heart failure and ischaemic heart disease

The management of the patient with angina and HF is largely accepted (see Chapter 10). Surgical or percutaneous coronary revascularization is indicated in patients with HF and refractory angina despite optimal medical therapy or acute coronary syndrome.

The Surgical Treatment for Ischaemic Heart Failure (STICH) trial addressed the broader role of surgical revascularization in patients with HFrEF and CAD. Patients with LVEF ≤35% and CAD who were suitable for surgery were randomized to coronary artery bypass graft (CABG) plus medical therapy or medical therapy alone. The patients enrolled were young, predominantly male, and 86% were in NYHA II/III. Two-thirds had three-vessel CAD and a similar proportion had severe proximal LAD disease. Despite this, 95% were in Canadian Cardiovascular Society angina classes 0–II. The primary outcome of all-cause mortality was not reduced by CABG, although the secondary outcomes of cardiovascular death (RRR 19%) and death from any cause or cardiovascular hospitalization (RRR 26%) were reduced.

The STICHES (Surgical Treatment for Ischaemic Heart Failure Extension Study) supports the practice of CABG compared against medical therapy in patients with HF and CAD with a 7% absolute reduction in mortality 10 years following revascularization.

Medical therapy is recommended in all patients with HF and IHD. Because of the peri-procedural risks of CABG surgery, with both morbidity and early mortality, it is reasonable to reassess the role of surgery after optimizing HF medical therapy first as this may improve the peri-operative course. Surgical coronary revascularization should be considered for 'prognostic' reasons in patients with HFrEF and CAD, particularly those with diabetes or multivessel CAD. Recommendations for revascularization in HFrEF are summarized in Table 7.1.

The role of percutaneous coronary intervention (PCI) with coronary angioplasty is less well established. It is an attractive option, as it would remove the necessity of the patient undergoing major surgery. Observational studies are difficult to interpret because patients undergoing PCI and not CABG have often been declined surgery because of severity of disease or comorbidity. REVIVED-BCIS-2 is the first RCT comparing PCI to medical therapy in patients with HFrEF and CAD. In 700 patients with LVEF ≤35% and extensive CAD, medical therapy plus revascularization with PCI did not improve mortality or HF hospitalization over a median follow-up of 41 months compared to medical therapy alone. There was no surgical arm to the study and the post-hoc analysis has highlighted a significant number of patients had angina (who typically would proceed to intervention if they had ongoing symptoms despite medical therapy). This has limited the utility of this study in the planning of patient care.

Ultimately, **the choice between medical therapy, and revascularization by PCI or CABG should be made by the heart team, including a HF specialist**, and be based on the extent of CAD, expected completeness of revascularization, associated valvular disease,

the presence of comorbidities and estimated risk of an interventional procedure (see Fig. 7.1).

Clinical trial evidence base

STICH (Surgical treatment for ischaemic heart failure) trial
STICHES (Surgical treatment for ischaemic heart failure extension study)
REVIVED-BCIS2 (Revascularisaton for ischaemic ventricular dysfunction) trial

Table 7.1 Recommendations for myocardial revascularization in patients with HFrEF. McDonagh TA, et al. ESC Scientific Document Group. CABG = coronary artery bypass graft; CCS = chronic coronary syndrome; HFrEF = heart failure with reduced ejection fraction; LAD = left anterior descending artery; LVAD = left ventricular assist device; OMT = optimal medical therapy; PCI = percutaneous coronary intervention; [a] Class of recommendation; [b] Level of evidence. 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. *Eur Heart J*. 2021;42:3599–3726.

Recommendations for myocardial revascularization in patients with heart failure with reduced ejection fraction.

Recommendations	Class[a]	Level[b]
CABG should be considered as the first-choice revascularization strategy, in patients suitable for surgery, especially if they have diabetes and for those with multivessel disease.[ss1,ss1.sas,s90]	IIa	B
Coronary re vascularization should be considered to relieve persistent symptoms of angina (or an angina-equivalent) in patients with HFrEF, CCS, and coronary anatomy suitable, for revascularization, despite OMT including anti-anginal drugs.	IIa	C
In LVAD candidates needing coronary revascularization, CABG should be avoided, if possible.	IIa	C
Coronary revascularization may be considered to improve outcomes in patients with HFrEF, CCS, and coronary anatomy suitable fur revascularization, after careful evaluation of the individual risk to benefit ratio, including coronary anatomy (i.e. proximal stenosis >90% of large vessels, stenosis of left main or proximal LAD), comorbidities, life expectancy, and patient's perspectives.	IIb	C
PCI may be considered as an alternative to CABG, based on Heart Team evaluation, considering coronary anatomy, comorbidities, and surgical risk.	IIb	C

Key references

Perera D, et al. Percutaneous revascularization for ischemic left ventricular dysfunction. *N Engl J Med.* 2022;387:1351–1360.

Velazquez EJ, et al. Coronary-artery bypass surgery in patients with left ventricular dysfunction. *N Engl J Med.* 2011;364:1607–1616.

Velazquez EJ, et al. Coronary-artery bypass surgery in patients with ischemic cardiomyopathy. *N Engl J Med.* 2016;374:1511–1520.

Assessment of myocardial viability

While coronary angiography details coronary anatomy it does not provide information about the myocardial perfusion or "viability" of the myocardium if perfusion was improved by revascularization.

The optimal method to assess for viability, and the benefit of that information, remains contentious. The choice of test depends on local availability and expertise; few studies have been performed that directly compare all the techniques in the same patient population.

Tests for assessing myocardial viability

- Stress perfusion cardiac magnetic resonance (CMR).
- Echocardiography—dobutamine stress and/or myocardial contrast.
- Myocardial perfusion imaging—thallium stress-redistribution-reinjection SPECT or thallium stress rest-redistribution SPECT or Technetium-sestamibi SPECT.
- FDG-positron emission tomography (PET) scanning.

The predictive accuracy of the tests for assessing for myocardial viability is illustrated in Fig. 7.1. However, nuclear imaging is now performed far less frequently, with stress perfusion CMR imaging offering a more detailed evaluation of hibernating myocardium.

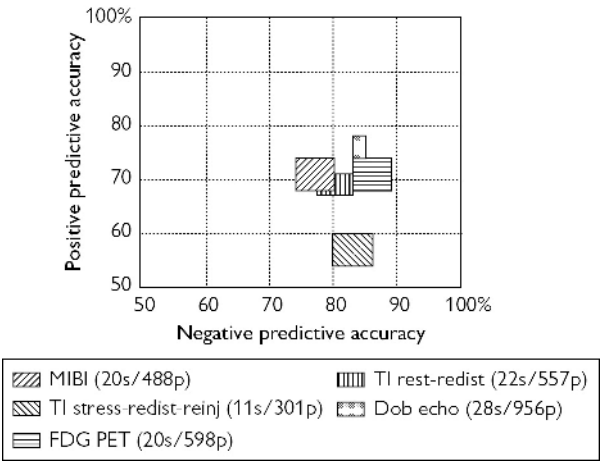

Fig. 7.1 Weighted mean positive and negative predictive accuracy of the different imaging tests for predicting recovery of segmental function after revascularization from a meta-analysis of patients with ischaemic LV dysfunction. The rectangles are centred on the weighted means, and the size of the rectangles indicates 95% confidence intervals. The number of averaged studies (s) and patients (p) for each technique is indicated. Underwood SR, et al. *Eur Heart J.* 2004;25:815–836 with permission from Oxford University Press.

Caution should be applied when assessing the myocardial viability scans, as the techniques depend on comparative blood flow, so 'balanced ischaemia' which can occur with, e.g. left main-stem stenosis, can mask severe ischaemia with potentially extensive areas of viable myocardium.

Myocardial viability was unrelated to outcomes after revascularization in the STICH trial and in a prespecified analysis from the REVIVED-BCIS-2 trial, viability testing did not identify patients with HF and CAD who benefit from PCI. There is not sufficient evidence to support the routine use of myocardial viability assessment, although it may be considered in individual cases.

Key references

Bonow RO, et al. Myocardial viability and survival in ischemic left ventricular dysfunction. *N Engl J Med*. 2011;364:1617–1625.

Perera D, et al. Viability and outcomes with revascularization or medical therapy in ischemic ventricular dysfunction: a prespecified secondary analysis of the REVIVED-BCIS2 trial. *JAMA Cardiol*. 2023;8:1154–1161.

Chapter 8

Cardiac transplantation

Introduction

Cardiac transplantation (CTx) is the final intervention for patients who remain symptomatic despite optimal medical and device therapy. However, while the patient's condition should be sufficiently severe to justify this procedure, the individual should also be free of significant comorbidities so that major cardiac surgery and the ensuing immunosuppressive regime can be tolerated.

In 1967, Christian Barnard performed the first human–human heart transplant in South Africa. CTx was revolutionized in 1976 with the discovery of ciclosporin (cyclosporin), which dramatically improved patient survival. However, the total number of heart transplants carried out is falling worldwide. Furthermore, the majority of heart transplant procedures are performed in small volume centres. In the 2021 ISHLT registry report:

- There were over 6,000 heart transplants performed worldwide.
- 72% of institutions performed <20 heart transplants/year.
- The primary indications for CTx were:
  - non-ischaemic cardiomyopathy (51%).
  - ischaemic cardiomyopathy (32%).
- The median age of the CTx recipient was 55 years and 74% were male (Table 8.1).
- The median age of the CTx donor was 35 years worldwide.
- 44% of recipients had an LVAD *in situ*.
- Median survival (for those transplanted 2001–2009) 12.1 years (see Fig. 8.1).

In the year to 31 March 2023, there was a 20% increase in heart transplantation in the UK to 214, most likely as a result of the 'opt-out' system now in place across the UK. Of these, 56% were urgent heart transplants and 25% were 'super-urgent' (patients maintained on short-term mechanical

Table 8.1 CTx recipient characteristics 2010–2018 (ISHLT registry data)

Variable	Value
Age	55 [25–68] years
Male	74 %
Weight	80 [54–109] kg
BMI	26.5 [19.6–34.6] kg/m2
Diabetes mellitus	27 %
Previous cardiac surgery	50.16%
Serum creatinine	106 [62–195] μmol/L
Pulmonary vascular resistance (PVR)	2.1 [0.6–5.1] Wood units
LVAD *in situ*	44%
Allograft ischaemic time	3.2 [1.5–.0] hrs

Khush KK et al. The Registry of the International Society for Heart and Lung Transplantation: 38th Adult Heart Transplant Report—2021. *J Heart Lung Transplant* 2021;40(10):1035–1049. Continuous factors expressed as median [5th–95th percentiles].

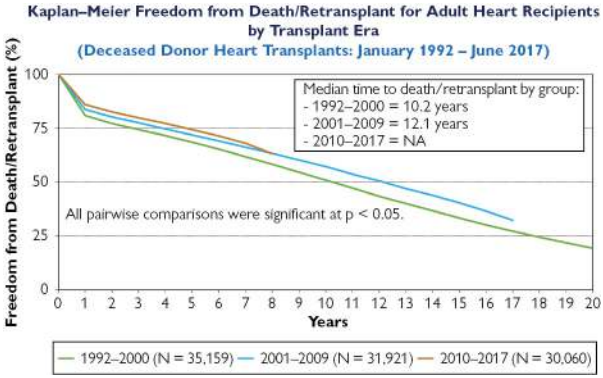

Fig. 8.1 Mehra M, et al. Outcome following heart transplantation by transplant era. *J Heart Lung Transplant*. 2023;42(10):1321–1333.

support while waiting for a heart transplant). Thus only 19% of heart transplant recipients received their heart while on the routine waiting list, and at that same timepoint there were 312 patients on the active heart transplant list. Of the 214 heart transplants performed in the UK, 55 (26%) were DCD (organ donation after circulatory death).

Combined organ transplantation is frequently discussed, but in reality, the absolute number of these procedures performed worldwide is actually very small. In 2015, the number of adult cases reported worldwide were:

• Heart–lung	36
• Heart–kidney	150
• Heart–liver	27
• Heart–kidney–pancreas	0

Key reference

Khush KK, et al. The Registry of the International Society for Heart and Lung Transplantation: 38th Adult Heart Transplant Report—2021. *J Heart Lung Transplant*. 2021;40(10):1035–1049.

Patient selection

The selection of patients for CTx is difficult and traditionally involves clinical assessment and an assimilation of markers for the severity of CHF (Fig. 8.2 and Tables 8.2 and 8.3). It is important to identify those patients at the highest risk of mortality prior to listing, as CTx is far from a benign surgical procedure, with a one-year mortality of approximately 17% (Fig. 8.1), and a median survival of 12.1 years. The assessment process also attempts to rule out the presence of any significant contraindication.

Conventional criteria

- Impaired LV systolic function with NYHA III/ IV symptoms.
- Receiving optimal medical and device therapy.
- Evidence of a poor prognosis (e.g. peak VO_2 max ≤12 mL/kg/min with an RER >1.05 on a beta-blocker or ≤12 mL/kg/min in patients intolerant of a beta-blocker), or a markedly elevated BNP/NT-proBNP).

Uncommon indications for CTx

- Refractory life-threatening arrhythmias.
- Intractable angina not amenable to revascularization or other methods of pain control.
- Restrictive and hypertrophic cardiomyopathy with persisting NYHA III/IV symptoms refractory to conventional treatment and/or recurrent admissions with decompensated HF.

Table 8.2 Recommended pre-transplant investigations

Demographics	Height, weight, and BMI
Blood tests	Urea and electrolytes, full blood count, liver function tests, thyroid function, iron studies, BNP/NT-proBNP, bone profile, lipids, HBA1C, blood group, and tissue typing
Microbiology/virology	Hepatitis B, hepatitis C, HIV, EBV, CMV, VZV, HSV, toxoplasma, MRSA screen
Respiratory lab	Pulmonary function tests, cardiopulmonary exercise test
Imaging	Echocardiogram, cardiac MRI, chest X-ray, Doppler studies (carotid and femoral arteries), ultrasound of the kidneys and liver (where indicated)
Device interrogation	Interrogate pacemaker/CRT/ICD function and history of arrhythmias
Urine	Cotinine (to ensure abstinence from smoking), toxicology, albumin/creatinine ratio
Invasive assessment	Right heart catheterization
Dental review	

Clinical indicators that should prompt consideration for referral

- Patients on optimal medical therapy who have limiting symptoms on exertion.
- ≥2 admissions with decompensated HF within the last 12 months despite adequate therapy and adherence.
- Persistent heart failure after optimized medical and device treatment.
- Increasing BNP/NT-proBNP levels despite adequate HF treatment.
- Calculated SHFM score indicating a >20% 1-year mortality.

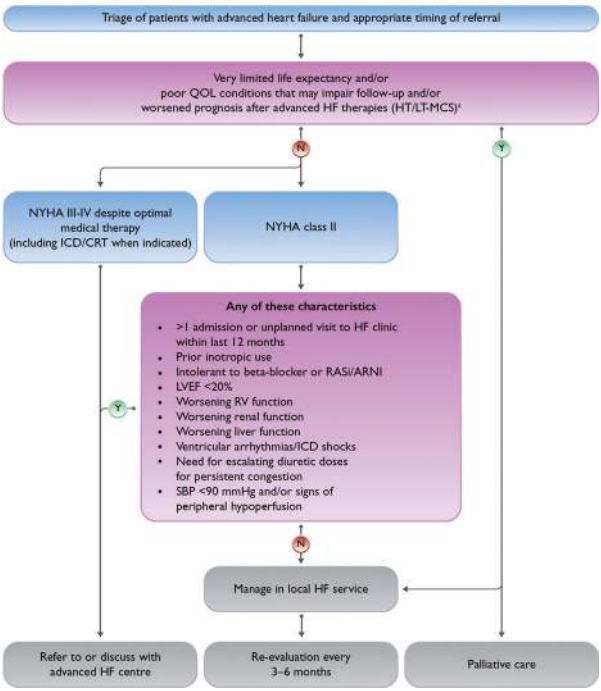

Fig. 8.2 Triage of patients with advanced heart failure and appropriate timing of referral. Adapted from ESC 2021 heart failure guidelines. McDonagh TA, et al. *Eur Heart J*. 2021;42(36):3599–3726.

ARNI = angiotensin receptor-neprilysin inhibitor; CRT = cardiac resynchronization therapy; HF = heart failure; HT = heart transplantation; ICD = implantable cardioverter-defibrillator; LT-MCS = long-term mechanical circulatory support; LVEF = left ventricular ejection fraction; NYHA = New York Heart Association; RASi = renin-angiotensin system inhibitor; RV = right ventricular; SBP = systolic blood pressure; QOL = quality of life. [a] Limited life expectancy may be due to major comorbidities such as cancer, dementia, end-stage organ dysfunction; other conditions that may impair follow-up or worsen post-treatment prognosis include frailty, irreversible cognitive dysfunction, psychiatric disorder, or psychosocial issues.

- Echocardiographic evidence of right ventricular dysfunction or increasing pulmonary artery pressure on optimal treatment.
- Deteriorating renal function attributable to heart failure or inability to tolerate diuretic dosages sufficient to clear congestion without change in renal function.
- Anaemia, involuntary weight loss, liver dysfunction, or hyponatraemia attributable to heart failure.
- Significant episodes of ventricular arrhythmia despite treatment.

Indications for urgent inpatient referral

- Requirement of continuous inotrope infusion or/and mechanical circulatory support (including intra-aortic balloon pump (IABP) to prevent multiorgan failure).
- No scope for revascularization in the setting of ongoing coronary ischaemia.
- Persisting circulatory shock due to a primary cardiac disorder.
- Refractory ventricular arrhythmia.
- An absence of contraindications to transplantation.

Contraindications

Advanced heart failure can lead to secondary organ dysfunction, which increases the risk associated with transplantation and may eventually become irreversible; referral should be considered before these complications become established. Whenever possible, intrinsic organ damage should be differentiated from potentially reversible abnormalities secondary to HF.

There are few *absolute* contraindications to CTx, but there are many factors which are associated with an adverse outcome following CTx.

Absolute contraindications

- Irreversible pulmonary hypertension (see Pulmonary hypertension p. 100).
- Irreversible pulmonary parenchymal disease (e.g. FEV_1 <50% predicted).
- Recent pulmonary embolus.
- Active malignancy.
- Life expectancy markedly compromised by other systemic disease.
- Advanced irreversible hepatic disease.
- Cerebrovascular disease not amenable to revascularization.
- Active infection.
- Inability to comply with medical therapy/immunosuppressive regime.
- Continuing alcohol misuse or substance misuse.

Relative contraindications/risk factors for an adverse outcome

- Age >65 years.
- Advanced irreversible renal disease (eGFR <30 mL/min).
- Diabetes mellitus with end-organ damage.
- Peripheral vascular disease not amenable to revascularization.
- Recent malignancy: collaborate with oncologists to establish risk stratification.

Table 8.3 'I Need Help' markers of advanced heart failure. From Supplementary table 14 McDonagh TA, et al. *Eur Heart J*. 2021;42(36):3599–3726.

I	Inotropes	Previous or ongoing requirement for dobutamine, milrinone, dopamine, or levosimendan
N	NYHA class/NP	Persisting NYHA class III or IV and/or persistently high BNP or NT-proBNP
E	End-organ dysfunction	Worsening renal or liver dysfunction in the setting of HF
E	Ejection fraction	Very low EF <20%
D	Defibrillator shocks	Recurrent appropriate defibrillator shocks
H	Hospitalizations	More than 1 hospitalization with HF in the last 12 months
E	Oedema/escalating diuretics	Persisting fluid overload and/or increasing diuretic requirement
L	Low blood pressure	Consistently low blood pressure with SBP <90 to 100 mmHg
p	Prognostic medication	Inability to uptitrate (or need to decrease/cease) ACE-Is, beta-blockers, ARNIs, or MRAs

- Hepatitis B, C, or HIV positive. May be considered if viral titres are undetectable on/following treatment with no evidence of other organ damage
- Severe obesity (BMI >35).
- Auto-immune conditions.
- Active peptic ulcer disease.
- Severe osteoporosis.
- Smoking.
- Learning disability/dementia.

Key references

Banner NR, et al. UK guidelines for referral and assessment of adults for heart transplantation. *Heart*. 2011;97:1520–1527.

Bhagra SK, et al. Cardiac transplantation: indications, eligibility and current outcomes. *Heart*. 2019;105:252–260.

Mehra MR, et al. Listing criteria for heart transplantation: International Society for Heart and Lung Transplantation guidelines for the care of cardiac transplant candidates. *J Heart Lung Transplant*. 2006;25:1024–1042.

Mehra MR, et al. Outcome following heart transplantation by transplant era. *J Heart Lung Transplant*. 2023;42(10):1321–1333.

Pulmonary hypertension

Irreversible pulmonary hypertension is regarded by most centres to be an absolute contraindication to CTx. If the PA systolic is >60 mmHg and there is one or more of the following three criteria, the risk of right heart failure and early death is increased:

- Pulmonary vascular resistance (PVR) >5 Wood units.
- PVR index (PVRI) >6.
- Transpulmonary gradient (TPG) ≥15 mmHg.

How to assess the reversibility of pulmonary hypertension

Reversibility of pulmonary hypertension should be assessed as follows:

- The Swan–Ganz catheter should remain *in situ*.
- Give oxygen therapy.
- Infuse a vasodilator (e.g. glyceryl trinitrate or sodium nitroprusside) while maintaining systolic blood pressure >85 mmHg.

If unsuccessful, the following can be considered:

- an infusion of dobutamine or milrinone.
- mechanical adjuncts, e.g. IABP or VAD.

If PVR is reversed, then the regime should be recorded in the notes. The PVR should then be checked every 3–6 months.

If the PVR can be reduced to <2.5 Wood units, but the systolic blood pressure falls <85 mmHg, the patient remains at high risk of right heart failure and mortality after cardiac transplantation.

Transpulmonary gradient (TPG) = Mean PAP–PCWP

PVR = TPG/cardiac output (measured in Wood units).

Example

Normal TPG approximately 6 mmHg.

Normal cardiac output (CO) approximately 5 L/minute.

PVR = 6/5 = 1.2 Wood units.

1 Wood unit = 80 dyne s/cm^5.

Normal range for pulmonary vascular resistance = 1.25–2.5 Wood units.

Normal range for pulmonary vascular resistance = 100–200 dyne s/cm^5.

Body surface area = square root of (height (cm) × weight (kg)/3600).

PVR index (PVRI) = PVR/body surface area.

Key references

Mehra MR, et al. Listing criteria for heart transplantation: International Society for Heart and Lung Transplantation guidelines for the care of cardiac transplant candidates. *J Heart Lung Transplant.* 2006;25:1024–1042.

Mosteller RD. Simplified calculation of body surface area. *N Engl J Med.* 1987;317:1098.

The CTx procedure

An orthotopic CTx in a patient with dilated cardiomyopathy is a relatively straightforward procedure in experienced hands. Conversely, transplants in patients who have undergone previous cardiac surgery (especially mechanical circulatory support—MCS), and those with abnormal anatomy can be technically challenging.

Donor compatibility

- Principal match is ABO blood group.
- Appropriate size matching (allowing for recipient sex and pulmonary hypertension).

Need to avoid specific donor HLA antigens in sensitized recipients.

The procedure (bicaval technique)

Prior to the procedure

- The immunosuppressive and antibiotic regime is commenced according to local protocol.
- The heart is transported in cold storage (4–8°C) to the transplant centre with a minimum of delay.
- The donor heart is inspected for any damage and for the presence of a persistent foramen ovale which, if present, should be closed (to eliminate the risk of right-to-left shunting if RV dysfunction should complicate the postoperative course).

The recipient cardiectomy is performed in such a way as to yield homograft valves for use in other patients. The recipient RA is resected by separating it from the SVC and IVC, and the posterior wall of the recipient's left atrium (LA) and surrounding tissue is left as a bridge between the recipient's four pulmonary veins.

The implant (Fig. 8.3): The LA anastomosis is performed first and requires particular attention because it will be relatively inaccessible at the end of the procedure. The donor and recipient PAs are then anastomosed end-to-end, followed by the donor and recipient aortas. The SVC and IVC anastomoses are usually performed before releasing the aortic cross-clamp, although this may be done before to minimize ischaemia time.

The majority of hearts spontaneously return to sinus rhythm following release of the aortic cross-clamp and restoration of coronary perfusion. However, some require internal cardioversion from ventricular fibrillation. Transient atrioventricular block is common but usually resolves within the first few hours. Initial sinus node dysfunction is also common. Thorough de-airing is essential at the end of the procedure including suction from the ascending aorta in order to protect the coronary and cerebral circulation.

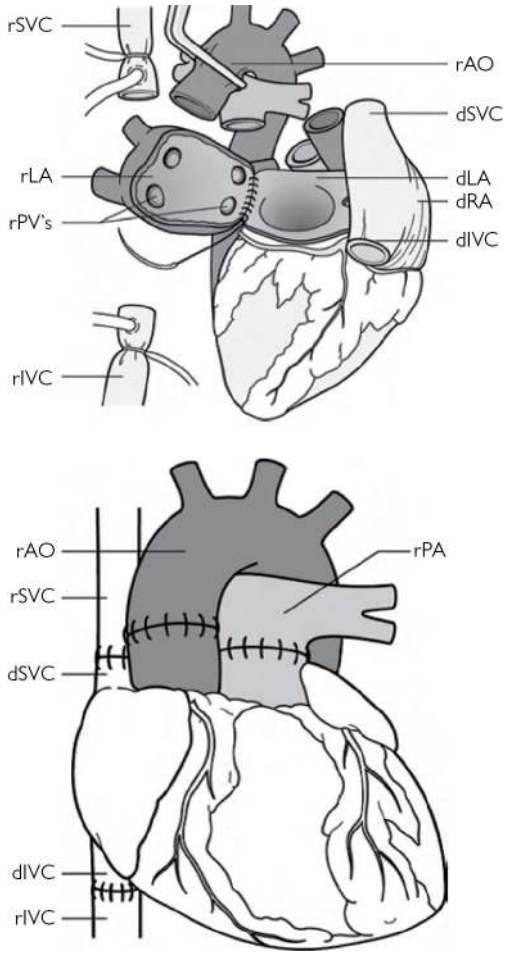

Fig. 8.3 Orthotopic heart transplantation using the bicaval technique. AO = aorta; d = donor; IVC = inferior vena cava; LA = left atrium; PA = pulmonary artery; PVs = pulmonary veins; r = recipient; RA = right atrium; SVC = superior vena cava.

Reproduced from McDonagh, Gardner, Clark & Dargie, *Oxford Textbook of Heart Failure*, 2011 with permission from Oxford University Press.

Post-transplant management

The immediate postoperative management of heart transplant recipients offers several unique challenges (Table 8.4). Patients should therefore be managed with a multidisciplinary approach. Common complications include:

Bleeding—of particular concern in patients undergoing redo surgery or following bridging with an LVAD. Early reversal of anticoagulation and the monitoring of haemostatic function with a thromboelastogram can be of assistance in the management of such patients. Platelet transfusion may be required, especially in those who have been receiving dual antiplatelet drug therapy, but the use of blood products appears to be associated with a higher risk of right heart failure.

Table 8.4 Common postoperative complications following orthotopic heart transplantation

- Bleeding
- Surgical
- Coagulopathy
- Acute right ventricular failure
- Pulmonary hypertension (recipient)
- Pulmonary artery stenosis/torsion
- Primary graft failure
- Acute biventricular failure
- Primary graft failure
- Rejection
- Pericardial effusion/tamponade
- Inflammatory response to surgery
- Bleeding
- Potential space after resection of previously enlarged heart
- Rarely: infection, rejection, drug-related (sirolimus)
- Anastomotic complications
- Secondary to stenosis of SVC, IVC, or pulmonary artery
- Vasoplegia
- Systemic inflammatory response
- Pre-existing infection
- Primary graft failure
- Prolonged cardiopulmonary bypass
- Pseudosepsis (milrinone accumulation in renal dysfunction)
- Infection
- Bacterial
- CMV
- Arrhythmia
- Sinus node dysfunction
- Atrioventricular block
- Atrial tachyarrhythmia (e.g. atrial flutter)
- Renal dysfunction
- Hypoalbuminaemia.

Acute RV failure—frequently seen in the immediate post-bypass period and is of critical importance. Pulmonary vascular resistance should be managed with inhaled and systemic and/or intravenous vasodilator therapy. Inhaled nitric oxide may be used prophylactically in patients with a known elevation of pulmonary vascular resistance and should be initiated early where there is any sign of right ventricular distension or dysfunction. A PAFC should be inserted to allow continuous monitoring of cardiac output and pulmonary artery pressures. Some surgeons also use a left atrial line to allow direct monitoring of left-sided filling pressures. Anastomotic complications, such as kinking or torsion at the pulmonary anastomosis, can contribute to postoperative right ventricular dysfunction.

Arrhythmia—sinus bradycardia and sinus arrest are common. Epicardial pacing wires must be placed on the atrium and ventricle at the time of surgery. Transient atrioventricular block is common but usually resolves within the first few hours. Ultimately, the implantation of a permanent pacemaker is required in ~5 % of recipients.

Vasoplegia—is a common condition post-heart transplant, characterized by persistent low systemic vascular resistance despite a normal or high cardiac index, resulting in profound and uncontrolled vasodilation. Risk factors include advancing age, preoperative and postoperative renal dysfunction, preoperative left ventricular assist device support, and prolonged cardiopulmonary bypass time.

Early graft failure—failure to achieve satisfactory haemodynamics with adequate cardiac output and acceptable filling pressures, without the use of excessive inotropic support, should prompt a complete diagnostic reassessment to exclude technical problems or rejection. Occasionally, short-term support with a VAD (e.g. Levotronix) or venoarterial extracorporeal membrane oxygenation (VA-ECMO) is necessary to avoid a slide into multisystem organ failure. Retransplantation for acute graft failure early after the original CTx has a 40–60% risk of death at one year.

Cardiac allograft rejection

Rejection can be either acute cellular (ACR) or antibody-mediated (AMR), although in the non-sensitized patient, cellular rejection is the most common form of acute rejection. ISHLT registry data suggests that ~30% of CTx recipients have a rejection episode in the first postoperative year. Risk factors include:

- Female sex.
- Younger patients.
- Patients receiving immunosuppressive induction therapy.

Patients who do not have an acute rejection episode in the first year have a better 3-year survival (94% vs. 88%, $p = 0.001$), and are less likely to develop cardiac allograft vasculopathy.

Early rejection is often asymptomatic but clinical signs suspicious of cardiac allograft rejection include:

- Pyrexia.
- Atrial arrhythmias.
- Changes in ECG voltage.
- Third heart sound.
- Heart failure.

Endomyocardial biopsy

(See ➔ Chapter 29.)

In 1973, Prof Philip Caves first described transvenous endomyocardial biopsy to diagnose cardiac allograft rejection (Table 8.5). Most centres continue to use this technique in the early phase after CTx, when the risk of rejection is highest, and while immunosuppressive therapy is slowly weaned to maintenance doses. This is generally performed from a right internal jugular approach, although the femoral route can be employed with the use of a long venous sheath. An example of a biopsy protocol is:

- Weekly for the first 6 weeks.
- Fortnightly from 6 weeks to 3 months.
- 6-weekly up to one year.
- Thereafter, only when rejection is clinically suspected.

Potential complications (total procedural risk of ~3%)

- Arrhythmias.
- Tamponade.
- Tricuspid valve trauma.
- Pneumothorax.
- Conduction disturbance.
- Air embolism.
- Nerve palsy.

Treatment of cardiac allograft rejection

- Maintain oral immunosuppressive therapy at optimum levels and ensure compliance.
- Grade 1R ACR without evidence of allograft dysfunction does not require further therapy.

Table 8.5 The 2005 revision of the working formulation for classification of acute cellular rejection of the heart

Grade	Category	Description
0	**No rejection**	
1R	**Mild ACR**	Multifocal interstitial and/or perivascular mononuclear infiltrates of lymphocytes, some macrophages and occasional eosinophils ± one focus of myocytolysis
2R	**Moderate ACR**	Two or more foci of mononuclear cell infiltrates expanding interstitium and with two or more foci of myocyte damage
3R	**Severe ACR**	Diffuse mononuclear cell infiltrates expanding interstitium ± oedema ± haemorrhage ± neutrophils ± widespread myocyte necrosis ± vasculitis

ACR, acute cellular rejection; R, revised (avoiding confusion with the grades used in the 1990 Working Formulation).

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- For Grades 2R and 3R ACR, one of the following additional measures is prescribed:
  - Methylprednisolone 1 g IV daily for 3 days.
  - Antithymocyte globulin (ATG) 0.5 mL/kg/day for 3 days.

Key reference

Colvin MM, et al. Antibody-mediated rejection in cardiac transplantation. *Circulation*. 2015;131(18):1608–1639.

Immunosuppressive agents

Patients are usually maintained on tacrolimus and mycophenolate mofetil (MMF) post-heart transplantation, with steroids used for the first 8–10 months.

Corticosteroids

- Intraoperative: 1 g methylprednisolone at release of cross-clamp.
- Days 1 and 2: 125 mg methylprednisolone IV 12-hourly, then oral prednisolone 60 mg/day decreasing by 5 mg each day towards a maintenance of 15 mg and then weaned and stopped after 8–10 months.
- Thereafter, steroids are given for acute rejection (given IV).

Tacrolimus

- Calcineurin inhibitor.
- Alternative to ciclosporin (cyclosporin).
- 0.15–0.3 mg/kg/day orally as two divided doses.

Mycophenolate mofetil (MMF)

- Antiproliferative immunosuppressant.
- As soon as the patient is able to take oral medications, MMF is commenced at a dose of 1 g bd (within 5 days of transplant).

Ciclosporin (cyclosporin)

- Calcineurin inhibitor.
- Commenced when haemodynamics are stable, without evidence of hepatic or renal failure.
- Starting dose: 4 mg/kg/day orally or 1.5 mg/kg/day IV in two divided doses (the IV dose is approximately a third of the oral dose).
- Subsequent dose depends on blood levels and renal function, and can be measured in two ways:
  - C_0—trough level.
  - C_2—2 hours post-dose.
- Target C_0 levels:
  - 300–400 micrograms/L for the first 4 weeks.
  - 200–250 micrograms/L from 4 weeks to 6 months.
  - 150–200 micrograms/L from 6 months to 1 year.
  - 100–150 micrograms/L after 1 year.

Azathioprine

- Antiproliferative immunosuppressant.
- Day 0: 4 mg/kg IV at induction.
- Postoperatively: 2 mg/kg/day as a single dose if white cell count >4.
- Discontinued when mycophenolate mofetil commenced.

► TPMT deficiency suggests risk of azathioprine toxicity.

Chapter 9

Mechanical circulatory support

Introduction

Mechanical circulatory support (MCS) is a collection of technologies that offer short- or long-term ventricular assistance for patients with heart failure. They are rapidly evolving and have an expanding indication. They can be classified as follows:

- Short-term ventricular support.
  - Intra-aortic balloon pump (IABP) (➔ see Chapter 30).
  - Axial flow pump (e.g. Impella).
  - Centrifugal pump (e.g. CentriMag) – peripheral or central; with or without an oxygenator to achieve extracorporeal membrane oxygenation (ECMO).
  - Pulsatile ventricular assist device (VAD).
- Long-term ventricular support.
  - Continuous-flow VAD (cVAD).
  - Pulsatile VAD (pVAD).
  - Total artificial heart (TAH).

Furthermore, these devices are commonly described according to their intended use (Table 9.1):

VADs are available to support the left ventricle (LVAD), right ventricle (RVAD), or both (BiVAD). In reality, LVADs account for the vast majority of long-term VADs (Fig. 9.1).

Currently, the HeartMate 3 (Abbott Laboratories) is the only durable LVAD used in the United States and Europe since the HeartWare HVAD was discontinued after reports of device malfunction and higher rates of stroke and mortality compared with the HeartMate 3.

Short-term devices are used in patients with acute heart failure and cardiogenic shock, with evidence of end-organ dysfunction as a bridge to decision (BTD), recovery (BTR), or transplantation (BTT). Extracorporeal membrane oxygenation—either peripheral or central—can also be used in

Table 9.1 Terms used to describe the use of MCS

Bridge to decision (BTD):	Use of MCS in patients with drug-refractory acute circulatory collapse and at immediate risk of death to sustain life until a full clinical evaluation can be completed and additional therapeutic options can be evaluated.
Bridge to candidacy (BTC):	Use of MCS to improve end-organ function in order to make an ineligible patient eligible for transplantation.
Bridge to transplantation (BTT):	Use of MCS to keep a patient at high risk of death before transplantation alive until a donor organ becomes available.
Bridge to recovery (BTR):	Use of MCS to keep patient alive until intrinsic cardiac function recovers sufficiently to remove MCS.
Destination therapy (DT):	Long-term use of MCS as an alternative to transplantation in patients with end-stage heart failure ineligible for transplantation.

* Destination therapy is not licensed in the UK.

this population. This and other short-term strategies used in acute heart failure will be covered in more detail in ➔ Chapter 26.

Long-term devices are generally reserved for patients with chronic heart failure, as a bridge to transplantation (BTT), transplant candidacy (BTC), myocardial recovery (BTR), or—in some countries—as destination therapy (DT). Currently, in the United Kingdom, long-term VADs are only indicated as BTT (Fig. 9.2).

INTERMACS

Seven clinical profiles were developed for the Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) to help characterize MCS recipients (Table 9.2):

1. Critical cardiogenic shock—'crash and burn'.
2. Progressive decline—'sliding on inotropes'.
3. Stable but inotrope dependent—'dependent stability'.
4. Resting symptoms.
5. Exertion intolerant.
6. Exertion limited—'walking wounded'.
7. Advanced NYHA class III.

Adverse prognostic factors

The INTERMACS registry (see Fig. 9.1) has identified adverse prognostic markers to VAD placement:

- Need for an RVAD.
- INTERMACS status 1 and 2.
- History of stroke.
- Advancing age.
- On a ventilator.
- History of or concomitant cardiac surgery.
- High BMI.
- Ascites.
- Diabetes.
- Renal dysfunction.

The right heart

The right heart is of great importance when considering LVAD placement. Evaluation of right ventricular function is crucial as postoperative right ventricular failure greatly increases perioperative mortality and reduces survival to, and after, transplantation. Consequently, BiVAD, rather than LVAD, support should be considered for BTT in patients with biventricular failure or at high risk of developing right ventricular failure after LVAD implantation. However, RVAD placement will be associated with an increased risk of an adverse outcome. Thus, referral before right ventricular failure develops is preferable.

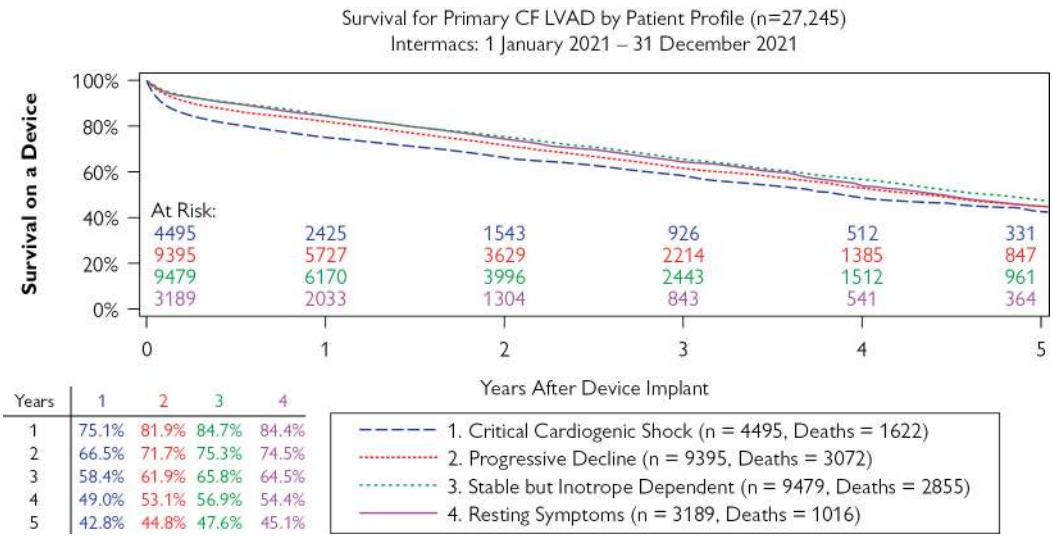

Fig. 9.1 Outcome following LVAD therapy stratified by INTERMACS status. Yuzefpolskaya et al. The Society of Thoracic Surgeons Intermacs 2022 Annual Report. *Ann Thorac Surg*. 2023;115:311–328.

Table 9.2 Interagency Registry for Mechanically Assisted Circulatory Support profile descriptions of patients with advanced heart failure. Adapted from ESC 2021 heart failure guidelines. McDonagh TA, et al. *Eur Heart J*. 2021;42(36):3599–3726.

Profile	Time frame for intervention
Profile 1. Critical cardiogenic shock Patient with life-threatening hypotension despite rapidly escalating inotropic support, critical organ hypoperfusion, often confirmed by worsening acidosis and/or lactate levels. 'Crash and burn.'	Definitive intervention needed within hours.
Profile 2. Progressive decline Patient with declining function despite i.v. inotropic support, may be manifest by worsening renal function, nutritional,depletion, inability to restore volume balance. 'Sliding on inotropes.' Also describes declining status in patients unable to tolerate inotropic therapy.	Definitive intervention needed within few days.
Profile 3. Stable on inotrope or inotrope dependent Patient with stable blood pressure, organ function, nutrition, and symptoms on continuous i.v. inotropic support (or a temporary circulatory support device or both) but demonstrating repeated failure to wean from support due to recurrent symptomatic hypotension or renal dysfunction. 'Dependent stability.'	Definitive intervention elective over a period of weeks to few months.
Profile 4. Frequent flyer Patient can be stabilized dose to normal volume status but experiences daily symptoms of congestion at rest or during activities of daily living. Doses of diuretics generally fluctuate at very high levels. More intensive management and surveillance strategies should be considered, wtii.ch may in some cases reveal poor compliance that would compromise outcomes with any therapy. Some patients may shuttle between 4 and 5.	Definitive intervention elective over a period of weeks to few months.
Profile 5. Housebound Comfortable at rest and with activities of daily living but unable to engage in any other activity living predominantly within the house. Patients are comfortable at rest without congestive symptoms, but may have underlying refractory elevated volume, status, often with renal dysfunction. If underlying nutritional status and organ function are marginal, patients may be more at risk than INTERMACS 4, and require definitive intervention.	Variable urgency. Depends upon maintenance of nutrition, organ function, and activity.

Table 9.2 (*Contd.*)

Profile	Time frame for intervention
Profile 6. Exertion limited Patient without evidence of fluid overload, comfortable at rest and with activities of daily living and minor activities outside-the home but fatigues after the first few minutes of any meaningful activity. Attribution to cardiac limitation requires careful measurement of peak oxygen consumption, in some cases with haemodynamic monitoring, to confirm severity of cardiac impairment. 'Walking wounded.'	Variable, depends upon maintenance of nutrition, organ function, and activity level.
Profile 7. Advanced HYHA class III symptoms Patient without current or recent episodes of unstable fluid balance, living comfortably with meaningful activity limited to mild physical exertion.	Heart transplantation or MCS may not be currently indicated.

Short-term MCS

Short-term mechanical circulatory support is indicated to reverse critical end-organ hypoperfusion in the setting of cardiogenic shock (patients in INTERMACS 1 and 2, see Fig. 9.2). Options include IABP, Impella, Centrimag VADs, and ECMO. It is useful for primary graft dysfunction post-cardiac transplantation, as well as for acute and severe cardiac dysfunction as a bridge to:

- Decision.
- Recovery.
- Heart transplantation.
- Long-term VAD (bridge to bridge).

Intra-aortic balloon pump

(See ➔ Chapter 30.)

An IABP comprises a 30–50 mL helium-filled balloon placed in the descending thoracic aorta, connected to a pneumatic pump. The pump is most frequently triggered from the ECG trace and inflates the balloon during diastole, and then rapidly deflates the balloon in systole. The balloon inflation augments diastolic blood pressure, resulting in improved coronary and cerebral perfusion. Balloon deflation reduces afterload and peripheral vascular resistance and increases stroke volume. Unlike inotropes and vasopressors, the benefits of the balloon pump are not accompanied by an increase in myocardial oxygen demand.

Impella

The Impella device is a percutaneous short-term VADs that is placed into the left ventricle via the femoral, subclavian, or axillary artery. A microaxial system pumps blood from the LV into the ascending aorta at a rate of 2–5 to 5 L/min depending on the device used. It is approved for use in high-risk percutaneous coronary intervention and cardiogenic shock.

There is recent evidence to support the use of Impella in the treatment of patients with STEMI-related cardiogenic shock. In the DanGer Shock trial, there was a lower risk of death from any cause at 180 days in those receiving Impella compared to standard care alone. However, the composite incidence of adverse events was higher with the use of the microaxial flow pump, including higher rates of bleeding, limb ischaemia, and sepsis.

Key reference

Møller JE, et al. Microaxial flow pump or standard care in infarct-related cardiogenic shock. *N Engl J Med*. 2024;390:1382–1393.

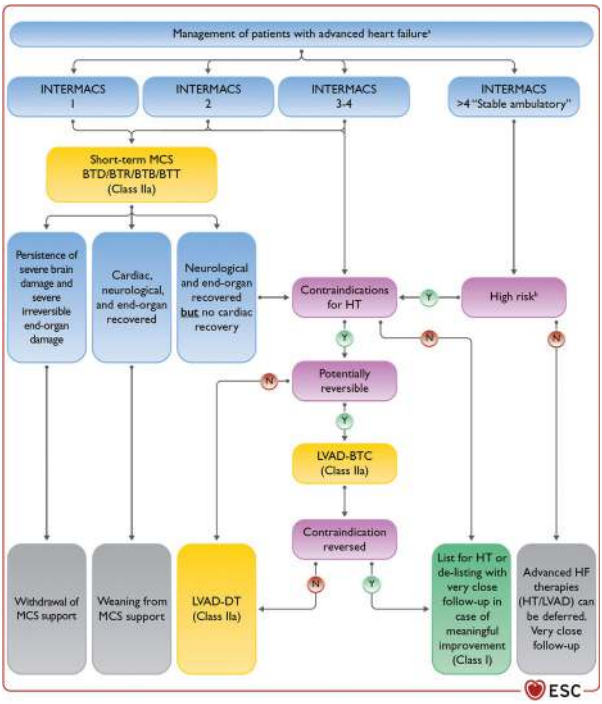

Fig. 9.2 Algorithm for the treatment of patients with advanced heart failure. BTB = bridge to bridge; BTC = bridge to candidacy; BTD = bridge to decision; BTR = bridge to recovery; BTT = bridge to transplantation; CA = cardiac amyloidosis; DT = destination therapy; ESC = European Society of Cardiology; HCM = hypertrophic cardiomyopathy; HF = heart failure; HFA = Heart Failure Association; HT = heart transplantation; INTERMACS = Interagency Registry for Mechanically Assisted Circulatory Support; LVAD = left ventricular assist device; LVAD-BTC = left ventricular assist device bridge to candidacy; LVAD-DT = left ventricular assist device destination therapy; MCS = mechanical circulatory support. Adapted from ESC 2021 heart failure guidelines. McDonagh TA, et al. *Eur Heart J*. 2021;42(36):3599–3726.

Long-term MCS

Cardiac transplantation remains an excellent treatment for selected patients with end-stage HF, with good long-term survival (see ➔ Chapter 8). However, with the increasing numbers of patients with end-stage HF, limited organ donation has meant that transplant waiting lists are growing—particularly for those patients who are blood group 'O'.

Increasingly, long-term LVADs are seen as an option to BTT. LVADs can also be used to permit recovery of end-organ dysfunction, so-called 'bridge to candidacy' (BTC), which may allow ineligible patients to become eligible for transplantation. This is particularly the case in patients who have pulmonary hypertension, or renal dysfunction thought due to hypoperfusion. In some countries, transplant ineligible patients are also considered for LVAD therapy as so-called DT.

In some instances, LV reverse remodelling and functional improvement during MCS permit removal of the VADs ('bridge to recovery'—BTR). This is more likely in patients with a non-ischaemic, non-infiltrative cardiomyopathy, or in individuals with a myocarditis (although this is less likely in patients with giant cell myocarditis).

VADs may ultimately become a more general alternative to cardiac transplantation, as survival rates in carefully selected patients receiving the latest continuous-flow devices are much better than with medical therapy alone. Although it is stated that patients receiving these devices also have a post-transplant survival rate similar to those not requiring bridging, this needs further clarification. However, LVADs remain significantly expensive, and, despite technological improvements, they are associated with a number of problems that require the patient to be monitored closely. The ESC recommends that such devices are only implanted and managed at tertiary heart failure centres with appropriately trained, specialist HF physicians and surgeons. Ideally these centres should also undertake cardiac transplantation.

Complications of the mechanical cardiac support devices

- Thromboembolism including cerebrovascular events; therefore, anticoagulation is essential.
- Bleeding.
- Device-related infection—particularly drive line.
- Mechanical dysfunction or failure.
- Haemolysis with the resulting need for transfusion, which is a concern in pre-transplantation patients due to the risk of antibody formation.
- Lack of RV support (in LVADs).

Long-term MCS devices

Although there are several different long-term LVADs said to be in development there is currently only one device routinely available: the Abbott HeartMate 3 (Figs. 9.3 and 9.4). This is indicated in selected patients who are in INTERMACS profiles 2–4, and possibly higher when they have high-risk characteristics. These third-generation LVADs have wide passages to reduce shear stress, are frictionless as there are no bearings and are designed to reduce stasis of blood that could result in thrombosis. Consequently, they have increased reliability, smaller size, and reduced complication rate—in particular pump thrombosis. They are used for BTT or to reverse contraindications to heart transplantation (BTC), or—in some countries—as DT. Current 2-year survival rates in patients receiving the latest continuous-flow LVADs are comparable to those after heart transplantation, although adverse events negatively affect QOL. Among patients with contemporary continuous-flow LVADs, actuarial survival is now reported to be 83% at 1 year and 52% at 5 years. Two-year survival was 84.5% and survival free of disabling stroke or need of reoperation for LVAD malfunction was 76.9% with a centrifugal-flow LVAD in MOMENTUM 3. Whether LVADs can match long-term prognosis compared to cardiac transplantation is uncertain.

HeartMate 3 LVAD

The HeartMate 3 (Fig. 9.3) is a continuous flow, centrifugal pump, with a bearing-less magnetically levitated rotor. It is currently the leading

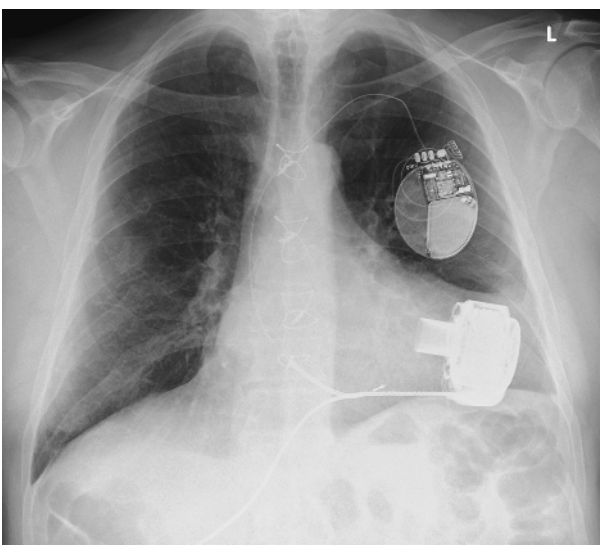

Fig. 9.3 Chest X-ray of HeartMate 3 LVAD (and single chamber ICD).

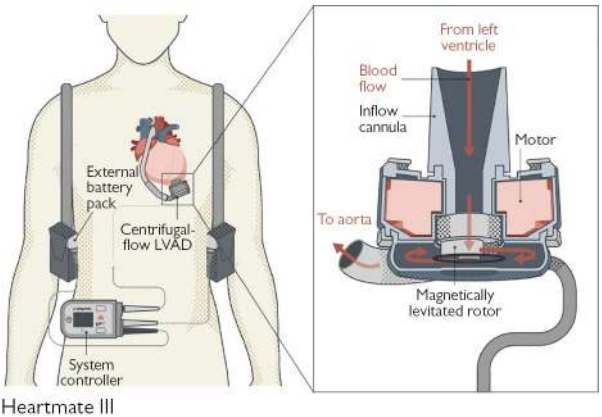

Fig. 9.4 Schematic of HeartMate 3 LVAD. From Akhtar W et al. British societies guideline on the management of emergencies in implantable left ventricular assist device recipients in transplant centres. *Intensive Care Med*. 2024 Apr;50(4):493–501.

continuous-flow long-term VADs used worldwide. The device is placed in the LV apex with the outflow into the ascending aorta, and an externalized driveline (Fig. 9.4). It has been implanted in more than 20,000 patients worldwide.

Total artificial heart (TAH)

These devices are inserted into the thorax in place of the patient's ventricles taking blood from the atria with outflow into the pulmonary artery and aorta. Although they are occasionally used as a bridge to transplantation, they only account for 1% of MCS implanted. NICE evaluated TAH in 2017 [IPG602] and found that data supporting their use were 'limited in quantity and quality' and therefore recommended that this procedure should 'only be used with special arrangements for clinical governance, consent and audit or research'.

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Yuzefpolskaya, et al. The Society of Thoracic Surgeons Intermacs 2022 Annual Report. *Ann Thorac Surg*. 2023;115:311–328.

Bridge to transplantation

Patients who await urgent cardiac transplantation have a higher mortality rate than those on the 'routine' list.

LVAD insertion as a BTT (Fig. 9.5) is usually considered because of deteriorating clinical status when it is felt the patient will not survive long enough to receive a donor organ. Alternatively, if the patient develops secondary organ dysfunction such that transplantation becomes contraindicated, support from the LVAD may allow renal function, nutritional status, and pulmonary vascular resistance to improve before subsequent transplantation, which usually takes several weeks or months. Transplantation should only be considered once these improvements have occurred (BTC).

The 2021 ESC guidelines recommend that an LVAD should be considered as a BTT in patients with >2 months of severe symptoms despite optimal medical and device therapy and more than one of the following:

- LVEF <25% and, if measured, peak VO_2 <12 mL/kg/min and/or <50% predicted value.
- ≥3 HF hospitalizations in the previous 12 months without an obvious precipitating cause.
- Dependence on i.v. inotropic therapy or temporary MCS.
- Progressive end-organ dysfunction (worsening renal and/or hepatic function) due to reduced perfusion and not to inadequate ventricular filling pressure (PCWP ≥20 mmHg and SBP ≤80–90 mmHg or CI ≤2 L/min/m^2).
- Deteriorating right ventricular function.

The timing of transplantation has been demonstrated to be very important in the outcome for patients receiving mechanical support devices. As stated previously, mechanical support improves survival to transplantation but the outcomes following cardiac transplantation are less certain.

An analysis of 466 patients who had received cardiac transplants after LVAD support demonstrated that those who received a transplant within 2

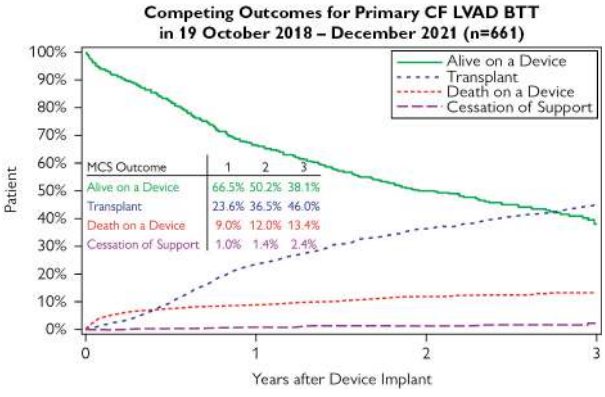

Fig. 9.5 Outcome following an LVAD as BTT. Yuzefpolskaya, et al. *Ann Thorac Surg*. 2023;115:311–328.

weeks of LVAD implant had a 1-year survival of 74%, while those who received their transplant more than 6 months after LVAD implant had a 1-year survival of 76%. By contrast, those who had a transplant 4–6 weeks after LVAD implantation had a 1-year survival of 92%.

An LVAD requires a window of time to facilitate resolution of end-organ dysfunction, particularly renal failure. However, complications from the LVAD, particularly thromboembolic and septic events can impact on subsequent transplantation success.

Bridge to recovery

There is increasing evidence that LVAD unloading, can result in recovery of myocardial function in a small proportion of patients. Ultimately, this may allow the LVAD to be removed, and the need for cardiac transplantation avoided. This is much more likely in patients with a non-ischaemic cardiomyopathies, or myocarditis, where the haemodynamic effects of mechanical cardiac support result in reverse remodelling of the myocardium.

The Harefield experience

In the Harefield Hospital, a strategy was adopted to maximize the incidence of myocardial recovery in selected patients with DCM, and to reduce the likelihood of deterioration following LVAD explantation. In two case series from this centre, 73% (11 out of 15) of such patients had sufficient myocardial recovery to remove the pump. This strategy combined:

- mechanical unloading with LVAD support.
- optimal medical therapy for heart failure.
- specific pharmacological therapy with clenbuterol—a β2 agonist.

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Destination therapy

In the future, as LVADs become less expensive, more reliable, and survival increases, it is likely that they will be more widely used as DT.

The first randomized, controlled trial of an LVAD in patients with advanced heart failure who are ineligible for cardiac transplantation (REMATCH) (Fig. 9.6), included 129 patients in NYHA class IV heart failure. They were randomized to receive either the HeartMate VE LVAD (a pulsatile device), or to optimal medical therapy. The primary endpoint of all-cause mortality was 48% lower in the group receiving the LVAD (p = 0.001). However, although mortality was statistically reduced, few patients in the group that received the assist device survived longer than 2 years and there were significant limitations with the device used, including infection, bleeding, and device failure. Despite this, the trial resulted in the FDA approving this LVAD as destination therapy in 2002.

Newer device designs with continuous flow have reduced complications and improved survival. Results of a trial randomizing the Heartmate II continuous-flow pump against the pulsatile Heartmate VE device saw a one- and 2-year survival of 68% and 58%, respectively, with the continuous-flow device and 55% and 24%, respectively, for the pulsatile device.

There were significant reductions in the rates of major adverse events (including device-related infection) and rehospitalization among patients with a continuous-flow device. The Heartmate II was approved for destination therapy by the FDA in 2009, and the HeartMate 3 in 2018.

Many other countries are awaiting further trials with newer devices and reduced costs before committing to such an expensive therapy for heart failure. However, the survival with modern long-term LVADs looks promising (Fig. 9.7).

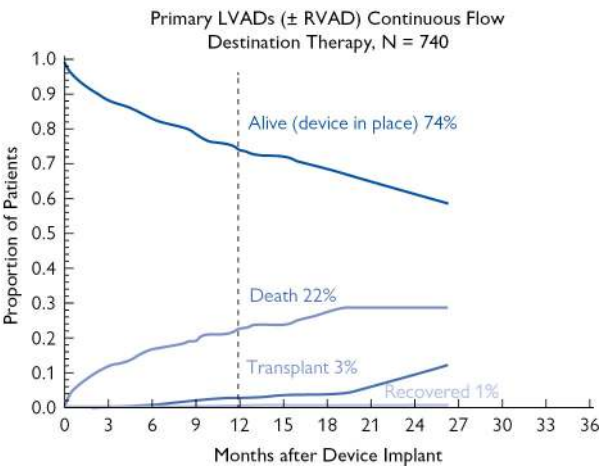

Fig. 9.6 Outcome following LVAD as DT.

Reprinted *J Heart Lung Transplant* 31, Kirklin et al. 4th INTERMACS Report 117–126, 2012.

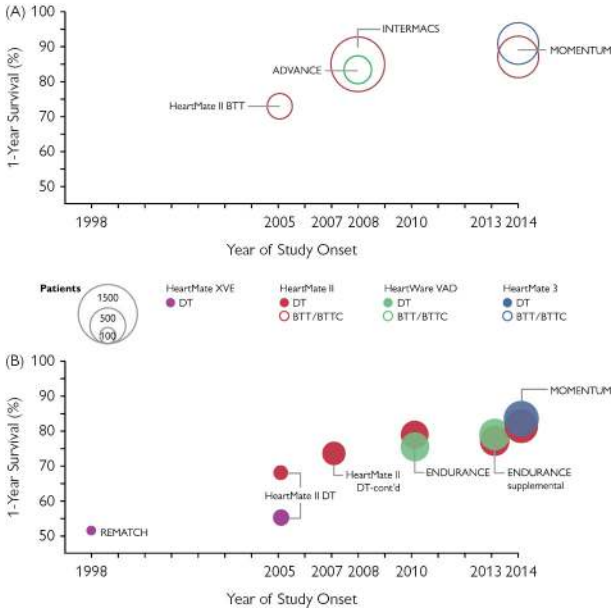

Fig. 9.7 Trends in the rate of 1-year survival across clinical study groups over time. A and B display the 1-year survival rates for patients enrolled in large studies of left VADs. **A**, Patients implanted as bridge-to-transplant or bridge-to-transplant candidacy (both represented as open circles). **B**, Patients implanted as destination therapy (solid circles). Data are shown according to the respective start dates of each study. Each circle is colour coded for each type of implanted device with purple for HeartMate XVE, maroon for HeartMate II, green for HeartWare, and blue for HeartMate 3. The area of each circle represents the sample size in each group (reference sizes are shown in the key). BTC indicates bridge to candidacy; BTT = bridge-to-transplant; BTTC = bridge-to-transplant candidacy; DT = destination therapy; and VAD, ventricular assist device. From: Chaudry S, et al. Left ventricular assist devices: a primer for the general cardiologist. *J Am Heart Assoc*. 2022;11:e027251.

Clinical trial evidence base

REMATCH (Randomized evaluation of mechanical assistance for the treatment of congestive heart failure) study

MOMENTUM 3 Goldstein DJ, et al. Association of clinical outcomes with left ventricular assist device use by bridge-to-transplant or destination therapy intent: the multicenter study of maglev technology in patients undergoing mechanical circulatory support therapy with HeartMate 3 (MOMENTUM 3) randomized clinical trial. *JAMA Cardiol*. 2020;5:411–419.

Tips and tricks

How to measure blood pressure on a VAD

As patients with LVADs invariably have a narrow arterial pulse pressure, their palpable pulse may be absent resulting in the inability of automated blood pressure machines to register BP accurately. The solution is to use a Doppler device to assess BP by finding the pressure at which the Doppler sound returns during cuff deflation. This pressure has been shown to correspond to the mean arterial pressure (MAP). This should be kept between 75–85 mmHg. A high MAP (>90 mmHg) has been shown to be associated with an increased risk of stroke and pump thrombosis, and a low MAP (≤75 mmHg) is associated with an increased risk of mortality.

Arrhythmias

Patients with HF commonly have both atrial and ventricular arrhythmias. Implantable cardioverter defibrillator (ICD) placement in LVAD recipients is slightly controversial, as sustained ventricular arrhythmias may be remarkably well-tolerated. However, many patients who receive an LVAD already have an ICD. While it is standard practice to reactivate a previously implanted ICD in an LVAD recipient, this should include discussion of the revised risks and benefits of ICD therapy following LVAD implantation. Patients should be warned that they might receive ICD shocks that may not be lifesaving. When ICDs are reactivated, device programming should minimize the risk of repeated shocks for non-sustained or well-tolerated ventricular arrhythmias. Implantation of a primary prevention ICD *after* implantation of an LVAD is not supported by current evidence, poses potential risks, and should be the subject of a clinical trial before it becomes standard practice.

LVAD emergencies and cardiopulmonary resuscitation

It should be remembered that patients with LVADs often do not have a palpable pulse. Where an assumed cardiac arrest situation is encountered, the first step is to auscultate the chest to hear if there is a mechanical LVAD noise, as well as assessing end-organ perfusion. If these are felt to be impaired, the driveline and controller should be examined to ensure they are appropriately connected and that flows are maintained. In patients with persistent low flow as well as evidence of end-organ dysfunction, such as significant hypotension (MAP <50), standard advanced cardiovascular life support and basic life support protocols should be followed. Current guidelines still recommend CPR in the patients who need it. However, in the event of LVAD failure and cardiac arrest, CPR may be deferred for a maximum of 2 min while immediate interventions are made to restore device function (see Fig. 9.8).

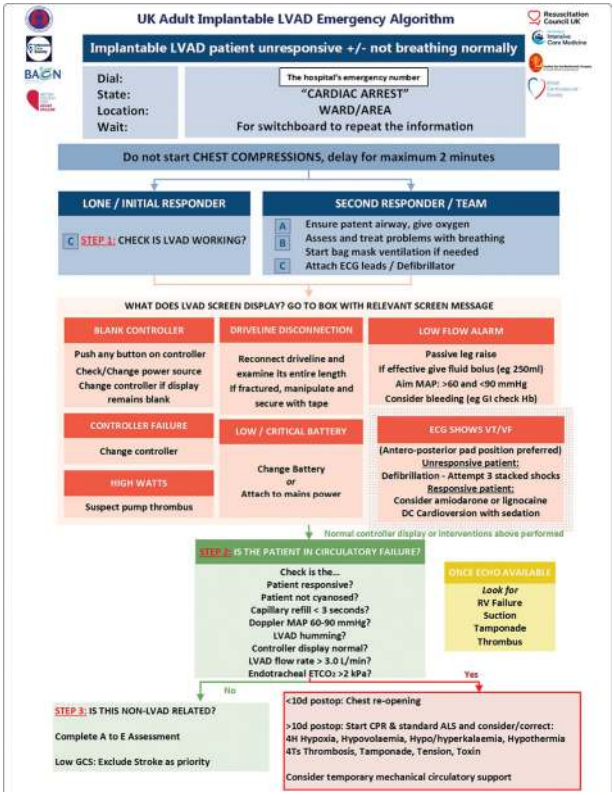

Fig. 9.8 A suggested LVAD emergency algorithm. Adapted from Akhtar W et al. British Societies guideline on the management of emergencies in implantable left ventricular assist device recipients in transplant centres. *Intensive Care Med*. 2024;50(4):493–501.

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Section III

Heart failure and comorbid/special conditions

Chapter 10

The patient with heart failure and angina

Introduction

The most common cause of HF in industrialized countries is ischaemic heart disease. Many of these patients have had previous myocardial infarction and are no longer troubled by anginal symptoms. As discussed in ➔ Chapter 1 and Chapter 7, the rigour with which the diagnosis of IHD is sought varies from centre to centre. Some perform invasive coronary angiography (or non-invasive CT coronary angiography) in all HF subjects, whereas others restrict the procedure to those with chest pain or evidence of ischaemia on non-invasive testing (exercise testing or myocardial perfusion imaging). The latter approach is often applied in those with comorbidities, which may increase the complication rate of angiography. The option of CT coronary angiography can be considered but is probably less appropriate in the context of ischaemic sounding chest pain where invasive angiography remains the gold standard. It should be noted that if there is concern regarding contrast induced nephropathy, invasive angiography is usually achievable at significantly lower contrast load than CT coronary angiography.

Although it is important to recognize that all patients, irrespective of the primary aetiology of the HF, may develop angina due to coronary disease, randomized trials of revascularization in HFrEF and coronary disease have failed to demonstrate consistently improved outcomes (➔ Chapter 7). However, if a patient attends the clinic with HF and describes chest pain the initial management should be directed to establishing whether this pain is cardiac in origin and then deciding how best to manage it.

Investigation

The initial investigation of the patient with HF and chest pain is similar to that of the patient without HF:

- History including risk factors:
  - Smoking.
  - Hyperlipidaemia.
  - Diabetes mellitus.
  - Hypertension.
  - Obesity.
  - Physical inactivity.
- Examination.
- Haematology and biochemistry profile.
- ECG.
- Echo.
  - Regional wall motion abnormality may indicate territory at risk.
  - Global hypokinesis may indicate multivessel disease, or a non-ischaemic aetiology.
- Exercise tolerance test ± myocardial perfusion imaging.

Further investigation depends on the results. If a non-cardiac cause of chest pain is suspected, e.g. oesophageal pain, then further assessment should be directed towards establishing that diagnosis.

Persistent angina despite optimization of medical therapy (including antianginal therapy) should prompt the consideration of coronary imaging (invasive or non-invasive CT coronary angiography) to guide suitability for revascularization.

Management

The key difference in the management of a patient with HF and angina is that fluid management is important in optimizing their angina symptoms. The reductions in ventricular size and pressures associated with achieving euvolaemia have an antianginal effect in themselves.

Risk factors for coronary artery disease should be identified and aggressively treated including treatment of hypertension, hyperlipidaemia, diabetes, anaemia, and obesity.

Non-pharmacological options

- Weight loss.
  - obese patients, target within 10% of ideal body weight.
- Smoking cessation.
- Increase in exercise, as symptoms allow.

Pharmacological options

All patients with HFrEF and angina should receive a beta-blocker as a first-choice anti-anginal unless there is a specific contraindication. The management of angina in HFrEF is summarized in Fig. 10.1

The following can also be considered, but their use—while established in angina—is somewhat contentious in heart failure patients:

- Anti-platelet therapy.
- Statin therapy.

There has been concern that **aspirin** may attenuate the beneficial effects of ACE inhibitors. Despite these concerns, ESC guidelines advocate the use of aspirin (75–100 mg) in all patients with coronary artery disease irrespective of HF diagnosis. In aspirin-intolerant patients **clopidogrel**, prasugrel, or ticagrelor are acceptable substitutes.

International guidelines support the use of **statins** in those with cardiovascular disease and those at high risk of cardiovascular disease to prevent or delay the onset of HF and prevent HF hospitalizations. Despite this, statin therapy is controversial in the HF population. Epidemiological studies have demonstrated an association between low cholesterol and poor prognosis. There have also been suggestions that statins are associated with reduced endotoxin removal, which may be important in patients with gastrointestinal oedema with potential for bacterial translocation. Also, statins reduce levels of ubiquinone and coenzyme Q, and this has been associated with reduced muscle function of both myocardium and skeletal muscle. CORONA (ischaemic cardiomyopathy) and GISSI-HF (ischaemic and non-ischaemic cardiomyopathy) have reported that the addition of a statin to established heart failure therapy did not reduce cardiovascular events. There was no evidence of harm with the addition of statins.

Other therapies that can be considered:

Ivabradine (see Chapter 5, Chapter 39) significantly reduces heart failure hospitalizations and cardiovascular death when added to optimal antianginal and heart failure therapy. The BEAUTIFUL study assessed the effect of ivabradine in patients with stable coronary artery disease and stable HFrEF on *optimal* medical therapy. In patients with a heart rate over 70 bpm in sinus rhythm, the addition of ivabradine significantly reduced

coronary events. In the SHIFT study, the addition of ivabradine to optimal heart failure therapy significantly reduced heart-failure-associated deaths and hospitalizations. NICE recommend the use of ivabradine in patients with ongoing heart failure symptoms despite *optimal* therapy with a heart rate of >75 bpm in sinus rhythm.

In addition, if the symptoms of angina remain poorly controlled then a long-acting **nitrate** can be added to therapy. This does not confer any survival benefit but has been demonstrated to be tolerated and improve symptoms in patients with angina and reduced LVEF.

Nicorandil has evidence of survival benefit in the management of chronic stable angina. There is no randomized trial evidence of its use in patients with angina and HF. Care should be taken if using nicorandil in these patients due to the blood-pressure-lowering side effect.

In β-adrenoreceptor antagonist intolerant patients, most calcium channel blockers should be used with caution because of their negative inotropic effect. **Amlodipine** and felodipine can be used in patients with angina and HF in whom β-blockers and nitrates have not been tolerated.

Trimetazidine and **ranolazine** are recognized in the ESC guidelines for the management of heart failure. Both agents inhibit fatty acid oxidation and improve the metabolic efficiency of the myocardium. Trimetazidine use is supported by meta-analysis data although a placebo-controlled trial did not demonstrate statistical benefit.

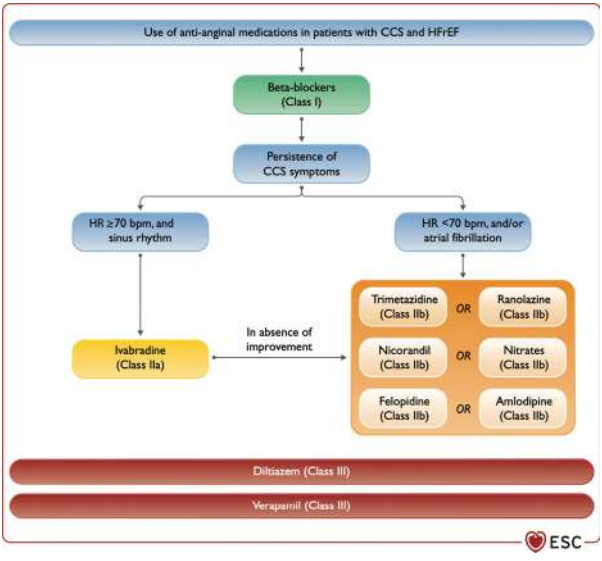

Fig. 10.1 Algorithm for the medical treatment of chronic coronary syndrome for patients with HFrEF. 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. *Eur Heart J*. 2021;42:3599–3726.

Interventional options

Surgical or percutaneous coronary revascularization is indicated in patients with HF and refractory angina despite optimal medical therapy. Ultimately, **the choice between medical therapy, and revascularization by percutaneous coronary intervention (PCI) or CABG should be made by the heart team, including a HF specialist**, and be based on the extent of CAD, expected completeness of revascularization, associated valvular disease, the presence of comorbidities and estimated risk of an interventional procedure (see Chapter 7).

Chapter 11

The patient with heart failure and arrhythmias

Introduction

Chronic heart failure and arrhythmias often co-exist. These include bradyarrhythmias and tachyarrhythmias of both ventricular and supraventricular origin. Up to 50% of deaths in the heart failure population are sudden and unexpected, although they may not all be arrhythmic. Sudden cardiac death is between six and nine times more common than in the general population.

Heart failure predisposes to arrhythmias; however, arrhythmias also predispose to heart failure. There are pathological processes that may be common to both diseases, including:

- Myocardial fibrosis.
- Alterations in intracellular calcium handling with changes in the action potential.
- Alterations in neuroendocrine function.
- Alterations in sympathetic tone.

Furthermore, the treatment of both bradyarrhythmias and tachyarrhythmias may result in deterioration in left ventricular systolic function that in itself is proarrhythmic.

The multifactorial nature of arrhythmias in heart failure has resulted in the 'multi-hit' hypothesis illustrated in Fig. 11.1, which was originally developed to describe the occurrence of sudden cardiac death but that could as easily relate to the development of arrhythmias in heart failure.

The assessment and management of arrhythmias should be integral to heart failure care. This includes prevention, accurate diagnosis, and treatment, both pharmacological and device or catheter intervention.

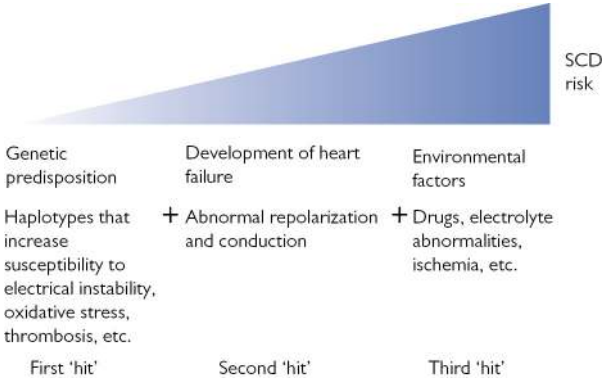

Fig. 11.1 Multi-hit hypothesis of the development of SCD. Heart failure serves to enhance the risk by the associated alterations in the myocardial substrate and increasing the frequency/intensity of triggers of malignant arrhythmias.

Reproduced from Tomaselli GF, Zipes DP. What causes sudden cardiac death in heart failure? *Circ Res*. 2004;95:754–763, 2nd edition had permission from Lippincott, Williams and Wilkins.

Overview of arrhythmia mechanisms

Arrhythmias are common in heart failure, irrespective of the aetiology. Arrythmia burden is higher in advanced disease. Although there are multiple factors that contribute to the proarrhythmic state, not all of these factors are modifiable.

There are three main mechanisms for ventricular arrhythmias:

- Automatism.
- Triggered activity.
- Re-entry.

In general, an arrhythmia is initiated by automatism or triggered activity and then sustained by re-entry.

Automatism is apparent in the healthy sino-atrial node as the pacemaker function. This is determined by the expression of channel proteins, including deactivation of the delayed K^+ current (I_{Kr} or I_{Ks}), activation of the pacemaker current, I_f, and activation of the T-type calcium channel I_{CaT}.

Under normal conditions, automatism is inhibited in ventricular cells by high K^+ conductance, which keeps the membrane hyperpolarized. I_f is absent or its activation voltage is too negative however, in pathological conditions such as ischaemic cardiomyopathy it may be re-expressed or its activation potential may be less negative.

Triggered activity is a term used to describe abnormal impulse initiation of which there are two types: Early after depolarizations (EADs) and delayed after depolarizations (DADs). The main mechanism in EADs is reactivation of the calcium current. EADs can also be induced by acceleration of the stimulation rate, especially when the cell is in a state of calcium overload. EADs, which are independent of $[Ca^{2+}]_i$, can occur in heart failure. DADs are triggered by the spontaneous release of Ca^{2+} from the sarcoplasmic reticulum in conditions of Ca^{2+} overload. Ventricular DADs are primarily due to $I_{Na/Ca}$. In heart failure, the Na/Ca exchanger is upregulated and I_{K1} (the inward rectifier current) is decreased. This destabilizes the membrane potential and results in increased triggered arrhythmias in heart failure.

It has been postulated that triggered activity is responsible for the initiation of almost all arrhythmias in non-ischaemic heart failure and about 50% of those in ischaemic heart failure.

Structural change in ischaemic and non-ischaemic cardiomyopathy

The interface between the myocardial scar and non-infarcted tissue acts as a source of unidirectional conduction block, slow conduction, and a heterogeneous refractory period, with potential for developing re-entry circuits. This border zone can also be a source of triggered activity, providing an extra stimulus that initiates re-entry to sustain an arrhythmia. Non-infarcted tissue also remodels with gradual hypertrophy of the non-infarcted ventricular cardiomyocytes as they adapt to the increased workload. This hypertrophy in itself may be proarrhythmic. There are extensive changes in the myocardial structure in non-ischaemic cardiomyopathy that result in a substrate for re-entry, including fibrosis and altered cell-to-cell coupling, with changes in the expression of connexins 43 and 45.

Bradyarrhythmias

The incidence of bradyarrhythmias associated with heart failure is increasing, reflecting the escalating use of β-adrenoreceptor antagonists. Profound bradycardias may result in clinical heart failure, as may be seen in the context of complete heart block.

Heart failure may result from the management of bradycardia. In 1925, Wiggers demonstrated that external stimulation of ventricular myocardium results in adverse changes in haemodynamics. These results have been replicated in several studies.

The DAVID trial compared VVI pacing (lower rate limit of 40 bpm) with DDDR pacing (lower rate limit of 70 bpm) after implantation of an implantable cardioverter defibrillators (ICD). At the time of data analysis, it was realized that the DDDR group had been paced 60% of the time while the VVI group were only paced 1% of the time. This has meant that the study is considered to demonstrate the effect of DDDR pacing compared with sinus rhythm. A significantly higher number of patients died or were hospitalized with heart failure in the group who were DDDR paced (27% v 16% in the VVI group). Such pacing is thought to induce mechanical dyssynchrony by effectively causing LBBB.

► Therefore, standard dual-chamber pacing is not recommended as a therapy for heart failure.

► The use of pacemakers to facilitate more aggressive β-adrenoreceptor blockade is also not advised, unless right ventricular pacing can be avoided. However, up-titration of β-blockers is often possible following CRT implantation in those suitable for such therapy. Otherwise, the target is to escalate the dose to the maximum tolerated level based on heart rate, blood pressure, and symptoms.

The BLOCK-HF trial compared CRT pacing with RV pacing in heart failure patients requiring a pacemaker for AV block. They concluded that CRT pacing reduced the incidence of urgent care visits for heart failure, death from any cause, or progression of heart failure.

► CRT implantation rather than a conventional pacemaker is recommended in patients with HFrEF who require pacing for the treatment of bradycardia. Dual-chamber pacing should be used as a backup only with pacing algorithms set to minimize paced beats.

Physiological pacing (also known as conduction system pacing, e.g. His bundle, or left bundle area pacing—see Chapter 6) is being increasingly adopted but more data are needed to confirm its role.

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Tachycardias

Tachycardias may cause heart failure: tachycardia-induced heart failure or tachycardiomyopathy. Heart failure may also result in tachycardias, including both atrial and ventricular fibrillation. The management of the arrhythmia may directly impact on systolic function, and many anti-arrhythmics are negatively inotropic.

Supraventricular tachyarrhythmias

Tachycardiomyopathy most frequently results from incessant atrial arrhythmias. The importance of the diagnosis lies in the recognition that it may be curable by radiofrequency ablation and that ventricular function may return to normal. Frequently the diagnosis is suspected when the LV systolic dysfunction is noted in combination with persistent tachycardia. The treatment initially centres on standard management of heart failure and negative chronotropic medication. The use of β-adrenoreceptor blockers often achieves both of these goals. The exact nature of the arrhythmia will determine the optimal definitive treatment strategy, but this should be planned with an electrophysiologist.

The most common supraventricular arrhythmia associated with heart failure is atrial fibrillation that will be discussed in the ➲ Atrial Fibrillation and heart failure section of this chapter, p. 142. Other supraventricular arrhythmias include atrial flutter and atrial tachycardias. The management of these arrhythmias focuses on restoration of sinus rhythm and prevention of recurrence of arrhythmia. Micro re-entrant arrhythmias such as AVNRT tend to be paroxysmal and are less implicated in heart failure.

Because of the negative inotropic effects of calcium channel blockers, they should be avoided in heart failure with reduced ejection fraction, although they are helpful in achieving rate control in patients with heart failure with preserved ejection fraction. The use of class I anti-arrhythmics are similarly discouraged. Therefore, the most useful agents are β-adrenoreceptor blockers, and where necessary, amiodarone. However, the SCD-HeFT study—the largest amiodarone study in heart failure—did not show a mortality benefit to those randomized to amiodarone. Digoxin may be used to achieve rate control but does not facilitate cardioversion or maintenance of sinus rhythm. Electrical cardioversion may be used to achieve sinus rhythm.

The role of anticoagulation in patients with atrial tachycardia is less clear than in atrial fibrillation. The presence of left ventricular systolic dysfunction is generally accepted as an indication that the risk of thromboembolism is significant. These patients should have consideration of anticoagulation irrespective of planned electrical cardioversion.

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Atrial fibrillation and heart failure

Atrial fibrillation (AF) and heart failure frequently co-exist and predispose to each other. The average prevalence of AF in all types of heart failure is around 25%, and the prognosis of those with AF and heart failure is worse than the combined risk of each alone.

AF has multiple mechanisms that contribute to heart failure, including:

- Loss of atrial contraction contributes up to 20% of optimal ventricular filling.
- An irregular ventricular rhythm.
- Tachycardia.
- Activation of neurohumoral systems.

Precipitating factors for AF should be considered, such as electrolyte disturbance, infection, valve disease, or hyperthyroidism. Treating heart failure and congestion relief may reduce the ventricular rate and increase the likelihood of spontaneous cardioversion to sinus rhythm. ACE inhibitors and angiotensin receptor blockers have both been shown to reduce the likelihood of developing AF and this reiterates the importance of these agents in the management of heart failure.

Anticoagulation remains an important issue in the care of AF and heart failure, whether the AF is paroxysmal, persistent, or permanent. The combination of AF and heart failure suggests a significant risk of thromboembolism such that formal anticoagulation is advised.

The use of thromboprophylaxis in AF is guided by the CHA_2DS_2-VASc score, and most patients with heart failure meet recommendation for formal anticoagulation. The patient's bleeding risk can be assessed with the HAS-BLED score, and if an individual scores ≥3 then careful consideration should be made about the risk/benefit profile.

Direct oral anticoagulants (DOACs) are now the preferred thromboprophylaxis in AF without severe mitral stenosis and have demonstrated similar efficacy to vitamin K antagonists and a lower risk of intracranial haemorrhage. It should be noted that DOACs are contraindicated in severe renal impairment (eGFR <15 mL/min) and in those with mechanical prosthetic heart valves.

Following cardioversion to sinus rhythm anticoagulation should be continued. The duration of therapy is not clear, possibly long-term due to the frequency of recurrence of AF in heart failure

There has been extensive discussion about the optimal management strategy for patients with AF, debating rate control and rhythm control. There is concern that patients with heart failure should be treated more aggressively with a goal of restoring and maintaining sinus rhythm in order to improve LV systolic function. Randomized trials in heart failure patients comparing rate control to pharmacological rhythm control have not demonstrated a clear benefit with either strategy.

Rate control can usually be achieved with β-adrenoreceptor blockers ± digoxin. Atrioventricular (AV) nodal ablation can be considered in those who are eligible with high ventricular rates resistant to medical treatment. Studies have demonstrated that AV nodal ablation for the management of AF, followed by RV apical pacing is associated with deterioration in heart failure symptoms and LV systolic function. Cardiac resynchronization therapy rather than RV apical pacing in this setting seems to confer benefits.

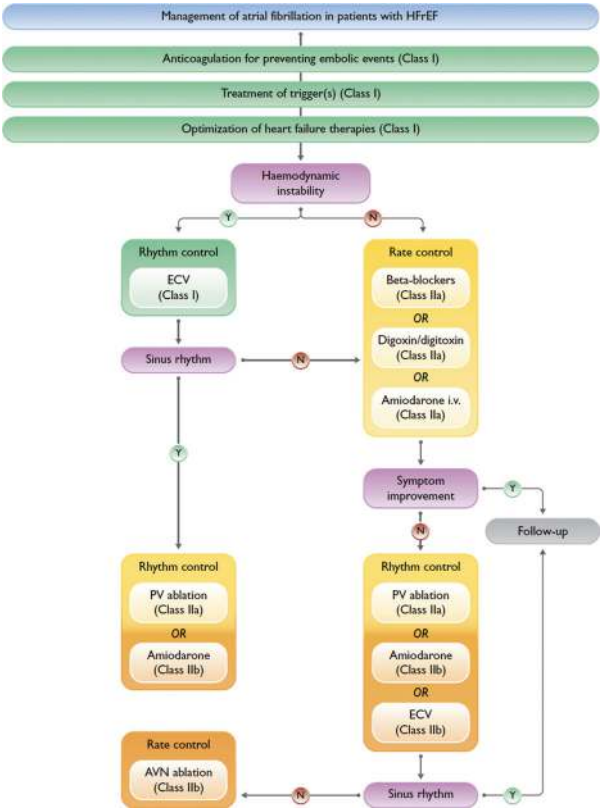

Fig. 11.2 Management of AF in patients with heart failure. From McDonagh TA et al. ESC HF guidelines 2021 (Fig. 14).

Rhythm control in heart failure can be attempted using pharmacology, electrical cardioversion, or catheter ablation.

Pharmacological options recommended by the ESC guidelines (Fig. 11.2) include amiodarone and dofetilide (not currently licensed for use in the UK). Amiodarone is relatively safe in patients with heart failure as it has little proarrhythmic effect (although monitoring of the QT interval is advised). It does, however, have considerable non-cardiac side effects. These include corneal deposits, thyroid disease, pulmonary fibrosis, hepatitis, cirrhosis, neuropathy, and photosensitivity. The interaction of amiodarone and warfarin is important, as there is an increased anticoagulant effect.

Close monitoring of the INR during the initiation of amiodarone is essential. However, the SCD-HeFT study—the largest amiodarone study in heart failure—did not show a mortality benefit to those randomized to amiodarone.

Sotalol is no longer considered as a first-line option due to the potential proarrhythmic effects. **Dronedarone, propafenone,** and **flecainide** are ***not*** recommended due to an association with worse outcomes in HFrEF.

Pharmacological cardioversion of AF is most effective when it occurs within the acute setting. In the context of the patient with heart failure, attempted cardioversion of AF of less than 48 hours duration can be performed with intravenous or oral amiodarone. However, the patient should then receive anticoagulation to cover the potential recurrence of AF.

Electrical cardioversion of AF may be considered acutely in patients with evidence of shock attributable to the onset of AF with fast ventricular heart rate. More commonly it is used in persistent AF after a period of anticoagulation to reduce the risk of thromboembolism. Studies have shown that an initial synchronized shock energy of 200 J for monophasic defibrillators and 100 J for biphasic defibrillators is associated with an improved success with reduced total shock energy.

Several randomized trials have now examined the impact of catheter ablation for rhythm control in AF and heart failure versus medical therapy. A recent meta-analysis reports a 39% relative risk reduction in all-cause mortality and 40% reduction in HF hospitalization in favour of catheter ablation. Guideline recommendations currently support consideration of AF catheter ablation in heart failure in those with a clear association between AF and worsening heart failure symptoms. Further trials are ongoing.

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Ventricular tachyarrhythmias

The association of ventricular tachyarrhythmias and heart failure with reduced ejection fraction is well established (Fig. 11.3). At least 50% of deaths in the heart failure population are thought to be sudden cardiac death, most often ventricular tachyarrhythmias.

Ventricular tachycardia is not only a complication of heart failure but can cause a tachycardiomyopathy if it is incessant or there are frequent paroxysms. There is evidence that tachycardiomyopathy may even result from frequent ventricular ectopics. The origin of ventricular tachycardia stable enough to induce tachycardiomyopathy is most often from the right ventricular outflow tract and has a specific morphology—LBBB with an inferior axis. This is an important finding as it can be cured with radiofrequency ablation and the LV systolic function is likely to return to normal.

Optimization of electrolyte balance is essential in the management of ventricular arrhythmias in heart failure (see Chapter 17); diuretic use frequently causes hypokalaemia and hypomagnesaemia, while ACEi/ARNI/ARBs, and MRAs are associated with hyperkalaemia. With the exception of ACE inhibitors, sacubitril/valsartan, MRAs, and β-adrenoreceptor blockers, pharmacological agents have not been shown to improve outcomes in the management of ventricular arrhythmias. In fact, many anti-arrhythmic agents increase the likelihood of sudden cardiac death because of their proarrhythmic effect.

Amiodarone or β-adrenoreceptor blockers can be used in combination with device therapy (ICD or CRT-D) to reduce the frequency of patient events, however SCD-HeFT demonstrated that amiodarone does not confer additional mortality benefit over best-medical therapy. In general terms there is an evidence gap and the optimal treatment strategy for ventricular arrhythmia in heart failure is not known.

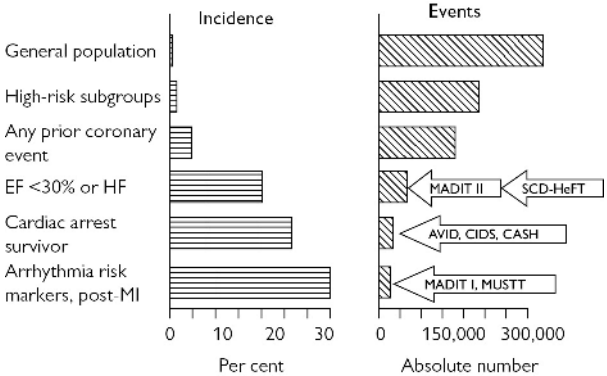

Fig. 11.3 Absolute numbers of arrhythmic events in different patient groups.

Zipes et al. ACC/AHA/ESC 2006 Guidelines for management of patients with ventricular arrhythmias and the prevention of sudden cardiac death, *European Heart Journal*, 2006:27 by permission of Oxford University Press for 2nd edition.

If there is a suggestion of an acute ischaemic aetiology to the evolution of ventricular arrhythmias in heart failure, then it is appropriate to consider coronary revascularization. In a pre-specified analysis from the recent REVIVED BCIS-2 trial in a population with chronic heart failure and ischaemic cardiomyopathy, coronary revascularization by PCI did not reduce fatal ventricular arrhythmias.

ICDs can reduce mortality in heart failure by aborting life-threatening ventricular arrhythmia. The SCD-HeFT trial simplified the management of ventricular arrhythmias in patients with an LVEF ≤35%. This study looked at both ischaemic *and* non-ischaemic cardiomyopathies and demonstrated that in those patients with NYHA II or III symptoms despite optimal medical therapy, an ICD achieved an absolute risk reduction in mortality at 5 years of 6.9% (29% in the ICD arm v 36% in the placebo arm). Of note, the more contemporary DANISH trial did not report an overall mortality benefit from ICD in those with non-ischaemic cardiomyopathy. Meta-analysis since support mortality benefits from primary prevention ICD in non-ischaemic cardiomyopathy but the benefits in this group appear to be less clear. The MADIT and MUSTT trials were studies of ICDs post-myocardial infarction rather than in heart failure. However, they confirm that there is a mortality benefit in treating patients with an LVEF ≤30%.

The current NICE guidance recommends primary prevention ICD in those with LVEF ≤35% and NYHA II-III functional limitation regardless of heart failure aetiology. ESC guidelines offer the strongest recommendation for primary prevention ICD only in those with ischaemic cardiomyopathy (see Table 6.6).

In patients with heart failure on optimal medical therapy with sinus rhythm and a QRS duration ≥150 ms with left bundle branch block morphology (or ≥120 ms with evidence of ventricular dyssynchrony) the CARE-HF arm demonstrated mortality benefit with CRT-P. The COMPANION study suggested that CRT-D reduced mortality in patients with NYHA III–IV heart failure, QRS duration ≥120 ms and LVEF ≤35%. However, the ECHO-CRT study has subsequently highlighted potential harm from CRT in those with a QRS <130 ms, and so CRT is not recommended in this group.

The role of CRT in NYHA II–IV patients in permanent AF is less clear outside some specific circumstances:

- pacemaker dependent following AV nodal ablation.
- pacemaker considered for slow ventricular rate.
- pacemaker considered for chronotropic incompetence on exercise.

The cost-implications of widespread use of ICDs or CRT-D have driven the search for a means of predicting those not at risk of ventricular arrhythmias who do not need an ICD. Despite initial promise, microvolt T-wave alternans has not been shown to discriminate adequately to allow prediction.

The decision making prior to device implantation has to include an assessment of the patient's prognosis. The ESC guidelines summarize this eloquently as an expectation 'to survive >1 year with good functional status'.

If a patient deteriorates then careful consideration should be made to the appropriateness of device deactivation for therapeutic interventions, i.e. maintain pacing functionality but switch off shock and overdrive pacing strategies. This would obviously require discussion with the patient and family.

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Chapter 12

The patient with heart failure and arthritis

Introduction

Arthritis can take many forms. Osteoarthritis is a frequent accompaniment to the ageing process. The interaction between inflammatory arthritis and heart failure is multifaceted, and continues to unfold at both pre-clinical and clinical trial levels:

- Chronic low-grade inflammation is associated with heart failure.
- Chronic low-grade inflammation is associated with atherosclerosis.
- Some treatments can be detrimental to fluid balance.
- Some of the treatments can cause an increase in cardiovascular events.

The balance between what is best in terms of cardiovascular status and maintenance of mobility can be difficult to achieve. In order to ensure optimal management, the treatment of patients with arthritis and heart failure should be coordinated by both a rheumatologist and cardiologist. Informed discussions with the patient are important in establishing a treatment plan.

>> The association of arthritis and heart failure requires investigation for an underlying cause, including the potential of sarcoidosis as a unifying cause (see Chapter 18).

Inflammatory arthritides and cardiovascular disease

There is an increasing body of evidence supporting the hypothesis that cytokine-driven inflammation is central in the pathogenesis not only of rheumatoid arthritis (RA) and systemic lupus erythematosis (SLE), but also atherosclerosis and heart failure. The levels of inflammatory mediators are orders of magnitude greater in rheumatological conditions compared with cardiac diseases. Therefore, one can hypothesize the interactions between these conditions. Inflammatory arthritis may initiate or promote cardiovascular disease through prolonged exposure to cytokines and related inflammatory mediators.

Both SLE and RA (and any of the other inflammatory arthritis conditions) have multiple cardiac manifestations, including:

- Pericarditis.
- Valvular heart disease (most often affecting the mitral valve).
- Myocarditis.
- Cardiac amyloidosis.
- Arrhythmias.
- Coronary artery vasculitis.
- Ischaemic heart disease.

Ischaemic heart disease and heart failure are more frequent and have an increased mortality in patients with inflammatory joint diseases than in the general population. Epidemiological and clinical studies indicate that RA is an independent risk factor for cardiovascular disease. The literature is not conclusive regarding the increased incidence of conventional cardiovascular risk factors. This again supports the central role of inflammatory mediators. Atorvastatin, ACEi, and ARBs are beneficial in reducing synovitis in RA and modifying vascular risk factors, and this may offer a combined strategy for these patients.

CVS risk factors in inflammatory arthritis

- Probably ↑ smoking rates in patients with RA.
- ↑ Diastolic BP.
- Inflammation tends to
  - ↓ Total cholesterol.
  - ↓ ↓ HDL.
  - ↑ LDL.

Overall, there is a pro-atherogenic effect with inflammatory arthritis. There is an increasing body of evidence suggesting that novel CVS risk factors, including endothelial dysfunction and insulin resistance, are more significant in the inflammatory arthritides.

Therefore, traditional risk calculators developed for the general public do not perform well in patients with inflammatory arthritis.

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Anti-inflammatory drugs and cardiovascular disease

The management of arthritis centres on the control of pain with restoration of function, and reduction of inflammation slowing disease progression.

The drugs in frequent use, as single agents or in combination, include:

- Analgesics
  - e.g. Paracetamol (acetominophen), tramadol.
- Non-steroidal anti-inflammatory drugs (NSAIDs).
  - Non-selective.
  - COX-2 selective.
- Steroids.
- Disease-modifying drugs.
  - Hydroxychloroquine.
  - Sulfasalazine.
  - Methotrexate.
  - Gold.
  - Penicillamine.
  - Leflunomide.
  - Steroid sparing (azathioprine and ciclosporin (cyclosporin)).
- Anti-cytokine agents.
  - Anti-tumour necrosis factor α agents (etanercept, adalimumab, and infliximab).
  - Interleukin-1 receptor antagonists (anakinra).
  - Anti-B cell therapies (rituximab).

Apart from the simple analgesics, all of these agents can have adverse cardiac effects. These are summarized in Table 12.1. In addition, there is a deleterious interaction between aspirin and non-selective NSAIDs, including ibuprofen, such that the beneficial effect of aspirin may be attenuated. However, studies suggest that this can be avoided by ensuring that aspirin is taken more than 2 hours before the NSAID.

There is evidence that some of the therapies for arthritis may in fact improve the CVS risk profile. For example, methotrexate reduced cardiovascular deaths in a study of patients with RA. Anti-tumour necrosis factor α agents increase mortality in established HF, but may reduce CVS risk in the general RA population. Anakinra continues to be studied for potential beneficial effects in HFpEF.

A Cochrane review suggested no increase in the frequency of heart failure in patients receiving biological agents.

Table 12.1 Summary of reported cardiovascular side effects with rheumatological treatments

	Fluid gain/ oedema	CVS vascular events/vasculitis	Cardiomyopathy
Non-selective NSAIDs	x	x	
COX-2 inhibitors	x	x	
Steroids	x		x
Hydroxychloroquine			x
Methotrexate		x	
Gold	x		
Penicillamine	x		
Leflunomide	x		
Ciclosporin (cyclosporin)	x		x
Anti-TNF α agents	x	x	x
Rituximab	x	x	x
Azathioprine	Caution with ACEi—may induce anaemia and severe leukopaenia		
Sulfasalazine	Pericarditis with potential for cardiac tamponade		

ACEi = angiotensin-converting enzyme inhibitor; COX-2 = cyclooxygenase 2; NSAID = non-steroidal anti-inflammatory drug.

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COX-2 inhibitors and cardiovascular disease

NSAIDs act by inhibiting cyclooxygenase (COX) and therefore blocking the conversion of arachidonic acid to prostaglandins, prostacyclin, and thromboxanes. There are two isoforms of COX: COX-1 and COX-2. These isoforms are differentially expressed. COX-1 is involved in gastric protection. The most frequent side effect of non-selective NSAIDs is dyspepsia. The development of COX-2 selective NSAIDs was hoped to herald an end to the gastrointestinal complications.

Risk factors for gastrointestinal bleeding with NSAIDs:

- Age >65 years.
- Anti-thrombotic use.
  - Aspirin.
  - Clopidogrel.
  - Warfarin.
  - Low molecular weight heparin.
- Corticosteroid use.
- Previous gastrointestinal bleed or active peptic ulcer disease.

The non-selective NSAIDs, including diclofenac and ibuprofen, have not been subjected to such rigorous study as the newer agents. There are NSAIDs considered to be non-selective but that are relatively more selective for COX-2, such as nabumetone and etodolac.

In a meta-analysis of COX-2 and traditional/non-selective NSAIDs, the incidence of serious vascular events was similar. The exception appeared to be naproxen, which was associated with the best CVS risk profile and no increase in vascular events. Unfortunately, trials of COX-2 inhibitors have demonstrated an increased risk of cardiovascular events, and this has led to the withdrawal of several agents.

- Rofecoxib was withdrawn from the market in 2004 after a study of colorectal adenomas demonstrated an increase in cardiovascular events approximately double that of the placebo arm. The number-needed-to-harm was 139.
- The MEDAL programme comprised three RCTs totalling 34,701 patients (24,913 with osteoarthritis and 9787 with RA). The primary aim was to compare thrombotic CVS events with long-term use of etoricoxib, selective COX-2, and diclofenac.
  - Similar rates of thrombotic cardiovascular events event rates of 1.24 and 1.30 per 100 patient-years, respectively.
  - CHF and oedema were increased with etoricoxib.

Key reference

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Management of patients with heart failure and arthritis

Osteoarthritis

- Where possible, simple analgesics should be used.
- When an NSAID is required, naproxen, even in high doses, is the agent that is not associated with an increase in vascular events. It should therefore be used as the first choice NSAID.
- If NSAIDs are required, an assessment of the risk of gastrointestinal bleeding should be made. If they have risk factors for bleeding, then the options are:
  - Non-selective NSAIDs + proton-pump inhibitor (PPI) or H_2 receptor antagonist cover.
  - Non-selective NSAIDs with misoprostol.
  - COX-2 selective NSAIDs.

A prior analysis suggests that the combination of non-selective NSAIDs and PPI or misoprostol is the most economically appropriate to prevent the need for endoscopy.

Inflammatory arthritis

Management of joint pain should be the same as for osteoarthritis.

If there is evidence of pre-existing cardiovascular disease including heart failure

- Baseline assessment of cardiovascular status should be performed with:
  - Echo for LVEF.
  - Exercise testing if appropriate and possible.
- COX-2 inhibitors should be avoided.
- Non-selective NSAIDs should be avoided if at all possible, or used at the lowest dose possible for the shortest time. Dosing should be timed to avoid interaction with aspirin (as mentioned previously).
- Disease-modifying drugs can be used but alterations in diuretic dose may be required.
- Azathioprine should be avoided if concomitant ACE inhibitor use.
- With the exception of anakinra, the recombinant human interleukin-1 receptor antagonist, anti-cytokine agents should be avoided if there is evidence of LVSD. If they are to be used then caution is required, and screening echoes performed to assess for deterioration in cardiac status.

If there is no evidence of pre-existing cardiovascular disease

- The development of heart failure symptoms should prompt assessment with echo to confirm the diagnosis.
- Suspicion of drug-induced heart failure should be high and potential agents withdrawn if possible.
- Standard HF management should be initiated.
- If symptoms of ischaemic heart disease develop, coronary angiography is usually appropriate and the possibility of coronary vasculitis should be considered.

Gout

Gout is commonly associated with HF, in part because of elevated plasma urate concentrations secondary to diuretic use. A raised plasma urate concentration has also been associated with an adverse prognosis.

The treatment of gout in the patient with HF is complicated by the relative contraindication to NSAIDs, COX-2 inhibitors, and corticosteroids. Therefore, acute exacerbations of gout should be managed with colchicine, and allopurinol is recommended to prevent recurrence.

Colchicine is given as a 1 mg initial dose, followed by 500 micrograms every 4 hours to a maximum dose of 6 mg in 3 days. Patients should be made aware of the common side effects, which include abdominal discomfort, vomiting, and diarrhoea.

Interestingly, several studies have postulated a beneficial effect in HF of targeted inhibition of xanthine oxidase with allopurinol. The suggested mechanism includes the reduction of free radical load and uric acid production. However, this has yet to be substantiated in clinical trials.

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Chapter 13

The patient with heart failure and cancer

Introduction

Cancer can occur at any age. It can be associated with heart failure in three ways:

- Heart failure as a consequence of cancer.
- Heart failure as a result of the treatment of cancer.
- Heart failure patients requiring treatment of malignancy.

The treatment of many cancers involves the use of potent chemotherapeutic agents and/or radiotherapy. These treatment modalities have radically improved survival in many cancers. However, the cost in the long term may include cardiotoxicity resulting in arrhythmias, coronary artery stenosis, or myocardial fibrosis or necrosis with resultant heart failure.

It has been increasingly recognized that the toxic cardiac effect is more often seen in multiagent body regimes. There is a synergistic cardiotoxicity associated with combining chemotherapy and mediastinal radiotherapy. The cardiac side effects of the therapy may take years to manifest. This raises difficult questions in considering whether there may be a role for the use of heart failure medications as prophylaxis and in how best to monitor for cardiotoxicity.

Malignancies more commonly associated with CHF

- Breast cancer.
- Lymphoma (especially Hodgkin's lymphoma).
- Lung.
- Leukaemia requiring haemopoietic cell transplant.
- Testicular germ cell tumours.

CHF as a consequence of malignancy

The majority of malignancies affecting the heart are secondary to remote primary disease. In a study of 1900 patients dying of cancer, 8% had cardiac metastases. The development of cardiomegaly, a new murmur, or arrhythmia may be the first sign of cardiac metastases. Heart failure may be due to cardiac or pericardial infiltration. Direct invasion or cardiac infiltration can result from primary mediastinal tumours and lung cancer.

Primary cardiac tumours include both benign and malignant lesions, although over 75% are benign. Myxomas, lipomas, and fibromas may cause symptoms of heart failure as a consequence of valvular obstruction. Malignant sarcomas have a poor prognosis and may be associated with heart failure due to myocardial infiltration.

Malignant pericardial effusions may cause symptoms of heart failure by restricting cardiac filling. They can present with haemodynamic compromise as cardiac tamponade. In the acute setting, the symptoms can be relieved with pericardiocentesis and placement of a pericardial drain. The drain is usually left in place until the effusion is drained completely. This is confirmed with echocardiography and that less than 30 mL has drained in the 24 hours prior to removal. This may require the drain to remain in place for 2–3 days.

The role of pericardial sclerosis by the instillation of a sclerosing agent is debatable. Initial studies used tetracycline but further small studies have used a wide range of chemotherapeutic agents, including bleomycin. There does not appear to be evidence of benefit from pericardial sclerosis over simple pericardial drainage. Patients may have significant side effects from the instillation of the sclerosing agent including chest pain and atrial arrhythmias.

Recurrent pericardial effusions may be managed by the creation of a pericardial window. Studies suggest that the subxiphoid approach for pericardiotomy is well tolerated with minimal complications. This approach avoids the need for a thoracotomy and lengthy procedure time which may be inappropriate given the prognosis of the primary disease.

Cardiac effects of cancer therapies

Radiotherapy

Studies of the effect of mediastinal radiation in animal models have demonstrated that there are three distinct phases to the myocardial reaction:

- Acute phase—neutrophil infiltration of all myocardial layers.
- Latent phase—no additional damage seen.
- Late phase—fibrotic reaction of the pericardium and myocardium. endovascular damage with resultant capillary obstruction.

The clinical manifestations of radiotherapy include:

- Pericarditis:
  - Acute.
  - Chronic.
  - Pericardial constriction.
- Pancarditis, including valve dysfunction.
- Coronary artery stenosis.
  - Most commonly ostial stenosis of the left anterior descending artery.
- Arrhythmias.
- Cardiomyopathy.

Strategies to reduce the cardiotoxic impact of radiotherapy include:

- Modification of cardiac risk factors.
  - Smoking.
  - Lipid profile.
- Tangential radiation beams.
- Respiratory gating.
- Limitation of radiation fraction size.

Management of radiation pericarditis

Clinical evidence of pericarditis may develop acutely after therapy, but more commonly it presents more than a year later. Approximately 50% of patients will develop severe constrictive pericarditis requiring surgical pericardiectomy. The operative mortality is significant (between 6% and 21%), and the 5-year postoperative survival is poor (between 1% and 27%).

Chemotherapy

The majority of patients receiving standard doses of chemotherapy do not suffer any adverse cardiac effects. However, these patients are at risk of developing cardiotoxicity. That cardiotoxicity can include the development of left ventricular dysfunction and heart failure. There is no universal consensus on the definition of cardiotoxicity, however most international statements are broadly similar. For the ESC definition relating to left ventricular dysfunction and HF, see Table 13.1.

The incidence and severity of cardiotoxicity depends on the patient's baseline cardiovascular risk and the cancer therapy to be given. Pre-treatment risk should be assessed using a multifactor risk stratification method, e.g. the HFA-ICOS risk assessment tool is recommended to stratify CV toxicity risk (PMID). Factors include age, cancer history, pre-existing cardiovascular risk factors (CVRFs), or cardiovascular disease (CVD) and previous cardiotoxic cancer therapy.

Table 13.1 ESC definition of cancer-therapy-related cardiac dysfunction. From Lyon A et al. 2022 ESC Guidelines on cardio-oncology. *Eur Heart J*. 2022 Nov 1;43(41):4229–4361.

CTRCD		
Symptomatic CTRCD (HF)[a,b]	Very severe	HF requiring inotropic support, mechanical circulatory support, or consideration of transplantation
	Severe	HF hospitalization
	Moderate	Need for outpatient intensification of diuretic and HF therapy
	Mild	Mild HF symptoms, no intensification of therapy required
Asymptomatic CTRCD	Severe	New LVEF reduction to <40%
	Moderate	New LVEF reduction by ≥10 percentage points to an LVEF of 40–49% *OR* New LVEF reduction by <10 percentage points to an LVEF of 40–49% AND either new relative decline in GLS by >15% from baseline OR new rise in cardiac biomarkers[c]
	Mild	LVEF ≥*50%* AND new relative decline in GLS by >15% from baseline AND/OR new rise in cardiac biomarkers[c]

The main causes of chemotherapy-related LV dysfunction are shown in Table 13.2.

Key points

- Anthracycline (AC) cardiotoxicity:
  - May occur acutely (rare), in less than 1 year (2–9%) and chronically after 1 year (1–9%).
  - Is associated with the lifetime dosage received.
  - Rises exponentially after 400 mg/mL /m² of doxorubicin.
  - Can portend a poor prognosis.
  - Early diagnosis and treatment can improve LV function.
- HER-2/ERB antagonists.
  - Monoclonal antibodies (MAB) used to treat breast cancer.
  - Asymptomatic LV dysfunction is common.
  - Use of AC increases risk.
- Immune checkpoint inhibitors (ICI).
  - Used for non-small cell lung cancer, melanoma, and renal carcinoma.
  - Can cause myocarditis.
  - Occurs early—within 3 months.
  - LVEF can be normal.

Table 13.2 Chemotherapy is most commonly associated with left ventricular dysfunction. Adapted from Slivnik J et al. Personalized approach to cancer treatment-related cardiomyopathy. *Curr Heart Fail Rep*. 2020 April;17(2):43–55.

Drug class	Drug	HF incidence
Anthracyclines	Doxorubicin	3.0–26%
	Epirubicin	0.9–3.3%
	Idarubicin	5.0–18%
Alkylating agents	Cyclophosphamide	7.0–28%
HER-2/ERB antagonists	Trastuzumab	2.0–28%
	Pertuzumab	0.9–16%
	Bevacizumab	1.0–10.9%
Tyrosine kinase inhibitors	Sorafenib	1.9–11%
	Sunitinib	1.0–27%
Proteasome inhibitors	Carfilzomib	7%
	Bortezomib	2–5%
Immune checkpoint inhibitors		1.1%

  - Poor outcomes with myocarditis reported with myocarditis—46% mortality, cardiogenic shock, cardiac arrest, or complete heart block.
- Cyclophosphamide.
  - Prognosis can be poor—up to 20% mortality.
- Proteasome inhibitors.
  - Bortezomib and caflizomib.
  - Used to treat myeloma.
- Tyrosine kinase inhibitors and MABs targeting vascular endothelial growth factor (VEGF).
  - Sorafenib, sunitinib, and bevacizumab.
  - Usually cause hypertension but can cause LVSD that usually responds to therapy.

Key references

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Swain SM, Whaley FS, Ewer MS. Congestive heart failure in patients treated with doxorubicin: a retrospective analysis of three trials. *Cancer*. 2003;97(11):2869–2879.

Diagnosis of chemotherapy-related cardiac dysfunction (CTRCD)

Imaging

- All patients should undergo evaluation of cardiac function prior to commencing potentially cardiotoxic therapy to provide a baseline for monitoring.
- Multiple imaging modalities help with the detection of CTRCD.
  - Echocardiography is the most widely used.
    - 3D volumetric analysis for LVEF is more accurate and reproducible.
    - Diastolic function and myocardial strain should also be measured.
  - Cardiac CMR is recommended for those with poor echo windows or complex pre-existing cardiac disease.
  - Nuclear imaging may be used. It provides an accurate assessment of LVEF. However, the radiation exposure makes it less useful for surveillance.
- The frequency of repeat imaging depends on the risk of the patient and the cardiotoxic agent being used.

Biomarkers

- Troponin.
  - Useful as a marker of early cardiotoxicity.
  - Mainly tested for AC.
    - Patients who develop raised TN are at greater risk of developing LVSD.
    - Currently being used in clinical trials to guide therapy.
  - Elevated TN is used for the diagnosis and treatment of ICI-induced myocarditis.
    - Trigger for CMR or endomyocardial biopsy.
- NT-proBNP.
  - More useful in the detection of later cardiotoxicity and HF in AC use.

Treatment of CTRCD

Primary prevention of CTRCD

Oncological measures

- Alteration of oncological regimen.
  - Consider non-cardiotoxic agents or dose reduction.
  - Altered preparations, liposomal doxorubicin reduce systemic effects but keep anti-tumour efficacy. Evidence suggesting reduced cardiotoxicity. It is not routinely used but should be considered in those at high/very high risk of CV toxicity with anthracyclines (AC).
- Dexrazoxane.
  - An iron chelator licensed for the prevention of AC-induced CTRCD.
  - Prevents iron-mediated reactive oxygen species production.
  - Use limited by concerns that it may reduce anti-tumour efficacy but should be considered in those at high/very high risk of CV toxicity with AC.

Cardiology interventions

- Management of CV risk factors according to CV prevention guidelines is recommended.
- Neurohormonal antagonists (ACEi/ARB/BB/MRA) have been studied for the prevention of AC and HER2-induced cardiotoxicity with equivocal results.
- BBs.
  - Studied in the CECCY trial: carvedilol versus placebo in 200 HER2-negative breast cancer patients being treated with AC. At 6 months there was no difference in decline in LVEF between the groups. There was less TN release and diastolic dysfunction in the carvedilol groups. They are not used routinely but should be considered in high/very high risk of CV toxicity with AC or other cancer therapies that may cause HF.
- ACEi/ARB.
  - Studies using them as preventive agents have shown mixed results.
    - ACEi has been shown to reduce the rate of CTRCD in those with TN rise after AC and other agents.
    - ARBs studied in breast cancer treated with AC and HER-2 therapies, no clinically significant effects on LVEF.
    - ACEi/ARB should be considered high/very high risk of CV toxicity with AC or anti-HER-2 therapies.
- MRA.
  - Mixed results from small trials, no indications to use as yet.

Treatment of CTRCD

Cardiology intervention

▶▶ Patients who develop LVSD or HF following chemotherapy should be offered standard guideline-directed therapy for HF (see Chapter 5).

Cancer therapy cessation

The decision to withhold/continue cardiotoxic cancer therapies should involve the treating oncologist and cardiologist. The aim is to continue lifesaving therapy whenever possible. Cardiologists should try to optimize

cardiac function to allow further chemotherapy especially if alternative treatments are unavailable.

Some general aids to management:

- Once the baseline risk assessment is performed, a personalized surveillance plan for patients to follow during treatment should be made. This ensures that the detection of early markers of cardiotoxicity, or cardiotoxicity itself, is identified as early so that treatment can be started as soon as possible if appropriate. Surveillance during treatment predominantly involves the use of cardiac imaging and cardiac biomarkers, and several pathways have recently been published (PMID: 35067533 and ESC guidelines).
- AC discontinuation is recommended in symptomatic severe CTRCD.
- Temporary discontinuation is recommended in those with symptomatic moderate CTRCD.
- With some agents, e.g. tratuzumab, it is possible to restart therapy after ACEi and BB have helped recover LV function.
- Three of the most common pathways for the use of AC, HER-2 targeted therapies, ICIs, and the management of LVSD and HF are shown in Figs. 13.1–13.3.

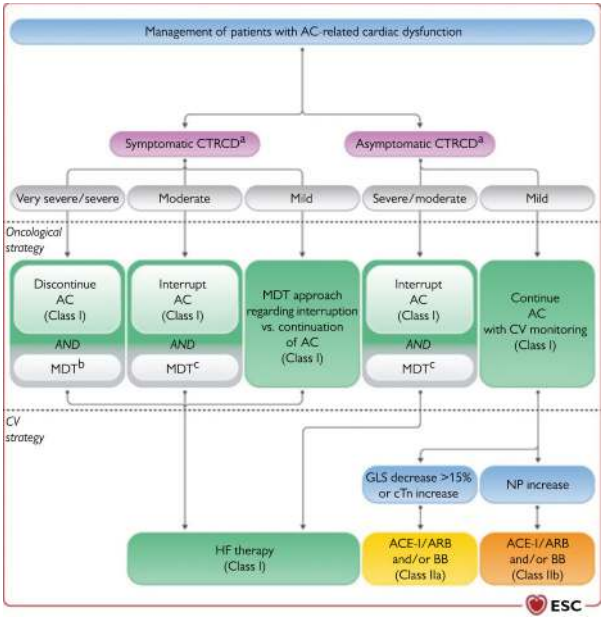

Fig. 13.1 Suggested pathway to manage anthracycline (AC)-related chemotherapy-related cardiac dysfunction (CTRCD). Lyon A et al. 2022 ESC Guidelines on cardio-oncology. *Eur Heart J*. 2022 Nov 1;43(41):4229–4361.

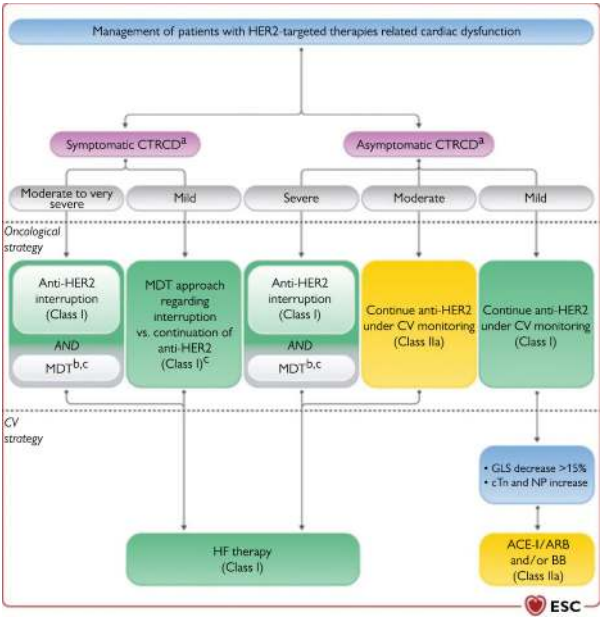

Fig. 13.2 Suggested algorithm for managing human epidermal receptor 2-targeted therapy-related cardiac dysfunction. Lyon A et al. 2022 ESC Guidelines on cardio-oncology. *Eur Heart J.* 2022 Nov 1;43(41):4229–4361.

Follow-up after cessation of cancer therapy

After the end of treatment:

- Risk assessment to identify those high-risk cancer survivors who require long-term CV surveillance (use a tool such as HFA-ICOS) (Table 13.3).
- Criteria for follow-up include:
  - Baseline high or very high risk based on HFA-ICOS risk assessment tools.
  - Cardiotoxic cancer therapy with a high risk of long-term CV complications.
  - Moderate or severe CTRCD diagnosed during cancer treatment.
  - New abnormalities in cardiac function by echocardiography, new elevated cardiac serum biomarkers, or new CV symptoms detected at the end-of-therapy assessment (3 or 12 months after treatment).

The timing of future CV assessment after cardiotoxic cancer treatment ends depends on the CV risk, the type of cancer therapy given, and whether CTRCD was diagnosed during treatment. Echocardiography and cardiac serum biomarkers can be measured in:

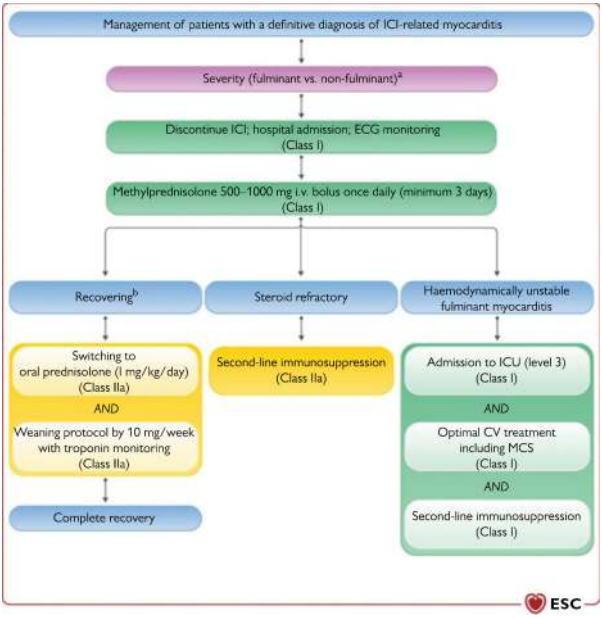

Fig. 13.3 suggested management of immune checkpoint inhibitor-related myocarditis. Lyon A et al. 2022 ESC Guidelines on cardio-oncology. *Eur Heart J*. 2022 Nov 1;43(41):4229–4361.

- Asymptomatic high-risk patient at 3 and 12 months.
- Asymptomatic moderate-risk patients—within 12 months.
- Asymptomatic low-risk patients may be considered within 12 months.

All patients started on ACEi/ARB/ARNI, BB, MRA, SGLT2i, for CTRCD should have:

- Clinical assessment, ECG, echocardiography, and cardiac serum biomarkers at 3, 6, and 12 months after completing cancer treatment.

An MDT-based approach to palliative and end-of-life care for patients with cancer with HF or LVSD, focusing on symptom relief, should be considered as appropriate (see Chapter 43).

Table 13.3 Risk factors for future cardiovascular disease. From Lyon A et al. 2022 ESC Guidelines on cardio-oncology. *Eur Heart J*. 2022 Nov 1;43(41):4229–4361 (Table 10).

High-risk conditions
High- and very-high baseline CV toxicity risk based on HFA-ICOS assessment
Specific anticancer treatment proven to have a high risk of long-term CV complications[a] Doxorubicin[b] >250 mg/m² RT>15 Gy MHD[c] Both doxorubicin[b] >100 mg/m² and RT 5–15 Gy MHD[d] High-risk HSCT patients[e]
Moderate or severe CTR-CVT during cancer treatment (especially CTRCD), CI-related myocarditis, cardiac arrhythmias, or severe vascular toxicities (ACS, stroke, PVD)
New CV symptoms or new asymptomatic abnormalities in echocardiography and/or cardiac serum biomarkers at the end-of-therapy assessment

ACS, acute coronary syndromes; CTR CD, cancer-therapy-related cardiac dysfunction; CTR-CVT, cancer-therapy-related cardiovascular toxicity; CV, cardiovascular; CVD, cardiovascular disease; CVRF, cardiovascular risk factors; GVHD, graft vs. host disease; Gy, Gray; HFA, Heart Failure Association; HSCT, haematopoietic stem cell transplantation; ICI, immune checkpoint inhibitors; ICOS, International Cardio-Oncology Society; MHD, mean heart dose; PVD, peripheral vascular disease; RT, radiotherapy.

[a]RT risk categorization based on MHD is recommended over categorization based on prescribed dose, which may not accurately reflect cardiac radiation exposure. Depending on dose distribution and exposure of specific cardiac substructures (as well as clinical risk factors), the treatment team may judge the patient to belong to a higher risk category. In addition, a patient may be judged to belong to a lower risk category if only a small part of the heart is exposed to a relatively high prescribed dose (i.e. RT to left breast or left chest wall only).

[b] Or doxorubicin equivalent.

[c] Or prescribed RT >35 Gy to a volume exposing the heart if MHD is not available.

[d] Or prescribed RT 15–34 Gy to a volume exposing the heart if MHD is not available.

[e] High-risk HSCT patients: allogenic HSCT; pre-existing CVD or multiple uncontrolled CVRF; cancer treatment history (mediastinal or mantle field radiation, alkylating agents, >250 mg/m² doxorubicin or equivalent); conditioning schemes (total body irradiation, alkylating agents); development of GVHD.

Key references

Bannister C et al. Cardiotoxicity of chemotherapeutic drugs: an update and future perspectives. *J Cardiovasc Pharmacol*. 2022;80:502–514.

Lyon A et al. Baseline cardiovascular risk assessment in cancer patients scheduled to receive cardiotoxic cancer therapies: a position statement and new risk assessment tools from the Cardio-Oncology Study Group of the Heart Failure Association of the European Society of Cardiology in collaboration with the International Cardio-Oncology Society. *Eur J Heart Fail*. 2020;22:1945–1960.

Non-anthracycline agents

Heart failure may result from direct cardiotoxicity, secondary to chemotherapy-related myocardial infarction, or due to pericardial effusion.

Direct cardiotoxicity is associated with:

- Alkylating agents
  - Cisplatin
  - Ifosfamide
  - Mitomycin
- Antimetabolites
  - Cytarabine
  - Pentostatin
- Antimicrotubules
  - Taxanes, including paclitaxel (especially if combined with anthracycline)
- Biological agents
  - Monoclonal antibodies, including bevacizumab and trastuzumab
  - Interferon alfa
- Amsacrine—topoisomerase II inhibitor
- Imatinib—specific tyrosine kinase inhibitor
- Tretinoin

Myocardial infarction may be due to coronary artery spasm:

- Alkylating agents
  - Cisplatin
- Antimetabolites
  - Capecitabine
  - Fluorouracil
- Antimicrotubules
  - Vinca alkaloids
- Biological agents
  - Interferon alfa

Pericardial effusion may be related to therapy with:

- Alkylating agents
  - Busulfan—which may also cause endomyocardial fibrosis
- Cyclophosphamide
- Imatinib
- Tretinoin

Key references

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Yeh ETH, Bickford CL Cardiovascular complications of cancer therapy: incidence, pathogenesis, diagnosis and management. *J Am Coll Cardiol.* 2009;53:2231–2247.

Trastuzumab (Herceptin®) and CHF

Recent developments in the management of breast cancer have offered improved survival, particularly for early-stage breast cancer. Patients are assessed for the need for adjuvant systemic therapy in addition to surgery. Determinants of the need for, and nature of, adjuvant therapy include:

- Estimated risk of disease recurrence.
- Pathology of the presenting breast tumour (hormone-responsive state).
- Overexpression of HER-2/neu cell surface molecule.

The possible options for adjuvant therapy include hormone therapy, chemotherapy that may include anthracyclines, cyclophosphamide, and taxanes, and the anti-HER2 monoclonal antibody trastuzumab.

Trastuzumab[1] is also effective in the management of metastatic breast cancer that overexpresses HER-2/neu. Therefore, there is a sizeable population of women who may benefit from this therapy. However, trastuzumab has significant potential cardiotoxicity, including both symptomatic and asymptomatic left ventricular systolic dysfunction and arrhythmias that does not appear to be dose-related. Unlike the anthracyclines this may not be reversible heart failure. The likelihood of developing heart failure is increased if trastuzumab is combined with anthracyclines and/or taxanes or cyclophosphamide. Other risk factors for the development of cardiomyopathy include previous anthracycline use, age >50 years, previous cardiac disease, and hyperlipidaemia.

The mechanism of the trastuzumab-induced heart failure is not entirely clear, however, there is evidence that Neuregulin-1 beta, a ligand of the HER-2/neu receptor, may attenuate doxorubicin-induced alterations of excitation-contraction coupling. Further evidence suggests that activation of this receptor improves systolic function in a number of cardiomyopathies. This may explain the increased incidence of heart failure in those receiving multimodality therapy.

The experience with trastuzumab to date has suggested guidelines for its use. Careful initial cardiac assessment is required, including documentation of LVEF (either by radionuclide ventriculography or echo). Therapy should not be commenced if the LVEF is <55%. At each subsequent visit, the patient is re-examined, and formal reassessment of LVEF is warranted if:

- Rise in heart rate from baseline.
  - baseline HR <80 bpm and increases to >90 bpm.
  - baseline HR >80 but <100 bpm and increases to >100 bpm.
  - baseline HR >100 bpm and increases to >120 bpm.
- Body weight increased by >2 kg in 1 week.
- Spontaneous report of breathlessness on exertion.

Routine repeat assessment of LVEF should occur every 3 months during therapy.

Trastuzumab should not be given if the baseline assessment identifies

- LVEF <55%.
- Uncontrolled hypertension.

1 Trastuzumab (Herceptin®) is not to be confused with ado-trastuzumab entansine (Kadcyla®).

- High-risk uncontrolled arrhythmias.
- Angina requiring medication.
- Clinically significant valve disease.
- Clinical history of heart failure.
- Evidence of transmural MI on ECG.

If LVEF falls by >10% and to below 50%

- Suspend therapy with trastuzumab.
- Commence heart failure therapy including ACE inhibitors + β blockers.
- Reassess LVEF.
  - If improved, consider restarting trastuzumab.
  - If static or worse, no further trastuzumab.

Key references

Keefe DL. Trastuzumab-associated cardiotoxicity. *Cancer.* 2002;95:1592–1600.

Liu X, et al. Neuregulin-1/erbB-activation improves cardiac function and survival in models of ischemic, dilated, and viral cardiomyopathy. *JACC.* 2006;48:1438–1447.

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Schuchter LM, et al. Neuregulin-1 beta attenuates doxorubicin-induced alterations of excitation-contraction coupling and reduces oxidative stress in adult rat cardiomyocytes. *J Mol Cell Cardiol.* 2006;41(5):845–854.

Suter TM, Cook-Bruns N, Barton C. Cardiotoxicity associated with trastuzumab (Herceptin) therapy in the treatment of metastatic breast cancer. *Breast.* 2004;13:173–183.

Measures to minimize cardiotoxic effects

Patients who may need to receive chemotherapeutic agents that are associated with potential cardiotoxicity should be screened prior to initiation of therapy. Screening should include:

- History.
  - CVRFs, including smoking and hyperlipidaemia.
  - Angina or previous myocardial infarction.
  - Previous clinical heart failure.
- Examination.
  - Hypertension.
  - Heart failure.
- Previous chemotherapy and radiotherapy.
- Planned concomitant chemotherapy and radiotherapy.

Risk factors should be addressed, and management of hypertension and heart failure initiated. Baseline assessment for those with a positive finding during screening should include documentation of LVEF. A clinical decision should then be made, balancing the risk of therapy-related cardiotoxicity with the potential benefit. There may be specific measures that can be taken to reduce cardiotoxicity, e.g. dexrazoxane, liposomal formulations, or infusion or bolus regimes. Clinical need for the use of therapy with potential cardiotoxicity should prompt the cardiologist to strive to pre-optimize the patient, and then a careful screening programme should be tailored to the individual patient.

Screening for the development of cardiotoxicity should be performed at the clinic follow-up. There is an increasing body of support for aggressive screening and early introduction of heart failure therapies. Symptoms or signs suggestive of developing heart failure should prompt reassessment of the LVEF. If there is evidence of a decline in LVEF then the planned therapy may need to be modified and referral made to a cardiologist for management of heart failure. The complexities of the issues around onco-cardiology are triggering the development of specialists in this field. Cardiac biomarkers may play a role in screening for LV dysfunction. There is preliminary evidence of a role for both Troponin (T or I) and NT-proBNP.

The role of 'prophylactic' heart failure medications for particularly potent combined regimes of chemotherapy +/or radiotherapy is not clear. In asymptomatic anthracycline-related left ventricular dysfunction, there are small trials assessing the effect of ACE inhibitors in the survivors of childhood cancers. While they do appear to be beneficial, they do not prevent progressive disease. There is evidence of the benefit of traditional heart failure medications in symptomatic heart failure related to cancer therapy. There may be a role for cardiac transplantation in the management of cancer-therapy-related CHF if the presentation is remote to the diagnosis of malignancy and the therapy has been curative.

Key references

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Chapter 14

The patient with heart failure and cardiomyopathy

Introduction

Cardiomyopathies are disorders of the heart muscle (Fig. 14.1). The ESC defines cardiomyopathy as 'a myocardial disorder in which the heart muscle is structurally and functionally abnormal, in the absence of coronary artery disease, hypertension, valvular disease, and congenital heart disease sufficient to cause the observed myocardial abnormality'

Cardiomyopathies can present at any age and may cause symptoms such as dyspnoea, chest pain, palpitations, or syncope. Cardiovascular comorbidities can act as disease modifiers that can trigger or aggravate an underlying cardiomyopathy. Asymptomatic individuals may be diagnosed following an incidental finding or during familial screening, although not all cardiomyopathies have an established pathogenic gene mutation.

In contrast to other fields within cardiology, there are few randomized control trials to guide treatment, and recommendations tend to come from observational cohort studies and expert consensus opinion. In broad terms, the pharmacological treatment of HF in the setting of cardiomyopathy does not differ from general HF management. In certain types of cardiomyopathy, specific therapeutic options are available and will be discussed in more detail.

Cardiomyopathy can be broadly classified according to clinical phenotype as:

- Dilated cardiomyopathy.
- Non-dilated left ventricular cardiomyopathy.
- Hypertrophic cardiomyopathy.
- Arrhythmogenic right ventricular cardiomyopathy.
- Restrictive cardiomyopathy.
- Other (hypertensive, LV non-compaction, tachycardiomyopathy, endomyocardial disease).

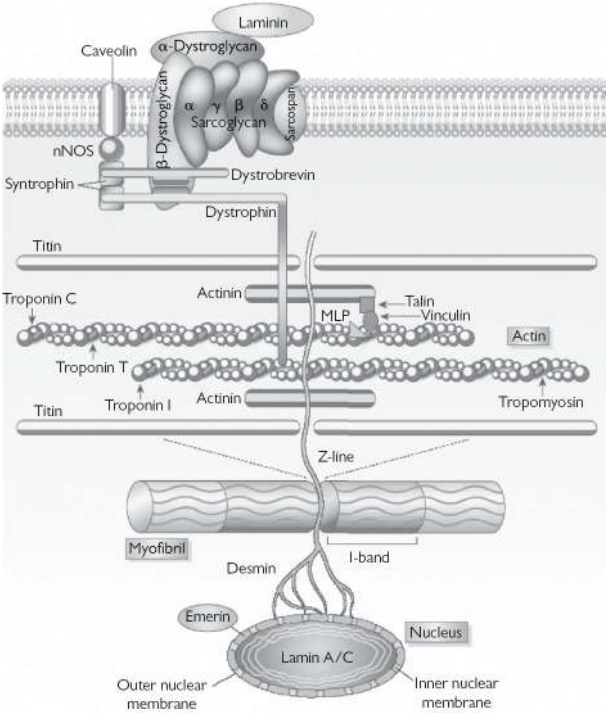

Fig. 14.1 Proteins and pathways involved in the development of cardiomyopathies. MLP = muscle; LIM = protein; nNOS = neuronal nitric oxide synthase.

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Dilated cardiomyopathy

In dilated cardiomyopathy (DCM) there is LV dilation and systolic dysfunction unexplained by coronary artery disease (ischaemic cardiomyopathy ➔ Chapter 10) or abnormal loading conditions (hypertension or valvular heart disease ➔ Chapter 24)

DCM is the most common cardiomyopathy phenotype with an estimated prevalence of up to 1 in 250. DCM comprises a heterogenous group with a wide range of aetiology that can be further classified as follows:

- Familial
- Infection
- Metabolic and endocrine
- Neuromuscular disorders
- Nutritional deficiency
- Peripartum
- Immune mediated
- Toxic and overload—for example, chemotherapy agents (discussed further in ➔ Chapter 13), alcohol, and haemochromatosis (➔ Chapter 18).

Non-dilated left ventricular cardiomyopathy

In non-dilated left ventricular cardiomyopathy (NDLVC) there is non-ischaemic LV scarring or fatty replacement in the absence of LV dilation with or without global or regional WMA or isolated global LV hypokinesia without scarring. As with DCM, this cardiomyopathy cannot be explained by CAD or abnormal loading conditions.

NDLVC is a recently described phenotype that used to be termed 'hypokinetic non-dilated cardiomyopathy' and can encompass those with clear evidence of cardiomyopathy, but who don't fully satisfy diagnostic criteria for other phenotypes. There is notable crossover with DCM-associated gene mutations and non-genetic aetiologies, e.g. laminopathy and infiltrative conditions. Cardiac MRI is the foremost imaging modality to confirm myocardial scar or fibrosis.

Familial dilated cardiomyopathy

Familial dilated cardiomyopathy is an inherited condition that represents a true 'primary' cardiomyopathy, rather than a heart muscle disorder in the context of other systemic pathology or altered physiological state. A familial link is now known to be present in up to 40% of patients with DCM. Numerous gene mutations have been identified, the majority of which are in the genes coding for cytoskeletal proteins. Approximately 90% of mutations are autosomal dominant with variable penetrance (Table 14.1). Inherited neuromuscular disorders that can cause dilated cardiomyopathy are discussed later in this chapter.

It is estimated that only around 35% of the genetic causes for familial cardiomyopathy have been identified. The presence of a mutation does not dictate whether an individual will show symptoms of a disorder, the severity of the symptoms, or its natural history. Equally, the presence of a

Table 14.1 Genetic test panels for multiple gene mutations

Protein	Gene	Transmission	Mutation frequency in DCM (%)	Association with HCM?
Titin	TTN	AD	10–20	Yes
Lamin A/C	LMNA	AD	5–10	
β-myosin heavy chain	MYH7	AD	5–10	Yes
Ribonucleic acid binding motif 20	RBM20	AD	3–6	
Cardiac troponin-T	TNNT2	AD	2–4	Yes
Desmoplakin	DSP	AD	2–4	
Cardiac sodium channel	SCN5A	AD	2–4	
BCL2-associated athanogene 3	BAG3	AD	1-2	Yes
α-Tropomyosin	TPM1	AD	1–2	Yes
Filamin C	FLNC	AD	1–2	Yes
Nexilin	NEXN	AD	1-2	Yes
Vinculin	VCL	AD	<1	Yes
Myosin binding protein C	MYBPC3	AD	<1	Yes
Phospholamban	PLN	AD	<1	Yes
Cardiac troponin I	TNNI3	AR	<1	Yes
Actin	ACTC	AD	<1	Yes
Cardiac troponin C	TNNC1	AD	<1	Yes
Desmin	DES	AD	<1	Yes
Dystrophin	DMD	X-linked	<1	

recognized gene variant does not exclude an alternative aetiology of DCM. Identifying a pathogenic variant can help with prognostication, guiding treatment (e.g. ICD), genetic counselling, and family screening.

Recommendations in patients with a new diagnosis of DCM

- Clinical history to include systemic disease and possible toxic agents.
- Careful extended family history and pedigree analysis.
- Clinical screening of first-degree relatives.
- Counselling of at-risk family members.
- Genetic testing and liaise with a geneticist.

Genetic testing and counselling

Genetic test panels assess for multiple gene mutations (those most robustly associated with cardiomyopathy—Table 14.1). Genetic testing must begin with identification of a causative mutation in an 'index' patient with cardiomyopathy. Cascade genetic testing and genetic counselling can then offered to first-degree relatives. Excluding the mutation in an at-risk family member can be extremely reassuring and avoid the need for periodic clinical screening.

Clinical screening

Clinical screening of first-degree relatives of patients with DCM is important in order to lead to earlier detection, and thus earlier treatment, of LVSD, particularly as the affected individuals may not manifest symptoms of heart failure or arrhythmias until late in the disease process. All first-degree relatives of patients with DCM should undergo clinical evaluation, ECG, and echocardiogram. Cardiac MRI should be considered. Those who do not carry the familial genetic variant and who do not have a cardiomyopathy phenotype can normally be discharged. Family members harbouring the identified genetic variant should undergo repeat screening at least every 5 years.

Key reference

Jordan E, et al. Evidence-based assessment of genes in dilated cardiomyopathy. *Circulation*. 2021;144:7–19.

Dilated cardiomyopathy and infection

It is possible to develop DCM when there is myocardial involvement from systemic infection caused by viruses, bacteria, mycobacteria, fungi, and parasites. The development of DCM following the inflammatory reaction in myocarditis is well recognized and can occur in up to 30% of cases (see Chapter 18).

A DCM phenotype in the context of sepsis and critical illness is increasingly recognized but not yet fully understood. This condition tends to present with acute but reversible DCM (complete recovery within weeks) and has been linked to certain infectious triggers, e.g. invasive streptococcus. Sepsis DCM could be a consequence of exaggerated immune response, or an infective trigger could act as a disease-modifying event that unmasks an underlying cardiomyopathy phenotype.

HIV cardiomyopathy

Cardiac involvement occurs in around 50% of patients with the human immunodeficiency virus (HIV), although this is infrequently clinically significant. The exact pathogenesis of HIV cardiomyopathy is not fully established but thought to include infection of myocardial cells with HIV type 1 (HIV-1), or a subsequent opportunistic infection, and cardiotoxicity from pharmacologic agents (e.g. nucleoside analogues and pentamidine). HIV-1 genomic material has been demonstrated within cardiac myocytes in patients with cardiomyopathy at autopsy.

In a 5-year echocardiographic follow-up study of 952 asymptomatic HIV patients, 8% developed a DCM. Of this group:

- The incidence was higher if the CD4 count was <400 cells/mm³.
- A histological diagnosis of myocarditis was made in 83%.
- HIV nucleic acid sequences were found in 76%.
- Inflammatory infiltrates were predominantly composed of CD3 and CD8 lymphocytes.
- In those with active myocarditis, patients were also infected with:
  - Coxsackie B (17%).
  - Cytomegalovirus (6%).
  - Epstein–Barr virus (3%).

⚠ Although this study was published in the *N Engl J Med.* (Barbaro G et al. Incidence of dilated cardiomyopathy and detection of HIV in myocardial cells of HIV-positive patients. *N Engl J Med.* 1998;339:1093–1099), the work was later retracted by the journal's editors (*N Engl J Med.* 2002;347:140) and therefore the validity of the data is uncertain.

Treatment

Conventional HF treatment may help improve cardiac function, even in asymptomatic HIV-positive patients. Caution should be employed when initiating lipid-lowering therapy, due to the interactions between HIV protease inhibitors and statins affecting cytochrome P450 function. Beware also the possible interaction between protease inhibitors and β-adrenoreceptor antagonists or digoxin due to the possible prolongation of AV conduction.

► A rare but important differential diagnosis of HIV cardiomyopathy is infective myocarditis (e.g. myocardial toxoplasmosis, aspergillosis, tuberculosis, cryptococcosis, histoplasmosis, candidosis, herpes simplex, cytomegalovirus) or cardiac malignancy. See ➔ Chapter 20.

Chagas heart disease

Chagas heart disease or Chagas cardiomyopathy is a protozoal myocarditis endemic to South and Central America, caused by the parasite *Trypanosoma cruzi*. It is estimated that 6 million people worldwide are infected with *T. cruzi*. About 70% of those infected are asymptomatic carriers and never develop any symptoms.

Acute Chagas disease tends to be diagnosed most frequently in children, although individuals of all ages can be infected. It can cause a severe myocarditis, particularly in the young, resulting in DCM, heart failure, and a high risk of mortality. However, if chronic disease occurs, the manifestations are usually delayed and typically do not arise until 20 years later. Whether the features that arise are due directly to parasite invasion or to secondary autoimmune mechanisms is not clear.

Transmission and pathophysiology

The major route of transmission of *T. cruzi* is directly from the reduviid bug. However, the infection can also arise from other routes, including food borne transmission, blood transfusion, organ transplantation, and vertical transmission. Organs involved show chronic inflammatory changes and diffuse fibrosis due antibody and cell-mediated immunity against *T. cruzi* antigens.

Clinical features

- Fatigue and fluid retention.
- Conduction system disease.
- Progressive cardiac dysfunction.
- Ventricular arrhythmias and sudden death.
- Thrombo-embolic disease.

Investigation

- Indirect immunofluorescence or ELISA.
- Echo—global LVSD with LV dilation, although in advanced disease there may be posterior and apical hypokinesis with relative sparing of the septum. An apical aneurysm may also be a feature.

Treatment

- Anti-parasitic agents (e.g. benznidazole, nifurtimox) reduce parasitaemia and can achieve parasitological cure in up to 90%.
- Standard heart failure therapy (not evidence based).
- Antiarrhythmic drugs (e.g. amiodarone).
- Anticoagulation (if indicated, e.g. AF, mural thrombus).

Key reference

Nunes MCP, et al. Chagas cardiomyopathy: an update of current clinical knowledge and management: a scientific statement from the American Heart Association. *Circulation*. 2018;138:e169–e209.

Lyme disease

Lyme disease is a multisystem disease caused by infection from a tick-borne spirochete (*Borrelia burgdorferi*). Early features include erythema migrans and constitutional upset, but the development of cardiac, neurological, and joint involvement may follow after weeks to months. In the USA, cardiac involvement occurs in up to 10% of untreated adults during the early disseminated phase of the disease—usually within the first two months after infection. This is less common in Europe, possibly related to infection by different organisms. Interestingly, although Lyme disease is seen to have a slight female predominance, the cardiac manifestations are much more common in males (3:1).

Clinical features

- Erythema migrans (approximately 90%).
- Early disseminated features (days to months later).
  - Carditis—the most common manifestation being conduction system disease—often progressing rapidly from first to higher degrees of block over a relatively short period of time, frequently requiring temporary transvenous pacing. Myopericarditis and cardiomyopathy (DCM) may also develop, but these are generally mild and self-limiting.
  - Neurological—e.g. lymphocytic meningitis, cranial nerve palsies.
  - Migratory polyarthritis (approximately 50%).
- Late features (weeks to years later).
  - Chronic arthritis.
  - Neurological problems, for example, dementia.

Diagnosis and investigation

- History of tick bite, and clinical features of Lyme disease.
- Serological studies with ELISA and western blot to confirm diagnosis.

Treatment

Lyme disease should generally be treated by those experienced in its management. Doxycycline is currently the antibacterial of choice for early Lyme disease, and intravenous ceftriaxone is recommended for Lyme disease associated with moderate to severe cardiac or neurological abnormalities, late Lyme disease, and Lyme arthritis. The duration of treatment is generally 2–4 weeks, although Lyme arthritis requires longer treatment with oral antibacterial drugs.

Metabolic and endocrine cardiomyopathy

Metabolic cardiomyopathies are generally caused by an underlying deficiency of energy production due to a wide variety of defects, including glycolipid, fatty acid, and glucose metabolism. Of these, Fabry and Pompe disease result in cardiac infiltration and are discussed in more detail in Chapter 18. Other metabolic cardiomyopathies include:

- Carnitine deficiency.
- Mitochondrial myopathies.

Endocrine conditions that can result in DCM, or act as aggravating factors to underlying cardiomyopathy, include:

- Hypo or hyperthyroidism.
- Diabetes mellitus (see Chapter 16).
- Phaemochromocytoma.
- Acromegaly.
- Cushing disease.
- Addison disease.

Neuromuscular disorders

There are a number of inherited progressive myopathic disorders that are associated with cardiac involvement. They include:

- Duchenne muscular dystrophy (DMD).
- Becker muscular dystrophy (BMD).
- Myotonic dystrophy.

The dystrophinopathies

Both Duchenne and Becker muscular dystrophies are X-linked recessive disorders of the dystrophin gene. DMD is more common than BMD, with an incidence of approximately 1:3500 male births compared with 1:30,000 male births. Proximal muscle weakness is the predominant symptom in both conditions, and the development of a DCM with conduction abnormalities and arrhythmias is well recognized (although less common in BMD). In general, DMD presents earlier, and has a more severe course, than BMD.

Clinical findings

- Pseudohypertrophy of the calf.
- Lumbar lordosis.
- Waddling gait.
- Shortening of the Achilles tendons.
- Hyporeflexia or areflexia.

Investigations

- Elevated creatine kinase (10–20 × normal).
- Electromyography—myopathic changes.
- Electrocardiogram—tall right precordial R waves with an increased R/S ratio and deep Q waves in lateral leads. Also associated with conduction disturbances.
- Muscle biopsy.
- Dystrophin analysis—marked reduction in dystrophin (DMD) or abnormal molecular weight (BMD).
- Genetic analysis.

Treatment

- Supportive.
- Standard heart failure therapy in those with a cardiomyopathy.
- Consider PPM/CRT in those with conduction abnormalities.

Myotonic dystrophy

Myotonic dystrophy is an autosomal dominant disorder of the myotonin gene affecting 1:20, 000 people. Myotonin is a protein kinase that transfers phosphate from ATP to other enzymes, and thus is involved in a diverse array of biochemical processes.

Symptoms typically occur in adolescence or adulthood, and include weakness and wasting affecting facial muscles, arms, and legs. Myotonia (delayed muscle relaxation after contraction), cataracts, and abnormal intellectual functioning are also the other features. Around 10% develop a cardiomyopathy, caused by myocardial fatty infiltration, fibrosis, and atrophy of the cardiac conduction system. Such patients are at risk of sudden death due to conductive system disease. However, the main cause of death is respiratory failure.

Investigations

- Electromyography (EMG).
- Mildly elevated serum CK concentration.
- Muscle biopsy.
- ECG—the presence of pathologic Q waves in the absence of coronary artery disease is an indicator of myocardial involvement.

► Beware of conduction system disease, which can progress rapidly.

- Echocardiography.
- Genetic testing—CTG trinucleotide repeat.

Treatment

- Supportive (no specific therapy).
- Standard heart failure therapy in those with a cardiomyopathy.
- Consider PPM/CRT in those with conduction abnormalities—patients should undergo yearly ECGs, or more frequently if conduction system involvement suspected.

Nutritional cardiomyopathy

Beriberi

Beriberi is caused by a deficiency in thiamine (vitamin B_1), which is an important co-enzyme in the hexose monophosphate shunt. It is prevalent in Asia where the diet consists of large quantities of polished rice, which is deficient in thiamine, and initially presents as a high-output cardiac failure. Beriberi can less commonly develop in patients on chronic diuretic therapy, due to increased urinary thiamine excretion.

Seven diagnostic criteria for classic beriberi heart disease have been proposed:

- ≥3 months of thiamine-deficient diet.
- Cardiomegaly, with normal sinus rhythm.
- Dependent oedema.
- Signs of neuritis, pellagra, or both.
- Minor ECG changes (e.g. non-specific ST/T abnormalities).
- No other identifiable cause for heart disease.
- Response to thiamine therapy or autopsy evidence.

Clinical features

- Wet beriberi—fatigue, malaise, and oedema.
- Dry beriberi—peripheral neuropathy, and a high cardiac output.
- Anaemia (if there is coexisting iron or folate deficiency).
- Painful glossitis.
- Hyperkeratinized skin lesions.
- Reduced thiamine, increased serum pyruvate and lactate, low red cell transketolase.

Treatment

Thiamine—the initial loading doses of thiamine are 100–500 mg intravenously, followed by 25–100 mg/day orally for at least 2 weeks. Patients often have a prompt improvement in cardiac function.

Other nutritional cardiomyopathies

Deficiencies in certain other micro- and macro-nutrients (e.g. selenium and zinc) have been implicated in the development of DCM. However, due to the complex individual diets in those with a non-ischaemic cardiomyopathy, this is usually impossible to unravel, and even more difficult to study!

Peripartum cardiomyopathy

Peripartum cardiomyopathy (PPCM) is a rare disorder where LVSD presents 'towards the end of pregnancy or in the months following delivery, where no other cause is found' (➔ Chapter 22).

Several mechanisms for PPCM have been investigated, including the shorter 16-kDa form of prolactin, nutritional disorders (e.g. selenium deficiency), autoimmune disease, myocarditis, abnormal hormonal regulation, viral triggers, and foetal microchimerism (foetal cells in maternal blood), causing the initiation of an autoimmune myocarditis. However, the aetiology remains unknown.

There is substantial overlap with DCM pathogenic gene mutations and genetic causes of cardiomyopathy are present in up to 20% of PPCM.

Possible risk factors for PPCM include:

- Extremes of childbearing age.
- Multiparity.
- Middle Eastern origin.
- Hypertension of pregnancy (although there is debate as to whether pre-eclamptic heart failure is a separate diagnosis).
- Use of tocolytics (medications used to suppress premature labour).
- Multiple pregnancy.
- Obesity.
- Smoking.

Clinical features

- Symptoms and signs of HF (may initially be masked by pregnancy).
- S_3 gallop.
- ECG—non-specific ST/T abnormalities are seen in the majority of cases; LVH by electrical criteria in two-thirds.
- Echo—dilated LV with LVSD; thrombus may be present.

Treatment

Standard HF therapy is indicated in PPCM following childbirth. In particular, β-adrenoreceptor antagonists are important in order to reduce the risks of arrhythmia and sudden death. However, ACE inhibitors, ARBs and ARNIs are known to be teratogenic and should therefore be replaced by hydralazine and nitrates until delivery. MRAs should also be avoided during pregnancy. Post-partum counselling about plans for breastfeeding is important in deciding what therapies can be initiated. β-adrenoreceptor antagonists and ACE inhibitors are generally accepted as safe even if breastfeeding proceeds. In very severe heart failure, the exertion and metabolic demands of breastfeeding should be recognized and consideration given to advising against breastfeeding.

Patients with PPCM are prothrombotic and prophylactic anticoagulation should be considered in all patients, with treatment-dose anticoagulation if confirmed thrombotic disease or AF.

Bromocriptine *may* be a novel disease-specific treatment for PPCM. A small randomized trial comparing two different dosing regimes reported high rates of LV recovery over 6 months and no mortality. Larger trials are underway and the latest European guidelines recommend *considering* bromocriptine use in PPCM.

Prognosis

Women with PPCM have a higher rate of spontaneous recovery of ventricular function than those with other forms of DCM. A recent European long-term population study describes LV recovery in 76% of cases over a median of 8.3 years. Recovery usually occurs in the first 6 months, although can take significantly longer. However, PPCM is still associated with a mortality of approximately 15%. For some, ventricular assist devices or cardiac transplantation become necessary—occasionally requiring urgent listing.

Subsequent pregnancy

There may be a significant risk for recurrence or death during subsequent pregnancies.

► **Pre-pregnancy counselling and contraceptive advice** are imperative as subsequent pregnancies may have the potential for maternal decompensation and death, particularly if there is persistent LV dysfunction.

Key references

Hilfiker-Kleiner D, et al. Bromocriptine for the treatment of peripartum cardiomyopathy: a multicentre randomized study. *Eur Heart J*. 2017;38:2671–2679.

Jackson AM, et al. A 20-year population study of peripartum cardiomyopathy. *Eur Heart J*. 2023;44:5128–5141.

Sliwa K, et al. Peripartum cardiomyopathy: from genetics to management. *Eur Heart J*. 2021;42:3094–3102.

Immune-mediated cardiomyopathy

Cardiac involvement is recognized in many systemic autoimmune diseases such as systemic lupus erythrmatosus (SLE) and inflammatory myopathies (e.g. dermatomyositis). SLE, for example, causes a pancarditis in approximately 10% of patients involving the pericardium, myocardium, endocardium, and coronary arteries, although patients may be asymptomatic.

The pathogenesis of myocardial dysfunction and immune response is incompletely understood. It is suggested that autoimmunity may contribute to the development of cardiac dysfunction in gene-positive familial DCM.

The inflammatory cardiomyopathy seen in acute myocarditis (particularly giant cell myocarditis) is caused by maladaptive immune response and carries a high mortality rate (see ➔ Chapter 20). Further evidence of immune-mediated cardiac toxicity can be seen with complications from immune checkpoint inhibitor therapy (see ➔ Chapter 18).

Alcoholic cardiomyopathy

Chronic excessive alcohol consumption is a leading cause of DCM. The majority of cases appear to be related to the direct toxic effect of alcohol on myocardial function, although nutritional deficiency (e.g. beriberi) and additives to alcohol (e.g. cobalt) have also been implicated in a minority of cases.

Up to one-third of alcoholics have evidence of LVSD. However, not all alcoholics develop cardiomyopathy as there appears to be a genetic predisposition to its development: those with a DD phenotype of the ACE gene polymorphism are significantly more likely to develop LVSD than those without. Genetic variants associated with DCM are common and TTN gene mutations have been identified in more than 10% of those with a diagnosis of alcoholic cardiomyopathy.

It is important to emphasize that alcohol-induced cardiomyopathy is a diagnosis of exclusion, and that recovery of cardiac function can occur if the disease is identified early and further alcohol intake halted.

Clinical features

- History of chronic alcohol excess.
- Symptoms and signs of a dilated cardiomyopathy of any aetiology.
- Atrial fibrillation is a relatively common finding.
- Possible signs of coexisting alcoholic liver disease.

Treatment

- Complete abstinence from alcohol.
- Standard heart failure therapy.
- Vitamin supplementation (e.g. thiamine, folic acid).

Hypertrophic cardiomyopathy

Hypertrophic cardiomyopathy (HCM) is a genetic disorder characterized by the presence of unexplained left ventricular hypertrophy (≥15 mm in any myocardial segment). This classically causes asymmetric hypertrophy of the interventricular septum (IVS), but there is significant heterogeneity in the extent of cardiac hypertrophy and degree of outflow obstruction, the latter of which is thought to affect 25% of individuals. By the time patients with HCM present with HF, the morphology may have changed from hypertrophic to dilated cardiomyopathy. The incidence is approximately 1:500.

Aetiology

HCM has an autosomal dominant inheritance, with incomplete penetrance. Several genes have been associated with HCM, each of them encoding cardiac sarcomere proteins (Table 14.1 (DCM section) and Table 14.2). Histologically, HCM has the distinctive appearance of myocyte disarray—where hypertrophied cardiomyocytes form abnormal intercellular connections—and fibrosis.

Clinical features

The majority of affected individuals are asymptomatic, are picked up incidentally, and have a normal life span. However, the first clinical manifestation may be sudden death, and therefore there is a significant variability in clinical course as well as outcome. Symptoms may include:

- Breathlessness—impaired ventricular filling (↑ LVEDP).
- Fatigue.
- Chest pain.
- Arrhythmias—both atrial and ventricular.
- Syncope.

Examination may be normal, although signs include:

- Jerky pulse.
- Prominent a-wave in JVP.
- Laterally displaced ± double apex beat.
- S_4.
- Harsh systolic murmur at left sternal edge, increasing with Valsalva manoeuvre, or on standing from a squat position.

Investigations

- ECG—usually abnormal (85%), with ST/T wave abnormalities and LVH, particularly in the mid-precordial leads. Prominent inferior or precordial Q waves are also frequently seen (in up to 50%) (Fig. 14.2).
- Echocardiography:
  - Degree and distribution of ventricular hypertrophy.
  - Small cavity size.
  - LV outflow tract obstruction (LVOTO)—caused by a thickened IVS and systolic anterior motion (SAM) of the anterior mitral valve leaflet.
  - Normal systolic function (although LVSD occurs in 5–10%).
- Cardiac MRI – late gadolinium enhancement present in 65%, typically patchy mid-wall pattern in areas of hypertrophy and anterior and posterior RV insertion points (In recent guidelines from ESC and ACC/AHA, CMR is now recognized as a key investigation in all patients with cardiomyopathy).

Table 14.2 Causes of left ventricular hypertrophy

Sarcomeric protein disease
- β-myosin heavy chain.
- Cardiac myosin binding protein C.
- Cardiac troponin I.
- Troponin-T.
- α-Tropomyosin.
- Essential myosin light chain.
- Regulatory myosin light chain.
- Cardiac α-actin.
- α-myosin heavy chain.
- Titin.
- Troponin C.

Metabolic disease
- (Glycogen storage disease II) Pompe disease.
- (Glycogen storage disease III) Forbes disease.
- Anderson-Fabry disease.
- Carnitine deficiency.
- Phosphorylase B kinase deficiency.
- Infant of a diabetic mother.
- AMP kinase (WPW, HCM, conduction disease).
- Debrancher enzyme deficiency.
- Hurler's syndrome.
- Hurler–Scheie disease.
- Hunter's syndrome.
- Mannosidosis.
- Fucosidosis.
- Total lipodystrophy.
- Mitochondrial cytopathy.
- MELAS.
- MERRF.
- LHON.

Syndromic HCM
- Noonan's syndrome.
- LEOPARD syndrome.
- Friedreich's ataxia.
- Beckwith–Wiedermann syndrome.
- Swyer's syndrome (pure gonadal dysgenesis).

Miscellaneous
- Obesity.
- Athletic training.
- Muscle LIM protein.
- Phospholamban promoter.
- Amyloidosis.
- Phaeochromocytoma.

HCM = hypertrophic cardiomyopathy; LHON = Leber's hereditary optic neuropathy; MELAS = mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes; MERRF = myoclonic epilepsy and ragged red fibres; WPW = Wolff–Parkinson–White syndrome.

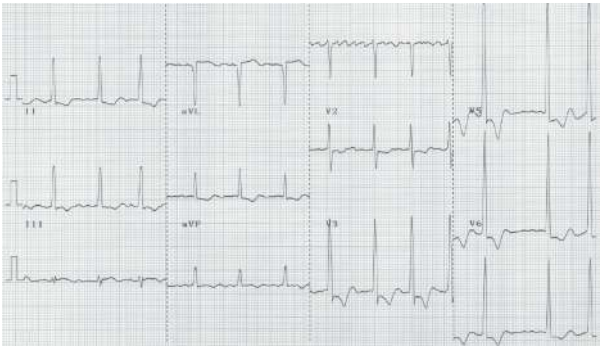

Fig. 14.2 ECG of HCM.

Reproduced from Myerson, Choudhury & Mitchell, *Emergencies in Cardiology*, 2006 with permission from Oxford University Press.

Other investigations

- Ambulatory ECG recording—to assess for arrhythmias.
- Exercise testing—to assess functional capacity and BP response.
- Genetic testing.
- Nuclear imaging—can be useful if diagnosis unclear and possibility of cardiac amyloidosis (see ➔ Chapter 18).

Treatment

The approach to HCM management depends on the presence or absence of symptoms and LVOTO. There are limited RCTs in HCM populations and treatment is generally empirical with the aim of reducing symptoms and improving functional capacity.

In patients without LVOTO, β-adrenoreceptor antagonists, non-dihydropyridine calcium channel blockers (e.g. verapamil or diltiazem) and low dose diuretics can be used. HF medical therapy is indicated in the setting of LVSD.

Typically, the treatment threshold for resting or provoked LV outflow tract gradient is ≥50 mmHg. The approach to management of symptomatic LVOTO in HCM is summarized in Fig. 14.3.

Pharmacological

- Non-vasodilating β-adrenoreceptor antagonists are the cornerstone of HCM therapy (e.g. metoprolol). By reducing heart rate, they reduce myocardial oxygen demand (and thus symptoms of angina and breathlessness), and the increase in outflow tract obstruction that accompanies exercise. β-Adrenoreceptor antagonists are also antiarrhythmic agents and may reduce the risk of syncope and SCD. Caution should be employed in the withdrawal of these agents due to rebound sympathetic sensitivity.

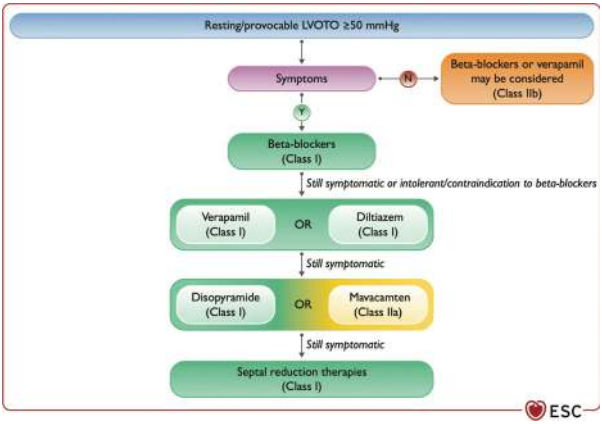

Fig. 14.3 Flow chart on the management of left ventricular outflow tract obstruction. LVOTO, left ventricular outflow tract obstruction. Arbelo E, et al. 2023 ESC Guidelines for the management of cardiomyopathies. *Eur Heart J*. 2023;44:3503–3626.

- Non-dihydropyridine calcium channel antagonists can be used in those who are intolerant to β-adrenoreceptor antagonists.
- Antiarrhythmic agents—disopyramide is a class 1A antiarrhythmic that can reduce the outflow gradient and may lead to symptomatic improvement, although these benefits may diminish with time. Amiodarone is an effective antiarrhythmic agent, but has not been shown to conclusively reduce the risk of SCD.
- Cardiac myosin ATPase inhibitors—mavacamten reduces myocardial contractility, resulting in reduced LVOT gradient and improved exercise capacity versus placebo in HCM patients with symptomatic LVOTO in the EXPLORER-HCM trial. Close echocardiographic monitoring is required and this drug class is contraindicated in those with LVEF <55%.
- In LVOTO, certain drugs should be avoided including vasodilating agents and digoxin.

Non-pharmacological

- Surgical myotomy–myectomy (Morrow procedure)—transaortic resection of IVS to debulk the septum. It may be combined with mitral valve repair or replacement in patients with significant SAM of the mitral valve. Symptomatic benefit is achieved in >80% and although procedural mortality ranges from 2 to 10%, long-term survival is comparable to the general population. LBBB is common postoperatively and there is a small risk of CHB.
- Alcohol septal ablation may be considered where there is favourable coronary anatomy. It is performed by inducing a localized septal

infarction. Alcohol is injected into the first or second septal perforator artery, following a contrast injection to ensure the correct septal distribution. The risk of CHB is approximately 15%.

- Dual chamber pacing may be considered in symptomatic individuals with an outflow tract gradient, who are not felt suitable for surgical myectomy or alcohol septal ablation. By programming a short a–v delay, the outflow gradient can be reduced by 50%.
- ICD—should be considered in high-risk individuals, particularly those with sustained ventricular arrhythmias and following resuscitated cardiac arrest. In the presence of outflow obstruction, a dual-chamber ICD is potentially of value (refer to dual-chamber pacing described previously).
- Cardiac transplantation may be an option for patients with progressive LV dysfunction refractory to other therapies.

Exercise

Undiagnosed HCM is the most common autopsy finding in competitive athletes who die suddenly. It is also true that around 50% of HCM deaths occur with or following exercise. This led to historically conservative recommendations to significantly limit exercise in HCM.

More recently, exercise programmes involving mild to moderate activity have demonstrated safety, as well as evidence of functional improvement and improved quality of life in symptomatic and asymptomatic HCM.

Risk factors for SCD in HCM

- Age.
- Maximum LV wall thickness.
- Left atrial size.
- LVOT gradient.
- Family history of SCD.
- Non-sustained VT.
- Unexplained syncope.

These factors can be used to estimate the risk of SCD at 5 years and inform decisions regarding ICD implantation: European guidelines suggest that if the 5-year SCD risk is <4% ICD is generally not indicated.

Arrhythmogenic cardiomyopathy

Arrhythmogenic cardiomyopathy (ACM), previously called arrhythmogenic right ventricular cardiomyopathy (ARVC), is characterized by the gradual replacement of myocytes by adipose and fibrous tissue primarily in the RV (hence why it was previously called ARVC). ACM is an important cause of sudden death in individuals <30 years (3% SCD/year), and diffuse RV, and occasionally LV, involvement may result in heart failure. The prevalence of ACM is approximately 1:5,000.

ACM is typically inherited as an autosomal dominant trait with variable (approximately 30%) penetrance and incomplete expression. Pathogenic gene variants are identified in 60% of cases. The genes responsible for ACM have been mapped to chromosomes 1, 2, 3, 10, and 14. It is understood to be a desmosome disease with defects in desmoplakin, desmoglein, desmocollin, plakoglobin, and plakophilin. Naxos disease is an autosomal recessive ACM mapped to chromosome 17, which is characterized by non-epidermolytic palmoplantar keratosis and woolly hair (Fig. 14.4).

Clinical features

ACM typically occurs in young adult males, and is usually asymptomatic. However, it should be considered in young patients presenting with syncope, VT (usually of RV origin—LBBB morphology), cardiac arrest, or in adult patients with heart failure. In the USA, ACM accounts for approximately 5% of SCD in those <65 years. Heart failure is predominantly right-sided, but may progress to biventricular failure. Most cases are diagnosed before the age of 40.

ACM can mimic the presentation of other cardiac pathology such as myocarditis, myocardial infarction (RV infarction), sarcoidosis, pulmonary hypertension or congenital cardiac abnormalities (e.g. Ebstein anomaly). Idiopathic RVOT tachycardia in particular, unlike ACM, is normally a benign condition and investigations are important to reach a clear diagnosis.

Investigation and diagnosis

The histological finding of transmural fibrofatty replacement of RV myocardium allows a definitive diagnosis of ARVC. Endomyocardial biopsy has a low sensitivity, since the disease is segmental and rarely involves the interventricular septum. ECG changes include abnormalities with ventricular depolarization and repolarization in the right precordial leads. Echocardiography reveals RV dilatation/dysfunction, and cardiac MRI can help to distinguish fat from muscle as well as providing information about RV wall motion and function. An expert consensus group has proposed the criteria for the diagnosis of ACM (outlined next).

Treatment

β-adrenoreceptor antagonists are first-line therapy for those with well-tolerated ventricular arrhythmias and for those with LVSD. Other antiarrhythmic drugs such as amiodarone, sotalol, or flecainide can be trialled if single-agent treatment has failed. Radiofrequency ablation can be considered in patients who are unresponsive or intolerant to antiarrhythmic drugs, although this has a limited success rate due to the diffuse and progressive nature of the disease and hasn't been shown to reduce SCD.

Patients who are considered to be at high risk for sudden cardiac death should receive an ICD (see arvcrisk.com). Avoidance of intense exercise may reduce ventricular arrhythmia burden and slow disease progression.

Criteria for diagnosis of ACM

A patient must demonstrate: two major criteria; or one major criterion plus two minor criteria; or four minor criteria.

1. Global or regional dysfunction and structural alterations

Major

By 2D echo:

- Regional RV akinesia, dyskinesia, or aneurysm.
- *and* any 1 of the following: PLAX RVOT ≥32 mm (or ≥19 mm/m^2), PSAX RVOT ≥36 mm (or ≥21 mm/m^2), fractional area change ≤33%.

By MRI:

- Regional RV akinesia, dyskinesia, or dyssynchronous RV contraction.
- *and* any 1 of the following: indexed RV EDV ≥110 mL/m^2 (male) or ≥100 mL/m^2 (female) or RV ejection fraction ≤40%.

By RV angiography:

- Regional RV akinesia, dyskinesia, or aneurysm.

Minor

By 2D echo:

- Regional RV akinesia or dyskinesia.
- *and* any 1 of the following: PLAX RVOT ≥29 to <32 mm (or ≥16 to <19 mm/m^2), PSAX RVOT ≥32 to <36 mm (or ≥18 to <21 mm/m^2), fractional area change >33% to ≤40%.

By MRI:

- Regional RV akinesia, dyskinesia, or dyssynchronous RV contraction.
- *and* any 1 of the following: indexed RV EDV ≥100 to <110 mL/m^2 (male) or ≥90 to <100 mL/m^2 (female) or RV ejection fraction >40% to ≤45%.

2. Tissue characterization of walls (endomyocardial biopsy)

Major

- Residual myocytes <60% by morphometric analysis (or <50% if estimated), with fibrous replacement of the RV free wall myocardium in ≥1 sample, with or without fatty replacement of tissue.

Minor

- Residual myocytes 60%-75% by morphometric analysis (or 50%-65% if estimated), with fibrous replacement of the RV free wall myocardium in ≥1 sample, with or without fatty replacement of tissue.

3. Repolarization abnormalities

Major

- Inverted T waves V1–V3 or beyond in individuals >14 years old (without RBBB).

Minor

- Inverted T waves in V1 and V2 in individuals >14 years old (without RBBB) or in V4, V5, or V6.
- Inverted T waves V1–V4 in individuals >14 years old with RBBB.

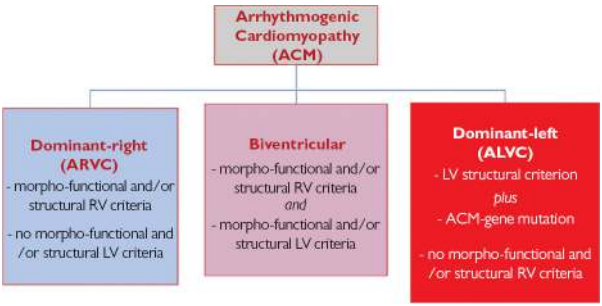

Fig. 14.4 Diagnosis of phenotypic variants of ACM in patients fulfilling the Padua criteria. Demonstration of morpho-functional and/or structural ventricular abnormalities is required for diagnosis of each phenotypic variant of ACM. Although dominant-right (ARVC) and biventricular disease variants can be diagnosed in those patients fulfilling RV and LV phenotypic criteria, the diagnosis of dominant-left (ALVC), without clinically demonstrable RV abnormalities, needs demonstration of an ACM-causing gene mutation, in association with a consistent LV phenotype(see text for details). From D. Corrado et al. *Int J Cardio*. 319(2020):106–114.

4. Depolarization/conduction abnormalities

Major

- Epsilon wave (low amplitude signal between the end of QRS and onset of T wave) in V1–V3.

Minor

- Late potentials by signal-averaged ECG (SAECG) in ≥1 of 3 parameters in the absence of a QRS duration of >110 ms on the standard ECG.
- Filtered QRS duration ≥114 ms.
- Duration of terminal QRS <40uV ≥38 ms.
- Root mean square voltage of terminal 40 ms ≤20uV.
- Terminal activation duration of QRS ≥55 ms (nadir of S wave to end of QRS, including R^{I}) in V1–V3 (without RBBB).

5. Arrhythmia

Major

- Ventricular tachycardia of LBBB morphology with superior axis.

Minor

- Ventricular tachycardia of RV outflow configuration (LBBB, inferior axis) or of unknown axis.
- >500 ventricular extrasystoles per 24 hours (Holter).

6. Family history

Major

- ARVC confirmed in a first-degree relative who meets diagnostic criteria.
- ARVC confirmed pathologically at autopsy or surgery in a first-degree relative.
- Identification of an ARVC associated (or probably associated) pathogenic mutation.

Minor

- ARVC confirmed in a first-degree relative but unclear if meets diagnostic criteria.
- Premature sudden death (<35 years old) due to suspected ARVC in a first-degree relative.
- ARVC confirmed pathologically or by diagnostic criteria in a second-degree relative.

Key references

Corrado D, et al. Diagnosis of arrhythmogenic cardiomyopathy: the Padua criteria. *Int J Cardiol*. 2020;319:106–114.

Marcus FI, et al. Diagnosis of arrhythmogenic right ventricular cardiomyopathy/dysplasia: proposed modification of the Task Force Criteria. *Eur Heart J*. 2010;31:806–814.

Restrictive cardiomyopathy

Restrictive cardiomyopathy is an uncommon condition in Western countries, characterized by impaired diastolic function secondary to reduced ventricular compliance in the absence of LVH. In certain geographical locations (particularly the tropics—Africa, India, South and Central America, and Asia), restrictive cardiomyopathy is a more important cause of death due to the higher incidence of endomyocardial fibrosis in those regions. Systolic function usually remains normal, at least early in the disease.

Aetiology

Although the aetiology is often obscure, there are several known causes of restrictive cardiomyopathy:

- Endomyocardial:
  - Endomyocardial fibrosis.
  - Hypereosinophilic syndrome (Löffler endocarditis).
  - Radiation.
- Myocardial:
  - Genetic—mutations involving sarcomeric and cytoskeletal proteins (TTNI3 most commonly)
  - Storage diseases (e.g. desmin).
- Conditions resulting in restrictive physiology (often with LVH):
  - Infiltrative (e.g. amyloidosis, sarcoidosis, haemochromatosis)—see ➔ Chapter 18.
  - Non-infiltrative (e.g. scleroderma).
  - Drug toxicity.
  - Malignancy.
  - End-stage HCM or DCM.

Clinical features

- Exercise intolerance (limited increase in cardiac output secondary to fixed stroke volume).
- Elevated filling pressures.
- Impalpable apex beat (unlike constrictive pericarditis).
- S_3/S_4.
- Peripheral oedema.
- Hepatomegaly and ascites.
- Kussmaul sign (inspiratory increase in JVP).
- Similar to HFpEF clinical phenotype.

Investigations

- ECG—P mitrale/pulmonale; low precordial QRS amplitude; atrial arrhythmias.
- Echocardiography—may initially appear unremarkable, with normal ventricular dimensions and systolic function. However, there is often marked bi-atrial enlargement secondary to elevated atrial pressures, and a restrictive inflow pattern seen on mitral Doppler.
- Cardiac catheterization to differentiate from constrictive pericarditis (Table 14.3).
- CT/MRI—assessment for infiltrative myocardial and endomyocardial disease, as well as imaging of the pericardium.

Table 14.3 Features differentiating constrictive pericarditis from restrictive cardiomyopathy

Clinical feature	Restrictive cardiomyopathy	Constrictive pericarditis
Past medical history	Infiltrative disease or endomyocardial fibrosis	Previous pericarditis, cardiac surgery, radiotherapy, trauma, connective tissue disease
Jugular venous waveform	Often increased	Normal or increased with 'flicking' X and Y dips
Cardiac auscultation	Later S_3, S_4 in some cases	Early S_3, high pitched 'pericardial knock'. No S_4
Paradoxical pulse	Rare	Often present
Mitral or tricuspid regurgitation	Often present	Rare
ECG	P waves reflect atrial hypertrophy. Conduction defects can be seen	P waves reflect intra-atrial conduction delay. Conduction defects less common
Chest X-ray	Pericardial calcification rare	Pericardial calcification may be present
MR/CT imaging	Thickened pericardium rare	Thickened pericardium often present
Ventricular septal movement in diastole	Abrupt septal movement in early diastole rare	Abrupt septal movement ('notch') in early diastole
Ventricular septal movement with respiration	Relatively little movement towards left ventricle	Movement towards left ventricle
Atrial enlargement	Pronounced	Slight or moderate in most cases
Respiratory variation in mitral and tricuspid flow velocity	Less	More
Equilibration of diastolic pressures in all cardiac chambers	Unlikely to be within 5 mmHg	Yes
Dip-plateau waveform in the right ventricular pressure waveform	End diastolic pressure often less than one-third of systolic	End diastolic pressure is often more than one-third of systolic pressure
Peak right ventricular systolic pressure	Elevated (often >40 mmHg)	Less likely to be elevated (often <40 mmHg)
Endomyocardial biopsy	May demonstrate amyloid, rarely other infiltrative disease	Normal, or non-specific abnormalities

Treatment

- Treat heart failure if present with medical therapy, and diuretics for fluid overload.
- Avoidance of, or rate control in, AF will help maintain ventricular filling time.
- Specific therapy directed towards underlying cause.
- Consider cardiac transplantation where appropriate.

► Beware of underfilling patients with restrictive cardiomyopathy, as a drop in filling pressure will have a marked impact on cardiac output.

► Differentiation from constrictive pericarditis is important as this can be treated surgically by pericardectomy (Table 14.3).

Prognosis

Restrictive cardiomyopathy has the worst prognosis of all cardiomyopathy phenotypes, and the most common cause of death is heart failure.

Endomyocardial disease

Endomyocardial fibrosis (EMF) is a disease of unknown aetiology that is characterized by fibrous endocardial involvement of either/both ventricles, often with associated atrioventricular valvular regurgitation. EMF typically occurs in equatorial Africa, where it is a frequent cause of restrictive cardiomyopathy and chronic heart failure, although the incidence of the disease appears to be declining. It is also recognized elsewhere: generally, within 15° of the equator.

Clinical features and investigation

- LV (40%), RV (10%), or biventricular involvement (50%).
- Symptoms and signs of left/right ventricular failure.
- Eosinophilia may be present.
- Mural thrombi common.
- ECG—small QRS voltages; ST/T wave abnormalities.
- Echo—apical obliteration of involved ventricle; dilated atria, pericardial effusion (may be large); MR/TR.
- CMR—late gadolinium enhancement in the endocardium—particularly affecting the apex and eventually the inflow tract of one or both ventricles. This is not confined to a coronary artery territory and usually spares the outflow tract orifices. Thrombus is often present.
- Endomyocardial biopsy may be diagnostic.

Treatment

- Diuretics.
- Anticoagulation if indicated.
- AF can be rate-controlled with digoxin, but its occurrence heralds a poor prognosis.
- Surgical removal of fibrotic endocardium leads to a significant improvement in symptoms, although recurrent fibrosis invariably occurs.

Löffler endocarditis (hypereosinophilic syndrome)

Hypereosinophilic syndrome (HES) is a clinical diagnosis where there is a sustained eosinophil count >1,500/mm³ for 6 months, with organ involvement. Most patients with HES have biventricular cardiac involvement (Löffler endocarditis), with eosinophilic myocarditis, mural thrombosis, and fibrotic change, resulting in a restrictive cardiomyopathy.

Clinical features and investigations

- Systemic upset—fever, weight loss, rash, cough.
- Symptoms and signs of heart failure.
- AF is common.
- Thromboembolic disease.
- Associated involvement of the lungs, bone marrow, brain, and kidneys.
- ECG—non-specific T-wave abnormalities.
- Echo—localized thickening of the LV basal posterior wall; restricted motion of the posterior mitral valve leaflet; preserved systolic function; dilated atria; apical thrombus.
- Cardiac MRI – diffuse sub-endocardial late gadolinium enhancement.

Treatment

- Diuretics and vasodilators.
- Anticoagulation if indicated.
- Early corticosteroid treatment.
- Interferon and tyrosine kinase inhibitors may be tried in advanced cases.
- Surgical removal of fibrotic endocardium.

Hypertensive cardiomyopathy

Hypertensive cardiomyopathy can be considered under the broader term of hypertensive heart disease and is a leading cause of chronic heart failure. Hypertension causes left ventricular hypertrophy as a compensatory mechanism to an increased afterload, by normalizing systolic wall stress and preserving contractile function. Anti-hypertensive drug therapy has been shown to prevent the development of LVH. In the face of persistent hypertension and elevated functional demand, the failure of further hypertrophy to normalize loading conditions results in progressive cardiac dysfunction and dilatation, as well as interstitial and perivascular fibrosis.

Cardiomyocyte apoptosis has been shown to be abnormally stimulated in the hypertrophied heart of patients with hypertension. This process is increased further in those who develop chronic heart failure, and therefore apoptosis may be one of the many mechanisms involved in the loss of contractile mass and function in hypertensive cardiomyopathy (Fig. 14.5).

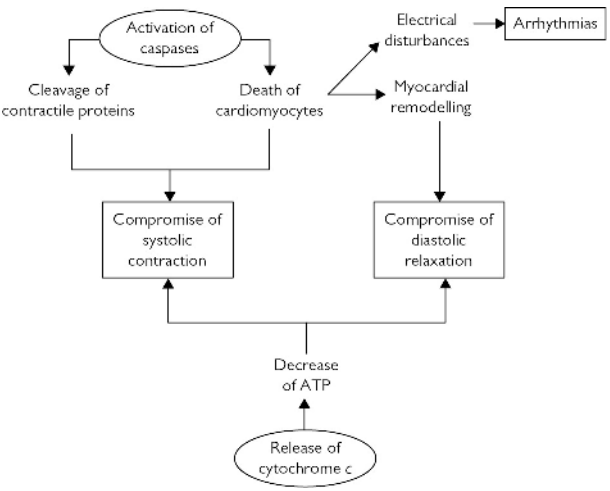

Fig. 14.5 Mechanisms activated by the apoptotic process in the cardiomyocyte that may contribute to a deterioration of cardiac function and alter the electrical activity of the myocardium in hypertensive cardiomyopathy. Cytochrome c plays a major role in ATP production through mitochondrial oxidative phosphorylation.

Caspases are proteases involved in the execution of the apoptotic process. Arantxa Gonzalez, Cardiomyocyte apoptosis in hypertensive cardiomyopathy. *Cardiovasc Res.* 2003;59(3), by permission of Oxford University Press.

Left ventricular hypertrabeculation

Previously known as left ventricular non-compaction (LVNC). LV hypertrabeculation is not strictly defined as a cardiomyopathy, but rather a ventricular phenotypic trait that is characterized by prominent trabeculation and deep intertrabecular recesses within the left ventricle with a thick endocardial layer and thin, compacted epicardial layer. These alterations are thought to be due to an intrauterine arrest of compaction of the myocardial fibres in the absence of any coexisting congenital lesions.

There is a familial link with around half of the patients having affected family members. The pattern of inheritance is generally autosomal dominant, although cases with X-linked inheritance have been recognized. Several mutations have been described, including genes coding for sarcomere, Z-disc, cytoskeleton, and nuclear envelope proteins.

Clinical features

LV hypertrabeculation can be either isolated or non-isolated. The latter form may be found in combination with septal defects, pulmonary stenosis, or hypoplastic left ventricle. There can be an association of LV hypertrabeculation with a high incidence of heart failure, thromboembolism, and ventricular arrhythmias. The appearance of LV hypertrabeculation can be seen transiently in athletes or during pregnancy, and is thought to represent increased prominence of normal myocardial architecture in these cases.

Mortality and morbidity rates are variable, but are high in those who have symptoms of severe heart failure, sustained ventricular arrhythmias, or left atrial enlargement.

Investigation

The diagnosis can be made by echocardiography or MRI with appearances of a non-compacted sub-endocardial layer of trabecularization with deep endomyocardial recesses. This most commonly involves the lateral, apical, and inferior walls of the left ventricle.

Treatment

- Standard HF therapy.
- Anticoagulation due to risk of thromboembolism.
- Family screening.
- Consideration of ICD.
- Cardiac transplantation.

Key reference

Lofiego C, et al. Wide spectrum of presentation and variable outcomes of isolated left ventricular non-compaction. *Heart.* 2007;93:65–71.

Tachycardiomyopathy

Incessant tachycardia is a recognized cause of cardiomyopathy. Indeed, atrial fibrillation, atrial flutter, ectopic atrial tachycardia, atrioventricular tachycardia (AVRT), atrioventricular nodal tachycardia (AVNRT), and ventricular tachycardia have all been shown to cause such a tachycardiomyopathy**.** Although the rate of the tachycardia appears to correlate with the degree of LVSD, the mechanism for myocardial dysfunction is not clear. However, as arrhythmias are frequently the result of cardiomyopathy, they are easily overlooked as the potential cause. Importantly, though, definitive treatment of the arrhythmia can result in complete reversal of the myocardial dysfunction. See ➔ Chapter 11.

Takotsubo syndrome

Takotsubo syndrome is characterized by transient regional systolic dysfunction, dilation and oedema involving the LV apex and/or mid-ventricle in the absence of obstructive coronary disease. Takotsubo is from the Japanese word defining an octopus trap that shares a similar appearance to the left ventricle in this syndrome.

The locus coeruleus in the pons regulates emotional response and is the primary origin of norepinephrine. The established pathophysiological theory in takotsubo syndrome centres on a triggered adrenergic surge and subsequent downstream direct or indirect myocardial damage.

Takotsubo syndrome is estimated to account for at least 3% of all presentations of acute coronary syndrome, and remains a diagnosis of exclusion.

Typical clinical features

- Postmenopausal women in the sixth decade (but can occur in men and women of all ages).
- Abrupt onset of chest pain.
- Preceding emotional or physical stress (e.g. concomitant illness—particularly acute intracranial events)—in one-third of cases there is no identifiable trigger.
- In severe cases—heart failure, cardiogenic shock, or ventricular arrhythmia.

Investigations

- ECG—ST-segment elevation or diffuse T wave inversion.
- Cardiac troponin—elevated cardiac troponin.
- Echo—typical WMA—transient LV outflow tract obstruction in 20%.
- Coronary angiography and left ventriculography—co-existing CAD present in 15%.
- MRI—helpful to distinguish from myocarditis and acute myocardial infarction—intense and diffuse myocardial oedema—elevated native T1/T2 and no persisting late gadolinium enhancement.

Treatment

- Diuretic if congestion.
- No evidence base to support long-term HF medical therapy in the setting of takotsubo syndrome and recovered LV function.
- Management of shock can be difficult as inotropic agents can aggravate systolic dysfunction driven by catecholamine excess.
- Anticoagulation if indicated (e.g. LV thrombus).
- Avoid QTc prolonging drugs to reduce likelihood of ventricular arrhythmia.

Prognosis

LV function usually completely recovers within days to weeks (although there is persisting myocardial oedema). It was once believed that takotsubo syndrome led a benign disease course based on recovered LV function and non-obstructed coronary arteries. However, more recent studies demonstrate in-hospital mortality comparable to acute ST elevation MI, and long-term outcomes significantly worse than the general population. Further research is underway.

Key reference

Singh T, et al. Takotsubo syndrome: pathophysiology, emerging concepts, and clinical implications. *Circulation*. 2022;145:1002–1019.

Chapter 15

The patient with heart failure and congenital heart disease

Introduction

Congenital heart disease has an incidence of approximately 8 cases per 1,000 live births. The term congenital heart disease covers a wide spectrum of lesions. At one end are the lesions of such severity that the child dies before reaching adulthood. At the opposite extreme, there are lesions that are small or that spontaneously resolve, e.g. small ventricular septal defects. However, the majority of the cases of congenital heart disease require ongoing multidisciplinary input.

The success of surgical and medical management has resulted in over 80% of patients with congenital heart disease reaching the age of 16. There are now more adults with congenital heart disease (i.e. survivors) than there are children.

The growth of the population of adults with congenital heart disease brings new challenges. They require monitoring of their original lesion and the consequences of any surgical repair. The timing and mode of further intervention, either surgical or percutaneous, remains open to debate.

It is becoming apparent that the long-term limitation of these patients results often from heart failure. The aetiology of the heart failure is different; not the myocardial necrosis of ischaemic heart disease. The heart failure of adult congenital heart disease (ACHD) results from a lifetime of abnormal cardiac pressure, volume, tension, and flow. The result is a combination of impaired contractility with abnormal preload and afterload.

Studies of heart failure in ACHD are being performed. A study examined the aerobic capacity in a range of six lesions:

- Closed atrial septal defect.
- Surgically corrected transposition of the great arteries (Fig. 15.1).
- Congenitally corrected transposition of the great arteries.
- Repaired tetralogy of Fallot (Fig. 15.2).
- Ebstein's anomaly.
- Fontan physiology (univentricular heart with diversion of the systemic venous return to the pulmonary artery).

All six of the groups had a mean peak VO_2 of <22 mL/kg/min, and in the Fontan group the mean peak VO_2 was only 16 mL/kg/min. This is comparable to New York Heart Association (NYHA) III in non-ACHD HF. The fact that such varying anatomical defects can result in reduced aerobic capacity has led postulation that the problem lies outwith the heart and is related to abnormalities of skeletal muscle—changes that are seen in other heart failure syndromes.

When considering HF in ACHD there are limited trials because of the varying anatomies and physiologies. Therefore, much of the advice is based on cohort reports and expert opinion with broad groupings of:

- Systemic left ventricular failure.
- Subpulmonary right ventricular failure.
- Systemic right ventricular failure.
- Single ventricle heart failure.

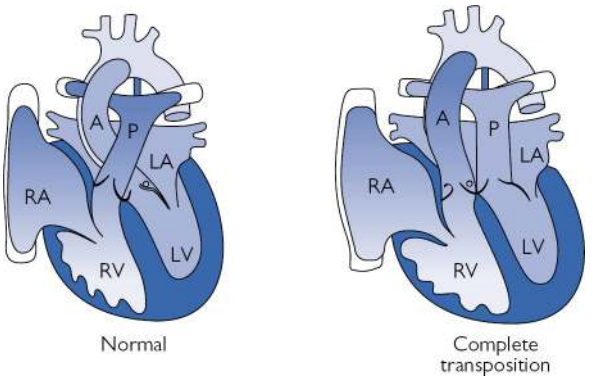

Fig. 15.1 Transposition and a normal heart for comparison.

Reproduced from Myerson, Choudhury & Mitchell, *Emergencies in Cardiology*, 2006 with permission from Oxford University Press.

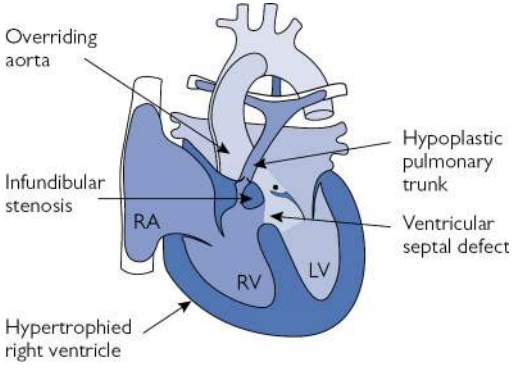

Fig. 15.2 Tetralogy of Fallot.

Reproduced from Myerson, Choudhury & Mitchell, *Emergencies in Cardiology*, 2006 with permission from Oxford University Press.

Key references

Bolger AP, et al. Congenital heart disease: the original heart failure syndrome. *Eur Heart J*. 2003;24:970–976.

Budts W, et al. Treatment of heart failure in adult congenital heart disease: a position paper of the Working Group of Grown-Up Congenital Heart Disease and the Heart Failure Association of the European Society of Cardiology. *Eur Heart J*. 2016;37:1419–1427.

Fredriksen PM, et al. Aerobic capacity in adults with various congenital heart diseases. *Am J Cardiol*. 2001;87:310–314.

Ladouceur M, et al. Cardiac drugs in ACHD cardiovascular medicine. *J Cardiovasc Dev Dis*. 2023;10:190.

Neurohumoral activation in ACHD with HF

'Classical' heart failure is associated with activation of sympathetic nervous system, renin–angiotensin–aldosterone system, endothelin, cytokines, and natriuretic peptides.

The role of these pathways in the evolution of heart failure in patients with ACHD has been investigated. Compared to age-matched controls, patients with ACHD had neurohumoral activation increasing in parallel with rising NYHA class or with deteriorating systemic ventricular function.

In patients with ACHD but without any symptoms of heart failure (NYHA class I) there is evidence of activation of natriuretic peptides, norepinephrine (noradrenaline) and endothelin-1.

However, while there was neurohumoral activation there was no difference between four anatomical groups of patients with ACHD:

- Tetralogy of Fallot.
- Systemic right ventricular physiology.
- Single ventricular physiology.
- Miscellaneous other lesions.

Neurohumoral activation in patients with ACHD correlated well with other standard measures of heart failure severity including:

- Cardiothoracic ratio on chest X-ray.
- QRS duration.
- Right and left atrial volumes.

The combination of neurohumoral activation and reduced aerobic capacity in a patient with ACHD equates with a diagnosis of heart failure, as it would in patients with other forms of cardiac disease.

The nature of the underlying cardiac lesion is important in assessing the likelihood and severity of resultant heart failure. Patients with cyanotic heart disease have lower aerobic capacity and higher neurohormonal activation than acyanotic patients. Patients with Fontan physiology have the most significant limitation in aerobic capacity.

Key references

Bolger AP, et al. Neurohormonal activation and the chronic heart failure syndrome in adults with congenital heart disease. *Circulation*. 2002;106:92–99.

Fredriksen PM, et al. Aerobic capacity in adults with various congenital heart diseases. *Am J Cardiol*. 2001;87:310–314.

Assessment of a patient with ACHD and HF

- Exclude non-cardiac causes for symptoms.
  - Thyroid function?
  - Anaemia?
  - Hypotension?
  - Iatrogenic, e.g. side-effects from medication?
- Assess for any haemodynamically significant lesion.
  - Does it require surgery or intervention?
- Is there an arrhythmia?
  - Does the patient require DC cardioversion?
  - Is there a role for electrophysiology study ± ablation?
- Establish the baseline NYHA status.
  - Consider formal cardiopulmonary exercise testing.
- Introduce tailored pharmacological therapy.
  - Diuretic therapy may help stabilize symptoms
  - ACE inhibitor often first drug initiated as disease-modifying therapy (as extrapolation of standard HF therapy).

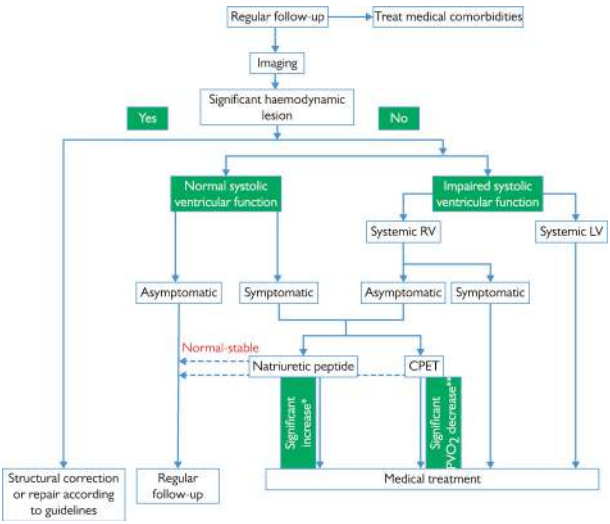

Fig. 15.3 Diagnosis—treatment algorithm. CPET = cardiopulmonary exercise test; PVO_2 = peak oxygen consumption; LV = left ventricle; RV = right ventricle. *two-fold increase of baseline natriuretic peptide value within 6 months ** > 25% decrease of peak oxygen consumption. Budts, W et al. Treatment of heart failure in adult congenital heart disease: a position paper of the Working Group of Grown-Up Congenital Heart Disease and the Heart Failure Association of the European Society of Cardiology. *Eur Heart J*. 2016;37:1419–1427.

- If evidence of dyssynchrony, consider CRT (± D) but recognize the limited data.
  - Early evidence suggesting possible harm with CRT in sub-pulmonary left ventricles.
- If deteriorating, consider role of advanced therapies.
  - Heart/lung/heart–lung transplantation?
  - Ventricular assist device?
- End-of-life issues including palliative care.
  - Recognition that advanced care planning should begin earlier in the patient pathway to allow informed decisions about social and financial issues: e.g. are pension contributions appropriate?

The diagnostic approach to HF in ACHD is summarized in Fig. 15.3.

Key references

Budts W, et al. Treatment of heart failure in adult congenital heart disease: a position paper of the Working Group of Grown-Up Congenital Heart Disease and the Heart Failure Association of the European Society of Cardiology. *Eur Heart J*. 2016;37:1419–1427.

Ringel RE, Peddy SB. Effect of high-dose spironolactone on protein-losing enteropathy in patients with Fontan palliation of complex congenital heart disease. *Am J Cardiol*. 2003;91:1031–1032.

Pharmacological options

Standard heart failure therapies have been well proven in the management of the majority of adult heart failure syndromes. However, there is a dearth of evidence for their use in patients with HF as a result of ACHD. These studies are difficult to achieve because of the smaller numbers of patients and the diversity of individual patient's initial anatomical and physiological presentation and subsequent surgical intervention. Pharmacological therapy options by ACHD phenotype are summarized in Table 15.1.

Diuretics: these are accepted in the management of symptoms of fluid overload. Loop diuretics are often very effective, although the dose may need to initially be given intravenously if there is chronic peripheral oedema. Patients with cyanotic heart disease will have abnormal renal function, requiring careful initiation and titration of diuretics. The main difference in the use of diuretics in ACHD patients is that consideration needs to be given to the preload-afterload balance of the individual patient. If they are dependent on their preload for cardiac output then caution must be applied in the prescription of diuretics. The addition of thiazide diuretics should be cautious as hypokalaemia may precipitate life-threatening arrhythmias.

Mineralocorticoid receptor antagonists (MRAs): do not have proven mortality benefit in this population. At higher doses they may be helpful in the management of patients with severe sub-pulmonic ventricular failure with ascites, or in patients with Fontan physiology who have developed protein-losing enteropathy.

ACE inhibitors and ARBs: not infrequently used in the patient with HF and ACHD. There are small studies in patients with specific ACHD lesions that have suggested little benefit in terms of aerobic capacity or haemodynamics. However, these studies were small and mainly retrospective. In systemic right ventricles there is evidence of benefit with both ACE inhibitors and ARBs. ACE inhibitors improved symptoms and quality of life in a small retrospective study of patients with cyanotic lesions. There is also emerging evidence of benefit in the use of ACE inhibitors in cyanotic patients with nephropathy and proteinuria.

Beta-blockers: there is very little published experience of the use of beta-blockers in the management of HF and ACHD. There is single centre evidence of benefit in their use in patients with left ventricular dysfunction resulting from tetralogy of Fallot and other right-sided congenital heart defects. There is also cautious use in patients with systemic right ventricular failure, although the dose may be limited by heart block and sinus node dysfunction.

SGLT2 inhibitors: early retrospective cohort experience suggests that SGLT2i generally seem safe, well-tolerated, and potentially beneficial in patients with ACHD. In one retrospective study, SGLT2i was associated with a 3-fold reduction in the 6-month HF hospitalization rate.

Angiotensin receptor-neprilysin inhibitors (ARNI): again there is little published experience in the management of HF and ACHD. There is a small cohort single centre data that suggests improvement with ARNI in biventricular circulations in ejection fraction, neurohumoral activation, and functional class. A second cohort reported benefit in patients with systemic right ventricles.

Most specialists caring for patients with ACHD and HF have taken a pragmatic approach in applying the evidence from the large heart failure trials to their patient group. Cautious use of these agents tailored to an individual patient appears to be a reasonable strategy. The inclusion of these patients in a registry may establish a body of experience to allow guidelines to be developed.

Table 15.1 Pharmacological therapy by ACHD phenotype

Phenotype-specific adult congenital heart disease	Use current HF recommendation guidelines Diuretic agents as needed ARNI/ACEi/ARB (ARNI preferred) and β blocker If NYHA FC II–IV and eGFR >30 mL/min/1.73 m^2 or creatinine <2.5 mg/dL in males or <2.0 mg/dL in females or K <5.0 mEq/L add aldosterone antagonist (MRA) If NYHA FC II–IV and eGFR >30 mL/min/1.73 m^2 add SGLT2i (dapagliflozin or empagliflozin) If **NYHA FC II-IV** eGFR >20 mL/min/1.73 m^2 add SGLT2i (empagliflozin) For persistently symptomatic patients despite all the above-mentioned therapy, consider hydralazine + isosorbide dinitrate For NYHA FC **II–III** with resting heart rate >70 bpm, on maximally tolerated β-blockade therapy in sinus rhythm, add ivabradine
Systolic failure of the systemic LV	In asymptomatic patients no medical therapy In symptomatic patients use standard HF therapy Considerations: β blockers may cause conduction abnormalities, i.e. symptomatic bradycardia especially in congenitally corrected TGA (complete heart block) and in TGA after atrial switch repair (sinus node dysfunction) Vasodilators may compromise ventricular filling in TGA after atrial switch repair due to rigid or/and obstructive baffles
Systolic failure of the systemic RV	In asymptomatic patients no medical therapy In symptomatic patients due to pulmonary arterial hypertension use PAH specific drugs; PDE5i, ERA, and prostacyclin analogues In symptomatic patients due to volume overload use loop diuretics

Table 15.1 (*Contd.*)

Fontan circulatory failure	In patients with single morphological LV and symptomatic patients with single morphological RV use standard HF therapy In asymptomatic patients with single morphological RV no medical therapy needed (ensure optimal Fontan circuit, consider thromboprophylaxis, improve BMI/physical conditioning, exclude arrhythmic targets) Use ERA and PDE5i in patients with elevated pulmonary pressure in the absence of elevated ventricular end diastolic pressure In symptomatic patients, employ standard HF guidelines with caution Considerations: Diuretics need to be uptitrated slowly and under close monitoring to avoid ventricular underfilling and decrease in cardiac output ARNI/ACEi/ARB in patients with intracardiac shunts may increase the right to left shunting by decreasing afterload and aggravate cyanosis ARNI/ACEi/ ARB may paradoxically decrease cardiac output and worsen HF symptoms in patients without preload reserve
Heart failure with preserved ejection fraction	Use diuretics and β blockers Consider ivabradine for patients in sinus rhythm and resting heart rate ≥ 70 bpm, on maximally tolerated β blockade

From: Brida M, et al. Heart failure in adults with congenital heart disease. *Int J Cardiol.* 2022;357:39–45.

Interventional options

The development of heart failure in a patient with ACHD requires review by an ACHD specialist. As described previously the evidence for pharmacological intervention is patchy. Assessment of the patient's anatomy is essential to consider whether further interventions may be beneficial.

Surgical issues: in patients with repaired tetralogy of Fallot, the development of pulmonary regurgitation is common. As the regurgitation increases the RV dilates and fails. Left ventricular dysfunction has been shown to correlate with RV dysfunction in this group. Pulmonary valve replacement improves right ventricular function and improves or prevents LV dysfunction. It improves aerobic capacity, reduces arrhythmias, and prevents further prolongation of the QRS duration. Timing of pulmonary valve replacement can be difficult but is optimally performed before irreversible RV dysfunction occurs. Percutaneous pulmonary valve replacements are being used in small numbers of patients.

A systemic morphologic right ventricle is likely to struggle in the long term. As the ventricle dilates it splints the interventricular septum reducing LV size but also inducing LV dysfunction. Pulmonary artery banding was initially intended to 'train' the LV prior to surgical arterial correction, however it has been recognized that it may be a therapeutic intervention in itself. The resistance of the pulmonary outflow has been suggested to result in LV remodelling and improved geometry including septal function, which in turn may improve the RV (systemic) ventricular function. There is inadequate evidence to support routine use of PA banding in systemic RV patients: as usual in ACHD patients, every case must be considered individually.

In patients who have had baffles or conduits formed as part of their surgical procedure (Fig. 15.4), CHF can develop gradually due to stenosis. The stenosis may be amenable to percutaneous dilatation ± stenting or may require more complex surgical repair.

Cardiac resynchronization: specific trials of CRT in patients with ACHD have not been performed. There is experience of benefit in patients with a systemic left ventricle. However, there is conflicting evidence in the use of CRT in ACHD with systemic RV dysfunction; evidence of both harm and benefit! There are also reports of CRT being used in tetralogy of Fallot and also in patients with transposition of the great arteries—either post-Mustard or in congenitally corrected TGA. The additional consideration in these patients is how and where to place the leads as the venous anatomy may preclude an entirely endovascular system. Sometimes an epicardial ventricular lead requires to be placed thoracoscopically or via mini-thoracotomy. International guideline recommendations for cardiac resynchronization pacing in ACHD are summarized in Fig. 15.5.

Implantable cardioverter defibrillators: ICDs, with or without cardiac resynchronization, are being considered for ACHD patients for either primary or secondary prevention of sudden cardiac death. The exact indications and timing of implantation are still being established. International guideline recommendations for ICDs in ACHD are described in Table 15.2. It has been demonstrated that in tetralogy of Fallot, QRSd >180 ms is associated with an increased risk of ventricular arrhythmia. Subcutaneous ICDs may extend the options for device use in ACHD (see Chapter 6).

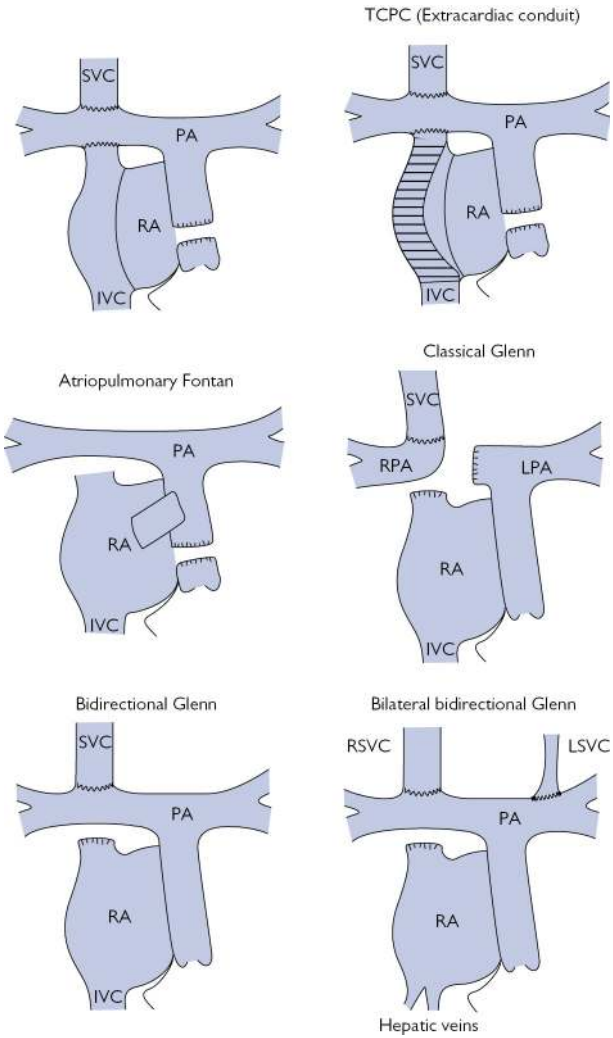

Fig. 15.4 Various Fontan operations.

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Recommendations for CHD

COR	LOE	Recommendations
2a	C-LD	1. In patients with CHD on GDMT with a systemic LV, LVEF <45%, and ventricular dyssynchrony (as defined by a QRS duration ≥ score of ≥3 or ventricular pacing ≥40%), CRT with BiV pacing is reasonable to reduce the risk of mortality or need for transplant.
2a	C-LD	2. In patients with CHD and a systemic single ventricle who require pacing, apical pacing is reasonable in preference to nonapical pacing.
2b	C-LD	3. In patients with CHD and a systemic single ventricle with symptomatic HF on GDMT, CRT with multisite ventricular pacing may be considered to maintain functional class or ventricular function.
2b	C-LD	4. In patients with CHD and a systemic RV with symptomatic HF on GDMT associated with ventricular electrical delay or requiring substantial ventricular pacing, CRT with BiV pacing may be considered to improve or maintain functional class or ventricular function.
2b	C-LD	5. In patients with CHD and a subpulmonary RV with RV dysfunction and RBBB, CRT with fusion-based pacing may be considered to improve RV function.
2b	C-LD	6. In patients with CCTGA and AV block in whom anatomic repair has not been performed, CSP with HBP or LBBAP may be considered to improve functional status.

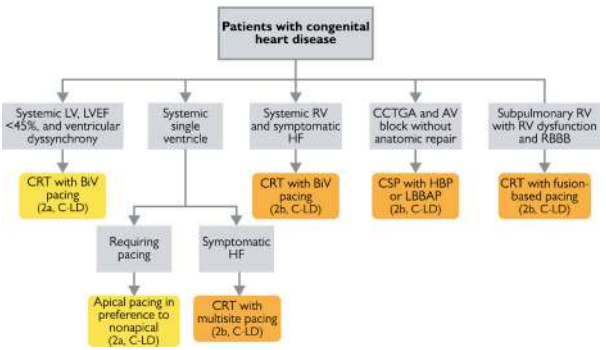

Fig. 15.5 Indications for cardiac resynchronization in ACHD. AV = atrioventricular; BiV = biventricular; CCTGA = congenitally corrected transposition of the great arteries; COR = class of recommendation; CHD = congenital heart disease; CRT = cardiac resynchronization therapy; CSP = conduction system pacing; GDMT = goal directed medical therapy; HBP = His bundle pacing; HF = heart failure; LBBAP = left bundle branch area pacing; LD = limited data; LOE = level of evidence; LV = left ventricle/ventricular; LVEF = left ventricular ejection fraction; RBBB = right bundle branch block; RV = right ventricle/ventricular. Chung MK, et al. 2023 HRS/APHRS/LAHRS guideline on cardiac physiologic pacing for the avoidance and mitigation of heart failure. *Heart Rhythm.* 2023;29(9):e17–e91.

The role of transplantation and mechanical circulatory support: End-stage heart failure can occur in young patients with ACHD. Some of them may be candidates for transplantation in the form of heart, lung, or heart and lung (although internationally the actual number of heart and lung transplants performed in such patients is very small), or mechanical circulatory support/ventricular assist device therapy. The decisions regarding these advanced therapies need to be made on an individual patient

Table 15.2 Indications for ICDs in ACHD

Recommendations	
Class I	1. ICD therapy is indicated in adults with CHD who are survivors of *cardiac arrest* due to ventricular fibrillation or hemodynamically unstable ventricular tachycardia after evaluation to define the cause of the event and exclude any completely reversible aetiology *(Level of evidence: B)*. 2. ICD therapy is indicated in adults with CHD and *spontaneous sustained ventricular tachycardia* who have undergone hemodynamic and electrophysiologic evaluation *(Level of evidence:* B). Catheter ablation or surgery may offer a reasonable alternative or adjunct to ICD therapy in carefully selected patients *(Level of evidence: C)*. 3. ICD therapy is indicated in adults with CHD and a *systemic left ventricular ejection* fraction < 35%, biventricular physiology, and NYHA class II or III symptoms *(Level of evidence: B)*.
Class IIa	ICD therapy is reasonable in selected adults with *tetralogy of Fallot* and multiple risk factors for sudden cardiac death, such as left ventricular systolic or diastolic dysfunction, nonsustained ventricular tachycardia, QRS duration ≥ 180 ms, extensive right ventricular scarring, or inducible sustained ventricular tachycardia at electrophysiologic study *(Level of evidence: B)*.
Class IIb	1. ICD therapy may be reasonable in adults with a *single or systemic right ventricular ejection fraction* <35%, particularly in the presence of additional risk factors such as complex ventricular arrhythmias, unexplained syncope, NYHA functional class II or III symptoms, QRS duration ≥ 140 ms, or severe systemic AV valve regurgitation *(Level of evidence: C)*. 2. ICD therapy may be considered in adults with CHD and a *systemic ventricular ejection fraction <35%* in the absence of overt symptoms (NYHA class I) or other known risk factors *(Level of evidence of: C)*. 3. ICD therapy may be considered in adults with CHD and *syncope of unknown origin* with hemodynamically significant sustained ventricular tachycardia or fibrillation inducible at electrophysiologic study *(Level of evidence: B)*. 4. ICD therapy may be considered for nonhospitalized adults with CHD *awaiting heart transplantation (Level of evidence: C)*. 5. ICD therapy may be considered for adults with syncope and moderate or complex CHD in whom there is a high clinical suspicion of ventricular arrhythmia and in whom thorough invasive and noninvasive investigations have failed to define a cause *(Level of evidence: C)*.

(*Continued*)

Table 15.2 (*Contd.*)

Recommendations. (Note: Class III = Not recommended)	
Class III	1. All Class III recommendations listed in current ACC/AHA/HRS guidelines apply to adults with CHD *(Level of evidence: C)*.[97] These include: a. Life expectancy with an acceptable functional status <1 year; b. Incessant ventricular tachycardia or ventricular fibrillation; c. Significant psychiatric illness that may be aggravated by ICD implantation or preclude systematic follow-up; d. Patients with drug-refractory NYHA class IV symptoms who are not candidates for cardiac transplantation or cardiac resynchronization therapy. 2. Adults with CHD and advanced pulmonary vascular disease (Eisenmenger syndrome) are generally not considered candidates for ICD therapy *(Level of evidence: B)*. 3. Endocardial leads are generally avoided in adults with CHD and intracardiac shunts. Risk assessment regarding hemodynamic circumstances, concomitant anticoagulation, shunt closure prior to endocardial lead placement, or alternative approaches for lead access should be individualized *(Level of evidence: B)*.

Khairy P, et al. PACES/HRS expert consensus statement on the recognition and management of arrhythmias in adult congenital heart disease. *Heart Rhythm* 2014;11.

basis. Early referral to a transplant centre allows consideration of all the issues in a multidisciplinary setting.

The initial diagnosis, surgical interventions, and complications of procedures and therapies can all result in additional problems at the time of transplantation and in postoperative care. For example, repeated surgical procedures may mean that the patient has limited vascular access, or has had multiple blood and blood product transfusions with the potential for blood-borne virus infection, e.g. hepatitis C infection, or multiple preformed antibodies.

Future care planning in end-stage HF

Care of the patient with end-stage heart failure is as important a stage as the acute care. There is an increasing appreciation of the importance of advanced care planning in this young population. Information has to be available to the individual patient about the possible impact of their congenital heart disease on their likely longevity. Explicit in such discussions must be an acknowledgement of the uncertainty of lifespan of many of the conditions in the current era with contemporary surgery, device, and medical interventions.

Recognition that they are in the final stages of their disease and the communication of this is vital to allow the patient and their family time. As discussed in section VII, the involvement of hospice care may be appropriate, as may the use of opiates.

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Pulmonary hypertension in ACHD

Pulmonary arterial hypertension is defined as an elevation in the *mean* pulmonary artery pressure greater than or equal to 20 mmHg at rest, with an end-expiratory wedge pressure of less than or equal to 15mmHg and a PVR of greater than or equal to 3 Wood units.

Pulmonary vascular disease can occur as a consequence of left-to-right flow through an intracardiac shunt, such as a VSD with resultant Eisenmenger's syndrome. It can also occur in association with connective tissue disease or as a primary lesion.

In the context of ACHD, breathlessness may be attributable to ventricular dysfunction or pulmonary hypertension. Both of these conditions may coexist and establishing the relative contributions of each may be challenging. The definition of pulmonary hypertension may be difficult to apply, for example, how does one define pulmonary hypertension in a patient with Fontan physiology? It has now been recognized that pulmonary hypertension in ACHD can fall into a number of categories.

There are three mechanisms that have been identified as potential therapeutic targets in the management of pulmonary hypertension:

- Endothelin receptors.
- Phosphodiesterase-5.
- Prostacyclins.

Bosentan is an endothelin-1 receptor antagonist that has been shown in the BREATHE-5 study to achieve symptomatic improvement and a significant improvement in pulmonary vascular resistance, pulmonary artery pressure, and 6-minute walk test distance. Alternative agents have been developed, particularly for patients who develop acute liver function test derangement on bosentan; such patients can be considered for treatment with ambrisentan. Studies have not shown additional benefit with macitentan in place of bosentan.

Sildenafil and Tadalafil are phosphodiesterase-5 inhibitors that block metabolism of nitric oxide. Studies have demonstrated an improvement in aerobic capacity and symptoms.

Prostacyclins are potent vasodilators and inhibitors of platelet activation. They can be given by intravenous infusion, subcutaneous infusion, inhaled aerosol, or oral preparation. Significant improvement has been demonstrated in exercise capacity and cardiopulmonary haemodynamics.

Short-term benefit has been demonstrated with these therapies. Longer follow-up will define the extent of these benefits. Work is ongoing to establish the optimal therapeutic strategy for these patients. Of particular interest is work that considers combinations of these therapies. Many of these patients are anticoagulated if there is any issue regarding pulmonary thromboembolic disease. Indeed, the very dilated pulmonary arteries may form thrombus *in-situ*.

▶ Acute management options of pulmonary hypertension

- Seek expert help.
- High flow oxygen.
- Consider specific agents: nitric oxide/iloprost/epoprostenol/sildenafil.
- Consider ECMO ± RVAD.
- Consider atrial septostomy.

► Acute management of heart failure in ACHD

Although this chapter addresses the patient with chronic heart failure and ACHD, it would be inappropriate to overlook the management of the acutely decompensated patient.

➲ The key issue in the management of these patients is an appreciation of the underlying physiology and then relating this to the acute presentation. Classical signs may be misleading, for example, an elevated JVP is appropriate for a patient with Fontan physiology, and aggressive diuresis to 'treat' it may have disastrous results. Some lesions are likely to result in systemic ventricular failure, presenting with 'left ventricular failure' signs and symptoms, while others may cause sub-pulmonic ventricular failure, with 'right heart failure' signs and symptoms. The most frequent presentation of acute ventricular failure is of sub-pulmonic failure.

►► Early involvement of an ACHD specialist is *always* appropriate.

The presentation of acute ventricular failure should prompt investigations to identify the cause. The possible causes include:

- Arrhythmias (most common cause)
- Obstruction of conduits
- Infection
- Ischaemia
- Anaemia
- Pulmonary thromboembolic disease.

ACHD lesions that may cause systemic ventricular failure:

- Mitral valve disease
- Acute severe aortic regurgitation
- Aortic stenosis
- Unrepaired coarctation
- Mustard repair with systemic ventricular failure
- Congenitally corrected transposition of the great arteries
- Systemic left ventricular failure (e.g. elderly Fallot's patient)
- Pulmonary vein obstruction
- Myocardial disease (e.g. Duchenne muscular dystrophy).

ACHD lesions that may cause sub-pulmonic ventricular failure:

- Fontan physiology
- Pulmonary hypertension
- Large atrial septal defects
- Tricuspid valve disease
- RV-pulmonary artery conduit obstruction (e.g. Rastelli procedure)
- Mustard repair with baffle obstruction
- Severe pulmonary regurgitation with RV dilatation (e.g. repaired Fallot's).

Key reference

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Initial management of the patient presenting in heart failure centres on initial resuscitation following a standard ABC approach. Thereafter the management needs to be focused on the patient's cardiac lesion. A suggested approach is:

- ABC
- Identify the underlying lesion—what is the anatomy?
  - Does this patient have a Fontan repair?
- Is there an acute haemodynamic lesion that needs urgent intervention (e.g. a ruptured mitral valve chordae)?
- Is the patient in sinus rhythm?
  - This may be difficult to assess, however even rate-controlled atrial flutter may be detrimental to a patient with Fontan physiology. Obtain a 12-lead ECG to aid diagnosis. If not sinus rhythm consider urgent cardioversion. Chemical cardioversion is often unsuccessful and so electrical cardioversion should be considered. TOE may be required to exclude intracardiac thrombus first.
- Is there evidence of sepsis—either systemic or endocarditis?
- Where is the problem?
  - Systemic or sub-pulmonic ventricle, or both?
- What is the primary problem?
  - Pulmonary oedema, peripheral oedema, or low cardiac output?

Once all these aspects have been considered specific management can be considered. The role of any drug has to be balanced against potential changes in filling pressures, renal perfusion, etc.

The final comment is that the venous anatomy of the patient with ACHD is often complex. Femoral veins may have been tied off after cardiac catheterization studies as a child. The neck veins may not connect in the expected fashion. Therefore, caution should be applied before placing lines.

►► Early involvement of an ACHD specialist is always appropriate.

Chapter 16

The patient with heart failure and diabetes

Introduction

Heart failure and diabetes mellitus (DM) commonly co-exist, but few clinicians are specialists in both areas. There can be difficulties managing these two conditions together, for example, some of the drugs used to control hyperglycaemia are relatively 'contraindicated' in heart failure. In recent years, randomized trials have demonstrated that newer anti-diabetic drugs (e.g. SGLT2 inhibitors) improve outcomes for patients with heart failure, even in the absence of DM.

Debate has focused on whether a specific 'diabetic cardiomyopathy' exists. There is evidence of myocardial fibrosis and steatosis, and subtle changes in LV morphology with remodelling of systolic and diastolic function seen on echocardiography in patients with diabetes but without heart failure. Whether these changes develop into a clinical heart failure syndrome is yet to be confirmed.

Definition

Diabetes can be considered as a group of metabolic diseases characterized by chronic hyperglycaemia resulting from defects to insulin secretion, resistance to insulin action, or both.

The ranges of blood glucose indicative of DM are as follows:

- Random venous plasma glucose ≥11.1 mmol/L; or
- Fasting plasma glucose ≥7.0 mmol/L; or
- Plasma glucose ≥11.1 mmol/L 2 hrs after a 75 g oral glucose tolerance test.

Epidemiology

- The prevalence of DM in the general population is approximately 4–7%.
- Around 12% of patients with DM in general population studies have heart failure, and in patients over 64 years of age, the prevalence of DM in heart failure rises to 22%.
- The prevalence of DM in clinical trial populations with symptomatic LVSD is around 30–40%.
- Epidemiological studies have identified that DM is an independent risk factor for heart failure (2–4-fold increased risk).
- The risk of developing DM is greatest in more advanced heart failure.
- 7.4% of patients with heart failure in the placebo arm of the CHARM programme developed DM over a median follow-up of 3.1 years.

Aetiology

Heart failure is a common manifestation of cardiovascular disease in people with DM. This may be due to the increased prevalence of other conditions such as coronary artery disease, hypertension, or obesity.

Insulin resistance, impaired fasting glucose, and hyperinsulinaemia in the absence of DM are common in heart failure. They are also risk factors for heart failure, independent of DM, and other established risk factors. Insulin resistance occurs in heart failure of both ischaemic and non-ischaemic aetiology. The relationship is likely to be multifactorial. Possible causes include:

- Sympathetic nervous system activation.
- Sedentary lifestyle.
- Endothelial dysfunction.
- Loss of skeletal muscle mass.
- Cytokines (e.g. TNF-α and leptin) on peripheral insulin sensitivity.

Investigations

Investigations indicated in the heart failure patient with DM include:

- Fasting glucose.
- HbA_1C.
- Urinalysis.
- Microalbuminuria.
- Fundoscopy.

Prognosis

- DM is an independent predictor of mortality in patients with heart failure.
- In heart failure patients with DM, cardiovascular mortality is increased by 50-90% compared to heart failure patients without DM.
- Increased mortality seems to be due to death by pump failure.
- Patients with DM and heart failure have a poorer functional state.
- Albuminuria is an independent predictor of first hospitalization for heart failure in patients with both DM and hypertension, with no previous history of MI or heart failure.

Management of diabetes in HF

Diabetic status does not reduce the efficacy of heart failure medical therapy. A general approach is to switch to agents with proven cardiovascular benefit and safety.

ACE inhibitors and ARBs

Blocking the RAAS reduces the development of DM in patients with heart failure. In a retrospective analysis of the SOLVD study, enalapril reduced the incidence of DM when compared to placebo (HR = 0.22 (0.10–0.46), $p < 0.0001$). In the CHARM study, candesartan also reduced the incidence of DM in patients with HF (HR = 0.78 (0.64–0.96), $p = 0.02$).

It should also be recognized that ACE inhibitors (micro-HOPE) and ARBs (LIFE), have been shown to reduce the incidence of heart failure in diabetic patients.

β-adrenoreceptor antagonists

Patients with heart failure and DM are less likely to be discharged from hospital on β-adrenoreceptor antagonists than patients with heart failure who do not have DM.

The major trials of β-adrenoreceptor antagonists in heart failure which demonstrated reductions in mortality and heart failure hospitalization included between 12 and 29% of patients with DM and sub-group analyses suggest that patients with and without DM have similar benefits.

There are concerns that β-adrenoreceptor antagonism may decrease hypoglycaemic awareness and blunt the compensatory increase in plasma glucose in insulin-treated diabetics. However, this appears to be less likely with the use of cardioselective β-adrenoreceptor antagonists.

Dipeptidyl peptidase 4 (DPP4) inhibitors

DPP4 inhibitors have mostly demonstrated neutral effects on cardiovascular events and mortality. The use of saxagliptin is cautioned in heart failure. In a randomized trial of saxagliptin therapy in patients with DM and high cardiovascular risk, there was an increase in heart failure hospitalization.

Glucagon-like peptide 1 (GLP-1) agonists

GLP-1 agonists are increasingly used in the treatment of DM and can result in significant weight loss. Notably, they cause a small increase in heart rate (3–5/minute). GLP-1 agonists have not been shown to improve heart failure outcomes or reduce incident heart failure in DM, but do lead to reductions in MI, stroke, and cardiovascular death in patients with DM.

Insulin

Insulin is a hormone that causes sodium retention. Insulin use has been demonstrated to independently predict both the development of heart failure and increased mortality in patients with DM. However, it is likely that insulin use is a marker for patients who have DM of longer duration and those with more extensive macrovascular disease.

Metformin

Metformin is commonly used in diabetics with heart failure, either alone, or in combination with sulphonylureas or insulin. There is believed to be a

small risk of lactic acidosis, although this has not been substantiated in clinical trials. Temporary withdrawal during periods of cardiac decompensation may be appropriate, particularly in those with hepatic or renal impairment.

Mineralocorticoid receptor antagonists (MRAs)

The EPHESUS trial recruited patients with post-MI heart failure or post-MI LVSD and DM: 32% of patients in the trial had DM. In a retrospective analysis of this cohort, the combined primary endpoint of cardiovascular mortality and cardiovascular hospitalization was reduced by 17% in those who received an MRA.

Sodium-glucose cotransporter 2 (SGLT2) inhibitors

SGLT2 inhibitors reduce cardiovascular death and hospitalization in heart failure with or without DM, and prevent heart failure in those with DM and CKD.

SGLT2 inhibitor therapy is recommended in all patients with heart failure and DM unless contraindicated; independent of HBA1c, other glucose-lowering medication, or LVEF.

See Chapter 27.

Sulphonylureas

Sulphonylureas stimulate endogenous insulin production. Historically, this class of drug tended to be used preferentially in patients with heart failure due to concerns relating to other oral hypoglycaemic agents.

Sulphonylureas are not contraindicated in heart failure, but symptoms should be monitored following initiation. In a non-randomized cohort study of patients with DM and heart failure, those with a new diagnosis of heart failure had a better 1-year mortality on metformin when compared to those on sulphonylureas (adjusted HR 0.66 (0.44–0.97)).

Thiazolidinediones (TZDs)

TZDs are peroxisome proliferator-activated receptor (PPAR-γ) agonists. The 2021 ESC guidelines for heart failure state that this drug class should not be used in patients with heart failure because they cause sodium retention, an increase in plasma volume, peripheral oedema, and weight gain (averaging between 1 and 3 kg). The risk of oedema increases in patients co-administered insulin. Fluid retention can be quickly reversed upon drug withdrawal and an increase in diuretics.

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Chapter 17

The patient with heart failure and electrolyte abnormalities

Introduction

Electrolyte abnormalities are common in ambulatory and hospitalized patients with heart failure and can often be attributed to neurohormonal activation or adverse effects from heart failure medical therapy.

Although deficiency of electrolytes is a more common problem in heart failure, it is possible to encounter elevated electrolyte levels, particularly in the context of multiorgan dysfunction. In rare cases, electrolyte abnormalities can offer clues about the aetiology of heart failure, e.g. low potassium in primary hyperaldosteronism (Conn's syndrome).

The depolarization of cardiac myocytes and maintenance of the resting membrane potential is dependent on electrolyte movement across the plasma membrane (Fig. 17.1). Abnormal systemic levels of electrolytes can destabilize the myocardium and predispose to life-threatening ventricular arrhythmia.

This chapter will describe common electrolyte abnormalities in heart failure including aetiology, pathophysiology, clinical implications, and treatment strategies.

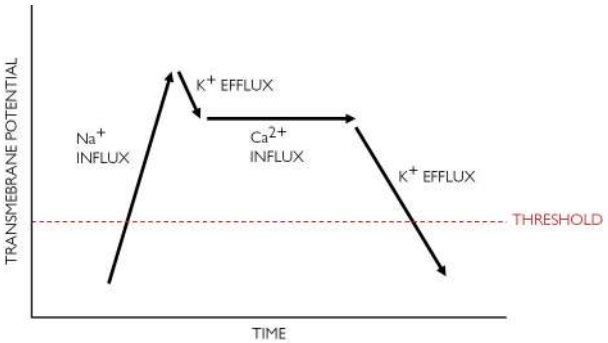

Fig. 17.1 Cardiac myocyte action potential.

Potassium (K^+)

Normal range ~3.5–5 mmol/L.

First isolated in the 1800s, potassium is the major intracellular cation, and is concentrated 30-fold over its extracellular concentration by the sodium-potassium pump (Na^+-K^+-ATPase enzyme) in the plasma membrane. Potassium movement in this way generates a current that maintains a negative resting membrane potential in cardiac myocytes. Myocardium is excitable tissue, and a negative resting membrane potential prevents spontaneous action potentials from generating premature extrasystoles during diastole that destabilize normal conduction and could potentiate sustained arrhythmia (Table 17.1).

Systemic potassium levels outside the normal range exert direct effects that promote cardiac arrhythmia, but also alter the cellular balance of other key electrolytes.

Derangement in serum potassium levels in heart failure is associated with increased mortality in a 'U-shaped' distribution with elevated risk at both ends of the spectrum.

Other physiological roles for potassium:

- Vasodilation.
- Reduced oxidative stress.
- Natriuresis.
- Endothelial function/integrity.

Table 17.1 Potassium abnormalities in heart failure

	Value mmol/L	Prevalence in HF	Electrophysiology	Clinical significance	Treatment	ECG changes	Possible causes
Hypokalaemia Severe hypokalaemia	<3.5 <2.5	Up to 50%	Inhibition of Na^+-K^+ pump, suppressed potassium transfer, and reduced repolarization reserve.	Myocardial excitability Atrial and ventricular arrhythmia Increased risk of digoxin toxicity	Oral supplementation • IV supplementation (consider <3 mmol/L) Addition of RAASi may be helpful • Dietary measures	• P wave amplitude increased • T wave flattening/ inversion • ST depression • U wave (best seen leads V1–V4) • QTc prolongation	Often attributed to loop and thiazide diuretic use Catecholamine surge (moves potassium intracellularly)
Hyperkalaemia Severe hyperkalaemia	>5 ≥6.5	Less than 5% but more common in CKD	Conduction block and development of re-entry circuits.	• Myocardial excitability • Atrial and ventricular arrhythmia	• Loop diuretics can be helpful • Potassium binders* • Dietary measures ! In severe hyperkalaemia: • IV calcium and insulin (facilitates intracellular potassium movement but rebound hyperkalaemia can occur) • Renal replacement therapy	• P wave flattening • T wave increased amplitude • AV block • QRS broadening • 'Sine wave' pattern in severe cases	• Associated with RAASi—particularly MRA** • Acute or chronic renal failure

* Oral potassium binding agents can be used in the acute or chronic setting to reduce potassium absorption or increase excretion in the GI tract. Potassium binders can be considered to facilitate the initiation of RAASi in those with hyperkalaemia, but there is no current trial evidence of improved clinical outcomes.

** A major cause of underuse of these agents.

Sodium (Na^+)

Normal range ~135–146 mmol/L.

Sodium is the most abundant serum electrolyte and a major intravascular ion. Osmolality, dictated by sodium concentration, equilibrates across the vascular membrane between vascular and interstitial spaces resulting in fluid shift.

Hyponatraemia can be present in up to 30% of hospitalized patients with heart failure and is a recognized marker of disease severity and prognosis.

In heart failure, activation of the sympathetic nervous system and RAAS impairs renal water excretion. Excess total body water relative to sodium results in hyponatraemia (haemodilution). Thiaizide diuretic use inhibits sodium reabsorption in the kidney and can also cause hyponatraemia (Fig. 17.2 and Table 17.2).

While there are reports of AV block and bradyarrhythmia in the context of hyponatraemia, severe sodium abnormalities typically manifest with CNS dysfunction rather than direct cardiac toxicity. Alterations to sodium channel function and subsequent myocardial conduction disturbance are more likely to be caused by other electrolyte abnormalities (K^+, Ca^{2+}) or medication (e.g. flecainide and other class I anti-arrhythmic agents).

Treatment of hyponatraemia in heart failure:

- Asymptomatic mild hyponatraemia (125–134 mmol/L) does not require emergency treatment, but rather investigation and correction of the underlying cause (including optimization of fluid status).

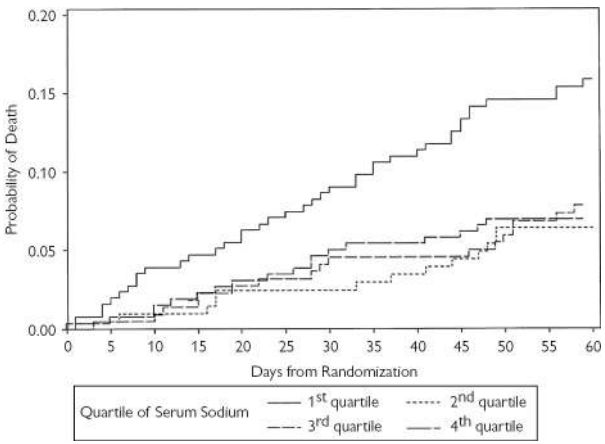

Fig. 17.2 Kaplan–Meier survival curves by serum sodium quartiles in patients enrolled in the outcomes of a prospective trial of intravenous milrinone for exacerbations of chronic heart failure (OPTIME-CHF). Reproduced from Klein L, et al. Lower serum sodium is associated with increased short-term mortality in hospitalized patients with worsening heart failure: results from the Outcomes of a Prospective Trial of Intravenous Milrinone for Exacerbations of Chronic Heart Failure (OPTIME-CHF) study. *Circulation*. 2005;111:2454–2460.

- The use of vasopressin antagonists (e.g. tolvaptan) can be considered under specialist guidance in cases of resistant hyponatraemia and congestion in heart failure. Vasopressin antagonists elevate serum sodium, but have not been shown to improve outcomes.
- In severe hyponatraemia (<125 mmol/L), hypertonic saline can be infused to raise serum sodium levels. Close monitoring is needed to ensure that sodium is corrected slowly (≤10 mmol/24 hrs) to prevent osmotic demyelination syndrome.

Hypernatraemia is caused by sodium gain or excess loss of free water (e.g. osmotic diuresis) and is less commonly associated with heart failure.

Key reference

Konstam MA, et al. Efficacy of vasopressin antagonism in heart failure outcome study with tolvaptan (EVEREST) investigators. Effects of oral tolvaptan in patients hospitalized for worsening heart failure: the EVEREST outcome trial. *JAMA*. 2007:28;297:1319–1331.

Other electrolyte deficiencies in heart failure

Table 17.2 Electrolyte deficiencies in heart failure

Electrolyte	Normal range (mmol/L)	Physiological function	Clinical significance of depletion	Causes for depletion in HF	ECG changes
Magnesium (Mg^{2+})	~0.70–1.05*	• Second most abundant intracellular cation • Mitochondrial structure and function • Regulates cellular uptake of K^+, Na^+ and Ca^{2+}	• Associated with depletion of other electrolytes • Stabilizes excitable membranes—reduced triggered automaticity by decreasing outward K^+ current and Ca^{2+} activity	• Loop diuretics • Poor absorption (congested HF states) • Alcohol excess	• PR prolongation • QTc prolongation • Torsades de pointes
Calcium (Ca^{2+})	~2.2–2.6	• Antagonizes effects of K^+ and Mg^{2+} at cell membrane (used in treatment of hyperkalaemia) • Myocardial contractility • Muscle contraction and neuromuscular function • Platelet aggregation	• Predisposes to arrhythmia	• Loop diuretics • Low Mg^{2+} • Respiratory alkalosis • Associated renal disease	• QTc prolongation • AV block
Chloride (Cl^-)	~95–108	• Acid-base homeostasis • Possible role in regulating RAAS and the diuretic response	• Independent predictor of disease severity and mortality in acute and chronic HF	• Loop and thiazide diuretics • Linked to low Na^+ (haemodilution)	• No specific changes

*Extracellular levels are albumin bound—serum levels may not reliably represent total body stores.

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Chapter 18

The patient with heart failure and infiltrative cardiac disease

Introduction

Conditions that result in the abnormal deposition of substances within cardiac myocytes or in the myocardial insterstitium can be classed as infiltrative cardiomyopathies.

Cardiac infiltration is typically associated with an inflammatory response and cardiac fibrosis, leading to ventricular wall rigidity and diastolic dysfunction. Clinical manifestations include heart failure (with both preserved and reduced ejection fraction), cardiac conduction abnormalities, and sudden death.

The presentation of infiltrative cardiomyopathy can be non-specific, and it is common for misclassification and delayed diagnosis. Depending on the underlying aetiology, specific disease-modifying treatments can be available.

Cardiac amyloidosis

Cardiac amyloidosis is an uncommon condition, but it is increasingly recognized and likely to be present, but undiagnosed, in a small proportion of older patients with left ventricular hypertrophy, HFpEF or aortic stenosis. The common feature of cardiac amyloidosis is the extracellular deposition of misfolded proteins in the heart, which demonstrate apple-green birefringence under polarized light when stained with Congo red (Fig. 18.1).

The two most common types of cardiac amyloidosis comprise >98% of all cases:

- Immunoglobulin light chain (AL)—a form of haematological malignancy associated with plasma cell dyscrasia.
- Transthyretin (ATTR)—>90% wild type (ATTRwt) and <10% hereditary (ATTRv).
  - ATTRwt is associated with ageing and is the most common type of cardiac amyloidosis worldwide.
  - ATTRv is a heterogenous condition that is autosomal dominant with high penetrance.

⚠ *The median survival* of untreated AL cardiac amyloidosis and heart failure is 6 months.

Cardiac amyloid deposits result in:

- Biventricular wall thickening, but not dilatation.
- Restrictive type cardiomyopathy.
- Systolic dysfunction in advanced disease.
- Atrial dilatation.
- Valvular thickening.

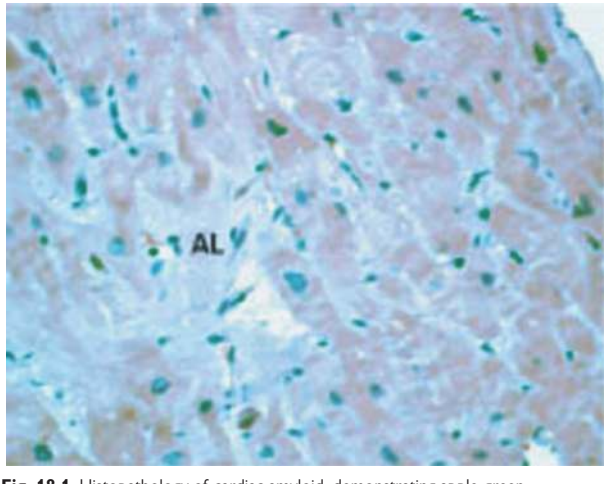

Fig. 18.1 Histopathology of cardiac amyloid, demonstrating apple-green birefringence with polarized light. Courtesy of Dr Allan McPhaden, Southern General Hospital, Glasgow (retired).

- Conduction system involvement.
- Perivascular involvement (particularly small vessels).

The clinical manifestations of cardiac amyloid deposition include:

- Heart failure—dyspnoea can be rapidly progressive and almost always associated with evidence of elevated right-sided filling pressure.
- Atrial fibrillation—high incidence of thromboembolism.
- Hypotension.
- Sudden death—common but not due to ventricular arrythmias.
- Chest pain—due to amyloid deposition in small vessels of the heart.
- Weight loss with peripheral oedema and ascites.

Cardiac amyloidosis should be suspected if LV wall thickness is ≥12 mm together with one or more red flags (Table 18.1).

Table 18.1 Cardiac and extracardiac amyloidosis red flags

CLINICAL	Heart failure aged ≥65
	Aortic stenosis aged ≥65
	Hypotension
	Sensory involvement or autonomic dysfunction/polyneuropathy
	Skin bruising*
	Bilateral carpal tunnel syndrome**
	Ruptured biceps tendon**
	Family history**
	Macroglossia*
	Deafness**
	Lumbar spinal stenosis**
LABORATORY	Proteinurea*
	Renal insufficiency*
	Disproportionate NT-proBNP elevation (to degree of clinical heart failure)
	Persistent troponin elevation
ELECTROCARDIOGRAM (ECG)	Conduction system disease
	Low QRS voltage
	Pseudoinfarct pattern
ECHOCARDIOGRAPHY	Reduced longitudinal strain with apical sparing pattern
	Pericardial effusion
	Granular myocardial appearance
	Increased RV wall thickness
	Increased valve thickness
CARDIAC MAGNETIC RESONANCE	Subendocardial LGE or increased extracellular volumes
	Elevated native T1 values
	Abnormal gadolinium kinetics

*typical of AL amyloidosis.

**typical of ATTR amyloidosis.

Investigations for cardiac amyloidosis

Electrocardiographic features

- Abnormal axis.
- Reduced voltage out of keeping with ventricular thickness.
- Bundle branch block is unusual (particularly LBBB), unless pre-existing.
- Conduction system disease.
- Pseudoinfarct pattern.

Echocardiographic features

- Non-dilated ventricles.
- Concentric biventricular thickening.
- Biatrial enlargement.
- Essentially normal ejection fraction until advanced disease.
- Granular infiltration of the atrial and ventricular septum.
- Restrictive Doppler pattern in advanced disease.
- Reduced longitudinal strain with apical sparing pattern.
- Pericardial effusion (Fig. 18.2).

Once cardiac amyloidosis is suspected the diagnosis can be confirmed using specific tests (Table 18.2):

Bisphosphonate scintigraphy: 99mTc-pyrophosphate (PYP), 99mTc-3, 3-diphosphono-1,2-propanodicarboxylic acid (DPD) or 99mTc-hydroxymethylene diphosphonate (HMDP) scintigraphy with single photon emission computed tomography (SPECT)

Assessments for monoclonal proteins (most to least sensitive)

- Serum free-light-chain assay.
- Serum and urine immunofixation.
- Urine electrophoresis.

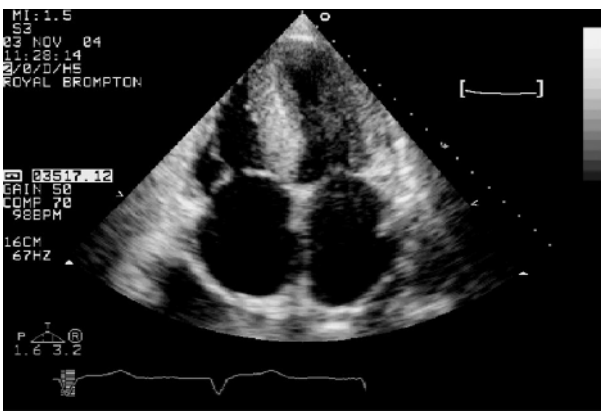

Fig. 18.2 Restrictive cardiomyopathy secondary to amyloid infiltration, with classical septal granular thickening and biatrial enlargement.

Table 18.2 Summary of diagnostic tests for cardiac amyloidosis

		SCINTIGRAPHY SCAN	
		< Grade 2 cardiac uptake	≥ Grade 2 cardiac uptake
MONOCLONAL PROTEIN	Negative	CA unlikely*	ATTR** → genetic testing
	Positive	Further investigation of AL amyloid → CMR*	Possible ATTR with concomitant haematological disorder → histology

AL = immunoglobulin light chain amyloidosis; ATTR = transthyretin amyloidosis; CA = cardiac amyloidoisis; CMR = cardiac magnetic resonance.

* If low-grade cardiac uptake histology is required to confirm diagnosis.

**ATTR can be diagnosed non-invasively.

*** If CMR inconclusive or supports amyloidosis histology is required to confirm diagnosis.

Histological diagnosis

- Cardiac—endomyocardial biopsy—tissue diagnosis when amyloid fibrils are found in cardiac tissue. Virtually 100% sensitive, because AL amyloid is widely deposited throughout the heart.
- Extracardiac—fine needle aspiration of the abdominal fat is positive for amyloid deposits in >70% of patients with AL amyloidosis.
  - Imaging criteria is required in combination with extracardiac tissue diagnosis to diagnose cardiac amyloidosis.

Treatment of cardiac amyloidosis

The treatment of cardiac amyloidosis often requires both specific disease-modifying treatments, as well as the management of complications including heart failure, aortic stenosis, atrial fibrillation, and conduction system disorders.

Disease-modifying treatment in cardiac amyloidosis

AL

- Chemotherapy or autologous stem cell transplantation.
  - Dependent on haematological disorder and multidisciplinary discussion.

ATTR

- Tafamidis—transthyretin stabilizer that inhibits amyloid formation and is the agent of choice in ATTR (with reasonable expected survival). Tafamidis reduces mortality (at 2 years) and hospitalization in ATTR cardiac amyloid as well as resulting in functional improvement within 6 months.
- IV patisaran—RNA interfering molecule—consider use in ATTRv.
- SC inotersen—antisense oligonucleotide—consider use in ATTRv.
- Diflunizal (off label).
- The definitive treatment is *liver* transplantation, which removes the source of transthyretin and thus the precursor of amyloid deposition. Cardiac transplantation can be considered in end-stage ATTRv.

Treatment of cardiac-related complications in cardiac amyloidosis

- Heart failure—the mainstay of heart failure therapy due to amyloidosis is diuretics. Achieving euvolaemia is key, but can be challenging due to loss of ventricular capacitance and medication intolerance due to orthostatic hypotension. The safety and efficacy of traditional heart failure medical therapy has not been established in cardiac amyloidosis. High doses of diuretic may be needed in coexisting nephrotic syndrome.
- Aortic stenosis—TAVI improves outcomes in amyloid-related severe AS.
- Atrial fibrillation—anticoagulation should be strongly considered due to the very high rate of thrombo-embolic events. ⚠ **Digoxin**—increased risk of digoxin toxicity because the drug binds avidly to amyloid fibrils, even with therapeutic serum digoxin levels.
- Conduction system disorders—pacemaker insertion according to standard indications. Cardiac amyloidosis is a risk factor for periprocedural AV block during TAVI).

Other amyloidosis subtypes with cardiac involvement

Secondary amyloidosis

Cardiac amyloid deposition in secondary amyloidosis is very rare, and hepatic and renal amyloid deposition dominates the clinical picture. It is associated with:

- Chronic infections.
- Rheumatoid arthritis.
- Other rheumatic disorders such as ankylosing spondylitis.
- Inflammatory bowel disease.

Isolated atrial amyloidosis

Isolated atrial amyloidosis is a common finding at autopsy, particularly in elderly patients, and involvement is strictly limited to the atria. It originates from atrial natriuretic peptide, and its significance is currently uncertain. However, it is more likely to be found in patients with atrial fibrillation.

Cardiac sarcoidosis

Sarcoidosis is a multisystem, non-caseating, granulomatous disease of unknown aetiology. It is estimated to affect 1:10,000 people, with marked geographical and racial variation, being three to four times more common in black patients. It typically affects young adults, and usually presents with either evidence of bilateral hilar lymphadenopathy or pulmonary infiltrates, or skin or eye lesions.

Sarcoidosis most commonly affects the lung. Cardiac involvement is uncommon, affecting only around 2–5% of patients with sarcoidosis, although autopsy studies indicate that sub-clinical cardiac involvement is more common (Fig. 18.3).

Pathophysiology

The aetiology of sarcoidosis is not clear. Several potential antigens have been suggested as triggers, including *Mycobacterium tuberculosis*, Mycoplasma species, aluminium, and pollen. T-helper cell activation leads to the formation of granuloma lesions, and interleukin-6 is thought to be involved in the maintenance of inflammation by inducing T cell proliferation. A positive association with cardiac sarcoidosis has been reported with HLA-DQB1*0601.

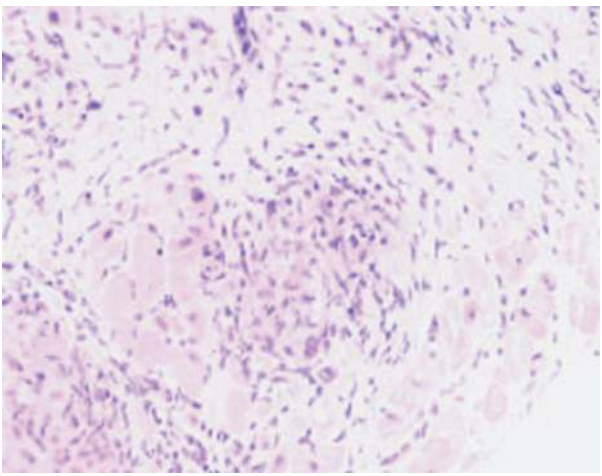

Fig. 18.3 Sarcoidosis. A central non-caseating granuloma is disrupting the myocardium with myocyte destruction and early replacement fibrosis. A second granuloma is present at the bottom left. Haematoxylin and eosin ×400. Courtesy of Dr Allan McPhaden, Southern General Hospital, Glasgow (retired).

Clinical features

The presentation of cardiac sarcoidosis can mimic multiple cardiomyopathy subtypes. Clinical sequelae are wide-ranging and, depending upon the location and extent of granulomatous inflammation, can include asymptomatic conduction abnormalities (the most common presenting feature) to fatal ventricular arrhythmias.

Cardiac manifestations include:

- Complete heart block, or other conduction abnormalities.
- Ventricular tachycardia/fibrillation.
- Supraventricular arrhythmias (e.g. re-entrant tachyarrhythmias, atrial flutter, fibrillation, and tachycardia).
- Heart failure.
- Pericardial effusion (rarely causing tamponade).
- Constrictive pericarditis.
- Valvular dysfunction (including mitral valve prolapse).

Prognosis

Most patients with cardiac sarcoidosis ultimately die from ventricular tachyarrhythmia, conduction disturbances, or progressive heart failure. Patients may be suitable for cardiac transplantation.

Diagnosis of cardiac sarcoidosis

Diagnostic criteria have been developed from multiple groups (primarily in America and Japan) with a focus on clinical and imaging parameters. There are differences in certain areas, but consistent criteria include:

- Non-caseating granuloma from endomyocardial biopsy.
- Histological diagnosis of extracardiac sarcoidosis.
- Mobitz type II 2nd degree heart block or 3rd degree heart block.
- Unexplained ventricular tachycardia.
- Patchy uptake on cardiac PET-CT.
- Typical multifocal late gadolinium enhancement on CMR (interventricular septum, left lateral free wall, right ventricle)

Investigations

The clinical findings of cardiac sarcoidosis are largely non-specific. As a result, diagnostic tests such as endomyocardial biopsy may be required, particularly in patients without other manifestations of sarcoidosis.

- Serum ACE.
- Kveim–Siltzbach test.
- Electrocardiography.
- 24-hour Holter monitoring.
- CXR.
- Magnetic resonance imaging.
- Echocardiography—the ventricular septum often appears hyperechogenic; evidence of LVSD or LV aneurysm.
- Endomyocardial biopsy (Fig. 18.3)—however, myocardial involvement can be patchy and more commonly occurs basally, whereas endomyocardial biopsy specimens are usually obtained from the apical septum.
- Nuclear imaging—particularly Thallium-201 scintigraphy.

Key references

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Terasaki F, Yoshinaga K. New guidelines for diagnosis of cardiac sarcoidosis in Japan. *Ann Nucl Cardiol*. 2017;3:42–45.

Treatment

The goal of immunosuppressive therapy in cardiac sarcoidosis is to stop active inflammation and prevent long-term recurrence. There are no placebo-controlled trials examining outcomes of immunosuppression in cardiac sarcoidosis.

Oral corticosteroids are thought to be capable of halting or slowing the progression of inflammation and fibrosis in sarcoidosis. There is no established optimal treatment regime, but the initial starting dose can be up to 80 mg of prednisone daily, with a gradual tapering of the dose to a lower maintenance level of 10–15 mg per day over a period of 6 months. Cushingoid side-effects are most common in doses over 7.5 mg. However, a possible association between corticosteroid treatment and formation of ventricular aneurysms has been described. Long-term immunosuppression is often required and steroid-sparing agents such as methotrexate, hydroxychloroquine, and biological therapies (e.g. TNF-alpha inhibitors) may be given to patients. PET-CT can be used to monitor treatment response, but there are no validated criteria.

A permanent pacemaker is indicated in patients with complete heart block or other high-grade conduction system disease, and consideration should be given for CRT in those with LVSD. An ICD/CRT-D is recommended in survivors of sudden death or patients with refractory ventricular tachyarrhythmias. Some also recommend a defibrillator for primary prevention due to the high rate of sudden death due to ventricular tachyarrhythmias in cardiac sarcoidosis.

Cardiac transplantation for cardiac sarcoidosis is rare. It remains, however, a possibility for younger patients with severe end-stage irreversible cardiac failure or resistant VT, although recurrent disease in the transplanted heart can occur. Other types of surgery may be occasionally required, such as correction of mitral valve disease or resection of ventricular aneurysms.

Key reference

Ueberham L, et al. Pathophysiological Gaps, Diagnostic Challenges, and Uncertainties in Cardiac Sarcoidosis. *s*. 2023;12:e027971.

Iron overload cardiomyopathy

Haemochromatosis is an autosomal recessive disorder and primary cause of iron overload in which mutations in the *HFE* gene (particularly *C282Y*—on the short arm of chromosome 6) cause increased intestinal iron absorption. The clinical manifestations of this disorder are related to excessive tissue iron deposition, particularly in the liver, pancreas, and pituitary, but also in the heart (Fig. 18.4). Iron overload cardiomyopathy accounts for around 30% of mortality in haemochromatosis but can also occur in conditions with secondary iron overload e.g. inherited haemoglobinopathies.

Clinical features

The clinical manifestations of iron accumulation include liver disease (ultimately leading to cirrhosis and an increased risk of hepatocellular carcinoma), skin pigmentation, diabetes mellitus, arthropathy, and hypogonadism. Cardiac effects in this setting are termed 'iron overload cardiomyopathy' and include LV dysfunction and conduction disease. This is the presenting manifestation in 15% of patients with haemochromatosis, with a predominance in young males.

Investigations

- Routine biochemistry including thyroid and liver function.
- Iron studies (ferritin, transferrin saturation, serum iron, TIBC).
- Genotyping (C282Y homozygosity).
- ECG.

Fig. 18.4 Haemochromatosis. Granular intracellular cardiac myocyte deposits of haemosiderin are stained blue. Perls stain ×400. Courtesy of Dr Allan McPhaden, Southern General Hospital, Glasgow (retired).

- Echo—typically restrictive or dilated cardiomyopathy.
- Cardiac MRI with T2* imaging.

Treatment

Venesection and chelation therapy can be associated with an improvement of ventricular dysfunction. However, irreversible myocardial dysfunction can occur in subjects with advanced disease.

Anderson–Fabry disease

Anderson–Fabry disease is an X-linked recessive glycolipid storage disease. It is caused by deficient activity of the lysosomal enzyme, α-galactosidase A, which results in the progressive accumulation of globotriaosylceramide in the vascular system, renal epithelial cells, myocardial cells, dorsal root ganglia, and autonomic nervous system.

The incidence of Anderson–Fabry disease is estimated to be 1:40,000. Expression of the clinical phenotype in heterozygous female carriers varies, with some females exhibiting severe signs of the disease because of random X-chromosome inactivation.

Clinical features

Clinical manifestations are invariably evident by 10 years of age, and initially include:

- Angiokeratomas in the groin, hips, and umbilical region.
- Peripheral neuropathy (with normal nerve conduction studies).
- Asymptomatic corneal dystrophy.

With advancing age, other disease becomes increasingly important:

- Cardiac involvement.
  - Cardiomyopathy—including LVH.
  - Conduction disease.
  - Myocardial infarction secondary to the accumulation of lipid moieties in angiographically normal coronary arteries.
  - Valvular defects—for example aortic stenosis and mitral regurgitation.
- Cerebrovascular disease leading to aneurysms, acute blindness, and stroke.
- Renal disease—initially evident as proteinuria, often progresses to renal failure by the time the patient reaches 30–40 years of age.

Investigation

There is a reduced or absent α-galactosidase A activity in plasma or peripheral leukocytes in affected males. Carriers may have normal enzyme activity and therefore this assay is not reliable and potential carriers should undergo genetic testing to confirm the diagnosis.

Treatment

No cure exists for Anderson–Fabry disease although genetic therapies are in development. Enzyme replacement with recombinant human α-galactosidase A is indicated in all symptomatic patients with classical disease and should be initiated early as efficacy is limited in advanced cases. Standard heart failure therapy should be initiated in Anderson–Fabry patients with cardiomyopathy, and other treatment directed against specific manifestations of the disease.

Glycogen storage disorders

Pompe disease

Pompe disease is an autosomal recessive glycogen storage disorder that results in a deficiency of acid α-glucosidase, a lysosomal enzyme that hydrolyses lysosomal glycogen to glucose. The accumulation of glycogen in certain tissues, especially muscles, impairs their ability to function normally and therefore muscle weakness is a prominent feature in all forms of Pompe disease.

Pompe disease is an extremely heterogeneous disorder that varies with respect to age at onset, rate of disease progression, and extent of organ involvement, with infantile-onset disease progressing much more rapidly than adult-onset disease and ultimately proving fatal, usually within the first year of life. It is thought to affect around 1:40,000 people.

Clinical features

The following are the features of adult-onset disease:

- Progressive proximal muscle weakness and exercise intolerance.
- Gait abnormalities.
- Hypotonia.
- Respiratory insufficiency.
- Sleep apnoea.
- Cardiomyopathies—typically HCM phenotype.

Investigation and treatment

The definitive test is the measurement of acid α-glucosidase, with muscle and skin fibroblasts providing the most reliable results. Genotyping is important in genetic counselling and may be of supportive diagnostic value.

Pompe disease leads to progressive muscular degeneration and premature death, mainly due to end-stage heart failure. There is no cure for Pompe disease but enzyme replacement therapy with alglucosidase alfa (rhGAA) is a treatment option that has been shown to reverse LVH in infants.

Danon disease

Danon disease is an X-linked glycogen storage disorder related to a defect in the *LAMP-2* gene. Abnormal glycogen deposition results in a clinical triad:

- Cardiomyopathy—HCM phenotype with massive LVH.
- Skeletal myopathy.
- Intellectual disability.

Other clinical features include retinal involvement and a short PR interval on ECG (ventricular pre-excitation). Genetic testing (specifically for LAMP-2 variants) can identify the condition but no treatment exists and the disease runs a malignant course.

Friedreich ataxia

Friedreich ataxia is an autosomal recessive disorder caused by a gene mutation in the *FTX* gene. Cardiac manifestations include HCM-type cardiomyopathy and frequent supraventricular arrythmia (e.g. atrial fibrillation). Other clinical features include progressive limb ataxia, diabetes mellitus and musculoskeletal abnormalities (including scoliosis and pes cavus).

Diagnosis is confirmed by identification of bi-co-allelic GAA expansion in first intron of *FTX* gene. No specific treatment is currently available.

Chapter 19

The patient with heart failure and anaemia

Introduction

Anaemia and iron deficiency are common in patients with chronic heart failure. The proportion of those who have anaemia increases with deteriorating NYHA functional class. A reduced haemoglobin is also associated with increased symptoms, more frequent hospitalizations and, in most studies, with an increased mortality rate (Fig. 19.1). Severe anaemia can also lead to high-output cardiac failure in the absence of heart disease.

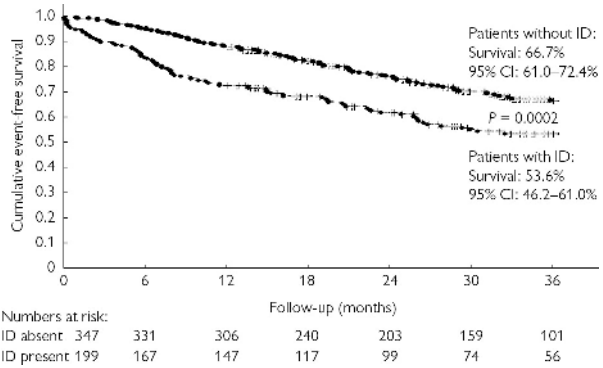

Fig. 19.1 Kaplan–Meier curves reflecting 3-year event-free survival rates in patients with systolic chronic heart failure with vs. without iron deficiency.

Reproduced from E Jankowska et al. Iron deficiency: an ominous sign in patients with systolic chronic heart failure, *European Heart Journal* 31, 2010: 1872–80, with permission of Oxford University Press.

Definition

There is significant variability in the definition of anaemia. The most commonly used definition is that of the WHO, taken from a document on iron deficiency anaemia:

- <12 g/dL in women.
- <13 g/dL in men.

This definition does not take into account postmenopausal women, a group that some would argue should have a similar haemoglobin to men.

Iron deficiency can be present without anaemia. Guideline recommendations define iron deficiency in heart failure as:

- Serum ferritin <100 ng/mL OR
- Serum ferritin 100–299 ng/mL with transferrin saturation (TSAT) <20%.

Prevalence

The prevalence of anaemia in heart failure varies considerably between studies, partly due the variability of the definition used. It is estimated that 30–50% of patients with heart failure have anaemia by WHO criteria, the proportion increasing with worsening heart failure. Iron deficiency can be present in up to 80% of acute heart failure presentations.

Aetiology

The causes of anaemia in heart failure are multifactorial, but it is likely that the mechanisms include:

- Iron deficiency—reduced absorption and possible downregulation of iron metabolism.
- Haemodilution.
- Reduced renal perfusion.
- Reduced bone marrow perfusion.
- Downregulation of erythropoietin (EPO) by ACE inhibitors.
- Angiotensin receptor blockers.
- Cytokines (e.g. TNFα).
- ↓ EPO in associated chronic renal disease.
- Other co-existing nutritional deficiency.

Investigations

- Full blood count.
- Mean corpuscular volume.
- Serum ferritin concentration.
- Transferrin saturation.
- Iron.
- Blood film.

Key references

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Prognosis

Many heart failure studies have identified co-existing anaemia as an adverse prognostic sign, with increasing mortality with lower haemoglobins (Fig. 19.2).

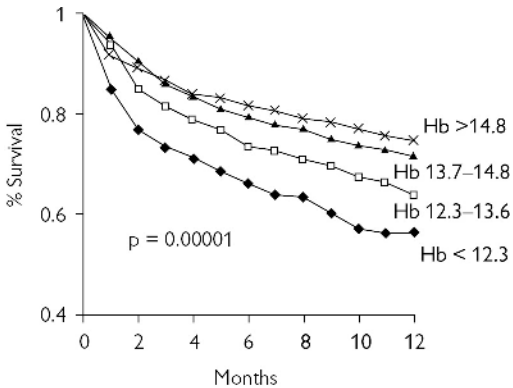

Fig. 19.2 Kaplan–Meier survival analysis in 1061 patients with heart failure stratified by Hb quartile.

Reprinted from *Journal of the American College of Cardiology*, Horwich et al. Anaemia is associated with worse symptoms, 1780–1786, Copyright 2002, with permission from Elsevier.

Treatment

Firstly, treat any reversible causes!

Aim for a haemoglobin >10 g/dL, transfusing as appropriate, acknowledging the risks associated with blood products. Blood transfusion can result in antibody formation that may impact on recipient suitability for cardiac transplantation.

Multiple randomized controlled trials have examined the benefits of IV iron replacement in heart failure and iron deficiency. The IRONMAN trial compared with IV ferric derisomaltose to usual care in 1137 patients with heart failure, iron deficiency and LVEF ≤45%. Results were neutral for the primary endpoint (a composite of total heart failure hospitalizations and cardiovascular death), however, in a pre-specified analysis that censored follow-up during the COVID-19 pandemic there was a reduction in the primary endpoint in those who received IV iron. A similar trend is seen in the analysis of the AFFIRM-AHF trial and subsequent meta-analyses have reported reduced risk of heart failure hospitalization with IV iron replacement. Of note, oral iron supplementation has not been shown to be effective in heart failure. Guideline recommendations support the consideration of IV iron replacement to improve symptoms and reduce heart failure hospitalization in patients with heart failure (LVEF <50%) and iron deficiency.

There is evidence that optimization of iron stores even in the non-anaemic patient improves exercise capacity. The FERRIC-HF trial confirmed that symptomatic patients with heart failure and abnormal iron profiles who received intravenous iron therapy had improved exercise capacity. This effect was more pronounced in the patients who were anaemic at baseline. A subgroup analysis of the FAIR-HF trial also confirmed symptomatic benefit following treatment of iron deficiency in heart failure irrespective of anaemia.

Erythropoietin stimulating agents are not indicated for the treatment of anaemia in heart failure. The RED-HF study considered the benefit of darbopoetin alfa in patients with HFrEF and anaemia who were iron replete. It did not reduce death or hospitalization and thromboembolic events were significantly increased.

Key references

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Chapter 20

The patient with heart failure and myocarditis

Myocarditis

Myocarditis is the inflammation of myocardium due to one of a large number of causes (see myocarditis subsections on classification and causes), including infection (either acute or as a post-infectious autoimmune response), systemic disease, drugs, and toxins. Currently, the most frequently implicated virus in developed countries is parvovirus B_{19}, although other viruses are commonly implicated.

Myocardial inflammation may be focal or diffuse, involving any or all cardiac chambers. The clinical course is variable—from full recovery to sudden death or the need for urgent cardiac transplantation. This variability appears, in part, to be due to the underlying aetiology.

Classification

- **Fulminant**—preceding flu-like illness, with a distinct onset of cardiac symptoms and rapid deterioration. Patients present with shock or symptoms and signs of severe LVSD. The clinical course is variable and patients either recover over the space of a few weeks or deteriorate rapidly, requiring consideration of CTx/MCS. Endomyocardial biopsy shows active myocarditis. Immunosuppressive therapy is often ineffective.
- **Acute**—unclear onset with gradual decline in cardiac function. Patients present with symptoms of progressive HF and ventricular dilatation with LVSD. There is active or borderline myocarditis on biopsy, which resolves with time. Patients either respond to heart failure therapy or progress to dilated cardiomyopathy.
- **Chronic active**—onset indistinct with progressive deterioration, present with heart failure with LVSD. Initial biopsy shows active or borderline myocarditis; however, subsequent biopsy reveals continued inflammation, fibrosis, giant cells, with eventual development of a dilated cardiomyopathy.
- **Chronic persistent**—no distinct onset of symptoms (primarily chest pain or palpitations) characterized by a persistent infiltrate on biopsy, often with foci of myocyte necrosis but without ventricular dysfunction. Immunosuppressive therapy does not affect myocardial infiltrate or clinical outcome.

Key reference

Lieberman EB, et al. Clinicopathologic description of myocarditis. *J Am Coll Cardiol.* 1991;18:1617–1626.

Causes of myocarditis

Infectious

- Viral—Adenovirus, Arbovirus (dengue fever, yellow fever), Arenavirus (Lassa fever), Coxsackie virus, Cytomegalovirus, Echovirus, Encephalomyocarditis virus, Epstein–Barr virus, hepatitis B, herpes virus, HIV-1, Influenza virus, Mumps virus, Poliomyelitis virus, rabies, Respiratory Syncytial virus, Rubella virus, Rubeola virus, Vaccinia virus, Varicella virus, Variola virus (Fig. 20.1).
- Bacterial—Brucellosis, Clostridia, Diphtheria, Francisella, Gonococcus, Haemophilus, Legionella, Meningococcus, Mycobacteria, Mycoplasma, Pneumococcus, Psittacosis, Salmonella, Staphylococcus, Streptococcus, *Tropheryma whippelii* (Whipple's disease).
- Fungal—Actinomycetes, Aspergillus, Blastomyces, Candida, Coccidioides, Cryptococcus, Histopalsma, Nocardia, Sporothrix.
- Rickettsial—Rocky Mountain spotted fever, Q fever, Scrub Typhus, Typhus.
- Spirochetal—Borrelia (Lyme's disease), Leptospira, Syphilis.
- Helminthic—Cysticercus, Echinococcus, Schistosoma, Toxocara (visceral larva migrans), Trichinella.
- Protozoal—Entamoeba, Leishmania, Trypanosoma (Chagas disease), Toxoplasmosis.

Non-infectious

- *Drug induced*
  - Toxic myocarditis—amphetamines, anthracyclines*, catecholamines, chloroquine, cocaine*, cyclophosphamide*, emetine, fluorouracil,

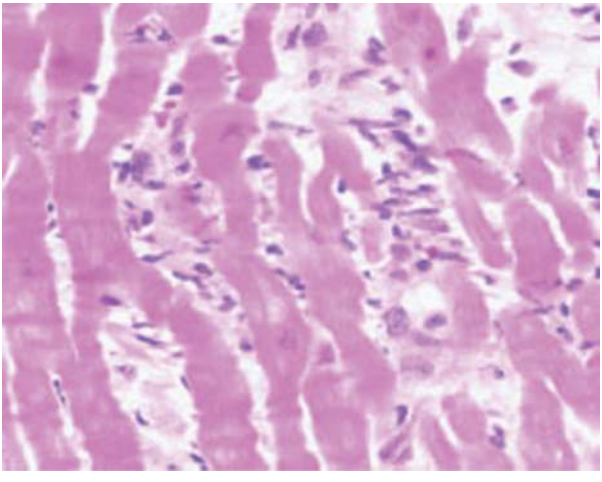

Fig. 20.1 Viral myocarditis. The myocardium contains focal interstitial infiltration by mononuclear cells, with associated cardiac myocyte degeneration. Haematoxylin and eosin ×400. Courtesy of Dr Allan McPhaden, Southern General Hospital, Glasgow (retired).

interferon alfa, interleukin-2*, lithium, paracetamol, thyroid hormone, immune-checkpoint inhibitors*.
  - Hypersensitivity myocarditis—acetazolamide, allopurinol, amitriptyline, amphotericin B, ampicillin*, carbamazepine, cefalotin, chlortalidone, colchicine, diclofenac, diphenhydramine, furosemide, hydrochlorothiazide*, indometacin, isoniazid, lidocaine, methyldopa*, methysergide, oxphenbutazone, para-aminosalicyclic acid, penicillins*, phenindione, phenylbutazone, phenytoin, procainamide, pyribenzamine, reserpine, spironolactone, streptomycin, sulfadiazine*, sulfamethoxazole*, sulfisoxazole*, sulfonylureas, tetracycline, trimethoprim.
- *Toxins*—arsenic, carbon monoxide, copper, iron, lead, mercury, phosphorus, scorpion stings, snake venom, spider bites, wasp sting.
- *Systemic diseases*—arteritis (giant cell, Takayasu), β-thalassaemia major, eosiophilic granulomatosis with polyangiitis (EGPA) vasculitis, Crohn's disease, cryoglobulinemia, dermatomyositis, diabetes mellitus, Hashimoto's thyroiditis, Kawasaki's disease*, mixed connective tissue disorder, myesthenia gravis, periarteritis nodosa, pernicious anaemia, pheochromocytoma, polymyositis, rheumatoid arthritis, sarcoidosis*, scleroderma, Sjogren's syndrome, systemic lupus erythematosus*, thymoma, ulcerative colitis, Wegener's granulomatosis.
- *Other*—cardiac rejection*, eosinophilic myocarditis, genetic, giant cell myocarditis*, granulomatous myocarditis, head trauma, hypothermia, hyperpyrexia, ionizing radiation, mononuclear myocarditis, peripartum myocarditis*.

Key reference

Pisani B, Taylor DO, Mason JW. Inflammatory myocardial diseases and cardiomyopathies. *Am J Med.* 1997;102:459–469.

* More common aetiologies

Clinical features

Myocarditis has a variable clinical course, but symptoms and signs include:

- May be asymptomatic.
- Prodromal viral illness—fever, myalgia, fatigue.
- Decreased exercise tolerance.
- Breathlessness.
- Chest pain (particularly in myopericarditis. However, myocarditis can mimic myocardial ischaemia, and therefore should be considered in patients with an acute coronary syndrome and normal coronary arteries).
- Raised JVP.
- S_3/S_4.
- MR/TR.
- Pericardial friction rub (in myopericarditis).
- Peripheral and pulmonary oedema.
- Cardiogenic shock.
- Ventricular arrhythmias and sudden death.

Investigation and diagnosis

- Cardiac troponin—raised concentrations indicate recent onset or ongoing myocardial necrosis.
- WCC/CRP—usually elevated.
- ECG—non-specifically abnormal: ST/T abnormalities, arrhythmias.
- CXR—may be normal; cardiomegaly ± pulmonary oedema.
- Echo—global, but variable degrees of cardiac dysfunction, MR, TR.
- MRI—may be useful in myocardial characterization, particularly with the use of gadolinium (Gd)-DTPA contrast-enhancement.
- PET CT scanning—may demonstrate myocardial cellular infiltration.
- PCR for the detection of the viral genome in selected cases, although false-positive tests do occur.
- Endomyocardial biopsy—may reveal a lymphocytic infiltrate ± myocardial necrosis. The sensitivity may be as low as 35% due to transient and patchy myocardial involvement. The Marburg histopathological criteria were devised in 1997:
  - **Acute (active) myocarditis**—A clear-cut infiltrate of ≥14 leukocytes/mm^2 and >7 T lymphocytes/mm^2 with necrosis or degeneration. The infiltrates are usually mononuclear, but may be neutrophilic or, occasionally, eosinophilic.
  - **Chronic myocarditis**—As acute myocarditis but no necrosis or degeneration.
  - **No myocarditis**—No infiltrating cells or <14 leukocytes/mm^2.

Treatment

- Refrain from exercise for at least 3 months.
- Usual HF therapy.
- Supportive therapy for cardiogenic shock—IABP, inotropes, consideration of VADs/urgent CTx.
- There is limited evidence of benefit from immunosuppressive therapy in myocarditis. High-dose intravenous corticosteroids are recommended in certain immune-mediated aetiologies, such as immune-checkpoint inhibitor myocarditis, hypereosinophilic syndromes, and giant cell myocarditis.

Giant cell myocarditis

Giant cell myocarditis is a rare form of myocarditis that presents with rapidly deteriorating cardiac dysfunction, heart block, and ventricular arrhythmias. Approximately 20% of patients have coexisting autoimmune disease, and the great majority of affected individuals (approximately 90%) are Caucasian. Endomyocardial biopsies reveal widespread necrosis and inflammation with the presence of lymphocytes, histiocytes, and eosinophils, as well as the characteristic multinucleated giant cells (Fig. 20.2).

The prognosis of giant cell myocarditis is very poor (<6 months). Overall, 89% of patients either die or require urgent transplantation. Identifying patients early will allow the immediate administration of cyclosporin-based multidrug immunosuppressive therapy, although this has limited success.

Due to the rapid deterioration of myocardial function, patients may require IABP or VAD therapy as a bridge to recovery, or a bridge to transplantation. It should be noted that a recurrence of giant cells occurs in 25% of transplanted hearts, but this usually occurs several years after surgery and appears to respond to an increase in immunosuppression.

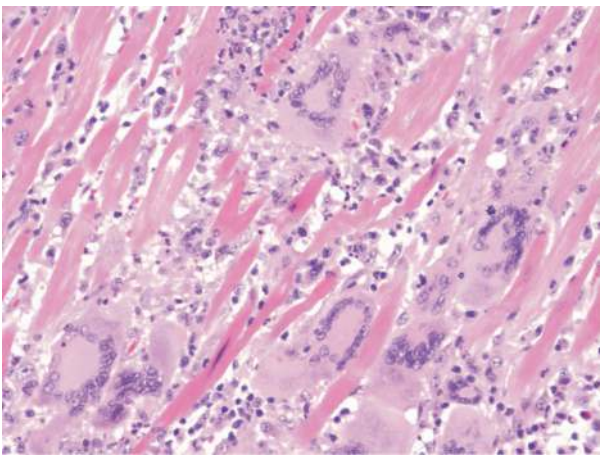

Fig. 20.2 Giant cell myocarditis. The myocardium is being damaged by a marked chronic inflammatory infiltrate that includes prominent multinucleated giant cells in the bottom half of the image. Haematoxlin and eosin. Courtesy of Dr Allan McPhaden, Southern General Hospital, Glasgow (retired).

Key references

Cooper LT, et al. Idiopathic giant cell myocarditis–natural history and treatment. *N Eng J Med.* 1997;336:1860–1866.

Murray LK, et al. Ventricular assist device support as a bridge to heart transplantation in patients with giant cell myocarditis. *Eur J Heart Fail.* 2012;14:312–318.

Chapter 21

The patient with heart failure and obstructive lung disease

Introduction

Obstructive lung disease is common in patients with HF, particularly those with HF of ischaemic aetiology due to the higher prevalence of smokers. It is also true that unrecognized HF exists in patients with COPD (one study estimated that as many as 21% of elderly patients with COPD had unrecognized heart failure), although those with advanced lung disease often have symptoms and signs of right ventricular failure.

The combination of HF and COPD/asthma presents particular diagnostic and therapeutic challenges.

Diagnostic

- Similar symptoms and signs.
- Poor echo windows in emphysematous patients.
- CXR—cardiothoracic ratio and evidence of pulmonary congestion unreliable in COPD.
- Assessing the severity of HF—which is the main cause of breathlessness?

Therapeutic

- Perceived contra-indication of β–adrenoreceptor antagonists.
- Difficulty assessing response to therapy.
- Significant airways disease is a relative contraindication to cardiac transplantation.
- High diuretic dose may cause hypoventilation due to a metabolic alkalosis.
- Digoxin can cause pulmonary vasoconstriction.

Diagnosis and investigation

Patients with suspected obstructive lung disease should have spirometric pulmonary function tests performed. The stage of lung disease can then be classified by the GOLD criteria (Fig. 21.1)

Other investigations indicated are those needed to confirm the presence of heart failure. These include:

- ECG.
- Chest X-ray.
- B-type natriuretic peptides—very useful at distinguishing between cardiac and pulmonary causes of dyspnoea. Caution should be applied in the interpretation of NT-proBNP in the context of severe COPD, as pulmonary hypertension can cause elevation of the biomarker.
- Echo.
- MRI/RNVG/ cardiac CT with functional assessment (if poor echo windows).

Contemporary recommendations suggest that there should be a low threshold for NT-proBNP +/– echocardiography in patients with COPD exacerbation. The differential diagnosis of suspected COPD exacerbation includes HF, pulmonary embolism, and pneumonia.

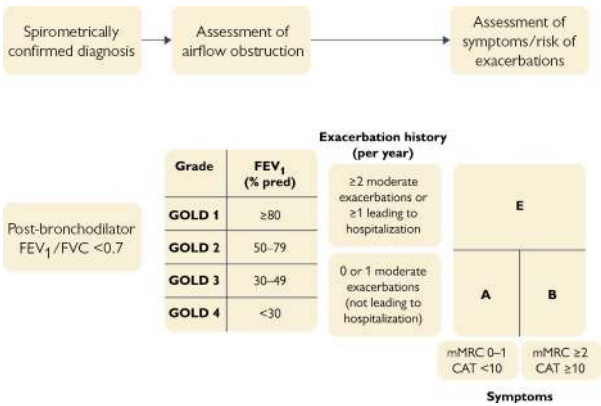

Fig. 21.1 GOLD ABE assessment tool. mMRC: modified Medical Research Council Dyspnea Questionnaire; CAT = COPD Assessment Test; FEV1 = forced expiratory volume in 1s; FVC = forced vital capacity. www.goldcopd.org

Treatment of HF in COPD/asthma

ARNI, ACE inhibitors, and ARBs may be potentially beneficial as they antagonize angiotensin-II, which is a potent bronchial constrictor. They may also decrease pulmonary inflammation and vasoconstriction, and thus improve alveolar membrane gas exchange.

β-adrenoreceptor antagonists—A Cochrane Review has shown that cardioselective β-adrenoreceptor antagonists do **not** produce adverse respiratory effects in the short term when given in mild-moderate reversible airway disease (i.e. asthma) or COPD.

► Given the recognized benefit of β-adrenoreceptor antagonists in heart failure, they should be cautiously administered to HF patients in the presence of mild-moderate reversible airway disease or COPD.

Mineralocorticoid receptor antagonists reduce alveolar-capillary membrane damage and so may have positive effects on gas diffusion.

Digoxin can cause pulmonary vasoconstriction, potentially adversely affecting long-term lung function, although this has not been subject to investigation.

Diuretics—standard doses have no noticeable effect on pulmonary function, but high doses may cause hypoventilation due to a metabolic alkalosis.

SGLT2 inhibitors—there is limited specific data looking at the impact of SGLT2 inhibitors on respiratory disease when used to treat heart failure. From the use of SGLT2i in type 2 diabetics, there was an association with reduced risks of respiratory events including pneumonia and respiratory failure.

Treatment of COPD/asthma in CHF

β_2-adrenoreceptor agonists are not highly selective and therefore myocardial β_1-receptors are often activated, causing tachycardia and increased myocardial oxygen consumption. Increased receptor stimulation may also encourage the down-regulation of these receptors and increase endogenous catecholamine production as a result.

Some studies have suggested that oral and inhaled short-acting β_2-adrenoreceptor agonists increase the risk of mortality and number of heart failure exacerbations in patients with left ventricular dysfunction. The same is not thought to be true of inhaled long-acting β_2-adrenoreceptor agonists and therefore they are the preferred option in COPD patients with HF.

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Abroug F, et al. Association of left heart dysfunction with severe exacerbation of chronic obstructive pulmonary disease: diagnostic performance of cardiac biomarkers. *Am J Crit Care Med.* 2006;174:990–996.

Agusti A, et al. Global Initiative for Chronic Obstructive Lung Disease 2023 Report: GOLD Executive Summary. *Am J Respir Crit Care Med*. 2023;207:819.

Au DH, et al. Risk of mortality and heart failure exacerbations associated with inhaled beta-adrenoceptor agonists among patients with known left ventricular systolic dysfunction. *Chest.* 2003;123:1964–1969.

Dransfield MT, et al. β-Blocker therapy and clinical outcomes in patients with moderate chronic obstructive pulmonary disease and heightened cardiovascular risk. An observational substudy of SUMMIT. *Ann Am Thorac Soc*. 2018;15:608–614.

Jeong HE, et al. Association of adverse respiratory events with sodium-glucose cotransporter 2 inhibitors versus dipeptidyl peptidase 4 inhibitors among patients with type 2 diabetes in South Korea: a nationwide cohort study. *BMC Med.* 2023;21:47.

Rutten FH, et al. Heart failure and chronic obstructive pulmonary disease: An ignored combination? *Eur J Heart Failure.* 2006;8:706–711.

Salpeter S, et al. Cardioselective beta-blockers for chronic obstructive pulmonary disease. *The Cochrane Library.* 2006;3:CD003566.

Chapter 22

The patient with heart failure and pregnancy

Introduction

Heart failure is a pathological state. Pregnancy is a physiological state, not an illness!

Heart failure can occur in pregnancy for a number of reasons, including:

- Pre-existing cardiac condition.
  - Cardiomyopathy (whether known or unknown).
  - Congenital heart disease.
  - Previous acute coronary syndrome.
  - Valvular heart disease.
  - Cardiac transplantation.
- Peripartum cardiomyopathy.
- Pre-eclampsia.

There is an assumption that there will be an optimal outcome for mother and baby throughout pregnancy. The risk of maternal death in the general population is estimated at 1 in 20,000. Severe systemic ventricular dysfunction is associated with high-risk pregnancy and a risk of maternal death of between 1 in 50 and 1 in 2.

The **Toronto scale** attempts to quantify risk of a cardiac event in pregnancy for women with pre-existing heart disease. A 'cardiac event' includes pulmonary oedema, arrhythmia, cerebrovascular event, cardiac arrest, or death. Risks factors for a cardiac event are:

- Prior cardiac event (TIA, CVA, arrhythmia, or HF).
- NYHA functional class III or IV, or cyanosis.
- Left heart obstruction (mitral valve area <2 cm^2, aortic valve area <1.5 cm^2, or peak left ventricular outflow tract gradient >30 mmHg).
- Systemic ventricular dysfunction (LVEF <40%).

If there are no risk factors, then the maternal risk is estimated at 5%, 1 risk factor implies a 27% risk of maternal cardiac event, and >1 risk factor attributes a maternal risk of 75% of a cardiac event.

The **Modified World Health Organization classification of maternal cardiovascular risk** was published in the European Society of Cardiology Guideline for the management of cardiovascular diseases during pregnancy published in 2018. It stratifies risk from low (class I) to high (class IV). Women with mild LVSD (LVEF >45%) are considered in mWHO class II–III suggesting a maternal event rate of 10-19%. Women with moderate left ventricular impairment (LVEF 30–45%), previous peripartum cardiomyopathy without any residual left ventricular impairment, or systemic right ventricle with good or mildly decreased ventricular function are considered mWHO class III, suggesting a maternal event rate of 19–27%. Women with severe systemic ventricular dysfunction (LVEF <30% or NYHA class III–IV) or previous peripartum cardiomyopathy with any residual left ventricular impairment are considered in mWHO class IV with a maternal event rate of 40–100%. These women in mWHO IV are at extremely high risk of maternal mortality or severe morbidity and are counselled that pregnancy would be very high risk and in the 2018 ESC guidance the advice is that pregnancy is 'contraindicated'.

The 2023 MBRRACE-UK report, Saving Lives, Improving Mothers' Care Core Report—Lessons learned to inform maternity care from the UK and Ireland Confidential Enquiries into Maternal Deaths and Morbidity 2019–21,

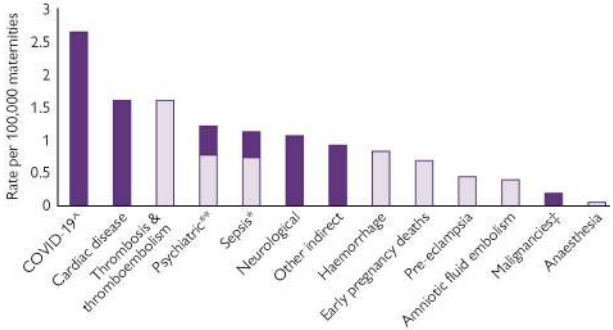

Fig. 22.1 Leading causes of maternal death per 100,000 maternities; UK 2019–20. Knight M et al. Saving Lives, Improving Mothers' Care Core Report—Lessons learned to inform maternity care from the UK and Ireland Confidential Enquiries into Maternal Deaths and Morbidity 2019–21. MBRRACE- UK. Oxford: National Perinatal Epidemiology Unit, University of Oxford 2023.

reported that cardiac disease, along with COVID-19, was the commonest cause of maternal death for the 2019–21 review. The deaths attributable to congenital heart disease and pulmonary hypertension are reducing, while maternal deaths from acquired heart disease including cardiomyopathies are increasing (Fig. 22.1).

The recurrent themes from MBRRACE-UK report include:

- Pre-pregnancy counselling is important and appropriate to any woman of childbearing age with a cardiac history (note that approximately 50% of pregnancies are not planned).
- Women with a known cardiac history MUST be referred for consultant-led obstetric care in a maternity unit where there is joint cardiac and obstetric care.
- Clear and prompt communication between specialties is key when managing a pregnant woman.
- Women with potentially serious medical conditions require immediate and appropriate multidisciplinary specialist care.

► A correlation has been demonstrated between maternal outcome and NYHA class: women with symptoms *greater* than NYHA II have a significantly higher chance of poor maternal outcome and poor foetal outcome.

Key references

Adamson DL, et al. *Heart Disease in Pregnancy*. Oxford University Press, 2011.

Knight M, et al. Saving Lives, Improving Mothers' Care Core Report—Lessons learned to inform maternity care from the UK and Ireland Confidential Enquiries into Maternal Deaths and Morbidity 2019–21. MBRRACE- UK. Oxford: National Perinatal Epidemiology Unit, University of Oxford 2023.

Regitz-Zagrosek V, et al. 2018 ESC Guidelines for the management of cardiovascular diseases during pregnancy. *Eur Heart J*. 2018;39:3165–3241.

Siu S, et al. Prospective multicenter study of pregnancy outcomes in women with heart disease (CARPREG). *Circ*. 2001;104:515–521.

Physiological changes of pregnancy

The **antenatal** changes in the cardiovascular system are significant and occur early in the first trimester. The changes affect preload, cardiac contractility, and afterload:

- There is a 50–70% increase in circulating blood volume.
- Left ventricular (LV) end-diastolic volume increases.
- Prostacyclin and the low impedence of the uterine vascular bed (which acts like an A–V fistula) combine to result in a fall in systemic vascular resistance between weeks 5 and 32. The SVR rises after week 32 through to term.
- Cardiac output increases by 30–50% due to an increase in stroke volume and heart rate.
- There is an increase in maternal oxygen consumption of 20–30% at term, which includes an increase in myocardial oxygen consumption.

During the **peripartum** period, there are further haemodynamic demands and changes that can be altered with analgesia and anaesthesia:

- Uterine contractions return up to 500 mL of volume back into the maternal circulation.
- Pain during labour increases catecholeamines, and consequently heart rate, blood pressure, and cardiac output.
- There is a sudden decompression of venous return through the inferior vena cava.

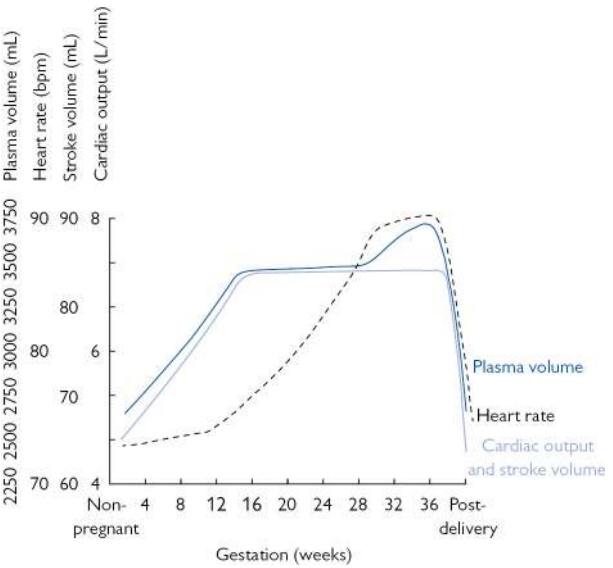

Fig. 22.2 Physiological changes during pregnancy.

Reprinted with permission from the American College of Cardiology 2014.

- Cardiac output returns to pre-labour levels at approximately 60 min post-delivery.

During the **post-partum** period, haemodynamics return to baseline over 3–6 months:

- Blood volume decreases by 10% by day 3 post-partum.
- Blood pressure falls initially then increases on days 3–7.
- SVR increases over the first 2 weeks post-partum to 30% above delivery levels (Fig. 22.2).

Heart failure and pregnancy

Heart failure can occur for the first time during pregnancy and can be dramatic in its presentation. However, heart failure can be a pre-existing condition that requires careful consideration in the pre-pregnancy setting. And finally, heart failure can present in the early post-partum period.

It is essential that there is close collaboration between obstetrics and cardiology. Primary care physicians, anaesthetists, intensive care specialists, and cardiothoracic surgeons are key members of the multidisciplinary team. Cross-specialty working demands prompt and clear communication for safe and effective patient care.

Equally it is imperative that there is education available for all these groups to improve recognition of early signs and symptoms of heart failure. Early recognition and management can improve maternal and foetal outcomes.

Pre-existing heart failure and pregnancy

If a woman of childbearing age is diagnosed with cardiac disease, there should be early consideration of pre-pregnancy counselling. Approximately 50% of pregnancies are unplanned.

Some of the cornerstones of therapy HFrEF are contraindicated in pregnancy. For example, ACE inhibitors and ARBs are associated with adverse foetal outcomes including renal tract malformations, and cardiac and neurological abnormalities. Spironolactone has anti-androgenic effects with high risk of feminization of a male foetus. Too little is known about the safety (or otherwise) of eplerenone in pregnancy, and therefore this should be avoided.

In addition, the aetiology of the heart failure needs to be considered:

- Congenital heart disease may have a significant impact on the likelihood of the offspring being affected with heart disease.
- Peripartum cardiomyopathy has specific concerns in terms of recurrence with future pregnancies—particularly if LV systolic function has not fully recovered.
- Ischaemic cardiomyopathy may have been treated with stents, demanding an anti-platelet regime that carries risks during pregnancy.
- Valvular heart disease may have anticoagulant requirements that demand careful management during pregnancy.

Pre-pregnancy counselling

Pre-pregnancy counselling offers the opportunity to ensure that each woman can discuss the potential impact of pregnancy on their health, including the potential risk of peripartum death or premature death with dependent children. It allows the planning of medication optimization prior to pregnancy (e.g. trial withdrawal of heart failure medications), and it allows consideration of the options for contraception.

►► Pre-pregnancy counselling should be performed by cardiologists and obstetricians with expertise in high-risk pregnancy. Counselling must highlight that a woman who proceeds with a high-risk pregnancy will continue to be supported by their medical team.

Suggested management of heart failure medications pre-pregnancy

After careful counselling highlighting the risks of destabilization of heart failure symptoms, cautious downtitration, and withdrawal of contraindicated medications can be attempted. Contraception should be continued during this trial of withdrawal of therapy.

Continue beta-blockers as risk of intrauterine growth retardation is relatively low with contemporary agents and dosage regimens.

- Initially the MRA should be withdrawn.
- Repeat echo after 4 weeks.
- If no change in LV function and symptoms are stable, SGLT2i should be withdrawn.
- Repeat echo after 4 weeks.
- If no change in LV function and symptoms stable, stepwise down-titrate ACEi/ARB/ARNI.
- Repeat echo after 3 months off ACEi/ARB/ARNI/SGLT2i/MRA.
- Perform functional assessment with exercise test off medication and update advice for pre-pregnancy counselling.
- If LVEF reduces and/or symptoms deteriorate with downtitration of medication, this suggests that pregnancy may not be tolerated without significant risk to maternal health.
  - Discuss contraceptive options.
  - Consider alternative methods of having a family (surrogacy or adoption).
- Pregnancy should be managed by experienced cardiac and obstetric teams with involvement from the local cardiac transplantation/mechanical circulatory support team.

Pre-pregnancy assessment for women with history of HF:

- ECG.
- Echo.
- Exercise testing for functional status.
- Baseline BNP/NT-proBNP may be helpful.

Key references

Singh K, et al. Brain natriuretic peptide in pregnant women with heart disease. *Obs Med.* 2020;13:25–29.

Stergiopoulos K, et al. Pregnancy in patients with pre-existing cardiomyopathies. *JACC.* 2011;58:337–350.

Pregnancy and prior cardiac transplantation

There is increasing experience in the care of women with previous cardiac transplantation who are pregnant. Women are usually fertile, and it is important to discuss contraception with young female transplant recipients.

Pre-pregnancy counselling is strongly recommended to review the potential risks of pregnancy and plan for maternal management through the pregnancy. The cause of the need for transplantation should be considered to allow counselling with regard to recurrence risk.

There is extensive experience in the use of immunosuppression during pregnancy, mainly from the renal transplant population. Calcineurin inhibitors (Tacrolimus and Ciclosporin) are generally continued in pregnancy as the benefits outweigh potential risks, although careful dose monitoring is required as the pregnancy-related changes in the volume of distribution and renal clearance of the drugs causes significant fluctuation in levels. Mycophenolate mofetil (MMF) appears to be teratogenic, and so it is usually switched to azathioprine pre-pregnancy.

There are both maternal and fetal considerations and risks. The maternal risks include:

- Pregnancy-induced hypertension.
- Pre-eclampsia.
- Renal impairment (often associated with ciclosporin use).
- Transplant rejection.

⚠ Remember the potential of premature coronary artery disease (allograft vasculopathy) in cardiac transplant recipients.

The foetal risks include the potential for premature delivery and low birth weight.

Key reference

Punnoose LR, et al. Pregnancy outcomes in heart transplant recipients. *J Heart Lung Transplant.* 2020;39(5):473–480.

HF presenting during pregnancy

Symptoms and signs of heart failure in pregnancy are the same as in the non-pregnant patient, but often are more difficult to elucidate early in their evolution. This is due to a combination of the patient being young and tolerating change relatively well, many symptoms being attributed to pregnancy, and clinicians not expecting to find serious cardiac pathology in usually well young women.

Clinical assessment, an ECG, and an echocardiogram can help to determine the cause of heart failure symptoms. There are a wide-range of potential cardiac causes including previously undiagnosed dilated cardiomyopathy, peripartum cardiomyopathy, ischaemic heart disease, and severe valvular heart disease. And there are a huge number of non-cardiac causes of pregnancy-related breathlessness that must be considered, including pulmonary embolism.

Investigations for heart failure symptoms should include:

- Clinical examination.
- BP.
- Urinalysis.
- ECG.
- Echo.
- Bloods including FBC (exclude significant anaemia), U&E for renal function, LFTs, TFTs (exclude hypo- or hyperthyroidism).
- NT-proBNP or BNP.

Pre-eclampsia is a condition that is important to appreciate in the obstetric population. It is often mentioned as a differential in the breathless patient, but relatively few women with pre-eclampsia have exertional breathlessness, while it is the presenting feature for the majority of new heart failure cases.

Pre-eclampsia is defined as new-onset hypertension occurring ≥20 weeks of gestation with proteinuria ≥0.3 g/24 hours. It is a multisystem disorder that is of uncertain aetiology. Clinical symptoms include:

- Progressive swelling.
- Headaches.
- Blurred vision (or visual disturbance).
- Nausea or vomiting.
- Epigastric or right upper quadrant pain.

If pre-eclampsia progresses it can develop into an aggressive maternal syndrome, with many complications including eclampsia, HELLP syndrome, renal failure, DIC, and pulmonary oedema.

Initial treatment of heart failure includes:

- Bed rest with ECG monitoring.
- Fluid management with fluid restriction and daily weight.
- Furosemide.
- Consider introduction of beta-blocker when euvolaemic.
- ACE inhibitors, ARB, and spironolactone contraindicated.
- Hydralazine and nitrates can be used during pregnancy.
- Full anticoagulation should be considered if severe LVSD.
- Targeted treatment if possible, e.g.
  - Balloon valvuloplasty for aortic stenosis or mitral stenosis.
  - Intervention if thrombosed mechanical valve prosthesis.

- Coronary angioplasty if myocardial ischaemia with culprit coronary stenosis.
- Correction of anaemia.
- Correction of thyroid dysfunction.

Peripartum cardiomyopathy (PPCM)

This is an important but rare cause of heart failure during the later stages of pregnancy and early post-partum period. It has been defined by the European Society of Cardiology as 'an idiopathic cardiomyopathy presenting with HF secondary to LV systolic dysfunction towards the end of pregnancy or in the months following delivery, where no other cause of HF is found'. It is a diagnosis of exclusion. The LV may not be dilated but the ejection fraction (EF) is nearly always reduced below 45%. A recent study highlighted that almost 25% of cases of confirmed PPCM had a normal ECG, therefore a normal ECG should not preclude echo assessment in peripartum women with possible heart failure.

There are known risk factors for PPCM including:

- Increased maternal age.
- Afro-Caribbean race.
- Multiparity.
- Multiple pregnancy.
- Hypertension (although there is debate as to whether pre-eclamptic heart failure is a separate diagnosis).

PPCM sometimes improves promptly with medical therapy post-partum, but others improve slowly and incompletely. Pre-pregnancy counselling and contraceptive advice are imperative as subsequent pregnancies may have the potential for maternal decompensation and death, particularly if there is persistent LV dysfunction.

There is a considerable interest in the underlying mechanisms in PPCM, including the potential role of prolactin. As such, there is some early work to suggest that bromocriptine may have a therapeutic role, although it is too early to recommend as it has not been assessed in a randomized trial against a control arm.

Children born to mothers with PPCM have worse clinical outcomes with perinatal complications including stillbirth and neonatal death.

⚠ Clinicians with new cases of PPCM are encouraged to register them with the ongoing ESC registry:

https://www.escardio.org/Research/registries/global-registries-and-surveys-programme/PeriPartum-CardioMyopathy-PPCM-Registry

Decompensated severe heart failure and peripartum care

Peripartum heart failure is a potentially life-threatening condition that demands an urgent multidisciplinary approach with experienced cardiology, obstetric, neonatal, and anaesthetic/intensivist inputs.

The plan for delivery needs to take into account the urgency of delivery. If steroids are suggested for fetal lung maturity, then cover the maternal bolus of steroids with diuretics.

Decisions about mode of delivery should be led by the obstetrician, and it should be noted that the haemodynamic shifts are likely to be less with an assisted vaginal delivery than a Caesarean section.

Decisions about analgesia and anaesthesia are determined by the anaesthetist. The severity of maternal symptoms, for example extreme orthopnoea, may mandate a specific approach, for example general anaesthesia. Optimal analgesia obviously reduces the stress and anxiety with benefit to the haemodynamics. Remember that in HCM, adequate filling is essential during delivery to minimize impact of LVOT obstruction.

The cardiologist has an important role in planning the back-up plans for the time of delivery. This can be directed by the aetiology of the heart failure. For example, is balloon valvuloplasty appropriate as a rescue strategy? It is important to have pre-discussed complex cases with the regional experts in mechanical circulatory support and cardiac transplantation. It may be most appropriate to transfer the woman pre-delivery to a cardiac centre that can provide the advanced therapies in the event of maternal collapse.

►► Post-partum, cardiology review is essential in establishing an aetiology for the HF and ensuring optimal recovery. Prior to discharge a plan for contraception should be enacted—combined oral contraception is not advised in impaired cardiac function.

Cardiac arrest

Cardiac arrest in the pregnant woman is uncommon. However, there are a number of differences in the ALS guidelines that are appropriate to consider:

- If cardiac arrest confirmed, initiate resuscitation but ensure that emergency calls are made to:
  - Consultant obstetrician.
  - Consultant neonatologist/paediatrician.
  - Consultant anaesthetist.
- Tilt the mother into a left lateral position to decompress the IVC. Practically, this means using pillows under the right pelvis and right side.
- Cardiac arrest may be caused by peripartum cardiomyopathy or amniotic fluid embolus, and all the traditional causes of cardiac arrest.
- After approximately 20 weeks of gestation, it is advised that the baby be delivered within **5 minutes** of cardiac arrest for MATERNAL survival.

Key references

Jackson A, et al. A 20 year population study of peripartum cardiomyopathy. *Eur Heart J.* 2023;44:5128–5141.

Regitz-Zagrosek V, et al. 2018 ESC Guidelines for the management of cardiovascular diseases during pregnancy *Eur Heart J.* 2018;39:3165–3241.

Chapter 23

The patient with heart failure and renal dysfunction

Introduction

Heart failure can be seen, as not only a cardiac disorder, but also a cardiorenal and neurohumoral syndrome.

Renal impairment is therefore common in patients with chronic heart failure and there are shared risk factors for both conditions such as diabetes and hypertension. The proportion of those who have renal dysfunction increases with deteriorating NYHA functional class. A reduced glomerular filtration rate (GFR) is also associated with increased symptoms, more frequent hospitalizations, and an increased mortality rate—particularly in the heart failure population with reduced left ventricular ejection fraction.

Definition

Serum creatinine concentration, which is often quoted as a barometer of renal impairment, is a poor indicator of renal function. Serum creatinine is determined by a number of factors other than GFR, such as gender, age, muscle mass, and ethnicity. Therefore, estimation of the GFR is preferred for the accurate assessment of renal function.

A 'normal' estimated GFR is regarded as being 120 ± 25 mL/min/1.73 m^2 (95th centiles). Males have a slightly higher GFR than females. With age, GFR tends to fall (to approximately 100 mL/min/1.73 m^2 at age 70), although serum creatinine does not rise substantially in healthy individuals. Therefore values >90 mL/min/1.73 m^2 can be regarded as normal for most patients. A GFR below 60 mL/min/1.73 m^2 is associated with complications of renal disease.

Prevalence

The prevalence of renal dysfunction in heart failure depends greatly on the population studied, and the definition used. In the CHARM trials, the overall prevalence of an eGFR<60 mL/min/1.73 m² was 36% (Fig. 23.1). In the more recent DAPA-HF trial, just over 40% of patients were within this category of renal dysfunction.

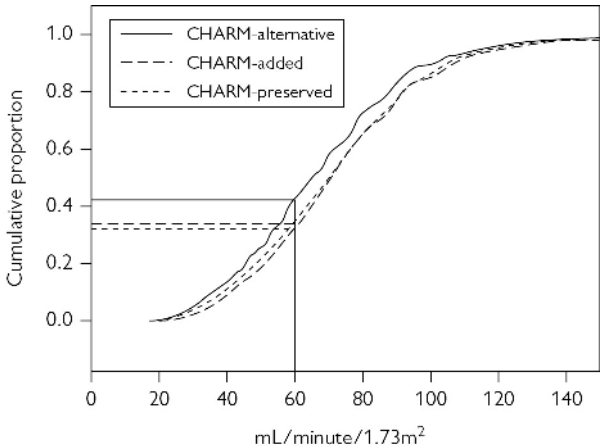

Fig. 23.1 Cumulative distribution of eGFR in patients with mild-moderate heart failure in the CHARM-Preserved, CHARM-Added, and CHARM-Alternative trials.

Reproduced from Hillege et al. Renal function as a predictor in a broad spectrum of patients with heart failure, *Circulation*, 113;5:671–678 with permission from Lippincott, Williams and Wilkins.

Aetiology

The causes of renal impairment in CHF are multifactorial, but it is likely that the mechanisms include:

- Renal hypoperfusion.
- Renal venous congestion.
- Renal artery stenosis.
- Diuretic treatment.
- Disease-modifying therapy (e.g. ARNI, ACEi, ARBs, MRAs).
- Other concomitant medication (e.g. NSAIDs).
- Comorbidities such as diabetes and amyloid.

Investigation

Investigations indicated in the heart failure patient with renal dysfunction include:

- Urea and electrolytes.
- Diabetic screen.
- eGFR.
- Urinalysis.
- Urinary microscopy.
- Renal ultrasound.
- Auto-antibodies (e.g. ANF, ANCA).
- Very rarely, a renal biopsy.

Until recently, it was not clear how best to estimate renal function in patients with heart failure. Traditionally, eGFR was calculated by means of inulin clearance or EDTA. However, the modification of diet in renal disease (MDRD) equations have been validated in patients with severe CHF.

Equations to estimate GFR

MDRD-1 equation:

$$\text{GFR}\left(\text{expressed in mL/min/1.73 m}^2\right) = 170 \times [\text{plasma creatinine}]^{-0.999}$$

$$\times [\text{age}]^{-0.176} \times [0.762 \text{ if patient is female}] \times [1.180 \text{ if patient is black}] \times$$

$$[\text{SUN}]^{-0.170} \times [\text{albumin}]^{+0.318}.$$

MDRD-2 (abbreviated) equation:

$$\text{GFR}\left(\text{expressed in mL/min/1.73 m}^2\right) = 186 \times [\text{plasma creatinine}]^{-1.154}$$

$$\times [\text{age}]^{-0.203} \times [0.742 \text{ if patient is female}] \times [1.212 \text{ if patient is black}].$$

Cockcroft–Gault formula normalized to a body surface area of 1.73 m², (creatinine clearance, expressed in mL/min/1.73 m²):

$$\text{GFR}(\text{males}) = 1.23 \times \text{weight (kg)} \times [140 - \text{age}] / \text{plasma creatinine}$$

$$(\mu\text{mol/L}) \times 1.73/\text{BSA GFR}(\text{females}) = 1.03 \times \text{weight (kg)}$$

$$\times [140\text{-age}] / \text{plasma creatinine}(\mu\text{mol/L}) \times 1.73/\text{BSA, where}$$

$$\text{BSA}\left(\text{m}^2\right) = \text{O [weight (kg)} \times \text{height (cm)}/3600].$$

Prognosis

Patients with CHF and renal dysfunction have been shown to be at greater risk of mortality and morbidity, including hospitalization, independent of LVEF and NYHA class. However, a low eGFR may be a more discerning marker of an adverse prognosis in patients with non-ischaemic heart failure, compared to those with heart failure of an ischaemic aetiology (Figs. 23.2 and 23.3).

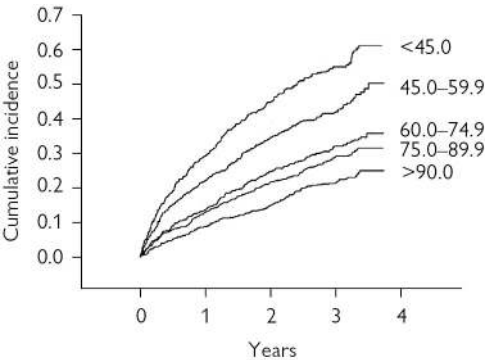

Fig. 23.2 Kaplan–Meier plot of cumulative incidence of cardiovascular death or unplanned admission to hospital for the management of worsening CHF stratified by a eGFR <45, 45 to 60, and >60 mL/min/1.73 m², in patients with a LVEF <40% enrolled in the CHARM trials.

Reproduced from Hillege et al. Renal function as a predictor in a broad spectrum of patients with heart failure, *Circulation*, 113;5:671–678 with permission from Lippincott, Williams and Wilkins.

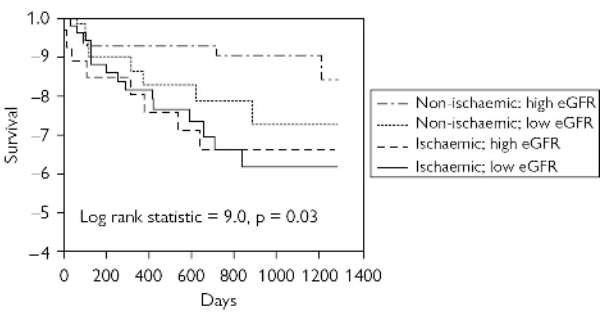

Fig. 23.3 Kaplan–Meier survival curve for eGFR in patients with ischaemic and non-ischaemic advanced heart failure.

Gardner RS, et al. Renal dysfunction, as measured by the modification of diet in renal disease equations, and outcome in patients with advanced heart failure. *Eur Heart J*. 2007;28:24 by permission of Oxford University Press.

Management

- Treat any reversible causes.
- Remove/modify potentially nephrotoxic drugs:
  - NSAIDs.
  - COX-2 inhibitors.
- Multidisciplinary approach with early nephrology input.
- Medical therapy—SGLT2 inhibitors and finerenone (a non-steroidal MRA) are both recommended for the prevention of heart failure in those with diabetic kidney disease.
- Dialysis where appropriate.
- Renal transplantation may be considered for patients with end-stage renal failure who develop heart failure.

What to do with heart failure therapy

Heart failure medical therapy has been shown to confer benefits in patients with CKD. However, in those with severe CKD (eGFR <30 mL/min/1.73 m²), there is little direct evidence to support medical therapy due to clinical trial exclusion criteria.

A transient worsening in renal function is recognized, particularly at initiation of RAAS inhibitors, ARNI, and SGLT2 inhibitors. This is not associated with worse outcomes, in fact long-term outcomes are better with a slower slope of GFR decline.

In view of the benefits of heart failure medical therapy, following initiation most clinicians will accept an increase in creatinine up to 50% from baseline (if <266 μmol/L or 3 mg/dL) or an eGFR decrease <10% from baseline (if >25 mL/min/1.73 m²). Careful monitoring of serum biochemistry is required and a more marked decline in renal function may lead to a decision to reduce the dose or stop the drug following specialist advice.

RAAS inhibitors—both ARBs and ACE inhibitors reduce progression to renal failure in CKD and improve survival in diabetic kidney disease. ACE inhibitors have been shown to provide renal protection in advanced renal insufficiency.

ARNI—sacubitril/valsartan can be started at a lower dose in the setting of CKD. In PARADIGM-HF there was no significant worsening renal function compared to ACE inhibitor (enalapril).

β-adrenoreceptor antagonists—the doses of bisoprolol, atenolol, and sotalol should be reduced in patients with renal dysfunction as these drugs are cleared renally. (NB: the latter two drugs do not have an evidence base in CHF.)

Mineralocorticoid receptor antagonists should not be started in patients with a creatinine above 220 μmol/L (above which patients were excluded from the trials), and the dose should be reduced or discontinued if creatinine rises significantly on treatment.

SGLT2 inhibitors should not be started in patients with severe CKD (eGFR <20 mL/min/1.73 m²).

Digoxin—the dose of digoxin will need to be reduced in renal impairment, particularly if there is an electrolyte imbalance.

Furosemide—higher doses of diuretics may be needed in patients with renal impairment.

Key references

Damman K, et al. Renal impairment, worsening renal function, and outcome in patients with heart failure: an updated meta-analysis. *Eur Heart J*. 2014;35:455–469.

Hou FF, et al. Efficacy and safety of benazepril for advanced chronic renal insufficiency. *NEJM*. 2006;354:131–140.

McDonagh TA, et al. ESC Scientific Document Group. 2023 focused update of the 2021 ESC guidelines for the diagnosis and treatment of acute and chronic heart failure. *Eur Heart J*. 2023;44:3627–3639.

Chapter 24

The patient with heart failure and valvular heart disease

Introduction

The relationship between heart failure and valve disease is complex. As a consequence of left ventricular dilatation, heart failure can result in regurgitation of the mitral, aortic, or tricuspid valves. Conversely, primary heart valve disease can lead to heart failure due to excess volume and pressure load (Fig. 24.1).

Valve intervention in the form of surgery or percutaneous transcatheter techniques may be required to improve symptoms of heart failure or symptoms from the valve disease (Fig. 24.2). Aortic valve intervention in severe aortic valve stenosis and heart failure reduces mortality. The timing of intervention can be difficult to judge. If surgery is planned for a valvular lesion, then consideration should be given to combining the surgery with the following:

- Additional valve lesions.
- Coronary revascularization.
- Surgery for atrial fibrillation.

The risk of operative intervention in the heart failure population should not be underestimated. The future for these patients may lie in percutaneous interventions including cardiac resynchronization or percutaneous valve replacements. There are percutaneous valves available for aortic and pulmonary valve disease, and potential transcatheter solutions for mitral regurgitation and tricuspid regurgitation. In selected cases valve stenosis may be managed with balloon valvuloplasty.

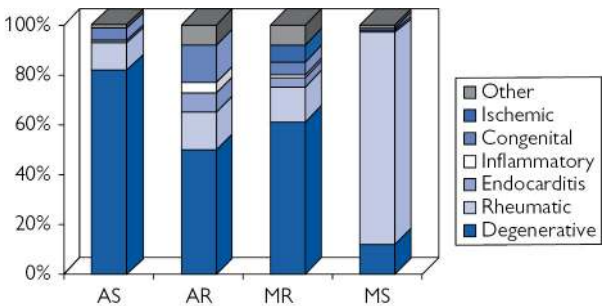

Fig. 24.1 Contributing factors for valve lesions. AR = aortic regurgitation; AS = aortic stenosis; MR = mitral regurgitation; MS = mitral stenosis.

Bernard Lung et al., A prospective survey of patients with valvular heart disease in Europe: the Euro Heart Survey on Valvular Heart Disease. *Eur Heart J.* 2003;24:1231–1243, by permission of Oxford University Press.

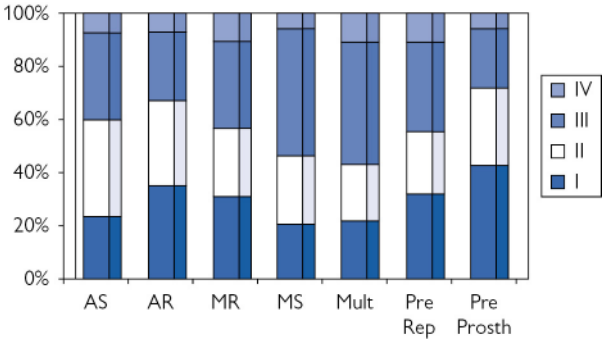

Fig. 24.2 Distribution of NYHA functional class in the Euro Heart survey on valvular heart disease.

Bernard Lung, et al. A prospective survey of patients with valvular heart disease in Europe: the Euro Heart Survey on Valvular Heart Disease. *Eur Heart J*. 2003;24(13):1231–1243, by permission of Oxford University Press.

Key reference

Vahanian A, et al. 2021 ESC/EACTS Guidelines for the management of valvular heart disease. *Eur Heart J*. 2022;43:561–632.

Aortic stenosis

Aetiology

Aortic stenosis (AS) is the most common primary valve lesion, and the prevalence is rising in Europe and North America. The most common aetiology is degenerative AS where there is annular calcification that progresses up the valve leaflets causing increasing limitation to flow. The underlying pathology of degenerative AS involves an inflammatory process that deposits lipids in the valve leaflets and then progresses to calcification.

Congenital AS is usually due to a bicuspid valve. Rheumatic AS causes fusion of the commissures and reduction in valve orifice.

Assessment

Aortic stenosis causes progressive obstruction of left ventricular (LV) outflow. Therefore, the key symptoms that identify critical AS are:

- Exertional chest pain.
- Exertional breathlessness.
- Exertional dizziness or syncope.

The clinical signs of AS include a slow-rising carotid pulse, a harsh ejection systolic murmur that radiates to the carotids, and a quiet, single S_2.

An ECG in AS may show LV hypertrophy. Echocardiography can confirm the diagnosis, allow examination of the valve morphology, calculate valve orifice area, and quantify the gradient through the valve. Table 24.1 summarizes the echo grading of AS.

Severe AS that has caused heart failure may present with a low-pressure low-gradient. Differentiating this scenario from heart failure and incidental mild to moderate AS is difficult. In true severe AS the stenotic valve causes an elevated afterload, decreased ejection fraction, and low stroke volume. In heart failure, contractile dysfunction results in reduced ejection fraction and low stroke volume.

►► To identify the patients who have true severe AS who may benefit from valve intervention further assessment is required. Assessing valve calcium score on cardiac CT or a dobutamine stress echo can be performed. A dobutamine stress echo in severe AS that will respond to valve intervention shows:

- Unchanged valve area.
- Increased stroke volume.
- Increased valve gradient.

Table 24.1 Echo grading of AS

	Aortic jet velocity	Mean gradient	Valve area
Normal	<1.5 ms^{-1}	<5 mmHg	3.0–4.0 cm^2
Mild	<3.0 ms^{-1}	<25 mmHg	>1.5 cm^2
Moderate	3.0–4.0 ms^{-1}	25–40 mmHg	1.0–1.5 cm^2
Severe	>4.0 ms^{-1}	>40 mmHg	<1.0 cm^2

Pharmacological therapy

Due to the inflammatory nature of degenerative AS, with its similarity to atherosclerosis, the role of statin therapy to slow progression of AS was studied and not shown to be beneficial. There is theoretical benefit in the use of ACE inhibitors but no proven outcome benefit.

Aggressive management of atrial fibrillation may be needed as the loss of atrial kick and uncontrolled ventricular rate may be disastrous to the patient's clinical condition.

Indications for intervention

Aortic valve intervention includes TAVI (transcatheter aortic valve implantation), SAVR (surgical aortic valve replacement) and balloon aortic

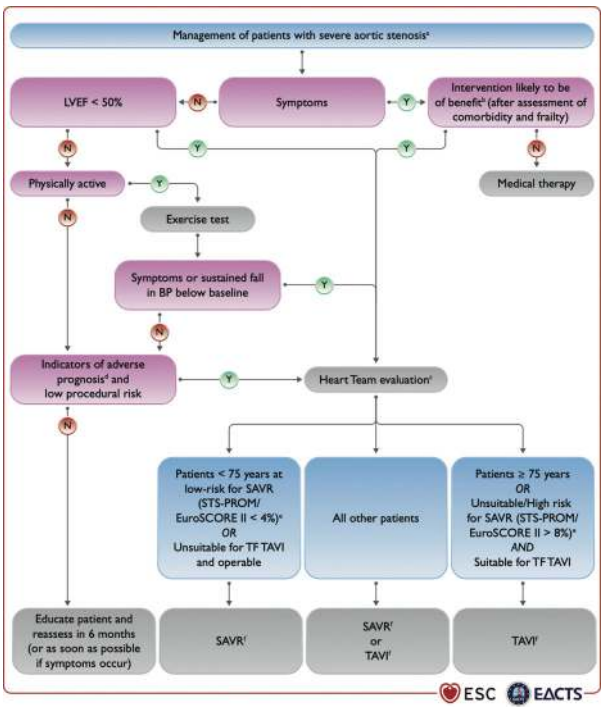

Fig. 24.3 Management of patients with severe aortic stenosis. BP: blood pressure; EuroSCORE: European System for Cardiac Operative Risk Evaluation; LVEF: left ventricular ejection fraction; SAVR: surgical aortic valve replacement; STS-PROM: Society of Thoracic Surgeons predicted risk of mortality; TAVI: transcatheter aortic valve implantation; TF = transfemoral. Vahanian A, et al. 2021 ESC/EACTS Guidelines for the management of valvular heart disease. *Eur Heart J*. 2022;43:561–632. By permission of Oxford University Press.

valvuloplasty—a temporary measure than can be considered in acute heart failure as a bridge to further therapy. Intervention is recommended in patients with heart failure symptoms and severe AS with an estimated life expectancy greater than one year. It is important to exclude and correct causes of high cardiac output and flow (e.g. hyperthyroidism or anaemia). The decision to proceed to aortic valve intervention should be made by the multidisciplinary Heart Team.

The ESC/EACTS guidelines for the management of patients with valvular heart disease have an algorithm for the management of severe AS (Fig. 24.3).

The use of TAVI has increased significantly in recent years. Trial data demonstrate non-inferiority to SAVR in patients with high and intermediate surgical risk over 5-year follow-up, and non-inferiority to SAVR in low-risk patients over 2-year follow-up. Compared to SAVR, TAVI offers shorter procedural times, no requirement for general anaesthetic and shorter hospital stays—in some cases same day discharge! It is recommended in patients over 75, or in those deemed to have high surgical risk.

Aortic regurgitation

Aetiology

Aortic regurgitation (AR) can result from aortic valve dysfunction or changes in aortic root geometry. Valve dysfunction may be congenital, rheumatic, or degenerative, because of, for example, chronic hypertension or myxomatous change. These usually produce chronic AR with slow, insidious LV dilation. LV dysfunction may be reversible if SAVR is performed soon after development. Chronic volume overload from AR may cause irreversible LV dysfunction even after SAVR.

Acute severe AR may be caused by infective endocarditis, aortic dissection, or trauma, and can result in catastrophic elevation of LV filling pressures and heart failure.

Assessment

The key symptoms that suggest severe AR include:

- Angina.
- Breathlessness.
- Symptoms of heart failure.

Clinical signs include collapsing pulses and an early diastolic murmur.

The ECG may show LV hypertrophy. Echocardiography can confirm the diagnosis, determine the severity, and assess the LV systolic function (Table 24.2).

Table 24.2 Echo grading of aortic regurgitation (AR)

	Mild AR	Severe AR
Diastolic flow reversal descending aorta	Absent	Present
Effective regurgitant orifice area	<0.1 cm^2	≥0.3 cm^2
Jet width (% of LVOT)	<25%	>60%
LV size	Normal	Dilated
Pressure half time	>500 ms	<200 ms
Vena contracta width	<0.3 cm	>0.6 cm

LVOT = left ventricular outflow tract.

Pharmacological therapy

There is trial evidence that supports the use of vasodilators, specifically nifedipine, to slow progression of AR. However, the presence of heart failure would discourage the use of nifedipine. In patients with chronic severe AR and heart failure, ACE inhibitors or ARBs are useful. β-adrenoreceptor antagonists should be used with caution as they prolong diastole and can worsen aortic valve regurgitation.

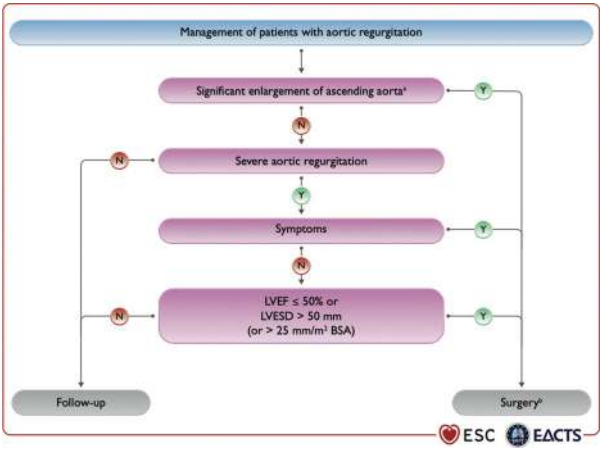

Fig. 24.4 Management of patients with aortic regurgitation. BSA = body surface area; LV = left ventricle/left ventricular; LVESD = left ventricle end-systolic diameter; LVEF = left ventricular ejection fraction. Vahanian A, et al. 2021 ESC/EACTS Guidelines for the management of valvular heart disease. *Eur Heart J*. 2022;43:561–632. By permission of: Oxford University Press.

Indications for intervention

Approximately 15% of valves can be repaired rather than replaced. The ESC/EACTS algorithm is illustrated (Fig. 24.4). TAVI can be considered as an intervention option in AR if the patient is ineligible for SAVR.

Key reference

Lancellotti P, et al. Scientific Document Committee of the European Association of Cardiovascular Imaging. Recommendations for the echocardiographic assessment of native valvular regurgitation: an executive summary from the European Association of Cardiovascular Imaging. *Eur Heart J Cardiovasc Imaging*. 2013;14:611–644.

Mitral stenosis

Aetiology

The vast majority of cases of mitral stenosis (MS) are due to rheumatic heart disease. There are a small number of cases attributable to congenital valve disease. Other rare causes include carcinoid disease (almost always in conjunction with an atrial right-to-left shunt, e.g. patent foramen ovale) and connective tissue diseases such as rheumatoid arthritis and systemic lupus erythematosus.

MS is associated with right heart failure with pulmonary hypertension. LV systolic function is usually preserved. Chronic afterload elevation and preload reduction causes reduced LV systolic dysfunction in about 25% of cases.

Assessment

The most common symptom of MS is exertional breathlessness. The development of atrial fibrillation may be associated with pulmonary oedema.

Clinical examination demonstrates a low, rumbling mid-diastolic murmur at the apex.

ECG findings include 'P mitrale' (evidence of left atrial enlargement) or atrial fibrillation.

Echocardiography confirms the diagnosis and can determine the severity of the lesion. It can also help plan the possible interventions. The options available are mitral valve replacement (with or without preservation of subvalvular apparatus) or percutaneous mitral commissurotomy (PMC).

PMC usually achieves a 100% increase in valve area. Contraindications include the presence of left atrial thrombus and significant mitral regurgitation (MR). Complication rates are significant:

- Failure rates 1–15%.
- Death 0–3%.
- Embolism 0.5–5%.
- Severe MR 2–10%.

Indications for intervention

The ESC/EACTS guidelines are shown (Fig. 24.5).

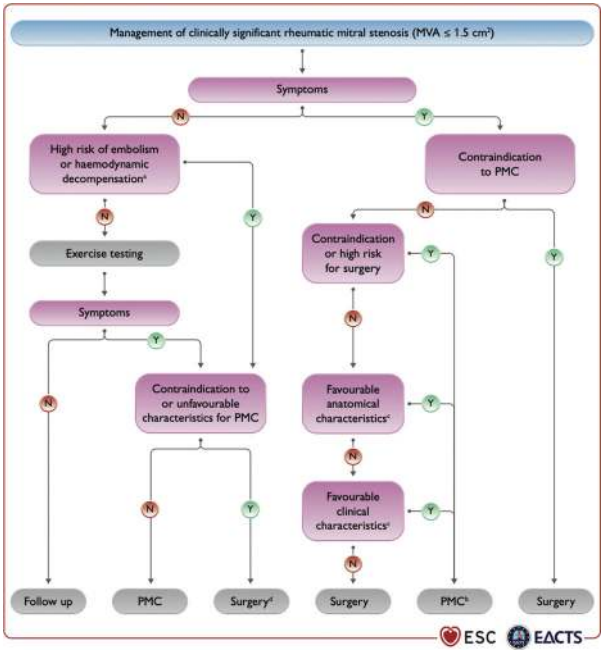

Fig. 24.5 Management of clinically significant rheumatic mitral stenosis (MVA <_ 1.5 cm²). AF = atrial fibrillation; LA = left atrium/left atrial; MVA = mitral valve area; NCS = non-cardiac surgery; PMC = percutaneous mitral commissurotomy. Vahanian A, et al. 2021 ESC/EACTS Guidelines for the management of valvular heart disease. *Eur Heart J*. 2022;43:561–632. By permission of Oxford University Press.

Mitral regurgitation

Aetiology

Mitral regurgitation (MR) can be due to:

- Primary lesion of one or more components of the mitral valve apparatus—'Primary MR'

e.g. rheumatic heart disease, infective endocarditis, mitral valve prolapse, connective tissue disease, ruptured chordae, or papillary muscle.

- Functional due to annular dilatation—'Secondary MR'

e.g. ischaemic cardiomyopathy.

The majority of patients with MR have a chronic progression of their symptoms. Those with infective endocarditis or failure of the mitral valve apparatus may present acutely, with severe heart failure.

Assessment

Patients with mild or even moderate MR may be entirely asymptomatic. The only physical sign may be the classic pansystolic murmur at the apex. Severe MR is usually symptomatic with symptoms of left-sided heart failure.

An ECG is helpful in establishing the rhythm, as many of these patients develop atrial fibrillation that may be responsible for symptomatic deterioration.

Transthoracic echocardiography confirms the diagnosis and documents the severity of the lesion. Echo can also help define the aetiology and consider whether pulmonary hypertension is developing (an ominous sign). Transoesophageal echo may be a useful adjunct, particularly in cases with symptomatic change without obvious change in the transthoracic echo assessment. Some of these patients may be found to have progressed to severe MR on transoesophageal studies.

Further assessment of MR can be made with cardiac catheterization or magnetic resonance scanning.

The severity of MR is notoriously difficult to judge. Severe MR is usually associated with left atrial dilatation. Transthoracic echocardiographic features that suggest severe MR are demonstrated in Table 24.3.

Table 24.3 Echocardiographic criteria for severe MR

	Severe MR
Effective regurgitant orifice area	≥0.4 cm^2
LV size	Dilated
Regurgitant fraction	≥50%
Regurgitant volume	≥60 mL
Vena contracta width	>0.7 cm

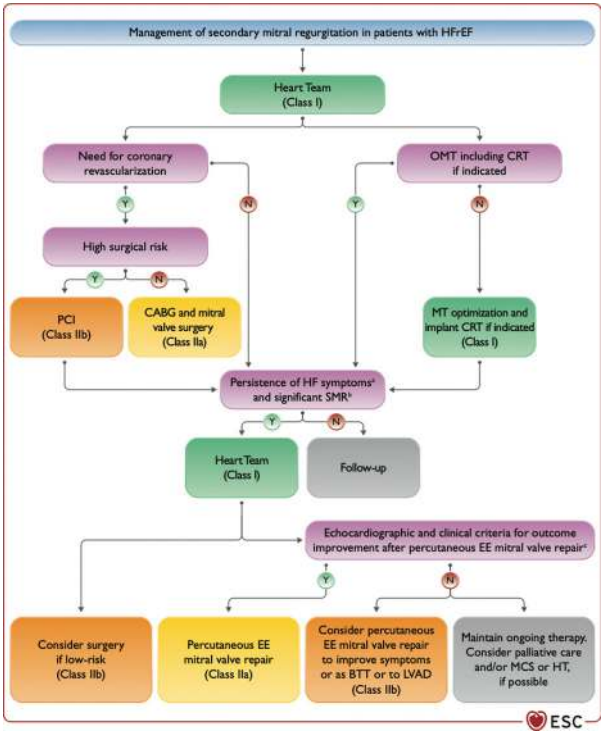

Fig. 24.6 Management of secondary mitral regurgitation in patients with heart failure with reduced ejection fraction. BTT = bridge to transplantation; CABG = coronary artery bypass graft; CRT = cardiac resynchronization therapy; EE = edge-to-edge; EROA = effective regurgitant orifice area; HF = heart failure; LVAD = left ventricular assist device; LVEF = left ventricular ejection fraction; LVESD = left ventricular end-systolic diameter; MCS = mechanical circulatory support; MT = medical therapy; NYHA = New York Heart Association; OMT = optimal medical therapy; PCI = percutaneous coronary intervention; SMR = secondary mitral regurgitation; TR = tricuspid regurgitation. McDonagh TA, et al. ESC Scientific Document Group. 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. *Eur Heart J.* 2021;42:3599–3726.

Indications for intervention

Surgical intervention is recommended in patients with severe primary MR and heart failure symptoms. The management of secondary MR in the setting of heart failure is outlined in Fig. 24.6.

At present there are a number of possible interventions for patients with MR and heart failure:

1. Pharmacology.
2. Cardiac resynchronization therapy.
3. Mitral valve repair ± annuloplasty.
4. Mitral valve replacement ± resection of subvalvular apparatus.
5. Percutaneous mitral valve repair.

Patients with MR and heart failure should be established on maximum tolerated heart failure medical therapy. Particular attention should be paid to optimization of ACE inhibitor and β-adrenoreceptor antagonists.

There is a small body of evidence considering the role of cardiac resynchronization therapy. LV dyssynchrony including the posterior mitral leaflet is important in the aetiology of MR. CRT may improve MR by restoring synchronous LV contraction acutely, and further improvements may be achieved by ventricular remodelling.

MV surgery, whether performed in isolation or in addition to coronary revascularization, can achieve significant improvements in symptoms of heart failure. However, the significant morbidity and mortality of cardiac surgery in this patient group with severe MR and heart failure should not be underestimated.

Mitral valve repair is the operation of choice when technically feasible based on evidence from patients with ischaemic and non-ischaemic cardiomyopathies. MV repair achieves beneficial effects of restoring the MV architecture and competence, without challenging the ventricle with a fully competent prosthetic valve replacement. MV repair can be combined with annuloplasty to further improve the MV architecture.

The subvalvular apparatus is well established in its importance in LV function after MV replacement. The MV apparatus achieves continuity between mitral annulus and LV free wall through the chordae and papillary muscles. The subvalvular apparatus is therefore preserved unless it is so diseased that it must be resected. There are prosthetic options that may facilitate repair of the apparatus.

Percutaneous end-to-end (EE) mitral valve repair should be considered in carefully selected cohorts of patients with HFrEF and severe secondary MR (Fig. 24.6). Randomized trials examining this technique demonstrate inconsistent results with regards to mortality and heart failure hospitalization when compared to medical therapy over 24-month follow-up. Transcatheter mitral valve replacement may emerge as an alternative treatment option in the future.

MV surgery may be combined with surgery for atrial fibrillation. There are a variety of techniques including the Maze procedure and radiofrequency ablation devices.

Key reference

Stone GW, et al. COAPT Investigators. Transcatheter mitral valve repair in patients with heart failure. *N Engl J Med*. 2018;379:2307–2318.

Tricuspid stenosis

Aetiology

This is a rare valve lesion in westernized countries. The causes of tricuspid stenosis (TS) are rheumatic disease and carcinoid syndrome. It most often occurs in conjunction with left-sided valve lesions, e.g. MS.

Assessment

Careful auscultation may detect a diastolic murmur that is louder in inspiration. Other clinical features are those of right heart failure.

Echocardiography is the diagnostic test of choice, although assessment of the tricuspid valve may be difficult, and stenosis can be overlooked. The normal tricuspid valve peak E wave is between 0.3–0.7 ms^{-1}. A mean pressure gradient >5 mmHg is consistent with severe TS.

Indications for intervention

Intervention is usually performed in the context of other valve surgery. In rare cases of isolated TS, balloon valvuloplasty may be considered. Otherwise, tricuspid valve replacement is the most frequent operation, usually with a bioprosthetic valve to reduce thrombotic risk.

Tricuspid regurgitation

Aetiology

The majority of tricuspid regurgitation (TR) is functionally related to right ventricular dysfunction, usually due to left-sided valve disease, LV dysfunction, or chronic obstructive pulmonary disease. Some TR is due to primary valve disease related to infective endocarditis or rheumatic heart disease.

Important aspects to the management of functional TR include optimization of heart failure medical therapy and adequate rate control for atrial fibrillation if present.

Assessment

Symptoms are usually those of right heart failure. Signs include a pansystolic murmur accentuated by inspiration, a raised JVP, and tender, pulsatile hepatomegaly.

Echocardiography confirms the diagnosis and the severity. Severe TR is associated with:

- Regurgitant volume >45 mL.
- Effective regurgitant orifice area >0.4 cm^2.

Indications for intervention

Intervention is usually considered at the time of surgery for left-sided valve lesions. Aetiology of TR and the extent of symptoms or pulmonary hypertension also guides decisions on intervention (Fig. 24.7).

Tricuspid valve annuloplasty is the surgical intervention of choice for functional TR. In primary valve disease, valve replacement may be required but this carries a high operative morality of between 7–40%.

Transcatheter interventions are now feasible treatment options. Randomized control trial data for tricuspid transcatheter edge-to-edge repair (TEER) demonstrates improved quality of life compared to medical therapy with a neutral impact on mortality and hospitalization.

Key references

Sorajja P, et al. TRILUMINATE Pivotal Investigators. Transcatheter repair for patients with tricuspid regurgitation. *N Engl J Med*. 2023;388:1833–1842.

Tang GH, et al. Tricuspid valve repair with an annuloplasty ring results in improved long-term outcomes. *Circulation*. 2006;114 (Suppl. 1):1577–1581.

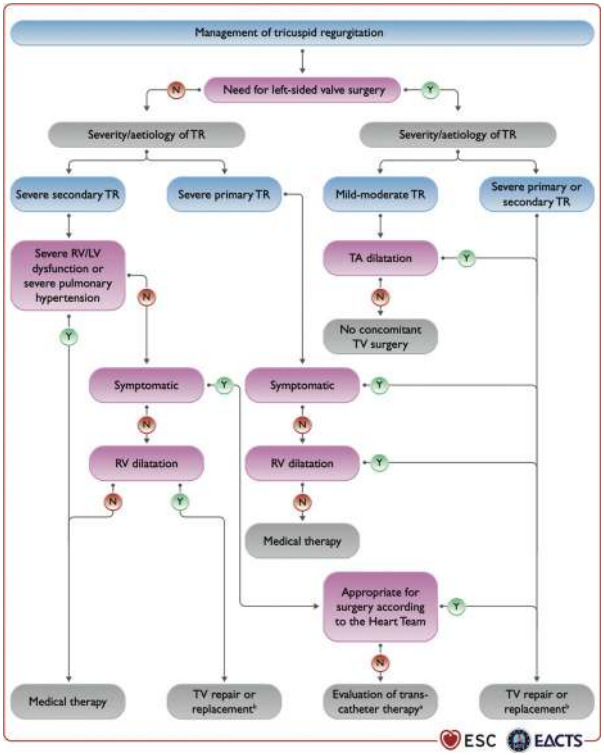

Fig. 24.7 Management of tricuspid regurgitation. LV = left ventricle/left ventricular; RV = right ventricle/right ventricular; TA = tricuspid annulus; TR = tricuspid regurgitation; TV = tricuspid valve. Vahanian A, et al. 2021 ESC/EACTS Guidelines for the management of valvular heart disease. *Eur Heart J*. 2022;43:561–632. By permission of Oxford University Press.

Pulmonary stenosis

Aetiology

The majority of pulmonary stenosis (PS) occurs as congenital heart disease in isolation or as a component of tetralogy of Fallot or Noonan's syndrome. In adults, few patients have symptomatic PS as it is usually mild or moderate, and related to thickening and doming of a morphologically normal valve in the absence of calcification (Table 24.4).

Assessment

Symptoms are usually mild and include breathlessness, progressing to right heart failure. Signs include an ejection systolic murmur in the pulmonary region, augmented by inspiration.

Echocardiography confirms the diagnosis and severity:

Cardiac catheterization is indicated if the transvalvular gradient is >3 ms^{-1}.

Indications for intervention

Percutaneous balloon valvotomy is recommended in symptomatic patients irrespective of gradient if the symptoms are felt to be due to the PS, or in asymptomatic patients with a gradient >64 mmHg with normal RV function. Bioprosthetic pulmonary valve replacement is reserved for patients with a severely dysplastic valve or if balloon intervention is unsuccessful.

Table 24.4 Echo grading of PS

• Mild PS	<3 ms^{-1}
• Moderate PS	3–4 ms^{-1}
• Severe PS	>4 ms^{-1}

Pulmonary regurgitation

Aetiology

Significant pulmonary regurgitation (PR) essentially only occurs in patients with congenital heart disease, e.g. following repair of tetralogy of Fallot. Occasional acquired cases of PR may be the result of infective endocarditis or carcinoid syndrome.

Assessment

Significant PR may present with symptoms of right or left heart failure, or arrhythmias. The murmur is an early diastolic murmur in the pulmonary region accentuated by inspiration.

Echocardiography confirms the diagnosis and the severity of the lesion. Severe PR is defined as the colour flow map of PR filling the RV outflow tract and a dense continuous wave Doppler signal with a short pressure half time (<90 ms).

Indications for intervention

In tetralogy of Fallot a QRS duration >180 ms has been shown to correlate with RV size and predicts malignant ventricular arrhythmias and sudden death. Pulmonary valve replacement (PVR) has been shown to reduce RV end-diastolic volume.

PVR is considered in symptomatic patients with severe PR, or patients with severe PR and progressive enlargement of the RV, or progressive RV dysfunction. In asymptomatic patients the timing of PVR remains unclear.

Transcatheter implantation of pulmonary valves is increasingly used as an alternative to open heart surgery, primarily in patients with congenital cardiac abnormalities and RVOT conduit stenosis/regurgitation.

Key references

Baumgartner H, et al. ESC Scientific Document Group. 2020 ESC Guidelines for the management of adult congenital heart disease. *Eur Heart J*. 2021;42:563–645.

Davlouros PA, et al. Timing and type of surgery for severe pulmonary regurgitation after repair of tetralogy of Fallot. *Int J Cardiol*. 2004;97:91–101.

Section IV

Acute heart failure

Chapter 25

Acute heart failure: from definition to diagnosis

Definition

Acute heart failure (AHF) is the term used to describe the rapid onset of, or change in, symptoms and signs of heart failure. It is life threatening, requires immediate medical attention, and usually results in admission to hospital. It may occur *de novo* or as an acute decompensation of chronic heart failure.

AHF can be classified into four main subgroups according to clinical presentation:

1. Acute decompensated heart failure—the most common AHF presentation. Gradual onset of systemic congestion, typically in patients with previous cardiac dysfunction (across the spectrum of LVEF). Does not fulfil the criteria for cardiogenic shock or acute pulmonary oedema.
2. Acute pulmonary oedema—caused by lung congestion. Dyspnoea with orthopnoea and respiratory failure.
3. Cardiogenic shock—primary cardiac dysfunction leading to reduced cardiac output and tissue hypoperfusion after the correction of preload. Reduced blood pressure (systolic BP <90 mmHg or a drop of mean arterial pressure >30 mmHg) and elevated ventricular filling pressures (PCWP >18 mmHg) with or without evidence of congestion.
4. Isolated right ventricular failure—increased RV and atrial pressure leading to systemic congestion. Systemic cardiac output can be reduced through ventricular interdependence. Increased jugular venous pressure, increased liver size, and hypotension.

Key reference

McDonagh TA, et al. ESC Scientific Document Group. 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. *Eur Heart J*. 2021;42:3599–3726.

Epidemiology

The mean age of an AHF presentation is 72 years in a US registry and 78 in a contemporary UK audit. The aetiology will vary with geography; however, ischaemic heart disease accounts for 60–70% of patients, particularly in the older population. In younger subjects, AHF frequently results from the many forms of dilated cardiomyopathy, arrhythmia, congenital or valvular heart disease, or myocarditis.

The ageing population, combined with the improved survival after acute myocardial infarction, has led to a marked increase in the number of patients currently living with chronic heart failure. Consequently, there has been an increase in hospitalizations for decompensated heart failure. The mortality and morbidity of AHF are high, with a risk of 1-year mortality of up to 37%. Furthermore, the 30-day risk of readmission is as high as 60%. The prognosis of AHF is particularly poor following acute myocardial infarction.

The management of heart failure is estimated to consume approximately 2% of healthcare expenditure in Western countries, with around 75% relating to inpatient care.

Aetiology

There are many underlying conditions that can lead to AHF across the spectrum of clinical presentations (Figs. 25.1 and 25.2). In addition to the underlying cause of the cardiac dysfunction, there is often a precipitant of the actual admission (Table 25.1).

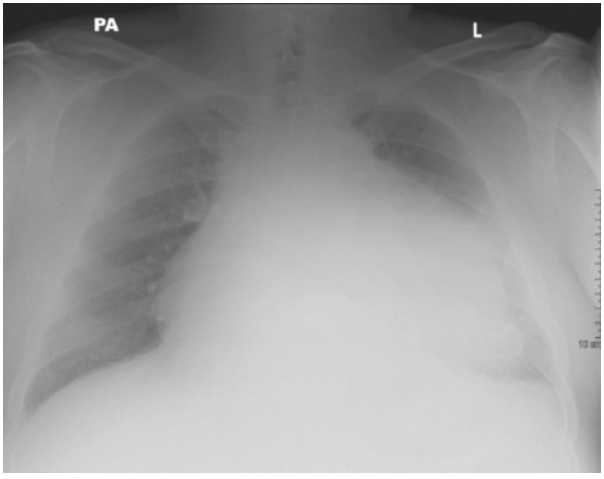

Fig. 25.1 CXR of a pericardial effusion.

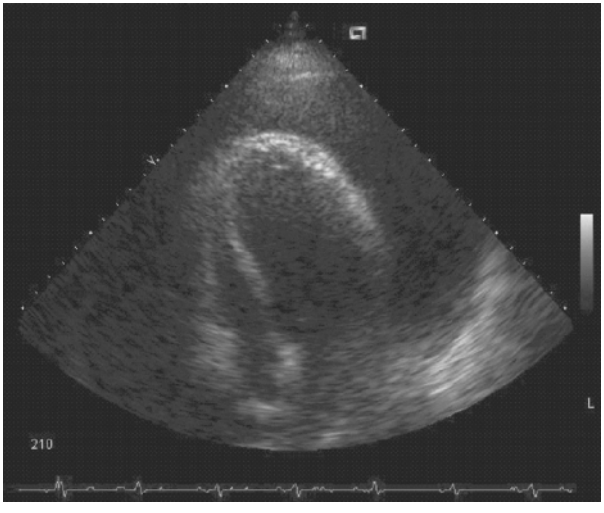

Fig. 25.2 An echocardiogram of a large pericardial effusion with significant collapse of the right ventricle.

Table 25.1 Causes and precipitants of acute heart failure

Events usually leading to rapid deterioration
• Tachyarrhythmia or severe bradycardia/conduction disturbance
• Acute coronary syndrome*
• Mechanical complication of acute coronary syndrome (e.g. ventricular septal defect, acute mitral regurgitation, free wall rupture)
• Acute pulmonary embolism*
• Hypertensive emergency
• Cardiac tamponade*
• Aortic dissection
• Surgery and perioperative problems
• Peripartum cardiomyopathy
• Increased sympathetic drive (e.g. Takotsubo syndrome)
Events usually leading to less rapid deterioration
• Infection (including infective endocarditis)
• Exacerbation of COPD/asthma*
• Severe anaemia
• Non-adherence to diet/drug therapy
• Iatrogenic causes (e.g. prescription of an NSAID or corticosteroid; drug interactions)
• Arrhythmias, bradycardia, and conduction disturbances not leading to sudden, severe change in heart rate
• Uncontrolled hypertension
• Hypothyroidism or hyperthyroidism
• Alcohol and drug abuse

Adapted from: McDonagh TA, et al. ESC Scientific Document Group. 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. *Eur Heart J*. 2021;42:3599–3726.

*Association with right ventricular failure (acute coronary syndrome—right ventricular myocardial infarction).

Pathophysiology of AHF

The key feature of AHF is a failure of the heart to maintain the circulation required for peripheral perfusion.

Many causes of AHF are partly, or wholly, reversible. As ischaemia is the most common precipitant of AHF, it is important to appreciate that cardiac dysfunction due to stunning or hibernation can return to normal when appropriately treated.

Myocardial stunning occurs following prolonged ischaemia and may persist in the short term even when normal blood flow is restored. The intensity and duration of stunning is dependent on the severity and duration of the preceding ischaemic insult.

Hibernation is due to a marked reduction in coronary blood flow despite the cardiomyocytes remaining intact. By improving blood flow and oxygenation, hibernating myocardium can return to normal function.

Clinical features of AHF

Symptoms

- Breathlessness.
- Orthopnoea/PND.
- Oedema.
- Fatigue.

Signs

- Tachycardia (or bradycardia; if this is the cause or, patient β-blocked).
- Hypotensive (or hypertensive in cases of hypertensive emergency).
- Thready rapid pulse.
- Elevated JVP.
- S3 gallop.
- Murmur (e.g. pan-systolic murmur of mitral regurgitation).
- Oliguria.
- Hepatomegaly.
- Ascites.
- Peripheral/sacral oedema.
- Pulmonary congestion with crepitations.

Haemodynamics

Fig. 25.3 describes four haemodynamic categories that the patient may present in based on perfusion status and the presence or absence of congestion: warm and dry, warm and wet, cold and dry, and cold and wet. Patients

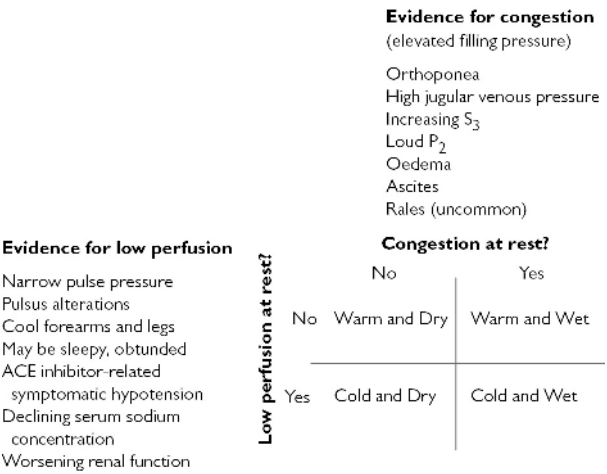

Fig. 25.3 A two-minute assessment of haemodynamic profile. Courtesy of Nohria A, Stevenson LW.

presenting wet and warm or wet and cold are at the highest risk of death or need of urgent cardiac transplantation.

Note that systemic hypotension is not always present in states of hypoperfusion. Young patients in particular can compensate well with low cardiac output and the only clinical sign can be mild confusion.

Killip classification

The Killip classification (Table 25.2) was designed to provide a clinical estimate of the severity of myocardial derangement in the treatment of acute myocardial infarction.

Table 25.2 The Killip classification

Stage I	No heart failure. No clinical signs of cardiac decompensation.
Stage II	Heart failure. Diagnostic criteria include crepitations and S3 gallop.
Stage III	Severe heart failure. Frank pulmonary oedema with crepitations throughout the lung fields.
Stage IV	Cardiogenic shock. Signs include hypotension and evidence of tissue hypoperfusion.

Key reference

Nohria A, et al. Clinical assessment identifies hemodynamic profiles that predict outcomes in patients admitted with heart failure. *J Am Coll Cardiol.* 2003;41:1797–1804.

Non-invasive investigation

The diagnosis of AHF is based on the symptoms and signs mentioned earlier, supported by the following investigations (see Fig. 25.4).

Pulse oximetry (SaO_2)—the pulse oximeter should be used continuously on any unstable patient. It may not transduce in the shocked patient.

ECG—a normal ECG is uncommon in acute heart failure. The ECG should be used to assess the rhythm and may help determine the aetiology of AHF (e.g. acute myocardial infarction). Continuous ECG monitoring is appropriate in these critically ill patients to identify cardiac arrhythmia.

CXR—to evaluate pre-existing chest or cardiac conditions (cardiac size and shape) and to assess pulmonary congestion. CXR allows the differential diagnosis of left heart failure from inflammatory or infectious lung diseases. A CT scan of the chest may be used to identify pulmonary pathology (including pulmonary embolism) or aortic dissection.

Laboratory tests—the following are recommended:

Natriuretic peptides (high negative predictive value)—for example, BNP or NT-proBNP.

- High sensitivity troponin (commonly elevated in AHF, may be helpful to exclude ACS).
- Full blood count.
- Urea and electrolytes.
- Iron status.

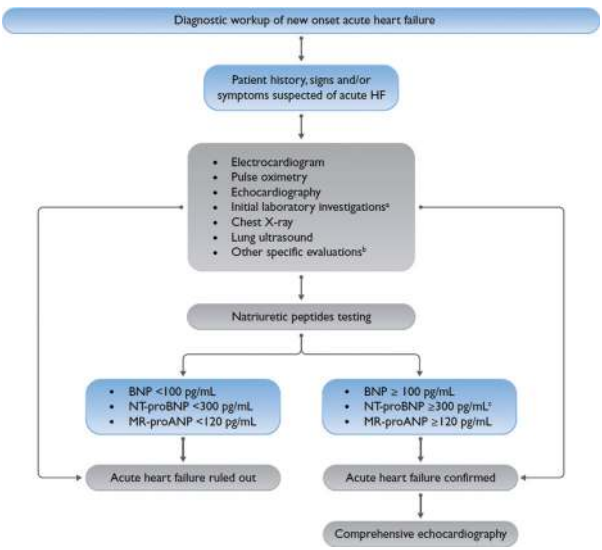

Fig. 25.4 Diagnostic workup of new onset acute heart failure. McDonagh TA, et al. ESC Scientific Document Group. 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. *Eur Heart J*. 2021;42:3599–3726.

- Thyroid function.
- Arterial blood gas (if respiratory failure).
- Lactate (if hypoperfusion suspected).
- INR (if patient anticoagulated or in severe heart failure).
- CRP, procalcitonin (if infection/pneumonia suspected).
- Blood glucose.

Echocardiography—An essential tool to evaluate regional and global ventricular function, as well as an assessment of valvular dysfunction. Echo is also used to diagnose pericardial pathology, and post-myocardial infarction VSDs.

► The diagnosis and management of AHF usually occur in parallel.

Consider

- Measurement of mixed venous O_2 saturation from a central vein estimates the total body oxygen supply–demand balance. A SvO_2 <70% is indicative of a low output state and inadequate tissue perfusion.
- D-dimer (recommended if pulmonary embolism suspected but may be falsely elevated).
- Urinalysis.
- Lung ultrasound (to identify signs of pulmonary congestion).

Invasive investigation

Urinary catheter

Aim for >0.5 mL/kg hourly volume output as an indicator of adequate renal perfusion.

Central venous pressure (CVP)

Right ventricular preload can be assessed from the CVP, with caution needed in the context of significant tricuspid regurgitation, acute right ventricular infarction or pulmonary hypertension (➔ Chapter 27).

Right heart catheterization (RHC)

In critically ill patients, or where the diagnosis is in doubt, an RHC can be helpful (➔ Chapter 28). As well as giving an estimation of left ventricular filling pressure, it can also be used to document cardiac output, pulmonary and systemic vascular resistance, and the presence of an intracardiac shunt.

Invasive arterial monitoring

Used for beat–beat blood pressure monitoring and titration of inotropic/vasodilator therapy. In addition, this facilitates close monitoring of acid status. An intra-aortic balloon pump (➔ Chapter 30) also allows arterial monitoring. In the era of radial approach coronary angiography, where possible, it is best to avoid using the right radial artery for a monitoring line in case of future need for angiography.

Coronary angiography

In the presence of an acute coronary syndrome, angiography, and subsequent revascularization has been shown to reduce mortality.

Chapter 26

Acute heart failure: management

Introduction

Having established the diagnosis of acute heart failure (AHF), the immediate aim is to implement resuscitation. If there is any evidence of airway compromise, including exhaustion or a reduced level of consciousness, an anaesthetic opinion should be sought as a matter of urgency. Thereafter measures should be instituted to stabilize and optimize breathing and circulation, aiming for a systolic pressure >90mmHg to ensure adequate coronary perfusion.

Much of the therapy for AHF to date, has not been subjected to rigorous clinical trial methodology, so much of the treatment remains empirical. Therefore, clinical guidelines incorporate and advocate their use but at a low level of evidence. There are, however, newer therapies and technologies that are currently under investigation.

It should be recognized that the patient with AHF is critically ill and therefore should be cared for by expert staff in a high-dependency environment. Particular care should be taken to minimize the risk of infection and to ensure adequate nutrition with normoglycaemia in diabetic patients.

An algorithm summarizing the immediate treatment of AHF is shown in Fig. 26.1. The various aspects will be discussed in more detail both in this chapter and in the detailed pharmacology (➔ Section VI).

It is also important to avoid certain drugs, which have been shown to worsen the outcome in AHF:

- Calcium antagonists (with the exception of amlodipine and felodipine).
- NSAIDs.
- Steroids.
- Tricyclic antidepressants.

The other common issue in the management of AHF is the role of β-adrenoreceptor antagonists. Patients established on this therapy for HFrEF, who are admitted due to worsening heart failure should be maintained on their current dose, unless inotropic support is needed. The dose could be reduced if signs of excessive dosage are suspected (that is, bradycardia and hypotension). However, there is no role for the initiation of β-adrenoreceptor antagonists in patients with decompensated heart failure. The same is true of RAAS inhibition in the acute setting. Heart failure medical therapy should be initiated once hemodynamically stable and prior to discharge in those with HFrEF (see ➔ Discharge planning).

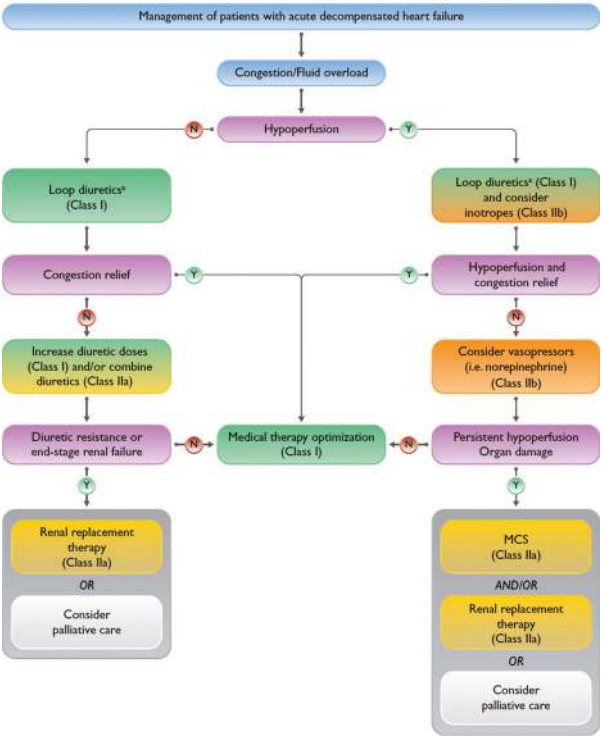

Fig. 26.1 Management of acute heart failure. MCS = mechanical circulatory support. aAcute mechanical cause: myocardial rupture complicating acute coronary syndrome (free wall rupture, ventricular septal defect, acute mitral regurgitation), chest trauma or cardiac intervention, acute native or prosthetic valve incompetence secondary to endocarditis, aortic dissection, or thrombosis. McDonagh TA, et al. ESC Scientific Document Group. 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. *Eur Heart J*. 2021;42:3599–3726.

Oxygen and ventilatory support

For those with oxygen saturations (SaO_2) less than 90% or pO_2 <8 kPa, oxygen therapy should be administered. The use of oxygen for those who are not hypoxic is not recommended due to the risk of vasoconstriction and reduced cardiac output. The maintenance of SaO_2 within the normal range is important to maximize tissue oxygenation.

For those patients who remain hypoxic, are in respiratory distress, or have a rising pCO_2, ventilatory support should be considered. In the first instance, non-invasive ventilation can be used. If the patient has contraindications to non-invasive ventilation or deteriorates despite it, then tracheal intubation and mechanical ventilation should be considered.

Non-invasive ventilation

There are two techniques that are possible options for the management of AHF:

- Continuous positive airways pressure (CPAP).
- Non-invasive positive pressure ventilation (NIPPV).

CPAP uses a tight-fitting mask and valve to deliver high-flow oxygen. CPAP achieves pulmonary recruitment and is associated with an increase in functional residual capacity. The improved pulmonary compliance, reduced transdiaphragmatic pressure swings, and decreased diaphragmatic activity can lead to a decrease in the overall work of breathing, and therefore a decreased metabolic demand from the body.

NIPPV is a more sophisticated technique that requires a ventilator. Addition of a PEEP to the inspiratory assistance results in a CPAP mode (also known as bi-level positive pressure support, BiPAP). The physiological benefits of this mode of ventilation are the same as for CPAP, but also include the inspiratory assist that further reduces the work of breathing and the overall metabolic demand.

CPAP and NIPPV decrease the need for endotracheal intubation, but there is no evidence that this translates into a reduction in mortality or improvement in long-term function. Blood pressure should be closely monitored throughout non-invasive ventilation as increased intrathoracic pressure decreases venous return and may decrease blood pressure.

Invasive mechanical ventilation

Invasive ventilation is indicated where the patient's airway is compromised by reduced conscious level (most commonly due to fatigue) or where there are contraindications to non-invasive ventilation, including facial trauma. Respiratory fatigue manifests as a decrease in respiratory rate, with a rising pCO_2 and confusion.

Invasive mechanical ventilation can be used to facilitate immediate intervention in a patient with pulmonary oedema and ST-elevation myocardial infarction.

Pharmacological therapy

Therapy for heart failure is given to relieve the symptoms and signs of peripheral and/or pulmonary congestion. The therapy given is usually determined by the patient's haemodynamic status (Fig. 26.1).

Diuretics (Chapter 38)

Diuretics are a fundamental treatment in AHF and fluid retention. They act by enhancing the excretion of water and sodium, leading to a decrease in plasma and extracellular fluid volume. Intravenous loop diuretics also exert an early venodilatory effect, prior to their diuretic action. This manifests as a reduction in preload. Diuretics should be used with caution in the acute setting if the systolic BP is <90 mmHg.

Intravenous loop diuretics (furosemide, bumetanide, torasemide) should be given as a bolus and can either be followed up by further boluses or by an infusion. The DOSE trial showed no difference between these two strategies. In those presenting with pulmonary oedema, 50 mg IV furosemide should be given. For those who have peripheral oedema or a known decompensation of chronic heart failure, 1–2× the dose of loop diuretic normally taken should be given IV.

Diuretic response can be evaluated by urine output (aiming for >100–150 mL/h over the first 6 hours) or measurement of urine sodium (aiming for >50–70 mmol/L at 2 hours). If diuretic response is inadequate despite uptitration of IV loop diuretic, combination diuretic therapies can be used, e.g. addition of a thiazide, metolazone, or acetazolamide. This approach can augment diuresis, but careful monitoring of renal function is required.

Inotropic agents and vasopressors (Chapter 40)

Inotropic agents can be considered in patients who, despite initial treatment, have low cardiac output, hypotension, and evidence of hypoperfusion.

► They should only be used in those who have an SBP <90 mmHg.

As discussed in (Chapter 40), there are significant detrimental effects of inotropes which may exacerbate the heart failure syndrome. These include:

- Increased myocardial oxygen demand.
- Altered calcium loading.
- Arrhythmias.

There are few controlled trials with inotropic agents in patients with AHF, and very few have assessed their effects on the symptoms and signs of heart failure and their long-term effects on prognosis.

In AHF, the inotropes most frequently used are **dopamine** and **dobutamine**. Tachycardia may be the limiting factor in the uptitration of these agents. In the presence of hibernating myocardium, dobutamine appears to achieve short-term increased contractility, but at the expense of myocyte necrosis.

The type-3-phosphodiesterase inhibitors (for example, **milrinone** and **enoximone**) are used to treat AHF in specific settings, including postoperative care of cardiac surgical patients.

Levosimendan was hoped to be the solution in inotropic therapy by achieving positive inotropic effect without calcium overload. It is a calcium-sensitizing agent that promotes inotropy by stabilizing troponin

C in a configuration which enhances the calcium sensitivity of cardiac myofilaments. Unfortunately, trials to date have been disappointing. Levosimendan is not currently licensed for use in the UK or USA.

Vasopressors are indicated in AHF when the patient has an optimal filling pressure (CVP 10–14 cmH_2O or PCWP 14–16 mmHg), and the addition of an inotropic agent fails to restore adequate organ perfusion. Caution should be applied as the use of vasopressors may increase the afterload and further reduce end-organ perfusion. **Norepinephrine** is the preferable first-line vasopressor based on a small number of limited trials in cardiogenic shock.

► In acute decompensated heart failure with significant renal dysfunction or hypotension, anti-RAAS therapy may need to be temporarily stopped.

Vasodilator therapy (Chapter 40)

Vasodilators reduce both preload and after-load and can be used to reduce congestion and improve symptoms in AHF if the patient's systolic blood pressure is >110 mmHg. IV vasodilators may be more effective than diuretic alone at treating pulmonary oedema in those with fluid redistribution and increased afterload, but this has not yet been clearly demonstrated in randomized trials. The vasodilators most commonly used in AHF are nitrates, although sodium nitroprusside is also used.

Nitrates

Nitrates exert their effects in a dose-dependent fashion: at low doses they reduce preload by venodilatation then, as the dose is increased, there is the additional effect of reduced afterload by arterial dilation.

Nitrates should be administered with careful BP monitoring. The dose should be reduced if systolic blood pressure falls below 90 mmHg, and discontinued permanently if blood pressure drops further. Caution is required in patients with LVH and/or severe aortic stenosis.

• s/l	2 puffs (400 micrograms) of glyceryl trinitrate every 5 minutes until IV infusion established.
• buccal	1–5 mg of isosorbide dinitrate.
• IV	GTN 20–200 micrograms/minute or isosorbide dinitrate 1–10 mg/hour.

Sodium nitroprusside

Can be used for patients who require a predominant reduction in afterload (for example, hypertensive crisis, acute aortic or mitral regurgitation, or acute VSD). The dose should be titrated cautiously with invasive arterial monitoring. Prolonged administration may be associated with toxicity from its metabolites, thiocyanide and cyanide, and should be avoided especially in patients with severe renal or hepatic failure. As this drug is photosensitive, it requires careful preparation.

Administration: Initially 0.3 micrograms/kg/minute uptitrating slowly to 5 micrograms/kg/minute.

Opiates

The *routine* use of opiates is not recommended due to the risk of respiratory depression. For those who are anxious or distressed intravenous morphine/diamorphine reduces anxiety, as well as the effort of breathing. Morphine induces venodilatation and mild arterial dilatation, and reduces heart rate by an indirect reduction in sympathetic activity. These features reduce both preload and afterload.

An initial dose of 5 mg morphine IV (2.5 mg diamorphine IV) should be given and repeated as necessary, along with an anti-emetic.

Thromboembolism prophylaxis

Patients with AHF are at risk of venous thromboembolism and should therefore be commenced on a low molecular weight heparin, for example, s/c enoxaparin 40 mg/day if renal function is normal (otherwise 20 mg/day) unless already receiving anticoagulation.

Digoxin

Cardiac glycosides produce a small increase in cardiac output and a reduction of filling pressures. However, digoxin is not indicated as an inotrope in AHF because of an associated increase in life-threatening arrhythmias. It is therefore paradoxical that the main indication for digoxin in AHF is to control the heart rate in tachyarrhythmias (e.g. AF with a rapid ventricular rate).

Non-pharmacological therapy

Intra-aortic balloon pump (➔ Chapter 30)

An intra-aortic balloon pump (IABP) can be used to improve coronary artery perfusion and provide haemodynamic support in AHF where initial treatment options have been unsuccessful, and either a definitive treatment is planned or recovery is anticipated. Indications include:

- Post-MI VSD.
- Post-MI mitral regurgitation (for example, papillary muscle infarction).
- Fulminant myocarditis.

Trials have been unable to demonstrate mortality benefit of IABP in post-MI cardiogenic shock and use in this setting is not routinely recommended in guidelines.

Mechanical circulatory support (➔ Chapter 9)

Short-term mechanical circulatory support should be considered in AHF and cardiogenic shock to support cardiac output and organ perfusion if there is the prospect of recovery, long-term support, or cardiac transplantation.

High-quality evidence is lacking and significant complications such as major bleeding and leg ischaemia warrant consideration. In recent years, temporary percutaneous devices have been developed that have the potential to bridge patients with AHF to stability/definitive therapy, while avoiding some of the risks of a major surgical procedure.

Extracorporeal membrane oxygenation (ECMO) uses cardiopulmonary bypass technology to provide prolonged cardiac or respiratory support.

Cardiac transplantation (➔ Chapter 8)

Urgent cardiac transplantation should be considered in patients with cardiogenic shock secondary to fulminant myocarditis or post-myocardial infarction where the prognosis would otherwise be poor.

Ultrafiltration

Ultrafiltration is not a new concept in AHF. However, a portable machine has now been developed with peripheral IV catheters, offering the potential for use of this technique outside of intensive care or dialysis units. To date studies have shown some conflicting results.

In the UNLOAD Trial 200 patients with decompensated CHF were randomized to UF versus usual care (with i.v diuretics). Those in the UF group had significantly greater fluid loss at 48 hours, with a similar effect on creatinine, and a lower readmission rate for HF at 90 days. However, the latest trial to date (CARRESS-HF), studied UF compared to an intensive diuretic regime in 188 patients with decompensated CHF. There was no change in the primary end point of a bivariate change from baseline in the serum creatinine level and body weight at 96 hours.

For now, UF has a modest (IIb C or 'may consider') in the ESC guidelines and should be confined to patients who fail diuretic therapy.

Key reference

Bart B, et al NEJM 2013 Ultrafiltration in decompensated heart failure with cardiorenal syndrome. *NEJM.* 2012;367:2296–2304.

Cardiogenic shock

Cardiogenic shock and acute coronary syndrome (ACS)

Cardiogenic shock is estimated to complicate 7-10% of ACS, usually involving ST-elevation MI, but non-ST-elevation acute coronary syndromes may also be the cause. The majority of cases result from severe left ventricular systolic dysfunction, while others have a mechanical defect (for example, acute VSD, acute RV infarction, or acute papillary muscle rupture). In-hospital mortality remains high at approximately 50%, irrespective of the presence or absence of ST elevation.

The patient with cardiogenic shock in the context of ACS needs to be recognized early and managed aggressively if appropriate to their comorbid condition. Immediate coronary angiography is recommended with a view to coronary revascularisaton of the infarct related or 'culprit' artery. The SHOCK trial included 302 patients with cardiogenic shock within 36 hours of an acute myocardial infarction. They were randomized to emergency revascularization (36% CABG, 64% PCI) or medical stabilization. At 30 days there was no difference in outcome. At 6 months and beyond, there was a statistically significant increased survival in the group that underwent early revascularization. In the CULPRIT-SHOCK trial, an initial primary PCI strategy addressing the culprit lesion only with possible staged revascularization was superior to immediate multivessel PCI. The management of cardiogenic shock is summarized in Fig. 26.2.

Predictors of mortality in AHF and ACS

- Increasing age.
- Previous MI.
- Poor peripheral perfusion at presentation (cold, clammy, and confused).
- Oliguria.
- Delay in pain-to-reperfusion therapy.
- Severe LVSD at baseline echo.
- Moderate or severe mitral regurgitation at baseline echo.

Key references

Byrne RA, et al. ESC Scientific Document Group. 2023 ESC guidelines for the management of acute coronary syndromes. *Eur Heart J*. 2023;44:3720–3826.

Hochman JS, et al. Early revascularization in acute myocardial infarction complicated by cardiogenic shock. *N Engl J Med*. 1999;341:625–634.

Thiele H, et al. PCI Strategies in patients with acute myocardial infarction and cardiogenic shock. *N Engl J Med*. 2017;377:2419–2432.

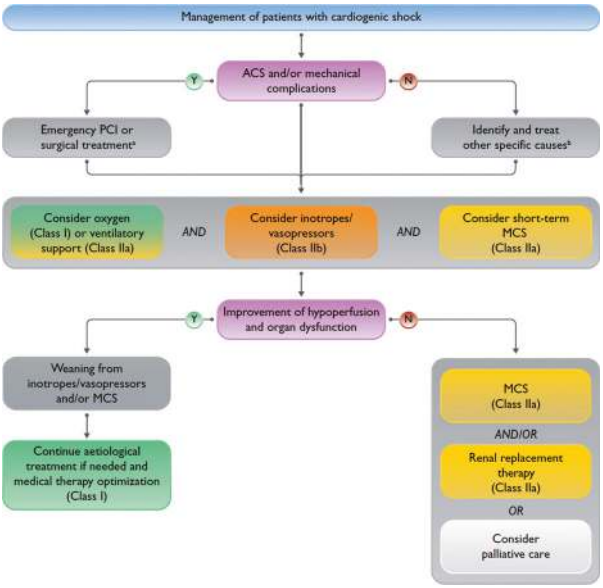

Fig. 26.2 Management of cardiogenic shock. ACS = acute coronary syndrome; BTT = bridge to transplantation; MCS = mechanical circulatory support; PCI = percutaneous coronary intervention. aPCI in ACS, pericardiocentesis in tamponade, mitral valve surgery in papillary muscle rupture. In case of interventricular septum rupture, MCS as BTT should be considered. bOther causes include acute valve regurgitation, pulmonary embolism, infection, acute myocarditis, arrhythmia. McDonagh TA, et al. ESC Scientific Document Group. 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. *Eur Heart J*. 2021;42:3599–3726.

Acute pulmonary oedema

Acute pulmonary oedema can be attributable to a number of conditions:
- Myocardial ischaemia.
- Acute aortic incompetence.
- Acute mitral regurgitation.
- Critical mitral stenosis.
- Hypertensive emergency (for example, secondary to phaeochromocytoma).
- Renal artery stenosis.
- Acute arrhythmia.

Acute pulmonary oedema is often associated with preserved systolic function. The differential diagnosis is:
- Pulmonary embolism.
- Pneumonia.
- Acute respiratory distress syndrome.

Specific investigation and management (see Fig. 26.3)

Hypertensive emergency is characterized by:
- Severe hypertension (BP >180/120 mmHg).
- Fundal changes: retinal haemorrhages, exudates, and papilloedema.
- CNS—headache, confusion, seizures, and coma.
- Renal—oliguria and uraemia.

Patients with AHF due to hypertensive emergency require management in a high-dependency/ intensive care setting with invasive arterial monitoring. Pharmacological therapy includes:
- Diuretics, for example, IV furosemide 50–80 mg bolus ± infusion of 10 mg/hour. It is not recommended to exceed 4 mg/minute except in single doses of up to 80 mg.
- Vasodilatators with nitrate moieties, for example, IV GTN 0.5–10 mg/hour.
- Adrenergic agents, for example, IV labetalol 2 mg/minute infusion.

Renal artery stenosis—recurrent episodes of acute pulmonary oedema in a patient with marked hypertension is an indication for the evaluation for renovascular disease; revascularization by percutaneous angioplasty should be considered if there is a ≥75% stenosis in one or both renal arteries.

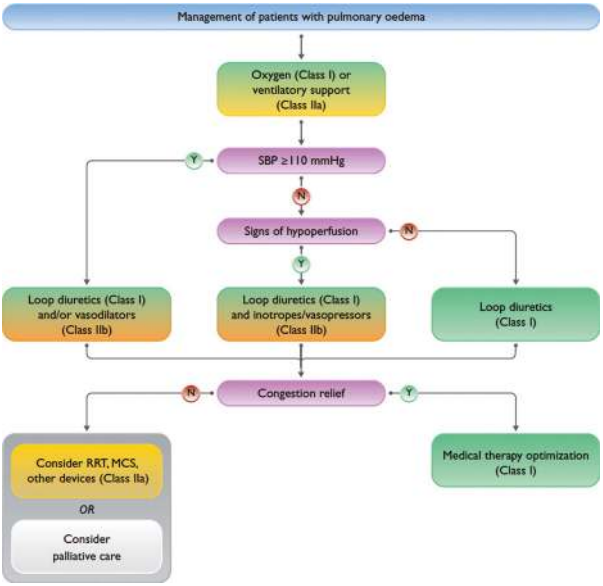

Fig. 26.3 Management of pulmonary oedema. MCS = mechanical circulatory support; RRT = renal replacement therapy; SBP = systolic blood pressure. McDonagh TA, et al. ESC Scientific Document Group. 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. *Eur Heart J*. 2021;42:3599–3726.

Isolated RV failure

RV failure is associated with increased RV and atrial pressure and systemic congestion RV failure may also impair LV filling, and ultimately reduce systemic cardiac output, through ventricular interdependence. The management of isolated RV failure is summarized in Fig. 26.4. Diuretics are often the first option of therapy for venous congestion. Noradrenaline and/or inotropes are indicated for low cardiac output and haemodynamic instability

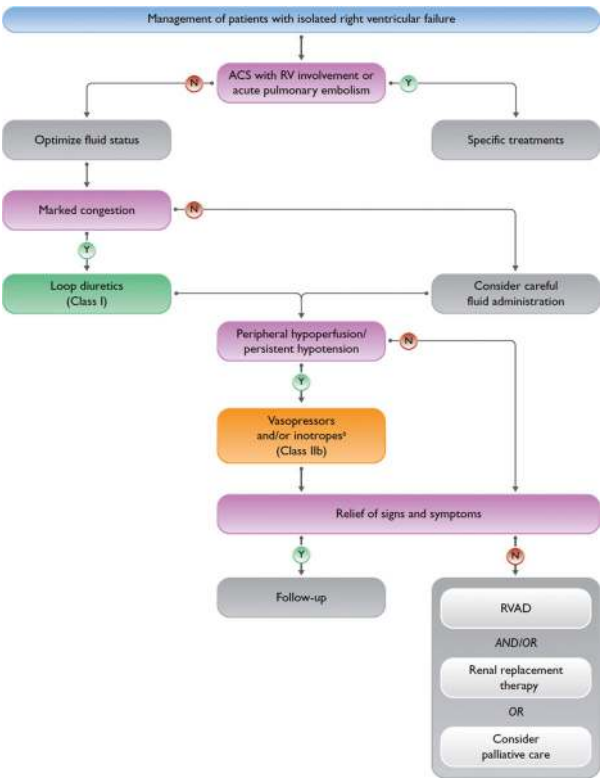

Fig. 26.4 Management of right ventricular failure. ACS = acute coronary syndrome; RV = right ventricular; RVAD = right ventricular assist device. aInotropes alone in case of hypoperfusion without hypotension. McDonagh TA, et al. ESC Scientific Document Group. 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. *Eur Heart J*. 2021;42:3599–3726.

Valvular heart disease and AHF

Acute heart failure can be secondary to valvular conditions (Chapter 24):

- Acute mitral valve incompetence.
- Acute aortic valve incompetence (including aortic dissection).
- Aortic stenosis.
- Mitral stenosis.
- Thrombosis of a prosthetic valve.
- Endocarditis.

In endocarditis, the initial management of the haemodynamically stable patient is conservative therapy with antibiotics. However, urgent surgery is indicated in patients with left-sided endocarditis and cardiogenic shock or pulmonary oedema.

AHF from prosthetic valve thrombosis is associated with a high mortality (between 8 and 20%). If valve thrombosis is suspected and there is evidence of AHF, then the patient should be examined with echocardiography (TTE ± TOE), fluoroscopy, or cardiac CT. Thrombolysis is associated with a risk of embolization of thrombotic material. This may cause pulmonary embolism from right-sided valves, or potentially cause cerebrovascular events from left-sided valves. These risks are in addition to the 'usual' risks of haemorrhage. Thrombolysis is used for right-sided prosthetic valves, and for high-risk surgical candidates. Surgery should be discussed for left-sided prosthetic valve thrombosis, particularly if large (>10 mm) or obstructive, but thrombolysis may be the initial treatment of choice.

The thrombolytics used are:

- Alteplase 10 mg IV bolus followed by 90 mg infused over 90 minutes + unfractionated heparin.
- Streptokinase 1.5 million IU over 60 minutes.

Arrhythmias and AHF

Arrhythmias are common in AHF. These can be either supraventricular (in particular atrial fibrillation) or ventricular. They may be a cause or consequence of AHF and can be life-threatening (see ➔ Chapter 11).

Bradycardias

Bradycardia in AHF patients occurs commonly in inferior myocardial infarction, usually as a result of right coronary artery occlusion. The other frequent cause is iatrogenic from drug therapies, such as digoxin and β-adrenoreceptor antagonists.

The management of haemodynamically significant bradycardia secondary to myocardial infarction is initially atropine (and isoprenaline if necessary), or with the early consideration of temporary pacing in the face of AHF. Digoxin-induced bradycardia should be managed similarly with the withdrawal of digoxin. Rarely, digoxin-specific antibody (e.g. Digibind™) may be required in cases of profound digoxin toxicity. In bradycardia secondary to β-adrenoreceptor antagonists, caution should be employed in stopping this therapy. Rather, the dose should be reduced in the first instance, where possible. However, glucagon can be used in cases of severe β-adrenoreceptor antagonist toxicity, unresponsive to atropine. The dose of glucagon is 2–10 micrograms in 5% glucose followed by an IV infusion of 50 micrograms/kg/hr.

Supraventricular tachycardia

Supraventricular tachycardias such as atrial fibrillation and atrial flutter are often poorly tolerated in patients with AHF, due to the reduction in ventricular filling time. Therefore, the control of the ventricular rate response is important. If haemodynamically compromised, this may be achieved with electrical cardioversion. If haemodynamics allow, then pharmacological cardioversion or rate control should be attempted.

It is important to ensure that patients with haemodynamically stable AF or atrial flutter are anticoagulated prior to cardioversion, unless the duration is <48 hours. The first-line drug of choice in the case of recent onset/anticoagulated is amiodarone; otherwise, rate control can be achieved with digoxin.

► The introduction of β-adrenoreceptor antagonists in decompensated HF is not advised.

Ventricular tachycardia/fibrillation

Ventricular fibrillation and pulseless ventricular tachycardia require immediate electrical cardioversion. Haemodynamically tolerated monomorphic ventricular tachycardia should initially be treated with intravenous amiodarone. Individuals who do not respond to amiodarone therapy should be considered for overdrive pacing, which allows the option of suppression pacing thereafter, or a synchronized shock under sedation/general anaesthetic.

Surgical intervention in AHF

- Ventricular dysfunction
  - Coronary reperfusion in cardiogenic shock and ACS if PCI not feasible.
  - Post-MI ventricular septal rupture.
  - Ventricular free wall rupture.
- Valve disease
  - Acute valve dysfunction.
  - Papillary muscle rupture.
  - Prosthetic valve failure or thrombosis.
- Aortic root disease
  - Type A aortic dissection.
  - Ruptured aneurysm of sinus of Valsalva.

Discharge planning

After stabilization of AHF, steps should be taken to initiate a discharge plan (see chapters 42 and 43). The patient should be free of dyspnoea and clinically euvolaemic. They should be at their dry weight, on oral diuretics with stable renal function, and off intravenous inotropic support for at least 48 hours.

Patients should be initiated on appropriate disease-modifying therapy, and arrangements made for review and uptitration within the following 1–2 weeks. In the STRONG-HF trial, 1078 haemodynamically stable patients who had been hospitalized with AHF were randomized to high intensity medical therapy (early and rapid intensification targeting full dose within 2 weeks of hospital discharge) or usual care. There was a significant reduction in the primary outcome of HF readmission or all-cause death at 180 days in the high intensity treatment group.

Patients should be able to mobilize around the ward, and complete basic activities of daily living. Prior to discharge, time should be invested to educate the patient and their family regarding:

- The heart failure syndrome.
- Fluid and salt restriction.
- Monitoring of daily weights.
- Medication.
- Exercise.

Patients should also be empowered to recognize clinical deterioration and appreciate when to call for help. This can be facilitated by involvement of heart failure liaison nurses.

Key reference

Mebazaa A, et al. Safety, tolerability and efficacy of up-titration of guideline-directed medical therapies for acute heart failure (STRONG-HF): a multinational, open-label, randomised, trial. *Lancet*. 2022;400(10367):1938–1952.

Section V

Procedures

Chapter 27

Central venous cannulation

Introduction

Central venous access is a key skill in the management of an ill patient. The Seldinger technique allows line placement into a variety of locations including veins and arteries but can also be used for catheter placement in body cavities such as pleural and pericardial spaces.

Indications for central vein cannulation include:

- Invasive pressure measurement.
- Pulmonary artery catheterization.
- Temporary pacing line.
- Infusion of inotropes, or anti-arrhythmics (e.g. amiodarone).

The location of a central venous catheter can be:

- Internal jugular vein.
- Subclavian vein.
- Femoral vein.

The internal jugular vein is most often used as, compared to the femoral site, the site can be kept sterile. The internal jugular vein allows the catheter to be inserted under direct ultrasound guidance, thus reducing the potential for complications such as carotid artery puncture or pneumothorax.

Potential complications of central venous cannulation include:

- Bleeding.
- Vascular damage including late vessel stenosis.
- Arterial puncture.
- Pneumothorax (↑ risk with subclavian vein, not with femoral vein!).
- Infection (↑ with femoral vein, ↓ subclavian or internal jugular vein).
- Arrhythmia.
- Air embolism.

Ultrasound guidance should be used for the placement of all central venous catheters.

The technique (Fig. 27.1)

A critical aspect of any invasive procedure is scrupulous attention to aseptic technique. The skin should be prepared and draped after choosing the site of approach. Local anaesthetic should be infiltrated into the skin and subcutaneous tissues. The catheter is flushed in preparation for insertion. The patient is positioned supine ± head down tilt.

- An incision is made in the skin then a needle is inserted into the vein.
- A J-tipped wire is advanced through the needle into the vein.
- The needle is removed leaving the wire in place.
- The skin is dilated with the dilator.
- The catheter can then be gently twisted into position.
- The guidewire is then removed.
- The catheter is sutured and the site covered with a sterile dressing.
- A check CXR should be performed except for femoral venous lines.

▶▶ Never advance the wire against resistance.

▶▶ Always ensure you have control and sight of the guidewire.

➲ Consider anatomy before cannulation in adult congenital heart disease.

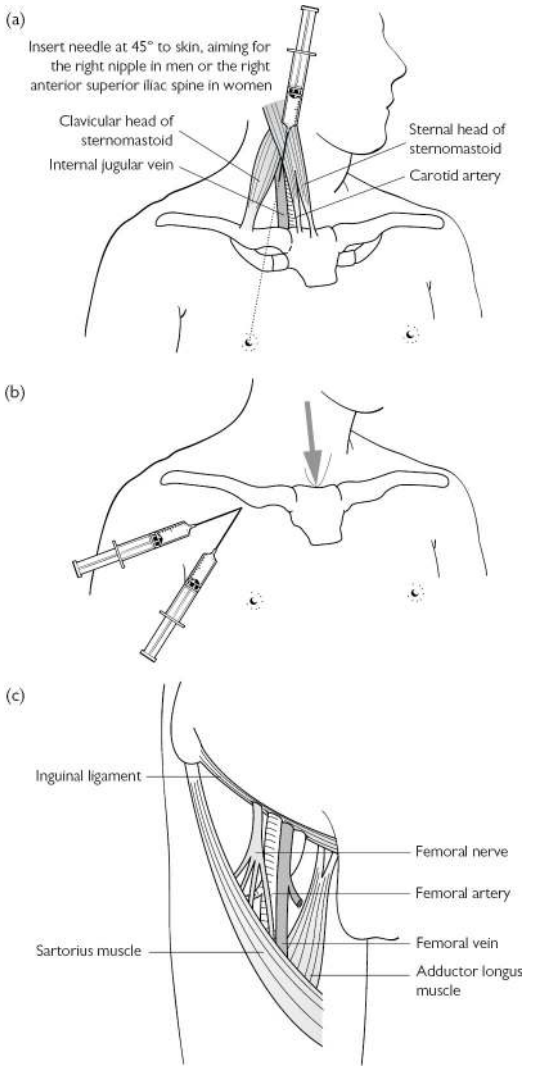

Fig. 27.1 (a) Anatomy of IJV. (b) Anatomy of subclavian vein. (c) Anatomy of femoral vein.

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Measurement of CVP

Following insertion of a central venous catheter into either the subclavian or internal jugular vein, central venous (i.e. right atrial) pressure can be calculated by:

- Connecting the distal port to a pressure monitoring kit (consisting of 500 mL 0.9% saline with 1000 iU of heparin to ensure line patency, pressure transducer, and three-way tap).
- Lie the patient flat.
- Carefully place the transducer at the level of the patient's right atrium—fourth intercostal space in the mid-axillary line.
- Zero the transducer by opening to atmospheric pressure.
- Open the three-way tap to the patient and off to atmospheric pressure.
- Measure CVP at end-expiration.
- A normal CVP is between 0 and 7 mmHg (10–15 cmH_2O).

Right atrial (RA) pressure is elevated in:

- RV infarction/failure.
- Fluid overload.
- Pulmonary hypertension.
- Tricuspid stenosis/regurgitation.
- Pulmonary stenosis.
- Left–right shunts (e.g. VSD).

The right atrial pressure waveform (Fig. 27.2) consists of:

- a wave—right atrial contraction (immediately follows the P wave on ECG).
- x descent—RA relaxation.
- c wave—closure of the tricuspid valve (TV).
- v wave—increasing right atrial pressure during RV systole.
- y descent—rapid fall in RA pressure following the opening of the TV.

Abnormalities of the RA waveform include:

- Cannon a waves are associated with a–v dissociation.
  - Ventricular tachycardia.
  - Ventricular pacing.
  - Complete heart block.
- Tall a waves seen in tricuspid stenosis.
- Tall v waves seen with tricuspid regurgitation.

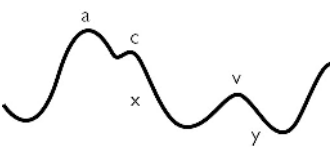

Fig. 27.2 The right atrial pressure waveform.

Chapter 28

Cardiac catheterization

Introduction

Cardiac catheterization is invasive, and hence has the potential to cause patient harm. However, despite advances in non-invasive imaging, there are frequent occasions when invasive investigation is required. Both right and left heart catheterization can offer valuable information about the patient.

Details of coronary angiography are not included, as this is the subject of entire books. Furthermore, there is no evidence base to recommend the routine use of coronary angiography in the diagnostic work-up of patients with heart failure, unless the patient experiences angina (➔ Chapters 7 and 10). However, coronary angiography is often performed at the time of invasive left ventricular assessment when this is felt necessary.

Pulmonary artery catheterization

Pulmonary artery flotation catheters (PACs) are used to measure pressure within the right heart (right atrium, right ventricle, and pulmonary artery), as well as indirectly assessing left atrial pressure (the pulmonary capillary wedge pressure). Furthermore, they can also be used to calculate cardiac output (using thermodilution or Fick equation) and pulmonary and systemic vascular resistance; measure mixed venous oxygen saturation; and detect intracardiac shunts (e.g. ventricular septal defects).

The basic PAC has a balloon for flotation and a single lumen at the catheter tip. The Swan–Ganz catheter for the measurement of cardiac output has at least four ports which include:

- Balloon inflation port.
- Distal port.
- Proximal port (usually in the RA when the catheter tip is in the PA).
- A thermistor (which measures temperature at the distal end of the catheter).

These catheters are ideally suited to be floated from the jugular/subclavian/axillary venous routes, however, with screening, the femoral route is possible (albeit more technically challenging).

Indications

- Cardiogenic shock.
- Pulmonary oedema.
- Right ventricular infarction.
- Shock of uncertain aetiology.
- Postoperative management of cardiac surgical patients.
- Massive pulmonary thromboembolism.
- Established LV systolic dysfunction with sepsis, acute hypovolaemia, or during perioperative care.
- Cardiac transplantation assessment.

Trials to study the benefits of PACs have been difficult to perform because of the extreme heterogeneity of the patient population. Two multicentre prospective trials have been published, which have reduced the use of PACs:

- In an intensive care population that included patients with acute myocardial infarction, the FACTT trial concluded that PACs did not improve survival or organ function but were associated with more catheter-related complications, mainly arrhythmias.
- The ESCAPE trial looked specifically at the use of pulmonary artery catheters in guiding the management of patients with decompensated chronic heart failure and concluded that there was no indication for the routine use of PACs.

PACs should be reserved for the patients being assessed for cardiac transplantation, those in whom there is clinical uncertainty as to their haemodynamic status (for example, right ventricular infarction), and those with established LV dysfunction and acute change in fluid status, for example, bleeding, sepsis, or renal failure.

The optimal filling pressure (PCWP) in the presence of LV systolic dysfunction is 14 mmHg.

Complications of PACs

- Complications of central venous cannulation.
- Arrhythmias—predominantly ventricular.
- Pulmonary haemorrhage.
- Pulmonary artery rupture.
- Pulmonary infarction.
- Valvular trauma—either tricuspid or pulmonary.
- Infection—potentially endocarditis.

Cautions

- Coagulopathy.
- Tricuspid valve disease—contraindicated in mechanical tricuspid valve replacement.

Key references

Binanay C, et al. Evaluation study of congestive heart failure and pulmonary artery catheterization effectiveness: the ESCAPE trial. *JAMA.* 2005;294:1625–1633.

Wheeler AP, et al. Pulmonary artery versus central venous catheter to guide treatment of acute lung injury. *N Engl J Med.* 2006;354:2213–2224.

Technique

The catheter is most easily manipulated through the superior vena cava from the internal jugular vein or the subclavian vein but can be introduced through the inferior vena cava from the femoral vein.

The potential for ventricular arrhythmias, particularly on crossing the tricuspid valve, requires that full resuscitation equipment should be available during manipulation of the PAC. Fluoroscopy should be used to place the PAC.

1. Ensure that IV access is patent, and that ECG monitoring is connected.
2. Insert a central venous introducer sheath into the central vein.
3. Flush all the lumens of the catheter and test the balloon with the required amount of air (usually ~1.5 mL).
4. Connect the pressure line, with the transducer zeroed at the level of the right atrium, to the distal port of the PAC.
5. Insert the catheter 15 cm, then inflate the balloon to assist with transit through the right heart.
6. Advance the catheter—the RV is usually entered with a catheter length of 25–35 cm, and the PA at 40–50 cm. Aim for the pulmonary artery serving the lower third of the lung. Record the waveforms in the RA, RV, and PA (Fig. 28.1). When the PCWP trace appears, stop advancing the catheter and deflate the balloon. If the PA trace does not appear, withdraw the catheter by 2 cm.
7. Gently re-inflate the balloon and measure the PCWP. A stable wedge position allows the catheter to be left in position with a PA trace that then shows a PCWP trace on balloon inflation. Measure PCWP at end-expiration (closest to atmospheric pressure).

►► The balloon should not be left inflated because of the potential for trauma or pulmonary artery rupture.

►► The balloon should not be inflated if resistance is felt.

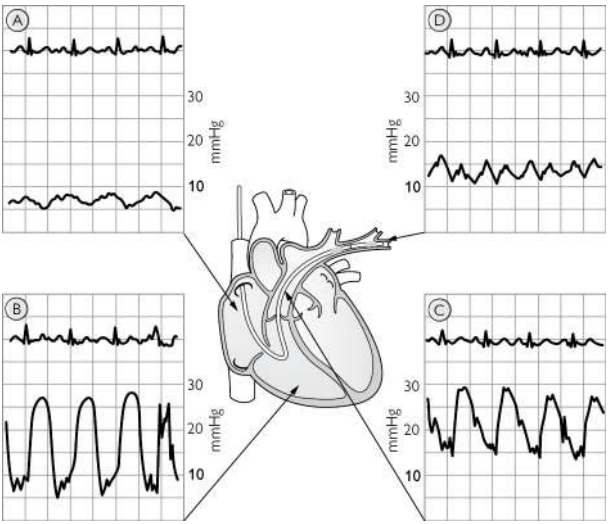

Fig. 28.1 Picture of waveforms.

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Troubleshooting

Difficulty accessing the pulmonary artery or crossing the pulmonary valve

- Try to torque the catheter anticlockwise after it crosses the tricuspid valve.
- Ask the patient to take a deep breath in or cough once the catheter is through the tricuspid valve.

From the femoral route, the catheter may point down into the right ventricular apex—force should not be applied to avoid perforation of the apex. If, despite the manoeuvres described, the tip does not point upwards, then a soft-tipped J-tipped wire (0.025 inch = 0.64 mm diameter) may be introduced to steer the wire up into the right ventricular outflow tract.

Poor wedge trace

A good wedge trace has the left atrial waveform with 'a' and 'v' waves. PCWP cannot be higher than PA diastolic pressure. If the trace continues to rise on balloon inflation, it suggests 'overwedging' and the balloon should be deflated and the catheter withdrawn by 2 cm before re-inflation. If the trace appears damped, the catheter may be kinked.

If balloon inflation fails to alter the trace, the tip may have become displaced and requires re-manipulation, or the balloon may have ruptured requiring replacement of the catheter. Imaging the catheter tip with fluoroscopy may differentiate between these possibilities.

Severe mitral regurgitation results in a prominent systolic wave that may cause the PCWP trace to resemble the PA trace—measure PCWP at the end of the 'a' wave.

Remember that PCWP does not equal left ventricular end-diastolic pressure (LVEDP) in mitral stenosis.

Catheter knotting

- Try to prevent by avoiding excessive catheter loops.
- Do not pull the catheter tight.
- Ask for help.
- Try advancing the catheter and manipulating it with a guidewire.

If unable to untie the knot, do not pull back through the internal jugular veins. A snare may be used to retrieve the catheter through the femoral vein, or vascular surgery referral may be required.

Cardiac calculations

Cardiac output

This technique uses a modification of the Fick principle. A fixed volume (usually 10 mL) of ice-cold saline is rapidly injected into the proximal port of the PAC. The rate of temperature change is detected by the thermistor at the catheter tip, 30 cm distal. A cardiac output monitor needs to be set up with the volume of saline injected and the temperature. At least five measurements should be taken and averaged—more if atrial fibrillation or unstable rhythm. The readings should fall within 10% of each other and those with irregular traces should be discarded (Table 28.1).

Potential errors

- Valve lesions—significant tricuspid regurgitation allows some of the bolus to fall back into the RA making interpretation potentially meaningless.
- Septal defects.
- Leak in the connections.

Mixed venous oxygen saturation

Assuming that there is no intracardiac shunt, mixed venous oxygen saturation can be measured from a pulmonary artery blood sample—this should be taken slowly from the distal port to avoid 'arterialization', that is, pulmonary venous sampling. Normal mixed venous oxygen saturation is 70–75%. Low-output states result in increased tissue oxygen extraction, and so low mixed venous saturation. High mixed venous saturations occur in high-output states including septic shock, or in low-output states where there is a left-to-right shunt, for example, an acquired VSD.

Plasma lactate

In shock, tissue hypoxia prevents aerobic metabolism of pyruvate into water and carbon dioxide. Instead, lactate is formed, and this can be measured offering useful data regarding tissue perfusion. A sample of either venous or arterial blood is collected into a heparin fluoride tube for analysis. Many arterial blood gas analysers now measure lactate as standard. Normal plasma lactate is 0.3–1.3 mmol/L. An initial rise in lactate may be seen after improving tissue perfusion, reflecting the washout from previously hypoperfused tissue.

Vascular resistance

Vascular resistance is the resistance to flow offered by a circulation (primarily small arterioles—'resistance vessels'), and is calculated by the fraction of pressure gradient and mean flow (i.e. cardiac output). Although pulmonary vascular resistance (PVR) is commonly quoted in Wood units, systemic vascular resistance (SVR) is usually measured in absolute units (dyne/s/cm^5), by multiplying by a factor of 79.9. The normal ranges are shown in Table 28.1.

PVR is the resistance to flow offered by the pulmonary vasculature, and relies on the transpulmonary gradient (TPG—the pressure difference between the mean pulmonary artery pressure (PAm) and mean left atrial

Table 28.1 Interpretation of PAC data. (A–V SaO_2 is the difference in arterial and mixed venous oxygen saturations)

Normal values		
Variable		**Normal range**
Stroke volume	SV	70–100 mL
Cardiac output	CO	4–6 L/minute
Right atrial pressure	RAP	0–5 mmHg
Right ventricular pressure	RVP	20–25/0–5 mmHg
Pulmonary artery pressure	PAP	20–25/10–15 mmHg
Pulmonary capillary wedge pressure	PCWP	6–12 mmHg
Mixed venous oxygen saturation	SVO_2	70–75%

Derived variables		
Variable	**Calculation**	**Normal range**
Cardiac index (CI)	Cardiac output/BSA	2.5–3.5 L/minute/m^2
Stroke index (SI)	Stroke volume/BSA	40–60 mL/m^2
Systemic vascular resistance (SVR)	(MAP–RAP × 79.9)/CO	800–1,400 dyne/s/cm^5
SVR Index	(MAP–RAP × 79.9)/CI	1760–2,600 dyne/s/cm^5/m^2
Pulmonary vascular resistance	(PAP–PCWP × 79.9)/CO	25–125 dyne/s/cm^5

	Hypovolaemia	Sepsis	LV failure	RV failure	Tamponade	Acquired VSD
CVP	↓	↓	↑	↑	↑	↑
PCWP	↓	↓	↑	↓	↑	↑
CO	↓	↑	↓	↓	↓	↓
SVR	↑	↓	↑	↑	↑	↑
A-V SVO_2	↑	↓	↑	↑	↑	↓

BSA: body surface area; MAP: mean arterial pressure.

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pressure (LAm)) and cardiac output (CO, in L/min), calculated using the following equations:

$$TPG = PA_m - LA_m \left(\text{or } PA_m - PCWP_m\right)$$

$$PVR = \frac{TPG}{CO}\left(in\,Wood\,Units\right) or$$

$$PVR = \frac{79.9 \times TPG}{CO}\left(dynes/\ sec/\ cm^{-5}\right)$$

- The calculation of PVR is particularly important in the assessment of patients for cardiac transplantation, because an elevated PVR is a risk factor for premature death after transplantation. An elevated PVR is commonly found in patients with chronic HF, particularly in the presence of valvular heart disease, and it may or may not be reversible.
- Irreversible pulmonary hypertension is an absolute contraindication to cardiac transplantation (➔ Chapter 8).

SVR is the resistance offered by the peripheral circulation and is almost invariably raised in patients with chronic HF, due to the activation of the renin–angiotensin–aldosterone and sympathetic nervous systems, as well as the endogenous release of vasoconstrictors such as endothelin. SVR is low in sepsis.

SVR is calculated using the mean aortic and right atrial pressures, and CO in the following equation:

$$SVR = \frac{79.9\,(\textit{mean aortic pressure} - \textit{mean RA pressure})}{\textit{Cardiac Output} \quad (\textit{in dyne.sec.cm}^{-5})}$$

Measurement of left ventricular end-diastolic pressure

The measurement of LVEDP contributes to the assessment of left ventricular filling pressures. The catheter is passed through the aortic valve from an arterial puncture as part of a left heart catheterization study. The traces should be recorded. A normal LVEDP is <12 mmHg. The LVEDP can be elevated because of mitral incompetence, aortic incompetence, ventricular septal defect, or LV systolic dysfunction. The LVEDP can also be elevated if the myocardium is hypertrophied (e.g. hypertensive heart disease, or hypertrophic cardiomyopathy) or restrictive (e.g. myocardial infiltration with amyloid, restrictive cardiomyopathy) (Figs. 28.2 and 28.3).

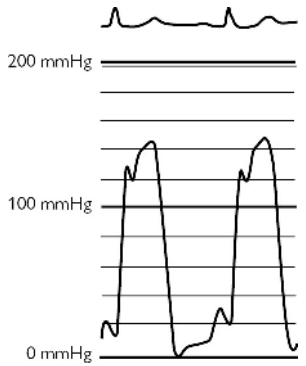

Fig. 28.2 The LV pressure trace with an ECG trace along the top.

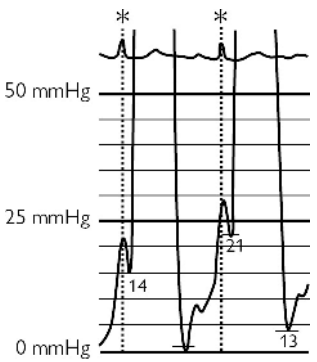

Fig. 28.3 This close-up view of the LVEDP has had the scale modified to ensure accurate measurement. The point to assess the LVEDP is indicated (*)—it is the point of the trace that equates to the peak of the R wave. The mean of several traces should be taken (3 if sinus rhythm, 5 if atrial fibrillation).

Contrast left ventriculography

Prior to cardiac MRI, contrast left ventriculography was considered to be the gold-standard assessment of LVEF. However, as contrast left ventriculography is invasive and uses contrast, and the quality of non-invasive imaging has improved significantly, it is now performed infrequently. It can be useful in cases of uncertainty.

Contrast left ventriculography is performed by passing a pigtail catheter into the LV cavity. Often, an angled pigtail is used to minimize the catheter entanglement in the mitral valve apparatus, and hence reduce ectopy. A power injector is then used to deliver contrast. Typical settings are 30–45 mL of contrast at a rate of 10–15 mL/second. The images are acquired in the following views (ideally with biplane imaging):

- 30° RAO projection.
  - Views high lateral, anterior, apical, and inferior walls.
- 45–60° LAO with 20° cranial tilt.
  - Views lateral and septal walls.
  - Best view to assess for VSD.

Indications for contrast left ventriculography

- Assessment of LVEF in patients with:
  - Ischaemic heart disease.
  - Valvular heart disease.
  - Cardiomyopathy.
- Assessment of regional wall motion abnormalities.
- Identification and assessment of ventricular septal defect.
- Assessment of mitral regurgitation.

Contra-indications to contrast left ventriculography

- Significant left main stenosis.
- Significant aortic valve stenosis.
- Renal impairment.
- LVEDP ≥25 mmHg.
- LV systolic pressure ≥180 mmHg.

Complications of contrast left ventriculography

- Cardiac arrhythmias.
- Intramyocardial staining.
- Embolism.
- Contrast reactions.

The images can be assessed after the procedure, and detailed measurements obtained of ventricular volumes, and hence LVEF, and regional wall motion. LVEF can be calculated from the following equation:

$$\text{(end-diastolic volume} - \text{end-systolic volume)} / \text{end-diastolic volume} \times 100$$

The severity of mitral regurgitation is assessed from the degree of opacification of the left atrium during contrast left ventriculography as illustrated in Fig. 28.4.

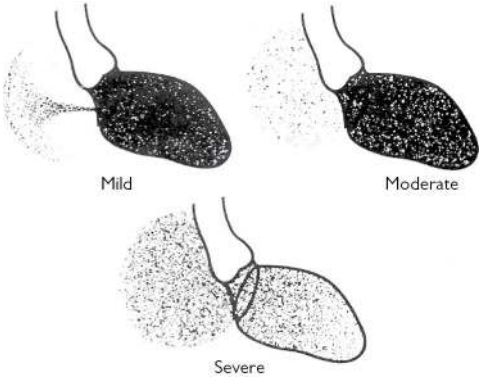

Fig. 28.4 Assessment of severity of mitral regurgitation from contrast left ventriculography.

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Wireless pulmonary artery pressure monitoring

A rise in diastolic pulmonary artery pressure may be one of the earliest signs of congestion. Monitoring devices can be placed in the pulmonary artery to assess pressure remotely using a wireless haemodynamic monitoring system (Fig. 28.5), although this requires patient cooperation as well as motivated clinical staff to review trends in data.

Using such technology, a preliminary trial (CHAMPION) showed a reduction in the risk of recurrent HF hospitalization in US patients with NYHA class III heart failure regardless of ejection fraction. However, a much larger and more contemporary trial (GUIDE-HF) which included NYHA II-IV HF patients did not show that haemodynamic-guided management resulted in a lower composite of mortality and total heart failure events.

Key trials

CHAMPION. Abraham WT, et al. *Lancet*. 2011; 377: 658–666.

GUIDE-HF. Lindenfeld J, et al. *Lancet*. 2021;398:991–1001.

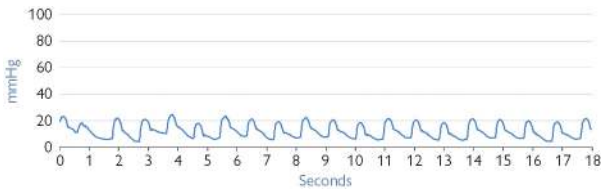

Fig. 28.5 Example of a pulmonary artery pressure trace obtained remotely using a wireless haemodynamic monitoring system.

Chapter 29

Endomyocardial biopsy

Introduction

In 1962, Sakakibara and Konno first reported their experience with transvascular cardiac biopsy (Fig. 29.1). In 1973, Caves et al. first described transvenous endomyocardial biopsy to diagnose cardiac allograft rejection.

There are a few occasions when an endomyocardial biopsy is necessary in patients with chronic heart failure. Rare exceptions are when an infiltrative cardiac condition is suspected, although diagnostic information can often be obtained by other methods. In an acute presentation of new heart failure, endomyocardial biopsy is indicated if giant cell myocarditis is suspected.

Right ventricular endomyocardial biopsies are common practice following cardiac transplantation to identify the evidence of allograft rejection, being traditionally performed weekly for the first 6 weeks, then fortnightly to 3 months, and then every 6 weeks for the remainder of the first postoperative year. However, with modern immunosuppressive regimes, the frequency of endomyocardial biopsies has lessened in many centres. Only in very rare instances is a left ventricular biopsy indicated (e.g. due to multiple previous RV biopsies) due to the risk of systemic embolization.

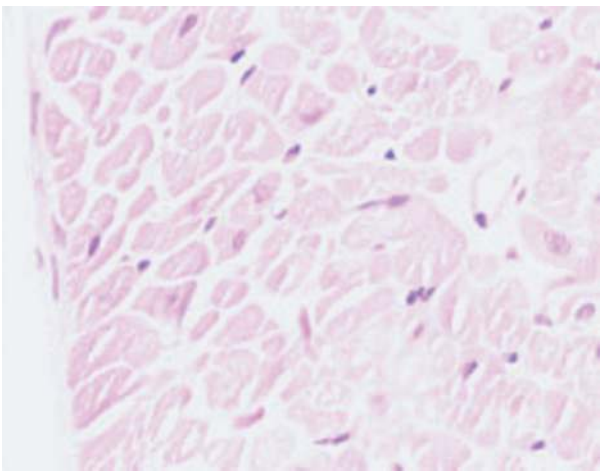

Fig. 29.1 Normal endocardium and myocardium. The endocardium on the left is a thin uniform layer with underlying myocardium that comprises cardiac myocytes, which are closely applied to one another with little intervening stroma that includes small blood vessels. Haematoxylin and eosin ×400. Courtesy of Dr Allan McPhaden, Glasgow (retired).

Indications

- Acute heart failure:
  - Giant cell myocarditis.
  - Hyper-eosinophilic myocarditis.
- Chronic heart failure:
  - Amyloidosis.
  - Sarcoidosis.
  - Haemochromatosis.
  - Chagas.
- Post-cardiac transplantation (rejection surveillance).
- Cardiac tumours.

Potential complications

Total procedural risk of approximately 1%.

- Arrhythmias.
- Tamponade.
- Pneumothorax.
- Conduction disturbance.
- Air embolism.
- Nerve palsy.

Procedure

Generally, a right internal jugular approach is undertaken, although the femoral route can be employed with the use of a long venous sheath (Table 29.1).

► Discuss the case with your pathologist beforehand:

- How many biopsy specimens are required?
- What should the samples be fixed in?
- Insert 7F RIJ sheath with haemostasis valve (➔ Chapter 27).
- Before use, the bioptome must first be checked to ensure:
  - The jaws approximate tightly.
  - The 90° bend lines up with the bioptome handle to aid guidance.
- Ask the patient to stop breathing when putting the bioptome into the sheath (and again when removing).
- Using fluoroscopy, direct the bioptome laterally along the SVC.
- In the mid-RA, rotate the bioptome anteriorly through the tricuspid valve.
- Advance into the RV gradually rotating posteriorly to the RV apex.
- Withdraw the tip slightly when it abuts the endocardium (seen fluoroscopically and felt as slight resistance).
- Open the bioptome jaws.
- Advance again onto the endocardial surface.
- Close the jaws of the bioptome and withdraw briskly but smoothly.
- Gently remove tissue sample from the jaws and place in an appropriate preservative.

For cardiac allograft rejection assessment:

- Four to six biopsy specimens are obtained from each procedure (due to the multifocal nature of rejection).
- Biopsies are fixed in 10% neutral buffered formalin.

Table 29.1 The 2005 revision of the Working Formulation for classification of acute cellular rejection of the heart

Grade	Category	Description
0	No rejection	–
1R	Mild ACR	Multifocal interstitial and/or perivascular mononuclear infiltrates of lymphocytes, some macrophages and occasional eosinophils ± one focus of myocytolysis (Fig. 29.2)
2R	Moderate ACR	Two or more foci of mononuclear cell infiltrates expanding interstitium and with two or more foci of myocyte damage
3R	Severe ACR	Diffuse mononuclear cell infiltrates expanding interstitium ±oedema ± haemorrhage ± neutrophils ± widespread myocyte necrosis ± vasculitis (Fig. 29.3)

ACR = acute cellular rejection; R = revised (avoiding confusion with the grades used in the 1990 Working Formulation).

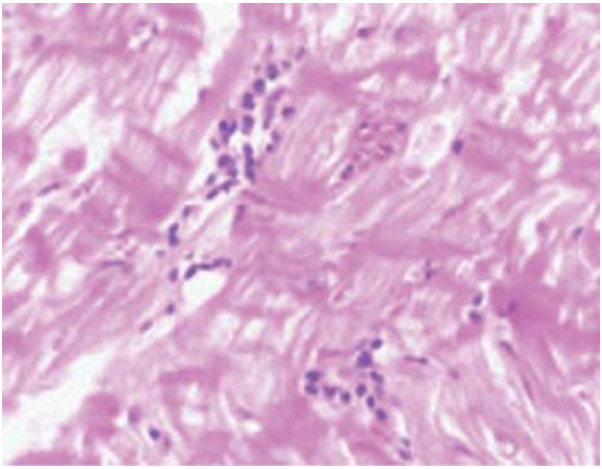

Fig. 29.2 Low-grade cardiac allograft rejection. The myocardium contains small perivascular aggregates of mononuclear cells (ISHLT Grade 1a). Haematoxylin and eosin ×400. Courtesy of Dr Allan McPhaden, Glasgow (retired).

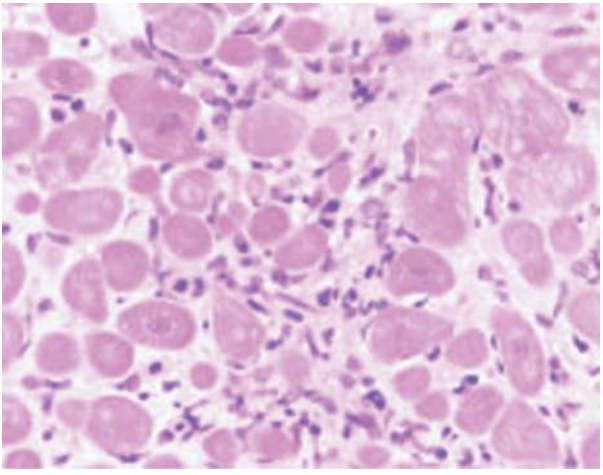

Fig. 29.3 High-grade cardiac allograft rejection. The myocardium contains perivascular aggregates of mononuclear cells with extension into the interstitium associated with multiple foci of cardiac myocyte degeneration. Haematoxylin and eosin ×400. Courtesy of Dr Allan McPhaden, Glasgow (retired).

Chapter 30

IABP insertion

Introduction

An intra-aortic balloon pump (IABP) comprises a 30–50 mL helium-filled balloon (size selected depending on the patient's height), placed in the descending thoracic aorta, and connected to a pneumatic pump. The pump can be triggered from the ECG trace (or less commonly from the pressure trace) and inflates the balloon during diastole, and then rapidly deflates the balloon in systole.

Balloon inflation augments diastolic blood pressure, resulting in improved coronary and cerebral perfusion. Balloon deflation reduces afterload and peripheral vascular resistance and increases stroke volume. Unlike inotropes and vasopressors, the benefits of the balloon pump are not accompanied by an increase in myocardial oxygen demand.

Indications

An IABP can be used to improve coronary artery perfusion and/or provide haemodynamic support in cardiogenic shock of any cause.

- Acute coronary ischaemia resistant to pharmacological therapy ± ventricular arrhythmias ± cardiogenic shock (bridge to PCI or CABG).
- Cardiogenic shock.
- Postoperative in cardiac surgery.
- Acute VSD or mitral regurgitation post-MI.
- Prophylactic use for high-risk PCI[2] or CABG.

Contraindications

- Known aortic dissection.
- Abdominal aortic aneurysm.
- Significant aortic regurgitation.
- Patent ductus arteriosus.
- Severe peripheral vascular disease.

Complications

- Limb ischaemia (5–19%).
- Aortic dissection (<5%).
- Aorto-iliac perforation.
- Infection.
- Haemorrhage.

Insertion

IABP can be inserted using a femoral artery sheath; however, fewer vascular complications occur if a sheathless technique is adopted. The IABP comes in a box complete with the guidewire and pressure and inflation lines. The size of balloon is determined by the patient's height correlated with the sizing chart on the IABP box.

- Prepare the inguinal region overlying the femoral artery for cannulation. Clean the skin down the medial aspect of the leg to the level of the knee. Drapes should cover a wide area to allow room to place the guidewire. Infiltrate the skin around the planned puncture site with local anaesthetic, ensuring adequate local anaesthesia around femoral artery.
- The Seldinger technique is used to cannulate the femoral artery, and then pass the guidewire up the aorta under fluoroscopic screening. The wire should be seen to sit in the aortic arch.
- For sheathless insertion, dilators are used to expand the skin and subcutaneous tissues before the IABP catheter is inserted over the wire into the femoral artery. Alternatively, the sheath provided is sited in the femoral artery and then the IABP catheter is placed.
- The tip of the IABP catheter should be advanced with fluoroscopic guidance until it sits below the left subclavian artery—no reduction in pulse character should be felt at the left radial artery.
- The catheter is then fixed in place with sutures both at the groin, and the shaft of the catheter is sutured to the medial aspect of the leg. The pressure lines and inflation lines should then be connected and the pump commenced.
- Systemic anticoagulation with intravenous heparin should be considered to reduce the risk of arterial thrombosis. The IABP should not be switched off for more than 1 minute at a time to minimize the risk of thrombus formation.

Removal

The heparin infusion should be stopped, and the activated clotting time allowed to fall to <150 seconds. To reduce trauma at the femoral puncture site, the balloon inflation lines should be disconnected before pulling the catheter. As the IABP creates a sizeable hole in the femoral artery, the wound is best compressed with a mechanical clamp for at least 30 minutes. Percutaneous vascular closure devices are routinely used in some centres.

IABP waveforms

Modern IABP have detailed algorithms that optimize the timing of inflation and deflation of the balloon. ECG leads should be connected as inflation is usually triggered by the R wave. In certain situations, the pressure trace may be used to trigger the balloon. Usually the balloon inflates with each cardiac cycle (1:1 augmentation), but this can be reduced to 1:2 or 1:3 augmentation either to allow adequate filling time during tachycardias or to allow weaning of IABP support (Figs. 30.1–30.5).

A patient with an IABP *in situ* requires close observation.

►► If blood is noted in the inflation lines, this indicates that the balloon has ruptured. To prevent the balloon from filling with blood and then clotting, the pump should be stopped and the balloon removed as soon as possible.

A = One complete cardiac cycle
B = Unassisted aortic end diastolic pressure
C = Unassisted systolic pressure
D = Diastolic augmentation
E = Reduced aortic end diastolic pressure
F = Reduced systolic pressure

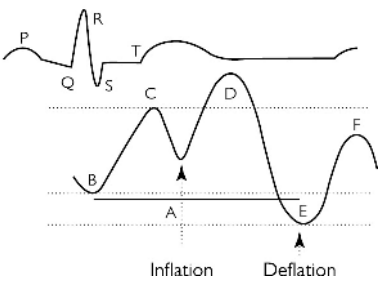

Fig. 30.1 Normal inflation/deflation cycle.

With permission from Maquet.

Inflation of the IAB prior to aortic valve closure

Waveform characteristics:

- Inflation of IAB prior to dicrotic notch.
- Diastolic augmentation encroaches onto sytole, (may be unable to distinguish).

Physiologic effects:

- Potential premature closure of the aortic value.
- Potential increase in LVEDV and LVEDP or PCWP
- Increased left ventricular wall stress or afterload.
- Aortic regurgitation.
- Increased MVO_2 demand.

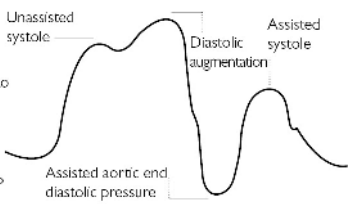

Fig. 30.2 Early inflation of IABP.

With permission from Maquet.

Inflation of the IAB markedly after closure of the aortic valve.

Waveform characteristics:

- Inflation of IAB after the dicrotic notch.
- Absence of sharp V.

Physiologic effects:

- Sub-optimal coronary artery perfusion.

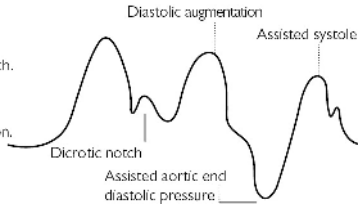

Fig. 30.3 Late inflation of IABP.

With permission from Maquet.

Premature deflation of the IAB during the diastolic phase.

Waveform characteristics:

- Deflation of IAB is seen as a sharp drop following diastolic augmentation.
- Sub-optimal diastolic augmentation.
- Assisted aortic end diastolic pressure may be equal to or less than the unassisted aortic end diastolic pressure.
- Assisted systolic pressure may rise.

Physiologic effects:

- Sub-optimal coronary perfusion.
- Potential for retrograde coronary and carotid blood flow.
- Sub-optimal afer load reduction.
- Increased MVO_2 demand.

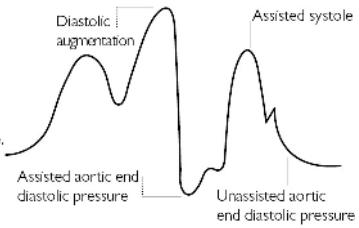

Fig. 30.4 Early deflation of IABP.

With permission from Maquet.

Waveform characteristics:

- Assisted aortic end diastolic pressure may be equal to the unassisted aortic end diastolic pressure.
- Rate of rise of assisted systole is prolonged.
- Diastolic augmentaion may appear widened.

Physiologic effects:

- Afterload reduction is essentially absent.
- Increased MVO_2 consumption due to the left ventricle ejecting against a greater resistance and a prolonged isovolumetric contraction phase.
- IAB may impede left ventricular ejection and increase the afterload.

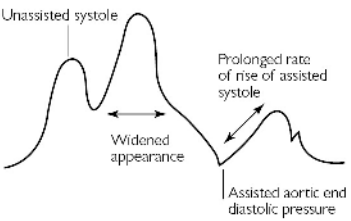

Fig. 30.5 Late deflation of IABP.

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Chapter 31

Cardiopulmonary exercise testing

Introduction

Cardiopulmonary exercise testing (CPET) is a non-invasive, dynamic study that provides an overall assessment of the physiological response to exercise. CPET is a better predictor of exercise performance and functional capacity than resting cardiac and pulmonary parameters. It has also been consistently related to morbidity and mortality.

Indications for CPET in CHF

Assessment of:

- Functional capacity (peak VO_2).
- Exercise-limiting symptoms.
- Breathlessness out-of-proportion to cardiac dysfunction.
- Prognosis.
- Selection for cardiac transplantation.

Measurements

The key measurements made during CPET include:

- VO_2: respiratory oxygen uptake.
- VCO_2: carbon dioxide production.
- RER: respiratory exchange ratio.
- Other ventilatory parameters:
  - Respiratory rate.
  - Tidal volume.
  - Minute ventilation (V_E). (Fig. 31.1).
  - Ventilatory threshold (V_T)—formerly known as anaerobic threshold—is the point at which V_E increases disproportionately to VO_2. It can be used to distinguish between cardiac and non-cardiac dyspnoea.
  - V_E/VCO_2.
  - Pulmonary gas exchange.
- Cardiac parameters including heart rate response.
- Borg scale rating of perceived dyspnoea.

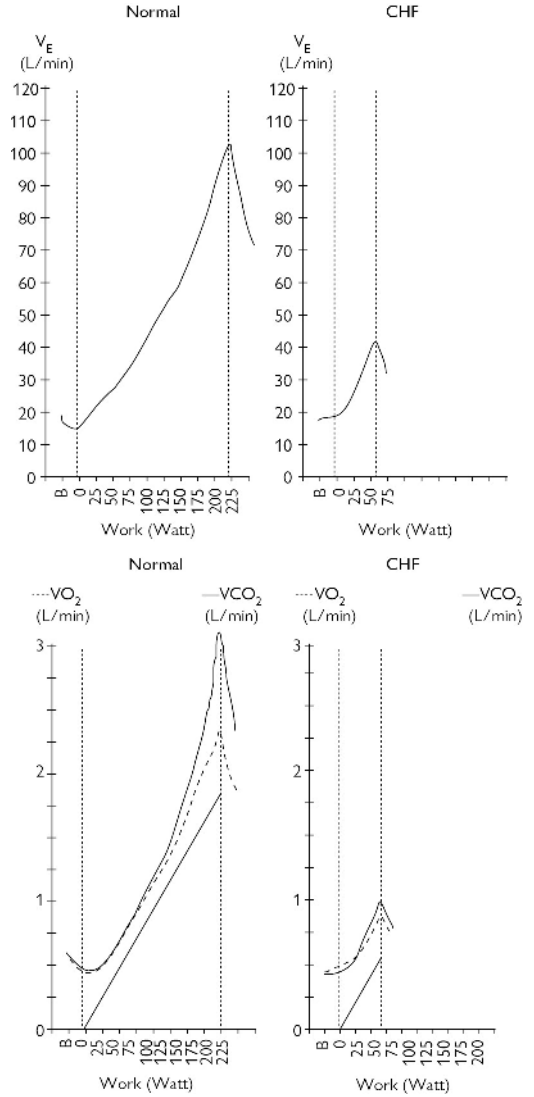

Fig. 31.1 Heart failure is associated with an increase in V_E due to increased dead space ventilation, poor ventilation/perfusion matching, and a reduced workload and peak VO_2. Images courtesy of Dr Roger Carter, Glasgow Royal Infirmary (retired).

Methodology

Patients undergoing a CPET exercise on either a bicycle ergometer or treadmill. They wear a nose clip and breathe through a mouthpiece or a tightly fitting face mask. pO_2 and pCO_2 may be measured by a gas analyser or pulse oximetry if the test is completely non-invasive. VO_2 and VCO_2 are calculated from the differences between inspired and expired gases and ventilatory volumes.

VO_2 max

VO_2 max represents the largest amount of oxygen an individual can use while performing dynamic exercise and is the maximal arterio-venous oxygen difference multiplied by cardiac output. This differs slightly from peak VO_2, which is the highest VO_2 achieved during graded exercise testing. VO_2 max is generally lower in:

- Women.
- Elderly individuals (declines with age).
- Those with a sedentary lifestyle.

VO_2 max is often quoted as a percentage of predicted value based on age, sex, weight, and height. Some would argue that this is a more important prognostic marker than VO_2 max, particularly in young patients.

In the presence of β-adrenoreceptor antagonism, a peak VO_2 ≤12 mL/kg/minute should be used to guide the listing for transplantation. In those intolerant of a β-adrenoreceptor antagonist, a peak VO_2 ≤14 mL/kg/minute should be used. It is important to note that listing for CTx is not solely on VO_2 (Fig. 31.2).

In obese patients (BMI >30 kg/m²), adjusting peak VO_2 to lean body mass may be considered appropriate (using an adjusted cut-off of ≤19 mL/kg/minute).

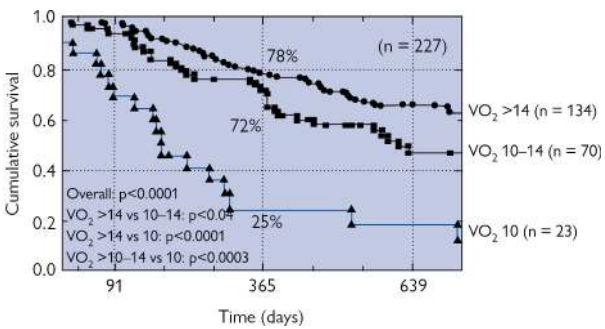

Fig. 31.2 Cumulative survival curves stratified by peak VO_2.

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Respiratory exchange ratio

The respiratory exchange ratio (RER) is the ratio between the CO_2 produced and the O_2 consumed. At rest, the RER is around 0.70–0.85, but to achieve a maximal test the RER should be >1.05 indicating that CO_2 production exceeds O_2 uptake, and that the anaerobic threshold has been exceeded.

Section VI

Detailed pharmacology and evidence base for chronic heart failure

Chapter 32

ACE inhibitors

The renin–angiotensin–aldosterone system (RAAS)

Angiotensin converting enzyme (ACE) inhibitors were first introduced because of their vasodilatory properties. It is now understood that the beneficial effects arise from the antagonism of the RAAS (Fig. 32.1).

As has been mentioned in (➔ Chapter 1), increased RAAS activity causes deleterious effects on the cardiovascular system and contributes to the poor prognosis in HF.

➔ Chapters 33–36 will demonstrate the rationale for the current pharmacological treatment for HF in the antagonism of the RAAS and sympathetic nervous systems.

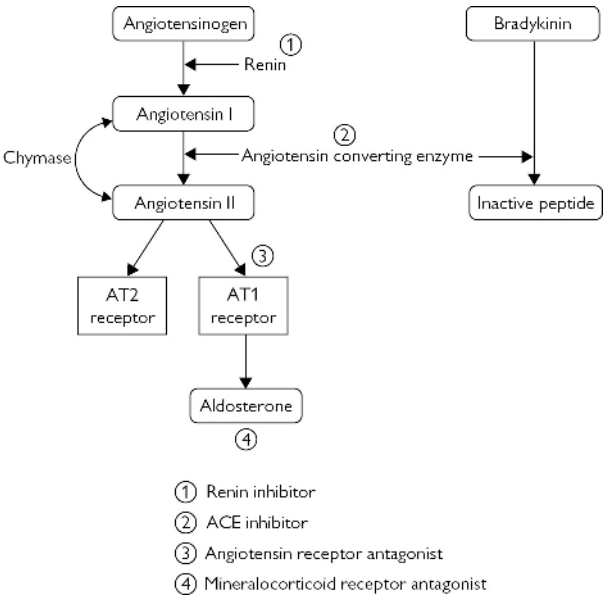

Fig. 32.1 The sites of action of antagonists of the RAAS.

The pharmacology of ACE inhibitors

ACE is a zinc metallopeptidase found on the surface of endothelial and epithelial cells. It leads to the production of angiotensin II and the breakdown of bradykinin. The wide distribution and multiple actions of these peptides suggest that ACE could be involved in various pathophysiological conditions.

It is now understood that ACE concentrations are under genetic control. This was initially thought to be due to an insertion/deletion (I/D) polymorphism in intron 16; however, this is subject to debate and varying opinion. This translates to stable plasma ACE concentrations in the same individual, whereas large interindividual differences are recognized.

The ACE inhibitor, captopril, was first described in 1977, and yet it was not until a decade had passed before the CONSENSUS study identified this class of drug to significantly reduce mortality in patients with severe HF. While current guidelines recommend sacubitril/valsartan (an angiotensin receptor-neprilysin inhibitor (ARNI)) as the initial therapy for patients with HFrEF (NYHA II-IV), ACE inhibitors remain an important therapy if the patient cannot tolerate an ARNI or there is unreliable access to ARNI for all stages of heart failure, as well as in patients with asymptomatic LVSD (Table 32.1).

Pharmacologically, there are three classes of ACE inhibitors:

- An active drug as well as active metabolites (e.g. captopril).
- A pro-drug, activated by hepatic metabolism (e.g. enalapril I enalaprilat).
- Water soluble and renally excreted unchanged (e.g. lisinopril).

Potential benefits of ACE inhibitors include reductions in:

- Myocardial hypertrophy and interstitial fibrosis.
- Atheroma.
- Oxidative stress.

Table 32.1 The pharmacokinetics of ACE inhibitors

ACE inhibitor	Zinc ligand	Pro-drug	Bio-availability (%)	Plasma protein binding (%)	Half-life (hours)	Elimination
Captopril	Sulphydril	No	60–75	30	2–3	Renal
Enalapril	Carboxyl	Yes	60*	50–60*	11	95% renal
Lisinopril	Carboxyl	No	6–60	Low	12	Renal
Perindopril†	Carboxyl	Yes	60	10–20	25–30	75% renal
Ramipril	Carboxyl	Yes	50–60*	56*	13–17	60% renal
Trandolapril	Carboxyl	Yes	40–60*	80–94	16–24	33% renal

* Reflects the data of the active drug.

† No evidence in heart failure.

- Fibrinogen.
- LV remodelling.

In HF, this translates to:

- A reduction in morbidity.
- A reduction in mortality.
- An improvement in LVEF.

How to initiate

(See also ➔ Chapter 5.)

- Recommended in NYHA I–IV HFrEF and asymptomatic LVSD.
- Caution/seek advice before initiation if K >5.0 mmol/L and/or significant renal dysfunction creatinine above 220 micromol/L or eGFR <35.
- Monitor blood pressure and renal function.
  - Aim for systolic BP >90 mmHg.
- Start with a low dose (Table 32.2).
- Double dose every 2–4 weeks if tolerated (could be increased more quickly in hospital with adequate monitoring of blood pressure and renal function).
- Aim for target dose (Table 32.2).

Table 32.2 The titration steps for ACE inhibitors

Drug	Start dose (mg)	Uptitration steps (mg)	Target dose (mg)	Frequency
Captopril	6.25	12.5–25–50	50	tds
Enalapril	2.5	5–10–20	20	bd
Lisinopril	5	10–20–30–40	35–40	od
Ramipril	2.5	2.5	5	bd
Trandolapril	0.5	1–2–4	4	od

► A small dose is better than no dose at all!

Contraindications to initiation

- Angio-oedema.
- Bilateral renal artery stenosis.
- Severe renal failure without renal replacement therapy.
- Hyperkalaemia.
- Pregnancy.
- The following are not absolute contraindications:
  - Moderate renal failure.
  - Moderate aortic stenosis.

Adverse effects

- Cough (5–15%).
- Hypotension.
- Hyperkalaemia.
- Renal dysfunction.
- Angio-oedema.
- Bronchospasm.

There is controversy regarding a possible interaction between aspirin and ACEIs, which might decrease the efficacy of the latter agents, (Hall D. The aspirin-angiotensin converting enzyme inhibitor trade-off: to halve and halve not. *J Am Coll Cardiol.* 2000;35:1808–1812). However, there is no evidence for the long-term use of aspirin in heart failure anyway.

Clinical trial evidence base

Drugs that have been shown to reduce mortality in patients with chronic heart failure or LVSD include:

- Captopril.
- Enalapril.
- Lisinopril.
- Ramipril.
- Trandolapril.

There are a number of large RCTs of ACE inhibitors in patients with HF. The main studies will be highlighted (Table 32.3).

Key references

CONSENSUS trial study group. Effects of enalapril on mortality in severe congestive heart failure. Results of the Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS). *New Eng J Med.* 1987;316:1429–1435.

Køber L, et al. A clinical trial of the angiotensin-converting-enzyme inhibitor trandolapril in patients with left ventricular dysfunction after myocardial infarction. Trandolapril Cardiac Evaluation (TRACE) Study Group. *New Eng J Med.* 1995;333:1670–1676.

Pfeffer MA, et al. Effect of captopril on mortality and morbidity in patients with left ventricular dysfunction after myocardial infarction. Results of the survival and ventricular enlargement trial. The SAVE Investigators *New Eng J Med.* 1992;327:669–677.

Packer M, et al. Comparative effects of low and high doses of the angiotensin-converting enzyme inhibitor, lisinopril, on morbidity and mortality in chronic heart failure. ATLAS Study Group. *Circulation.* 1999;100:2312–2318.

The Acute Infarction Ramipril Efficacy (AIRE) Study Investigators. Effect of ramipril on mortality and morbidity of survivors of acute myocardial infarction with clinical evidence of heart failure. *Lancet.* 1993;342:821–828.

Table 32.3 Summary of ACE inhibitor RCTs in HF/LVSD

Trial (Drug versus placebo)	Number of patients	NYHA class	Mean LVEF (%)	Mean follow-up (years)	Mortality reduction (%)	Withdrawal due to intolerance (% versus placebo)
SAVE Captopril	2231	Post-MI LVSD		3.5	19	—
CONSENSUS Enalapril	253	IV	—	0.5	40	14% versus 17%
SOLVD Enalapril	2569	90% II/III	27	3.4	16	—
ATLAS Lisinopril—Low versus high dose	3164	16% II 77% III 7% IV	23	3.8	—	17% versus 18%
AIRE Ramipril	2006	Post-MI HF	—	1.25	27	35% versus 32%
TRACE Trandolapril	1749	Post-MI LVSD	—	2.4	22	37% versus 36%

Chapter 33

Angiotensin receptor-neprilysin inhibitors

Introduction

Sacubitril/valsartan is the first-in-class angiotensin receptor-neprilysin inhibitor (ARNI) and has become an important component of comprehensive disease-modifying medical therapy in the management of HFrEF.

Sacubitril/valsartan is a combination of two distinct compounds and exhibits a multimodal mechanism of action. LBQ657 (sacubitrilat) is the active metabolite of the prodrug sacubitril and acts to inhibit neprilysin—a neutral endopeptidase which degrades several endogenous vasoactive peptides including the natriuretic peptides. Neprilysin inhibition therefore increases the concentration of beneficial vasoactive peptides, but also angiotensin II—a peptide known to mediate long-term adverse effects on the cardiovascular system. The addition of the angiotensin receptor blockers (ARB) valsartan blocks the angiotensin II type-1 (AT_1) receptor (see Chapter 34), therefore inhibiting the damaging cardiovascular effects of renin-angiotensin-aldosterone system (RAAS) upregulation, while enhancing the cardioprotective response of the natriuretic peptide system.

Initial clinical trials of neprilysin inhibition combined these agents with ACE inhibitors but higher rates of bradykinin-mediated angioedema led to the development of the ARNI drug class, combining neprilysin inhibition with an ARB. In the PARADIGM-HF trial (Prospective Comparison of ARNI with angiotensin-converting enzyme inhibitors (ACEI) to Determine Impact on Global Mortality and Morbidity in Heart Failure), sacubitril/valsartan reduced the primary endpoint of cardiovascular mortality or heart failure hospitalization by 20% compared to treatment with the ACE inhibitor enalapril. Furthermore, there was a reduction in all-cause mortality of 16%. Circulating concentrations of NT-proBNP were significantly reduced at 4 weeks in those taking sacubitril/valsartan, suggesting reduced left ventricular wall stress, as this natriuretic peptide is not a direct substrate of the neprilysin enzyme (Table 33.1).

It is recommended that an ACE inhibitor or ARB be replaced by sacubitril/valsartan in patients with HFrEF who remain symptomatic despite optimal medical therapy. Initiation of ARNI can also be considered as initial therapy in those with HFrEF who are not receiving a RAAS inhibitor.

Table 33.1 The pharmacokinetics of sacubitril/valsartan

ARNI	Active metabolite	Bio-availability (%)	Plasma protein binding (%)	Half-life (hours)	Metabolism and elimination
Sacubitril/valsartan*	Sacubitrilat	60	97	11.5	Sacubitril undergoes ester hydrolysis to form sacubitrilat 52–68% renal excretion

* Valsartan pharmacokinetics Table 34.1

Additional benefits of sacubitril/valsartan vs. enalapril in PARADIGM-HF:
- Reduced incidence of diabetes requiring insulin treatment.
- Reduced decline in eGFR.
- Reduced rate of hyperkalaemia.
- Reduced loop diuretic requirement.

Potential benefits of ARNI include:
- Reduced myocardial hypertrophy and interstitial fibrosis.
- Reverse cardiac remodelling.
- Vasodilation.
- Natriuresis.
- Diuresis.

In heart failure, this translates to:
- A reduction in morbidity.
- A reduction in mortality.
- An improvement in symptoms and quality of life.

How to initiate

- Recommended in ambulatory or hospitalized patients with HFrEF as a replacement for ACEi or ARB, and can be considered as *de novo* therapy in those who are ACEi/ARB naïve.
- If converting from ACE inhibitor to sacubitril/valsartan, the ACEi should be stopped for at least 36 hours prior ('wash out' period to reduce risk of angioedema).
- Start with a low dose and double dose at no less than two-week intervals, aiming for the target dose (Table 33.2).
- Monitor blood pressure.
- Monitor renal function and electrolytes.

NOTE: PARADIGM-HF enrolled those with SBP >95 mmHg. Symptomatic hypotension was more common with sacubitril/valsartan compared with enalapril, but even in those who developed hypotension, there was evidence of clinical benefit.

Table 33.2 Titration steps for ARNI

Drug	Start dose (mg)	Target dose (mg)
Sacubitril/valsartan	49/51* bd	97/103 bd

* 24/26 mg can be used as a starting dose in selected patients (e.g. low blood pressure, RAASi naïve, or CKD)

Contraindications to initiation

- History of angioedema.
- Known bilateral renal artery stenosis.
- Pregnancy or breastfeeding.
- eGFR <30 mL/min/1.73m^2.
- Symptomatic hypotension or SBP <90 mmHg.
- Co-prescription of ACEi or ARB.

Adverse effects

- Hypotension—no change in therapy required if asymptomatic. Dizziness is common and often improves with time. Reconsider the need for other vasodilators and review diuretic use if no signs of congestion.
- Cough—consider alternative causes (lung disease, pulmonary oedema). If the cough is attributed to ARNI, substitution for ARB is recommended.
- Worsening renal function—a small rise in creatinine, K^+, and urea is expected. Review concomitant nephrotoxic drugs. eGFR reduction to no less than 30 mL/min/1.73m^2 and K^+ increase up to 5.5mmol/L is acceptable. If greater than these limits, then ARNI may need to be reduced or stopped—seek specialist advice.

Clinical trial evidence base

Table 33.3 Summary of major randomized controlled trials (RCTs) of sacubitril valsartan in heart failure

Trial	Drug vs. comparator	Number of patients	NYHA class	Inclusion LVEF	Mean LVEF (%)	Median follow-up (years)	Mortality reduction (%)
PARADIGM-HF*	SV vs. enalapril	8442	II–IV	≤40%	29**	2.25	16
PARAGON-HF	SV vs. valsartan	4822	II–IV	≥45%	57	2.9	ns

* Trial stopped early due to clear benefit

** Trial inclusion changed to LVEF <35%

SV, sacubitril valsartan

ns, not significant

NOTE: There is no RCT evidence of mortality benefit of ARNI in HFpEF and the drug class is not licensed for this indication in the UK. However, sacubitril valsartan has been approved in the USA by the FDA for HF and an LVEF less than normal

Sacubitril/valsartan

PARADIGM-HF (Prospective Comparison of ARNI with ACEI to Determine Impact on Global Mortality and Morbidity in Heart Failure)—see Table 33.3.

Key references

Ayalasomayajula S, et al. Clinical pharmacokinetics of sacubitril/valsartan (LCZ696): a novel angiotensin receptor-neprilysin inhibitor. *Clin Pharmacokinet*. 2017;56:1461–1478.

Docherty KF et al. Sacubitril/Valsartan: neprilysin inhibition 5 years after PARADIGM-HF. *JACC Heart Fail*. 2020; 8:800–810.

McMurray JJ, et al. PARADIGM-HF investigators and committees. Angiotensin-neprilysin inhibition versus enalapril in heart failure. *N Engl J Med*. 2014;371:993–1004.

Chapter 34

Angiotensin receptor antagonists

Introduction

The renin–angiotensin–aldosterone system (RAAS) is activated in patients with heart failure and, as mentioned in ➔ Chapter 1, contributes to many of the detrimental effects seen in these patients. The RAAS is not completely blocked by ACE inhibition, since angiotensin II is also produced through the mechanisms distinct from ACE pathways. The development of antagonists to the angiotensin II type-1 (AT_1)-receptor (ARBs) provides a pharmacologically different mechanism of inhibiting the RAAS (Fig. 34.1). In theory, inhibition of the RAAS by blockade of the AT_1-receptor can result in a more complete inhibition of the adverse cardiovascular effects of angiotensin II, while the other potentially desirable actions modulated by different angiotensin II receptors are potentially left unopposed. However, not all the effects of unopposed stimulation of the AT_2-receptor may be beneficial. Unlike ACE inhibitors, ARBs do not inhibit bradykinin breakdown and thus are much less likely to cause side effects associated with ACE inhibitors, such as cough, bronchospasm, and angio-oedema.

The effects of angiotensin II on the principal receptors are:

AT_1 receptor

- Vasoconstriction.
- Sodium and water retention.
- Aldosterone synthesis and secretion.
- Increased vasopressin secretion.
- Cardiac hypertrophy.

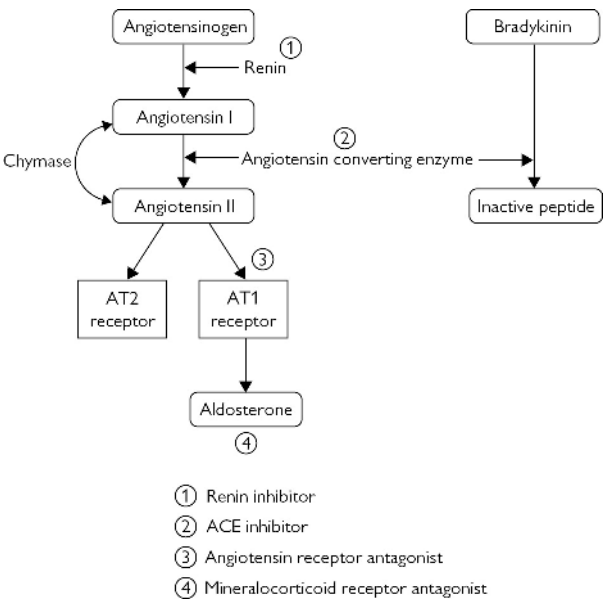

Fig. 34.1 The sites of action of antagonists of the RAAS.

AT_2 receptor

- Inhibition of cell growth.
- Vasodilation.
- Apoptosis.
- Modulation of extracellular matrix.
- Cellular differentiation.

ARBs with an evidence base in CHF

Drugs that have been subject to randomized controlled trials in patients with CHF include (Table 34.1):

- Candesartan.
- Losartan.
- Valsartan.

Table 34.1 The pharmacokinetics of angiotensin receptor antagonists

Angiotensin receptor antagonists	Bioavailability (%)	Plasma protein binding (%)	Half-life (hours)	Metabolism and elimination
Candesartan	34	>99	9	Largely unchanged via urine and faeces
Losartan	33	>99	2 (6–9)†	14% converted to active metabolite; 35% urinary and 58% faecal excretion
Valsartan	23	94–97	1–9	Unchanged in faeces (83%) and urine (13%)
Irbesartan*	60–80	96	11–15	Hepatic metabolism via P450; 80% excreted unchanged in faeces

* Irbesartan does not have an evidence base in patients with HFrEF but is displayed here for comparison.

† Active metabolite.

How to initiate

(See also ➔ Chapter 5.)

- Indicated only in HFrEF patients who are truly ARNI or ACEi-intolerant (unless contra-indication exists).
- No longer the first-choice recommendation in HF patients who remain symptomatic despite optimal treatment with an ACE-inhibitor and beta-blocker. Rather, a mineralocorticoid receptor antagonist is the preferred option due to the data from EMPHASIS-HF and RALES trials (➔ Chapter 35) which demonstrated a further reduction in all-cause mortality. ARB 'add-on' treatment has not shown such an effect and is no longer recommended.
- Start at a low dose and uptitrate (Table 34.2).

Contra-indications to initiation

- Bilateral renal artery stenosis.
- Severe renal failure without renal replacement therapy.
- Pregnancy.

Side effects

- Hypotension.
- Renal dysfunction.
- Hyperkalaemia.
- Hyponatraemia.

Table 34.2 The titration steps for angiotensin receptor antagonists

Drug	Start dose (mg)	Uptitration steps (mg)	Target dose (mg)	Frequency
Candesartan	4	8–16	32	od
Losartan*	25	50	100	od
Valsartan	40	80	160	bd
Irbesartan†	75	150	300	od

* Target dose in ELITE and ELITE II was 50 mg od.

† Irbesartan does not have an evidence base in HF but is being shown here for comparison.

Clinical trial evidence base

There are a number of large RCTs of angiotensin receptor antagonists in patients with CHF. The main studies will be highlighted (Table 34.3).

Table 34.3 Summary of RCTs of angiotensin receptor antagonists in HFrEF

Trial (Drug versus placebo, or active comparator)	Number of patients	NYHA class (%)	Mean LVEF (%)	Mean follow-up (years)	Mortality reduction (%)	Increase in LVEF (%)	Withdrawal due to intolerance (% versus placebo)
CHARM-Overall Candesartan	7599	45 II 52 III 3 IV	39	3.1	9*	–	23 versus 19
CHARM-Alternative Candesartan	2028	47 II 49 III 4 IV	30	2.8	17†	–	24 versus 22*
CHARM-Added Candesartan	2548	24 II 73 III 3 IV	28	3.4	–	–	25 versus 18
CHARM-Preserved Candesartan	3023	61 II 37 III 2 IV	54	3.0	–	–	22 versus 18
ELITE Losartan versus captopril	722	65 II 34 III 2 IV	31	0.9	–	–	18.5 versus 30
ELITE II Losartan versus captopril	3152	52 II 43 III 5 IV	31	1.5	–	–	10 versus 15
HEAAL High dose vs. low dose Losartan	3846	69 II 30 III 1 IV	33	4.7	–	–	1.99 versus 1.83
Val-HeFT Valsartan	5010	62 II 36 III 2 IV	27	1.9	–	4.5 versus 3.2	9.9 versus 7.7

* Not significant.

† Adjusted figures.

Candesartan

CHARM-Overall (candesartan in heart failure: assessment of reduction in mortality and morbidity)

CHARM-Alternative

CHARM-Added

CHARM-Preserved

Losartan

ELITE (evaluation of losartan in the elderly study)
ELITE II (evaluation of losartan in the elderly study)
HEAAL (evaluation of losartan in the elderly study)

Valsartan

Val-HeFT (valsartan-heart failure trial)

Chapter 35

Beta-adrenoreceptor antagonists

The adrenoreceptors

The concept of adrenoreceptors can be dated back to Langley in 1905. The theory of reducing myocardial oxygen demand in angina by antagonizing the β-adrenoreceptor was conceived by Sir James Black, led to his invention of pronethalol and propranolol between 1959 and 1962. Since then, many more such compounds have been created with differing affinities for the adrenoreceptors (Table 35.1), which have subsequently been classified as:

Table 35.1 Actions of commonly used β-adrenoreceptor antagonists in CHF

Drug	α_1	β_1	β_2	Other properties
Bisoprolol	–	+++	–	–
Carvedilol	+	++	+	Antioxidant
Metoprolol	–	++	–	–
Nebivolol	–	++	–	Activate nitric oxide

α_1-adrenoreceptors

- Post-synaptic.
- Stimulation causes peripheral vasoconstriction and venoconstriction.

α_2-adrenoreceptors

- Pre-synaptic.
- Stimulation causes pre-synaptic sympathetic inhibition.

β_1-adrenoreceptors

- Found mainly in the heart, intestine, and renin-secreting tissue of the kidney.
- Stimulation causes positive chronotropy and inotropy and increased a–v conduction.

β_2-adrenoreceptors

- Present predominantly in bronchial and vascular smooth muscle.
- Also found in GI tract, uterus, pancreas, and heart.
- Stimulation causes bronchial dilatation and peripheral vasodilatation.

The heart contains β-adrenoreceptors in the ratio 70% β_1:30% β_2.

The sympathetic nervous system in heart failure

Deleterious effects of the sympathetic nervous system in heart failure

- ↑ HR, contractility.
- Electrical instability.
- Apoptosis.
- Myocardial toxicity.
- LV dilatation and hypertrophy.
- Renin release.

Mechanism of action of β-adrenoreceptor antagonism in CHF

- Reduction in:
  - Renin release.
  - Angiotensin-II and aldosterone.
  - Myocardial oxygen demand.
  - Catecholamine-induced free fatty acid release from adipose tissue.
  - Myocardial oxidative stress.
- Improvement in cardiac function.
- Anti-arrhythmic effect.

Proven benefits of β-adrenoreceptor antagonism in CHF

- Reduction in all-cause mortality.
- Reduction in sudden cardiac death and pump failure.
- Improvement in left ventricular ejection fraction.
- Improvement in medium–long-term morbidity (with the possibility of short-term deterioration).
- Reduction in hospitalization.
- Reduction in the need for cardiac transplantation.
- May reduce cases of new-onset diabetes mellitus.

Pharmacokinetics

The major determinant of the pharmacokinetics of β-adrenoreceptor antagonists is their lipid solubility (Table 35.2).

Table 35.2 The pharmacokinetics of β-adrenoreceptor antagonists

β-blocker	Bio-availability (%)	Plasma protein binding (%)	Lipid solubility	Half-life (hours)	Metabolism and elimination
Bisoprolol	90	30	Moderate	10–12	50% hepatic metabolism; renal excretion
Carvedilol	25	98	Moderate	6–10	Extensive hepatic metabolism; faecal excretion
Metoprolol	50–75	12	Moderate	3–7	Hepatic metabolism; faecal excretion
Nebivolol	12–100	98	High	10–50	Hepatic metabolism; faecal excretion
Atenolol*	50	10	Low	6–10	Renal excretion

►* Atenolol does not have an evidence base in patients with chronic heart failure but is displayed here for comparison. Patients with CHF may be already on this drug. However, readers are encouraged to practice evidence-based medicine.

Lipophilic β-adrenoreceptor antagonists (e.g. nebivolol) are generally:
- Well absorbed from the GI tract.
- Metabolized in the liver.
- Large volume of distribution (Vd), including across the blood–brain barrier (therefore can cause sleep disturbance).
- Highly protein bound.
- Short-acting.

Hydrophilic β-adrenoreceptor antagonists (e.g. atenolol) are generally:
- Less well absorbed from the GI tract.
- Excreted virtually unchanged by the kidney (therefore caution in renal impairment).
- Lower volume of distribution (in particular, less likely to cross blood–brain barrier).
- Low protein bound.
- Longer acting.

How to initiate

(See also ➔ Chapter 5.)

- Recommended in NYHA I–IV CHF.
- Patients should be euvolaemic.
- 'Start low, go slow'.
- Monitor heart rate, blood pressure, and for signs of fluid retention.
  - Aim for pulse >50/min and systolic BP >90 mmHg.
- Double dose every 1–4 weeks if tolerated.
- Aim for target dose (Table 35.3).

► A small dose is better than no dose at all!

Table 35.3 The titration steps for β-adrenoreceptor antagonists

Drug	Start dose (mg)	Uptitration steps (mg)	Target dose (mg)	Frequency
Carvedilol	3.125	6.25–12.5–25–50*	25/50*	bd
Bisoprolol	1.25	2.5–5–7.5–10	10	od
Metoprolol†	12.5†/25	25–50–100–200	200 CR/XL	od
Nebivolol	1.25	2.5–5–10	10	od

* Where patient is >85 kg.

† Evidence base is only for metoprolol succinate not tartrate, which is the shorter-acting preparation available in the United Kingdom.

Contra-indications to initiation

- Asthma.
- Significant bradycardia (<50/min).
- Mobitz type II or complete heart block.
- Cardiac decompensation.
- The following are not absolute contra-indications:
  - COPD without significant reversibility.
  - PVD.

Adverse effects

- Bradycardia/heart block.
- Hypotension.
- Cold extremities.
- Fluid retention (treat with diuretics).
- Fatigue.
- Masking of symptoms of hypoglycaemia.
- Initial worsening of symptoms including breathlessness (often improves).
- Sexual dysfunction.
- Sleep disturbance (particularly lipophilic drugs).

⚠ Abrupt discontinuation

Due to the upregulation of β-adrenoreceptors during treatment with β-adrenoreceptor antagonists, abrupt discontinuation can lead to:

- Arrhythmia.
- Exacerbation of angina.
- Worsening pump failure.
- Reflex hypertension.

Clinical trial evidence base

The β-adrenoreceptor antagonists that have been shown to improve outcome in patients with chronic heart failure include:

- Bisoprolol.
- Carvedilol.
- Metoprolol (succinate).
- Nebivolol.

There are a number of large RCTs of β-adrenoreceptor blockade in patients with CHF. The main studies are highlighted (Table 35.4).

Bisoprolol

CIBIS (cardiac insufficiency bisoprolol study). *Circulation*. 1994;90: 1765–1773.
CIBIS-II (cardiac insufficiency bisoprolol study II). *Lancet*. 1999;353:9–13.

Carvedilol

US Carvedilol. Packer M, et al. *N Engl J Med*. 1996;334:1349–1355.
Australia/New Zealand. *Lancet*. 1997;349:375–380.
MOCHA. Bristow MR, et al. *Circulation*. 1996;94:2807–2816.
COPERNICUS (carvedilol prospective randomized cumulative survival study). Packer M, et al. *N Engl J Med*. 2001;344:1651–1658.
COMET (carvedilol or metoprolol European trial). Poole-Wilson P, et al. *Lancet*. 2003;362:7–13.

Metoprolol

► Evidence base is only for metoprolol succinate not tartrate, which is the shorter-acting preparation available in the United Kingdom.
MERIT-HF (metoprolol CR/XL randomized interventional trial in heart failure). *Lancet*. 1999;353:2001–2007.

Nebivolol

SENIORS (study of the effects of nebivolol intervention on outcomes and re-hospitalization in seniors with heart failure). Flather M, et al. *Eur Heart J*. 2005;26:215–225.

Table 35.4 Summary of RCTs of β-adrenoreceptor antagonists in CHF

Trial (drug versus placebo)	Number of patients	NYHA class	Mean LVEF (%)	Mean follow-up (years)	Mortality reduction (%)	Increase in LVEF (%)	Withdrawal due to intolerance (% versus placebo)
CIBIS Bisoprolol	641	95% III 5% IV	25	1.9	–	–	23 versus 26
CIBIS-II Bisoprolol	2647	83% III 17% IV	28	1.3	34	–	15 versus 15
US Carvedilol	389	85%II 15% III	23	0.6	77	10	7.3 versus 10.4
Aus/NZ Carvedilol	415	30% I 54% II 16% III	28	1.6	–	5.3	17.6 versus 14.6
MOCHA Carvedilol	345	46% II 52% III 2% IV	23	0.5	73	8*	11 versus 13
Copernicus Carvedilol	2289	IV	19	0.9	39	–	14.8 versus 18.5
COMET Carvedilol versus metoprolol	3029	48% II 48% III 4% IV	26	4.8	17	–	32 versus 32
MERIT-HF Metoprolol	3991	41% II 55% III 4% IV	28	1.0	34	–	9.8 versus 11.7
SENIORS Nebivolol	2128	3% I 56% II 39% III 2% IV	36	1.8	–	–	26.7 versus 24.6

* In a dose-response manner with greatest improvement on 25 mg bd.

Chapter 36

Mineralocorticoid receptor antagonists (MRAs)

Introduction

The final process in the renin–angiotensin–aldosterone system (RAAS) is the production of the mineralocorticoid aldosterone in the adrenal glands (Fig. 36.1). Aldosterone has an important role in the pathophysiology of heart failure, and concentrations of aldosterone are 20-fold higher in patients with HF compared to normal individuals. By acting on the distal convoluting tubule and collecting ducts in the kidney, aldosterone is a major regulator of extracellular fluid volume. It promotes the re-absorption of sodium and is an important determinant of potassium and magnesium excretion. Aldosterone also causes sympathetic activation, parasympathetic inhibition, myocardial and vascular fibrosis, baroreceptor dysfunction, and impairment of arterial compliance.

It is well known that ACE inhibitors and ARBs only transiently suppress the production of aldosterone. Other mechanisms are involved in the mechanism of aldosterone release, including the response of the adrenal cortex to changes in K^+ concentration, as well as the action of adrenocorticotrophic hormone (ACTH). This has led to the successful trial of mineralocorticoid receptor antagonists (previously known as aldosterone antagonists) in patients with symptomatic chronic HFrEF and symptomatic HFrEF following myocardial infarction.

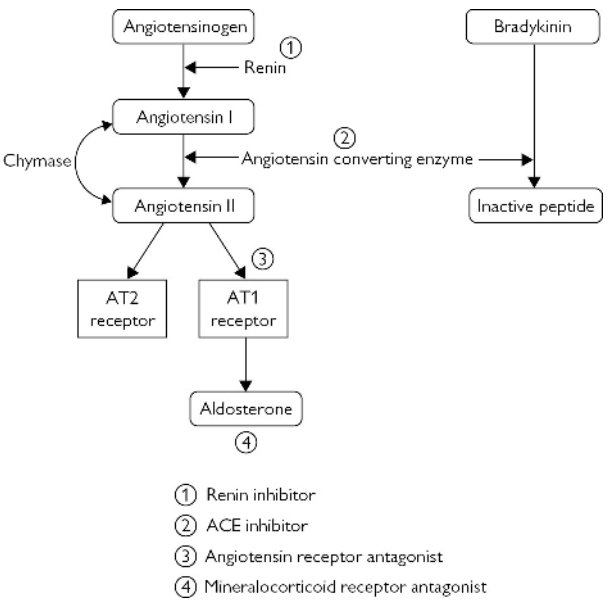

Fig. 36.1 The sites of action of antagonists of the RAAS.

Proven benefits of aldosterone antagonism in HF

- Reduction in mortality.
- Reduction in hospitalization for worsening HF.
- Improvement in functional class.

MRAs with an evidence base in HF

Mineralocorticoid receptor antagonists—MRAs (aldosterone antagonists) are now considered as a 'Core-4' therapy for patients with HFrEF (Table 36.1).

MRAs that have been subject to randomized controlled trials in patients with HF and post-MI HF are:

- Spironolactone—NYHA classes III/IV.
- Eplerenone—NYHA class II, and post-MI heart failure with LVSD.

These MRAs:

- Increase sodium excretion.
- Reduce potassium loss at distal renal tubule.
- Reduce oxidative stress.
- Improve endothelial function.
- Attenuate platelet aggregation.
- Decrease activation of matrix metalloproteinases.
- Improve ventricular remodelling.
- Improve heart-rate variability.

Pharmacology

Spironolactone

- Competitive aldosterone antagonist.
- Also binds to androgen and progesterone receptors, therefore can cause gynaecomastia and impotence among men.
- Well-absorbed orally.
- Principally metabolized to active metabolites: sulphur-containing metabolites (80%) and canrenone (20%).
- Although the plasma half-life of spironolactone itself is short (1.3 hours), the half-lives of the active metabolites are longer (2.8–11.2 hours).
- Elimination of metabolites occurs primarily in the urine and secondarily through biliary excretion in the faeces.
- The renal action of a single dose of spironolactone reaches its peak after 7 hours, and activity persists for at least 24 hours.

Eplerenone

- Competitive selective MRA (greater selectivity for the mineralocorticoid receptor than spironolactone).

Table 36.1 Pharmacokinetics of the mineralocorticoid receptor antagonists

Mineralocorticoid receptor antagonist	Bioavailability (%)	Plasma protein binding (%)	Half-life (hours)	Metabolism pathway and elimination
Spironolactone	90	90	1.3	Extensively to active drug 50% renal
Eplerenone	69	50	3–5	P450 (CYP3A4) 67% renal

- Metabolism is primarily mediated via cytochrome P450 (CYP3A4).
- No active metabolites of eplerenone have been identified in human plasma.
- Less than 5% of an eplerenone dose is recovered as unchanged drug in urine and faeces. Approximately 32% of the dose is excreted in faeces and 67% in urine.
- The elimination half-life of eplerenone is approximately 3–5 hours.

The selective non-steroidal MRA ***finerenone*** has been shown to reduce HF hospitalization in populations with diabetes mellitus and chronic kidney disease. The Finerenone in Heart Failure Patients (FINEARTS-HF) trial explored the effect of finerenone in a symptomatic HF population with LVEF ≥40% and demonstrated a reduction in worsening heart failure events and cardiovascular mortality. As such, the treatment options in HFmrEF and HFpEF are expanding and this will likely be reflected in future guidelines.

Key reference

Agarwal R, et al. Cardiovascular and kidney outcomes with finerenone in patients with type 2 diabetes and chronic kidney disease: the FIDELITY pooled analysis. *Eur Heart J*. 2022;43:474–484.

Solomon SD et al. *Finerenone in Heart Failure with Mildly Reduced or Preserved Ejection Fraction*. N Engl J Med 2024;391:1475–1485.

How to initiate

(See also ➔ Chapter 5.)
See Table 36.2.

- Caution/seek advice before initiation if the baseline creatinine is >220 μmol/L or eGFR <30 mL/min/1.73 m².
- Monitor at 1 and 4 weeks after starting/increasing dose for renal dysfunction and hyperkalaemia.
- Use with caution in older people.
- Stop mineralocorticoid receptor antagonist temporarily during episodes of diarrhoea and/or vomiting.
- Consider dose uptitration after 4–8 weeks.

Contraindications to initiation

- Known allergic reaction.
- Significant renal impairment.
- Hyperkalaemia.

Side-effects

- Hyponatraemia.
- Hyperkalaemia.
- Renal dysfunction—recent evidence demonstrates that patients with HF whose eGFR falls below 30 mL/min/1.73 m² are at very high risk. The benefit of MRA is substantial therefore careful consideration is required in managing the medical therapy in these patients (see ➔ Chapter 23).
- Gynaecomastia—spironolactone*.
- Impotence—spironolactone*.

Table 36.2 Titration steps for mineralocorticoid receptor antagonists

Drug	Start dose (mg)	Target dose (mg)	Frequency
Spironolactone	25	50	od
Eplerenone	25	50	od
Finerenone	20	40	od

* Does not apply to eplerenone, which can be substituted on such occasions.

* Does not apply to eplerenone, which can be substituted on such occasions.

Clinical trial evidence base

See Table 36.3.

Table 36.3 Summary of RCTs of MRAs in HF

Trial (drug versus placebo)	Number of patients	NYHA class (%)	Mean LVEF (%)	Mean follow-up (years)	Mortality reduction (%)	Withdrawal due to intolerance (% versus placebo)
RALES Spironolactone	1663	0.5 II 70.5 III 29 IV	25	1.9	30	8 versus 5
TOPCAT Spironolactone	3445	3 I 64 II 33 III <1 IV	56*	3.3	ns**	6 versus 11
EPHESUS Eplerenone	6632	Post-MI	33	1.3	15	4 versus 3
EMPHASIS-HF Eplerenone	2737	II	26	1.75	24	14 versus 16
FINEARTS-HF; Finerenone		69 II 30 III	53	2.7	ns	20.4 versus 20.6

* Median.

** RCTs of spironolactone in HFpEF have failed to demonstrate benefit. Although the TOPCAT trial was neutral, subgroup analysis of those recruited in the Americas, and 9 analysis of those with LVEF <55% showed significant reductions in outcome measures.

Spironolactone

RALES (Randomized aldactone evaluation study)

TOPCAT (Treatment of preserved cardiac function heart failure with an aldosterone antagonist)

Eplerenone

EPHESUS (Eplerenone post–acute myocardial infarction heart failure efficacy and survival study)

EMPHASIS-HF (Eplerenone in Mild Patients Hospitalization and Survival Study in Heart Failure)

Key references

Matsumoto S, et al. Mineralocorticoid receptor antagonists in patients with heart failure and impaired renal function. *JACC*. 2024;83(24):2426–2436.

Pitt B, et al. The effect of spironolactone on morbidity and mortality in patients with severe heart failure. Randomized Aldactone Evaluation Study Investigators. *New Engl J Med*. 1999; 341:709–717.

Pitt B, et al. Eplerenone reduces mortality 30 days after randomization following acute myocardial infarction in patients with left ventricular systolic dysfunction and heart failure. J Am Coll Cardiol. 2005;46(3):425–431.

Pitt B, et al. Spironolactone for heart failure with preserved ejection fraction. *N Engl J Med*. 2014;370:1383–1392.

Pfeffer MA, et al. Regional variation in patients and outcomes in the Treatment of Preserved Cardiac Function Heart Failure With an Aldosterone Antagonist (TOPCAT) trial. *Circulation*. 2015;131:34–42.

Solomon SD, et al. Sacubitril/valsartan across the spectrum of ejection fraction in heart failure. *Circulation*. 2020;141:352–361.

Zannad F, et al. EMPHASIS-HF Study Group. Eplerenone in patients with systolic heart failure and mild symptoms. *New Engl J Med*. 2011;364:11–21.

Chapter 37

SGLT2 inhibitors

Introduction

Phlorizin was first isolated from apple tree bark by French chemists De Koninck and Stas in 1835 and was discovered to induce glycosuria and reduce hyperglycaemia by Von Mering in 1888. Phlorozin acts as a non-selective inhibitor of sodium glucose co-transporter (SGLT) proteins in the proximal tubule of the kidneys and the GI tract but suffers from poor intestinal absorption and low bioavailability.

In the 1980s, renewed efforts began to refine derivatives of phlorizin into a compound for use in the treatment of diabetes that acted selectively on the SGLT2 protein in the proximal tubules of the kidneys to increase glucosuria and reduce hyperglycaemia (Fig. 37.1). Further adaptations, including resistance to enzyme-mediated hydrolysis, and thus a clinically useful half-life, led to the introduction of modern SGLT2 inhibitors as a treatment for diabetes in 2014.

Trials of the drug class in diabetic and renal populations revealed improved cardiovascular outcomes unrelated to glycaemic effect. Benefits have since been confirmed in patients with heart failure in the absence of diabetes. Dapagliflozin was the first SGLT2 inhibitor licensed for the treatment of chronic heart failure in 2020 followed shortly thereafter by empagliflozin, and now these agents have since received approval for use in chronic heart failure across the range of LV ejection fraction.

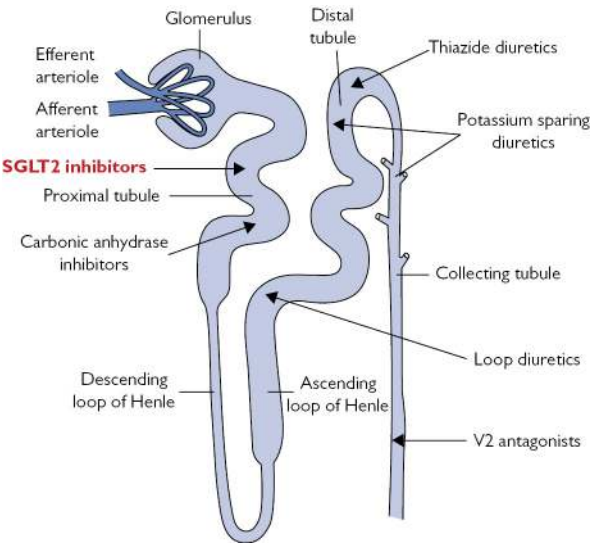

Fig. 37.1 The site of action of SGLT2 inhibitors and diuretics on the nephron.

Possible mechanisms resulting in cardiovascular benefit

- Natriuresis and osmotic diuresis.
- Attenuation of adverse cardiac remodelling.
- Reduced ventricular arrythmia risk and sudden death.
- Anti-inflammatory properties.
- Increased myocardial efficiency.

The pharmacology of SGLT2 inhibitors

The sodium-dependent glucose transporter 2 (SGLT2), part of the human solute carrier family, is a membrane associated transport protein expressed in the brush border membrane on the luminal surface of the proximal renal tubule. The kidney is a site of significant glucose handling and glucose is freely filtered in the glomerulus. SGLT2 is the primary site of glucose re-absorption from the glomerular filtrate (~97%) as well as facilitating ~5% of renal sodium absorption in normal physiology.

The sodium potassium adenosine triphosphatase active transporter (Na^+/K^+ ATPase) on the basolateral membrane establishes a concentration gradient that drives Na, and therefore glucose into the cell via SGLT2.

SGLT2 inhibitors are filtered at the glomerulus and act from the extracellular surface of the tubule lumen to increase sodium and glucose excretion resulting in osmotic diuresis. SGLT2 inhibitors are unable to completely block the transport protein and achieve a maximum inhibition of ~50% of the filtered glucose load regardless of drug dose (Table 37.1).

Potential benefits of SGLT2 inhibitors include reductions in:

- Blood glucose and glycated haemoglobin.
- Blood pressure.
- Arterial stiffness and vascular resistance.
- Visceral adiposity.
- Albuminuria.
- Plasma urate.
- Adverse renal outcomes.

In CHF, this translates to:

- Improved quality of life and a reduction in heart failure symptoms.
- A reduction in morbidity.
- A reduction in mortality.

Table 37.1 The pharmacokinetics of SGLT2 inhibitors approved for use in heart failure

SGLT2 inhibitor	Selectivity for SGLT2 vs. SGLT1	Bio-availability (%)	Plasma protein binding (%)	Half-life (hours)	Elimination (% renal)
Dapagliflozin	x1200	78	91	13	75
Empagliflozin	x2500	78	86	12	54
Sotagliflozin	x20	25	93	29	57

How to initiate

- Recommended in NYHA II–IV heart failure across the spectrum of LV ejection fraction.
- Monitor blood pressure—aim for systolic BP >90 mmHg.
- Monitor renal function—a small, reversible reduction in eGFR can be expected on initiation.
- Monitor glucose in those with type II diabetes on other diabetic drugs, which may predispose to hypoglycaemia.
- Monitor fluid balance—diuretic effect at initiation so may require diuretic dose alteration.
- No dose up-titration required (dapagliflozin and empagliflozin).
- Sick day rules—discontinue if unable to maintain fluid intake and resume with normal diet.

Contra-indications to initiation

- Pregnancy or breastfeeding.
- Severe CKD (eGFR <15 mL for dapagliflozin or eGFR <20 mL for empagliflozin).
- Symptoms of hypotension or SBP <95 mmHg.

NOTE: SGLT2 inhibitors are not recommended in those with Type 1 diabetes.

Adverse effects

- Genital mycotic infections (5–15% and more common in females).
- Diabetic ketoacidosis (rare and in trials only in those with diabetes; can be euglycaemic).

Table 37.2 SGLT2 inhibitor dosing in HF and renal impairment

Drug	Dose (mg)	Dose adjustment in renal impairment	Studied lower eGFR threshold
Dapagliflozin	10	No	25
Empagliflozin	10	No	20
Sotagliflozin	200–400	No	25

Clinical trial evidence base

Drugs that have been shown to reduce CV mortality and HF hospitalization in patients with HFrEF include:

- Dapagliflozin.
- Empagliflozin.
- Sotagliflozin (only in those with type II diabetes; see Table 37.2).

There are a number of large RCTs of SGLT2 inhibitors in patients with heart failure. The main studies will be highlighted (Table 37.3)

Dapagliflozin

DAPA-HF (Dapagliflozin in patients with heart failure and reduced ejection fraction). McMurray JJ, et al. *N Engl J Med*. 2019;381:1995–2008.
DELIVER (Dapagliflozin in heart failure with mildly reduced or preserved ejection fraction). Solomon S, et al. *N Engl J Med*. 2022;387:1089–1098.

Empagliflozin

EMPEROR-Reduced (Cardiovascular and renal outcomes with empagliflozin in heart failure). Packer M, et al. *N Engl J Med*. 2020;383:1413–1424.
EMPEROR-Preserved (Empagliflozin in heart failure with a preserved ejection fraction). Anker S, et al. *N Engl J Med*. 2021;385:1451–1461.

Sotagliflozin

SOLOIST-WHF (Sotagliflozin in patients with diabetes and recent worsening heart failure). Bhatt D, et al. *N Engl J Med*. 2021;384:117–128.

Table 37.3 Summary of SGLT2 inhibitor RCTs in heart failure

Trial (Drug versus placebo)	No. of patients	NYHA class	Mean LVEF (%)	Median follow-up (years)	Patients with diabetes (%)	eGFR enrolment threshold
DAPA-HF Dapagliflozin	4744	II–IV	31	1.5	42	>30
EMPEROR-Reduced Empagliflozin	3730	II–IV	27	1.3	50	>20
SOLOIST-WHF Sotagliflozin	1222	I–IV	35 (median)	0.8	100	>30
EMPEROR-Preserved Empagliflozin	5988	I–IV	54	2.2	49	>20
DELIVER Dapagliflozin	6263	II–IV	54	2.3	45	>25

Chapter 38

Diuretics and aquaretics

Introduction

Na^+ and Cl^- are the major determinants of extracellular fluid volume. Therefore, the role of diuretics is to increase the net loss of sodium and water by interfering with sodium, chloride, and water transport in the renal tubular cell membrane. As a large proportion of sodium and water that passes through the nephron is re-absorbed, even a small reduction in re-absorption can result in a marked increase in excretion.

Diuretics are commonly classified into the following groups (Fig. 38.1 and Table 38.1):

- Loop (e.g. furosemide, bumetanide).
- Thiazide (e.g. bendroflumethiazide).
- MRAs (e.g. spironolactone).
- Potassium-sparing (e.g. amiloride).
- Osmotic diuretics (e.g. mannitol).
- Carbonic anhydrase inhibitors (e.g. acetazolamide).

The latter group, the carbonic anhydrase inhibitors, have limited usefulness as diuretics. In contrast, loop diuretics form the cornerstone of therapy for patients with HF and evidence of fluid retention. HF patients may also require the addition of a thiazide to augment diuresis, and potentially overcome diuretic resistance that can often be seen with higher doses of loop diuretic.

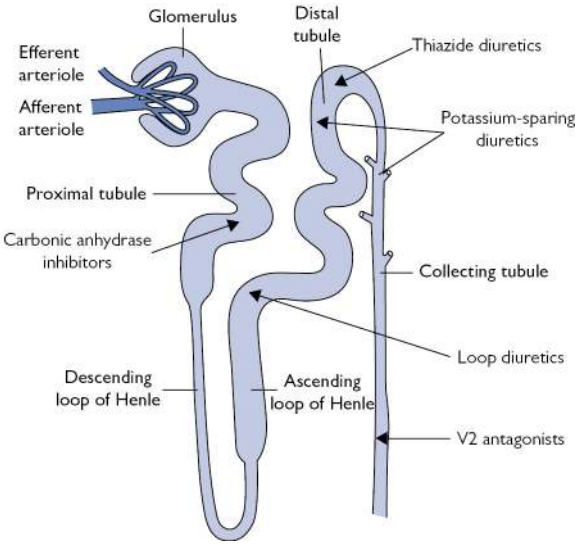

Fig. 38.1 The site of action of diuretics on the nephron.

Table 38.1 The pharmacokinetics of diuretics

Diuretic	Class	Bioavailability (%)	Onset of action, minutes (oral/iv)	$t_{½}$ (hours)	Metabolism and elimination (%)
Furosemide	Loop	52	40/5 Peak = 90	1.5	60 R 40 M
Bumetanide	Loop	85	40/5 Peak = 90	1	65 R 35 M
Torasemide	Loop	85	40/10 Peak = 90	3	30 R 70 M
Bendroflumethiazide	Thiazide	99	120/–	3	30 R 70 M
Metolazone	Thiazide-like	65	60/–	4–5	80 R 10 B 10 M
Spironolactone	MRA	65	120/–	1.3	100 M
Amiloride	K^+ sparing	50	120/–	6–9	100 R
Triamterene	K^+ sparing	30–70	120/–	2	50 M 50 R

B = excretion of intact drug into bile; M = metabolized; R = renal excretion of intact drug.

► It is important to ensure that those patients with HF who require diuretic therapy are commenced on an appropriate salt and fluid restriction (usually 1.5 L/day), and counselled on fluid balance and daily weights.

Diuretic resistance

In established HF, patients often require escalating doses of diuretic to maintain euvolaemia. This reduced response to diuretics is described as 'diuretic resistance'. Patients may be refractory to diuretics for several reasons:

- Renal hypoperfusion—low mean arterial BP and high venous pressure reduces the renal perfusion gradient.
- Worsening renal function.
- Reduced bioavailability of oral diuretics due to gut oedema.
- 'Braking': rebound sodium reabsorption when there is no diuretic at the site of action. TDS dosing (8am, 12 noon, 4pm) of oral loop diuretics can help here.
- Increased intraluminal protein binding of the diuretic.
- Reduced tubular secretion (renal failure, NSAIDs).
- Hypertrophy of distal nephron resulting in renal adaptation.
- Tubuloglomerular feedback (mediated by adenosine α_1-receptor).
- Non-compliance with drugs or diet (high sodium intake).

Diuretic resistance can be combated by sequential nephron blockade, where both loop and thiazide diuretics are used together, or by delivering parenteral diuretics.

Loop diuretics

Loop diuretics are inhibitors of the Na^+–K^+–$2Cl^-$ carrier in the luminal membrane of the cells of the thick ascending loop of Henle. They are the most powerful of all diuretics (often referred to as 'high ceiling diuretics'), capable of excreting approximately 20% of filtered sodium.

Examples of loop diuretics include:

- Furosemide.
- Bumetanide.
- Torasemide.

Administration

Table 38.2 shows recommended starting doses of the principle loop diuretics. These can be titrated—both up and down—as required. High doses are sometimes necessary in patients with coexisting chronic renal failure. However, the lowest effective dose should be used at all times, in conjunction with a fluid restriction. Indeed, a retrospective study by Neuberg et al. suggests that high diuretic doses are an independent risk factor for mortality.

Table 38.2 The titration steps of loop diuretics

Loop diuretic	Equivalent doses (mg)	Starting dose	Maximum daily dose
Furosemide	40	40 mg od	Titrated to response
Bumetanide	1	1 mg od	Titrated to response
Torasemide	10	5 mg od	Normal max 40 mg (up to 200 mg)

Once patients are on furosemide 80 mg bd (or equivalent), the addition of a thiazide diuretic (e.g. bendroflumethiazide 2.5 mg) is often preferable to escalating doses of loop diuretic, with careful monitoring of electrolytes and renal function.

Undesirable effects

- Hypokalaemia, hypocalcaemia, hypomagnesaemia, hyponatraemia.
- Hypotension.
- Hyperuricaemia.
- Metabolic alkalosis.
- Ototoxicity.

Key reference

Neuberg GW, et al. Diuretic resistance predicts mortality in patients with advanced heart failure. *Am Heart J.* 2002;144:31–38.

Thiazide diuretics

Thiazides exert their diuretic effect by inhibiting the active reabsorption of sodium and accompanying chloride in the early distal convoluted tubules, resulting in up to 10% of sodium in the filtrate being excreted. They, therefore, elicit a weaker diuretic response compared with the loop diuretics.

Examples of thiazide diuretics include:

- Bendroflumethiazide.
- Hydrochlorothiazide.
- Metolazone.

Metolazone is a thiazide-like diuretic that primarily exerts its effects on the distal tubule. However, it also appears to have a significant proximal diuretic effect, which would increase the fraction of the filtered Na^+ that reaches the loop of Henle. This is potentially desirable in patients with a markedly reduced GFR, as metolazone also prevents any compensatory increase in distal Na^+ reabsorption.

Indapamide is a non-thiazide sulfonamide, which has a greater hypotensive effect that may limit its utility in many patients with HF on contemporary medical therapy. The initial dose is 2.5 mg daily that can be increased to 5 mg daily if required.

Administration

Thiazide diuretics are generally not administered to HF patients, except those who are already established on loop diuretics, and require escalation of therapy due to fluid retention. This combination can result in a profound diuresis, and the patient should therefore be supervised closely, with the monitoring of renal function, electrolytes, and fluid status.

A thiazide, when added to a loop diuretic, should be tailored to each patient. Some only require, for example, bendroflumethazide 2.5 mg once weekly on top of their normal daily furosemide regimen of 80 mg bd. Others may require daily thiazide administration (Table 38.3).

Table 38.3 The titration steps of thiazide diuretics

Thiazide diuretic	Relative potency	Starting dose	Maximum daily dose
Bendroflumethiazide	10	2.5 mg thrice weekly	10 mg od mane
Hydrochlorothiazide	1	12.5 mg od	50 mg
Metolazone	10	2.5 mg thrice weekly	20 mg od mane

► Sanofi-Aventis no longer manufacture and distribute metolazone in the UK. Generic manufacturers have produced a number of preparations, but the Medicines and Healthcare products Regulatory Agency (MHRA) has recommended caution in switching between preparations due to variable bioavailabilty.

Most studies of combination therapy (loop + thiazide) have used metolazone, but one study* has shown that metolazone and bendrofluazide were equally effective in inducing diuresis in patients with resistant oedema when added to intravenous furosemide.

Undesirable effects

- Hypotension.
- Hypokalaemia, hypomagnesaemia, hyponatraemia.
- Hypercalcaemia.
- Hyperglycaemia.
- Pancreatitis.
- Metabolic alkalosis.

► Thiazide and loop diuretic combination therapy can cause a marked hyponatraemia or deterioration in renal function, and patients should be monitored closely.

Key reference

Channer KS, et al. Combination diuretic treatment in severe heart failure: a randomised controlled trial. *Br Heart J.* 1994;71:146–150.

Potassium-sparing diuretics

Potassium-sparing diuretics are of limited diuretic efficacy, causing excretion of about 5% of the sodium in the filtrate. They include amiloride, triamterene, and spironolactone. Their principal sites of action are the distal convoluted tubule and the collecting tubules, inhibiting both sodium reabsorption and potassium excretion.

Amiloride and triamterene act by blocking the Na^+ channels in the luminal membrane of the principal cells of the cortical collecting ducts. This reduces the Na^+ entry through the luminal membrane, and hence the net reabsorption of NaCl. Spironolactone and eplerenone are mineralocorticoid receptor antagonists, and are discussed in more detail in Chapter 36.

Administration

Amiloride and triamterene are occasionally used for their potassium-sparing properties, in addition to, for example, a loop diuretic (Table 38.4). However, hypokalaemia in heart failure patients can usually be managed with the use of ACEi/ARNI/ARB and MRAs.

Undesirable effects

- Hyperkalaemia.
- Hyponatramia.
- Postural hypotension.
- GI disturbance.
- Dry mouth.
- Photosensitivity.

Table 38.4 Titration steps of potassium-sparing diuretics

K^+ sparing diuretic	Starting dose	Maximum daily dose
Amiloride	5 mg od	20 mg od
Triamterene	150 mg alt days	250 mg od
Spironolactone	25 mg od	400 mg od*
Eplerenone	25 mg od	50 mg od

* Maximum dose of spironolactone used in the RALES study was 50 mg od.

Aquaretics

Aquaretics are arginine vasopressin (AVP) receptor antagonists. Unlike diuretics, which cause simultaneous loss of sodium and water, aquaretics only result in a loss of water.

AVP (also known as anti-diuretic hormone—ADH) is released from the posterior pituitary in response to a fall in osmolality or blood pressure. It has a homeostatic role in the maintenance of a constant plasma osmolality, and its effects are mediated through two main receptors:

- V_1 receptor—predominantly vascular; mediates vasoconstriction.
- V_2 receptor—found in the renal collecting ducts; allows water to return to the circulation from the urine along an osmotic gradient.

There are currently three AVP antagonists being evaluated for use in HF:

- Tolvaptan and lixivaptan—selective V_2 receptor antagonists—aquaretics.
- Conivaptan—a dual V_1 and V_2 antagonist—aquaretic/vasodilator.

The role for AVP antagonists in heart failure is currently uncertain. In the largest trial of AVP antagonists to date (EVEREST), Tolvaptan had no effect on total mortality or HF hospitalization but did lead to an improvement in breathlessness and weight loss in the first day and weight loss at 1 week.

A more promising role for AVP antagonists is in the management of HF patients with hyponatraemia. Hyponatraemia is common in end-stage HF and is associated with a very poor prognosis. In EVEREST, patients with hyponatraemia had a significant increase in serum sodium.

►► The MHRA issued an alert regarding over-rapid increase in serum sodium and risk of serious neurological events. Therefore, serum sodium should be closely monitored in patients receiving AVP receptor antagonists (see ➔ Chapter 17).

Clinical trial evidence base

Tolvaptan

EVEREST (The Efficacy of Vasopressin Antagonism in Heart Failure Outcome Study With Tolvaptan)

Key reference

Konstam MA, et al. Effects of oral tolvaptan in patients hospitalized for worsening heart failure: the EVEREST outcome trial. *JAMA*. 2007;297(12):1319–1331.

Chapter 39

Rate-limiting therapy

Only so many heart beats?

It is well known that smaller mammals have higher resting heart rates and shorter life spans than larger species. The inverse relationship between heart rate and life expectancy has prompted speculation that heart rate lowering may lead to a longer life expectancy (Fig. 39.1). However, it is incredibly interesting that, ultimately, all mammals appear to have the same number of heart beats in their lifetime (Fig. 39.2) >~10 x 10^8 heartbeats/lifetime.

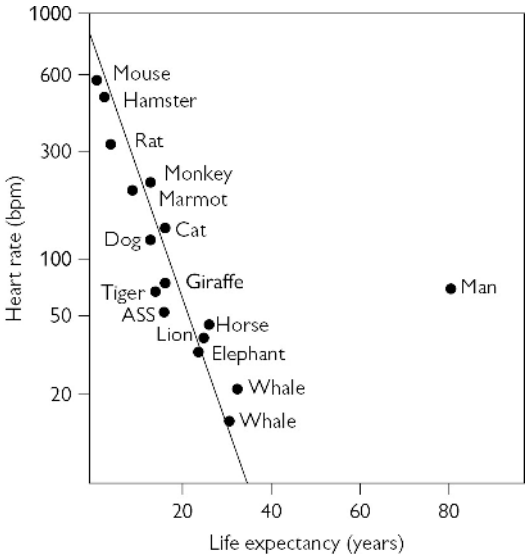

Fig. 39.1 Semilogarithmic relationship between resting heart rate and life expectancy in mammals.

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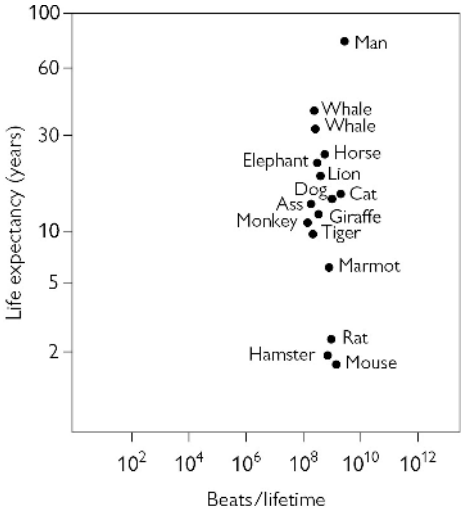

Fig. 39.2 Relation between life expectancy and total heart beats/lifetime.

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Heart rate and heart failure

In 1987, the Framingham Study confirmed suspicion that an elevated resting heart rate is a strong predictor of cardiovascular morbidity and mortality in the general population. Subsequently, a raised resting heart rate has also been consistently shown to predict an adverse outcome in patients with heart failure (Fig. 39.3).

Pathophysiologically, a relative tachycardia in the failing heart results from activation of the neurohumoral systems (particularly, the sympathetic nervous system). Intrinsically, a raised heart rate could be considered to be beneficial. Cardiac output is a directly related to heart rate (cardiac output = heart rate × stroke volume), and where the heart's ability to increase stroke volume is impaired, a rise in cardiac output necessitates an increase in heart rate.

However, failing human myocardium has a negative force-frequency association. Thus, a reduction in heart rate can improve myocardial contractility, and improve energy supply while reducing expenditure.

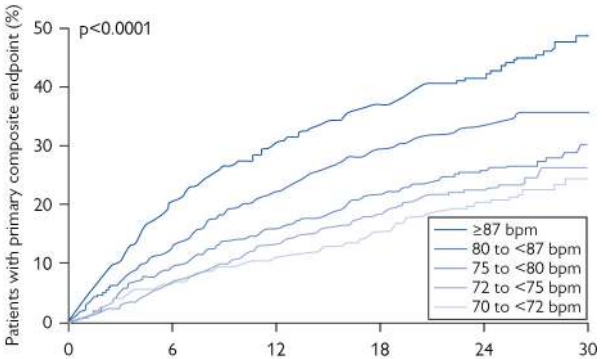


Fig. 39.3 Kaplan–Meier cumulative event curves for cardiovascular hospitalization or cardiac death according to heart rate at baseline in the SHIFT study.

Ivabradine

Ivabradine is a specific inhibitor of the I_f current in the sino-atrial node and, in therapeutic doses, it has no action on other channels in the heart or vascular system. As such, ivabradine does not modify myocardial contractility or intracardiac conduction. Furthermore, in view of its mode of action, ivabradine only has pharmacological effects in patients who are in sinus rhythm. It does not slow the ventricular rate in atrial fibrillation (AF).

► Ivabradine is not indicated for patients in AF.

Indications

- Should be considered for patients with HF and NYHA II–IV functional classification, with a heart rate ≥70/min and LVEF ≤35%, despite treatment with evidence-based doses of disease-modifying therapy (see Chapter 5):
  - ARNI/ACEi (or ARB).
  - Beta-blocker.
  - Mineralocorticoid receptor antagonist.
  - SGLT2 inhibitor.
- May be considered to reduce the risk of HF hospitalization in patients in sinus rhythm with an EF ≤35% and a heart rate ≥70/min who are unable to tolerate a beta-blocker (e.g. true asthmatics). Patients should also receive an ARNI/ACE inhibitor (or ARB), mineralocorticoid receptor antagonist, and SGLT2 inhibitor.

► The European Medicines Agency (EMA) has approved ivabradine for HF patients with a heart rate ≥75/min in sinus rhythm, and with an LVEF<35%.

Undesirable effects

- Symptomatic bradycardia.
- Visual side effects (phosphenes) in ~3%.

How to initiate

- Optimize evidence-based therapy for heart failure (including maximally tolerated dose of beta-blocker).

If, despite this, the patient is in sinus rhythm >70/min, commence on:

- Ivabradine 5 mg bd.

After two weeks:

- HR >60/min—increase ivabradine to 7.5 mg bd.
- HR 50–60/min—maintain ivabradine dose at 5 mg bd.
- HR <50/min, or the patient has signs or symptoms related to bradycardia—reduce the dose to 2.5 mg bd.

Clinical trial evidence base

SHIFT (Systolic heart failure treatment with the I_f inhibitor ivabradine trial)

Key reference

Swedberg K, et al. Ivabradine and outcomes in chronic heart failure (SHIFT): a randomised placebo-controlled study. *Lancet.* 2010;376:875–885.

Cardiac glycosides

Cardiac glycosides increase the force of myocardial contraction and reduce conductivity within the atrioventricular (AV) node. The most commonly used cardiac glycoside is digoxin. The current recommendations are to introduce this drug in patients who remain symptomatic, despite maximal, medical therapy, or to provide rate control for patients with AF.

With the growing interest in heart rate as a target in heart failure, the spotlight has returned to digoxin and its properties as a heart rate lowering agent in heart failure. Indeed, the relative reduction in the combined endpoints of CV death or hospitalizations for HF in the DIG trial (the same endpoint as SHIFT) was 15% with digoxin—very similar to the 18% relative risk reduction (RRR) observed with ivabradine in the SHIFT trial. Furthermore, digoxin has pharmacological effects in AF.

Current indications

- Symptomatic improvement in advanced chronic heart failure (in patients already established on maximally tolerated disease-modifying therapy—see ➔ Chapter 5), aiming for serum digoxin concentrations of 0.65–1.0 nmol/L (0.5–0.8 ng/mL).
- The control of ventricular rate in persistent AF (as an adjunct to beta-blockade).

Undesirable effects

- Narrow therapeutic window.
- Multiple side effects.
- Pro-arrhythmic.
- Dose adjustment made in renal impairment.

Therefore, caution is advised in elderly patients and those who are frail. Also, those patients who are hypokalaemic or malnourished are at increased risk of undesirable effects from digoxin.

Toxicity

- Discontinue digoxin.
- Digibind (digoxin-specific antibody fragments) can be given for more haemodynamically significant digoxin toxicity.

Important interactions

- Increased cardiac toxicity with digoxin and hypokalaemia.
- The plasma concentration of digoxin is increased with:
  - Amiodarone—half dose of digoxin.
  - Propafenone and quinidine.
  - Diltiazem, verapamil, and nifedipine (none of which should be used in the HFrEF patient anyway).
  - Spironolactone.
  - Ciclosporin.

Clinical trial evidence base

DIG Study (the effect of digoxin on mortality and morbidity in patients with heart failure)

► Patients with AF were excluded from the DIG study.

Post-hoc analyses of DIG study suggest:

- Digoxin therapy is associated with an increased risk of all-cause mortality in women (23% relative risk increase, $p = 0.014$), but not men. Rathore SS, et al. Sex-based differences in the effect of digoxin for the treatment of heart failure. *N Engl J Med*. 2002;347:1403–1411.
- Higher serum digoxin concentrations (SDC) are associated with increased mortality in men. The authors suggest a SDC of 0.64–1 nmol/L (0.5–0.8 ng/mL). Rathore SS, et al. Association of serum digoxin concentration and outcomes in patients with heart failure. *JAMA*. 2003;289:871–878.

Key references

Castagno D, et al. Should we SHIFT our thinking about digoxin? Observations on ivabradine and heart rate reduction in heart failure. *Eur Heart J*. 2012;33:1137–1141.

Digitalis Investigation Group. The effect of digoxin on mortality and morbidity in patients with heart failure. *New Eng J Med*. 1997;336:525–533.

Chapter 40

Inotropes and vasopressors

Principles of inotropes

Inotropes are often used to provide haemodynamic support for patients with decompensated heart failure. Their sites of action are depicted in Fig. 40.1. Although several drugs with inotropic activity are available, it has become increasingly evident that these drugs are associated with important negative effects. The positive inotropic actions of many of these agents are due to an increase in intracellular calcium concentration, which may also augment myocardial energy consumption and arrhythmias. Importantly, guidelines do not recommend the routine use of inotropes due to these safety concerns, unless the patient has symptomatic hypotension and evidence of hypoperfusion.

More recently, myotropes have been developed that improved myocardial function by directly augmenting cardiac sarcomere function (e.g. omecamtiv mecarbil, a cardiac myosin activator), although their role is yet to be fully established in the management of heart failure patients.

Inotropic/myotropic agents are classified according to their mode of action (Table 40.1):

- β-adrenergic agonists—induce an increase in intracellular cAMP activity by the stimulation of cellular receptors.
- Dopexamine.
- Cardiac glycosides.
- Phosphodiesterase inhibitors.
- Calcium sensitizers.
- Cardiac myosin activators.

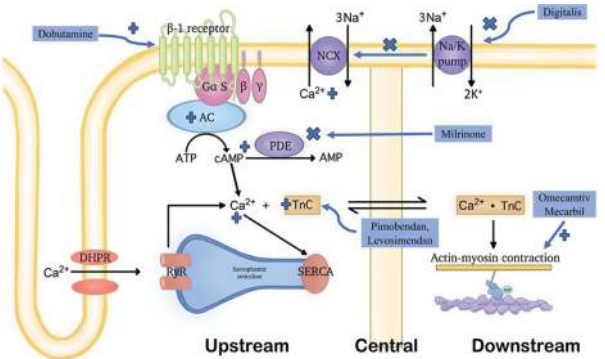


Fig. 40.1 Inotropic mechanisms and current inotropic interventions. Zhou et al. *Front Cardiovasc Med*, 19 March 2024 Sec. *Cardiovascular Pharmacology and Drug Discovery*. Volume 11, 2024 | https://doi.org/10.3389/fcvm.2024.1337154.

Table 40.1 Currently available and developmental direct inotropic agents

Pharmacological agent	Mechanism	dP/dt	Hemodynamic effects	Patient Outcomes
Cardiac calcitropes				
Dobutamine	Catecholamine: β-adrenergic receptor → cAMP → ↑ Ca^{2+}	↑	↑ Cardiac output	↑ Mortality
Dopamine	Catecholamine: β-adrenergic receptor → cAMP → ↑ Ca^{2+}	↑	↑ Cardiac output	↑ Mortality
Epinephrine	Catecholamine: β-adrenergic receptor → cAMP → t Ca^{2+}	↑	↑ Cardiac output	↑ Mortality
Milrinone	Phosphodiesterase-3 inhibitor: cAMP → ↑ Ca^{2+}	↑	↑ Cardiac output	↑ Mortality
Levosimendan	Phosphodiesterase-3 inhibitor (and calcium sensitizer): ↓ Troponin and tropomyosin inhibition; cAMP → ↑ Ca^{2+}	↑	↑ Cardiac output	? ↑ Mortality
Cardiac glycosides	Na^{+}-K^{+} ATPase inhibitor: 1- NCX ca2+ extrusion → ↑ Ca^{2+}	↑	↔ Cardiac output	? ↔ Mortality ↓ Hospitalizations
Istaroxime	Na^{+}-K^{+} ATPase Inhibitor & SERCA2a Activator: ↓ Ca^{2+} extrusion → ↑ Ca^{2+}, ↑ SERCA2a → ↑ Ca^{2+} in SR	↑	↑ Cardiac output	?
Cardiac myotropes				
Omecamtiv mecarbil	Direct myosin activator ↑ Myosin participation in systole	↔	↑ Cardiac output	?
Cardiac mitotropes				
Perhexiline	Carnitine palmitoyl transferase inhibitor: ↓ Mitochondrial fatty acids → ↑ Glucose metabolism	↔	↑ Cardiac output	?
Trimetazidine	Thiolase I inhibitor:! Fatty acid oxidation → ↑ Glucose metabolism	↑	↑ Cardiac output	?
Elamipretide	Cardiolipin stabilizer ↑ Adenosine triphosphate synthesis	?	?	?

From Pstoka et al. Cardiac calcitropes, myotropes, and mitotropes. *J Am Coll Cardiol*. 2019;73:2345–2353.

Dobutamine

Dobutamine is a synthetic catecholamine with β_1-, β_2-, and α_1-adrenergic activity.

Properties

- Inotropic.
- Chronotropic.
- Vasodilator at higher doses.

Undesirable effects

- Increases myocardial oxygen demand.
- Pro-arrhythmic secondary to abnormal calcium loading.
- Leads to hypotension at higher doses.
- Tachyphylaxis—prolonged infusion over 96 hours has been associated with a decrease in the haemodynamic effect by as much as 50%.

Pharmacology

- Onset of action 1–2 minutes; peak effect within 10 minutes.
- Plasma half-life is 2 minutes.
- Metabolites are excreted via kidneys.

Common interactions

There is a risk of severe hypertension with:

- β-adrenoreceptor antagonists (unopposed α1-adrenergic activity).
- Monoamine oxidase inhibitors (MAOIs).

Administration

- Ideally should be given centrally due to possible phlebitis.
- Administered in doses from 2.5–25 micrograms/kg/min (Table 40.2 and 40.3).

⚠ Beneficial short-term action encouraged investigators to use the drug in patients with CHF on an outpatient basis. Intermittent therapy was found to increase the quality of life and haemodynamics. However, a clinical trial had to be stopped prematurely because of an increase in mortality in the dobutamine-treated group.

Table 40.2 Infusion chart for dobutamine

	Dobutamine (2 mg/mL) infusion rate (mL/hour)							
	Patient body weight (kg)							
Dose (microgram/ kg/ minute)	40	50	60	70	80	90	100	110
2.5	3	4	4.5	5	6	7	7.5	8
5	6	7.5	9	10.5	12	13.5	15	16.5
7.5	9	11	13.5	16	18	20	22.5	25
10	12	15	18	21	24	27	30	33
15	18	22.5	27	31.5	36	40.5	45	49.5
20	24	30	36	42	48	54	60	66
25	30	37.5	45	52.5	60	67.5	75	82.5

500 mg of dobutamine made up to 250 mL with either 5% glucose (dextrose) or 0.9% saline.

Table 40.3 Infusion chart for dobutamine

	Dobutamine (1 mg/mL) infusion rate (mL/hour)							
	Patient body weight (kg)							
Dose (microgram/kg/ minute)	40	50	60	70	80	90	100	110
2.5	6	7.5	9	10.5	12	13.5	15	16.5
5	12	15	18	21	24	27	30	33
7.5	18	22.5	27	31.5	36	40.5	45	49.5
10	24	30	36	42	48	54	60	66
15	36	45	54	63	72	81	90	99
20	48	60	72	84	96	108	120	132
25	60	75	90	105	120	135	140	155

250 mg of dobutamine made up to 250 mL with either 5% glucose (dextrose) or 0.9% saline.

Dopamine

Dopamine is an endogenous precursor of norepinephrine, with predominantly β_1-receptor activity. However, at low doses, it acts on dopamine receptors (DA_1) causing dilation of smooth muscles in renal arteries, which can augment diuresis in combination with diuretics. At higher doses, it has inotropic effects through β_1 receptors, and vasoconstrictor effects via α_1 and 5HT receptors.

Properties

- May augment diuresis.
- Inotropic.
- Minor effects on heart rate or blood pressure except at higher doses.

Undesirable effects

- Extravasation may cause local necrosis.
- Pro-arrhythmic secondary to abnormal calcium loading.

Pharmacology

- Steady state reached within 5–10 minutes.
- Plasma half-life of 9 minutes.
- Widely distributed throughout the body.
- Does not cross the blood–brain barrier.
- Metabolized by monoamine oxidase (MAO) and catechol-O-methyltransferase (COMT) in the liver, kidney, and plasma.

Common interactions

Potentiated by:

- Monoamine oxidase inhibitors (MAOIs). In patients who have received MAOIs within the previous 2–3 weeks, the initial dopamine dose should be no greater than 10% of the usual dose.
- Tricyclic antidepressants.

Antagonized by:

- β-adrenoreceptor antagonists.

Hypotension and bradycardia have been observed in patients receiving phenytoin.

Administration

- Ideally through a central vein to avoid extravasation (Table 40.3 and 40.4).
- To augment diuresis in patients with decompensated HF, use at low dose with IV diuretics (diuretic-dose dopamine). A small study by Giamouzis et al. showed that low-dose dopamine and furosemide preserved renal function when compared to high dose furosemide alone (as described in Tables 40.4 and 40.5). In the ROSE-HF Study, where renal dose dopamine was compared to iv nesiritide in patients with decompensated HF, there was no difference in death or hospitalizations for HF.
- Do not discontinue abruptly—decrease dose gradually.

Table 40.4 The dose-dependent effects of dopamine

Dose	0.5–3.0 micrograms/kg/minute	3.0–5.0 micrograms/kg/minute	>5.0 micrograms/kg/minute
Predominant action	DA_1	β_1	5HT and α_1
Cardiovascular	↑ Cardiac output	↑ Myocardial contractility	↑ Heart rate vasoconstriction
Renal	↓ Proximal tubular Na re-absorption Renal blood flow	↑ Renal blood flow	Variable effect on renal blood flow
Gastro-intestinal	↑ Splanchnic blood flow	↑ Splanchnic blood flow	Variable effect on splanchnic blood flow

Table 40.5 Infusion chart for dopamine

	Dopamine (1.6 mg/mL) infusion rate (mL/hour)							
	Patient body weight (kg)							
Dose (microgram/kg/minute)	40	50	60	70	80	90	100	110
2.5	4	5	6	7	8	8	9	10
5	8	9	11	13	15	17	19	20
7.5	12	14	17	20	23	25	28	30
10	15	19	23	26	30	34	38	39
15	23	28	34	39	45	51	56	59
20	30	38	45	53	60	68	75	79

400 mg dopamine made up to 250 mL with 5% glucose (dextrose) or 0.9% saline.

Key references

Chen HH, et al. Low dose dopamine or low dose nesiritide in acute heart failure with renal dysfunction: the ROSE acute heart failure randomized trial. JAMA. 2013;310(23):2533–2543.

Giamouzis G, et al. Heart failure patients: results of the dopamine in acute decompensated heart failure (DAD-HF) trial. *J Cardiac Fail.* 2010;16:922–930.

Epinephrine (adrenaline)

Epinephrine is a direct-acting sympathomimetic agent, exerting its effect on β_1, β_2, and α_1 adrenoreceptors. Generally, it does not have a role in the management of acute heart failure.

Properties

- Inotropic.
- Chronotropic.
- Vasoconstriction.
- Bronchodilator.

Undesirable effects

- Increases myocardial oxygen demand.
- Pro-arrhythmic secondary to abnormal calcium loading.
- Hypertension.
- Hyperglycaemia.
- Hypokalaemia.
- Increased renin secretion.
- Increased after-load.
- Reduction in renal blood flow with higher doses.

Pharmacology

- Rapid onset of action.
- Plasma half-life is 5–10 minutes.
- 50% protein bound.
- Rapidly metabolized in the liver and tissues and excreted in the urine.

Administration

- Use with extreme caution.
- Indicated in cardiac arrest or in severe cardiogenic shock with haemodynamic monitoring (Table 40.6).

Table 40.6 Infusion chart for epinephrine

	Epinephrine (16 micrograms/mL) infusion rate (mL/hour)							
	Patient body weight (kg)							
Dose (microgram/kg/minute)	40	50	60	70	80	90	100	110
0.03	4.5	6	7	8	9	10	11	12
0.05	7.5	9	11	13	15	17	19	21
0.1	15	19	23	26	30	34	38	41
0.2	30	38	45	52	60	68	75	83
0.3	45	57	68	78	90	102	114	124
0.4	60	75	90	104	120	135	150	165
0.5	75	94	112	130	150	169	188	206

4 mg epinephrine made up to 250 mL with 5% glucose (dextrose). At larger doses and therefore volumes, the concentration of the infusion can be increased (double strength, triple strength, etc.), thereby reducing the necessary infusion rate and volume load to patient.

Norepinephrine (noradrenaline)

Norepinephrine is an endogenous agonist at α_1 and α_2 adrenoreceptors. It has a modest effect on β_1 adrenoreceptors. Generally, it does not have a role in the management of acute heart failure, as SVR is usually high in these patients.

Properties

- Vasoconstriction.

Undesirable effects

- Reduced renal blood flow.
- Splanchnic and distal limb ischaemia.
- Increased pulmonary vascular resistance.
- Uterine contraction.
- Metabolic acidosis.
- Arrhythmia secondary to abnormal calcium loading.

Pharmacology

- Inactive orally.
- Extensively metabolized.
- Only small amounts are excreted unchanged in the urine.

Administration

- Use with extreme caution.
- Administer centrally with haemodynamic monitoring.
- Dilute in 5% glucose (dextrose).
- Initial infusion rates are between 2 and 12 micrograms/minute (Table 40.7).
- Indicated in septic shock.

Table 40.7 Infusion chart for norepinephrine

	Norepinephrine infusion rate (mL/hour)							
	Patient body weight (kg)							
Dose (microgram/kg/minute)	40	50	60	70	80	90	100	110
0.03	4.5	6	7	8	9	10	11	12
0.05	7.5	9	11	13	15	17	19	21
0.1	15	19	23	26	30	34	38	41
0.2	30	38	45	52	60	68	75	83
0.3	45	57	68	78	90	102	114	124
0.4	60	75	90	104	120	135	150	165
0.5	75	94	112	130	150	169	188	206
1.0	150	186	224	260	300	338	375	412

4 mg norepinephrine made up to 250 mL with 5% glucose (dextrose) (16 micrograms/mL). At larger doses and therefore volumes, the concentration of the infusion can be increased (double strength, triple strength, etc.), thereby reducing the necessary infusion rate and volume load to patient.

Dopexamine

Dopexamine is a synthetic analogue of dopamine. It stimulates adrenergic β_2-receptors and peripheral dopamine receptors, and inhibits the neuronal re-uptake of noradrenaline.

Properties

- Increase in cardiac output mediated by after-load reduction (β_2, DA1).
- Mildly inotropic (β_2, uptake-1 inhibition).
- Increase in blood flow to vascular beds (DA1) such as the renal and mesenteric beds.
- Does not cause vasoconstriction.

Undesirable effects

- Tachycardia/tachyarrhythmia.
- Hypertension.

Pharmacology

- Rapid onset of action.
- Plasma half-life of around 11 minutes in patients with cardiac failure.
- Subsequent elimination of the metabolites is by urinary and biliary excretion.

Common interactions

- Enhances effects of epinephrine and norepinephrine.
- Risk of hypertensive crisis with MAOIs.

Administration

- By intravenous infusion into central or large peripheral vein.
- Dose: 0.5–6 micrograms/kg/minute.

Phosphodiesterase inhibitors

Phosphodiesterase inhibitors inhibit cAMP breakdown, with inotropic and vasodilatory effects. However, in large-scale placebo-controlled trials in patients with CHF, selective type III phosphodiesterase inhibitors (PDEI) were associated with an increase in mortality. Their use is, therefore, kept to short-term administration in decompensated patients in a critical care setting.

Properties

- Reduce after-load.
- Decrease filling pressures.
- Increase cardiac index.
- Increase the rate of contractility and relaxation.

Undesirable effects

- Increased mortality with long-term use.
- Pro-arrhythmic.

Pharmacology

- Enoximone
  - Variable elimination half-life (3–8 hours in HF patients).
  - 85% protein bound.
  - Metabolized in the liver and excreted in the urine mainly as metabolites.
- Milrinone
  - Elimination half-life of 2–3 hours.
  - 70% protein bound.
  - Elimination mainly in the urine (83% unchanged drug).

Administration

- Enoximone
  - By intravenous infusion, initially 90 micrograms/kg/minute over 10–30 minutes, followed by continuous infusion of 5–20 micrograms/kg/minute.
  - Total dose over 24 hours should not usually exceed 24 mg/kg.
- Milrinone
  - By intravenous injection, 50 micrograms/kg over 10 minutes followed by intravenous infusion at a rate of 375–750 ng/kg/minute, if blood pressure satisfactory.
  - Maximum daily dose 1.13 mg/kg.
  - Lower dose in renal impairment.

Calcium channel sensitizers

Levosimendan

Levosimendan is a calcium-sensitizing agent that promotes inotropy by stabilizing troponin C in a configuration which enhances the calcium sensitivity of cardiac myofilaments. Furthermore, levosimendan also leads to vasodilatation via the opening of ATP-dependent potassium channels. These two properties have led to the term 'inodilator'.

► Levosimendan is currently not licensed for heart failure in the UK, but is being used in the USA and parts of Europe.

Properties

- Inotropic.
- Vasodilatation.
- Reduces PCWP.
- Active metabolites may exert action for 5–7 days after treatment discontinued.

Undesirable effects

- Pro-arrhythmic (particularly atrial fibrillation).
- Headache.
- Hypotension.
- May increase long-term mortality.

Pharmacokinetics

Levosimendan is:

- 98% bound to plasma protein.
- Undergoes complete metabolism, with some active metabolites.
- Elimination $t_{½}$ is approximately 1 hour.

Administration (where licensed)

Given intravenously:

- Loading dose—12–24 micrograms/kg over 10 minutes, followed by:
- Maintenance dose—IV infusion of 0.05–0.2 micrograms/kg/minute, titrated to response.

Clinical trial evidence base

LIDO study (levosimendan infusion versus dobutamine study)

REVIVE-II (randomized multicentre evaluation of intravenous levosimendan efficacy versus placebo in the short-term treatment of decompensated heart failure)

SURVIVE

PERSIST

Phase 2 study of oral form of levosimendan in approximately 300 patients with severe CHF failed to improve clinical outcomes; therefore, phase 3 study not proposed.

LION-HEART

In this small pilot study, intermittent administration of levosimendan to ambulatory patients with advanced systolic heart failure reduced plasma concentrations of NT-proBNP, worsening of HRQoL, and hospitalization for heart failure.

Cardiac myosin activators

There is a great deal of interest in developing safer inotropes. Omecamtiv mecarbil—a cardiac myosin activator—promotes actin-dependent phosphate release moving the cross-bridge into its strongly bound force producing state and early research held this compound in great promise.

However, the GALACTIC-HF study assessed the efficacy and safety of omecamtiv mecarbil in over 8000 HFrEF patients from both the inpatient and outpatient setting and the primary endpoint of a first HF event or CV death was reduced by only 8% in relative terms and there was no significant reduction in CV mortality. In the future, the role of omecamtiv mecarbil may be clarified but currently this drug is not licensed for use in HF, and the FDA declined approval in 2023.

Chapter 41

Vasodilators

Hydralazine

Hydralazine is principally an arteriolar dilator, although it has an uncertain mode of action. It has been shown to increase cardiac output with little effect on filling pressures. Hydralazine can also reduce the degree of mitral regurgitation. It is used in combination with isosorbide dinitrate (ISDN) in moderate to severe chronic heart failure in:

- Patients intolerant to ACE inhibitors or ARBs.
- African Americans already established on ACE inhibitors or ARBs.

Clinical effects

- ↓ Afterload.
- ↑ Cardiac output.

Undesirable effects

- Tachycardia.
- Fluid retention (renin release).
- Headache.
- Lupus syndrome (more likely to develop in slow acetylators).

Pharmacokinetics

- Rapidly absorbed from the gut (peak concentration 1–2 hours).
- Bioavailability: 26–55%.
- Peak plasma concentrations: 0.5–1.5 hours.
- Plasma protein binding: 90%.
- $t_{½}$: 2–3 hours, but up to 16 hours in severe renal failure (CrCl <20 mL/minute, therefore reduce dose).
- Largely excreted as acetylated and hydroxylated metabolites, some of which are conjugated with glucuronic acid.

Administration

- Aim to uptitrate every 2 weeks if tolerated, paying particular caution in severe heart failure or in hypotensive patients.
- Starting dose: Hydralazine 25 mg qds and isosorbide dinitrate 10 mg qds
- Target dose: Hydralazine 75 mg qds and isosorbide dinitrate 40 mg qds.

Clinical trial evidence base

V-HeFT I (veterans' administration cooperative study)
V-HeFT II
A-HEFT 2004-efficacy in African Americans (*N Engl J Med.* 2004;351:2049–2057).

Nitrates

Nitrates relieve pulmonary congestion in acute heart failure by increasing vasodilatory cyclic GMP in vascular smooth muscle. At low doses, nitrates principally induce venodilation, but as the dose increases they cause arterial dilation. Recent trial evidence (the ELISABETH Trial) has not confirmed their efficacy for use in acute heart failure. They are drugs that may be considered to aid symptoms in AHF.

Clinical effects

- ↓ Pre-load.
- ↓ Afterload.
- ↓ Myocardial oxygen demand.

Undesirable effects

- Headache.
- Hypotension.

Pharmacokinetics

Exposure to nitrates results in the rapid development of tolerance (particularly when given IV in high doses), limiting their effectiveness to 16–24 hours.

- Glyceryl trinitrate.
  - Large volume of distribution.
  - Rapidly metabolized to dinitrates and mononitrates.
  - $t_{½}$: 1–4 minutes.
  - 30–60% plasma protein bound.
  - The principal metabolite is glyceryl mononitrate, which is inactive.
- Isosorbide dinitrate (ISDN).
  - Bioavailability: 80% (oral).
  - $t_{½}$: 2 hours (oral).
  - $t_{½}$: 0.7 hours (IV).
  - Metabolized to active metabolites (isosorbide mononitrate).

Administration

Nitrates should be administered with careful BP monitoring. The dose should be reduced if systolic blood pressure falls <90 mmHg, and discontinued permanently if blood pressure drops further.

- s/l 2 puffs (400 micrograms) of glyceryl trinitrate every 5 minutes.
- buccal 1–5 mg of isosorbide dinitrate.
- IV GTN 20–200 micrograms/minute or isosorbide dinitrate 1–10 mg/hour.

Key reference

Freund Y, et al. The ELISABETH trial. *JAMA*. 2020;324(19):1948–1956.

Sodium nitroprusside

Sodium nitroprusside (SNP) causes peripheral vasodilation by a direct action on vascular smooth muscle. Prolonged administration may be associated with toxicity from its metabolites, thiocyanide and cyanide, and should be avoided especially in patients with severe renal or hepatic failure.

SNP should be uptitrated cautiously with invasive arterial monitoring. Likewise, SNP should be downtitrated slowly to avoid rebound hypertension. Controlled trials with SNP in AHF are lacking, and its administration in AMI has yielded equivocal results. In AHF caused by acute coronary syndromes, nitrates are favoured over SNP as SNP may cause 'coronary steal syndrome'.

Clinical effects

- Vasodilatation—reduction in both pre- and afterload.

Undesirable effects

- Hypotension.
- Headache.
- Nausea.

Pharmacokinetics

Sodium nitroprusside is rapidly metabolized and excreted entirely as metabolites, principally thiocyanate. The elimination half-life of thiocyanate is 2.7–7 days when renal function is normal, but is longer in patients with impaired renal function or hyponatraemia. Toxic symptoms begin to appear at plasma thiocyanate concentrations of 50–100 micrograms/mL, and fatalities have been reported at concentrations of 200 micrograms/mL.

Administration

- Intravenous infusion of 0.3–5 micrograms/kg/minute, uptitrating carefully.

Soluble guanylate cyclase stimulator

Vericiguat

Vericiguat is a novel oral soluble guanylate cyclase stimulator which enhances the cGMP pathway. Early study in patients with worsening HFrEF saw a reduction in NT-proBNP concentrations.

The VICTORIA trial, involving 5050 recently hospitalized patients (or those who had received intravenous diuretics) with symptomatic HF and an LVEF <45%, to guideline directed medical therapy with or without vericiguat. Over a relatively short median follow-up of just under 11months, the composite primary endpoint of death from CV causes or first hospitalization for heart failure was 10% lower in those receiving vericiguat, although there was no effect on either all-cause or CV mortality.

Furthermore, though there was a relatively consistent effect of vericiguat across the prespecified subgroups, there was a signal that those with very high NT-proBNP concentrations may be too advanced for a favourable effect from vericiguat. As such, the VICTOR study is underway in patients with HFrEF who have **not** been hospitalized for 6 months.

The 2021 ESC guidelines state that vericiguat may be considered in addition to standard therapy for HFrEF (Table 41.1). Although it has been approved by the FDA, it does not yet have marketing authorization in the UK.

Clinical trials

VICTORIA—Armstrong PW, et al. *N Engl J Med*. 2020;382:1883–1893.

VICTOR—ClinicalTrials.gov ID NCT05093933.

Table 41.1 Titration steps for vericiguat

Drug	Start dose (mg)	Target dose (mg)
Vericiguat	2.5 mg od	10 mg od

Other vasodilators

Serelaxin

Serelaxin is recombinant human relaxin-2, which has been shown to increase arterial compliance, cardiac output, and renal blood flow. In the RELAX-HF study of 1161 acute heart failure patients the primary endpoint of breathlessness was improved with serelaxin. Interestingly, serelaxin reduced CV death at 180 days, but not hospitalization for heart failure. However, in the much larger RELAX-AHF II trial involving 6545 patients hospitalized for acute HF, an infusion of serelaxin did not lower the incidence of cardiovascular death or worsening HF. As such, it is not marketed in the Western World.

Ularitide

Ularitide is a synthetic form of urodilatin—a renally produced natriuretic peptide that promotes sodium excretion, improves renal blood flow, and is a vasodilator. However, despite reducing NT-proBNP, it did not affect a clinical composite endpoint or reduce cardiovascular mortality in the TRUE-HF trial.

Nesiritide

Nesiritide is recombinant human B-type natriuretic peptide, manufactured from *Escherichia coli*. It has the same 32-amino acid sequence as the endogenous peptide, which is produced by the ventricular myocardium. Although it led to a fall in wedge pressure and a reduction in preload and afterload, trial evidence from ASCEND-HF showed no effect on outcome and it was withdrawn from use in the USA. It was never licensed in the UK.

Clinical trials

RELAX-AHF-2—Metra M, et al. *N Engl J Med*. 2019;381:716–726.
TRUE-HF—Packer M, et al. *N Engl J Med*. 2017;376:1956–1964.
ASCEND-HF—O'Connor C, et al. *N Engl J Med*. 2011;365:32–43.

Section VI

Multiprofessional heart failure care

Chapter 42

Heart failure services

Introduction

The management of chronic HF is underpinned by one of the strongest evidence bases in medicine. Following large randomized controlled drug treatment trials from the late 1980s and early 1990s, numerous guidelines outlining the pharmacological treatment of heart failure have been written (ESC, ACC/AHA, NHFA/CSANZ, SIGN, and NICE). Despite this, registry data show a low uptake of evidence-based therapies in the community, and both morbidity and mortality remain high. This has led to a paradigm shift away from concentration on the prescription of individual drug therapies, to the systems of care in which these treatments are delivered, that is, within organized multiprofessional heart failure services.

Complexity of HF

The need for multiprofessional HF services arises from the increasing complexity of diagnosing and managing HF. Patients are asked to make lifestyle changes, take multiple drugs, and are increasingly exposed to device therapy. In addition, the average age of a HF patient at diagnosis is 78 years—that is, it is predominantly a 'cardiogeriatric syndrome'. Patients affected have frequent and multiple comorbidities, and the therapies themselves have numerous side effects.

In the midst of all this, the HF patient has to make multiple visits to hospital clinics, often seeing numerous doctors. This can sow the seeds for enormous confusion likely to result in patchy adherence to therapy.

Evidence for heart failure services

Many RCTs of multiprofessional versus usual care have now been carried out. Seminal ones include:

- Rich et al. 1995 (Fig. 42.1)
  - Nurse directed multiprofessional HF intervention versus usual care in HF patients aged >70 years at high risk of readmission.
  - The interventional arm included education, dietary advice, cardiology review, home visits, and telephone contact.
  - 44% reduction in all-cause readmissions at 90 days ($p = 0.035$).
- Stewart et al. 1999 (Fig. 42.2)
  - Randomized patients to usual care versus home visit from nurse for education about medication after an admission for HF.
  - Significant reduction in event-free survival at 1 year ($p = 0.037$).
- Blue et al. 2001 (Fig. 42.3)
  - 165 admissions with HF, randomized to nurse intervention/usual care.
  - ↓ All-cause admissions (86 versus 114, $p = 0.018$).
  - ↓ HF admissions (19 versus 45, $p < 0.001$).
  - Fewer days in hospital for HF (3.43 versus 7.46, $p = 0.0051$).

Other evidence

Numerous other trials of multidisciplinary strategies have been reported, but they are heterogeneous in terms of the models of care they have employed. Models have included:

- Multiprofessional HF clinics.
- Multidisciplinary follow-up without HF clinics.
- Telephone contact.
- Primary care follow-up.
- Enhanced patient self-care.

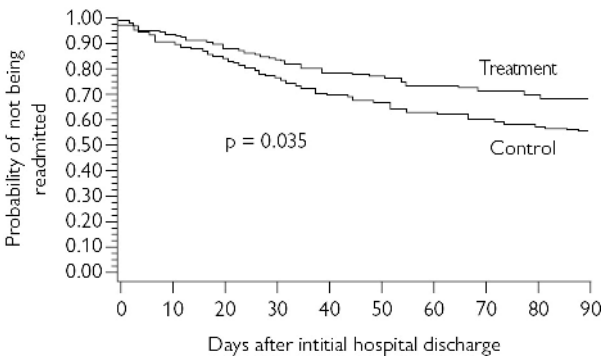
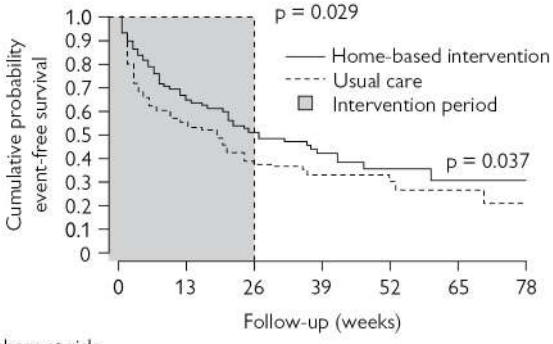


Fig. 42.1 Kaplan–Meier curve for the probability of not being re-admitted to the hospital during the 90-day period of follow-up.

From Rich M, et al. A multidisciplinary intervention to prevent the readmission of elderly patients with congestive heart failure. *N Engl J Med.* 1995;333:1190–1195 with permission from Massachusetts Medical Society (for 2nd edition).

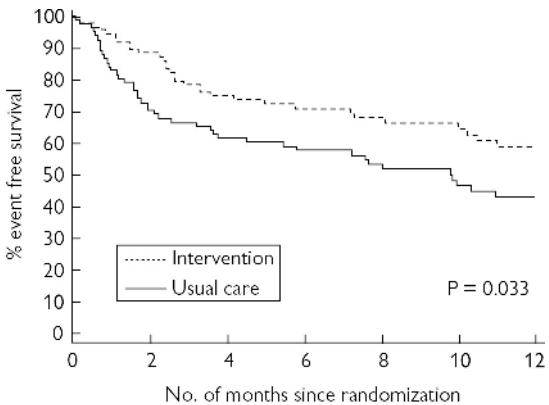


Numbers at risk

Intervention	100	66	51	23	13	6	4
Usual care	100	57	38	17	9	5	2

Fig. 42.2 Cumulative probability of event-free survival during follow-up.

Reprinted from *The Lancet*, 354: Stewart S, et al. Effects of a multidisciplinary, home-based intervention on unplanned readmissions and survival among patients with chronic congestive heart failure: a randomised controlled study, 1077–1083, Copyright 1999, with permission from Elsevier (for 2nd edition).



Numbers at risk:

Usual care	81	57	50	42	35	27	22
Intervention	84	74	60	49	44	34	28

Fig. 42.3 Time to first event (death from any cause or hospital admission or heart failure) in usual care and nurse intervention groups.

Reproduced from BMJ. Randomised controlled trial of specialist nurse intervention in heart failure, Blue LM, et al. 323:715, Copyright 2001 with permission from BMJ Publishing Group Limited.

In a recent meta-analysis, nurse home visits and disease management clinics were shown to be associated with reduced all-cause mortality (↓ 22%) and all-cause readmission (↓ 35%). Disease management programmes also lead to higher rates of prescribing of disease-modifying therapy, improved adherence to therapy, and most strategies are cost saving.

Key reference

Van Spall HGC, et al. Comparative effectiveness of transitional care services in patients discharged from the hospital with heart failure: a systematic review and network meta-analysis. *Eur J Heart Fail*. 2017;19:1427–1443.

Guidelines

Most society guidelines now recommend that HF care be delivered in a multiprofessional manner, and the Heart Failure Association of the ESC have produced a position statement on the delivery of heart failure care outlining the main components of such programmes. The most recent ESC guidelines summarize the most important characteristic and elements of a HF management programme (Table 42.1).

Table 42.1 Important characteristic and elements of a HF management programme

Characteristics

1. Patient/person-centred
2. Multidisciplinary
3. The focus of the programme should be flexible and include:
   - prevention of disease progression
   - symptom control
   - maintaining patients in their preferred place of care for end-stage heart failure
4. Competent and professionally educated staff
5. Encourage patient/carer engagement in the understanding and management of their condition

Components

1. Optimized management; lifestyle choices, pharmacological, and devices
2. Patient education, with special emphasis on self-care and symptom management
3. Provision of psychosocial support to patients and family caregivers
4. Follow-up after discharge (clinic; home visits; telephone support or telemonitoring)
5. Easy access to healthcare, especially to prevent and manage decompensation
6. Assessment of (and appropriate intervention in response to) an unexplained change in weight, nutritional, and functional status, quality of life, sleep problems, psychosocial problems, or other findings (e.g. laboratory values)
7. Access to advanced treatment options: supportive and palliative care

European Society of Cardiology HF Guidelines 2021. McDonagh TA, et al. *Eur Heart J.* 21;42(36):3599–3726.

Essential components

Most HF services have unique features specific to their geographical location, disease prevalence, local resources, and barriers to optimal care. Many are evolving into HF networks to provide comprehensive care for a community. Essential components seem to include:

- Specially trained HF nurses with a role in educating the patient about HF and its precipitating factors, dietary advice, adjustment of diuretics, and the need for adherence to therapy.
- Access to clinicians trained in HF. The essential topics which should be covered during patient education are listed in Table 42.2.

Table 42.2 Essential topics for patient education

Educational topic	Patient skills and self-care behaviours
Definition and aetiology	• Understand the cause of heart failure and why symptoms occur
Prognosis	• Understand important prognostic factors and make realistic decisions
Symptom monitoring and self-care	• Monitor and recognize signs and symptoms • Record daily weight and recognize rapid weight gain • Know how and when to notify healthcare provider • In the case of increasing dyspnoea or oedema or a sudden unexpected weight gain of >2 kg in 3 days, patients may increase their diuretic dose and/or alert their healthcare team • Use flexible diuretic therapy if appropriate and recommended after appropriate education and provision of detailed instructions
Pharmacological treatment	• Understand indications, dosing, and effects of drugs • Recognize the common side effects of each drug prescribed
Adherence	• Understand the importance of following treatment recommendations and maintaining motivation to follow treatment plan • Sodium restriction may help control the symptoms and signs of congestion in patients with symptomatic heart failure classes III and IV
Diet	• Avoid excessive fluid intake: fluid restriction of 1.5–2 L/day may be considered in patients with severe heart failure to relieve symptoms and congestion. Restriction of hypotonic fluids may improve hyponatraemia. Routine fluid restriction in all patients with mild to moderate symptoms is probably not of benefit. Weight-based fluid restriction (30 mL/kg body weight, 35 mL/kg if body weight >85 kg) may cause less thirst • Monitor and prevent malnutrition • Eat healthily and keep a healthy weight (see Section 11)

(*Continued*)

Table 42.2 (*Contd.*)

Educational topic	Patient skills and self-care behaviours
Alcohol	• Modest intake of alcohol: abstinence is recommended in patients with alcohol-induced cardiomyopathy. Otherwise, normal alcohol guidelines apply (2 units per day in men or 1 unit per day in women). 1 unit is 10 mL of pure alcohol (e.g. 1 glass of wine, 1/2 pint of beer, 1 measure of spirit)
Smoking and drugs	• Stop smoking and/or taking illicit drugs
Exercise	• Understand the benefits of exercise • Perform exercise training regularly • Be reassured and comfortable about physical activity
Travel and leisure	• Prepare travel and leisure activities according to physical capacity • When travelling, carry a written report of medical history and current medication regimen and carry extra medication. Monitor and adapt fluid intake particularly during flights and in hot climates. Beware adverse reactions to sun exposure with certain medications (e.g. amiodarone)
Sexual activity	• Be reassured about engaging in sex and discuss problems with healthcare professionals. Stable patients can undertake normal sexual activity that does not provoke undue symptoms
Immunization	• Receive immunization against COVID, influenza, and pneumococcal disease according to local guidelines and practice
Sleep and breathing disorders	• Recognize preventive behaviour such as reducing weight in obese patients, smoking cessation, and abstinence from alcohol • Learn about treatment options if appropriate
Psychosocial aspects	• Understand that depressive symptoms and cognitive dysfunction are common in patients with heart failure and the importance of social support • Learn about treatment options if appropriate

Adapted from 2021 ESC guidelines. European Society of Cardiology HF Guidelines 2021. McDonagh TA, et al. *Eur Heart J*. 21;42(36):3599–3726.

Key references

McDonagh TA, et al. European Society of Cardiology Heart Failure Association standards for delivering heart failure care. *Eur J Heart Fail.* 2011;13:235–241.

McDonagh TA, et al. European Society of Cardiology 2021 HF Guidelines. *Eur Heart J.* 2011;42(36):3599–3726.

Van Spall HGC, et al. Comparative effectiveness of transitional care services in patients discharged from the hospital with heart failure: a systematic review and network meta-analysis. *Eur J Heart Fail*. 2017;19:1427–1443.

Telemonitoring and remote monitoring

Many disease management programmes for HF include options for telemonitoring. This enables patients to provide digital health information to help optimize their care, remotely.

Examples include:

Non-invasive

- Symptoms.
- Weight.
- Heart rate and rhythm.
- Blood pressure.

Invasive

- Pulmonary artery pressure monitoring (see ➔ Chapter 28).
- IVC area and collapsibility (e.g. FIRE1).
- Thoracic impedance.
- Device derived data from ICDs, CRT and loop recorders (e.g. HeartLogic, CorVue, TRIAGE-HF).

Home telemonitoring is an efficient method for aiding delivery of HF care, but it should be adapted to work in parallel with existing HF services. Non-invasive home telemonitoring *may* reduce CV and HF hospitalizations and CV death. Monitoring of pulmonary artery pressure may be considered in HF patients to improve HF outcomes.

Towards HF networks

A multiprofessional HF service must:
- Have local guidelines to be used across all levels of care.
- Be able to manage HF in both primary and secondary care to ensure consistency of approach.
- Include medical therapy guidelines that can be used to allow nurse prescribing and optimization of therapy.
- These should be based around the existing practice guidelines for the management of CHF.

Ideally, a HF service should be centred on a HF clinic. The HF clinic should:
- Be multidisciplinary: involving cardiologists, GPs, care of the elderly physicians, specialist nurses, and pharmacists, as appropriate.
- Provide a supportive milieu for healthcare professionals (HCPs).
- Provide places for supervision and training.
- Facilitate better time management for nurses with patients who are able to attend compared with more time-consuming home visits.
- Allow rapid access to heart failure expertise for primary and secondary care physicians, other specialist HCPs, and patients.

The aims of such a service are to:
- Provide an accurate diagnosis.
- Instigate appropriate investigation.
- Roll out a management plan.

A heart failure service should be available to the HF patient wherever they enter their healthcare journey, whether that is in primary care, as a HF admission to an internal medicine ward, or the CCU, or as a referral to secondary or tertiary care.

The management for most patients will be rolled out in primary care, aided by HF nurses, and cardiology liaison from secondary/tertiary care. Some patients need to attend HF clinics for more intensive management, and others require access to advanced HF care for the consideration of device therapy and rarer and more rationed therapies, such as cardiac transplantation and LV assist devices. Selected patients will require palliative care services. The aim of a HF service is to improve the outcomes for all HF patients, regardless of their entry point to healthcare (Fig. 42.4).

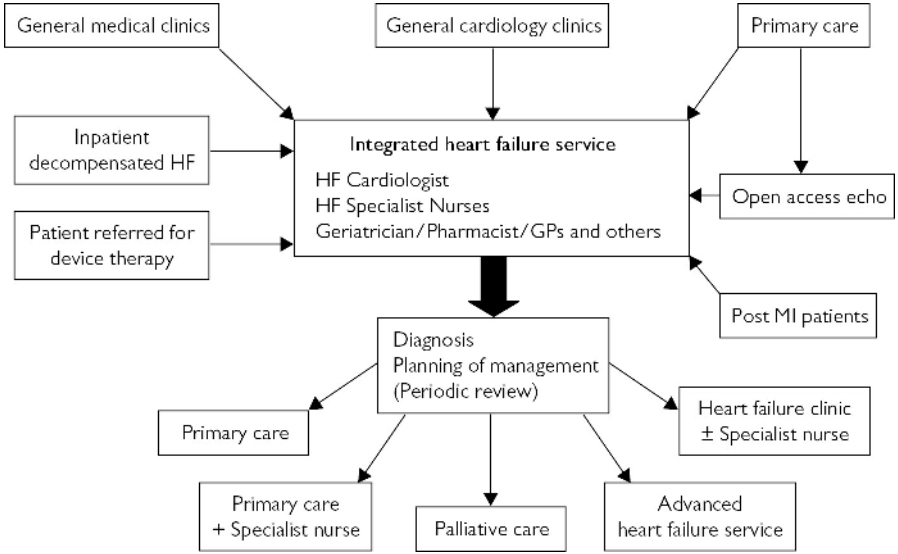


Fig. 42.4 An ideal HF network.

Reproduced with permission from The British Society for Heart Failure.

Chapter 43

Palliative care

The need for palliative care in HF

Palliative care, or 'end-of-life therapies' for heart failure (HF), really refers to a shift in the focus of care from management primarily aimed at prolonging life to that concerned chiefly with the relief of symptoms.

Mortality and morbidity of advanced HF

According to the HF treatment trials, the annual mortality rate of HFrEF, when we look at the incremental effects of disease-modifying therapy, is now around 5% per annum.

Despite this, HF remains a fatal disease for most patients—as they are not representative of those enrolled in the landmark trials. These real-world HF patients are much older (mean age at diagnosis of 78 years) and have frequent comorbidities. Their mortality rates are greater than those of the most common cancers—diseases for which there is well-established palliative care. For those reaching end of life, symptoms are frequent and include:

- Lack of energy.
- Breathlessness (60%).
- Weakness or fatigue.
- Pain—78% (comparable to lung/colon cancer).
- Insomnia.
- Depression.

Patient's and carer's view

Boyd and co-workers studied how patients and their carers viewed health and social care in the last year of life in NHYA IV HF. They conducted serial interviews with 20 patients, 27 carers, and 30 healthcare professionals. They found that quality of life was severely reduced by physical and psychological morbidity. In addition, psychosocial care, patient and carer education, and coordination of care between primary and secondary care were poor. A palliative care approach was rare.

Key references

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Croft JB, et al. Heart failure survival among older adults in the United States. *Arch Intern Med.* 1999;159:505–510.

Hershberger RE, et al. Care processes and clinical outcomes of continuous outpatient support with inotropes (COSI) in patients with refractory end-stage heart failure. *J Card Fail.* 2003;9:180–187.

Rose EA, et al. Long-term mechanical left ventricular assistance for end-stage heart failure. *N Engl J Med.* 2001;345:1435–1443.

Timing

Disease progression in heart failure

Timing of palliative care in HF is difficult. The disease trajectory is fundamentally different to cancers, where there is often a fairly predictable and inexorable decline towards death once response to treatment fails. In HF, half of all the patients die suddenly, although this proportion is smaller in those with advanced heart failure where most succumb to progressive pump failure (Fig. 43.1).

Despite a plethora of prognostic markers in HF, none provide much help on their own for deciding when palliative care should begin, although they can help provide confirmatory evidence of advanced disease.

For whom?

There is a growing appreciation that patients benefit from the opportunity for advanced planning towards their end-of-life care. Palliative care should be considered for those with:

- Severe functional limitation.
- Chronic poor quality of life with NYHA Class IV symptoms.
- End organ hypoperfusion, despite optimized medical therapy.

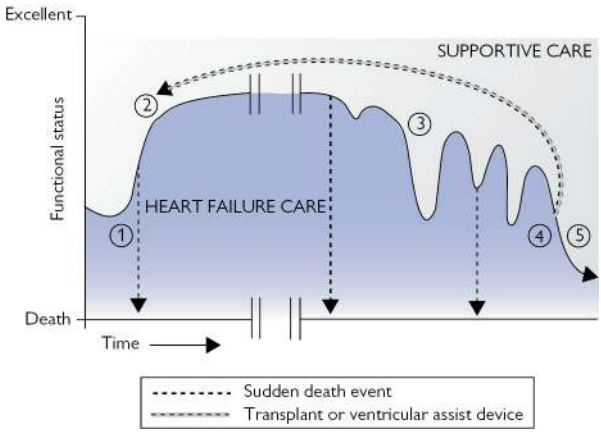

Fig. 43.1 The disease trajectory in HF. Schematic course of stage C and D heart failure. The stages refer to the ACC/AHA Classification Stages of HF—Stage C: patients with left ventricular dysfunction and with current or prior symptoms; Stage D: end stage. Sudden death may occur at any point along the course of illness. (1) Initial symptoms of heart failure (HF) develop, and HF treatment is initiated. (2) Plateaus of variable length may be reached with initial medical management, or after mechanical support, or heart transplant. (3) Functional status declines with variable slope, with intermittent exacerbations of HF that respond to rescue efforts. (4) Stage D HF, with refractory symptoms and limited function. (5) End-of-life.

Reproduced from *Journal of Cardiac Failure 2004*, 10: Goodlin S et al. Consensus statement: Palliative and supportive care in advanced heart failure, 200–9.

- Cardiac cachexia/low serum albumin.
- Significant disease progression in the previous 6 months:
  - Multiple hospital admissions.
  - Loss of ability to perform activities of daily living.
  - No remediable/exacerbating factors.
  - Ineligible for transplantation/MCS (see Chapters 8 and 9).

Guidelines

The ESC Guidelines recommend that the key components of palliative care should include (Table 43.1):

Table 43.1 Key components of palliative care service in patients with heart failure. ICD = implantable cardioverter-defibrillator; MCS = mechanical circulatory support; QOL= quality of life.

Focus on improving or maintaining the QOL of a patient and his/her family as well as possible until he/she dies.
Frequent assessment of symptoms (including dyspnoea and pain) resulting from advanced heart failure and other comorbidities and focus on symptom relief.
Access for the patient and his/her family to psychological support and spiritual care according to need.
Advanced care planning, taking into account preferences for place of death and resuscitation (which may include deactivating devices, such as ICD or long-term MCS that may require a multidisciplinary team decision).

Managing end-stage HF

Conventional HF therapy

This is difficult—especially in considering which drugs to stop as many disease-modifying drugs for HF also reduce symptoms. These include

- ACE inhibitors/ARNI/ARB.
- β-adrenoreceptor antagonists.
- Mineralocorticoid receptor antagonists.
- SGLT2 inhibitors.
- Diuretics.
- Digoxin.

In general, these should be continued but may require reduction or cessation if they are causing symptomatic hypotension, tiredness, or renal dysfunction.

Devices

- CRT improves HF symptoms in NYHA II–IV subjects.
- ICDs can alter the mode of death from sudden to progressive pump failure. Consideration should be given to switching the defibrillation function off after discussion with the patient and their family (see Chapter 6).

Specific palliative therapies: breathlessness

Opioids

Evidence from a small (n = 10) RCT, with a double-blinded crossover design in NYHA III/IV HF subjects, using 5 mg oral morphine 4-hourly, demonstrated a significant reduction in breathlessness without any adverse effect in terms of sedation. 2.5 mg morphine was used if the serum creatinine was >200 μmol/L. The treatment was combined with an anti-emetic haloperidol 1.5 mg at night and lactulose if necessary (Fig. 43.2). Repeat doses of opioids may be considered for the relief of dyspnoea, but patients should be counselled about the side effects of opioids such as constipation, nausea, and mental status change. Patients should also avoid driving while prescribed opioids.

Oxygen

A small study showed that oxygen therapy improved dyspnoea, but not effort or functional capacity.

IV inotropes

- Are used infrequently in the community in Europe: there is more experience in the USA.
- They are usually used in hospitalized HF patients with a low cardiac output.
- They can provide symptomatic relief.
- In those who are inotrope dependent, that is, cannot be weaned, home IV support is an option in some areas.

Specific palliative therapies: tiredness

- Sleep-disordered breathing occurs in 50% of advanced HF.

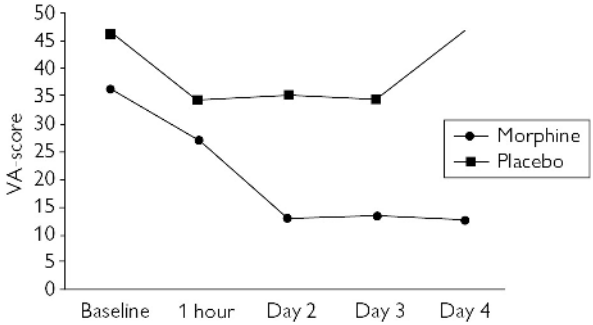

Fig. 43.2 The effect of morphine on dyspnoea in heart failure. Median breathlessness scores on placebo and morphine.

Johnson MJ, McDonagh TA, Harkness A, McKay SE, Dargie HJ. Morphine for the relief of breathlessness in patients with chronic heart failure—a pilot study. *Eur JHeart Fail.* 2002;4(6):753–756 by permission of Oxford University Press (for second edition).

- Some studies show that CPAP can improve LV function and neurohormonal profile in central sleep apnoea. This should be assessed and treated if necessary.
- The role of psychostimulants remains to be determined.

Specific palliative therapies: anxiety and depression

Patients should be offered conventional support via local psychology services.

Specific palliative therapies: pain

Patients should be offered non-pharmacological management. Further options include opioids, oxycodone, and fentanyl in conjunction with palliative care services.

Delivery of care

Interdisciplinary supportive care should be delivered. The key features are:

- Communication is essential.
- End-of-life planning is required.
- Concurrent with 'multiprofessional HF' care.
- Should focus on patients and families.

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Comin-Colet J, et al. Efficacy and safety of intermittent intravenous outpatient administration of levosimendan in patients with advanced heart failure (LION-HEART). *Eur J Heart Fail.* 2018;20:1128–1136.

Johnson MJ, McDonagh TA, Harkness A, McKay SE, Dargie HJ. Morphine for the relief of breathlessness in patients with chronic heart failure–a pilot study. *Eur J Heart Fail.* 2002;4:753–756.

Oxberry SG, et al. Repeat dose opioids may be effective for breathlessness in chronic heart failure if given for long enough. *J Palliat Med.* 2013;16:250–255.

The SUPPORT study demonstrated that 50% of seriously ill hospitalized patients, who survived 10 days, preferred care focused on comfort. Most patients prefer quality of life rather than longevity.

The palliative care given should relieve symptoms and provide holistic interdisciplinary support for patients and family. It can occur in several settings:

- Home based.
- Integrated HF care.
- Hospice based.

How to deliver care

How best to deliver end-of-life care causes anxiety and confusion for healthcare professionals. Should all end-stage HF patients be referred to a palliative care physician? This is clearly impractical, despite the fact that non-cancer palliative care is increasing. They would be unable to cope with the numbers. However, access to a palliative care consultative service is essential for those patients who require it.

The St George's experience of integrated HF care demonstrates a good model of care delivery. They studied 121 consecutive deaths between 1999 and 2002 in their hospital, with the following outcome:

- They developed a model of integrated, consultative, palliative care within a comprehensive HF management programme.
- They empowered HF nurse specialists, GPs, cardiologists, and internists to deliver palliative care.
- Ultimately, only 8.3% needed formal palliative care, 2.5% needed community palliative care services, and 4.1% hospice care (Figs. 43.3 and 43.4).

Palliative care consultation arrangements should be integrated into the existing multidisciplinary HF management programmes, so that this important end-of-life care can be delivered to those who need it.

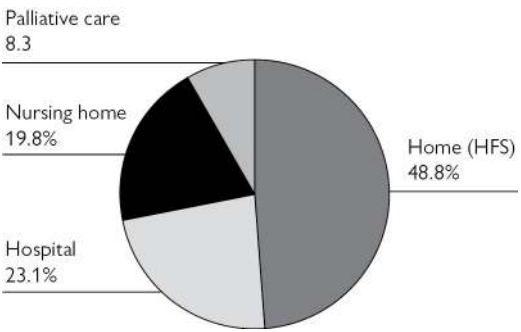

Fig. 43.3 The St George's integrated palliative care service—place of death of patients in collaborative heart failure programme. HFS indicates heart failure service (a community-based heart failure disease management programme).

Reproduced from Davidson et al. Integrated, collaborative palliative care in heart failure: the St. George Heart Failure Service experience 1999–2002. *J Cardiovasc Nurs.* 2004;19:68–75 with permission from Lippincott, Williams and Wilkins.

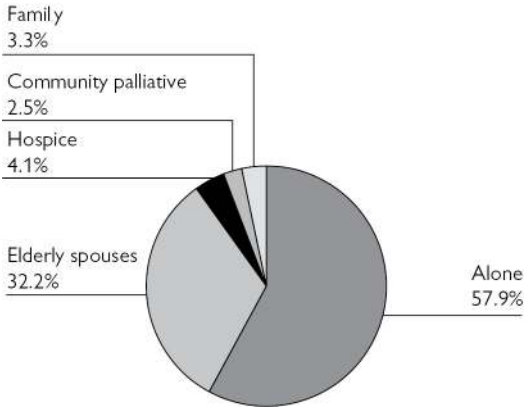

Fig. 43.4 The St George's integrated palliative care service—level of support for patients in a home-based collaborative care programme.

Reproduced from Davidson et al. Integrated, collaborative palliative care in heart failure: the St. George Heart Failure Service experience 1999–2002. *J Cardiovasc Nurs.* 2004;19:68–75 with permission from Lippincott, Williams and Wilkins.

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Future research

Palliative care in end-stage HF is an area where there has to be a focus on future research, especially within the domains of:

- Prognosis and illness trajectory.
- Symptom treatments, for example, opioids, interventions for fatigue, and antidepressants.
- Patient and family support.
- Models of integration of HF services with palliative care services.

Index

For the benefit of digital users, indexed terms that span two pages (e.g., 52–53) may, on occasion, appear on only one of those pages.

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