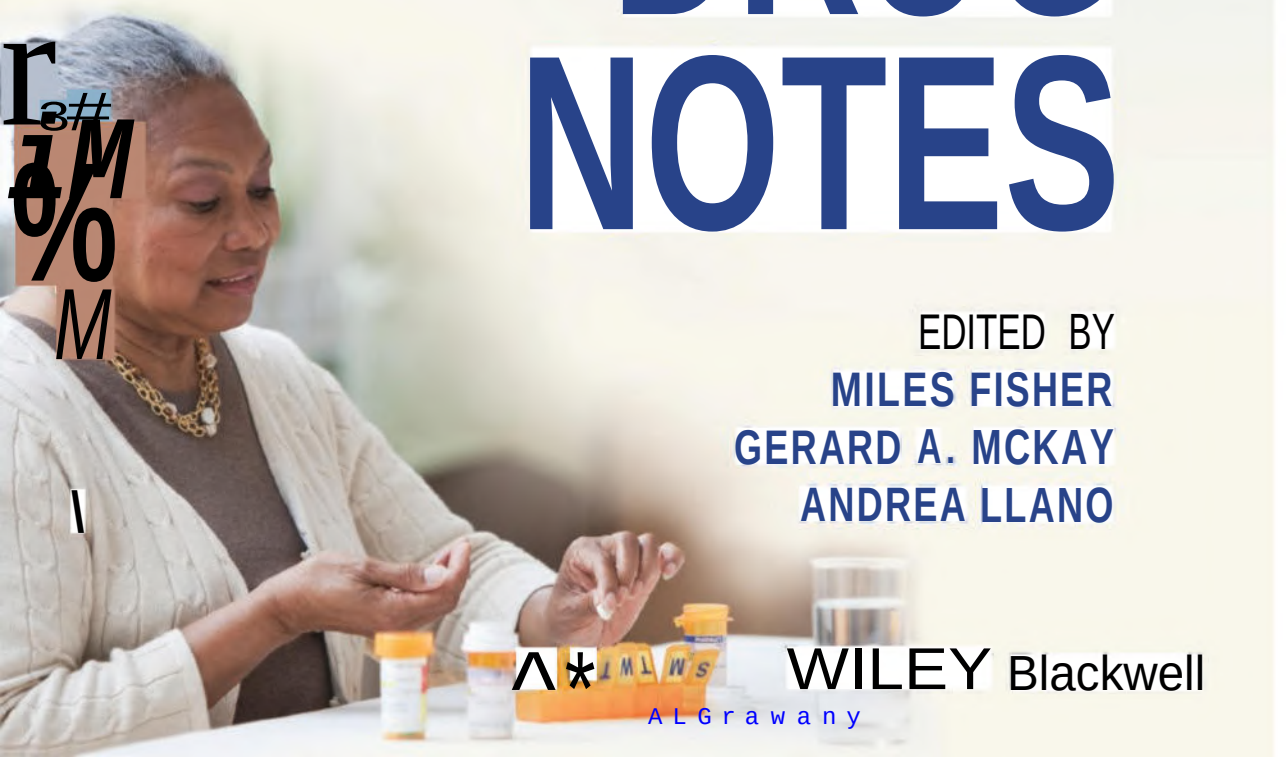
DIABETES DRUG NOTES



EDITED BY
MILES FISHER
GERARD A. MCKAY
ANDREA LLANO

WILEY Blackwell

Diabetes Drug Notes

A L G r a w a n y

Diabetes Drug Notes

Edited by

MILES FISHER,
GERARD A. MCKAY, AND ANDREA LLANO
Glasgow Royal Infirmary, Glasgow, UK

WILEY Blackwell

This edition first published 2022

Registered Offices
John Wiley & Sons, Inc., 111 River Street, Hoboken, NJ 07030, USA
John Wiley & Sons Ltd, The Atrium, Southern Gate, Chichester, West Sussex, PO19 8SQ, UK

Editorial Office
9600 Garsington Road, Oxford, OX4 2DQ, UK

For details of our global editorial offices, customer services, and more information about Wiley products visit us at www.wiley.com.

Wiley also publishes its books in a variety of electronic formats and by print-on-demand. Some content that appears in standard print versions of this book may not be available in other formats.

Library of Congress Cataloging-in-Publication Data
Names: Fisher, Miles, editor. | McKay, Gerard A., editor. | Llano, Andrea, editor.
Title: Diabetes drug notes / edited by Miles Fisher, Gerard A. McKay, Andrea Llano.
Description: Hoboken, NJ : Wiley-Blackwell, 2022. | Includes bibliographical references and index. | Contents: Clinical pharmacology of antidiabetic drugs / Andrea Llano, Gerry McKay, and Ken Paterson -- Metformin / Joseph Timmons and James Boyle -- Sulfonylureas and meglitinides -- Joseph Timmons and James Boyle -- DPP-4 inhibitors / Sharon Mackin and Gemma Currie -- SGLT2 inhibitors / Miles Fisher, Andrea Llano, and Gerry McKay -- GLP-1 receptor agonists / Catherine Russell and John Petrie -- Animal and human insulin / Ken Paterson -- Short-acting insulin analogues / Kate Hughes and Gerry McKay -- Long-acting Insulin Analogues / Robert Lindsay -- Devices / David Carty -- Acarbose and alpha glucosidase inhibitors / Miles Fisher -- Glitazones and glitazars / Miles Fisher -- Other antidiabetic drugs / Maroria Oroko, Andrea Llano, and Miles Fisher -- Future antidiabetic drugs / Emma Johns and Miles Fisher -- Guidelines / Miles Fisher and Russell Drummond -- Prescribing antidiabetic drugs / Andrea Llano, Gerry McKay, Frances McManus, Catriona McClements, Joyce McKenzie, and Deborah Morrison.
Identifiers: LCCN 2022020904 (print) | LCCN 2022020905 (ebook) | ISBN 9781119785002 (paperback) | ISBN 9781119785019 (pdf) | ISBN 9781119785026 (epub) | ISBN 9781119785033 (ebook)
Subjects: MESH: Hypoglycemic Agents--pharmacology | Glycoside Hydrolase Inhibitors--pharmacology | Insulins--pharmacology | Diabetes Mellitus--drug therapy
Classification: LCC RC661.I6 (print) | LCC RC661.I6 (ebook) | NLM WK 825 | DDC 616.4/62061--dc23/eng/20220608
LC record available at https://lccn.loc.gov/2022020904
LC ebook record available at https://lccn.loc.gov/2022020905

Cover image: © Milos Dimic/Getty Images, Jose Luis Pelaez/Getty Images, MirageC/Getty Images
Cover design by Wiley

Set in 10/12pt STIXTwoText by Integra Software Services Pvt. Ltd, Pondicherry, India

Contents

Foreword

As the prevalence of diabetes continues to escalate, the delivery of individualised, effective, and well-tolerated treatment has become ever more prescient. Achieving adequate glycaemic control is a fundamental therapeutic objective across the spectrum of diabetes presentations in order to defer and address complications and co-morbidities. Type 2 diabetes accounts for the majority of people with diabetes, and the management of this disease is made particularly difficult by its heterogeneity and variable natural history. Type 1 diabetes requires the fine-tuning of insulin replacement to maintain quality and quantity of life. Recent years have seen the availability of an increasing range of therapies that target different aspects of the pathophysiology, but how can these drugs be used to best effect?

This book explains the rationale that underpins the selection of antidiabetic drugs and offers clear practical know-how advice to guide healthcare professionals through the pharmacotherapy of diabetes. Each class of antidiabetic drug receives comprehensive coverage, supported by evidence from key clinical trials and 'real-world' usage. The text is conveniently structured for a duality of purpose, such that it successfully provides detailed pharmacology for the specialist while also offering straightforward clinical pointers for the non-specialist.

Optimising the management of diabetes requires clinicians to take full advantage of the variety of antidiabetic drugs, and this book brings a much welcomed informative and authoritative resource to serve this need.

Clifford J. Bailey
Professor emeritus
Aston University, Birmingham, UK

Preface

At Glasgow Royal Infirmary historically diabetes and clinical pharmacology were linked with specialists in each discipline contributing to one of the medical units in the provision of general medical care to the inhabitants of the east of Glasgow whilst delivering specialist expertise. A few miles north of the Royal Infirmary, Stobhill Hospital in its prime had physicians delivering care who were also delivering academic excellence in the Department of Materia Medica at the University of Glasgow. In 2011 the two hospitals in the northeast of Glasgow merged to provide in patient care on one site and in doing so brought together the prospect of having a combined Department of Diabetes, Endocrinology and Clinical Pharmacology.

In addition to having a long-standing reputation for recruiting patients to commercial studies, the Royal Infirmary has strong links with the University of Glasgow, with senior academics continuing to provide both general and specialist patient care, and the University of Strathclyde Institute of Pharmacy and Biomedical Sciences, specifically around training independent pharmacy prescribers.

Education and training have been hallmarks of the department and in 2008 a series of Drug Notes was established for *Practical Diabetes*, covering drugs used in those with diabetes but not necessarily ones for lowering blood glucose, encouraging trainees to be first authors. The series is still going, suggesting that an understanding of drugs is an essential part of being a healthcare provider with an interest in diabetes. Antidiabetic drugs were covered in two separate series for the British Journal of Cardiology, again with trainees aspiring to be specialists in diabetes and endocrinology being first authors and to consider clinical pharmacology as a key knowledge skill.

With the emergence of new therapies for diabetes that are now providing benefits beyond glycaemic control, it seemed like the right time to bring together one definitive text that provides the prescriber with the background information and evidence that will help underpin their practice. We chose to ask colleagues in our department to contribute with the help of trainees working on a formula that has worked before but also because the clinical expertise within our department has specialists in both fields and contributed significantly to the Scottish Intercollegiate Guideline Network (SIGN) guideline for diabetes (SIGN116) but also to the Clinical Pharmacological update for type 2 diabetes in 2017 owing to the emergence of new classes of drugs to treat type 2 diabetes (SIGN154).

We are grateful to colleagues and trainees in the Department of Diabetes, Endocrinology and Clinical Pharmacology for taking on the challenge of contributing to this book. As is often the case when taking on a task like this, it became incredibly time consuming, particularly as we neared completion, and therefore we owe a debt of gratitude to our families for their patience, understanding and support.

Miles Fisher
Andrea Llano
Gerry McKay

Editors and contributors

Editors

Miles Fisher, MBChB, MD, FRCP
Formerly Consultant Physician, Department of Diabetes, Endocrinology and Clinical Pharmacology, Glasgow Royal Infirmary, 84 Castle Street, Glasgow G4 0SF, UK
Honorary Professor, University of Glasgow, Glasgow, UK
miles.fisher@ggc.scot.nhs.uk

Gerard A. McKay, BSc (Hons), MBChB, FRCP, FBPhS
Consultant Physician, Department of Diabetes, Endocrinology and Clinical Pharmacology, Glasgow Royal Infirmary, 84 Castle Street, Glasgow G4 0SF, UK
Honorary Clinical Associate Professor, University of Glasgow, Visiting Professor, University of Strathclyde, Glasgow, UK
gerard.mckay@ggc.scot.nhs.uk

Andrea Llano, BSc (Hons), MBChB, MRCP
Consultant Physician, Department of Diabetes, Endocrinology and Clinical Pharmacology, Glasgow Royal Infirmary, 84 Castle Street, Glasgow G4 0SF, UK
Honorary Clinical Lecturer, University of Glasgow, Glasgow, UK
andrea.llano@ggc.scot.nhs.uk

Contributors

James Boyle, MBChB, MD, MSc, FRCP
Consultant Physician, Department of Diabetes, Endocrinology and Clinical Pharmacology, Glasgow Royal Infirmary, 84 Castle Street, Glasgow G4 0SF, UK
Honorary Clinical Associate Professor, University of Glasgow, Glasgow, UK

David Carty, MBChB, PhD, FRCP
Consultant Physician, Department of Diabetes, Endocrinology and Clinical Pharmacology, Glasgow Royal Infirmary, 84 Castle Street, Glasgow G4 0SF, UK
Honorary Clinical Senior Lecturer, University of Glasgow, Glasgow, UK

Gemma Currie, MBChB, MRCP, PhD
Consultant Physician, Department of Diabetes, Endocrinology and Clinical Pharmacology, Glasgow Royal Infirmary, 84 Castle Street, Glasgow G4 0SF, UK
Honorary Clinical Senior Lecturer, University of Glasgow, Glasgow, UK

Russell Drummond, BSc (Hons), MBChB, MD, FRCP
Consultant Physician, Department of Diabetes, Endocrinology and Clinical Pharmacology, Glasgow Royal Infirmary, 84 Castle Street, Glasgow G4 0SF, UK
Honorary Clinical Associate Professor, University of Glasgow, Glasgow, UK

Miles Fisher, MBChB, MD, FRCP
Formerly Consultant Physician, Department of Diabetes, Endocrinology and Clinical Pharmacology, Glasgow Royal Infirmary, 84 Castle Street, Glasgow G4 0SF, UK
Honorary Professor, University of Glasgow, Glasgow, UK

Kate Hughes, MBChB, MRCP, PhD
Consultant Physician, Department of Diabetes, Endocrinology and Clinical Pharmacology, Glasgow Royal Infirmary, 84 Castle Street, Glasgow G4 0SF, UK

Emma Johns, MBChB, MRCP, PhD
Specialty Trainee in Diabetes and Endocrinology, Department of Diabetes, Endocrinology and Clinical Pharmacology, Glasgow Royal Infirmary, 84 Castle Street, Glasgow G4 0SF, UK

Robert Lindsay, BSc, MBChB, PhD, FRCP
Reader in Diabetes and Endocrinology, Institute of Cardiovascular and Medical Sciences, University of Glasgow, Glasgow, UK
Honorary Consultant Physician, NHS Greater Glasgow and Clyde, Glasgow, UK

Andrea Llano, BSc (Hons), MBChB, MRCP
Consultant Physician, Department of Diabetes, Endocrinology and Clinical Pharmacology, Glasgow Royal Infirmary, 84 Castle Street, Glasgow G4 0SF, UK
Honorary Clinical Lecturer, University of Glasgow, Glasgow, UK

Sharon Mackin, MBChB (Hons), MRCP (Diabetes and Endocrinology), MD
Consultant Physician, Department of Diabetes, Endocrinology and Clinical Pharmacology, Glasgow Royal Infirmary, 84 Castle Street, Glasgow G4 0SF, UK
Honorary Clinical Senior Lecturer, University of Glasgow, Glasgow, UK

Catriona McClements, MBChB
Senior Clinical Fellow, Department of Diabetes, Endocrinology and Clinical Pharmacology, Glasgow Royal Infirmary, Glasgow, UK

Gerard A. McKay, BSc (Hons), MBChB, FRCP, FBPhS
Consultant Physician, Department of Diabetes, Endocrinology and Clinical Pharmacology, Glasgow Royal Infirmary, 84 Castle Street, Glasgow G4 0SF, UK
Honorary Clinical Associate Professor, University of Glasgow, Visiting Professor, University of Strathclyde, Glasgow, UK

Joyce McKenzie, BSc, MBChB, MD
Specialty Doctor in Diabetes, Department of Diabetes and Endocrinology, New Stobhill Hospital, Glasgow, UK

Frances McManus, BSc (MedSci), MBChB, MRCP, PhD
Consultant Physician, Consultant Physician, Department of Diabetes, Endocrinology and Clinical Pharmacology, Glasgow Royal Infirmary, 84 Castle Street, Glasgow G4 0SF, UK

Deborah Morrison, MBChB, MRCP, PhD, MRCGP
General Practitioner with a special interest in diabetes, Department of Diabetes and Endocrinology, New Stobhill Hospital, Glasgow, UK
Honorary Clinical Lecturer, University of Glasgow, Glasgow, UK

Maroria Oroko, BSc (Hons), MBChB, MRCP
Specialty Trainee in Diabetes and Endocrinology, Department of Diabetes, Endocrinology and Clinical Pharmacology, Glasgow Royal Infirmary, 84 Castle Street, Glasgow G4 0SF, UK

Ken Paterson, MBChB, FRCP, FFPM, FBPhS
Formerly Consultant Physician, Department of Diabetes, Endocrinology and Clinical Pharmacology, Glasgow Royal Infirmary, 84 Castle Street, Glasgow G4 0SF, UK
Honorary Senior Research Fellow, University of Glasgow, Glasgow, UK

John Petrie, BSc (Hons), MBChB, PhD, FRCP
Professor of Diabetic Medicine, Institute of Cardiovascular and Medical Sciences, University of Glasgow, Glasgow, UK
Honorary Consultant Physician, Department of Diabetes, Endocrinology and Clinical Pharmacology, Glasgow Royal Infirmary, 84 Castle Street, Glasgow G4 0SF, UK

Catherine Russell, MBChB, MRCP
Specialty Trainee in Diabetes and Endocrinology, Department of Diabetes, Endocrinology and Clinical Pharmacology, Glasgow Royal Infirmary, Glasgow, UK

Joseph Timmons, BMSc (Hons), MBChB (Hons), MRCP
Clinical Lecturer in Diabetes and Endocrinology, Institute of Cardiovascular and Medical Sciences, University of Glasgow, Glasgow, UK
Honorary Specialty Trainee in Diabetes and Endocrinology, NHS Greater Glasgow and Clyde, Glasgow, UK

Introduction

Diabetes Drug Notes is an expansion of the approach that we used for the Drug Notes series in *Practical Diabetes*. That series features drugs used in people with diabetes to manage cardiovascular disease, diabetic complications, and other effects of diabetes, but not the management of glycaemia. Each note in *Practical Diabetes* had a short introduction, a description of the pharmacology, evidence for efficacy and safety, any specific evidence for use in people with diabetes, and a short discussion. Three or four key points summarised the review, and references are kept to a minimum. Diabetes Drug Notes follows a broadly similar approach with key points, short introductions, sections on pharmacology, evidence for glycaemic efficacy and safety, results from outcome trials in diabetes, and refences that are focussed on glycaemic efficacy and outcome trials.

In Chapter 1 we describe the basic principles of clinical pharmacology with a focus on how these principles apply to antidiabetic drugs (we have adopted this term as it is used in the British National Formulary, which will be familiar to many readers, rather than alternatives such as 'glucose-lowering agents' or 'hypoglycaemic agents').

In Chapters 2–14, following a short introduction, we describe the pharmacology of the drugs, including descriptions of the mechanisms of action, relevant pharmacokinetic considerations, and doses for drugs that are available in the UK. Glycaemic efficacy is described, including in comparison with other antidiabetic drugs, followed by safety and side effects. We then detail outcome trials with the drugs, covering cardiovascular outcome trials, renal outcome trials, and other outcome trials such as the prevention of diabetes or use in overweight and obesity. For metformin, sulfonylureas and animal and human insulin we also include information about the history of the drugs. Each chapter finishes with a discussion of the place of the drug/s in current and future clinical practice. Detailed references are provided for efficacy and outcome trials, but other sections have minimal referencing.

Chapter 15 on guidelines focusses on the drugs rather than wider aspects of diabetes care. For patients with type 2 diabetes there are many guidelines dedicated to antidiabetic drugs, but for patients with type 1 diabetes, and for diabetes and pregnancy, information has been extracted from more comprehensive guidelines. Chapter 16 describes how antidiabetic drugs are prescribed in patients with diabetes depending on clinical features and comorbidities and includes patient journeys for a patient with type 1 diabetes and a patient with type 2 diabetes.

It is not the intention that the book should be read in order from first to last chapter, and we have provided detailed cross-referencing within the chapters. For example, a reader might start with the chapter on DPP-4 inhibitors, go to Chapter 1 to understand why the cardiovascular outcome trials were conducted, dip into Chapter 12 on glitazones for more information on the rosiglitazone controversy, move on to Chapter 6 to see how GLP-1 receptor agonists compare with DPP-4 inhibitors, see what guidelines say about these drugs in Chapter 15, and finish with prescribing issues for them in Chapter 16.

Miles Fisher
Andrea Llano
Gerry McKay

CHAPTER 1

Clinical Pharmacology of Antidiabetic Drugs

Andrea Llano, Gerry McKay, and Ken Paterson

KEY POINTS

- Clinical pharmacology studies the relationship between drugs and the body and has a crucial role in the development of new therapies.
- Pharmacodynamics describes how a drug exerts its actions and pharmacokinetics is the processes a drug undergoes (absorption, distribution, metabolism and excretion).
- The drug development and regulatory process is lengthy and new medicines need to demonstrate safety, efficacy and quality. In addition, drugs intended to be used in diabetes require demonstration of cardiovascular safety.
- Pharmacoeconomics allows the provision of cost-effective therapies to those who need them and is an important tool when there is an increasing demand for healthcare and limited resource.

Introduction

Clinical pharmacology describes all aspects of the relationship between drugs and humans. An understanding not only allows for the discovery and development of new drugs that influence the course of disease, but also a better understanding of how drugs work can aid the prescriber in partnership with the patient to ensure that the most appropriate drug is chosen. This is relevant for prescribing in diabetes

Diabetes Drug Notes, First Edition. Edited by Miles Fisher, Gerard A. McKay, and Andrea Llano.

given the increase in antidiabetic drugs that are now available for glucose lowering, many with additional benefits. Choosing the correct antidiabetic drug ('antihyperglycaemic' and 'oral hypoglycaemic' are other terms used) is complicated in many cases by the need for wider cardiovascular risk management and the polypharmacy that can result from managing established complications and other co-morbidities. Before getting to the individual with diabetes, antidiabetic drugs have to go through a lengthy development process underpinned by the requirement to show safety, efficacy and quality.

A serendipitous approach to drug discovery and development based on observations and careful measurement of response has been replaced by a deeper understanding of biochemical and pathophysiological processes that influence disease. This has led to the synthesis of specific agents (chemical or biological) with specific actions. Measurement of drug concentrations in plasma and correlation with effect have aided drug development. The development of genomics and proteomics has added further sophistication such that individualisation of drug choice is a much more realistic prospect.

Clinical Pharmacology

Introduction

The dose–response relationship within an individual is a measure of sensitivity to a drug. This has two components: pharmacokinetics and pharmacodynamics. Pharmacokinetics describes the dose–concentration relationship, and pharmacodynamics describes the concentration–effect relationship. Understanding pharmacodynamics and pharmacokinetics is fundamental to the process of drug development, e.g. selecting the appropriate dose to ensure that the concentration of drug at the site of action is likely to have a therapeutic effect. Understanding pharmacokinetics and pharmacodynamics is relevant to clinical practice as it allows optimisation of therapeutic interventions for the individual being treated [1].

Pharmacodynamics

The effect that a drug has on the body can often be explained through a specific mechanism of action. This can be through action on specific receptors, enzymes or membrane ionic channels or by a direct cytotoxic action.

Action on a Receptor A receptor is normally a protein situated on the cell membrane or within the cell. Drugs bind to the receptors and can act in three ways:

- An agonist stimulates the receptor to produce an effect.
- An antagonist blocks the receptor from being activated by an agonist.

- A partial agonist stimulates the receptor to a limited extent but blocks it from being stimulated by naturally occurring agonists.

For antidiabetic drugs the main type of effect seen at receptors is an agonist effect. This can be seen for sulfonylureas, which bind to SU receptors on beta cells, and PPAR gamma agonists, which act on nuclear receptors to increase transcription of insulin-sensitive genes.

Action on an Enzyme Enzymes are proteins that, through interaction with substrates, result in activation or inhibition. Although the mechanism of action of metformin is poorly understood, part of its effect in diabetes is through activated AMP kinase. Another diabetes class acting through an effect on enzymes is DPP-4 inhibitors. These drugs inhibit the action of dipeptidyl peptidase-4, allowing for the prolongation of the action of endogenous incretins GLP-1 and GIP.

Membrane Channels Some drugs exert their action through an effect on membrane channels. SGLT 2 inhibitors work by blocking the sodium glucose co-transporter 2, resulting in the loss of glucose and sodium in urine.

Cytotoxic This mechanism of action is more relevant to drugs used to treat cancer.

Dose–Response Relationship When thinking about drugs an understanding of dose response is important. Dose–response relationships can be steep or flat (Figure 1.1). In the treatment of diabetes with insulin, a flat dose–response curve is

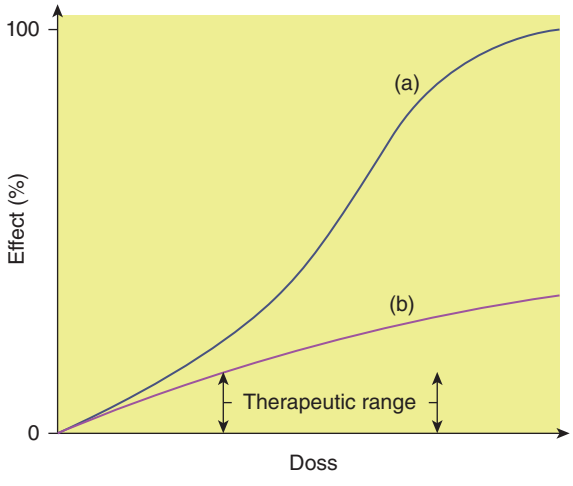


FIGURE 1.1 Dose–response relationships for drugs. Schematic examples of a drug (a) with a steep dose– (or concentration–) response relationship in the therapeutic range, and (b) a flat dose– (or concentration–) response relationship within the therapeutic range.

desirable for background insulin, but a steep dose–response curve is desirable for prandial insulin. In clinical practice the maximum therapeutic effect might not be achieved because of the emergence of undesirable effects. In drug development, if too high a dose is chosen it may be that the success of the drug is hampered by the side effects, e.g. in the case of the DPP-4 inhibitor vildagliptin, at a higher dose liver function tests need to be monitored, which is not the case for other drugs in the class. It is very important to consider this in drug development both for the desired effect and for adverse effects. This leads to the concept of therapeutic range. The difference between the concentration causing a desired effect and the concentration causing an adverse effect is termed the therapeutic index, a measure of a drug's safety.

Dose–response curves can be influenced by genetics, environment and disease, and have two components: dose–plasma concentration and plasma concentration–effect. The ability to develop assays to measure drug concentration has allowed a better understanding of the variability in response between individuals but also for some drugs with a narrow therapeutic index the ability to perform therapeutic drug monitoring.

Pharmacokinetics

Absorption After drugs have been given orally, they can be considered to have an absorption rate and bioavailability. By slowing absorption, the dose–concentration relationship can be smoothed out, giving a more sustained effect and minimising side effects, e.g. Glucophage SR® (slow-release metformin). Subcutaneous absorption of insulin can also be manipulated to provide the desired effect, both to make absorption quicker, which is desirable for prandial insulin, and to make it slower, which is desirable for basal insulin. Bioavailability is a term used to describe the fraction of drug that gets into the systemic circulation. GLP-1 receptor agonists like most peptide-based drugs generally cannot be given orally owing to them being digested, so they need to be given parenterally to get sufficient quantities into the systemic circulation. However, one oral preparation of GLP-1 receptor agonist is now available that relies on a sophisticated delivery method and at a much higher dose than the parenteral preparation to achieve sufficient systemic exposure for the desired clinical effect (see Chapter 6). Other orally administered drugs can undergo extensive first-pass metabolism in the liver, resulting in a significant reduction in systemic exposure and clinical effect.

Distribution/Plasma Protein Binding When a drug gets into the systemic circulation it is then distributed to the tissues. This process will be dependent on the properties of the drug, in particular protein binding and lipid solubility factors. In practice protein binding has little in the way of clinical relevance, but if a drug has low protein binding and is highly lipid soluble, it will have only a small amount in the circulation and thus will be considered to have a high volume of distribution. In real terms this has more of an impact on drug development.

Clearance Clearance is the sum of all of the drug eliminated from the body and mostly depends on hepatic metabolism and renal excretion. If a drug is given by intravenous infusion or repeated doses orally, there will come a point at which a balance is reached between the drug entering and the drug leaving the body. This results in a steady-state concentration in the plasma or serum (C_{ss}). A constant-rate intravenous infusion will yield a constant C_{ss}, while a drug administered orally at regular intervals will result in fluctuation between peak and trough concentrations (Figure 1.2). Clearance depends on the liver and/or kidneys eliminating a drug and will be affected by diseases that affect these organs either directly or via blood flow to these organs. In stable clinical conditions when clearance remains constant it is directly proportional to dose rate, so-called first-order or linear kinetics. Few drugs show zero-order kinetics, e.g. alcohol when eliminating enzymes become saturated. Following a single intravenous bolus dose, it is possible to work out the time that it takes for elimination to result in half the original concentration of the drug being present (the half-life or $t_{1/2}$) and through a number of complex equations, the time at which steady state will be achieved after starting a regular treatment schedule or after any change in dose can be predicted. Generally this takes four to five half-lives.

Drug Metabolism and Elimination Drugs that are already water soluble are generally excreted unchanged by the kidney. Lipid-soluble drugs are not easily excreted by the kidney because, following glomerular filtration, they are largely reabsorbed from the proximal tubule. The first step in the elimination of such lipid-soluble drugs is metabolism to more polar (water-soluble) compounds. This is achieved mainly in the liver.

Metabolism generally occurs in two phases:

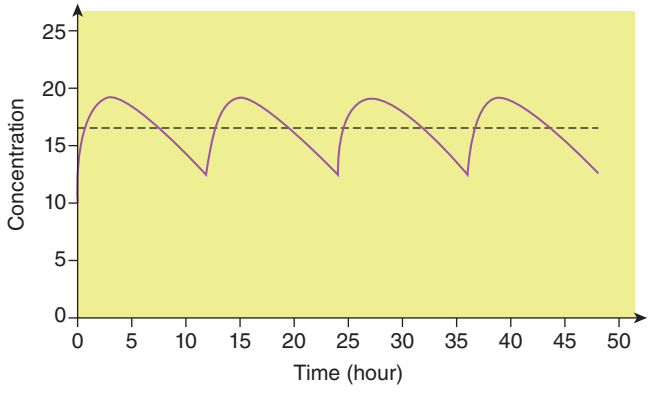


FIGURE 1.2 Steady-state concentration–time profile for an oral dose (—) and a constant rate intravenous infusion (- - - - -).

Phase 1. Mainly oxidation, but also reduction or hydrolysis to a more polar compound. Oxidation can occur in various ways at carbon, nitrogen or sulfur atoms and *N*- and *O*-dealkylation. These reactions are catalysed by the cytochrome P450-dependent system of the endoplasmic reticulum. Knowledge of P450, which exists as a superfamily of similar enzymes (isoforms), has increased greatly recently, and it is divided into a number of families and subfamilies. Although numerous P450 isoforms are present in human tissue, only a few of these have a major role in the metabolism of drugs. These enzymes, which display distinct but overlapping substrate specificity, include CYP1A2, CYP2C9, CYP2C19, CYP2D6, CYP2E1 and CYP3A4.

Phase 2. Conjugation usually by glucuronidation or sulfation to make the compound more polar. This involves the addition of small endogenous molecules to the parent drug, or to its phase 1 metabolite, and almost always leads to abolition of pharmacological activity. Multiple forms of conjugating enzymes are also known to exist, although these have not been investigated to the same extent as the P450 system.

Enzyme Induction and Inhibition Enzyme induction or inhibition can result in a pharmacokinetic drug interaction diminishing clinical efficacy or resulting in side effects, respectively. Induction is the result of a drug prolonging the action and activity of drug-metabolising enzymes. In clinical practice rifampicin, carbamazepine and phenytoin are potent enzyme inducers, as is 'over the counter' St John's Wort. These agents increase the activity of drug metabolising enzymes and increase the metabolism of medicines metabolised by the same route. Inhibition reduces metabolism and prolongs the action of a drug. In clinical practice macrolide antibiotics (e.g. clarithromycin) can inhibit cytochrome P450, prolonging the action of some drugs that are commonly used in diabetes patients, e.g. simvastatin, which should be stopped whilst on macrolide treatment.

Renal Excretion Glomerular filtration is the most common route of renal elimination. Free drug is cleared by filtration and the protein-bound drug remains in the circulation. Active secretion in the proximal tubule, which can affect both weak acids and weak bases, has specific secretory sites in proximal tubular cells and can also be a mechanism for elimination and also passive reabsorption in the distal tubule. If renal function is impaired, for example by disease or old age, then the clearance of drugs that normally undergo renal excretion is decreased. The effect of reduced renal excretion on dose for antidiabetic drugs is summarised in Chapter 16, Table 16.3.

Drug Development and Clinical Trials

Introduction

The development of drugs for therapeutic use is complex and lengthy and necessarily subject to extensive regulatory requirements. The three pillars of drug development are safety, efficacy and quality. Safety and efficacy of an investigational product are

required to be shown in well-designed and robust clinical trial programmes before regulatory approval is granted so that a drug can be marketed. This is governed by Good Clinical Practice. Quality needs to be shown in manufacturing processes and is governed by Good Manufacturing Practice. Drugs intended for use in patients with type 2 diabetes are also required to demonstrate their cardiovascular safety using outcomes such as cardiovascular mortality, myocardial infarction and stroke. There have been many changes in the development process and its regulation over the last century. The process of drug development and approval is summarised in Figure 1.3. It can take more than 12 years to take a drug into the market, at a considerable cost (>£1 billion).

Preclinical Development

Historically, remedies and treatments were derived from plants and herbs, and many drugs were discovered serendipitously. The use of *Galega officianalis* (biguanide) to treat symptoms of hyperglycaemia has been documented as far back as medieval times. Sulfonylureas were initially investigated for use in the treatment of typhoid and incidentally found to cause hypoglycaemia. SGLT2 inhibitors were derived from phlorizin,

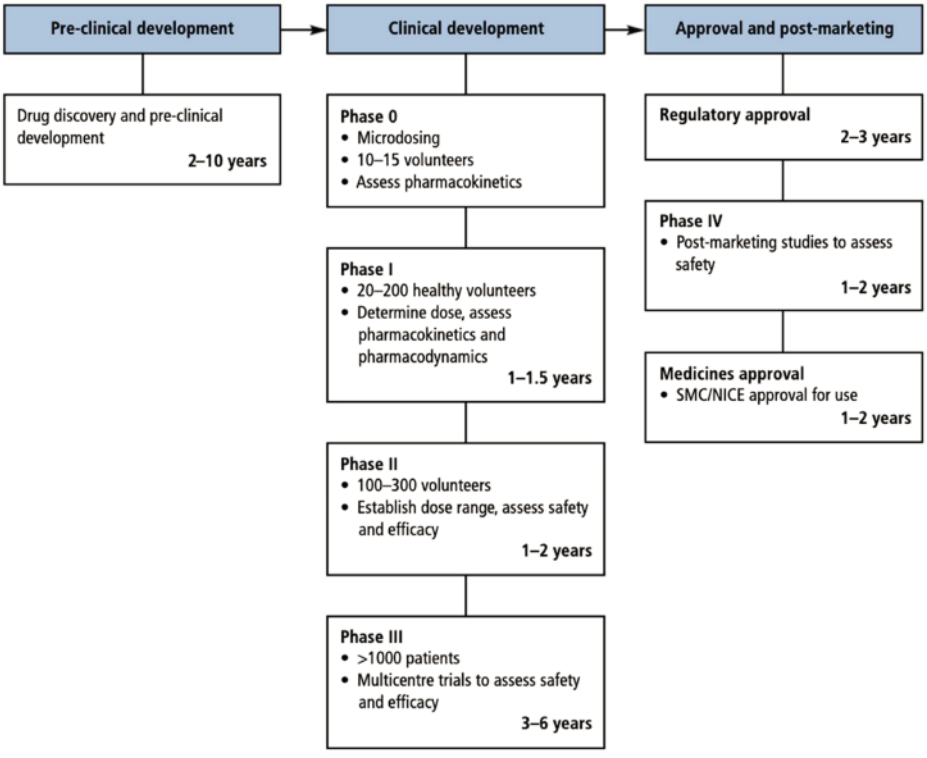


FIGURE 1.3 Drug development and approval. Clinical development consists of Phase 0, Phase I (or 1), Phase II (or 2) and Phase III (or 3). Phase IV (or 4) is part of post-marketing.

a compound derived from apple tree bark that was initially used in fever but was found to also cause glycosuria.

Advances in the understanding of the pathological processes involved in disease at the cellular and molecular levels have led to more sophisticated methods of drug discovery and a more methodical approach to drug development. Biological targets are first selected and compounds which are active at this site are identified. These compounds can be designed according to the target's chemical structure or selected from a pharmaceutical research organisation's extensive compound library. Several thousand molecules are usually identified at the beginning of this process. Candidate drug molecules then enter a process known as lead optimisation where they undergo further selection and/or modification to achieve the desired pharmacological activity. Preclinical testing involves extensive *in vivo* studies undertaken to determine a compound's affinity and selectivity in cell disease models. This period takes 2–10 years and approximately 50% of lead compounds do not progress beyond this point. Various animal models are used to establish the compound's pharmacokinetic characteristics (absorption, distribution, metabolism and excretion). *In vivo* toxicology studies are used to determine the maximum nontoxic dose of the drug and establish reproductive toxicity (adverse effects on fertility, foetal development and lactation).

This is a crucial stage in drug development as the costs increase exponentially once a drug gets into clinical development in humans. If a drug shows potential toxicity in animal studies, it is important to understand that this is generally at higher concentrations than would be used clinically and does not necessarily result in it not getting tested in humans. An example of this is the GLP-1 receptor agonist liraglutide, which was shown to increase the risk of thyroid cancer in mice and rat models, but at doses 8 times higher than what humans would receive. In subsequent clinical trials the risk of developing medullary thyroid cancer, which is very rare, has not been shown. However, the animal results have meant that this potential side effect has been highlighted as something to look out for in subsequent clinical trials in the development programme.

Chemical properties such as stability and formulation are also established, and manufacturing processes developed to ensure that the lead compound can be produced in sufficient quantity and quality for clinical studies. Towards the end of this period, applications to regulatory bodies are prepared to proceed to investigation in humans [2].

Regulatory Approval

Prior to the 1960s there was no formal process of drug approval or regulation, and it was not a legal requirement to demonstrate the efficacy or safety of a drug. Thalidomide was first marketed in 1956 as a sedative and hypnotic and was used as a treatment for nausea and vomiting associated with pregnancy. No formal clinical trials or reproductive toxicology studies had been carried out prior to its marketing. It was soon noted to cause an increase in birth defects and was banned in 1961.

These findings prompted regulatory reformations necessitating that a drug's safety and efficacy be vigorously demonstrated. The Food and Drug Administration (FDA)

produced the Drug Amendments Act of 1962 in the US, and the Medicines Act 1968 in the UK set down the legal framework by which medicines are licensed and controlled. These amendments ensure that manufacturers demonstrate a drug's safety and efficacy using controlled clinical studies in appropriate study participants and that post-marketing surveillance is carried out.

Prior to testing in humans, regulatory approval must be obtained from the relevant regulatory authority, including the European Medicines Agency (EMA) in Europe and the FDA in the US (Table 1.1). Along with the third large regulatory authority in Japan, the International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH) was established and continues to meet to bring together the regulatory authorities and pharmaceutical industry to discuss scientific and technical aspects of drug registration.

On 31 January 2020, the UK formally left the European Union and entered a transition period that ended on 1 January 2021. Following Brexit, the regulation of all medicines and devices has transferred from the EMA to the UK's Medicines and Healthcare Products Regulatory Agency (MHRA) [3]. This is likely to prove challenging as previously many of the submissions to the EMA were contracted out to the MHRA. Therefore, more work will be required as a consequence of its new status as a stand-alone regulatory body, but without the external resources coming in from the EMA. The other complicating factor is that its regulatory role only relates to approval in England, Scotland and Wales, not Northern Ireland. However, there are mechanisms in place to ensure mutual recognition, particularly given the harmonisation of regulatory approach, which may allow a more responsive process with the potential advantage of marketing authorisations being fast tracked, particularly for drugs with clear potential benefits. This process has been clearly illustrated through the granting of marketing authorisations for COVID-19 vaccines.

All clinical trials must be registered in a clinical trials database and have ethics approval. Trials must be conducted in line with Good Clinical Practice, a set of international standards covering the design, conduct, recording and reporting of clinical trials, and manufactured in line with Good Manufacturing Practice, a set of international standards ensuring the quality of the investigational product.

TABLE 1.1 The main regulatory authorities and their functions

Regulatory authority	Function
Medicines and Healthcare Regulatory products Agency (MHRA)	Formed in 2003. Functions include: regulation of clinical trials, assessment and authorisation of medicinal products in the UK; operates post-marketing drug surveillance. It will have a new role post Brexit operating separately from the EMA
European Medicines Agency (EMA)	Established in 1995. Coordinates the evaluation and supervision of the new medicinal products, grants opinion on licensing and oversees pharmacovigilance across member states
Food and Drug Administration (FDA)	Established in 1927. Responsible for regulation and supervision of drug safety: drug assessment and authorisation, post-marketing surveillance

Clinical Trials

Once the efficacy and safety of a drug have been determined in preclinical studies, it can move into investigation in the human population. Drugs progress through different stages of clinical trials prior to gaining regulatory approval and entering clinical use. Although these stages are described separately, in practice they often overlap [2].

Microdosing Microdosing was introduced in 2003 to improve the efficiency of drug development. It aims to improve the selection of preclinical candidate drugs by assessing *in vivo* human pharmacokinetic and pharmacokinetic data. It takes place after preclinical development but prior to phase 1 clinical trials and is often referred to as phase 0. Microdosing assumes that the pharmacological parameters of a drug can be determined in humans using minute doses (one hundredth of the planned dose), thereby avoiding significant side effects and eliminating candidate drugs with undesirable profiles early on in the process.

Phase 1 Trials Phase 1 trials are nontherapeutic, exploratory studies and prior to the introduction of microdosing they traditionally bridged the gap between animal and human studies. They are typically carried out in small numbers of healthy volunteers. They test pharmacodynamics, including a detailed safety screen and pharmacokinetics. In order for drugs to be tested in humans, safety data needs to be shown in two different species. Even if this is the case, sometimes unexpected toxicity has been seen, e.g. the clinical trial of TGN1412 in Northwick Park Hospital that resulted in multi-organ failure for the six healthy volunteers. So-called 'First in Human' studies generally start with low doses to establish safety, then move on to dose-ranging studies. At this stage sometimes signals of efficacy can be seen, e.g. evidence of effect on an enzyme system, but with safety established then the therapeutic potential of a drug can be tested in phase 2 and 3 clinical studies. Phase 1 studies will also continue in parallel, including studies testing for drug interactions or to answer a specific safety question, e.g. does the drug cause QTc prolongation?

Phase 2 Trials Phase 2 trials are often referred to as 'proof of concept' studies. They are undertaken in 100–300 patients who have the target condition and are generally conducted by specialists in treating the condition. They are designed to assess efficacy or markers of efficacy. For antidiabetic drugs this could be using HbA1c, capillary blood glucose monitoring or continuous glucose monitoring. The primary aim is to decide whether it is likely that the signal of efficacy is good enough and the side effect profile acceptable to justify progression into larger, more expensive phase 3 clinical trials. Phase 2 studies are usually randomised controlled trials of the drug compared with placebo or active comparator.

Phase 3 Trials Phase 3 trials are large-scale randomised controlled trials often involving several thousand patients across multiple sites. The candidate drug is usually assessed against placebo and/or existing therapies. The aim is to quantify the

extent to which the drug is effective and in which particular patients. Given that the studies are larger with more patient exposure, less common side effects may emerge. These studies are often referred to as 'pivotal' studies as it is these that are used to inform regulatory approval, labelling and patient information once the drug is marketed. Usually, two separate pivotal trials are required for each new medicine, although there are exceptions to this rule. Traditional phase 3 studies tend to be double-blind, randomised and controlled in matched groups, but are sometimes adapted for practical reasons. Ideally the primary endpoint should be clinically relevant and measurable. The trials should aim to have as much complete data as possible and to be analysed on an intention-to-treat basis. The trials also need to be large enough to be powered to detect differences between treatment groups. Further phase 3 trials often take place after a drug gets regulatory approval, e.g. to widen the licensed indication or to test on different patient populations.

Phase 4 Trials Phase 4 trials are studies that are conducted after marketing authorisation. These may be carefully designed marketing studies, but more often are considered as post-marketing surveillance or pharmacovigilance with particular emphasis on safety (see later in this chapter). Observational studies have been used to assess both safety and efficacy in clinical practice, and are sometimes referred to as real-world studies. As observational studies they sit below meta-analysis and randomised control trials in the evidence-based hierarchy. They should not be considered a substitute for a well-designed randomised controlled trial against placebo or an appropriate comparator, but rather as a reassurance that the results seen in the pivotal trials used to underpin regulatory approval are realised in clinical practice.

Drug Licensing of Antidiabetic Drugs

Each regulatory body has guidance on the clinical development of drugs to be used to lower blood glucose in patients with diabetes. These stipulate that clinical trial participants must be representative of the target population in terms of age, ethnicity, presence of comorbidities and metabolic control. Long-term glucose control is measured using HbA1c and reduction in HbA1c is associated with reduced risk in the development of microvascular complications. HbA1c is therefore a primary endpoint for treatments to be used in diabetes and should measure the difference in baseline HbA1c between the investigational drug and comparators.

Cardiovascular Outcome Trials

Cardiovascular disease is the leading cause of death in people with diabetes. Prior to 2008, there were no specific requirements for new therapies for people with type 2 diabetes to demonstrate cardiovascular safety and it was only necessary to demonstrate glycaemic efficacy and safety. This change in legislation was a consequence of a

meta-analysis of individual patient data which suggested that rosiglitazone was associated with a greater incidence of myocardial infarction, and possibly an increase in cardiovascular death (see Chapter 12).

In the rosiglitazone meta-analysis there were significant weaknesses; across the studies there was no standard method for identifying or validating outcomes and events in eligible or ineligible trials may have been missed or misclassified. Also, the total number of events was relatively small. The meta-analysis was controversial at the time, and even today it is uncertain whether rosiglitazone is associated with an increase in atherosclerotic cardiovascular events or not. Regardless, the response of the FDA was to make significant changes to regulations for the licensing of new antidiabetic drugs and this was closely followed by the EMA for licensing in Europe.

The major changes were:

- The phase 3 study population should include subjects at high risk of cardiovascular events, including patients with long-standing diabetes, existing cardiovascular disease or chronic kidney disease and the elderly.
- All cardiovascular events in the development programme should be blindly adjudicated and analysed.
- Long-term safety data (greater than two years) was required, and this was generally collected as part of a dedicated cardiovascular outcome trial (CVOT).
- As the concerns around rosiglitazone were for atherosclerotic events, the particular focus of the FDA was on either three-point MACE (major adverse cardiovascular events, a composite of cardiovascular death, nonfatal myocardial infarction and nonfatal stroke) or four-point MACE (MACE plus hospitalisation for unstable angina), and hospitalisation for heart failure was a secondary concern.
- If it was deemed by the regulator that there was sufficient cardiovascular data from the development programme to indicate cardiovascular safety then the CVOT could be completed after licensing, which was the situation for most new antidiabetic drugs.
- If completed post-licensing, the first safety analysis of the new drug with the comparator was for noninferiority, and if noninferiority was demonstrated, the data could then be analysed for possible superiority.
- If the data from the phase 3 programme was deemed insufficient to demonstrate cardiovascular safety, then the CVOT would need to be completed and show noninferiority before licencing, as happened for alogliptin and lixisenatide in the US.
- As an alternative to demonstrate safety before licensing, a smaller CVOT could be performed and analysed for noninferiority, as happened for oral semaglutide.

Cardiovascular outcome trials have been completed and published for most of the newer antidiabetic drugs, and many drugs not only demonstrate cardiovascular safety but also show cardiovascular benefit compared with placebo, for example empagliflozin, canagliflozin, dapagliflozin, liraglutide, dulaglutide and semaglutide (see Chapters 4–6, and summary in Chapter 16). On review in 2020 the FDA noted that none of the CVOTs had identified an increase in the risk of ischaemic cardiovascular

events, so they removed the requirement for a bespoke CVOT. The importance of cardiovascular safety data was not removed, but the dedicated CVOT was replaced with a wider safety database with data from controlled clinical trials and clinical trial extensions, including:

- at least 4000 patient years of exposure to the new drug in phase 3 clinical trials;
- at least 1500 patients exposed to the new drug for at least one year;
- at least 500 patients exposed to the new drug for at least two years;
- at least 500 patients with stage 3/4 chronic kidney disease exposed to the new drug;
- at least 600 patients with established cardiovascular disease exposed to the new drug;
- at least 600 patients older than 65 years of age exposed to the new drug.

This new guidance was issued for feedback in draft form in 2020 during the COVID-19 pandemic and has now replaced the 2008 guidance on the FDA website [4].

Marketing Authorisation

Following completion of phase 3 trials, a Marketing Authorisation Application is submitted to the relevant licensing authority. Product registration is in important aspect of the regulatory process and is required prior to marketing a drug. The Marketing Authorisation Application contains a product's quality, safety and efficacy data. Each licensing authority has a panel of specialists comprising clinicians, statisticians and scientists, who review the application before recommending whether a marketing authorisation should be granted. The timeline of events leading to the marketing authorisation of dapagliflozin, as an example of antidiabetic drug development, is described in Table 1.2.

Development and Licensing of Insulin

Insulin Regulatory Approval

The regulatory approval for new insulins, like with any drug, requires safety and efficacy to be established through a clinical trial programme. The EMA published guidelines to sponsors of clinical trials for all drugs being developed for use in diabetes and insulin is considered separately. Studies need to be done in both type 1 and type 2 diabetes. Pharmacokinetic studies are required to be done in all types of patients for whom treatment is intended, including the young and the elderly, the former an important group given that their glycaemic variability and susceptibility to hypoglycaemia are higher compared with adults. Pharmacokinetic (PK) data need to include peak insulin concentration, time to peak concentration, area under the insulin–time curve and half-life. It is also necessary to show that the PK characteristics remain the same if the insulin is used in mixtures. Although insulin analogues are usually developed for

TABLE 1.2 **Dapagliflozin timeline as an example of antidiabetic drug development [5]**

Date	Event
1835	Phlorizin isolated from apple tree bark
1886	Phlorizin noted to cause glycosuria in animals
1930s	Phlorizin given i.v. in human subjects and noted to cause glycosuria Used to investigated renal blood flow and glomerular filtration
1950s	Phlorizin used to characterise SGLT receptors
1960s	Phlorizin derivatives developed (e.g T095) with better bioavailability and less gastrointestinal upset
1990s	Phlorizin and derivatives blunt glucose rises in animal models, used to investigate glucose metabolism
2008	Pre-clinical studies with dapagliflozin published
2009–2015	Phase 1–3 studies published
2012	EMA approval for use in type 2 diabetes
2014	FDA approves dapagliflozin for use in type 2 diabetes
2019	Approval of dapagliflozin as an adjunct in patients with type 1 diabetes
2020	Approval of dapagliflozin for treatment of heart failure
2021	Approval of dapagliflozin for treatment of chronic kidney disease

novel PK properties, differences in parameters of PK/PD (pharmacodynamics) alone cannot be used on their own to claim superiority. Pharmacodynamic data in insulin-sensitive type 1 diabetes are important to compare insulins with the glucose-clamp technique, the preferred method to assess time–action profiles.

In short-term exploratory studies, the efficacy outcome is usually 24 h glucose profiles, and in confirmatory studies of longer duration (6–12 months) using an appropriate insulin as a comparator. Outcomes should include achieving glycaemic targets (HbA1c and variability in glycaemic control). In trials in type 1 diabetes a run-in period is required to define the variability in glycaemic control and frequency of hypoglycaemia in each group before active comparison begins. Hypoglycaemia is the major obstacle to achieving good glycaemic control. Continuous glucose monitoring can be used to identify hypoglycaemia. The incidence and rate of both overall hypoglycaemia overall and severe hypoglycaemia should be determined in all clinical trials. Definitions of hypoglycaemia need to be harmonised across studies and the EMA guidelines cite the International Hypoglycaemic Study Group recommendations (Table 1.3) [6]. There has been some debate as to what the glucose alert value adds, but with increased use of continuous glucose monitoring, asymptomatic hypoglycaemia may be helpful in comparing different insulins in clinical trials whilst perhaps being less useful as a definition in the clinical setting.

Additional adverse effects seen that are specific for insulin are local reactions, toxicity and immunogenicity. Specifically for insulin analogues, affinity for the IGF-1

TABLE 1.3 **Proposed glucose levels when reporting hypoglycaemia in clinical trials**

Level	Definition
Level 1 (glucose alert value)	Glucose level 3.9mmol/l (70 mg/dl) or less
Level 2 (serious, clinically important hypoglycaemia)	Glucose level of <3.0 mmol/l (<54 mg/dl)
Level 3 (severe hypoglycaemia)	Severe cognitive impairment requiring external assistance for recovery

Source: Based on [6].

and insulin receptors is required and if increased it is recommended that longer-term studies should include fundal photographs to look for any retinal changes. The FDA guidance that resulted in the need for CVOTs in all new treatments in development for treating type 2 diabetes specifically excluded insulin because it was considered a life-saving treatment in type 1 diabetes and that such studies would be impractical.

Development and Approval of Biosimilar Insulin

Introduction Biosimilars are manufactured copies of previously approved biological drugs. Owing to variation in their manufacture and final protein molecule, they cannot be considered identical versions of their reference drug, hence the term biosimilar [7]. The biopharmaceutical market is rapidly growing with many such products, for example biosimilars of infliximab, filgrastim and erythropoietin. Three biosimilar insulins are available at present: Abasaglar® (insulin glargine), Semglee® (insulin glargine) and Admelog® (insulin lispro). Another insulin glargine, Lusduna®, was approved by the FDA and EMA but withdrawn in 2018.

Insulin Production The manufacture of insulin has evolved significantly since it was first isolated in 1922. Initially, insulin was derived from bovine or porcine pancreatic extracts. Nowadays, insulin is manufactured using recombinant DNA technology which makes use of *Escherichia coli* or *Saccharomyces cerevisae* expression systems. DNA is isolated from human cells and inserted into an appropriate vector before transfer into the host cell. The recombined host cell then produces its product, which is recovered and refolded to a pro-insulin like-molecule. After C-peptide is removed, the insulin product undergoes purification and storage. Extensive testing is undertaken to assure the purity and stability of the product. As living cells are used, the manufacturing process can be affected by changes to physical conditions which introduce subtle changes to the end product. This is of importance as the biological activity may also be affected.

This manufacturing process is complex and the exact details closely guarded. Even once a patent expires, pharmaceutical companies are not obliged to make manufacturing details available. Once a patent expires, other companies will be unable to identically replicate the production process.

Biosimilar vs. Generic Drugs The nature of chemical drug molecules allows them to be readily reproduced and generic drugs have identical chemical structures and pharmacological profiles. Biologics in contrast, are larger and more complex, with several layers of structure. Unlike drugs that are synthesised chemically, biological molecules require expression systems. Reproduction of a biologic produces a biosimilar, and the complexities of production (which are not shared after patent expiry) and the final protein molecule mean that the end product is not identical and cannot be considered generic (Table 1.4). While generic drugs offer bigger savings (up to 80%), biosimilars offer less expensive alternatives, costing up to 20–30% less than their originator drug, thereby providing significant cost savings. This is important in expanding competition in a market dominated by a few pharmaceutical companies and in increasing access to treatment.

Regulatory Considerations for Biosimilars Marketing Authorisation Applications for both generic and biosimilars can only be submitted on patent expiry of the reference drug. Regulatory submissions must provide evidence that the generic product is identical in structure, strength and formulation (pharmaceutical equivalence) and approval requires demonstration of bioequivalence. This term refers to the absence of a significant difference in the bioavailability between a generic and its reference drug. If both drugs have equivalent biosimilarity they can be considered to have the same clinical effects. The maximum plasma concentration (C_{max}) and area under the plasma concentration–time curve (AUC) are used to determine bioequivalence and there should be no more than a 20% difference in these pharmacokinetic parameters [8].

TABLE 1.4 **Comparison of biosimilar and generic drugs**

	Generic	Biosimilar
Size	Small	Large, complex
Structure	Structurally identical to reference product	Similar to reference product but not identical owing to natural variability in protein molecule and manufacturing process
Manufacture	Chemical synthesis	Recombinant DNA technology in cell lines
Equivalence	Bioequivalence and therapeutic equivalence must be demonstrated	No clinical significant differences in terms of purity, safety and potency
Interchangeability	Interchangeable with reference product	Not interchangeable
Name	Generic name is used	Should be prescribed by brand name
Cost savings	Up to 80%	20–30%
Development time	2–3 years	8–10 years
Development costs	$1–5 million	$100–200 million

The regulatory requirements for biosimilars were first published in 2005 by the EMA and include specific guidance relating to insulin biosimilars [9]. Post-Brexit, biosimilars are regulated by the MHRA under the Human Medicine Regulation 2012. Comparability with its reference product in terms of safety, purity and potency must be established. Manufacturers are required to provide details of the structural and functional characteristics of the product, its manufacturing process and quality control. Comparability studies are carried out to demonstrate that the pharmacokinetic and pharmacodynamic profiles are not significantly different between a biosimilar and its originator drug.

Safety of Biosimilars Immunogenicity is an important safety aspect in the use of biological medicines. Antibody formation can be stimulated following the use of any biological drug, which can result in adverse reactions such as allergy and anaphylaxis in addition to altering the biologic's therapeutic action. Pharmaceutical companies are therefore required carry out safety studies detailing antibody testing strategies and the incidence of antibody formation to the biosimilar.

Post-marketing surveillance is important with biological drugs as unexpected adverse effects are more likely. A risk-management plan must be submitted with information on pharmacovigilance monitoring.

Interchangeability and Substitution A biosimilar is considered interchangeable if biosimilarity has been established and the same therapeutic effect is achieved in each patient. There should be no impact on safety or efficacy if the reference drug is switched with the biosimilar. This an important safety aspect as it may result in the substitution of a prescribed biological medicine with a biosimilar without the prescriber's knowledge, an action termed automatic substitution. Guidance regarding substitution varies throughout the world. In the UK, the MHRA advises against automatic substitution of a biological drug and states that, unlike chemical drugs normally prescribed by generic name, biosimilars must be prescribed by brand name [10].

Prescribing Considerations for Biosimilars A diverse and large armoury of insulins is available and the introduction of biosimilars could add confusion to an already complex prescribing situation. Position statements on the prescribing of insulin biosimilars have been published by Diabetes UK [11] and the Association of British Clinical Diabetologists [12] that recommend consideration of the factors outlined in Box 1.1.

Box 1.1 Prescribing considerations for biosimilar insulin

- Biosimilar insulin should be considered when initiating insulin.
- Ensure biosimilar is prescribed using brand name and delivery device is stated.
- Changing to a biosimilar should be done with the mutual consent of the prescriber and the patient.
- Adverse reactions should be reported using the Yellow Card scheme.
- It is not recommended that patients who are established on insulin and stable are changed to biosimilar insulin.

Source: Adapted from [12].

Pharmacovigilance

When a new medicine enters clinical use following marketing authorisation, it will have shown a positive risk: benefit assessment in clinical trials, usually of relatively short duration (6–24 months) and involving commonly 5000–10 000 subjects chosen to match the entry criteria of the clinical trials. Efficacy will have been shown and common adverse effects will have been identified and deemed acceptable or manageable. There are still important unknowns for a new medicine:

- Are there rare (but serious) adverse effects which were not seen in the clinical trials?
- Are there significant adverse effects apparent in subjects who would have been excluded from the clinical trials?
- Are there significant adverse effects which are only apparent in long-term use?

Monitoring the new medicine to look for such adverse events is known as 'pharmacovigilance'. Structured pharmacovigilance surveillance of new medicines is a condition of regulatory approval and is the responsibility of the manufacturer of the medicine. Relatively rare side effects are often not identified in clinical trials as too few events occur to be detected and linked to the medicine. As Table 1.5 shows, an event with a frequency of 1 in 1000 needs 3000 subjects to be exposed to the medicine to be 95% sure of seeing just one case, and larger numbers to see the two or three cases that would be needed to trigger a potential signal that the event was drug related. Rarer events need even larger numbers. Pharmacovigilance procedures fall into one of two broad categories, passive and active.

Passive Pharmacovigilance

Passive pharmacovigilance rests on prescribers (or patients) reporting suspected adverse drug reactions to the regulatory authority and/or the manufacturer of the medicine. The manufacturer will forward all such reports to the regulator so that they have a full picture of events reported and can assess whether any safety 'signals' can be identified. Signals are then further evaluated to decide whether they were related to the drug or a coincidence. In the UK, newly licensed medicines have a 'black triangle' (▼) as part of their documentation and packaging, inviting the reporting of *all* suspected events related to the medicine, not only events seen as serious or significant. This ensures intensive monitoring for newly authorised medicinal products. Prescribers, pharmacists and patients are encouraged to report events in what is known as the 'Yellow Card Scheme', founded in 1964 after the thalidomide incident. Many reports now are submitted online, but the process retains its old name.

Passive reporting (also known as a spontaneous reporting scheme) is useful in identifying rare, and sometimes unusual, events but is limited by requiring the individual reporting the event to have made the link (or at least suspected the link) between the medicine and the event. Signal detection of possible adverse drug reactions is the main objective of a spontaneous reporting scheme.

TABLE 1.5 **The numbers of patients needed to observe to have a 95% chance of detecting one, two, or three cases of an adverse reaction at a given incidence of the reaction**

Expected incidence	Number of patients to be observed to detect one event	Number of patients to be observed to detect two events	Number of patients to be observed to detect three events
1 in 100	300	480	650
1 in 200	600	960	1 300
1 in 1 000	3 000	4 800	6 500
1 in 2 000	6 000	9 600	1 300
1 in 10 000	30 000	48 000	6 500

Spontaneous reporting of suspected adverse drug reactions is poor at assessing the true frequency of events as it is often estimated that only around 10% of events are actually reported. It is also poor at providing reassurance that events are not occurring, given the low reporting rates.

Active Pharmacovigilance

Active pharmacovigilance involves undertaking active surveillance of recipients of the new medicine, often identified from primary care prescription data or secondary care disease registries and other sources. Identified recipients of the medicine in question are 'followed' over months or even years and all health-related events recorded. The overall dataset can then be reviewed and any events that appear to be in excess of predicted numbers can be investigated. This methodology records all events, and so does not require any link to the medicine to have been made.

Often, data on a comparator group are collected simultaneously, the subjects having the same underlying diagnosis but not receiving the new medicine. This allows the background event rate to be known with reasonable certainty, and thus allows any excess events in the subjects receiving the new medicine to be reasonably confidently attributed to the medicine and the magnitude of the excess event rate established. A key principle in pharmacovigilance is to compare the frequency of events observed in users of a new medicine with what would be expected if these patients received the standard existing treatment or no treatment (observed vs. expected).

Active pharmacovigilance can not only detect rare or unusual events but can also detect an increased frequency of common events related to a new medicine. It is, for example, unlikely that an individual prescriber would attribute an acute vascular event (e.g. acute coronary syndrome) in a subject with type 2 diabetes to a new medicine

(but rather to the diabetes), but active pharmacovigilance could pick up an increased incidence of such events across a larger population.

As all events are recorded, data from active pharmacovigilance can also provide evidence of the absence of any increased risk related to a new medicine. This was important when cases of acute pancreatitis were reported in subjects treated with GLP-1 receptor agonists at rates above the population rate. Pharmacovigilance data showed an increased rate of acute pancreatitis in subjects with type 2 diabetes (compared with the nondiabetic population), but no increased risk specifically in those taking GLP-1 receptor agonists, reassuring prescribers and patients alike.

Active pharmacovigilance clearly has many advantages over passive surveillance, but it is expensive, often difficult to undertake and has to be time delimited, so eventually only passive surveillance can continue. The two approaches are complementary.

Pharmacoeconomics

Introduction

Scarcity of resource is a feature of all healthcare systems. If the system cannot do everything, then it must make choices amongst interventions, usually aiming to choose interventions that provide the maximum health benefits for the resources expended. Using economic evaluation, pharmacoeconomics aims to provide a structured approach to making such choices, looking at the full clinical benefits of a new intervention such as a new medicine, but also looking at all the costs associated with its use, comparing these with the benefits and costs of existing therapies. It also is mindful that resources can only be used once, so any use of a new medicine will come at the expense of another intervention somewhere in the healthcare system which will not be undertaken, the opportunity cost of adopting the new medicine. Pharmacoeconomics is a relatively inexact science, but it does offer a structured approach to assessing the clinical value and cost-effectiveness of new medicines [13]. As in diabetes there is a wide range of proven interventions of good efficacy available at reasonable cost, it is vital that new medicines are fully assessed and only adopted if their benefits justify their cost and the opportunity cost of their introduction.

Different countries use different approaches to their analysis of costs and benefits and overall assessment of cost-effectiveness. In the UK, the approach favoured by NICE (the National Institute for Health and Care Excellence) and the SMC (Scottish Medicines Consortium) is a cost–utility analysis. This captures the benefits of a medicine for both duration of life (= survival) and for quality of life and combines these into a single metric, the Quality Adjusted Life Year (or QALY). Figure 1.4 shows the health benefits of a new medicine over current therapy, the gain in A being in quality of life, while the gain in B shows a survival benefit. The overall benefit of the new medicine is thus A + B.

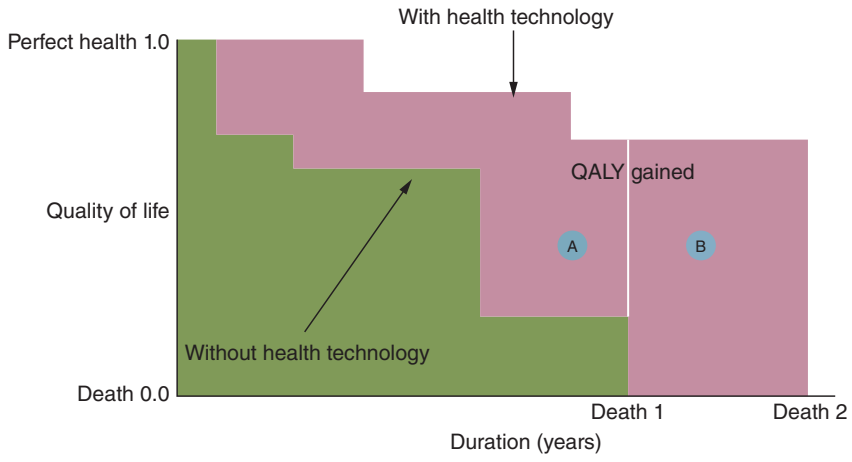


FIGURE 1.4 Health benefits of a new medicine over current therapy, the gain in A being in quality of life, while the gain in B shows a survival benefit. The overall benefit of the new medicine is A + B. *Source:* From [1].

Cost–utility analysis has the advantage of being able to evaluate health benefits independently of the disease involved, and thus allow comparison of interventions amongst diseases, for example a new diabetes medicine compared with new medicines for dementia and/or lung cancer. With the QALY as the outcome measure, it is even possible to compare the cost-effectiveness of new medicines with that of nonmedical interventions (e.g. surgery).

The costs of using a new medicine are not limited to its acquisition costs, but also to costs (or savings) associated with the administration, monitoring and the management of any adverse effects. Economic evaluation should also take into account any downstream changes in the resources used in disease management, e.g. reductions in hospitalisations or physician visits owing to better symptom control with the new treatment. Once all costs have been identified, it is possible to create an incremental cost-effectiveness ratio (ICER), in which the costs are divided by the benefits to create a 'Cost per QALY'.

$$\text{ICER} = \frac{\text{incremental cost of new treatment } (£)}{\text{incremental benefit of new treatment } (\text{QALY})}$$

New treatments across disease areas can be compared, the one with the lowest ICER representing the best 'value for money'. To aid decision-making and ensure consistency over time, NICE and SMC use informal ICER thresholds such that a medicine with an ICER <£20 000 will usually be accepted for NHS use while a medicine with ICER >£30 000 will not usually be accepted. Medicines with ICERs in the range £20 000–30 000 may or may not be accepted depending on factors such as the extent of unmet clinical need, the tolerability of existing therapies and the quality of the evidence supporting the ICER estimation. Medicines with an ICER >£30 000 may also be accepted for use if, for example, there is a high level of unmet clinical need or other special circumstances.

Utility Values

Utility values are a measure of quality of life and can range from 1, meaning perfect health, to 0, equivalent to death. They describe in numerical form the quality of life experienced by patients in different health states and are a crucial part of the calculation of QALYs, especially for medicines that improve symptoms but may not affect overall survival. Ideally utility values are derived from actual patients in individual health states, although in some circumstances healthy people may be asked to imagine disease states and respond to whichever technique is being used to elicit utility values. There is no perfect way to elicit utilities, but most involve balancing the benefits of improved health against reduced survival (Box 1.2).

An alternative approach to utility derivation is frequently used by NICE and is based on a five-item questionnaire (EuroQol 5 Dimensions or EQ-5D), a frequently used Patient Reported Outcome measure in clinical trials. EQ-5D asks patients to grade themselves across five domains (mobility, self-care, usual activities, pain and discomfort, and anxiety and depression). An algorithm has been developed that allows responses to the questionnaire to be converted into a utility value. This method has been criticised as possibly not capturing all aspects of quality of life but has nevertheless found widespread use. Obviously utility values may differ according to the methodology used to derive them. The effects of this can be tested by varying utility values in sensitivity analysis (see below).

Health Economic Modelling

Clinical trials of new medicines in a chronic disease such as diabetes are usually of relatively short duration (6–24 months). Pharmacoeconomics ideally seeks to see the costs and benefits of a new medicine over a much longer time horizon,

Box 1.2 Examples of eliciting utility values

Time Trade-off
With time trade-off the subject is asked to assume that they will live for (say) 10 years in their present state of health and is then asked how much of that 10 years they would forego to return to full health. The more survival they are willing to give up, the worse their current quality of life is assumed to be. If they give up 2 years, their utility value will be 0.8, if they give up 5 years, it will be 0.5.

Standard Gamble
With standard gamble the subject is told that a treatment exists that could return them to full health, but which also has a chance of causing instant death. They are asked what risk of death they are willing to take to be 'cured'. Once again, the greater the risk they are willing to accept, the lower their current quality of life, and hence utility value, is assumed to be.

10–20 years or even a lifetime. In addition, clinical trials usually collect data on surrogate outcomes (e.g. HbA1c, blood pressure) and not on the endpoints that really matter to patients such as survival, incidence of vascular events, incidence of visual loss, etc. Health economic modelling is the mechanism that is used to bridge these gaps. The aim of such modelling is to extrapolate the trial data to a longer time horizon and to translate the surrogate outcomes into meaningful clinical outcomes for patients [13].

Modelling uses data from epidemiological and interventional studies to predict differences in outcome with different treatments and thus evaluate the overall health gain from a new treatment to populate the 'incremental benefit' part of the ICER calculation. Diabetes has extensive datasets from both disease registries and interventional studies which allow the modelling to be reasonably robust and credible in a pharmacoeconomic evaluation.

For example, if a new medicine leads to, on average, a reduction in HbA1c of 8 mmol/mol compared with the current therapy, it is possible to derive from existing datasets the impact that this will have on long-term survival and the incidence of myocardial infarction, visual loss, end-stage renal disease, etc., which then forms part of the estimation of the QALY associated with the new treatment. There are a variety of modelling techniques, but one that is commonly used would see the creation of an 'imaginary' cohort of perhaps 1000 patients with diabetes reflecting the demographics of the relevant UK diabetes population. This cohort would then be 'treated' with existing therapy (and all outcomes recorded) and then with the new therapy, again recording all outcomes, all simulated using computer programs. Survival gain can be estimated, as can reductions in diabetes-associated co-morbidities. By applying a reduction in quality of life to each of the co-morbidities, the differences in both survival and quality of life, the essential components of the QALY, can be estimated.

Sensitivity Analysis

It will be obvious from the above that health economic assessment relies heavily on extrapolation of clinical trial data, estimates of utility values and assumptions about other parameters that have not been formally measured in clinical trials. This extrapolation and assumption introduce considerable uncertainty into assessment of the ICER, uncertainty that is tested in sensitivity analysis. In one-way sensitivity analysis, individual parameters are varied across a plausible range of possibilities to see which have the biggest impact on the ICER and which are less important. It may then be possible to try to find data from other sources that can inform the estimate of the most important parameters and reduce the uncertainty in the ICER assessment.

In probabilistic sensitivity analyses, multiple parameters are varied simultaneously within plausible ranges and according to defined data distributions for each parameter (e.g. normal distribution). This creates both an 'average' ICER but also a range of possible ICERs which may be useful in decision-making. Finally, several parameters may be varied at the same time within, or to the extremes of, their ranges in scenario analyses, aiming to establish the likeliest true value of the ICER and best and worst case scenarios.

Ultimately, while health economists can undertake modelling, extrapolation and sensitivity analyses, it is for decision-makers at NICE or SMC (for example) to decide, based on their clinical knowledge and the available data, which estimate(s) of the ICER

they find most plausible and then make their decisions based on this while fully aware of the extent of the prevailing uncertainty.

For example, the NICE Technology Appraisal for dapagliflozin with insulin for treating type 1 diabetes (TA597) was presented with a base case ICER by the manufacturer of £6,618 per QALY [14]. NICE was not persuaded by some of the assumptions in the base case, and when these were removed the ICER rose to £19,122, a significant increase, taking the ICER much closer to NICE's usual threshold for acceptance, although still allowing the medicine to be accepted for NHS use in this indication.

A number of health economic models of diabetes (type 1, type 2 or both) have been developed and refined over many years and are used frequently to estimate the cost-effectiveness of interventions [15]. Each model uses slightly different data inputs and modelling assumptions and thus the outputs vary somewhat. Commonly used models include the UKPDS Outcomes Model, the CORE Model, the Sheffield Model and the Cardiff Model. No model is perfect, but the Mount Hood Diabetes Challenge Network brings model developers together every two years to encourage further model development and refinement.

Discounting

Discounting is the way in which economic evaluations are adjusted for the fact that individuals (and societies) are not ambivalent about when they receive a benefit or incur a cost, the so-called time preference. The convention in the UK is to regard current benefits of interventions (not just in healthcare) as more 'valuable' than future benefits, discounting the value of future benefits by 3.5% per year. Costs are similarly discounted, but this situation may be problematic in a chronic disease such as diabetes, where costs may be incurred in the present and short-term future to avoid long-term complications many years later. A health gain of 1 QALY is, for example, valued at only 0.55 QALY if it occurs in 20 years' time, almost doubling the ICER. This has been identified as a significant problem in chronic diseases and there are currently suggestions that the discount rate be reduced to 1.5% (which would increase the QALY in the above example to 0.82 QALY).

Indirect Comparison and Network Meta-analysis

It is often the case that the clinical trials with a new medicine have not been undertaken with an active comparator, but against a placebo. Alternatively, the trials may have been undertaken with an active comparator therapy but not the appropriate comparator in current clinical practice. In these circumstances some form of indirect comparison against current practice is necessary. This, at its simplest, involves finding data on the new medicine and the appropriate comparator each compared with a common intervention (either placebo or another medicine). The common intervention helps to correct for differences in the study populations and thus the true effects of the new medicine and its comparator can be seen. An example is shown in Box 1.3.

In diabetes there are many clinical trials and other sources of efficacy information on a wide range of medicines, some compared with placebo and others with two medicines compared 'head-to-head'. All of these data can be combined into a network of

Box 1.3 Example of an indirect comparison

Current therapy: HbA1c reduced by 10 mmol/mol (placebo 4 mmol/mol)
New therapy: HbA1c reduced by 14 mmol/mol (placebo 7 mmol/mol)

At first sight the new medicine appears considerably more effective than current therapy, but once the difference in placebo response is factored in, the advantage of the new medicine is quite small (7 mmol/mol more than placebo vs. 6 mmol/mol more than placebo). A simple indirect comparison such as this cannot completely adjust for differences in the patient populations studied but is significantly better than just comparing the unadjusted efficacy numbers.

comparative efficacies, into which data on a new medicine can be incorporated. Such a network meta-analysis is, given the multiple comparisons made, more robust than the simple indirect comparison described above. Network meta-analysis can allow comparisons between medicines in different classes (e.g. GLP-1 receptor agonists vs. DDP-4 inhibitors) or assessment of the relative efficacy of medicines within a class (NICE Technology Appraisal TA390 compared three different SGLT2 inhibitors, for instance) [14]. As with economic modelling, indirect comparison is a relatively inexact science and is dependent on the data used – NICE TA390 assessed four different indirect comparisons, one from each of the manufacturers of the three medicines considered and a fourth developed by NICE itself. Indirect comparison is thus better than naive unadjusted comparison, but nothing is as good a reflection of relative efficacy as an actual head-to-head trial against the appropriate comparator.

Network meta-analyses are frequently described as showing that (for example) Medicine A is 'better' than Medicine B. No such 'value judgment' can be drawn as the analysis will simply show that, at the doses used in clinical studies, Medicine A showed greater efficacy than Medicine B, the latter possibly showing other features (such as ease of administration or better tolerability) that might make it 'better' overall.

Future Developments in Diabetes Clinical Pharmacology

Drug Development

Advances in the genetics and molecular biology are changing the traditional process of drug discovery and development. Proteomics, the study of proteins and their role in biological functions, has had an important role in the identification of biomarkers and drug targets. A better understanding of the molecules involved in the pathophysiology of type 2 diabetes has led to the development of several new classes of drugs with many other classes in the pipeline (see Chapter 14). Proteins such as interleukin

6, adiponectin and leptin and their role in type 2 diabetes are being characterised and could lead to novel drug therapies.

Inter-individual drug variability has been explained in part by pharmacogenomics, the study of the genomics of the drug response. Individuals with reduced function CYP2CP alleles metabolise sulfonylureas more slowly and have a better glycaemic response than those with normal function copies [16]. Information from genome-wide association studies has been used to determine the association between nucleotide variations and an individual's response to drugs. These studies have been used to show that the response to metformin is in part due to nucleotide variations in genes such as ATM and SLC22A1. A greater understanding of the factors underlying variability in drug response can help personalise medicine and ensure that patients receive the maximal therapeutic benefit with minimal side effects.

Pharmacovigilance

The increasing use of electronic medical records and the ability to link different databases offer the possibility to incorporate active pharmacovigilance into routine practice within healthcare systems. This leads to the concept of 'big data', where large amounts of anonymised data are collected and analysed, looking for patterns that might suggest drug safety signals. Of course, with such large patient numbers and large quantities of data, apparent associations between events and drug use will inevitably arise by chance. Considerable care is needed to avoid over-reacting to chance findings of associations if unnecessary 'drug scares' are to be avoided. A variety of techniques are available. One relatively straightforward technique is to divide the dataset into two and look for associations in one half of the data. Any associations found can then be looked for in the other half of the dataset; only if the association is found again is it possibly of significance. Possible benefits from the application of artificial intelligence and machine learning to analyse big datasets are being explored. Assessment of any medicine is based on balancing risks and benefits, the latter hopefully outweighing the former. Pharmacovigilance has focussed on identifying and quantifying risks but has rarely looked at confirming and quantifying benefits in the 'real-world' use of medicines. The availability of larger linked datasets opens up the possibility of pharmacovigilance being about ongoing risk–benefit assessment, which is more valuable to patients, prescribers and regulators than looking at risks in isolation.

Pharmacoeconomics

Traditionally, pharmacoeconomic assessment of new medicines has been undertaken after regulatory approval, but this has been criticised as delaying access to potentially valuable new medicines. In some countries, including the UK, pharmacoeconomic assessment is set to occur alongside regulatory assessment, such that both will reach their conclusions virtually simultaneously.

While this streamlined approach may speed the availability of new medicines, it does mean that the pharmacoeconomic assessment will be made using less mature data than might have been available previously, introducing more uncertainty into the assessment. Indeed, the final details of the indication for therapy may not be clear when the pharmacoeconomic assessment is begun, requiring close coordination of the regulatory and pharmacoeconomic assessment processes to ensure that they remain aligned.

References

1. McKay, G., Walters, M., and Ritchie, N. (2021). *Lecture Notes: Clinical Pharmacology and Therapeutics*, 10th edn. Wiley Blackwell.
2. Blass, B. (2021). *Basic Principles of Drug Discovery and Development*, 2nd edn. London: Academic Press.
3. Medicines and Healthcare Products Regulatory Agency (2020). New guidance and information for industry from the MHRA. https://www.gov.uk/government/collections/new-guidance-and-information-for-industry-from-the-mhra (accessed 27 September 2021).
4. Chong, W.H., Yanoff, L.B., Andracac-Carrere, E., and Hai, M.T. (2020). Asessing the safety of glucose-lowering drugs – a new focus for the FDA. N Engl J Med 383: 1199–1202.
5. National Institute for Health and Care Excellence (NICE) (2016). Technology appraisal guidance [TA390]: canaglilfozin, dapagliflzoin and empagliflozin as monotherapies for treating type 2 diabetes. https://www.nice.org.uk/guidance/ta390 (accessed 27 March 2021).
6. International Hypoglycaemia Study Group (2017). Glucose concentrations of less than 3.0 mmol/l (54 mg/dl) should be reported in clinical trials: a joint position statement of the American Diabetes Association and the European Association for the Study of Diabetes. Diabetes Care 40: 155–157.
7. Llano, A., Fisher, M., and McKay, G. (2017). Biosimilar insulin: the current landscape. Practical Diabetes 34 (2): 51–54.
8. Committee for Medicinal Products for Human Use (CHMP) (2014). Guideline on similar biological medicinal products. https://www.ema.europa.eu/documents/scientific-guideline/guideline-similar-biological-medicinal-products-rev1_en.pdf (accessed 27 September 2021).
9. Committee for Medicinal products for Human Use (CHMP) (2015). Guideline on non-clinical and clinical development of similar biological medicinal products containing recombinant human insulin and insulin analogues. https://www.ema.europa.eu/documents/scientific-guideline/guideline-non-clinical-clinical-development-similar-biological-medicinal-products-containing_en-0.pdf (accessed 27 September 2021).
10. Medicines and Healthcare Products Regulatory Agency (MHRA) (2021). Guidance on the licensing of biosimilar products. https://www.gov.uk/government/publications/guidance-on-the-licensing-of-biosimilar-products/guidance-on-the-licensing-of-biosimilar-products (accessed 27 September 2021).
11. Diabetes UK (2019). Position statement: biosimilar insulins. https://www.diabetes.org.uk/resources-s3/2019-09/Biosimilars%20PS%20Final.pdf (accessed 27 September 2021).
12. Jayagobal, J., Drummond, R., and Nagi, D. (2018). Association of British Clinical Diabetologists (ABCD) position statement on the use of biosimilar insulin. Br J Diabetes 18: 171–174.

13. Walley, T. and Haycox, A. (1997). Pharmacoeconomics: basic concepts and terminology. Br J Clin Pharmacol 43: 343–348.
14. National Institute for Health & Care Excellence (NICE) (2019). Technology Appraisal Guidance [TA592]: dapagliflozin with insulin for treating type 1 diabetes. https://www.nice.org.uk/guidance/ta597 (accessed 27 September 2021).
15. Henriksson, M., Jindal, R., Sternhuvud, C. et al. (2016). A systematic review of cost-effectiveness models in type 1 diabetes mellitus. Pharmacoeconomics 34: 569–585.
16. Pearson, E. (2019). Diabetes: is there a future for pharmacogenomics guided treatment? Clin Pharmacol Ther 106: 329–337.

CHAPTER 2

Metformin

Joseph Timmons and James Boyle

KEY POINTS

- Metformin provides benefit in improving glycaemic control with approximately a 1% (11 mmol/mol) reduction in HbA1c.
- The major serious side effect of metformin is lactic acidosis, which is rare, with a dose reduction required in renal impairment.
- Metformin was shown to have cardiovascular benefits in a substudy of the United Kingdom Prospective Diabetes Study.
- Metformin is first-line treatment for the management of people with type 2 diabetes in most international guidelines.
- Metformin may have a role as adjunctive therapy in people with type 1 diabetes.

Introduction

Metformin is positioned as the 'first-line' antidiabetic drug for the management of type 2 diabetes (see Chapter 15). It is cheap, effective and well tolerated. Despite the emerging evidence for novel antidiabetic drugs for the management of people with type 2 diabetes, metformin has retained its position as the first-line monotherapy in most UK, European and US guidelines [1, 2]. Despite being a well-established drug, there remains incomplete understanding as to the mechanisms of action of metformin [3]. The application of this drug in the management of people with type 1 diabetes [4] and potential renal benefits are beginning to emerge. As such, the story of how metformin should be used to the optimal benefit of people with diabetes is likely to continue to expand.

Diabetes Drug Notes, First Edition. Edited by Miles Fisher, Gerard A. McKay, and Andrea Llano.

History of Biguanides

Metformin (dimethylbiguanide) has been used in Europe since the 1950s and in the US since the 1990s. It is derived from the herb *Galega officinalis*, otherwise known by several names including French lilac. Despite this name, the herb is native to many European countries including Britain. The medicinal properties of *G. officinalis* have been known since the early Middle Ages and it has been used to treat a variety of maladies. As increasing knowledge of the existence and concept of diabetes mellitus became apparent, its medicinal properties became better known. Indeed, the seventeenth-century physician John Hill recommended *G. officinalis* for the treatment of thirst and frequent urination [5].

Animal studies in the early twentieth century demonstrated that guanidine, the active compound in *G. officinalis*, had glucose-lowering properties, but there were concerns regarding toxicity. This research paved the way for the formulation of less toxic diguanidines, later termed biguanides, synthalin A (decamethylene diguanide) and synthalin B (dodecamethylene diguanide). The isolation of insulin for therapeutic use in 1922, coupled with an increasing awareness of the potential toxicity of these agents, led to their discontinuation as a treatment modality. Despite this, research into similar molecules continued though the late 1920s and 1930s. Metformin was initially synthesised in 1922, but its full potential in glucose-lowering was not realised at the time. Medicinal products belonging to the biguanide class were developed for various conditions in the interim period, including malaria and influenza, e.g. metformin was used as an 'anti-influenza' drug named flumamine. While it was thought to help with the symptoms of influenza, its glucose-lowering side effects were also noted. The interesting observation of coincidental blood glucose lowering gained the attention of the French physician and clinical pharmacologist Jean Sterne.

While working at the Hôpital de la Pitie in Paris, Sterne started conducting experiments to examine the glucose-lowering properties of galegine. Although this was disappointing, it led in the mid 1950s to the investigation of metformin at Aron Laboratories and the Hôpital Laennec in Paris. In clinical trials of people with juvenile-onset diabetes and maturity-onset diabetes, glucose-lowering was achieved in the absence of hypoglycaemia. In 1957, Sterne published work on 1,1-dimethylbiguanide hydrochloride, the chemical name for metformin. Evoking the image of a 'glucose-eating' drug, he proposed the name glucophage. This was introduced the following year in many European countries to treat diabetes. Metformin was only one of the biguanide class that was being simultaneously investigated, and trials of buphormin in Germany and phenformin in the US were also published in the late 1950s. Initially these agents were favoured for their more potent glucose-lowering effects. Arguably, it is this association with other similar agents in the same class that dampened the early enthusiasm for metformin and tempered its use worldwide for decades [5, 6].

Phenformin and Lactic Acidosis

Ungar and colleagues developed phenformin (phenethylbiguanide) in the US in the late 1950s. The blood glucose reduction achieved by phenformin was, if anything, more

potent than that of metformin. In the US, it was regarded as a good alternative to sulfonylureas. Such was the success of phenformin in the US that neither metformin nor buphormin were introduced. Nevertheless, in Europe both were in use to a greater or lesser extent, with metformin preferred in the UK and buphormin preferred in Germany. Despite approval of metformin in the UK in 1958, it was not widely prescribed there or in the rest of Europe. It was known that lactic acidosis was a safety issue with these drugs from the beginning, but this only met with regulatory restriction in the US in the 1970s. This started with the withdrawal of phenformin from a major US trial. Concern escalated in 1978 when phenformin was removed completely from the US market. Unfortunately, the reputation of phenformin as having an unacceptably high risk of lethal metabolic acidosis tarnished the entire biguanide class. Although these drugs remained available in Europe in the interim period, the class did not recover in North America until the early 1990s [5, 6].

From clinical use, it was understood that the risk of lactic acidosis appeared to be less in metformin compared with other members of the biguanide class. Research continued throughout the 1980s examining the multitude of effects of metformin including decreasing hepatic gluconeogenesis and improving insulin sensitivity. Serendipitously, this coincided with a growing appreciation of the pathophysiology of type 2 diabetes and the role that insulin resistance played in this. Reassuring results from efficacy studies in the 1980s, coupled with a desire by the European pharmaceutical company Lipha, eventually yielded acceptance by the FDA when safety data was satisfactory. US approval of metformin was eventually granted in December 1994. The landmark UKPDS (United Kingdom Prospective Diabetes Study) was ongoing through the late 1970s until the late 1990s. The results of the UKPDS were practice changing and led to a paradigm shift in glycaemic targets. Moreover, the benefits of metformin in reducing macrovascular complications and deaths spurred on the ascent of metformin to being the most prescribed oral drug for the management of type 2 diabetes.

Pharmacology

Mechanism of Action

Despite its long history and the extensive research on metformin in clinical trials, the exact mechanisms of action have not been precisely defined (Figure 2.1) [7]. Indeed, multiple novel mechanisms of action have been described over the past decade but remain incompletely elucidated in the literature. In broad terms metformin works to achieve glucose reduction in the following ways:

- inhibition of hepatic glucose production;
- reduced insulin resistance; and
- intestinal effects.

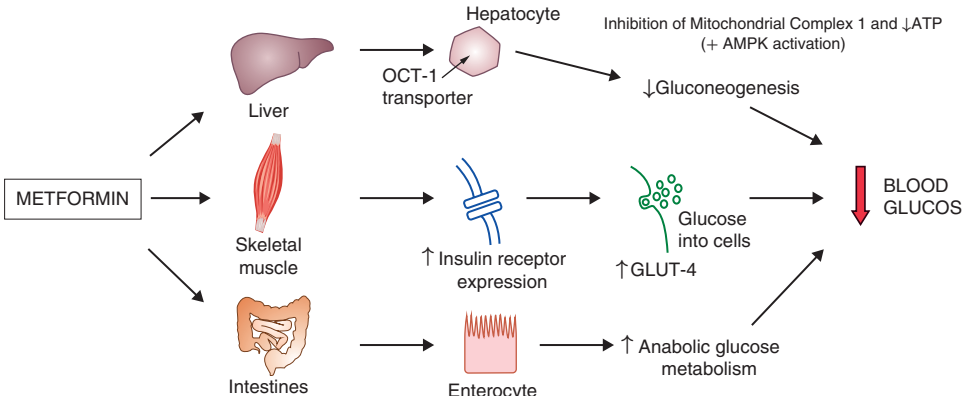


FIGURE 2.1 Mechanism of action of metformin. Metformin is considered to have its effect through several mechanisms in the liver, peripheral tissue including skeletal muscle, and intestines. In the liver it is taken up into hepatocytes under the action of Organic Cation Transporter 1, accumulating around mitochondria, inhibiting complex I within the respiratory chain, leading to reduction in ATP, which is required for gluconeogenesis. Although not precisely elucidated, AMPK activation by metformin is part of this process. Through several mechanisms, including activation of GLUT-4 receptor expression, metformin reduces insulin resistance in skeletal muscle. In the intestine metformin increases anaerobic metabolism in enterocyte cells, in turn reducing glucose absorption, and may also have a direct effect on GLP-1 secretion [7].

Inhibition of Hepatic Glucose Production Inhibition of glucose production in the liver is generally accepted as the primary modality through which metformin exerts its glucose-lowering effects. Hepatic glucose production is the complex sum of several physiological processes, namely gluconeogenesis, glycogen synthesis and glycolysis. Metformin is believed to exert its primary effect on glycaemic control by reducing hepatic gluconeogenesis. Gluconeogenesis is the process whereby the liver produces glucose *de novo* from amino acid precursors in the fasting state. Gluconeogenesis plays an important role in fasting glycaemia and as such metformin reduces fasting glycaemia with overall glycaemic benefits [3, 7, 8].

The mechanism through which metformin reduces gluconeogenesis is complex and remains incompletely understood. Metformin is taken up by hepatocytes under the action of OCT-1 (Organic Cation Transporter 1). Metformin then accumulates in the hepatocytes and particularly around mitochondria, which occurs because metformin is a positively charged molecule and there is a membrane potential across the mitochondrial wall. Here metformin inhibits complex I within the respiratory chain. This leads to a reduction in ATP production. Gluconeogenesis is an energy-rich process, indeed for each glucose molecule produced six ATP equivalents are required. Therefore, any inhibition of this energy production reduces gluconeogenesis. Nevertheless, some rodent models have raised questions as to how important this really is in reducing hepatic gluconeogenesis. For example, another mitochondrial mechanism of action has been proposed involving inhibition of the glycerophosphate shuttle. This

is important in the recycling of cytoplasmic NADH for oxidative phosphorylation and energy production [3].

AMP-activated protein kinase (AMPK) is probably the best-known pathway associated with the actions of metformin. AMPK is a cellular energy sensor that is activated by metformin. Alterations to the cellular energy state suggest that a reduced cellular energy balance activates AMPK. As such, some of the molecular mechanisms we have discussed above, undoubtedly in conjunction with other mechanisms, alter the cellular energy balance and ultimately lead to AMPK activation. Changes to the ADP:ATP (adenosine diphosphate:adenosine triphosphate) and AMP:ATP (adenosine monophosphate:adenosine triphosphate) ratios which reflect this state of cellular energy depletion are important. AMPK acts to restore the cellular energy balance by promoting catabolic pathways designed to increase the energy yield in the form of ATP and inhibits processes that will further deplete the cell of energy, including gluconeogenesis. Interestingly, there is ongoing debate based on *in vitro* models as to whether concentrations of metformin correlating with normal dosing regimens lead to cellular energy depletion and thus AMPK activation. There is also evidence that another mechanism of direct AMPK activation via the lysosome may be important. Currently, it appears clear that, while AMPK activation is important, the exact mechanism through which metformin achieves this outcome is complex and requires further research [3, 7].

Reduced Insulin Resistance The pathophysiology of type 2 diabetes is characterised by a resistance to the effect of insulin in peripheral tissue such as skeletal muscles. As a result, the action of insulin in allowing peripheral glucose uptake is reduced. Metformin reduces the insulin resistance that characterises type 2 diabetes and lowers blood glucose levels by increasing the uptake of glucose in peripheral muscles through enhancing the action of insulin in these insulin-resistant cells. It is likely that metformin exerts this effect via several mechanisms. Potential mechanisms include increasing the activity of the tyrosine kinase insulin receptors, coupled with increased GLUT-4 receptor expression. GLUT-4 receptors are the primary means of glucose uptake into cells, so by increasing GLUT 4 expression it can be seen why more glucose will be taken up by peripheral muscle and why blood glucose is lowered [3, 7, 8].

Intestinal Effects The intestinal side effects of metformin are well known, and the role of the intestine in the glucose-lowering effect of metformin is increasingly appreciated. There is evidence to suggest that metformin increases anaerobic metabolism of glucose in the enterocyte cells within the gut. This in turn reduces the absorption of glucose from the gut, lowering glucose levels. There is also evidence that metformin may lead to GLP-1 secretion. GLP-1 is responsible for increasing pancreatic insulin secretion and reducing glucagon secretion, reducing blood glucose levels (see Chapter 4). Furthermore, there is emerging evidence that the gut microbiome (the bacteria that are ordinarily present in the gut) is altered by metformin, but how this may contribute to is glucose-lowering effects remains unknown [3, 9].

Pharmacokinetics

Metformin has good bioavailability when taken orally. Approximately 60% is absorbed with 30% excreted unchanged via the gut. The C_{max} is reached at approximately 2.5 hours (time to maximum concentration, T_{max}) following ingestion and it takes 24–48 hours to reach a plasma steady state. Metformin is not metabolised but excreted unchanged in the urine via glomerular filtration and tubular secretion in the nephron. The conventional formulation is immediately released and has a plasma half-life of between four and eight hours, so has to be given multiple times over the day. A modified, or extended, release formulation is more slowly absorbed, allowing for once daily dosing.

Prescribing in Renal Impairment Given that it is excreted unchanged in urine, metformin can accumulate in patients with renal impairment and exert a toxic effect. Metformin should not be commenced if the estimated glomerular filtration rate (eGFR) is <30 ml/min/1.73 m^2. Similarly, in people who have acute kidney injury, metformin should be temporarily stopped. It can then be restarted when renal function has returned to baseline. If medications which may affect renal function are to be initiated, such as ACE inhibitors, then care should be taken to monitor renal function when this is being done. In a hospital setting, conditions which are likely to provoke an acute kidney injury, such as diarrhoea, dehydration and sepsis, should be indications to pre-emptively stop metformin temporarily.

Prescribing point: *Prior to initiation of metformin therapy, renal function should be assessed then annually thereafter as part of a routine screening investigations, biannually in those who are at increased risk of a reduction in renal function.*

Prescribing in Liver Disease There is no hepatic metabolism of metformin and no specific requirement to reduce metformin dosing in liver disease. However, one of the primary adverse events associated with metformin therapy is lactic acidosis, and liver disease can lead to tissue hypoxia, which exacerbates the risk of lactic acid formation, so it is important that metformin is used with care in this setting.

Prescribing in Heart Failure In a similar way to liver disease, there is increased risk of tissue hypoperfusion associated with heart failure. Heart failure also increases the risk of lactic acidosis. As such, in a similar way to liver disease, care should be taken to reduce or stop metformin in those with decompensated heart failure who are at increased risk of tissue hypoperfusion.

Prescribing in Pregnancy Metformin is safe in pregnancy. It can be used in pregnancy by women with pre-existing type 2 diabetes and women who develop gestational diabetes (see also Chapter 15). Metformin may be used while breastfeeding.

Dose

- Metformin should be started at a dose of 500 mg and should be taken once daily with breakfast for one week.

- Further up-titration of the dose should be continued as required to a maximum of 2 g per day.
- Metformin modified release should be taken initially at 500 mg daily, increased if necessary every 10–15 days up to 2 g once daily, to be taken with the evening meal.
- Metformin is also available at a dose of 850 mg to be taken three times daily.
- Metformin is available as fixed-dose combinations with commonly used DPP-4 inhibitors (see Chapter 4) and SGLT2 inhibitors (see Chapter 5).

Glycaemic Efficacy

Broadly speaking, metformin, sulfonylureas and glitazones have similar efficacies and are more efficacious than acarbose and DPP4 inhibitors, but less efficacious than GLP-1 receptor agonists or insulin. Following approval for the use of metformin in the US, two randomised control studies were undertaken to evaluate the glycaemic efficacy of metformin alone or with another treatment given over 29 weeks to moderately obese participants with type 2 diabetes not controlled by diet (protocol 1; metformin vs. placebo; 289 patients) or diet plus glyburide (protocol 2; metformin and glyburide vs. metformin vs. glyburide; 632 patients) [10]. Glyburide is also known as glibenclamide in Europe.
In protocol 1:

- The metformin-treated group compared with placebo had lower mean fasting glucose concentrations (10.6 ± 0.3 vs. 13.7 ± 0.3 mmol/l; $p < 0.001$).
- The metformin-treated group compared with placebo had lower mean HbA1c ($7.1 \pm 0.1\%$ vs. $8.6 \pm 0.2\%$; $p < 0.001$).

In protocol 2:

- Metformin and glyburide treatment compared with glyburide alone was more effective in reducing fasting plasma glucose (10.5 ± 0.2 vs. 14.6 ± 0.2 mmol/l; $p < 0.001$) and HbA1c ($7.1 \pm 0.1\%$ vs. $8.7 \pm 0.1\%$, $p < 0.001$).
- The effect of metformin alone was similar to that of glyburide alone.

A more detailed assessment of glycaemic efficacy was outlined in the Scottish Intercollegiate Guidelines Network (SIGN) guideline 154 [11]:

- For glycaemic control with metformin vs. placebo or diet the evidence suggests greater reduction of HbA1c (standardised mean difference, SMD, 0.97, 95% confidence interval, CI, −1.25 to −0.69 and SMD −1.06, 95% CI 1.89 to −0.22, respectively).
- A review of the evidence identified two systematic reviews showing similar efficacy to sulfonylureas, a randomised controlled trial (RCT) showing similar efficacy to the SGLT2 inhibitor canagliflozin and an RCT showing marginally less efficacy than the GLP-1 receptor agonist dulaglutide.

- Metformin as monotherapy gave a greater reduction in HbA1c than DPP-4 inhibitors (pooled between-group difference –0.4% (–4.37 mmol/mol), 95% CI –0.5 to –0.3% (–5.46 to –3.28 mmol/mol)) in a meta-analysis of six short-duration studies.

The ADOPT trial (A Diabetes Outcome Progression Trial; see Chapter 12) compared metformin, glyburide and rosiglitazone in drug-naive patients with type 2 diabetes. Similar short-term efficacy was identified. Longer-term efficacy was best for rosiglitazone, then metformin, with glyburide having the least durability of action.

Prescribing point: *When adding in metformin as monotherapy, review of clinical response is required as it might not be expected to provide more than a 1% improvement in HbA1c and additional treatment may be required.*

Safety and Side Effects

Metformin may be associated with several adverse effects and the most common is gastrointestinal upset. This may take the form of abdominal discomfort, decreased appetite, diarrhoea, or nausea and vomiting. When this occurs, there should be some reassurance given to the patient that it is likely that these unpleasant effects will diminish in time. In a proportion of patients these side effects will be serious enough to lead to discontinuation of therapy, and this may occur in up to 30% of people. Gastrointestinal side effects are more common when higher doses of metformin are used. Modified-release preparations of metformin can be considered if adverse gastrointestinal side effects persist. Metformin does not cause weight gain and may be associated with modest weight loss (on average 1–2 kg), which adds to the favourable profile of the drug. More rarely hepatitis can occur owing to metformin therapy. There can be adverse skin reactions such as rash and rarely a reduction in vitamin B12 absorption.

Prescribing point: *Metformin should be titrated up slowly to reduce the risk of gastrointestinal side effects.*

Lactic Acidosis

Lactic acidosis is a serious medical emergency characterised by the buildup of lactic acid in the bloodstream. This is a rare but serious complication of metformin therapy. It is characterised by fatigue, nausea and vomiting, dyspnoea, abdominal pain and muscle cramps. This can progress to coma and death. Biochemically there is a metabolic acidosis (with a raised anion gap) and an elevated lactate level (>2.5 mmol/l). The mortality associated with lactic acidosis can be as high as 25% when fully established [12, 13].

Lactate formation occurs most commonly in the context of anaerobic respiration owing to tissue hypoperfusion. This can occur in any condition where cellular perfusion is reduced. We have already considered several of these situations. In clinical practice, we also often see an elevated lactate in severe infections and sepsis. It is in these situations that particular care must be taken to stop metformin pre-emptively and therefore reduce the risk of lactic acidosis.

Metformin may contribute to lactic acidosis via several mechanisms. Firstly, it inhibits the uptake of lactate by the liver for use in gluconeogenesis – which it inhibits. Secondly, as we have already discussed, it may increase the production of lactate within the gut. It is likely, however, that inhibition of hepatic uptake of lactate for gluconeogenesis is the predominant cause of lactic acidosis associated with metformin [12, 13].

A common clinical scenario is that of a patient with type 2 diabetes who takes metformin undergoing a surgical procedure. In cases of major surgery involving a general anaesthetic or spinal anaesthetic, it is recommended that metformin therapy is temporarily stopped and not restarted until 48 hours post-operatively if renal function remains stable. Where CT imaging using iodinated contrast agents is required, this too can provoke contrast-induced nephropathy, increasing the risk of lactic acidosis. In such circumstances metformin should also be temporarily discontinued and restarted 48 hours following contrast administration if renal function remains stable.

Prescribing point: *Metformin-associated lactic acidosis can be prevented by withholding during an intercurrent illness and around times when patients are at increased risk, including when undergoing surgical intervention.*

Outcome Trials

Cardiovascular Outcome Trials

UKPDS UKPDS (United Kingdom Prospective Diabetes Study) was a landmark trial led by Dr Robert Turner and his colleagues at the University of Oxford [14]. It was one of the most important trials in creating a paradigm shift in the management of type 2 diabetes. The UKPDS commenced in the 1970s and results were published in 1998. The Diabetes Complications and Control Trial, which was published in 1993, had examined whether tight glycaemic control improved the long-term risk of microvascular complications in type 1 diabetes [15]. However, debate continued as to whether tight glycaemic control would reduce the risk of such complications in people with type 2 diabetes. The primary outcome of the UKPDS was to examine whether tighter glycaemic control in type 2 diabetes also reduced this risk. The secondary outcome of this trial was to examine whether different therapeutic agents also preferentially reduced the risk of negative outcomes when used to achieve tight glycaemic control.

A total of 5102 participants at 23 centres across the UK took part in the main trial. There was a median follow-up of 10.7 years. Those with a new diagnosis of type 2 diabetes and a fasting blood glucose >6 mmol/l were included. There was a three to four month period of optimisation of diet. Fasting plasma glucose was then rechecked. If fasting glucose was found to be between 6 and 15 mmol/l, then participants were randomised. This involved randomisation to a 'conventional policy' of fasting plasma glucose targets of <15 mmol/l or 'intensive policy' of fasting plasma glucose targets <6 mmol/l. One of sulfonylurea, insulin therapy or metformin (overweight participants only) was administered (after randomisation) to help achieve this target.

In participants who initially managed to attain a fasting blood glucose of <6 mmol/l with diet alone, this approach was continued and if fasting blood glucose rose above 6 mmol/l they were then eligible for randomisation also. Participants who despite dietary intervention had a blood glucose greater than 15 were automatically randomised to the intensive policy arm of the trial. If monotherapy failed in those in the intensive arm, then combination therapy was instituted.

Three aggregate endpoints were used in this trial. The first outcome was any diabetes-related endpoint. This umbrella term encompassed both macrovascular and microvascular complications. Diabetes-related death was the second outcome reported, and the third outcome was all-cause mortality. Importantly, the UKPDS found that the intensive control based on treatment with sulfonylurea or insulin showed a reduction in any diabetes-related endpoint, but did not initially demonstrate a reduction in diabetes mortality (see also Chapters 3 and 7).

The UKPDS specifically examined the effect of metformin in 342 overweight patients with type 2 diabetes compared with overweight patients in the conventional control group (<15 mmol/l) and intensive control via any of the other treatment modalities.

- Metformin therapy was associated with a 32% reduction (95% CI 13–47; $p = 0.002$) for any diabetes-related endpoint, a 42% reduction for diabetes-related death (95% CI 9–63; $p = 0.017$) and a 36% reduction for all cause mortality (95% CI 9–55; $p = 0.011$) compared with conventional control (Table 2.1, Figure 2.2).
- Myocardial infarction was reduced by 39% (95% CI 41–69; $p = 0.010$) and macrovascular outcomes (myocardial infarction, sudden death, angina, stroke and peripheral vascular disease) were reduced by 30% (95% CI 5–48%; $p = 0.020$) in the metformin group, relative to the controls.
- In participants randomised to the intensive glycaemic control arm, metformin therapy demonstrated a reduction in any diabetes-related endpoint compared with intensive glycaemic control using sulfonylureas and insulin.
- Metformin was not associated with weight gain or hypoglycaemia.

Following the UKPDS, epidemiological follow-up of patients continued for a further ten years. In this post-trial monitoring subjects who had started on metformin therapy demonstrated continued reductions for any diabetes-related endpoint, myocardial infarction or death from any cause [16].

HOME Study The HOME study (Hyperinsulinaemia: the Outcome of its Metabolic Effects) looked at the benefits of continuing metformin in people with type 2 diabetes who had been commenced on insulin. Unlike UKPDS, this study comprised people with longstanding diabetes, not those who were newly diagnosed. It was a multicentre clinical trial in 390 people with type 2 diabetes on insulin treatment who were randomised to metformin vs. placebo to be given in addition to insulin. The primary endpoint was an aggregate of microvascular and macrovascular morbidity and mortality outcomes. Secondary endpoints looked at other microvascular and macrovascular outcomes. Additionally, they examined the effect of metformin on other parameters such as haemoglobin A1C, insulin requirements, lipid levels, blood pressure, body weight

TABLE 2.1 Cardiovascular trials with metformin [14, 18, 19, 29]

Trial	UKPDS [14]	HOME [18]	SPREAD-DIMCAD [19]	REMOVAL [29]
Intervention	Intensive control with metformin up to 2550 mg daily	Metformin 850 mg one to three times daily	Metformin up to 1.5 g daily	Metformin 1 g twice daily
Comparator	Conventional control with diet alone	Placebo	Glipizide up to 30 mg daily	Placebo
Population size	Total 753 Metformin 342 Diet 411	390	304	428
Age (years)	53	61	63	55
Duration of diabetes (years)	Recently diagnosed	13	6	34
Follow-up (years)	11	4	5	3
Atherosclerotic CVD (%)	0	33	100	12
Heart failure (%)	0	NA	Excluded	
Primary outcome	Significant reductions in any diabetes-related endpoint, diabetes-related death, all-cause mortality	Aggregate of microvascular, macrovascular morbidity and mortality no difference	Cardiovascular composite metformin superior	No difference in mean progression of cIMT
Other outcomes	Myocardial infarctions significantly reduced	Macrovascular morbidity significantly reduced	No significant differences	Maximal cIMT significantly reduced

CVD = cardiovascular disease, cIMT = carotid intima media thickness.

and body mass index (BMI) [17, 18]. As there were baseline differences in age, sex, smoking, statin use and previous cardiovascular disease, these were accounted for in the analysis, but this weakens the findings:

- The HOME study failed to demonstrate a significant difference in the primary outcome (Table 2.1).
- Metformin was associated with a reduction in macrovascular events (hazard ratio, HR 0.60; 95% CI 0.40–0.92; $p = 0.04$) with an absolute risk reduction of 6.1% and a number needed to treat of 16 to prevent one macrovascular event.

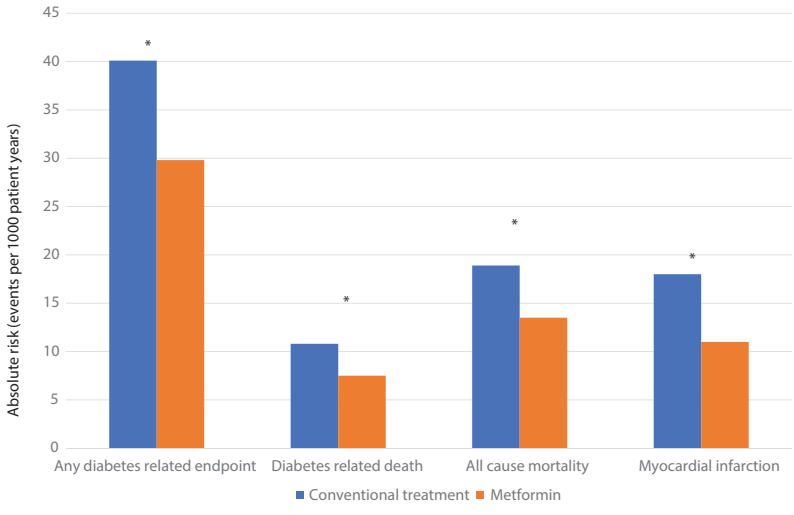


FIGURE 2.2 Event rates (events per 1000 patient years) comparing metformin and conventional treatment in the UKPDS metformin substudy. UKPDS had three aggregate endpoints of any diabetes-related endpoint, diabetes-related death, and all-cause mortality. Myocardial infarction was a secondary endpoint. Statistically significant differences are marked with an asterisk. *Source:* Based on [14].

The benefit was thought to be at least partially explained by a mean reduction of 3.07 kg in the metformin group and there was no reduction in microvascular endpoints with metformin therapy. Additionally, in the HOME study metformin was associated with a number of metabolic benefits. There was a reduction in insulin dosage and in HbA1c in the metformin group. There was also a reduction in body weight and BMI along with a reduced waist-to-hip ratio. There was no change, however, in blood pressure or lipid profile. Importantly there was no increase over 4.3 years of follow-up in the number of hypoglycaemic events.

SPREAD-DIMCAD SPREAD-DIMCAD (Study on the Prognosis and Effect of Antidiabetic Drugs on Type 2 Diabetes Mellitus with Coronary Artery Disease) was a Chinese multicentre randomised, double-blind, placebo-controlled trial examining whether metformin in comparison with the sulfonylurea glipizide led to beneficial cardiovascular outcomes in people with type 2 diabetes and pre-existing coronary artery disease (previous myocardial infarction or >50% stenosis of coronary artery) [19]. A total of 304 participants were enrolled in the study. There was a reduction in glycated haemoglobin in both the glipizide group and the metformin group to 7.1 and 7%, respectively (from baseline 7.6% in both groups).

- In those who were randomised to metformin after a median of five years' follow-up, the adjusted hazard ratio for a composite of cardiovascular events was

0.54 (95% CI 0.30–0.90; $p = 0.026$) in comparison with the glipizide group (Table 2.1, Figure 2.3).

- Metformin demonstrated a significantly lower BMI in comparison with the glipizide group.

This study added further evidence that metformin therapy exerts additional benefits beyond glucose lowering for people with type 2 diabetes. It was postulated by the authors that metformin may exert this effect through anti-inflammatory actions.

Renal Effects

There is emerging evidence to suggest that metformin may have beneficial effects on the kidney in diabetic kidney disease. However further research is required before any recommendations are made regarding metformin administration in people who have reduced renal function [20–22].

Prevention of Type 2 Diabetes

DPP The DPP (Diabetes Prevention Programme) recruited adults over the age of 25 years with risk factors for the development of diabetes (elevated fasting plasma glucose/impaired glucose tolerance/overweight or obese) in the US between 1996 and 2001 [23]. Participants were randomised to metformin 850 mg twice daily, intensive

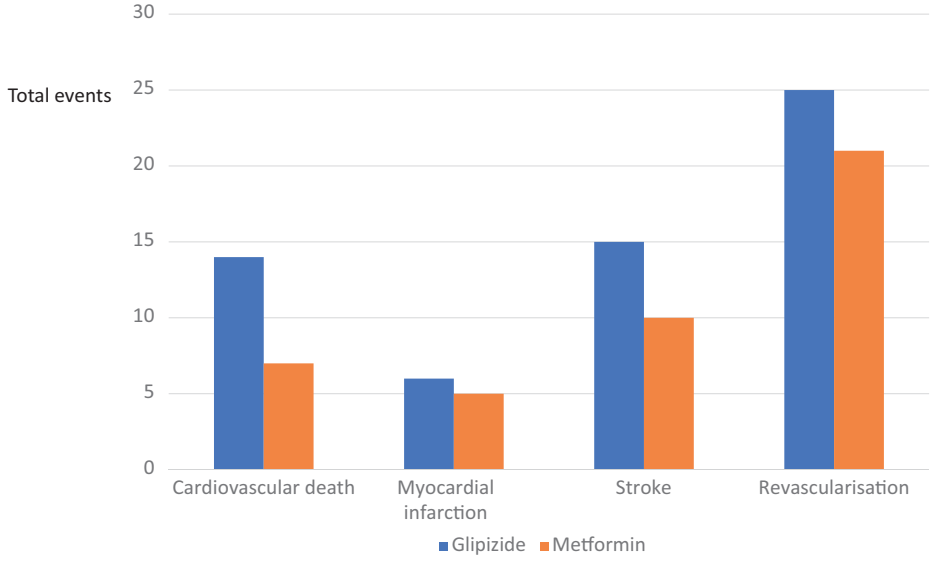


FIGURE 2.3 Total events comparing metformin and glipizide in the SPREAD-DIMCAD. *Source:* Based on [19].

lifestyle modification (aiming for 7% weight loss and 150 minutes of moderate to intensive exercise per week) or placebo (see Table 2.2). A total of 3234 participants were recruited and followed up over 2.8 years. The trial was stopped early owing to the emerging evidence for the efficacy of both lifestyle intervention and metformin therapy.

- Metformin was associated with a 31% reduction in the incidence of diabetes compared with placebo (95% CI 17–43%) while intensive lifestyle intervention was associated with a 58% (95% CI 48–66%) reduction.

Of the participants in the DPP, 88% continued into the DPPOS (DPP Outcomes Study) that followed up participants for 15 years [24]. Those on metformin remained on this (although now open label). Those in the lifestyle intervention group were given intermittent lifestyle reinforcement advice. Placebo was discontinued.

- Metformin was associated with an 18% reduction in the incidence of diabetes at 15 years compared with those in the discontinued placebo group. Risk reduction in the lifestyle group was 27% compared with placebo.

TABLE 2.2 **Studies on the prevention of diabetes with metformin [23, 25, 26]**

Trial	DPP [23]	IDDP [25]	CANOE [26]
Intervention	Metformin 850 mg twice daily	Metformin up to 500 mg twice daily,	Combination rosiglitazone 2 mg plus metformin 500 mg twice daily
Comparator(s)	Placebo, a lifestyle modification programme	Control, lifestyle modification alone, lifestyle modification plus metformin	Placebo
Population size	3234	531	207
Age (years)	51	46	52
Follow-up (years)	3	3	4
Primary outcome for metformin	31% reduction in incidence of diabetes with metformin	27% reduction in incidence of diabetes with metformin	34% reduction in the incidence of diabetes with rosiglitazone plus metformin
Primary outcome for comparators	58% reduction in incidence of diabetes with lifestyle modification	28% reduction in incidence of diabetes with lifestyle modification, 28% reduction with both	Placebo comparison only

This study suggested that, while metformin appeared to reduce the risk of developing type 2 diabetes, lifestyle intervention was more efficacious. In three groups, however, metformin was approximately as efficacious as lifestyle interventions: obese people with BMI >35 kg/m^2, people younger than 60 and women with previous gestational diabetes. These groups have been included in the American Diabetes Association Standards of Care as being groups in whom metformin may be considered as a therapeutic intervention to reduce the risk of type 2 diabetes [2].

IDPP The IDPP (Indian Diabetes Prevention Programme) was a non-blinded study of 531 Asian Indian subjects. This trial had four arms with median follow-up of 30 months: (i) control; (ii) lifestyle intervention; (iii) metformin (at 250 mg twice daily); and (iv) lifestyle intervention with metformin [25].

- The three year cumulative incidences of diabetes were 55.0, 39.3, 40.5 and 39.5% in groups 1–4, respectively.
- The relative risk reduction was 28% with lifestyle modification (95% CI 20.5–37.3; $p = 0.018$), 26% with metformin (95% CI 19.1–35.1; $p = 0.029$) and 28% with lifestyle modification with metformin (95% CI 20.3–37.0; $p = 0.022$), as compared with the control group.

CANOE The CANOE (Canadian Normoglycaemia Outcomes Evaluation) study examined whether a combination pill comprising rosiglitazone 2 mg and metformin 500 mg taken twice daily vs. placebo reduced the incidence of type 2 diabetes in 207 people with impaired glucose tolerance over 3.9 years of follow-up [26].

- Incident diabetes occurred in significantly fewer individuals in the active treatment group ($n = 14(14\%)$) than in the placebo group ($n = 41$ (39%); $p < 0.0001$).
- The relative risk reduction was 66% (95% CI 41–80) and the absolute risk reduction was 26% (95% CI 14–37).
- Seventy (80%) patients in the treatment group regressed to normal glucose tolerance compared with 52 (53%) in the placebo group ($p = 0.0002$).

The evidence that metformin is associated with a reduction in the risk of developing type 2 diabetes and in certain groups has led to it being recommended for this purpose in some international guidelines. However, lifestyle intervention appears to be more efficacious in reducing risk and should be considered as the first-line approach in people at high risk of developing type 2 diabetes and current European guidelines suggest this approach.

Metformin in Type 1 Diabetes

While metformin has its primary use in type 2 diabetes, it also can have a role in people with type 1 diabetes. Data from a Scottish cohort demonstrated that 8% of the population with type 1 diabetes were currently prescribed metformin and up to 15% had been prescribed metformin in the past [4]. The potential benefits of metformin therapy in type 1 diabetes are clear. Given that we know that metformin has cardiovascular benefits in type 2 diabetes, it has been extrapolated that this may also apply to people with type 1 diabetes. In addition to this, the concept of double diabetes has gained increasing momentum over the last decade. 'Double diabetes' is the concept that, in addition to the autoimmune beta cell destruction seen in type 1 diabetes, there is also the emergence of insulin resistance with age and weight gain [27]. This dual pathology is exacerbated by insulin-induced weight gain, which worsens insulin resistance in those who are genetically susceptible to this [28]. The majority of people with type 1 diabetes are in the overweight or obese category. In society generally, there is an increasing epidemic of type 2 diabetes. It therefore makes sense that in people who have been diagnosed with type 1 diabetes, like the rest of the population, are also at risk of developing a type 2 phenotype. This concept makes metformin with its known reduction of insulin requirement and reduction of insulin resistance a very appealing theoretical prospect in this group.

REMOVAL

The REMOVAL (Removing with Metformin Vascular Adverse Lesions) trial was an international multicentre placebo-controlled trial evaluating whether metformin therapy in addition to insulin reduced cardiovascular risk and improved other metabolic and cardiovascular parameters. Participants were people with type 1 diabetes of five years' duration or more, over the age of 40 with three or more pre-specified cardiovascular risk factors [29]. Participants were randomised to metformin vs. placebo in addition to their usual insulin over three years of follow-up. The primary endpoint was progression of mean far-wall carotid intima media thickness (cIMT), which is a surrogate marker for the presence of atherosclerosis. This was measured annually over a three year period.

- Metformin failed to demonstrate any benefit in averaged far-wall cIMT (the primary endpoint), and Metformin attenuated averaged maximal far-wall cIMT (another way of measuring cIMT), one of the tertiary outcomes.
- There were several metabolic benefits seen with metformin therapy in REMOVAL, including a modest reduction in HbA1c (−0.13%; $p = 0.006$), bodyweight (−1.17 kg; $p < 0.0001$) and LDL cholesterol (−0.13 mmol/l; $p = 0.001$).
- The decline in eGFR was attenuated in the metformin group vs. placebo 4.00 ml/min/1.73 m^2 (2.19 to 5.81; $p < 0.001$) over the three years of REMOVAL follow-up, suggesting possible renal benefits in this population.

Prescribing point: *Metformin is not licensed in the UK as an adjunctive glucose-lowering therapy in people with type 1 diabetes who are unable to reach their glycaemic targets with insulin therapy, but may be used off label. This approach must, however, be on an individual patient basis under the close supervision of the diabetes team.*

Place of Metformin in Current and Future Practice

Metformin is an important drug in the management of type 2 diabetes and remains 'first line' after lifestyle interventions in many European and North American diabetes guidelines, despite some advocating the first-line use of SGLT2 inhibitors because of the more robust cardiovascular outcome trial data. Given the established glycaemic efficacy, some evidence of cardiovascular benefit, well-established safety profile and affordability, it is likely to remain at the forefront of the treatment for type 2 diabetes going forward. However, there is considerable debate as to whether the evidence emerging for newer antidiabetic drugs should place them before metformin in guidelines (see Chapters 5 and 15).

The use of metformin as an adjunctive therapy in type 1 diabetes is likely to increase with the increase in prevalence of obesity and a role in delaying progression of diabetic kidney disease is under investigation. It used in the treatment of polycystic ovary syndrome and is a licensed indication in the UK. There is potential for the use of metformin in any condition associated with insulin resistance.

References

1. Buse, J.B., Wexler, D.J., Tsapas, A. et al. (2020). 2019 update to: management of hyperglycaemia in type 2 diabetes, 2018. A consensus report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). *Diabetes Care* 43: 487–493.
2. American Diabetes Association. (2021). Pharmacologic approaches to glycemic treatment: standards of medical care in diabetes 2021. *Diabetes Care* 44 (Supplement 1): S111–S114.
3. Rena, G., Hardie, D.G., and Pearson, E.R. (2017). The mechanisms of action of metformin. *Diabetologia* 60: 1577–1585.
4. Livingstone, R., Boyle, J.G., and Petrie, J.R. (2017). A new perspective on metformin therapy in type 1 diabetes. *Diabetologia* 60: 1594–1600.
5. Bailey, C. and Day, C. (2004). Metformin: its botanical background. *Pract Diabetes* Int 21: 115–117.
6. Bailey, C.J. (2017). Metformin: historical overview. *Diabetologia* 60: 1566–1576.
7. Glossmann, H.H. and Lutz, O.M.D. (2019). Pharmacology of metformin – an update. *Euro J Pharmacol* 865: 17278. doi: 10.1016/j.ejphar.2019.172782.

8. Rena, G., Pearson, E.R., and Sakamoto, K. (2013). Molecular mechanism of action of metformin: old or new insights? Diabetologia 56: 1898–1906.
9. Bailey, C.J., Wilcock, C., and Scarpello, J.H.B. (2008). Metformin and the intestine. *Diabetologia* 51: 1552–1553.
10. Defronzo, R.A. and Goodman, A.M. and the Metformin Multicentre Study Group (1995). Efficacy of metformin n patients with non-insulin dependent diabetes mellitus. *N Engl J Med* 333: 541–549.
11. SIGN (2017). SIGN 154. Pharmacological management of glycaemic control in people with type 2 diabetes. A national clinical guideline. https//www.sign.ac.uk/media/1090/sign154.pdf (accessed 27 September 2021).
12. Defronzo, R., Fleming, G.A., Chen, K., and Bicsak, T.A. (2016). Metformin-associated lactic acidosis: current perspectives on causes and risk. *Metabolism* 65: 20–29.
13. Chu, P.Y., Hackstadt, A.J., Chipman, J. et al. (2020). Hospitalization for lactic acidosis among patients with reduced kidney function treated with metformin or sulfonylureas. *Diabetes Care* 43: 1462–1470.
14. UK Prospective Diabetes Study Group (1998). Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34). *Lancet* 352: 854–865.
15. Nathan, D.M., Genuth, S., Lachan, J. et al. (1993). The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. *N Engl J Med* 329: 977–986.
16. Holmann, R., Paul, S.K., Bethyl, A. et al. (2008). 10-year follow-up of intensive glucose control in type 2 diabetes. *N Engl J Med* 359: 1577–1589.
17. Wulffelé, M.G., Kooy, A., Lehert, P. et al. (2002). Combination of insulin and metformin in the treatment of type 2 diabetes. *Diabetes Care* 25: 2133–2140.
18. Kooy, A., de Jager, J., Lehert, P. et al. (2009). Long-term effects of metformin on metabolism and microvascular and macrovascular disease in patients with type 2 diabetes mellitus. *Arch Intern Med* 169: 616–625.
19. Hong, J., Zhang, Y., Lai, S. et al. (2013). Effects of metformin versus glipizide on cardiovascular outcomes in patients with type 2 diabetes and coronary artery disease. *Diabetes Care* 36: 1304–1311.
20. Corremans, R., Vervaet, B.A., dddd'Haese, P.C., Neven, E., and Verhulst, A. (2019). Metformin: a candidate drug for renal diseases. *Int J Mol Sci* 20. doi:10.3390/ijms20010042.
21. Borges, C.M., Fujihara, C.K., Malheiros, D.M. et al. (2020). Metformin arrests the progression of established kidney disease in the subtotal nephrectomy model of chronic kidney disease. *Am J Physiol Renal Physiol* 318: F1229–1236.
22. Petrie, J.R., Rossing, P.R., and Campbell, I.W. (2020). Metformin and cardiorenal outcomes in diabetes: a reappraisal. *Diabetes Obes Metab* 22: 904–915.
23. Diabetes Prevention Programme Research Group (2002). Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. *N Engl J Med* 346: 393–403.
24. Nathan, D.M., Barrett-Connor, E., Crandall, J.P. et al. (2015). Long-term effects of lifestyle intervention or metformin on diabetes development and microvascular complications over 15-year follow-up: the Diabetes Prevention Program Outcomes Study. *Lancet Diabetes Endocrinol* 3: 866–875.
25. Ramachandran, A., Snehalatha, C., Mary, S. et al. (2006). The Indian Diabetes Prevention Programme shows that lifestyle modification and metformin prevent type 2 diabetes in Asian Indian subjects with impaired glucose tolerance (IDPP-1). *Diabetologia* 49: 289–297.
26. Zinman, B., Harris, S.B., Neuman, J. et al. (2010). Low-dose combination therapy with rosiglitazone and metformin to prevent type 2 diabetes mellitus (CANOE trial): a double-blind randomised controlled study. *Lancet* 376: 103–111.

27. Kietsiriroje, N., Pearson, S., Campbell, M., Ariëns, R.A., and Ajjan, R.A. (2019). Double diabetes: a distinct high-risk group? *Diabetes Obes Metab* 21: 2609–2618.
28. Cleland, S.J., Fisher, B.M., Colhoun, H.M., Sattar, N., and Petrie, J.R. (2013). Insulin resistance in type 1 diabetes: what is 'double diabetes' and what are the risks? *Diabetologia* 56: 1462–1470.
29. Petrie, J.R., Chaturvedi, N., Ford, I. et al. (2017). Cardiovascular and metabolic effects of metformin in patients with type 1 diabetes (REMOVAL): a double-blind, randomised, placebo-controlled trial. *Lancet Diabetes Endocrinol* 5: 597–609.

CHAPTER 3

Sulfonylureas and Meglitinides

Joseph Timmons and James Boyle

KEY POINTS

- Sulfonylureas are among the most commonly prescribed drugs for type 2 diabetes. They are administered orally and are associated with a reduction in HbA1c of approximately 1.0–2.0% (11–22 mmol/mol).
- Meglitinides have a similar profile but have a shorter duration of action, a characteristic that limits their use.
- The main adverse effects of insulin secretagogues are hypoglycaemia and weight gain.
- Sulfonylureas were included in the intensive treatment arm of the UKPDS and reduced microvascular complications but not macrovascular complications.
- The CAROLINA trial was a modern cardiovascular outcome trial to examine the cardiovascular safety of the DPP-4 inhibitor linagliptin, with the sulfonylurea glimepiride as a comparator, and demonstrated that neither were associated with excess adverse cardiovascular outcomes.

Introduction

Sulfonylurea drugs remain amongst the commonest drugs prescribed in people with type 2 diabetes. Like metformin, they are amongst the oldest oral agents available to lower blood glucose levels. They are cheap and efficacious but have the major side effects of hypoglycaemia and weight gain to consider [1]. Despite these side effects, sulfonylureas have retained a prominent position in international guidelines as a second-line agent after metformin. Indeed, up to 31% of patients in the US and 45% of

Diabetes Drug Notes, First Edition. Edited by Miles Fisher, Gerard A. McKay, and Andrea Llano.

patients in the UK are prescribed a sulfonylurea as part of their treatment regimen [1]. Meglitinides comprise a similar class of drugs which act via the same receptor as sulfonylureas and are less commonly prescribed in current practice [2].

History of Sulfonylureas

In the late 1930s, there was increasing understanding that some sulfur-based compounds could lead to low blood glucose levels. Around five years after this observation was first made, in 1942, Marcel Janbon and colleagues noted that the antibiotic paraamino sulfonamide-isopropyl-thiadiazole, used at the time to treat typhoid, caused hypoglycaemia. With parallels to the development of metformin, it was the observation of this adverse event that catalysed further research into chemically similar agents for use in diabetes [1].

In 1946 further research was conducted by the French physician Auguste Loubatieres. He discovered that it was the aryl-sulfonylurea compounds within these agents that caused hypoglycaemia by stimulating the release of insulin from the beta cells. This research paved the way in the 1950s for the first sulfonylureas to be used clinically. Carbutamide was the first agent of this class to be used, but it was withdrawn as it caused toxic myelosuppressive effects on the bone marrow.

Tolbutamide was the first successful sulfonylurea to be used clinically in Germany with further first-generation sulfonylureas such as chlorpropamide, acetohexamide and tolazamide quickly following. With further parallels to metformin, these agents were more widely used in Europe initially before broader uptake in North America. Second-generation sulfonylureas such as glibenclamide (also known as glyburide), glipizide and gliclazide were then developed. The history of sulfonylurea drugs, like many other antidiabetic drugs, is marred by early safety concerns. The University Group Diabetes Project (UGDP) was a trial using, among other agents, tolbutamide [3]. It was stopped early owing to concerns of excess cardiovascular risk in the sulfonylurea group. Despite methodological flaws and the mortality difference not reaching significance, tolbutamide and the entire class were temporarily withdrawn from the US market and it was not until 1984 that sulfonylureas were finally reintroduced.

The second generation of sulfonylureas (glibenclamide, glipizide and gliclazide) exerted a more potent hypoglycaemic effect. The UKPDS examined the role of sulfonylureas (as well as insulin and metformin) in attaining tight glucose control (fasting plasma glucose <6 mmol/l) [4]. This trial demonstrated the benefits of tight glycaemic control in avoiding diabetes complications. This was true regardless of which agent was used to attain intensive glycaemic control. There was no increased cardiovascular risk associated with sulfonylureas in comparison with other treatments. The third-generation sulfonylurea glimepiride became available in the mid 1990s. Despite the plethora of newer drugs available for the glycaemic management of type 2 diabetes, sulfonylureas have retained an important role as a second-line agent in many international guidelines [5, 6].

Pharmacology

Insulin Secretion from Beta Cells

Beta cells account for approximately 50–70% of the total cells within the islets of Langerhans. Beta cells contain stored insulin for immediate release and have the capacity to make more to replenish this following its liberation. A key component of beta cell physiology is the ability of these cells to sense the plasma glucose level and respond appropriately to this by secreting insulin. This is known as glucose-stimulated insulin secretion.

Glucose is taken up into the beta cells via the GLUT 2 transporter down its concentration gradient into the cell. Here glucose undergoes glycolysis and further metabolism to yield ATP and a change in the beta cell ATP:ADP ratio. This change is important because as blood glucose rises, the ATP:ADP ratio rises and activates the ATP-sensitive potassium channel (K_{ATP}) in the beta cell membrane, causing it to close. By closing this channel, the outward movement of positively charged K^+ ions is stopped and the resting cell membrane potential is disrupted, causing cellular depolarisation. The cellular depolarisation leads to the movement of calcium ions (Ca^{2+}) down their concentration gradient through voltage-gated calcium channels and into the beta cell. Intracellular influx of calcium ions leads to the release of insulin, which is prestored in vesicles via exocytosis. Insulin is then released into the hepatic portal vein and travels around the body to facilitate cellular glucose uptake and lower blood glucose levels.

Mechanism of Action

Sulfonylureas work to reduce plasma glucose by a combination of effects on insulin secretion and extra-pancreatic actions.

Insulin Secretion

Sulfonylureas are insulin secretagogues which act on the beta cells and lead to glucose-independent insulin secretion. They do so by directly activating the K_{ATP} channel. The K_{ATP} channel is an octameric structure formed from four sulfonylurea receptor 1 (SUR1) molecules and four potassium inward rectifier channels (KIR 6.1). Sulfonylurea drugs bind to SUR1 receptors at one or both binding sites and cause closure of the K_{ATP} channel and beta cell depolarisation. A cascade of calcium ion movement into the cell via the voltage-gated calcium receptor then occurs with resultant insulin exocytosis (Figure 3.1). Different sulfonylureas have differing characteristics of SUR binding. This explains the differences in onset and duration of action found in this class of drugs.

Given the fact that sulfonylureas lead to beta cell depolarisation and insulin secretion, their ability to exert beneficial glycaemic effects is entirely dependent on the presence of functioning beta cells. In the context of longstanding type 2 diabetes, sulfonylureas cease to function as effectively as before as beta cell mass is lost [1, 7, 8].

Extra-pancreatic Actions

There are several other mechanisms of action attributed to sulfonylureas. There is some variability between drugs within the class. Broadly

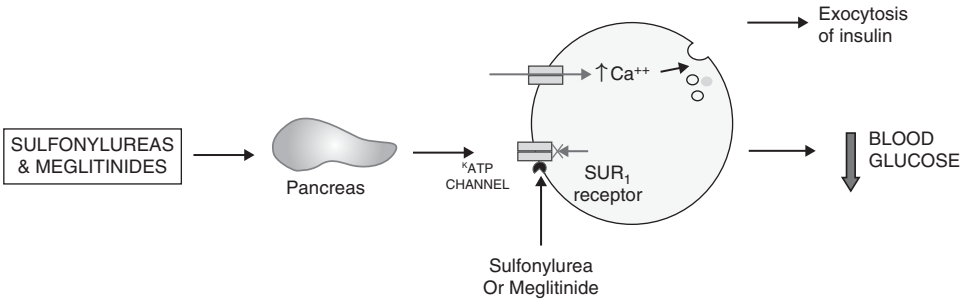


FIGURE 3.1 Mechanism of action of sulfonylureas. Sulfonylureas (and meglitinides) act on the beta cells and lead to glucose-independent insulin secretion by directly activating the ATP-sensitive potassium channel (K_{ATP}). Sulfonylureas (and meglitinides) bind to SUR1 receptors at one or both binding sites and cause closure of the K_{ATP} channel and beta cell depolarisation. A cascade of calcium ion movement into the cell via the voltage-gated calcium receptor then occurs with resultant insulin exocytosis.

speaking they are associated with an enhanced response to insulin and therefore increased carbohydrate uptake in skeletal muscle. There is evidence that these drugs also exert effects on the liver, the net effect of which is a reduction in hepatic glucose output. These extra-pancreatic actions are very much a small part of how sulfonylureas work in comparison with the direct effect on beta cells.

Pharmacokinetics

In the UK and EU, gliclazide and glimepiride are the most commonly used sulfonylureas. Glipizide and tolbutamide are also available but less commonly used. Sulfonylureas are well absorbed orally and each has its own absorption characteristics. They should be taken approximately half an hour before meals to enable maximal absorption.

Prescribing point: *Glibenclamide is widely used globally but owing to a long half-life carries an increased risk of hypoglycaemia.*

Gliclazide

Gliclazide is the most commonly prescribed sulfonylurea in the UK. It is well absorbed and maximum plasma concentrations occur at two to six hours. It is 95% plasma protein bound and is mainly metabolised in the liver. It is excreted in the urine with an elimination half-life of approximately 10–12 hours.

Dose

- Gliclazide is started at 40 mg once or twice daily before meals.
- It is adjusted according to response to a maximum of 160 mg twice daily.
- It is also available as a modified release preparation, 30–120 mg once daily.

Glimepiride Glimepiride is also well absorbed with good bioavailability. Its maximum serum concentration is reached approximately 2.5 hours after ingestion. Like gliclazide, it is extensively protein bound (>99%). Mean serum half-life is around five to eight hours. It is metabolised in the liver and excreted in the urine and via the gut.

Dose

- Glimepiride is started at 1 mg per day with the main meal.
- It should be titrated to a total of 4 mg per day, in split doses with meals.
- A maximal total daily dose of 6 mg is only recommended in exceptional circumstances.

Prescribing point: *Caution should be taken when prescribing sulfonylureas in patients with renal impairment owing to the increased risk of hypoglycaemia.*

Prescribing point: *Sulfonylureas are not recommended in severe hepatic impairment owing to the risk of hypoglycaemia.*

Glycaemic Efficacy

Sulfonylureas can be expected to reduce the blood glucose concentration by approximately 20%. HbA1c is reduced by approximately 1.0–2.0% (11–22 mmol/mol) when sulfonylureas are initiated as monotherapy. In a systematic review examining 31 trials, monotherapy with sulfonylureas was associated with a reduction in HbA1c of 1.51% compared with placebo [9]. This is broadly comparable with the reduction achieved using metformin. In a systematic review of 27 trials where second-line agents were added to metformin, sulfonylureas were associated with a 0.79% further reduction in HbA1c [10].

The benefits of sulfonylureas compared with newer SGLT2 inhibitors have recently been investigated as an add-on therapy to metformin. Glipizide gave a more rapid initial reduction in HbA1c than dapagliflozin but with a similar reduction in HbA1c at 12 months (–0.50 vs. –0.48%). In a four year extension to this study, dapagliflozin produced sustained reductions in HbA1c when compared with glipizide (0.3%) [11].

ADOPT

ADOPT (A Diabetes Outcome Progression Trial) examined the durability of the effect of sulfonylureas and other drugs (metformin and rosiglitazone) in 4360 patients recently diagnosed with type 2 diabetes on no treatment. Participants were treated with rosiglitazone, metformin or glibenclamide [12].

- Sulfonylurea monotherapy demonstrated good glucose-lowering efficacy for up to 2.75 years before an additional drug was required to maintain optimal glycaemic control, so it was the least durable treatment.
- The risk of treatment failure was reduced by 32% (95% CI 15–45) with rosiglitazone as compared with metformin and by 63% (95% CI 55–70) with rosiglitazone as compared with glibenclamide ($p < 0.001$).

UKPDS

The details of the UKPDS have been discussed in Chapter 2, and cardiovascular results for the sulfonylurea group are described later in the 'Outcome Trials' section. The sulfonylureas that were used in the intensive treatment group were chlorpropamide, glibenclamide and glipizide. Following the initial run-in with intensive education on diet, subjects who were randomised to sulfonlyureas had an approximate 1.0% reduction in HbA1c. Over ten years the average HbA1c was 7.9% in the control group and 7.0% in the intensive treatment group, but HbA1c rose steadily in the sulfonylurea group, again suggesting a lack of a durable effect in reducing HbA1c [4].

GRADE Study

The GRADE (Glycaemic Reduction Approaches in Diabetes: A Comparative Effectiveness) study compared the addition of glimepiride, sitagliptin, liraglutide or basal insulin in 5047 patients with type 2 diabetes treated with metformin [13]. The trial aimed to provide guidance as to the most effective second-line therapy. The preliminary results have been recently reported.

- Over an average five year follow-up period, the proportion of patients with an HbA1c of 53 mmol/mol or more was highest in those taking sitagliptin (77%) and glimepiride (72%) and lowest in those randomised to insulin glargine and liraglutide (67 and 68% respectively).
- The cardiovascular endpoint (which included MACE, heart failure requiring hospitalisation, unstable angina or transient ischaemic attack) was met in 5.8% of patients randomised to liraglutide compared with 7.6% patients taking insulin glargine, 8.0% for glimepiride and 8.6% for sitagliptin.

These initial results suggest that liraglutide and insulin are associated with improved glycaemic control compared with glimepiride and sitagliptin. The trial unfortunately did not include SGLT 2 inhibitors, which limits the applicability of the results in the modern type 2 diabetes population.

Safety and Side Effects

Weight Gain

An important side effect of sulfonylureas is weight gain. Sulfonylureas are associated with an approximate 2 kg weight gain. However, the absolute weight gain associated with each sulfonylurea differs. In UKPDS, participants taking glibenclamide gained 4 kg over the first three years before their weight stabilised. Conversely, in the ADVANCE (Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation) trial, where intensive glycaemic control was primarily achieved using gliclazide modified release (>90% participants), weight gain at the end of the trial was 0.7 kg in the intensive control group [14]. A systematic review of 27 RCTs which included weight data for sulfonylureas concluded that as a class weight gain was 2 kg [10]. It is therefore recommended that if weight gain is a particular issue, an alternative agent associated with weight neutrality or loss should be considered instead. It should be noted that the degree of weight gain associated with sulfonylureas is ordinarily less than that associated with insulin.

Hypoglycaemia

The most important side effect associated with sulfonylureas is hypoglycaemia. This occurs because of the glucose-independent insulin secretion caused by these drugs. The risk of hypoglycaemia is higher with longer acting drugs such as chlorpropamide and glibenclamide [1]. Hypoglycaemia often occurs owing to a mismatch between dose and the patient's oral intake and activity levels. The elderly are vulnerable to hypoglycaemia, particularly in the presence of intercurrent illness or when hospitalised. In certain groups hypoglycaemia risk may be too high to justify the use of a sulfonylurea. People who are dependent on alcohol or have renal failure or chronic liver disease are at particular risk.

Other Side Effects

Nausea, diarrhoea and abdominal pain have also been reported. Uncommon side effects include vomiting and deranged liver function. Rarely or very rarely, disorders of haematopoiesis such as cytopenia and agranulocytosis may occur. Allergic skin reactions including allergic dermatitis can occur, usually within the first six to eight weeks of therapy.

Prescribing point: *Gliclazide should be used with caution in the elderly owing to the risk of hypoglycaemia.*

Outcome Trials

Cardiovascular Safety and Sulfonylureas

Since the FDA ruling in 2008 that owing to safety concerns around rosiglitazone, novel antidiabetic drugs must have proven cardiovascular safety, we now have assurance that novel diabetes drugs have cardiovascular safety or indeed (as has been demonstrated for SGLT2 inhibitors and certain GLP-1 receptor agonists) cardiovascular benefit. Older diabetes drugs like sulfonylureas have not had this rigorous requirement and so do not have the same guarantee of cardiovascular safety or benefit [15].

There is a theoretical scientific justification as to why sulfonylureas may be associated with increased cardiovascular risk. Firstly, hypoglycaemia induced by these drugs and negative consequences such as autonomic activation can be associated with deleterious cardiovascular outcomes. Secondly, the ATP-sensitive SUR receptors are found not only in the pancreatic beta cells, but also in the myocardium and vasculature. At these sites, activation of ATP-sensitive SUR receptors in the presence of ischaemia leads to opening of the central channel with subsequent vasodilatation and a reduction in cardiac afterload. This is known as ischaemic preconditioning. Sulfonylurea drugs are thought to block the opening of these channels and therefore attenuate or prevent these benefits [1].

UGDP

The UGDP (University Group Diabetes Program) first raised the spectre of increased cardiovascular risk associated with sulfonylureas [3]. In this study, it was reported that tolbutamide was associated with an increased risk of cardiovascular mortality compared with titrated insulin therapy or placebo. These conclusions have been challenged. The trial was not designed as a cardiovascular outcome trial in the way current trials for this purpose are and the incidence of cardiovascular disease at baseline was not matched in the groups. There were in fact few cardiovascular deaths overall with only 26 in the tolbutamide group and 10 in the placebo group. Despite this, a complete ban on sulfonylureas was instituted in the US [1].

It was approximately 20 years following this that the UKPDS demonstrated a reduction in microvascular complications associated with tight glycaemic control using among other agents sulfonylurea drugs. There was no appreciable increased risk of cardiovascular mortality in this trial [4]. Nevertheless, the suspicion created by the UGDP has remained. No consistent association this class and adverse cardiovascular outcomes was demonstrated in any of these meta analyses. However, these studies were not specifically designed to examine MACE. Arguably it has not been until the recently published CAROLINA study (Cardiovascular Outcome Study of Linagliptin versus Glimepiride in Patients with Type 2 Diabetes; discussed further below), that the cardiovascular safety of a drug in this class has definitively been determined [16].

UKPDS

The aim of the UKPDS was to examine whether tight glycaemic control aiming for fasting blood glucose less than 6 mmol/l led to a reduction in adverse microvascular outcomes compared with best achievable blood glucose control using diet and lifestyle measures alone [4].

In the UKPDS, 3867 patients with a new diagnosis of type 2 diabetes who had received three months of lifestyle modification and had fasting plasma glucose between 6.1 and 15 mmol/l were randomised to lifestyle intervention or intensive glycaemic control using either a sulfonylurea (chlorpropamide, glibenclamide, or glipizide) or insulin. The endpoints were any diabetes-related endpoint (an aggregate of sudden death, death from hyperglycaemia or hypoglycaemia, fatal or nonfatal myocardial infarction, angina, heart failure, stroke, renal failure, amputation (of at least one digit), vitreous haemorrhage, retinopathy requiring photocoagulation, blindness in one eye or cataract extraction), diabetes-related death and all-cause mortality.

- There was a 12% reduction (95% CI 0.79–0.99; $p = 0.29$) in any diabetes-related endpoint in the intensive control group (Figure 3.2).
- There was a 10% numerical reduction in diabetes-related mortality (95% CI 0.73–1.11; $p = 0.34$), and there was no difference in diabetes-related deaths.
- The reduction in the any diabetes-related endpoint was primarily driven by a significant reduction in microvascular endpoints (25% relative risk; 95% CI 7–40%; $p = 0.0099$), including the need for photocoagulation.

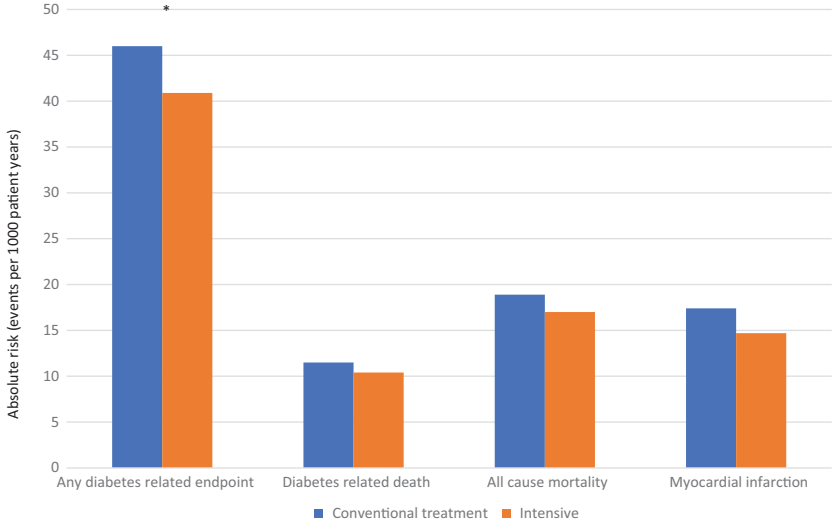


FIGURE 3.2 Event rates comparing intensive treatment with sulfonylureas or insulin and conventional treatment in the UKPDS [4]. The UKPDS had three aggregate endpoints of any diabetes-related endpoint, diabetes-related death, and all-cause mortality. Myocardial infarction was a secondary endpoint. Statistically significant differences are marked with an asterisk.

- There was no significant reduction in macrovascular disease when these endpoints were considered individually, but the investigators reported that the reduction in risk was of borderline significance for myocardial infarction ($p = 0.052$).

In the intensive control group, hypoglycaemia was higher than with lifestyle modification. Overall, the rate of severe hypoglycaemia was 0.7% per year in the conventional arm, 1.0% for chlorpropamide, 1.4% with for glibenclamide and 1.8% for those allocated to insulin therapy. Weight gain was also increased in the intensive control group with a mean additional weight gain of 2.9 kg over the ten years of follow-up. The greatest weight gain, however, was in those allocated to insulin, with an average gain of 4.0 kg. This is compared with a weight gain of 1.7 kg in those on glibenclamide and 2.6 kg in those on chlorpropamide.

The UKPDS demonstrated that intensive glycaemic control (whether using insulin or sulfonylureas) was associated with a significant reduction in diabetes-related endpoints – driven particularly by a reduction in microvascular disease. There was no increase in deleterious cardiovascular outcomes seen in the UGDP. Hypoglycaemia and weight gain were increased in the sulfonylurea group.

A ten year post-trial epidemiological follow-up study of the UKPDS was published in 2008 [17]. The aim of this follow-up study was to determine whether the early intensive glycaemic control achieved in the trial had lasting beneficial effects on the incidence of complications over time. Of the participants initially randomised, 3277 participants were followed up at annual clinics over a period of five years or via annual questionnaires if they were unable to attend. Thereafter from years 6 to 10 post-trial, all participants were asked to complete a questionnaire assessment. Participants were not maintained in their preassigned therapy groups following cessation of the trial. Within one year the difference in HbA1c between the groups was lost. Prespecified aggregate outcomes were examined by treatment group during the active trial.

In the group allocated to sulfonylurea/insulin to maintain intensive therapy (despite not being bound to previous treatment modality and an equilibration between the intensive and conventional group HbA1c levels) there appeared to be a continuing beneficial effect from early intensive glycaemic control:

- There was a relative risk reduction of 9% (95% CI 0.83–0.99; $p = 0.04$) in the aggregate of any diabetes-related endpoint.
- Diabetes-related death was reduced by 17% (95% CI 0.73–0.96; $p = 0.01$) and all-cause mortality by 13% (95% CI 0.79–0.96; $p = 0.007$).
- Reductions of 24% (95% CI 0.64–0.89; $p = 0.001$) in microvascular disease and a 15% reduction (95% CI 0.74–0.97; $p = 0.01$) in myocardial infarction were noted in the sulfonylurea/insulin group at ten years.

The lack of ongoing glycaemic differences between groups suggests that early intensive glycaemic control following diagnosis with sulfonylurea or insulin had beneficial legacy effects on the risk of diabetes-related complications and death over the following ten years in UKPDS participants.

ADVANCE

ADVANCE was another major trial which followed the UKPDS in providing evidence that reductions in HbA1c and blood pressure are protective against vascular complications in type 2 diabetes [14]. The primary outcome of the trial was in examining whether tight glycaemic control to target HbA1c values of less than 6.5% (48 mmol/mol) reduced the incidence of micro- and macrovascular complications compared with standard glucose lowering. In a factorial design, participants were additionally randomised to either blood pressure control with perindopril/indapamide combination tablet (Preterax®) or placebo (regardless of baseline blood pressure).

ADVANCE was a large-scale international trial recruiting participants in 215 collaborating centres spanning four continents. Participants were over the age of 55 had pre-existing type 2 diabetes and additional vascular risk factors. A total of 11 140 participants were randomised to the trial. The median period of follow-up was five years. In the intensive glycaemic control arm gliclazide-modified release was used to achieve glycaemic targets. At follow-up, in addition to lifestyle factors, any other oral agent or insulin could be added to maintain glycaemic targets. In those who were allocated to standard of care the treatment given was dependent on local routine practice.

The primary outcome of the trial was a composite of microvascular and macrovascular events including stroke, myocardial infarction and cardiovascular death, in addition to nephropathy or retinopathy incidence and progression. HbA1c was 6.5% in the intensive control group compared with 7.3% in the standard control group.

- In the intensive group, there was a reduction in the incidence of the composite of microvascular and macrovascular events (HR 0.90; 95% CI 0.82–0.98; $p = 0.01$).
- Intensive glycaemic control was associated with a reduction in major microvascular events (9.4 vs. 10.9%; HR 0.86; 95% CI 0.77–0.97; $p = 0.01$).
- There was a 21% relative risk reduction in diabetic nephropathy in the intensive group (4.1 vs. 5.2%; HR 0.79; 95% CI 0.66–0.93; $p = 0.006$).
- Intensive glycaemic control had no significant effects on major macrovascular events (HR with intensive control, 0.94; 95% CI 0.84–1.06, $p = 0.32$) or death from cardiovascular causes (HR with intensive control 0.88; 95% CI 0.74–1.04, $p = 0.12$).
- Episodes of severe hypoglycaemia were uncommon but more likely to occur in the intensively control group (2.7 vs. 1.5%; HR 1.86; 95% CI 1.42–2.40; $p < 0.001$).

The reduction in the composite outcome was driven by a reduction in microvascular events (14% relative risk reduction), in particular by the reduction in incidence or progression of diabetic nephropathy (21% relative risk reduction). Importantly, ADVANCE examined mortality data and found no significant difference in mortality between intensive control and standard control. These data demonstrated that intensive glycaemic control could safely be achieved. Nevertheless, there was an increase in admissions to hospital in the intensive control group. As may be expected, severe hypoglycaemia was more frequent, as were minor episodes of hypoglycaemia.

This trial also looked at the effect of more intensive blood pressure control in people with type 2 diabetes. Participants were randomised to a combination pill of perindopril

and indapamide or placebo. Those randomised to the combination tablet had lower incidences of coronary events and nephropathy and overall reduced mortality. This was independent of the initial blood pressure.

In summary, ADVANCE demonstrated that intensive glycaemic targets of HbA1c less than 6.5% led to a significant reduction in the incidence of microvascular events (particularly nephropathy) but not macrovascular events. This trial also demonstrated that such reductions could be safely achieved without an increase in mortality.

Prescribing point: *Prescribing in type 2 diabetes will usually involve identifying and prescribing medication for other cardiovascular risk factors including hypertension and hyperlipidaemia.*

CAROLINA

CAROLINA was a cardiovascular safety trial with the DPP-4 inhibitor linagliptin and used the sulfonylurea glimepiride as an active comparator (see Chapter 4) [16]. The trial was designed to demonstrate the cardiovascular noninferiority of linagliptin compared with glimepiride. A total of 6042 participants were randomised and followed up over a mean duration of 6.3 years. The population in this trial was at high cardiovascular risk; indeed 42% had already had macrovascular disease. The primary outcome was time to major cardiovascular events (cardiovascular death, nonfatal myocardial infarction or nonfatal stroke).

- Over the follow-up period, the primary outcome occurred in 11.8% for the linagliptin group and in 12.0% for the glimepiride group (HR 0.98; 95% CI 0.84–1.14; $p < 0.001$ for noninferiority).

There was no evidence of superiority of linagliptin in comparison with glimepiride. This trial was the first to demonstrate the cardiovascular safety of a sulfonylurea. It demonstrated that glimepiride was safe with no increase in adverse cardiovascular outcomes even in this high-risk population.

TOSCA.IT

TOSCA.IT (Thiazolidinediones Or Sulfonylureas Cardiovascular Accidents Intervention Trial) compared pioglitazone and sulfonylureas on cardiovascular outcomes in 3028 patients with type 2 diabetes when used as second-line therapy with metformin [18]. The trial is discussed in more detail in Chapter 12. There were no differences in the primary endpoint (composite of all-cause mortality, myocardial infarction, stroke and urgent coronary revascularisation) between those treated with sulfonylureas and those treated with pioglitazone. However, the methodology of the trial does not allow firm conclusions to be drawn about the cardiovascular safety of either pioglitazone or sulfonylureas.

Prescribing point: *Sulfonylureas are not associated with cardiovascular or renal protective effects.*

Meglitinides

Meglitinides are also insulin secretagogues and were first synthesised later in the 1980s. They are closely related to the sulfonylureas and act via the same mechanism. Like sulfonylureas, meglitinides bind to receptors on the SUR1 channel in the pancreatic beta cells and lead to conformational changes causing channel closure. Channel closure leads to depolarisation of the beta cell and insulin secretion as described in detail above. Meglitinides have similar blood glucose-lowering efficacy to sulfonylureas in terms of absolute HbA1c reduction [2, 19].

The key difference between meglitinides and sulfonylureas is the affinity with which they bind to receptors. Meglitinides bind less avidly and therefore have a much shorter duration of action. The rapid onset of action and reduced affinity to the receptor means that meglitinides characteristically lower postprandial glucose levels with little to no effect on fasting plasma glucose.

The side-effect profile is largely similar to that of sulfonylureas. Hypoglycaemia is a particular concern and patients should be selected carefully in view of this. Weight gain also occurs with meglitinides.

Nateglinide

Nateglinide is derived from phenylalanine. It is rapidly and completely absorbed following oral injection and is extensively albumin bound. There is a dose-dependent insulin peak following administration of these drugs with maximal concentration in the serum at approximately 45 minutes for nateglinide following ingestion. It is metabolised by the liver and largely excreted by the kidneys.

Nateglinide was started at a dose of 60 mg taken three times daily and up-titrated as necessary to a maximum dose of 180 mg three times daily. As nateglinide is predominantly renally excreted, dose reductions were required in severe renal impairment. Nateglinide was discontinued by Novartis in 2020.

Repaglinide

Repaglinide is derived from benzoic acid and displays similar pharmacokinetic properties to nateglinide. Following rapid absorption, peak serum concentrations are reached at 60 minutes. Repaglinide also has a dose-dependent insulin peak. Metabolism is primarily hepatic and excretion via bile. Repaglinide does not undergo significant renal excretion and it can therefore be used with caution in severe renal impairment. Repaglinide was first developed by Novo Nordisk under the brand name Prandin® and is now available in generic form.

Dose

- Repaglinide can be started at 0.5 mg and titrated at intervals of one to two weeks to a maximum daily dose of 16 mg.

- It should be taken approximately half an hour before meals to obtain the maximum postprandial effect.

Prescribing point: *Repaglinide has a shorter duration of action compared with sulfonylureas and needs to be taken more frequently.*

Outcome Trials

NAVIGATOR

NAVIGATOR (Effect of Nateglinide on the Incidence of Diabetes and Cardiovascular Events) examined whether short-acting insulin secretagogues could reduce the incidence of type 2 diabetes and cardiovascular events in people with impaired fasting glucose and either existing cardiovascular disease or risk factors for cardiovascular disease [20] (Table 3.1).

A total of 9306 participants were enrolled in this double-blind placebo control randomised controlled trial and were followed up for five years for incident diabetes. In a 2-by-2 factorial design, participants were randomised to either nateglinide or placebo with either the angiotensin receptor blocker valsartan or placebo. Pharmacological intervention was combined with lifestyle modification in all participants, with a target of 5% weight loss in combination with 150 minutes of exercise weekly. The three co-primary outcomes were the development of diabetes, a core cardiovascular outcome (death from cardiovascular causes, nonfatal myocardial infarction, nonfatal stroke or hospitalisation for heart failure) and an extended cardiovascular outcome (composite of the individual components of the core composite cardiovascular outcome, hospitalisation for unstable angina, or arterial revascularisation).

- Diabetes developed in 1674 (36.0%) participants in the nateglinide group and in 1580 (33.9%) participants in the placebo group (HR with nateglinide, 1.07; 95% CI 1.00–1.15; $p = 0.05$).
- The core composite cardiovascular outcome occurred in 365 participants in the nateglinide group (7.9%) and in 387 participants in the placebo group (8.3%) (HR ratio with nateglinide, 0.94; 95% CI 0.82–1.09; $p = 0.43$).
- The extended composite cardiovascular outcome occurred in 658 participants in the nateglinide group (14.2%) and in 707 participants in the placebo group (15.2%) (HR with nateglinide, 0.93; 95% CI 0.83–1.03; $p = 0.16$).

NAVIGATOR demonstrated no significant reduction in the incidence of type 2 diabetes nor any reduction in adverse cardiovascular events or death. The incidence of hypoglycaemia was predictably increased in the participants who received repaglinide. It was therefore concluded that repaglinide should not be used as a therapeutic approach in delaying the onset of diabetes.

Prescribing point: *Meglitinides are not associated with cardiovascular protective effects.*

TABLE 3.1 **Cardiovascular trials with sulfonylureas and nateglinide [4, 14, 16, 18, 20]**

Trial	UKPDS [4]	ADVANCE [14]	CAROLINA [16]	TOSCA. IT [18]	NAVIGATOR [20]
Intervention	Intensive control with sulfonylurea or insulin	Intensive glucose control based on gliclazide modified release	Glimepiride 4 mg once daily	Metformin plus sulfonylurea	Nateglinide up to 60 mg three times daily
Comparator	Conventional control with diet alone	Standard glucose control	Linagliptin 5 mg	Metformin plus pioglitazone 15–45 mg	Placebo
Population size (*n*)	3 867	11 140	6 042	3 028	9 306
Age (years)	53	67	64	62	64
Duration of diabetes (years)	Recently diagnosed	8	6	8	Subjects had impaired glucose tolerance
Follow-up (years)	10	5	6	5	5
Atherosclerotic CVD (%)	0	32	42	11	24
Heart failure (%)	0	NA	4	Patients with heart failure excluded	NA

(*Continued*)

TABLE 3.1 (*Continued*)

Trial	UKPDS [4]	ADVANCE [14]	CAROLINA [16]	TOSCA. IT [18]	NAVIGATOR [20]
Primary outcome(s)	12% reduction in any diabetes-related endpoint No difference in diabetes-related death No difference in all-cause mortality	10% reduction in combined MACE and major microvascular events 14% reduction in major microvascular events No difference in MACE	MACE noninferior	No difference in extended cardiovascular composite	No difference in the development of diabetes, no difference in a core cardiovascular outcome, no difference in an extended cardiovascular outcome
Secondary outcomes	Myocardial infarctions numerically reduced	No difference in death from CV causes or death from any cause	Increased risk of hypoglycaemia with glimepiride	Increased risk of hypoglycaemia with sulfonylureas	Increased risk of hypoglycaemia with nateglinide

CV = cardiovascular, CVD = cardiovascular disease, MACE = major adverse cardiovascular events.

Place of Sulfonylureas and Meglitinides in Current and Future Practice

Sulfonylureas remain one of the most commonly prescribed treatments for type 2 diabetes despite being one of the oldest. They are efficacious in lowering blood glucose levels and HbA1c alone or as an additive agent to metformin. In many international guidelines, they remain second-line treatment options after metformin monotherapy, a position that may change in updated guidelines given the advent of newer drugs. Sulfonylureas are low cost for healthcare systems, where this factor is a substantial influence in decision making. The use of sulfonylureas is limited by two important side effects – hypoglycaemia and weight gain – although the impact of both is less than with insulin.

Despite previous concerns regarding cardiovascular safety, several meta-analyses and the CAROLINA trial have provided reassurance that these drugs are safe to prescribe in this high cardiovascular risk group. Unlike metformin, and like DPP-4 inhibitors, there is no evidence for cardiovascular benefits with sulfonylureas. For patients with existing cardiovascular disease or who are at a high risk of developing cardiovascular disease, SGLT2 inhibitors or GLP-1 receptor agonists are better options, and for patients in this category who are well controlled on a combination of metformin and a sulfonylurea a switch to the combination of metformin plus SGLT2 inhibitor should be considered.

While meglitinides are also insulin secretagogues with a similar adverse effect profile to sulfonylureas, they need to be taken several times a day, limiting their clinical use, and they have also largely been superseded by other classes of antidiabetic drugs.

References

1. Khunti, K., Chatterjee, S., Gerstein, H.C., Zoungas, S., and Davies, M.J. (2018). Do sulfonylureas still have a place in clinical practice? *Lancet Diabetes Endocrinol* 6: 821–832.
2. Landgraf, R. (2000). Meglitinide analogues in the treatment of type 2 diabetes mellitus. *Drugs and Aging* 17: 411–425.
3. Miller, M., Knatterud, G.L., and Hawkins, B.S. (1976). A study of the effects of hypoglycemic agents on vascular complications in patients with adult onset diabetes. VI. Supplementary report on nonfatal events in patients treated with tolbutamide. *Diabetes* 25: 1129–1153.
4. UK Prospective Diabetes Study (UKPDS) Group. (1998). Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). *Lancet* 352: 837–854.
5. Buse, J.B., Wexler, D.J., Tsapas, A. et al. (2020). 2019 update to: management of hyperglycaemia in type 2 diabetes, 2018. A consensus report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). *Diabetes Care* 43: 487–493.
6. American Diabetes Association (2021). Pharmacologic approaches to glycemic treatment: standards of medical care in diabetes 2021. *Diabetes Care* 44 (Supplement 1): S111–S114.

7. Thulé, P.M. and Umpierrez, G. (2014). Sulfonylureas: a new look at old therapy topical collection on pharmacologic treatment of type 2 diabetes. *Curr Diabetes Rep* 14: 1–8.
8. Sola, D., Rossi, L., Schianca, G.P.C. et al. (2015). Sulfonylureas and their use in clinical practice. *Arch Med Sci* 11: 840–848.
9. Hirst, J.A., Farmer, A.J., Dyar, A., Lung, T.W.C., and Stevens, R.J. (2013). Estimating the effect of sulfonylurea on HbA1c in diabetes: a systematic review and meta-analysis. *Diabetologia* 56: 973–984.
10. Phung, O.J., Scholle, J.M., Talwar, M., and Coleman, C.I. (2010). Effect of noninsulin antidiabetic drugs added to metformin therapy on glycemic control, weight gain, and hypoglycemia in type 2 diabetes. *JAMA* 303: 1410–1418.
11. Del Prato, S., Nauck, M., Durán-Garcia, S. et al. (2015). Long-term glycaemic response and tolerability of dapagliflozin versus a sulphonylurea as add-on therapy to metformin in patients with type 2 diabetes: 4-year data. *Diabetes Obes Metabol* 17: 581–590.
12. Viberti, G., Kahn, S.E., Greene, D.A. et al. (2002). A Diabetes Outcome Progression Trial (ADOPT): an international multicenter study of the comparative efficacy of rosiglitazone, glyburide, and metformin in recently diagnosed type 2 diabetes. *Diabetes Care* 25: 1737–1743.
13. Nathan, D.M., Buse, J.E., Kahn, S.E. et al. (2013). Rationale and design of the glycemia reduction approaches in diabetes: a comparative effectiveness study (GRADE). *Diabetes Care* 36: 2254–2261.
14. The ADVANCE Collaborative Group (2008). Intensive blood glucose control and vascular outcomes in patients with type 2 diabetes. *N Engl J Med* 358: 2560–2572.
15. Pop, L.M. and Lingvay, I. (2017). The infamous, famous sulfonylureas and cardiovascular safety: much ado about nothing? *Curr Diabetes Rep* 17: 1–9.
16. Rosenstock, J., Kahn, S.E., Johansen, O.E. et al. (2019). Effect of linagliptin vs glimepiride on major adverse cardiovascular outcomes in patients with type 2 diabetes: the CAROLINA randomized clinical trial. *JAMA* 322: 1155–1166.
17. Holman, R.R., Paul, S.K., Bethel, M.A. et al. (2008). 10-Year follow-up of intensive glucose control in type 2 diabetes (UKPDS 80). *N Engl J Med* 359: 1577–1589.
18. Vaccaro, O., Masulli, M., Nicolucci, A. et al. (2017). Effects on the incidence of cardiovascular events of the addition of pioglitazone versus sulfonylureas in patients with type 2 diabetes inadequately controlled with metformin (TOSCA.IT): a randomised, multicentre trial. *Lancet Diabetes Endocrinol* 5: 887–897.
19. Blicklé, J.F. (2006). Meglitinide analogues: a review of clinical data focused on recent trials. *Diabetes Metabol* 32: 113–120.
20. Holman, R.R., Haffner, S.M., McMurray, J.J. et al. (2010). Effect of nateglinide on the incidence of diabetes and cardiovascular events. *N Engl J Med* 362: 1463–1476.

CHAPTER 4

DPP-4 Inhibitors

Sharon Mackin and Gemma Currie

KEY POINTS

- Dipeptidyl peptidase-4 (DPP-4) inhibitors provide modest benefits in glycaemic control with HbA1c reductions of 0.3–0.6% (3–7 mmol/mol) and they are best used in combination therapy with other antidiabetic drugs.
- Within this class individual drugs differ in their metabolism and excretion pathways and the choice of drug should be tailored to the renal and hepatic function of the patient.
- DPP-4 inhibitors are usually well tolerated but more serious adverse effects include a small increased risk of pancreatitis and a possible increased risk of heart failure with saxagliptin and alogliptin, and caution is advised in patients who are at an increased risk of these conditions.

Introduction

Dipeptidyl peptidase-4 (DPP-4) inhibitors, colloquially known as 'gliptins', are a class of oral antidiabetic drugs used to treat people with type 2 diabetes. Owing to their modest effects on blood glucose and HbA1c, the DPP-4 inhibitors are most optimally used in combination with other diabetes medications as second- or third-line adjunctive therapy. In the UK, Europe and the US medicines licensed for use within this class are saxagliptin, sitagliptin, alogliptin and linagliptin, and vildagliptin is licensed in the UK and EU. There are other DPP-4 inhibitors available for use in the wider international community. All DPP-4 inhibitors share some common clinical and pharmacological features, but individual drug pharmacokinetic and side-effect profiles differ, and these need to be considered when making personalised therapeutic plans.

Diabetes Drug Notes, First Edition. Edited by Miles Fisher, Gerard A. McKay, and Andrea Llano.

Pharmacology

Structure and Function of Dipeptidyl Peptidase-4

DPP-4 (or DPP-IV) is a 766 amino acid serine protease enzyme widely expressed in epithelial, endothelial and immune cells, and across a variety of tissues including the small intestine, kidney, pancreas, prostate and parathyroid gland. DPP-4 consists of a transmembrane domain that acts as an anchor for the protein to the cell, with an attached cytoplasmic *N*-terminal and a large extracellular *C*-terminal at alternate sides. The large extracellular domain contains the catalytic region which is responsible for enzymatic cleavage of peptide hormones. The extracellular component can remain attached to the cell or can be spliced from the transmembrane stalk to form a soluble circulating DPP-4 molecule. Circulating DPP-4 can be found in serum and other bodily fluids. It is unclear whether circulating soluble DPP-4 has more enzymatic effects than the membrane enzymatic region. In addition to its proteolytic properties, DPP-4 has nonenzymatic functions. It binds to and alters a variety of ligands and has regulatory roles including cellular proliferation, T-cell-mediated immunity and inflammation.

The effects of DPP-4 on glucose physiology occur through its enzymatic properties. Within the gastrointestinal tract, DPP-4 cleaves and rapidly inactivates the incretin hormones glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP). GLP-1 is described in further detail in Chapter 6 and is one of the main targets of DPP-4. GLP-1 is produced in the small intestine and acts to increase pancreatic insulin release following carbohydrate ingestion, suppresses glucagon release, modulates gut motility to promote earlier satiety and has central effects on the brain to regulate appetite. It has a very short half-life of two minutes. GIP is produced in the small intestine and has similar prandial insulinotropic effects, but in contrast does not affect glucagon, gastric emptying or satiety.

Mechanism of Action

Studies have shown that incretin effects are diminished in people with type 2 diabetes [1]. Specifically, insulin secretory responses to an oral glucose load are significantly lower in subjects with type 2 diabetes than in healthy controls [2]. This appears to be driven predominantly by diminished GIP effects on insulin secretion, with only mildly reduced or preserved effects from GLP-1 [3]. As such, there has been interest in preserving the effects of GIP and/or potentiating the effects of the preserved GLP-1 in the treatment of type 2 diabetes.

DPP-4 cleaves both hormones to inactivate them, and inhibition of this enzyme by DPP-4 inhibitors is a mechanism to prolong the activity of GLP-1 and GIP, thereby enhancing their insulinotropic and appetite suppressant effects (Figure 4.1). An advantage of DPP-4 inhibitors is that, because they act by prolonging the action of the incretin hormones and stimulating insulin release in a glucose-dependent manner, the risk of hypoglycaemia is low.

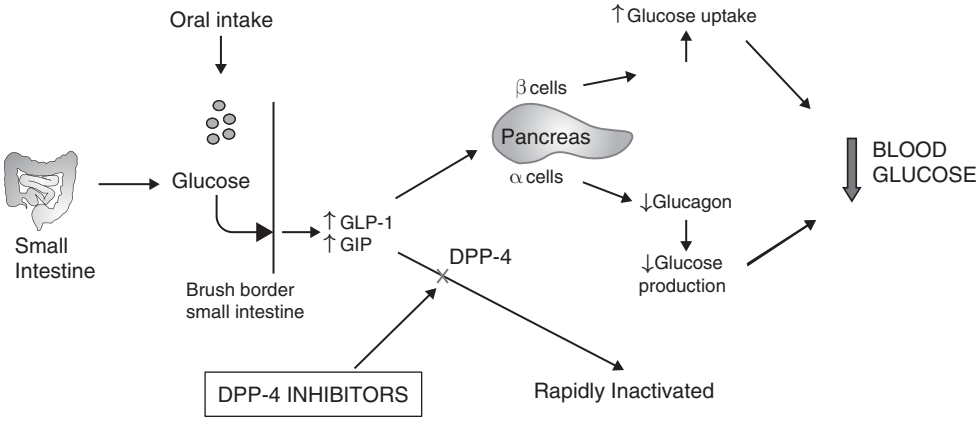


FIGURE 4.1 Mechanism of action of DPP-4 inhibitors. Absorption of glucose results in the release of the incretin hormones GLP-1 (glucagon-like peptide-1) and GIP (glucose-dependent insulinotropic polypeptide), which have several effects that result in lowering of glucose including effects on the pancreas (see Figure 6.1). DPP-4 cleaves both hormones to inactivate them, and inhibition of this enzyme by DPP-4 inhibitors is a mechanism to prolong the activity of GLP-1 and GIP.

Pharmacodynamics and Pharmacokinetics

There are several DPP-4 inhibitors marketed internationally, each differing slightly in pharmacology. Broadly, they all act to bind DPP-4 and block its degradative effects on incretin hormones. High selectivity for DPP-4 over other structurally homologous DPP inhibitors and proteases (DPP-VIII, DPP-IX and Fibroblast Activation Protein (FAP)) is important to the side-effect profile, with those inhibitors showing the least activity on other proteases less likely to cause side effects. Significant inhibition of these other proteases, particularly DPP-VIII and DPP-IX, has been associated with severe and fatal immune-mediated toxicities in animal models. DPP-4 inhibitors can be classified as peptidomimetic where structurally they form peptide or amide bonds, or nonpeptidomimetic where peptide bonds are not a key feature.

The pharmacology and prescribing considerations for sitagliptin, vildagliptin, saxagliptin, linagliptin and alogliptin are summarised in Table 4.1.

Sitagliptin Sitagliptin is a peptidomimetic DPP-4 inhibitor with a phenethylamine-based structure. It competitively binds noncovalently to DPP-4 binding sites and is highly selective for DPP-4, showing more than 1000-fold selectivity for DPP-4 over structurally similar enzymes. Plasma concentrations of sitagliptin increase proportionally with higher ingested dose and reach a maximum concentration (T_{max}) between 1.5 and 6 hours. This effect is no different whether animals are in the fed or fasted state. Bioavailability of oral sitagliptin is high at 87%. Its terminal half-life has been demonstrated to lie between 10 and 12 hours. Sitagliptin is mostly renally excreted and a small amount is metabolised by cytochrome P450 enzymes and is then excreted in urine or faeces.

TABLE 4.1 Prescribing considerations for commonly prescribed DPP-4 inhibitors

Medicine	Frequency of administration	Excretion	Prescribing considerations
Sitagliptin	Once daily	Renal	Dose reduction in CKD
Vildagliptin	Twice daily	Renal	Dose reduction in CKD LFT monitoring recommended
Saxagliptin	Once daily	Renal	Dose reduction in CKD
Linagliptin	Once daily	Biliary	No dose reduction in CKD
Alogliptin	Once daily	Renal	Dose reduction in CKD

CKD = chronic kidney disease, LFT = liver function test.

Prescribing point: *Sitagliptin is administered once daily and the dose should be reduced in patients with chronic kidney disease (CKD).*

Sitagliptin, marketed as Januvia® by Merck, was the first DPP-4 inhibitor made available for the treatment of type 2 diabetes in 2007. It is an oral treatment currently approved by the FDA and the EMA and more widely as an oral antidiabetic drug as a monotherapy or combined with other treatments for type 2 diabetes.

Dose

- Sitagliptin 100 mg once daily in patients with eGFR ≥ 45 ml/min/1.73 m^2.
- 50 mg once daily in patients with eGFR 30–44 ml/min/1.73 m^2.
- 25 mg once daily in patients with eGFR < 30 ml/min/1.73 m^2.
- Sitagliptin is also available as a fixed-dose combination with metformin (Janumet® 50 mg/1000 mg), one tablet twice daily.

Saxagliptin Saxagliptin is a peptidomimetic DPP-4 inhibitor with a cyanopyrrolidine ring that binds covalently to a serine hydroxyl binding site in DPP-4. It is highly selective for DPP-4 and has tenfold higher potency for DPP-4 inhibition than other DPP-4 inhibitors such as sitagliptin and vildagliptin. Saxagliptin is rapidly absorbed with peak concentrations reached within 0.5–2 hours of ingestion and has an oral bioavailability of 50%. The half-life is 27 hours. Saxagliptin undergoes metabolism by CYP3A4 and CYP3A5 to 5-hydroxysaxaglitpin, which is biologically active, and other lesser metabolites. Dose reduction should be considered in patients who are receiving concomitant CYP3A4/5 inhibitors as peak plasma concentrations can increase more than twofold. Approximately 75% of saxagliptin is excreted in urine and 25% in faeces.

Pharmacokinetic studies have shown that renal impairment significantly increases active drug exposure, at least doubling exposure to sitagliptin and 5-hydroxysaxagliptin, and prescribing recommendations suggest dose reduction to 2.5 mg once daily in those with moderate or severe renal impairment (eGFR < 45 ml/min/1.73 m^2).

In hepatic impairment, saxagliptin exposure is increased compared with patients without liver disease, but to a more modest level (up to 1.8-fold higher). Interestingly, patients with liver disease show less capacity to metabolise saxagliptin, and metabolite 5-hydroxysaxagliptin levels are lower in this population compared with healthy subjects. The manufacturer advises caution in moderate hepatic impairment and avoidance if there is severe impairment.

Prescribing point: *Saxagliptin is administered once daily and the dose should be reduced in patients with CKD.*

Saxagliptin, marketed as Onglyza®, is an oral DPP-4 inhibitor produced by AztraZeneca. It was first approved for use in type 2 diabetes in 2009 by the FDA and is now widely accepted by several regulatory bodies worldwide.

Dose

- Saxagliptin 5 mg once daily in patients with eGFR ≥ 45 ml/min/1.73 m^2.
- 2.5 mg once daily in patients with eGFR < 45 ml/min/1.73 m^2 or in patients prescribed drugs that inhibit cytochrome P450 enzymes (CYP3A4 and CYP3A5).
- Saxagliptin is also available as a fixed-dose combination with metformin (Kombiglyze® 2.5 mg/850 mg and Komboglyze® 2.5 mg/1000 mg), one tablet twice daily, and with dapagliflozin (Qtern® 5 mg/10 mg) once daily.

Vildagliptin Similar to saxagliptin, vildagliptin is a cyanopyrrolidine-based peptidomimetic DPP-4 inhibitor. Vildagliptin forms a covalent bond with the catalytic region of DPP-4, which hydrolyses and inactivates vildagliptin. Whilst bound to DPP-4, DPP-4 cannot bind other substrates such as GLP-1 and GIP, limiting its degradative effect. Inactivated vildagliptin dissociates slowly from DPP-4 (half-life one hour). Vildagliptin does not exhibit as much selectivity for DPP-4 over other protease substrates compared with other inhibitors.

Vildagliptin is rapidly absorbed and reaches peak plasma concentrations at 1.5 hours. It has a high oral bioavailability of 85%. Vildagliptin is metabolised via several different pathways. Importantly, CYP450 does not have a significant role in the metabolism of vildagliptin, making it less susceptible to interactions with P450 inducers or inhibitors. Vildagliptin and its metabolites are predominantly renally excreted (85%), and the remainder is found in faeces.

In patients with renal impairment of increasing severity there is a significantly increased exposure to the drug (up to twofold higher), despite minimal increases in the peak plasma concentration (30%), and dosing frequency should be reduced in moderate and severe renal impairment. Small pharmacokinetic studies have shown no significant differences in vildagliptin exposure or peak concentrations in liver disease, but vildagliptin is not recommended in liver disease owing to its potential hepatic side effects.

Prescribing point: *Vildagliptin is administered twice daily, monitoring of liver function tests is recommended and the dose should be reduced in patients with CKD.*

Vildagliptin is an oral DPP-4 inhibitor marketed as Galvus® by Novartis as a twice daily treatment for use in combination therapy of type 2 diabetes, or as monotherapy where metformin is inappropriate. It was first approved by the EMA in 2007 for use in Europe and the UK, followed by the regulatory bodies in Japan and China in 2010 and 2011 respectively. It is now marketed in over 100 countries. Vildagliptin has not been approved by the FDA, and Novartis have previously reported communication from the FDA in 2007 that it was approvable but further studies were requested to be performed to evaluate safety and efficacy in populations with renal impairment.

Dose

- Vildagliptin 50 mg twice daily in patients with creatinine clearance ≥ 50 ml/min.
- A 50 mg once daily dose if creatinine clearance is <50 ml/min or concomitant prescribing with secretagogues such as a sulfonylurea.
- Vildagliptin is also available as a fixed-dose combination with metformin (Eucreas® 50 mg/850 mg and Eucreas® 50 mg/850 mg), one tablet twice daily.

Alogliptin Alogliptin is a xanthine-based nonpeptidomimetic inhibitor that binds noncovalently to DPP-4. It is highly selective with >14 000-fold greater selectivity for DPP-4 compared with DPP-VIII, DPP-IX and FAP. Alogliptin is rapidly absorbed with almost 100% oral bioavailability regardless of fed state. It reaches peak plasma concentrations within an hour post-ingestion and has a very long half-life of 21 hours. The majority of alogliptin is excreted unchanged in the urine (60%). The two main metabolites, M1 (*N*-demethylated), which is biologically active and M2 (*N*-acetylated), which is inactive, account for very small proportions of urine and plasma concentrations (<2 and <6% respectively). Alogliptin does not interact significantly with P450 enzymes.

A pharmacokinetic study in subjects with renal impairment showed that drug exposure after a single dose of alogliptin was 1.7-, 2.1-, 3.2- and 3.8-fold higher in those with mild, moderate, severe and end-stage renal impairment, with similar peak plasma concentrations reached compared with healthy controls, and dosing adjustments are recommended in these patients.

In mild and moderate liver impairment, limited evidence has suggested no clinically significant change in pharmacokinetics. This seems logical given that clearance is predominantly renally mediated. There are concerns, however, that alogliptin may be associated with hepatotoxicity (see 'Safety and Side Effects'). The manufacturer recommends the avoidance of alogliptin in patients with severe liver disease.

Alogliptin is an oral therapy first approved for use in Japan in 2010, before later gaining approval by the EMA and FDA in 2013. It was developed by Takeda in Japan and is marketed under the brand name Nesina® in most worldwide regions, but as Vipidia® in the UK and European regions. Fixed-dose combinations exist with metformin and with pioglitazone, but the combination with pioglitazone is not available in the UK or EU.

Dose

- Alogliptin 25 mg once daily in patients with creatinine clearance > 50 ml/min.
- A 12.5 mg once daily dose in patients with creatinine clearance ≥ 30 to ≤ 50 ml/min.
- A 6.25 mg once daily dose in patients with creatinine clearance < 30 ml/min (manufacturer advises use with caution).
- Alogliptin is also available as a fixed-dose combination with metformin (Vipomet® 12.5 mg/1000 mg), one tablet twice daily.

Prescribing point: *Alogliptin is administered once daily and the dose should be reduced in patients with CKD.*

Linagliptin Linagliptin is a xanthine-based, nonpeptidomimetic DPP-4 inhibitor and has some unique pharmacokinetics compared with other DPP-4 competitors. It has over 10 000-fold selectivity for DPP-4 over the other DPP inhibitors, and 90-fold higher selectivity than for FAP. It has been shown to be a more potent inhibitor of DPP-4 than the other DPP-4 inhibitors and exhibits nonlinear pharmacokinetics. Linagliptin is rapidly absorbed and reaches peak plasma concentrations at 1.5 hours. Unlike the other DPP-4 inhibitors, which are largely unbound in plasma, linagliptin is predominantly protein bound and follows saturation kinetics. Linagliptin is largely eliminated from the body in its unchanged form. The unbound proportion is eliminated first, followed by the remainder as it slowly dissociates from DPP-4. Around 10% is metabolised to form inactive metabolites. The majority of alogliptin (85% of combined unchanged drug and metabolites) is excreted via the hepatobiliary system into faeces, with only minor renal excretion (comprising 5% unchanged drug in urine).

Prescribing point: *Linagliptin is administered once daily and as it is excreted into bile it does not require dose reduction in patients with CKD.*

Linagliptin is a once daily oral DPP-4 marketed as Trajenta® by Boehringer Ingelheim and Eli Lilly. It was first approved for use by the US FDA in 2011, and in Europe and the UK in 2012. It is widely available in several other countries, including Canada, Australia and Japan.

Dose

- Linagliptin 5 mg once daily.
- Linagliptin is also available as a fixed-dose combination with metformin (Jentaduo® 2.5 mg/850 mg and Jentaduo® 2.5 mg/1000 mg) one tablet twice daily, and with empagliflozin as Glyxambi® 10 mg/5 mg once daily, increasing to Glyxambi® 25 mg/5 mg once daily if necessary.

Other DPP-4 Inhibitors Several other DPP-4 inhibitors have been developed that are not approved in the UK, EU or the US but are approved for use in some Asian and South American countries. The pharmacology and prescribing considerations for these other DPP-4 inhibitors are summarised in Table 4.2. Several peptido-

TABLE 4.2 Prescribing considerations for other DPP-4 inhibitors

Medicine	Frequency of administration	Excretion	Prescribing considerations
Anagliptin	Once or twice daily	Renal	Dose reduction in CKD
Gemigliptin	Once daily	Renal and hepatic	Caution in moderate or severe CKD
Teneligliptin	Once daily	Metabolised then renal and biliary	Caution in severe liver disease
Evogliptin	Once daily	Mainly hepatic, up to one-third renal	Caution with concomitant potent CYP3A4 inhibitors Caution in severe hepatic impairment and moderate or severe CKD Avoid in end-stage CKD
Trelagliptin	Once weekly	Renal	100 mg dose not recommended in moderate or severe CKD
Omarigliptin	Once weekly	Renal	Dose reduction in severe or end-stage CKD

CKD = chronic kidney disease.

metic DPP-4 inhibitors have been marketed for daily administration. These include anagliptin (Sanwa Kagaku Kenkyusho and Kowa Pharmaceuticals), gemigliptin (LG Life Sciences), teneligliptin (Mitsubishi Tanabe Pharma) and evogliptin (Dong-A ST Co. Ltd).

There are also two once weekly oral DPP-4 inhibitors. Trelagliptin (Takeda) was the first to be developed and is approved for use in Japan. FDA and EMA approvals were sought for use in the US and Europe, but the high costs of the approval process for these regions led to the withdrawal of these applications by the developer. Omarigliptin (Merck) is the other once weekly DPP-4 inhibitor and it has been approved for use in Japan since 2015. Both of these drugs show similar efficacies in HbA1c reduction (approximately 0.3%, 3 mmol/mol) as compared with other daily administered DPP-4 inhibitors. FDA approval processes were also started for omarigliptin and a randomised, double-blind, placebo-controlled cardiovascular outcome trial was initiated, but costs again proved prohibitive to the developer and the study was halted early for commercial reasons. The data obtained from this cardiovascular outcome study was incomplete and it was not powered to detect differences in cardiovascular outcomes, so caution in interpretation of the available data needs to be considered [4]. The available data included over 4202 participants with type 2 diabetes and established

cardiovascular disease followed up for a median of 96 weeks (range 1–178 weeks). Major adverse cardiovascular events, a composite of cardiovascular death, nonfatal myocardial infarction and nonfatal stroke, appeared similar between groups (3 per 100 patient years for both groups) and there was no apparent difference in heart failure hospitalisations.

Prescribing point: *When deciding on a DPP-4 inhibitor, the choice of medicine and dose is largely decided by considering drug pharmacokinetics with concurrent clinical factors such as renal or liver disease, clinician familiarity and regional access (*Tables 4.1 *and* 4.2*).*

Glycaemic Efficacy

As monotherapy, DPP-4 inhibitors contribute modest reductions to measures of glycaemic control in patients with type 2 diabetes. Table 4.3 outlines some of the key randomised control study results for DPP-4 inhibitor used as a monotherapy [5–9]. Broadly, used in this way prescribers can expect to see HbA1c reductions in the region of 0.3–0.6% (3–7 mmol/mol) with up to 1 mmol/l improvement in fasting blood glucose concentrations. Some of the studies have reported more pronounced glycaemic benefits in patients with type 2 diabetes who have higher baseline HbA1c compared with those who are well controlled. For example, a study with sitagliptin showed larger improvements in those with higher baseline HbA1c concentrations, with a reduction of 1.2% (13 mmol/mol) in those with HbA1c greater than 9% and a reduction of 0.4% (4 mmol/mol) in those with HbA1c less than 9%. [6].

Whilst the data shown in Table 4.3 show efficacy as monotherapy in randomised, controlled trials, real-world data have confirmed similar glycaemic improvements in populations with type 2 diabetes [10, 11]. This is important since patients in the clinical setting will have different levels of healthcare worker interaction, comorbid conditions and complications, will be more likely to use DPP-4 in combination with other antidiabetic drugs and may have different motivations for managing their diabetes compared with those involved in strict trial protocols. DPP-4 inhibitors have been studied in combination with metformin, sulfonylurea, pioglitazone, SGLT2 inhibitors and insulin, and can be used in combination with these drugs. The results of meta-analyses exploring DPP-4 inhibitors used in combination with other antidiabetic therapies are described in Table 4.4 [12–16]. DPP-4 inhibitors can be useful adjuncts to other diabetes medications and show similar improvements in HbA1c whether used as a monotherapy or in combination. The risk of hypoglycaemia is increased if prescribed alongside sulfonylurea, and many prescribers would exert similar caution if used alongside insulin.

VERIFY

VERIFY (Vildagliptin Efficacy in Combination with Metformin for Early Treatment of Type 2 Diabetes) was a randomised controlled trial comparing metformin monotherapy with early combination treatment with metformin and vildagliptin in a cohort of 2001 patients

TABLE 4.3 **Glycaemic efficacy of DPP-4 inhibitors when used as monotherapy [5–9]**

	Saxagliptin	Sitagliptin	Vildagliptin	Alogliptin	Linagliptin
Duration of study	24 weeks	18 weeks	24 weeks	26 weeks	18 weeks
Study population ($n =$)	401 randomised 1:1:1:1 Average age 53 years, average BMI 31–32 kg/m^2 across all groups and equal numbers of male and female recruits Over 80% were of white race	521 randomised 1:2:2 for placebo: sitagliptin groups Mean age 54.5–55.5 years with similar mean BMI 32 kg/m^2 across groups. Male participants comprised 50–62% of participants Approximately two-thirds were of white race	354 randomised 1:1:1:1 Average age 50–52 years with mean BMI 31.9–32.7 kg/m^2 across groups. Approximately 55% male, and 50–60% white race across groups	329 randomised 1:2:2 to placebo: alogliptin groups Average age 53.4 years with 53% male, and two-thirds of white race	227 randomised 1:2 to placebo: linagliptin Treatment-naive patients unable to take metformin Average age 56.4–56.7 and mean BMI 29–30 kg/m^2. Males comprised 40% of the group; 70% were of white race
Dose	2.5, 5 or 10 mg once daily	100g or 200 mg once daily	50 mg once daily, 50 mg twice daily, 100 mg once daily	12.5 or 25 mg once daily	5 mg once daily
Mean HbA1c at entry, % (all groups)	7.8–8.0% across groups	8.0–8.1% across groups	8.3–8.5% across groups	7.9% for entire study population	8.1% both groups

	Saxagliptin	Sitagliptin	Vildagliptin	Alogliptin	Linagliptin
Mean change in HbA1c, % at end of study period	–0.43 at 2.5 mg –0.46 at 5 mg –0.55 at 10 mg	–0.48 at 100 mg –0.36 at 200 mg	–0.5 at 50 mg once daily –0.7 at 50 mg twice daily –0.8 at 100 mg once daily	–0.56 at 12.5 mg –0.59 at 25 mg	–0.39
Mean change in fasting blood glucose (mmol/l)	–0.8 at 2.5 mg –0.5 at 5 mg –0.9 at 10 mg	–0.7 at 100 mg –0.6 at 200 mg	n.s. at 50 mg once daily –1.2 at 50 mg twice daily –1.1 at 100 mg once daily	–0.6 at 12.5 mg –0.9 at 25 mg	–0.7
Change in two hour postprandial glucose (mmol/l)	–2.5 at 2.5 mg –2.4 at 5 mg –3.0 at 10 mg	–2.3 at 100 mg –2.7 at 200 mg	Not reported	Not reported	Not reported

TABLE 4.4 **Glycaemic efficacy and side effects of DPP-4 inhibitors used in combination with other antidiabetic therapies [12–16]**

Study design	Glycaemic parameters	Side effect profile
DPP-4 inhibitor and metformin combination vs. metformin monotherapy [12]	HbA1c reduction 0.5% (0.4–0.57) greater using combination DPP-4 inhibitor with metformin Fasting blood glucose 0.8 mmol/l lower (95% CI 0.74–0.87)	Less weight loss with combination therapy compared with metformin monotherapy No difference in hypoglycaemia or gastrointestinal side effects
DPP-4 inhibitor in combination with metformin and sulfonylurea vs. metformin and sulfonylurea dual therapy [13]	HbA1c improved 0.69% (0.37–1.02) in triple therapy group compared with the comparator	Weight gain was higher (0.9 kg) in the triple therapy group compared with comparator Risk of hypoglycaemia was 2.3-fold in the triple therapy group, compared with metformin and sulfonylurea group
DPP-4 inhibitor and pioglitazone combination vs. pioglitazone monotherapy [14]	HbA1c reduction of 0.64% (0.55–0.73) in combined DPP-4 inhibitor and pioglitazone group vs. pioglitazone monotherapy Fasting blood glucose 0.94 mmol/L lower (0.76–1.12) in the combined group	No difference in hypoglycaemia or gastrointestinal side effects. No increase in oedema reported but should be noted that studies included alogliptin, vildagliptin and sitagliptin only
DPP-4 inhibitor and SGLT2 inhibitor combination vs. SGLT2 inhibitor monotherapy [15]	HbA1c reduction of 0.31% (0.24–0.38) in DPP-4 inhibitor/SGLT2 inhibitor combined group compared with SGLT2 inhibitor alone Both fasting and post-prandial glucose reduced by 0.5 mmol/l in combination of DPP-4 inhibitor and SGLT2 inhibitors compared with SGLT2 inhibitor alone	No increase in hypoglycaemia Further studies into whether combining DPP-4 inhibitors with SGLT2 inhibitors may reduce the rates of SGLT2 inhibitor induced genital infection are warranted.
DPP-4 inhibitor and insulin combination vs. insulin monotherapy [16]	HbA1c reductions were 0.53% (0.43–0.63) greater in the combination group vs. insulin monotherapy Fasting blood glucose levels were no different between groups, but post-prandial glucose was 1.65 mmol/L (0.96–2.34) lower in the combination group Insulin dosage was 2.2 units/day lower in the combined group	Hypoglycaemia rates were no different between groups, nor was weight gain

within two years of the diagnosis of type 2 diabetes [17]. Time to treatment failure (defined as two separate HbA1c measurements of at least 7.0% (53 mmol/mol) at two consecutive visits 13 weeks apart) and safety parameters were measured over a five year period.

- Incidence of initial treatment failure was significantly lower in the combination therapy group compared with subjects on treatment with metformin monotherapy (44 vs. 64%; HR 0.51; 95% CI 0.45–0.58; $p < 0.001$), and the relative risk of time to initial treatment failure was halved in the combination group.
- Early combination therapy was found to be safe and well tolerated with low rates of hypoglycaemia, pancreatic pathology and malignancy seen in similar numbers across both groups.

VERIFY was not designed nor powered to assess cardiovascular safety, but similar rates of first macrovascular events (cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, hospital admission for heart failure) were recorded in each group (2.4 vs. 3.3% in combination and metformin monotherapy), suggesting possible neutral effects on cardiovascular risk. This needs to be interpreted with caution as heart failure risk is a concern from other drugs in this class and was not commented on specifically in this study.

GRADE

As described in Chapter 3, the GRADE study compared the addition of glimepiride, sitagliptin, liraglutide or basal insulin in 5047 patients with type 2 diabetes treated with metformin [18]. The trial aimed to provide guidance as to the most effective second-line therapy.

- Over an average five year follow-up period, the proportion of patients with an HbA1c of 7.0% (53 mmol/mol) or more was highest in those taking sitagliptin (77%) and glimepiride (72%) and lowest in those randomised to insulin glargine and liraglutide (67 and 68%, respectively).
- The cardiovascular endpoint (which included MACE, heart failure requiring hospitalisation, unstable angina or transient ischaemic attack) was observed in 5.8% of patients randomised to liraglutide compared with 7.6% of patients taking insulin glargine, 8.0% for glimepiride and 8.6% for sitagliptin.

These results suggest that the HbA1c-lowering effects of sitagliptin (and by extension other DPP-4 inhibitors) are less than other comparable therapies.

Safety and Side Effects

DPP-4 inhibitors are generally safe and well tolerated. The risk of hypoglycaemia is low owing to the glucose-dependent insulinotropic effects of the incretin system, and these drugs are not associated with the weight gain seen with some other therapies such as sulfonylureas. However, unlike SGLT2 inhibitors and GLP-1 receptor agonists, they do not promote weight loss.

Side Effects

As with all pharmacotherapy, DPP-4 inhibitors have associated side effects. For the most part these are minor, self-limiting gastrointestinal side effects such as nausea, abdominal pain, constipation and diarrhoea. Some of the recognised side effects of DPP-4 inhibitors are shown in Table 4.5. Nasopharyngitis and pancreatitis are two of the most unique side effects in this class. Intra-class side-effect profiles vary depending on the drug used. For instance, saxagliptin has been associated with increased frequency of adverse cardiometabolic side effects compared with the others, whilst vildagliptin is more associated with adverse hepatic effects.

It is recommended that renal and liver function are checked before starting treatment with saxagliptin, vildagliptin or alogliptin. Patients treated with vildagliptin should have three-monthly liver function tests checked in the first year of treatment. In patients prescribed alogliptin and saxagliptin, renal function should be monitored. This allows for the detection of side effects as well as dose adjustment.

Pancreatitis and Pancreatic Cancer

Owing to the stimulatory effects of the incretin system on pancreatic beta and alpha cells, researchers have been interested in exploring clinical sequelae associated with incretin therapy on pancreatic complications. One postmortem

TABLE 4.5 **Side effects associated with DPPP-4 inhibitors. More common side effects (up to 5% of patients) are highlighted in bold**

System	Side effect
Gastrointestinal	**Nausea, abdominal pain, altered bowel habit**, pancreatitis
Respiratory	**Nasopharyngitis, upper respiratory tract infections**, interstitial lung disease (rare, few case reports with vildagliptin and sitagliptin)
Neurological	**Headache, dizziness**, tremor
Hepatic	Elevated liver enzymes
Renal	Acute renal impairment with sitagliptin
Cardiovascular	Peripheral oedaema (saxagliptin and vildagliptin)
Skin	Rash pruritis, cutaneous vasculitis, Steven–Johnson syndrome
Musculoskeletal	Arthralgia, myalgia

study found that pancreata from patients with type 2 diabetes who had received incretin-based therapy (DPP-4 inhibitors or GLP-1 receptor agonists) showed increased exocrine cellular proliferation, alpha cell hyperplasia and subclinical dysplasia compared with those treated with other therapies [19]. Around the same time, data from the FDA adverse events reporting system had suggested a 6- and 2.7-fold risk of pancreatitis and pancreatic cancer, respectively [20], but this database relies on accurate and complete reporting of adverse events by physicians and is subject to bias. With potential mechanisms and signals for serious adverse pancreatic outcomes with DPP-4 inhibitor use, the FDA and EMA conducted independent analysis. Using multiple methodologies that included meta-analysis of over 200 clinical trials and data from animal models relating to measures of pancreatic function, they found no increased risk of pancreatic malignancy [21]. Biochemical measures of pancreatic function (lipase and amylase) were higher in those receiving incretin-based therapies but were not associated with the clinical symptoms of pancreatitis. As such, they concluded that there was insufficient evidence to support a causal link between incretin therapy and pancreatitis, but further evidence should be acquired over time, and so an advisory of potential increased risk of pancreatitis was applied to DPP-4 inhibitors and GLP1 receptor agonists.

Multiple meta-analyses have been published since to answer this ongoing debate and the results have also been conflicting [22–25]. These meta-analyses are summarised in Table 4.6. In summary, there may be an increased risk of pancreatitis with DPP-4 inhibitors, but the absolute risk is small, with meta-analyses suggesting a number needed to harm of >1000 patients [26]. Furthermore, results from two of the large cardiovascular outcome trials (TECOS and SAVOR TIMI) have shown no increased risk of pancreatic cancer [27, 28].

TABLE 4.6 **Meta-analysis of pancreatitis and pancreatic cancer risk with DPP-4 inhibitor treatment [21–25]**

Meta-analysis	Study description	Pancreatitis	Pancreatic malignancy
Roshanov, 2015 [22]	>36 000 participants in three cardiovascular outcome trials • SAVOR-TIMI53 – saxagliptin • EXAMINE – alogliptin • TECOS – sitagliptin	Odds ratio 1.82 (1.17–2.82) Absolute events 0.4% treatment vs. 0.2% control	Not analysed
Li, 2014 [23]	19,241 participants in 28 RCT • DPP-IV inhibitors included sitagliptin, saxagliptin, linagliptin, alogliptin, vildagliptin	Odds ratio 1.06 (0.46–2.45) Absolute events 0.12% for both groups	Not analysed

(*Continued*)

TABLE 4.6 (*Continued*)

Meta-analysis	Study description	Pancreatitis	Pancreatic malignancy
Engel, 2013 [24]	>14 000 participants in 25 RCTs • Pooled analysis of outcomes with sitagliptin 100 mg	No difference between groups Incidence rate 0.1 per 100 patient years	No difference between groups Incidence rate 0.05 (treatment) and 0.06 (control) per 100 patient years
Dicembrini, 2019 [25]	>130 000 participants in 164 trials • Included alogliptin, linagliptin, omarigliptin, saxagliptin, sitagliptin, teneligliptin, vildagliptin	Odds ratio 1.14 (0.86–1.47) Absolute events 0.3% both groups	Odds ratio 0.86 (0.60–1.24) Absolute events 0.2% both groups

Hepatic Side Effects of Alogliptin

Data from the large EXAMINE cardiovascular outcome trial showed an increase in liver enzymes in the alogliptin group compared with placebo, but the proportion of patients reaching clinically significant levels of greater than three times the upper limit of normal was similar between groups [29]. Other studies have shown no increase in the incidence of hepatobilary disorders in patients treated with alogliptin [30]. Analysis of the real-world FDA adverse events-reporting database similarly found no increase in liver injury with alogliptin [31]. Regulatory authorities in Europe and the US have highlighted cases of severe hepatotoxicity in patients taking alogliptin and subsequently issued warnings that liver function tests should be monitored on alogliptin [32].

Outcome Trials

Cardiovascular Outcome Trials

Safety concerns surrounding the risk of myocardial infarction and heart failure with the thiazolidinedione drug class (see Chapter 12) led regulatory bodies in the US and Europe to mandate that all novel diabetes therapies demonstrate cardiovascular safety over a minimum of two years in dedicated CVOTs either pre- or post-licensing (see Chapter 1). Consequently, the last decade has seen the emergence of a raft of CVOTs for

TABLE 4.7 **Summary of cardiovascular outcome trials with DPP-4 inhibitors [29, 34, 37–39]**

Trial	SAVOR-TIMI 53 [34]	EXAMINE [29]	TECOS [37]	CARMELINA [38]	CAROLINA [39]
DPP-4 inhibitor	Saxagliptin 5 mg (2.5 mg if eGFR ≤50)	Alogliptin 25 mg (12.5 mg if eGFR 30–60, 6.25 mg if eGFR <30)	Sitagliptin 100 mg (50 mg if eGFR 30–50)	Linagliptin 5 mg	Linagliptin 5 mg
Comparator	Placebo	Placebo	Placebo	Placebo	Glimepiride 4 mg once daily
Population size	16 492	5 380	14 671	6 991	6 042
Age (years)	65	61	66	66	64
Duration of diabetes (years)	10	7	9.4	15	6
Follow-up (years)	2.1	1.5	3.0	2.2	6.3
Atherosclerotic CVD (%)	79	100	100	58	42
Heart failure (%)	13	28	18	27	4
Primary outcome	MACE noninferior	MACE noninferior	MACE noninferior	MACE noninferior	MACE noninferior
Heart failure outcomes	HFH increased	HFH increased in subgroup	No increase in HFH	No increase in HFH	No increase in HFH

CVD = cardiovascular disease, eGFR = estimated glomerular filtration rate, HFH = hospitalisation for heart failure, MACE = major adverse cardiovascular events.

the newer antidiabetic drugs, with some even demonstrating unprecedented cardiovascular protective effects. Cardiovascular safety data have been published for four DPP-4-inhibitor therapies (saxagliptin, sitagliptin, alogliptin and linagliptin). The CVOTs with DPP-4 inhibitors are summarised in Table 4.7.

SAVOR-TIMI 53 Saxagliptin was licensed for use in the US and Europe in 2009. The following year saw the publication of a systematic assessment of cardiovascular outcomes from the phase 2 and 3 studies where post-hoc blinded adjudication of prespecified endpoints was conducted by an independent clinical events committee. Data were available for a total of 4607 randomised participants treated with saxagliptin or a comparator (placebo, metformin or glibenclamide) and no increased risk of cardiovascular death, myocardial infarction or stroke was observed in those assigned to active treatment with saxagliptin [33].

SAVOR-TIMI 53 (Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus-TIMI 53) was a multicentre, randomised, placebo-controlled double-blind trial evaluating the safety and efficacy of saxagliptin in 16 492 subjects with type 2 diabetes at high cardiovascular risk, defined as having established cardiovascular disease or at least two cardiovascular risk factors [34]. Most participants were recruited from North America and Europe, mean age was 65 years and mean duration of diabetes was 12 years. Hypertension and dyslipidaemia were prevalent in the study population (81 and 71%, respectively) and 13% were smokers. Of those with established cardiovascular disease 38% had prior myocardial infarction, 22% had been diagnosed with significant coronary artery stenosis, 24% had undergone coronary artery bypass grafting, 13% had preexisting heart failure and 13% had prior ischaemic stroke. The majority of participants were on at least one antidiabetic drug at randomisation (5% no medication; 25% one oral antidiabetic drug; 28% two or more oral drugs; 41% insulin). The primary efficacy and safety endpoint was MACE, a composite of cardiovascular death, nonfatal myocardial infarction and nonfatal ischaemic stroke. Secondary efficacy endpoints also included hospitalisation for heart failure, unstable angina or coronary revascularisation. Participants were followed up over a median of 2.1 years.

- A primary endpoint occurred in 613 (7.3%) participants in the saxagliptin group compared with 609 (7.2%) in the comparator placebo group (HR 1.00; 95% CI 0.89–1.12; $p < 0.001$ for noninferiority, $p = 0.99$ for superiority), while major secondary endpoints occurred in 1059 (12.8%) participants in the saxagliptin group compared with 1034 (12.4%) in the placebo group (HR 1.02; 95% CI, 0.94–1.11; $p = 0.66$).
- These results established noninferiority but not superiority and were similar in elderly participants and subjects with renal impairment.
- Unexpectedly, more patients in the saxagliptin group were hospitalised for heart failure (3.5 vs. 2.8%; HR 1.27; 95% CI 1.07–1.51; $p = 0.007$; Figure 4.2), a finding that the investigators felt merited further investigation and confirmation in other studies.

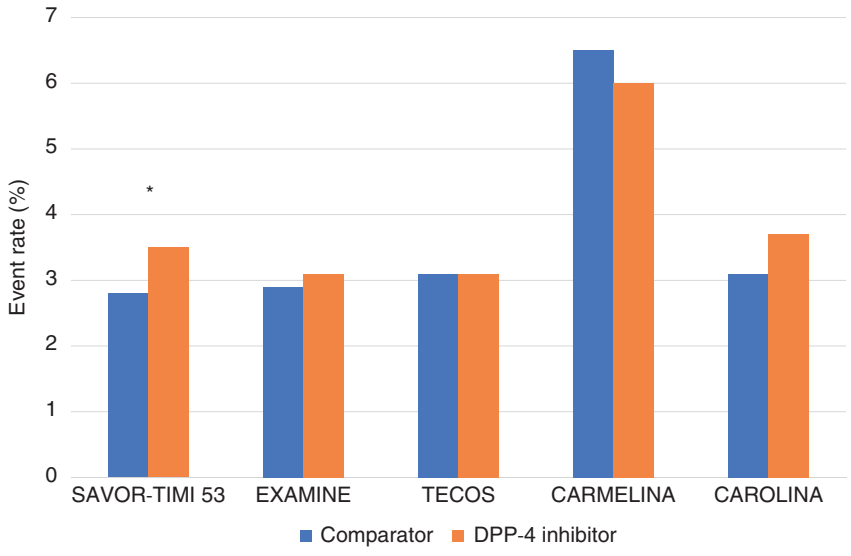


FIGURE 4.2 Hospitalisation for heart failure (HFH) event rates from the cardiovascular outcome trials with DPP-4 inhibitors: saxagliptin (SAVOR-TIMI 53) [34], alogliptin (EXAMINE) [29], sitagliptin (TECOS) [37] and linagliptin (CARMELINA and CAROLINA) [38, 39]. In SAVOR-TIMI 53, EXAMINE, TECOS and CARMELINA the comparator was placebo, and in CAROLINA the comparator was glimepiride. Statistically significant differences are marked with an asterisk.

EXAMINE Alogliptin was licensed for use in the US and Europe in 2013. Systematic assessment of cardiovascular outcomes across the phase 2 and 3 studies was published in the same year. This analysis included 6107 patients treated with alogliptin (4162), placebo (687) or comparator antidiabetic drugs (1168). The majority of participants had established cardiovascular risk factors, although the prevalence of cardiovascular disease was low. The incidence of major adverse cardiovascular events (MACE) was not significantly different between alogliptin and comparator groups [35].

EXAMINE was a multicentre, randomised, placebo-controlled double-blind trial conducted at over 800 centres across 49 countries [25]. A total of 5380 subjects who had experienced an acute coronary syndrome within 15–90 days of randomisation were included. The median age of participants was 61 years and the median duration of diabetes was seven years. The majority of participants were white (73%) or Asian (20%). Hypertension was prevalent in the study population (83%) and 13% were smokers. The majority of participants had experienced previous myocardial infarction (87%) or percutaneous coronary intervention (62%), while a smaller number had previous coronary bypass grafting (13%). Preexisting heart failure was present in 28% and 7% had a history of previous ischaemic stroke. Around 30% of the study population had established chronic kidney disease with an eGFR of <60 ml/min/1.73 m^2. Inclusion criteria required that patients recruited were taking antidiabetic drugs. Metformin was prescribed in around 60% of participants, sulfonylureas in 45% and insulin in 30%, while 2% were taking thiazolidinediones. The primary endpoint was MACE, a

composite of cardiovascular death, nonfatal myocardial infarction and nonfatal stroke, while the secondary endpoint also included urgent revascularisation owing to unstable angina within 24 hours of hospital admission. Hospitalisation for heart failure was not included as an individual endpoint, although it was included in an exploratory MACE composite. The median follow-up period was 1.5 years.

- The primary endpoint occurred in 11.3% of the alogliptin group compared with 11.8% of the placebo group (HR 0.96; upper boundary of the one-sided repeated confidence interval 1.16; $p < 0.001$ for noninferiority), while 13.4% of the alogliptin group experienced a secondary endpoint in comparison with 12.7% of the comparator group (HR 0.95; upper boundary of the one-sided repeated confidence interval 1.14; $p = 0.26$).

In keeping with the SAVOR-TIMI 53 trial, these results established noninferiority but not superiority. Although not a focus of the index publication, a later publication described the incidence of heart failure hospitalisation in the EXAMINE trial [36].

- There was no significant difference in the exploratory endpoint including heart failure hospitalisation and cardiovascular death between alogliptin and placebo-treated patients (HR 0.98; 95% CI 0.86–1.12). However, unexpectedly, a significant increase in hospitalisation for heart failure was seen in participants with no prior history of heart failure at baseline (HR 1.76; 95% CI 1.07–2.90; $p = 0.026$).

TECOS Sitagliptin was licensed for use in the US in 2006 and European licensing followed in 2007. Pooled analysis of safety and tolerability outcomes from 14 161 patients (7726 sitagliptin; 6885 comparator agent) across 25 phase 2 and 3 studies were published in 2013. At baseline 10% of patients included in this analysis had cardiovascular disease while 81% had cardiovascular risk factors beyond established type 2 diabetes. The exposure-adjusted incidence of MACE was similar between sitagliptin-treated and comparator groups [37].

As both SAVOR-TIMI 53 and EXAMINE had demonstrated increased incidence of heart failure hospitalisation, the results of TECOS (Trial Evaluating Cardiovascular Outcomes with Sitagliptin) were of particular interest. Despite being planned before the publication of the FDA guidance on CVOTs, the design and analysis of TECOS were consistent with these recommendations [34]. TECOS was a randomised, double-blind, placebo-controlled trial to assess the cardiovascular safety of sitagliptin. A total of 14,724 participants were recruited from 38 countries and randomised to receive sitagliptin or placebo. The mean age of participants was 66 years, 68% were Caucasian and median diabetes duration was 9.4 years. Hypertension was prevalent in the study population (86%), 77% had hyperlipidaemia and 51% were current or previous smokers. Cardiovascular disease was a prerequisite for inclusion in TECOS. Previous myocardial infarction was present in 43% of the trial population, 39% had previous percutaneous coronary intervention, 25% had undergone coronary artery bypass grafting and 18% had a diagnosis of congestive heart failure. Seventeen per cent of the study population had experienced previous ischaemic stroke and 17% had preexisting peripheral arterial disease. For diabetes therapy at inclusion, 53% were on

single-drug treatment, 38% were on dual therapy and 23% were insulin treated. The primary endpoint was MACE plus hospitalisation for unstable angina (also called four-point MACE) while hospitalisation for heart failure was included among the secondary outcome measures of interest.

- Over a median follow-up period of three years the primary endpoint occurred in 839 (11.4%) individuals in the sitagliptin arm and 851 (11.6%) placebo-treated participants, demonstrating noninferiority but not superiority (HR 0.98; 95% CI 0.88–1.09; $p < 0.001$ for noninferiority).
- Interestingly there was no significant difference in rates of hospitalisation for heart failure between active and placebo groups (HR 1.00; 95% CI 0.83–1.20; $p = 0.98$), a result that was at odds with previous DPP-4 inhibitor CVOTs (SAVOR-TIMI 53 and EXAMINE).

CARMELINA and CAROLINA Linagliptin was licensed for use in the US in 2011 and the following year in Europe. Two CVOTs were published assessing the safety of linagliptin in 2018 and 2019: CARMELINA (Cardiovascular and Renal Microvascular Outcome Study with Linagliptin) [38] and CAROLINA [39].

CARMELINA aimed to evaluate the impact of linagliptin on cardiovascular and renal outcomes in a cohort of patients with type 2 diabetes at high risk of vascular and renal events. This randomised, placebo-controlled, double-blind trial was conducted in 605 centres across 27 countries. A total of 6991 participants were randomised to receive linagliptin (3499) or placebo (3492) and followed up for a median of 2.2 years. The mean age of participants was 66 years and mean diabetes duration was 15 years. The majority (90%) had a history of hypertension and 10% were current smokers. Heart failure was more prevalent at baseline than in most of the other CVOTs described in this chapter (27%), 58% had a background of ischaemic heart disease, 80% had some degree of albuminuria and just over 60% had an eGFR of <60 ml/min/1.73 m^2. Most participants were taking more than one antidiabetic drug at inclusion (97%) and 58% were insulin treated. The primary outcome was three-point MACE (cardiovascular death, nonfatal myocardial infarction and nonfatal stroke), while the secondary outcome was a composite of end-stage renal disease, renal death or a 40% decline in eGFR from baseline. Hospitalisation for heart failure was among a number of prespecified tertiary outcomes. CARMELINA was particularly well suited to addressing the heart failure dilemma given the high burden of heart failure in the trial population at baseline in comparison with the other DPP-4 inhibitor CVOTs.

- The primary outcome occurred in 12.4% of the active treatment group compared with 12.1% of those randomised to placebo, meeting the criteria for noninferiority but not superiority (HR 1.02; 95% CI 0.89–1.17; $p < 0.001$ for noninferiority).
- In line with the TECOS findings, there was no significant difference in hospitalisations for heart failure between the treatment groups (6.0% active group vs. 6.5% placebo-treated; HR 0.90; 95% CI 0.74–1.08; $p = 0.26$).

CAROLINA was a multicentre, randomised, double-blind active controlled clinical trial examining the cardiovascular safety of linagliptin in comparison with the sulfonylurea glimepiride in patients with type 2 diabetes and established cardiovascular disease or risk factors. A total of 6042 participants recruited from 607 centres across 43 countries were followed up for a median of 6.3 years. Participant mean age was 64 years and median diabetes duration was 6 years. Most of the trial population had a history of hypertension (90%) and 20% were smokers. Forty-two per cent of participants had established cardiovascular disease in at least one territory; 32% had coronary artery disease, 12% had cerebrovascular disease and 7% had peripheral arterial disease. Heart failure was less prevalent than in the previous DPP-4-inhibitor CVOTs at only 4% of the trial population. The majority of trial participants were taking metformin at inclusion (84%) and 29% were prescribed a sulfonylurea. Insulin therapy was among the trial exclusion criteria. The primary endpoint was three-point MACE while hospitalisation for heart failure was among the secondary endpoints.

- The primary endpoint occurred in 11.8% of the linagliptin group compared with 12% of those treated with glimepiride, meeting the criterion for noninferiority but not superiority (HR 0.98; 95% CI 0.84–1.14; $p < 0.001$ for noninferiority).
- In line with findings from TECOS and CARMELINA, hospitalisations for heart failure were not significantly different between the two groups (HR 1.21; 95% CI 0.92–1.59).

Vildagliptin Meta-analysis Unlike the other DPP-4-inhibitors, there has not been a large, multicentre, randomised placebo-controlled cardiovascular safety study conducted to evaluate vildagliptin. In 2015 a retrospective meta-analysis of prospectively adjudicated cardiovascular events across 40 double-blind randomised controlled phase 3 and 4 studies with vildagliptin was published [40]. This included pooled data on 17 446 patients, 9599 receiving vildagliptin and 7847 receiving comparator therapy (36% placebo, 33% sulfonylurea, 10% thiazolidinedione, 15% metformin and 6% other) over a mean exposure duration of 50 weeks. Mean age was slightly lower than the CVOTs at 56 years, mean diabetes duration was also lower at 5.5 years and 18% had suffered a previous cardiovascular event. There was no significant difference in cardiovascular outcomes between the groups; MACE occurred in 0.86% of vildagliptin-treated and 1.2% of comparator-treated patients. The incidence of adjudicated heart failure events was not significantly different between active and comparator groups.

VIVIDD (Vildagliptin in Ventricular Dysfunction Diabetes), published in 2018, was a small mechanistic study designed to address the conflicting evidence pertaining to heart failure risk with the DPP-4 inhibitor class and to determine the effect of vildagliptin on left ventricular function [41]. Investigators recruited 254 patients with type 2 diabetes and heart failure defined as ejection fraction below 40%. Participants were randomised to receive vildagliptin or placebo over a 52 week follow-up period with the primary objective to demonstrate that vildagliptin was at least noninferior to placebo with regards change in left ventricular ejection fraction (LVEF) from baseline. The adjusted mean change in LVEF was 4.95% in the vildagliptin group and 4.33% in the placebo group, demonstrating noninferiority.

Summary of Cardiovascular Outcome Trials Following the completion of these five large trials evaluating the cardiovascular safety of DPP-4-inhibitors we can conclude that these agents seem to be relatively safe from the cardiovascular standpoint. All trials demonstrated cardiovascular noninferiority, but none suggested any degree of cardiovascular benefit, at least in the short term. The heart failure signal unexpectedly seen with saxagliptin and alogliptin in SAVOR-TIMI 53 and EXAMINE was not borne out with sitagliptin or linagliptin in TECOS, CARMELINA or CAROLINA, confirming that this is not a class-specific effect.

Prescribing point: *DPP-4 inhibitors do not reduce cardiovascular outcomes and for patients with existing cardiovascular disease, or a high risk of developing cardiovascular disease, SGLT2 inhibitors or GLP-1 receptor agonist are a better treatment choice.*

Renal Outcomes

Diabetic kidney disease (DKD), defined as raised albumin to creatinine ratio (ACR > 30 mg/g) with or without a consistent reduction in eGFR (<60 ml/min/1.73 m^2), is a leading cause of end stage renal disease (ESRD) globally. Until recently, management strategies for patients affected by DKD were based on risk factor management focusing on glycaemic control and blood pressure, and the only drugs with any proven benefit for these patients were ACE inhibitors and angiotensin receptor blockers. These drugs have been shown to reduce the incidence of ESRD and doubling of serum creatinine, but despite their almost universal prescribing and inclusion in key clinical guidelines, there remains an unacceptably high degree of progression to ESRD among people with diabetes. Published studies on the impact of glucose-lowering therapies have often reported renal endpoints as secondary or tertiary endpoints, or have performed retrospective analyses to determine the impact of these agents on DKD. More recently dedicated renal outcome trials have been conducted with some of the newer antidiabetic drugs. The evidence for renal benefits of other agents such as SGLT2 inhibitors and GLP-1 receptor agonists is much stronger than that for DPP-4-inhibitors.

A 2019 meta-analysis reported that the use of DPP-4 inhibitors was associated with reduction in albuminuria but no effect on eGFR [42]. Postulated mechanisms underpinning these observations include effects on oxidative stress, inflammation, fibrosis and endothelial function at a renal level [43]. There has only been one DPP-4 inhibitor trial which prospectively specifically focused on renal outcomes (CARMELINA), while renal outcome data from the other CVOTs have been analysed retrospectively.

Saxagliptin At inclusion, 16% of SAVOR-TIMI 53 participants had eGFR <50 ml/min/1.73 m^2. In terms of albumin excretion, 59% of trial subjects were normoalbuminuric, 27% had microalbuminuria and 10% had macroalbuminuria. The group treated with saxagliptin saw stable or improved ACR compared with placebo-treated patients with a mean difference of −34.3 mg/g between active and comparator groups. This was mainly driven by changes in ACR in the subgroup of participants with heavy albuminuria at baseline. There was no difference in 'hard' renal endpoints, including the doubling of creatinine, the development of ESRD/commencement of renal replacement therapy or renal death [44].

Alogliptin In the EXAMINE trial cohort 29% of participants had eGFR <60 ml/min/1.73 m^2 at baseline, while albuminuria data were not reported. Similarly, at end of the study there was no analysis of changes in urine albumin–creatinine ratio (UACR) between treatment and control groups. The authors did, however, note that there was no significant difference in eGFR at end of the study between patients treated with alogliptin or placebo, nor was there any difference in the proportion of participants starting on dialysis during the study, although numbers were small (0.9% alogliptin group vs. 0.8% placebo group) [25].

Sitagliptin A retrospective analysis of data from the TECOS study evaluated changes in eGFR and to a lesser extent UACR in individuals receiving sitagliptin compared with placebo [45]. Mean baseline eGFR in this cohort was 75 ml/min/1.73 m^2. Urinary albumin data were only collected for a small subset of trial participants (5148 out of a total of 14 671); the majority of this subgroup were normoalbuminuric (3710, 72%), 1200 (23%) had microalbuminuria and 247 (5%) had overt albuminuria. For UACR outcome analysis a subgroup of 3832 with baseline UACR and eGFR as well as at least one post-baseline UACR measurement was used. The mean eGFR reduction over the four year trial period was marginally greater in the sitagliptin group (–4.0 vs. –2.8 ml/min/1.73 m^2), although the mean rate of decline was not significantly different between the study groups. The UACR was marginally lower in participants treated with sitagliptin compared with placebo in this small subset of study subjects.

Linagliptin Several early studies hypothesised that linagliptin in particular may have renoprotective potential. For example, administration of linagliptin to streptozotocin-induced diabetic mice was shown to inhibit renal fibrosis [46], and preliminary early phase 3 clinical data suggested an anti-albuminuric effect in adults with type 2 diabetes and renal impairment [47]. The MARLINA-T2D (Efficacy, Safety and Modification of Albuminuria in Type 2 Diabetes Subjects with Renal Disease with Linagliptin) study was subsequently performed in 360 patients with type 2 diabetes and albuminuria [48] and demonstrated reductions in HbA1c with linagliptin vs. placebo, but linagliptin did not significantly lower albuminuria.

While most DPP-4 inhibitors are renally excreted, linagliptin is primarily excreted via the gut. It was therefore anticipated that this agent could be used safely without dose adjustment in patients with CKD. CARMELINA was the first of the DPP-4 inhibitor outcome trials to include patients with established renal disease up to CKD stage 5. At baseline 74% of participants had eGFR 30–59 ml/min/1.73 m^2 while 15.2% had eGFR < 30 ml/min/1.73 m^2. Furthermore, the study protocol included a pre-specified combined renal endpoint (renal death, development of ESRD or 40% decline in eGFR from baseline) as a secondary outcome measure [38].

- The risk of the composite renal outcome was not significantly different between linagliptin and placebo groups (HR 1.04; 95% CI 0.89–1.22; $p = 0.62$).
- Similar results were seen for the exploratory composite of sustained ESRD, renal death or a 50% drop in eGFR from baseline (HR 0.98; 95% CI 0.82–1.18; $p = 0.87$).
- Transition in the albuminuria category did, however, occur less frequently in the linagliptin-treated group compared with those treated with placebo (35.3 and

38.5%, respectively) and this different was statistically significant (HR 0.86; 95% CI 0.78–0.95; $p = 0.03$).

While this result is of interest and in line with preclinical data it should be borne in mind that albuminuria is considered a surrogate rather than a hard renal endpoint.

Summary of Renal Effects While there is evidence that some DPP-4 inhibitors may slow progression of albuminuria in individuals with type 2 diabetes, as yet no data have confirmed significant impact on the hard renal endpoints of death, ESRD or doubling of serum creatinine. Evidence is more consistent and convincing for the other novel antidiabetic drugs. However, cardiovascular outcome studies for DPP-4 inhibitors have not shown any evidence of renal harm and these agents can be safely used with dose adjustment in patients with established CKD. The exception is linagliptin, which does not require dose adjustment owing to the alternate excretory pathway. None of these trials included dialysis patients. It should be borne in mind that patients with established CKD are at risk of heart failure and pragmatically agents that have raised safety concerns regarding heart failure hospitalisation should be avoided in the patients with CKD.

Prescribing point: *For patients who are at an increased risk of developing heart failure SGLT2 inhibitors are a better treatment choice than DPP-4 inhibitors. If DPP-4 inhibitors are to be used in these patients, then sitagliptin and linagliptin are the drugs of choice.*

The Place of DPP-4 Inhibitors in Current and Future Practice

The completion of five large clinical trials evaluating the cardiovascular safety of DPP-4 inhibitors confirms that these drugs are safe and well tolerated from the cardiovascular standpoint. They do not confer clear cardiovascular benefit or renoprotection, whereas other novel antidiabetic drugs have very strong evidence of benefit in these areas. Furthermore, these drugs have a modest effect on glycaemic control, although they do come without significant risk of hypoglycaemia or excessive weight gain. DPP-4 inhibitors, and linagliptin in particular, can be used safely in patients with CKD with dose adjustment (with the exception of linagliptin). The SAVOR-TIMI 53 and EXAMINE trials raised concern about an increased incidence of heart failure with use of DPP-4 inhibitors but this was not borne out in TECOS, CARMELINA or CAROLINA, thus allaying concerns that this signal was a class-specific effect.

DPP-4 inhibitors are recommended as second- or third-line treatment options in NICE and SIGN guidelines and ADA/EASD (American Diabetes Association/European Association for the Study of Diabetes) consensus reports (Chapter 15). However, SIGN and ADA/EASD in particular highlight the importance of tailoring therapy to the individual patient in terms of hypoglycaemia risk, weight status and cardiovascular risk. The lack of a protective effect from complications of diabetes means that these

drugs are unlikely to remain key therapies for diabetes management, particularly when considered in the context of the SGLT2 inhibitor and GLP-1 receptor agonist trials, as both SIGN and ADA/EASD recommend that drugs with proven cardiovascular benefit be prescribed in patients with vascular disease. DPP-4 inhibitors may remain a useful add-on oral option in a small group of patients and provide an alternative to sulfonylurea without risk of hypoglycaemia or weight gain.

References

1. Holst, J.J., Knop, F.K., Vilsbøll, T., Krarup, T., and Madsbad, S. (2011). Loss of incretin effect is a specific, important and early characteristics of type 2 diabetes. *Diabetes Care* 34: S251–S257.
2. Nauck, M., Stöckmann, F., Ebert, R., and Creutzfeldt, W. (1986). Reduced incretin effect in type 2 (non-insulin-dependent) diabetes. *Diabetologia* 29: 46–52.
3. Nauck, M.A., Heimesaat, M.M., Orskov, C. et al. (1993). Preserved incretin effect of glucagon-like peptide 1 [7–36 amide] but not of synthetic human gastric inhibitory polypeptide in patients with type-2 diabetes mellitus. *J Clin Invest* 91: 301–307.
4. Gantz, I., Chen, M., Suryawanshi, S. et al. (2017). A randomized, placebo-controlled study of the cardiovascular safety of the once-weekly DPP-4 inhibitor omarigliptin in patients with type 2 diabetes. *Cardiovasc Diabetol* 16: 112.
5. Rosenstock, J., Aguilar-Salinas, C., Klein, K. et al. (2009). Effect of saxagliptin monotherapy in treatment-naïve patients with type 2 diabetes. *Curr Med Res Opin* 25: 2401–2411.
6. Raz, I., Hanefield, M., Xu, L. et al. (2006). Efficacy and safety of the dipeptidyl peptidase-4 inhibitor sitagliptin as monotherapy in patients with type 2 diabetes mellitus. *Diabetologia* 49: 2564–2571.
7. Pi-Sunyer, F.X., Schweizer, A., Mills, D., and Dejager, S. (2007). Efficacy and tolerability of vildagliptin monotherapy in drug-naive patients with type 2 diabetes. *Diabetes Res Clin Pract* 76: 132–138.
8. DeFronzo, R.A., Fleck, P.R., Wilson, C.A., Mekki, Q., and on behalf of Alogliptin Study 010 Group. (2008). Efficacy and safety of the dipeptidyl peptidase-4 inhibitor alogliptin in patients with type 2 diabetes and inadequate glycemic control: a randomized, double-blind, placebo-controlled study. *Diabetes Care* 31: 2315–2317.
9. Barnett, A.H., Patel, S., Harper, R. et al. (2012). Linagliptin monotherapy in type 2 diabetes patients for whom metformin is inappropriate: an 18-week randomized, double-blind, placebo-controlled phase III trial with a 34-week active-controlled extension. *Diabetes Obes Metab* 14: 1145–1154.
10. Fadini, G.P., Bottigliengo, D., D'Angelo, F. et al. (2018). Comparative effectiveness of DPP-4 inhibitors versus sulfonylurea for the treatment of type 2 diabetes in routine clinical practice: a retrospective multicenter real-world study. *Diabetes Ther* 9: 1477–1490.
11. Carls, G.S., Tuttle, E., Tan, R.D. et al. (2017). Understanding the gap between efficacy in randomized controlled trials and effectiveness in real-world use of GLP-1 RA and DPP-4 therapies in patients with type 2 diabetes. *Diabetes Care* 40: 1469–1478.
12. Wu, D., Li, L., and Liu, C. (2014). Efficacy and safety of dipeptidyl peptidase-4 inhibitors and metformin as initial combination therapy and as monotherapy in patients with type 2 diabetes mellitus: a meta-analysis. *Diabetes Obes Metab* 16: 30–37.

13. Downes, M.J., Bettington, E.K., Gunton, J.E., and Turkstra, E. (2015). Triple therapy in type 2 diabetes; a systematic review and network analysis. *Peer J* 3: e1461.
14. Wang, B., Sun, Y., Sang, Y., Liu, X., and Liang, J. (2018). Comparison of dipeptidyl peptidase-4 inhibitors and pioglitazone combination therapy versus pioglitazone monotherapy in type 2 diabetes – a system review and meta-analysis. *Med* 97 (46): e12633.
15. Li, D., Shi, W., Wang, T., and Tang, H. (2018). SGLT2 inhibitor plus DPP-4 inhibitor as combination therapy for type 2 diabetes: a systematic review and meta-analysis. *Diabetes Obes Metab* 20: 1972–1976.
16. Yang, W., Cai, X., Gao, X., Chen, Y., Chen, L., and Ji, L. (2018). Addition of dipeptidyl peptidase-4 inhibitors to insulin treatment in type 2 diabetes patients: a meta-analysis. *J Diabetes Investig* 9: 813–821.
17. Matthews, D.R., Paldánius, P.M., Proot, P. et al. (2019). Glycaemic durability of an early combination therapy with vildagliptin and metformin versus sequential metformin monotherapy in newly diagnosed type 2 diabetes (VERIFY): a 5-year, multicentre, randomised, double-blind trial. *Lancet* 394: 1519–1529.
18. Nathan, D.M., Buse, J.E., Kahn, S.E. et al. (2013). Rationale and design of the glycemia reduction approaches in diabetes: a comparative effectiveness study (GRADE). *Diabetes Care* 36: 2254–2261.
19. Butler, A.E., Campbell-Thompson, M., Gurlo, T., Dawson, D.W., Atkinson, M., and Butler, P.C. (2013). Marked expansion of exocrine and endocrine pancreas with incretin therapy in humans with increased exocrine pancreas dysplasia and the potential for glucagon-producing neuroendocrine tumors. *Diabetes* 62: 2595–2604.
20. Elashoff, M., Matveyenko, A.V., Gier, B., Elashoff, R., and Butler, P.C. (2011). Pancreatitis, pancreatic, and thyroid cancer with glucagon-like peptide-1-based therapies. *Gastroenterol* 141: 150–156.
21. Egan, A.G., Blind, E., Dunder, K. et al. (2014). Pancreatic safety of incretin-based drugs – FDA and EMA assessment. *N Engl J Med* 370: 794–797.
22. Roshanov, P.S. and Dennis, B.B. (2015). Incretin-based therapies are associated with acute pancreatitis: meta-analysis of large randomized controlled trials. *Diabetes Res Clin Pract* 110 (3): e13–e17.
23. Li, L., Shen, J., Bala, M.M. et al. (2014). Incretin treatment and risk of pancreatitis in patients with type 2 diabetes mellitus: systematic review and meta-analysis of randomised and non-randomised studies. *BMJ* 348: g2366.
24. Engel, S.S., Round, E., Golm, G.T., Kaufman, K.D., and Goldstein, B.J. (2013). Safety and tolerability of sitagliptin in type 2 diabetes: pooled analysis of 25 clinical studies. *Diabetes Ther* 4: 119–145.
25. Dicembrini, I., Montereggi, C., Nreu, B. et al. (2020). Pancreatitis and pancreatic cancer in patients treated with Dipeptidyl Peptidase-4 inhibitors: an extensive and updated meta-analysis of randomized controlled trials. *Diabetes Res Clin Pract* 159: 107981.
26. Pinto, L.C., Rados, D.V., Barkan, S.S., Leitão, C.B., and Gross, J.L. (2018). Dipeptidyl peptidase-4 inhibitors, pancreatic cancer and acute pancreatitis: a meta-analysis with trial sequential analysis. *Sci Rep* 8: 782.
27. Raz, I., Bhatt, D.L., Hirshberg, B. et al. (2014). Incidence of pancreatitis and pancreatic cancer in a randomized controlled multicenter trial (SAVOR-TIMI 53) of the dipeptidyl peptidase-4 inhibitor saxagliptin. *Diabetes Care* 37: 2435–2441.
28. Buse, J.B., Bethel, M.A., Green, J.B. et al. (2017). Pancreatic safety of sitagliptin in the TECOS study. *Diabetes Care* 40: 164–170.
29. White, W.B., Cannon, C.P., Heller, S.R. et al., for the EXAMINE investigators. (2013). Alogliptin after acute coronary syndrome in patients with type 2 diabetes. *N Engl J Med* 369: 1317–1326.

30. Ueki, K., Tanizawa, Y., Nakamura, J. et al. (2021). Long-term safety and efficacy of alogliptin, a DPP-4 inhibitor, in patients with type 2 diabetes: a 3-year prospective, controlled, observational study (J-BRAND registry). *BMJ Diab Res Care* 9: e001787.
31. Raschi, E., Poluzzi, E., and De Ponti, F. (2015). Comment on: 'Pharmacokinetics in patients with chronic liver disease and hepatic safety of incretin-based therapies for the management of type 2 diabetes mellitus'. *Clin Pharmacokinet* 54: 447–448.
32. Barbehenn, E., Almashat, S., Carome, M., and Wolfe, S. (2014). Hepatotoxicity of alogliptin. *Clin Pharmacokinet* 53: 1055–1056.
33. Frederich, R., Alexander, J.H., Fiedorek, F.T. et al. (2010). A systematic assessment of cardiovascular outcomes in the saxagliptin drug development program for type 2 diabetes. *Postgrad Med* 122: 16–27.
34. Scirica, B.M., Bhatt, D.L., Braunwald, E. et al., for the SAVOR-TIMI 53 Steering Committee and Investigators. (2013). Saxagliptin and cardiovascular outcomes in patients with type 2 diabetes mellitus. *New Engl J Med* 369: 1317–1326.
35. White, W.B., Pratley, R., Fleck, P. et al. (2013). Cardiovascular safety of the dipeptidyl peptidase-4 inhibitor alogliptin in type 2 diabetes mellitus. *Diabetes Obes Metab* 15: 668–673.
36. Zannad, F., Cannon, C.P., Cushman, W.C. et al., for the EXAMINE investigators. (2015). Heart failure and mortality outcomes in patients with type 2 diabetes taking alogliptin versus placebo in EXAMINE: a multicentre, randomised double-blind trial. *Lancet* 385: 2067–2076.
37. Green, J.B., Bethel, M.A., Armstrong, P.W. et al., for the TECOS Study Group. (2015). Effect of sitgaliptin on cardiovascular outcomes in type 2 diabetes. *N Engl J Med* 373: 232–242.
38. Rosenstock, J., Perkovic, V., Johansen, O.E. et al. (2019). Effect of linagliptin vs placebo on major cardiovascular events in adults with type 2 diabetes and high cardiovascular and renal risk. The CARMELINA randomised clinical trial. *JAMA* 321: 69–79.
39. Rosenstock, J., Kahn, S.E., Johansen, O.E. et al. (2019). Effect of lingliptin vs glimepiride on major adverse cardiovascular outcomes in patients with type 2 diabetes. The CAROLINA randomized clinical trial. *JAMA* 322: 1155–1166.
40. McInnes, G., Evans, M., Del Prato, S. et al. (2015). Cardiovascular and heart failure safety profile of vildagliptin: a meta-analysis of 17000 patients. *Diabetes Obes Metab* 17: 1085–1092.
41. McMurray, J.J.V., Ponikowski, P., Bolli, G.B. et al. (2018). Effects of vildagliptin on ventricular function in patients with type 2 diabetes mellitus and heart failure. *JACC: Heart Fail* 6: 8–17.
42. Bae, J.H., Kim, S., Park, E.G. et al. (2019). Effects of dipeptidyl peptidase-4 inhibitors on renal outcomes in patients with type 2 diabetes: a systematic review and meta-analysis. *Endocrinol Metab* 34: 80–92.
43. Kanasaki, K. (2018). The role of dipeptidyl dipeptidase-4 in kidney disease: renal effects of dipeptidyl ipetidase-4 inhibitors with a focus on linagliptin. *Clin Sci* 132: 489–507.
44. Mosenzon, O., Leibowitz, G., Bhatt, D.L. et al. (2017). Effect of saxagliptin on renal outcomes in the SAVOR-TIMI 53 trial. *Diabetes Care* 40: 69–76.
45. Cornel, J.H., Bakris, G.L., Stevens, S.R. et al. (2016). Effect of sitagliptin on kidney and respective cardiovascular outcomes in type 2 diabetes: outcomes from TECOS. *Diabetes Care* 39: 2304–2310.
46. Kanasaki, K., Shi, S., Kanasaki, M. et al. (2014). Linagliptin-mediated DPP-4 inhibition ameliorates kidney fibrosis in streptozotocin-induced diabetic mice by inhibiting endothelial-to-mesenchymal transition in a therapeutic regimen. *Diabetes* 63: 2120–2131.
47. Groop, P.H., Cooper, M.E., Perkovic, V. et al. (2013). Linagliptin lowers albuminuria on top of recommended standard treatment in patients with type 2 diabetes and renal dysfunction. *Diabetes Care* 36: 3460–3468.
48. Groop, P.H., Cooper, M.E., Perkovic, V. et al. (2017). Linagliptin and its effects on hyperglycaemia and albuminuria in patients with type 2 diabetes and renal dysfunction: the randomised MARLINA-T2D trial. *Diabetes Obes Metab* 19: 1610–1619.

CHAPTER 5

SGLT2 Inhibitors

Miles Fisher, Andrea Llano, and Gerry McKay

KEY POINTS

- SGLT2 inhibitors inhibit the reabsorption of glucose in the proximal convoluted tubule of the kidney, promoting glycosuria and weight loss with moderate reductions in HbA1c in people with diabetes.
- The main side effect is an increase in genital thrush, and the most series side effect is an increased incidence of diabetic ketoacidosis in at-risk patients with type 1 and type 2 diabetes; the risk can be reduced by the careful selection of patients for therapy and education of the patient.
- Cardiovascular outcome trials with empagliflozin (EMPA-REG OUTCOME), canagliflozin (CANVAS) and dapagliflozin (DECLARE-TIMI 58) in people with type 2 diabetes have demonstrated remarkable early reductions in major adverse cardiovascular events (MACE, a composite of cardiovascular death, nonfatal myocardial infarction and nonfatal stroke) in patients with established atherosclerosis, and reductions in heart failure events in a wider group of patients with type 2 diabetes.
- A dedicated trial of canagliflozin in people with diabetic kidney disease (CREDENCE) demonstrated a significant reduction in renal outcomes, and similar reductions in renal outcomes were observed in a study of dapagliflozin in chronic kidney disease (DAPA-CKD), regardless of whether the patent had diabetes or not.
- In outcome trials of patients with well-characterised heart failure dapagliflozin (DAPA-HF) and empagliflozin (EMPEROR-Reduced and EMPEROR-Preserved) have demonstrated reductions in heart failure events and cardiovascular mortality.
- SGLT2 inhibitors are now established treatments for the management of patients with type 2 diabetes, chronic kidney disease and heart failure.

Diabetes Drug Notes, First Edition. Edited by Miles Fisher, Gerard A. McKay, and Andrea Llano.

Introduction

Phlorizin is a naturally occurring polyphenol found in unripe apples and the root bark of some apple and other fruit trees. It is a competitor of both sodium–glucose cotransporter-1 (SGLT1) and sodium–glucose cotransporter-2 (SGLT2), with greater affinity for SGLT2. When phlorizin was studied in a rat model of diabetes, it was shown to increase glycosuria and reduce hyperglycaemia without causing hypoglycaemia. When taken by mouth phlorizin has poor systemic bioavailability and it is metabolised in the gastrointestinal tract to phloretin, so it was useful as an investigational product but not as a possible long-term treatment for people with diabetes. Phlorizin derivatives were subsequently explored looking for molecules that had increased resistance to enzymatic degradation and increased systemic bioavailability.

Dapagliflozin, canagliflozin, empagliflozin and ertugliflozin have all been demonstrated to be safe and effective SGLT2 inhibitors for the treatment of diabetes and have satisfied the cardiovascular safety requirements of the FDA and the EMA (see Chapter 1). Indeed, highly significant reductions in the numbers of cardiovascular events were seen with empagliflozin, canagliflozin and dapagliflozin. Dapagliflozin and empagliflozin have been further developed as treatments for chronic kidney disease, and dapagliflozin and empagliflozin have been further developed as treatments for heart failure. Other SGLT2 inhibitors are available in some countries as treatments for type 2 diabetes. Sotagliflozin is a combined SGLT1 and SGLT2 inhibitor that was under development as a possible treatment for type 1 and type 2 diabetes, but development was halted for commercial reasons.

Pharmacology

Physiology of Sodium-dependent Glucose Transporters

Glucose transport across cell membranes is mediated by the active sodium–glucose transporter (SGLT). There are six isoforms of this transporter of which SGLT1 and SGLT2 are the best characterised. SGLT2 is a low-affinity, high-capacity glucose transporter found in the renal tubules and is responsible for reabsorbing approximately 90% of filtered glucose. SGLT1 is found in the gastrointestinal tract where it is responsible for glucose absorption, as well as in renal tubules where it is responsible for the other 10% of glucose reabsorption (Figure 5.1). In contrast to SGLT2, SGLT1 is a high-affinity, low-capacity glucose transporter.

Intestinal SGLT1 expression is affected by dietary intake, and diets high in glucose or sodium increase the expression of SGLT1 receptors in the small bowel, providing a regulatory mechanism. In the kidney glucose is transported by SGLT1 and SGLT2 through the apical membrane of the proximal convoluted tubule using a sodium gradient maintained by a Na^+/K^+ ATPase at the basolateral cell membrane. Glucose is then passively transported by GLUT1 and 2 into the renal interstitium.

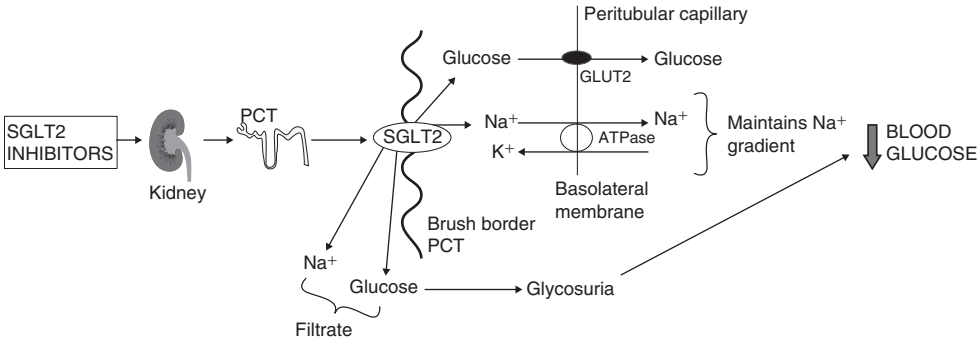


FIGURE 5.1 Mechanism of action of SGLT2 inhibitors. Glucose transport across cell membranes is mediated by the active sodium–glucose transporter (SGLT). SGLT2 are the best characterised. SGLT2 is a low-affinity high-capacity glucose transporter found in the renal tubules and is responsible for reabsorbing approximately 90% of filtered glucose. SGLT2 inhibitors block SGLT2 in the proximal convoluted tubule (PCT) of the kidney, reducing the reabsorption of glucose and promoting glycosuria.

The renal glucose transport system becomes saturated when blood glucose levels exceed 11.1 mmol/L and glucose spills over into urine, causing glycosuria. In patients with diabetes the expression of SGLT2 is increased, which contributes to hyperglycaemia by increasing glucose reabsorption.

Mechanism of Action

SGLT2 inhibitors block SGLT2 in the proximal convoluted tubule of the kidney, reducing the reabsorption of glucose and promoting glycosuria (Figure 5.1). This mechanism of action is particularly relevant as SGLT2 expression is increased in patients with diabetes. SGLT2 inhibitors reduce renal glucose reabsorption by 30–50% and can reduce HbA1c by 0.6–0.9% (7–10 mmol/mol). Their effects are dependent on serum glucose levels and independent of insulin, a characteristic that means that they carry a low risk of causing hypoglycaemia. Their glycaemic efficacy is dependent on glomerular filtration, and they are less efficacious in renal impairment.

Pharmacodynamics and Pharmacokinetics

Dapagliflozin Dapagliflozin is a competitive, reversible, highly selective and orally active inhibitor of SGLT2. The oral bioavailability of dapagliflozin is 78% and peak concentration is reached two hours after administration. Dapagliflozin has a half-life of 12–15 hours. It undergoes renal and hepatic metabolism and 75% of dapagliflozin is excreted via the kidneys. It is recommended to initially use a lower dose (5 mg) in severe hepatic impairment.

The phase 3 development programme of dapagliflozin included 11 placebo-controlled and active comparator studies (comparators were glipizide and sustained-release metformin) in nearly 7000 patients with type 2 diabetes. It included drug-naive subjects, patients already on oral antidiabetic drugs and patients on insulin. The programme included two studies in patients with diabetes and hypertension and a small-body composition study using dual energy X-ray absorptiometry (DEXA).

Dapagliflozin (Forxiga®) was approved by the EMA in 2012 and by the FDA in 2014. The cardiovascular outcome trial with dapagliflozin (DECLARE-TIMI 58) was started in 2013 and completed in 2018 [1]. Dapagliflozin is licensed for use in the management of people with type 2 diabetes and was previously approved as an adjunct in patients with type 1 diabetes with a BMI ≥ 27 kg/m^2 who had suboptimal glycaemic control. Dapagliflozin is also licenced for the treatment of symptomatic chronic heart failure with reduced ejection fraction in patients with and without diabetes, and for chronic kidney disease with and without diabetes.

Dose

- Type 2 diabetes, dapagliflozin 10 mg once daily.
- Dapagliflozin is also available as a fixed-dose combined preparation with metformin (Xigduo® 5 mg/850 mg and 5 mg/1000 mg).
- Heart failure, 10 mg once daily.
- Chronic kidney disease, 10 mg once daily.

Canagliflozin Canagliflozin is a competitive, reversible, selective and orally active inhibitor of SGLT2. It is slightly less selective for SGLT2 than dapagliflozin and has slightly greater affinity for SGLT1 than dapagliflozin. Canagliflozin has a bioavailability of 65% and a half-life of 10–13 hours. Canagliflozin is metabolised by the liver and is largely excreted in faeces.

The phase 3 development programme included ten placebo-controlled studies and two active comparator studies with glimepiride (CANTATA-SU) and sitagliptin (CANTATA-D) in nearly 8000 patients with type 2 diabetes. It included a small study in patients with renal impairment (eGFR 30–50 ml/min/1.73 m^2) and a study in older subjects looking at bone safety and body composition.

Canagliflozin (Invokana®) was licensed by the EMA and FDA in 2013. The cardiovascular outcome trial with canagliflozin (CANVAS) was started in 2009 and completed in 2017 [2]. Canagliflozin is licensed for the treatment of type 2 diabetes and for the treatment of diabetic kidney disease.

Dose

- Type 2 diabetes, canagliflozin 100 mg once daily, increased if tolerated to 300 mg once daily if required.

- Canagliflozin is also available as a fixed-dose combined preparation with metformin (Vokanamet® 50 mg/850 mg and 50 mg/1000 mg).
- Diabetic kidney disease, 100 mg once daily.

Empagliflozin Empagliflozin is a competitive, reversible, selective and orally active inhibitor of SGLT2. It has a bioavailability of 78% and a half-life of 12 hours. It does not undergo significant metabolism and is excreted via urine and faeces.

The EMPA-REG phase 3 development programme included around 5000 patients with type 2 diabetes and included six placebo-controlled monotherapy or add-on combination studies and one study as an add-on to metformin compared with glimepiride (EMPA-REG H2H-SU), plus a study in patients with CKD stage 2 and 3 (EMPA-REG RENAL) and a study in patients with diabetes and hypertension (EMPA-REG BP).

Empagliflozin (Jardiance®) was approved for use in the management of people with type 2 diabetes in 2014 by the FDA and the EMA. Empagliflozin was the third SGLT2 inhibitor to be marketed internationally but was the first to have a completed cardiovascular outcome trial in EMPA-REG OUTCOME, which was started in 2010 and completed in 2015 [3].

Dose

- Type 2 diabetes, empagliflozin 10 mg once daily, increased to 25 mg once daily if necessary and if tolerated.
- Empagliflozin is also available as four fixed-dose combined preparations with metformin (Synjardy® 5 mg/850 mg, 12.5 mg/850 mg, 5 mg/850 mg, 12.5 mg/1000 mg) and two fixed-dose combined preparations with linagliptin (Glyxambi® 10 mg/5 mg and 25 mg/5 mg).
- Heart failure, 10 mg once daily.

Ertugliflozin Ertugliflozin possesses a high selectivity for SGLT2 vs. SGLT1 and other glucose transporters (GLUT1-4). It has a bioavailability of 70–90% and a half-life of 11–17 hours. It undergoes hepatic metabolism and is excreted in urine and faeces.

The VERTIS phase 3 development programme for ertugliflozin included seven placebo-controlled and active comparator studies (the comparators were glimepiride and sitagliptin) in over 4000 patients with type 2 diabetes. It included a study in patients with moderate renal impairment (stage 3 CKD).

The VERTIS-CV cardiovascular outcome trial started in 2013 and was completed in 2019 [4]. Ertugliflozin (Steglatro®) was licensed for use in 2017 by the FDA and 2018 by the EMA.

Dose

- Ertugliflozin, 5 mg once daily, increased to 15 mg once daily if necessary and if tolerated.
- Ertugliflozin is available in many countries in the EU as four fixed-dose combined preparations with metformin (Segluromet® 2.5 mg/850 mg, 2.5 mg/1000 mg,

7.5 mg/850 mg, 7.5 mg/1000 mg) and two combinations with sitagliptin (Steglujan® 5 mg/100 mg and 15 mg/100 mg), but these fixed-dose combinations are not available in the UK.

Sotagliflozin Sotagliflozin is a dual inhibitor of SGLT1 and SGLT2. Inhibition of SGLT1 decreases the absorption of glucose in the proximal intestine, resulting in a blunting and delay of postprandial hyperglycaemia, and it was hoped that this dual effect might increase glycaemic efficacy, particularly in patients with CKD.

The initial phase 2 development of sotagliflozin was performed by Lexicon Pharmaceuticals in patients with type 1 and type 2 diabetes. Phase 3 development was then taken over by Sanofi Aventis and included three studies in people with type 1 diabetes, and eight studies in people with type 2 diabetes including a comparison with glimepiride (SOTA-GLIM), the effects of sotagliflozin on bone measured by DEXA scan (SOTA-BONE) and studies in patients with CKD stage 3 (SOTA-CKD3) and stage 4 (SOTA-CKD4). The reductions in HbA1c in people with CKD were not clinically meaningful. The development programme for sotagliflozin in diabetes also included the SCORED cardiorenal outcome trial [5] and the SOLOIST-WHF trial in heart failure [6]. In addition to the usual side effects of SGLT2 inhibitors, diarrhoea was significantly increased with sotagliflozin in these studies.

Sotagliflozin (Zynquista®) was approved by the EMA in Europe at a dose of 200 mg for use as an adjunct therapy in combination with insulin for people with type 1 diabetes based on the results of four phase 2 studies and three phase 3 studies, but it has never been available to prescribe for patients as the development of sotagliflozin was halted by Sanofi for commercial reasons.

Other SGLT2 Inhibitors Dapagliflozin, canagliflozin, empagliflozin and ertugliflozin have been approved by the EMA in Europe and the FDA in the US. Each has undergone a detailed development programme, including the undertaking of cardiovascular outcome trials which are described below. Several other SGLT2 inhibitors are available in other parts of the world: ipragliflozin, luseogliflozin and tofogliflozin are available in Japan and remogliflozin is available in India.

The licensing of drugs in these countries has been based on short-term efficacy information, up to 52 weeks, and longer-term safety data is generally lacking. To date there have been no randomised controlled trials undertaken on whether these drugs reduce cardiovascular events or not. Small numbers of patients treated with these SGLT2 inhibitors were included in the CVD-REAL international pharmaco-epidemiological studies.

Glycaemic Efficacy

SGLT2 inhibitors have been described as moderately effective in reducing HbA1c [7]. When used as monotherapy the reduction in HbA1c is comparable with that for metformin, with reductions of around 0.8% (9 mmol/mol). The reduction is greater in people with a higher baseline HbA1c. A slight further decrease in HbA1c

to around 0.9% (10 mmol/mol) occurs if a larger dose of canagliflozin (300 mg) or empagliflozin (25 mg) is used. When SGLT2 inhibitors are added to metformin as second-line therapy the reduction is around 0.6% (7 mmol/mol), and when added to insulin reductions in HbA1 of 0.5–0.6% (5–7 mmol/mol) are observed. Head-to-head comparator studies in phase 3 development programmes have shown a greater reduction in HbA1c with SGLT2 inhibitors than with sitagliptin. Rates of hypoglycaemia with SGLT2 inhibitors are like those with metformin and significantly less than those with sulfonylureas. Unfortunately, SGLT2 inhibitors were not included in the GRADE study, a comparative efficacy study of major antidiabetic therapies added to metformin (glimepiride, sitagliptin, liraglutide and insulin glargine), as SGLT2 inhibitors were not clinically available when the study was launched (see Chapters 3 and 4).

Because of the mechanism of action of SGLT2 inhibitors they are less effective at reducing HbA1c in people with diabetic kidney disease and a reduced eGFR. When SGLT2 inhibitors were first introduced as a treatment for type 2 diabetes the licences for the drugs recommended starting if the eGFR was >60 ml/min/1.73 m^2, reducing the dose for canagliflozin and empagliflozin if the eGFR fell to between 60 and 45 ml/min/1.73 m^2 and withdrawing the drug if the eGFR fell below 45 ml/min/1.73 m^2, and this information is still contained in the summary product characteristics. Since then, there is evidence, described below, that SGLT2 inhibitors reduce renal events in patients with chronic kidney disease and heart failure events in people with heart failure, many of whom also have a reduced eGFR, and licences have been changed to reflect these new indications for use.

Prescribing point: *SGLT2 inhibitors are less effective at reducing HbA1c in patients with an eGFR of <60 ml/min/1.73 m^2. It is recommended that practitioners should check up to date summary product characteristics for information about the eGFR criteria for the prescribing of individual SGLT2 inhibitors.*

Comparisons of SGLT2 Inhibitors with GLP-1 Receptor Agonists

A key area of interest has been the comparison of SGLT2 inhibitors with GLP-1 receptor agonists. To date, three head-to-head studies, all sponsored by manufacturers of GLP-1 receptor agonists, have compared the two drug classes (Table 5.1). The once weekly formulation of exenatide was comprehensively studied in the DURATION development programme. DURATION-8 was a 28 week double-blind, phase 3 study comparing exenatide once weekly 2 mg, dapagliflozin 10 mg and the combination of exenatide plus dapagliflozin [8], which was then extended to 52 and 104 weeks [9, 10].

- At all three time points (28, 52 and 104 weeks) exenatide was more effective than dapagliflozin at reducing HbA1c, and the combination of exenatide plus dapagliflozin was more effective than either single drug.
- The reduction in body weight was greater with dapagliflozin than with exenatide.

TABLE 5.1 **Studies comparing the glycaemic efficacy of SGLT2 inhibitors and GLP-1 receptor agonists [8–12]**

Study	DURATION-8 [8–10]	SUSTAIN 8 [11]	PIONEER 2 [12]
SGLT2 inhibitor	Dapagliflozin 10 mg	Canagliflozin 300 mg	Empagliflozin 25 mg
Comparator(s)	Exenatide prolonged release 2 mg once weekly Combination therapy	Semaglutide 1 mg once weekly	Oral semaglutide 14 mg daily
Study population ($n =$)	695	788	822
Duration of study	28 weeks (extended to 52 and 104 weeks)	52 weeks	52 weeks
HbA1c results	Greater reduction with exenatide than dapagliflozin at 28 weeks	Greater reduction with semaglutide at 52 weeks	Greater reduction with semaglutide at 26 and 52 weeks
Body weight results	Greater weight reduction with dapagliflozin than exenatide at 28 weeks	Greater reduction with semaglutide at 52 weeks	Greater reduction with semaglutide at 52 weeks

The subcutaneous once weekly formulation of semaglutide was studied in the SUSTAIN development programme and SUSTAIN 8 compared semaglutide 1 mg with canagliflozin 300 mg [11]. At 52 weeks semaglutide was more effective than canagliflozin at reducing HbA1c and weight. The study design did not include a group receiving both drugs. A similar study design was used for PIONEER 2 comparing oral semaglutide 14 mg daily with empagliflozin 25 mg [12]. A greater reduction in HbA1c was seen with semaglutide, and the reduction in body weight was similar comparing the two drugs.

Additional Effects of SGLT2 Inhibitors

SGLT2 inhibitors have several other beneficial actions in addition to their glucose-lowering effects, and some of these may contribute to the cardiovascular and renoprotective benefits discussed later in the chapter.

Body Weight SGLT2 inhibitors result in the daily loss of 60–80 g of glucose, resulting in a caloric deficit. Randomised controlled trials have reported a weight loss of between 2 and 3 kg with their use. A meta-analysis of 39 studies reported that doses of 10 mg dapagliflozin, 25 mg empagliflozin and 300 mg canagliflozin were associated with weight losses of −1.80, −1.81 and −2.66 kg, respectively, compared with placebo [13]. In comparator trials, weight loss with SGLT2 inhibitors was greater than with metformin, DPP-4 inhibitors or sulfonylureas.

Blood Pressure SGLT2 inhibitors decrease systolic blood pressure by 5–6 mmHg and diastolic blood pressure by 1–2 mmHg, and this may partly be secondary to their natriuretic effect. The effect is more pronounced in patients with a higher baseline systolic blood pressure and is independent of renal function [14].

Prescribing point: *In addition to lowering blood pressure, the osmotic diuresis associated with SGLT2 inhibitors can increase the risk of fluid depletion and caution should be exercised in certain patient groups such as the elderly, patients taking loop diuretics or patients with impaired renal function.*

Side Effects and Safety

Genitourinary Infections

The use of SGLT2 inhibitors has been associated with an increased risk of genital mycotic infections. These are more common in female patients and those with a previous history of genital infections. They are generally mild to moderate in severity and respond to standard treatment. A meta-analysis found that empagliflozin, dapagliflozin and canagliflozin were associated with a higher risk of genital fungal infections compared with placebo with odds ratios of 3.64 (95% CI 2.87–4.63), 4.51 (95% CI 3.37–6.04) and 4.99 (95% CI 3.74–6.67) respectively [15].

Prescribing point: *Patients starting on SGLT2 inhibitors should be given advice about genital hygiene, and if thrush occurs it usually responds to conventional topical or oral antifungal therapy.*

A small number of patients develop recurrent thrush and will wish to stop treatment. Some patients may wish to continue with treatment if this has been associated with weight loss, and the patient should be involved in the decision as to whether to discontinue treatment or not.

A possible increased incidence of bacterial urinary tract infections (UTIs) has been reported with the use of SLGT2 inhibitors, but the data is inconsistent and not definitive. One meta-analysis analysed the risk of SGLT2 inhibitors as a class on the incidence of UTIs and found no significant risk, but a subgroup analysis of individual agents in the class found an increased risk of UTIs with dapagliflozin (RR 1.21; 95% CI 1.02–1.43) [16].

Diabetic Ketoacidosis

Diabetic ketoacidosis (DKA) is an uncommon but serious complication of SGLT2 inhibitor use in patients with type 2 diabetes, which can present as euglycaemic ketoacidosis, where there is a severe metabolic acidosis, ketonuria, but only a marginally raised blood glucose concentration, leading to delays in recognition and treatment. Although reports of DKA during clinical trials of SGLT2 inhibitors were infrequent, post-market-

ing surveillance studies found a significant association and all SGLT2 inhibitors now carry safety warnings for DKA.

Several mechanisms contribute to DKA in patients with type 2 diabetes:

- SGLT2 inhibitor-mediated increase in glucagon secretion which in turn increases gluconeogenesis, lipolysis and ketogenesis.
- An osmotic diuresis and volume depletion increasing counterregulatory hormones and further increasing lipolysis and ketogenesis.
- A reduction in glycosuria and renal excretion of ketone bodies.
- Reductions in insulin dosing.

DKA rates of 0.09 vs. 0.04% (treatment vs. placebo) were reported in EMPA-REG OUTCOME, which were not significantly different [3]. In the CANVAS trial there were 0.6 vs. 0.3 events per 1000 patient years, respectively [2], while DECLARE-TIMI 58 reported nonstatistically significant event rates of 0.3 vs. 0.1% [1]. Post-marketing data show a much higher incidence of DKA. A recent systematic review and meta-analysis of 39 randomised controlled trials and 60 580 patients found an increased risk of DKA associated with SGLT2 inhibitor use in patients with type 2 diabetes compared with placebo or other therapies with an OR of 2.13 (95%CI 1.38–3.27) [17].

DKA tends to occur within the first six weeks of treatment with SGLT2 inhibitors and cases are often precipitated by acute illness, reduced oral intake or surgery. Retrospective case analysis in the type 2 population has suggested that some episodes of DKA were associated with use in patients with undiagnosed type 1 diabetes or in those with low beta cell function. At the time of starting therapy with SGLT2 inhibitors patients should be advised about the signs and symptoms of DKA and to seek medical advice if these occur. During acute illness SGLT2 inhibitors should be temporarily withheld (along with ACE inhibitors, angiotensin-II receptor antagonists, diuretics, metformin and nonsteroidal anti-inflammatories) and restarted once the patient has recovered from the acute illness. Testing for ketones should be done by medical staff or by patients who are already testing for ketones, but it is not practical to start ketone testing in all patients who start SGLT2 inhibitors.

Prescribing point: *SGLT2 inhibitors should be used with caution in patients at risk of DKA, particularly those with low endogenous insulin secretion. SGLT2 inhibitors should be stopped temporarily if a patient is undergoing major surgery or during serious illness.*

Prescribing point: *SGLT2 inhibitors should not be restarted in patients who experience DKA during use unless a clear cause for DKA was identified and resolved.*

Amputation

Reports of lower limb amputation with SGLT2 inhibitor use have been inconsistent. An unexpected increased risk of lower limb amputation was detected during the CANVAS Program [2]. Canagliflozin was associated with an approximately twofold increased risk of lower limb amputation compared with the placebo group (6.3 vs. 3.4 events per

1000 patient years, $p < 0.001$). The later CREDENCE trial with canagliflozin found no significant risk in lower limb amputations with canagliflozin compared with placebo (HR 1.11; 95% CI 0.79–1.56) [18]. There was a numerical increase in toe amputations with ertugliflozin in the VERTIS CV trial, but this safety signal was not seen with empagliflozin or dapagliflozin.

The OBSERVE-4D study analysed data from four observational databases and found no increased risk of lower limb amputation between 142 800 new users of canagliflozin and 110 897 new users of other SGLT2 inhibitors and placebo [18]. Another population-based cohort study found a twofold increased risk of amputation with SGLT2 inhibitors, which was largely associated with canagliflozin [19].

Other Adverse Effects

A possible increase in Fournier's gangrene was an initial safety concern with SGLT2 inhibitors, but in the cardiovascular outcome trials the rates of this serious condition were similar in those the SGLT2 inhibitor and placebo groups.

SLGT2 inhibitors modulate calcium and phosphate homeostasis. Canagliflozin has been reported to increase fracture risk with mild decreases in bone mineral density [20], and there was an increase in fractures in the canagliflozin patients in the CANVAS Program (15.4 vs. 11.9 events per 1000 patient years, $p = 0.02$) [2]. This association has not been seen with dapagliflozin, empagliflozin or ertugliflozin.

Outcome Trials

Cardiovascular Outcome Trials in Diabetes

As for all drugs being developed for use in type 2 diabetes, SGLT2 inhibitors have had to be tested in large clinical trials to show cardiac safety as mandated by the FDA in the US and the EMA following the concerns about increased cardiovascular risk owing to rosiglitazone (see Chapters 1 and 12). These CVOTs have been designed to meet the FDA/EMA requirements to show noninferiority over a two-year period. Most of the trials recruited people with type 2 diabetes and established atherosclerotic cardiovascular disease or those with risk factors for cardiovascular disease. Secondary endpoints have included heart failure and renal outcomes.

EMPA-REG OUTCOME EMPA-REG OUTCOME (Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients) included 7020 patients with type 2 diabetes and established atherosclerotic cardiovascular disease, although a small number of subjects were randomised who were subsequently characterised as having increased cardiovascular risk rather than established atherosclerotic cardiovascular disease [3]. Ten per cent also had baseline heart failure recorded by the local clinical investigator (Table 5.2). Randomisation was in a 1:1:1 ratio to treatment with empa-

TABLE 5.2 Cardiovascular outcome trials with SGLT2 inhibitors [1–4]

Trial	EMPA-REG OUTCOME [3]	CANVAS Program [2]	DECLARE-TIMI 58 [1]	VERTIS CV [4]
SGLT2 inhibitor	Empagliflozin 10 and 25 mg	Canagliflozin 100–300 mg	Dapagliflozin 10 mg	Ertugliflozin 5 and 15 mg
Comparator	Placebo	Placebo	Placebo	Placebo
Population size	7 020	10 142	17 160	8 246
Age (years)	63	63	64	64
Duration of diabetes (years)	57% over 10 years	14	11	13
Follow-up (years)	3	4	4	3
Atherosclerotic CVD (%)	99	72	41	100
Heart failure (%)	10	14	10	23
Results for primary outcome(s)	16% reduction in MACE	15% reduction in MACE	(1) Dapagliflozin noninferior for MACE (2) 17% reduction in CV death/HFH	Ertugliflozin noninferior for MACE
Secondary outcomes	HFH reduced Renal composite reduced	HFH reduced Renal composite reduced	HFH reduced Renal composite reduced	HFH reduced

CV = cardiovascular, CVD = cardiovascular disease, HFH = heart failure hospitalisation, MACE = major adverse cardiovascular events.

gliflozin 10 mg, empagliflozin 25 mg or placebo with a median follow-up of 3.1 years. The two empagliflozin treatment groups were combined for analysis:

- The primary three-point MACE endpoint (cardiovascular death, nonfatal myocardial infarction and nonfatal stroke) was significantly reduced with empagliflozin compared with placebo (10.5 vs. 12.1%; HR, 0.86; 95% CI 0.74–0.99; $p = 0.04$ for superiority; Figure 5.2).
- Empagliflozin resulted in a significant reduction in cardiovascular death (HR 0.62; 95% CI 0.49–0.77; $p < 0.001$), all-cause mortality (HR 0.68; 95% CI 0.57–0.82; $p < 0.001$) and HFH, which was a secondary outcome (HR 0.65; 95% CI 0.50–0.85; $p = 0.002$) (Figure 5.3).
- Adverse events were similar between groups, but there was a significant increase in genital fungal infections in the empagliflozin group (6 vs. 2%). There was no significant difference in the occurrence of hypoglycaemia or diabetic ketoacidosis.

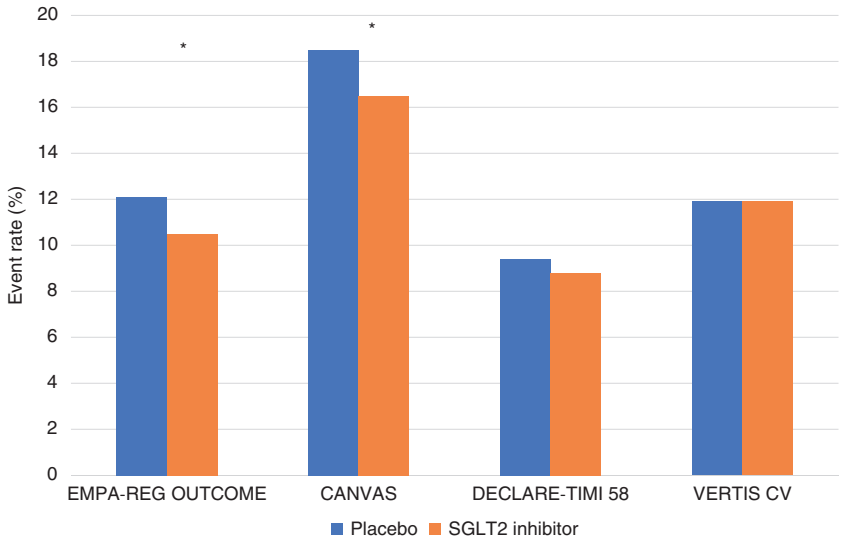


FIGURE 5.2 Major adverse cardiovascular event rates (%) from the cardiovascular outcome trials with SGLT2 inhibitors: empagliflozin (EMPA-REG OUTCOME) [3], canagliflozin (CANVAS) [2], dapagliflozin (DECLARE-TIMI 58) [1], and ertugliflozin (VERTIS CV) [4]. Statistically significant differences are marked with an asterisk.

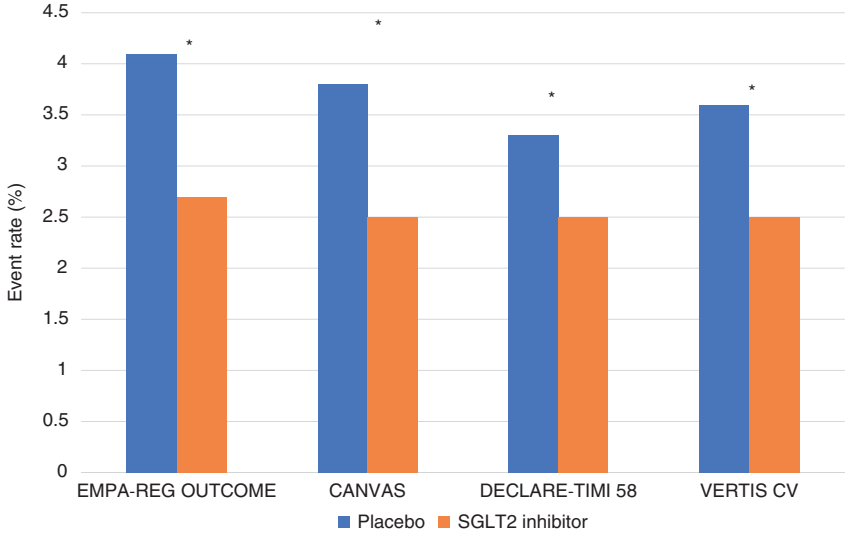


FIGURE 5.3 Hospitalisation for heart failure (HFH) event rates (%) from the cardiovascular outcome trials with SGLT2 inhibitors: empagliflozin (EMPA-REG OUTCOME) [3], canagliflozin (CANVAS) [2], dapagliflozin (DECLARE-TIMI 58) [1], and ertugliflozin (VERTIS CV) [4]. Statistically significant differences are marked with an asterisk.

The CANVAS Program The CANVAS Program consisted of CANVAS (Canagliflozin Cardiovascular Assessment Study) and CANVAS-R (CANVAS-Renal). These trials were designed to show the cardiovascular safety of canagliflozin in patients with type 2 diabetes, and the results of the two trails were amalgamated for the safety analysis [2]. CANVAS was a cardiovascular safety trial used to establish cardiovascular safety and CANVAS-R was a similar study undertaken to be jointly analysed with CANVAS to meet a post-approval cardiovascular safety commitment of regulatory authorities. The CANVAS Program included 10 142 participants with established atherosclerotic cardiovascular disease (72%) or two or more cardiovascular risk factors (28%). CANVAS randomised patients on a 1:1:1 basis to canagliflozin 100 mg, canagliflozin 300 mg or placebo whilst CANVAS-R randomised patients on a 1:1 basis to canagliflozin 100 mg or placebo with the option to increase the dose to 300 mg or matching placebo at week 13 with a median follow-up across both trials of 126.1 weeks. In the CANVAS Program:

- The primary three-point MACE endpoint was significantly reduced for canagliflozin compared with placebo (HR, 0.86; 95% CI 0.75–0.97; $p = 0.02$ for superiority).
- There was no statistically significant reduction for the individual components of the three-point MACE or total mortality, but HFH was significantly reduced (HR 0.67; 95% CI 0.52–0.87).
- Although the number of overall adverse events was lower in the canagliflozin-treated patients there was an increase in genital mycotic infections. As mentioned earlier, there was a small nonsignificant increase in diabetic ketoacidosis and an unexpected increase in amputations and lower extremity fractures in the canagliflozin group.

DECLARE-TIMI 58 DECLARE-TIMI 58 (Dapagliflozin Effect on Cardiovascular Events-Thrombolysis in Myocardial Infarction 58) included 17 160 patients with type 2 diabetes with either established cardiovascular disease (41%) or at increased cardiovascular risk, the latter representing the majority of those recruited (59% of patients) [1]. There were coprimary endpoints of three-point MACE, and the composite of cardiovascular (CV) death and HFH. Patients were randomised on a 1:1 basis to dapagliflozin 10 mg or placebo with a median follow-up of 4.2 years:

- There was a statistically significant reduction in the composite endpoint of CV death or HFH (HR 0.83; 95% CI 0.73–0.95; $p = 0.005$) owing to the reduction in HFH (HR 0.73; 95% CI 0.61–0.88).
- Dapagliflozin met the prespecified criterion for noninferiority with respect to three-point MACE, but there was no statistical difference in the outcome of three-point MACE for those treated with dapagliflozin vs. placebo (HR 0.93; 95% CI 0.84–1.03; $p = 0.17$).
- In a prespecified analysis of subjects with a prior myocardial infarction at baseline there was a significant reduction in three-point MACE with dapagliflozin (HR 0.84; 95% CI 0.72–0.99; $p = 0.039$).
- Genital fungal infections and diabetic ketoacidosis were more common with dapagliflozin, but there was no difference in the rate of fractures or amputations.

VERTIS CV VERTIS CV (Evaluation of Ertugliflozin Efficacy and Safety Cardiovascular Outcomes Trial) included 8246 patients with type 2 diabetes and established atherosclerotic cardiovascular disease. Patients were randomised on a 1:1:1 basis to ertugliflozin 5 mg, ertugliflozin 15 mg or placebo and median follow-up was three years [4]. The initial intention was to recruit 4000 subjects and to test for noninferiority of MACE, but when the EMPA-REG OUTCOME trial results were published the protocol was amended without the knowledge of any interim results to double the sample size and to include efficacy objectives for superiority with respect to cardiovascular and renal outcomes.

- Ertugliflozin was noninferior compared with placebo for three-point MACE (HR 0.97; 95% CI 0.85–1.11; $p < 0.001$ for noninferiority) but was not superior.
- There was no difference in the composite of cardiovascular death and HFH for ertugliflozin compared with placebo (HR 0.88; 95% CI 0.75–1.03, $p = 0.11$ for superiority).
- There was a reduction in HFH for ertugliflozin (HR 0.70; 95% CI 0.54–0.90), although this was not a predefined endpoint for statistical testing.

It is not clear why VERTIS-CV did not demonstrate a statistically significant reduction in MACE with ertugliflozin, as the study population was very similar to EMPA-REG OUTCOME, and significant reductions in MACE were observed in CANVAS and in subjects with a prior myocardial infraction in DECLARE-TIMI 58.

Meta-analysis of Cardiovascular Outcome Trials As each CVOT with a SGLT2 inhibitor has completed there has been a fresh meta-analysis of cardiovascular and kidney outcomes with SGLT2 inhibitors. An updated meta-analysis included six trials comprising 46 969 patients with type 2 diabetes, 66% of whom had established atherosclerotic cardiovascular disease [21]. SGLT2 inhibitors were associated with a reduced risk of cardiovascular events (HR 0.90; 95% CI 0.85–0.95; Q statistic, $p = 0.27$), HFH/CV death (HR = 0.78; 95% CI 0.73–0.84; Q statistic, $p = 0.09$) and kidney outcomes (HR, 0.62; 95% CI 0.56–0.70; Q statistic, $p = 0.09$). Outcomes for HFH were consistent across the trials (HR 0.68; 95% CI 0.61–0.76; $I^2 = 0.0\%$), but there was significant heterogeneity of associations with outcome for CV death (HR, 0.85; 95% CI 0.78–0.93; Q statistic, $p = 0.02$; $I^2 = 64.3\%$), reflecting that EMPA-REG OUTCOME had a strongly positive effect, VERTIS a lack of effect on CV death, or both. The presence or absence of atherosclerotic cardiovascular disease did not modify the association with outcomes for major adverse cardiovascular events, HFH/CV death or kidney outcomes.

Real-world Evidence of Cardiovascular Benefits Real-world evidence has been increasingly used to see if randomised control trial evidence is observed in clinical practice. CVD-REAL (Comparative Effectiveness of Cardiovascular Outcomes in New Users of SGLT2 Inhibitors), CVD-REAL 2 and CVD-REAL 3 were a series of observational cohort studies looking at the use of SGLT2 inhibitors in the real world [22–24]. CVD-REAL was a cohort study of 309 056 patients from the US and Europe with type 2 diabetes newly initiated on either SGLT2 inhibitors or other antidiabetic drugs with 154 528 in each group [22]. The groups were well matched by baseline characteristics. Those prescribed SGLT2

were on canagliflozin, dapagliflozin and empagliflozin (53, 42 and 5%, respectively). There were 215 622 patients in the US, Norway, Denmark, Sweden and the UK, of whom death occurred in 1334 (incidence rate 0.87/100 person years) and HFH or death in 1983 (incidence rate 1.38/100 person years). The use of SGLT2 inhibitors compared with other antidiabetic drugs was associated with better outcomes for HFH (HR 0.61; 95% CI 0.51–0.73; $p < 0.001$), death (HR 0.49; 95% CI 0.41–0.57; $p < 0.001$) and HFH or death (HR 0.54; 95% CI 0.48–0.60; $p < 0.001$) with no significant heterogeneity by country. Similar outcomes were observed in CVD-REAL 2 in patients from Asia-Pacific, the Middle East and North America [23].

As a part of the CVD-Real observational studies, CVD-Real Nordic used data from Denmark, Norway and Sweden of 22 830 patients with type 2 diabetes who were commenced on SGLT2 inhibitor compared with 68 490 commenced on other antidiabetic drugs matched by the use of propensity scores [25]. Compared with other antidiabetic drugs, the use of SGLT2 inhibitors was associated with a decreased risk of cardiovascular mortality (HR 0.53; 95% CI 0.40–0.71), major adverse cardiovascular events (HR 0.78; 95% CI 0.69–0.87) and hospital events for heart failure (HR 0.70; 95% 0.61–0.81; $p < 0.0001$ for all).

Renal Outcome Trials

In addition to increasing the reabsorption of glucose, SGLT2 inhibitors reduce the reabsorption of sodium in the proximal convoluted tubule. This increases the delivery of sodium to the macula densa, a process known as tubuloglomerular feedback. This in turn causes afferent vasoconstriction and decreased hyperfiltration (Figure 5.4). As

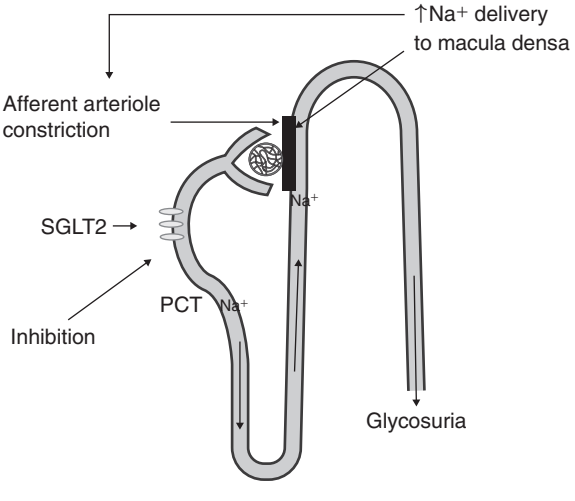


FIGURE 5.4 Tubuloglomerular feedback. Decreased delivery of sodium to the macula densa with subsequent impaired tubuloglomerular feedback and vasodilation of the afferent arteriole in early diabetic kidney disease leads to hyperfiltration. SGLT-2 inhibition reduces reabsorption of sodium increasing delivery to the macula densa. This improves tubuloglomerular feedback with vasoconstriction of the afferent arteriole and decreased hyperfiltration.

hyperfiltration is an early feature of diabetic nephropathy it was hypothesised that SGLT2 inhibitors might reduce the progression of diabetic kidney disease [26], and the CREDENCE trial was performed to test this hypothesis. The CVOTs all provided supporting evidence that SGLT2 inhibitors might be useful in the management of diabetic kidney disease, prompting studies which include nondiabetic subjects to look at this as a primary outcome.

CREDENCE In the CANVAS Program there was a 40% reduction in a secondary renal composite outcome (40% reduction in eGFR, renal replacement therapy or renal death) for canagliflozin compared with placebo (HR 0.60; 85% CI 0.47–0.77) [2].

The CREDENCE (Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation) trial included 4401 patients with type 2 diabetes and DKD comparing canagliflozin 100 mg with placebo in patients with lower levels of eGFR (30–89 ml/min/1.73 m^2) than the CVOTs for SGLT2s with a median follow-up of

TABLE 5.3 Cardiorenal outcome trials with SGLT2 inhibitors [5, 27, 31, 34]

Trial	CREDENCE [27]	DAPA-CKD [31]	SCORED [5]	EMPA-KIDNEY [34]
SGLT2 inhibitor	Canagliflozin 100 mg	Dapagliflozin 10 mg	Sotagliflozin 200–400 mg	Empagliflozin 10 mg
Comparator	Placebo	Placebo	Placebo	Placebo
Population size	4 401	4 304	10 584	6 609
Age (years)	63	62	69	64
Diabetes population (%)	100	68	100	46
Follow-up (years)	3	2	1	3
Atherosclerotic CVD (%)	50	38	20% previous myocardial infarction	27
Heart failure (%)	15	11	31	10
Results for primary outcome	30% reduction in renal composite outcome	39% reduction in renal composite outcome	26% reduction in CV death/HFH or urgent visits for heart failure	Results awaited
Secondary outcomes	MACE reduced CV death/ HFH reduced	CV death/ HFH reduced	HFH or urgent visits reduced	Results awaited

CV = cardiovascular, CVD = cardiovascular disease, HFH = heart failure hospitalisation, MACE = major adverse cardiovascular events, NA = not available.

2.6 years [27] (Table 5.3). The primary outcome was a composite of end-stage kidney disease (dialysis, transplantation or eGFR < 15 ml/min/1.73 m^2), doubling of serum creatinine and death from renal or cardiovascular disease. The trial was stopped early on the recommendation of the data and safety monitoring committee after a planned interim analysis showed significant reductions in the risk of kidney failure and cardiovascular events as follows:

- The primary composite renal outcome was significantly reduced for canagliflozin compared with the placebo (HR 0.70; 95% CI 0.59–0.82; $p = 0.00001$).
- A renal specific composite outcome excluding death from cardiovascular disease was significantly reduced (HR 0.66; 95% CI 53–0.0.81; $p < 0.001$), as was end-stage kidney disease on its own (HR 0.68; 95% CI 0.54–0.86; $p = 0.002$).
- The canagliflozin group had a lower risk of three-point MACE (HR 0.80; 95% CI 0.67–0.95; $p = 0.01$) and HFH (hazard ratio, 0.61; 95% CI 0.47–0.80; $p < 0.001$), but there was no significant difference in all-cause mortality.
- Reassuringly given the results in the CANVAS Program, there was no increase in amputations in the canagliflozin treatment group.

DAPA-CKD In DECLARE-TIMI 58 there was a reduction in the secondary renal composite outcome (sustained decrease of 40% or more in eGFR, new end-stage renal disease or death from renal or cardiovascular causes) for the dapagliflozin group compared with placebo (HR 0.76; 95% CI 0.67–0.87) [1]. Dapagliflozin has also been studied in several trials in populations with diabetes and/or renal disease. The DERIVE trial was an efficacy and safety trial of 24 weeks' duration in 321 patients with type 2 diabetes and chronic kidney disease stage 3A (eGFR 45–59 ml/min/1.73 m^2), showing that treatment with dapagliflozin resulted in greater reductions in HbA1c, body weight and systolic blood pressure compared with placebo and with no increase in adverse events [28]. DELIGHT included 461 subjects with type 2 diabetes, increased albuminuria and an eGFR of 25–75 ml/min/1.73 m^2, who were randomised 1:1:1 to dapagliflozin 10 mg, dapagliflozin 10 mg plus saxagliptin 2.5 mg or placebo [29]. At 24 weeks the urinary albumin excretion rate was reduced by dapagliflozin, −21.0% (95% CI −34.1 to −5.2; $p = 0.011$, and dapagliflozin plus sitagliptin, −38.0% (−48.2 to −25.8; $p < 0.0001$).

DIAMOND was a randomised, double-blind, placebo-controlled, cross-over mechanistic study in 53 nondiabetic participants with CKD and proteinuria (24 hour urinary excretion >500 mg and ≤3500 mg), who were stable on a renin–angiotensin system blockade [30]. Participants were assigned to receive dapagliflozin 10 mg then placebo or vice versa. The primary outcome, percentage change from baseline in proteinuria with dapagliflozin compared with placebo, was not significant at 0.9% (95% CI −16.6–22.1; $p = 0.93$), but change in measured GFR, a secondary endpoint, was significant with dapagliflozin treatment at −6.6 ml/min/1.73 m^2 (95% CI −9.0 to −4.2; $p < 0.0001$).

The definitive DAPA-CKD (Dapagliflozin and Prevention of Adverse Outcomes in Chronic Kidney Disease) trial randomly assigned the 4304 participants with an eGFR of 25–75 ml/min/1.73 m^2 and a urinary albumin creatinine ratio of 200–5000 (mg/g) to dapagliflozin 10 mg or placebo [31]. The primary outcome was a composite of a sustained decline in eGFR of at least 50%, end-stage kidney disease, or death from

renal or cardiovascular causes. The study was stopped early after a median follow-up of 2.4 years as an interim analysis showed benefits:

- The primary composite endpoint was significantly reduced for dapagliflozin compared with placebo (HR 0.61; 95% CI 0.51–0.72; $p < 0.001$).
- The renal specific composite outcome excluding death from cardiovascular disease was significantly reduced (HR 0.56; 95% CI 0.45–0.68; $p < 0.001$).
- The composite outcome of death from cardiovascular causes or HFH was significantly reduced for dapagliflozin compared with placebo (HR 0.71; 95% CI 0.55–0.92; $p = 0.009$) as was all-cause mortality (HR 0.69; 95% CI 0.53–0.88; $p = 0.004$).
- Some 32 and 33% of participants in the dapagliflozin and placebo groups, respectively, did not have type 2 diabetes and the outcomes were similar.

SCORED As described earlier, the combined SGLT1 and SGLT2 inhibitor sotagliflozin was withdrawn from the market by its sponsor before the completion and publication of two large outcome trials in patients with type 2 diabetes with established CKD and heart failure. SCORED (Effect of Sotagliflozin on Cardiovascular and Renal Events in Patients with Type 2 Diabetes and Moderate Renal Impairment Who are at Cardiovascular Risk) had 10 584 participants with diabetes and CKD, who were randomised to sotagliflozin (200 mg daily titrated to 400 mg if tolerated) or placebo on a 1:1 basis and followed for a median of 16 months [5]. Owing to COVID-19 and a withdrawal of funding, SCORED was stopped early. The primary endpoint was changed to the composite of cardiovascular death and hospitalisations or urgent visits for heart failure:

- Sotagliflozin significantly reduced the composite of cardiovascular deaths and hospitalisations or urgent visits for heart failure (HR 0.74; 95% CI 0.63–0.88; $p < 0.001$).
- Sotagliflozin significantly better reduced the original coprimary endpoint of occurrence of three-point MACE (HR 0.84; 95% CI 0.72–0.99).
- Sotagliflozin also reduced the other original coprimary endpoint of the first occurrence of death from cardiovascular causes or HFH (HR 0.77; 95% CI 0.66–0.91).
- The benefits were seen for patients across the full range of eGFR with micro- or macroalbuminuria, the effect becoming apparent within three months.

Empagliflozin EMPA-REG RENAL was an efficacy and safety trial of 24 weeks' duration in 741 patients with type 2 diabetes and CKD [32]. Empagliflozin reduced HbA1c, body weight and blood pressure in subjects with stage 2 CKD (eGFR of 60–89 ml/min/1.73 m^2) and stage 3 CKD (eGFR of 30–59 ml/min/1.73 m^2), but empagliflozin was not effective at reducing HbA1c in patients with stage 4 CKD (eGFR of 15–29 ml/min/1.73 m^2).

In EMPA-REG OUTCOME empagliflozin was associated with a significant reduction in a prespecified secondary renal endpoint defined as 'incident or worsening nephropathy', which was a composite of progression to macroalbuminuria, doubling of serum creatinine level, initiation of renal-replacement therapy or death from renal

disease (HR 0.61; 95% CI 0.53–0.70; $p < 0.001$) [33]. Further analysis of renal data from EMPA-REG OUTCOME has shown:

- Doubling of serum creatinine and the need for renal replacement was seen less for those on empagliflozin (relative risk reduction of 44% and 55% respectively).
- In the early phase of treatment (weeks baseline to week 4) there was a short-term decrease in eGFR in both dose groups compared with placebo (0.62 ± 0.04 ml/min/1.73 m^2 in the 10 mg group and 0.82 ± 0.04 ml/min/1.73 m^2 in the 25 mg group), as compared with a small increase (of 0.01 ± 0.04 ml/min/1.73 m^2) in the placebo group ($p < 0.001$).
- During longer-term treatment eGFR remained stable in the empagliflozin-treated groups compared with placebo where eGFR declined steadily (adjusted estimates of annual decreases of 0.19 ± 0.11 ml/min/1.73 m^2 in the 10 and 25 mg empagliflozin groups, as compared with a decrease of 1.67±0.13 ml/min/1.73 m^2 in the placebo group ($p < 0.001$).

EMPA-KIDNEY (The Study of Heart and Kidney Protection with Empagliflozin) recruited 6609 participants with chronic kidney disease with or without diabetes [34]. The primary endpoint for the study is a composite of time to first occurrence of kidney disease progression (defined as end-stage kidney disease, a sustained decline in eGFR to < 10 ml/min/1.73 m^2, renal death or a sustained decline of ≥40% in eGFR from randomisation) or cardiovascular death. The trial was stopped early due to clear positive efficacy following a formal interim assessment, and detailed results are expected later in 2022.

Ertugliflozin Although in VERTIS CV there was no difference in the prespecified renal composite outcome (death from renal causes, renal replacement therapy or doubling of serum creatinine) for ertugliflozin compared with placebo (HR 0.81; 95% CI 0.63–1.04), the authors argued that doubling of serum creatinine had too much influence on the statistically nonsignificant finding. They explored replacing this outcome with a sustained 40% decrease from baseline eGFR [35]:

- The composite endpoint of sustained reduction in eGFR from a baseline of 40%, end-stage renal disease or renal death occurred at a lower event rate for those treated with ertugliflozin (HR 0.66; 95% CI 0.5–0.88).
- Ertugliflozin was associated with a consistent decrease in UACR and attenuation of eGFR decline across subgroups.

Meta-analysis of Renal Outcomes A meta-analysis of four studies (EMPA REG, CANVAS, CREDENCE and DECLARE-TIMI 58) included 38 723 participants and showed that SGLT2 inhibitors substantially reduced the risk of dialysis, transplantation or death owing to kidney disease (RR 0.67; 95% CI 0.52–0.86; $p = 0.0019$). SGLT2 inhibitors reduced end-stage kidney disease (0.65; 0.53–0.81; $p < 0.0001$) and acute kidney injury (0.75; 0.66–0.85; $p < 0.0001$) [36]. There was evidence of benefit for all eGFR subgroups, including for participants with a baseline eGFR 30–45 ml/min/1.73 m^2 (RR 0.70; 95% CI 0.54–0.91; $p = 0.0080$).

Real-world Evidence of Renal Benefit The CVD-REAL 3 (Comparative Effectiveness of Cardiovascular Outcomes in New Users of SGLT2 Inhibitors) study was a multinational cohort study [24]. After propensity matching there were 35 561 episodes of SGLT2 initiation (mainly dapagliflozin 58%, empagliflozin 34% and canagliflozin 6%) with a comparator group of the same size. SGLT2 inhibitor initiation was associated with reduced eGFR decline (1.53 ml/min/1.73 m^2 per year, 95% CI 1.34–1.72; $p < 0.0001$). There was a mean follow-up of 15 months and a composite kidney endpoint (a sustained reduction in eGFR of 50% or more (confirmed by a second measurement) or end-stage kidney disease (ESKD), which was defined as an eGFR of less than 15 ml/min/1.73 m^2 (confirmed at a subsequent measurement), dialysis for 30 days or more, or kidney transplantation) was also significantly reduced in the SGLT2 treatment group (HR 0.49; 95% CI 0.35–0.67; $p < 0.0001$).

Box 5.1 Possible mechanisms of cardiovascular and/or renal protection with SGLT2 inhibitors

Reduction in cardiovascular risk factors:
- weight reduction and reduction in visceral and subcutaneous adipose tissue;
- reduction in blood pressure;
- improved glycaemic control.

Renal effects:
- reduced intraglomerular pressure;
- osmotic diuresis;
- natriuresis;
- reduced albuminuria;
- reduced interstitial oedema.

Haemodynamic effects:
- reduction in intracellular and extracellular volume;
- improved cardiac preload and afterload.

Cardiac effects:
- improved myocardial metabolism;
- reduced left ventricular mass;
- reduced interstitial fibrosis;
- reduced macrophage infiltration;
- reduced pericardial fibrosis and fat.

Effects on atherosclerosis:
- improved endothelial function and vasodilation;
- reduced oxidative stress and increasing availability of nitric oxide;
- reduced circulating markers of inflammation and fibrosis.

Heart Failure Outcome Trials

The observations from EMPA-REG OUTCOME of an early reduction in cardiovascular death and hospitalisation for heart failure with empagliflozin prompted a series of dedicated cardiovascular studies in patients with cardiovascular disease. There have been scores of small investigator-initiated, mechanistic studies trying to identify potential mechanisms of cardiovascular and/or renal benefit of SGLT2 inhibitors, and some of these potential mechanisms of benefit are described in Box 5.1.

There have also been large outcome trials funded by pharmaceutical companies in patients with heart failure with and without diabetes. In contrast to the diabetes CVOTs, where the clinical diagnosis of heart failure was made by the local clinician, these trials required accurate documentation of the ejection fraction for inclusion in the study. The first studies were in patients with heart failure and a reduced ejection fraction [37, 38] and these have been followed by studies in patients with heart failure and a preserved ejection fraction [39, 40]. These have been complemented by shorter (12–16 weeks) investigator-initiated and pharmaceutical company studies on the effects of SGLT2 inhibitors on biomarkers and quality of life in patients with heart failure, which have shown improvements in the quality of life.

DAPA-HF DAPA-HF (Dapagliflozin in Patients with Heart Failure and Reduced Ejection Fraction) randomised 4744 patients with heart failure (New York Heart Association class II, III or IV and an ejection fraction of 40% or less) to dapagliflozin 10 mg or placebo [37] (Table 5.4).

- The primary composite outcome of worsening heart failure (hospitalisation or an urgent visit resulting in intravenous therapy for heart failure) or cardiovascular death occurred significantly less in the dapagliflozin treatment group (HR 0.74; 95% CI 0.65–0.85; $p < 0.001$).
- The incidence of the secondary composite outcome of HFH or CV death was lower for dapagliflozin compared with placebo (HR 0.75; 95% CI 0.65–0.88; $p < 0.001$).
- The results in patients with diabetes were similar to those in patients without diabetes (42% of participants had diabetes).
- Adverse events of volume depletion, renal dysfunction and hypoglycaemia did not differ between treatment groups, and diabetic ketoacidosis was not increased.

DELIVER (Dapagliflozin Evaluation to Improve the LIVEs of Patients With Preserved Ejection Fraction Heart Failure) was a multinational randomised controlled trial assessing the possible benefit of dapagliflozin in patients with heart failure and a preserved ejection fraction [40]. A total of 6263 participants were enrolled and preliminary results are reported as showing a reduction in the primary composite endpoint. Full results are expected later in 2022.

The EMPEROR Trials Program The EMPEROR-Reduced (Empagliflozin Outcome Trial in Patients with Chronic Heart Failure and a Reduced Ejection Fraction) trial comprised 3730 participants with heart failure (New York Heart Association class II, III or IV heart failure and an ejection fraction of 40%) [38]. Patients were randomised to empa-

TABLE 5.4 **Heart failure outcome trials with SGLT2 inhibitors [6, 37–40]**

Trial	DAPA-HF [37]	EMPEROR-Reduced [38]	SOLOIST WHF [6]	EMPEROR-Preserved [39]	DELIVER [40]
SGLT2 inhibitor	Dapagliflozin 10 mg	Empagliflozin 10 mg	Sotagliflozin 200–400 mg	Empagliflozin 10 mg	Dapagliflozin 10 mg
Comparator	Placebo	Placebo	Placebo	Placebo	Placebo
Population size (n =)	4 744	3 730	1 222	5 988	6 263
Age (years)	66	67	69	73	72
Diabetes population (% of subjects)	42	50	100	49	45
Follow-up (months)	18	16	9	26	NA
Heart failure (% of subjects)	100	100	100	100	100
Ejection fraction (%)	31	28	35	54	54
Results for primary outcome	30% reduction in worsening heart failure or CV death	25% reduction in HFH or CV death	33% reduction in CV death/ HFH or urgent visits for heart failure	21% reduction in HFH or CV death	Results awaited
Secondary outcomes	Worsening heart failure reduced CV death reduced	Total number of hospitalisations for heart failure reduced Mean slope of change in eGFR reduced	HFH or urgent visits reduced	Total number of hospitalisations for heart failure reduced Mean slope of change in eGFR reduced	Results awaited

CV = cardiovascular, CVD = cardiovascular disease, HFH = heart failure hospitalisation, MACE = major adverse cardiovascular events, NA = not available.

gliflozin 10 mg or placebo for a median of 18 months with a primary composite endpoint of HFH or CV death:

- Empagliflozin significantly reduced the incidence of HFH and CV death (HR 0.75; 95% CI 0.65–0.86; $p < 0.001$) and the effect was consistent regardless of the presence or absence of diabetes.
- HFH was lower for empagliflozin compared with placebo (HR 0.70; 95% CI 0.58–0.85; $p < 0.001$).

- Empagliflozin slowed the decline in the estimated glomerular filtration rate compared with placebo (−0.55 vs. −2.28 ml/min/1.73 m^2; $p < 0.001$).

The EMPEROR-Preserved (Empagliflozin Outcome Trial in Patients with Chronic Heart Failure and a Preserved Ejection Fraction) trial randomised 5988 participants with heart failure and preserved ejection fraction [39]. In clinical practice, patients with heart failure and a preserved ejection fraction are treated with the same drugs as patients with heart failure and a reduced ejection fraction, but none of these treatments (ACE inhibitors or angiotensin-II receptor antagonists, beta blockers, mineralocorticoid receptor agonists, etc.) has been demonstrated to improve prognosis in this group. Patients in EMPEROR-Preserved were randomised to empagliflozin 10 mg or placebo for a median of 26 months with a primary composite endpoint of HFH or CV death:

- Empagliflozin significantly reduced the incidence of HFH and CV death (HR 0.79; 95% CI 0.69–0.90; $p < 0.001$), and the effect was consistent regardless of the presence (49%) or absence (51%) of diabetes.
- HFH was lower for empagliflozin compared with placebo (HR 0.73; 95% CI 0.61–0.88; $p < 0.001$).
- Uncomplicated genital and urinary infections and hypotension were more common in patients treated with empagliflozin.

SOLOIST-WHF In addition to the data from the SCORED study already discussed, where patients benefitted in a reduction in HFH across a range of CKD, there has also been a trial looking at the efficacy and safety of sotagliflozin in patients with unstable heart failure [6]. SOLOIST-WHF (Effect of Sotagliflozin on Cardiovascular Events in Patients with Type 2 Diabetes Post Worsening Heart Failure) randomised 1222 patients on a 1:1 basis to sotagliflozin or placebo initiated before or shortly after discharge from hospital. The trial was stopped early owing to loss of funding from the sponsor. The revised primary endpoint was the total number of deaths from cardiovascular causes and hospitalisations and urgent visits for heart failure (first and subsequent events):

- Sotagliflozin reduced the total number of deaths from cardiovascular causes and hospitalisations and urgent visits for heart failure (HR 0.67; 95% CI 0.52–0.85; $p < 0.001$).
- Sotagliflozin did not significantly reduce the rate of death from cardiovascular causes compared with placebo.

Canagliflozin and Ertugliflozin To date there have been no large heart failure outcome trials undertaken for canagliflozin or ertugliflozin, although there has been some further analysis of the data from the CANVAS Program and VERTIS CV, and the effect of canagliflozin on the quality of life of patients with heart failure is being studied in a small study.

Meta-analysis of DAPA-HF and EMPEROR-Reduced Among 8474 patients combined from DAPA-HF and EMPEROR-Reduced trials, the estimated treatment effect

was a 13% reduction in all-cause death (pooled HR 0.87; 95% CI 0.77–0.98; $p = 0.018$) and a 14% reduction in cardiovascular death (0.86; 0.76–0.98; $p = 0.027$) [41]. SGLT2 inhibition was accompanied by a 26% relative reduction in the combined risk of cardiovascular death or first hospitalisation for heart failure (0.74; 0.68–0.82; $p < 0.0001$) and by a 25% decrease in the composite of recurrent hospitalisations for heart failure or cardiovascular death (0.75; 0.68–0.84; $p < 0.0001$). The risk of the composite renal endpoint was also reduced (0.62; 0.43–0.90; $p = 0.013$). All tests for heterogeneity of effect size between trials were not significant. The pooled treatment effects showed consistent benefits for subgroups based on age, sex, diabetes, treatment with an angiotensin receptor-neprilysin inhibitor (ARNI) and baseline eGFR, but suggested treatment-by-subgroup interactions for subgroups based on New York Heart Association functional class and race.

SGLT2 Inhibitors in Type 1 Diabetes

For people with type 1 diabetes insulin is an essential therapy but, despite modern innovations in insulin treatment that are described in Chapters 8–10, many patients have suboptimal glycaemic control. Side effects of insulin treatment include weight gain and hypoglycaemia, and data from registries have shown that, just like the non-diabetic population, many people with type 1 diabetes are overweight or obese. The mode of action of SGLT2 inhibitors is independent of pancreatic beta cell function, and SGLT2 inhibitors are associated with significant weight loss when used in people with type 2 diabetes. SGLT2 inhibitors have been extensively studied as possible adjunct therapies in people with type 1 diabetes and have confirmed reductions in HbA1c and body weight in that population, but at the expense of a significant increase in the risk of diabetic ketoacidosis (Table 5.5).

Dapagliflozin in Type 1 Diabetes

Following a proof of concept phase 2 study using dapagliflozin at doses from 1 to 10 mg, the efficacy and safety of dapagliflozin 5 and 10 mg vs. placebo was studied in the phase 3 DEPICT trials. DEPICT-1 included 833 patients with type 1 diabetes and HbA1c between 7.7 and 11.0% (61–97 mmol/mol) [42]:

- The baseline HbA1c of 8.53% was significantly reduced at 24 weeks by 0.42% with dapagliflozin 5 mg and 0.45% with dapagliflozin 10 mg.
- Body weight was reduced by 2.8% (5 mg) and 3.6% (10 mg), and insulin doses were reduced by 8 units (5 mg) and 13 units (10 mg).
- Adjudicated definite diabetic ketoacidosis occurred in four patients (1%) in the 5 mg group, five patients (2%) in the 10 mg group and three (1%) in the placebo group.

DEPICT-2 compared dapagliflozin 5 mg, dapagliflozin 10 mg and placebo in 813 subjects with type 1 diabetes and HbA1c 7–5–10.5% [43]:

TABLE 5.5 **Efficacy and safety of SGLT2 inhibitors in patients with type 1 diabetes [42–47]**

Study	DEPICT-1 [42]	DEPICT-2 [43]	inTandem1 [44]	In Tandem2 [45]	inTandem3 [46]	EASE-2 [47]	EASE-3 [47]
SGLT2 inhibitor	Dapagliflozin 5 and 10 mg	Dapagliflozin 5 and 10 mg	Sotagliflozin 200 and 400 mg	Sotagliflozin 200 and 400 mg	Sotagliflozin 400 mg	Empagliflozin 10 and 25 mg	Empagliflozin 2.5, 10 and 25 mg
Comparator	Placebo	Placebo	Placebo	Placebo	Placebo	Placebo	Placebo
Number of subjects ($n =$)	833	813	793	782	1402	730	975
Study duration	24 weeks with a further 28 week extension	24 weeks with a further 28 week extension	24 weeks for HbA1c 52 weeks for HbA1c, weight	24 weeks for HbA1c 52 weeks for HbA1c, weight	24 weeks	52 weeks	26 weeks
Baseline HbA1c	8.5% (70 mmol/mol)	8.4%	7.6%	7.8%	8.2%	8.1%	8.2%
HbA1c results compared with placebo	5 mg – 0.42% 10 mg – 0.45% Less at 52 weeks	5 mg – 0.37% 10 mg – 0.42% Less at 52 weeks	200 mg – 0.36% 400 mg – 0.41% Less at 52 weeks	200 mg – 0.37% 400 mg – 0.35% Less at 52 weeks	−0.46%	10 mg 25 mg	2.5 mg 10 mg 25 mg
Weight results compared with placebo	5 mg – 3.0% 10 mg – 3.7% Sustained at 52 weeks	5 mg – 3.2% 10 mg – 3.7% Sustained at 52 weeks	200 mg – 3.14 kg 400 mg – 4.3 kg	200 mg – 2.18 kg 400 mg – 2.92 kg	-2.98 kg	10 mg – 3.2 kg 25 mg – 3.6 kg	2.5 mg – 1.8 kg 10 mg – 3.0 kg 25 mg – 3.4kg
DKA events	5 mg five patients (2%) 10 mg eight patients (3%) Placebo two patients (1%)	5 mg seven patients (3%) 10 mg six patients (2%) Placebo zero patients (0%)	200 mg nine patients (3%) 400 mg 11 patients (4%) Placebo one patient (0.4%)	200 mg six patients (2%) 400 mg nne patients (3%) Placebo zero patients (0%)	400 mg 21 patients (3%) Placebo four patients (0.6%)	Pooled with EASE 3	2.5 mg two patients (0.8%) 10 mg 21 patients (4%) 25 mg 16 patients (3%) Placebo nine patients (1%)

- The baseline Hba1c of 8.43% was significantly reduced at 24 weeks by 0.37% with dapagliflozin 5 mg and 0.42% with dapagliflozin 10 mg.
- Total daily insulin dose and body weight were reduced in the dapagliflozin groups.
- Adjudicated definite diabetic ketoacidosis occurred in seven patients (2.6%) in the 5 mg group, six patients (2.2%) in the 10 mg group, and none (0%) in the placebo group.

Both DEPICT studies were followed to 52 weeks, and the reductions in HbA1c were less marked at 52 weeks. Pooled analysis of continuous glucose monitoring data from both DEPICT studies showed an improved time spent in range without an increase in the range indicating hypoglycaemia.

Sotagliflozin in Type 1 Diabetes

Following a phase 2, 12 week dose ranging study of sotagliflozin 75, 200 and 400 mg vs. placebo in people with type 1 diabetes, the efficacy and safety of sotagliflozin were studied in the inTandem series of phase 3 clinical trials. The inTandem1 study was performed in North America and compared sotagliflozin 200 mg, sotagliflozin 400 mg and placebo in 793 adults with type 1 diabetes [44]. The inTandem2 study was performed in Europe and compared sotagliflozin 200 mg, sotagliflozin 400 mg and placebo in 782 adults with type 1 diabetes [45]. The inTandem3 study was preformed worldwide and compared sotagliflozin 400 mg and placebo in 1402 subjects with type 1 diabetes [46]:

- HbA1c was reduced by 0.35–0.41% at 24 weeks and 0.21–0.32% at 52 weeks in the sotagliflozin groups.
- Body weight, insulin dose and systolic blood pressure were reduced in patients receiving sotagliflozin.
- Confirmed diabetic ketoacidosis was increased when sotagliflozin was added to insulin compared with insulin alone.

Efficacy and Safety of Other SGLT2 Inhibitors in Type 1 Diabetes

The EASE (Empagliflozin as Adjunctive to Insulin Therapy) programme included two double-blind, placebo-controlled phase 3 trials of empagliflozin in people with type 1 diabetes [47]. EASE-2 studied empagliflozin 10 or 25 mg, or placebo in 730 patients with 52 weeks of treatment, and EASE-3 studied empagliflozin 2.5, 10 or 25 mg or placebo in 975 patients with 26 weeks of treatment. Similar to the studies with dapagliflozin and sotagliflozin, patients in the empagliflozin groups had reductions in HbA1c, body weight and total daily insulin dose, and an increase in time in range.

Canagliflozin has not been extensively studied in people with type 1 diabetes; a phase 2 study of 351 patients comparing canagliflozin 10 and 25 mg was only 18 weeks in duration and demonstrated an increase in DKA [48]. There are no plans at present to study ertugliflozin in people with type 1 diabetes.

Diabetic Ketoacidosis

The incidence of SGLT2 associated DKA in patients with type 1 diabetes using adjunctive therapy is an important safety concern. A meta-analysis involving 7109 patients found that after six months the benefits on glycaemia were weakened (see also Table 5.5**)**, but the risk of DKA was if anything increased [49]. A lower incidence of DKA was observed following the implementation of an enhanced risk mitigation plan inTandem1, suggesting that the risk of DKA can be managed with patient education.

Mitigation strategies for patients with type 1 diabetes taking SGLT2 inhibitors are described in Box 5.2 [50]. The use of SGLT2 inhibitors in patients with type 1 diabetes

Box 5.2 Strategies to reduce the risk of diabetic ketoacidosis with SGLT2 inhibitors in people with type 1 diabetes.

Patient education:
- causes and symptoms of diabetic ketoacidosis (DKA);
- importance of ketone monitoring;
- use of ketone monitoring (training in testing procedure, proactive monitoring, and situations when monitoring is indicated);
- treatment protocol for addressing ketosis;
- guidance on when to seek medical attention.

Clinician education:
- criteria for patient selection;
- training and educational needs of patients;
- potential for missed DKA with euglycaemic DKA;
- STICH protocol recommended for treatment –
  - STop SGLT inhibitor treatment for a few days,
  - Insulin administration,
  - Carbohydrate consumption, and
  - Hydration with a suitable drink.

Risk communication:
- product labelling;
- medication guide;
- patient alert card;
- website;
- healthcare professional education.

Source: Adapted from [50].

remains controversial, as the reductions in HbA1c are modest and diminish at 52 weeks, whereas the risk of DKA, and possible mortality related to DKA, may be much higher in the real world outside the tightly controlled and supported environment of a clinical trial.

Regulatory Approval in Type 1 Diabetes

Based on these data dapagliflozin was approved by the EMA in Europe at a dose of 5 mg daily for use in people with type 1 diabetes. In late 2021 AstraZeneca, in agreement with the EMA, decided to remove this indication for dapagliflozin, and recommended discontinuing dapagliflozin in patients with type 1 diabetes as soon as clinically practical. Sotagliflozin was approved by the EMA for use in people with type 1 diabetes, but as mentioned above, this drug is not commercially available. In Japan, dapagliflozin and ipragliflozin are approved for use in type 1 diabetes. In contrast, in the US the FDA rejected the applications for approval of dapagliflozin and sotagliflozin in type 1 diabetes because of safety concerns about rates of diabetic ketoacidosis.

Use of SGLT2 Inhibitors in Other Diseases

DARE-19

Based on the observations and results of the diabetes cardiovascular outcome trials further detailed studies were performed in patients with chronic kidney disease and heart failure. During the COVID-19 pandemic it was observed that people with diabetes, renal disease or cardiac disease were at a high risk of morbidity and mortality with coronavirus infection, and that in addition to respiratory failure COVID-19 causes multiorgan failure, cardiovascular decompensation and acute kidney injury. DARE-19 (Dapagliflozin in Respiratory Failure in Patients with COVID-19) was an investigator-initiated trial in 1250 subjects from 95 sites in seven countries who were hospitalised with suspected coronavirus infection and had comorbidities of type 2 diabetes, hypertension, atherosclerotic cardiovascular disease, heart failure or chronic kidney disease [51]. Half of the subjects had type 2 diabetes. Subjects were randomised to dapagliflozin 10 mg or placebo for a 30 day treatment period, followed by a further 60 day observational follow-up period. DARE-19 had dual primary endpoints looking at prevention of major clinical events (time to organ failure or death) and recovery from illness:

- There were numerically fewer major clinical events in the placebo group (86 events, 14%) compared with the dapagliflozin group (70 events, 11%), but this was not statistically significant (HR 0.80; 95% CI 0.58–1.10; $p = 0.168$).
- There was no effect on the recovery from illness.

It remains uncertain if dapagliflozin might be of benefit in patients with COVID-19, and in retrospect a larger study would have been better. Most treatment recommendations recommend stopping SGLT2 inhibitors at the time of acute illness, including COVID-19, because of concerns about DKA or acute kidney injury. The

DARE-19 investigators concluded that the results did not support discontinuation of SGLT2 inhibitors in the setting of COVID-19 if patients are closely monitored.

Place of SGLT2 Inhibitors in Current and Future Practice

Type 2 Diabetes

SGLT2 inhibitors were the third new class of modern antidiabetic drugs after DPP-4 inhibitors and GLP-1 receptor agonists. DPP-4 inhibitors are likely to be displaced by SGLT2 inhibitors as these offer the advantages of greater efficacy in reducing HbA1c with secondary benefits of reductions in weight and systolic blood pressure in addition to reducing atherosclerotic events, heart failure events and the progression of renal disease.

In comparison with GLP-1 receptor agonists SGLT2 inhibitors may be slightly less effective at reducing HbA1c and weight, but they are all oral treatments, and in addition to reducing atherosclerotic events like the GLP-1 receptor agonists, they reduce heart failure events and the progression of renal disease in people with type 2 diabetes. As the mechanisms of action of SGLT2 inhibitors and GLP-1 receptor agonists are different, and the patterns of cardiac and renal benefits are different, there is a strong argument for combining the drugs for maximum cardiorenal benefit.

A large group of potential patients with type 2 diabetes where SGLT2 inhibitors could not previously be prescribed owing to licensing restrictions were those with CKD. Evidence has emerged that there are many patients who may benefit from SGLT2 inhibitors in terms of safety in this patient group but who also may benefit prognostically.

There is ongoing debate about whether SGLT2 inhibitors should displace metformin as first-line therapy in people with type 2 diabetes. In the diabetes cardiovascular outcome trials the subjects had longstanding diabetes, and cardiovascular benefits were observed regardless of whether the patient was on metformin or not. Some European cardiology guidelines now recommend SGLT2 inhibitors first line for newly diagnosed patients with type 2 diabetes and existing cardiovascular disease (see Chapter 15). An open-label, registry-based, PROBE design randomised trial from Sweden (SMARTEST) aims to compare dapagliflozin 10 mg with metformin up to 3 g daily in 4300 subjects with type 2 diabetes who are treatment naive or on one antidiabetic drug [52]. Importantly, patients with existing cardiovascular disease are excluded, and the primary endpoint is a composite of death, myocardial infarction, stroke, heart failure, diabetic nephropathy, retinopathy or foot ulcer. The trial is estimated to complete in 2025 and has the potential to elevate SGLT2 inhibitor therapy to first-line treatment for most people with type 2 diabetes.

Chronic Kidney Disease and Heart Failure

SGLT2 inhibitors have been proven to reduce the progression of CKD in people with and without diabetes, and to reduce heart failure events in people with heart failure

with and without diabetes. Licences for individual SGLT2 inhibitors are changing in the UK, EU and US to reflect the results of these trials. Dapagliflozin is approved for the treatment of heart failure and chronic kidney disease, empagliflozin is approved for the treatment of heart failure and canagliflozin is approved for the treatment of diabetic kidney disease. If future trials are positive, e.g. the renal outcome trial with empagliflozin, then its licence will change further, and if ongoing trials of SGLT2 inhibitors are positive then future licensing may include other groups of cardiological patients, e.g. patients with acute heart failure, patients with resistance heart failure or patients following an acute coronary syndrome.

Initiation of SGLT2 inhibitors for renal or cardiological reasons in patients who do not have diabetes is relatively straightforward as to date no episodes of DKA have been identified in subjects who did not have diabetes. Potential patients should still be warned about potential genital mycotic infection.

In populations of people with heart failure or chronic kidney disease up to one-third will have diabetes, and in many the diabetes will be undiagnosed. Some diabetes services run joint clinics with renal physicians, and a very small number run joint clinics with cardiology. Diabetologists can assist cardiologists and renal physicians in identifying people with diabetes using HbA1c criteria, classifying the diabetes and highlighting people on sulfonylureas or insulin who are at risk of hypoglycaemia and people with certain clinical characteristics or a high HbA1c concentration who are at risk of DKA when SGLT2 inhibitors are initiated. This can include agreed pathways of care, with assessment by diabetologists of individual patients with heart failure or chronic kidney disease as required.

Type 1 Diabetes

There is considerable interest in adjuvant therapy in addition to insulin for treating type 1 diabetes, particularly in those who are overweight and likely to have insulin resistance. Studies have demonstrated efficacy at reducing HbA1c and weight in people with type 1 diabetes but at the expense of a fourfold increase in diabetic ketoacidosis. The risk for DKA should be assessed for the individual and if there are any high-risk features such as recurrent DKA this should prompt an alternative treatment strategy.

Only dapagliflozin (at a dose of 5 mg) and sotagliflozin were given regulatory approval (by the EMA but not FDA) for the treatment of selected patients with type 1 diabetes, and as described earlier this indication has now been removed. Despite this, dapagliflozin can still be prescribed off label to people with type 1 diabetes. Given the safety concerns specifically with regards to DKA, dapagliflozin should only be used in individuals with type 1 diabetes who fulfil the criteria previously specified in the summary of product characteristics and who are attending specialist diabetes clinics with the experience and expertise to safely educate and manage these patients.

References

1. Wiviott, S.D., Bonaca, M.P., Mosenzon, O. et al., for the DECLARE-TIMI 58 investigators. (2019). Dapagliflozin and cardiovascular outcomes in type 2 diabetes. *N Engl J Med* 380: 347–357.
2. Neal, B., Perkovic, V., Mahaffey, K.W. et al., for the CANVAS Program Collaborative Group. (2017). Canagliflozin and cardiovascular and renal events in type 2 diabetes. *N Engl J Med* 377: 644–657.
3. Zinman, B., Wanner, C., Lachin, J.M. et al., for the EMPA-REG OUTCOME investigators. (2015). Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. *N Engl J Med* 373: 2117–2128.
4. Cannon, C.P., Pratley, R., Dagogo-Jack, S. et al., for the VERTIS CV Investigators. (2020). Cardiovascular outcomes with ertugliflozin in type 2 diabetes. *N Engl J Med* 383: 1425–1435.
5. Bhatt, D.L., Szarek, M., Pitt, B. et al., for the SCORED Investigators. (2021). Sotagliflozin in patients with type 2 diabetes and chronic kidney disease. *N Engl J Med* 384: 129–139.
6. Bhatt, D.L., Szarek, M., Steg, P.G. et al., for the SOLOIST-WHF Trial Investigators (2021). Sotagliflozin in patients with diabetes and recent worsening heart failure. *N Engl J Med* 384: 117–128.
7. SIGN 154 (2017 November). Pharmacological management of glycaemic control in people with type 2 diabetes. https://www.sign.ac.uk/media/1090/sign154.pdf (accessed 27 September 2021).
8. Frias, J.P., Guja, C., Hardy, E. et al. (2016). Exenatide once weekly plus dapagliflozin once daily versus exenatide or dapagliflozin alone in patients with type 2 diabetes inadequately controlled with metformin monotherapy (DURATION-8): a 28 week, multicentre, double-blind, phase 3, randomised controlled trial. *Lancet Diabetes Endocrinol* 4: 1004–1016.
9. Jabbour, S.A., Frias, J.P., Hardy, E. et al. (2018). Safety and efficacy of exenatide once weekly plus dapagliflozin once daily versus exenatide or dapagliflozin alone in patients with type 2 diabetes inadequately controlled with metformin monotherapy: 52-week results of the DURATION-8 randomized controlled trial. *Diabetes Care* 41: 2136–2146.
10. Jabbour, S.A., Frias, J.P., Ahmed, A. et al. (2020). Efficacy and safety over 2 years of exenatide plus dapagliflozin in the DURATION-8 Study: a multicenter, double-blind, phase 3, randomized controlled trial. *Diabetes Care* 43: 2528–2536.
11. Lingvay, I., Catarig, A.-M., Frias, J.P. et al. (2019). Efficacy and safety of once-weekly semaglutide versus daily canagliflozin as add-on to metformin in patients with type 2 diabetes (SUSTAIN 8): a double-blind, phase 3b, randomised controlled trial. *Lancet Diabetes Endocrinol* 7: 834–844.
12. Rodbard, H.W., Rosenstock, J., Canani, L.H. et al. (2019). Oral semaglutide versus empagliflozin in patients with type 2 diabetes uncontrolled on metformin: the PIONEER 2 trial. *Diabetes Care* 42: 2272–2281.
13. Pinto, L.C., Rados, D.V., Remonti, L.R. et al. (2015). Efficacy of SGLT2 inhibitors in glycemic control, weight loss and blood pressure reduction: a systematic review and meta-analysis. *Diabetol Metab Syndr* 7 (Suppl 1): A58.
14. Cherney, D.Z.I., Cooper, M.E., Tikkanen, I. et al. (2018). Pooled analysis of Phase III trials indicate contrasting influences of renal function on blood pressure, body weight, and HbA1c reductions with empagliflozin. *Kidney Int* 93: 231–244.
15. Li, D., Wang, T., Shen, S., Fang, Z., Dong, Y., and Tang, H. (2017). Urinary tract and genital infections in patients with type 2 diabetes treated with sodium-glucose co-transporter 2 inhibitors: a meta-analysis of randomized controlled trials. *Diabetes Obes Metab* 19: 348–355.

16. Donnan, J.R., Grandy, C.A., Chibrikov, E. et al. (2019 02). Comparative safety of the sodium glucose co-transporter 2 (SGLT2) inhibitors: a systematic review and meta-analysis. *BMJ Open* 9 (1): e022577.
17. Liu, J., Li, L., Li, S. et al. (2020). Sodium-glucose co-transporter-2 inhibitors and the risk of diabetic ketoacidosis in patients with type 2 diabetes: a systematic review and meta-analysis of randomized controlled trials. *Diabetes Obes Metab* 22: 1619–1627.
18. Ryan, P.B., Buse, J.B., Schuemie, M.J. et al. (2018). Comparative effectiveness of canagliflozin, SGLT2 inhibitors and non-SGLT2 inhibitors on the risk of hospitalization for heart failure and amputation in patients with type 2 diabetes mellitus: a real-world meta-analysis of 4 observational databases (OBSERVE-4D). *Diabetes Obes Metab* 20: 2585–2597.
19. Udell, J.A., Yuan, Z., Rush, T., Sicignano, N.M., Galitz, M., and Rosenthal, N. (2018). Cardiovascular outcomes and risks after initiation of a sodium glucose cotransporter 2 inhibitor. *Circulation* 137: 1450–1459.
20. Alba, M., Xie, J., Fung, A., and Desai, M. (2016). The effects of canagliflozin, a sodium glucose co-transporter 2 inhibitor, on mineral metabolism and bone in patients with type 2 diabetes mellitus. *Curr Med Res Opin* 32: 1375–1385.
21. McGuire, D.K., Shih, W.J., Cosentino, F. et al. (2021). Association of SGLT2 inhibitors with cardiovascular and kidney outcomes in patients with type 2 diabetes. A meta-analysis. *JAMA Cardiol* 6: 148–158.
22. Kosiborod, M., Cavender, M.A., Fu, A.Z. et al. (2017). Lower risk of heart failure and death in patients initiated on sodium-glucose cotransporter-2 inhibitors versus other glucose-lowering drugs: the CVD-REAL Study (Comparative effectiveness of cardiovascular outcomes in new users of sodium-glucose cotransporter-2 inhibitors). *Circulation* 136: 249–259.
23. Kosiborod, M., Lam, C.S.P., Kohsaka, S. et al. (2018). Cardiovascular events associated with SGLT2 inhibitors versus other glucose-lowering drugs: the CVD-REAL 2 Study. *J Am Coll Cardiol* 71: 2628–2639.
24. Heerspink, H.J.L., Karasik, A., Thuresson, M. et al. (2020). Kidney outcomes associated with the use of SGLT2 inhibitors in real-world clinical practice (CVD-REAL 3): a multinational observational cohort study. *Lancet Diabetes Endocrinol* 8: 27–35.
25. Birkeland, K.I., Jorgensen, M.E., Carstensen, B. et al. (2017). Cardiovascular mortality and morbidity in patients with type 2 diabetes following initiation of sodium-glucose co-transporter-2 inhibitors versus other glucose-lowering drugs (CVD-REAL Nordic): a multinational observational analysis. *Lancet Diabetes Endocrinol* 5: 709–717.
26. Cherney, D.Z.I., Perkins, B.A., Soleymanlou, N. et al. (2014). Renal hemodynamic effect of sodium-glucose cotransporter 2 inhibition in patients with type 1 diabetes mellitus. *Circulation* 129: 587–597.
27. Perkovic, V., Jardine, M.J., Neal, B. et al., for the CREDENCE Trial Investigators. (2019). Canagliflozin and renal outcomes in type 2 diabetes and nephropathy. *N Engl J Med* 380: 2295–2306.
28. Fioretto, P., Del Prato, S., Buse, J.B. et al. (2018). Efficacy and safety of dapagliflozin in patients with type 2 diabetes and moderate renal impairment (chronic kidney disease stage 3A): the DERIVE Study. *Diabetes Obes Metab* 20: 2532–2540.
29. Pollock, C., Stefansson, B., Reyner, D. et al. (2019). Albuminuria-lowering effect of dapagliflozin alone and in combination with saxagliptin and effect of dapagliflozin and saxagliptin on glycaemic control in patients with type 2 diabetes and chronic kidney disease (DELIGHT): a randomised, double-blind, placebo-controlled trial. *Lancet Diabetes Endocrinol* 7: 429–441.
30. Cherney, D.Z., Dekkers, C.C., Barbour, S.J. et al. (2020). Effects of the SGLT2 inhibitor dapagliflozin on proteinuria in non-diabetic patients with chronic kidney disease (DIAMOND): a randomised, double-blind, crossover trial. *Lancet Diabetes Endocrinol* 8: 582–593.

31. Heerspink, H.J.L., Stefansson, B.V., Correa-Rotter, R. et al. (2020). Dapagliflozin in patients with chronic kidney disease. *N Engl J Med* 383: 1436–1446.
32. Barnett, A.H., Mithal, A., Manassie, J. et al. (2014). Efficacy and safety of empagliflozin added to existing antidiabetes treatment in patients with type 2 diabetes and chronic kidney disease: a randomised, double-blind, placebo-controlled trial. *Lancet Diabetes Endocrinol* 2: 369–384.
33. Wanner, C., Inzucchi, S.E., Lachin, J.M. et al., for the EMPA-REG OUTCOME Investigators. (2016). Empagliflozin and progression of kidney disease in type 2 diabetes. *N Engl J Med* 375: 323–334.
34. Herrington, W.G., Preiss, D., Haynes, R. et al. (2018). The potential for improving cardiorenal outcomes by sodium-glucose co-transporter-2 inhibition in people with chronic kidney disease: a rationale for the EMPA-KIDNEY study. *Clin Kidney J* 11: 749–761.
35. Cherny, D.Z., Charbonnel, B., Cosentino, F. et al. (2021). Effects of ertugliflozin on kidney composite outcomes, renal function and albuminuria in patients with type 2 diabetes mellitus: an analysis from the randomised VERTIS CV trial. *Diabetologia* 64: 1256–1267.
36. Neuen, B.L., Young, T., Heerspink, H.J. et al. (2019). SGLT2 inhibitors for the prevention of kidney failure in patients with type 2 diabetes: a systematic review and meta-analysis. *Lancet Diabetes Endocrinol* 7: 845–854.
37. Jjv, M., Solomon, S.D., Inzucchi, S.E. et al, for the DAPA-HF Trial Committees and Investigators. (2019). Dapagliflozin in patients with heart failure and reduced ejection fraction. *N Engl J Med* 381: 1995–2008.
38. Packer, M., Anker, S.D., Butler, J. et al., for the EMPEROR-Reduced Trial Investigators. (2020). Cardiovascular and renal outcomes with empagliflozin in heart failure. *N Engl J Med* 383: 1413–1424.
39. Anker, S.D., Butler, J., Filipatos, G. et al., for the EMPEROR-Preserved Trial Investigators. Empagliflozin in heart failure with a preserved ejection fraction. *N Engl J Med* Aug 27. doi: 10.1056/NEJMoa2107038. Online ahead of print.
40. Solomon, S.D., de Boer, R.A., DeMets, D. et al. (2021). Dapagliflozin in heart failure with preserved and mildly reduced ejection fraction: rationale and design of the DELIVER trial. *Eur J Heart Fail* 23: 1217–1225.
41. Zannad, F., Ferreira, J.P., Pocock, S.J. et al. (2020). SGLT2 inhibitors in patients with heart failure with reduced ejection fraction: a meta-analysis of the EMPEROR-Reduced and DAPA-HF trials. *Lancet* 396: 819–829.
42. Dandona, P., Mathieu, C., Phillip, M. et al. (2017). Efficacy and safety of dapagliflozin in patients with inadequately controlled type 1 diabetes (DEPICT-1): 24 week results from a multicentre, double-blind, phase 3, randomised controlled trial. *Lancet Diabetes Endocrinol* 5: 864–876.
43. Mathieu, C., Dandona, P., Gillard, P. et al. (2018). Efficacy and safety of dapagliflozin in patients with inadequately controlled type 1 diabetes (the DEPICT-2 Study): 24-week results from a randomized controlled trial. *Diabetes Care* 41: 1938–1946.
44. Buse, J.B., Garg, S.K., Rosenstock, J. et al. (2018). Sotagliflozin in combination with optimized insulin therapy in adults with type 1 diabetes: the North American in Tandem1 study. *Diabetes Care* 41: 1970–1980.
45. Danne, T., Cariou, B., Banks, P. et al. (2018). HbA1c and hypoglycemia reductions at 24 and 52 weeks with sotagliflozin in combination with insulin in adults with type 1 diabetes: the European inTandem2 Study. *Diabetes Care* 41: 1981–1990.
46. Garg, S.K., Henry, R.H., Banks, P. et al. (2017). Effects of sotagliflozin added to insulin in patients with type 1 diabetes. *N Engl J Med* 377: 2337–2348.
47. Rosenstock, J., Marquard, J., Laffel, L.M. et al. (2018). Empagliflozin as adjunctive to insulin therapy in type 1 diabetes: the EASE trials. *Diabetes Care* 41: 2560–2569.

48. Henry, R.R., Thakkar, P., Tong, C., Polidori, D., and Alba, M. (2015). Efficacy and safety of canagliflozin, a sodium glucose cotransporter 2 inhibitor, as add-on to insulin in patients with type 1 diabetes. *Diabetes Care* 38: 2258–2265.
49. Rao, L., Ren, C., Luo, S., Huang, C., and Li, X. (2021). Sodium–glucose cotransporter 2 inhibitors as an add-on therapy to insulin for type 1 diabetes mellitus: meta-analysis of randomized controlled trials. *Acta Diabetologia* 58: 869–880.
50. Danne, T., Garg, S., Peters, A.L. et al. (2019). International consensus on risk management of diabetic ketoacidosis in patients with type 1 diabetes treated with sodium–glucose cotransporter (SGLT) inhibitors. *Diabetes Care* 42: 1147–1154.
51. Kosiborod, M.N., Esterline, R., Furtado, R.H.M. et al. (2021). Dapagliflozin in patients with cardiometabolic risk factors hospitalised with COVID-19 (DARE-19): a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet Diabetes Endocrinol* 9: 586–594.
52. Sundstrom, J., Kristofi, R., Ostlund, O. et al. (2021 October). A registry-based randomised trial comparing an SGLT2 inhibitor and metformin as standard treatment of early stage type 2 diabetes (SMARTEST): rationale, design and protocol. *J Diabetes Complications* 35 (10): 107996. doi: 10.1016/j.jdiacomp.2021.107996. Epub 2021 Jul 21.

CHAPTER 6

GLP-1 Receptor Agonists

Catherine Russell and John Petrie

KEY POINTS

- GLP-1 receptor agonists are highly effective antidiabetic drugs that reduce HbA1c and body weight in patients with type 2 diabetes without increasing the risk of hypoglycaemia, unless they are combined with sulfonylurea or insulin therapy.
- Meta-analysis of large cardiovascular outcome trials indicates that improved cardiovascular and renal outcomes may be a class effect.
- GLP-1 receptor agonist treatment should be considered for all patients with type 2 diabetes and established atherosclerotic cardiovascular disease.
- Gastrointestinal symptoms are transient in most but lead to discontinuation in about 5% of individuals.

Introduction

Glucagon-like peptide 1 (GLP-1) receptor agonists have revolutionised the treatment of type 2 diabetes by improving HbA1c whilst also reducing body weight without increasing the risk of hypoglycaemia. Other important effects include reductions in glucagon concentrations, decreased appetite and enhanced satiety. While early GLP-1 receptor agonists such as exenatide required twice daily subcutaneous administration, there are now several once weekly preparations available and more recently an oral preparation of semaglutide has been licensed.

Diabetes Drug Notes, First Edition. Edited by Miles Fisher, Gerard A. McKay, and Andrea Llano.

Pharmacology

Glucagon-like Peptide-1 and the Incretin Effect

Incretins are hormones secreted from the gastrointestinal tract in response to nutrient ingestion which enhance glucose-stimulated insulin secretion. In humans, glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide-1 (GLP-1) are responsible for 50–70% of total insulin secretion in response to an oral glucose load. GLP-1 is secreted by intestinal L-cells in response to meal ingestion but is also under the control of the autonomic nervous system and neurotransmitters such as gastrin-releasing peptide. In addition to stimulating insulin secretion from pancreatic beta cells, GLP-1 also inhibits glucagon secretion from alpha cells and delays gastric emptying. People with type 2 diabetes have some impairment of the incretin axis with consequent higher peak plasma glucose in response to increasing oral glucose loads, making this a useful therapeutic target [1] (see also Chapter 4).

Mechanism of Action

Pancreatic Actions Binding of GLP-1 to its receptor on pancreatic beta cells activates a heterotrimeric G-protein which promotes adenylate cyclase activity, resulting in cAMP formation which in turn results in glucose-dependent insulin secretion. GLP-1 also increases beta cell proliferation and neogenesis while inhibiting apoptosis and improves glucose sensitivity in glucose-resistant cells. Both upregulation of insulin secretion and inhibition of glucagon secretion by GLP-1 are glucose dependent and therefore, importantly, do not occur in conditions of hypoglycaemia. The circulating half-life of native GLP-1 is less than two minutes owing to its rapid degradation by DPP-4. As a continuous intravenous infusion would not be practical therapeutically, drug design has focused either on inhibition of the action of DPP-4 (Chapter 4) or stimulation of the GLP-1 receptor with agonists more resistant to degradation by DPP-4 (Figure 6.1).

Extra-pancreatic Actions GLP-1 has other actions aside from insulin secretion (Figure 6.1). Delayed gastric emptying is mediated via direct stimulation of gastric parietal cells and vagal nerve stimulation. It is usually transient but may contribute to reduced appetite and reduced postprandial blood glucose in the initial weeks of treatment in patients with type 2 diabetes.

Peripheral administration of GLP-1 receptor agonists promotes satiety, reduces energy intake and results in weight loss. This effect is mediated by GLP-1 receptors located on hypothalamic nuclei (e.g. nucleus accumbens). GLP-1 receptors located on the nodose ganglion on afferent fibres of the abdominal vagal nerves connecting to the brainstem may also play a role.

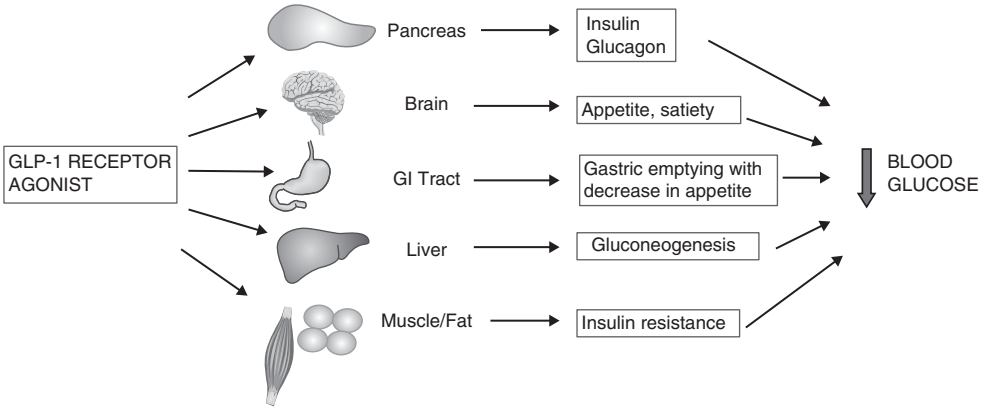


FIGURE 6.1 Mechanism of action of GLP-1 receptor agonists. The circulating half-life of native GLP-1 is less than two minutes owing to its rapid degradation by dipeptidyl peptidase 4 (DPP-4). GLP-1 receptor agonists are more resistant to degradation by DPP-4. GLP-1 has other actions aside from insulin secretion including delayed gastric emptying mediated via direct stimulation of gastric parietal cells and vagal nerve stimulation, and increased satiety through a direct action in the hypothalamus. GLP-1 receptor agonists may also decrease gluconeogenesis in the liver and peripheral insulin resistance.

Pharmacodynamics and Pharmacokinetics

The first GLP-1 receptor agonists were derived from exendin-4, a 39 amino acid molecule first isolated from the salivary secretions of the Gila monster lizard, which is native to the Arizona desert. Exendin has only 53% sequence homology to native GLP-1 but binds to the GLP-1 receptor with a similar affinity [2]. Analogues of exendin-4 include exenatide, lixisenatide and efpeglenatide. Newer GLP-1 receptor agonists such as liraglutide, dulaglutide, albiglutide and semaglutide are analogues of native GLP-1 (Box 6.1). GLP-1 receptor agonists are administered subcutaneously to prevent degradation in the stomach. The exception to this is the oral preparation of semaglutide (Rybelsus®).

Box 6.1 Derivation of GLP-1 receptor agonists

Analogues of exendin-4:

- exenatide;
- lixisenatide;
- efpeglenatide.

Analogues of native GLP-1:

- liraglutide;
- dulaglutide;
- albiglutide;
- semaglutide.

Exenatide Exenatide was the first GLP-1 receptor agonist to be licensed. It is rendered resistant to degradation by DPP-4 via a single substitution of glycine for alanine (Figure 6.2). Immediate-release exenatide reaches peak concentration in 2.1 hours and has a half-life of 2.4 hours. It requires twice daily administration. The prolonged release suspension of exenatide uses biodegradable biospheres to prolong the half-life to 96 hours and thus permits weekly injections. Both preparations are renally excreted and undergo proteolytic degradation following glomerular filtration. Exenatide should be avoided in severe renal impairment (eGFR <30 ml/min/1.73 m^2). It has not been studied in liver impairment but dose adjustment is not needed in patients with hepatic dysfunction as it is does not undergo hepatic metabolism.

Prescribing point: *Exenatide can be administered twice daily or once weekly according to patient preference. It should be avoided in severe renal impairment.*

Exenatide (Byetta®) and the prolonged release suspension of exenatide (Bydureon®) were released in 2006 and 2011, respectively, and are currently produced by AstraZeneca. They are licensed for use in combination with insulin and oral antidiabetic drugs

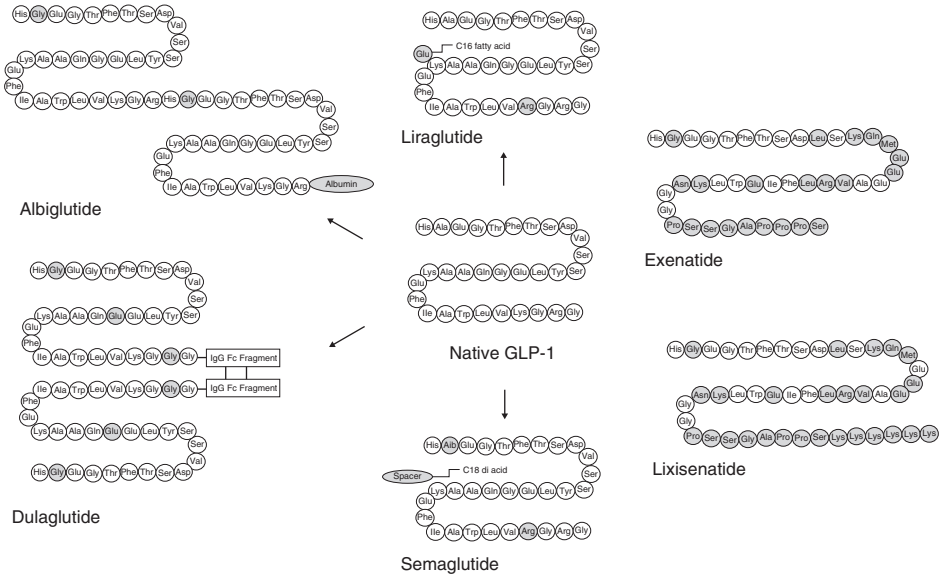


FIGURE 6.2 Structure of GLP-1 receptor agonists. GLP-1 receptor agonists can be categorised as those derived from exendin-4 (exenatide, lixisenatide) or those with more homogeneity with native GLP-1 (liraglutide, semaglutide, dulaglutide and albiglutide). Those derived from exendin-4 have a considerable number of differences in amino acid sequence. Liraglutide has the addition of long fatty acid side chains, which facilitate binding to albumin, promote stability and increase half-life. Dulaglutide is attached to the Fc fragment of IgG4 which limits renal clearance and prolong half-life. Semaglutide has a similar structure to liraglutide but has a glycine amino acid substitution and fatty acid chain which prevent its degradation by DPP-4 and increase its affinity for albumin, thereby increasing its half-life. Albiglutide comprises two GLP-1 molecules fused to albumin to promote stability and prolong half-life.

(metformin, sulfonylureas, pioglitazone and SGLT2 inhibitors). As Bydureon required reconstitution before injection it was reformulated in 2021 with biodegradable microspheres (Bydureon Bcise®). Exenatide ITCA 650, a small titanium, matchstick-sized osmotic minipump placed in the subdermis of the abdominal wall to deliver subcutaneous exenatide continuously for three to six months was in development but failed to secure FDA approval in both 2017 and 2020 [3].

Dose

- Exenatide (Byetta) 5 μg twice daily increased to 10 μg twice daily if necessary.
- Exenatide (Bydureon) 2 mg once weekly.
- Byetta 5 and 10 μg and Bydureon 2 mg are available as prefilled pens.

Lixisenatide Lixisenatide is a GLP-1 receptor agonist which has six additional lysine residues and a proline residue deleted at the *C*-terminus. It is administered subcutaneously once daily and has a half-life of three hours. It is renally metabolised and excreted. Lixisenatide is not recommended in severe or end-stage renal disease. It has not been studied in hepatic impairment but dose adjustment is not needed in patients with hepatic dysfunction as it does not undergo hepatic metabolism.

Lixisenatide (Lyxumia®) is produced by Sanofi and received marketing authorisation in 2013 in the EU and in 2016 in the US, following completion of the ELIXA cardiovascular outcome trial. It is licensed for use in combination with insulin or oral antidiabetic drugs.

Prescribing point: *Lixisenatide is administered by subcutaneous injection once daily. It is less effective at reducing HbA1c than other GLP-1 receptor agonists.*

Dose

- Lixisenatide 10 μg once daily for two weeks, then increased to 20 μg daily.
- Lixisenatide 10 and 20 μg are available as prefilled pens.
- Lixisenatide is also available in two combinations with insulin glargine (Suliqua®) as prefilled pens (Suliqua 100 units/ml plus 33 μg/ml and Suliqua 100 units/ml plus 50 μg/ml). Each dose step contains 1 unit of insulin glargine and 0.33 or 0.5 μg of lixisenatide.

Liraglutide Liraglutide is an analogue of GLP-1 and shares 97% homology with native GLP-1. The addition of long fatty acid side chains facilitates binding to albumin and promotes stability and an increased half-life. Maximum serum concentrations are reached in 8–12 hours following subcutaneous administration. It is metabolised to smaller polypeptides by DPP-4 without a specific target organ for elimination.

Liraglutide can be used in moderate to severe renal disease but should be avoided in end-stage kidney disease. Exposure of liraglutide is reduced with declining hepatic function. Liraglutide is not recommended in severe hepatic impairment.

Liraglutide is marketed by Novo Nordisk and is available as Victoza® and Saxenda®. Victoza was approved by the EMA in 2009 and in 2010 by the FDA for the treatment of type 2 diabetes in combination with insulin and oral antidiabetic drugs. Saxenda was licensed as an adjunct for weight loss by the EMA in 2015.

Prescribing point: *Liraglutide is administered subcutaneously once daily. It can be used in moderate to severe renal impairment.*

Dose

- Liraglutide (Victoza) 0.6 mg once daily increased in increments to 1.8 mg for type 2 diabetes.
- Liraglutide (Saxenda) 0.6 mg once daily increased in steps to a maximum of 3 mg in treatment of obesity.
- Victoza and Saxenda are available as prefilled pens.
- Liraglutide is also available as a combination preparation in a prefilled pen with insulin degludec (Xultophy®). Each dose step has 1 unit of insulin degludec and 0.036 mg of liraglutide.

Dulaglutide Dulaglutide is a GLP-1 receptor agonist with 90% sequence homology to native GLP-1. It is attached to the Fc fragment of IgG4 which limits renal clearance and prolongs its half-life. These modifications also reduce its immunogenic potential. Peak plasma concentrations are reached in 48 hours and it has a half-life of 4.5 days. It is degraded by general protein catabolism pathways. Dulaglutide can be used in severe renal disease but there is a lack of evidence to support use in end-stage renal disease. It can be used in hepatic impairment.

Dulaglutide (Trulicity®) is made by Eli Lilly and was approved in 2014 by the EMA and FDA.

Dose

- Dulaglutide 0.75 mg as monotherapy or 1.5 mg in combination with other antidiabetic drugs, increased in weekly increments to a maximum of 4.5 mg.
- Dulaglutide is available in prefilled pens of 0.75, 1.5, 3 and 4.5 mg doses.

Prescribing point: *Dulaglutide is administered subcutaneously once weekly. It can be used in moderate to severe renal impairment.*

Semaglutide Semaglutide is a GLP-1 receptor agonist with 94% sequence homology to native GLP-1. It is currently unique amongst GLP-1 agonists in that it is available in both subcutaneous and oral preparations. The subcutaneous preparation of semaglutide has a similar structure to liraglutide but has a glycine amino acid substitution and fatty acid chain which prevents its degradation by DPP-4 and increases its affinity for albumin, thereby increasing its half-life. Maximum concentrations are reached in one to three days following administration and it has a terminal half-life of seven days. It undergoes proteolytic degradation and is excreted via the urine and faeces.

Oral semaglutide incorporates an absorption enhancer, sodium *N*-(8-[2-hydroxybenzoyl] amino) caprylate ('SNAC'), which protects it from proteolytic degradation in the stomach and enhances absorption across the gastric mucosa. It is predominantly absorbed in the stomach and has an approximate bioavailability of 1%. Its absorption is improved following a period of fasting. Maximum concentrations are reached in 1.5 hours and terminal half-life is 145 hours. It is extensively metabolised by proteolysis and excreted in urine and faeces.

Renal and hepatic impairment have not been shown to have any clinically significant effects on either oral or subcutaneous semaglutide.

Semaglutide was developed by Novo Nordisk and is available for administration once weekly as a subcutaneous injection (Ozempic®) or daily as an oral tablet (Rybelsus®). Ozempic was approved by the FDA in 2017 and by the EMA in 2018 at doses up to 1 mg weekly. Semaglutide 2 mg weekly has been approved by the EMA and FDA but is not yet available for clinical use. The oral preparation of semaglutide was approved in the US in 2019 and in Europe in 2020.

Prescribing point: *Oral semaglutide should be taken after six hours of fasting in the absence of food or other medications to maximise its absorption.*

Dose

- Semaglutide (Ozempic) 0.25 mg subcutaneously once weekly, increased in increments to maximum of 1 mg.
- Semaglutide is available in prefilled pens of 0.25, 0.5 and 1 mg.
- Semaglutide (Rybelsus) 3 mg once daily orally increased to 7 and 14 mg in monthly intervals.

Other GLP-1 Receptor Agonists There are several other GLP-1 receptor agonists which have previously been approved or are available in other countries. Albiglutide shares 95% homology with native GLP-1 and comprises two GLP-1 molecules fused to albumin to promote stability. The half-life of albiglutide is estimated at seven days and it is metabolised by proteolytic enzymes. Albiglutide was withdrawn from the market on commercial (rather than safety or efficacy) grounds in 2018.

A further once weekly GLP-1 receptor agonist, efpeglenatide, was under development by Sanofi as a once weekly injection, but development was halted for commercial reasons. It has one amino acid modification from native exendin with half-life prolonged by conjugation of this residue to an IgG4 Fc fragment (in phase 2 trials it has been successfully administered with monthly rather than weekly dosing) [4].

Taspoglutide was a daily GLP-1 receptor agonist but phase 3 development was halted owing to injection site, gastrointestinal and hypersensitivity reactions.

Polyethylene glycol loxenatide (PEX168) is a once weekly GLP-1 receptor agonist like exendin-4 with several amino acid substitutions and the addition of polyethylene glycol. Two small phase 3 studies demonstrated efficacy in HbA1c and weight lowering as monotherapy and in combination with metformin [5, 6]. It is available in China but as no large-scale cardiovascular safety trials have been commissioned it is unlikely to reach European or US markets.

Glycaemic Efficacy and Effect on Weight

GLP-1 receptor agonists are described as highly effective drugs at lowering blood glucose, with associated weight loss. Relative glycaemic and weight-lowering efficacy are best demonstrated through well-designed and -conducted phase 3 clinical studies using various antidiabetic drugs as comparators with prespecified HbA1c as the primary outcome. CVOTs do not have these primary endpoints and the other drugs used along with the antidiabetic drug under investigation will contribute to achieving the target HbA1c in both the active and placebo groups.

Comparisons within Class

Trials comparing different GLP-1 receptor agonists against others in the class are summarised in Table 6.1. In general, GLP-1 receptor agonists with structural homology with the native molecule have greater glucose-lowering efficacy than those based on exendin-4, but this may be related to duration of action rather than amino acid sequence per se [7–22].

TABLE 6.1 **Summary of head-to-head trials comparing GLP-1 receptor agonists**

Trial, number of subjects (n)	Duration (weeks)	GLP-1 receptor agonist	Comparator(s)	HbA1c reduction	Body weight reduction
LEAD-6 [8] $n = 464$	26	Liraglutide 1.8 mg once daily	Exenatide 10 μg twice daily	<7.0%: 54 vs. 43% ($p = 0.0015$)	Similar (≈ – 3kg) in each group
DURATION-1 [9] $n = 295$	30	Exenatide extended release 2 mg once weekly	Exenatide 10 μg twice daily	1.9 vs. 1.5% (noninferior)	3.7kg vs. 3.6kg ($p = 0.89$)
DURATION-5 [10] $n = 252$	24	Exenatide extended release 2 mg once weekly	Exenatide 10 μg twice daily	1.6 vs. 0.9% ($p < 0.0001$)	2.3kg vs. 1.4kg ($p < 0.05$)
DURATION-6 [11] $n = 911$	26	Exenatide extended release 2 mg once weekly	Liraglutide 1.8 mg once daily	1.28 vs. 1.48% ($p = 0.02$)	2.68 vs. 3.57 kg ($p = 0.0005$)
GETGOAL-X [12] $n = 634$	24	Lixisenatide 20 μg once daily	Exenatide 10 μg twice daily	0.79 vs. 0.96% (noninferior)	2.96 vs. 3.98kg (noninferior)
Nauck et al. [13] $n = 404$	26	Liraglutide 1.8 mg once daily.	Lixisenatide 20 μg once daily	1.8 vs. 1.2% ($p < 0.0001$)	4.3 vs. 3.7 kg ($p = 0.23$)

(*Continued*)

TABLE 6.1 (*Continued*)

Trial, number of subjects (*n*)	Duration (weeks)	GLP-1 receptor agonist	Comparator(s)	HbA1c reduction	Body weight reduction
AWARD-1 [14] $n = 978$	52	Dulaglutide 1.5 mg Dulaglutide 0.75 mg once weekly	Exenatide 10 μg twice daily and placebo	<7.0%: 78 and 66 vs. 52 vs. 43% (both doses Dulaglutide vs. exenatide and placebo ($p < 0.001$)	–1.3kg, +0.2kg, –1.07kg, +1.2kg ($p = <0.001$, $p = 0.01$ and $p < 0.001$ vs. placebo respectively) (dulaglutide 1.5 mg vs. exenatide $p = 0.474$) (significant weight gain for dulaglutide 0.75 mg vs. exenatide $p < 0.001$)
AWARD-6 [15] $n = 599$	26	Dulaglutide 1.5 mg once weekly[2]	Liraglutide 1.8 mg once daily	1.42 vs. 1.36% (noninferior)	3.6 vs. 2.9 kg ($p = 0.011$)
SUSTAIN-3 [16] $n = 813$	56	Semaglutide 1.0 mg once weekly[3]	Exenatide extended release 2 mg once weekly	1.5 vs. 0.9% ($p < 0.0001$)	5.6 vs. 1.9 kg ($p < 0.0001$)
SUSTAIN-7 [17] $n = 1201$	40	Semaglutide 0.5 mg once weekly Semaglutide 1.0 mg once weekly	Dulaglutide 0.75 mg Dulaglutide 1.5 mg once weekly	1.5 vs. 1.1% ($p < 0.0001$) 1.8 vs. 1.4% ($p < 0.0001$)	4.6 kg vs. 2.3 kg ($p < 0.0001$) 6.5 kg vs. 3.0 kg ($p < 0.0001$)
SUSTAIN-10 [18] $n = 577$	30	Semaglutide 1.0 mg once weekly	Liraglutide 1.2 mg once daily	1.7 vs. 1.0% ($p < 0.0001$)	5.8 kg vs. 1.9 kg (p < 0.0001)
PIONEER-4 [19] $n = 711$	52	Oral semaglutide up to 14 mg once daily	Liraglutide 1.8 mg once daily	1.3 vs. 1.1% ($p < 0.0001$)	4.4 vs. 3.1 kg ($p = 0.0003$)
PIONEER-9 [20] (Japan) $n = 243$	26	Oral semaglutide 14 mg once daily	Liraglutide 0.9 mg once daily	<7.0%: 81 vs. 53% ($p = 0.0152$)	–2.4 vs. 0 kg (p < 0.0001)

(*Continued*)

TABLE 6.1 (*Continued*)

Trial, number of subjects (*n*)	Duration (weeks)	GLP-1 receptor agonist	Comparator(s)	HbA1c reduction	Body weight reduction
PIONEER-10 [21] (Japan) $n = 458$	52	Oral semaglutide 14 mg once daily	Dulaglutide 0.75 mg	<7.0%: 71 vs. 51% ($p = 0.0016$)	–1.6 kg vs. +1 kg ($p < 0.001$)
SUSTAIN FORTE [22] $n = 961$	40	Semaglutide 2.0 mg once weekly	Semaglutide 1.0 mg once weekly	2.2 vs. 1.9% ($p = 0.0003$)	–6.9 kg vs. 6.0 kg ($p = 0.015$)

Source: Based on [8–22].

Comparisons with Other Antidiabetic Drugs

DPP-4 Inhibitors Sitagliptin 100 mg daily has been compared with lixisenatide 20 μg once daily, exenatide 2 mg once weekly, liraglutide 1.2 and 1.8 mg per day, albiglutide 50 mg once weekly, dulaglutide 0.75 and 1.5 mg per week, semaglutide 0.5 and 1.0 mg per week and oral semaglutide 7 and 14 mg per day in phase 3 trials (aimed primarily at establishing market position [23]).

- All GLP-1 receptor agonists showed a statistically significant greater reduction in HbA1c compared with sitagliptin 100 mg except for lixisenatide and (low-dose) oral semaglutide 3 mg once daily.
- All GLP-1 receptor agonists also showed greater weight reduction except for (low-dose) oral semaglutide 3 mg, once weekly dulaglutide 0.75 mg and albiglutide 50 mg.

SGLT2 Inhibitors The PIONEER-2 trial compared oral semaglutide 14 mg and empagliflozin 25 mg in participants with uncontrolled type 2 diabetes on metformin monotherapy [24].

- The mean reduction in HbA1c at 26 weeks was 1.3% in the semaglutide group vs. 0.9% for empagliflozin ($p < 0.0001$) at 26 weeks and was maintained at 52 weeks.
- By 52 weeks there was a marginally significantly greater reduction in body weight with oral semaglutide vs. empagliflozin (−4.7 vs. −3.8 kg, $p = 0.0114$).

Other trials comparing GLP-1 receptor agonist with SGLT2 inhibitors are described in Chapter 5.

Insulin A meta-analysis compared the results of 19 'head-to-head' studies on the efficacy of short- and long-acting GLP-1 receptor agonists vs. insulin treatment [25]. Participants were also treated with oral antidiabetic drugs. Sixteen studies compared

GLP-1 receptor agonists and basal insulin, seven of which involved the short-acting twice daily exenatide, while the rest compared the long-acting GLP-1 receptor agonists albiglutide, dulaglutide, exenatide once weekly and liraglutide. Three studies compared GLP-1 receptor agonists (albiglutide, exenatide twice daily and liraglutide) with a basal bolus regimen.

- Exenatide twice daily showed no significant difference in mean HbA1c compared with treatment with insulin.
- Overall, long-acting GLP-1 receptor agonists showed a significantly greater reduction in mean HbA1c compared with insulin of 0.17% ($p < 0.0001$).
- Exenatide twice daily achieved a greater difference in weight vs. insulin treatment than its longer-acting counterparts, with differences of −5.1 vs. −3.3 kg, respectively ($p < 0.0001$). The overall reduction compared with insulin was −3.7 kg ($p < 0.0001$).

Other Antidiabetic Drugs There have been few studies comparing sulfonylureas with GLP-1 receptor agonists. Metformin was often used as a 'foundational' drug for participants with type 2 diabetes in drug trials and therefore head-to-head data are unavailable. The HARMONY-3 study compared albiglutide with sitagliptin, glimepiride and placebo in participants taking metformin [26].

- The mean difference in HbA1c between those assigned to albiglutide compared with glimepiride was −0.3% ($p = 0.0033$). Weight was reduced by 1.21 kg with albiglutide but increased by 1.17 kg with glimepiride ($p < 0.0001$).

As described in Chapters 3 and 4, the GRADE study compared the addition of glimepiride, sitagliptin, liraglutide or basal insulin in 5047 patients with type 2 diabetes treated with metformin with favourable outcomes for liraglutide compared with other treatments in terms of percentage at target for HbA1c and number of cardiac events [27].

Efficacy of Combinations of GLP-1 Receptor Agonists with Insulin

Combinations of long-acting insulin analogues and GLP-1 receptor agonists provide convenient once daily injection and are suitable for use in many patients who would previously have required basal bolus regimens (i.e. four injections per day).

As described above, Xultophy is a fixed-ratio combination of insulin degludec and liraglutide. Dosing ranges from 10 to 50 dose steps in increments of 1 unit of insulin degludec and 0.036 mg of liraglutide such that 50 dose steps contains 50 units of long-acting insulin and 1.8 mg of liraglutide (the highest dose licensed for the treatment of diabetes). It is provided with support materials that encourage up- and down-titration by 2 units according to three day average fasting blood glucose. DUAL VII compared the efficacy and safety of insulin degludec/liraglutide with basal bolus insulin in 506 insulin-treated people with type 2 diabetes in a multicentre, randomised, open-label trial [28].

- Mean HbA1c decreased from 8.2% (66 mmol/mol) at baseline to 6.7% (50 mmol/mol) at 26 weeks with insulin degludec/liraglutide and from 8.2% (67 mmol/mol) to 6.7% (50 mmol/mol) with basal bolus ($p < 0.0001$ for noninferiority).
- Symptomatic hypoglycaemia was much lower with insulin degludec/liraglutide than with basal bolus (19.8 vs. 52.6%) with a estimated risk ratio of 0.39 (95% CI 0.29–0.51; $p < 0.0001$).
- There was a reduction in mean body weight of 0.9 kg with insulin degludec/liraglutide and an increase with basal bolus of 2.6 kg (estimated treatment difference, ETD, −3.6 kg; 95% CI −4.2 to −2.9; $p < 0.0001$).
- Total daily insulin dose increased to a mean of 40 units with insulin degludec/liraglutide and 84 units with basal-bolus (ETD −44.5 units; 95% CI −48.3 to −40.7; $p < 0.0001$).

Suliqua is a fixed-ratio combination of insulin glargine and lixisenatide delivered via a single daily injection. The Lixi-Lan L trial compared fixed-ratio combination insulin glargine/lixisenatide with insulin glargine in 736 participants with type 2 diabetes with inadequate control on basal insulin plus up to two oral antidiabetic drugs [29]. Insulin glargine/lixisenatide was administered via two pens: either a ratio of 2 units of insulin glargine to 1 μg of lixisenatide (pen A) or a ratio of 3 units of insulin glargine to 1 μg of lixisenatide (pen B). This allowed for delivery of insulin glargine over a range of 10–60 units/day while ensuring that the lixisenatide dose did not exceed the recommended dose of 20 μg/day.

- HbA1c reduction was greater with insulin glargine/lixisenatide than with glargine (−1.1 vs. −0.6%, $p < 0.0001$), with a final mean HbA1c of 6.9% (52 mmol/mol) compared with 7.5% (58 mmol/mol) for insulin glargine.
- Mean body weight decreased by 0.7 kg with the iGlarLixi group and increased by 0.7 kg in the insulin glargine group (1.4 kg difference, $p < 0.0001$).
- Hypoglycaemia was comparable between groups.

In clinical practice Xultophy has gained greater market share because of its greater efficacy in reducing HbA1c combined with simplicity of use. Suliqua has been less used as it appears to be less effective than Xultophy at reducing HbA1c, reflecting the fact that lixisenatide is less effective than liraglutide at reducing HbA1c in head-to-head trials [13].

Other Effects of GLP-1 Receptor Agonists

Cardiovascular System As detailed later in this chapter, most GLP-1 receptor agonists are cardioprotective, and all others have demonstrated cardiovascular safety. All are associated with a persistent increase in heart rate via activation of the sinoatrial node (in which GLP-1 receptors are present) and enhanced sympathetic nervous system activity. In long-term use, systolic blood pressure is reduced, and this may be independent of weight loss. Mechanisms may include natriuresis, vasodilatation and possibly other as yet unidentified neurohormonal mechanisms.

Lipids Treatment with GLP-1 receptor agonists reduces total and LDL cholesterol as well as postprandial hypertriglyceridaemia and levels of free fatty acids. In addition to improvements in lipoprotein metabolism secondary to weight loss, GLP-1 receptor agonism also directly reduces intestinal lipoprotein synthesis (i.e. fewer triglycerides and chylomicrons reach the circulation after oral lipid administration).

Side Effects and Safety

Side Effects

The main adverse events associated with GLP-1 receptor agonists are in the gastrointestinal system: nausea, vomiting and diarrhoea (Box 6.2). Nausea and vomiting are probably related to both delayed gastric emptying and central (hypothalamic) effects but the mechanism for diarrhoea is less well understood. Gastrointestinal side effects are dose related, and usually mild to moderate. They can be minimised by slow and programmed dose escalation over a period of weeks, diminishing in most cases over time.

Box 6.2 Side effects and safety of GLP-1 receptor agonists

- Predictable – gastrointestinal (nausea, vomiting, diarrhoea).
- Thyroid cancer – no concerns shown in clinical trials and practice.
- Pancreatitis/pancreatic cancer – no concerns in clinical trials and practice.
- Cholelithiasis – there is an increased risk during treatment.

Safety

Thyroid Cancer Concerns were raised during the development of GLP-1 receptor agonists regarding the possibility of increased rates of medullary thyroid cancer after it was discovered that mice and rats exposed to a once daily injection of liraglutide developed an increased rate of C-cell abnormalities with some developing C-cell carcinomas. Further experiments with cell lines originating from rodent C-cells showed increased production of cAMP and stimulation of calcitonin production in response to exposure to exenatide and liraglutide. These responses could not be replicated using human cell lines and experience with long-term clinical use of liraglutide and other agents has not supported an increase in calcitonin levels [30]. It is thought that a difference in GLP-1 receptor expression between rodent and human C-cells may account for the difference in response to GLP-1 exposure. Caution is recommended in treating individuals at high risk of medullary thyroid cancers (family or personal history of multi-

ple endocrine neoplasia or familial medullary thyroid carcinoma) with incretin therapies.

Pancreatitis and Pancreatic Cancer Concerns around GLP-1 receptor agonist use and pancreatitis arose after case reports of patients developing acute pancreatitis. Studies in rodents also reported that exposure to GLP-1 was associated with proliferation of pancreatic duct glands and acinar cells, potentially exacerbating chronic pancreatitis, and resulting in pancreatic intraepithelial neoplasia. After considerable controversy, available data were formally reviewed by the FDA and EMA, who found no evidence of a causal link between incretin therapies and pancreatitis or pancreatic cancer [31]. In addition, meta-analysis of long-term exposure in cardiovascular outcome trials has no shown clear association [32].

Cholelithiasis Treatment with GLP-1 receptor agonists is associated with an increased risk of cholelithiasis. The proposed mechanisms include rapid weight loss, altered bile acid production and secretion, and inhibition of gallbladder contraction/emptying leading to sludge and gallstone formation. In addition, exenatide has been shown to reduce cholecystokinin-induced gallbladder emptying compared with placebo in healthy subjects [33].

Outcome Trials

Cardiovascular Outcome Trials

Since 2008, the FDA has required pharmaceutical companies to conduct large-scale, double-blind, randomised, CVOTs to assess the effects of new antidiabetic drugs on rates of MACE, a composite endpoint of cardiovascular death, nonfatal myocardial infarction or nonfatal stroke (see Chapter 1). As these trials compare the investigational agent with 'placebo plus standard of care' and use a 'treat-to-target' strategy, they are not designed to assess the efficacy of GLP-1 receptor agonists on HbA1c and weight reduction and do not allow comparison between drugs; differences in HbA1c or weight reduction between trials of different drugs more reflect how well the trial protocol was implemented (i.e. how rigorously these targets were pursued).

ELIXA ELIXA (Evaluation of Lixisenatide in Acute Coronary Syndrome) was the first completed CVOT with a GLP-1 receptor agonist and was carried out to assess the effects of lixisenatide vs. placebo (1:1) on cardiovascular morbidity and mortality in 6068 patients with type 2 diabetes at high cardiovascular risk [34] (Table 6.2). It included only participants who had recently had a cardiovascular event (an acute coronary syndrome in the previous 180 days) and was a multicentre, randomised, double-blind, placebo-controlled trial. The primary endpoint was an extended version of MACE that included hospitalisation for unstable angina, sometimes termed 'MACE plus'. Over a mean follow-up of 25 months, 96% of participants completed

TABLE 6.2 **Cardiovascular outcome trials with GLP-1 receptor agonists**

Trial	ELIXA [34]	LEADER [35]	SUSTAIN-6 [36]	EXSCEL [39]	REWIND [40]	Harmony Outcomes [41]	PIONEER 6 [42]	AMPLITUDE-O [44]
GLP-1 receptor agonist	Lixisenatide 20 ug	Liragutide 1.8 mg	Semaglutide 0.5 mg and 1.0 mg	Exenatide extended release 2 mg	Dulaglutide 1.5 mg	Albiglutide 30–50 mg	Oral semaglutide 14 mg	Efpeglenatide 4 and 6 mg
Comparator	Placebo	Placebo	Placebo	Placebo	Placebo	Placebo	Placebo	Placebo
Population size	6 068	9 340	3 297	14 752	9 901	9 463	3 183	4 076
Age (years)	60	63	65	62	66	64	66	64
Duration of diabetes (years)	9	13	14	13	57% over 10 years	14	15	16
Follow-up (years)	2	4	2	3	5	4	1	2
Atherosclerotic CVD (%)	100	81	59	73	31	100	85	90
Heart failure (%)	22	13	24	16	9	20	12	18
Results for primary outcome(s)	Lixisenatide noninferior for MACE plus hospitalisation for unstable angina	13% reduction in MACE	26% reduction in MACE	Exenatide noninferior for MACE	22% reduction in MACE	22% reduction in MACE	Oral semaglutide noninferior for MACE	27% reduction in MACE
Renal outcomes	Reduction in new-onset macroalbuminuria	Reduction in composite renal outcome including macroalbuminuria	Reduction in composite renal outcome including macroalbuminuria	Reduction in composite renal outcome including macroalbuminuria	Reduction in composite renal outcome including macroalbuminuria	NA	NA	Reduction in composite renal outcome including macroalbuminuria

CV = cardiovascular, CVD = cardiovascular disease, HFH = heart failure hospitalisation, MACE = major adverse cardiovascular events.
Source: Based on [34, 36, 39–42, 44].

the study with similar study drug discontinuation rates in both groups. Lixisenatide was well tolerated with 2591 of 3031 patients (85%) randomised to active treatment taking the maximum dose (20 μg/day) at the time of their last study visit. Mean systolic blood pressure was lower in the lixisenatide group vs. placebo by 0.8 mmHg (95% CI 1.3–0.3; $p = 0.001$).

- Lixisenatide was noninferior to placebo with regards to the extended MACE primary outcome which occurred in 406 patients (13.4%) randomised to lixisenatide group vs. 399 (13.2%) allocated to placebo (HR 1.02; 95% CI 0.89–1.17; $p < 0.001$ for noninferiority, $p = 0.81$ for superiority). Thus, cardiovascular safety was demonstrated but there was no evidence of cardiovascular benefit.
- Lixisenatide was noted to be associated with reduced progression of urinary albumin excretion compared with placebo.

Adverse events causing permanent discontinuation of the study drug occurred in 347 patients (11%) in the lixisenatide group and in 217 (7%) in the placebo group ($p < 0.001$). The most frequent adverse effects were gastrointestinal, affecting 149 patients (5%) in the lixisenatide group vs. 37 (1%) in the placebo group ($p < 0.001$). There was no excess of pancreatitis or pancreatic cancer which occurred respectively in 8 vs. 5 and 9 vs. 3 participants randomised to lixisenatide vs. placebo.

LEADER LEADER (Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results) was a multicentre, double-blind CVOT carried out to assess the long-term effects of liraglutide vs. placebo and standard of care on cardiovascular outcomes (MACE) and other clinically important events in 9340 people with type 2 diabetes [35]. It targeted a high-risk (although lower risk than ELIXA) population, either aged over 50 years with mean HbA1c over 7.0% and at least one preexisting cardiovascular condition or aged over 60 years with no history of cardiovascular disease but at least one of the following cardiovascular risk factors: microalbuminuria/proteinuria, hypertension and left ventricular hypertrophy, left ventricular systolic or diastolic dysfunction, or low ankle brachial index. Ultimately 81% were in the group that had established cardiovascular disease. The median daily dose of liraglutide was 1.78 mg and the median follow-up was 3.8 years.

- LEADER was the first CVOT with a GLP-1 receptor agonist to demonstrate a reduction in the rate of MACE, with 608 MACE events in 4668 participants randomised to liraglutide (13.0%) and 694 in 4672 allocated to placebo (14.9%) (HR 0.87; 95% CI 0.78–0.97; $p < 0.001$ for noninferiority, $p = 0.01$ for superiority).
- There were also fewer deaths from cardiovascular causes with 219 (4.7%) with liraglutide vs. 278 (6.0%) with placebo (HR 0.78; 95% CI 0.66–0.93; $p = 0.007$) and fewer deaths from any cause with 381 (8.2%) vs. 447 (9.6%) (HR, 0.85; 95% CI 0.74–0.97; $p = 0.02$) with liraglutide vs. placebo.
- Systolic blood pressure was 1.2 mmHg (95% CI 1.9–0.5) lower at 36 months in the liraglutide group.

As expected, the most common reason for discontinuing study medication was gastrointestinal side effects. There was a statistically significant increase in the development of acute (145 vs. 90 cases) and severe (40 vs. 31 cases) cholecystitis in the liraglutide group compared with the placebo group. There appeared to be a possible imbalance in development of pancreatic cancer with liraglutide compared with placebo (13 vs. 5, $p = 0.06$). Many of these events occurred early in the trial, before prolonged exposure to liraglutide. Acute pancreatitis affected 18 patients in the liraglutide group compared with 23 in the placebo group. Only one case of medullary thyroid cancer occurred, and this was in the placebo group.

SUSTAIN-6 SUSTAIN-6 (Trial to Evaluate Cardiovascular and Other Long-Term Outcomes in Subjects with Type 2 Diabetes) was a CVOT carried out to assess the cardiovascular safety of once weekly semaglutide (0.5 or 1.0 mg weekly) in the treatment of type 2 diabetes [36]. SUSTAIN-6 was a smaller trial than ELIXA or LEADER and was performed prior to licensing. The sample size calculation ($n = 3297$) was based on demonstrating noninferiority of semaglutide vs. placebo and standard of care with respect to MACE, and it was not formally designed to detect cardiovascular superiority. The inclusion criteria were almost identical to those of LEADER, i.e. only the younger group of participants were required to have had a previous cardiovascular event. Included participants were therefore at very similar cardiovascular risk to subjects in LEADER at baseline, with 80% having established cardiovascular disease. A total of 826 participants were randomised to semaglutide 0.5 mg, 822 to semaglutide 1.0 mg, 824 to placebo matching 0.5 mg semaglutide and 825 to placebo matching 1.0 mg semaglutide. The mean observation time was 2.1 years. Rates of discontinuation of treatment were similar across the groups.

- Cardiovascular safety was clearly demonstrated with the primary composite MACE outcome occurring in 108 of 1648 patients (6.6%) in the semaglutide groups and 146 of 1649 (8.9%) in the placebo groups (HR 0.74; 95% CI 0.58–0.95; $p < 0.001$ for noninferiority).
- In further nonprespecified testing, semaglutide was superior to placebo ($p = 0.02$) for MACE reduction and in preventing nonfatal stroke, which occurred in 27 subjects (1.6%) in the semaglutide group and 44 subjects (2.7%) in the placebo group (HR 0.61; 95% CI 0.38–0.99; $p = 0.04$).
- A prespecified secondary retinal outcome (composite of requirement for photocoagulation, treatment with intravitreal agents, vitreous haemorrhage or diabetes-related blindness) occurred in more participants allocated to semaglutide than placebo, 50 in the semaglutide group (3.0%) and 29 in the placebo group (1.8%) (HR 1.76; 95% CI 1.11–2.78; $p = 0.02$).

This unexpected finding occurred very early following randomisation, and almost exclusively in participants also on insulin therapy. It has generated considerable discussion and several subgroup analyses. In participants with no known retinopathy at baseline there was no safety signal while 83.5% (66/79) of those affected had preexisting retinopathy at baseline [36]. Of the five participants who developed diabetes-related blindness on semaglutide, all had preexisting (treated) proliferative retinopathy. On this basis, it

has been hypothesised that the increased risk of retinopathy seen with semaglutide was related to an initial rapid decline in blood glucose levels in participants at particular risk. This phenomenon, known as 'early worsening' or 'normoglycaemic re-entry' has previously been reported in type 1 diabetes, most notably in the Diabetes Control and Complications Trial [37]. SUSTAIN-6 was the only CVOT with a GLP-1 receptor agonist in which participants with advanced diabetic retinopathy were included and no upper limit of HbA1c was stipulated. In response to these data, regulators suggested caution in using semaglutide in insulin-treated patients with type 2 diabetes and requested the commissioning of further research. The FOCUS trial is currently underway with the primary objective of assessing the long-term effects of treatment with semaglutide compared with placebo on diabetic retinopathy (primary outcome at least three-step progression on the Early Treatment of Diabetic Retinopathy Study scale), with an estimated completion date of 2027 [38].

As with other GLP-1 receptor agonists, gastrointestinal adverse events were more common in the semaglutide group compared with placebo and were the most common reason for discontinuation. Acute pancreatitis and pancreatic cancer occurred in numerically fewer participants with semaglutide than placebo. There were no cases of medullary thyroid cancer.

Prescribing point: *Semaglutide should be avoided in insulin-treated patients with active diabetic eye disease.*

EXSCEL No CVOT was conducted with standard release exenatide as this was approved and introduced before the regulatory requirement for the assessment of cardiovascular safety in new antidiabetic drugs. This was not the case for the extended release once weekly formulation and EXSCEL (Exenatide Study of Cardiovascular Event Lowering) was designed as a large, double-blind, placebo-controlled CVOT designed to assess the cardiovascular safety and efficacy of extended-release exenatide compared with placebo and standard of care in 14 752 people with type 2 diabetes (1:1 randomisation) [39]. EXSCEL was the largest CVOT with a GLP-1 receptor agonists conducted to date and included adults over 60 years of age with a wide range of HbA1c (48–96 mmol/mol), 73% with a history of a previous cardiovascular event. The primary outcome was the first occurrence of any of the components of MACE. Secondary outcomes included a composite of death from cardiovascular causes or hospitalisation for heart failure, revascularisation, initiation of antidiabetic drugs other than the trial regimen and changes from baseline in HbA1c level, body weight, blood pressure and lipid levels.

EXSCEL was conducted somewhat pragmatically, for example with relatively light study monitoring after randomisation of the subjects. As a result, there was lower retention on study medication compared with other trials; premature permanent discontinuation of treatment occurred in 3164 (43%) of those randomised to exenatide and 3343 (45%) of those taking placebo. The predominant reason for discontinuation was participant decision rather than adverse effects. It should be noted that EXSCEL used the older injection device for extended release exenatide, which required suspension in a diluent prior to injection and was less easy to use than modern pre-

filled pens. Event-driven by design, EXSCEL was stopped once 1744 participants had experienced a confirmed primary outcome, which occurred after a median of 3.2 years of follow-up.

- The main results indicated cardiovascular safety (i.e. noninferiority) of exenatide LAR ($p < 0.0001$) for MACE with the primary outcome occurring in 839 participants of 7356 participants (11.4%) in the exenatide arm compared with 905 of 7396 participants (12.2%) on placebo. However, the superiority of exenatide LAR vs. placebo plus standard of care in reducing MACE was not demonstrated (HR 0.91; 95% CI 0.83–1.00; $p = 0.06$).
- There was a numerical reduction in death from any cause with 507 deaths in the exenatide group (6.9%) and 584 deaths in the placebo group (7.9%) (HR 0.86; 95% CI 0.77–0.99), but as the primary outcome was not significantly reduced, this result should be considered exploratory.

In other results, fewer participants randomised to exenatide required additional antidiabetic drugs (HR 0.67; 95% CI 0.63–0.71; $p < 0.001$), including insulin initiation (HR 0.61; 95% CI 0.54–0.68; $p < 0.001$). There was no difference between groups in the incidence of serious adverse events or events of clinical interest such as acute pancreatitis and cancers and no difference rates of severe hypoglycaemia.

REWIND REWIND (Researching Cardiovascular Events with a Weekly Incretin in Diabetes) was a randomised, double-blind CVOT carried out to assess whether adding once weekly dulaglutide to the diabetes treatment regimen of middle-aged and older participants with type 2 diabetes reduced the incidence of cardiovascular disease (MACE) compared with placebo [40]. Inclusion criteria were designed to recruit participants at lower risk of cardiovascular disease than in ELIXA, LEADER, or EXSCEL. Subjects aged 50–59 years had to have sustained a previous cardiovascular event but those over 60 years of age were eligible if they had two of a set of cardiovascular risk factors including smoking, hypertension and dyslipidaemia. There was no lower limit of HbA1c and individuals with newly diagnosed diabetes were eligible for inclusion in the trial. Secondary outcomes included a composite clinical microvascular outcome of diabetic retinopathy or renal disease, hospital admission for unstable angina, death and heart failure requiring either hospital admission or an urgent visit requiring therapy.

A total of 9901 patients were randomised (1:1) and median follow-up was 5.4 years. Loss to follow-up was low with primary composite outcome status known in 9610 (97%) participants. Compared with EXSCEL there was reasonable retention on study medication with 3621 (73%) assigned to dulaglutide and 3520 (71%) assigned to placebo taking the study drug at the last visit and good tolerability with 451 (9%) participants assigned to dulaglutide and 310 (6%) assigned to placebo permanently discontinuing the study drug owing to adverse events.

- The primary MACE outcome was significantly reduced by dulaglutide, occurring in 594 (12.0%) participants assigned to dulaglutide and 663 (13.4%) participants assigned to placebo (HR 0.88; 95% CI 0.79–0.99; $p = 0.026$).

- There was a significant reduction in stroke (HR 0.76; 0.62–0.94; $p = 0.010$), but no significant differences were observed in secondary outcomes of cardiovascular death (HR 0.91; 95% CI 0.78–1.06; $p = 0.21$) or myocardial infarction (HR 0.96; 0.79–1.15; $p = 0.65$).
- No difference was detected in a composite ophthalmic microvascular outcome (requirement for photocoagulation, intravitreal injection therapy, or vitrectomy; HR 1.24, 95% CI 0.92–1.68; $p = 0.16$).

As with other trials with GLP-1 receptor agonists, gastrointestinal adverse events were common, occurring in 47% of participants allocated to dulaglutide compared with 34% assigned to placebo ($p < 0.0001$), but there was no significant increase in serious gastrointestinal adverse events with dulaglutide. Rates of pancreatitis were similar with dulaglutide compared with placebo, with 23 (0.5%) vs. 13 (0.3%) events ($p = 0.11$) and this was also the case for medullary thyroid cancer (one case with dulaglutide and none with placebo, $p = 0.32$) and pancreatic cancer (19 cases with dulaglutide and 12 with placebo, $p = 0.22$).

Harmony Outcomes The Harmony Outcomes trial was part of the Harmony phase 3 development programme for albiglutide, a once weekly GLP-1 receptor agonist that was available in the US and UK from 2014 to 2017 [41]. Harmony Outcomes was completed and published in 2018 after the drug had been withdrawn by the manufacturer GSK for commercial reasons. Like ELIXA, Harmony Outcomes was designed to include high-risk participants with type 2 diabetes and a history of established coronary artery, cerebrovascular or peripheral vascular disease, but was larger with 9463 participants randomised (1:1) and shorter median follow-up (1.6 years). Albiglutide was reasonably well tolerated with 1140 (24%) subjects discontinuing study medication prematurely compared with 1297 (27%) in the placebo group.

- The primary composite MACE outcome occurred in 338 (7%) of 4731 participants in the albiglutide group and in 428 (9%) of 4732 participants in the placebo group (HR 0.78; 95% CI 0.68–0.90), demonstrating superiority compared with placebo ($p < 0.0001$ for noninferiority; $p = 0.0006$ for superiority).
- A significant reduction in a secondary outcome of fatal or nonfatal myocardial infarction was also observed (HR 0.75; 95% CI 0.61–0.90, $p = 0.003$).

Rates of pancreatitis and pancreatic cancer were similar in the two treatment groups and thyroid cancer was not observed in either group.

PIONEER 6 The PIONEER 6 (Peptide Innovation for Early Diabetes Treatment) trial was a CVOT designed to assess the cardiovascular safety of the oral formulation of semaglutide (14 mg daily) compared with placebo and standard of care (1:1 randomisation) in the treatment of type 2 diabetes [42]. Like SUSTAIN-6 with weekly injectable semaglutide, PIONEER 6 was a prelicensing trial designed to demonstrate noninferiority and was not designed to have the statistical power to detect superiority (i.e. reduction in rates of MACE). As the inclusion criteria were similar to those in SUSTAIN-6 and LEADER, the 3183 participants recruited had similar

characteristics with around 80% having established cardiovascular disease. Median follow-up was 15.9 months and the trial was stopped when 122 primary endpoints had been accrued in accordance with the event-driven design. Some 85% of those allocated to oral semaglutide completed the trial on treatment compared with 90% with placebo.

- The primary MACE composite outcome occurred in 61 of 1591 participants (3.8%) in the semaglutide group compared with 76 of 1592 (4.8%) of those in the placebo group (HR 0.79; 95% CI 0.57–1.11; $p < 0.001$ for noninferiority). A prespecified test for superiority (included in the statistical analysis plan following the experience of SUSTAIN-6) did not show statistical significance ($p = 0.17$).
- Death from cardiovascular causes (a secondary outcome) was lower in the semaglutide group with an incidence of 15 (0.9%) vs. 30 (1.9%) in the placebo group (HR 0.49; 95% CI 0.27–0.92) as was death from all causes (23 participants (1.4%) in the oral semaglutide group vs. 45 (2.8%) in the placebo group (HR 0.51; 95% CI 0.31–0.84).
- Adverse events related to diabetic retinopathy occurred in 113 of 1591 patients (7.1%) with oral semaglutide and 101 of 1592 (6.3%) with placebo.

Gastrointestinal adverse events occurred in 108 of 1591 patients (6.8%) in the oral semaglutide group compared with 26 of 1592 (1.6%) in the placebo group and were the main driver for treatment discontinuation. Acute pancreatitis occurred in one patient in the semaglutide group and three patients in the placebo group. There was one case of medullary thyroid cancer reported in the semaglutide group in a patient with preexisting thyroid nodules and an elevated baseline calcitonin level.

The cardiovascular effects of oral semaglutide are being further investigated in the SOUL trial of 9642 patients with type 2 diabetes with an estimated study completion in 2024 [43].

AMPLITUDE-O AMPLITUDE-O was a CVOT designed to assess cardiovascular safety and efficacy of the once weekly GLP-1 receptor agonist efpeglenatide (4 mg weekly or 6 mg weekly) in comparison with placebo and standard of care (1:1:1) in 4076 participants with type 2 diabetes [44]. Efpeglenatide was a once weekly GLP-1 receptor agonist under phase 3 development by Sanofi when the development was halted for commercial reasons. Efpeglenatide consists of a modified exendin-4 molecule conjugated with an IgG4 Fc fragment. As AMPLITUDE-O was conducted in the era of SGLT2 inhibitors, the randomisation was stratified for their use. Secondary outcomes included an expanded MACE (MACE, coronary revascularisation or hospitalisation for unstable angina) and a composite renal outcome (incident macroalbuminuria, increase in UACR ≥30% from baseline, sustained reduction in eGFR of >40% for >30 days or renal replacement therapy for >90 days). The median follow-up was 1.8 years and information regarding the primary outcome was known for 3941 of the 4076 participants (96.7%). Efpeglenatide was well tolerated with 89% of participants taking active therapy for follow-up compared with 91% for placebo.

- In the main results, 189 out of 2717 (7.0%) of participants assigned to either dose of efpeglenatide had an incident MACE event compared with 125 out of 1359 (9.2%)

for placebo (HR 0.73; 95% CI 0.58–0.92; $p < 0.001$ for noninferiority, $p = 0.007$ for superiority), demonstrating the cardiovascular safety of efpeglenatide and superiority to placebo in reducing MACE.

- The combined efpeglenatide groups also reported a significant reduction in the incidence of the expanded MACE composite events (HR 0.79; 95% CI 0.65–0.96; $p = 0.02$).

Meta-analysis of Cardiovascular Outcome Trials An updated systematic review and meta-analysis of the cardiovascular, mortality and renal outcomes with GLP-1 receptor agonists in patients with type 2 diabetes was published following the publication of AMPLITUDE-O [32]. Eight trials with 60 080 patients were included: ELIXA, LEADER, SUSTAIN-6, EXSCEL, HARMONY, REWIND, PIONEER 6 and AMPLITUDE-O. This showed that treatment with a GLP-1 receptor agonist vs. placebo led to a 14% reduction in MACE (HR 0.86; 95% CI 0.80–0.93; $p < 0.0001$) and a reduction in the risk of cardiovascular death (HR 0.87; 95% CI 0.80–0.94; $p = 0.001$), fatal or nonfatal stroke (HR 0.83; 95% CI 0.76–0.92; $p < 0.001$), and fatal or nonfatal myocardial infarction (HR 0.90; 95% CI 0.83–0.98; $p = 0.043$). Risk of death from any cause was reduced by 12% (HR 0.88; 95% CI 0.82, 0.94; $p = 0.001$) compared with placebo. The number needed to treat to prevent one MACE was 65 (95% CI 45–130) over three years. The risk of hospital admission for heart failure was also significantly reduced by 11% in those treated with a GLP-1 receptor agonist (HR 0.89, 95% CI 0.82–0.98; $p = 0.013$).

In the meta-analysis the incidences of severe hypoglycaemia, pancreatitis, pancreatic and thyroid cancer did not differ between GLP-1 receptor agonist treatment and placebo.

Summary of Cardiovascular Outcome Trials It has been debated in recent years whether the effect of GLP-1 receptor agonists on cardiovascular outcomes is homogenous across the class. In previous meta-analyses, point estimates for reduction of MACE events appeared to differ somewhat between the GLP-1 receptor agonists based on exendin-4 (exenatide and lixisenatide; HR 0.95; 95% CI 0.85–1.06) and those with structural homology with native GLP-1 (liraglutide, semaglutide, albiglutide, dulaglutide; HR 0.84; 95% CI 0.79–0.90; *p*-value for interaction 0.06), leading to the suggestion that this was a decisive factor in determining cardiovascular efficacy. There were other differences between the trials which might explain the differences (proportion with established cardiovascular disease, length of study, drug duration of action, drug dosing interval, baseline HbA1c). For example, the ELIXA trial of lixisenatide (a short-acting exendin-based GLP-1 receptor agonist) recruited only participants with recent acute coronary syndrome. Given a high risk of cardiovascular disease it should in theory have been easier to detect a treatment effect even with a smaller sample size, but on the other hand, cardiovascular disease may have been too advanced to be amenable to intervention.

The recent publication of AMPLITUDE-O and its inclusion in a revised meta-analysis has provided a new insight as the revised hazard ratios were similar between the exendin- and nonexendin-based drugs. Indeed, hazard ratios were almost identical in a sensitivity analysis that excluded the ELIXA trial, with a hazard ratio of 0.84 (95% CI 0.68–1.03) for exendin-based drugs compared with a hazard ratio of 0.84

(95% CI 0.79–0.91) for those with structural homology (p-value for interaction = 1.00). This suggests that adequate GLP-1 agonism per se may be sufficient for cardiovascular benefit without the need for structural homology to native GLP-1. In this context it can be speculated that the EXSCEL trial with the exendin-based exenatide LAR might have converted its marginal result for MACE reduction to a significant one had fewer participants discontinued treatment (40% of the population), reducing its statistical power.

The reduction in the risk of hospitalisation for heart failure (11%) in this meta-analysis of diabetes CVOTs was relatively modest compared with the reductions in the risk of hospital admission with heart failure that have been seen in a recent SGLT2 inhibitor meta-analysis (32%) [45] (see Chapter 5). Whilst there have been some early clinical studies in patients with type 2 diabetes and heart failure, to date there have been no dedicated outcome trials of GLP-1 receptor agonists in a stable heart failure population. GLP-1 receptor agonists may be considered as an alternative in people with diabetes who do not tolerate an SGLT2 inhibitor for this indication.

Prescribing point: *GLP-1 receptor agonists should be prescribed for people with diabetes and established atherosclerotic heart disease.*

Renal Outcomes

Diabetic nephropathy is the commonest cause of end-stage renal failure globally and is the primary renal diagnosis for 20% of patients starting renal replacement therapy in the UK. It is a diagnosis based on persistent albuminuria >30 mg/g creatinine and/or an eGFR <60 ml/min/1.73 m^2.

Renal Outcomes from Cardiovascular Outcome Trials There was considerable hope for the effects of GLP-1 receptor agonists on renal outcomes and the first trial to report, ELIXA, detected a reduction in new-onset albuminuria. At the time this was reported with some caution by the investigators but in a later *post hoc* analysis there was also a reduction in new-onset macroalbuminuria following adjustment for baseline HbA1c (HR 0.81; 95% CI 0.66–0.99; $p = 0.04$) [46] and this has since been corroborated by trials with other GLP-1 receptor agonists that have demonstrated improvements in renal outcomes.

Six trials with GLP-1 receptor agonists have reported renal data to date (i.e. all but Harmony Outcomes and PIONEER 6; Table 6.2). In LEADER, rates of nephropathy (defined as new-onset macroalbuminuria or doubling of serum creatinine with an eGFR < 45 ml/min/1.73 m^2, the need for renal replacement therapy or death from renal disease) were significantly lower with liraglutide compared with placebo (1.5 vs. 1.9 events per 100 patient years of observation; HR 0.78; 95% CI 0.67–0.92; $p = 0.003$), and this was driven primarily by reduced rates of new-onset albuminuria [47]. In REWIND, a composite renal outcome (first occurrence of new macroalbuminuria, sustained decline in estimated glomerular filtration rate of ≥30% from baseline, or initiation of renal replacement therapy) was reduced by dulaglutide compared with placebo (HR 0.85; 95% CI 0.77–0.93; $p = 0.0004$) [48].

Meta-analysis of Renal Outcomes from Cardiovascular Outcome Trials Meta-analysis has shown that GLP-1 receptor agonists reduce rates of a renal composite outcome consisting of new macroalbuminuria, worsening kidney function (doubling of serum creatinine or 40% or greater decline in eGFR), end-stage kidney disease or kidney-related death by 21% (HR 0.79, 95% CI 0.73–0.87, $p < 0.0001$) [32]. This may not be entirely driven by new-onset macroalbuminuria (which can be regarded as a surrogate outcome) as a composite outcome including only the clinically important components was nominally significant when ELIXA was excluded in a sensitivity analysis (HR 0.82, 95% CI 0.69–0.98, $p < 0.03$). The FLOW trial is now in progress to assess whether semaglutide 1.0 mg weekly reduces rates of a composite renal outcome in people with type 2 diabetes with renal impairment (reduced eGFR and albuminuria) over five years [49].

Mechanistically, GLP-1 receptor agonists, as well as reducing body weight and blood pressure, promote natriuresis and may have a role in electrolyte regulation and homeostasis by influencing fluid intake and the transport of electrolytes within the gut and the kidneys themselves. It is also hypothesised that they may have a role in renal haemodynamics, reducing glomerular hyperfiltration.

Use of GLP-1 Receptor Agonists in Other Diseases

Overweight and Obesity

Obesity is a chronic metabolic disease characterised by increased body fat stores, the aetiology of which encompasses complex interactions of biological, behavioural, social and environmental factors. It is an increasing global public health challenge and is one of the leading causes of disability and death. Pathogenic effects of adipose cell hypertrophy include impaired adipogenesis, dysregulation of adipokines, increased circulating free fatty acids, inflammation and oxidative stress, adipose tissue hypoxia, lipotoxicity and altered energy storage. These effects can directly stimulate atherosclerosis and endothelial cell dysfunction as well as promote cardiometabolic disease via hypertension, insulin resistance, diabetes mellitus and dyslipidaemia. As noted above, treatment with GLP-1 receptor agonists in people with type 2 diabetes has been shown to cause weight loss by increasing satiety and reducing the response of hypothalamic reward centres, leading to decreased intake. Studies have therefore been carried out to investigate the role of GLP-1 receptor agonists as a treatment for obesity in non-diabetic individuals. These have investigated higher doses than were used in type 2 diabetes trials.

In the SCALE trial of liraglutide 3 mg ($n = 3731$), subjects allocated to liraglutide (2:1 randomisation) had lost a mean of 8.0 ± 6.7% (8.4±7.3 kg) of their body weight at 56 weeks compared with 2.6 ± 5.7% (2.8 ± 6.5 kg) in the placebo group [50]. Nearly a third of participants taking liraglutide 3.0 mg daily lost greater than 10% of their

body weight. In a three year extension to the trial the time to onset of type 2 diabetes was 2.7 times longer with liraglutide than with placebo (95% CI 1.9–3.9; $p < 0.0001$) corresponding with a hazard ratio of 0.21 (95% CI 0.13–0.34) [51]. In 2020, NICE recommended the use of liraglutide for the treatment of obesity in the UK under certain conditions (Box 6.3) [52].

Box 6.3 NICE recommendations on the use of liraglutide (Saxenda) 3.0 mg for the treatment of obesity in the UK

- Use alongside calorie restriction and increased physical activity in adults.
- BMI of at least 35kg/m^2 (with adjusted thresholds for minority ethnic groups).
- Nondiabetic hyperglycaemia (HbA1c 42–47 mmol/mol or fasting plasma glucose 5.5–6.9 mmol/l).
- High risk of cardiovascular disease, e.g. history of hypertension and dyslipidaemia.
- Prescribed in secondary care by a multidisciplinary tier 3 weight management service.

Source: Modified from [52].

At the time of writing (April 2022) semaglutide had been approved for the weight loss indication in both the US and Europe with global launch pending. Supporting data was from the STEP-1 and STEP-2 trials that investigated a 2.4 mg dose for the treatment of obesity in nondiabetic and diabetic subjects [53, 54]. STEP-1 ($n = 1961$), which was carried out in nondiabetic individuals over 68 weeks (2:1 randomisation), demonstrated a mean weight loss of −15.3 kg with semaglutide compared with −2.6 kg with placebo (estimated treatment difference −12.7 kg; 95% CI −13.7 to −11.7). In addition 86% of subjects on semaglutide lost greater than 5% of their body weight compared with 32% with placebo ($p < 0.001$; co-primary endpoints). Adverse events (mainly gastrointestinal) leading to discontinuation of randomised therapy occurred in 7% of participants on semaglutide compared with 3% on placebo.

STEP-2 had a similar design but was carried out in people with recently diagnosed type 2 diabetes with a 1:1:1 randomisation to semaglutide 2.4 mg vs. semaglutide 1.0 mg weekly vs. placebo (64 = 90). It demonstrated a mean weight loss of −9.6 kg with semaglutide 2.4. mg compared with −3.4 kg with placebo (estimated treatment difference −6.21 kg; 95% CI −7.28 to −5.15) while 69% of subjects lost greater than 5% of their body weight compared with 28% with placebo ($p < 0.001$; co-primary endpoints). Effects for all body weight outcomes were intermediate (dose dependent) for semaglutide 1.0 mg weekly but HbA1c reductions were similar for the two doses (placebo-corrected 1.2 and 1.1%, respectively, from baseline HbA1c 8.1%).

Evidence to date suggests that the GLP-1 receptor agonists liraglutide and semaglutide can be used to achieve substantial and sustained weight loss in recently diagnosed people with diabetes as well as in nondiabetic individuals. This is likely to impact on longer-term outcomes, and the effect of semaglutide on cardiovascular outcomes in people with overweight and obesity is being examined in the SELECT

(Semaglutide Effects on Heart Disease and Stroke in Patients with Overweight or Obesity) trial [55]. This large trial aims to recruit 17 500 participants and is estimated to complete in 2023.

Nonalcoholic Fatty Liver Disease

Nonalcoholic fatty liver disease (NAFLD) has a reported estimated prevalence as high as 25% in the general European population and has been linked to rising levels of obesity. In the context of obesity, it is associated with infiltration of the liver by immune cells which produce cytokines and interleukins contributing to a low-grade, chronic intrahepatic inflammatory process. Deleterious effects of lipotoxicity and glucotoxicity on hepatocytes cause mitochondrial defects, endoplasmic reticulum stress and oxidative stress, which contribute to the formation of simple steatosis and progression to nonalcoholic steatohepatitis (NASH). Prolonged inflammation leads to fibrosis in which replacement of hepatocytes which have undergone apoptosis is unsuccessful. This can lead to cirrhosis and hepatocellular carcinoma. NAFLD is now the fastest growing indication for liver transplantation.

The LEAN (Liraglutide Safety and Efficacy in Patients with Nonalcoholic Steatohepatitis) trial was a randomised, double-blind, placebo-controlled trial of liraglutide 1.8 mg vs. placebo for 48 weeks in 52 individuals with or without diabetes (HbA1c < 9.0%), BMI > 25 kg/m^2 and a histological diagnosis of nonalcoholic steatohepatitis [56]. Forty-five (87%) of patients completed treatment and had paired liver biopsies performed. Thirty-nine per cent of patients (9/23) in the liraglutide arm had resolution of NASH with no worsening of fibrosis (primary outcome) compared with 9% (2/22) in the placebo group.

In a more recent and larger trial ($n = 320$) over 78 weeks with semaglutide in doses of 0.1–0.4 mg daily (i.e. equivalent to 0.7–2.8 mg weekly), 40% in the 0.1 mg group, 36% in the 0.2 mg group, 59% in the 0.4 mg group and 17% in the placebo group had resolution of NASH with no worsening of fibrosis [57]. It is thought that GLP-1 receptor agonists may protect hepatocytes from lipoapoptosis by inhibiting the endoplasmic reticulum stress response and by the reduction of fatty acid accumulation by activation of both macro- and chaperone-mediated autophagy, preventing progression of underlying steatosis in patients with NAFLD.

Place of GLP-1 Receptor Agonists in Current and Future Practice

Over the last decade, GLP-1 receptor agonists have established themselves as highly effective and generally well-tolerated drugs for the treatment of type 2 diabetes. Cardiovascular outcome trials initially designed to assess safety have shown that GLP-1 receptor agonists reduce rates of MACE, particularly strokes. The most recent data indi-

cate that this is broadly a class effect, with the exception of lixisenatide with its short duration of action. It is surprising, therefore, that while clinical use of SGLT2 inhibitors in patients with diabetes has accelerated following the publication of the results of CVOTs, the use of GLP-1 receptor agonists has only increased modestly. This may reflect the fact that until recently GLP-1 receptor agonists were an injected treatment, requiring more education to initiate than a SGLT2 inhibitor, and may change with the availability of oral semaglutide.

It is rational to combine a GLP-1 receptor agonist and a SGLT2 inhibitor to further reduce HbA1c and potentially maximise reductions in cardiovascular and renal outcomes, as the mechanisms of benefit seem to be different for the two classes of drugs. It is important to avoid therapeutic inertia, delaying the use of effective drugs until complications are established (see Chapter 16), but cost-effectiveness must also be a factor in cost-constrained healthcare systems (see Chapter 1).

Going forward, GLP-1 receptor agonists are likely to be increasingly used earlier in the course of type 2 diabetes, especially for weight control in patients with diabetes who have been recently diagnosed or have nonalcoholic fatty liver disease. A wider role in the management of overweight, obesity and nonalcoholic fatty liver disease in nondiabetic subjects is likely if once weekly GLP-1 receptor agonists are licensed at a cost-effective price for these indications.

There is also interest in the use of GLP-1 receptor agonists for neuroprotection in Parkinson's disease or following an acute stroke in those with or without diabetes. Animal models in these diseases have shown some benefits of GLP-1 receptor agonists, particularly in Parkinson's disease, and small preliminary clinical studies have shown some benefits in humans. Further well-designed randomised, controlled clinical trials will be required to test these potential clinical indications.

References

1. Nauck, M., Stöckmann, F., Ebert, R. et al. (1986). Reduced incretin effect in type 2 (non-insulin-dependent) diabetes. *Diabetologia* 29: 46–52.
2. Donnelly, D. (2012). The structure and function of the glucagon-like peptide-1 receptor and its ligands. *Br J Pharmacol* 166: 27–41.
3. Rosenstock, J., Buse, J.B., Azeem, R. et al. (2018). Efficacy and safety of ITCA 650, a novel drug-device GLP-1 receptor agonist, in type 2 diabetes uncontrolled with oral antidiabetes drugs: the FREEDOM-1 Trial. *Diabetes Care* 4: 333–340.
4. Del Prato, S., Kang, J., Trautmann, M.E. et al. (2020). Efficacy and safety of once-monthly efpeglenatide in patients with type 2 diabetes: results of a phase 2 placebo-controlled, 16-week randomized dose-finding study. *Diabetes Obes Metab* 22: 1176–1186.
5. Shuai, Y., Yang, G., Zhang, Q. et al. (2021). Efficacy and safety of polyethylene glycol loxenatide monotherapy in type 2 diabetes patients: a multicentre, randomized, double-blind, placebo-controlled phase 3a clinical trial. *Diabetes Obes Metab* 23: 116–124.
6. Gao, F., Lv, X., Mo, Z. et al. (2020). Efficacy and safety of polyethylene glycol loxenatide as add-on to metformin in patients with type 2 diabetes: a multicentre, randomized, double-blind, placebo-controlled, phase 3b trial. *Diabetes Obes Metab* 22: 2375–2383.

7. Trujillo, J.M., Nuffer, W., and Smith, B.A. (2021). GLP-1 receptor agonists: an updated review of head-to-head clinical studies. *Ther Adv Endocrinol Metab* 12: 1–15.
8. Buse, J.B., Rosenstock, J., Sesti, G. et al. (2009). Liraglutide once a day versus exenatide twice a day for type 2 diabetes: a 26-week randomised, parallel-group, multinational, open-label trial (LEAD-6). *Lancet* 374: 39–47.
9. Drucker, D.J., Buse, J.B., Taylor, K. et al. (2008). Exenatide once weekly versus twice daily for the treatment of type 2 diabetes: a randomised, open-label, non-inferiority study. *Lancet* 372: 1240–1250.
10. Blevins, T., Pullman, J., Malloy, J. et al. (2011). DURATION-5: exenatide once weekly resulted in greater improvements in glycemic control compared with exenatide twice daily in patients with type 2 diabetes. *J Clin Endocrinol Metab* 96: 1301–1310.
11. Buse, J.B., Nauck, M., Forst, T. et al. (2013). Exenatide once weekly versus liraglutide once daily in patients with type 2 diabetes (DURATION-6): a randomised, open-label study. *Lancet* 38: 117–124.
12. Rosenstock, J., Raccah, D., Korányi, L. et al. (2013). Efficacy and safety of lixisenatide once daily versus exenatide twice daily in type 2 diabetes inadequately controlled on metformin: a 24-week, randomized, open-label, active-controlled study (GetGoal-X). *Diabetes Care* 36: 2945–2951.
13. Nauck, M., Rizzo, M., Johnson, A. et al. (2016). Once-daily liraglutide versus lixisenatide as add-on to metformin in type 2 diabetes: a 26-week randomized controlled clinical trial. *Diabetes Care* 39: 1501–1509.
14. Wysham, C., Blevins, T., Arakaki, R. et al. (2014). Efficacy and safety of dulaglutide added onto pioglitazone and metformin versus exenatide in type 2 diabetes in a randomized controlled trial (AWARD-1). *Diabetes Care* 37: 2159–2167.
15. Dungan, K.M., Povedano, S.T., Forst, T. et al. (2014). Once-weekly dulaglutide versus once-daily liraglutide in metformin-treated patients with type 2 diabetes (AWARD-6): a randomised, open-label, phase 3, non-inferiority trial. *Lancet* 384: 1349–1357.
16. Ahmann, A.J., Capehorn, M., Charpentier, G. et al. (2018). Efficacy and safety of once-weekly semaglutide versus exenatide ER in subjects with type 2 diabetes (SUSTAIN 3): a 56-week, open-label, randomized clinical trial. *Diabetes Care* 41: 258–266.
17. Pratley, R.E., Aroda, V.R., Lingvay, I. et al. (2018). Semaglutide versus dulaglutide once weekly in patients with type 2 diabetes (SUSTAIN 7): a randomised, open-label, phase 3b trial. *Lancet Diabetes Endocrinol* 6: 275–286.
18. Capehorn, M.S., Catarig, A.M., Furberg, J.K. et al. (2020). Efficacy and safety of once-weekly semaglutide 1.0mg vs. once-daily liraglutide 1.2mg as add-on to 1–3 oral antidiabetic drugs in subjects with type 2 diabetes (SUSTAIN 10). *Diabetes Metab* 46: 100–109.
19. Pratley, R., Amod, A., Hoff, S.T. et al. (2019). Oral semaglutide versus subcutaneous liraglutide and placebo in type 2 diabetes (PIONEER 4): a randomised, double-blind, phase 3a trial. *Lancet* 394: 39–50.
20. Yamada, Y., Katagiri, H., Hamamoto, Y. et al. (2020). Dose–response, efficacy, and safety of oral semaglutide monotherapy in Japanese patients with type 2 diabetes (PIONEER 9): a 52-week, phase 2/3a, randomised, controlled trial. *Lancet Diabetes Endocrinol* 8: 377–391.
21. Yabe, D., Nakamura, J., Kaneto, H. et al. (2020). Safety and efficacy of oral semaglutide versus dulaglutide in Japanese patients with type 2 diabetes (PIONEER 10): an open-label, randomised, active-controlled, phase 3a trial. *Lancet Diabetes Endocrinol* 8: 392–406.
22. Frias, J.P., Auerbach, P., Bajaj, H. et al. (2021). Efficacy and safety of once-weekly semaglutide 2.0 mg versus 1.0 mg in patients with type 2 diabetes (SUSTAIN FORTE): a double-blind, randomised, phase 3B trial. *Lancet Diabetes Endocrinol* 9: 563–574.
23. Gilbert, M.P. and Pratley, R.E. (2020). GLP-1 Analogs and dpp-4 inhibitors in type 2 diabetes therapy: review of head-to-head clinical trials. *Front Endocrinol* (Lausanne) 178: 1–13.

24. Rodbard, H.W., Rosenstock, J., Canani, L.H. et al. (2019). Oral semaglutide versus empagliflozin in patients with type 2 diabetes uncontrolled on metformin: the PIONEER 2 trial. *Diabetes Care* 42: 2272–2281.
25. Abd El Aziz, M.S., Kahle, M., Meier, J.J. et al. (2017). A meta-analysis comparing clinical effects of short- or long-acting GLP-1 receptor agonists versus insulin treatment from head-to-head studies in type 2 diabetic patients. *Diabetes Obes Metab* 19: 216–227.
26. Ahrén, B., Johnson, S.L., Stewart, M. et al. (2014). HARMONY 3: 104-week randomized, double-blind, placebo- and active-controlled trial assessing the efficacy and safety of albiglutide compared with placebo, sitagliptin, and glimepiride in patients with type 2 diabetes taking metformin. *Diabetes Care* 37 (8): 2141–2148.
27. Nathan, D.M., Buse, J.E., Kahn, S.E. et al. (2013). Rationale and design of the glycemia reduction approaches in diabetes: a comparative effectiveness study (GRADE). *Diabetes Care* 36: 2254–2261.
28. Billings, L.K., Doshi, A., Gouet, D. et al. (2018). Efficacy and safety of IDegLira versus basal-bolus insulin therapy in patients with type 2 diabetes uncontrolled on metformin and basal insulin: the DUAL VII randomized clinical trial. *Diabetes Care* 4: 1009–1016.
29. Aroda, V.R., Rosenstock, J., Wysham, C. et al., LixiLan-L Trial Investigators. (2016). Efficacy and safety of LixiLan, a titratable fixed-ratio combination of insulin glargine plus lixisenatide in type 2 diabetes inadequately controlled on basal insulin and metformin: the LixiLan-L randomized trial. *Diabetes Care* 39: 1972–1980.
30. Hegedüs, L., Moses, A.C., Zdravkovic, M. et al. (2011). GLP-1 and calcitonin concentration in humans: lack of evidence of calcitonin release from sequential screening in over 5000 subjects with type 2 diabetes or nondiabetic obese subjects treated with the human GLP-1 analog, liraglutide. *J Clin Endocrinol Metab* 96: 853–860.
31. Monami, M., Nreu, B., Scatena, A. et al. (2017). Safety issues with glucagon-like peptide-1 receptor agonists (pancreatitis, pancreatic cancer and cholelithiasis): data from randomized controlled trials. *Diabetes Obes Metab* 19: 1233–1241.
32. Sattar, N., Lee, M.M.Y., Kristensen, S.L. et al. (2021). Cardiovascular, mortality, and kidney outcomes with GLP-1 receptor agonists in patients with type 2 diabetes: a systematic review and meta-analysis of randomised trials. *Lancet Diabetes Endocrinol* 9: 653–662.
33. Keller, J., Trautmann, M.E., Haber, H. et al. (2012). Effect of exenatide on cholecystokinin-induced gallbladder emptying in fasting healthy subjects. *Regul Pept* 179: 77–83.
34. Pfeffer, M.A., Claggett, B., Diaz, R. et al., for the ELIXA Investigators (2015). Lixisenatide in patients with type 2 diabetes and acute coronary syndrome. *N Engl J Med* 373: 2247–2257.
35. Marso, S.P., Daniels, G.H., Brown-Frandsen, K. et al., for the LEADER Steering Committee on behalf of the LEADER Trial Investigators (2016). Liraglutide and cardiovascular outcomes in type 2 diabetes. *N Engl J Med* 375: 311–322.
36. Marso, S.P., Bain, S.C., Consoli, A. et al., for the SUSTAIN-6 Investigators (2016). Semaglutide and cardiovascular outcomes in patients with type 2 diabetes. *N Engl J Med* 375: 1834–1844.
37. Bain, S.C., Klufas, M.A., Ho, A., and Matthews, D.R. (2019). Worsening of diabetic retinopathy with rapid improvement in systemic glucose control: a review. *Diabetes Obes Metab* 21: 454–466.
38. A research study to look at how semaglutide compared to placebo affects diabetic eye disease in people with type 2 diabetes (FOCUS). https://clinicaltrials.gov/ct2/show/NCT03811561 (accessed 7 November 2021).
39. Holman, R.R., Bethel, M.A., Mentz, R.J. et al., for the EXSCEL Study Group (2017). Effects of once-weekly exenatide on cardiovascular outcomes in type 2 diabetes. *N Engl J Med* 377: 1228–1239.

40. Gerstein, H.C., Colhoun, H.M., Dagenais, G.R. et al., for the REWIND Investigators. (2019). Dulaglutide and cardiovascular outcomes in type 2 diabetes (REWIND): a double-blind, randomised placebo-controlled trial. *Lancet* 394: 121–130.
41. Hernandez, A.F., Green, J.B., Janmohamed, S. et al., for the Harmony Outcomes Committees and Investigators (2018). Albiglutide and cardiovascular outcomes in patients with type 2 diabetes and cardiovascular disease (Harmony Outcomes): a double-blind, randomised placebo-controlled trial. *Lancet* 392: 1519–1529.
42. Husain, M., Birkenfeld, A.L., Donsmark, M. et al., for the PIONEER 6 Investigators (2019). Oral semaglutide and cardiovascular outcomes in people with type 2 diabetes. *N Engl J Med* 381: 841–851.
43. A heart disease study of semaglutide in patients with type 2 diabetes (SOUL). https://clinicaltrials.gov/ct2/show/NCT03914326 (accessed 7 November 2021).
44. Gerstein, H.C., Sattar, N., Rosenstock, J. et al, for the AMPLITUDE-O Trial Investigators (2021). Cardiovascular and renal outcomes with efpeglenatide in type 2 diabetes. *N Engl J Med* 385: 896–907.
45. McGuire, D.K., Shih, W.J., Cosentino, F. et al. (2021). Association of SGLT2 Inhibitors with cardiovascular and kidney outcomes in patients with type 2 diabetes: a meta-analysis. *JAMA Cardiol* 6: 148–158.
46. Muskiet, M.H.A., Tonneijck, L., Huang, Y. et al. (2018). Lixisenatide and renal outcomes in patients with type 2 diabetes and acute coronary syndrome: an exploratory analysis of the ELIXA randomised, placebo-controlled trial. *Lancet Diabetes Endocrinol* 6: 859–869.
47. Mann, J.F.E., Orsted, D.D., Brown-Frandsen, K. et al., for the LEADER Steering Committee and Investigators (2017). Liraglutide and renal outcomes in type 2 diabetes. *N Engl J Med* 377: 839–848.
48. Gerstein, H.C., Colhoun, H.M., Dagenais, G.R. et al., for the REWIND Investigators (2019). Dulaglutide and renal outcomes in type 2 diabetes: an exploratory analysis of the REWIND randomised, placebo-controlled trial. *Lancet* 394: 131–138.
49. A research study to see how semaglutide works compared to placebo in people with type 2 diabetes and chronic kidney disease (FLOW). https://clinicaltrials.gov/ct2/show/NCT03819153 (accessed 7 November 2021).
50. Pi-Sunyer, X., Astrup, A., Fujioka, K. et al., for the SCALE Obesity and Prediabetes NN8022-1839 Study Group (2015). A randomized, controlled trial of 3.0 mg of liraglutide in weight management. *N Engl J Med* 373: 11–22.
51. le Roux, C.W., Astrup, A., Fujioka, K. et al., for the SCALE Obesity Prediabetes NN8022-1839 Study Group (2017). 3 years of liraglutide versus placebo for type 2 diabetes risk reduction and weight management in individuals with prediabetes: a randomised, double-blind trial. *Lancet* 389: 1399–1409.
52. Liraglutide for managing overweight and obesity. https://www.nice.org.uk/guidance/ta664 (accessed 12 November 2021).
53. Wilding, J.P.H., Batterham, R.L., Calanna, S. et al., for the STEP 1 Study Group (2021). Once-weekly semaglutide in adults with overweight or obesity. *N Engl J Med* 384: 989–1002.
54. Davies, M., Færch, L., Jeppesen, O.K. et al. (2021). Semaglutide 2.4 mg once a week in adults with overweight or obesity, and type 2 diabetes (STEP 2): a randomised, double-blind, double-dummy, placebo-controlled, phase 3 trial. *Lancet* 397: 971–984.
55. Ryan, D.H., Lingvay, I., Colhoun, H.M. et al. (2020). Semaglutide effects on cardiovascular outcomes in people with overweight or obesity (SELECT) rationale and design. *Am Heart J* 229: 61–69.

56. Armstrong, M.J., Gaunt, P., Aithal, G.P. et al. (2016). Liraglutide safety and efficacy in patients with non-alcoholic steatohepatitis (LEAN): a multicentre, double-blind, randomised, placebo-controlled phase 2 study. *Lancet* 387: 679–690.
57. Newsome, P.N., Buchholtz, K., Cusi, K. et al, for the NN9931-4296 Investigators (2021). A placebo-controlled trial of subcutaneous semaglutide in nonalcoholic steatohepatitis. *N Engl J Med* 384: 1113–1124.

CHAPTER 7

Animal and Human Insulins

Ken Paterson

KEY POINTS

- Insulin was discovered in 1921 and entered clinical use from 1922, proving life saving for people with type 1 diabetes.
- Subsequent developments in insulin therapy included improved purification of beef and pork insulins, prolongation of the time–action profile, and the development of U100 insulins as a unified formulation.
- The remainder of the twentieth century saw progressive development of and improvements to the insulins in clinical use, culminating in the availability of biosynthetic human insulin.
- Large prospective studies have proved the benefits of tight glycaemic control in avoiding long-term diabetes complications in both type 1 and type 2 diabetes.
- Efforts to tighten glycaemic control highlighted the limitations of available insulin formulations and the need for insulins more closely meeting the needs and lifestyles of insulin users.

Introduction

Insulin Structure

Insulin is the major anabolic hormone in mammals and other species, being responsible for regulating the synthesis of carbohydrates, proteins and fats. It is a peptide hormone,

Diabetes Drug Notes, First Edition. Edited by Miles Fisher, Gerard A. McKay, and Andrea Llano.

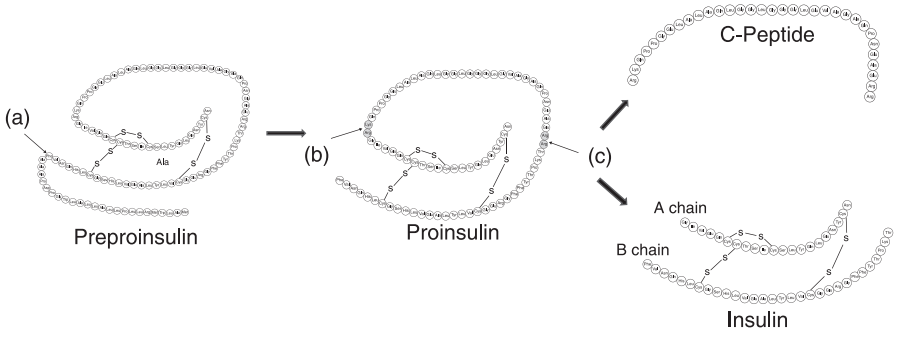


FIGURE 7.1 Insulin structure. Preproinsulin is rapidly broken down to a single 86 amino acid chain (proinsulin). Proinsulin then folds to achieve the correct three-dimensional structure to allow its physiological actions before the central portion of the proinsulin chain is removed, leaving two chains (A and B chains) linked by disulfide bonds and the cleaved portion, known as C-peptide.

synthesised and released by the beta cells of the islets of Langerhans in the pancreas. Insulin is initially synthesised as a larger peptide (preproinsulin), which is rapidly broken down to a single 86 amino acid chain (proinsulin). Proinsulin then folds to achieve the correct three-dimensional structure to allow its physiological actions before the central portion of the proinsulin chain is removed, thus leaving two chains (known as A and B chains) linked by disulfide bonds and the cleaved portion, known as C-peptide (Figure 7.1).

The insulin A chain has 21 amino acids and the B chain has 30 amino acids. The structure of insulin is highly conserved across species, allowing insulins from animal sources to be used to treat human diabetes. Insulin from beef cattle differs from human insulin by only three amino acids and pork insulin differs from human insulin by only one amino acid.

Insulin Receptors

Insulin exerts its effects via its receptor, a tyrosine kinase receptor which comprises two alpha and two beta subunits. Binding of insulin to the alpha subunits present on the cell surface triggers autophosphorylation of the beta subunit tyrosine kinase and subsequent activation of several downstream pathways via IRS-1 (insulin receptor substrate 1) shown in Figure 7.2.

The metabolic effects of insulin are mediated by the PI3K (phosphatidylinositol 3-kinase) pathway. Here, PKB (protein kinase B) is activated and stimulates the translocation of a glucose transporter, GLUT4, into the cell membrane, resulting in glucose uptake. Glycogen synthesis is stimulated by PKB, which phosphorylates and deactivates glycogen synthase kinase-3, which in turn prevents the deactivation of glycogen synthase. This pathway also results in glucose and protein synthesis.

In addition, the MAPK (mitogen activated protein kinase) pathway activates a cascade of transcription factors and protein kinases that are important for cell growth and differentiation.

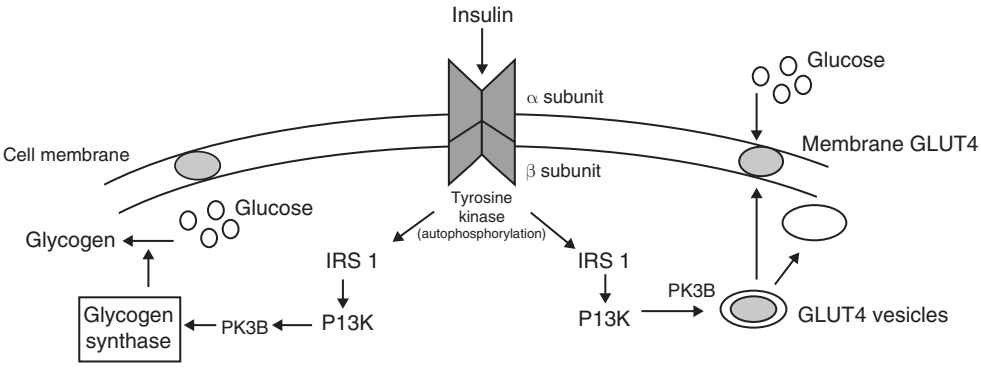


FIGURE 7.2 Insulin receptors. Binding of insulin to the alpha subunits present on the cell surface triggers autophosphorylation of the beta subunit tyrosine kinase and subsequent activation of several downstream pathways via IRS-1 (insulin receptor substrate 1). The metabolic effects of insulin are mediated by the PI3K (phosphatidylinositol 3-kinase) pathway. PKB (protein kinase B) is activated and stimulates the translocation of a glucose transporter, GLUT4 into the cell membrane, resulting in glucose uptake. Glycogen synthesis is stimulated by PKB which phosphorylates and deactivates glycogen synthase kinase-3, which in turn prevents the deactivation of glycogen synthase.

Insulin Physiology

Insulin is the principal anabolic hormone in the human body, acting to promote uptake of nutrients by many tissues and thereafter their metabolism for energy or utilisation in the synthesis of glycogen, protein and triglycerides (Box 7.1). The actions of insulin oppose those of catabolic hormones such as glucagon, cortisol, growth hormone and adrenaline. Insulin has key, but slightly different, roles in the fasting and fed states. On a daily basis, roughly 50% of insulin released is in the fasting state, the other 50% being in response to food ingestion (Figure 7.3).

In the fasting (or 'basal') state, the continuous secretion of low levels of insulin acts to prevent uncontrolled catabolism, which would otherwise see the breakdown of tissue fat and protein and also the metabolism of stored glycogen in liver and muscle to produce glucose. Unchecked, this would lead to the metabolic abnormalities seen in diabetic ketoacidosis, with marked hyperglycaemia from the released glucose and a metabolic acidosis from the metabolism of free fatty acids. Insulin has a pivotal role in maintaining homeostasis and controlling the balance between anabolism and catabolism while fasting.

In the fed (or 'prandial') state, insulin is essential in most tissues (except the brain) for ensuring the uptake of glucose and amino acids and the subsequent utilisation of these as either energy sources within cells or precursors of larger storage and structural molecules such as glycogen, triglyceride and proteins.

Following food ingestion, and largely triggered by the consequent rise in plasma glucose levels owing to food absorption, plasma insulin levels rise quickly (within minutes) as preformed insulin already stored within beta cells is released. This very rapid initial action is followed by ongoing synthesis and release of insulin until the nutrients in the meal have been fully absorbed and distributed. The precise pattern of insulin

Box 7.1 Actions of insulin

Fasting	
Carbohydrate	Inhibition of breakdown of liver glycogen stores Inhibition of breakdown of liver glycogen stores
Protein	Inhibition of protein breakdown in muscle Control of amino acid release for liver conversion to glucose
Lipid	Inhibition of triglyceride breakdown in adipose tissue Control of free fatty acid release as alternative energy source
Fed	
Carbohydrate	Promotion of glucose uptake by most tissues (except brain) Reduced liver glucose output
Protein	Promotion of amino acid uptake (especially by muscle) Increased synthesis of protein
Lipid	Promotion of glucose uptake into adipose tissue Increased conversion of glucose to free fatty acids and hence synthesis of triglyceride

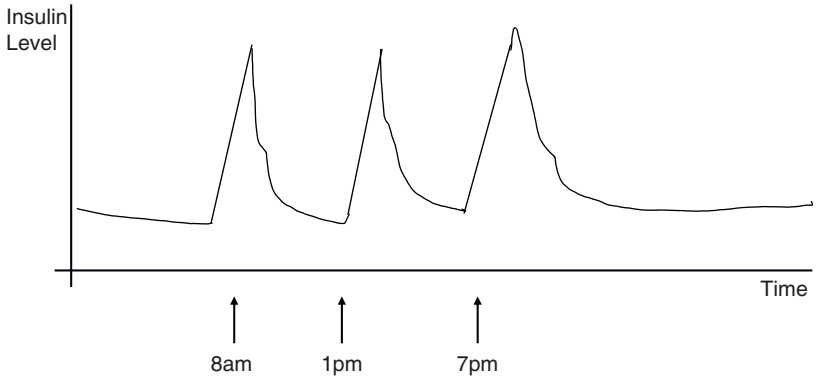


FIGURE 7.3 Physiological insulin profile. In normal healthy individuals 50% of insulin released is in the fasting state, the other 50% being in response to food ingestion. The figure illustrates increased insulin release in response to prandial carbohydrate intake.

release is governed by many factors, particularly the rate at which food leaves the stomach to enter the upper small intestine. Foods high in fibre, particularly soluble fibre, tend to slow gastric emptying, leading to a slower and more prolonged delivery of nutrients and a lesser but more sustained insulin response. A similar effect may be seen with drugs which slow gastric emptying such as opiates and anticholinergic drugs.

Foodstuffs that contain largely complex carbohydrates in the form of starches also slow nutrient absorption compared with foods containing mostly simpler sugars. This leads to the concept of 'glycaemic index', a measure of the likely impact of different foods on plasma glucose levels (simpler sugars have a higher glycaemic index than more complex carbohydrates).

Insulin has a very short plasma half-life (10–15 minutes) and so has the central role in the real-time 'minute to minute' control of plasma glucose levels. It also adapts to day-to-day and meal-to-meal differences in nutrient delivery and absorption, as well as differences in physical activity and other factors which may influence plasma glucose levels. This crucial, but highly flexible, role for insulin is readily delivered by endogenous insulin from the islets of Langerhans but is a real challenge for exogenous insulin administered in the treatment of diabetes.

Production and Pharmacokinetic Modifications

Following the initial discovery of insulin in Toronto in 1921 and its first clinical use in humans in January 1922, the only source of insulin was beef pancreas, from which insulin was extracted, purified and dissolved in buffer, hence known as 'soluble' insulin ('regular' in the US). Soluble insulin has an onset of action about 45–60 minutes after subcutaneous administration and a duration of action of around six hours, so several injections were required each day to try to achieve control of diabetes over 24 hours.

The next seven to eight decades saw efforts to 'improve' on soluble beef insulin along four main lines:

- improved purification;
- changes to the time–action profile of insulin, especially prolongation of action to reduce the number of doses required daily;
- unified formulation; and
- change of insulin source species.

The commercial development of insulin the US was done by Eli Lilly and Company, and Eli Lily remain a major international producer of insulin. In Europe, the commercial development of insulin included the use of pigs as a source of insulin in Denmark. The two large European pharmaceutical companies producing insulin internationally are Novo Nordisk and Sanofi Aventis.

Improved Purification

Following the discovery of insulin, difficulties with purification led to delays in it being tried in human patients. Eventually enough progress was made to allow its use in humans, and shortly thereafter, when the pharmaceutical company Eli Lilly and

Company became involved, the technique of isoelectric precipitation was introduced. This allowed large quantities of purified insulin to be produced commercially to meet the needs of patients. Insulin produced in this way, however, still contained contaminants such as proinsulin, C-peptide and even some slightly denatured insulin. While these contaminants had little effect on the metabolic action of the insulin with which they were associated, they were almost certainly responsible for some of the allergy problems seen.

In the 1970s, improvements in insulin-purification techniques, and particularly the use of chromatography, allowed the production of insulin with virtually no contaminants at all. Whether beef or pork in origin, these highly purified insulins were often known as 'monocomponent' insulins, and certainly seemed to be associated with far fewer allergy problems than the less purified products. Rapidly all insulins were monocomponent, so human insulins were monocomponent from their introduction in the 1980s.

Time Action Prolongation

As noted above, the time–action profile of soluble beef insulin showed an onset of action of around 45–60 minutes post-injection and a duration of action of around six hours. Pork and human insulins show slightly shorter time to onset (around 30–45 minutes) and slightly shorter duration of action (four to five hours). Multiple daily injections would be required to achieve control of glycaemia over 24 hours, so from the very earliest days of insulin therapy the hunt was on to find ways to prolong the time–action profile of insulin and reduce the frequency of injections (Table 7.1).

Insulin Zinc Suspension The addition of zinc (usually as zinc chloride) to soluble insulin resulted in the formation of insulin–zinc complexes, which are relatively insoluble. This delayed the onset of action of insulin after injection, but also prolonged

TABLE 7.1 Insulin time–action profiles

Insulin	Onset of action	Duration of action
Soluble	20–40 minutes	4–8 hours
Semilente	1 hour	12–16 hours
Lente	1 hour	24–30 hours
Isophane (NPH)	1.5–2 hours	16–24 hours
Biphasic	20–40 minutes	16–24 hours
Protamine zinc	4 hours	24–36 hours
Ultralente	6–8 hours	30–36 hours

In general, human and pork insulins act more quickly and have a shorter duration of action than beef insulins.

the duration of action. When small amounts of zinc were added, the resultant insulin was known as 'insulin zinc suspension amorphous' (also known as 'semilente') and had an onset of action of around 1–1.5 hours and a duration of action of 12–14 hours. If larger amounts of zinc were added, crystals of insulin zinc formed, and the resultant formulation was known as 'insulin zinc suspension crystalline' (also known as 'ultralente'). Its onset of action was around six hours after injection with a duration of action of 30 hours or even longer.

A popular compromise, to achieve the benefits of the rapid onset of semilente with the long duration of ultralente was 'lente' insulin, which comprised 30% semilente and 70% ultralente. This was usually given just once daily and was often reserved for older patients or for patients with type 2 diabetes and significant endogenous insulin reserves to cover mealtime glucose fluctuations. It was possible to mix soluble insulin with insulin zinc suspensions (IZSs) in the same syringe, but the onset of action of the soluble component was probably slightly delayed.

IZS insulins do not contain any protein (other than the insulin itself) and so are less prone to local allergic reactions than some other longer-acting insulins (see below). As a suspension (as opposed to a solution), IZSs had to be resuspended by gentle agitation before each injection.

Protamine Zinc Insulin The addition of protamine, a protein derived from fish sperm, to insulin and zinc produced a crystalline suspension with a delayed onset of action (four hours after injection) and a prolonged duration of action (24–30 hours). It was often used in combination with soluble insulin, the latter providing insulin action before the protamine zinc insulin (PZI) began to act. Soluble insulin and PZI could not be mixed in the same syringe as the excess zinc in the PZI simply complexed with the soluble insulin, in effect converting it to more PZI.

Being a protein, protamine could occasionally cause allergic reactions, although these were usually limited to local itching and inflammation at injection sites. Globin, a protein derived from haemoglobin, was sometimes used as an alternative to protamine if allergy was a problem (hence globin zinc insulin).

Isophane or Neutral Protamine Hagedorn Insulin The addition of protamine alone to insulin led to the formation of an insulin–protamine complex that was relatively insoluble at physiological pH. The complex is in suspension within its buffering solution. This was also named neutral protamine Hagedorn (NPH) after its inventor, Hans Cristian Hagedorn.

Prescribing point: *Isophane insulin has to be resuspended before each injection by gently agitating the insulin vial (or pen injector cartridge). Failure to adequately resuspend the complex can lead to incorrect doses being administered.*

The complex slowly broke apart at the injection site. This delayed the onset of action of the insulin to 1.5–2 hours but prolonged the action of the insulin to 12–16 hours, allowing full 24 hour insulin action from just two injections per day. Importantly, the preparation contained no excess protamine, so if soluble insulin was mixed in the same syringe with isophane, each insulin retained its own time–action profile, allowing the soluble component to act rapidly and the isophane component to offer longer-term

action. Mixing insulins was rather tricky for some patients, leading to the popularity of biphasic insulins, premixed combinations of soluble and isophane insulins. As noted above, protamine allergy was an occasional problem.

Biphasic Insulins These premixed combinations of soluble and isophane insulins allowed patients to benefit from doses of two different insulins taken as a single injection from a single insulin vial or pen injector cartridge. Because they contained isophane insulin, care had to be taken to fully resuspend the isophane component before each injection, otherwise the proportions of soluble and isophane insulins injected would be different from the planned proportions.

At the height of usage of biphasic insulin preparations (1980s and 1990s), the available proportions of soluble insulin included 10, 20, 25, 30, 40 and 50% of the total dose. Proportions of 30 and 50% were most widely used. Biphasic preparations lacked the flexibility of 'free mixtures' (when the insulin user made the mix for each injection and could thus vary the proportions to account for changes in diet and physical activity), but had the benefit of simplicity, with a low possibility of significant dosage errors being made. Currently available insulin fixed mixtures are described Chapter 9, Table 9.3.

Unified Formulation

When insulin was first commercialised and made available for use by people with diabetes, it was formulated at a concentration of 20 units (Un)/ml (= U20). Insulin syringes were calibrated in units on the basis of this insulin concentration. To reduce the volume of injection (and associated discomfort), insulin began to be marketed in two additional concentrations, namely 40 Un/ml (= U40) and 80 Un/ml (= U80). These rapidly became the standard formulations, but the syringes remained calibrated for U20 insulin.

This led to immense possibilities for confusion over dosages. Many insulin users regarded their 'dose' as being the number of 'marks' on the syringe that they used to measure the volume to be injected, whereas their actual dose was either twice (if using U40) or four times (if using U80) the marking on the syringe. Accidental underdosage and overdosage were not uncommon, especially in healthcare settings when insulin users were perhaps not self-administering their insulin.

In the early 1980s, it was decided to adopt a single concentration for all insulin formulations, the concentration being 100 Un/ml (= U100). Insulin syringes were recalibrated to the new standard such that the numbers on the syringe corresponded with the actual units of insulin. A widespread education exercise was required to make the switch and remove U40 and U80 from use, but this was successful and removed the earlier possibilities of confusion.

Since then, more concentrated insulins in U200, U300 and U500 strengths have become available, either to reduce the volume of insulin that needs to be injected, or in the case of U300 insulin glargine, to further prolong the time–action profile (see Chapter 9). Currently available more concentrated insulins (U200, U300 and U500) and their perceived benefits are described in Box 7.2.

Box 7.2 Currently available more concentrated insulins (U200, U300, U500) and their perceived benefits

Humalog U200 (Insulin lispro) – smaller volume of injection
Degludec U200 (Insulin degludec) – smaller volume of injection
Glargine U300 (Toujeo) – prolonged time–action profile
Humulin R U500 (Regular insulin) – smaller volume for patients with severe insulin resistance, not licensed for use in the UK

Sources of Insulin

Beef Insulin Although highly metabolically active, and thus life saving for people with type 1 diabetes, insulin derived from cattle pancreas has drawbacks. The three amino acid difference from human insulin led, in some patients, to stimulation of the immune system and allergic reactions. Mostly these were limited to inflammation at sites of injection, which was generally manageable. However more generalised allergic reactions were not uncommon, sometimes necessitating the use of immunosuppressive therapy such as corticosteroids to allow insulin therapy to be continued in the hope that immune tolerance would develop. Development of such tolerance was, thankfully, the norm, but it often took considerable time.

A particularly severe local reaction was the atrophy of subcutaneous fat (insulin lipodystrophy) at the site(s) of frequent injection. This was an immune-mediated inflammatory response, perhaps triggered in part by impurities in the injected insulin as well as the bovine origin of the insulin. It was unsightly, but also led to different rates of insulin absorption compared with 'normal' subcutaneous tissue, adversely affecting the day-to-day reproducibility of insulin action and hence glycaemic control.

Pork Insulin The immunological issues seen with beef insulin led to the introduction and gradual adoption of pork insulin as the insulin source of choice. While there was little difference in the biological activities and time–action profiles (and hence overall glycaemic control) between beef and pork insulins, insulin allergy in all of its forms was much less frequently seen with pork insulin.

Prescribing point: *Porcine insulin is rarely used and is available in soluble isophane and premixed formulations. Bovine insulin is no longer available in the UK.*

Human Insulin The 'Holy Grail' of insulin therapy in the late 1970s was seen to be the ability to treat insulin deficiency in humans with bioidentical human insulin. Initially efforts were made to convert pork insulin to human insulin by changing the single amino acid which differed between them, but the major change came about with the development of genetic engineering techniques which allowed the insulin gene to be inserted into, and be expressed by, single-celled organisms. Both bacteria (*Escherichia coli*) and yeast (*Saccharomyces*) were initially used for insulin

production, the end products being effectively identical to each other and to native human insulin.

The time–action profiles of human insulins were very similar to those of pork insulins, so the effects on overall glycaemic control were minimal. Allergic issues were even less frequent than with pork insulin, and insulin lipodystrophy was very unusual. Biosynthetic production using genetically engineered organisms provided greater certainty about long-term insulin supplies as the need for cadaveric animal pancreas was completely avoided.

Hypoglycaemia and Human Insulin

Following the initial introduction of human insulins in the early 1980s, anecdotal reports of severe hypoglycaemia began to appear in both the medical and lay press [1, 2]. This was a surprise, as no significant increase in hypoglycaemia had been seen in the pivotal clinical trials. It led to many patients refusing to change from animal insulins to human insulin and to demands that animal insulin production be continued (plans having been to gradually run this down).

Pharmacovigilance studies were undertaken which failed to show any overall increased risk of hypoglycaemia, and it appears that the concerns were a form of post hoc fallacy, in which events that occur after a change has been made are deemed to have been caused by the change [3]. Significant hypoglycaemia at that time occurred in roughly 10% of insulin-treated patients each year, so by chance 1% of patients would have a significant hypoglycaemic event in any five to six week period. If that five to six week period happened to occur just after a change to human insulin, human nature tends to attribute the hypoglycaemia to the change of insulin rather than the play of chance, hence the small but significant number of cases reported.

Concern about hypoglycaemia specifically related to human insulin has diminished with time and animal insulin usage is now minimal. This story shows the importance of pharmacovigilance in identifying adverse events, but also in refuting allegations of adverse events (see also Chapter 1).

Limitations of Older Insulins

While the development of biosynthetic human insulin had seemed to be the ‘end of the road’ for insulin developments, replacing the missing (or insufficient) natural hormone with its exact replica, it is readily apparent that treatment with human insulin has significant drawbacks. While human insulin delivered from the pancreas into the portal venous system is ‘ideal’, it is clear that human insulin, in all of its formulations, administered subcutaneously by injection or even continuous infusion using a pump, is far from ideal and has significant limitations. Efforts to intensify treatment in both type 1 and type 2 diabetes merely served to highlight the limitations.

Short-acting Insulins

Soluble human insulin, administered as a bolus subcutaneously, begins to act in about 30–45 minutes and lasts for around four to five hours. Nutrient absorption (particularly carbohydrate absorption) following a meal begins about 15 minutes after the meal is ingested and takes around two to three hours depending on the foods eaten. There is thus a mismatch between the time–action profile of the insulin and the requirement to handle the absorbed carbohydrate and other nutrients.

To get around this, it is suggested that the insulin bolus be taken 20–30 minutes before the start of the meal to give time for the insulin to begin to work. This is a bit of a 'counsel of perfection' as most patients find it too difficult and burdensome to plan ahead in such detail, especially in their workplace, and are concerned about the risk of hypoglycaemia if, having taken their insulin, their food ingestion is then delayed. Very many patients, if asked, admit to routinely taking their premeal insulin just 5–10 minutes before eating, meaning that food absorption is likely to begin before the premeal insulin is starting to act. This can lead to significant hyperglycaemia in the first hour after eating, perhaps taking another hour or more to fully resolve.

However, once the carbohydrate from the main meal is fully dealt with, the insulin continues to act with a risk of late post-meal hypoglycaemia. In an effort to avoid this, between-meal snacks are usually recommended, but these could be difficult for patients at work with limited opportunities for snacking and are also a problem for patients trying to reduce calorie intake to control their weight.

Soluble human insulin thus does not match ideally the needs of people with diabetes, who struggle to match its time–action profile with their physiological needs and lifestyles, and this stimulated the development of short-acting analogue insulins (Chapter 8).

Formulations of human soluble insulin

- Actrapid® is available in a vial.
- Humulin S® is available in vials and cartridges (also known as Humulin R® in the US).
- Insuman Rapid® is available in cartridges.

Prescribing point: *Soluble insulin should be taken 30 minutes before a meal.*

Intermediate and Long-acting Insulins

All of the available intermediate and long-acting human insulins achieve their altered time–action profile by creating an insulin depot at the site of injection, from which the biologically active insulin monomer is released over a number of hours. This process has significant drawbacks:

Time–Action Profile It is an inevitable feature of the time–action profile of an insulin which extends its profile by delaying absorption from an injection site that there will be a delay in the onset of insulin action, a peak of insulin action roughly

midway through the absorption process and a progressive reduction in insulin action thereafter. It follows, therefore, that none of the intermediate and long-acting insulins has a 'flat' profile, effectively providing basal insulin at a fixed level; all have peaks and troughs of action. In the daytime, it is often possible to manage the peaks and troughs by dietary manipulation (even if this is not very popular with, or acceptable to, insulin users), but overnight, and the problems of morning hyperglycaemia, are a particular challenge. The issues are less of a problem in the management of type 2 diabetes as residual endogenous insulin secretion, under physiological control, can often even out the peaks and troughs of exogenous insulin action, but this is not possible in type 1 diabetes.

Formulations of human isophane insulin

- Humulin I® is available in a vial, cartridge and prefilled pen.
- Insulatard® is available in a vial, cartridge and prefilled pen.
- Insuman Basal® is available in a vial, cartridge and prefilled pen.

Formulations of premixed human insulin

- Humulin M3® (70% insulin isophane human, 30% insulin soluble human) is available as a vial, cartridge or prefilled pen.
- Insuman Comb 25® (75% insulin isophane human, 25% insulin soluble human) is available as a cartridge or prefilled pen.
- Insuman Comb 50® (50% insulin isophane human, 50% insulin soluble human) is available as a cartridge.

Prescribing point: *Premixed insulins reduce the number of injections required and are best suited to those with predictable meals and activity levels.*

Morning (Fasting) Hyperglycaemia Hyperglycaemia on waking (i.e. before breakfast) is a very common problem, and has a significant impact on overall glycaemic control. Two possible scenarios are seen, either separately or, less frequently, together:

- dawn phenomenon; and
- the Somogyi effect.

Dawn phenomenon Part of the normal physiological response to the end of sleep and impending waking is an increase in a variety of hormone levels, most particularly catecholamines and cortisol. These hormones all have an action to raise blood glucose levels in anticipation of the day to come, but their raised levels come just as most intermediate and long-acting insulin preparations are reaching the tail end of their time–action profiles, producing a 'perfect storm' of raised levels of 'anti-insulin' hormones just as insulin action is diminishing. Clearly, if this is the cause of morning hyperglycaemia, an increased dose of intermediate or long-acting insulin may be helpful, if this does not lead to hypoglycaemia at the time of peak insulin action.

Somogyi effect Depending on the timing of administration of intermediate and long-acting insulins, there is the potential for significant hypoglycaemia in the early hours of the morning, at a time of deep sleep. The hypoglycaemia often does not lead to wakening but triggers the activation of counter-regulatory responses to hypoglycaemia, such as release of catecholamines and cortisol. This physiological response overcomes the early nocturnal hypoglycaemia, but at the expense of significant hyperglycaemia on waking the following morning. The solution to this 'effect' is to reduce the amount of insulin action overnight and avoid the overnight hypoglycaemia and thus its consequent morning hyperglycaemia, precisely opposite to the management of the 'dawn phenomenon'.

Differentiation of the dawn phenomenon from the Somogyi effect is difficult, and often necessitates overnight blood glucose checks, which disturb sleep and the very profiles they seek to assess. Even more difficult is the fact that both phenomena can exist at the same time in the same insulin user: early nocturnal hypoglycaemia (Somogyi) followed by dawn phenomenon owing to waning insulin action in the face of the 'new day'. The limitations of the available intermediate- and long-acting insulins are clearly to blame.

Variability

The absorption of soluble insulin varies by 20–25% on a daily basis and between different injection/administration sites. Insulin absorption from a subcutaneous depot is even more variable as the 'behaviour' of the depot is another factor subject to injection site differences. This means that the precise time–action profile of intermediate and long-acting insulins can vary very significantly from day to day and from administration site to site. This is largely unpredictable, and therefore not open to any helpful interventions, but undermines efforts to improve glycaemic control as people with diabetes are reluctant to tighten control for fear of unpredictable hypoglycaemia.

Thus, neither short-acting nor intermediate or long-acting preparations of human insulin are really able to meet all the requirements of patients who are increasingly anxious to optimise overall glycaemic control and hence avoid long-term diabetes complications. Patients and clinicians alike were looking for better options.

Intensified Insulin Therapy

DCCT and EDIC

Despite the detailed observational data on over 4400 insulin-treated patients published in 1977 by Belgian physician Jean Pirart [4], the question of whether improving glycaemic control in type 1 diabetes really did reduce long-term diabetes complications was felt, at least by some, to be open. To obtain positive proof from a prospective, randomised and controlled study, the Diabetes Control and Complications Trial (DCCT)

was undertaken between 1983 and 1993 at 29 centres in the US [5]. A total of 1441 patients were randomly assigned to either conventional therapy (once or twice daily insulin, a largely fixed-dose strategy and three monthly follow-up) or intensive therapy (three or more daily insulin doses or insulin pump therapy, daily dose adjustment to achieve preset target blood glucose results and monthly (or more frequent) follow-up). The primary outcome was progression of diabetic retinopathy.

The intensive therapy cohort had an HbA1c roughly 2.0% (22 mmol/mol) lower than the conventional therapy group over a mean 6.5 years of follow-up. Intensive therapy reduced the risk of developing new diabetic retinopathy by 76% in those with no retinopathy at the start of the study and reduced the risk of progression of preexisting background retinopathy by 54%. Similar effects were seen on secondary endpoints such as microalbuminuria, neuropathy and macrovascular events, although the last was not statistically significant owing to low event rates in a relatively young study population. The case for intensive therapy reducing diabetic complications was widely regarded to be proven [6].

The question as to whether benefits would be maintained in the long term is the subject of the Epidemiology of Diabetes Interventions and Complications (EDIC) Study [5]. This has followed the DCCT study cohorts but allowed intensification of therapy in the cohort treated conventionally while reducing the level of supervision in the cohort treated intensively. HbA1c levels rapidly equalised, but it was 18 years after the end of the DCCT study before retinopathy prevalence roughly equalised and even after 30 years of follow-up macrovascular events are still less frequent in those who were originally randomised to intensive therapy [7], giving rise to the poorly understood concept of 'metabolic memory'. The EDIC study is due to complete in 2022.

The combined results of DCCT and EDIC made intensified insulin therapy the sought after 'gold standard' for the great majority of patients with type 1 diabetes.

UKPDS

The question as to whether improved glycaemic control would improve long-term outcomes also applied in type 2 diabetes, leading to a large, prospective study of over 5000 patients with type 2 diabetes treated at 23 centres in the UK. Fuller details of the study are contained in Chapters 2 and 3. The study, like DCCT, compared 'conventional' treatment with 'intensive' treatment, and one of the intensive treatment arms used insulin. The insulin used was a once daily dose of ultralente insulin, initially beef ultralente, and later human ultralente. The treatment target was a fasting plasma glucose <6 mmol/l [8].

The intensive treatment arm had a mean HbA1c of 7.0% (53 mmol/mol) compared with 7.9% (63 mmol/mol) in the conventional treatment arm. After ten years of follow-up, diabetes-related endpoints were reduced by 12% in the intensively treated cohort, showing the benefits of improved glycaemic control. All of the interventions in the intensively treated cohort (insulin or one of three sulfonylureas) were equally effective but, as in DCCT, both weight gain and hypoglycaemia were greater in patients treated with insulin than in the other treatment groups (conventional and sulfonylureas) [9].

The UKPDS outcomes stimulated increased efforts to improve glycaemic control in people with type 2 diabetes but reserved insulin use for patients in whom adequate

control could not be achieved with oral medicines. Human ultralente insulin was withdrawn from the European market in 2005 so it is no longer possible to replicate the insulin regimen used in UKPDS.

Side Effects of Intensified Insulin Therapy

Intensified insulin therapy was not without its drawbacks, the two major side effects being hypoglycaemia and weight gain.

Hypoglycaemia The incidence of severe hypoglycaemia, defined as hypoglycaemia requiring the assistance of a third party to provide treatment, was threefold higher in the intensively treated cohort of the DCCT as compared with those on conventional therapy [9]. Hospitalisation for treatment of hypoglycaemia was 50% more likely in those on intensive therapy. Within the DCCT study itself, these differences in hypoglycaemia rates were not associated with any observable changes in cognitive or neuropsychological function, but many other studies have shown significant concerns about long-term cognitive function in subjects with one or more severe hypoglycaemic events [10], and severe hypoglycaemia is not liked (and is even feared) by many patients, so it is a major limiting factor to intensification of insulin therapy. Clinical features of the symptoms, signs and treatment of hypoglycaemia are described in Box 7.3.

Box 7.3 Symptoms, signs, causes, diagnosis and treatment of hypoglycaemia

Symptoms and signs

- Sweating
- Fatigue
- Dizziness
- Pallor
- Weakness
- Hunger
- Tachycardia
- Blurred vision
- Confusion
- Reduced consciousness
- Coma

Causes

- Excessive dose of insulin
- Reduced food intake
- Delayed food intake
- Exercise
- Alcohol

Diagnosis and treatment

- Capillary blood glucose <4.0 mmol/l
- Clinical diagnosis alone in an emergency
- Oral fast-acting carbohydrate (glucose tablets, sweets, sugary drinks. etc.)
- Glucose gel (on buccal mucosa – gums, cheeks)
- Glucagon 1 mg subcutaneously (see Chapter 16)
- Intravenous dextrose (150–200 ml of 10% dextrose)

Weight Gain In DCCT weight gain in patients receiving intensified therapy for five years was 4.6 kg more than in patients on conventional therapy, with a doubling of the rise in BMI and a 33% increase in the risk of becoming overweight, defined as a body weight more than 120% of ideal body weight. The difference in body weight disappeared during follow-up in the EDIC study (as all subjects tended to gain weight) and, as noted above, the increased weight in the intensively treated cohort did not prevent them having lower rates of macrovascular events in the long term. Weight gain is, however, often seen as undesirable, even unacceptable, by some patients and is another limiting factor to the use of intensified insulin therapy regimens.

Place of Human Insulin in Current and Future Therapy

Insulin can be used in the management of both type 1 diabetes, in which its use is essential, and in type 2 diabetes, in which it forms one of the many treatment options for patients that are discussed in detail in this book. The demands on insulin therapy differ significantly between the two types of diabetes.

Insulin Therapy in Type 1 Diabetes

In type 1 diabetes, within a short time (a few months) after diagnosis there is usually no clinically significant residual insulin secretion from the pancreas, the pancreatic beta cells having virtually disappeared as a result of the disease process. Exogenous insulin therapy is thus aiming to provide all aspects of the patient's insulin needs, including both basal and prandial components, and requires the flexibility to cope with different patterns of food ingestion, different meal sizes and constituents and varying lifestyle factors such as physical exercise and intercurrent illness. The use of human insulin in people with type 1 diabetes has largely been replaced by the use of short- and long-acting insulin analogues (Chapter 8 and 9) or subcutaneous insulin pumps (Chapter 10), unless cost or the availability of insulin is an issue (see also Chapter 15).

Insulin Therapy in Type 2 Diabetes

In type 2 diabetes, the situation is somewhat more straightforward as most patients starting on insulin therapy will still have clinically significant residual insulin secretion from their own pancreas, albeit not enough to meet their full insulin demands (hence their diabetes). Often, simple provision of supplemental basal insulin is adequate to improve glycaemic control, the residual endogenous insulin being adequate to meet the prandial insulin requirements. The endogenous insulin is also still secreted under physiological control and can cope with varying insulin requirements on a day-to-day basis.

It should be noted, however, that type 2 diabetes is usually a progressive disease, with a slow but ongoing reduction in beta cell capacity, and that, over time, even patients with type 2 diabetes initially well controlled with only supplemental basal insulin may require intensification of their insulin regimen with, for example, prandial insulin supplementation.

Current treatment guidelines for type 2 diabetes in the UK recommend consideration of the use of insulin where adequate glycaemic control is not being achieved by the use of recommended combinations of two oral antidiabetic drugs, although the alternative option of adding a third antidiabetic drug or a GLP-1 receptor agonist is also recommended (see Chapter 15). Because of the greater frequency of hypoglycaemia in insulin-treated patients, the introduction of a third oral antidiabetic drug might be preferred in patients for whom hypoglycaemia could be potentially hazardous (e.g. frailer patients or those with limited mobility, patients living alone).

If insulin is to be used, it is recommended that once daily isophane human insulin administered at bedtime should be offered first. Assuming metformin has been tolerated and is not contraindicated, this should be continued along with insulin. The insulin dose can be titrated on the basis of fasting plasma glucose as in UKPDS. A second dose of isophane insulin at breakfast may be needed if daytime glucose levels are elevated, and biphasic insulins may be used if post-meal glucose levels are a particular problem.

All use of insulin must come with a structured education package. Current guidelines are some years old, but do note the possible advantages, for some patients, of newer insulin analogues. It is important to refer to current guidelines when actually managing patients to ensure that the most up to date advice is being followed.

References

1. Teuscher, A. and Berger, W.G. (1987). Hypoglycaemia unawareness in diabetics transferred from beef/porcine insulin to human insulin. *Lancet* 2 (8555): 382–385.
2. Gale, E.A. (1989). Hypoglycaemia and human insulin. *Lancet* 2 (8674): 1264–1266.
3. Richter, B. and Neises, G. (2005). 'Human' insulin versus animal insulin in people with diabetes mellitus. *Cochrane Database Syst Rev* 2005 (1): CD003816.
4. Pirart, J. (1978). Diabetes mellitus and its degenerative complications: a prospective study of 4,400 patients observed between 1947 and 1973. *Diabetes Care* 1 (4): 168–188.

5. Epidemiology of Diabetes Interventions and Complications (EDIC) (1999). Design, implementation, and preliminary results of a long-term follow-up of the Diabetes Control and Complications Trial cohort. *Diabetes Care* 22: 99–111.
6. The Diabetes Control and Complications Trial Research Group (1993). The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. *N Engl J Med* 329: 977–986.
7. The Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications Study Research Group (2016). Intensive diabetes treatment and cardiovascular outcomes in type 1 diabetes: the DCCT/EDIC Study 30-year follow-up. *Diabetes Care* 39: 686–693.
8. UK Prospective Diabetes Study (UKPDS) Group (1998). Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). *Lancet* 352: 837–853.
9. The Diabetes Control and Complications Trial Research Group (1995). Adverse events and their association with treatment regimens in the Diabetes Control and Complications Trial. *Diabetes Care* 18: 1415–1427.
10. Lacy, M.E., Gilsanz, P., Eng, C. et al. (2020). Severe hypoglycemia and cognitive function in older adults with type 1 diabetes: the Study of Longevity in Diabetes (SOLID). *Diabetes Care* 43: 541–548.

CHAPTER 8

Short-acting Insulin Analogues

Kate Hughes and Gerry McKay

KEY POINTS

- The development of short-acting (prandial) insulin analogues has been key in the development of more flexible insulin strategies attempting to mirror physiological insulin secretion and reduce the time before a meal that the insulin needs to be taken.
- Several methods have been used to alter the pharmacokinetics and pharmacodynamics of human insulin using recombinant DNA techniques, rendering them faster acting, either by altering the molecule or by adapting the excipients as a means of trying to quicken absorption.
- The first fast-acting insulin analogues improved absorption by changes to the amino acid sequence, and second-generation ultrafast-acting insulin analogues by changes to the formulation.

Introduction

As outlined in Chapter 7, soluble insulin has a relatively slow onset of action. In the fasting state, where the pancreas is working normally, insulin and glucagon are secreted together to maintain normal blood glucose. At mealtimes there is an increase in insulin secretion into the portal circulation with up to 60% cleared by the liver. Recombinant DNA techniques allowed for the development of human insulin, but since these soluble insulins are subcutaneously delivered like their animal predecessors, they must be administered 30 minutes before eating to avoid excess postprandial hyperglycaemia. This is because there is an inevitable delay between insulin absorption in the subcutaneous fat and insulin

Diabetes Drug Notes, First Edition. Edited by Miles Fisher, Gerard A. McKay, and Andrea Llano.

reaching liver, muscle and fat where it acts. With the emergence of structured education, basal bolus dosing and increased sophistication of monitoring, the limitations of soluble insulin have become more apparent. Alongside attempts to lengthen the time–action profile to produce more predictable basal insulins (described in Chapter 9), human insulin has also been manipulated to shorten the time–action profile. Improving prandial insulin delivery was also an important strategy in trying to improve blood glucose control.

Factors Affecting Absorption and Metabolism of Short-acting Insulin

Good injection technique and practices are especially important for short-acting insulin delivery because it is injected multiple times per day to cover mealtimes as part of a basal bolus treatment strategy. External factors that can adversely affect the absorption of subcutaneous inulin and thus cause poor glucose control can be addressed by education. The key issues frequently encountered in diabetes clinics are over-used injection sites, resulting in lipohypertrophy and lipoatrophy, incorrect injection site, e.g. into muscle, and poor injection technique (e.g. not doing an 'air shot' prior to administration, not changing needles each injection and not storing insulin correctly).

Other factors leading to variable insulin requirements include differences in the site of injection (upper abdominal absorption is quicker than the thigh or hip) and in the volume of insulin injected (larger volumes may be absorbed less rapidly). Adherence to therapy, lifestyle factors (alcohol intake, diet and exercise, temperature) and other medical conditions, e.g. thyroid, renal, adrenal disease and complications from diabetes such as impaired gut motility resulting in gastroparesis, can also affect the pharmacokinetics and hence the effective dose.

Some medications can alter glucose metabolism. Those that may reduce insulin requirements include concomitant use of oral antidiabetic drugs, beta-blockers, ACE inhibitors and salicylates. Conversely, oral contraceptives, thiazides, glucocorticoids and growth hormone may increase insulin requirements.

Manufacturing Insulin Analogues

The initial strategy to improve insulin absorption targeted using recombinant DNA technology to alter the sequence of amino acids in the peptide, in an attempt to make it less likely to aggregate into dimers and hexamers. There were considerable concerns about the likelihood of side effects, with earlier studies halted owing to concerns of toxicity. In 1988 Novo Nordisk announced the development of their prototype analogue, B10Asp which, as a consequence of slight modification of the human insulin molecule, did not aggregate as much as human insulin and was absorbed from subcutaneous tissue 15 minutes earlier. Initial clinical studies did not seem to show much benefit

with regards to improvements in HbA1c, and development was halted in 1992 when it was shown to promote breast cancer in rats.

The first commercially available analogue in the UK was the fast-acting insulin lispro (Humalog®) approved in 1996. This was followed by insulin aspart (Novorapid®), which also caused safety concerns, particularly given that it was closer in structure to insulin-like growth factor 1 (IGF-1) than human insulin [1], and insulin glulisine (Apidra®) (Table 8.1). Insulin lispro and insulin aspart were also developed as mixed insulins along with intermediate-acting human insulin and some of these are still available for clinical use (Table 8.2). More recently further modifications of the formulations of insulin aspart and insulin lispro have been made to provide for an ultrafast-acting effect marketed as Fiasp® and Lyumjev® respectively. All fast-acting insulin analogues have a faster onset and a shorter duration of action than soluble human insulin but, by design, equipotent glucose-lowering activity.

TABLE 8.1 **Approximate onset, peak and duration of action of short-acting insulin analogue**

Insulin analogue	Trade name/company	Onset of action	Peak	Duration of action
Insulin lispro	Humalog® Eli Lilly	10–20 minutes	1–3 hours	3–5 hours
Insulin aspart	NovoRapid® Novo Nordisk	10–20 minutes	1–3 hours	3–5 hours
Insulin glulisine	Apidra® Sanofi	10–20 minutes	2–3 hours	3–5 hours
Fast-acting insulin aspart	FiASP® Novo Nordisk	5–10 minutes	1–2 hours	3–4 hours
Ultra rapid insulin lispro	Lyumjev® Eli Lilly	5–10 minutes	1–2 hours	3–4 hours

Source: Based on [1].
The total exposure to insulin for faster acting insulin analogues compared with insulin analogues is the same but seen earlier.

TABLE 8.2 **Fixed mixtures containing short-acting insulin analogues**

Humalog Mix25® (Eli Lilly)	25% insulin lispro, 75% insulin lispro protamine suspension
Humalog Mix50® (Eli Lilly)	50% insulin lispro, 50% insulin lispro protamine suspension
NovoMix 30® (Novo Nordisk)	30% insulin aspart, 70% protamine crystallised insulin
Ryzodec IDegAsp® (Novo Nordisk)	30% insulin aspart, 70% inslin degludec

Short-acting Insulin Analogues

Insulin Lispro

There is transposition of proline and lysine at positions 28 and 29 in the *C*-terminus of the B chain (Figure 8.1) in insulin lispro and it is manufactured by Eli Lilly under the brand name Humalog. At physiological concentrations insulin lispro exists in solution as a monomer, allowing better absorption. When insulin lispro is injected subcutaneously, the onset of action occurs within 15 minutes of injection, the maximum effect is reached at one to three hours and the duration of action is three to five hours. In a small study comparing lispro and regular human insulin before a carbohydrate-rich meal in people with type 1 diabetes, prandial blood glucose excursions after a meal were shown to be reduced in the insulin lispro group [2].

Insulin lispro was the first short-acting insulin analogue approved for use by the EMA in 1996. It was approved for use on the basis of a development programme that included eight clinical trials, four in people with type 1 diabetes and four in people with type 2 diabetes. Six of the trials were in people with previously diagnosed diabetes and two in newly diagnosed diabetes (one in type 1 diabetes, one in type 2 diabetes) [3].

These trials included a total of 2951 patients randomised to insulin lispro or Humulin R (recombinant soluble rDNA human insulin) along with once or twice daily basal insulin (NPH or ultralente – see Chapter 7). The main findings were as follows:

- There were no statistically significant differences in HbA1c or fasting blood glucose.
- The glucose excursions at one hour and at two hours were lower with insulin lispro, although statistical differences were not achieved in four of eight studies at one hour and in two of eight studies for the two hour levels despite being given just before meals.

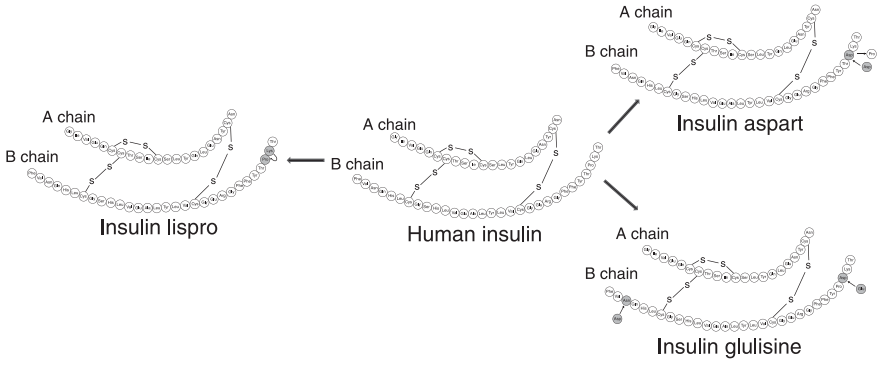


FIGURE 8.1 Structures of short-acting insulin analogues. Insulin lispro has a transposition of proline and lysine at positions 28 and 29, insulin aspart has an aspartic acid molecule that replaces a proline amino acid in position 28 and insulin glulisine has a lysine amino acid that replaces asparagine at position B3 of the molecule and a glutamic acid that replaces a lysine at position B29 of the B chain.

- The rate (episodes/30 days) of hypoglycaemia was significantly reduced in type 1 subjects on insulin lispro.
- No relevant findings have been found in relation to toxicity.

Subsequent studies in children and pregnancy showed similar benefits.

Formulations

- Insulin lispro (Humalog) U100 is available in vials, cartridges and pre-filled pens.
- Insulin lispro is also available in U200 strength in a disposable pen.
- Insulin lispro is available as a premixed insulin as Humalog Mix 25® (25% insulin lispro, 75% insulin lispro protamine suspension) and Humalog Mix 50® (50% insulin lispro, 50% insulin lispro protamine suspension).

Prescribing point: *Care is required when prescribing Humalog, Humalog Mix25 and Humalog Mix50 as prescribing errors have been documented when the patient has been given the wrong formulation.*

Insulin Aspart

An aspartic acid molecule replaces a proline amino acid in position 28 of the molecule (Figure 8.1) in insulin aspart, which makes it less likely to aggregate, and it is manufactured under the brand name NovoRapid by Novo Nordisk. When insulin aspart is injected subcutaneously, the onset of action occurs within 15 minutes of injection, the maximum effect is reached at one to three hours and the duration of action is three to five hours (Table 8.1).

Insulin aspart was first approved for use by the EMA in 1999. The regulatory approval was on the basis of one exploratory four-week cross-over phase 2 clinical study (104 randomised, 90 completers) and three six-month phase 3 clinical studies, two in people with type 1 diabetes (1954 participants randomised) and one in people with type 2 diabetes (182 participants randomised) comparing insulin aspart and human insulin [4]. The main findings were as follows:

- In type 1 diabetes insulin aspart reduced HbA1c levels by 0.12 and 0.15% more than human insulin after six months.
- In type 2 diabetes no significant differences were observed, but according to preplanned criteria, noninferiority of insulin aspart to human insulin was observed.
- For type 1 diabetes mean postprandial blood glucose levels at six months were significantly lower in the insulin aspart group compared with the human insulin group after all three meals.
- There was no treatment difference between pre- and postprandial blood glucose levels or bedtime and nighttime blood glucose levels in type 2 diabetes.
- There were no relevant differences between treatment groups noted regarding the incidence of hypoglycaemic events.
- No relevant findings have been found in relation to toxicity.

In subsequent studies in pregnancy women with type 1 diabetes or gestational diabetes, no differences in safety parameters were observed in those treated with insulin aspart compared with human insulin [5].

One of the clinical studies comparing insulin aspart and human insulin, both with basal NPH, in a multicentre, prospective randomised trial, was published with more details and showed lower HbA1c levels at six months and lower postprandial blood glucose levels. There was less overnight and late postprandial hypoglycaemia in the insulin aspart group [6].

Formulations

- Insulin aspart (NovoRapid) U100 is available in vials, cartridges and pre-filled pens.
- NovoRapid PumpCart® is a 100 units/ml preparation of insulin aspart that can be used in insulin pumps where basal insulin is provided by a continuous infusion of short-acting insulin (see Chapter 10).
- Insulin aspart is available as a premixed insulin as NovoMix 30® (30% insulin aspart, 70% protamine crystallised insulin aspart), and in the EU but not the UK as Ryzodec® (30% insulin aspart, 70% insulin degludec).

Prescribing point: *Care is required when prescribing NovoRapid and NovoMix 30® as prescribing errors have been documented when the patient has been given the wrong formulation. Errors can also happen at the point of dispensing and administration.*

Insulin Glulisine

A lysine amino acid replaces asparagine at position B3 of the molecule and glutamic acid replaces a lysine at position B29 in insulin glulisine (Figure 8.1). It is manufactured under the brand name Apidra by Sanofi. When injected subcutaneously, the glucose-lowering activity will begin within 10–20 minutes, peaking at one to three hours, and the duration of action is three to five hours. (Table 8.1).

Insulin glulisine was first approved for use by the EMA in 2004. The regulatory approval was on the basis of four studies, three in people with type 1 diabetes (two with a total of 1549 adults and in one with 572 children and adolescents aged 4–17 years) and one in people with type two diabetes (878 adults randomised) comparing insulin glulisine with human insulin or insulin lispro [7]. The main findings were:

- In the first study of adults with type 1 diabetes there was a decrease of 0.14% for both the group treated with insulin glulisine and the comparator insulin lispro.
- Similar findings were seen in the second study in type 1 diabetes which compared insulin glulisine with human insulin.
- In the study in children and adolescents, insulin glulisine and comparator insulin lispro produced similar changes in HbA1c, but not enough evidence to show whether it was effective in children under the age of 6 years.
- In type 2 diabetes HbA1c was reduced by 0.46% for insulin glulisine compared with 0.30% for human insulin.

A study comparing premeal insulin glulisine and human insulin in subjects with type 1 diabetes demonstrated lower glucose excursions with insulin glulisine [8].

Formulations

- Insulin glulisine (Apidra) U100 is available in vials, cartridges and pre-filled pens.

Meta-analysis of Short-acting Insulin Analogues

A meta-analysis of studies looking at short-acting insulin analogues has been undertaken to clarify whether they add value to the management of people with diabetes. When undertaking these studies important primary outcomes include improved glycaemic control but also postprandial glucose excursions and episodes of hypoglycaemia.

In a meta-analysis of 22 studies ($n = 6235$) in people with type 1 diabetes [9], short-acting insulin analogues were associated with:

- A decrease in total hypoglycaemic episodes (rate ratio, RR 0.93; 95% CI 0.87–0.99; 6235 patients; $I^2 = 81\%$), nocturnal hypoglycaemia (RR 0.55; 95% CI 0.40–0.76; 1995 patients; $I^2 = 84\%$) and severe hypoglycaemia (RR 0.68; 95% CI 0.60–0.77; 5945 patients; $I^2 = 0\%$).
- Lower postprandial glucose levels (mean difference, MD, −19.44 mg/dl; 95% CI −21.49 to −17.39; 5031 patients; $I^2 = 69\%$).
- Lower HbA1c (MD −0.13%; IC 95% −0.16 to −0.10; 5204 patients; $I^2 = 73\%$) levels.

I^2 is a measure of the heterogeneity of the studies included in the meta-analysis. Heterogeneity as determined by the chi-square test was considered non-significant for I^2 values between 0 and 50%, moderate for values between 51 and 79% and significant for values between 80 and 100%. Thus, the results should be interpreted with caution.

In a meta-analysis looking at the use of short-acting insulin analogues, 27 studies ($n = 7452$) including use in people with type 2 diabetes, were included [10]. The following findings were reported:

- The difference in postprandial glucose between short-acting analogue insulin vs. short-acting human insulin was significant in subjects with type 1 diabetes (−22.2 mg/dl; 95% CI −27.4 to −17.0 mg/dl; $p < 0.0001$).
- There was no significant difference in postprandial glucose in subjects with type 2 diabetes.
- For preprandial glucose, there was a nonsignificant trend favouring regular human insulins in type 1 diabetes; no data were available for patients with type 2 diabetes. In patients with type 1 diabetes, the between-group difference in end of treatment HbA1c favoured rapid-acting insulin analogues.

TABLE 8.3 Biosimilar short-acting insulin analogues

Biosimilar insulin	Company	EMA approval	Available
Insulin lispro (Admelog)	Sanofi	2017	2018
Insulin aspart (Trurarpi)	Sanofi	2020	2021
Insulin aspart (Kirsty)	Viatris	2021	No

Biosimilar Short-acting Insulin Analogues

There are three fast-acting prandial biosimilar insulin analogues that have been approved for use in the EU. The process of getting regulatory approval driven by the potential for cost savings for healthcare systems is much simpler than the standard approval process and is described in Chapter 1. In order to get regulatory approval similar pharmacokinetic and pharmacodynamic properties have to be shown and the three available (Table 8.3) have similar benefits mainly with regard to reducing postprandial glucose excursions and reducing hypoglycaemia whilst being able to be injected with meals. To date, two of these (Admelog®, Sanofi, and Trurapi®) have been made available for clinical use.

Formulations

- Insulin lispro (Admelog) U100 is available in vials, cartridges and pre-filled pens.
- Insulin aspart (Trurapi) U100 is available in vials, cartridges, and pre-filed pens.

Prescribing point: *Prescribing biosimilar insulins provide an opportunity for healthcare providers to make cost savings.*

Second-generation Ultrafast-acting Insulin Analogues

Rather than changing the molecule further by recombinant DNA technology, research has gone into developing formulations for fast-acting analogues that would render them more absorbable from subcutaneous tissue. There are currently two ultrafast-acting insulin analogues, fast-acting insulin aspart (FiASP®), manufactured by Novo Nordisk, and ultra-rapid insulin lispro (Lyumjev®), manufactured by Eli Lilly.

Fast-acting Insulin Aspart

Fast-acting insulin aspart has the addition of L-arginine and niacinamide (vitamin B3). Niacinamide promotes a more rapid absorption of faster aspart by accelerating the dis-

sociation of hexamers into monomers, and L-arginine, a naturally occurring amino acid, acts as a stabilising agent, resulting in an accelerated initial absorption (Table 8.1).

In a pooled analysis of 218 adult subjects with type 1 diabetes from six randomised, double-blind cross-over trials in the faster aspart clinical development programme it was clearly shown that the pharmacokinetic and pharmacodynamic profiles were left-shifted for faster aspart vs. insulin aspart [11]:

- Onset of appearance occurred 4.9 min earlier for fast-acting insulin aspart compared with aspart (95% CI −5.3 to −4.4; $p < 0.001$).
- Early exposure (AUC) was two times greater (estimated ratio of faster aspart/insulin aspart 2.01; 95% CI 1.8 to −2.17; $p < 0.001$).
- Offset of exposure (t) occurred 12.2 min earlier (95% CI −17.9 to −6.5; $p < 0.001$).

As a consequence of the pharmacokinetic changes, the pharmacodynamic benefits of fast-acting insulin aspart compared with aspart are:

- Onset of action occurred 4.9 min earlier (95% CI −6.9 to −3.0; $p < 0.001$).
- Early glucose-lowering effect was 74% greater (1.74; 95% CI 1.47–2.10; $p < 0.001$).
- Offset of glucose effect occurred 14.3 min earlier (95% CI −22.1 to −6.5; $p < 0.001$).
- Total exposure and total glucose-lowering effect did not differ significantly between treatments.

Onset 1 was a 26 week randomised, double-blind, basal bolus (BB), treat-to-target trial including 1143 adults with type 1 diabetes where subjects had mealtime faster aspart ($n = 381$), insulin aspart ($n = 380$) or open-label post-meal faster aspart ($n = 382$), all in combination with basal insulin detemir [12]. The following results were found:

- There was noninferiority to insulin aspart for both mealtime and post-meal faster aspart in HbA1c reduction ($p < 0.0001$).
- Mealtime faster aspart statistically significantly reduced HbA1c compared with insulin aspart ($p = 0.0003$).
- Compared with insulin aspart, faster aspart provided superior mealtime postprandial glucose control.
- There was no difference in overall rate of severe or blood glucose-confirmed hypoglycaemia.

In an additional treatment period for Onset 1, taking it out to 52 weeks and including 761 adults with type 1 diabetes on either mealtime faster aspart or insulin aspart, each with once or twice daily insulin detemir, the following results were reported [13]:

- Mean change in baseline in HbA1c levels for faster aspart was −0.8% and that for insulin aspart was +0.01%.
- Changes from baseline in one hour postprandial glucose increment significantly favoured faster aspart.
- There was no difference in overall severe or blood glucose-confirmed hypoglycaemia.

Onset 2 was a 26 week, double-blind, BB, treat-to-target trial in 699 adults with type 2 diabetes where subjects had mealtime faster aspart ($n = 345$) or aspart ($n = 344$) in addition to basal insulin glargine and metformin [14]. The following results were found:

- There was noninferiority of faster aspart vs. insulin aspart in reducing HbA1c (Estimated treatment difference −0.02%; 95% CI −0.15–0.10).
- Compared with insulin aspart, faster aspart provided superior one hour but not two to four hour mealtime postprandial glucose control.
- There was no difference in overall rate of severe or blood glucose-confirmed hypoglycaemia but an increase in post-meal hypoglycaemia with faster aspart.

Onset 3 was an open-label, randomised, 18 week trial in adults ($n = 236$) with inadequately controlled type 2 diabetes receiving basal insulin and oral antidiabetic drugs to receive a BB regimen or to continue basal insulin both with metformin [15].

- The estimated treatment difference in HbA1c was 0.94% (95% CI −1.17 to −0.720); −10.3 mmol/mol (95% CI −12.8 to −7.8; $p < 0001$).
- Reductions from baseline in overall mean two hour post-prandial glucose and overall post-prandial glucose increment for all meals (self-measured plasma glucose profiles) were statistically significant in favour of BB treatment ($p < 0001$).
- Severe/blood glucose-confirmed hypoglycaemia rate (12.8 vs. 2.0 episodes per patient year of exposure), total daily insulin (1.2 vs. 0.6 U/kg) and weight gain (1.8 vs. 0.2 kg) were greater with BB than with basal-only treatment.

Formulations

- Insulin aspart (Fiasp) U100 is available in vials, cartridges, pre-filled pens and pump cartridges.

Prescribing point: *When prescribing fast-acting prandial insulin it is important that the user understands that there cannot be a delay in eating owing to the risk of hypoglycaemia. The risk is outweighed by the clear benefits of being able to take prandial insulin when eating.*

Ultra-rapid Insulin Lispro

Ultra-rapid insulin lispro has the addition of citrate, to aid vasopermeability, and treprostinil, to aid vasodilation, allowing for faster absorption. It is produced by Eli Lilly under the name Lyumjev. A phase 1 study demonstrated ultra-rapid insulin lispro achieving the greatest numerical reduction in postprandial glucose at two hours post-meal [16].

PRONTO-T1D was a 26 week treat-to-target phase 3 trial in adults with type 1 diabetes evaluating the efficacy of ultra-rapid insulin lispro vs. insulin lispro. There was an eight week run-in to optimise basal insulin glargine or degludec before randomisation to double-blind mealtime ultra-rapid lispro ($n = 451$) or insulin lispro ($n = 442$), or open-label post-meal ultra-rapid insulin lispro ($n = 329$). The primary endpoint was change to baseline HbA1c with multiplicity-adjusted objectives for postprandial glucose excursions after a meal test. The results were as follows:

- Both mealtime and post-meal ultra-rapid insulin lispro were noninferior to insulin lispro for HbA1c: the estimated treatment difference for mealtime ultra-rapid insulin lispro was −0.08% (95% CI −0.16–0.00) and for post-meal ultra-rapid insulin lispro was +0.13% (95% CI 0.04–0.22).
- Mealtime ultra-rapid insulin lispro was superior to insulin lispro in reducing one and two hour postprandial glucose excursions during the meal test (estimated treatment difference, −1.55 mmol/l (95% CI −1.96 to −1.14) at one hour and −1.73 mmol/l (95% CI −2.28 to −1.18) at two hours (both $p < 0.001$)).
- The rate and incidence of severe, documented and postprandial hypoglycaemia (<3.0 mmol/l) were similar between treatments, but mealtime ultra-rapid insulin lispro demonstrated a 37% lower rate in the period more than four hours after meals ($p = 0.013$)
- Injection site reactions were reported by 2.9% of patients on mealtime ultra-rapid insulin lispro, 2.4% of those on post-meal ultra-rapid insulin lispro and 0.2% of those on insulin lispro.

PRONTO 2 was a double-blind 26 week study in people with type 2 diabetes [17]. After an eight week lead-in to optimise basal insulin glargine or insulin degludec in combination with prandial insulin lispro treatment, patients were randomised to blinded ultra-rapid insulin lispro ($n = 336$) or insulin lispro ($n = 337$) injected zero to two minutes prior to meals. Patients could continue metformin and/or a sodium-glucose cotransporter 2 inhibitor. The primary endpoint was a change in HbA1c from baseline to 26 weeks. The results showed:

- Noninferiority of ultra-rapid insulin lispro vs. insulin lispro in HbA1c reduction.
- Improved post-meal plasma glucose for ultra-rapid insulin lispro.
- No significant treatment differences in rates of severe or documented hypoglycaemia (<3.0 mmol/l).

Formulations

- Insulin lispro (Lyumjev) U100 is available in vials, cartridges and pre-filled pens.
- Insulin lispro (Lyumjev) is also available in U200 strength in a pre-filled pen.

Other Attempts to Improve Insulin Absorption and Inhaled Insulin

Despite the advances in absorption of short-acting insulin analogues over human insulin, delivery through subcutaneous tissue remains a cause of a significant delay in the entry of insulin into the bloodstream. Further strategies have been investigated to address this issue and there have been several attempts to overcome this problem, but

so far none has been adopted into routine clinical practice. For example, coadministration of recombinant human hyaluronidase enzyme with analogue insulins has been shown to accelerate insulin absorption and cause faster onset of insulin action and a shorter duration of action, but has not progressed into phase 3 clinical trials [18].

Other investigators have studied the use of dispersed boluses to aid absorption via increasing the surface area to which the insulin is delivered [19]. The use of heating devices, e.g. InsuPatch®, to increase absorption by increasing local blood flow, has also been studied [20], but neither has entered routine clinical use.

There has been considerable interest in inhaled insulin, to allow patients to avoid the inconvenience of injections as well as the risks of infection and insulin-related skin issues. The FDA previously approved Exubra®, an inhaled insulin produced by Pfizer, for use in diabetes. It was not commercially successful, perhaps owing to the inconvenience of carrying the large device needed to deliver the drug, and it was withdrawn from all markets.

Technosphere Inhaled Insulin

One inhaled insulin powder is currently available, Technosphere insulin (Afrezza®, Mannkind). This product is adsorbed onto particles which dissolve on inhalation and are absorbed from the lungs into the pulmonary vasculature before being rapidly dispersed through the systemic circulation [21]. The time to peak concentration is 12–17 minutes. Despite this potentially faster route of absorption than via adipose tissue, Afrezza did not achieve faster onset of activity compared with insulin lispro but was noninferior with regards to HbA1c reduction [22]. Afrezza has been approved by the FDA for glycaemic control in adults with diabetes. However, it must be used with a basal insulin in type 1 diabetes and cannot be used for treatment of DKA or in patients who smoke. Initial data from the STAT study reported improved time in range and postprandial glucose levels in patients with type 1 diabetes who used additional inhalations as directed [23].

Place of Short-acting Insulin Analogues in Current and Future Practice

Intensive Insulin Therapy

The DCCT study showed that intensive insulin treatment of type 1 diabetes reduces the risk of microvascular complications (see Chapter 7). If this is to be achieved, however, insulin regimens must closely mimic the normal physiology. This has meant that simple twice daily regimens based on mixed (short- and long-acting) insulins (such as Humulin M3 and NovoMix 30) have for most patients been superseded by modern insulin regimens for people with type 1 diabetes.

Modern insulin regimens are designed to recreate the normal physiological fluctuations of endogenous pancreatic insulin secretion, allow a flexible lifestyle and achieve the glycaemic targets recommended in guidelines, thereby reducing the risk of microvascular complications and hypoglycaemia. These flexible regimens involve both a basal dose and multiple doses of short-acting insulin per day. The former is intended to replace background pancreatic function and the latter is designed to replace prandial insulin secretion, and so must be varied according to food intake, the current blood glucose levels and planned exercise.

This approach is referred to as basal bolus therapy requiring a combination of long- and short-acting insulin analogues. The former are covered in Chapter 9 and short-acting insulin analogues infused continuously in an insulin pump are covered in Chapter 10.

Structured Education

Structured education programmes are a key aspect of diabetes management, empowering individuals to self-manage their diabetes. These courses not only improve an individual's knowledge of diabetes, but also aid insulin adjustment through carbohydrate counting. This in turn can be used to teach patients how to manage their insulin during illnesses, exercise and social activities in order to maintain blood glucose levels within target ranges. For type 1 diabetes, structured education courses available include ASPIRE, DAFNE (Dose Adjustment For Normal Eating) and BERTIE (Beta Cell Education Resources for Training in Insulin and Eating). An important factor making insulin adjustment possible is the availability of short-acting insulin analogues which can mimic prandial insulin secretion.

Carbohydrate counting is a key principle in self-management and insulin adjustment in diabetes. In carbohydrate counting, the individual measures the number of grams of carbohydrate in a particular meal and the dose of prandial insulin administered is calculated for that amount. Each individual has a specific ratio of insulin to carbohydrate which is used to calculate the prandial insulin dose, e.g. 1 unit of prandial insulin per 10 g of carbohydrate. This ratio may vary at different times of the day and also with insulin sensitivity, body weight and activity levels. In addition, the amount of insulin required also depends on the prevailing blood glucose level, any illness or any planned activity. Extra doses of short-acting analogue insulin can be taken, e.g. for hyperglycaemia. This is termed a correction dose, which was not possible with older regimens using longer-acting or mixed insulins. Correction doses can be calculated using an insulin sensitivity factor which refers to how much the blood glucose will fall with 1 unit of short-acting insulin.

Alternative Routes of Insulin Delivery

Prospects for future developments in this area include novel delivery methods for prandial insulins, to prevent the delay from insulin administration to insulin action and also to reduce the burden of fluctuations in glucose levels and calculations needed to

ensure an adequate insulin dose. One such product available in some countries is Generex's Oral-Lyn buccal human insulin [24]. This is a liquid insulin that is sprayed into the mouth and the insulin is absorbed via the buccal musosa and could provide an alternative to prandial insulin injections. In addition, smart insulin patches which have the ability to sense the need for insulin and deliver it are being investigated [25]. These patches are made from a glucose-sensing polymer that is encapsulated with insulin. Microneedles are attached to the patch and, when placed, penetrate under the skin and sense blood glucose levels, allowing the patch to automatically respond to changing blood glucose levels by releasing more or less insulin as required.

References

1. Amiel, S.A. (1998). Learning to use a new drug – the fast acting insulin analogues. Diabet Med 15: 537–538.
2. Heinemann, L., Heise, T., Wahl, L.C. et al. (1996). Prandial glycaemia after a carbohydrate-rich meal in type 1 diabetic patients: using the rapid acting insulin analogue [Lys(B28), Pro(B29)] human insulin. Diabet Med 13: 625–629.
3. Insulin Lispro Scientific Discussion (2005). https://www.ema.europa.eu/en/documents/scientific-discussion/humalog-epar-scientific-discussion_en.pdf (accessed 19 December 2021).
4. Insulin Aspart Scientific Discussion (2004). https://www.ema.europa.eu/en/documents/scientific-discussion/novorapid-epar-scientific-discussion_en.pdf (accessed 19 December 2021).
5. Mathiesen, E.R., Kinsley, B., Amiel, S.A. et al. (2007). Maternal glycaemic control and hypoglycaemia in type 1 diabetic pregnancy: a randomised trial of insulin aspart versus human insulin in 322 pregnant women. Diabetes Care 30: 771–776.
6. Home, P.D., Lindholm, A., and Riis, A. (2000). Insulin aspart vs. human insulin in the management of long-term blood glucose control in Type 1 diabetes mellitus: a randomized controlled trial. Diabet Med 17: 762–770.
7. Insulin Glulisine Scientific Discussion (2005). https://www.ema.europa.eu/en/documents/scientific-discussion/apidra-epar-scientific-discussion_en.pdf (accessed 19 December 2021).
8. Arave, K., Klein, O., Frick, A.D., and Becker, R.H. (2006). Advantage of premeal-injected insulin glulisine compared with regular human insulin in subjects with type 1 diabetes. Diabetes Care 29: 1812–1817.
9. Melo, K.F., Bahia, L.R., Pasinato, B. et al. (2019). Short-acting insulin analogues versus regular human insulin on post prandial glucose and hypoglycemia in type 1 diabetes mellitus: a systematic review and meta-analysis. Diabetol Metab Syndr 11: 2–13.
10. Nicolucci, A., Ceriello, A., Di Bartolo, P. et al. (2020). Rapid-acting insulin analogues versus regular human insulin: a meta-analysis of effects on glycemic control in patients with diabetes. Diabetes Ther 11: 573–584.
11. Heise, T., Pieber, T.R., Danne, T., Erichsen, L., and Haahr, H. (2017). A pooled analysis of clinical pharmacology trials investigating the pharmacokinetic and pharmacodynamic characteristics of fast-acting insulin aspart in adults with type 1 diabetes. Clin Pharmacokinet 56: 551–559.
12. Russell-Jones, D., Bode, B.W., De Block, C. et al. (2017). Fast-acting insulin aspart improves glycemic control in basal-bolus treatment for type 1 diabetes: results of a 26-week multicenter, active-controlled, treat-to-target, randomized, parallel-group trial (Onset 1). Diabetes Care 40: 943–950.

13. Mathieu, C., Bode, B.W., Franek, E. et al. (2018). Efficacy and safety of fast-acting aspart in comparison with insulin aspart in type 1 diabetes (onset 1): a 52-week, randomized, treat-to-target, Phase III trial. Diabetes Obes Metab 20: 1148–1155.
14. Bowering, K., Case, C., Harvey, J. et al. (2017). Faster aspart versus insulin aspart as part of a basal-bolus regimen in inadequatley controlled type 2 diabetes: the onset 2 trial. Diabetes Care 40: 951–957.
15. Rodbard, H.W., Tripathy, D., Velazquez, M.V. et al. (2017). Adding fast-acting insulin to basal insulin significantly improved glycaemic control in patients with type 2 diabetes: a randomised, 18 week, open label, phase 3 trial (Onset 3). Diabetes Obes Metab 19: 1389–1396.
16. Klaff, L., Dachuang, C., Dellva, M.A. et al. (2020). Ultra rapid lispro improves postprandial glucose control compared with lispro in patients with type 1 diabetes: results from the 26-week PRONTO-T1D Study. Diabetes Obes Metab 22: 1799–1807.
17. Blevins, T., Zhang, Q., Frias, J.P. et al. (2020). Randomized double-blind clinical trial comparing ultra rapid lispro with lispro in a basal-bolus regimen in patients with type 2 diabetes: PRONTO-T2D. Diabetes Care 43: 2991–2998.
18. Morrow, L., Muchmore, D.B., Hompesch, M., Ludington, E.A., and Vaughn, D.E. (2013). Comparative pharmacokinetics and insulin action for three rapid-acting insulin analogs injected subcutaneously with and without hyaluronidase. Diabetes Care 36 (2): 273–275.
19. Mader, J.K., Birngruber, T., Korsatko, S. et al. (2013). Enhanced absorption of insulin aspart as the result of a dispersed injection strategy tested in a randomized trial in type 1 diabetic patients. Diabetes Care 36: 780–785.
20. Landau, Z., Klonoff, D., Nayberg, I. et al. (2014). Improved pharmacokinetic and pharmacodynamic profiles of insulin analogues using InsuPatch, a local heating device. Diabetes Metab Res Rev 30: 686–692.
21. Rave, K., Potocka, E., Boss, A.H. et al. (2009). Pharmacokinetics and linear exposure of AFRESA™ compared with the subcutaneous injection of regular human insulin. Diabetes Obes Metab 11: 715–720.
22. Bode, B.W., McGill, J.B., Lorber, D.L. et al. (2015). Inhaled Technosphere insulin compared with injected prandial insulin in type 1 diabetes: a randomized 24-week trial. Diabetes Care 38: 2266–2273.
23. Snell-Bergeon, J.K., Akturk, H.K., Rewers, A. et al. (2018). Improved time-in-range (tir) on continuous glucose monitor (cgm) with Technosphere Inhaled Insulin (TI) compared with insulin aspart in t1d patients. Diabetes Technol Ther 20: 639–647.
24. Oral-Lyn – Oral spray formulation of human insulin for types 1 and 2 diabetes. https://www.clinicaltrialsarena.com/projects/oral-lyn (accessed 19 December 2021).
25. Smart insulin. https://www.diabetes.co.uk/insulin/smart-insulin.html (accessed 19 December 2021).

CHAPTER 9

Long-acting Insulin Analogues

Robert Lindsay

KEY POINTS

- The development of longer-acting insulins has been key to more flexible insulin strategies attempting to mirror physiological insulin secretion.
- Several methods have been used to alter the pharmacodynamics of insulin analogues and render them longer acting, predominantly supporting dimerisation and hexamerisation at injection sites or increasing protein binding, particularly to albumin.
- First- and second-generation, genetically engineered, long-acting insulin analogues offer pharmacodynamic advantages with less of a peak of insulin action and a longer duration of action. This in turn has translated into fewer hypoglycaemic episodes compared with isophane insulin. These benefits are most marked in people with type 1 diabetes and differences between the novel insulins themselves are less marked.
- These modifications have allowed reliable strategies of once daily rather than twice daily dosage and with the most recent formulations may allow once weekly dosage.
- Owing to the alteration of molecular structure, there were theoretical concerns over an increased propensity of insulin analogues to be associated with side effects and unexpected effects, including diabetes complications and even malignancy. These concerns have not been borne out in longer-term evidence but will be an important point of scrutiny with each new agent.

Diabetes Drug Notes, First Edition. Edited by Miles Fisher, Gerard A. McKay, and Andrea Llano.

Introduction

Insulin injected subcutaneously has a short duration of action and initially had to be administered several times a day. A key early pharmacological aim was extension of the half-life of insulin after injection, eventually leading to the range of long-acting insulins available today and different clinical patterns of insulin administration.

Older Strategies to Extend the Action of Insulin

Several strategies have been used to extend the half-life and action of insulin. Physiologically, insulin eventually circulates and binds to receptors as monomers. By contrast, during the synthesis of insulin intracellularly, after cleavage from proinsulin, insulin forms dimers and hexamers stabilised with zinc atoms. Secretory vesicles in beta cells contain microcrystals of insulin at acid pH (5.5), which dissociate after secretion into the circulation. As discussed in detail in Chapter 7, the early development of longer-acting insulins used some of these properties. Zinc was used to stabilise insulin crystals and protamine, a highly basic protein, was used to stabilise insulin after injection, allowing slower release. Hagedorn subsequently developed NPH insulin, a combination of insulin and protamine in 'isophane' (equal) proportions at a neutral pH, with a small amount of zinc giving critical stability and slower release with subcutaneous injection. 'Lente' insulins were developed using suspension, again with zinc, but without foreign proteins, and led to the development of the trio of semilente, lente and ultralente insulins depending on the concentration of zinc.

Once longer-acting insulins were available, different clinical strategies of insulin administration became possible using patterns of either administration of short- and long-acting insulin (basal bolus patterns) or fixed mixtures of short- and long-acting insulin. These mixtures were initially developed with isophane insulin but have now also been developed with long-acting insulin analogues.

Factors Affecting the Absorption and Action of Insulin

From early in the development of insulin it became apparent that there was between-subject variability in insulin action which in turn might be explained by physiological differences between people, such as underlying insulin resistance. To an extent this is less concerning as it can be overcome by establishing the dose for an individual patient. In addition to this there was considerable intra-subject variability (within a single individual). Clinically this is much more troublesome as it translates into quite different clinical effects of insulin (essentially hypoglycemia and hyperglycemia) between different days. There may be a number of reasons for this, including variable absorption in the presence of lipohypertrophy at injection sites, and failure to adequately mix insulins such as isophane that require resuspension, but it also reflects the underlying pharmacology of the different formulations. This within-subject variation appears to be relatively marked with isophane insulin and is clinically important, particularly in more insulin-deficient people. Further, physiologically, in

sulin is delivered to the portal circulation and up to 60% is cleared by the liver. This is quite different from pharmacological injection into the subcutaneous space, which results in a relative overexposure to insulin in the systemic space and underexposure in the hepatic space. At least in theory, hepatic under-insulinisation and systemic relative insulin overexposure might account for some of the adverse effects of insulin, including weight gain. More recently some insulins have aimed to differentially target insulin action towards the liver to restore this more physiological pattern.

Development of Long-acting Insulin Analogues

The next era of long-acting insulin development came with modification of the insulin molecule at the molecular level. This included most notably the development of insulin glargine, detemir and degludec. Within this, detemir and glargine at 100 units/ml (U100) concentration are sometimes termed 'first-generation' analogues and degludec (at U100 and later U200 concentrations) and glargine at 300 units/ml (U300), 'second-generation' insulin analogues.

There were several aims in developing these insulins:

1. Alteration of insulin pharmacokinetic and pharmacodynamic profiles with slower delivery of the insulin molecule to target tissues, allowing both longer duration of action after injection and less peak of action. This peak, particularly with insulin injected in the evening, was believed to be particularly responsible for nocturnal hypoglycaemic episodes.
2. Improved predictability of action between doses.
3. Overcoming the relative systemic over-insulinisation and hepatic under-insulinisation with the subcutaneous administration of insulin.

Strategies to Modify the Action of Long-acting Insulin Analogues

Several strategies have been used to modify the pharmacokinetics and pharmacodynamics of insulins:

- The addition of fatty acid residues to increase albumin binding and thus half-life, a feature in insulin detemir, degludec and particularly insulin icodec, whose very long half-life allows once weekly dosage.
- Molecular modification to encourage the creation of dimers and hexamers, leading to crystallisation and slower release at the injection site. Insulin glargine and detemir use this strategy.

- Changes in insulin concentration to try to exaggerate some of these features, a modification used with both insulin glargine in the U300 formulation and degludec in the U200 formulation.
- Development of insulins in solution. Isophane insulin is formulated as a suspension that requires mixing prior to administration. Failure to mix this insulin prior to administration is common and leads to increased day-to-day variability of drug action so the development of insulins that are in solution would be expected to reduce some of this variability.
- Modification to reduce enzymatic degradation, an example being insulin icodec.
- Development of prodrugs – insulin glargine is a prodrug requiring metabolism to active forms for action, which again may increase its half-life.

Long-acting Insulin Analogues

Insulin Glargine

This analogue insulin was introduced by Sanofi in 2000 initially in a 100 units/ml form (U100 glargine) under the trade name Lantus®. A more concentrated U300 formulation (300 units/ml) was introduced later and is considered below. Glargine has two molecular modifications with the addition of two arginine residues inserted at position B30 of the insulin molecule and replacement of asparagine with glycine at position A21 [1] (Figure 9.1). These changes lead to a molecule that is stable and

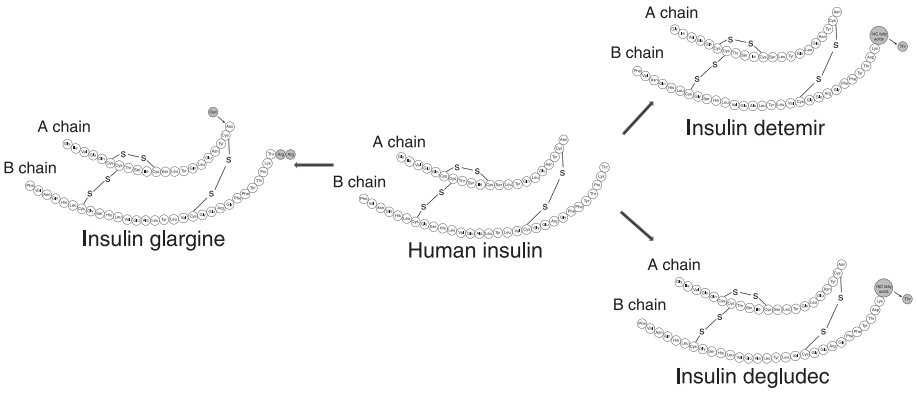


FIGURE 9.1 Structures of glargine, detemir, degludec and glargine U300. Insulin glargine has two molecular modifications with the addition of two arginine residues inserted at position B30 of the B chain and replacement of asparagine with glycine at position A21 on the A chain. Insulin detemir has the threonine deleted at position B30 of the B chain and a 14C fatty acid (myristic acid) residue added to the lysine at position B29. Insulin degludec has the threonine deleted at position B30 of the B chain and the addition of a 16C fatty diacid to lysine at position B29.

soluble in acid solution, but which precipitates at neutral pH at the injection site, causing slower release [2]. Glargine forms hexamers that are more stable than native insulin and metabolic activity lasts for up to 30 hours as compared with 12–14 hours for isophane [3]. Importantly these modifications also result in less of a peak of action after injection in comparison with isophane insulin, which has a marked peak in action four to six hours after injection when assessed in studies assessing the rate of glucose infusion required to maintain euglycaemia after injection [3, 4]. Variability of insulin effect (intra-subject variability) appears modestly better than isophane insulin [5]. Notably from early in its development glargine was known to have greater insulin-like growth factor 1 (IGF1) binding capacity than insulin, a feature which led to theoretical concerns that it might increase the development of tumours, but this has not been seen as a safety issue in clinical practice.

Formulations

- Insulin glargine (Lantus) U100 is available in vials, cartridges and pre-filled pens.
- Lantus is also available as two fixed combinations with lixisenatide (Suliqua®, lixisenatide 33 μg/ml, insulin glargine 100 units/ml and lixisenatide 50 μg/ml, insulin glargine 100 units/ml) in pre-filled pens.

Prescribing point: *Insulin glargine is normally prescribed once daily but, in some patients twice daily dosing is required.*

Glycaemic Efficacy and Risk of Hypoglycaemia with Glargine The 'Treat-to-Target' trial published in 2003 examined the use of insulin glargine or isophane insulin when added to oral therapy in patients with type 2 diabetes to achieve an HbA1c of <7% (53 mmol/mol) [6]. A total of 756 overweight men and women with type 2 diabetes and HbA1c > 7.5% on one or two oral antidiabetic drugs were included.

- The trial demonstrated reduced rates of hypoglycaemia with insulin glargine compared with NPH insulin.
- Improvements appeared most marked for nocturnal hypoglycaemia with, for example, a 42% reduction in all reported nocturnal hypoglycaemic events (4.0 vs. 6.9 per patient per year; $p < 0.001$) and a 48% reduction in confirmed nocturnal hypoglycaemia of ≤3.1 mmol/l (1.3 vs. 2.5; $p < 0.002$).

The GRADE study has been described in Chapters 3, 4 and 6. It compared second-line therapy with glimepiride, sitagliptin, liraglutide and glargine when added to metformin, and the results suggested that glargine and liraglutide gave better glycaemic control than glimepiride or sitagliptin.

ORIGIN Glargine was approved by licensing authorities in Europe and the US before the introduction of the requirement to demonstrate cardiovascular safety of new antidiabetic drugs (see Chapter 1). The ORIGIN (Outcome Reduction with an Initial Glargine Intervention) trial reported in 2012 and was an investigator-initiated randomised trial of early use of insulin glargine to normalise fasting plasma glucose in

12537 people with dysglycaemia (impaired fasting glucose, impaired glucose tolerance or type 2 diabetes) compared with standard of care [7]. The active treatment group aimed for self-monitored glucose of <5.3 mmol/l. The aim of the trial was to examine potential cardiovascular benefits of this strategy. Although this was an investigator-initiated trial, the approach was similar to subsequent FDA-mandated cardiovascular safety trials. ORIGIN had coprimary endpoints of MACE, a composite of cardiovascular death, nonfatal myocardial infarction and nonfatal stoke, and a composite of these events plus revascularisation or hospitalisation for heart failure.

After a median follow-up of 6.2 years:

- Rates of incident cardiovascular outcomes were similar in the insulin glargine and standard care groups (Figure 9.2).
- Rates of severe hypoglycaemia were increased at 1.00 vs. 0.31 per 100 person years.

While predominantly designed to demonstrate the potential effects of early normalisation of fasting glucose, the trial demonstrated reassuring results in terms of the cardiovascular safety of glargine in this very large trial.

Insulin Detemir

Insulin detemir, launched by Novo Nordisk under the trade name Levemir®, was the second extensively commercialised long-acting insulin analogue produced by

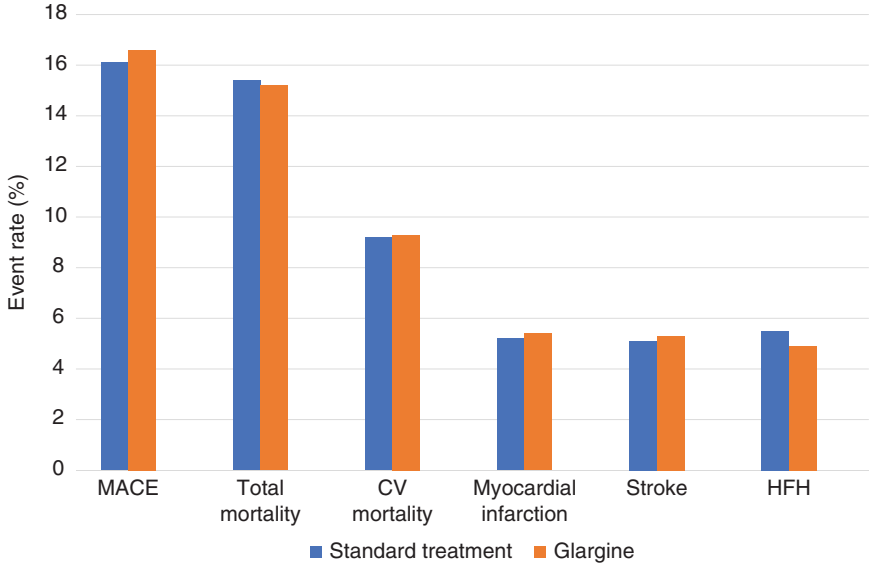


FIGURE 9.2 Six year event rates (%) comparing glargine and standard treatment in the ORIGIN trial [7]. MACE = major adverse cardiovascular events, a composite of cardiovascular death, nonfatal myocardial infarction and nonfatal stroke, HFH = hospitalisation for heart failure. *Source:* Based on [7].

recombinant DNA technology. The amino acid threonine at position B30 of the human insulin molecule was deleted and a 14C fatty acid (myristic acid) residue was added to the e-amino group of the lysine residue at position B29 (Figure 9.1). Combined, these changes resulted in increased self-association (both in hexamers and because of hexamer–hexamer interaction) and much higher albumin binding in interstitial fluid and plasma. These changes in turn result in a longer action than isophane insulin and less pronounced peak of action [8]. The prolongation of action was much less pronounced than that of insulin glargine, a feature which has often led to insulin detemir being used twice daily in clinical practice. Importantly, the within-subject variation appeared improved compared with both NPH and glargine [5] (Table 9.1).

Formulations

- Insulin detemir (Levemir) U100 is available in vials, cartridges and pre-filled pens.

Prescribing point: *Insulin detemir is a basal insulin normally given twice daily which allows more flexibility around dose adjustment on a day-to-day basis, e.g. decreasing the dose on an evening when undertaking physical activity.*

Glycaemic Efficacy and Risk of Hypoglycaemia with Detemir A meta-analysis of 30 trials (27 randomised controlled trials) in 7496 people with type 1 diabetes suggested that:

- Insulin glargine and detemir were associated with a modest (−0.26 to −0.39%, −2 to −5 mmol/mol) but clinically significant improvement in HbA1c in comparison with isophane insulin.
- Insulin glargine and detemir were associated with a clinically significant reduction in particularly nocturnal hypoglycaemia [9].

TABLE 9.1 Comparison of glargine (U100), detemir, degludec and glargine (U300)

Comparison (vs. isophane insulin or standard of care)	Glargine U100	Detemir	Degludec	Glargine U300
Duration of action	~30 hours (vs. 12–14 hours for isophane)	6–24 hours depending on dose	Over 24 hours	Over 24 hours
Nocturnal hypoglycaemic episodes	Reduced	Reduced	Reduced	Reduced
CV outcomes	Noninferior	No direct RCTs	Noninferior	No direct RCTs
Biosimilars available	Yes	No	No	No

CV = cardiovascular, RCT = randomised controlled trial.
Source: Based on [5].

Two adult trials have compared insulin detemir with glargine in type 1 diabetes, suggesting that there is no difference in HbA1c, weight gain or severe or nocturnal hypoglycaemia [10]. Comparison of the newer insulins with isophane in people with type 2 diabetes also supports a suggested reduction in nocturnal hypoglycaemia with both insulin detemir and insulin glargine [11].

4-T The 4-T (Treating to Target in Type 2 Diabetes) trial was a three year, open-label study performed in the UK examining intensification strategies of insulin detemir (once or twice daily if required), biphasic insulin aspart twice daily and prandial insulin aspart three times daily in 708 people with type 2 diabetes [12].

- With similar mean levels of HbA1c in each group, the use of insulin detemir was associated with lower rates of hypoglycaemia than biphasic or before-meal insulin.
- The mean weight gain was also higher in the prandial insulin group. The results supported the initial addition of basal insulin to oral antidiabetic drugs, with subsequent intensification to a basal prandial regimen.

Insulin Degludec

The insulin degludec molecule is altered from the human insulin amino acid sequence by deletion of ThrB30 and the addition of a 16-carbon fatty diacid to LysB29. In vitro this facilitates the creation of multihexamers and slows absorption from subcutaneous sites (Figure 9.1). This is in turn associated with a longer duration of action but also increased stability compared with U100 glargine [13]. Insulin degludec was launched by Novo Nordisk under the trade name Tresiba®.

Formulations

- Insulin degludec (Tresiba) U100 is available in cartridges and pre-filled pens.
- Degludec is also available in U200 strength in pre-filled pens.
- Degludec is available as a fixed combination with liraglutide (Xultophy®, liraglutide 3.6 mg/ml, insulin degludec 100 units/ml) in pre-filled pens.

Prescribing point: *Insulin degludec has a long time–action profile and it will take two to three days to see the effects of any adjustment in dose.*

Glycaemic Efficacy and Risk of Hypoglycaemia with Degludec The open-label BEGIN series of studies [14] examined a variety of clinical situations in type 1 and type 2 diabetes and demonstrated that:

- Significantly lower rates of overall confirmed, nocturnal confirmed and severe hypoglycaemic episodes were reported with degludec compared with glargine in insulin-naive subjects with type 2 diabetes: estimated rate ratio (RR) 0.83 (95% CI 0.70–0.98), RR 0.64 (0.48–0.86) and RR 0.14(0.03–0.70).
- In all people with type 2 diabetes, significantly lower rates of overall confirmed and nocturnal confirmed episodes were reported with insulin degludec compared with U100 glargine: RR 0.83 (0.74–0.94) and RR 0.68 (0.57–0.82).

- In the type 1 diabetes subjects, the rate of nocturnal confirmed episodes was significantly lower with insulin degludec compared with U100 glargine during maintenance treatment: RR 0.75(0.60–0.94).

The double-blind cross-over SWITCH 1 [15] and SWITCH 2 [16] trials published in 2017 compared the use of insulin degludec with that of U100 insulin glargine in people with type 1 and type 2 diabetes, respectively. The trials recruited people with at least one risk factor for hypoglycaemia (such as one or more severe hypoglycaemic episode in the year before the trial, moderate renal impairment eGFR 30–59 ml/min/1.73 m^2, hypoglycaemia unawareness or a previous episode of hypoglycaemia < 3.9 mmol/l) in a blinded randomised cross-over design. Treat-to-target designs were used and HbA1c outcomes found to be similar.

In SWITCH 1, in people with type 1 diabetes:

- The insulin degludec group had reductions in symptomatic hypoglycaemia (RR) of 0.89 (95% CI 0.85–0.94) and a nocturnal symptomatic hypoglycaemia RR of 0.64 (95% CI 0.56–0.73).
- The insulin degludec group had reductions in severe hypoglycaemia during the maintenance period of the trial: 10.3% (95% CI 7.3–13.3%) vs. 17.1% (95% CI 13.4–20.8%), respectively.

In SWITCH 2, in people with type 2 diabetes:

- Insulin degludec was associated with a reduction in overall symptomatic hypoglycaemia (RR = 0.70; 95% CI 0.61–0.80) and nocturnal symptomatic hypoglycaemia (RR = 0.58; 95% CI 0.46–0.74).
- No significant differences in severe hypoglycaemia were observed.

DEVOTE DEVOTE (Trial Comparing Cardiovascular Safety of Insulin Degludec vs. Insulin Glargine in Patients with Type 2 Diabetes at High Risk of Cardiovascular Events) was a large FDA-mandated, double-blind, cardiovascular outcome trial in 7637 people with type 2 diabetes designed to assess cardiovascular safety [17]. DEVOTE compared insulin degludec and insulin glargine U100. Glargine U100 was chosen as the comparator as several of the phase 3 studies with degludec used open-label glargine as the comparator, and cardiovascular endpoint data were available for glargine U100 from the ORIGIN trial.

In DEVOTE:

- There was no significant difference in the primary outcome of the incidence of MACE, a composite of cardiovascular death, nonfatal myocardial infarction and nonfatal stroke (Figure 9.3).
- The use of insulin degludec (compared with U100 glargine) was associated with a reduction in severe hypoglycaemia from 6.6% with glargine to 4.9% with degludec, an absolute difference of 1.7% (RR 0.60, $p < 0.001$ for superiority) over 24 months

The DEVOTE and ORIGIN trials are compared in Table 9.2.

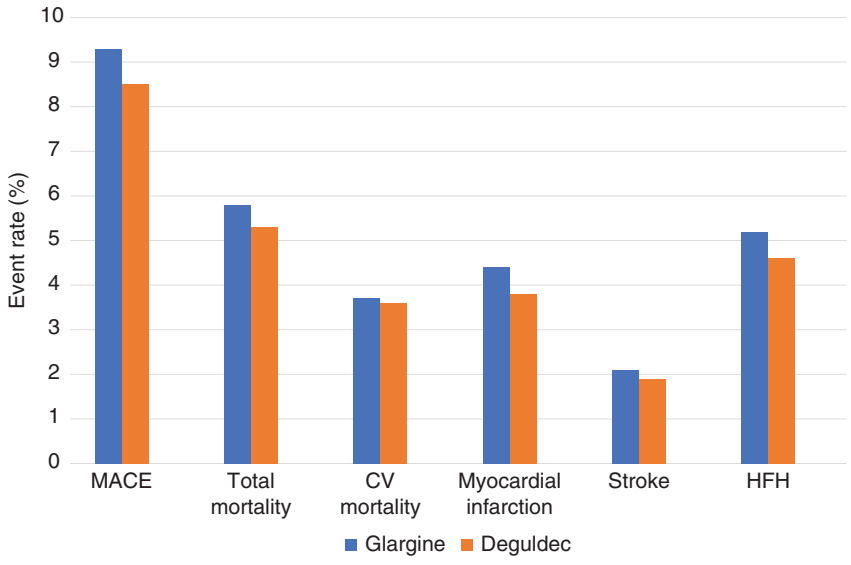


FIGURE 9.3 24 month event rates (%) comparing degludec and placebo in the DEVOTE trial [17]. MACE = major adverse cardiovascular events, a composite of cardiovascular death, nonfatal myocardial infarction and nonfatal stroke, HFH = hospitalisation for heart failure. *Source:* Based on [17].

U300 Glargine

The property of precipitation of glargine at injection sites as the principal retarding action led to the potential that more concentrated formulations might increase this effect (Figure 9.1). The U300 formulation was developed and shown to have longer duration of action than U100 glargine with improved stability of action [18]. It was launched by Sanofi under the trade name Toujeo®.

Formulations:

- Toujeo is available as a pre-filled pen.

Prescribing point: *Toujeo is only available in a pre-filled pen to reduce the risk of administration error as it is a concentrated insulin (300 units/ml) and might be confused with insulin glargine (100 units/ml).*

Glycaemic Efficacy and Risk of Hypoglycaemia with U300 Glargine

The EDITION trial programme was a series of studies examining U300 vs. U100 glargine [19, 20]:

- In EDITION 1 U300 glargine was associated with a reduction in confirmed (≤3.9 mmol/l) or severe nocturnal hypoglycaemic events (RR 0.79; 95% CI 0.67–0.93).
- Meta-analysis of patient-level data across the EDITION series of studies supported a more sustained reduction in HbA1c and reduced risk of nocturnal confirmed hy-

TABLE 9.2 Cardiovascular outcome trials with long-acting insulin analogues

Trial	ORIGIN [7]	DEVOTE [17]
Insulin	Glargine U100	Degludec
Comparator	Standard treatment	Glargine U100
Population size (n =)	12 537	7 637
Age (years)	64	65
Duration of diabetes (years)	5	16
Follow-up (years)	6	2
Atherosclerotic CVD (%)	59	85% CVD or CKD
Heart failure (%)	NA	12
Primary outcome(s)	MACE noninferior MACE plus revascularisation or HFH noninferior	MACE noninferior
Secondary outcomes	Body weight and hypoglycaemia increased with glargine	Weight noninferior, severe hypoglycaemia reduced with degludec

CKD = chronic kidney disease, CVD = cardiovascular disease, MACE = major adverse cardiovascular events, NA = not available, HFH = hospitalisation for heart failure.

poglycaemia (≤3.9 mmol/l) or severe hypoglycaemia at night (RR 0.85; 95% CI 0.77–0.92) or at any time of day (RR 0.94; 95% CI 0.90–0.98) in people with type 2 diabetes.

- In people with type 1 diabetes, nocturnal confirmed or severe hypoglycaemia was lower with U300 (RR 0.69; 95% CI 0.53–0.91), but only in the first eight weeks of the study.

The BRIGHT study was a head-to-head randomised comparison of the two second-generation insulin analogues U300 glargine and insulin degludec in over 900 insulin-naive people with type 2 diabetes [21]:

- There were no major changes in outcomes with a small advantage to lower hypoglycaemia with U300 glargine in the titration phase only.

In contrast, the CONCLUDE trial [22] examined U300 glargine head-to-head against a different formulation of insulin degludec (U200) in 1609 people with insulin-treated type 2 diabetes:

- There was no difference in the primary endpoint of overall symptomatic hypoglycaemia but a lower rate of nocturnal symptomatic hypoglycaemia (RR 0.63; 95% CI 0.48–0.84) and severe hypoglycaemia (RR 0.20; 95% CI 0.07–0.57) with U200 degludec.

It is difficult to be definitive regarding these contrasting results. The CONCLUDE trial has been criticised on methodological grounds (accuracy of glucometers) and patients differed from the BRIGHT study in being insulin naive as well as in the primary outcomes of the trials [23]. It remains possible that there is a genuine advantage of U200 degludec over U300 glargine, but further trial evidence would be needed to support this.

Biosimilar Long-acting Insulin Analogues

The development of biosimilar drugs has been discussed in Chapter 1. These are of particular importance in long-acting insulin analogues as biosimilars based on insulin glargine have been clinically available for several years and have been widely used [24, 25]. Abasaglar® was the first insulin biosimilar approved in the UK and Europe and launched by Eli Lilly. Its reference product is Lantus, an insulin glargine whose patent expired in 2015. Abasaglar was approved by the EMA in 2014 and became available in the UK in 2015.

Biosimilarity was demonstrated with five phase 1 and three phase 3 studies. Phase 1 studies included both healthy volunteers and those with type 1 diabetes and were used to demonstrate comparable bioavailability, pharmacokinetic and pharmacodynamic properties between Abasaglar and Lantus. In the phase 3 multisite randomised studies Abasaglar was noninferior and safety was demonstrated in comparison with insulin glargine. These studies included people with type 1 diabetes (ELEMENT 1) and people with type 2 diabetes (ELEMENT 2 and 5), including a trial of those who were solely insulin naive (ELEMENT 2). HbA1c, weight gain and hypoglycaemia were comparable between groups, as were important safety measures such as antibody formation and weight gain [26–28].

A later biosimilar glargine marketed by Mylan as Semglee® was examined in the INSTRIDE programme, again with trials in type 1 and type 2 diabetes and no important safety or efficacy concerns [29–31].

Formulations

- Insulin glargine (Abasaglar) U100 is available in cartridges and pre-filled pens.
- Insulin glargine (Semglee) U100 is available in pre-filled pens.

Prescribing point: *Biosimilar insulins should be prescribed by their brand name.*

Other Long-acting Insulin Analogues

Not all attempts to create novel long-acting insulin analogues have been successful. Basal Insulin Peglispro (LY2605541 or BIL) was a modified form of the short-acting insulin analogue lispro with the addition of a polyethylene glycol, which led to slow release from subcutaneous tissues. It showed an interesting pharmacodynamic profile with prolonged action and was expected to preferentially increase hepatic insulinisation. Weight gain appeared to be lower than with other agents. Unfortunately, the drug was withdrawn owing to unforeseen effects of transaminitis and raised triglycerides [32].

Combinations of Long- and Short-acting Insulin Analogues

Fixed mixtures of short- and long-acting insulins have been available for some time using original human sequence insulin and long-acting isophane insulin (see Chapter 7). Such mixtures have fallen out of favour in the treatment of people with type 1 diabetes but are still used in some patients with type 2 diabetes. Insulin glargine was not suitable for mixture as the pattern of crystal deposition at the site of injection appears to also lead to retardation of the short-acting component [33]. Similarly, mixing short-acting insulin with insulin detemir alters the pharmacodynamics of the short-acting insulin [34]. In contrast, insulin degludec can be mixed with short-acting insulin, leading to the development of premixed degludec and insulin aspart in a 70/30% mixture, Ryzodec®, and this has been studied in both people with type 1 and type 2 diabetes [35]. This insulin is available in many countries but is not commercially available in the UK.

Further combination insulins are available in the fixed mixtures of short-acting insulin analogues such as insulin aspart and lispro with protamine-stabilised forms of the same molecule. Thus 'biphasic insulin aspart' in a 70% long-acting and 30% short-acting and insulin lispro mixtures in 50/50 or 75/25 ratios have been tested. While biphasic insulin aspart appears to be superior to U100 glargine alone in certain groups with type 2 diabetes [36], overall results have been inconsistent [37]. Currently available fixed mixtures of short- and long-acting insulin and insulin analogues are described in Table 9.3.

TABLE 9.3 **Currently available fixed mixtures of short- and long-acting insulin and insulin analogues**

Name	Manufacturer	Short acting insulin	Long acting insulin	Injection devices
Human insulins				
Humulin M3	Eli Lilly	30% soluble insulin	70% isophane insulin	Cartridge, pre-filled pen, vial
Insuman Comb25	Sanofi	25% soluble insulin	75% crystalline protamine insulin	Cartridge, pre-filled pen
Insuman Comb50	Sanofi	50% soluble insulin	75% crystalline protamine insulin	Cartridge
Insulin analogues				
Humalog Mix25	Eli Lilly	25% insulin lispro	75% insulin lispro protamine suspension	Cartridge, pre-filled pen, vial
Humalog Mix50	Eli Lilly	50% insulin lispro	50% insulin lispro protamine suspension	Cartridge, pre-filled pen
NovoMix 30	Novo Nordisk	30% insulin aspart	70% protamine crystallised insulin aspart	Cartridge, pre-filled pen
Ryzodec	Novo Nordisk	30% insulin aspart	70% insulin degludec	Not available in the UK

Meta-analysis of Glycaemic Efficacy of Long-acting Insulin Analogues

Type 1 Diabetes

A large network meta-analysis of trials of insulin glargine and detemir using data to January 2013 and a total of 27 trials [38] concluded that:

- Both were superior to NPH for HbA1c: insulin glargine vs. NPH, −0.39% (−0.59 to −0.19%); insulin detemir once daily vs. NPH, − 0.26% (−0.48 to −0.03%); insulin detemir twice daily vs. NPH, −0.36% (−0.65 to −0.08%).
- First-generation insulin analogues (analysis not conducted separately) offered an advantage over NPH for hypoglycaemia: combined data, 0.62 (95% CI 0.42–0.91).

In contrast comparisons between the analogues suggest smaller differences. A meta-analysis of available studies in 2019 suggested no difference between degludec and detemir (two trials) for HbA1c or hypoglycaemia, but slightly (but significantly) greater weight gain of around 1 kg more with degludec compared with detemir. Comparison of degludec with glargine (four studies) again suggested no difference in HbA1c but a lower rate of nocturnal hypoglycaemia with degludec (RR 0.68; 95% CI 0.56–0.81). There were no differences in weight gain [10].

For the direct comparison of detemir with glargine in type 1 diabetes, there were only two adult trials, which suggested no difference in HbA1c, weight gain or severe or nocturnal hypoglycaemia [10]. For the comparison of the two available concentrations of insulin glargine (U300 and U100; two trials), overall HbA1c or hypoglycaemia did not differ between the two preparations [10].

Type 2 Diabetes

A recent Cochrane review examined treatment with long-acting insulin analogues with NPH in adults with type 2 diabetes mellitus [11]. A total of 24 trials to the end of 2019 were included with trials ranging between 24 weeks and five years in duration. Only trials using NPH as comparator were included and while trials of insulin glargine U100 and U300, insulin detemir and insulin degludec were sought, there was only sufficient data against the NPH comparator for insulin detemir and U100 glargine. In general, changes in HbA1c were similar between the two insulins with no significant overall differences between treatments, probably reflecting similar treat-to-target strategies. Both detemir and glargine were associated with reduced rates of confirmed nocturnal hypoglycaemia and for detemir serious hypoglycaemia (Table 9.4). However, the absolute risk reduction was small (under 1%), reflecting the relative rarity of these effects in the populations studied. There were no significant changes in other outcomes, including cardiovascular disease outcomes or other diabetes complications.

There are fewer comparisons in meta-analysis between analogues. In 2011 a Cochrane review including four trials suggested no major clinical differences between detemir and glargine in patients with type 2 diabetes [39]. A later meta-analysis of available studies in 2019 found no suitable direct comparisons of degludec and detemir in people with type 2 diabetes. Comparison of degludec with glargine (nine studies) found no difference in HbA1c (10). This included the very large DEVOTE and SWITCH2 trials with a combined total of over 8000 patients.

- Severe (RR 0.7; 95% CI 0.54–0.96) and nocturnal (0.73; 95% CI 0.65–0.82) hypoglycaemia were reduced with degludec compared with glargine, although the absolute rates of these complications were relatively low (severe hypoglycaemia, 3.3% vs. 5.5% degludec vs. glargine), although clearly within the range of potential clinical importance.
- There were no differences in mortality, cancer rates, the number of cardiovascular events (ten) or weight gain.

For the direct comparison of detemir with glargine in type 2 diabetes, no differences in HbA1c or severe or nocturnal hypoglycaemia were found (10). For comparison of the two available concentrations of insulin glargine (U300 and U100; four trials):

- HbA1c effects were similar.
- There were lower rates of nocturnal hypoglycaemia with U300 (RR 0.74; 95% CI 0.66–0.82) earlier in trials (two to six months), but this was not sustained to 12 months.

TABLE 9.4 **Meta-analysis of the effects of long-acting insulin analogues vs. human isophane insulin in people with type 2 diabetes**

	Comparison vs. NPH (95% CI)					
	Severe hypoglycaemia		**Serious hypoglycaemia**		**Confirmed nocturnal hypoglycaemia (≤3.1 mmol/l)**	
	Risk ratio hypoglycaemia	Absolute risk reduction	Risk ratio hypoglycaemia	Absolute risk reduction	Risk ratio	Absolute risk reduction
Glargine	0.68 (0.46–1.01)	−1.2% (−2.0–0)	0.75 (0.52–1.09)	−0.7% (−1.3–0.2%)	**0.88 (0.81–0.96)**	**−0.3 (−0.41 –0.17)**
Detemir	0.45 (0.17–1.20)	−0.09 (−0.14–0.04)	**0.16 (0.04–0.61)**	**−0.09 (−0.11 to −0.04)**	**0.32 (0.16– 0.63)**	**−0.27 (−0.34 to −0.15)**

Source: Based on [43].

Statistically significant differences ($p < 0.05$) are highlighted in bold. No trials were found for glargine U300 or degludec

Safety of Long-acting Insulin Analogues

As discussed in Chapter 1, concern over the cardiovascular safety of glucose-lowering therapies in general led to a mandate by the FDA of very large cardiovascular safety trials of diabetes therapies, including degludec insulin. Across a similar time, there was also important speculation about potential off-target effects and the potential for increased mitogenesis with analogue insulins and glucose-lowering therapies [40]. In part, this related to recognition that different insulins had different affinities to receptors related to the insulin receptor – most notably IGF-1 [41]. It was posited that insulin glargine in particular had greater affinity for this receptor than native insulin and there was speculation that this might in turn influence the malignancy risk or the risk of complications such as retinopathy [40]. This was, and is, an important issue but a complex one. First, the last 20 years have seen developing evidence of the association of both type 2 diabetes and obesity with malignancy in large population studies [42]. Second, such influences would be exerted over long time courses. Large-scale, long-term trial data and the use of observational, registry data would be needed to clarify these issues. Importantly, for malignancy, large trials have been reassuring, although the numbers of incident cases of malignancy are usually small [17], and in addition registry data, perhaps more relevant given that very long-term exposure might be needed, have not supported increases in cancer incidence [42].

The Place of Long-acting Insulin Analogues in Current and Future Practice

Advantages of Insulin Analogues

The development of insulin analogues has undoubtedly been of benefit to people with type 1 and type 2 diabetes. The clinical evidence would suggest that these insulins are clearly longer acting, more stable and offer definite benefits in reduced risk of hypoglycaemia. This seems most apparent for nocturnal hypoglycaemia and in patients who are most insulin deficient, predominantly people with type 1 diabetes. Most people with type 1 diabetes are likely to benefit from these insulin analogues compared with older types of insulin. For type 2 diabetes this benefit may be confined to those aiming at tighter control and with less endogenous insulin secretion, or those who are clinically perceived as at risk of hypoglycaemia, but nevertheless a substantial number of people may benefit. It should not be missed that these insulins have also allowed stable once rather than twice daily dosing, again being a considerable convenience for patients. In addition, the agents have been subjected to and have benefitted from scrutiny over longer-term potential benefits and adverse effects on cardiovascular and cancer outcomes. Data have been reassuring, and use needs to be balanced with the increased cost of the analogues, but with the competition generated by biosimilar insulin analogues, costs are reducing.

Patterns of Insulin Administration

The advent of long-acting insulin analogues allowed the development of basal bolus patterns of insulin administration, where a long-acting insulin supplying a steady, lower level of circulating (basal or background) insulin is paired with boluses of short-acting insulin at mealtimes (preprandial or bolus). This is now the standard treatment for people with type 1 diabetes from the time of diagnosis. These bolus patterns are generally in either a fixed-dose pattern or varied with the accompanying carbohydrate pattern as used in structured education programmes such as DAFNE, published in 2002 [43], in turn based on pioneering approaches developed in Dusseldorf [44] (see also Chapter 8). The original DAFNE programme was based on twice daily isophane insulin along with short-acting insulin. With time, it and similar programmes have adopted analogue insulins. Randomised evidence is not available but observationally people with type 1 diabetes using twice daily (usually detemir or isophane) rather than once daily insulin have better overall results [45].

In people with type 2 diabetes patterns of insulin administration can be more varied with approaches of once daily long-acting insulin along with oral antidiabetic drugs, short-acting insulin only at mealtimes, basal bolus and the use of fixed mixtures all being possible. Trials such as the 4T trial have explored these different options, although given the heterogeneity of type 2 diabetes a rationale for varying approaches can be made in individual patients.

Future Long-acting Insulin Analogues

Much longer-acting insulins such as the once weekly icodec may allow even more innovative patterns of insulin use in selected patient groups. Insulin icodec is modified by three amino acid substitutions in positions 14, 16 and 25 and the addition of a C20 fatty diacid containing a side chain at B29K. This results in a remarkably long half-life of 196 hours in part owing to albumin binding in the circulation and reduced degradation. This insulin is early in its clinical life and more limited trial information is available but in 2020 in a trial of 247 insulin-treated people with type 2 diabetes similar outcomes were achieved with once weekly icodec in comparison with daily injection of U100 glargine [46].

Other once weekly insulins are in development including Basal Insulin Fc, a fusion protein combining a novel single-chain variant of insulin with a fragment of human immunoglobulin (human IgG2 Fc domain). These include molecules from both Eli Lilly Ltd (LY3209590) and Hanmi (LAPS Insulin 115: HM12470). Intriguingly such molecules could also potentially be combined with weekly incretin analogues, suggesting future potential developments.

More broadly, there is a long history of attempts to create glucose-sensitive insulins: systems of insulin delivery sensitive to glucose levels at a molecular level (as opposed to closed loop systems discussed in Chapter 10) [47]. It remains to be proved whether these systems will be reactive rapidly enough to offer clinical benefits. Taken together

the innovation of insulin analogues has been of huge benefit, perhaps most enduringly in the convenience of timing of administration, and in that light further innovation, particularly to even longer acting insulins, is eagerly anticipated.

References

1. Owens, D.R. (2011). Insulin preparations with prolonged effect. *Diabetes Technol Ther* 13 (Suppl 1): S5–14.
2. Hirsch, I.B. (2005). Insulin analogues. *N Engl J Med* 352: 174–183.
3. Heinemann, L., Linkeschova, R., Rave, K. et al. (2000). Time-action profile of the long-acting insulin analog insulin glargine (HOE901) in comparison with those of NPH insulin and placebo. *Diabetes Care* 23: 644–649.
4. Lepore, M., Pampanelli, S., Fanelli, C. et al. (2000). Pharmacokinetics and pharmacodynamics of subcutaneous injection of long-acting human insulin analog glargine, NPH insulin, and ultralente human insulin and continuous subcutaneous infusion of insulin lispro. *Diabetes* 49: 2142–2148.
5. Heise, T., Nosek, L., Rønn, B.B. et al. (2004). Lower within-subject variability of insulin detemir in comparison to NPH insulin and insulin glargine in people with type 1 diabetes. *Diabetes* 53: 1614–1620.
6. Riddle, M.C., Rosenstock, J., and Gerich, J. (2003). The treat-to-target trial: randomized addition of glargine or human NPH insulin to oral therapy of type 2 diabetic patients. *Diabetes Care* 26: 3080–3086.
7. Gerstein, H.C., Bosch, J., Dagenais, G.R. et al. (2012). Basal insulin and cardiovascular and other outcomes in dysglycemia. *N Engl J Med* 367: 319–328.
8. Heinemann, L., Sinha, K., Weyer, C. et al. (1999). Time–action profile of the soluble, fatty acid acylated, long-acting insulin analogue NN304. *Diabet Med* 16: 332–338.
9. Tricco, A.C., Ashoor, H.M., Soobiah, C. et al. (2013). Safety, effectiveness, and cost of long-acting versus intermediate-acting insulin for type 1 diabetes: protocol for a systematic review and network meta-analysis. *Syst Rev* 2: 73.
10. Holmes, R.S., Crabtree, E., and McDonagh, M.S. (2019). Comparative effectiveness and harms of long-acting insulins for type 1 and type 2 diabetes: a systematic review and meta-analysis. *Diabetes Obes Metab* 21: 984–992.
11. Semlitsch, T., Engler, J., Siebenhofer, A. et al. (2020). (Ultra-)long-acting insulin analogues versus NPH insulin (human isophane insulin) for adults with type 2 diabetes mellitus. *Cochrane Database Syst Rev* 11: Cd005613.
12. Holman, R.R., Thorne, K.I., Farmer, A.J. et al. (2007). Addition of biphasic, prandial, or basal insulin to oral therapy in type 2 diabetes. *N Engl J Med* 357: 1716–1730.
13. Heise, T., Hermanski, L., Nosek, L. et al. (2012). Insulin degludec: four times lower pharmacodynamic variability than insulin glargine under steady-state conditions in type 1 diabetes. *Diabetes Obes Metab* 14: 859–864.
14. Ratner, R.E., Gough, S.C., Mathieu, C. et al. (2013). Hypoglycaemia risk with insulin degludec compared with insulin glargine in type 2 and type 1 diabetes: a pre-planned meta-analysis of phase 3 trials. *Diabetes Obes Metab* 15: 175–184.
15. Lane, W., Bailey, T.S., Gerety, G. et al. (2017). Effect of insulin degludec vs insulin glargine U100 on hypoglycemia in patients with type 1 diabetes: the SWITCH 1 randomized clinical trial. *JAMA* 318: 33–44.

16. Wysham, C., Bhargava, A., Chaykin, L. et al. (2017). Effect of insulin degludec vs insulin glargine U100 on hypoglycemia in patients with type 2 diabetes: the SWITCH 2 randomized clinical trial. *JAMA* 318: 45–56.
17. Marso, S.P., McGuire, D.K., Zinman, B. et al. (2017). Efficacy and safety of degludec versus glargine in type 2 diabetes. *N Engl J Med* 377: 723–732.
18. Becker, R.H., Dahmen, R., Bergmann, K. et al. (2015). New insulin glargine 300 units · mL^{-1} provides a more even activity profile and prolonged glycemic control at steady state compared with insulin glargine 100 units · mL^{-1}. *Diabetes Care* 38: 637–643.
19. Riddle, M.C., Bolli, G.B., Ziemen, M. et al. (2014). New insulin glargine 300 units/mL versus glargine 100 units/mL in people with type 2 diabetes using basal and mealtime insulin: glucose control and hypoglycemia in a 6-month randomized controlled trial (EDITION 1). *Diabetes Care* 37: 2755–2762.
20. Home, P.D., Bergenstal, R.M., Bolli, G.B. et al. (2015). New insulin glargine 300 units/mL versus glargine 100 units/ml in people with type 1 diabetes: a randomized, phase 3a, open-label clinical trial (EDITION 4). *Diabetes Care* 38: 2217–2225.
21. Rosenstock, J., Cheng, A., Ritzel, R. et al. (2018). More similarities than differences testing insulin glargine 300 units/ml versus insulin degludec 100 units/ml in insulin-naive type 2 diabetes: the randomized head-to-head BRIGHT trial. *Diabetes Care* 41: 2147–2154.
22. Philis-Tsimikas, A., Klonoff, D.C., Khunti, K. et al. (2020). Risk of hypoglycaemia with insulin degludec versus insulin glargine U300 in insulin-treated patients with type 2 diabetes: the randomised, head-to-head CONCLUDE trial. *Diabetologia* 63: 698–710.
23. Del Prato, S. (2020). How conclusive is the CONCLUDE trial? *Diabetologia* 63: 692–697.
24. Davies, M., Dahl, D., Heise, T., Kiljanski, J., and Mathieu, C. (2017). Introduction of biosimilar insulins in Europe. *Diabet Med* 34: 1340–1353.
25. Tieu, C., Lucas, E.J., DePaola, M., Rosman, L., and Alexander, G.C. (2018). Efficacy and safety of biosimilar insulins compared with their reference products: a systematic review. *PLoS One* 13 (4): e0195012.
26. Blevins, T.C., Dahl, D., Rosenstock, J. et al. (2015). Efficacy and safety of LY2963016 insulin glargine compared with insulin glargine (Lantus®) in patients with type 1 diabetes in a randomized controlled trial: the ELEMENT 1 study. *Diabetes Obes Metab* 17: 726–733.
27. Pollom, R.K., Ilag, L.L., Lacaya, L.B., Morwick, T.M., and Ortiz Carrasquillo, R. (2019). Lilly insulin glargine versus lantus(®) in insulin-naïve and insulin-treated adults with type 2 diabetes: a randomized, controlled trial (ELEMENT 5). *Diabetes Ther* 10: 189–203.
28. Rosenstock, J., Hollander, P., Bhargava, A. et al. (2015). Similar efficacy and safety of LY2963016 insulin glargine and insulin glargine (Lantus®) in patients with type 2 diabetes who were insulin-naïve or previously treated with insulin glargine: a randomized, double-blind controlled trial (the ELEMENT 2 study). *Diabetes Obes Metab* 17: 734–741.
29. Blevins, T.C., Barve, A., Raiter, Y. et al. (2020). Efficacy and safety of MYL-1501D versus insulin glargine in people with type 1 diabetes mellitus: results of the INSTRIDE 3 phase 3 switch study. *Diabetes Obes Metab* 22: 365–372.
30. Blevins, T.C., Barve, A., Sun, B., and Ankersen, M. (2018). Efficacy and safety of MYL-1501D vs insulin glargine in patients with type 1 diabetes after 52 weeks: results of the INSTRIDE 1 phase III study. *Diabetes Obes Metab* 20: 1944–1950.
31. Blevins, T.C., Barve, A., Sun, B. et al. (2019). Efficacy and safety of MYL-1501D versus insulin glargine in patients with type 2 diabetes after 24 weeks: results of the phase III INSTRIDE 2 study. *Diabetes Obes Metab* 21: 129–135.
32. Muñoz-Garach, A., Molina-Vega, M., and Tinahones, F.J. (2017). How can a good idea fail? Basal Insulin Peglispro [LY2605541] for the treatment of type 2 diabetes. *Diabetes Ther* 8: 9–22.

33. Cengiz, E., Tamborlane, W.V., Martin-Fredericksen, M., Dziura, J., and Weinzimer, S.A. (2010). Early pharmacokinetic and pharmacodynamic effects of mixing lispro with glargine insulin: results of glucose clamp studies in youth with type 1 diabetes. *Diabetes Care* 33: 1009–1012.
34. Cengiz, E., Swan, K.L., Tamborlane, W.V. et al. (2012). The alteration of aspart insulin pharmacodynamics when mixed with detemir insulin. *Diabetes Care* 35: 690–692.
35. Rendell, M. (2019). Premix insulins in type 1 diabetes: the coming of degludec/aspart. *Expert Opin Drug Metab Toxicol* 15: 341–348.
36. Rys, P., Wojciechowski, P., Siejka, S. et al. (2014). A comparison of biphasic insulin aspart and insulin glargine administered with oral antidiabetic drugs in type 2 diabetes mellitus–a systematic review and meta-analysis. *Int J Clin Pract* 68: 304–313.
37. Hong, T., Lu, J., Zhang, P. et al. (2019). Efficacy and safety of basal analog regimens in type 2 diabetes mellitus: systematic review and meta-analysis of randomized controlled trials. *Diabetes Ther* 10: 1051–1066.
38. Tricco, A.C., Ashoor, H.M., Antony, J. et al. (2014). Safety, effectiveness, and cost effectiveness of long acting versus intermediate acting insulin for patients with type 1 diabetes: systematic review and network meta-analysis. *BMJ* 349: g5459.
39. Swinnen, S.G., Simon, A.C., Holleman, F., Hoekstra, J.B., and Devries, J.H. (2011). Insulin detemir versus insulin glargine for type 2 diabetes mellitus. *Cochrane Database Syst Rev* 2011 (7): Cd006383.
40. Smith, U. and Gale, E.A. (2009). Does diabetes therapy influence the risk of cancer? *Diabetologia* 52: 1699–1708.
41. Le Roith, D. (2007). Insulin glargine and receptor-mediated signalling: clinical implications in treating type 2 diabetes. *Diabetes Metab Res Rev* 23: 593–599.
42. Colhoun, H.M. (2009). Use of insulin glargine and cancer incidence in Scotland: a study from the Scottish Diabetes Research Network Epidemiology Group. *Diabetologia* 52: 1755–1765.
43. DAFNE Study Group (2002). Training in flexible, intensive insulin management to enable dietary freedom in people with type 1 diabetes: dose adjustment for normal eating (DAFNE) randomised controlled trial. *BMJ* 325 (7367): 746.
44. Mühlhauser, I., Jörgens, V., Berger, M. et al. (1983). Bicentric evaluation of a teaching and treatment programme for type 1 (insulin-dependent) diabetic patients: improvement of metabolic control and other measures of diabetes care for up to 22 months. *Diabetologia* 25: 470–476.
45. Hopkinson, H.E., Jacques, R.M., Gardner, K.J., Amiel, S.A., and Mansell, P. (2015). Twice- rather than once-daily basal insulin is associated with better glycaemic control in Type 1 diabetes mellitus 12 months after skills-based structured education in insulin self-management. *Diabet Med* 32: 1071–1076.
46. Rosenstock, J., Bajaj, H.S., Janež, A. et al. (2020). Once-weekly insulin for type 2 diabetes without previous insulin treatment. *N Engl J Med* 383: 2107–2116.
47. Hoeg-Jensen, T. (2021). Review: glucose-sensitive insulin. *Mol Metab* 46: 101107.

CHAPTER 10

Devices

David Carty

KEY POINTS

- Insulin pumps have improved hugely over the last two decades and are now widely used internationally.
- Continuous glucose monitoring has been shown to improve glycaemic control and reduce hospital admissions.
- Integrated pump/continuous glucose monitoring 'closed-loop' systems are likely to be the future of management of people with type 1 diabetes.
- Identifying which individuals with type 1 diabetes will benefit most from certain technologies remains a challenge.

Introduction

Since the introduction of insulin therapy 100 years ago, there have been major advances in diabetes management. Despite this, glycaemic control remains poor, with only 26% of people with type 1 diabetes reaching an HbA1c below the target of 7.5% (58 mmol/mol) in Scotland [1]. As described in Chapters 8 and 9, modern insulin formulations offer the potential to improve glycaemic control further, reducing the risk of complications, reducing hypo- and hyperglycaemia and improving the quality of life. The use of modern technologies may further improve glycaemic control and the quality of life of people with type 1 diabetes.

Diabetes Drug Notes, First Edition. Edited by Miles Fisher, Gerard A. McKay, and Andrea Llano.

Insulin Pens

History

Before the development of insulin pens, the administration of insulin was a laborious process, involving drawing up insulin from a bottle with a glass syringe and injecting using reusable wide-bore metal needles that required sterilisation and sharpening. This was simplified when disposable plastic insulin syringes were introduced, but it was the introduction in the early 1980s of a reusable convenient pen with prefilled plastic insulin cartridges, first reported in the *Lancet* by Drs Reith and Ireland and colleagues from Glasgow, that revolutionised diabetes care [2]. Insulin injection became quicker, more discrete and less painful.

Modern Insulin Pens

Modern insulin pens are plastic, lightweight and disposable, requiring smaller needles and less force to inject than their predecessors. Memory function technology allows 'smart' pens to keep track of the dosage and time of injection. This information can then be sent remotely using Bluetooth technology or can be directly scanned using near-field technology (similar to scanning a contactless bank card) to integrated phone applications. The smart pen apps can help calculate insulin dosage and log blood sugar readings alongside insulin doses to provide personalised reports for use in the clinic**.** Smart pens also have reminders to prevent missed doses and can alert the user that insulin has expired or exceeded its temperature range. Those with visual impairment can count the 'clicks' on an insulin pen to calculate the dose, while half-unit pens have also been developed for use, particularly, in small children.

Prescribing point: *Smart pens are useful for the clinician and person with diabetes to understand when and how much insulin is given relative to glucose measurements.*

Insulin Pumps

History

The idea that insulin could be delivered continuously to the subcutaneous tissues was first developed and tested in the 1960s with systems developed by Arnold Karnish and the Biostator device. While providing valuable insights, these contraptions were the size of a backpack and were too large and cumbersome to be of clinical utility. The Mill Hill infuser pump, developed in London in the late 1970s, had a dual infusion rate with basal rates and prandial rates which were adjusted using a button on the side of the apparatus. In the 1980s the 'big blue brick' or 'autosyringe' developed by the American inventor Dean Kamer had some commercial success, but problems with

battery life, the requirement for a screwdriver to adjust infusion rates and high rates of complications meant that they were only used in a minority of patients.

Modern Insulin Pumps

Modern insulin pumps and have several features that offer potential benefits over insulin pens:

- Pumps allow a more physiological and flexible delivery of insulin that can be adjusted hour by hour, depending on requirement.
- For many this helps to counter the effect of 'dawn phenomenon' caused by cortisol and other stress hormones in the early hours of the morning.
- This can also be used to adjust for other factors such as exercise, menstrual cycle, working shift patterns and alcohol ingestion.

Mealtime bolus insulin is also delivered by the pump. Insulin pumps have a bolus calculator, which helps users to calculate a dose based upon carbohydrate intake, insulin sensitivity and blood sugar readings (either entered manually or automatically from the blood glucose meter via Bluetooth or similar technologies). The duration of the bolus can also be adjusted, using extended 'square wave' or 'dual wave' programmes to prolong release, for example for high-fat meals such as pizza. Insulin pumps can also allow a very precise amount of insulin to be delivered, with increments of 0.05 units/hour, which can be particularly useful in the paediatric setting.

Modern insulin pumps have several different features designed to suit the needs of their consumers. Most insulin pumps are worn in a pocket or attached to a belt and contain a cartridge of insulin that is delivered via tubing to a subcutaneous cannula, usually inserted into the abdomen. An alternative is the 'patch' pump that is applied directly to the skin and has a cannula attaching directly from the pump under the skin. The lack of tubing and the waterproof features mean that these pumps are often popular with sports enthusiasts. A key feature with current insulin pumps is their ability to communicate with continuous glucose monitors (see below).

Glycaemic Efficacy of Insulin Pumps

Since they became more widely available in the first part of the twenty-first century, data has been gathering about the effectiveness of insulin pumps. Several early meta-analyses showed that HbA1c levels were overall reduced with insulin pump therapy compared with multiple daily injections, with reductions of around 0.3–0.6% (3–7 mmol/mol), but with a significant reduction in insulin dose and in episodes of severe hypoglycaemic [3]. Differences in patient selection between studies, different levels of control and training at baseline, and different methods of analysis across studies, however, have meant that uncertainty about their overall benefit remains.

The REPOSE (Relative Effectiveness of Pumps over MDI and Structured Education) study delivered DAFNE-structured education to 300 adults with type 1 diabetes across the UK and then randomised participants to either pump therapy or multiple daily injections (MDIs) [4]. REPOSE showed that both groups had significant improvements in HbA1c and reductions in severe hypoglycaemia; adding an insulin pump did not lead to a substantial improvement in glycaemia control but did improve treatment satisfaction and quality of life. Patient selection is important and there remains a proportion of 'non-responders' to insulin pump therapy; ongoing studies will determine whether psychological interventions or additional technologies such as linked continuous glucose monitors improve their effectiveness.

Prescribing point: *Novorapid and Humalog are the most used insulin preparations in insulin pumps, but fast-acting insulin aspart (Fiasp) is also available (see Chapter* 8*).*

Safety of Insulin Pumps

Despite their widespread use, and despite the potential risks associated with insulin pump therapy, available evidence on their efficacy and safety is limited. This is in part because insulin pumps, being classed as devices, are not necessarily subject to the same levels of scrutiny prior to release as medications would be. Information on their safety is not always shared in a sufficiently transparent manner, and once a pump is on the market, real-world data on their use are not always made publicly available. Further, modifications to pumps and their software systems are often made post-release without necessarily undergoing clinical studies.

Regulation also varies between different countries. In the US, the FDA classes insulin pumps as Class 2 (moderate risk) devices; those that have an integrated system with continuous glucose monitoring (CGM) are deemed Class 3 (higher risk). In the EU insulin pumps are graded as Class 2b devices, but the level of scrutiny required for them to be certified (CE mark) can vary significantly between different countries. In 2015 the ADA and the EASD published a joint statement calling for increased funding for research into insulin pump safety, for improved transparency of pre- and post-marketing data, and for a standardised safety approach internationally [5].

Potential Disadvantages of Pump Therapy

Although continuous subcutaneous insulin delivery systems offer several advantages, it is important that wearers are aware of potential hazards associated with pump therapy. Firstly, there is often a misconception that pump therapy makes the management of diabetes simpler when in fact the opposite can be true; the complexities involved often require more work and training rather than less. It is also important for individuals and their families to understand the risks involved with pump therapy. While those on basal bolus therapy have the 'safety net' of basal insulin in their system, any interruption to the delivery of insulin via the pump (from a kinked infusion tubing, battery failure or trauma) can lead to complete insulin deficiency and diabetic ketoacidosis.

For this reason, pump users are always advised to ensure that they have spare insulin pens as a backup for holidays, etc.

Prescribing point: *Ensure that patients on an insulin pump have a supply of subcutaneous insulin (long and short acting) in the event of pump failure.*

The costs associated with insulin pump therapy have also been a limitation in their uptake. Insulin pumps cost approximately £2500–3000, and there are recurring costs for consumables such as reservoirs, cannulas and batteries, as well as the costs of the training required.

Self-monitoring of Blood Glucose

Blood Glucose Monitors

Home blood glucose monitoring became the standard of care in the 1980s, and along with the development of the measurement of HbA1c, this revolutionised diabetes care, leading ultimately to the development of landmark studies such as the DCCT (see Chapter 7).

Since that time there have been significant improvements in the accuracy and battery life of meters, which themselves are smaller and lighter. The relative costs of meters and testing strips have fallen, and there have been reductions in the amount of blood required and time taken for results, particularly since calibration is no longer required. Meters now have features that allow users to record insulin doses, carbohydrate intake and exercise, while 'speaking' meters have been designed for individuals with visual impairment.

Most companies manufacturing glucose monitors have associated apps that use Bluetooth and other technologies to provide an interface allowing sugar readings to be displayed in an easy to interpret format. This can be used by the individual to provide an overview of daily patterns and time in range and can be used to relay data to healthcare professionals.

Prescribing point: *There are many capillary blood glucose monitors available and often healthcare providers will choose from a limited number to realise cost savings. It is essential that the correct strips are prescribed for the particular monitor.*

Continuous Glucose Monitoring

Although there have been significant improvements in home blood glucose monitoring in recent years, there remains the inconvenience of fingertip blood sampling, and the inability to know what is happening to sugar levels between checks, particularly in the overnight period. Continuous glucose monitoring, using a subcutaneous sensor to measure interstitial fluid glucose levels, measures glucose readings every few minutes, building up a complete picture of trends over the course of an entire day (Box 10.1).

Box 10.1 Glossary of glucose monitoring terms

Self-monitoring of blood glucose (SMBG)

- Self-sampling of blood using a fingerstick for capillary glucose measurement using a meter
- Episodes of hyperglycaemia or hypoglycaemia are harder to detect since sampling is performed intermittently

Continuous glucose monitoring (CGM)

- Minimally invasive subcutaneous sensors which sample interstitial glucose at regular intervals, e.g. every 5–15 minutes
  - Retrospective CGM
    - Glucose levels are not visible while the device is worn
    - A report is generated for evaluation after the device is removed
  - Real-time CGM (rtCGM)
    - Sensors transmit and/or display glucose levels throughout the day
    - The patient can review glucose levels and adjust treatment as required
  - Intermittently scanned CGM
    - Also know as flash GM or FGM
    - Glucose levels can be seen when the device is worn and when the device is queried

Source: Adapted from [9].

Continuous glucose monitoring systems consist of a sensor, a small wire inserted under the skin of either the stomach or back of the arm, which detects glucose in the interstitial fluid. The sensor is usually held in place with an adhesive and is connected to a transmitter. The transmitter wirelessly sends information on blood glucose levels to a receiver, a reader or a smart phone/smartwatch app to display the data. Trend arrows allow the wearer to detect when sugar levels are rising or falling rapidly. It should be noted that, since CGM measures interstitial fluid rather than blood glucose, a 'lag' time of up to 20 minutes has been reported.

Prescribing point: *Given that there is a 'lag' time patients should be advised to also measure blood glucose at times when their symptoms, or the device, indicate hypoglycaemia.*

There are two types of CGM currently available: intermittently scanned (flash) CGM, which requires the wearer to actively scan the sensor every six to eight hours, and 'real-time' CGM. Although more expensive than flash CGM, real-time CGM systems have the advantage that they can link with insulin pumps, they have in built alarms to alert the wearer to hypo- and hyperglycaemia, and do not need to be scanned regularly.

Intermittently Scanned (Flash) Continuous Glucose Monitoring The 'flash' glucose monitoring device Freestyle Libre was first launched in Europe in 2014 and came into widespread use in the UK in late 2017 when it was added to the NHS drug tariff. The system consists of a sensor worn on the upper arm; each sensor lasts for two weeks (Figure 10.1). The sensor measures glucose every minute, and stores one value every 15 minutes. Libre needs to be actively scanned by the wearer to obtain glucose information, and if the individual scans every six to eight hours a continuous trace of sugar levels is developed, which can then be analysed using the accompanying app (Libreview) by the wearer or a healthcare professional. The sensor can be scanned using either a reader or a smartphone to find out current interstitial fluid glucose levels. Unlike other CGM devices, the Libre system needs to be read by the wearer, and so does not alarm if sugars are low or high, although the Libre 2 system, released in early 2021, has in-built alarm features.

Early Libre use in Scotland was first reported in 2019, in a study in which 900 people with type 1 diabetes and Freestyle Libre were compared with 518 people without Libre [6]. An overall reduction in HbA1c of 0.6% (7 mmol/mol) was seen in the Libre group. Significant reductions in admissions for diabetic ketoacidosis and high levels of wearer satisfaction were reported in the Libre arm, although there was an associated increase in self-reported hypoglycaemia. The more widespread use of Libre through-

FIGURE 10.1 Freestyle Libre flash glucose monitoring system (Abbott Diabetes Care). This comprises a sensor worn on the back of the arm. A small subcutaneous filament measures interstitial blood glucose every minute and stores data every 15 minutes. The device can be scanned using a dedicated reader or smartphone. The reader shows the glucose level and trend using arrows. An ambulatory glucose profile is also produced which allows for pattern analysis. *Source:* FreeStyle Libre is a trademark of Abbott or its related companies. Reproduced with permission of Abbott, © 2021. All rights reserved.

out the UK was then analysed in an audit run by the UK Association of British Clinical Diabetologists, studying over 10 000 individuals from 102 hospitals, and reported in 2020 [7]. Overall, a 0.5% (5 mmol/mol) reduction in HbA1c was seen, as well as reductions in hypoglycaemia, diabetes distress, paramedic callouts and hospital admissions for hypo- and hyperglycaemia.

Real-time Continuous Glucose Monitoring The first CGM system was introduced by Medtronic in 1999. Like conventional blood glucose meters, they have developed over the years and are now smaller, lighter and more accurate, require less calibration and have a longer battery life than early models.

Several CGM devices are now commercially available. Using Bluetooth technology, live glucose readings can be analysed using the wearer's smartphone or watch. Modern sensors are waterproof, small and lightweight. Software allows the wearer to log food intake, insulin dosage and physical activity. Sugar data can be uploaded to a cloud-based system, allowing multiple users to access data.

The currently most widely used sensors include the Dexcom G6 (sensor lasts up to ten days), the Medtronic Guardian Sensor 3 (sensor lasts up to seven days) and the 'Eversense' implantable CGM, which is inserted into the upper arm like a contraceptive implant, and lasts up to 90 days.

Accuracy of Continuous Glucose Monitoring The accuracy of CGM is of critical importance, particularly since interstitial fluid rather than blood glucose is being measured. The mean absolute relative difference (MARD) is the most commonly used metric to analyse measurement performance between different CGM systems and is calculated by averaging the differences between CGM system measurement results and the corresponding comparator, the capillary blood glucose measurement. While early CGM systems had a MARD of around 20%, this has improved in the last two decades. Modern systems have a MARD of 9–14% [8]. It is important to note that the accuracy of CGM can vary, particularly at the extremes of glucose measurements.

Ambulatory Glucose Profiles Modern blood glucose monitors, and particularly continuous glucose monitors, provide an enormous amount of data to the wearer and the healthcare professional. Analysing this data in a way that can help the individual to improve their diabetes control can be challenging. As a result, most CGM analysis platforms use an ambulatory glucose profile, which combines one to two weeks of CGM data in a graphical format. Median glucose levels across the day are demonstrated, with 25/75th and 5/95th centiles shown. These can target which times of day require an adjustment of insulin dose or adjustments to pump settings.

Another way to analyse CGM data, and one which is now beginning to be widely used in clinical practice, is to examine how much time is spent in glycaemic 'target ranges'.

Time in Range The concept of 'time in range' has a number of potential advantages over HbA1c. Measuring HbA1c simply gives an average of blood glucose levels over a two to three month period and individuals with diabetes who are having recurrent hypo- and hyperglycaemia may have a perfect HbA1c, since the extremes of gly-

caemia average out. Furthermore, HbA1c can be affected by several conditions including pregnancy, anaemia and haemoglobinopathies. Time in range (TIR) provides an overall picture of glycaemic control, and since it is a concept that most people can easily understand, the individual and their family can be motivated to improve time in range on a day-to-day basis. Individuals with diabetes can be encouraged to use their smartphone app to examine TIR on a daily or weekly basis, and to use this as an incentive to improve their control.

The target range for most people with type 1 diabetes has been established as 3.9–10 mmol/l. An international consensus was published in 2018 [9] and set a target for most people with type 1 diabetes to aim to have 70% of CGM within the target range (Figure 10.2). To support these recommendations, a retrospective analysis of seven-point blood glucose profiles from the DCCT demonstrated that TIR is strongly associated with the development of microvascular complications and should be considered an acceptable endpoint for clinical trials [10]. Data linking CGM-derived TIR with microvascular complications is limited, although preliminary data on 515 CGM users from Belgium showed that increasing TIR was associated with decreasing risk for microvascular complications.

Measuring time below range can also give useful information on the frequency and risk of hypoglycaemia. For most people the target is to spend less than 4% of time (or one hour per day) below 3.9 mmol/l. These targets can be modified; for example, in older individuals or those at particular risk of hypoglycaemia, a target of 50% 'time

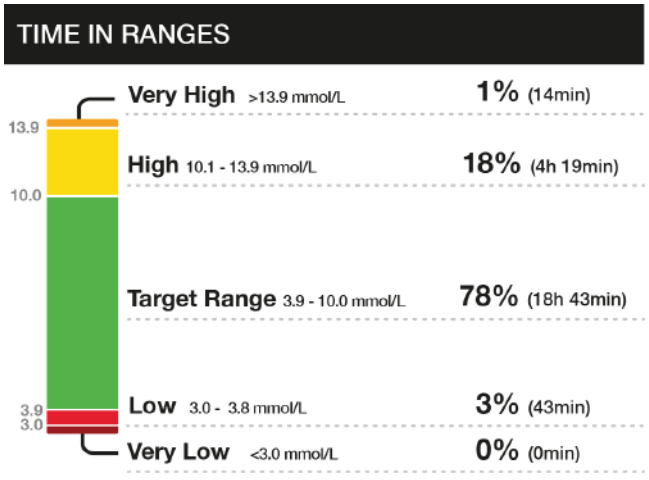


FIGURE 10.2 Time in range is a metric of glycaemic control taken from the ambulatory glucose profile and defined as the percentage of time spent within predetermined glucose levels. It includes the percentage of time per day spent within the target glucose (TIR), below the target glucose range (TBR) and above the target glucose range (TAR). For most patients with type 1 and type 2 diabetes, a TIR of >70% (3.9–10.0 mmol/l), TBR <4% (<3.9) and TAR <25% (>10) are recommended. *Source:* Reproduced with permission of Abbott, © 2021. All rights reserved.

in range' and <1% of time below range has been recommended. Pregnant women with type 1 diabetes have a tighter target range of 3.5–7.8 mmol/l, with an aim of having at least 70% of sugars within this range.

Efficacy of Continuous Glucose Monitoring Several large studies in recent years have provided robust evidence of the effectiveness of CGM, including the Glycaemic Control and Optimisation of Life Quality in Diabetes (GOLD) study, the CGM Intervention in Teens and Young adults (CITY) study, the multiple Daily Injections and Continuous Glucose Monitoring in Diabetes (DIAMOND) study and the Sensing with Insulin Pump Therapy to Control HBA1c (SWITCH) study. A recent meta-analysis of 15 randomised controlled trials showed that CGM was associated with an overall reduction in HbA1c of –0.17%, an increase in TIR of 70 minutes per day and significantly less time spent in hyper- and hypo-glycaemia. CGM has been shown to be effective in both pump and multidose insulin users, in adults and in young people, and although the benefits have been most clearly seen in people with type 1 diabetes, there were also benefits reported in people with type 2 diabetes [11]. In pregnancy, the Continuous Glucose Monitoring in Pregnant Women with Type 1 Diabetes (CONCEPTT) trial in 2017 showed that CGM in pregnancy led to a reduction in HbA1c, as well as a reduction in outcomes such as large for gestational age babies and requirement for neonatal intensive care unit admissions [12].

Linkage of Continuous Glucose Monitoring to Insulin Pumps

A key feature of CGM systems is their ability to communicate with insulin pumps, and a key area of research in the last 20 years has been the aim of developing a fully 'closed-loop' artificial pancreas system (APS) for managing people with type 1 diabetes. Improvements in the accuracy of CGM and secure wireless communication between pumps and CGM have led to significant advances along this path in recent years.

Low-glucose Suspend

The first step towards a closed-loop system came with the concept of 'low-glucose suspend' features from the Medtronic MiniMed Veo system, first approved in 2009. Insulin delivery could be suspended for up to two hours when sensor glucose fell below a certain level; this system was thought to be particularly beneficial in children or in those with severe hypoglycaemia. Early studies showed that use of a threshold-suspend sensor augmented pump led to a reduction in hypoglycaemia in all patient groups, compared with those without the threshold-suspend feature, with a 32% reduction in nocturnal hypoglycaemia and no difference in HbA1c [13].

The next step was the development of a predictive low-glucose suspend feature, in which insulin pumps would suspend when an algorithm predicted that glucose would fall below a certain threshold. Using the Tandem T-slim pump alongside the Dexcom G5 sensor, the Predictive Low-glucose Suspend for Reduction of Low Glucose (PROLOG) trial reported a 31% reduction in time in hypoglycaemic range, again without any corresponding increase in hyperglycaemia [14].

Hybrid Closed Loop

The currently most advanced available systems are known as 'hybrid' closed loop [15]. Hybrid systems mean that the user will manually enter mealtime insulin, but apart from mealtimes, including the overnight period, basal insulin delivery is controlled automatically by the algorithm. The first hybrid closed-loop system, the Medtronic 670G, was approved by the FDA in 2016, and currently there are three that are commercially available (Table 10.1): the Medtronic 780G (Medtronic, Northridge, California, US, using the Guardian 3 sensor), the Tandem T-slim Control IQ system (Tandem Inc., San Diego, California, US, along with the Dexcom G6 sensor) and the CamAPS system (Cambridge, UK, using the Dana RS pump and the Dexcom G6 sensor). The Medtronic and Tandem systems have the glucose algorithm built into the pump software, while the CamAPS uses a smartphone app which connects via Bluetooth to the pump and sensor.

A potential drawback of hybrid closed-loop systems, such as the Medtronic 780G

TABLE 10.1 **Currently commercially available hybrid closed-loop systems**

	Medtronic 780G – Guardian 3 Sensor	**Tandem T-Slim-Dexcom G6 – Control IQ**	**CamAPS FX Dana RS – Dexcom G6**
Integrated pump	780G	Tandem T-slim X2	Dana RS
Sensor	Guardian 3	Dexcom G6	Dexcom G6
Sensor duration	7 days	10 days	10 days
Glycaemic target	6.7, 6.1 or 5.5 mmol/l	Target range 6.2–8.9 mmol/l	5.8 mmol/l (customisable)
TIR	73% Adolescents, 75% adults	71% (adolescents and adults)	76% (well controlled adults)
Waterproof?	Up to 12 ft	Pump up to 3 ft, sensor up to 8 ft	Pump fully waterproof, sensor to 8 ft
Approximate yearly cost if new to pump (UK NHS)	£5698.50	£5171	£5560

Source: Adapted from [15].

and Tandem systems, is that the algorithm aims for a pre-programmed glycaemic target range that is nonadjustable, meaning that the target is sometimes not sufficiently tight for those who require tighter control, such as pregnant women. All systems have passed safety regulations in the UK.

Efficacy of Closed Loop Systems

Positive data has arisen from the addition of CGM to insulin pumps. The International Diabetes Closed Loop (iDCL) trial studied 168 individuals and compared the Control IQ closed-loop system with a sensor-augmented pump without automated insulin adjustment. Those randomised to the Control IQ closed-loop system had an increase from 61% TIR at baseline to 71% TIR over six months of therapy; those in the control group had no change in TIR across the trial [16]. In addition, the closed-loop system led to less hypoglycaemia, less hyperglycaemia and better HbA1c levels. A further study of 101 children used the Control IQ system and TIR increased from 53% at baseline to 67% after 16 weeks; those in the closed-loop arm had 2.6 hours per day less hyperglycaemia than those in the control group [17].

DIY Closed Loop

As a result of perceived slow progress in the development of closed-loop systems, a few 'do it yourself' APSs have arisen in the last few years. A mainly online community has supported the development of open access closed-loop systems, which appear quickly since they have not undergone the usual regulatory approval. Individuals must build and maintain their own systems, but do this with the support of a large worldwide online community. Current systems include Open APS, Android APS and Loop, although it is important to note that no longitudinal randomised controlled trials have been undertaken to evaluate their safety and effectiveness.

Guidelines on the Use of Devices

Insulin Pumps

Insulin pump use is increasing year on year but varies significantly across the world, in part depending on the funding of healthcare systems; in the US it is estimated that 30–40% of people with type 1 diabetes use a pump, while in Scotland overall 14% of people with type 1 diabetes are registered pump users.

Guidance on insulin pump use varies internationally. The NICE guidelines from 2015 recommended the use of insulin pumps for children and young people with type 1 diabetes as an alternative to basal bolus insulin regimens from the time of diagnosis if MDIs were deemed impractical or inappropriate [18]. Insulin pump therapy

was also recommended as a treatment option for adults and children 12 years and older with type 1 diabetes mellitus if attempts to achieve target HbA1c levels with MDIs result in the person experiencing disabling hypoglycaemia, for those with lack of hypoglycaemic awareness, and those with gastroparesis. NICE guidelines on the management of type 1 diabetes were updated in March 2022 [19]. The guidance on pump therapy is unchanged but the use of integrated sensor-augmented pumps is to be updated as a multiple technology appraisal.

The guidance of SIGN for people with type 1 diabetes was last produced in 2010 (see Chapter 15). It identified that insulin pump therapy was associated with modest improvements in glycaemic control and recommended that it should be considered in patients who were unable to achieve their glycaemic targets with MDIs, or patients who were experiencing recurring episodes of severe hypoglycaemia [20]. As a good practice point it recommended that multidisciplinary pump clinics should be available for pump users, and that structured education should be part of the process. In addition, as a good practice point SIGN recommended insulin pump therapy for those with very low basal insulin requirements (such as infants and young children), for whom even small doses of basal insulin may result in hypoglycaemia. SIGN has in development updated guidelines on the management of type 1 diabetes, including technologies, with an estimated publication date in 2022.

The ADA 'Standards of Medical Care' 2021 has broader guidance, derived from expert opinion, indicating that insulin pump therapy should be considered an option for all adults, children and adolescents with type 1 diabetes who are able to safely manage the device [21]. The recent consensus report from the ADA and the EASD on the management of type 1 diabetes in adults details the attributes of insulin pump therapy in comparison with injected insulin regimens with regards to flexibility, risk of hypoglycaemia and cost, and notes that either MDI or insulin pump therapy can be used to mimic physiology as closely as possible [21].

Continuous Glucose Monitoring

Within the UK, until recently intermittently scanned CGM has been available for all people with type 1 diabetes who fulfil certain criteria. With the higher costs involved, real-time CGM, has been less widely available except in pregnancy, where it has been widely used following the CONCEPTT study. NICE guidelines updated in March 2022, however, recommend access to CGM for all people with Type 1 Diabetes- a major widening of access to this technology [19]. The choice between real time CGM and intermittently scanned CGM is dependent upon individual preferences, needs, characteristics and the functionality of devices available [18]. The guidelines also recommend that intermittently scanned CGM is offered to those with type 2 diabetes on multiple daily insulin injections who have impaired hypoglycaemic awareness, or who have a condition or disability that means they cannot self monitor capillary blood glucose.

The consensus report from the ADA and the EASD on the management of type 1 diabetes in adults details the advantages of CGM and describes standardised metrics for clinical care but does not recommend specific groups of patients that might benefit from CGM [22].

Place of Devices in Current and Future Practice

There have been huge developments in recent years in insulin pump and CGM technologies, which have the potential to revolutionise diabetes care. The use of CGM and the ability to review sugars remotely have been enormously beneficial during the increase in telemedicine that has arisen from the COVID-19 pandemic. While the majority of research on technologies such as pumps and CGM has been undertaken in people with type 1 diabetes, it is expected that their use in people with type 2 diabetes will increase in the coming years.

One of the challenges, particularly in countries with publicly funded healthcare systems, is working out which individuals will benefit most from which system. Regardless of the technology used, training in carbohydrate counting, management of hypoglycaemia and insulin sensitivity are essential. Formal structured training such as DAFNE should be offered to all people with type 1 diabetes. Even with the hybrid close loop system, the most advanced technology currently available, good glycaemic control can only be achieved with careful and accurate calculation of bolus doses.

Insulin development has progressed hugely over recent years and using more modern, quicker acting insulins analogues such as Fiasp and Lyumjev, with a time of onset of only a few minutes, along with modern technologies is likely to lead to further improvements in care for people with diabetes. Diabetes management in pregnancy can be particularly challenging and is an area where modern technologies may be widely adopted. The Automated Insulin Delivery Amongst Pregnant Women with Type 1 Diabetes (AiDAPT) study is examining closed-loop insulin systems in pregnancy throughout the UK. If this and similar studies demonstrate positive outcomes, they are likely to lead to a significant increase in the use of closed-loop insulin systems in this setting.

Finally, within the next five years, it is expected that refinement of closed-loop systems, including the use of 'bihormonal' pumps which include glucagon to prevent hypoglycaemia, will lead to further improvements in diabetes management as they become increasingly commercially available.

References

1. Scottish Diabetes data Group. Scottish Diabetes Survey (2019). https://www.diabetesinscotland.org.uk/wp-content/uploads/2020/10/Diabetes-Scottish-Diabetes-Survey-2019.pdf (accessed 11 October 2021).
2. Paton, J.S., Wilson, M., Ireland, J.T., and Reith, S.B. (1981). Convenient pocket insulin syringe. *Lancet* 1 (8213): 189–190.
3. Pickup, J.C. (2012). Insulin-pump therapy for type 1 diabetes mellitus. *N Engl J Med* 366: 1616–1624.
4. REPOSE Study Group (2017). Relative effectiveness of insulin pump treatment over multiple daily injections and structured education during flexible intensive insulin treatment for type 1 diabetes: cluster randomised trial (REPOSE). *BMJ* 356: j1285.

5. Heinemann, L., Fleming, G.A., Petrie, J.R. et al. (2015). Insulin pump risks and benefits: a clinical appraisal of pump safety standards, adverse event reporting, and research needs: a joint statement of the European Association for the Study of Diabetes and the American Diabetes Association Diabetes Technology Working Group. *Diabetes Care* 38: 716–722.
6. Tyndall, V., Stimson, R.H., Zammitt, N.N. et al. (2019). Marked improvement in HbA1c following commencement of flash glucose monitoring in people with type 1 diabetes. *Diabetologia* 62: 1349–1356.
7. Deshmukh, H., Wilmot, E.G., Gregory, R. et al. (2020). Effect of flash glucose monitoring on glycemic control, hypoglycemia, diabetes-related distress, and resource utilization in the Association of British Clinical Diabetologists (ABCD) nationwide audit. *Diabetes Care* 43: 2153–2160.
8. Freckmann, G. (2020). Basics and use of continuous glucose monitoring (CGM) in diabetes therapy. *J Lab Med* 44: 71–79.
9. Battelino, T., Danne, T., Bergenstal, R.M. et al. (2019). Clinical targets for continuous glucose monitoring data interpretation: recommendations from the international consensus on time in range. *Diabetes Care* 42: 1593–1603.
10. Beck, R.W., Bergenstal, R.M., Riddlesworth, T.D. et al. (2019). Validation of time in range as an outcome measure for diabetes clinical trials. *Diabetes Care* 42: 400–405.
11. Maiorino, M.I., Signoriello, S., Maio, A. et al. (2020). Effects of continuous glucose monitoring on metrics of glycemic control in diabetes: a systematic review with meta-analysis of randomized controlled trials. *Diabetes Care* 43: 1146–1156.
12. Feig, D.S., Donovan, L.E., Corcoy, R. et al., on behalf of the CONCEPTT Collaborative Group (2017). Continuous glucose monitoring in pregnant women with type 1 diabetes (CONCEPTT): a multicentre international randomised controlled trial. *Lancet* 390: 2347–2359.
13. Bergenstal, R.M., Klonoff, D.C., Garg, S.K. et al. (2013). Threshold-based insulin-pump interruption for reduction of hypoglycemia. *N Engl J Med* 369: 224–232.
14. Forlenza, G.P., Zoey, L., Buckingham, B.A. et al. (2018). Predictive low-glucose suspend reduces hypoglycemia in adults, adolescents, and children with type 1 diabetes in an at-home randomized crossover study: results of the PROLOG Trial. *Diabetes Care* 41: 2155–2161.
15. Leelarathna, L., Choudhary, P., Wilmot, E.G. et al. (2021). Hybrid closed-loop therapy: where are we in 2021? *Diabetes Obese Metab* 23: 655–660.
16. Brown, S.A., Kovatchev, B.P., Raghinaru, D. et al. (2019). Six-month randomized, multicenter trial of closed-loop control in type 1 diabetes. *N Engl J Med* 381: 1707–1717.
17. Breton, M.D., Beck, R.W., and Wadwa, R.P. (2020). A randomized trial of closed-loop control in children with type 1 diabetes. *N Engl J Med* 383: 836–845.
18. NICE guidelines [NG18] Diabetes (type 1 and type 2) in children and young people: diagnosis and management. https://www.nice.org.uk/guidance/ng18/chapter/Recommendations (accessed 11 April 2022)
19. NICE guidelines [NG17] (2015). Type 1 diabetes in adults: diagnosis and management. https://www.nice.org.uk/guidance/ng17/chapter/Recommendations (accessed 11 April 2022).
20. SIGN 116 (2010 March). Management of diabetes. A national clinical guideline, 30–38. https://www.sign.ac.uk/media/1054/sign116.pdf (accessed 11 October 2021).
21. American Diabetes Association Standards of Medical Care in Diabetes (2022). Diabetes technology, S85–S99. https://care.diabetesjournals.org/content/44/Supplement_1/S73 (accessed 11 October 2021).
22. Holt, R.I.G., DeVries, J.H., Hess-Fischl, A. et al. (2021 September 30). The management of type 1 diabetes in adults. A consensus report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). *Diabetologia* 64: 2609–2652.

CHAPTER 11

Acarbose and Alpha Glucosidase Inhibitors

Miles Fisher

KEY POINTS

- Alpha glucosidase inhibitors (acarbose, voglibose, miglitol) are moderately effective at reducing postprandial hyperglycaemia and mildly effective at reducing HbA1c in people with type 2 diabetes.
- Clinical use of alpha glucosidase inhibitors as a treatment for type 2 diabetes is limited by gastrointestinal side effects.
- Meta-analysis of three large studies in subjects with impaired glucose tolerance demonstrated no reduction in cardiovascular outcomes and alpha glucosidase inhibitors are not indicated for cardiovascular protection.
- Alpha glucosidase inhibitors delay the progression to diabetes in subjects with impaired glucose tolerance.

Introduction

Alpha glucosidase inhibitors (AGIs) are an oral antidiabetic drug for type 2 diabetes. Acarbose was the first clinically available AGI, followed by voglibose and miglitol. The clinical use of AGIs in Europe and the US has been limited as the effects on reducing HbA1c have been modest and gastrointestinal side effects have been frequent and occasionally distressing for the patient. In contrast, AGIs are widely used in South and East Asia where the diet contains more complex carbohydrate and where AGIs appear to be better tolerated and more efficacious than in Europe and the US.

Diabetes Drug Notes, First Edition. Edited by Miles Fisher, Gerard A. McKay, and Andrea Llano.

Pharmacology

Polysaccharides and oligosaccharides in the diet are poorly absorbed and are broken down to monosaccharides by alpha glucosidase in the brush border of the small intestine. These monosaccharides are then easily absorbed. Many natural products contain AGI activity. Acarbose is a pseudooligosaccharide derived from the *Actinoplanes* strain of fungi. Voglibose was first isolated from the bacterium *Streptomyces hygroscopicies var. limonons*. In contrast, miglitol is a semisynthetic AGI derived from deoxynojirimycin, which is found in mulberry tea.

Mechanism of Action

Alpha glucosidase inhibitors have several possible mechanisms of action:

- They competitively and reversibly inhibit alpha glucosidase, slowing the absorption of carbohydrates and leading to reductions in postprandial hyperglycaemia (Figure 11.1).
- The inhibition of carbohydrate absorption increases the availability of substrates for gut fermentation in the distal intestine, leading to changes in the gut microbiota, which may also have a therapeutic effect.
- They have been shown to increase postprandial GLP-1 concentrations and decrease postprandial insulin and GIP concentrations.
- Acarbose also has a weak inhibitory effect on pancreatic alpha amylase.

Acarbose

Acarbose acts locally in the gastrointestinal tract and is not absorbed. It is metabolised in the intestine by bacteria and digestive enzymes. Some metabolites are absorbed and

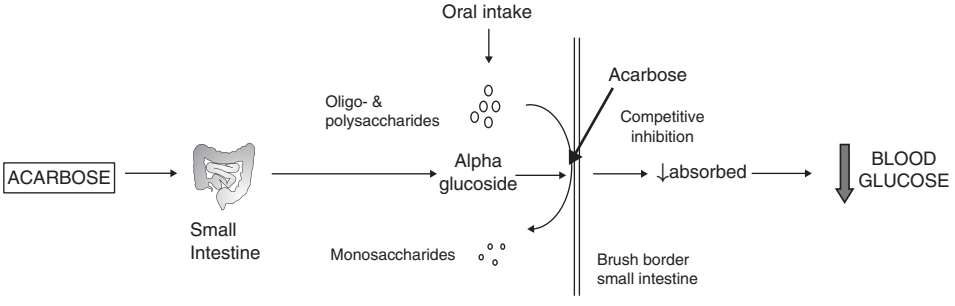


FIGURE 11.1 Mechanism of action of alpha glucosidase inhibitors. Alpha glucosidase inhibitors (e.g. acarbose) competitively and reversibly inhibit alpha glucosidase, slowing the absorption of carbohydrates and leading to reductions in postprandial hyperglycaemia. The inhibition of carbohydrate absorption increases the availability of substrates for gut fermentation in the distal intestine.

excreted by the kidney and the other metabolites are excreted in faeces. Acarbose has few significant drug interactions; it may decrease the bioavailability of digoxin and valproate.

Acarbose was the first clinically available AGI and was developed by Bayer, a European pharmaceutical company. Acarbose was launched in Switzerland as Glucobay® in 1986, in China in 1994 and in the US in 1995. Acarbose is the only AGI available in the UK and is available as a generic drug.

Dose

- Acarbose initially 50 mg daily.
- Increased to 50 mg three times a day for six to eight weeks.
- Increased, if necessary, to 100 mg three times a day.
- Maximum 200 mg three times a day.

Other Alpha Glucosidase Inhibitors

Voglibose is also poorly absorbed and is excreted in faeces. In contrast, miglitol is absorbed completely from the gut, is not metabolised and is excreted by the kidneys.

Voglibose was launched in Japan in 1994 by Takeda, a Japanese pharmaceutical company, and is also available in India, China and South Korea. Miglitol was initially developed by Bayer then licensed out. It was first available in The Netherlands in 1996 followed by multiple other countries in the EU, the US, Japan, Taiwan, India and China.

Glycaemic Efficacy

Acarbose is described as having modest glycaemic efficacy and reduces HbA1c by between 0.55 and 0.8% (6–9 mmol/mol). The efficacy of acarbose was examined in a three-year double-blind, placebo-controlled substudy of the UKPDS (United Kingdom Prospective Diabetes Study), published in 1999 [1]. The substudy included 1946 of the UKPDS patients who were randomised to acarbose maximum dose 100 mg three times daily or placebo for three years. At three years the HbA1c was 0.5% (5 mmol/mol) lower in subjects on acarbose who were able to remain on the treatment, but more than half of the subjects had to stop taking acarbose because of flatulence or diarrhoea.

This substudy of the UKPDS was included in a Cochrane systematic review and meta-analysis of AGIs in patients with type 2 diabetes [2]. Forty-one studies of at least 12 weeks' duration were included: 30 studies with acarbose, seven with miglitol, one with voglibose and three combined. Compared with placebo, beneficial effects of AGIs on HbA1c were found (acarbose –0.8% (–9 mmol/mol) and miglitol –0.7% (–8 mmol/mol)). Fasting blood glucose decreased by 1.1 mmol/l with acarbose and 0.5 mmol/l with miglitol. Post-load glucose decreased by 2.3 mmol/l with acarbose and 2.7 mmol/l with miglitol. Doses of acarbose higher than 50 mg three times daily increased the

gastrointestinal side effects but did not further reduce HbA1c. Effects on body mass index were minimal, and no effect on plasma lipids was detected. There was no evidence for an effect on morbidity or mortality.

A more recent systematic review and meta-analysis examined the efficacy of acarbose in patients with an Eastern or Western diet [3]. Forty-six studies were included in the analysis, and in patients on an Eastern diet the reduction in HbA1c was 1.0% (11 mmol/mol) vs. 0.5% (5 mmol/mol) in those on a Western diet, and in those on an Eastern diet efficacy was comparable with that of metformin or sulfonylureas. There is also some suggestion that gastrointestinal side effects may be less common in people on an Eastern diet.

Several small studies, mostly from Europe and the US, have examined the effects of acarbose as an adjunctive therapy to diet and insulin in patients with type 1 diabetes. As for patients with type 2 diabetes, the effects on HbA1c were modest, gastrointestinal side effects were common and many patients discontinued treatment.

Safety and Side Effects

Gastrointestinal side effects are common with acarbose, and these include flatulence, diarrhoea, gastrointestinal discomfort and abdominal pain. Some patients get meteorism, a combination of bloating sensation, abdominal discomfort and abdominal distension.

Prescribing point: *To mitigate gastrointestinal side effects, acarbose should be started at a dose of 50 mg daily, then slowly increased to a maximum of 200 mg three times daily. A diet high in complex carbohydrates and low in simple sugars may also reduce gastrointestinal side effects.*

Acarbose has a good safety profile, which may be explained by its local action in the gastrointestinal tract and lack of systemic absorption. There have been no cardiovascular concerns with acarbose, and the possibility of cardiovascular benefit is discussed below. Acarbose has been associated with increases in hepatic enzymes and rare cases of hepatotoxicity, with a small number of fatal cases.

Hypoglycaemia is rare with acarbose, but hypoglycaemia can occur when acarbose is combined with insulin or sulfonylureas.

Outcome Trials

Prevention of Type 2 Diabetes

STOP-NIDDM The use of AGIs to prevent the progression from prediabetes to diabetes was studied in two large outcome trials [4, 5]. The STOP-NIDDM (Study to Prevent Non-insulin-dependent Diabetes Mellitus) trial tested the hypothesis that

acarbose would improve postprandial hyperglycaemia and increase insulin sensitivity by reducing stress on the pancreatic beta cells, so preventing or delaying the progression from impaired glucose tolerance to diabetes (Table 11.1). Subjects were recruited mainly through newspaper advertisements. Following screening, 1429 subjects who had impaired glucose tolerance on a glucose tolerance test were randomised to acarbose or placebo. To avoid or minimise gastrointestinal side effects acarbose was started at 50 mg daily and titrated every two weeks to 100 mg three times daily or the maximum tolerated dose. The primary endpoint was the development of diabetes on the basis of an annual glucose tolerance test and subjects were followed for a mean of 3.3 years. Secondary outcomes were changes in blood pressure, lipid profile, insulin sensitivity, morphometric profile and cardiovascular events.

In STOP-NIDDM:

- A total of 221 (32%) patients randomised to acarbose and 285 (42%) randomised to placebo developed diabetes (HR 0.75; 95% CI 0.63–0.90; $p = 0.0015$).
- The most frequent side effects of acarbose were flatulence and diarrhoea. Out of 682 patients in the acarbose group, 211 (31%) discontinued treatment early, com-

TABLE 11.1 Outcome trials with alpha glucosidase inhibitors

Trial	STOP-NIDDM [4, 6]	Voglibose Ph-3 [5]	ACE [12]
Drug	Acarbose 100 mg three times daily	Voglibose 0.2 mg three times daily	Acarbose 50 mg three times daily
Comparator	Placebo	Placebo	Placebo
Population size ($n =$)	1429	1780	6522
Age (years)	54	56	64
Follow-up (years)	3.3	4	5
Atherosclerotic CVD (%)	5	NA	100
Heart failure (%)	NA	NA	4
Primary outcome	25% reduction in the development of diabetes	41% reduction in the development of diabetes	No difference in five-point MACE
Secondary outcomes	Cardiovascular events reduced Myocardial infarctions reduced		No difference in three-point MACE Reduced development of diabetes

CHD = coronary heart disease, CV = cardiovascular, CVD = cardiovascular disease, MACE = major adverse cardiovascular events, NA = not available.
Source: Based on [4–6, 12].

pared with 130 (19%) of 686 on placebo, and the commonest single cause of early discontinuation was gastrointestinal side effects.

- At the end of the study, treatment with placebo for three months was associated with an increase in conversion from impaired glucose tolerance to diabetes.

The authors concluded that acarbose delayed the progression to type 2 diabetes in subjects with impaired glucose tolerance. They made comparisons with studies that used changes in lifestyle to delay the progression to diabetes (Da Qing, Diabetes Prevention Program, Finnish Diabetes Prevention Study) and noted the greater effect of lifestyle changes. They suggested that these trials were not blinded and so bias could have affected the outcome of these trials. The STOP-NIDDM investigators did not consider that their own trial may have been biased as subjects and investigators were not fully blinded as they were recording gastrointestinal side effects! Instead, they commented that the benefits of acarbose in delaying progression to diabetes were underestimated as one-third of subjects randomised to acarbose discontinued this prematurely.

Secondary endpoints in STOP-NIDDM were the development of a composite of major adverse cardiovascular events and the development of new hypertension [6]. Major adverse cardiovascular events were defined as cardiovascular death, coronary heart disease (myocardial infarction, new angina, coronary revascularisation), congestive heart failure, cerebrovascular disease or peripheral vascular disease. These were adjudicated by three cardiologists who were blinded to treatment. In this analysis of cardiovascular events:

- Acarbose was associated with a 49% relative risk reduction in the development of cardiovascular events (HR 0.51; 95% CI 0.28–0.95; $p = 0.03$), but the number of events was very small, with 32 events in the placebo group and 15 events in the acarbose group (Figure 11.2).
- Acarbose was also associated with a reduction in the incidence of new hypertension (blood pressure ≥140/90).

The authors stated that the reductions in MACE were due to the decrease in postprandial hyperglycaemia with acarbose, but in fact postprandial glucose concentration was not measured in STOP-NIDDM!

Voglibose Ph-3 Study The other large trial that examined the effects of an AGI in delaying the progression from impaired glucose tolerance to diabetes was the Voglibose Ph-3 study [5]. This randomised double-blind, placebo-controlled trial randomised 1780 Japanese subjects with impaired glucose tolerance to voglibose 0.2 mg three times daily or placebo. The primary endpoint was the development of diabetes and the secondary endpoint was normoglycaemia. The trial was supposed to run for a minimum of three years but was halted early by the data monitoring committee after an interim analysis showed a significant reduction in the development of diabetes with voglibose over a mean duration of 48 weeks:

- Patients treated with voglibose had a lower risk of progression to type 2 diabetes than those on placebo (50 of 897 vs. 106 of 881; HR 0.595; 95% CI 0.43–0.82; $p = 0.0014$).

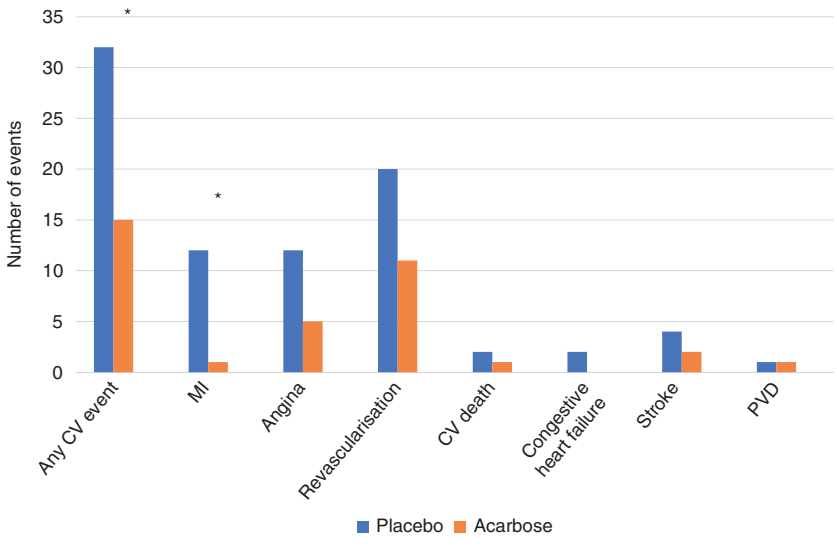


FIGURE 11.2 Cardiovascular events (total events) comparing acarbose and placebo in the STOP-NIDDM trial [6]. Statistically significant differences are marked with an asterisk. CV = cardiovascular, MI = myocardial infarction, PVD = peripheral vascular disease. *Source:* Based on [6].

- More people in the voglibose group achieved normoglycaemia than in the placebo group.
- Adverse effects were more common in the voglibose group, including gastrointestinal side effects such as diarrhoea, flatulence and abdominal distension (13 vs. 5%).

These findings are broadly similar to the results from STOP-NIDDM. The number of cardiovascular events was very small, with 12 in the voglibose group and 18 in the placebo group.

Cardiovascular Outcome Trials

Meta-analysis of Cardiovascular Events with Acarbose The cardiovascular results from STOP-NIDDM were combined with cardiovascular events from six other efficacy trials of acarbose in a controversial meta-analysis [7]. This meta-analysis showed reductions in myocardial infarctions and major cardiovascular events with acarbose, and the result was driven by a reduction in myocardial infarctions from STOP-NIDDM. This meta-analysis was heavily criticised because of publication bias, heterogeneity, detection bias and confounding factors [8]. The controversy was revisited one year later when other authors identified what they thought were several flaws in STOP-NIDDM, including selection bias, inadequate blinding, bias in data analysis and data reporting, plus potential sponsoring bias [9], suggesting that STOP-NIDDM

and the meta-analysis of selected studies with acarbose were seriously flawed and no conclusions could be drawn from the published data [10]. The STOP-NIDDM investigators countered that the STOP-NIDDM results were scientifically sound and credible and that the criticisms were unfounded and flawed by misinterpretations, biases and inappropriate valued judgments [11]!

ACE The ACE (Acarbose Cardiovascular Evaluation) trial was a phase 4 investigator-initiated randomised, placebo-controlled study to definitively test the hypothesis generated in the post hoc analysis of STOP-NIDDM that acarbose would reduce cardiovascular events in subjects with impaired glucose tolerance [12]. This large cardiovascular outcome trial recruited 6522 Chinese subjects with coronary heart disease and impaired glucose tolerance from 176 outpatient clinics in China. Subjects were randomised to placebo or acarbose 50 mg three times daily and were followed up for a median of five years. The primary outcome was a composite of cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, hospitalisation for unstable angina and hospitalisation for heart failure:

- There was no difference in the primary outcome with 470 cardiovascular events in the acarbose group and 479 in the placebo group (HR 0.98; 95% CI 0.86–1.11; $p = 0.73$) (Figure 11.3).
- There was no significant difference in any of the secondary cardiovascular outcomes.
- Acarbose significantly delayed the progression to diabetes by 18% (HR 0.82; 95% CI 0.71–0.94, $p = 0.005$), which was a secondary outcome.

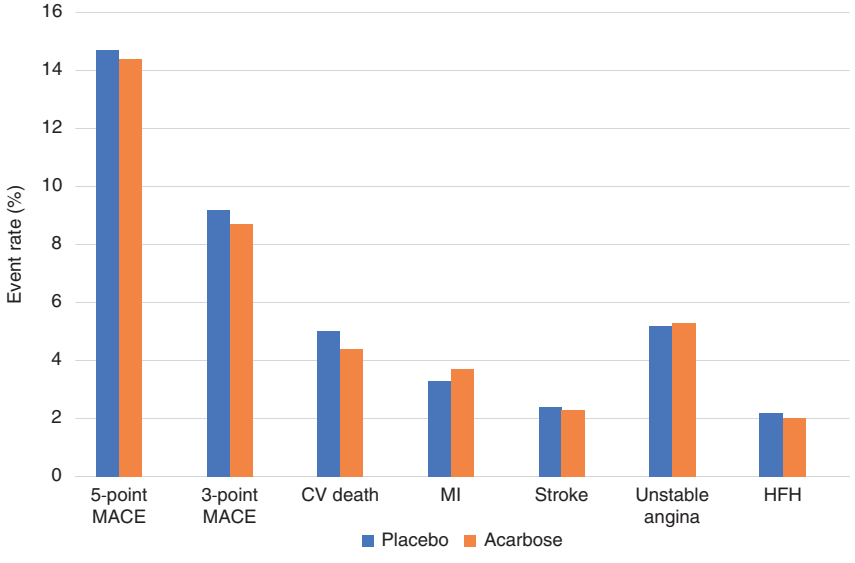


FIGURE 11.3 Cardiovascular event rate (%) comparing acarbose and placebo in the ACE trial [12]. There were no statistically significant differences. CV = cardiovascular, MI = myocardial infarction, HFH = hospitalisation for heart failure, MACE = major adverse cardiovascular events. *Source:* Based on [12].

Meta-analysis of Cardiovascular Events with Alpha Glucosidase Inhibitors The ACE study investigators performed a meta-analysis on the effects of alpha glucosidase inhibitors on incident diabetes and cardiovascular outcomes [13]. They included studies with more than 500 participants and/or more than 100 endpoints of interest. Based on meta-analysis of data from STOP-NIDDM, Voglibose Ph-3 and ACE they observed a 23% reduction in incident diabetes (HR 0.77; 95% CI 0.67–0.88; $p < 0.0001$) and based on cardiovascular data from the acarbose subgroup of UKPDS plus the same three studies, no difference in cardiovascular outcomes was observed (HR 0.98; 95% CI 0.89–1.10; $p = 0.85$). They concluded that the effect of AGIs on cardiovascular outcomes was neutral, so AGIs could not be indicated for cardiovascular protection.

Place of Alpha Glucosidase Inhibitors in Current and Future Practice

Alpha glucosidase inhibitors are infrequently used as antidiabetic drugs in the UK, most of Europe and the US, owing to perceived modest effects in reducing HbA1c, and major gastrointestinal side effects which limit adherence to these medications. With the availability of DPP-4 inhibitors and SGLT2 inhibitors, which are much better tolerated by people with diabetes, AGIs are now infrequently mentioned in guidelines and consensus reports on the management of people with type 2 diabetes. For example, in the joint American Diabetes Association/European Association for the Study of Diabetes consensus report it is noted that no new scientific information has emerged on AGIs in recent years, and they are not mentioned as treatment options where there is a compelling need to avoid hypoglycaemia or cost is a major issue [14]. They are widely used, however, as a treatment for type 2 diabetes in parts of the world where the diet is high in carbohydrates such as China, India and Japan.

The results of the ACE trial showed beyond reasonable doubt that acarbose does not reduce cardiovascular events in subjects with established coronary heart disease and impaired glucose tolerance. Given the costs of running these large cardiovascular outcome trials it seems unlikely that a similar outcome trial will be performed in subjects with diabetes. On the available evidence the effects of AGIs on cardiovascular events in people with diabetes is neutral, and AGIs should not be indicated for cardiovascular protection in people with diabetes.

The trials on the prevention of diabetes have consistently demonstrated that AGIs delay the progression to diabetes, and they are used in some parts of the world for that recommendation in subjects with prediabetes. The NICE guideline on preventing type 2 diabetes in individuals at high risk mentions only metformin [15].

References

1. Holman, R.R., Cull, C.A., and Turner, R.C. (1999). A randomized double-blind trial of acarbose in type 2 diabetes shows improved glycemic control over 3 years (U.K. Prospective Diabetes Study 44). *Diabetes Care* 22: 960–964.
2. Van de Laar, F.A., Lucassen, P.L., Akkermans, R.P. et al. (2006 October 18). Alpha-glucosidase inhibitors for type 2 diabetes mellitus. *Cochrane Database Syst Rev* (4): CD005061. doi: 10.1002/14651858.CD005061.pub2.
3. Zhu, Q., Tong, Y., Wu, T., Li, J., and Tong, N. (2013). Comparison of the hypoglycemic effect of acarbose monotherapy in patients with type 2 diabetes mellitus consuming an Eastern or Western diet: a systematic meta-analysis. *Clin Ther* 35: 880–899.
4. Chiasson, J.-L., Josse, R.G., Gomis, R. et al., for the STOP-NIDDM Trial Research Group (2002). Acarbose for prevention of type 2 diabetes mellitus: the STOP- NIDDM randomised trial. *Lancet* 359: 2072–2077.
5. Kawamori, R., Tajima, N., Iwamoto, Y. et al., on behalf of the Ph-3 Study Group. (2009). Voglibose for prevention of type 2 diabetes mellitus: a randomised, double-blind trial in Japanese individuals with impaired glucose tolerance. *Lancet* 373: 1607–1614.
6. Chiasson, J.-L., Josse, R.G., Gomis, R. et al., for the STOP-NIDDM Trial Research Group. (2003). Acarbose treatment and the risk of cardiovascular disease and hypertension in patients with impaired glucose tolerance: the STOP-NIDDM trial. *JAMA* 290: 486–494.
7. Hanefeld, M., Cagatay, M., Petrowitsch, T. et al. (2004). Acarbose reduces the risk for myocardial infarction in type 2 diabetic patients: meta-analysis of seven long-term studies. *Eur Heart J* 25: 10–16.
8. Van de Laar, F.A. and Lucassen, P.L.B.J. (2004). No evidence for a reduction of myocardial infarctions by acarbose. *Eur Heart J* 25: 1179–1180.
9. Kaiser, T. and Sawicki, P.T. (2004). Acarbose for prevention of diabetes, hypertension and cardiovascular events? A critical analysis of the STOP-NIDDM data. *Diabetologia* 47: 575–580.
10. Sawicki, P.T. and Kaier, T. (2004). Response to Chiasson et al.: acarbose for the prevention of Type 2 diabetes, hypertension and cardiovascular disease in subjects with impaired glucose tolerance: facts and interpretations concerning the critical analysis of the STOP-NIDDM Trial data. *Diabetologia* 47: 976–977.
11. Chiasson, J.-L., Josse, R.G., Gomis, R. et al., for the STOP-NIDDM Trial Research Group. (2004). Acarbose for the prevention of Type 2 diabetes, hypertension and cardiovascular disease in subjects with impaired glucose tolerance: facts and interpretations concerning the critical analysis of the STOP-NIDDM Trial data. *Diabetologia* 47: 969–975.
12. Holman, R.R., Coleman, R.L., Chan, J.C.N. et al., for the ACE Study Group. (2017). Effects of acarbose on cardiovascular and diabetes outcomes in patients with coronary heart disease and impaired glucose tolerance (ACE): a randomised, double-blind, placebo-controlled trial. *Lancet Diabetes Endocrinol* 5: 877–886.
13. Coleman, R.L., Scott, C.A.B., Lang, Z. et al. (2019). Meta-analysis of the impact of alpha-glucosidase inhibitors on incident diabetes and cardiovascular outcomes. *Cardiovasc Diabetol* 18: 135.
14. Davies, M.J., D'Alessio, D.A., Fradkin, J. et al. (2018). Management of hyperglycaemia in type 2 diabetes, 2018. A consensus report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). *Diabetologia* 61: 2461–2498.
15. NICE. (2012 July). Preventing type 2 diabetes: risk identification and interventions for individuals at high risk. NICE public health guidance 38. https://www.nice.org.uk/guidance/PH38 (accessed 28 September 2021).

CHAPTER 12

Glitazones and Glitazars

Miles Fisher

KEY POINTS

- Pioglitazone is an oral antidiabetic drug with moderate efficacy in reducing HbA1c and the side effects of weight gain, fluid retention and an increased risk of bone fractures.
- Pioglitazone reduced atherosclerotic events in cardiovascular outcome trials in people with type 2 diabetes and existing atherosclerotic cardiovascular disease (PROactive), and in nondiabetic patients with insulin resistance and a recent stroke (IRIS), but also demonstrated increases in heart failure events and bone fractures.
- Rosiglitazone was the subject of a major controversy when it was suggested in a meta-analysis that it was associated with an increased risk of myocardial infarctions in people with type 2 diabetes.
- Evidence for an increase in myocardial infarctions with rosiglitazone is limited, but the controversy stimulated a major change in the way that new antidiabetic drugs were licensed in the US and Europe.

Introduction

Thiazolidinediones, also known as glitazones, are an oral treatment for type 2 diabetes. Troglitazone, the first commercially available glitazone, was introduced to clinical practice in the UK, US and Japan in 1997. Troglitazone was withdrawn from the UK market the same year following reports of liver toxicity and deaths from liver failure, but it was not until three years later that troglitazone was withdrawn from the US and Japan.

Rosiglitazone, the second glitazone to market, was approved in 1999 in the US and Japan, and in 2000 in Europe, followed shortly afterwards by pioglitazone.

Diabetes Drug Notes, First Edition. Edited by Miles Fisher, Gerard A. McKay, and Andrea Llano.

Rosiglitazone was the focus of an intense controversy in 2007 following the publication of a meta-analysis which suggested an increase in myocardial infarctions in patients treated with rosiglitazone compared with placebo or active comparators [1]. The licence for rosiglitazone was suspended in Europe during the controversy and rosiglitazone was withdrawn from use in Europe in 2010. Following a period of restricted availability, the clinical use of rosiglitazone in the US dropped. Restrictions were lifted in the US in 2013 and rosiglitazone is still available there, although it has been withdrawn from many other countries in the world. Pioglitazone remains available in generic form in the UK and EU but is seldom used as there are modern alternatives with fewer adverse effects.

Pharmacology

Mechanism of Action

Insulin resistance is one of the fundamental pathophysiological abnormalities in people with type 2 diabetes. Glitazones act as insulin sensitisers to counter insulin resistance and are ligands for nuclear peroxisome-proliferator activator gamma (PPAR gamma) receptors. PPAR gamma receptors act as sensors of metabolites, hormones and vitamins and are expressed on adipose tissue, with lesser expression at other sites such as pancreatic beta cells, skeletal muscle, liver and the vascular endothelium. Ligand binding at the PPAR gamma receptor regulates the transcription of target genes which regulate fatty acid metabolism, glucose uptake and adipocyte differentiation (Figure 12.1). In adipose tissue glitazones promote lipogenesis, with reduced serum concentrations of free fatty acids. In addition, glitazones increase

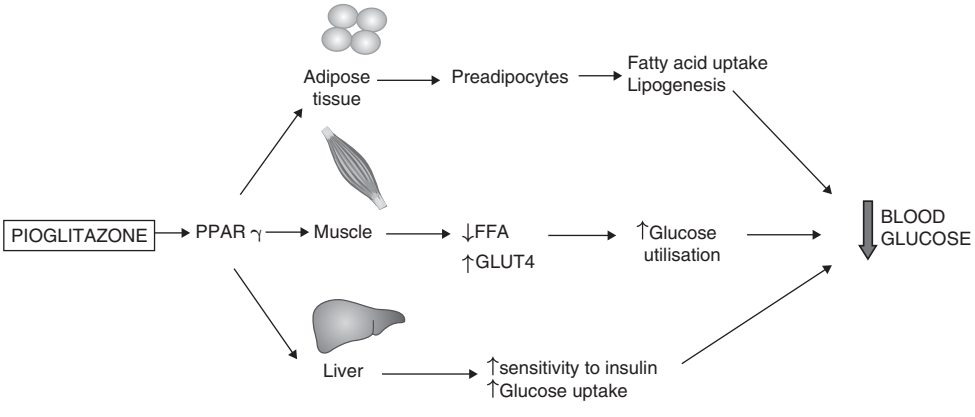


FIGURE 12.1 Mechanism of action of glitazones. Ligand biding at the PPAR gamma receptor regulates the transcription of target genes which regulate fatty acid metabolism, glucose uptake, and adipocyte differentiation, which results in a reduction in blood glucose.

the transcription of GLUT-4 glucose transporters, which directly facilitate glucose uptake into skeletal muscle and adipocytes.

Pharmacokinetics

Pioglitazone Pioglitazone is rapidly absorbed, with peak serum concentrations one to two hours after ingestion, and a half-life of three to seven hours. Absorption may be slightly delayed by food, but this is not clinically meaningful, and food does not alter the extent of absorption, which is almost complete. Pioglitazone is highly bound to albumin and other serum proteins (>99%) and concentrations in serum are low. Pioglitazone is metabolised in the liver by hydroxylation and oxidation, which are then conjugated with sulfate and glucuronic acid. Some metabolites are metabolically active with a longer half-life than pioglitazone. Elimination of pioglitazone from the body is by excretion of unchanged drug in bile or as metabolites in faeces. Pioglitazone has few significant drug interactions; clopidogrel and gemfibrozil increase the exposure to pioglitazone.

Pioglitazone was launched by Takeda under the brand name Actos®. Pioglitazone remains available in the UK and throughout the world as a generic drug, so it is inexpensive compared with modern branded antidiabetic drugs.

Dose

- Pioglitazone initially 15–30 mg once daily.
- Adjusted according to response to 45 mg once daily.
- In elderly patients initiate with the lowest possible dose and increase gradually.
- Pioglitazone is also available as a generic fixed-dose combination at a dose of 15 mg with metformin 850 mg.

Glycaemic Efficacy

Pioglitazone is described as being moderately effective at reducing HbA1c when used as monotherapy and in combination as dual or triple therapy with metformin, sulfonylureas, DPPP-4 inhibitors and insulin. Reductions in HbA1c with pioglitazone in combination therapy range from 0.6 to 1.3% (7–14 mmol/mol).

ADOPT

Type 2 diabetes is a progressive disorder and over time beta cell function declines and hyperglycaemia increases despite treatment. The availability of glitazones as a third major class of antidiabetic drugs following the biguanides and sulfonylureas allowed for detailed comparisons of the durability of glycaemic control between the different classes. ADOPT (A Diabetes Outcome Progression Trial) was a large trial involving 4360 patients with type

2 diabetes who were treatment naive [2]. Rosiglitazone 4 mg twice daily, metformin 1 g twice daily and glibenclamide 7.5 mg twice daily were compared as the first-line monotherapy and patients were treated for a mean of four years. Treatment failure with monotherapy was defined as a fasting glucose concentration over 10 mmol/mol.

- Treatment failure was less with rosiglitazone than the comparators, occurring in 15% of the rosiglitazone group, 21% of the metformin group and 34% of the glibenclamide group ($p < 0.001$ for both comparisons).
- Rosiglitazone was associated with more weight gain and oedema than either metformin or glibenclamide, but with fewer gastrointestinal side effects than metformin and less hypoglycaemia then glibenclamide ($p < 0.001$ for all comparisons).

The ADOPT study investigators concluded that potential risks and benefits, including adverse events and drug costs, should be considered to inform the choice of pharmacotherapy for people with type 2 diabetes.

Cardiovascular events in ADOPT were collected as adverse events and were increased in the rosiglitazone group, with numerical increases in nonfatal myocardial infarction and congestive heart failure. Cardiovascular data from ADOPT was subsequently included in the meta-analysis by Nissen and Wolski [1].

Other Effects of Glitazones

Glitazones have been shown to have effects on several cardiovascular risk factors and markers in addition to effects on reducing HbA1c. The effects of pioglitazone and rosiglitazone on lipid profiles differed markedly in a double-blind comparator study, where pioglitazone reduced triglycerides levels, but these were increased with rosiglitazone [3]. Additionally, the increase in HDL cholesterol was greater with pioglitazone than rosiglitazone, and the increase in LDL cholesterol concentration was less. The effects on LDL particles also differed: pioglitazone reduced the LDL particle concentration whereas rosiglitazone increased the LDL particle concentration, and LDL particle size increased more with pioglitazone. These effects of pioglitazone on lipids might be explained by pioglitazone acting as a ligand for PPAR alpha, like the fibrate class of lipid-lowering drugs.

Safety and Side Effects

Side Effects

Common side effects of glitazones are weight gain and fluid retention. Fluid retention in the legs is a common reason for discontinuing therapy with pioglitazone. Glitazones cause weight gain through at least two mechanisms:

- They increase storage of free fatty acids in subcutaneous adipose tissue by activating PPAR gamma.

- They increase sodium and fluid reabsorption in the proximal convoluted tubule and renal collecting duct.
- There is also the possibility that they may increase vascular permeability, promoting oedema and weight gain.

In addition to peripheral oedema, macular oedema has been occasionally reported in patients receiving pioglitazone therapy.

Safety

Cardiovascular Safety Rosiglitazone was the centre of a major controversy in 2007 around its possible effects on cardiovascular morbidity and mortality. Steve Nissen and Kathy Wolski, a cardiologist and a biostatistician from Cleveland Clinic, Ohio, published a meta-analysis of myocardial infarctions and death from cardiovascular causes with rosiglitazone, based on data from 42 studies [1]. Selection criteria for the meta-analysis included a study duration of more than 24 weeks, a randomised control group not receiving rosiglitazone and the availability of outcome data for myocardial infarction and cardiovascular death. As well as published literature, they included summary data from the website of the FDA and summary data from a clinical trials registry maintained by GlaxoSmithKline, the manufacturers of rosiglitazone. Most of the published studies were studies of glycaemic efficacy, but they also included data from the ADOPT and DREAM trials (see below). They identified the following results:

- There was a significant increase in myocardial infarctions in the rosiglitazone group with 86 myocardial infarctions compared with 72 in the control group (OR 1.43; 95% CI 1.03–1.98; p= 0.03).
- There were 39 cardiovascular deaths in the rosiglitazone group and 22 in the control group (OR 1.64; 95% CI 0.98–2.74; $p = 0.06$), which was not statistically significant.
- They suggested that a possible explanation for the increase in cardiovascular events was the effect of rosiglitazone in increasing LDL cholesterol, and that pioglitazone did not appear to have the same adverse effects on lipids or on cardiovascular outcomes.

Nissen and Wolski believed that their meta-analysis raised important issues around regulatory pathways for the development of drugs to treat diabetes, as the pathways focussed on the ability to demonstrate a sustained reduction in blood glucose concentrations and not on long-term cardiovascular effects. They suggested that the RECORD cardiovascular outcome trial with rosiglitazone might provide useful further information, and in the short term recommended an urgent need for a comprehensive evaluation of the source data to clarify the cardiovascular risk of rosiglitazone.

Interim analysis of RECORD was published shortly afterwards and showed no difference in the primary endpoint, but the number of events was low with 217 primary events in the rosiglitazone group and 202 in the control group at that time [4]. Later in 2007 a different meta-analysis including studies of rosiglitazone of over 12 months'

duration confirmed a significant increase in myocardial infarctions and heart failure, but no increase in cardiovascular mortality was evident [5].

When Nissen and Wolski updated their meta-analysis in 2010 they included 56 studies, including the RECORD cardiovascular outcome trial [6]. The risk for myocardial infarction was again increased with 159 myocardial infarctions in the rosiglitazone group and 136 in the control group (OR 1.28; 95% CI 1.02–1.63; $p = 0.04$), and a similar nonsignificant increase in cardiovascular deaths.

In 2007 the same group of investigators from the Cleveland Clinic published a meta-analysis of the cardiovascular effects of pioglitazone [7]. Studies were included in the meta-analysis if they were randomised, double-blind and controlled with either an active or a placebo comparator. Individual patient data from 19 studies, including the PROactive cardiovascular outcome trial, was provided by the manufacturer (Takeda) [8]. For this meta-analysis the primary outcome was a composite of all-cause mortality, myocardial infarction or stroke, and secondary outcomes included what was termed 'the incidence of serious heart failure'. Pioglitazone was associated with a statistically significant lower risk of the primary outcome, and a significant increase in serious heart failure, and they noted that the increase in heart failure was without an associated increase in mortality.

Heart Failure Fluid retention and ankle oedema was an early observation in the clinical development of glitazones. Once glitazones were widely used in clinical practice there were reports from large cohort studies of increases in heart failure. A meta-analysis and systematic review performed in 2007 included seven double-blind clinical trials in patients with diabetes or prediabetes given pioglitazone or rosiglitazone. The risk of congestive heart failure was nearly doubled with both glitazones, indicating a class effect, and the risk was increased across a wide background of cardiac risk [9].

A meta-analysis from 2020 of the effects of antidiabetic drugs on heart failure in randomised cardiovascular outcome trials showed a 40% increase in heart failure with glitazones [10]. A possible explanation for this finding is that fluid retention is unmasking undiagnosed heart failure and glitazones are contraindicated in patients with known heart failure. Patients should be closely monitored for signs of heart failure when starting pioglitazone, especially if they are at increased risk of heart failure because of atherosclerotic cardiovascular disease or concomitant insulin therapy, and pioglitazone should be stopped if symptoms or signs of heart failure are detected.

Prescribing point: *Pioglitazone should not be used in patients with a history of heart failure. Patients on pioglitazone should be monitored for signs of heart failure and pioglitazone should be discontinued if heart failure is suspected.*

Bone Fractures Glitazones are associated with an increase in bone fractures. This was first noticed in the ADOPT trial with rosiglitazone. Publication of fracture data was not reported in the main ADOPT publication and it was two years later that it was reported that fractures of the upper and lower limbs were increased in women who received rosiglitazone [11]. Similar increases in fractures were subsequently found in the RECORD trial with rosiglitazone and the PROactive trial with pioglitazone, suggesting a possible class effect [12, 13]. Initially it was suggested that the increase was mostly in distal fractures in postmenopausal women, but observational data from a

cohort study in Scotland showed a clear association between the use of rosiglitazone or pioglitazone and hospitalisation for hip fracture in men and women [14]. The IRIS trial in patients with insulin resistance and a recent stroke confirmed a significant increase in serious bone fractures, defined as requiring hospitalisation or surgery [15].

An understanding of the mechanism for this increase in fractures has come from preclinical and clinical studies. Preclinical studies have demonstrated that PPAR gamma is expressed on stromal cells of the bone marrow. PPAR receptor activation by glitazones diverts mesenchymal stem cells into adipocytes rather than osteoblasts, reducing bone formation, and bone resorption may also be increased by the stimulation of osteoclast activity. This is supported by clinical trials which have shown decreased bone turnover, accelerated bone loss and reduced bone mineral density in diabetic patients treated with glitazones.

Prescribing point: *Pioglitazone should be avoided in patients with established osteoporosis or who have an increased risk of fracture such as postmenopausal women, people with a previous fracture and people over 65 years of age.*

Bladder Cancer A slight numerical increase in bladder cancer was observed in the PROactive trial, with 14 cases in the pioglitazone group and six cases in the placebo group [8]. Results from meta-analyses have shown variable results. Some meta-analyses have demonstrated a slight but statistically significant increase in bladder cancer in patients who received pioglitazone treatment compared with comparator patients who had not received pioglitazone, with increased risk related to the dose and duration of pioglitazone therapy. Other meta-analyses have failed to demonstrate an increase in bladder cancer with pioglitazone. The EMA advises that pioglitazone should not be used in patients with active bladder cancer or a history of bladder cancer, or in patients with uninvestigated macroscopic haematuria. The EMA also advises that risk factors for bladder cancer should be assessed before initiating pioglitazone treatment and risks should be considered carefully both before initiating and during treatment in the elderly as the risk of bladder cancer increases with age.

Prescribing point: *Before starting treatment with pioglitazone patients should be assessed for risk factors for bladder cancer including age, smoking status, exposure to certain occupational or chemotherapy agents, and previous radiation therapy to the pelvic region.*

Outcome Trials

Cardiovascular Outcome Trials

RECORD The RECORD (Rosiglitazone Evaluated for Cardiac Outcomes and Regulation of Glycaemia in Diabetes) trial had a very different study design to the modern cardiovascular outcome trials which are performed in accordance with the FDA requirements of 2008 [4, 16]. RECORD was an open-label noninferiority study using a PROBE (Prospective Randomised Open Blinded Endpoint) study design and involved 4447 patients with type 2 diabetes and inadequate glycaemia control on metformin or

sulfonylurea (Table 12.1). A total of 2220 patients were randomised to receive add-on rosiglitazone and 2227 to receive the combination of metformin plus sulfonylurea. The primary endpoint was hospitalisation or death from cardiovascular causes (sudden death, myocardial infarction, heart failure, stroke, unstable angina, transient ischaemic attack, unplanned cardiovascular revascularisation, amputation of extremities). Overall, the subjects were at low cardiovascular risk, and only 17% of subjects had ischaemic heart disease at baseline. Outcome measures were adjudicated by an independent clinical endpoint committee who were unaware of the patient study group.

TABLE 12.1 Cardiovascular outcome trials with glitazones [8, 16, 19, 20]

Trial	RECORD [16]	PROactive [8]	IRIS [19]	TOSCA.IT [20]
Intervention	Rosiglitazone plus metformin or sulfonylurea	Pioglitazone 15–45 mg	Pioglitazone 15–45 mg	Metformin plus pioglitazone 15–45 mg
Comparator	Metformin plus sulfonylurea	Placebo	Placebo	Metformin plus sulfonylurea
Population size (n =)	4447	5238	3876	3028
Age (years)	58	62	64	62
Duration of diabetes (years)	7	8	Nondiabetic subjects only	8
Follow-up (years)	5.5	3	5	5
Atherosclerotic CVD (%)	28	100	100	11
Heart failure (%)	0.5	Patients with heart failure excluded	Patients with heart failure excluded	Patients with heart failure excluded
Primary outcome	No difference in cardiovascular hospitalisation or cardiovascular death	No difference in extended cardiovascular composite	24% reduction in fatal or nonfatal stroke or myocardial infarction	No difference in extended cardiovascular composite
Secondary outcomes	HFH significantly increased	MACE significantly reduced Serious heart failure significantly increased	Serious heart failure no significant difference	Treatment failure reduced

CVD = cardiovascular disease, HFH = hospitalisation for heart failure, MACE = major adverse cardiovascular events.

Results from RECORD have been published on three separate occasions [4, 16, 17]. Following the publication of the Nissen and Wolski meta-analysis, an unplanned interim analysis of RECORD was performed at four years which showed no difference in the primary endpoint. As indicated previously, the number of events was low with 217 primary events in the rosiglitazone group and 202 in the control group. When looked at as separate endpoints there were no differences in myocardial infarction or death from cardiovascular causes. Of note, heart failure events (hospitalisation or death) were doubled in the rosiglitazone group [4].

The second publication of RECORD results followed the planned completion of the study at a mean of 5.5 years of follow-up [16]. The results were similar:

- There were 321 primary events with rosiglitazone and 323 in the control group, meeting the criteria for noninferiority (HR 0.99; 95% CI 0.85–1.16).
- Heart failure admission to hospital or death was significantly increased in the rosiglitazone group (HR 2.10; 95% CI 1.35–3.27; $p = 0.0003$)
- There were no significant differences in myocardial infarction or cardiovascular death.
- New data were provided for bone fractures, and upper and distal limb fractures were increased with rosiglitazone, mainly in women.

The results of the RECORD trial together with other safety data, were reviewed by the FDA in 2010. The FDA requested an independent reevaluation of cardiovascular outcomes from the RECORD trial database using RECORD endpoint definitions and new FDA endpoint definitions, and this was published in 2013 [17]. A modest number of further events was identified, and no significant differences were found for cardiovascular or unknown deaths, myocardial infarction or stroke, or for the composite endpoint of cardiovascular death, myocardial infarction or stroke (Figure 12.2).

TIDE With ongoing uncertainty about the possible cardiovascular safety of rosiglitazone and the possible cardiovascular benefits of pioglitazone, the TIDE (Thiazolidinedione Intervention with Vitamin D Evaluation) trial was a complex study which aimed to assess the effects of rosiglitazone and pioglitazone on major cardiovascular events (cardiovascular death, nonfatal myocardial infarction, nonfatal stroke), and vitamin D on cancers and mortality [18]. TIDE was a large multicentre trial with a three-by-two factorial design so subjects could be randomised to rosiglitazone, pioglitazone or placebo for the glitazone part of the trial, and cholecalciferol or placebo for the vitamin D part of the trial. TIDE was halted when the FDA officially withdrew its support for the trial after public concerns about the safety of the rosiglitazone intervention. Less than 10% of the proposed number of patients had been recruited when the trail was halted, so no conclusions can be drawn from the results [18].

PROactive PROactive (PROspective pioglitAzone Clinical Trial in macroVascular Events) was a double-blind, placebo-controlled trial comparing pioglitazone 15–45 mg vs. placebo in 5238 patients with type 2 diabetes and atherosclerotic cardiovascular disease, with an average follow-up of three years [8]. PROactive was completed in 2005 before the new regulations for antidiabetic drugs were introduced but was very similar in design to

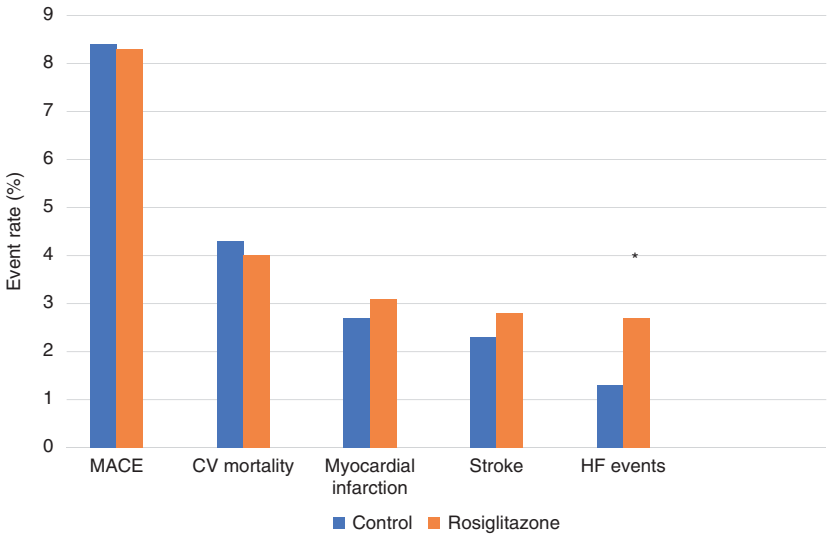


FIGURE 12.2 Event rates (%) comparing rosiglitazone and control groups in the re-evaluation of the RECORD trial. Statistically significant differences are marked with an asterisk. *Source:* Based on [17]. MACE = major adverse cardiovascular events, CV = cardiovascular, HF = heart failure.

the later FDA-mandated cardiovascular safety trials. All subjects had established atherosclerotic cardiovascular disease, it was double-blind and placebo-controlled, and events were adjudicated blindly. The major difference to FDA mandated trials was the primary endpoint, which in PROactive was a composite of all-cause mortality, nonfatal myocardial infarction, stroke, acute coronary syndrome, endovascular or surgical intervention in the coronary or leg arteries, or amputation above the ankle. Patients with New York Heart Association class II–IV heart failure were excluded, and unfortunately there was no collection of a history of possible heart failure at baseline.

- A numerical reduction in the primary endpoint was observed with 514 events with pioglitazone and 572 with placebo but this was not statistically significant (HR 0.90; 95% CI 0.80–1.02; $p = 0.095$).
- Before the trial was completed, and the results unblinded, the investigators defined a 'main secondary' endpoint which was a composite of all-cause mortality, nonfatal myocardial infarction and nonfatal stroke, which was significantly reduced by 16% (HR 0.84; 95% CI 0.72–0.98; $p = 0.027$; Figure 12.3).
- Heart failure events in PROactive were not adjudicated and were collected as serious adverse events. Any report of heart failure was increased with pioglitazone (10.8 vs. 7.5% for placebo) with increases in heart failure needing hospitalisation and heart failure not needing hospitalisation, but there was no difference in fatal heart failure.

When the ADOPT study identified bone fractures as a possible side effect of rosiglitazone, the PROactive database was reanalysed and showed a significantly increased rate of bone fractures in female patients (5.1% with pioglitazone vs. 2.5% with placebo) [13].

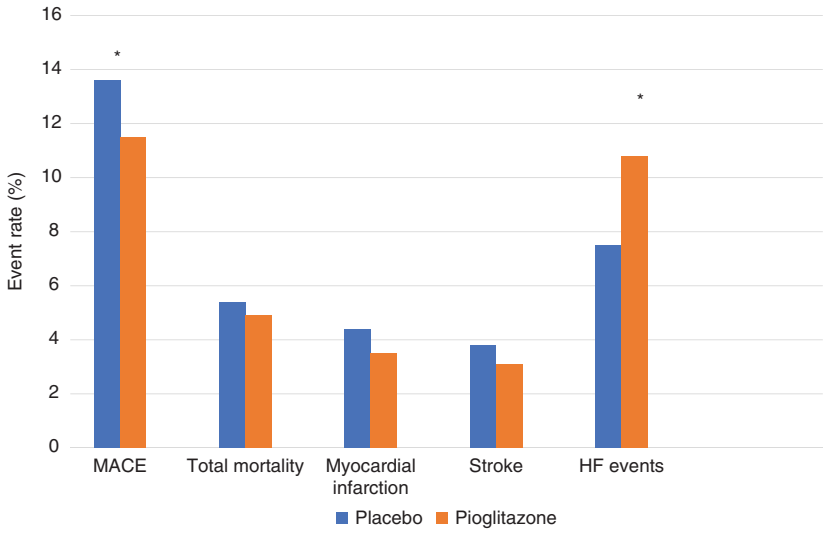


FIGURE 12.3 Event rates (%) comparing pioglitazone and placebo groups in the PROactive trial. Statistically significant differences are marked with an asterisk. *Source:* Based on [8]. MACE = major adverse cardiovascular events, HF = heart failure.

IRIS The IRIS (Insulin Resistance Intervention after Stroke) trial was a double-blind, placebo-controlled, investigator-initiated study to determine if pioglitazone would reduce cardiovascular events in nondiabetic subjects [19]. IRIS compared pioglitazone 15–45 mg vs. placebo in 3876 patients with a recent stroke or transient ischaemic attack and insulin resistance, defined as a value of more than 3.0 on the homeostasis model assessment of insulin resistance (HOMA-IR) index. Subjects with New York Heart Association class III or IV heart failure were excluded, as were subjects with class II heart failure and a reduced ejection fraction. The primary endpoint was a composite of fatal or nonfatal stroke or myocardial infarction, and subjects were followed for median of 4.8 years.

- The primary endpoint was significantly reduced in the pioglitazone group with 175 events and 228 in the placebo group (HR 0.76; 95% CI 0.62–0.93; $p = 0.007$; Figure 12.4).
- The development of diabetes was significantly reduced with 73 patients in the pioglitazone group and 149 patients in the control group (HR 0.48; 95% CI 0.33–0.69; $p < 0.001$).
- There was no difference in all-cause mortality or heart failure events.
- Bone fractures requiring surgery or hospitalisation were significantly increased [15, 19].

The IRIS investigators calculated that for patients who were at a low risk of fracture pioglitazone prevented 2.0 strokes or myocardial infarctions for every fracture caused, compared with preventing 0.5 strokes or myocardial infarctions for every fracture caused in patients who were at a high risk of fractures.

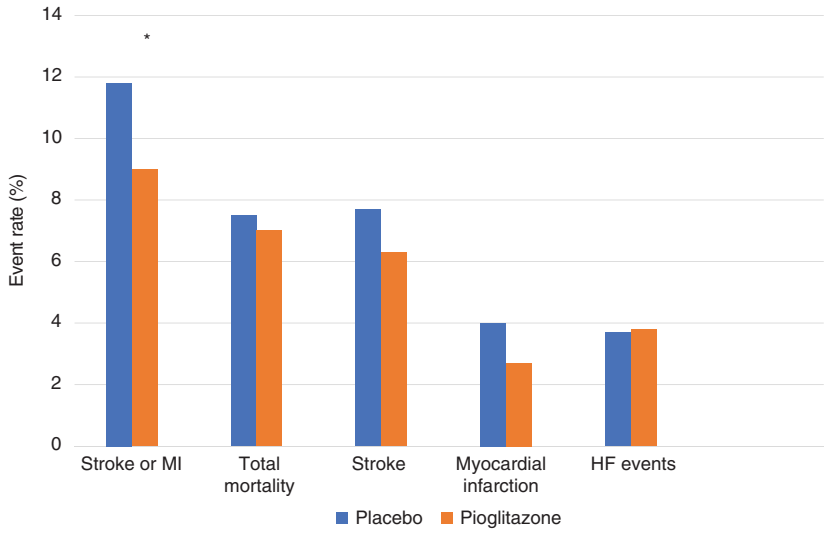


FIGURE 12.4 Event rates (%) comparing pioglitazone and placebo groups in the IRIS trial. Statistically significant differences are marked with an aserisk. *Source:* Based on [19].

MI = myocardial infarction, HF = heart failure.

TOSCA. IT TOSCA. IT (Thiazolidinediones Or Sulfonylureas Cardiovascular Accidents Intervention Trial) was designed to test the hypothesis that pioglitazone would reduce cardiovascular events compared with sulfonylureas when added second line to people with diabetes who were not controlled with metformin monotherapy [20]. It was an investigator-initiated trial with a PROBE design. This design has lower costs than a double-blind, randomised, placebo-controlled trial and may have greater similarity to standard clinical practice. Indeed, TOSCA. IT was performed in 57 diabetes clinics in Italy, and compared pioglitazone with various sulfonylureas that were used in Italy.

TOSCA.IT recruited 3028 subjects who were followed for a median of 57 months when the study was stopped because of futility. No difference was seen in the primary endpoint, which was a composite of all-cause mortality, myocardial infarction, stroke and urgent coronary revascularisation. The overall cardiovascular event rate was low, and small doses of drugs were used, with mean doses of pioglitazone 23 mg, glibenclamide 8 mg, gliclazide 42 mg and glimepiride 2.5 mg. These methodological shortcomings mean that TOSCA.IT cannot inform us about the cardiovascular efficacy or safety of pioglitazone or sulfonylureas. One of many secondary outcomes in TOSCA.IT was treatment failure, defined as an HbA1c of greater than 8.0% on two consecutive visits, and this was significantly less with metformin plus pioglitazone than metformin plus sulfonylureas, and so similar to the results of ADOPT with rosiglitazone.

Prescribing point: *SGLT2 inhibitors and GLP-1 receptor agonists are better options than pioglitazone to reduce cardiovascular events in patients with established atherosclerotic cardiovascular disease.*

Prevention of Type 2 Diabetes

People with impaired glucose tolerance or raised fasting glucose are at an increased risk of developing type 2 diabetes. Many interventions have been explored to delay the progression from prediabetes to diabetes, and these can broadly be divided into lifestyle interventions and pharmacological interventions. The US DPP (Diabetes Prevention Program) showed that lifestyle change, a mixture of changes in diet and physical activity, was more effective than pharmacological intervention with metformin in delaying the progression to diabetes [21]. One other pharmacological intervention group at the start of the DPP was randomisation to troglitazone [22]. That arm of the study was halted early because of liver toxicity. During the mean 0.9 years that subjects received troglitazone there was a significant reduction in the incidence of diabetes, but during the three years after withdrawal the diabetes incidence rate was almost identical to that in the placebo group, suggesting that troglitazone was delaying rather than preventing the progression to diabetes.

Another small study TRIPOD (Troglitazone In Prevention of Diabetes) showed that compared with placebo troglitazone improved insulin sensitivity and delayed the progression to diabetes in 266 Hispanic women with previous gestational diabetes during a median follow-up of 30 months [23]. That trial had to be stopped early when troglitazone was withdrawn from the market, so the investigators followed this with a second study PIPOD (Pioglitazone in Prevention of Diabetes) using pioglitazone or placebo in 86 women who had not developed diabetes by that time [24]. The findings were similar, with an increase in insulin sensitivity and a reduction in the risk of diabetes in the pioglitazone group.

DREAM DREAM (Diabetes Reduction Assessment with Ramipril and Rosiglitazone Medication) was a large double-blind, randomised, controlled trial with a two-by-two factorial design comparing rosiglitazone 8 mg and placebo and ramipril and placebo in 5269 subjects with impaired fasting glucose or impaired glucose tolerance [25]. Subjects were followed for a median of three years and the primary outcome was a composite of incident diabetes or death. Rosiglitazone, but not ramipril, significantly reduced the incidence of diabetes (Table 12.2). Deaths were not different comparing rosiglitazone and placebo groups, but a cardiovascular events composite was numerically increased, and confirmed heart failure was significantly increased comparing rosiglitazone and placebo groups.

Other Trials on the Prevention of Diabetes With a growing awareness of the adverse effects of full dose rosiglitazone the CANOE (Canadian Normoglycema Outcomes Evaluation) trial investigated a combination of low-dose rosiglitazone (2 mg) and low-dose metformin (500 mg) twice daily in 207 subjects with impaired glucose tolerance [26]. The development of diabetes was reduced by 66% in the intervention group, and the main side effect was an increase in diarrhoea, presumably owing to the metformin component of the intervention. An even greater relative reduction in the development of diabetes was recorded in the ACT NOW (Actos NOW) study with pioglitazone, which compared pioglitazone 45 mg with placebo in 602 subjects with impaired glucose tolerance and demonstrated a 72% risk reduction [27]. Weight gain and oedema were more common in the pioglitazone group.

The IDPP-2 (Indian Diabetes Prevention Programme-2) in 407 subjects with impaired glucose tolerance compared lifestyle modification plus pioglitazone 30 mg

TABLE 12.2 **Diabetes prevention trials with glitazones [25–28]**

Trial	DREAM [25]	CANOE [26]	ACT NOW [27]	IDPP-2 [28]
Intervention	Rosiglitazone 8 mg daily	Combination rosiglitazone 2 mg plus metformin 500 mg twice daily	Pioglitazone	Pioglitazone 30 mg plus lifestyle modification
Comparator	Placebo	Placebo	Placebo	Placebo plus lifestyle modification
Population size ($n =$)	5269	207	602	407
Age (years)	55	52		45
Follow-up (years)	3	4	2	3
Primary outcome	60% reduction in the incidence of diabetes or death	34% reduction in the incidence of diabetes	72% reduction in the incidence of diabetes	No difference in the incidence of diabetes
Other results	62% reduction in the incidence of diabetes Increase in body weight with rosiglitazone		Greater increase in body weight with pioglitazone	

with lifestyle modification plus placebo and showed no difference in conversion from impaired glucose tolerance to diabetes on three years of follow-up, but there was no group receiving pioglitazone alone in that study [28]. Further analysis of the IRIS trial in subjects with insulin resistance and a recent stroke showed that pioglitazone 45 mg reduced the development of diabetes by 52% compared with placebo, and that this was predominantly driven by subjects with an initial impaired fasting glucose or elevated HbA1c, i.e. those with prediabetes [29].

Glitazars

The fibrate class of lipid-lowering drugs are agonists of PPAR alpha. Glitazars are a class of drugs distinct from glitazones which act as dual agonists of PPAR alpha and gamma. Glitazars were being developed as a potential treatment for type 2 diabetes that might have wider effects on features of the metabolic syndrome through effects on PPAR alpha. None of the glitazars reached clinical practice in the US or Europe because of either side effects or toxicity. Muraglitazar had completed phase 3 clinical development and was initially approved by the FDA in 2005. However, a meta-analysis

of the phase 2 and 3 clinical trials by Steve Nissen and colleagues demonstrated an increase in major adverse cardiovascular events and heart failure comparing muraglitazar with placebo or pioglitazone, and further development was discontinued in 2006. The development of tesaglitazar was also terminated in 2006 because of renal toxicity identified in the phase 3 development programme.

Aleglitazar

Results from the phase 3 development programme for aleglitazar showed that it significantly reduced HbA1c, triglycerides and increased HDL cholesterol compared with placebo, with some weight gain as an expected side effect. The development programme for aleglitazar was halted in 2013 when the AleCardio cardiovascular outcome trial was stopped by the data and safety monitoring committee because of futility for cardiovascular efficacy and an increase in serious adverse events with aleglitazar [30]. This phase 3 trial had recruited 7226 subjects with diabetes and an acute coronary syndrome and aimed to satisfy FDA safety criteria and explore the possibility of cardiovascular benefit with aleglitazar. The serious events reported with aleglitazar included increased heart failure, renal dysfunction and gastrointestinal haemorrhage. At the same time, no reduction in the primary endpoint of major adverse cardiovascular events was observed.

Saroglitazar

Saroglitazar is a combined PPAR alpha and gamma agonist that has been developed and approved in India for the treatment of hyperglycaemia in type 2 diabetes as an add-on therapy to metformin, for diabetic dyslipidaemia in patients with type 2 diabetes, and for NASH. The approval process did not include the large, long-term cardiovascular safety data required to satisfy regulators in the US and Europe. It is also approved in Mexico for the treatment of diabetic dyslipidaemia. The efficacy effects on dyslipidaemia were demonstrated in several phase 3 trials, and reductions in HbA1c were noninferior to pioglitazone 30 mg. Safety was examined in these trials out to 56 weeks, and longer-term safety data for saroglitazar is currently lacking. Saroglitazar is under further investigation as a possible treatment for NASH, NAFLD and primary biliary cholangitis.

Place of Glitazones and in Current and Future Practice

Type 2 Diabetes

There were high expectations when glitazones were introduced that this new class of antidiabetic drugs might have a major place in the management of people with diabetes, and glitazones were widely used as second- and third-line therapies and as an

alternative to starting insulin. There was also the suggestion that by addressing insulin resistance, glitazones might reduce the development of diabetes, slow the deterioration of hyperglycaemia in people with established diabetes and reduce the development of atherosclerotic cardiovascular disease in people with diabetes. Although pioglitazone reduced atherosclerotic events in the PROactive trial, this was at the expense of an increase in side effects including heart failure, and SGLT2 inhibitors and GLP-1 receptor agonists have replaced pioglitazone as drugs of choice with established atherosclerotic cardiovascular disease.

Pioglitazone is now a generic drug so it has a lower cost than modern antidiabetic drugs which are branded medications. Pioglitazone featured as a second-line treatment in the NICE guideline from 2015 for that reason, and pioglitazone is included in the joint ADA/EASD consensus statement as a second-line alternative to sulfonylureas for patients without atherosclerotic cardiovascular disease who are not controlled on metformin therapy where cost is a major issue (see Chapter 15). Because of the side-effect profile and safety concerns it is anticipated that few patients will now be started on pioglitazone.

Prevention of Diabetes

Large outcome trials showed some evidence that glitazones delayed the progression to diabetes and that reductions in HbA1c were longer lasting than those with either metformin or sulfonylureas, but also identified serious side effects. Lifestyle change is more effective than pharmacological interventions at delaying the progression to diabetes in people with prediabetes. Where lifestyle change is not possible, some guidelines recommend the use of metformin as a cost-effective intervention with few side effects. Because of its side-effect profile plus concerns about long-term safety, pioglitazone is not recommended for clinical use in that group of subjects.

References

1. Nissen, S.E. and Wolski, W. (2007). Effect of rosiglitazone on the risk of myocardial infarction and death from cardiovascular causes. *N Engl J Med* 356: 2457–2471.
2. Kahn, S.E., Haffner, S.M., Heise, M.A. et al., for the ADOPT Study Group (2006). Glycemic durability of rosiglitazone, metformin, or glyburide monotherapy. *N Engl J Med* 355: 2427–2443.
3. Goldberg, R.B., Kendall, D., Deeg, M.A. et al., for the GLAI Study Investigators (2005). A comparison of lipid and glycemic effects of pioglitazone and rosiglitazone in patients with type 2 diabetes and dyslipidemia. *Diabetes Care* 28: 1547–1554.
4. Home, P.D., Pocock, S.J., Beck-Nielsen, H. et al., for the RECORD Study Group (2007). Rosiglitazone evaluated for cardiovascular outcomes – an interim analysis. *N Engl J Med* 357: 28–38.
5. Singh, S., Loke, Y.K., and Furberg, C.D. (2007). Long-term risk of cardiovascular events with rosiglitazone: a meta-analysis. *JAMA* 298: 1189–1195.

6. Nissen, S.E. and Wolski, W. (2010). Rosiglitazone revisited: an updated meta-analysis of risk for myocardial infarction and cardiovascular mortality. *Arch Intern Med* 170: 1191–1201.
7. Lincoff, A.M., Wolski, K., Nicholls, S.J., and Nissen, S.E. (2007). Pioglitazone and risk of cardiovascular events in patients with type 2 diabetes mellitus: a meta-analysis of randomized trials. *JAMA* 298: 1180–1188.
8. Dormandy, J.A., Charbonnnel, B., Eckland, D.J.A. et al., on behalf of the PROactive Investigators (2005). Secondary prevention of macrovascular events in patients with type 2 diabetes in the PROactive Study (PROspective pioglitAzone Clinical Trial In macroVascular Events): a randomised controlled trial. *Lancet* 366: 1279–1289.
9. Lago, R.M., Singh, P.P., and Nesto, R.W. (2007). Congestive heart failure and cardiovascular death in patients with prediabetes and type 2 diabetes given thiazolidinediones: a meta-analysis of randomised clinical trials. *Lancet* 370: 1129–1136.
10. Ghosh-Swaby, O.R., Goodman, S.G., Leiter, L.A. et al. (2020). Glucose-lowering drugs or strategies, atherosclerotic cardiovascular events, and heart failure in people with or at risk of type 2 diabetes: an updated systematic review and meta-analysis of randomised cardiovascular outcome trials. *Lancet Diabetes Endocrinol* 8: 418–435.
11. Kahn, S.E., Zinman, B., Lachin, J.M. et al., for the A Diabetes Outcome Progression Trial (Adopt) Study Group (2008). Rosiglitazone-associated fractures in type 2 diabetes: an analysis from A Diabetes Outcome Progression Trial (ADOPT). *Diabetes Care* 31: 845–851.
12. Jones, N.P., Curtis, P.S., and Home, P.D. (2015). Cancer and bone fractures in observational follow-up of the RECORD study. *Acta Diabetol* 52: 539–546.
13. Dormandy, J., Bhattacharya, M., van Troostenburg de Bruyn, A.-R., and on behalf of the PROactive Investigators (2009). Safety and tolerability of pioglitazone in high-risk patients with type 2 diabetes: an overview of data from PROactive. *Drug Saf* 32: 187–202.
14. Colhoun, H.M., Livingstone, S.J., Looker, H.C. et al., on behalf of the Scottish Diabetes Research Network Epidemiology Group (2012). Hospitalised hip fracture risk with rosiglitazone and pioglitazone use compared with other glucose-lowering drugs. *Diabetologia* 55: 2929–2937.
15. Viscoli, C.M., Inzucchi, S.E., Young, L.H., and for the IRIS Trial Investigators (2017). Pioglitazone and risk for bone fracture: safety data from a randomized clinical trial. *J Clin Endocrinol* 102: 914–922.
16. Home, P.D., Pocock, S.J., Beck-Nielsen, H. et al., for the RECORD Study Group (2009). Rosiglitazone evaluated for cardiovascular outcomes in oral agent combination therapy for type 2 diabetes (RECORD): a multicentre, randomised, open-label trial. *Lancet* 373: 2125–2135.
17. Mahaffey, K.W., Hafley, G., Dickerson, S. et al. (2013). Results of a reevaluation of cardiovascular outcomes in the RECORD trial. *Am Heart J* 166: 240–249.
18. The TIDE Trial Investigators (2012). Design, history and results of the Thiazolidinedione Intervention with vitamin D Evaluation (TIDE) randomised controlled trial. *Diabetologia* 55: 36–45.
19. Kernan, W.N., Viscoli, C.M., Furie, K.L. et al., for the IRIS Trial Investigators (2016). Pioglitazone after ischemic stroke or transient ischemic attack. *N Engl J Med* 374: 1321–1331.
20. Vaccaro, O., Masulli, M., Nicolucci, A. et al., for the Thiazolidinediones or Sulfonylureas Cardiovascular Accidents Intervention Trial (TOSCA.IT) Study Group under the Mandate of the Italian Diabetes Society (2017). Effects on the incidence of cardiovascular events of the addition of pioglitazone versus sulfonylureas in patients with type 2 diabetes inadequately controlled with metformin (TOSCA.IT): a randomised, multicentre trial. *Lancet Diabetes Endocrinol* 5: 887–897.
21. Diabetes Prevention Program Research Group (2002). Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. *N Engl J Med* 346: 393–403.

22. The Diabetes Prevention Program Research Group (2005). Prevention of diabetes with troglitazone in the Diabetes Prevention Program. *Diabetes* 54: 1150–1156.
23. Buchanan, T.A., Xiang, A.H., Peters, R.K. et al. (2002). Preservation of pancreatic B-cell function and prevention of type 2 diabetes by pharmacological treatment of insulin resistance in high-risk Hispanic women. *Diabetes* 51: 2796–2803.
24. Xiang, A.H., Peters, R.K., Kjos, S.L. et al. (2006). Effect of pioglitazone on pancreatic B-cell function and diabetes risk in Hispanic women with prior gestational diabetes. *Diabetes* 55: 517–522.
25. The DREAM (Diabetes Reduction Assessment with Ramipril and Rosiglitazone Medication) Trial Investigators (2006). Effect of rosiglitazone on the frequency of diabetes in patients with impaired glucose tolerance or impaired fasting glucose: a randomised controlled trial. *Lancet* 368: 1096–1105.
26. Zinman, B., Harris, S.B., Neuman, J. et al. (2010). Low-dose combination therapy with rosiglitazone and metformin to prevent type 2 diabetes mellitus (CANOE trial): a double-blind randomised controlled study. *Lancet* 376: 103–111.
27. DeFronzo, R.A., Tripathy, D., Schwenke, D.C. et al., for the ACT NOW Study (2011). Pioglitazone for diabetes prevention in impaired glucose tolerance. *N Engl J Med* 364: 1104–1115.
28. Ramachandran, A., Snehalatha, C., Mary, S. et al. (2009). Pioglitazone does not enhance the effectiveness of lifestyle modification in preventing conversion of impaired glucose tolerance to diabetes in Asian Indians: results of the Indian Diabetes Prevention Programme-2 (IDPP-2). *Diabetologia* 52: 1019–1026.
29. Inzucchi, S.E., Viscoli, C., Young, L.W. et al., for the IRIS Trial Investigators (2016). Pioglitazone prevents diabetes in patients with insulin resistance and cerebrovascular disease. *Diabetes Care* 39: 1684–1692.
30. Lincoff, A.M., Tardif, J.-C., Schwartz, G.G. et al., for the AleCardio Investigators (2014). Effect of aleglitazar on cardiovascular outcomes after acute coronary syndrome in patients with type 2 diabetes mellitus: the AleCardio randomized clinical trial. *JAMA* 311: 1515–1525.

CHAPTER 13

Other Antidiabetic Drugs

Maroria Oroko, Andrea Llano, and Miles Fisher

KEY POINTS

- Pramlintide is an injected amylin analogue that promotes satiety and reduces postprandial hyperglycaemia, leading to modest reductions in HbA1c in patients with type 1 and type 2 diabetes when added to insulin treatment.
- Colesevelam is a lipid-lowering drug with modest HbA1c-lowering effects in people with type 2 diabetes and frequent but generally mild gastrointestinal side effects.
- Bromocriptine quick release has modest effects on HbA1c when used in patients with type 2 diabetes and showed noninferiority in a small cardiovascular safety trial with a low number of cardiovascular events, but a larger cardiovascular outcome trial has not been performed.
- Hydroxychloroquine is approved in India as an add-on antidiabetic drug for patients with uncontrolled type 2 diabetes.
- Antiobesity drugs (orlistat, naltrexone/bupropion, phentermine/topiramate) are associated with minor reductions in HbA1c secondary to weight loss in people with diabetes and may delay the progression to diabetes in people with prediabetes.

Introduction

In addition to the common antidiabetic drugs that are widely available in many countries for the treatment of type 1 and type 2 diabetes, a small number of drugs are approved in a limited number of countries. These drugs are generally deemed to have low efficacy in reducing HbA1c, significant side effects or both. For many the mechanism of reduction of hyperglycaemia is not completely understood. In the US pramlintide is approved as an injected adjunct to insulin therapy for people with type 1 and type 2 diabetes. Colesevelam

Diabetes Drug Notes, First Edition. Edited by Miles Fisher, Gerard A. McKay, and Andrea Llano.

and bromocriptine are also approved for the treatment of type 2 diabetes in the US, and hydroxychloroquine is approved in India for the treatment of type 2 diabetes.

Pramlintide

Insulin treatment is often associated with weight gain in people with type 1 and type 2 diabetes. The administration of prandial pramlintide by subcutaneous injection has been shown to decrease postprandial plasma glucose and HbA1c and minimise the weight gain that is associated with insulin therapy. Pramlintide (Symilin®) was licensed by the FDA in 2005 as an adjuvant treatment in patients with type 1 and type 2 diabetes who take prandial insulin. Safety concerns involving hypoglycaemia have prevented its licensing in the UK and EU.

Pharmacology

Amylin, or islet amyloid polypeptide, is a 37 amino acid peptide hormone. It is stored with insulin in pancreatic beta cells and co-secreted with insulin in response to a glucose load. Like insulin, the secretion of amylin is pulsatile, and its release is augmented by meals. It acts on the AMY1 receptor in the brain, resulting in several synergistic effects which reduce postprandial glucose:

- the promotion of satiety;
- the slowing of gastric emptying; and
- the reduction of the post-prandial hyperglucagonaemia which is typical of insulin-treated diabetes.

Amylin secretion is deficient in people with type 1 diabetes and insulin-treated type 2 diabetes, making it an attractive therapeutic target. Human amylin cannot be therapeutically administered as it forms amyloid fibres which are relatively insoluble. Pramlintide is a synthetic analogue of amylin made soluble by the substitution of several amino acids with proline residues (Figure 13.1). Its onset of action occurs 20 minutes after subcutaneous injection, and it has a half-life of 48–55 minutes. It is largely metabolised by the kidneys, and no dosage adjustment is required in renal impairment. Pramlintide precipitates above pH 5.5, which currently makes it unsuitable for coformulation with injectable insulin.

Gastrointestinal side effects are the most common side effects with pramlintide therapy and appear to be more common in patients with type 1 diabetes. Mild to moderate nausea, vomiting and anorexia occur in people with type 1 diabetes, and nausea is the commonest side effect in people with type 2 diabetes. In type 1 diabetes, nausea seems to reduce with time and after a year of therapy nausea is uncommon.

Pramlintide is administered subcutaneously at mealtimes along with rapid-acting insulin at a dose of 15 μg rapidly titrated to 30–60 μg three to four times daily, or at 60 μg with one-step titration to 120 μg as tolerated in people with type 2 diabetes.

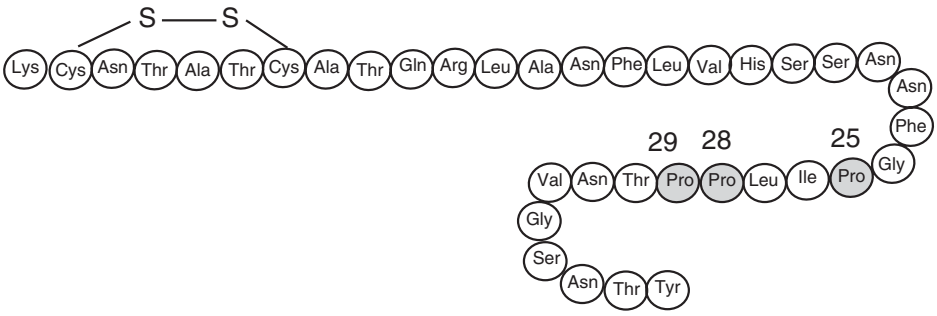


FIGURE 13.1 Structure of pramlintide. The amino acid sequences at positions 25, 28 and 29 in the amylin molecule have been substituted with proline residues, producing a stable and soluble drug which mimics the effects of endogenous amylin.

Glycaemic Efficacy

Efficacy in Type 1 Diabetes A small number of studies comparing pramlintide with placebo in people with type 1 diabetes have demonstrated small but significant reductions in postprandial hyperglycaemia, HbA1c and body weight with the addition of pramlintide to insulin therapy over a period of 29–52 weeks. A meta-analysis from 2010 included three RCTs in people with type 1 diabetes and three RCTs in people with type 2 diabetes [1]. A significant improvement in HbA1c of 0.2–0.3% (2–3 mmol/mol) with pramlintide therapy compared with placebo was observed in patients with type 1 diabetes and suboptimal glycaemic control, but reductions in HbA1c were not observed in subjects who were well controlled. The meta-analysis observed weight loss in the pramlintide group of 0.4–1.3 kg, and weight gain in the placebo group (0.8–1.2 kg), and there was some suggestion that weight may be regained in the pramlintide group after 52 weeks of treatment.

Overall, no significant reduction in insulin requirements was observed in the meta-analysis, but in one RCT in 296 people with type 1 diabetes the doses of prandial insulin were proactively cut by 30–50% at initiation of pramlintide therapy [2]. No significant difference was seen in rates of severe hypoglycaemia between the groups in this study, other than in the group which was limited to the lower 30 μg dose, owing in large part to higher rates of moderate nausea and vomiting. In this group, who might otherwise be expected to be at high risk of hypoglycaemia owing to reduced or unpredictable carbohydrate intake, the rate of severe hypoglycaemia remained elevated for the full 29 week study period at 0.79–1.10 events/patient year, whereas the rate in the placebo group was 0.28–0.42 events/patient year [2].

A more recent meta-analysis identified 10 RCTs in people with type 1 diabetes. Compared with placebo, the addition of pramlintide reduced HbA1c by up to 0.4% (5 mmol/mol), with reduced insulin requirements but an increase in hypoglycaemia and gastrointestinal side effects [3].

Efficacy in Type 2 Diabetes In the first meta-analysis the three RCTs comparing pramlintide with placebo in people with type 2 diabetes treated with insulin demonstrated reductions in postprandial hyperglycaemia, HbA1c and body weight [1]. The

studies used different doses of prandial pramlintide ranging from 60 to 150 μg two to three times daily. The meta-analysis of these studies observed that higher doses of pramlintide (120 μg twice daily and 150 μg three times daily) significantly reduced HbA1c over placebo by roughly 0.4% (5 mmol/mol). While weight increased with placebo, it decreased with pramlintide therapy and a significant weight difference was observed between the groups of 1.5–2.5 kg. There was no significant difference in insulin requirements between groups.

Another meta-analysis identified four studies in people with type 2 diabetes, the same three plus one additional study, and four studies in people with obesity [4]. Modest reductions in HbA1c (−0.3%, 3 mmol/mol) and weight (−2.2 kg) were observed, and a doubling of nausea as a side effect. Rates of severe hypoglycaemia were higher in patients taking pramlintide compared with placebo but appeared to fall to similar levels with placebo after the initial four week period where dosage titration occurred.

Safety

A six month post-regulatory approval trial was conducted which evaluated the incidence of severe hypoglycaemia in 766 patients with type 1 diabetes and in 531 insulin-treated patients with type 2 diabetes [5]. In this phase 4, open-label, observational study the incidence of severe hypoglycaemia was higher in the first three months of treatment with 4.8% and 0.33 events/patient year in patients with type 1 diabetes and 2.8% and 0.19 events/patient year in patients with type 2 diabetes. This declined in the subsequent three months to 1.8 and 0.3% respectively and 0.08 and 0.02 events/patient year in patients with type 1 or type 2 diabetes. The summary of product characteristics for pramlintide carries a warning about the risk of severe hypoglycaemia.

Prescribing point: *Pramlintide is injected subcutaneously before main meals in addition to insulin. When pramlintide is initiated, doses of mealtime insulin should be reduced by 50%.*

Colesevelam

Colesevelam is an intestinal bile acid sequestrant (BAS) incidentally noted to have glucose-lowering effects. Colesevelam was primarily developed as a treatment for dyslipidaemia, particularly for patients with raised low-density lipoprotein (LDL) cholesterol concentrations, with fewer side effects and a higher affinity for bile acids than the earlier BAS drugs colestyramine and colestipol. Colesevelam (Welchol®) was approved by the FDA in 2008 as a treatment for adults with type 2 diabetes in combination with metformin, sulfonylurea or insulin.

Pharmacology

Bile acids are synthesised in the liver from cholesterol, stored in the gallbladder, then secreted into the small intestine. They bind to fats and fat-soluble vitamins, aiding

absorption into the systemic circulation, and 95% of bile acids are then resorbed into the enterohepatic circulation for reuse. Colesevelam and other BAS drugs bind to bile acids in the intestine, preventing resorption and resulting in their excretion in faeces. This causes an upregulation of cholesterol 7-alpha hydroxylase enzyme, which increases the production of bile acids from its precursor, cholesterol. Owing to this effect, the activity of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase is upregulated and there is increased hepatic expression of LDL receptors which results in an increased clearance of LDL cholesterol from the blood.

The mechanism by which BAS drugs exert their glycaemic-lowering effects is unclear. One study of glucose metabolism in patients with type 2 diabetes treated with colesevelam ($n = 30$) or placebo ($n = 30$) for 12 weeks showed that colesevelam [6]:

- increased fasting plasma GLP-1 concentrations;
- increased total GLP-1 and GIP concentrations;
- increased plasma glucose clearance in the fasting and postprandial state; and
- improved beta cell function as measured by beta cell response for the degree of insulin resistance present.

Colesevelam had no effects on enteric glucose absorption or hepatic gluconeogenesis, and it was proposed that colesevelam improves beta cell function by increasing plasma levels of the incretin hormones GLP-1 and GIP.

Colesevelam is administered orally at a dose of 3.75 g once daily or 1.875 g twice daily. It should be taken separately four hours before or after the administration of other drugs as it can impair their absorption. The affected drugs include glibenclamide, phenytoin, ciclosporin, levothyroxine and ethinyloestradiol. Absorption of fat-soluble vitamins may also be impaired and vitamin supplementation may be required with long-term use.

Colesevelam is generally well tolerated, adverse events are uncommon and treatment discontinuation is no greater among subjects taking colesevelam than those taking a placebo. It is a weight-neutral drug. Unsurprisingly given its mechanism of action, the most frequent side effects are gastrointestinal, and constipation is the most common side effect. A rise in triglyceride levels with colesevelam therapy has been observed in some patients and so caution is advised if prescribing in patients with high triglyceride levels.

Glycaemic Efficacy

A Cochrane systematic review identified six studies of colesevelam in patients with type 2 diabetes and estimated a reduction in HbA1c of 0.5% (6 mmol/mol) with colesevelam [7]. A more recent systematic review and meta-analysis of 17 studies including either colesevelam or colestimide (another BAS) over 8–26 weeks observed an improvement in HbA1c of 0.55% (7 mmol/mol) vs. placebo with treatment [8]. Fasting plasma glucose was reduced significantly by 1.1 mmol/l, and LDL cholesterol was reduced by 0.33 mmol/l compared with placebo. There was no effect on body weight.

Cardiovascular Safety

Colesevelam was approved prior to the change in regulatory requirements necessitating cardiovascular outcome trials and as such there is no cardiovascular trial data for colesevelam. It is worth noting that the LRC-CPPT (Lipid Research Clinics Coronary Primary Prevention Trial), an early randomised controlled trial of colestyramine in 3806 men with primary hypercholesterolaemia with an average follow-up of seven years, showed significant reductions in cardiovascular death (24%) and nonfatal myocardial infarction (19%) in the colestyramine group vs. the placebo group [9].

Bromocriptine

Bromocriptine is an ergot alkaloid derivative which is used in the medical management of prolactin-producing pituitary tumours and in Parkinson's disease. It was approved by the FDA in 2009 in a quick release formulation (Cycloset®) for use in type 2 diabetes, where there is evidence of benefit in reducing fasting glucose and HbA1c. Bromocriptine is weight neutral with a low risk of causing hypoglycaemia.

Pharmacology

Bromocriptine acts on dopamine receptors in the corpus striatum. It is an agonist at the D2 receptor and an antagonist at the D1 receptor. It also inhibits the release of glutamate and has varying actions on serotoninergic pathways. Bromocriptine undergoes significant first-pass metabolism and is metabolised in the liver by cytochrome P450 3A4. It has a half-life of two to eight hours and is largely excreted in bile.

Bromocriptine improves insulin resistance and reduces free fatty acids and hepatic glucose production. Its mechanism of action in reducing hyperglycaemia has not been fully elucidated. Knockout mice lacking D2 receptors are glucose intolerant and antipsychotic drugs that inhibit dopamine release can cause glucose intolerance in humans. Its effects on glycaemia are thought to be largely centrally mediated and include:

- the regulation of hypothalamic noradrenaline output;
- the modulation of appetite 'reward' pathways;
- circadian hypothalamic inputs on peripheral insulin sensitivity;
- direct dopaminergic innervation of pancreatic beta cells by the hypothalamic paraventricular nucleus via the vagus nerve; and
- a reduction in prolactin levels.

For the management of type 2 diabetes, bromocriptine is taken in the morning at a starting dose of 0.8 mg, increased weekly to a maximum tolerated dose of 1.6–4.8 mg.

The most common side effects of bromocriptine are nausea, vomiting, headache, dizziness, hypotension, fatigue and nasal stuffiness. These usually improve after two

to three weeks of therapy and can be limited by ingestion with food. Later side effects include constipation, blurred vision, digital vasospasm and neuropsychiatric effects such as confusion and impulse control disorders. It is relatively contraindicated in patients sensitive to other ergot drugs and is absolutely contraindicated in syncopal migraine. It is best avoided in patients with psychotic disorders and in breastfeeding women, where it will probably inhibit lactation.

There appears to be a dose-dependent association between ergot-derived dopamine agonists (bromocriptine, cabergoline, pergolide and dihydroergocriptine) and fibrotic disorders such as cardiac valvulopathies, pulmonary fibrosis, retroperitoneal fibrosis, pericardial thickening and pleural effusions.

Glycaemic Efficacy

A recent systematic review and meta-analysis assessed the trial evidence for dopamine agonists in diabetes and included six trials involving bromocriptine and three involving cabergoline [10]. Cabergoline, like bromocriptine, is an ergot-derived dopamine agonist, but it is not licensed for use in diabetes. The meta-analysis found that dopamine agonists reduced HbA1c by 0.7% (8 mmol/mol) compared with placebo, with a reduction in fasting plasma glucose of 1.7 mmol/l and no difference in effect size between bromocriptine and cabergoline.

Cylcoset Safety Trial

The cardiovascular safety of bromocriptine quick release was assessed in the Cylcoset Safety Trial, a 52 week randomised double-blinded placebo-controlled noninferiority trial in 3095 patients with type 2 diabetes [11] (Table 13.1). Patients were randomised in a 2:1 ratio to their usual antidiabetic regimen plus bromocriptine quick release or placebo. The primary outcome was an extended MACE endpoint, which comprised myocardial infarction, stroke, coronary revascularisation and hospitalisation with angina or heart failure.

- Numerically fewer cardiovascular events were observed in subjects treated with bromocriptine (HR 0.60; 95% CI 0.35–0.96) showing statistical noninferiority.
- The number needed to treat to prevent one event would be 79 patients over 1 year.

It should be noted that this was a short trial in mostly hypertensive subjects on one or two oral antidiabetic drugs, and the event rate was low with 37 events (1.8%) in the bromocriptine quick release group and 32 events (3.1%) in the placebo group. A post hoc analysis using the more usual MACE endpoint definition of cardiovascular death, myocardial infarction or stroke identified 14 events in the bromocriptine quick release group (0.7%) and 15 (1.5%) in the placebo group [12]. Modest improvements in fasting triglyceride levels, blood pressure and heart rate were observed in the trial. There was no effect on body weight observed in the intervention group. There was no increase in hypoglycaemic events. More subjects discontinued bromo-

TABLE 13.1 **Cycloset cardiovascular safety trial with bromocriptine quick release [11, 12]**

Trial	Cycloset Safety Trial [11, 12]
Drug	Bromocriptine quick release up to 4.8 mg
Comparator	Placebo
Population size (n =)	3095
Age (years)	60
Duration of diabetes (years)	8
Follow-up	52 weeks
Atherosclerotic CVD	'One third'
Heart failure	Not described
Primary outcome	Extended MACE noninferior
Secondary outcome	Three-point MACE noninferior

criptine owing to adverse events than placebo (24% vs. 11%), the most common of which was nausea. These results should be treated as preliminary, and it would take a longer cardiovascular outcome trial in higher-risk subjects, with a much larger number of events, to determine if bromocriptine quick release significantly reduces cardiovascular events or not.

Hydroxychloroquine

Hydroxychloroquine is an antimalarial drug derived from the hydroxylation of quinine in the 1940s, when it was observed to be less toxic than other antimalarials. Its anti-inflammatory properties have since established it as a useful disease-modifying agent in the treatment of rheumatological conditions such as systemic lupus erythematosus (SLE) and rheumatoid arthritis. A prospective, multicentre observational study ($n = 4905$) with 21 years of follow-up compared the incidence of new-onset diabetes in nondiabetic patients with rheumatoid arthritis who were started on hydroxychloroquine vs. those who were not [13]. The use of hydroxychloroquine was associated with a significant reduction in the incidence of diabetes (5.2 vs. 8.9 diagnoses per 1000 patient years of observation, $p < 0.001$) and an adjusted relative risk of developing diabetes (0.23, 95% CI 0.11–0.50). A growing recognition of possible antidiabetic properties led to prospective studies that showed modest reductions in HbA1c when used in patients with type 2 diabetes. It is licensed as an add-on antidiabetic drug in India for patients with uncontrolled type 2 diabetes.

Pharmacology

The chemical properties of 4-aminoquinolines such as hydroxychloroquine result in their accumulation in acidic compartments such as lysosomes and inflamed tissues. This inhibits lysosomal activity and autophagy, and disrupts membrane stability. They interfere with toll-like receptor signalling pathways and can reduce production of inflammatory cytokines such as IL-1, IL-6, TNF and IFN-γ *in vitro*. Hydroxychloroquine has been shown to reduce the production of the cytokine TNF in peripheral blood mononuclear cells in patients with SLE. Hydroxychloroquine is considered an immunomodulatory rather than an immunosuppressant drug and its use is not associated with an increased risk of infection or malignancy.

It is unclear how hydroxychloroquine and chloroquine exert their effects on glucose metabolism. Chloroquine has been observed to reduce the metabolic clearance of and boost fasting C-peptide secretion, increasing the rate of systemic glucose uptake, and possibly increasing endogenous insulin secretion. Hydroxychloroquine use may reduce beta cell dysfunction and its anti-inflammatory effect may play a role as patients with higher baseline levels of high-sensitivity C-reactive protein may have better glycaemic response to hydroxychloroquine than those with lower levels [14]. Hydroxychloroquine may also increase plasma levels of the adipokine adiponectin, which has anti-inflammatory and insulin-sensitising effects.

Hydroxychloroquine is well absorbed with good oral bioavailability. It has a long half-life of 40–60 days and is largely excreted by the kidneys. Hydroxychloroquine binds strongly to melanin, which may be an important mechanism in its role managing dermatological manifestations of SLE and in its adverse ocular effects such as retinopathy. Side effects are generally mild and gastrointestinal in nature, but a major and serious adverse effect is hydroxychloroquine retinopathy.

Glycaemic Efficacy

There have been two recent meta-analyses involving hydroxychloroquine. The first included 15 clinical studies in patients with and without diabetes and demonstrated that hydroxychloroquine improved metabolic parameters and lowered HbA1c, fasting serum glucose and postprandial glucose levels [15]. Another meta-analysis included 11 RCTs and found that treatment with hydroxychloroquine in patients with type 2 diabetes or prediabetes was associated with reductions in fasting glucose (−8.05 mg/dl; 95% CI −11.17 to −4.93; $p < 0.0001$), two hour postprandial glucose (−15.52 mg/dl; 95% CI −20.61 to −10.42; $p < 0.00001$) and HbA1c (−0.19%; 95% CI −0.37 to −0.02; $p = 0.03$) [$p16$].

Antiobesity Drugs

Several drugs have been developed as weight-reducing drugs for people with overweight or obesity and when studied in people with diabetes have demonstrated modest

reductions in HbA1c related to weight loss. In contrast, GLP-1 receptor agonists were first developed as a treatment for type 2 diabetes and were observed to be associated with significant reductions in weight. They were then further developed as weight-reducing treatments for people with overweight or obesity (see Chapter 6).

Orlistat

Orlistat is the most established of a small selection of drugs which have been approved for weight loss. It was approved for prescription in 1998 by the EMA and in 1999 by the FDA at a dose of 120 mg under the brand name Xenical®. The FDA then approved it for over-the-counter use in 2007 followed by the EMA in 2009. In the UK the over-the-counter preparation is available at a 60 mg strength under the brand name Alli®. Orlistat inhibits intestinal fat absorption, thus reducing calorific intake. It has a significant effect not just on weight, but also on other cardiometabolic parameters such as HbA1c, fasting plasma glucose and various indices of hyperlipidaemia. In patients with obesity, it reduces progression to impaired glucose tolerance and to type 2 diabetes. It is licensed for use in adults aged 18–75 years who have a BMI of 30 kg/m^2 or more, or who are overweight with a BMI of 28 kg/m^2 or more with risk factors such as type 2 diabetes, hypertension or hypercholesterolaemia.

Pharmacology Orlistat works by forming covalent bonds with the active serine site of gastric and pancreatic lipases, impairing their ability to hydrolyse dietary triglycerides into free fatty acids and monoglycerides. These triglycerides are therefore not absorbed, reducing calorific intake. This inhibitory effect on lipases in the stomach and small intestine, which is long acting but reversible, leads to a 30% reduction in dietary fat absorption. It also leads to fatty stools, particularly after high-fat meals, which is the most prominent adverse effect of the drug. Orlistat is metabolised in the luminal wall and has little systemic absorption. Its effects persist for 24–48 hours and faecal fat content will return to normal at 48–72 hours after discontinuation. Orlistat is a safe drug and generally well tolerated amongst patients motivated to lose weight, such as participants in clinical trials, but in the real world adherence to therapy is lower because of gastrointestinal side effects.

Dose

- Orlistat 120 mg up to three times a day to be taken immediately before, during or up to one hour after each main meal.
- Continue treatment beyond 12 weeks if weight loss since the start of treatment exceeds 5% and use clinical judgement if weight loss is less than 5% in people with type 2 diabetes or prediabetes.

Glycaemic Efficacy Several studies have demonstrated an improvement in glycaemic measures following treatment with orlistat. A meta-analysis of 10 RCTs with

orlistat in 7718 subjects found that mean weight reductions of 2.39 kg (95% CI −3.34 to −1.45) were associated with a reduction of 0.12 mmol/l (95% CI −0.20 to −0.04) in fasting blood glucose in patients treated with orlistat [17]. A subsequent meta-analysis of 12 RCTs in overweight or obese patients with type 2 diabetes found that lifestyle intervention plus orlistat was associated with a mean reduction in weight of 2.10 kg (95% CI −2.3 to −1.8), a mean reduction in fasting blood glucose of −1.16 mmol/l (95% CI −1.4 to −0.80) and a mean HbA1c reduction of −0.5% (−6.12 mmol/mol; 95% CI −10.3 to −1.9 mmol/mol; $p < 0.004$) compared with lifestyle intervention alone [18].

XENDOS The XENDOS (Xenical in the Prevention of Diabetes in Obese Subjects) study was a multicentre, double-blind RCT of 3305 obese individuals without diabetes aged 30–60 years with primary endpoints of onset of new diabetes on an oral glucose tolerance test and weight loss, over a four year period [19]. Participants were randomised to orlistat 120 mg three times daily with lifestyle changes or placebo with lifestyle changes. Some 52% of subjects in the intervention group and 34% of subjects in the placebo control group completed treatment. Gastrointestinal upset was the most common reason for withdrawal.

- After four years of treatment the incidence of type 2 diabetes was 6.2% in the orlistat group and 9.0% in the placebo group, corresponding to a risk reduction of 37% in risk of developing diabetes ($p = 0.0032$).
- Mean weight loss was greater with orlistat than with placebo (5.8 vs. 3.0 kg with placebo, $p < 0.001$).
- There were significant improvements in several cardiovascular risk factors with orlistat compared with placebo, including systolic blood pressure (−4.9 vs. −3.4 mmHg, $p < 0.01$), diastolic blood pressure (−2.6 vs. −1.9 mmHg, $p < 0.01$), total cholesterol (−7.9 vs. −2.3%, $p < 0.01$), LDL cholesterol (−12.8 vs. −5.1%, $p < 0.01$) and waist circumference (−6.4 vs. −4.4 cm, $p < 0.01$).

The risk reduction for the development of diabetes was greater in the subgroup with impaired glucose tolerance (IGT) (52% reduced incidence), and among these IGT subjects 10 people needed to be treated with orlistat for 4 years to prevent one from developing diabetes. This result is supported by a small pooled analysis of 675 obese subjects in three double-blind, placebo-controlled RCTs lasting 104 weeks where 3.0% of patients with IGT went on to develop diabetes on orlistat compared with 7.6% of subjects on placebo [20].

In the XENDOS study, 8% of subjects on orlistat withdrew from the study owing to adverse events as compared with 4% on placebo, with the difference mostly attributed to gastrointestinal events. Most gastrointestinal events were rated as mild to moderate in intensity and were more common in the first year (91% compared with 65% on placebo) than in the fourth year (36% vs. 23% on placebo).

Prescribing point: *To maximise the efficacy and minimise side effects of orlistat patients should be on a nutritionally balanced, mildly hypocaloric diet, rich in fruit and vegetables, and containing approximately 30% of calories from fat.*

Naltrexone/Bupropion

Pharmacology Naltrexone is a μ-receptor antagonist used in the treatment of drug and alcohol dependence. Bupropion is a dopamine and noradrenaline reuptake inhibitor used to aid smoking cessation. Both naltrexone and bupropione act on the hypothalamic melanocortin system where pro-opiomelanocortin cells produce peptides such as α-melanocyte stimulating hormone (MSH) and β-endorphin. α-MSH is anorexigenic, promoting energy expenditure and appetite reduction, while β-endorphin autoinhibits pro-opiomelanocortin cells via μ-opioid receptors. Bupropion augments the release of α-MSH and β-endorphin while naltrexone inhibits β-endorphin action. Individually they have little to no effect on weight; however, when given in combination, their synergistic effects produce significant weight loss.

Peak concentrations are reached in two to three hours, and steady-state concentrations in roughly seven days. Bupropion is metabolised by cytochrome P450 while naltrexone is not. Naltrexone/bupropion is largely renally excreted.

Naltrexone/bupropion is licensed as an adjunct in the management of obesity in individuals with a BMI of 30 kg/m^2 or more or in individuals with a BMI of 27 kg/m^2 or more who have weight-related risk factors. It has been approved by the FDA and the EMA, but its use is not recommended by NICE in the UK.

Efficacy A meta-analysis of the use of weight-reducing drugs compared with placebo for at least one year identified four large RCTs comparing naltrexone/bupropion with placebo. Accepting significant heterogeneity between the studies, the effect size was estimated to be a weight reduction of 5.0 kg at one year of therapy (95% CI 4.4–5.5 kg) [21].

Specific Evidence for Use in Diabetes The COR-Diabetes study was one of the four studies included in the meta-analysis [22]. It was a 56 week study comparing naltrexone/bupropion with placebo in 505 patients with diabetes. This trial had a slightly lower effect size than the others in the meta-analysis:

- Naltrexone/bupropion resulted in a greater weight reduction than placebo (−5.0 vs. −1.8%; $p < 0.001$).
- Naltrexone/bupropion also resulted in significantly greater reduction in HbA1c (−0.6 vs. −0.1%; 6.6 vs. 1.1 mmol/mol; $p < 0.001$).

Cardiovascular Safety There were initial concerns around cardiovascular safety with naltrexone/bupropion as data from phase 3 trials demonstrated a small increase in heart rate and blood pressure. A large cardiovascular outcome trial ($n = 8910$) was started in 2012 to demonstrate the noninferiority of naltrexone/bupropion vs. placebo, with a primary endpoint of MACE, defined as cardiovascular death, nonfatal myocardial infarction or nonfatal stroke [23].

The trial was terminated prematurely after public release of confidential interim data by the sponsor as a patent publication. The academic leadership of the study

recommended termination of the trial owing to the breach of confidentiality and the sponsor agreed. After 25 and 50% of the planned events the hazard ratio for MACE did not exceed 2.0, but it was not possible to assess for noninferiority for the prespecified upper limit of 1.4, so the cardiovascular safety of naltrexone/bupropion has not yet been definitively answered.

Gastrointestinal side effects, chiefly nausea, were the most common cause of drug discontinuation and occurred in 14% of participants who stopped taking naltrexone/bupropion, significantly more than for placebo (2%). Other side effects significantly associated with naltrexone/bupropion included central nervous complaints in 5% (tremor, dizziness, headache) and psychiatric complaints in 3% (insomnia, anxiety, hallucinations) in patients who discontinued naltrexone/bupropion. The FDA has issued a black box warning from the FDA for suicide and suicidal ideation associated with the use of naltrexone/bupropion.

A recent systematic review and meta-analysis examined the cardiovascular safety of naltrexone, bupropion and naltrexone/bupropion, and an additive network meta-analysis model for random effects found no association between treatment and major adverse cardiovascular events [24].

Phentermine and Phentermine/Topiramate

Pharmacology Phentermine is an atypical amphetamine analogue that inhibits noradrenaline reuptake in the hypothalamus. Its appetite-suppressant effect has been used in combination with lifestyle change to tackle obesity since 1959. Topiramate is an anticonvulsant that centrally modulates voltage-gated ion channels, augments λ-aminobutyric acid (GABA) neurotransmitter activity at GABA-A receptors, antagonises the AMPA/kainite subtype of the glutamate receptor and inhibits carbonic anhydrase isoenzymes II and IV. It effects weight loss by an as yet unclear mechanism that seems linked to reduced caloric intake in humans. Although independently effective, topiramate in monotherapy is frequently poorly tolerated, with paraesthesia, depression, poor concentration and memory impairment commonly reported. This led to the combination use of extended release topiramate with phentermine with hopes of 'balancing out' these depressive effects.

Phentermine/topiramate (PHEN/TPM) was approved by the FDA in 2012 at doses of 3.75 mg/23 mg (low dose), 7.5 mg/46 mg (mid dose), 11.25 mg/69 mg (three-quarter dose) and 15 mg/92 mg (high dose). In the US it is licensed for use in patients with BMI ≥ 30 kg/m^2 or those with BMI ≥ 27 kg/m^2 with at least one weight-related comorbidity. It was not approved in the EU because of concerns regarding its cardiovascular and psychiatric safety. PHEN/TPM is taken once daily and its bioavailability has not been established. Phentermine is readily absorbed whereas extended release topiramate is released later in the day and they are largely excreted unchanged in the urine.

Efficacy A pooled analysis of two large RCTs comparing lifestyle intervention and PHEN/TPM with lifestyle intervention alone showed mean percentage weight losses of 4.7, 8.2 and 10.4% with low, mid and high dose PHEN/TPM at 56 weeks, respectively

(1.5% weight loss with lifestyle and placebo, $p < 0.0001$) [25]. A meta-analysis found similar effects with a dose-dependent average weight loss of 7.73 kg (95% CI 6.60–8.85) compared with placebo, along with significant improvements in blood pressure (systolic −6.9–9.1 mmHg depending on dose), non-HDL-cholesterol, HDL-cholesterol and triglycerides above placebo [26]. The drug was well tolerated, with lower dropout rates than placebo in one of the trials. The most common side effects were paraesthesia, dizziness, dysgeusia, insomnia, constipation and dry mouth and were generally mild to moderate in severity.

Specific Evidence for Use in Diabetes These results were echoed in a specifically type 2 diabetic population in the DM-230 continuation of the OB-202 trial [27]. Subjects ($n = 130$) received 28 weeks of 15 mg phentermine and topiramate 100 mg before switching to high-dose PHEN/TPM for a further 28 weeks and saw a 9.6% weight loss at 56 weeks vs. 2.6% in the placebo group ($p < 0.0001$). In addition to improvements in the same cardiometabolic parameters as the above studies, HbA1c improved by 17.5 mmol/mol, compared with 13.1 mmol/mol in the placebo group ($p < 0.05$).

Further post hoc pooled analysis from the phase 3 development programme for phentermine/topiramate has shown a reduction in the incidence of new diabetes in nondiabetic subjects [28], which is most obvious in patients with the highest cardiometabolic disease staging [29], but this has not yet been formally tested in an RCT on the prevention of type 2 diabetes.

Cardiovascular Safety PHEN/TPM has been associated with reductions in blood pressure and a mild increase in heart rate of 1.2–1.7 beats/minute. By technical calculations of the rate pressure product (a proxy measure for myocardial demand) from the two large RCTs, this small increase was deemed unlikely to promote ischaemia in patients with preexisting coronary heart disease [25]. There is no prospective cardiovascular outcome study. A large retrospective study was done including 14 586 real-world patients on PHEN/TPM [30]. The study found that the incident rate ratio for major adverse cardiac events in the PHEN/TPM group was 0.24 (95% CI 0.03–1.70). The finding was nonsignificant with a wide confidence interval despite the relatively large sample population, which seems to be due to the low number of events captured. This may itself be in part linked to a high proportion of the sample being female (80%) and non-obese (44%), so this was not a representative sample for diabetic populations.

Place of Other Drugs in Current and Future Practice

Type 1 Diabetes

The cornerstone of the pharmacological treatment of people with type 1 diabetes is the replacement of insulin, using either a combination of modern short- and

long-acting insulin analogues (Chapters 8 and 9) or insulin pump therapy (Chapter 10). Despite these innovations in insulin therapy, weight gain and hypoglycaemia remain common side effects of insulin treatment. Several drugs have been studied as possible adjunctive therapies in people with type 1 diabetes, which might facilitate the use of lower insulin doses for the same glycaemic effect, limiting weight gain and/or hypoglycaemia. Several drugs that are mainly used as antidiabetic drugs in people with type 2 diabetes have been studied, including metformin, glitazones, acarbose, SGLT2 inhibitors and GLP-1 receptor agonists. Of these drugs, only off-label metformin (Chapter 2) and SGLT2 inhibitors which are approved for use in Europe and Japan (Chapter 5) are regularly used in routine clinical practice in people with type 1 diabetes.

Pramlintide is approved in the US, but usage has been low as its effects are modest and it requires additional subcutaneous injections. Interest in pramlintide as a treatment in type 1 diabetes has recently been renewed now that the patent has expired, and preliminary short-term clinical studies have shown interesting results when continuous subcutaneous insulin infusion is combined with separate continuous pramlintide infusion. Longer-term research will be required before this approach can be considered in routine clinical care. Interestingly, a long-acting amylin analogue named cagrilintide, with agonistic effects on native amylin and calcitonin receptors, is under early investigation in combination with subcutaneous semaglutide as a treatment for type 2 diabetes or overweight and obesity .

Type 2 Diabetes

Bromocriptine and colesevelam are approved in the US and hydroxychloroquine is approved in India for the treatment of type 2 diabetes. It is hard to envisage a role for these drugs used off label in other countries as their effects on HbA1c are modest, side effects are common and much better modern antidiabetic drugs are available (Chapters 4–6). Currently available oral antiobesity drugs also have modest effects on glycaemia when used in people with diabetes. Some also slow the progression to diabetes in high-risk individuals, and NICE recommends considering the use of orlistat in individuals who are at risk of the development of type 2 diabetes and are unable to lose weight by lifestyle change alone, or are unable to participate in physical activity because of a disability or for medical reasons.

GLP-1 receptor agonists were first developed as a treatment for type 2 diabetes (Chapter 6). They were observed to be associated with significant reductions in weight and were then further developed as weight-reducing treatments for people with overweight or obesity who did not have diabetes. Drugs that have the potential to be treatments for diabetes and for obesity in nondiabetic individuals are commercially attractive to pharmaceutical companies. Many of the multiagonist therapies currently under development (see Chapter 14) are being studied simultaneously as possible treatments for diabetes and for overweight/obesity.

References

1. Lee, N.J., Norris, S.L., and Thakurta, S. (2010). Efficacy and harms of the hypoglycemic agent pramlintide in diabetes mellitus. *Ann Fam Med* 8: 542–549.
2. Edelman, S., Garg, S., Frias, J. et al. (2006). A double-blind, placebo-controlled trial assessing pramlintide treatment in the setting of intensive insulin therapy in type 1 diabetes. *Diabetes Care* 29: 2189–2195.
3. Qiao, Y.-C., Ling, W., Pan, Y.-H. et al. (2017). Efficacy and safety of pramlintide injection adjunct to insulin therapy in patients with type 1 diabetes mellitus: a systematic review and meta-analysis. *Oncotarget* 8: 66504–66515.
4. Singh-Franco, D., Perez, A., and Harrington, C. (2011). The effect of pramlintide acetate on glycemic control and weight in patients with type 2 diabetes mellitus and in obese patients without diabetes: a systematic review and meta-analysis. *Diabetes Obes Metab* 13: 169–180.
5. Pencek, R., Roddy, T., Peters, Y. et al. (2010). Safety of pramlintide added to mealtime insulin in patients with type 1 or type 2 diabetes: a large observational study. *Diabetes Obes Metab* 12: 548–551.
6. Beysen, C., Murphy, E.J., Deines, K. et al. (2012). Effect of bile acid sequestrants on glucose metabolism, hepatic de novo lipogenesis, and cholesterol and bile acid kinetics in type 2 diabetes: a randomised controlled study. *Diabetologia* 55: 432–442.
7. Ooi, C.P. and Loke, S.C. (2012). Colesevelam for type 2 diabetes. *Cochrane Database Syst Rev* 12: art. no.: CD009361. doi: 10.1002/14651858.CD009361.pub2.
8. Hansen, M., Sonne, D.P., Mikkelsen, K.H. et al. (2017). Bile acid sequestrants for glycemic control in patients with type 2 diabetes: a systematic review with meta-analysis of randomized controlled trials. *J Diabetes Complications* 31: 918–927.
9. [No authors listed] (1984). The Lipid Research Clinics Coronary Primary Prevention Trial results. I. Reduction in incidence of coronary heart disease. *JAMA* 251: 351–364.
10. Andersen, I.B., Andreassen, M., and Krogh, J. (2021). The effect of dopamine agonists on metabolic variables in adults with type 2 diabetes: a systematic review with meta analysis and trial sequential analysis of randomized clinical trials. *Diabetes Obes Metab* 23: 58–67.
11. Gaziano, J.M., Cincotta, A.H., O'Connor, C.M. et al. (2010). Randomized clinical trial of quick-release bromocriptine among patients with type 2 diabetes on overall safety and cardiovascular outcomes. *Diabetes Care* 33: 1503–1508.
12. Gaziano, J.M., Cincotta, A.H., Vinik, A. et al. (2012). Effect of bromocriptine-QR (a quick-release formulation of bromocriptine mesylate) on major adverse cardiovascular events in type 2 diabetes subjects. *J Am Heart Assoc* 1 (5): e002279. doi: 10.1161/JAHA.112.002279. Epub 2012 Oct 25.
13. Wasko, M.C.M., Hubert, H.B., Lingala, V.B. et al. (2007). Hydroxychloroquine and risk of diabetes in patients with rheumatoid arthritis. *JAMA* 298: 187–193.
14. Misra, D.P., Gasparyan, A.Y., and Zimba, O. (2020). Benefits and adverse effects of hydroxychloroquine, methotrexate and colchicine: searching for repurposable drug candidates. *Rheumatol Int* 40: 1741–1751.
15. Wondafrash, D.Z., Desalegn, T.W., Yimer, E.M. et al. (2020 February 27). Potential effect of hydroxychloroquine in diabetes mellitus: a systematic review on preclinical and clinical trial studies. *J Diabetes Res* 2020: 5214751.doi: 10.1155/2020/5214751. eCollection 2020.
16. Simental-Mendía, L.E., Simental-Mendía, M., Sanchez-Garcia, A., and Linden-Torres, E. (2021 May 19). Effect of hydroxychloroquine on glucose control in patients with and without diabetes: a systematic review and meta-analysis of randomized controlled clinical trials. *Eur J Clin Pharmacol*. doi: 10.1007/s00228-021-03144-7. Online ahead of print.

17. Zhou, Y.-H., Ma, X.-Q., Wu, C. et al. (2012). Effect of anti-obesity drug on cardiovascular risk factors: a systematic review and meta-analysis of randomized controlled trials. *PLoS One* 7 (6): e39062. doi: 10.1371/journal.pone.0039062.
18. Aldekhail, N.M., Logue, J., McLoone, P. et al. (2015). Effect of orlistat on glycaemic control in overweight and obese patients with type 2 diabetes mellitus: a systematic review and meta-analysis of randomized controlled trials. *Obes Rev* 16: 1071–1080.
19. Torgerson, J.S., Hauptman, J., Boldrin, M.N. et al. (2004). XENical in the Prevention of Diabetes in Obese Subjects (XENDOS) study. *Diabetes Care* 27: 155–161.
20. Heymsfield, S.B., Segal, K.R., Lucas, C.P. et al. (2000). Effects of weight loss with orlistat on glucose tolerance and progression to type 2 diabetes in obese adults. *Arch Intern Med* 160: 1321–1326.
21. Khera, R., Murad, M.H., Chander, A.K. et al. (2016). Association of pharmacological treatments for obesity with weight loss and adverse events: a systematic review and meta-analysis. *JAMA* 315: 2424–2434.
22. Hollander, P., Gupta, A.K., Plodkowski, R. et al. (2013). Effects of naltrexone sustained-release/bupropion sustained-release combination therapy on body weight and glycemic parameters in overweight and obese patients with type 2 diabetes. *Diabetes Care* 36: 4022–4029.
23. Nissen, S.E., Wolski, K.E., Prcela, L. et al. (2016). Effect of naltrexone–bupropion on major adverse cardiovascular events in overweight and obese patients with cardiovascular risk factors: a randomized clinical trial. *JAMA* 315: 990–1004.
24. Sposito, A.C., Bonilha, I., Luchiari, B. et al. (2021). Cardiovascular safety of naltrexone and bupropion therapy: systematic review and meta-analyses. *Obes Rev* 22: e13224. doi: 10.1111/obr.13224. Epub 2021 Apr 1.
25. Jordan, J., Astrup, A., Engeli, S. et al. (2014). Cardiovascular effects of phentermine and topiramate: a new drug combination for the treatment of obesity. *J Hypertens* 32: 1178–1188.
26. Lei, X.-G., Ruan, J.-Q., Lai, C. et al. (2021). Efficacy and safety of phentermine/topiramate in adults with overweight or obesity: a systematic review and meta-analysis. *Obesity* 29: 985–994.
27. Garvey, W.T., Ryan, D.H., Bohannon, N.J.V. et al. (2014). Weight-loss therapy in type 2 diabetes: effects of phentermine and topiramate sustained release. *Diabetes Care* 37: 3309–3312.
28. Garvey, T.W., Ryan, D.H., Henry, R. et al. (2014). Prevention of type 2 diabetes in subjects with prediabetes and metabolic syndrome treated with phentermine and topiramate extended release. *Diabetes Care* 37: 912–921.
29. Guo, F. and Garvey, W.T. (2017). Cardiometabolic disease staging predicts effectiveness of weight-loss therapy to prevent type 2 diabetes: pooled results from phase III clinical trials assessing phentermine/topiramate sustained release. *Diabetes Care* 40: 856–862.
30. Ritchey, M.E., Harding, A., Hunter, S. et al. (2019). Cardiovascular safety during and after use of phentermine and topiramate. *J Clin Endocrinol Metab* 104: 513–522.

CHAPTER 14

Future Antidiabetic Drugs

Emma Johns and Miles Fisher

KEY POINTS

- Tirzepatide, a once weekly GLP-1/GIP dual agonist, has demonstrated superior glycaemic efficacy and weight-lowering effects compared with the GLP-1 receptor agonist semaglutide.
- The main side effects of tirzepatide relate to gastrointestinal tolerability and appear to occur early during treatment in the dose titration phase.
- The effect of tirzepatide on cardiovascular events, including major adverse cardiovascular events, is being examined in the SURPASS-CVOT trial which is estimated to complete at the end of 2024.
- The GLP-1/glucagon receptor dual agonist cotadutide has demonstrated favourable effects on liver enzymes, biomarkers of liver fibrosis and liver fat content and along with efinopegdutide (a GLP-1/glucagon dual agonist) and LAPS triple agonist (a GLP-1/GIP/glucagon triple agonist) is being investigated as possible therapy for NASH.
- Imeglimin has a unique mechanism of action targeting multiple pathophysiological defects in type 2 diabetes and demonstrates modest HbA1c-lowering capacity when used as monotherapy or in combination with other antidiabetic drugs.

Introduction

Whilst intensive lifestyle interventions and bariatric surgery are promising management options for people with type 2 diabetes, most people with type 2 diabetes will continue to rely on antidiabetic drugs for disease management. There is a need to expand and improve the range of antidiabetic drugs that are available to offset the growing burden of morbidity and mortality relating to type 2 diabetes and its complications. Research is ongoing to find new and improved antidiabetic drugs which may offer unique or additive benefits to the existing range of antidiabetic drugs that are currently

Diabetes Drug Notes, First Edition. Edited by Miles Fisher, Gerard A. McKay, and Andrea Llano.

used routinely in clinical practice and described in detail in this book. Many novel drug targets and drug classes have been studied over the years and development has been abandoned because of lack of efficacy or toxicity. As examples, glucokinase inhibitors increase insulin secretion and hepatic glucose metabolism, but studies to date have shown modest reductions in HbA1c that have not been sustained long term, and G-protein coupled receptors on beta cells are activated by fatty acids, enhancing insulin secretion, but the development of the fatty acid receptor agonist fasiglifam was halted following reports of liver toxicity.

Results from the phase 2 and phase 3 development programmes for the drugs described in this chapter have been presented over the last few years at national and international scientific meetings, and if development is successfully completed some of these drugs may enter clinical practice in the next few years.

Dual and Triple Agonists

Physiology

GLP-1 The incretin system is the intestinal hormone system which promotes insulin secretion following the oral administration of carbohydrates. This system is impaired in patients with type 2 diabetes (see also Chapter 4) [1]. Glucagon-like peptide-1 and GIP are the two hormones clearly identified as incretins in humans. Dipeptidyl peptidase-4 (DPP-4) inhibitors increase systemic GLP-1 and GIP levels by preventing their enzymatic breakdown, have a modest glucose-lowering effect and are weight neutral. The physiological actions of GLP-1, along with the glycaemic, weight loss and cardiovascular benefits of GLP-1 receptor agonist therapy in patients with type 2 diabetes, are discussed in detail in Chapter 6.

GIP The physiological actions of GIP, also known as glucose-dependent insulinotropic polypeptide, are summarised in Box 14.1. Enthusiasm for GIP as a drug target was previously dampened based on evidence that the pancreatic beta cell response to GIP was significantly impaired in subjects with type 2 diabetes compared with nondiabetic subjects, in contrast to a relatively preserved response to GLP-1. Administration of GLP-1 was also shown to significantly reduce postprandial increases in blood glucose, leading to an initial focus on GLP-1 as a promising glucose-lowering target. The loss of the insulinotropic response to GIP highlights the important contribution of GIP in the abnormal glucose regulation found in people with type 2 diabetes and whilst GLP-1 and GIP have additive actions in the incretin effect in people with normal glucose tolerance, GIP has been hypothesised to play a greater role [2]. Importantly, the impaired beta cell response to GIP in patients with type 2 diabetes has been shown to improve with correction of hyperglycaemia, at least in part owing to increased GIP receptor expression in the islet cells [3, 4]. This supports the hypothesis that the incretin system is impaired as a secondary result of hyperglycaemia, rather than primarily driving it [5].

Box 14.1 Structure and functions of GLP-1, GIP and glucagon

GLP-1 (Glucagon-like Peptide-1)

- Thirty amino acid peptide derived from proglucagon.
- Released from intestinal L cells in response to oral glucose ingestion (also secreted continuously at low basal levels).
- GLP-1 receptor (GLP-1R) locations include pancreatic beta cells, lung, kidneys, heart and peripheral and central nervous system.
- Effects of GLP-1 binding include increased insulin secretion and suppression of glucagon secretion in a glucose-dependent manner, slowing of gastric emptying and increased satiety.

GIP (glucose-dependent insulinotropic polypeptide)

- Forty-two amino acid peptide.
- Secreted from enteroendocrine K cells predominantly located in the duodenum and jejunum.
- Secreted continuously at low basal levels, rapid increase in release following nutrient intake.
- Stimulates insulin release in a glucose-dependent manner by binding its receptor on pancreatic beta cells.
- GIP receptor (GIPR) expressed in pancreas, stomach, bone, small intestine, adipose tissue, lung and multiple regions of the central nervous system.

Glucagon

- Twenty-nine amino acid peptide.
- Derived from precursor peptide proglucagon.
- Synthesised in and secreted from pancreatic alpha cells.
- Extra-pancreatic secretion has been observed in pancreatectomised patients and is hypothesised to originate from proglucagon-producing intestinal cells.
- Acts in opposition to insulin to maintain glucose homeostasis and prevent hypoglycaemia.
- Increases hepatic glucose output through glycogenolysis and gluconeogenesis.
- Other important actions in the liver (reduced lipid synthesis, increased fatty acid oxidation and improved hepatocyte survival) and brain (increased satiety and control of hepatic glucose output).
- Glucagon receptor (GCGR) expressed abundantly in the liver and kidneys, and to a lesser degree in the brain, pancreatic islet cells (predominantly beta and also alpha cells), heart, gastrointestinal tract, adipocytes and adrenal glands

Glucagon The structure and function of glucagon are summarised in Box 14.1. Type 2 diabetes is characterised by inappropriately high glucagon levels in the fasting and postprandial states, which contribute to hyperglycaemia. There is growing interest in the potential benefits of glucagon receptor agonism in the management of coexistent type 2 diabetes and obesity. Glucagon increases energy expenditure by inducing thermogenesis in brown adipose tissue, and glucagon administration promotes satiety and reduces food intake. Glucagon agonism has the potential to offer benefits in the management of obesity, particularly when co-administered with another peptide, which can counterbalance the deleterious effects of glucagon agonism on blood glucose levels.

Pharmacology of Multiagonist Therapies

The development of new incretin-based therapies which combine the benefits of GLP-1 receptor agonists with additional improvements in glucose lowering and weight loss is an exciting prospect. Multiagonist drugs are now in development which target the receptors of two or three peptides (GLP-1, GIP and/or glucagon) in combination. Multiagonist therapies are single-molecule peptides which have been developed to provide mixed-agonist activity at the receptors of GIP and/or glucagon in addition to GLP-1. By exploiting the combined effects of more than one peptide, and the distribution of these receptors in different organ systems, they aim to achieve synergistic metabolic effects, and perhaps improved side-effect profiles. Multiagonists with activity at two types of receptor are termed 'dual agonists', whilst 'triple-agonists' or 'tri-agonists' have activity at three receptors.

GLP-1, GIP and glucagon appear ideal targets for multiagonist therapy. GLP-1 and glucagon are both derived from pro-glucagon, and all three hormones are structurally similar in terms of their peptide sequence and secondary structure (the shape of amino acid segments within a peptide). All three hormones act as class B G-protein coupled receptors which are structurally distinct yet have cross-reactivity for the other peptide ligands.

There are two distinct types of single molecule multiagonist peptides (Figure 14.1):

1. Peptide fusion molecules (also known as peptide conjugates) attach multiple unchanged peptides together into a single structure, forming a molecule which is larger than the component parts.
2. Chimeric or co-agonist peptides (also known as hybrid molecules) fuse the amino acid sequences of two or more hormones into a single molecule, maintaining a similar size to the constituent peptides.

The latter has been the preferred option in the development of incretin system multiagonists owing to the similarity in the structure of these hormones and their receptors. By altering the composition of the hybrid peptide, the relative potency of the molecule at its target receptors can be manipulated, potentially altering the beneficial and adverse effects induced by the drug. A balanced agonist refers to one which has equal activity at each receptor, whereas a preferential agonist has been designed to have greater and lesser potency at specific receptors.

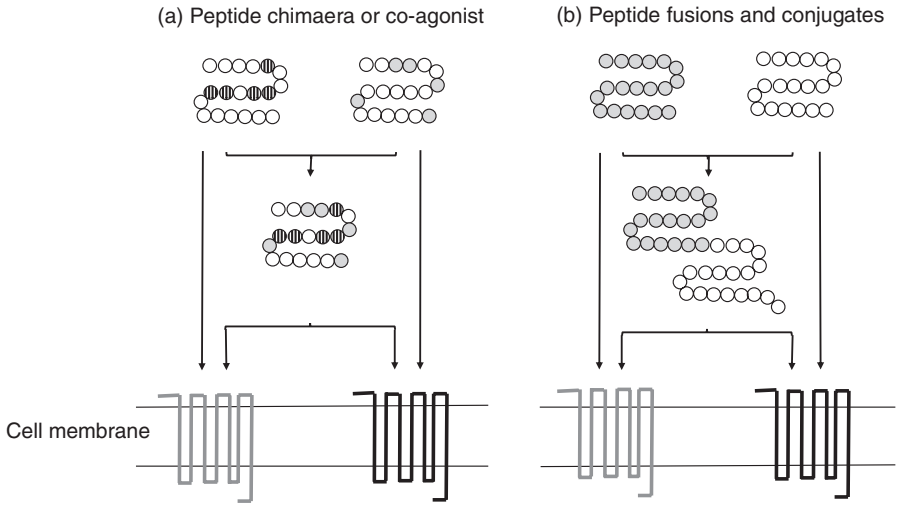


FIGURE 14.1 The two main types of single molecule multiagonist peptides. (a) Peptide chimaera or co-agonist drugs fuse the amino acid sequences from two or more peptides into a single molecule. (b) Peptide fusion or conjugate drugs attach two or more unchanged molecules together into a single structure.

GLP-1/GIP Receptor Dual Agonists

Tirzepatide Tirzepatide (LY3298176, Eli Lilly) is a synthetic hybrid 39 amino acid peptide based on the amino acid structure of GIP (Figure 14.2) [6, 7]. This linear peptide structure is conjugated to a C20 fatty diacid moiety, facilitating binding to albumin and prolonging the duration of action, allowing once weekly subcutaneous injection. Tirzepatide has agonist activity at GLP-1 and GIP receptors, with evidence of greater binding affinity for the GIP receptor in preclinical studies [6].

The efficacy and safety of tirzepatide were examined in a phase 2b randomised, double-blind, placebo-controlled trial in 318 adults with type 2 diabetes [7]. Subjects were randomly assigned to six parallel treatment groups: tirzepatide 1, 5, 10 or 15 mg, dulaglutide 1.5 mg or placebo injected subcutaneously once weekly for 26 weeks. Subjects had a duration of diabetes of at least six months, with a mean disease duration of nine years. Baseline HbA1c ranged from 7.0 to 10.5% (mean 8.1%; 53–91 mmol/mol, mean 65 mmol/mol) and BMI ranged from 23 to 50 kg/m^2 (mean 32.6 kg/m^2). Most subjects were treated with metformin monotherapy at baseline (≥86% per group) with the remainder managed with diet. After 26 weeks of treatment:

- Dose-dependent reductions in HbA1c were observed with tirzepatide: −1.06% (1 mg), −1.73% (5 mg), −1.89% (10 mg) and −1.94% (15 mg), compared with −1.21% (dulaglutide) and −0.06% (placebo).
- Changes in mean body weight were also observed in the same pattern across the range of tirzepatide doses, ranging from −0.9 to −11.3 kg (compared with −2.7 kg for dulaglutide and −0.4 kg for placebo).

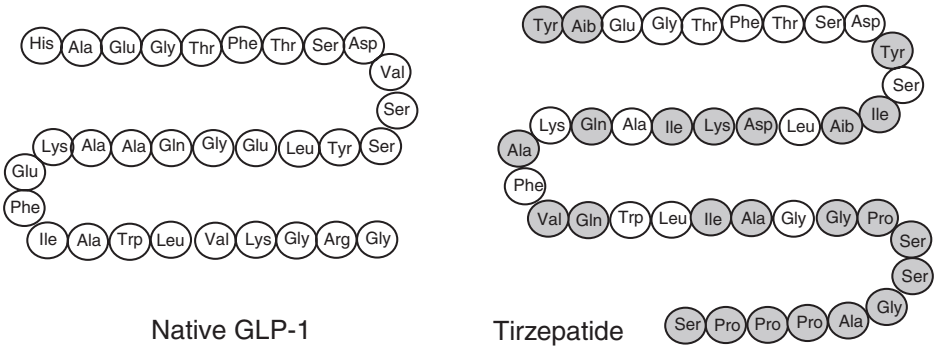


FIGURE 14.2 Structure of tirzepatide. Tirzepatide is a synthetic hybrid 39 amino acid peptide based on the amino acid structure of GIP, conjugated to a C20 fatty diacid moiety.

After 26 weeks of treatment, 14–71% of those treated with tirzepatide achieved a weight loss of ≥5% body weight (compared with 22% on dulaglutide) and 6–39% achieved a ≥10% reduction in body weight (compared with 9% on dulaglutide). Overall, tirzepatide at a dose of 5–15 mg was associated with a greater reduction in HbA1c and bodyweight than dulaglutide. After 26 weeks, tirzepatide was associated with greater reductions in triglyceride concentration than dulaglutide and placebo at the 10 and 15 mg doses (mean reduction from baseline –0.8 mmol/l at 15 mg). Changes in mean total cholesterol ranged from 0.2 to −0.3 mmol/l and were similar to those in the dulaglutide and placebo arms.

Gastrointestinal side effects (nausea, diarrhoea and vomiting) and reduced appetite were the most commonly reported side effects. The incidence of gastrointestinal side effects ranged from 23% (1 mg) to 66% (15 mg) compared with 43% (dulaglutide) and 10% (placebo). All gastrointestinal side effects were more common in the 15 mg group compared with dulaglutide. Compared with the dulaglutide group, the 5 and 10 mg tirzepatide groups experienced similar rates of nausea and vomiting, but diarrhoea was more commonly reported with tirzepatide. Gastrointestinal side effects were generally noted to be transient, of mild to moderate intensity, and to occur early in the treatment course. Two cases of acute pancreatitis were recorded in the 5 mg tirzepatide group. The incidences of hypoglycaemia were similar across all groups and there were no reports of severe hypoglycaemia. The proportion of participants discontinuing study medication owing to adverse events was highest in the 15 mg group (24%), compared with 11% of dulaglutide.

The first completed phase 3 trials involving tirzepatide were SURPASS-1 and SURPASS-2 [8, 9]. In SURPASS-1, 478 people with type 2 diabetes, mean duration 4.7 years and mean HbA1c 7.9% (63 mmol/mol) were randomised to receive double-blind tirzepatide (5, 10 or 15 mg) or placebo in a 1:1:1:1 ratio [8]. Some 54% of participants were treatment naive and the remainder had received no antidiabetic drug for at least three months. All participants randomised to the tirzepatide arms commenced treatment at 2.5 mg once weekly and completed a step-wise dose increase of 2.5 mg at four weekly intervals until the target dose was achieved.

- After 40 weeks, tirzepatide at all doses was associated with significant reductions in HbA1c and body weight compared with placebo.
- These were greatest in the 15 mg dose group (placebo-adjusted HbA1c reduction −2.11% and placebo-adjusted weight reduction −8.8 kg at 40 weeks).
- In this group, 52% of participants achieved an HbA1c < 5.7% (39 mmol/mol) and 88% achieved HbA1c < 7.0% (53 mmol/mol).

The most commonly reported adverse events were gastrointestinal, including nausea (18% in 15 mg group), diarrhoea (12%), constipation (7%) and vomiting (6%). Adverse events typically occurred in the dose-titration period and were of mild to moderate severity. There were no reports of severe hypoglycaemia in the tirzepatide treatment arms. Treatment discontinuation rates ranged from 9% (5 mg) to 21% (15 mg), compared with 15% in the placebo group. Most discontinuations in the 15 mg and placebo arms were not related to adverse events, but to non-drug factors including the COVID-19 pandemic.

SURPASS-2 was an open-label trial involving 1879 patients with type 2 diabetes who were randomised in equal numbers to receive tirzepatide 5, 10 or 15 mg, or semaglutide 1 mg once weekly [9].

- After a treatment period of 40 weeks, tirzepatide at all doses was superior to semaglutide in terms of HbA1c lowering and reductions in body weight.
- A dose-dependent treatment response to tirzepatide was evident, with maximal improvements in HbA1c (−2.3%, estimated treatment difference vs. semaglutide −0.45%) and body weight (−11.2 kg, estimated treatment difference vs. semaglutide −5.5 kg) in the 15 mg group.

Overall, the gastrointestinal side-effect profile of tirzepatide was similar to that of semaglutide.

Following this evidence of efficacy in improving glycaemia and body weight in people with type 2 diabetes, the effect of tirzepatide on cardiovascular outcomes is an important question. Could this drug exceed the cardiovascular benefits of the GLP-1 receptor agonists described in Chapter 6? The large, international, cardiovascular outcome trial SURPASS-CVOT (NCT04255433) will address this question, comparing tirzepatide with dulaglutide in an estimated enrolment of 12 500 participants. Inclusion criteria include type 2 diabetes, confirmed atherosclerotic cardiovascular disease, HbA1c 7.0–10.5% and BMI ≥25 kg/m^2. The primary outcome, the usual three-point MACE (i.e. cardiovascular death, nonfatal myocardial infarction or nonfatal stroke), will be assessed over an approximate maximum treatment period of 54 months. This trial commenced enrolment in 2020 and is expected to complete at the end of 2024.

SURPASS-1, SURPASS-2 and SURPASS-CVOT are part of a large phase 3 development programme designed to further assess the efficacy and safety of tirzepatide in a range of patient populations, including people with type 2 diabetes and non-diabetic subjects with obesity (or overweight with related comorbidities; THis table is spear over 4 pages. For one the 'n' column is bold but it is in regular case for 2 others. Also see if some of the hyphenation can be improved.Table 14.1).

TABLE 14.1 **Tirzepatide phase 3 clinical trial programme (see Appendix 1 for conversion of HbA1c from % to mmol/mol)**

Trial (ClinicalTrials.gov Identifier)	Study design	Participants	Comparator	*n*	Primary outcome measure(s)	Estimated primary completion date
SURPASS-1 (NCT03954834)	Randomised, double-blind, placebo-controlled trial Duration 40 weeks	• T2DM diet controlled • HbA1c 7.0–9.5% • BMI ≥ 23 kg/m^2	Placebo	478	Change from baseline HbA1c (week 40)	October 2020
SURPASS-2 (NCT03987919)	Randomised, open-label, active-comparator trial Duration 40 weeks	• T2DM on MF • HbA1c 7.0–10.5% • BMI ≥ 25 kg/m^2	Semaglutide (s.c. once weekly)	1881	Change from baseline HbA1c (week 40)	January 2021
SURPASS-3 (NCT03882970)	Randomised, open-label, active-comparator trial Duration 52 weeks	• T2DM on MF (±SGLT2i) • HbA1c 7.0–10.5% • BMI ≥ 25 kg/m^2	Insulin degludec	1420	Change from baseline HbA1c (week 52)	December 2020
SURPASS-4 (NCT03730662)	Randomised, open-label, active-comparator trial Duration 52 weeks	• T2DM on 1–3 OHAs (excluding DPP4i and GLP1RA) • Increased CV risk • BMI ≥ 25 kg/m^2	Insulin glargine	1878	Change from baseline HbA1c (week 52)	May 2021

(*Continued*)

TABLE 14.1 (*Continued*)

Trial (ClinicalTrials.gov Identifier)	Study design	Participants	Comparator	*n*	Primary outcome measure(s)	Estimated primary completion date
SURPASS-5 (NCT04039503)	Randomised, double-blind, placebo-controlled trial Duration 40 weeks	• T2DM on insulin glargine (±MF) • HbA1c 7.0–10.5% • BMI ≥ 23 kg/m^2	Placebo	472	Change from baseline HbA1c (week 40)	December 2020
SURPASS J-combo (NCT03861039)	Randomised, open-label, parallel group trial Duration 52 weeks Japanese market	• T2DM on OHA monotherapy • HbA1c 7.0–10.9% • BMI ≥ 23 kg/m^2	N/A	441	Number of participants with ≥1 SAE considered to be related to study drug administration	February 2021
SURPASS J-mono (NCT03861052)	Randomised, double-blind, parallel group trial Duration 52 weeks Japanese market	• T2DM • Treatment naive or OHA monotherapy • HbA1c 7.0–10.0% • BMI ≥ 23 kg/m^2	Dulaglutide (0.75 mg once weekly)	636	Mean change in HbA1c from baseline to week 52	March 2021
SURPASS-AP-COMBO (NCT04093752)	Randomised, open-label trial Duration 40 weeks	• T2DM on MF ± SU • HbA1c 7.5–11.0% • BMI ≥ 23 kg/m^2	Insulin glargine (once daily, dose titrated)	917	Mean change in HbA1c from baseline to week 40	February 2022
SURPASS-CVOT (NCT04255433)	Randomised, double-blind, parallel group trial Duration 54 months	• T2DM • Atherosclerotic CV disease • HbA1c 7.0–10.5% • BMI ≥25 kg/m^2	Dulaglutide (once weekly)	12,500	Time to first occurrence of death from CV causes, MI, or stroke (MACE-3)	October 2024

SYNERGY-NASH (NCT04166773)	Randomised, double-blind, placebo-controlled trial Duration 52 weeks	• BMI 27–50 kg/m^2 • Histologic diagnosis of NASH with stage 2 or 3 fibrosis • T2DM or no T2DM • HbA1c ≤9.5% if T2DM	Placebo	196	Percentage of participants with absence of NASH with no worsening of fibrosis on liver histology after 52 weeks	June 2022
SURMOUNT-1 (NCT04184622)	Randomised, double-blind, placebo-controlled trial Duration 72 weeks (plus two year extension)	• No diabetes • BMI ≥ 30 kg/m^2 *or* BMI ≥ 27 kg/m^2 with at least one of: HTN, dyslipidaemia, OSA or CVD • At least one unsuccessful effort to lose weight with diet	Placebo	2400	• Percentage change in body weight from baseline to week 72 • Percentage of participants who achieved ≥5% reduction in body weight from baseline to week 72	April 2022
SURMOUNT-2 (NCT04657003)	Randomised, double-blind, placebo-controlled trial Participants with T2DM and overweight/obesity Baseline therapy may include diet/exercise or any oral diabetes therapy except DPP4i or GLP1RA	• T2DM diet controlled *or* on any OHA except DPP-4i • HbA1c 7.0–10.0% • BMI ≥ 27 kg/m^2 • At least one unsuccessful effort to lose weight with diet	Placebo	900	• Percentage change in body weight from baseline to week 72 • Percentage of participants who achieved ≥5% reduction in body weight from baseline to week 72	July 2023

(*Continued*)

TABLE 14.1 (*Continued*)

Trial (ClinicalTrials.gov Identifier)	Study design	Participants	Comparator	*n*	Primary outcome measure(s)	Estimated primary completion date
SURMOUNT-3 (NCT04657016)	Randomised, double-blind, placebo-controlled trial (intervention following intensive lifestyle modification programme) Duration 72 weeks	• No diabetes • BMI ≥ 30 kg/m² *or* BMI ≥ 27 kg/m² with at least one of: HTN, dyslipidaemia, OSA or CVD • At least one unsuccessful effort to lose weight with diet	Placebo	800	• Percentage change in body weight from baseline to week 72 • Percentage of participants who achieved ≥5% reduction in body weight from baseline to week 72	August 2023
SURMOUNT-4 (NCT04660643)	Randomised, double-blind, placebo-controlled trial Lead in phase: all participants take tirzepatide Treatment phase: participants randomised to tirzepatide or switch to placebo	• No diabetes • BMI ≥ 30 kg/m² *or* BMI ≥ 27 kg/m² with at least one of: HTN, dyslipidaemia, OSA or CVD • At least one unsuccessful effort to lose weight with diet	Placebo	750	Percentage change in body weight from baseline to week 36	August 2023

All trials phase 3 except SYNERGY-NASH (phase 2).Tirzepatide administered in three parallel dose arms (5, 10 and 15 mg once weekly) in all trials except SURMOUNT-2 (10 and 15 mg once weekly) and SURPASS-CVOT, SURMOUNT-3 and SURMOUNT-4 (dose not specified).Details regarding trials obtained from www.ClinicalTrials.gov.Abbreviations: BMI = body mass index, CV = cardiovascular, CVD = cardiovascular disease, DPP4i = dipeptidyl peptidase-4 inhibitor, GLP1RA = Glucagon-like peptide-1 receptor agonist, HTN = hypertension, MACE = major adverse cardiovascular event, MF = metformin, MI = myocardial infarction, OHA = oral hypoglycaemic agent, OSA = obstructive sleep apnoea, SAE = serious adverse event, SGLT2i = sodium-glucose cotransporter-2 inhibitor, SU = sulfonylurea, T2DM = type 2 diabetes mellitis

NNC0090-2746 NNC0090-2746 (also known as RG7697) is a fatty acylated peptide administered as a once daily subcutaneous preparation. It has balanced agonist activity at GIP and GLP-1 receptors. NNC0090-2746 was under development by Novo Nordisk but did not enter phase 3 development. NNC0090-2746 was evaluated over a 12 week period in a randomised, double-blind, parallel group, placebo-controlled phase 2 trial [10]. A total of 108 patients with type 2 diabetes who were inadequately controlled on metformin (mean HbA1c 8.3%, mean BMI 33.0 kg/m^2) were randomised to receive 1.8 mg of NNC0090-2746, placebo or open-label liraglutide (titrated over 2 weeks to 1.8 mg daily). Overall, NNC0090-2746 led to similar reductions in bodyweight and HbA1c to liraglutide. However, improvements in body weight were only observed amongst participants with baseline HbA1c < 8.5%. From this preliminary data, treatment with NNC0090-2746 would appear to have lesser effects than tirzepatide.

GLP-1/Glucagon Receptor Dual Agonists

Cotadutide Cotadutide (MEDI0382, AstraZeneca) is a 30 amino acid synthetic linear peptide designed with a palmitic acid side chain to extend its plasma half-life [11]. This molecule has a fivefold relative potency at the GLP-1 receptor compared with the glucagon receptor. It is administered as a once daily subcutaneous injection and has an approximate half-life of eight to nine hours [12].

The results of two randomised, double-blind, placebo-controlled phase 2a trials of cotadutide have been published [12, 13]. The studies involved 177 participants and were performed across multiple sites in Germany, and both recruited overweight and obese adults (BMI 27–40 kg/m^2) with type 2 diabetes and HbA1c 6.5–8.5%. Metformin monotherapy was permitted in both trials, and a four week washout period of other antidiabetic drugs was performed in both. Subjects receiving current or recent GLP-1receptor agonists or insulin therapy were excluded. The trials administered cotadutide for slightly different treatment durations (41 vs. 49 days) and had individual dose-titration schedules, with respective dose ranges of 50–300 and 100–300 μg. In both trials, compared with placebo, cotadutide was associated with a significant reduction in the glucose area under the curve (0–4 hours) following a mixed-meal tolerance test (mean difference −27.84%, $p < 0.001$ and −22.6%, $p < 0.0001$ respectively). Evaluation of fasting plasma glucose and continuous glucose monitoring data suggested comparable glucose-lowering efficacy at the 50 μg dose compared with higher doses [12]. Cotadutide was associated with a significant reduction in body weight in both studies (mean difference −3.33%, $p = 0.003$ and −2.14 kg, $p = 0.0008$ respectively), with the greatest weight loss observed in participants who received a 300 μg dose for 28 days [12]. These weight-loss effects were speculated to be more pronounced than those reported with GLP-1 receptor agonist treatment in other trials of similar duration [13].

Cotadutide was generally well tolerated but associated with an increase in gastrointestinal side effects compared with placebo, in particular nausea and vomiting, and decreased appetite. Whilst a dose-dependent relationship was not apparent, gastrointestinal adverse events were less frequently reported in the cotadutide-treated partici-

pants in the trial that used a lower starting dose of 50 μg [12]. The authors concluded that the safety profile of cotadutide was similar to that of GLP-1 receptor agonists at the equivalent stage of development [12].

A phase 2b trial assessing the efficacy of cotadutide in 834 overweight and obese participants with metformin-treated type 2 diabetes has been completed [14]. This double-blind trial compared cotadutide administered at three doses (100, 200 and 300 μg) with placebo and open-label liraglutide 1.8 mg.

- After 54 weeks of treatment, cotadutide was associated with significant reductions in HbA1c compared with placebo (−1.03, −1.16 and −1.19% with increasing doses, compared with −1.17% (liraglutide) and −0.45% (placebo)).
- Whilst all doses of cotadutide were associated with significant reductions in body weight compared with placebo, only the 300 μg dose was associated with a significantly greater reduction when compared with liraglutide (−5.02 vs. −3.33%, $p < 0.01$).
- Nausea and vomiting were the most commonly reported adverse events and were experienced in a greater proportion of those receiving cotadutide (35 and 17%, respectively) compared with liraglutide or placebo.

Gastrointestinal adverse events were noted to decrease over time, a pattern similar to that observed with GLP-1 receptor agonist therapy. The authors speculate that these effects may relate to cotadutide delaying gastric emptying and suggest that further experience in dose titration may improve the tolerability of this drug.

The phase 2 development programme for cotadutide includes trials assessing the effects of cotadutide on hepatic glycogen levels in obese patients with type 2 diabetes (NCT03555994) and its safety and efficacy in patients with type 2 diabetes and chronic kidney disease (NCT04515849).

Bamadutide Bamadutide (SAR425899, Sanofi) is a once daily subcutaneous preparation with preferential activity at the GLP-1 receptor. Bamadutide showed efficacy in reducing fasting plasma glucose, HbA1c and body weight over 4 weeks in a phase 1 placebo-controlled study involving 36 overweight and obese patients with type 2 diabetes [15]. A subsequent phase 2 study compared bamadutide with metformin, liraglutide and placebo in 296 patients with type 2 diabetes [16]. Over the 26 week treatment period, approximately 25% of those in the bamadutide arm dropped out of the trial owing to tolerability issues, primarily related to gastrointestinal side effects [17]. These results were announced in a 2018 press release by Sanofi, which concluded the preparation was 'not acceptable for clinical use' at that point. The results were attributed to relative activity at the GLP-1 receptor being higher than expected compared with preclinical data, rendering the dose titration schedule too aggressive. This unbalanced activity profile was supported by a recently published phase 1 trial which reported that bamadutide has very low occupancy at the glucagon receptor, based on the appearance of PET/CT images in six subjects [18]. Further investigation to optimise the dose titration schedule in the hope of improving tolerability was planned but further development of bamadutide was halted for commercial reasons.

GLP-1/Glucagon Receptor Dual Agonists in Non-alcoholic Fatty Liver Disease There is growing interest in the potential for GLP-1/glucagon receptor dual agonists to benefit patients with NASH, a form of NAFLD characterised by hepatitis, liver cell damage and hepatic fat accumulation. Type 2 diabetes and obesity are highly prevalent in this patient population. In post-hoc analysis, significant reductions in ALT, AST and PRO-C3 (a biomarker of hepatic fibrosis) were observed in patients who received 300 μg cotadutide for 54 weeks, but not lower doses, compared with liraglutide and placebo [14]. A 39% reduction in hepatic fat was also reported following six weeks of cotadutide treatment, a change which exceeds that associated with a six month course of liraglutide 1.2 mg [19]. It is hypothesised that these benefits may be attributed to the promotion of fatty acid oxidation by glucagon receptor agonism, resulting in increased hepatic fat clearance [13]. A phase 2 study assessing the safety, tolerability and pharmacodynamics of cotadutide in obese patients with biopsy-confirmed NAFLD/NASH completed in 2021 and results are awaited (NCT04019561).

Efinopegdutide (HM12525A, JNJ-64565111, Merck) is a GLP-1/glucagon receptor agonist with once weekly dosing. Following evidence of safety in phase 2 trials involving class 2 and 3 obese patients with and without type 2 diabetes (NCT03586830, NCT03486392), future phase 2 trials will focus on the role of this drug as a potential treatment for NASH.

Triple Agonists

In preclinical studies of mice with diet-induced obesity, a triple agonist of the incretin system with balanced activity at the GLP-1, GIP and glucagon receptors was associated with superior improvements in glycaemia, body weight and hepatic lipid content compared with dual agonists (GLP-1/glucagon and GIP/glucagon) or liraglutide [20]. It was considered that tri-agonists could offer clinically important beneficial features over dual agonists. Owing to the additional buffering activity of GIP in addition to GLP-1, more potent agonism at the glucagon receptor and the related benefits could be achieved with less risk of hyperglycaemia (this is in contrast to GLP-1/glucagon co-agonists which to date are unbalanced towards greater activity at GLP-1). In addition, balanced agonism may reduce the likelihood of GLP-1-related gastrointestinal side effects.

The once weekly subcutaneous preparation LAPS Triple Agonist (HM15211, Hanmi Pharmaceuticals) is the only triple agonist preparation currently progressing through the clinical trial pipeline, and development of several other tri-agonists was discontinued following the completion of phase 1 trials. Based on preclinical results showing a beneficial effect on hepatic fibrosis and inflammation, LAPS triple agonist has recently been awarded fast track designation by the FDA as a possible treatment for NASH. It was generally well tolerated in a phase 1 study of a single ascending dose in healthy obese patients [21]. The results of a 12 week phase 1 multiple ascending dose trial in obese patients with NAFLD are awaited (NCT03744182). A phase 2, placebo-controlled trial to assess safety, efficacy and tolerability in patients with biopsy-confirmed NASH is currently underway and is estimated to complete by the end of 2022 (NCT04505436).

Imeglimin

Pharmacology

Mechanism of Action Imeglimin (Poxel Pharma) is the first in a new class of oral antidiabetic drugs known as the 'glimins'. It is a tetrahydrotriazine-containing drug which inhibits the oxidative phosphorylation process in the mitochondria of aerobic cells [22]. Mitochondria play a crucial role in the cellular metabolism of glucose and mitochondrial dysfunction has been shown to play an important role in the pathogenesis of type 2 diabetes [23]. The molecular effects of imeglimin include improved mitochondrial function, leading to increased ATP synthesis, lipid oxidation and reduced production of reactive oxygen species [24].

In preclinical studies, imeglimin exposure was associated with several beneficial effects in pancreatic beta cells including increased glucose-dependent insulin release, increased cell mass and improved cell survival [22, 24]. In addition, increased skeletal muscle insulin sensitivity and suppression of hepatic gluconeogenesis have been reported [25]. Preclinical results also suggest that imeglimin may have a protective effect on endothelial function [26, 27]. Owing to this unique mechanism of action, imeglimin may offer additive benefits when used in combination with other antidiabetic drugs.

Pharmacokinetics The absorption of imeglimin involves an active transport process in addition to passive paracellular absorption. Absorption is up to 80% but decreases with larger doses owing to probable saturation of active transport. After absorption it is rapidly distributed to target organs. In the circulation, it has very low protein binding capacity (1–8%) and a half-life of 12–20 hours. Imeglimin undergoes very low hepatic metabolism and is renally excreted.

Glycaemic Efficacy and Safety

The efficacy and safety of imeglimin have been assessed in phase 2 trials performed in Europe, the US and Japan. Imeglimin monotherapy showed similar efficacy to metformin with regards to glucose lowering, assessed by comparing the plasma glucose response after four weeks (with a three hour oral glucose tolerance test) and eight weeks (with a prolonged meal test) of treatment [28]. The glucose-lowering effects of imeglimin were superior at the 1000 mg twice daily dose (compared with 2000 mg once daily) and 1500 mg twice daily dose (compared with 850 mg twice daily) in the four and eight week studies, respectively. A dose-ranging study performed over 24 weeks using imeglimin doses from 500 to 2000 mg twice daily found that the glucose-lowering effects were maximal at the 1500 mg twice daily dose (placebo-corrected HbA1c reduction −0.63%, $p < 0.001$), and that maximal efficacy for all doses was achieved by 18 weeks [29]. A 24 week dose-ranging study performed in Japanese participants found that reductions in HbA1c were similar in the 1000 mg twice daily and 1500 mg twice daily groups (placebo-corrected change −0.94 and −1.0% respectively), but the 1500 mg

twice daily dose was less well tolerated, in part owing to a greater number of gastrointestinal side effects [30].

Imeglimin as an add-on therapy was assessed in two randomised, double-blind, placebo-controlled trials involving participants with type 2 diabetes and HbA1c ≥ 7.5% taking metformin or sitagliptin monotherapy [31, 32]. After a 12 week treatment period, imeglimin 1500 mg twice daily significantly reduced HbA1c compared with placebo in the metformin (−0.65 vs. −0.21%, $p < 0.001$) and sitagliptin (−0.60 vs. 0.12%, $p < 0.001$) trials. A meta-analysis of three phase 2 placebo-controlled trials reported a mean reduction in HbA1c of −0.63% (95% CI −0.84 to −0.42) and a mean reduction in fasting plasma glucose of −0.52 mmol/l (95% CI −0.80 to −0.24) with imeglimin 1500 mg twice daily as monotherapy or add-on therapy (to metformin or sitagliptin) [33].

These results from dose-ranging studies informed the decision to administer the 1000 mg twice daily dose in subsequent phase 3 trials performed in Japan. For submission to the Japanese licensing authority imeglimin was assessed in the phase 3 TIMES (Trials of Imeglimin for Efficacy and Safety) programme involving more than 900 Japanese participants with type 2 diabetes. TIMES 1 was a randomised, double-blind, placebo-controlled trial assessing the glycaemic efficacy of imeglimin monotherapy [34]. A total of 213 patients (78% male) with type 2 diabetes managed with diet and exercise ± a single oral antidiabetic drug were recruited. Patients were randomised to imeglimin (1000 mg twice daily) or placebo in a 1:1 ratio for 24 weeks. Patients previously taking a single antidiabetic drug completed a 12 week washout period, and a four week placebo run-in was completed by all participants. Baseline characteristics included mean age 62 years, mean HbA1c 7.9%, mean duration of diabetes 7.5 years and mean BMI 26 kg/m^2. In TIMES 1:

- The primary outcome of the change in HbA1c at 24 weeks was significantly improved by imeglimin with a placebo-corrected reduction of −0.87% ($p < 0.001$).
- A reduction in fasting plasma glucose (placebo-corrected reduction −1.1 mmol/l, $p < 0.001$) and an increased proportion of participants achieving HbA1c <7% (35.8 vs. 7.5%, $p < 0.001$) were also observed after 24 weeks in the imeglimin arm.

A similar proportion of participants in the imeglimin and placebo arms experienced adverse events (44 and 45%), gastrointestinal symptoms (11 and 8%) and adverse events leading to treatment discontinuation (3 and 6%). No cases of serious adverse events relating to study drug or severe hypoglycaemia were recorded in either arm.

TIMES 2 evaluated the efficacy of imeglimin as an add-on therapy for a duration of 52 weeks [35]. A total of 510 participants (73.7% male) received open-label imeglimin (1000 mg twice daily) in addition to an existing single oral antidiabetic drug. The following baseline therapies were prescribed in similar numbers: alpha glucosidase inhibitor, biguanide, DPP4 inhibitor, glinide, SGLT2 inhibitor and thiazolidinedione ($n = 63$–65 per group), and a larger group of 127 participants were taking a sulfonylurea. At baseline, mean age ranged from 56 to 60 years amongst groups, mean BMI was 24–27 kg/m^2, mean HbA1c was 8.16–8.72%, and mean duration of diabetes was 7.5–10.6 years.

- After 52 weeks, an HbA1c reduction was reported in all groups, ranging from −0.56% in the sulfonylurea group to −0.92% in the DPP-4 inhibitor group.

Adverse events were experienced in a considerable proportion of participants, ranging from 51.6% (alpha glucosidase inhibitor) to 84.4% (glinide). Most of these events were not considered to be related to the study drug. The highest rate of drug-related adverse events occurred in the biguanide group ($n = 24$, 38%). The proportion of participants who experienced adverse events leading to drug discontinuation ranged from seven (11%) in the biguanide group to one (2%) in the glinide and SGLT2 inhibitor groups. No cases of a serious drug-related adverse event or severe hypoglycaemia were recorded in any group.

TIMES 3 assessed the safety and efficacy of imeglimin in addition to insulin therapy [36]. This trial comprised a 16 week double-blind, placebo-controlled phase, followed by an open-label 36 week extension phase. A total of 215 participants (62.8% male) with insulin-treated type 2 diabetes were randomised to receive imeglimin (1000 mg twice daily) or placebo in a 1:1 ratio. Participants continued their existing insulin regimen (either basal or pre-mixed) at a fixed dose throughout the trial. Approximately 20% of participants were also prescribed a single oral antidiabetic drug at baseline, and this was withdrawn during a 12 week washout period prior to randomisation. Baseline characteristics of the cohort included mean age 58 years, mean HbA1c 8.8%, mean duration of diabetes 13 years and mean BMI 25 kg/m^2.

- After 16 weeks, a placebo-corrected reduction in HbA1c of −0.60% ($p < 0.001$) was observed in the imeglimin group.

Adverse events leading to discontinuation were experienced in one (0.9%) and four (3.7%) participants in the imeglimin and placebo groups, respectively. Hypoglycaemia was evident at similar rates in both groups (imeglimin 21.3%, placebo 15.9%), and no episodes of severe hypoglycaemia were reported. TIMES 3 continued with an open-label 36 week extension period involving 208 participants, where all participants from the placebo group switched to receive imeglimin in addition to their existing insulin therapy. After the total trial duration of 52 weeks, a reduction in HbA1c of −0.54% was evident in the group initially randomised to placebo. Amongst those who had received imeglimin throughout, a −0.64% reduction was observed.

Regulatory Status

Overall, imeglimin has been well tolerated in clinical trials. Dose-dependent gastrointestinal symptoms are the most commonly reported adverse events. No severe hypoglycaemia or cardiovascular events have been reported to date. Imeglimin appears to be weight neutral and to have no significant effect on blood pressure or lipid profile. Based on the results of the completed TIMES trials imeglimin has been approved for use in Japan.

There is a theoretical risk that imeglimin may cause severe hypoglycaemia in patients with chronic kidney disease based on its mechanism of action. While a small number of participants in the TIMES 1 cohort had CKD stage 3A ($n = 21$ in the imeglimin treatment group), all participants in TIMES 2 and 3 had normal renal function (eGFR ≥60 ml/min/1.73 m^2). A phase 3 programme of trials with a focus on participants with type 2 diabetes and CKD stage 3B/4 is currently in development with a view to submitting imeglimin for approval in the US and Europe. This will also require an expansion of the clinical trial programme, including further data on the long-term safety profile of imeglimin and its impact on cardiovascular events.

Place of New Antidiabetic Drugs in Future Practice

Single-molecule multiagonists of the incretin system and imeglimin are the drug classes which appear most likely to enter clinical practice in the next few years. In phase 2 and 3 trials of up to 40 weeks' duration the GLP-1/GIP dual agonist tirzepatide has demonstrated striking glucose-lowering and weight-loss effects in patients with type 2 diabetes, most of whom are overweight or obese. Tirzepatide appears to cause gastrointestinal side effects in a similar proportion of patients to GLP-1 receptor agonists, and gradual dose titration is required to maximise tolerability. The cardiovascular effects of tirzepatide are being compared with those of dulaglutide in a trial of 12,500 participants expected to complete in 2024. If tirzepatide is associated with similar reduction in cardiovascular events to dulaglutide, tirzepatide may replace GLP-1 receptor agonists as the preferred first-line incretin system agonist.

Drugs with agonist activity at the glucagon receptor appear most promising as future therapeutic options for patients with NASH, many of whom are obese and have type 2 diabetes. Cotadutide (a GLP-1/glucagon dual agonist) was associated with reductions in liver enzymes, liver fat content and a biomarker of liver fibrosis in a 54 week phase 2b trial. Future trials of cotadutide, in addition to efinopegdutide (another GLP-1/glucagon dual agonist) and LAPS triple agonist (a GLP-1/GIP/glucagon triple agonist) will focus on this potential therapeutic avenue.

Imeglimin has a unique mechanism of action with evidence of effects in the pancreatic islet cells, liver and skeletal muscle in preclinical studies. Phase 3 studies in Japan have shown that imeglimin has modest glycaemic efficacy when used as monotherapy, or in addition to oral antidiabetic drugs or insulin. It is generally well tolerated with low risk of hypoglycaemia and was approved for use in Japan in 2021. The results of future trials examining the efficacy of imeglimin in patients with chronic kidney disease and the cardiovascular safety of this drug will be crucial to inform the progression of this drug into routine clinical practice in Europe and the US.

References

1. Holst, J.J., Knop, F.K., Vilsboll, T., Krarup, T., and Madsbad, S. (2011). Loss of incretin effect is a specific, important, and early characteristic of type 2 diabetes. *Diabetes Care* 34 (Supplement 2): S251–7.
2. Nauck, M.A., Bartels, E., Orskov, C., Ebert, R., and Creutzfeldt, W. (1993). Additive insulinotropic effects of exogenous synthetic human gastric inhibitory polypeptide and glucagon-like peptide-1-(7-36) amide infused at near-physiological insulinotropic hormone and glucose concentrations. *J Clin Endocrinol Metab* 76: 912–917.
3. Højberg, P.V., Vilsbøll, T., Rabøl, R. et al. (2009). Four weeks of near-normalisation of blood glucose improves the insulin response to glucagon-like peptide-1 and glucose-dependent insulinotropic polypeptide in patients with type 2 diabetes. *Diabetologia* 52: 199–207.

4. Piteau, S., Olver, A., Kim, S.-J. et al. (2007). Reversal of islet GIP receptor down-regulation and resistance to GIP by reducing hyperglycemia in the Zucker rat. *Biochem Biophys Res Commun* 362: 1007–1012.
5. Knop, F.K., Vilsbøll, T., Højberg, P.V. et al. (2007). Reduced incretin effect in type 2 diabetes. *Diabetes* 56: 1951–1959.
6. Coskun, T., Sloop, K.W., Loghin, C. et al. (2018). LY3298176, a novel dual GIP and GLP-1 receptor agonist for the treatment of type 2 diabetes mellitus: from discovery to clinical proof of concept. *Mol Metab* 18: 3–14.
7. Frias, J.P., Nauck, M.A., Van, J. et al. (2018). Efficacy and safety of LY3298176, a novel dual GIP and GLP-1 receptor agonist, in patients with type 2 diabetes: a randomised, placebo-controlled and active comparator-controlled phase 2 trial. *Lancet* 392: 2180–2193.
8. Rosenstock, J., Wysham, C., Frias, J.P. et al. (2021). Efficacy and safety of a novel dual GIP and GLP-1 receptor agonist tirzepatide in patients with type 2 diabetes (SURPASS-1): a double-blind, randomised, phase 3 trial. *Lancet* 398: 143–155.
9. Frias, J.P., Davies, M.J., Rosenstock, J. et al. (2021). Tirzepatide versus semaglutide once weekly in patients with type 2 diabetes. *N Engl J Med* 385: 503–515.
10. Frias, J.P., Bastyr, E.J., Vignati, L. et al. (2017). The sustained effects of a dual GIP/GLP-1 receptor agonist, NNC0090-2746, in patients with type 2 diabetes. *Cell Metab* 26: 343–352.
11. Henderson, S.J., Konkar, A., Hornigold, D.C. et al. (2016). Robust anti-obesity and metabolic effects of a dual GLP-1/glucagon receptor peptide agonist in rodents and non-human primates. *Diabetes Obes Metab* 18: 1176–1190.
12. Parker, V.E.R., Robertson, D., Wang, T. et al. (2020). Efficacy, safety, and mechanistic insights of cotadutide, a dual receptor Glucagon-Like Peptide-1 and glucagon agonist. *J Clin Endocrinol Metab* 105: 803–820.
13. Ambery, P., Parker, V.E., Stumvoll, M. et al. (2018). MEDI0382, a GLP-1 and glucagon receptor dual agonist, in obese or overweight patients with type 2 diabetes: a randomised, controlled, double-blind, ascending dose and phase 2a study. *Lancet* 391: 2607–2618.
14. Nahra, R., Wang, T., Gadde, K.M. et al. (2021). Effects of cotadutide on metabolic and hepatic parameters in adults with overweight or obesity and type 2 diabetes: a 54-week randomized Phase 2b study. *Diabetes Care* 44: 1433–1442.
15. Tillner, J., Posch, M.G., Wagner, F. et al. (2019). A novel dual glucagon-like peptide and glucagon receptor agonist SAR425899: results of randomized, placebo-controlled first-in-human and first-in-patient trials. *Diabetes Obes Metab* 21: 120–128.
16. A study to assess the safety and efficacy of SAR425899 in patients with type 2 diabetes mellitus. https://clinicaltrials.gov/ct2/show/NCT02973321 (accessed 1 February 2021).
17. GI toxicity hits midstage Sanofi GLP-1 drug as patients drop out. FierceBiotech. https://www.fiercebiotech.com/biotech/gi-toxicity-hits-midstage-poc-sanofi-glp-1-drug-as-patients-drop-out (accessed 1 February 2021).
18. Eriksson, O., Haack, T., Hijazi, Y. et al. (2020). Receptor occupancy of dual glucagon-like peptide 1/glucagon receptor agonist SAR425899 in individuals with type 2 diabetes. *Sci Rep* 10: 16758.
19. Petit, J.-M., Cercueil, J.-P., Loffroy, R. et al. (2017). Effect of liraglutide therapy on liver fat content in patients with inadequately controlled type 2 diabetes. The Lira-NAFLD study. *J Clin Endocrinol Metab* 102: 407–415.
20. Finan, B., Yang, B., Ottaway, N. et al. (2015). A rationally designed monomeric peptide triagonist corrects obesity and diabetes in rodents. *Nat Med* 21: 27–36.
21. Choi, J.D., Baek, S., Kim, Y. et al. (2019). 982-P: a double-blinded, placebo controlled, single ascending dose study for safety, tolerability, pharmacokinetics, and pharmacodynamics after subcutaneous administration of novel long-acting GLP-1/GIP/Glucagon Triple Agonist (HM15211) in healthy obese subjects. *Diabetes* 68 (Supplement 1): 982–P.

22. Yaribeygi, H., Maleki, M., Sathyapalan, T., Jamialahmadi, T., and Sahebkar, A. (2020). Molecular mechanisms by which imeglimin improves glucose homeostasis. *J Diabetes Res* 2020: 1–5.
23. Pinti, M.V, Fink, G.K., Hathaway, Q.A., Durr, A.J., Kunovac, A., and Hollander, J.M. (2019). Mitochondrial dysfunction in type 2 diabetes mellitus: an organ-based analysis. *Am J Physiol Metab* 316: E268–85.
24. Vial, G., Chauvin, M.-A., Bendridi, N. et al. (2015). Imeglimin normalizes glucose tolerance and insulin sensitivity and improves mitochondrial function in liver of a high-fat, high-sucrose diet mice model. *Diabetes* 64: 2254–2264.
25. Fouqueray, P., Leverve, X., Fontaine, E., Baquié, M., and Wollheim, C. (2011). Imeglimin – a new oral anti-diabetic that targets the three key defects of type 2 diabetes. *J Diabetes Metab* 2 (4); doi:10.4172/2155-6156.1000126.
26. Detaille, D., Vial, G., Borel, A.-L. et al. (2016). Imeglimin prevents human endothelial cell death by inhibiting mitochondrial permeability transition without inhibiting mitochondrial respiration. *Cell Death Discov* 2: 15072.
27. Lachaux, M., Souille, M., Remy-Jouet, I. et al. (2018). Acute imeglimin treatment improves metabolic syndrome-related cardiac and coronary endothelial dysfunction in the zucker fa/fa rat. *Eur Heart J* 39 (suppl_1).
28. Pirags, V., Lebovitz, H., and Fouqueray, P. (2012). Imeglimin, a novel glimin oral antidiabetic, exhibits a good efficacy and safety profile in type 2 diabetic patients. *Diabetes Obes Metab* 14: 852–858.
29. Fouqueray, P., Bolze, S., Pirags, V. et al. (2015). Dose-ranging study to determine the optimum dose for imeglimin, a novel treatment for type 2 diabetes. *Diabetes* 64: abstract 3016464.
30. Dubourg, J., Ueki, K., Grouin, J.-M., and Fouqueray, P. (2021). Efficacy and safety of imeglimin in Japanese patients with type 2 diabetes: a 24-week, randomized, double-blind, placebo-controlled, dose ranging phase 2b trial. *Diabetes Obes Metab* 23: 800–810.
31. Fouqueray, P., Pirags, V., Inzucchi, S.E. et al. (2013). The efficacy and safety of imeglimin as add-on therapy in patients with type 2 diabetes inadequately controlled with metformin monotherapy. *Diabetes Care* 36: 565–568.
32. Fouqueray, P., Pirags, V., Diamant, M. et al. (2014). The efficacy and safety of imeglimin as add-on therapy in patients with type 2 diabetes inadequately controlled with sitagliptin monotherapy. *Diabetes Care* 37: 1924–1930.
33. Crabtree, T.S., DeFronzo, R.A., Ryder, R.E.J., and Bailey, C.J. (2020). Imeglimin, a novel, first in-class, blood glucose-lowering agent: a systematic review and meta-analysis of clinical evidence. *Br J Diabetes* 20: 28–31.
34. Dubourg, J., Fouqueray, P., Thang, C., Groulin, J.-M., and Ueki, K. (2021). Efficacy and safety of imeglimin monotherapy versus placebo in Japanese patients with type 2 diabetes (TIMES 1): a double-blind, randomized, placebo-controlled, parallel-group, multicenter phase 3 trial. *Diabetes Care* 44: 952–959.
35. Kaku, K., Dubourg, J., Thang, C., Kaneko, T., and Fouqueray, P. (2020). Long-term treatment with imeglimin as add-on to oral antidiabetes therapy in Japanese patients with type 2 diabetes mellitus (TIMES 2). http://www.interscience.wiley.com/jpages/1462-8902%5Cnhttp://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=emed18&NEWS=N&AN=603864026 (accessed 26 September 2021).
36. Dubourg, J., Watada, H., Thang, C., Kaneko, T., and Fouqueray, P. (2020). Efficacy and safety of imeglimin in combination with insulin in Japanese patients with type 2 diabetes: results of TIMES 3 trial. *Diabetologia* (Supplement 1): P637.

CHAPTER 15

Guidelines on Antidiabetic Drugs

Miles Fisher and Russell Drummond

KEY POINTS

- Many national and international guidelines contain detailed recommendations on the use of newer antidiabetic drugs in people with type 2 diabetes.
- At a UK level, the SIGN guidelines on the pharmacological management of glycaemic control in people with type 2 diabetes were updated in 2017 to reflect the results of CVOTs.
- NICE guidelines on the management of type 2 diabetes in adults from 2015 were finally updated in 2022, and endorse the wider use of SGLT2 inhibitors.
- The ADA/EASD consensus report on the management of hyperglycaemia in type 2 diabetes and the European Society of Cardiology guideline on diabetes, prediabetes and cardiovascular diseases have several similarities with regards to the positioning of specific antidiabetic drugs but also some important differences.
- Guidelines on the management of type 1 diabetes from NICE and SIGN endorse the use of short- and long-acting insulin analogues, whereas for people with type 2 diabetes isophane is recommended as the insulin of choice.
- The World Health Organization and International Diabetes Federation have developed international guidelines for the management of diabetes which focus on the cost and availability of antidiabetic drugs, especially insulin.
- Guidelines on pregnancy and diabetes make recommendations on the use and safety of individual insulins and oral antidiabetic drugs.

Diabetes Drug Notes, First Edition. Edited by Miles Fisher, Gerard A. McKay, and Andrea Llano.

Introduction

Evidence-based Guidelines

Clinical practice guidelines in diabetes are systematically developed, evidence-based statements whose role is to assist practitioners and patients in making and understanding care decisions about diabetes. There are internationally recognised standards for developing, maintaining and updating guidelines. The evidence base should be obtained using an unbiased and transparent process that systematically reviews and appraises published clinical research. Following appraisal, the evidence is synthesised into recommendations for clinical practice. The type of evidence used depends on the type of review question, and ranges from meta-analysis or systematic review of randomised controlled trials, through observational data from case-controlled or cohort studies, to expert opinion.

Guidelines for the management of type 2 and type 1 diabetes, and diabetes in pregnancy, exist at international, national and local levels, and contain detailed recommendations on the use of antidiabetic drugs.

Consensus Reports

Evidence-based guidelines on diabetes have replaced consensus reports in many parts of the world. In the US few diabetes organisations follow this internationally standardised guideline methodology and recommendations on diabetes care are more often based on consensus statements and reports. This typically involves a group of experts meeting and producing a series of recommendations based on the consensus of the group and their knowledge of the literature at that time. Consensus reports can be more prone to bias depending on the opinions and character of those involved in the reports and are more often based on a limited literature review which may miss publications that would be identified in a systematic review, particularly if the results are negative.

Common Approaches and HbA1c Targets

Guidelines that have been developed by diabetes organisations and associations on the use of antidiabetic drugs in people with type 1 and type 2 diabetes have the goal of managing hyperglycaemia with the aim of reducing the microvascular and macrovascular complications of diabetes.

Guidelines for the management of hyperglycaemia in type 2 diabetes have several similarities of approach. Firstly, an HbA1c target is agreed with the patient. Most guidelines have a common HbA1c target for most patients, with higher or lower targets for specific patient groups. For patients with type 2 diabetes the targets are based on extrapolation from the results of the UKPDS, ADVANCE, ACCORD (Action to Control Cardiovascular Risk in Diabetes) and VADT (Veterans Affairs Diabetes Trial) trials (see Chapter 16, Tables 16.7 and 16.8). Box 15.1 gives examples of HbA1c targets for people with type 2 diabetes from some commonly used guidelines [1–4].

Box 15.1 Recommendations on HbA1c targets for type 2 diabetes from selected guidelines

National Institute for Health and Care Excellence (NICE) 2015 [1]

- Aim for an HbA1c level of 48 mmol/mol (6.5%) on lifestyle interventions, and with a single drug not associated with hypoglycaemia.
- For adults on a drug associated with hypoglycaemia, aim for a target HbA1c level of 53 mmol/mol (7.0%).
- Intensify drug treatment if HbA1c levels are not adequately controlled by a single drug and rise to 58 mmol/mol (7.5%) or higher.

Scottish Intercollegiate Guideline Network (SIGN) 2017 [2]

- An HbA1c target of 7.0% (53 mmol/mol) is reasonable to reduce the risk of microvascular and macrovascular disease.
- A target of 6.5% (48 mmol/mol) is reasonable at diagnosis.
- Targets should be set with individuals to balance benefits with harms, in particular hypoglycaemia and weight gain.

Irish College of General Practitioners (ICGP) 2019 [3]

- The target Hba1c for the majority of patients with type 2 diabetes should be ≤53mmol/mol (≤7.0%).
- More stringent goals such as <48 mmol/mol may be considered for selected patients if this can be achieved without significant hypoglycaemia or other adverse effects of treatment.
- Consider relaxing the HbA1c target such as <58 mmol/mol (<8.0%) on a case-by-case basis, with particular consideration for people who are older or frail.

International Diabetes Federation (IDF) 2017 [4]

- General targets for glucose control should be less than 7.0% (53 mmol/mol).
- Lower targets are desirable as long as hypoglycaemia and weight gain can be avoided using appropriate treatments.
- Values of HbA1c above 8.0% (64 mmol/mol) are generally unacceptable.

Source: Based on [1–4].

The general approach at the time of diagnosis of type 2 diabetes is either a period of initial lifestyle change followed by metformin monotherapy or a combination of lifestyle change plus metformin from the start. Some guidelines now suggest a possible combination of metformin plus a SGLT2 inhibitor regardless of the HbA1c level for patients with cardiovascular or renal disease, and many suggest consideration of insulin for patients who are very symptomatic and losing weight. Thereafter, if HbA1c targets are not reached after three to six months of monotherapy then a stepwise approach is adopted and dual therapy is recommended, with a similar stepwise approach after a further three to six months when triple therapy is recommended, and this may include injected treatment with a GLP-1 receptor agonist or insulin.

Common themes throughout national and international guidelines for type 1 diabetes are recommendations to provide evidence-based, practical advice to maximise quality of life and minimise the short- and long-term risks both of the disease but

also of the treatment. Whilst life expectancy in people with type 1 diabetes is increasing, it remains lower than for people without diabetes, and despite improvements in insulin pharmacology, delivery device and glucose monitoring (see Chapters 8–10), the majority of people with type 1 diabetes have HbA1c targets that are above agreed target levels, and rates of diabetic ketoacidosis remain unacceptable. For patients with type 1 diabetes the HbA1c targets are based on extrapolation from the DCCT/EDIC trial (see Chapter 7). Box 15.2 describes HbA1c targets for people with type 1 diabetes [5–8].

Box 15.2 Recommendations on HbA1c targets for type 1 diabetes from selected guidelines and the ADA standards of care

NICE 2015 [5]

- Support adults with type 1 diabetes to aim for a target HbA1c level of 48 mmol/mol (6.5%) or lower, to minimise the risk of long-term vascular complications.
- Agree an individualised HbA1c target with each adult with type 1 diabetes, taking into account factors such as the person's daily activities, aspirations, likelihood of complications, comorbidities, occupation and history of hypoglycaemia.

SIGN 2010 [6]

- Targets recommended by different authorities vary between 6.5 and 7.5% (48 and 58 mmol/mol).
- Targets can also vary within an individual even over a very short period of time depending on a variety of clinical and nonclinical circumstances.
- The guideline development group concluded that identifying a single target for all people with type 1 diabetes was not appropriate, but that patients should discuss this with their healthcare professionals, in the knowledge that the overall aim is to achieve the lowest HbA1c as possible which does not interfere with the patient's quality of life.

American Diabetes Association (ADA) Standards of Medical Care in Diabetes 2022 [7]

- An HbA1c goal for many nonpregnant adults of <7% (53 mmol/mol) without significant hypoglycaemia is appropriate.
- On the basis of provider judgment and patient preference, achievement of lower HbA1c levels than the goal of 7% may be acceptable, and even beneficial, if they can be achieved safely without significant hypoglycaemia or other adverse effects of treatment.
- Less stringent A1C goals, such as <8% (64 mmol/mol), may be appropriate for patients with limited life expectancy, or where the harms of treatment are greater than the benefits.

IDF 2017 [8]

- For diabetes in childhood and adolescence in under-resourced countries the target for all age groups is a value less than 7.5% (58 mmol/mol).

Source: Based on [5–8].

Guidelines on the Use of Antidiabetic Drugs in Type 2 Diabetes

NICE

The role of NICE is to improve outcomes for people using the NHS and other public health and social services, for use in England, Wales and Northern Ireland. A key component of this is the production of evidence-based guidance and advice for health, public health and social care practitioners. NICE guidelines on type 1 diabetes [5], type 2 diabetes [1] and diabetes in pregnancy [9] were last produced in 2015, with partial updates of the type 1 diabetes and type 2 diabetes guidelines in 2022.

The recommendations contained in NICE guideline on the management of type 2 diabetes now include evidence from cardiovascular outcome trials (CVOTs). The approach recommended by NICE is initial therapy with metformin monotherapy, with the addition of a SGLT2 inhibitor as soon as metformin tolerability is confirmed for those with chronic heart failure, established atherosclerotic cardiovascular disease, chronic kidney disease, or those at high risk of cardiovascular disease (CVD). If metformin is contraindicated it recommends SGLT2 inhibitor alone for these patients, and a DPP-4 inhibitor, pioglitazone, sulfonylurea or SGLT2 inhibitor for those not at high CVD risk (Table 15.1).

TABLE 15.1 **NICE [1], SIGN [2], ICGP [3], IDF [4] and WHO [21] guidelines on the management of type 2 diabetes compared**

	NICE 2015	SIGN 2017	ICGP	IDF
HbA1c target	HbA1c <58 mmol/mol (7.5%)	HbA1c <53 mmol/mol (7.0%) (key recommendation)	HbA1c <58 mmol/ml (7.0%)	HbA1c <58 mmol/ml (7.0%)
First line	Metformin, metformin plus SGLT2 inhibitor if HF, ASCVD, CKD, or high CVD risk	Metformin (key recommendation)	Metformin	Metformin
Second line	Metformin plus DPP-4i, pioglitazone, SU, or SGLT2i dual therapy	Metformin plus SU, SGLT2i, DPP-4i, or pioglitazone dual therapy	SGLT2i or GLP-1 RA	Metformin plus SU, DPP-4i, or SGLT2i alpha glucosidase inhibitor can be used as well
Third line	Metformin plus DPP-4i plus SU triple therapy Metformin plus pioglitazone plus SU triple therapy Insulin	Metformin, SU, SGLT2i, DPP-4i, pioglitazone triple therapy GLP-1 RA triple therapy Basal insulin triple therapy	Other class above, consider referral to secondary care	Insulin Triple therapy with three oral glucose-lowering drugs GLP-1 RA

(*Continued*)

TABLE 15.1 (*Continued*)

	NICE 2015	SIGN 2017	ICGP	IDF
Fourth line	Metformin, SU plus GLP-1 RA triple therapy	Additional agent from third-line options	Seek expert opinion	NA
DPP-4 inhibitors	Dual therapy, triple therapy with metformin	Second, third, fourth line	Refer to ADA/EASD consensus report	Second, third line
SGLT2 inhibitors	First line with metformin, dual therapy, triple therapy with metformin	Second, third, fourth line Consider in people with established CVD (key recommendation)	Second, third line	Second, third line Established CVD may be taken into consideration
GLP-1 receptor agonists	Combination therapy with metformin and SU if triple oral therapy not effective	Third, fourth line Consider in people with established CVD (key recommendation)	Second, third line	Dual therapy if weight loss is a priority and the drug is affordable Triple therapy as an alternative to insulin if weight loss has been insufficient Established CVD may be taken into consideration
Blood glucose monitoring	'do not routinely offer ... unless the person is on insulin ...'	Recommended in older guideline for patients using insulin Not recommended for people using oral glucose-lowering drugs with the exception of SUs	Routine self-monitoring of blood glucose in people with uncomplicated type 2 diabetes using oral hypoglycaemic agents is not recommended	Mandatory for patients using insulin

ADA = American Diabetes Association, CVD = cardiovascular disease, DPP-4i = DPP-4 inhibitor, EASD = European Association for the Study of Diabetes, GLP-1 RA = GLP-1 receptor agonist, SU = sulfonylurea

This is followed by first intensification to dual therapy with metformin plus a DPP-4 inhibitor, pioglitazone, or a sulfonylurea, with the comment that treatment with combinations of medications including SGLT2 inhibitor may be appropriate for some people with type 2 diabetes. At the point of second intensification triple

therapy with metformin, a DPP-4 inhibitor and a sulfonylurea or triple therapy with metformin, pioglitazone and a sulfonylurea are recommended, as is starting insulin-based therapy. A combination of triple therapy with metformin, sulfonylurea and a GLP-1 receptor agonist may be considered if triple therapy with oral drugs is not effective, not tolerated, or contraindicated and the patient satisfies certain obesity related criteria.

SIGN

The objective of the SIGN is to improve the quality of healthcare for patients in Scotland by reducing variation in practice and outcome, through the development and dissemination of national clinical guidelines containing recommendations for effective practice based on current evidence.

SIGN produced updated guidance on the pharmacological management of glycaemic control in people with type 2 diabetes in 2017 [2]. This included evidence from the CVOTs that had been completed at that time. As the CVOTs that had been completed had included predominantly people with established atherosclerotic cardiovascular disease, the key recommendations on the specific use of SGLT2 inhibitors and GLP-1 receptor agonists focused on these patients rather than patients with increased cardiovascular risk without established cardiovascular disease.

Four key recommendations were highlighted by SIGN (Box 15.1, Table 15.1):

1. An HbA1c target of 7.0% (53 mmol/mol) among people with type 2 diabetes is reasonable to reduce the risk of microvascular and macrovascular disease. A target of 6.5% (48 mmol/mol) may be appropriate at diagnosis. Targets should be set with individuals in order to balance benefits with harms, in particular hypoglycaemia and weight gain.
2. Metformin should be considered as the first-line oral treatment option for people with type 2 diabetes.
3. In individuals with type 2 diabetes and established cardiovascular disease, SGLT2 inhibitors with proven cardiovascular benefit should be considered.
4. For individuals with type 2 diabetes and established cardiovascular disease, GLP-1 receptor agonist therapies with proven cardiovascular benefit should be considered.

The SIGN guideline contains detailed recommendations for the commonly used oral and injected antidiabetic drugs in type 2 diabetes (Box 15.3) and are combined in an algorithm which summarises evidence from the guideline in the context of the clinical experience of the guideline group.

ICGP

In Ireland guidelines on the diagnosis and management of uncomplicated type 2 diabetes in adults have been produced by the ICGP (Irish College of General Practice). The guidelines were updated in 2019 as a succinct practical guide for Irish

Box 15.3 SIGN recommendations on specific antidiabetic drugs and drug classes. Amended from SIGN 154 on the pharmacological management of glycaemia control in people with type 2 diabetes

Metformin

- Metformin should be considered as the first-line oral treatment option for people with type 2 diabetes.

Sulfonylureas

- Sulfonylureas should be considered as first-line oral agents in people who are intolerant of or have contraindications to metformin.
- Sulfonylureas should be considered as add-on second-line treatment to other oral therapies and may be useful in triple oral therapy.

Pioglitazone

- Pioglitazone should be considered, usually as dual or triple therapy, for lowering HbA1c.
- Pioglitazone should not be used in patients with heart failure.
- The risk of fracture should be considered during long-term use of pioglitazone.

DPP-4 inhibitors

- DPP-4 inhibitors should be considered, usually as dual or triple therapy, for lowering HbA1c.

SGLT2 inhibitor

- SGLT2 inhibitors should be considered as an add-on therapy to metformin in people with type 2 diabetes.
- In individuals with type 2 diabetes and established cardiovascular disease, SGLT2 inhibitors with proven cardiovascular benefit should be considered.

GLP-1 receptor agonists

- GLP-1 receptor agonist therapy should be considered in people with a body mass index of ≥30 kg/m^2 (or ethnicity-adjusted equivalent) in combination with oral glucose-lowering drugs or basal insulin (or both) as third- or fourth-line treatment, when adequate glycaemic control has not been achieved with these drugs.
- GLP-1 receptor agonist therapy should be considered as an alternative to insulin in people for whom treatment with combinations of oral glucose-lowering drugs has been inadequate.
- For individuals with type 2 diabetes and established cardiovascular disease, GLP-1 receptor agonist therapies with proven cardiovascular benefit should be considered.

Insulin

- Oral metformin therapy should be continued when insulin therapy is initiated to maintain or improve glycaemic control.
- Once daily bedtime NPH insulin should be used when adding insulin to metformin. Basal insulin analogues should be considered according to hypoglycaemia risk, for example in those who suffer from recurrent episodes of hypoglycaemia or require assistance with insulin injections.
- When commencing insulin therapy, bedtime basal insulin should be initiated and the dose titrated against morning (fasting) glucose. If the HbA1c level does not reach target then addition of prandial insulin should be considered.
- Soluble human insulin or rapid-acting insulin analogues can be used when intensifying insulin regimens to improve or maintain glycaemic control.

Source: From [2]/SIGN.

general practice [3]. This includes a concise section on manging glycaemia in people with uncomplicated type 2 diabetes and endorses the use of newer antidiabetic drugs. It recommends metformin first line 'for everyone', an SGLT2 inhibitor or GLP-1 receptor agonist second line, and third line the other class of SGLT2 inhibitor or GLP-1 receptor agonist or a DPP-4 inhibitor and consideration of referral to secondary care (Table 15.1).

EASD and ADA Consensus Reports

The aims of the European Association for the Study of Diabetes (EASD) are to encourage and support research in the field of diabetes, the rapid diffusion of acquired knowledge and facilitation of its application. The EASD has worked jointly with other specialty associations in the US and Europe to produce guidelines and consensus reports, and these contain detailed recommendations on the use of antidiabetic drugs. Two of these have been widely discussed and have the potential to make significant changes to the way that newer antidiabetic drugs are used.

Since 2009 the ADA and the EASD have produced a series of consensus reports on the management of hyperglycaemia in type 2 diabetes. A consensus report contains a comprehensive examination of the literature, is authored by an expert panel and represents the panel's collective analysis, evaluation and opinion. The joint ADA/EASD consensus report on the management of type 2 diabetes was comprehensively revised in 2018 to reflect the results of the cardiovascular outcome trials in diabetes [10], with a further smaller update in 2019 [11]. It is important to note that consensus reports do not follow the detailed methodology to produce guidelines and are potentially more prone to bias depending on opinions of those involved in the process. The expert panel

was composed of diabetologists and lacked representation from cardiologists, nephrologists, primary care or people with diabetes.

Key features of the recommendations on antidiabetic drugs from the ADA/EASD consensus report are detailed in Box 15.4. The 2018 report has a traditional approach with metformin monotherapy as the preferred initial treatment for most people. Thereafter, if the patient is not at HbA1c target, dual or triple therapy is chosen based on whether the patient has:

- atherosclerotic cardiovascular disease, heart failure or chronic kidney disease;
- a compelling need to minimise hypoglycaemia;
- a compelling need to minimise weight gain or promote weight loss; or
- cost is a major issue.

Box 15.4 Consensus recommendations on antidiabetic drugs from the 2018 ADA/EASD consensus report

- Facilitating medication adherence should be specifically considered when selecting glucose-lowering medications.
- Among patients with type 2 diabetes who have established atherosclerotic cardiovascular disease (ASCVD), SGLT2 inhibitors or GLP-1 receptor agonists with proven cardiovascular benefit are recommended as part of glycaemic management.
- Among patients with ASCVD in whom heart failure coexists or is of special concern, SGLT2 inhibitors are recommended.
- For patients with type 2 diabetes and CKD, with or without CVD, consider the use of an SGLT2 inhibitor shown to reduce CKD progression or, if contraindicated or not preferred, a GLP-1 receptor agonist shown to reduce CKD progression.
- Metformin is the preferred initial glucose-lowering medication for most people with type 2 diabetes.
- The stepwise addition of glucose-lowering medication is generally preferred to initial combination therapy.
- The selection of medication added to metformin is based on patient preference and clinical characteristics. Important clinical characteristics include the presence of established ASCVD and other comorbidities such as heart failure or CKD and the risk for specific adverse medication effects, particularly hypoglycaemia and weight gain, as well as safety, tolerability and cost.
- Intensification of treatment beyond dual therapy to maintain glycaemic targets requires consideration of the impact of medication side effects on comorbidities, as well as the burden of treatment and cost.

- In patients who need the greater glucose-lowering effect of an injectable medication, GLP-1 receptor agonists are the preferred choice to insulin. For patients with extreme and symptomatic hyperglycaemia, insulin is recommended
- Patients who are unable to maintain glycaemic targets on basal insulin in combination with oral medications can have treatment intensified with GLP-1 receptor agonists, SGLT2 inhibitors or prandial insulin.
- Access, treatment cost and insurance coverage should all be considered when selecting glucose-lowering medications.

Source: From [10]/Springer Nature.

The 2019 consensus report was updated to reflect the results from further cardiovascular and renal outcome trials [11]. Two important changes from the 2018 report are in the general recommendations, where initial combination therapy can be considered in new-onset diabetes, and treatment with a GLP-1 receptor agonist or SGLT2 inhibitor can be considered independently of HbA1c levels in appropriate high-risk individuals with established type 2 diabetes to reduce cardiovascular or renal events (Box 15.5).

Box 15.5 Changes to consensus recommendations on antidiabetic drugs from the 2019 ADA/EASD consensus report

General considerations

- In appropriate high-risk individuals with established type 2 diabetes, the decision to treat with a GLP-1 receptor agonist or SGLT2 inhibitor to reduce MACE, hospitalisation for heart failure, CV death or CKD progression should be considered independently of baseline HbA1c or individualised HbA1c target.
- Providers should engage in shared decision-making around initial combination therapy in new-onset cases of type 2 diabetes.

GLP-1 receptor agonist recommendations

- For patients with type 2 diabetes and established atherosclerotic CV disease (such as those with prior myocardial infarction, ischaemic stroke, unstable angina with ECG changes, myocardial ischaemia on imaging or stress test, or revascularisation of coronary, carotid or peripheral arteries), where MACE is the gravest threat, the level of evidence for MACE benefit is greatest for GLP-1 receptor agonists.
- To reduce risk of MACE, GLP-1 receptor agonists can also be considered in patients with type 2 diabetes without established cardiovascular disease (CVD) with indicators of high risk, specifically, patients aged 55 years or older with coronary, carotid or lower extremity artery stenosis >50%, left ventricular hypertrophy, eGFR <60 ml/min/1.73 m^2 or albuminuria.

SGLT2 inhibitor recommendations

- For patients with or without established atherosclerotic CVD, but with heart failure with reduced ejection fraction (ejection fraction <45%) or CKD (eGFR 30 to ≤60 ml/min/1.73 m^2 or UACR >30 mg/g, particularly UACR >300 mg/g), the level of evidence for benefit is greatest for SGLT2 inhibitors.
- SGLT2 inhibitors are recommended in patients with type 2 diabetes and heart failure, particularly those with heart failure with reduced ejection fraction, to reduce HFH, MACE and CV death.
- SGLT2 inhibitors are recommended to prevent the progression of CKD, HFH, MACE and CV death in patients with type 2 diabetes with CKD.
- Patients with foot ulcers or at high risk for amputation should only be treated with SGLT2 inhibitors after careful shared decision-making around risks and benefits with comprehensive education on foot care and amputation prevention.

Source: From [11]/American Diabetes Association.

ESC

Between the publication of the 2018 and 2019 ADA/EASD consensus reports the ESC (European Society of Cardiology) published comprehensive evidence-based guidelines on diabetes, prediabetes and cardiovascular disease which were developed in collaboration with the EASD [12]. These covered multiple aspects of cardiovascular care including cardiovascular risk assessment, blood pressure, lipids, management of coronary artery disease, heart failure, arrhythmias, peripheral arterial disease and chronic kidney disease. The ESC guideline contains multiple recommendations on antidiabetic drugs that are summarised in Box 15.6. The section on heart failure and diabetes also contains several recommendations on the use of antidiabetic drugs, emphasising the benefits of SGLT2 inhibitors in reducing hospitalisation for heart failure (Box 15.7).

The ESC guideline contains some important and controversial differences from the ADA/EASD consensus report. Metformin is changed from first-line therapy for all patients with type 2 diabetes to overweight patients with type 2 diabetes without cardiovascular disease and at moderate cardiovascular risk. For drug-naive patients with atherosclerotic cardiovascular disease (ASCVD) or high/very high cardiovascular risk monotherapy with a SGLT2 inhibitor or GLP-1 receptor agonist is recommended regardless of HbA1c, with the addition of metformin if HbA1c is above target. For patients with ASCVD or high/very high cardiovascular risk on metformin monotherapy the ESC guideline also recommends the addition of an SGLT2 inhibitor or GLP-1 receptor agonist independent of HbA1c.

A similar approach has been recommended in the consensus report of the American College of Clinical Endocrinologists and American College of Endocrinology, which indicates that SGLT2 inhibitor or GLP-1 receptor agonist monotherapy may

Box 15.6 Recommendation on antidiabetic drugs from the 2019 ESC guidelines on diabetes, prediabetes and cardiovascular disease developed in collaboration with the EASD

SGLT2 inhibitors

- Empagliflozin, canagliflozin, or dapagliflozin are recommended in patients with type 2 diabetes and CVD, or at very high/high CV risk, to reduce CV events.
- Empagliflozin is recommended in patients with type 2 diabetes and CVD to reduce the risk of death.

GLP-1 receptor agonists

- Liraglutide, semaglutide, or dulaglutide are recommended in patients with type 2 diabetes and CVD, or at very high/high CV risk to reduce CV events.
- Liraglutide is recommended in patients with type 2 diabetes and CVD, or at very high/high CV risk to reduce the risk of death.

Biguanides

- Metformin should be considered in overweight patients with type 2 diabetes without CVD and at moderate CV risk.

Insulin

- Insulin-based glycaemic control should be considered in patients with acute coronary syndromes with significant hyperglycaemia (>10 mmol/l or >180 mg/dl), with the target adapted according to comorbidities.

Thiazolidinediones

- Thiazolidinediones are not recommended in patients with heart failure.

DPP-4 inhibitors

- Saxagliptin is not recommended in patients with type 2 diabetes and a high risk of heart failure.

Source: From [12]/European Society of Cardiology.

be preferable to metformin in those with ASCVD and/or CKD independent of glycaemic control [13].

The difference between the ESC guideline and the ADA/EASD consensus report narrowed with the 2019 update where GLP-1 receptor agonist and SGLT2 inhibitors can be considered independently of baseline or target HbA1c in appropriate high-risk individuals with established type 2 diabetes (Box 15.5).

Box 15.7 Recommendation on diabetes treatment to reduce heart failure risk adapted from the 2019 ESC guidelines on diabetes, prediabetes and cardiovascular disease developed in collaboration with the EASD

- SGLT2 inhibitors (empagliflozin, canagliflozin, or dapagliflozin) are recommended to lower risk of heart failure hospitalisation.
- Metformin should be considered in patients with diabetes mellitus and heart failure if eGFR >30 ml/min/1.73 m^2.
- GLP-1 receptor agonists and DPP-4 inhibitors sitagliptin and linagliptin have a neutral effect on risk of heart failure and may be considered.
- Insulin treatment in heart failure may be considered.
- DPP-4 inhibitor saxagliptin in heart failure is not recommended.
- Thiazolidinediones (pioglitazone and rosiglitazone) in heart failure are not recommended.

Source: From [12]/European Society of Cardiology.

One explanation for the difference between the ESC guideline and ADA/EASD consensus reports is a gap in the evidence for the treatment of newly diagnosed patients with type 2 diabetes, as these patients and those with established cardiovascular disease were mostly excluded from the UKPDS trial. The cardiovascular outcome trials of SGLT2 inhibitors and GLP-1 receptor agonists included patients with a duration of diabetes of around ten years, many of whom were already on metformin, sulfonylureas or insulin. However, mediation analysis has shown that reductions in cardiovascular events occurred regardless of whether the patient was on metformin or not. Another possible explanation for the difference is that many treatments for cardiological conditions such as coronary heart disease or heart failure are given for prognostic benefits and the measured effects on biomarkers such as blood pressure or lipids are a lesser consideration for cardiologists.

Aware that the difference between the two reports might contribute to confusion and clinical inertia, a subset of the writing groups of the ADA/EASD consensus report and the ESC guidelines was convened as an expert panel [14]. The expert panel emphasised the overall commonalities of approach and the need to ensure that people with type 2 diabetes, cardiovascular disease, heart failure or chronic kidney disease are treated appropriately with an SGLT2 inhibitor or GLP-1 receptor agonist. The panel concluded that this approach should be initiated independently of background therapy, glycaemic control or individualised treatment goals. Hopefully the differences between the two organisations can be resolved in the future.

IDF

The IDF has worked jointly with other organisations to produce guidelines on the management of diabetes people with type 2 diabetes [4], in childhood and adolescence [8], and during Ramadan [15]. The IDF (International Diabetes Federation) clinical

practice recommendations for managing type 2 diabetes in primary care also cover multiple aspects of comprehensive diabetes care, including lifestyle changes, targets for glucose control, initial pharmacological therapy, add-on therapy and the management of cardiovascular risk factors [4]. They recommended that the general target for glucose control is less than 7.0% (53 mmol/mol). Self-monitoring of blood glucose is recommended as mandatory for patients using insulin. A stepwise approach is recommended with metformin followed by sulfonylurea, a DPP-4 inhibitor or SGLT2 inhibitor (Table 15.1).

Guidelines on the Management of Type 1 Diabetes

NICE

The current 'Type 1 diabetes in adults: diagnosis and management' NICE guidelines originate from 2015 and were updated in 2022 [5]. The key priorities for implementation focused on education and blood glucose management, with the recent update focussing on flash and continuous glucose monitoring, which have been described in Chapter 10. All patients should be offered a structured education programme of proven benefit containing carbohydrate counting, ideally between 6 and 12 months after diagnosis. In general, a target HbA1c of 48 mmol/mol (6.5%) or lower is recommended (Box 15.2). Blood glucose targets within the NICE guidelines are 5–7 mmol/l on waking, 4–7 mmol/l prior to other meals and 5–9 mmol/l if measured postprandially (at least 90 minutes after a meal). In the NICE guideline, multiple daily injection basal bolus regimens, rather than twice daily mixed regimens are advocated as the insulin regimen of choice (Box 15.8). Twice daily insulin detemir is recommended as the choice of long-acting insulin, but once daily detemir or insulin glargine is an alternative. With respect to adjunctive therapy, metformin may be considered in some patients as an off-label use in patients with a BMI of 25 kg/m^2 (23 kg/m^2 for people from South Asian and related minority ethnic groups).

In Ireland, the Irish Department of Health national clinical guideline from 2018 on adult type 1 diabetes mellitus guideline derives its recommendations from the NICE guidance from 2015 and contextualises these for Ireland, so it is synchronous with the NICE guidance on education, glycaemic targets, choice of insulin and monitoring recommendations [16].

SIGN

SIGN guidelines for the management for type 1 diabetes (and diabetes in pregnancy) were last published in March of 2010 and clearly require updating [6]. In comparison with the NICE guidelines the SIGN guidelines acknowledge that improved glycaemic

Box 15.8 NICE recommendations on insulin therapy in people with type 1 diabetes

Insulin regimen

- Offer multiple daily injection basal bolus insulin regimens, rather than twice daily mixed insulin regimens, as the insulin injection regimen of choice for all adults with type 1 diabetes. Provide the person with guidance on using multiple daily injection basal bolus insulin regimens.
- Do not offer adults newly diagnosed with type 1 diabetes nonbasal bolus insulin regimens (that is, twice daily mixed, basal only, or bolus only).

Long-acting insulin

- Offer twice daily insulin detemir as basal insulin therapy for adults with type 1 diabetes.
- Consider, as an alternative basal insulin therapy for adults with type 1 diabetes:
- An existing insulin regimen being used by the person who is achieving their agreed targets;
- Once daily insulin glargine or insulin detemir if twice daily basal insulin injection is not acceptable to the person, or once daily insulin glargine if insulin detemir is not tolerated.
- Once daily insulin degludec if there is a particular concern about nocturnal hypoglycaemia.
- Once daily ultra long-acting insulin such as degludec for people who need help from a carer or healthcare professional to administer injections.
- When starting an insulin for which a biosimilar is available, use the product with the lowest acquisition cost.

Rapid-acting insulin

- Offer rapid-acting insulin analogues injected before meals, rather than rapid-acting soluble human or animal insulins, for mealtime insulin replacement for adults with type 1 diabetes.
- Do not advise routine use of rapid-acting insulin analogues after meals for adults with type 1 diabetes.
- If an adult with type 1 diabetes has a strong preference for an alternative mealtime insulin, respect their wishes and offer the preferred insulin.

Mixed insulin

- Consider a twice daily human mixed insulin regimen for adults with type 1 diabetes if a multiple daily injection basal bolus insulin regimen is not possible and a twice daily mixed insulin regimen is chosen.
- Consider a trial of a twice daily analogue mixed insulin regimen if an adult using a twice daily human mixed insulin regimen has hypoglycaemia that affects their quality of life.

Source: From [5]/NICE.

control reduces both microvascular and macrovascular complications, but no evidence was identified on outcomes associated with treatment to specific targets and no single HbA1c target was identified. Nevertheless, the SIGN guideline states that 6.5–7.5% (45–58 mmol/mol) is the target used by other authorities. The consensus was that the individualised HbA1c target was to achieve the lowest HbA1c possible that does not interfere with the patient's quality of life (Box 15.2).

Multiple daily injections, rather than premixed twice daily regimens, are advocated with basal insulin analogues recommended in adults with type 1 diabetes who are experiencing severe or nocturnal hypoglycaemia. Insulin pump therapies are noted to be associated with modest improvements in glycaemic control and should be considered for patients unable to achieve their glycaemic targets or who experience recurring episodes of severe hypoglycaemia. Patients who experience hypoglycaemia or fail to achieve their glycaemic targets should have access to a structured education programme based upon adult-learning theories. With respect to adjunctive therapy, medications other than insulin were deemed to have no role in the management of type 1 diabetes.

ADA

The ADA standards of medical care in diabetes are updated annually. These are intended to provide the components of diabetes care, general treatment goals and recommendations generated by a multidisciplinary expert committee. These standards of care are more up to date with regards to diabetes technology (see Chapter 10). They suggest that an HbA1c goal of less than 7.0% (53 mmol/mol) for many nonpregnant adults without significant hypoglycaemia is appropriate, with a less stringent HbA1c goals such as 8.0% (64 mmol/mol) for patients with limited life expectancy, or where the harms of treatment are greater than the benefits [7]. Multiple daily injections of prandial and basal insulin, or continuous subcutaneous insulin infusion, are recommended for most people with type 1 diabetes. Rapid-acting insulin analogues are recommended in most individuals to reduce the risk of hypoglycaemia, and they recommend that patients should receive education on how to match prandial insulin doses to carbohydrate intake, premeal blood glucose and anticipated physical activity [17].

ADA/ESD Consensus Report on the Management of Type 1 Diabetes in Adults

Following on from the consensus reports on the management of type 2 diabetes, the ADA and EASD have recently produced a consensus report on the management of type 1 diabetes in adults [18]. This extensive report covers many aspects of clinical care including the diagnosis of type 1 diabetes, the aims and goals of management, schedules of care, diabetes self-management education and support, the monitoring of glucose levels and hypoglycaemia. Each section contains a detailed narrative but in contrast to the consensus report on type 2 diabetes, no specific recommendations are detailed in this report.

There is a section on insulin therapy that endorses the use of multiple daily injections with short- and long-acting insulin analogues, or continuous infusion of a rapid-acting insulin analogue via a pump. The report acknowledges that the cost of insulin analogues or pumps is a barrier for some people, so it also describes alternative insulin regimens that might be used but at a cost of higher glucose variability with a higher risk of hypoglycaemia and less flexibility of lifestyle. These include two daily injections with regular human insulin plus isophane insulin, and premixed insulins. This is an example of the bias that can enter into a consensus report and evidence-based guidelines would have sought evidence of the best insulin regimens and synthesised the findings into specific recommendations.

Special Patient Groups

Use of Antidiabetic Drugs in Pregnancy

There are national and international guidelines on the management of pregnancy and diabetes. These are usually comprehensive guidelines and include recommendations on all aspects of management from preconception to the postnatal period. A detailed description of these guidelines is beyond the scope of this book. Most provide recommendations on the use of specific insulins and oral antidiabetic drugs when required in women with existing diabetes or gestational diabetes (Box 15.9). There are minor differences among guidelines and standards of care with respect to both the type of insulin utilised and whether oral antidiabetic drugs may be recommended in pregnancy.

The NICE guideline from 2015 states that the available evidence on rapid-acting insulin analogues does not show an adverse effect on pregnancy or the health of the baby [9]. The SIGN guideline from 2010 similarly recommends that rapid-acting insulin analogues (lispro and aspart) appear safe and should be considered where hypoglycaemia is problematic [19]. Both NICE and SIGN suggest that isophane insulin should be the insulin of choice for long-acting insulin during pregnancy but that long-acting insulin analogues (specifically insulin detemir or insulin glargine) should be considered in women who have established good diabetes control before pregnancy. Current guidelines do not comment on the newer long-acting insulin analogues degludec and U300 glargine.

For oral antidiabetic drugs there are larger differences. For patients with type 2 diabetes SIGN recommends that metformin or sulfonylureas may be continued (Box 15.9) and similar recommendations are contained in the IDF guideline on the management of diabetes in childhood and adolescence in under-resourced countries [8]. SIGN also recommends that metformin or glibenclamide may be considered as initial pharmacological glucose-lowering treatment in women with gestational diabetes. NICE guidelines indicate that metformin (off label) may be utilised during the preconception period and during pregnancy but glibenclamide is no longer suggested as an alternative to insulin as an option for the treatment of gestational diabetes. The

Box 15.9 Recommendations on the use of antidiabetic drugs from pregnancy guidelines

NICE 2015 [9]

Safety of medicines before and during pregnancy

- Women with diabetes may be advised to use metformin as an adjunct or alternative to insulin in the preconception period and during pregnancy, when the likely benefits from improved blood glucose control outweigh the potential for harm. Stop all other oral blood glucose-lowering agents before pregnancy and use insulin instead.
- Be aware that the available evidence on rapid-acting insulin analogues (aspart and lispro) does not show an adverse effect on the pregnancy or the health of baby.
- Use isophane insulin (also known as NPH insulin) as the first choice for long-acting insulin during pregnancy. Consider continuing treatment with long-acting insulin analogues (insulin detemir or insulin glargine) for women with diabetes who have established good blood glucose control before pregnancy.

Gestational diabetes

- If blood glucose targets are not met with diet and exercise changes within one to two weeks, offer metformin.
- If metformin is contraindicated or unacceptable to the woman, offer insulin.
- If blood glucose targets are not met with diet and exercise changes plus metformin, offer insulin as well.

SIGN 2010 [19]

- Women with diabetes initially treated in early pregnancy with metformin or sulfonylureas should be advised that these medications do not appear to carry additional risk of teratogenesis or early pregnancy loss.
- Rapid-acting insulin analogues (lispro and aspart) appear safe in pregnancy and may be considered in individual patients where hypoglycaemia is problematic.
- Metformin or glibenclamide may be considered as initial pharmacological, glucose-lowering treatment in women with gestational diabetes.

American Diabetes Association [20]

Management of preexisting type 1 diabetes and type 2 diabetes in pregnancy

- Insulin should be used for the management of type 1 diabetes in pregnancy. Insulin is the preferred agent for the management of type 2 diabetes in pregnancy.
- Either multiple daily injections or insulin pump technology can be used in pregnancy complicated by type 1 diabetes.

Management of gestational diabetes

- Insulin is the preferred medication for treating hyperglycaemia in gestational diabetes. Metformin and glyburide (glibenclamide) should not be used as first-line agents, as both cross the placenta to the foetus. Other oral and noninsulin glucose-lowering medications lack long-term safety data.
- Metformin, when used to treat polycystic ovary syndrome, should be discontinued by the end of the first trimester.

Source: Based on [9, 17 and 18].

ADA standards of care suggest, more strongly, that insulin is the preferred treatment of choice for gestational diabetes, as oral antidiabetic drugs may cross the placenta, and indeed if metformin has been utilised as part of a regimen to facilitate ovulation induction, for example in polycystic ovarian syndrome, it should be discontinued at the end of the first trimester [20].

Use of Antidiabetic Drugs in Patients with Kidney Disease

KDIGO KDIGO (Kidney Disease Improving Global Outcomes) is a global nonprofit organisation developing and implementing evidence-based clinical practice guidelines in kidney disease. KDIGO published updated clinical practice guidelines for diabetes management in CKD in 2020 [21]. This included a combination of recommendations supported by practice points and covered comprehensive care, glycaemic monitoring and targets, lifestyle interventions, antidiabetic drugs and approaches to the management of patients with diabetes and CKD. Under the heading of antidiabetic drugs there were four key recommendations:

1. Glycaemic management for patients with type 2 diabetes and CKD should include lifestyle therapy, first-line treatment with metformin and an SGLT2 inhibitor, and additional drug therapy as needed for glycaemic control.
2. We recommend treating patients with type 2 diabetes, CKD and an eGFR $\geq$ 30 ml/min/1.73 m^2 with metformin.
3. We recommend treating patients with type 2 diabetes, CKD and an eGFR $\geq$ 30 ml/min/1.73 m^2 with an SGLT2 inhibitor.
4. In patients with type 2 diabetes and CKD who have not achieved individualised glycaemic targets despite use of metformin and SGLT2 inhibitor, or who are unable to use those medications, we recommend a long-acting GLP-1 receptor agonist.

Practice points were also advised by KIDGO where no systematic review was conducted, where there was insufficient evidence, where evidence was inconclusive, or the alternative option was illogical.

ABCD ABCD (the Association of British Clinical Diabetologists) is a national organisation of consultant physicians in Britain who specialise in diabetes. One of its aims is to ensure the high quality of care for diabetic patients both in hospital and in primary care. ABCD has published position papers and guidelines on multiple aspects of inpatient and outpatient diabetes care.

Two recent guidelines produced with the Renal Association have been on managing hyperglycaemia in patients with diabetic kidney disease and detecting and managing diabetes following solid organ transplantation [22, 23]. The guideline on managing hyperglycaemia in patients with diabetic kidney disease is very detailed and contains specific recommendations covering eight antidiabetic drug classes [22]. Some of these recommendations on metformin, SGLT2 inhibitors and GLP-1 receptor agonists are similar to the recommendations and practice points from the KDIGO guidelines, but also included are practice points on older antidiabetic drugs. Simplified key recommendations on the other antidiabetic drugs are described in Box 15.10.

Box 15.10 Therapeutic recommendations on managing hyperglycaemia in patients with diabetic kidney disease. Adapted from the Association of British Clinical Diabetologists and Renal Association guidelines on managing hyperglycaemia in patients with diabetes and diabetic nephropathy–chronic kidney disease

Insulin therapy

- In people who are less likely to be able to comply with the requirements of a basal bolus regime, once daily regimes with longer-acting insulins should be considered.
- If people have troublesome hypoglycaemia on NPH insulin, conversion to analogue insulins may be of benefit.
- There is no evidence of benefit from biphasic premixed insulin administered once, twice or three times daily in people with CKD stages 3–5. This regimen, however, may be useful in individuals who have poorly controlled diabetes on a once daily insulin regimen.
- Care should be taken when combining insulin with a sulfonylurea in people with CKD stages 3–5, owing to the high risk of hypoglycaemia.

Sulfonylureas

- Gliclazide and glipizide are metabolised in the liver and are therefore the preferred sulfonylureas for people with type 2 diabetes and CKD. Given the absence of excess cardiovascular events in a randomised trial, gliclazide should be the preferred choice of drug.
- A submaximal dosage of gliclazide and glipizide is used in people with an eGFR of <45 ml/min/1.73 m^2.
- Sulfonylureas should be avoided alongside insulin in people with an eGFR of <45 ml/min/1.73 m^2, unless there is clear evidence of the absence of hypoglycaemia.

- Gliclazide and glipizide should be avoided when a person's eGFR is <30 ml/min/1.73 m^2, as this therapy is off licence in this scenario.
- The safety profiles and pharmacokinetics of glibenclamide, glimepiride and tolbutamide do not support their use in people with CKD, and we suggest that they should be avoided in such individuals.

Meglitinides

- Meglitinides can be considered for use in people with type 2 diabetes and CKD as a monotherapy (repaglinide) or in addition to metformin (nateglinide and repaglinide) if other drugs are not tolerated.
- Meglitinide dose reduction is advised in people with CKD stages 4 and 5 who are on dialysis. In these individuals, owing to hepatic metabolism, repaglinide is advised in preference to nateglinide.

Thiazolidinediones: pioglitazone

- People with type 2 diabetes and CKD of all stages can be considered for treatment with pioglitazone.
- Caution is required when commencing treatment in people who have evidence of fluid overload. These individuals should be monitored for fluid retention initially after two weeks, and three to six monthly thereafter.

Dipeptidyl peptidase-4 inhibitors

- People with type 2 diabetes and CKD of all stages are suitable for treatment with DPP-4 inhibitors.
- Doses of DPP-4 inhibitors are appropriately reduced in accordance with the degree of renal impairment (including maintenance haemodialysis) except linagliptin.
- People with type 2 diabetes and CKD can be safely prescribed DPP-4 inhibitors without the risk of hypoglycaemia or weight gain at all stages of renal disease.

Source: Based on [22].

The guideline on detecting and managing diabetes following solid organ transplantation includes recommendations, future research and suggested audit standards for the management of post-transplant diabetes, and five of the recommendations are on glycaemic targets and the use of antidiabetic drugs (Box 15.11) [23].

Use of Antidiabetic Drugs during Ramadan

The IDF has jointly produced practical guidelines on diabetes and Ramadan with the Diabetes & Ramadan International Alliance, and these were updated in 2021 [15].

Box 15.11 Recommendations on the management of post transplantation diabetes mellitus (PTDM). Adapted from the Association of British Clinical Diabetologists and Renal Association guidelines on the detection and management of diabetes post solid organ transplant

- Glycaemic target for people with PTDM should be around 7% (53 mmol/mol), but adjusted according to degree of chronic kidney disease, age, co-morbidity, ability to self manage and patient preference.
- In patients with a stable eGFR >30 ml/min/1.73 m^2 and BMI >25 kg/m^2, metformin (dose adjusted for eGFR) should be considered first-line oral therapy for people with confirmed PTDM.
- Other therapies which may be used safely in PTDM include sulfonylureas, meglitinides, DPP-4 inhibitors, pioglitazone and GLP-1 receptor agonists. The use of sulfonylureas and meglitinides should be undertaken with care especially in those at risk of hypoglycaemia, and doses should be adjusted according to eGFR.
- SGLT2 inhibitors should be used with caution in patients with stable eGFR >30 ml/min/1.73 m^2 and poor glycaemic control in patients at low risk of urinary tract infection, after careful discussion with nephrology and diabetes specialists.
- Insulin therapy should be considered in all patients who have inadequate glucose control, or who have symptomatic hyperglycaemia.

Source: Based on [23].

These comprehensive guidelines include detailed descriptions on the epidemiology of diabetes and fasting during Ramadan, risk stratification, pre-Ramadan risk assessment and education, nutrition plans, etc. They acknowledge that most recommendations are based on expert opinion rather than clinical evidence. They include a final chapter that highlights key recommendations and the evidence base for these. Recommendations on the use of antidiabetic drugs in management of type 1 and type 2 diabetes during Ramadan are summarised in Box 15.12.

Use of Antidiabetic Drugs in Under-resourced Countries

The biggest international challenge for the World Health Organization (WHO) for people with type 1 diabetes is the availability and affordability of insulin and associated devices. In 2018 the WHO published a guideline on second- and third-line medicines and type of insulin for the control of blood glucose levels in nonpregnant adults with diabetes [24]. The objective was to provide guidance for managing hyperglycaemia in type 1 and type 2 diabetes in primary care in low-resource settings.

For people with type 2 diabetes, metformin is recommended as first-line treatment. Sulfonylureas are recommended for second-line treatment to patients who do not achieve glycaemic control, defined as a fasting glucose over 7 mmol/

Box 15.12 Key recommendations on adjustment of antidiabetic drugs for Ramadan. Adapted from Diabetes and Ramadan Practical Guidelines 2021

Type 2 diabetes

- Metformin and acarbose are safe and require no dose modifications for people with type 2 diabetes who fast during Ramadan.
- No dose modifications are needed for thiazolidinediones for people with type 2 diabetes when fasting during Ramadan.
- Modern sulfonylureas are preferred over older sulfonylureas to reduce the risk of hypoglycaemia in people with type 2 diabetes who fast during Ramadan.
- The daily dose of short-acting insulin secretagogues (based on three-meal dosing) may be reduced or redistributed to two doses during Ramadan according to meal sizes.
- Dipeptidyl peptidase-4 inhibitors can be used to reduce incidence of hypoglycaemia compared with sulfonylureas during Ramadan.
- Sodium-glucose co-transporter-2 inhibitors should be used with caution during Ramadan.
- As long as GLP-1 receptor agonists have been appropriately dose titrated prior to Ramadan, no further treatment modifications are required.
- Dose reductions need to be made to long- and short-acting insulin therapies and premixed insulin therapies.
- Second-generation long-acting insulin analogues have been reported to be safe with lower risks of hypoglycaemia compared with older-generation mixed insulin for people with type 2 diabetes.
- Dose reductions need to be made in individuals on multiple antidiabetic medications.

Type 1 diabetes

- Fasting during Ramadan in individuals with type 1 diabetes mellitus can be safe provided that strict criteria are met.
- A reduction of basal insulin dose by 10–30% in people with type 1 diabetes when fasting during Ramadan is recommended.
- The use of premixed insulin should be discouraged.
- The use of continuous glucose monitoring or flash glucose monitoring is superior to the traditional blood glucose monitoring and should be the method of choice if available.

Source: From [15]/International Diabetes Federation.

mol, or for first-line treatment if metformin is contraindicated. Basal human insulin is then recommended with metformin and/or sulfonylurea for patients who do not achieve glycaemic control as in many countries human insulin is available at lower prices than the three newer oral antidiabetic drug classes, with the comment that if insulin is unsuitable a DPP-4 inhibitor, SGLT2 inhibitor or thiazolidinedione may be added.

Human insulin is recommended for people with type 1 diabetes and in adults with type 2 diabetes for whom insulin is indicated. The recommendation covers short-acting (regular) human insulin and intermediate-acting (NPH) human insulin. Long-acting insulin analogues detemir or glargine are recommended in adults with type 1 or type 2 diabetes who have frequent severe hypoglycaemia with human insulin. Short-acting insulin analogues are not recommended by the WHO.

The IDF worked jointly with the International Society for Paediatric and Adolescent Diabetes to produce guidelines for the management of diabetes in childhood and adolescence in under-resourced countries, which take into account resource- and cost-related issues affecting diabetes care for children and youth with diabetes in developing countries [8]. This guideline covers insulin treatment and blood glucose monitoring as well as multiple other aspects of comprehensive diabetes care including the management of diabetic ketoacidosis, nutritional management, diabetes education, psychological care, etc. They recommend a target HbA1c for all age groups as a value of less than 7.5% (58 mmol/mol). They highlight that human insulin in short-acting form, e.g. Actrapid, Humulin R and Insuman Rapid, and intermediate-acting form (NPH insulin), e.g. Humulin NPH, Protophane and Insulatard, are options as well as premixed short- and intermediate-acting insulins in the combination 30/70 or 25/75. This recognises that analogue insulins, which are also available in some countries, are substantially more expensive. They recommend a basal bolus regimen as the preferred option over twice daily insulin. The guidelines include recommended blood glucose targets of 4–7 mmol/l before meals, 5–10 mmol/l after meals, 6–10 mmol/l at bedtime and 5–8 mmol/l at 3.00 am.

Place of Guidelines in Current and Future Practice

As described in previous chapters, there have been multiple developments in antidiabetic drugs and devices over the last decade and it is a challenge for the developers of guidelines for them to be up to date at the time of publication. NICE addressed this problem in its guideline on the management of type 2 diabetes by indicating that they would await the completion of all CVOTs, but this left a vacuum for some clinical prescribers who were uncertain how to integrate the results of these CVOTs into routine clinical practice. The SIGN update was performed when several CVOTs had been completed so it included these in its evidence gathering and synthesis of recommendations, but there is now evidence of benefit using different SGLT2 inhibitors and GLP-1 receptor agonists, and in patients other than those with existing atherosclerotic disease.

Owing to the COVID pandemic, many guideline programmes have been paused to focus on guidelines on multiple aspects of COVID. NICE has updates in development on the management of type 1 diabetes, the management of type 2 diabetes in adults, diabetes in pregnancy and diabetes in children. SIGN has in development updated

guidelines on type 1 diabetes and type 2 diabetes prevention. The guideline on type 1 diabetes will include insulin therapies, regimes and technologies, adjunctive oral pharmacological therapies, and the application of novel glucose monitoring sensing technologies. The guideline on type 2 diabetes will include pharmacological interventions that prevent progression to type 2 diabetes in individuals at increased risk. The estimated publication date for these is 2022.

The ADA/EASD consensus report on patients with type 2 diabetes sought to future proof its expert opinions by predicting the results of pending outcomes trials in cardiac and renal populations but did not include cardiology or renal representation. The differences between the consensus report and the evidence-based guidelines from the ESC have caused further confusion as to the place of the new antidiabetic drugs in routine clinical practice. There is a clear need to rationalise these recommendations at a European level plus a wider need for evidence-based guidelines to replace expert opinion to minimise the chance of conflicting recommendations in the future.

It has been suggested that the place of newer antidiabetic drugs as first-line treatments for people with type 2 diabetes can only be successfully resolved with a randomised, controlled trial comparing metformin with an SGLT2 inhibitor or GLP-1 receptor agonist [25]. Perhaps a more radical rethink about the treatment of people with type 2 diabetes is required, with a complete move away from a stepwise approach at the time of diagnosis to a pillars of therapy approach where all people with newly diagnosed type 2 diabetes receive structured education, lifestyle advice, metformin and an SGLT2 inhibitor. This would be a pragmatic, if costly, way of resolving the current uncertainty while potentially offering a better outlook for people with type 2 diabetes.

References

1. NICE (2015, 2 December). Type 2 diabetes in adults: management. NICE Guideline (NG28). https://www.nice.org.uk/guidance/ng28 (accessed 12 April 2022).
2. SIGN 154 (2017, November. Pharmacological management of glycaemic control in people with type 2 diabetes. A national clinical guideline. https://www.sign.ac.uk/our-guidelines/pharmacological-management-of-glycaemic-control-in-people-with-type-2-diabetes. (accessed 22 November 2021).
3. ICGP (2019). Quality and safety in Practice Committee. Diagnosis and management of uncomplicated type 2 diabetes in adults (T2DM). A succinct practical guide for Irish General Practice: Quick Reference Guide. https://www.icgp.ie/go/library/catalogue/item/635EAD13-8305-4A73-9A19FB346193CBD5 (accessed 22 November 2021).
4. International Diabetes Federation (2017). IDF Clinical Practice Recommendations for Managing Type 2 Diabetes in Primary Care. https://www.idf.org/e-library/guidelines/128-idf-clinical-practice-recommendations-for-managing-type-2-diabetes-in-primary-care.html (accessed 22 November 2021).
5. NICE (2015, 26 August). Type 1 diabetes in adults: diagnosis and treatment. NICE Guideline. https://www.nice.org.uk/guidance/ng17 (accessed 12 April 2022).
6. SIGN 116 (2010, March). Management of diabetes. A national clinical guideline, 30–38. https://www.sign.ac.uk/media/1054/sign116.pdf (accessed 22 November 2021).

7. American Diabetes Association (2022). Glycemic targets: standards of medical care in diabetes – 2022. *Diabetes Care* 45: S83–S96. https://doi.org/10.2337/dc22-S006.
8. *Pocketbook for Management of Diabetes in Childhood and Adolescence in Under-Resourced Countries*, 2nd edn. https://www.idf.org/e-library/guidelines/89-pocketbook-for-management-of-diabetes-in-childhood-and-adolescence-in-under-resourced-countries-2nd-edition.html (accessed 22 November 2021).
9. NICE (2015, 25 February). Diabetes in pregnancy: management from preconception to the postnatal period. NICE guideline. https://www.nice.org.uk/guidance/ng3 (accessed 22 November 2021).
10. Davies, M.J., D'Alessio, D.A., Fradkin, J. et al. (2018). Management of hyperglycaemia in type 2 diabetes, 2018. A consensus report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). *Diabetologia* 61: 2461–2498.
11. Buse, J.B., Wexler, D.J., Tsapas, A. et al. (2020). 2019 update to: management of hyperglycaemia in type 2 diabetes, 2018. A consensus report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). *Diabetologia* 63: 221–228.
12. Cosentino, F., Grant, P.J., Aboyans, V. et al. (2019). ESC Guidelines on diabetes, pre-diabetes, and cardiovascular diseases developed in collaboration with the EASD. The Task Force for diabetes, pre-diabetes, and cardiovascular diseases of the European Society of Cardiology (ESC) and the European Association for the Study of Diabetes (EASD). *Euro Heart J* 41: 255–323.
13. Garber, A.J., Handelsman, Y., Grunberger, G. et al. (2020). Consensus statement by the American Association of Clinical Endocrinologists and American College of Endocrinology on the comprehensive type 2 diabetes management algorithm – 2020 executive summary. *Endocr Pract* 26: 107–139.
14. Marx, N., Davies, M.J., Grant, P.J. et al. (2021). Guideline recommendations and positioning newer drugs in the management of type 2 diabetes. *Lancet Diabetes Endocrinol* 9: 46–52.
15. IDF-DAR practical guidelines 2021. Diabetes and Ramadan. Practical guidelines 2021. https://www.idf.org/e-library/guidelines/165-idf-dar-practical-guidelines-2021.html (accessed 22 November 2021).
16. Department of Health (2018, June). Adult type 1 diabetes mellitus. National Clinical Guideline No. 17. https://www.diabetes.ie/wp-content/uploads/2018/06/NCG-No-17-Adult-T1-DM_-Web-ready-copy-1.pdf (accessed 22 November 2021).
17. American Diabetes Association (2022). Pharmacological approaches to glycemic treatment: standards of medical care in diabetes – 2022. *Diabetes Care* 45: S125–S143.
18. Holt, R.I.G., DeVries, J.H., Hess-Fischl, A. et al. (2021). The management of type 1 diabetes in adults. A consensus report by the American Diabetes Association (ADA) and the European association for the Study of Diabetes (EASD). *Diabetologia*. doi: 10.1007/s00125-021-05568-3.
19. SIGN 116 (2010, March). Management of diabetes. A national clinical guideline, 56–68. https://www.sign.ac.uk/media/1054/sign116.pdf (accessed 22 November 2021).
20. American Diabetes Association (2022). Management of diabetes in pregnancy: standards of medical care in diabetes – 2022, S232–S243. https://doi.org/10.2337/dc22-S016 (accessed 22 November 2021).
21. de Boer, I.H., Caramori, M.L., Chan, J.C.N. et al. (2020). Executive summary of the KIDIGO diabetes management in CKD guideline: evidence-based advances in monitoring and treatment. *Kidney Int* 98: 839–848.

22. Bain, S.C., Chowdhury, T.A., De, P. et al. (2021 update). Clinical practice guidelines for management of hyperglycaemia in adults with diabetic kidney disease. https://abcd.care/resource/abcd-and-renal-association-clinical-practice-guidelines-management-hyperglycaemia-adults (accessed 22 November 2021).
23. Chowdhury, T.A., Wahba, M., Mallik, R. et al. (2021 January 12). Association of British Clinical Diabetologists and Renal Association guidelines on the detection and management of diabetes post solid organ transplantation. *Diabetic Med* e14523. doi: 10.1111/dme.14523.
24. World Health Organization (2018). Guidelines on second-and third-line medicines and type of insulin for the control of blood glucose levels in non-pregnant adults with diabetes mellitus. http://apps.who.int/iris/bitstream/handle/10665/272433/9789241550284-eng.pdf?ua=1 (accessed 11 November 2021).
25. Zaccardi, F., Khunti, K., Marx, N., and Davies, M.J. (2020). First-line treatment for type 2 diabetes: is it too early to abandon metformin? *Lancet* 396: 1705–1707.

CHAPTER 16

Prescribing Antidiabetic Drugs

Andrea Llano, Gerry McKay, Frances McManus, Catriona McClements, Joyce McKenzie, and Deborah Morrison

KEY POINTS

- Consideration should be taken when prescribing in extremes of age, pregnancy and renal and liver impairment as well as in the presence of comorbidities such as ischaemic heart disease and heart failure.
- SLGT2 inhibitors should be considered in patients with diabetes and heart failure or cardiovascular disease, or who are at high risk of developing cardiovascular disease.
- GLP-1 receptor agonists have demonstrated cardiovascular benefits and should be considered in these patient groups.
- Polypharmacy is common and often appropriate in patients with diabetes, but it can result in nonadherence. In the elderly polypharmacy can be inappropriate and caution should be exercised in this group as they are more likely to suffer adverse effects.

Introduction

Prescribing is one of the main interventions available for the treatment and prevention of disease and there is now an armoury of pharmacological drugs available for the management of diabetes. In this chapter, several aspects of prescribing will be discussed with respect to diabetes, including therapeutic inertia, polypharmacy and adherence. A variety of diseases and conditions such as pregnancy, cardiovascular disease and renal

Diabetes Drug Notes, First Edition. Edited by Miles Fisher, Gerard A. McKay, and Andrea Llano.

and hepatic impairment can coexist with diabetes, which can influence prescribing of antidiabetic drugs, and these will be considered.

Why Prescribe?

A prescription is defined as an instruction written by a medical practitioner (or qualified independent prescriber) that authorises a patient to be issued with a drug or treatment, but before this there needs to be an accurate assessment based on history, examination and investigations to ensure an appropriate working diagnosis.

In chronic disease management such as type 2 diabetes the diagnosis is already established, and it is up to the clinician to understand what the target of treatment at that time is, which may not only be about glycaemic control. In terms of glycaemic control it is important to have an understanding of where on the pathophysiological disease journey the patient is to ensure the drug chosen is likely to have the benefit desired.

In general, when considering reasons for prescribing a drug the aim is to improve symptoms and/or prognosis on the one hand, while balancing with the potential to cause harm or side effects on the other. Improvement in prognosis can be a hard endpoint such as prolonging life or improved outcomes implied by a surrogate endpoint, e.g. in diabetes improvement in HbA1c. There are several factors that should be taken into consideration when prescribing and these are outlined in Box 16.1.

Therapeutic Inertia

Introduction

Clinical or therapeutic inertia is a widespread phenomenon found within many chronic conditions. In patients with diabetes, it often refers to the failure to start or intensify treatment in patients who have not reached their HbA1c target, but can also be seen when patients have suboptimal blood pressure or cholesterol measurements.

Box 16.1 Good prescribing

- Each drug should have a clear indication.
- The patient should be involved in the decision-making process; why they are taking the drug, what are the potential adverse effects, are these acceptable to the patient, do they want to take more medicines?
- The benefits of the drug should outweigh the adverse effects.
- Avoid cascade prescribing: review each new symptom as a potential adverse effect before additional prescribing.
- Consider drug interactions with patients' regular or over-the-counter medications.
- Stop treatments that are no longer efficacious.

Despite an increasing number of classes of drugs and substantial evidence of the benefits of optimising metabolic control, many patients fail to achieve their therapeutic targets. Scottish data from 2019 shows that 45% of patients have an HbA1c >58 mmol/mol [1]. In Europe and the US, up to 60% of patients with type 2 diabetes have suboptimal glycaemic control [2, 3]. Data from the National Health and Nutrition Examination Survey found that a third of patients with diabetes had not met their HbA1c target [4]. Another study in patients with type 2 diabetes found that a quarter of patients with an HbA1c over 58 mmol/mol did not receive treatment intensification and that a delay of intensification of a year significantly increased the risk of cardiovascular complications such as myocardial infarction, stroke and heart failure [5]. Further data from over 80 000 patients with type 2 diabetes in the UK found delays of over seven years to intensification with further oral antidiabetic drugs or insulin [6]. There is also evidence for therapeutic inertia in patients with hypertension and hypercholesterolaemia [7, 8]. Patients being managed in primary care are more likely to experience delays in intensification [9, 10].

Causes of Therapeutic Inertia

The complex causes of therapeutic inertia can be categorised into three main groups which are summarised in Table 16.1. A case example of therapeutic inertia is given in Box 16.2.

Clinician-related Factors These are factors associated with the healthcare provider and are found in up to half of cases of therapeutic inertia. They include lack of knowledge and familiarity with pharmacological therapies used in type 2 diabetes. Over the last ten years there have been significant changes in the management of hyperglycaemia in type 2 diabetes with several new classes of drugs available. Many clinicians may choose to rely on older, more familiar therapies such as metformin, sulfonylureas and insulin, and fail to use newer antidiabetic drugs which have greater efficacy and additional cardiovascular benefits. Concerns about adverse effects, e.g. diabetic ketoacidosis with SGLT2 inhibitors, hypoglycaemia and weight gain with insulin and sulfonylureas, can also prevent intensification of therapy.

TABLE 16.1 Factors associated with therapeutic inertia

Clinician factors	Patient factors	Healthcare system factors
Lack of up-to-date knowledge	Adverse effects	Resource constraints
Lack of experience	Complex drug regimens	• staff
Variations in guidelines	High tablet burden	• technologies
Fear of adverse effects	Poor understanding or denial of disease and complications	• funding
Time constraints	Lack of symptoms	
Reactive vs. proactive management	Reluctance to take insulin	
Poor communication	Poor communication	

Box 16.2 Therapeutic inertia clinical case

A 56-year-old man has had type 2 diabetes for ten years. He has hypertension and hypercholesterolaemia and had a non-ST elevation myocardial infarction (NSTEMI) three years ago. He attends for diabetes screening annually and there have been no changes made to his drug regimen for some time.

His medications include: metformin 1 g twice daily, gliclazide 160 mg twice daily, ramipril 5 mg, amlodipine 10 mg and aspirin 75 mg. He was intolerant of atorvastatin.

His HbA1c is 69 mmol/mol, with eGFR >60 ml/min, cholesterol 6.2mmol/l, blood pressure 148/87 mmHg and BMI 28 kg/m^2,

Discussion

A case of therapeutic inertia is illustrated here. This man has had suboptimally controlled diabetes for many years despite having high cardiovascular risk. He should be aggressively managed, aiming for an HbA1c between 48 and 58 mmol/mol. blood pressure should be <130/80 mmHg and he requires treatment of his hypercholesterolaemia.

- Intensification with an SGLT2 inhibitor would be appropriate given their cardioprotective effects.
- An alternative statin should be trialled. If this is not tolerated, ezetimibe could be considered.
- Blood pressure is above target; ramipril should be maximised and a beta blocker should be added next as this will also improve prognosis following non-ST elevation myocardial infarction.

Clinicians often overestimate the care they provide and assume that their patients have better diabetes management than they do. They may also find ways to unconsciously avoid prescribing, attributing clinical findings to external factors, e.g. blood pressure above target as the patient has been rushing for their appointment, and not making plans to recheck until their next appointment in several months' time.

Finally, it is recognised that the clinical approach to glycaemic control is often reactive, and that additional therapy is instituted once HbA1c has climbed rather than being target orientated. This is likely to contribute to inertia and will result in patients experiencing longer periods of hyperglycaemia.

Patient-related Factors Patient-related factors are estimated to account for about 30% of treatment inertia. These include factors such as poor adherence, poor understanding of the disease and complex therapeutic regimens with multiple medications. A lack of adequate communication between a clinician and patient can also

contribute to inertia. One study found that approximately a quarter of patients in whom insulin was prescribed were reluctant to commence it, leading to a failure to improve glycaemic control, termed psychological insulin resistance [11]. This may be in part due to a fear of needles and to the belief that they have somehow failed. Adverse effects such as gastrointestinal upset, weight gain and hypoglycaemia can also limit a patient's use of pharmacological therapy.

Healthcare System Factors About 20% of therapeutic inertia is caused by healthcare system factors. In the UK this can include the availability of resources such as specialist nurses, dieticians, new technologies, and access to specialist services. The increasing number of patients with diabetes and other chronic diseases has placed rising demands on both primary and secondary care. Patients are often not able to receive reviews within the desired timescales.

Overcoming Inertia

Having considered the factors associated with therapeutic inertia, interventions to address it can be designed. The importance of education cannot be overemphasised. The number of drugs available to manage type 2 diabetes has increased dramatically in the last 30 years, many of which have beneficial effects on cardiovascular and renal outcomes. Healthcare providers require education and up-to-date guidelines to manage patients optimally. Other successfully trialled strategies have included computerised reminders providing target recommendations and a multidisciplinary approach using nurse practitioners, specialist diabetes nurses and pharmacists [12].

Patient education with regards to the management of their diabetes is also important. Many patients often have a poor understanding of diabetes and its complications. Treatment regimens should be acceptable to patients and clear goals should be set and agreed.

Polypharmacy

Introduction

Polypharmacy refers to the concurrent use of multiple medications by an individual. While several definitions exist, it often refers to the use of five or more medications. The prevalence of polypharmacy has increased significantly in recent years, largely because of an ageing and multimorbid population. Many patients now find themselves under the care of several different specialists, each prescribing according to their own guidelines. A Scottish study found that between 1995 and 2010, the number of patients prescribed five or more medications doubled to 21% and the number prescribed 10 or more medications tripled to 6% [13]. The number of prescriptions to manage diabetes has increased by 14% between 2015 and 2020 in England.

Polypharmacy can be considered appropriate in many situations, e.g. the use of multiple medications for a patient with several diseases, each prescribed with the intent of reducing morbidity and mortality and improving quality of life based on the best available evidence. Polypharmacy can be necessary in patients with type 2 diabetes who require multiple medications not only to manage glycaemia and cardiovascular risk but also for associated complications such as heart failure, and exists in 57–99% of patients with diabetes [14]. Data show that patients with type 2 diabetes take between five and seven medications each day for the management of hyperglycaemia, blood pressure and dyslipidaemia. Polypharmacy is more common in older patients who frequently require treatment for other comorbidities and elderly patients can often find themselves taking 20 or more tablets each day.

While appropriate polypharmacy is necessary and improves quality of life and expectancy in many situations, it can have negative unintended effects. Problematic polypharmacy occurs when several medications are inappropriately prescribed and can result in adverse drug reactions, drug interactions and increased healthcare costs. There is a direct relationship between the number of medications an individual takes and the frequency of adverse effects [15]. One study found that just under half of patients prescribed 10 or more medications had prescribing errors [16].

A greater pill burden or the increasing complexity of a drug regimen increases the likelihood of poor adherence. From a patient's perspective, polypharmacy can have a negative impact on their quality of life. An important adverse effect in patients with diabetes is hypoglycaemia, associated with the use of insulin and sulfonylureas. Hypoglycaemia is more common in older patients because of factors such as altered pharmacokinetics and reduced or erratic oral intake and is important because of its correlation with increased mortality and morbidity.

Inappropriate polypharmacy can be associated with a prescribing cascade where a drug is prescribed to treat another drug's adverse effects which have been misinterpreted as a new condition. An example of a prescribing cascade is the development of gout with thiazide diuretics which is then treated with allopurinol.

Elderly patients are an important group to consider in terms of prescribing as they are particularly susceptible to polypharmacy. It takes eight to ten years of intensive glucose control before the microvascular benefits can be seen. For many patients, particularly older individuals, their life expectancy may be such that they are unlikely to gain much benefit from tight glycaemic control. Intensive glycaemic control also increases the risk of hypoglycaemia by up to threefold and in turn is associated with increased morbidity and mortality. In elderly patients, it can increase the risk of hospital admission, increase the length of stay and contribute to delirium. It is therefore crucial that the benefits and harms of glycaemic control are considered carefully, and decisions made with the patient's wishes in mind.

Detecting and Managing Polypharmacy

Many tools have been developed to help prescribers recognise and manage problematic pharmacy. The STOPP/START tool and Beer's criteria are most widely known and were developed for use in patients over 65 years of age as they are the most vulnerable

group who are likely to suffer adverse events because of polypharmacy [17, 18]. The STOPP/START screening tool provides a list of criteria to use when reviewing a patient's medications. This tool is broken down into STOPP (Screening Tool of Older People's potentially inappropriate Prescriptions) and START (Screening Tool to Alert doctors to Right (i.e. appropriate, indicated) Treatments) and provides recommendations categorised according to the system. The advice specific to diabetes is given in Box 16.3.

Beer's criteria provide a list of drugs which carry a significant risk of adverse effects. Drugs included in this list are anticholinergic drugs, benzodiazepines, selective serotonin reuptake inhibitors and warfarin. A list of patients who are susceptible to adverse effects is also given where caution must be taken, particularly when prescribing high-alert drugs. Such groups include patients with diabetes, Parkinson's disease, chronic kidney disease and the elderly.

The main disadvantage of these tools is their complexity. They are not particularly user friendly, and recommendations can become outdated quickly, particularly in the pharmacological management of diabetes. They also do not take patient preferences into account, nor their frailty or life expectancy. A case example of polypharmacy in diabetes is given in Box 16.4.

Box 16.3 The STOPP/START criteria in diabetes

STOP:

- Sulfonylureas with a long duration of action (e.g. glibenclamide, chlorpropamide, glimepiride) with type 2 diabetes mellitus (risk of prolonged hypoglycaemia).
- Metformin if eGFR below 30 ml/min/1.73 m^2 (risk of lactic acidosis).
- Pioglitazone in patients with heart failure (risk of exacerbation of heart failure).

START:

- ACE inhibitor or angiotensin II receptor agonist (if intolerant of ACE inhibitor) in diabetes with evidence of renal disease, i.e. dipstick proteinuria or microalbuminuria (greater than 30 mg/24 hours) with or without serum biochemical renal impairment.

Box 16.4 Polypharmacy clinical case

A 79-year-old woman is seen at the diabetes clinic. She has type 2 diabetes, hypertension and chronic kidney disease. She takes metformin, gliclazide, empagliflozin, atorvastatin, rampiril, bendroflumethiazide and amlodipine. She dislikes the polyuria associated with her medication and the number of medications she takes. She does not have frequent episodes of hypoglycaemia.

HbA1c is 68 mmol/mol, eGFR is 43 ml/min and blood pressure is 119/68 mmHg.

Individualise targets – the benefits of tight glycaemic control can take ten years. Her life expectancy is unlikely to exceed this. Intensive blood pressure control in the elderly can be associated with an increased risk of falls.

Consider patient preferences – she has polyuria most likely owing to an SGLT2 inhibitor and diuretic. She has a significant pill burden and needs to take eight tablets in the morning, two tablets with her evening meal and one before bed.

Recommendations

- Relax HbA1c target while avoiding extremes of glycaemia. Empagliflozin can be discontinued given its urinary side effects. While it is renoprotective, this has to be balanced with her quality of life and anticipated life expectancy.
- Relax blood pressure target – her blood pressure is a little low and increases her risk of symptomatic postural hypotension. Stopping bendrofluemthaizde would reduce urinary frequency and increase her blood pressure.
- Fixed dose combinations and modified release preparations may be considered to reduce her tablet burden.

Nonadherence

Introduction

Nonadherence is often used interchangeably with terms such as compliance, concordance and persistence. The term compliance is no longer recommended as it has negative connotations regarding a patient's behaviour. Nonadherence refers to the extent to which a patient takes medications as prescribed by a healthcare provider. There are different forms of adherence. Primary nonadherence occurs when a patient fails to obtain or start prescribed medication. It may be considered intentional where a patient deliberately decides to take medication or nonintentional where factors such as cost or ability (e.g. poor cognition, inability to understand instructions) prevents an individual from taking prescribed medications. Nonconforming occurs when doses are missed or taken in excess or incorrect doses or times used.

There are many reasons for nonadherence. Patients may forget to take their medication and complex treatment regimens, a high pill burden, adverse effects and a poor understanding of their condition and its potential complications can contribute. Insulin-specific reasons for nonadherence can include a fear of needles, fear of hypoglycaemia and time pressures.

A variety of studies have suggested that nonadherence can be found in up to 93% of patients with type 2 diabetes [19]. Risk factors associated with nonadherence include

male gender, age (young adults and elderly), long duration of diabetes, low level of education and the presence of depression [20]. The consequences of poor adherence to therapy in diabetes include increased risk of microvascular complications, hospitalisation and cardiovascular mortality. There are also economic implications of nonadherence in terms of wasted medicines and costs associated with complications.

Improving Adherence

Nonadherence should not be viewed as the patient's fault and a nonjudgmental approach should be taken when discussing the subject. Patients should be given opportunities to discuss adherence both at planned reviews and when new medications are being prescribed. It is important to understand barriers to adherence and interventions to improve it should explore a patient's reasons for taking medication and their understanding of their condition. Good communication between a prescriber and the patient is crucial and the importance of education cannot be overemphasised. Patients should understand their conditions and the reasons for treatment. Discussion of adverse effects and methods to minimise these, e.g. reducing the dose, may be considered. In addition to patient education, a variety of interventions to improve adherence have been studied. Patient reminders such as daily text messages or phone calls have been demonstrated to have some success but are expensive. Simplifying treatment regimens and medication packaging (e.g. blister packs) can also help adherence.

The Patient with Problematic Hypoglycaemia

Introduction

Hypoglycaemia is common adverse event in patients using insulin, sulfonylureas or meglitinides, occurring in up to 76% of patients with diabetes [21], and is one of the main barriers to good glycaemic control. Mild hypoglycaemia can occur once or twice a week in patients with type 1 diabetes. Severe hypoglycaemia, defined as a hypoglycaemic episode which requires third-party assistance, occurs in up to 25% of patients with type 1 diabetes and 6% of patients with type 2 diabetes [22]. Glucagon administered by a third party is often required in the treatment of severe hypoglycaemia (see Box 16.5).

Hypoglycaemia is not only unpleasant for patients but is associated with an increased risk of cardiovascular disease, mortality, cognitive impairment and decreased quality of life. Repeated episodes of hypoglycaemia can result in impaired hypoglycaemic awareness, where autonomic activation to hypoglycaemia is blunted and an individual is unable to detect hypoglycaemic symptoms. The prevalence of impaired hypoglycaemic awareness has been reported to be between 20 and 25% in patients with type 1 diabetes.

Box 16.5 Glucagon

Glucagon is the main counterregulatory hormone to insulin. It is released from pancreatic islet alpha cells in response to falling glucose and stimulates hepatic glycolysis and gluconeogenesis. The release of glucagon in response to hypoglycaemia is diminished in people with type 1 diabetes and people with type 2 diabetes who are treated with insulin.

It is useful in the management of severe hypoglycaemia because it can be given intramuscularly or subcutaneously by relatives or carers. It reaches peak concentrations in a few minutes and raises serum glucose within ten minutes.

Glucagon is administered at a dose of 1 mg subcutaneous or intramuscularly. It is usually supplied as a powder with solvent (GlucaGen®, Novo Nordisk) and has to be reconstituted prior to injection. An intranasal preparation (Baqsimi®) has been approved by the FDA and EMA but awaits marketing authorisation in the UK.

Problematic Hypoglycaemia

Problematic hypoglycaemia is defined as two or more episodes of severe hypoglycaemia in 12 months, an episode of severe hypoglycaemia over a 12 month period associated with impaired hypoglycaemia awareness, more than two episodes of asymptomatic hypoglycaemia which interfere with daily activities or an extreme fear of hypoglycaemia [23].

There are many risk factors associated with problematic hypoglycaemia. Advancing age results in impaired counterregulatory responses to hypoglycaemia, whilst longer duration of diabetes increases the cumulative number of hypoglycaemic episodes and increases the risk of the development of impaired hypoglycaemia awareness. The presence of renal impairment and autonomic neuropathy can also increase the risk of problematic hypoglycaemia.

Modifiable factors associated with problematic hypoglycaemia include incorrect insulin dosing, inappropriate insulin regimens, poor injection technique, the presence of lipohypertrophy, mismatch between insulin and activity and the presence of gastroparesis. These should be identified and addressed.

Management of Problematic Hypoglycaemia

A useful approach to the patient with problematic hypoglycaemia is outlined below [23]. HbA1c should be also individualised taking into account balancing hypoglycaemic awareness against microvascular complications.

Identify and Characterise Hypoglycaemia The presence of hypoglycaemia should be reviewed at each consultation and should include the following:

- the frequency of hypoglycaemic episodes including the occurrence of severe hypoglycaemia;
- the presence of impaired hypoglycaemic awareness which can be determined using scoring systems such as the Gold and Clarke scores (Table 16.2);
- the identification of precipitating causes of hypoglycaemia;
- the presence of hypoglycaemic warning symptoms and the threshold that they occur at.

Review Risk Factors for Problematic Hypoglycaemia Risk factors associated with problematic hypoglycaemia include:

- impaired hypoglycaemic awareness
- older age
- cognitive impairment
- depression/diabetes distress
- long-standing diabetes
- lipohypertrophy
- autonomic neuropathy
- renal impairment
- extreme glycaemic variability and
- adrenal insufficiency, malabsorptive states, e.g. coeliac disease, pancreatic insufficiency.

Review Patient Education and Behaviour Patients with type 1 diabetes should be offered a structured education programme, e.g. DAFNE. Such educational interventions have been shown to reduce the frequency of severe hypoglycaemic episodes.

TABLE 16.2 Establishing the risk of problematic hypoglycaemia

Gold score [20]	Clarke score [21]
A patient is asked 'Do you know when you are having a hypo?' Response is graded between 1, always aware, and 7, never aware. Scores ≥4 are suggestive of impaired hypoglycaemic awareness	Eight-item questionnaire which asks question regarding symptoms of hyperglycaemia, frequency, number of incidences of severe hypoglycaemia and threshold for onset of symptoms. Score ≥4 implies reduced hypoglycaemic awareness

Behaviours such as the following should be addressed:

- postmeal bolusing – rapid acting insulin should be taken 15 mins before a meal;
- rage bolusing – the administration of excessive insulin doses as a response to hyperglycaemia;
- insulin stacking – repeated doses of insulin taken over a short time period.

Review Insulin

- Insulin analogue and basal bolus regimens are associated with a reduced risk of hypoglycaemia and should be used where possible.
- Ensure an appropriate balance between basal and prandial insulin (50% basal, 50% bolus).
- Estimation of carbohydrate intake and insulin dose should be reviewed.
- Technique and appropriateness of needle length should be checked; lipohypertrophy should be avoided.

Further options to address problematic hypoglycaemia include technological interventions such as interstitial ('flash') glucose monitoring, which has become increasingly available for use in patients using insulin in the UK (see Chapter 10). In some patients, CGM and continuous subcutaneous insulin infusion may be considered. Newer CGM devices are set to alarm when blood glucose reaches a preset level, which can then alert the individual or a carer to hypoglycaemia or impending hypoglycaemia. Finally, pancreatic or islet cell transplantation can restore endogenous insulin secretion and may be considered for patients who have failed to respond to the other interventions.

Prescribing in Renal Impairment

Introduction

Most drugs are excreted by the kidneys and the presence of renal impairment can therefore affect a drug's pharmacokinetics and alter its therapeutic action. Renal impairment is common in patients with diabetes; up to 30% of patients with type 1 diabetes and up to 40% of those with type 2 diabetes will develop kidney disease and over 25% of patients on dialysis have diabetes [24]. An understanding of the pharmacokinetics of antidiabetic drugs is therefore important when prescribing in this patient group.

The degree of renal impairment is typically classified using eGFR. There are several equations to calculate eGFR and it is recommended that the Cockcroft Gault equation is used as it provides a more reliable estimate of renal function in obesity, a common finding in patients with type 2 diabetes.

Many therapies used to manage hyperglycaemia in the presence of renal impairment will require dose adjustments and these are considered separately below. They are summarised in Table 16.3. Until recently, the management of hyperglycaemia in

TABLE 16.3 Prescribing in renal impairment

Antidiabetic drug	Renal impairment	Dose adjustment
Metformin	eGFR >60ml/min/1.73m^2	Up to 3g per day
	eGFR <45–59ml/min/1.73m^2	Up to 2g per day
	eGFR <30–44ml/min/1.73m^2	Up to 1g per day
	eGFR <30ml/min/1.73m^2	Avoid use
	Dialysis	Contraindicated
Sulfonylureas		
Gliclazide and Glimepiride	Mild to moderate renal impairment	Use with care
	Severe renal impairment	Avoid
Pioglitazone	All stages of CKD	No dose adjustment
DPP-4 inhibitors		
Sitagliptin	eGFR 30–45ml/min/1.73m^2	Reduce dose to 50mg/daily
	eGFR <30ml/min/1.73m^2	Reduce dose to 25mg/daily
Vildagliptin	CrCl <50ml/min	Reduce dose to 50mg/daily
Saxagliptin	Moderate to severe renal impairment	Reduce dose to 2.5mg/daily
Linagliptin	All stages of CKD	No dose adjustment
Aloglpitin	CrCl 30–50ml/min	Reduce dose to 12.5mg/daily
	CrCl <30ml/min	Reduce dose to 6.25mg/daily
SGLT2 inhibitors		
Dapagliflozin	eGFR <45ml/min/1.73m^2	Reduced efficacy, may be used for CKD or heart failure
	eGFR <15ml/min/1.73m^2	Avoid initiation
Empagliflozin	eGFR <30–60ml/min/1.73m^2	Use 10 mg
	eGFR <30ml/min/1.73m^2	Not recommended for T2DM
	eGFR<20ml/min/1.73m^2	Not recommended for heart failure
Canagliflozin	eGFR <60ml/min/1.73m^2	Use 100 mg
	eGFR <30ml/min/1.73m^2	Avoid initiation
Ertugliflozin	eGFR <60ml/min/1.73m^2	Avoid initiation
	eGFR <45ml/min/1.73m^2	Avoid

(*Continued*)

TABLE 16.3 (*Continued*)

Antidiabetic drug	Renal impairment	Dose adjustment
GLP-1 receptor agonists		
Liraglutide	CrCl <30 ml/min	Avoid
Dulaglutide	All stages of CKD	No specific advice
Semaglutide	End stage renal disease	Avoid
Insulin (all types)	All stages of CKD	Reduced doses will be required

CrCl, Creatinine clearance.

diabetes and chronic kidney disease was largely with insulin owing to a lack of evidence on the safety and efficacy of other classes of drugs, but a variety of drugs can now be used in the presence of severe renal impairment.

Renal impairment can alter a drug's pharmacokinetics in several ways as discussed below. Its impact is not always predictable.

Reduced Absorption Uraemia associated with chronic kidney disease can cause GI upset and oedema, which in turn can reduce the absorption of drugs from the stomach and duodenum. Higher doses may be required.

Increased Bioavailability Chronic kidney disease can reduce the activity of CP450 enzymes, thereby reducing the first-pass metabolism of drugs and increasing their bioavailability. This can result in toxicity and necessitate a dose reduction (or dose increase for prodrugs).

Reduced Renal Clearance A drug's renal clearance is dependent on the glomerular filtration rate. As renal function declines, the rate of clearance falls and serum levels remain elevated, which can result in toxicity. Dose reductions can be required.

Metformin

Metformin is associated with lactic acidosis, a risk that is increased in the presence of renal impairment. Although this risk is rare, guidance still recommends that metformin is avoided in conditions where there is an increased risk of tissue hypoperfusion, including renal impairment. Doses should be reduced once the eGFR falls below 45 ml/min/1.73 m^2 and discontinued below 30 ml/min/1.73 m^2. It should not be used in dialysis and should be withheld in acute kidney impairment.

Pioglitazone

Pioglitazone is metabolised by the liver and largely excreted in bile. Although it can be given in renal impairment, this is not recommended owing to concerns of fluid retention and congestive heart failure. There are differing recommendations on its use in dialysis.

Acarbose

Acarbose has very limited systemic absorption and is largely excreted unchanged. However, it is not recommended in severe renal impairment owing to a lack of experience.

Sulfonylureas and Meglitinides

Sulfonylureas are metabolised by the liver but can accumulate in renal impairment and increase the risk of hypoglycaemia. They are not recommended when eGFR <30 ml/min.

Repaglinide and nateglinide also undergo metabolism by the liver. Repaglinide is excreted in bile and nateglinide by the kidneys. They can be used in CKD, although a dose reduction is recommended in CKD stages 4 and 5 or those on dialysis. Repaglinide should be used preferentially in this patient group based on its pharmacokinetic profile.

Incretin-based Therapies

DPP-4 inhibitors have different routes of elimination from the systemic circulation, which influence prescribing guidance in renal disease. Linagliptin can be used at all stages of CKD including dialysis. Alogliptin, vildagliptin and sitagliptin can be used in CKD with dose adjustments. Saxagliptin should be avoided when eGFR is <30. In dialysis, saxagliptin and vildagliptin should be avoided.

Exenatide and lixisenatide are renally excreted and should be avoided in moderate to severe renal impairment. Liraglutide, dulaglutide and semaglutide are degraded by proteolytic enzymes and can be initiated and continued at all stages of renal impairment. Their use is not recommended in end-stage renal failure owing to a lack of data.

SGLT2 Inhibitors

SGLT2 inhibitors undergo extensive metabolism to inactive metabolites in the liver and are excreted in part via bile or urine. They are less effective at reducing HbA1c in patients with a reduced eGFR because of their mechanism of action. Licensing is rapidly changing as evidence accumulates. Empagliflozin can be initiated if eGFR is ≥30ml/min in patients with type 2 diabetes. It is also licensed for heart failure in patients with and without diabetes if eGFR ≥20ml/min. Empagliflozin should be reduced to 10 mg once the eGFR falls below 60 ml/min.

Canagliflozin can be used for glucose lowering at 300 mg if the eGFR is >60 or 100 mg if the eGFR is 45–60 ml/min. It is licensed for the treatment of diabetic kidney disease and can be continued at 100 mg daily for renal protection until dialysis. Dapagliflozin can be used for heart failure in patients at all stages of CKD and is also licensed for the treatment of CKD in patients with and without type 2 diabetes. It can be initiated when eGFR is ≥15 ml/min. SGLT2 inhibitors are not recommended for use in dialysis.

Insulin

The clearance of exogenous insulin decreases with GFR and there is an increased risk of hypoglycaemia. Dose reductions may be needed in renal impairment and an increase in the frequency of monitoring is recommended.

Prescribing in Liver Disease

Introduction

The liver is the main site of drug metabolism. Here drugs are modified into more lipophilic compounds which can then be excreted by the kidney. Prodrugs such as enalapril and dabigatran also require metabolism by the liver to convert them into pharmacologically active compounds. The presence of liver disease can therefore have a significant impact on a drug's pharmacokinetic and pharmacodynamic profile and drugs metabolised by the liver are likely to require dose adjustments. It can, however, be difficult to accurately predict the effect of liver disease on drug metabolism. Liver function tests do not correlate well with the degree of hepatic impairment and its effect on drug metabolism. Furthermore, the high metabolic reserve that the liver has means that alterations in drug metabolising capacity are not often seen until severe liver disease is present. The Child Pugh Score can be used to define liver disease according to the presence of decompensation and synthetic capacity (Table 16.4).

Liver Disease and Diabetes

The prevalence of chronic liver disease in patients with diabetes has been reported to range from 19 to 71%, making it important to be aware of the modifications that need to be made when prescribing antidiabetic drugs (Table 16.5**)**.

TABLE 16.4 Determination of Child Pugh score

	Points		
	1	**2**	**3**
Encephalopathy	None	Grade 1–2	Grade 3–4
Ascites	None	mild-moderate	Severe
Bilirubin (mmol/l)	<35	35 to 50	>50
Albumin (g/l)	>35	28 to 35	<28
International Normalised Ratio	<1.7	1.7 to 2.3	>2.3

A point is allocated according to each parameter. Child Pugh grade A (score 5–6), well-functioning liver; grade B (score 7–9), significant functional compromise; grade C (score 10–15), decompensation

TABLE 16.5 Prescribing in liver impairment

Drug	Advice
Metformin	Avoid in severe hepatic impairment
Sulfonylureas	Avoid in hepatic impairment
Repaglinide	Avoid in hepatic impairment – insufficient data
Nateglinide	No data available regarding use in severe liver disease – avoid
Pioglitazone	Avoid in hepatic impairment
DPP-4 Inhibitors	
Linagliptin	No dose adjustment in hepatic impairment Avoid in severe hepatic impairment
Alogliptin	No dose in mild to moderate hepatic impairment
Sitagliptin	No dose in mild to moderate hepatic impairment Avoid in severe hepatic impairment
Saxagliptin	Caution in moderate hepatic impairment Avoid in severe hepatic impairment
Vildagliptin	Avoid in hepatic impairment
GLP-1 receptor agonists	
Liraglutide	Avoid in severe hepatic impairment
Semaglutide	Caution in severe hepatic impairment (owing to limited experience)
Exenatide	No dose adjustment in hepatic impairment
Lixisenatide	No dose adjustment in hepatic impairment
Dulaglutide	No dose adjustment in hepatic impairment
SGLT2 Inhibitors	
Dapagliflozin	Dose reduction recommended in severe hepatic impairment Avoid in severe hepatic impairment
Empagliflozin	Avoid in severe hepatic impairment – insufficient data
Canagliflozin	Avoid in severe hepatic impairment – insufficient data
Ertugliflozin	
Insulins	Safe in hepatic impairment but increased frequency of monitoring recommended

There are several factors to consider when prescribing in patients with liver disease, as listed below.

Reduced Drug Absorption The presence of ascites and oedema can reduce drug absorption, necessitating the use of larger doses. In cholestatic liver disease, the absorption of fat-soluble drugs may be reduced, thereby requiring an increase in dose.

Increased Volume of Distribution In the presence of ascites, the volume of distribution of hydrophilic drugs such as furosemide is increased, meaning that higher doses are required to achieve the intended therapeutic effect.

Altered Protein Binding Hypalbuminaemia affects highly protein bound drugs, resulting in an increase in serum drug levels and increased risk of adverse effects. A reduction in dose may be required if a drug is highly protein bound.

Reduced Metabolism Hepatocellular damage can reduce the liver's metabolising capacity. This can result in reduced first-pass metabolism, leading to an accumulation of active drug and the potential for adverse effects. Conversely, pro-drugs may not be activated and their therapeutic effect is lost. With cholestatic disease, the reduction in bile acids can impair the absorption and clearance of fat-soluble drugs.

Hepatic Blood Flow Liver disease can reduce hepatic blood flow and the presence of portosystemic shunting can redirect blood from the liver. This affects drugs with a high extraction index which under normal circumstances undergo rapid metabolism and have a low bioavailability. In liver impairment, drugs with a high extraction index are likely to have increased bioavailability owing to reduced first-pass metabolism and will require a reduction in the oral dosage.

Reduced Excretion In drugs which undergo biliary excretion, the presence of hepatic impairment can lead to an accumulation of metabolites.

Metformin

Metformin does not undergo hepatic metabolism and has a good safety profile in liver disease. Guidelines advise against the use of metformin in patients with severe liver impairment owing to the small but clinically important risk of lactic acidosis.

Pioglitazone

Pioglitazone is predominantly metabolised by the liver and is largely excreted in bile. There is some evidence of hepatocellular injury associated with pioglitazone and periodic monitoring of liver function tests is recommended. It should not be used in hepatic dysfunction.

Sulfonylureas and Meglitinides

Both sulfonylureas and meglitinides undergo significant hepatic metabolism by the CP450 system and are extensively protein bound so in hypalbuminaemia their concentrations rise. Their use in the presence of hepatic impairment can increase the risk of hypoglycaemia. This risk is often compounded by concomitant malnutrition in patients with chronic liver disease.

Repaglinide is largely excreted in the bile. There is insufficient data regarding its use in liver disease and it should therefore be avoided in hepatic impairment. In contrast, nat-

eglinide is predominantly eliminated renally and can be used in mild to moderate hepatic impairment. It is not recommended in severe hepatic impairment owing to a paucity of data.

Incretin-based Therapies

GLP-1 receptor agonists and DPP-4 inhibitors do not undergo significant hepatic metabolism and are predominantly excreted by the kidneys. GLP-1 agonists are extensively bound to plasma proteins (>98%) while DPP-4 inhibitor protein binding varies from <10 to >90%. They are largely considered safe in patients with liver disease but there are individual exceptions to this based on pharmacokinetic data (Table 16.5).

SGLT2 Inhibitors

This class of drugs is predominantly metabolised by the liver via glucuronidation. They are predominantly protein bound (>90%) but hepatic impairment does not have any impact on the extent of protein binding. There is limited data regarding their safety in severe hepatic impairment and for this reason they are only recommended for use in patients with mild to moderate liver disease. Dapagliflozin, however, can be used at a lower dose in patients with severe hepatic impairment.

Insulin

Insulin is predominantly metabolised by the liver. In decompensated cirrhosis, there is reduced gluconeogenesis and reduced insulin clearance, which can affect insulin requirements.

Acarbose

Only 1–2% of acarbose is absorbed into the systemic circulation. It is extensively metabolised within the gut. Elevations in transaminases have been reported to occur which resolve on cessation of acarbose. While the US has no specific restrictions on its use in hepatic impairment, in the UK the Summary of Product Characteristics advises that it should be avoided in the presence of in liver disease.

Prescribing in Cardiovascular Disease

Diabetes and Coronary Artery Disease

The association of diabetes and macrovascular disease is well established and people with diabetes have roughly double the risk of developing cardiovascular disease compared with the general population. Atherosclerosis is more prevalent in patients with diabetes and around a third of patients with diabetes have cardiovascular disease [25]. It is the leading cause of death in patients with diabetes.

TABLE 16.6 Risk factors associated with type 2 diabetes

Risk factor	Association with diabetes	Recommendations
Obesity	Common in patients with type 2 diabetes Increases risk of type 2 diabetes Several antidiabetic drugs promote weight gain, e.g. gliclazide, insulin	• Encourage weight loss • Choose weight-neutral drugs or those which cause weight loss over those wthat promote weight gain • Consider referral to specialist weight management service
Diet	Increased intake of processed foods and high calorie diet associated with development of insulin resistance and type 2 diabetes	• Encourage healthy eating • In patients with type 2 diabetes, low-carbohydrate diets recommended • Consider input from specialist dieticians • Encourage attendance at structured education programmes (e.g. DAFNE)
Sedentary lifestyle	Regular exercise maintains healthy weight, improves insulin resistance	• Encourage regular exercise (150 minutes moderate exercise each week or 75 minutes of vigorous exercise)
Smoking	Associated with endothelial dysfunction and inflammation Increases CV risk	• Encourage smoking cessation
Hypertension	Common in patients with diabetes Increases risk of micro- and macro-vascular complications	• <140/90 mmHg for patients with type 2 diabetes and hypertension • <130/80 mmHg for patients with microvascular disease • ACE-I/ARB first-line antihypertensives
Lipids	Dyslipidaemia associated with atherosclerosis	• Offer a statin to all those >40 years of age with diabetes

Box 16.6 Prescribing points for patients with diabetes and coronary artery disease

- Consider ACE inhibitor and beta-blocker
- Aim for blood pressure <140/90 mmHg
- Long-term aspirin 75 mg
- High-dose statin atorvastatin (80 mg)
- Consider SGLT2 inhibitors and GLP-1 receptor agonists in patients with type 2 diabetes.

Box 16.7 Prescribing points for patients with diabetes and heart failure

- Consider SLGT2 inhibitors
- ACE inhibitors should be used unless contraindicated
- Beta blocker therapy should be commenced in stable patients unless contraindicated; this can reduce mortality and hospitalisation
- Thiazolidinediones and saxagliptin should not be used in patients with heart failure

The management of cardiovascular risk in patients with diabetes requires a multifaceted approach with consideration given to each of the risk factors associated with cardiovascular disease (Table 16.6). The STENO-2 trial demonstrated that intensive multifactorial control of hypertension, hyperlipidaemia, hyperglycaemia and micro-albuminuria was effective in reducing cardiovascular death by as much as 50% [26]. The key prescribing points for managing patients with diabetes, coronary artery disease and heart failure are given in Boxes 16.6 and 16.7.

Glycaemic Control The role of glycaemic control in the prevention and progression of microvascular complications has been well established in many landmark trials and is discussed in other chapters. Intensive glycaemic control (HbA1c <53 mmol/mol),

TABLE 16.7 **Landmark trials of intensive glucose control designed to assess cardiovascular outcomes**

Trial	UKPDS	ACCORD	ADVANCE	VADT
Intervention	Intensive control with sulfonylurea or insulin	Intensive therapy	Intensive glucose control based on gliclazide modified release	Intensive glucose control
Comparator	Conventional control with diet alone	Standard therapy	Standard glucose control	Standard glucose control
Population size (*n*)	3 867	10 251	11 140	1 791
Age (years)	53	62	67	60
Duration of diabetes (years)	Recently diagnosed	10	8	11
Follow-up (years)	10	3.5	5	6
Atherosclerotic CVD (%)	0	35	32	40

(*Continued*)

TABLE 16.7 (*Continued*)

Trial	UKPDS	ACCORD	ADVANCE	VADT
Heart failure (%)	0	5	NA	NA
Primary outcome	No differences in any diabetes-related endpoint, diabetes-related death, all-cause mortality	No difference in MACE	Reduction in combined MACE and major microvascular events Reduction in major microvascular events No difference in MACE	No difference in an extended MACE outcome
Secondary outcomes	Myocardial infarctions numerically reduced	Increased total mortality and deaths from cardiovascular causes with intensive therapy	No difference in death from CV causes or death from any cause	No difference in death from any cause

TABLE 16.8 **Long-term epidemiological follow-up of the landmark studies**

Trial	UKPDS Post Trial Monitoring	ACCORDION	ADVANCE-ON	VADT
Intervention	Previous intensive control with sulfonylurea or insulin	Previous intensive therapy	Previous intensive glucose control based on gliclazide modified release	Previous intensive glucose control
Comparator	Previous conventional control with diet alone	Previous standard therapy	Previous standard glucose control	Previous standard glucose control
Population size (*n*)	2 998	8 601	8 494	1 391
Age (years)	53	62	67	60
Duration of diabetes (years)	0	10	8	11

(*Continued*)

TABLE 16.8 (*Continued*)

Trial	UKPDS Post Trial Monitoring	ACCORDION	ADVANCE-ON	VADT
Total follow-up (years)	20	9	10	15
Atherosclerotic CVD (%)	0	35	32	40
Heart failure (%)	0	5	NA	NA
Primary outcome	Significant reductions in any diabetes-related endpoint, diabetes-related death and death from any cause	No difference in MACE	No difference in MACE or major microvascular events	No difference in an extended MACE outcome
Secondary outcomes	Significant reductions in myocardial infarction and microvascular disease	Significantly increased cardiovascular-related deaths	Reduction in end-stage renal disease No difference in death from CV causes or death from any cause	Reduction in renal composite No difference in death from CV causes or death from any cause

however, has not been associated with improved macrovascular outcomes as demonstrated by ADVANCE, ACCORD and VADT, and furthermore is associated with an increased risk of hypoglycaemia [27–29]. This is of particular significance because hypoglycaemia is associated with poor cardiovascular outcomes. Most guidelines (see Chapter 15) therefore advocate a target of HbA1c <58 mmol/mol and emphasise that glycaemic control should be not pursued at the expense of hypoglycaemia. The outcomes of the landmark trials designed to assess whether glycaemic control improves cardiovascular outcomes and longer-term epidemiological follow-up of trial patients are summarised in Tables 16.7 and 16.8.

Over recent years, there has also been a shift from glycaemic control as the focus of care in patients with diabetes. Evidence from cardiovascular outcome trials of class-specific improvements in cardiorenal outcomes has led to a change in the management of cardiovascular risk. Guidelines now advocate the use of antidiabetic drugs with proven cardiovascular and renal benefit over with drugs which solely impact HbA1c. However, despite the availability of cardio- and reno-protective drugs in diabetes, many patients continue on traditional therapies.

Choosing Antidiabetic Drugs with Cardiovascular Benefit SGLT2 inhibitors and GLP-1 receptor agonists have proven cardiovascular benefits in patients with diabetes (Chapters 5 and 6) and should be offered to type 2 diabetes patients with established cardiovascular disease or high cardiovascular risk where appropriate.

In patients with cardiovascular disease or cardiovascular risk factors, empagliflozin, dapagliflozin and canagliflozin have been shown to improve cardiovascular outcomes. Semaglutide, dulaglutide and liraglutide have all been associated with significant reductions in cardiovascular risk. The exact mechanisms by which these protective effects occur are uncertain but are thought to be mediated by reductions in blood pressure and improvements in lipid profile as well as via reductions in inflammation, platelet reactivity and endothelial dysfunction.

Management of Other Cardiovascular Risk Factors

Blood Pressure Management Hypertension is a well-established risk factor for both cardiovascular disease and microvascular complications and is common in patients with diabetes, with a reported prevalence of approximately 80%. Trials such as ADVANCE and ACCORD have demonstrated the benefits of good blood pressure control in patients with diabetes.

A target blood pressure of less than 140/90 mmHg is recommended by NICE in people with diabetes and ACE inhibitors or angiotensin receptor blockers should be used as first-line drugs [30]. In the presence of microalbuminuria or diabetic kidney disease, a lower target of <130/80 mmHg should be used to prevent the progression of renal disease. Other guidelines, including SIGN, advocate this lower target for all patients with type 2 diabetes.

Lipid Management Dyslipidaemia is a common abnormality in patients with diabetes and contributes to the increased cardiovascular risk. Patients with diabetes will typically have raised triglycerides and low HDL cholesterol. Statins lower total cholesterol and have a modest effect on triglycerides, and there is substantial evidence supporting their role in the reduction of cardiovascular morbidity and mortality [31]. Statins are recommended as primary prevention for all patients over the age of 40 with diabetes. Second-line therapies for the management of dyslipidaemia include ezetimibe and PCSK9 inhibitors.

Antiplatelet Therapy In contrast to secondary prevention, there is a lack of evidence for the benefit of antiplatelet drugs such as aspirin or clopidogrel in the primary prevention of cardiovascular disease. As such, most guidelines do not recommend their use in patients with diabetes who do not have cardiovascular disease.

Acute Coronary Syndromes

Approximately two-thirds of patients admitted to hospital with acute coronary syndromes (defined as unstable angina or myocardial infarction) have hyperglycaemia (blood glucose ≥11 mmol/l) and many do not have underlying diabetes. The presence of

hyperglycaemia with acute coronary syndromes is a strong predictor of poorer short- and long-term outcomes, including increased mortality. However, despite this, the evidence supporting tight glycaemic control in acute coronary syndromes has been conflicting.

The DIGAMI (Diabetes Mellitus, Insulin Glucose Infusion in Acute Myocardial Infarction) study compared an insulin infusion with standard therapy in patients with diabetes who presented with myocardial infarction and a serum glucose of >11.1 mol/l [32]. The treatment arm included a multidose insulin regimen post-infusion designed to maintain normoglycaemia for three months. Intensive glucose control was associated with a 29% reduction in mortality. DIGAMI 2 failed to confirm these results [33]. This trial compared insulin infusions followed by insulin or standard glucose control or routine glucose control in patients with type 2 diabetes and acute myocardial infarction. There were no differences in outcomes in each of the three groups.

The Hyperglycaemia: Intensive Insulin Infusion In Infarction (HI-5) study also failed to demonstrate a benefit of maintaining glucose control <10 mmol/l using intravenous insulin [34].

Current guidance recommends that blood glucose levels are maintained at <11 mol/l while avoiding hypoglycaemia. A dose-adjusted insulin infusion may be used but intensive intravenous insulin therapy is not recommended [35].

Diabetes and Heart Failure

Heart failure is a common complication of diabetes and its presence doubles the risk of mortality. The prevalence of diabetes in patients with heart failure ranges from 10 to 47% while the prevalence of heart failure in patients with diabetes is between 9 and 22% [36]. Despite this association, heart failure-related outcomes are poorly characterised and under-represented in cardiovascular outcome trials. There is, however, evidence of opposing effects on heart failure with certain classes of drugs used in the management of glycaemia. SLGT2 inhibitors have well-known benefits in heart failure while thiazolidinediones and certain DPP-4 inhibitors have been associated with deleterious effects (Box 16.7).

Pioglitazone Thiazolidinediones are associated with oedema and fluid retention, adverse effects which are more common in patients with heart failure. In the PROactive trial, pioglitazone was associated with a 50% increased risk in hospitalisation for heart failure compared with placebo in patients with type 2 diabetes [37].

Saxagliptin The SAVOR-TIMI 53 trial (see Chapter 4) showed that saxagliptin was associated with a 27% increased risk of heart failure in patients treated with saxagliptin (HR 1.27; 95% CI 1.07–1.51). This association with heart failure is not seen with other DPP-4 inhibitors. Saxagliptin is not recommend in patients with, or at risk of, heart failure.

GLP-1 Receptor Agonists Despite clear benefits in atherosclerotic cardiovascular disease, GLP-1 agonists have not demonstrated any positive outcomes with regards heart failure in any individual CVOT. Meta-analysis has shown minimally significant reductions in hospitalisation for heart failure (see Chapter 6).

SGLT2 Inhibitors SGLT2 inhibitors are the only class with proven benefits in heart failure and are associated with a 30–35% reduction in hospitalisation for heart failure. This class is covered in detail in Chapter 5. Empagliflozin was the first in its class to demonstrate a significant benefit with a respect to heart failure with a reduction in hospitalisation for heart failure in patients with type 2 diabetes and established atherosclerotic cardiovascular disease. Canagliflozin and dapagliflozin were subsequently also associated with reductions in hospitalisation for heart failure. Two trials specifically examined the effect of SGLT2 inhibitors in the heart failure population and found their protective effects are not restricted to patients with diabetes.

The DAPA-HF trial (Dapagliflozin and Prevention of Adverse Outcomes in Heart Failure) examined dapagliflozin in 4744 patients with heart failure and a reduced ejection fraction and found a 26% risk reduction in the combined outcome of worsening heart failure or cardiovascular death [38]. The EMPEROR-Reduced trial examined empagliflozin in 3730 patients with heart failure and a reduced ejection fraction and found a 25% reduction in cardiovascular death or hospitalisation for heart failure in those treated with empagliflozin [39]. As a result of this evidence, SLGT2 inhibitors have been incorporated into guidelines on the management of heart failure with a reduced ejection fraction in both patients with and those without diabetes.

The mechanisms underlying the benefits of SGLT2 inhibitors in heart failure are unclear. Their antihypertensive and diuretic effects are thought to be involved as well as direct effects on the myocardium (see Chapter 5) [40].

Prescribing in Pregnancy

Introduction

The prevalence of diabetes, in particular type 2 diabetes and gestational diabetes, in females of childbearing age has increased. It is estimated that in patients who are pregnant and have diabetes, 14% of these cases are due to previous type 1 or type 2 diabetes and 86% have gestational diabetes [41]. Diabetes increases the risk of complications to both the mother and the foetus and as such, good glycaemic control perinatally is important with a target HbA1c of 48 mmol/mol being advised.

The first trimester of pregnancy when organogenesis occurs is a period when the embryo is particularly susceptible to drugs. Many medications which are routinely used in diabetes such as statins and antihypertensives as well as antidiabetic drugs are either known to be teratogenic or there is a lack of evidence regarding their safety during pregnancy, thus contraindicating their use.

Antidiabetic Drugs in Pregnancy

Guidelines for the management of blood glucose in pregnancy are outlined in Chapter 15. Given its well-established safety in pregnancy, metformin is used as a monother-

TABLE 16.9 Blood glucose targets in pregnancy and diabetes

Time	Target capillary blood glucose
Fasting	< 5.3 mmol/l
One hour after meals	< 7.8
Two hours after meals	< 6.4
If taking insulin, aim capillary blood glucose >4 mmol/l	

apy in patients with type 2 or gestational diabetes or as an adjunct to insulin if blood glucose readings exceed 7 mmol/l [42]. Blood glucose targets in patients with diabetes are given in Table 16.9. It is important that these are not reached at the expense of problematic hypoglycaemia.

Other Drugs Used in Pregnancy

ACE inhibitors, angiotensin receptor blockers and diuretics should be stopped. Hypertension during pregnancy should be managed initially with labetalol. Second- and third-line options include nifedipine and methyldopa, respectively. A target of <135/85 mmHg is recommended [43]. Statins should be discontinued prior to conception or immediately on becoming pregnant.

Breastfeeding

Metformin is excreted into breast milk in small quantities not demonstrated to have significant adverse effects for the infant and it may be used in patients with preexisting type 2 diabetes. While insulin can be excreted into the breast milk, it is degraded in the gastrointestinal tract and will not have any impact on the infant's glucose metabolism. There can be a significant reduction in insulin requirements postpartum and with breastfeeding [42].

There is no evidence regarding the safety of the other classes of antidiabetic drugs and their use is not recommended while breastfeeding.

Prescribing in the Young

There are significant physiological differences between adults and children which require consideration when prescribing. The term 'children' include neonates to 16-year-olds. There are several pharmacokinetic differences which include:

- increased gastric pH and larger surface area to volume ratio (which can reduce absorption);

- increased extracellular water and body fat (which can influence the volume of distribution);
- altered CP450 activity and increased hepatic blood flow (altered bioavailability and metabolism); and
- reduced glomerular filtration (reduced excretion).

Type 2 diabetes is uncommon in this age group and therefore there is little evidence to guide the prescribing of antidiabetic drugs. There is much more experience of insulin use in children given the incidence and prevalence of type 1 diabetes in this group. Insulin requirements change with rapid changes in growth as well as a period of insulin resistance during puberty, and dose changes are often necessary.

Prescribing in the Elderly

Introduction

Several pharmacokinetic and pharmacodynamic changes occur with increasing age. These changes are of particular relevance given that elderly patients have many co-morbidities and are often prescribed several medications. Age-related changes occur

TABLE 16.10 Pharmacokinetic changes in the elderly

Process	Physiological change	Effect	Potential consequence
Absorption	↓ gastric acid/↑ pH ↓ gastric emptying ↓ bowel surface area ↓ muscle mass	↓ in drug absorption	↓ drug effect
Distribution	↓ body fat ↓ total water content hypalbuminaemia	↑ distribution of lipid-soluble drugs ↓ distribution of water soluble drugs ↓ drug binding	↓ half life ↓ half life ↓ drug effect
Metabolism	↓ liver mass ↓ reduced phase 1 metabolism ↓ hepatic and portal blood flow	↓ bioavailability	↓ drug effect
Excretion	↓ renal blood flow ↓ renal filtration	↓ excretion of renally excreted drugs	↓ drug effect

in each of the pharmacokinetic parameters and are summarised in Table 16.10. There is no evidence in the data so far to demonstrate clinically significant changes in the pharmacokinetic properties of drugs to manage diabetes. Renal impairment is the main factor to consider when prescribing in the elderly and is discussed earlier in this chapter.

Hypoglycaemia in the Elderly

Hypoglycaemia is a common complication in patients with diabetes treated with sulfonylureas or insulin. Elderly patients are more vulnerable to hypoglycaemia as a consequence of age-related autonomic dysfunction. Hypoglycaemia is more likely to present with neuroglycopenic symptoms rather than adrenergic, and can make its recognition more challenging. Hypoglycaemia is important as it is associated with significant mortality and morbidity, particularly in older adults. The SOLID study (Study of Longevity in Diabetes) found an association between severe hypoglycaemia and impaired cognition [44].

As discussed earlier, the management of diabetes in the older age group should take into account frailty and life expectancy. Strict glycaemic targets should not be pursued at the expense of hypoglycaemia.

The Patient with Type 1 Diabetes: a Therapeutic Journey (an Illustrative Case)

A 21-year-old woman presents with osmotic symptoms and weight loss and is diagnosed with type 1 diabetes. Her HbA1c at diagnosis is 120 mmol/mol. She is commenced on a basal bolus regimen of insulin. Twice daily basal insulin and bolus prandial rapid-acting insulin analogue are used to mimic physiological insulin secretion and doses are calculated at 0.3 U/kg/day.

Initial education regarding injection sites, insulin pens, treatment of hypoglycaemia, exercise and driving is given over the weeks following diagnosis. Initially her insulin needs are minimal as she enters the 'honeymoon period', but over the next 18 months her insulin doses are titrated up by the multidisciplinary diabetes team. She also receives guidance on the counting of carbohydrates in her diet. Planning for a pregnancy is discussed and contraceptive advice given with the progestogen-only preparation being recommended.

Eighteen months after diagnosis her HbA1c has fallen to 64 mmol/mol and all weight lost prior to diagnosis has been regained. She attends the DAFNE education programme for further education and optimisation of glycaemic control. She is now on Levemir 12 units twice daily and Novorapid in a ratio of 1 unit per 10 g of carbohydrate. After completing structured education and in preparation for a planned pregnancy she uses flash glucose monitoring to maximise control (see Chapter 10). Pre-pregnancy HbA1c is 48 mmol/mol. She starts folic acid 5 mg daily.

Although glycaemic control during pregnancy remains within range, hypoglycaemic awareness is reduced. Continuous glucose monitoring is used to improve glycae-

Box 16.8 The patient with type 1 diabetes: key points

- Education and regular support from specialist healthcare professionals is essential in the long-term management of type 1 diabetes.
- Good glycaemic control pre- and during pregnancy reduces the risk of miscarriage, foetal anomalies, macrosomia, stillbirth, pre-eclampsia, neonatal hypoglycaemia and respiratory distress syndrome.
- Flash glucose monitoring is available for all patients with type 1 diabetes and insulin pumps may be considered for patients who have difficulty achieving glycaemic targets owing to hypoglycaemia and/or despite multiple daily insulin injections.

mic control in pregnancy rather than flash glucose monitoring. She receives intensive support during her pregnancy from the team and further education is offered regarding appropriate alterations in insulin doses to attain maximal physiological glucose control. Her time in range target of 3.9–7.8 mmol/l is optimised to >70% to decrease macrosomia and complications postnatally. To achieve this, prandial insulin is changed to insulin aspart at 15 weeks and the timing of mealtime insulin emphasised. Microvascular complications are monitored during pregnancy and no deterioration is seen.

She delivers a 2.3 kg healthy baby at 38 weeks after induction. The baby does not require any input from the Special Care Baby Unit. During pregnancy her insulin doses rise to approximately twice pre-pregnancy levels but immediately revert to these postnatally.

Over the next two years control remains good, but the patient has difficulties with the dawn phenomenon and since she desires another pregnancy and is not able to maintain her HbA1c at target without frequent hypoglycaemic events, the patient is started on an insulin pump. Key points for managing people with type 1 diabetes are outlined in Box 16.8.

The Patient with Type 2 Diabetes: a Therapeutic Journey (an Illustrative Case)

A 49-year-old woman presents to her GP with recurrent urinary tract infections. She has a past medical history of type 2 diabetes with previous gestational diabetes between her second and third pregnancies. A miscarriage two years ago is noted. Her BMI was 26 kg/m^2 before her first pregnancy and is now 38 kg/m^2. She also has hypertension and depression. She has not attended for any chronic disease reviews for several years.

The GP notes that she is prescribed metformin 500 mg twice daily but this has not been requested in the last six months and was only requested sporadically before then. There is a similar pattern with ramipril 5 mg. She smokes 20 cigarettes a day, stopping only during her pregnancies. She does not drink alcohol. She is her mother's main carer.

The GP addresses the urinary tract infection, and also enquires about the patient's diabetes and medication adherence. The patient reports osmotic symptoms and confirms that she does not take metformin or ramipril. There is no recent HbA1c. Her blood

pressure is found to be 156/87. She is asked to restart her metformin and ramipril and agrees to return later in the week to see the practice nurse for bloods and a diabetes review.

Unfortunately, she does not attend her review appointment with the nurse. The GP contacts her by phone to explain why they want to see her and the importance of improving her diabetes. The patient explains that she is feeling very low about her health, especially her diabetes. She has poor sleep because of her low mood, which is exacerbated by nocturia. She is frustrated that she continues to gain weight. She is the main carer for her mother who has vascular dementia and is approaching end-stage renal failure owing to poorly controlled diabetes. She does not feel that diabetes medications helped her mother and from her perspective made things worse, as she gained weight and developed complications despite drug therapy.

The GP explains to her that the management of type 2 diabetes has changed significantly. Newer therapies not available to her mother are not only effective at controlling blood glucose but also protect against micro- and macrovascular complications and promote weight loss rather than weight gain. The GP helps her to understand that she is not on the same trajectory as her mother.

She agrees to attend a screening appointment. The results are shown below:

HbA1c 90 mmol/mol
eGFR >60 min/ml
ACR 45 mg/mmol
cholesterol 6.5 mmol/l
HDL 1.7 mmol/l
Blood pressure 154/87 mmHg
BMI 38 kg/m^2
Feet – low risk
Retinopathy – mild background changes only

The GP makes a list of areas requiring attention:

- high HbA1c
- hypertension
- hyperlipidaemia
- smoking
- obesity
- evidence of microvascular changes

The patient identifies that her main worries are weight and her risk of having the same complications as her mother. To keep her engaged the GP prioritises her main worries and takes a stepwise approach.

The GP discusses the benefits and side effects of both SGLT2 inhibitors and GLP-1 receptor agonists with the woman. She worries about thrush and urinary frequency and prefers to try the GLP-1 receptor antagonist first.

She attends three months later for review on full-dose metformin and GLP-1 receptor agonist. She restarts ramipril. The latest results are shown below:

Box 16.9 The patient with type 2 diabetes: key points

- All patients with diabetes should receive annual reviews to include measurement and review of HbA1c, blood pressure, cholesterol, urinary albumin, serum creatinine, weight check, smoking, eye screening and foot screening.
- Drugs with cardio- or reno-protective properties should be considered when managing a patient with type 2 diabetes.
- Polypharmacy and nonadherence are common in diabetes and should be addressed at each review.

HbA1c 65 mmol/mol
eGFR >60 min/ml
blood pressure 137/83 mmHg
BMI 34 kg/m^2

She feels positive about the weight loss and improvement in osmotic symptoms. The GP explains the targets and suggests that adding in an SGLT2 inhibitor now would be preferable as this will provide cardio-renal protection and continue to support weight loss. The GP takes this opportunity to talk about lifestyle in more detail and broaches again the benefits of referral to local weight-management services. A cardiovascular risk decision aid is used to illustrate her risk of cardiovascular disease and demonstrate the benefits of a statin. The patient agrees to try it.

Six months later she attends for review. Her HbA1c, blood pressure and lipids are all within target and her microalbuminuria has resolved. She has chosen to access local commercial weight-management which is available to her for free and has lost further weight; her BMI is 28.5 mg/m^2. She is encouraged to continue with lifestyle improvements and attend diabetes reviews regularly. Key points to consider when managing type 2 diabetes are outlined in Box 16.9.

Future Developments in Prescribing in Diabetes

As life expectancy and multimorbidity increase, individualised management plans will become more important to minimise polypharmacy, reduce adverse effects and improve adherence and quality of life. The development of clinical trial evidence to support the use of specific drugs in certain groups in addition to the emerging evidence for pharmacogenomics (see Chapter 1) provides the potential for highly targeted treatment choices made for individual patients. While doctors have traditionally been responsible for prescribing, independent prescribers have become commonplace. They can prescribe drugs for any medical condition

within their competence and have an important role in increasing capacity within the NHS, ensuring cost-effective prescribing and improving patient care. Patients with diabetes are increasingly cared for by pharmacists or specialist nurses who are also independent prescribers and function within the wider multidisciplinary team which also includes diabetologists, podiatrists and dieticians. This wider multidisciplinary team approach has the potential to allow patients needing intervention to be identified and started on treatment earlier, and allows more opportunities to educate patients on the benefits of taking drugs to improve symptoms and prognosis.

References

1. Scottish Diabetes Data Group (2020). Scotttish Diabetes Survey 2019. https://www.diabetesinscotland.org.uk/wp-content/uploads/2020/10/Diabetes-Scottish-Diabetes-Survey-2019.pdf (accessed 23 March 2021).
2. Stone, M.A., Charpentier, G., Doggan, K. et al. (2013). Quality of care of people with type 2 diabetes in eight European countries. Findings from the Guideline Adherence to Enhance Care (GUIDANCE) study. Diabetes Care 36: 2628–2638.
3. Palta, P., Huang, E.S., Kalyani, R.R., Golden, S.H., and Hsin-Chieh, Y. (2017). Hemaglobin A1c and mortality in older adults with and without diabetes: results from the national health and nutrition examination surveys (1988–2011). Diabetes Care 40: 453–460.
4. Carls, G., Huynh, J., Tuttle, E., Yee, J., and Edelman, S.V. (2017). Achievement of glycated hemaglobin goals in the US remains unchanged through 2014. Diabetes Ther 8: 863–873.
5. Paul, S., Klein, K., Thorsted, B.L., Wolden, M.L., and Khunti, K. (2015). Delay in treatment intensification increases the risks of cardiovascular events in patients with type 2 diabetes. Cardiovasc Diabetol 14: 100.
6. Khunti, K., Wolden, M.L., Thorsted, B.L., Anderson, M., and Davies, M.J. (2013). Clinical inertia in people with type 2 diabetes. Diabetes Care 34: 3411–3417.
7. Yusuf, S., Islam, S., Chow, C.K. et al. (2011). Use of secondary prevention drugs for cardiovascular disease in the community in high-income, middle-income, and low-income countries (the PURE Study): a prospective epidemiological survey. Lancet 378: 1231–1243.
8. Kotseva, K., De Backer, G., De Bacquer, D. et al. (2019). Lifestyle and impact on cardiovascular risk factor control in coronary patients across 27 countries: results from the European Society of Cardiology ESC-EORP EUROASPIRE V registry. Eur J Prev Cardiol 26: 824–835.
9. Balkau, B., Bouee, S., Avignon, A. et al. (2012). Type 2 diabetes treatment intensification in general practice in France in 2008–2009: the DIAttitude Study. Diabetes Metab 38 (Supplement3): S29–35.
10. Mata-Cases, M., Benito-Badorrey, B., Roura-Olmeda, P. et al. (2013). Clinical inertia in the treatment of hyperglycemia in type 2 diabetes patients in primary care. Curr Med Res Opin 29: 1495–1502.
11. Polonsky, W.H., Fisher, L., Guzman, S., Villa-Cabllero, L., and Edelman, S.V. (2005). Psychological insulin resistance in patients with type 2 diabetes: the scope of the problem. Diabetes Care 28: 2543–2545.
12. Khunti, S., Khunti, K., and Seidu, S. (2019). Therapeutic inertia in type 2 diabetes: prevalence, causes, consequences and methods to overcome inertia. Ther Adv Endocrinol Metab 10: 2042018819844694.

13. Guthrie, B., Makubate, B., Hernandez-Santiago, V., and Dreischulte, T. (2015). The rising tide of polypharmacy and drug-drug interactions: population database analysis 1995–2010. BMC Medicine 13: 74.
14. Van Oort, S., Rutters, F., Warle-van Herwaarden, M.F. et al. (2021). Characteristics associated with polypharmacy in people with type 2 diabetes: the Dutch Diabetes Pearl cohort. Diabet Med 38: e14406.
15. Johnell, K. and Klarin, I. (2007). The relationship between number of drugs and potential drug-drug interactions in the elderly: a study of over 600,000 elderly patients from the Swedish Prescribed Drug Register. Drug Saf 30: 911–918.
16. Avery, T., Barber, N., Ghaleb, N. et al. (2012). Investigating the prevalence and causes of prescribing errors in general practice: the PRACtICe Study (PRevalence And Causes of prescrIbing errors in general practiCe). A report for the GMC. https://www.rpharms.com/Portals/0/Documents/Old%20news%20documents/news%20downloads/gmc-report.pdf (accessed 14 April 2021).
17. O'Mahony, D., O'Sullivan, D., Byrne, S. et al. (2015). STOPP/START criteria for potentially inappropriate prescribing in older people: version 2. Age and Ageing 44: 213–218.
18. Croke, L. (2020). Beers criteria for inappropriate medication use in older patients: an update from the AGS. Am Fam Physician 101: 56–57.
19. Krass, I., Schieback, P., and Dhippayom, T. (2015). Adherence to diabetes medication: a systematic review. Diabet Med 32: 725–737.
20. Horii, T., Momo, K., Yasu, T., Kabeya, U., and Atsuda, K. (2019). Determination of factors affecting medication adherence in type 2 diabetes mellitus patients using a nationwide claim-based database in Japan. PLoS One 14: e0223431.
21. Alwafi, H., Alsahrif, A.A., Wei, L. et al. (2020). Incidence and prevalence of hypoglycaemia in type 1 and type 2 diabetes individuals: a systematic review and meta-analysis. Diabetes Res Clin Pract 170: 108522.
22. Edridge, C.L., Dunkley, A.J., Bodicoat, D.H. et al. (2015). Prevalence and incidence of hypoglycaemia in 532,542 People with type 2 diabetes on oral therapies and insulin: a systematic review and meta-analysis of population based studies. PLoS One 10: e0126427.
23. Choudhary, P., Rickels, M.R., Senior, P.A. et al. (2015). Evidence-informed clinical practice recommendations for treatment of type 1 diabetes complicated by problematic hypoglycemia. Diabetes Care 38: 1016–1029.
24. Reutens, A.T. and Atkins, R.C. (2011). Epidemiology of diabetic nephropathy. Contrib Nephrol 170: 1–7.
25. La Sala, L., Prattichizzo, F., and Ceriello, A. (2019). The link between diabetes and atherosclerosis. Eur J Prev Cardiol 26: 15–24.
26. Gaede, P., Vedel, P., Parving, H.H., and Pedersen, O. (1999). Intensified multifactorial intervention in patients with type 2 diabetes mellitus and microalbuminuria: the Steno type 2 randomised study. Lancet 353: 617–622.
27. Patel, A., MacMahon, S., Chalmers, J. et al. (2008). Intensive blood glucose control and vascular outcomes in patients with type 2 diabetes. N Engl J Med 358: 2560–2572.
28. Gerstein, H.C., Miller, M.E., Byington, R.E. et al. (2008). Effects of intensive glucose lowering in type 2 diabetes. N Engl J Med 358: 2545–2559.
29. Duckworth, W., Abraira, C., Moritz, T. et al. (2009). Glucose control and vascular outcomes in veterans with type 2 diabetes. N Engl J Med 360: 129–139.
30. NICE (2019). Hypertension in adults: diagnosis & management (NG136). https://www.nice.org.uk/guidance/ng136 (accessed 5 August 2021).
31. Sillars, A. and Sattar, N. (2019). Management of lipid abnormalities in patients with diabetes. Curr Cardiol Rep 21: 147.

32. Malmberg, K., Ryden, L., Efendic, F. et al. (1995). Randomized trial of insulin-glucose infusion followed by subcutaneous insulin treatment in diabetic patients with acute myocardial infarction (DIGAMI study): effects on mortality at 1 year. J Am Coll Cardiol 26: 57–65.
33. Malmberg, K., Ryden, L., Weder, H. et al. (2005). Intense metabolic control by means of insulin in patients with diabetes mellitus and acute myocardial infarction (DIGAMI 2): effects on mortality and morbidity. Eur Heart J 26: 650–661.
34. Cheung, N.W., Wong, V.W., and McLean, M. (2006). The Hyperglycemia: Intensive Insulin Infusion In Infarction (HI-5) study. Diabetes Care 29: 765–770.
35. NICE (2011). Hyperglycaemia in acute coronary syndromes: management of hyperglycaemia in people with acute coronary syndromes. https://www.nice.org.uk/guidance/ng185/evidence/k-hyperglycaemia-in-acute-coronary-syndromes-2011-evidence-reviews-pdf-8949422995 (accessed 7 August 2021).
36. Packer, M. (2018). Heart failure: the most important, preventable, and treatable cardiovascular complication of type 2 diabetes. Diabetes Care 41: 11–13.
37. Dormandy, J.A., Charbonnnel, B., Eckland, D.J.A. et al., on behalf of the PROactive Investigators. (2005). Secondary prevention of macrovascular events in patients with type 2 diabetes in the PROactive Study (PROspective pioglitAzone Clinical Trial In macroVascular Events): a randomised controlled trial. Lancet 366: 1279–1289.
38. McMurray, J.J., Solomon, S.D., Inzucchi, S.E. et al. (2019). Dapagliflozin in patients with heart failure and reduced ejection fraction. N Engl J Med 381: 1995–2008.
39. Packer, M., Anker, S.D., Butler, J. et al. (2020). Cardiovascular and renal outcomes with empagliflozin in heart failure. N Engl J Med 383: 413–424.
40. Joshi, S.S., Singh, T., Newby, D., and Singh, J. (2021). Sodium-glucose co-transporter 2 inhibitor therapy: mechanisms of action in heart failure. Heart 107: 1032–1038.
41. International Diabetes Federation (2019). Diabetes Atlas. https://www.diabetesatlas.org/upload/resources/material/20200302_133351_IDFATLAS9e-final-web.pdf (accessed 28 June 2021).
42. NICE (2015). Diabetes in pregnancy: management from preconception to the postnatal period. https://www.nice.org.uk/guidance/ng3 (accessed 28 June 2021).
43. Webster, K., Fishburn, S., Maresh, M. et al. (2019). Diagnosis and management of hypertension in pregnancy: summary of updated NICE guidance. BMJ 366: l5119.
44. Lacy, M.E., Gilsanz, P., Eng, C. et al. (2020). Severe hypoglycemia and cognitive function in older adults with type 1 diabetes: the Study of Longevity in Diabetes (SOLID). Diabetes Care 43: 541–548.

Appendix

APPENDIX 1 **HbA1c conversion chart**

HbA1c (%)	HbA1c (mmol/mol)	HbA1c (%)	HbA1c (mmol/mol)
4.0	20	8.1	65
4.1	21	8.2	66
4.2	22	8.3	67
4.3	23	8.4	68
4.4	25	8.5	69
4.5	26	8.6	70
4.6	27	8.7	72
4.7	28	8.8	73
4.8	29	8.9	74
4.9	30	9.0	75
5.0	31	9.1	76
5.1	32	9.2	77
5.2	33	9.3	78
5.3	34	9.4	79
5.4	36	9.5	80
5.5	37	9.6	81
5.6	38	9.7	83
5.7	39	9.8	84
5.8	40	9.9	85
5.9	41	10.0	86
6.0	42	10.1	87
6.1	43	10.2	88
6.2	44	10.3	89
6.3	45	10.4	90
6.4	46	10.5	91
6.5	48	10.6	92
6.6	49	10.7	93
6.7	50	10.8	95
6.8	51	10.9	96

(*Continued*)

APPENDIX 1 (*Continued*)

HbA1c (%)	HbA1c (mmol/mol)	HbA1c (%)	HbA1c (mmol/mol)
6.9	52	11.0	97
7.0	53	11.1	98
7.1	54	11.2	99
7.2	55	11.3	100
7.3	56	11.4	101
7.4	57	11.5	102
7.5	58	11.6	103
7.6	60	11.7	104
7.7	61	11.8	105
7.8	62	11.9	107
7.9	63	12.0	108
8.0	64		

Old unit = NGSp unit = %HbA1c, new unit = IFCC unit = mmol/mol

Index

Diabetes Drug Notes, First Edition. Edited by Miles Fisher, Gerard A. McKay, and Andrea Llano.

D

I

R

S

T

WILEY END USER LICENSE AGREEMENT

Go to www.wiley.com/go/eula to access Wiley’s ebook EULA.