The increasing incidence of diabetes, often in association with cardiovascular and renal disease, constitutes one of the major healthcare challenges of the 21st century. However, physicians can now deploy a wide range of therapeutic agents, singly and in combination, to help lower and stabilise blood sugar levels. Drawing on the expertise of internationally-recognised authorities in their fields, this new volume describes the modes of action of each of these types of treatment and evaluates their effectiveness.

In the first section of the book the authors review the various agents used to manage blood sugar, and the mechanisms by which their therapeutic effect is achieved. The second section of the book deals with the treatment of associated cardiovascular problems in the diabetic patient, including antihypertensive, lipid-lowering, and anti-platelet therapies, as well as the management of other complications associated with diabetes, including polyneuropathy. Therapeutic Strategies in Diabetes reviews the evidence for all of these new treatments, evaluates the potential for new and emerging therapies, and presents an informed view of current recommendations for best-practice management.

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Edited by
Coen D. A. Stehouwer
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Preface

We are witnessing a global epidemic of diabetes and obesity, and, in their wake, of cardiovascular and renal disease. Prevention and treatment will require an in-depth understanding of therapeutic options. It is therefore timely and appropriate that this book has been dedicated to the topic of therapeutic strategies in diabetes and its cardiovascular complications. It is meant for all physicians who care for individuals with diabetes.

In many parts of the world, individuals with diabetes are treated by physicians who received their primary training either in diabetology (and often feel less familiar with cardiovascular treatment options), or by physicians who received their primary training in cardiovascular disease (and often feel less familiar with metabolic treatments). This book specifically aims to provide a bridge between these traditions.

As editors, we are fortunate to have persuaded leading authorities in the field to provide detailed discussions of current concepts and challenges. We have deliberately sought a balance between the metabolic and the cardiovascular perspectives. Accordingly, we have divided the book in two parts, with chapters on metabolic and cardiovascular treatment options, respectively.

In the first part, the opening chapter, by Marc Evans and Rajesh Peter, gives an overview of glucose lowering strategies, both old and new, and their rationale. As a variety of blood glucose lowering drugs are now available, with different modes of actions and safety profiles, the treatment of type 2 diabetes is rapidly gaining in complexity. This chapter sets the stage for the next five chapters. The first two of these provide in-depth discussions of the use of insulin analogues by Geremia Bolli and of specific novel ways of insulin administration (continuous subcutaneous insulin infusion, continuous intraperitoneal insulin infusion, and inhaled insulin administration) by Eric Renard. In the next chapter, Allan Vaag and Søren Lund discuss old and new uses of arguably the most important oral antidiabetic drug available, namely metformin. Andries Gilde and Bart Staels discuss the somewhat contentious issue of the use of glitazones (rosiglitazone and pioglitazone), which are PPARγ agonists, and of a new class of PPAR activators, the glitazars, which are agonists of both PPARα (like fibrates) and of PPARγ (like glitazones). In the final chapter of this section, Tina Vilsbøll and co-workers discuss the exciting development of incretin hormone mimetics as a treatment for type 2 diabetes. These drugs are either activators of the receptor for glucagon-like peptide-1 (GLP-1), or inhibit the breakdown of endogenous GLP-1 (so-called DPP-4 inhibitors), and appear to ameliorate many important aspects of the pathophysiology of type 2 diabetes.

One of the most important lessons learnt in the past decade is that what works for primary and secondary prevention of cardiovascular disease in individuals without diabetes, works as well, if not better, in individuals with diabetes. Thus, in the second part of this book, John Reckless, Frank Visseren, and Gillian Marshall and co-workers discuss the appropriate use of statins and other lipid-lowering treatments; John McKnight and colleagues, and Julián Segura and Luis Rulope summarize the management of high blood pressure both from a cardiovascular and a renal perspective; and John Colwell explains how and when to use antiplatelet therapy in diabetes.
Are other options on the horizon? Hyperhomocysteinaemia is a particularly strong risk factor for cardiovascular disease in diabetes. Coen van Guldener and Yvo Smulders explain that homocysteine levels can be reduced by folic acid, but that the jury is still out on whether such treatment will reduce cardiovascular disease risk.

The final chapter of this book, by Eleanna Salgami and Andrew Boulton, is on the treatment of symptomatic diabetic neuropathy. Although strictly speaking this is not a cardiovascular disease, we have included it here because it often is an extremely distressing complication of diabetes, and because all practitioners who treat individuals with diabetes need to be aware of the available treatment options.

We hope that you will enjoy reading these chapters, as we have, and that you will find them both practical and thought-provoking.

Coen D.A. Stehouwer
Nicolaas Schaper
Part 1

Metabolic considerations
INTRODUCTION

The results of the randomised, multicentre United Kingdom Prospective Diabetes Study (UKPDS) confirmed the importance of long-term glycaemic control in limiting the complications associated with type 2 diabetes [1]. Indeed the long-term benefits of intensive blood glucose control were demonstrated by the UKPDS follow-up analysis in which despite a loss of glycaemic differences between the intensive and standard therapy groups on completion of the randomised phase of the study, emergent risk reductions for mortality and myocardial infarction during 10 years of post-trial follow-up [2]. Hence tight glucose control early in the natural history of type 2 diabetes appears to confer long-term benefits, even if control deteriorates, while the benefits of blood pressure control are only apparent as long as control is maintained [2]. Such data drives current clinical practice in which treatment is directed towards the attainment of near normal glycaemia (glycosylated haemoglobin [HbA1c] concentrations <7%). While such targets maybe difficult to attain for many patients there is clear consensus that chronic hyperglycaemia should be optimally managed, weighing safety and quality of life considerations on an individual basis. The safety considerations of glycaemic control were highlighted by the recent Action to Control Cardiovascular Risk in type 2 Diabetes (ACCORD) study in which intensive glycaemic control (HbA1c 6.4%) was associated with an increased risk of all cause mortality compared with conventional control (HbA1c 7.4%) [3]. Such an observation may at least in part be attributable to hypoglycaemia, indeed hypoglycaemia is a major consideration in the management of blood glucose in patients with type 2 diabetes. Symptomatic hypoglycaemia is reported by up to 38% of patients with type 2 diabetes taking oral glucose lowering medications, being associated with detrimental effects on quality of life, treatment satisfaction and therapy adherence [4]. Glycaemic control is just one aspect of the overall management plan of patients with type 2 diabetes; which should also encompass effective blood pressure and lipid management. The benefits of intensive multiple risk factor intervention on vascular complications have been shown to be both clinically and cost-effective in reducing morbidity and mortality [5] and has given rise to the genesis blood pressure and cholesterol treatment targets in patients with type 2 diabetes, as outlined by the recent Joint British Societies’ (JBS) 2 Guidelines [6]. While evidence of the clinical effectiveness of such inter-
ventions is available the translation of this approach into population based therapy presents a considerable challenge.

Insulin resistance along with defective insulin secretion are the cardinal metabolic features of type 2 diabetes, with subtle abnormalities of both being evident even at the earliest stages of glucose intolerance. Whilst insulin resistance is highly prevalent, linked to obesity and physical inactivity, near normal glucose tolerance can be maintained as long as β-cell insulin secretion is maintained. The development of glucose intolerance and thus type 2 diabetes is therefore dependent on progressive β-cell dysfunction. The initial management of a newly diagnosed person with type 2 diabetes involves advice and education relating to the potential benefits of dietary modification and lifestyle change. The objectives of this being to improve metabolic control through reductions in body weight that may help improve insulin sensitivity. The majority of patients will, however, require pharmacological therapy in the medium to long term. In UKPDS only 25% of patients maintained an HbA1c level <7% after 9 years without either oral agents or exogenous insulin [7]. Not only was drug therapy required but the need for escalating polypharmacy was also clearly demonstrated. This phenomenon was further illustrated in the A Diabetes Outcome Progression Trial (ADOPT) study, in which only 21.9%, 21% and 16.5% respectively of patients treated with either rosiglitazone, metformin or glyburide monotherapy demonstrated sustained blood glucose control after 4 years of treatment [8].

Gradual decline in β-cell function is held to be the major determinant of this progressive hyperglycaemia. Other factors such as weight gain and concordance failure with therapy or lifestyle modification may also contribute.

The selection of initial pharmacotherapy is based on the clinical and biochemical characteristics of the patient. Safety considerations must always be carefully considered since few, if any, oral hypoglycaemic agents are completely devoid of risk. Patients presenting with weight loss or failing to respond rapidly to oral hypoglycaemic therapy, despite optimum compliance with both treatment and lifestyle advice, usually signals the need for early insulin initiation. Exogenous insulin is otherwise usually reserved for patients who fail to respond oral therapies, or in whom safety considerations dictate its use as the agent of choice.

Several classes of oral hypoglycaemic agents are currently available with considerable expansion in recent years. Based on data from UKPDS [9], metformin is currently accepted as the initial oral pharmacotherapy of choice in the management of overweight people with type 2, the addition of further hypoglycaemic agents being indicated once glycaemic control is suboptimal (HbA1c concentration >7%) despite maximally tolerated initial oral therapy. This so called step-wise approach to the glycaemic management of people with type 2 diabetes has resulted in the genesis of both national and international treatment guidelines (Figure 1.1).

The current therapies available for the management of blood glucose in type 2 diabetes maybe divided according to their principle mode of action:

- Those agents that increase insulin secretion (insulin secretagogues).
- Those agents that improve insulin sensitivity.
- Drugs that facilitate weight loss.
- Drugs that delay the rate of digestion and absorption of carbohydrates.
- Drugs that mimic the physiological effects of gut hormones (incretin mimetics).

In this chapter we reflect on the mode of action, pharmacokinetics, indications and contraindications, efficacy, safety, tolerability and current place in management of these classes of drugs.
INSULIN SECRETAGOGUES

SULPHONYLUREAS

Sulphonylureas have been used extensively for treating type 2 diabetes for over 50 years. They exert blood glucose lowering effects primarily by stimulating insulin secretion from β-cells. By the 1960s several different agents were available including tolbutamide, tolazamide and chlorpropamide. Doubts about safety were raised in the 1970s, but a review of the available literature provides little in the way of convincing evidence of cardiovascular toxicity and the UKPDS demonstrated no increased risk of myocardial infarction among patients treated with sulphonylureas compared with patients randomised to insulin as monotherapy [1], while the benefits of glucose lowering with sulphonylureas in the STENO-2 study are clearly apparent [5]. More potent second generation sulphonylures emerged in the 1970s and 80s including glimepiride, glibenclamide, gliclazide and glipizide. The ADVANCE study (Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation) study has demonstrated the utility of these agents in limiting microvascular complications but no impact on cardiovascular outcomes has been demonstrated [10].

Mode of action

Sulphonylureas bind to the β-cell sulphonylurea receptor (SUR1), which is part of a transmembrane complex, the activation of which results in closure of K⁺ ATP channels reducing cellular potassium efflux, thus favouring membrane depolarisation [11] (Figure 1.2). As a consequence, voltage-dependent calcium channels open resulting in an influx of calcium thus activating calcium-dependent proteins, which control the release of insulin. When sulphonylureas bind to the SUR1, a prompt release of pre-formed insulin takes place adjacent to the plasma cell membrane – the so-called first phase of insulin release [12]. Sulphonylureas also increase the extended or second phase of insulin release, which begins approximately 10 minutes later as insulin granules are translocated to the membrane from within the β-cell [12]. A protracted stimulation of the second phase of insulin release involves the secretion of newly formed insulin granules, which continues while there is ongoing drug stimulation, provided there are sufficient β-cell reserves. Sulphonylureas can thus cause hypoglycaemia...
since insulin release is initiated even when glucose concentrations are below the normal threshold for glucose-stimulated insulin secretion (<5 mmol/l).

The principle distinguishing feature between individual sulphonylureas is their pharmacokinetic profile, with duration of action varying from <12 h for tolbutamide to >24 h for chlorpropamide [13]. This arises as a result of differences in rates of metabolism, activity of metabolites and rates of elimination. These properties have important implications for the risk of sulphonylurea-associated hypoglycaemia. All sulphonylureas are well absorbed, reaching peak plasma concentrations within 2–4 h. They are all primarily metabolised in the liver, although metabolites and subsequent routes of elimination vary. Since all sulphonylureas are highly plasma protein bound they have the potential to interact with other drugs sharing this banding, for example salicylates, sulphonamides and warfarin. Displacement from circulating proteins has been implicated in cases of severe sulphonylurea-induced hypoglycaemia.

**Indications and contraindications**

Since metformin is considered as the first-line oral hypoglycaemic for the majority of patients, sulphonylureas are a commonly used second-line agent. They may also be used as a first-line therapy; customarily, they are preferred for patients who are not overweight since
weight gain is an associated feature of sulphonylurea therapy [13]. Sulphonylureas are commonly used in combination therapy with agents from other treatment classes, with the exception of other insulin secretagogues. Daytime sulphonylurea treatment may also be used in combination with bedtime insulin and may reduce insulin requirement by up to 50% [14]. Sulphonylureas should be introduced at a low dose, increased over 2–4 weeks until glycaemic targets are achieved. If hypoglycaemia ensues it is advisable to return to the previous dose. Improved \(\beta\)-cell capacity resulting from alleviation of glucose toxicity and fatty acid toxicity may contribute to an increased risk of hypoglycaemia in some patients. In general, patients achieving a lesser degree of fasting hyperglycaemia following diet and exercise are more likely to develop hypoglycaemic symptoms than those with more marked fasting hyperglycaemia [13]. The maximal blood glucose lowering effect of sulphonylurea therapy is usually achieved at doses below the recommended maximum, probably reflecting the fact that maximum \(\beta\)-cell stimulation occurs at submaximal doses.

**Efficacy**

When used as monotherapy, sulphonylureas can reduce fasting plasma glucose by 2–4 mmol/l, accompanying a 1–2% reduction in HbA1c, although individual responses may vary. Since the hypoglycaemic effects of sulphonylureas relates to increased insulin secretion, the effectiveness of these agents is dependent on adequate \(\beta\)-cell reserve. The rate of decline of \(\beta\)-cell function appears to be the main determinant of loss of sulphonylurea efficacy and this may be greater with sulphonylurea than with insulin sensitising therapy [8]. The deterioration in glycaemic control associated with sulphonylureas is occasionally termed ‘secondary sulphonylurea failure’ and occurs at a rate of approximately 15% of patients per annum [8]. In essence, this is a reflection of disease progression rather than a true therapeutic failure.

The plasma insulin concentration achieved during sulphonylurea therapy does not usually extend beyond the normal physiological range observed in non-diabetic individuals. Consequently, the suggestion that sulphonylurea-induced hyperinsulinaemia may increase the detrimental insulin-related effects on the cardiovascular system remains largely unsubstantiated.

Sulphonylureas usually have modest effects on lipid profiles with small decreases in plasma triglyceride levels, most likely linked to improved glycaemic control. When a sulphonylurea is used in combination with another oral hypoglycaemic agent, the glucose lowering efficacy of both agents is additive, with the response again being dependent on the preservation of adequate \(\beta\)-cell function. Thus, following monotherapy failure, early use of combination therapy is a key approach to the maintenance of optimal glycaemic control.

**Adverse events**

Hypoglycaemia, whether subclinical, minor, or occasionally life-threatening, is the most common and serious adverse effect of sulphonylureas. The reported incidence of sulphonylurea hypoglycaemia in clinical studies ranges from 10–40% [8, 15]. Patients thus receiving sulphonylurea therapy should receive education on the recognition and prevention of hypoglycaemia. Severe protracted hypoglycaemia is more likely with longer acting sulphonylureas such as glibenclamide, while shorter acting agents such as gliclazide have a lower risk. Patient specific factors may also influence hypoglycaemia risk including irregular eating habits, excessive alcohol consumption and in those with tight glycaemic control as a manifest by HbA1c concentrations within or just above the non-diabetic range. More severe hypoglycaemia (i.e. requiring assistance) has been estimated to occur in about 1% of sulphonylurea treated patients (0.2–2.5 episodes per 1000 patient-years) with a mortality risk from such severe episodes being calculated at between 0.014–0.033 per 1000 patient-years, with longer-acting agents appearing to carry the greater mortality risk [16]. The development of new onset sulphonylurea-related hypoglycaemia should alert the clinician to the
possibility of other confounding factors such as occult malignancy, renal failure or hepatic impairment. Severe episodes of sulphonylurea-induced hypoglycaemia require treatment with intravenous dextrose infusions, while diazoxide and somatostatin may also be of benefit.

Other potential adverse events related to sulphonylureas include uncommon hypersensitivity reactions, which are usually transient. Fever, jaundice, blood dyscrasias and acute porphyria in predisposed individuals are also recognised rare adverse events. Weight gain is recognised as a class-related side-effect in sulphonylurea therapy ranging from 1–4 kg in the first six months of treatment and stabilising thereafter.

The issue of cardiovascular safety relating to the sulphonylureas was raised by the discovery of isoforms of the sulphonylurea receptor on both cardiac and vascular smooth muscle (SUR2A, 2B). Sulphonylureas containing a badenzamido group (gliclazide, glibenclamide, glipizide and glimepiride) can bind to these receptors where as those without demonstrate very little interaction [17]. The effects of the K+ channel-opening nicorandil are blocked by such badenzamido-containing sulphonylureas, however, the clinical implications of these observations remain unclear. Indeed, in two recent megatrials, namely ADOPT and RECORD no increased adverse cardiovascular signal was seen in association with sulphonylurea therapy [8, 18]. However, very high concentrations of sulphonylureas may cause contraction of cardiac and vascular muscle, although this is thought unlikely to be of any clinical significance at the therapeutic drug concentrations.

RAPID-ACTING PRANDIAL INSULIN RELEASERS

The first phase of glucose-stimulated insulin secretion is diminished early in the natural history of type 2 diabetes [19]. Early phase insulin secretion is important for postprandial glucose regulation and it is increasingly recognised that postprandial hyperglycaemia precedes fasting hyperglycaemia [20]. Furthermore, the contribution of postprandial glucose is the predominant contributor to excess glycaemia relatively well controlled (HbA1c <7.5%) patients, while the contribution of fasting glucose increases as glycaemia deteriorates [20]. Postprandial blood glucose excursions would thus appear to be a relevant therapeutic target. Rapid-acting prandial insulin releasers are available, which are taken orally immediately before a meal and produce rapid, but short-lived, insulin secretion. These agents, meglitinide derivatives, (netaglinide, repaglinide) are promoted as prandial glucose regulators but in fact also impact to a lesser extent on fasting hyperglycaemia.

Mode of action

These agents bind to the SUR1 in the β-cell membrane at a site distinct from the sulphonylurea binding site (Figure 1.2). Since the K+ ATP channel is closed when either the sulphonylurea binding site or the meglitinide binding site is occupied by its respective agonist, there is no advantage in combining a prandial insulin releaser with a sulphonylurea. The short half-life of these meglitinide agents results in enhancement of first phase and early second phase insulin secretion, which is less sustained than that seen with sulphonylureas.

Pharmacokinetics

Repaglinide is rapidly and almost completely absorbed following oral administration with peak plasma concentrations at around 1 h [21]. It is rapidly metabolised in the liver, with its metabolites excreted in bile. When taken around 15 minutes before a meal, repaglinide produces a prompt insulin release, which is limited to a period of around 3 h. Netaglinide has a slightly faster onset and shorter duration of action with its binding to target receptors lasting only a matter of seconds.
Blood glucose lowering therapies

Indications and contraindications
These agents maybe used as monotherapy or in combination with agents other than sulphonylureas. Suitable candidates include individuals with irregular eating patterns, while the lower risk of hypoglycaemia makes repaglinide an attractive option for individuals at risk of hypoglycaemia. The need for multiple daily dosing is a potential disincentive while the dosing regimen may also be confusing. Repaglinide should be ideally taken 15–30 minutes prior to a meal, starting at the lowest dose of 0.5 mg before each meal with dose titration over a subsequent 2–4 week period to a maximum of 4 mg before each meal according to response. Unlike some sulphonylureas and metformin, repaglinide is suitable for patients with moderate renal impairment, although careful dose titration and glucose monitoring is still required [21].

Efficacy
Overall reductions in HbA1c are similar in order of magnitude to those observed in sulphonylureas (1–2%). When used in combination with metformin, reductions in HbA1c of a similar order of magnitude are observed.

Adverse events
The overall incidence of hypoglycaemia is lower than with sulphonylureas. Sensitivity reactions, usually transient, may occur. Small increases in body weight maybe expected but these are minimal when compared to sulphonylurea therapy and there is little effect seen on weight when these agents are used in combination with metformin.

ALPHA-GLUCOSIDASE INHIBITORS
Inhibitors of intestinal α-glucosidase enzymes reduce the rate of carbohydrate ingestion, thereby providing an alternative means to reducing postprandial glucose levels [22]. Acarbose is the only agent licensed in the UK and does not cause weight gain, can reduce postprandial hyperinsulinaemia and has lowered plasma triglyceride concentrations in some studies [22].

Mode of action
These agents inhibit the activity of α-glucosidase enzymes in the brush border lining the intestinal villi. This prevents the cleaving of polysaccharide substrates into monosaccharides prior to absorption. This defers the completion of carbohydrate digestion until further along the intestinal tract, consequently causing glucose absorption to be delayed. The displacement of glucose absorption more distally along in the intestinal tract alters glucose-dependent release of intestinal hormones that enhance nutrient induced insulin secretion.

Pharmacokinetics
Acarbose is absorbed only to a trivial degree (<2%) and is degraded by amylases in the small intestine. Some of these products may be absorbed and are eliminated in the urine over a period of about 24 h.

Indications and contraindications
Acarbose maybe a useful first-line treatment in patients who have only slightly raised fasting glucose concentrations and more marked postprandial hyperglycaemia; the STOP-NIDDM study confirmed the utility of acarbose in delaying progression from impaired glucose tolerance to type 2 diabetes [23]. These agents maybe used either as monotherapy
or in combination with other oral agents and when starting treatment it is important to ensure a patient’s diet is rich in complex carbohydrates rather than simple sugars. Acarbose should be taken before meals, commencing with low dose (15 mg/day) with slow titration over several weeks, with a maximum dose often being limited by gastrointestinal (GI) symptoms. Intuitively, therefore, patients experiencing gastrointestinal adverse effects with metformin may not be the optimum candidates for such an agent, while a history of chronic intestinal disorders may also theoretically represent a contraindication to acarbose. As with all other hypoglycaemic agents, pregnancy and breast-feeding are traditionally regarded to be contraindications, mainly due to a lack of safety data rather than evidence of detrimental effects.

Efficacy
Used in patients who comply with dietary modification, acarbose will typically reduce prandial glucose concentrations by 1–4 mmol/l. As with prandial glucose regulators, there also appear to be small reductions in fasting glycaemia of up to 1 mmol/l. The decrease in HbA1c is usually around 0.5–1% providing that a sufficient dose of the drug is tolerated and dietary compliance is maintained.

Adverse effects
The most commonly reported adverse effect of acarbose is gastrointestinal upset occurring with a frequency of up to 31% in the STOP-NIDDM trial [23]. If the dosage of drug is too high relative to the amount of complex dietary carbohydrate, undigested oligosaccharides pass into the large bowel and become fermented by intestinal flora causing flatulence, abdominal discomfort and diarrhoea. Hypoglycaemia is only likely to be encountered in combination with either a sulphonylurea or insulin and no clinically significant drug interactions have been reported.

INSULIN SENSITISERS
Insulin resistance is a prominent metabolic abnormality in many patients with type 2 diabetes and therefore represents an attractive therapeutic target. The biguanides and thiazolidinediones are regarded as insulin sensitising drugs [24].

BIGUANIDES
Metformin is currently the only available biguanide and since it is both the least expensive oral hypoglycaemic, combined with data suggesting cardiovascular benefits in overweight patients with type 2 diabetes [8], it is now considered as the first-line agent for the majority of patients.

Mode of action
Metformin has a variety of metabolic effects (Table 1.1), many of which extend beyond glucose lowering. The true molecular mechanism of metformin action is, however, not fully understood. At the cellular level, metformin may improve insulin sensitivity via post-receptor signalling pathways for insulin [25]. Recent data have also suggested that adenosine V monophosphate activated protein kinase (AMPK) is a possible intracellular target for metformin, which, via phosphorylation pathways, acts as a regulator of cellular energy metabolism [26]. Metformin does not stimulate insulin release and small reductions in fasting insulin concentrations are often observed. The predominant glucose-lowering effect of metformin appears to be the reduction of excess hepatic glucose release (Figure 1.3). Metformin attenuates gluconeogenesis by increasing hepatic sensitivity to insulin and
Blood glucose lowering therapies

Table 1.1 Summary of metabolic and vascular effects of metformin

<table>
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<th>Antihyperglycaemic action</th>
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<tr>
<td>- Suppresses hepatic glucose production</td>
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<tr>
<td>- Increase insulin mediated glucose utilisation</td>
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<tr>
<td>- Decrease fatty acid oxidation</td>
</tr>
<tr>
<td>- Increase splanchnic glucose turnover</td>
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<tr>
<td>Weight stabilisation or reduction</td>
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<tr>
<td>Improved lipid profile</td>
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<td>- Reduction in plasma triglyceride</td>
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<td>- Reduction in plasma fatty acids</td>
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<td>Improved insulin sensitivity</td>
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<td>Vascular effects</td>
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<td>- Improved endothelial function</td>
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<td>- Increased fibrinolysis</td>
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decreasing hepatic extraction of certain gluconeogenic substrates such as lactate. Hepatic glycogenolysis is also reduced, while insulin-stimulated glucose uptake in skeletal muscle may also be increased to some extent [25]. Metformin also acts in an insulin-dependent manner to suppress the oxidation of fatty acids, thus reducing triglyceride levels and further reducing the energy supply for hepatic gluconeogenesis [25]. Glucose metabolism in the splanchnic bed may also be increased by metformin in an insulin-dependent fashion. This may further contribute to blood glucose lowering effects and also aid in the prevention of weight gain.

Pharmacokinetics

Metformin is a hydrophilic biguanide that is completely absorbed and eliminated unchanged in the urine. Consequently, renal impairment represents a contraindication to metformin as sufficient renal function is required to avoid accumulation of the drug. Renal clearance is achieved more by tubular secretion than by glomerular filtration. Metformin is not metabolised and therefore does not interfere with co-administered drugs. It is widely distributed, being retained in the walls of the gastrointestinal tract, providing a reservoir from which plasma concentrations are maintained. Peak plasma metformin concentrations are, however, short-lived – in patients with normal renal function, the half-life for metformin is 2–5 h, with 90% of an administered dose being eliminated within 12 h [25].

Indications and contraindications

Metformin is the first-line therapy of choice for obese patients with type 2 diabetes and may be equally effective in patients of normal weight. Metformin may be used in combination with any other oral hypoglycaemic agent or with insulin. The drug is contraindicated in patients with impaired renal function (serum creatinine >150 µmol/l, glomerular filtration rate [GFR] <60 ml/min). Conditions predisposing to tissue hypoxia also represent a contraindication, along with severe liver disease, alcohol abuse and a history of metabolic acidosis. Metformin may be used in the elderly, provided that renal insufficiency and other exclusions are not present. The improvement in insulin sensitivity may also cause ovulation to resume in cases of polycystic ovarian syndrome and it has been used in this condition (unlicensed) to enhance fertility. Metformin should be taken with meals or immediately before eating in order to minimise gastrointestinal side-effects. Treatment should be commenced ordinarily at a dose of 500 mg once or twice daily with slow dosage increase (one tablet at a time) at intervals of around 2–3 weeks until a target level of glycaemic control is achieved. The maximal effective dosage appears to be around
2 g/day given in divided doses, the maximum being 3000 g/day. A slow-release formulation of metformin is available and is said to have fewer in the way of gastrointestinal side-effects. During long-term treatment with metformin, it is advisable to monitor patients for the development of contraindications, in particular renal dysfunction. Metformin may also reduce gastrointestinal absorption of Vitamin B₁₂; while anaemia is very rare, an annual haemoglobin measurement and B₁₂ assessment is prudent. It is advisable to stop metformin treatment temporarily during intravenous radiographic contrast administration, surgery and any other inter-current situation that may invoke the exclusion criteria, in particular renal dysfunction.

**Efficacy**

As monotherapy, or in combination therapy, metformin typically reduces fasting plasma glucose levels by 2–4 mmol/l with a corresponding decrease in HbA₁c of between 1–2%. The effect is largely independent of body weight, age and duration and diabetes, however, given the progressive nature of type 2 diabetes, metformin monotherapy alone is often
Blood glucose lowering therapies

insufficient to maintain adequate glycaemic control with data from the recent ADOPT study suggesting an annual failure rate of up to 10% [8]. Metformin is unlikely to cause significant hypoglycaemia, body weight tends to stabilise or decrease slightly, while small improvements in lipid profiles maybe observed with reductions in plasma triglyceride concentrations, fatty acid levels and low-density lipoprotein cholesterol levels and high-density lipoprotein (HDL) cholesterol tends to increase, all of which appear to be independent of blood glucose lowering. These attributes may contribute to the putative cardiovascular benefits of metformin [9], although no clear dose response relationship is evident, suggesting that patients who can only tolerate low doses of metformin may benefit in terms of cardiovascular outcomes from continuing with the drug, even if other agents need to be added to optimise glycaemic control. Detracting from the generally favourable notion of cardiovascular benefits related to metformin there was evidence of an initially greater mortality when metformin was added to sulphonylurea therapy in a UKPDS substudy [9]. Longer term follow up has, however, demonstrated that the cardiovascular benefits of metformin were maintained, with one potential explanation being at least in part a spuriously low mortality rate in the comparator sulphonylurea monotherapy group. Similar findings of an increased cardiovascular mortality have been suggested in observational studies assessing combination metformin and sulphonylurea therapy [27]. However, data from large US studies and a variety of patient source databases have provided considerable reassuring evidence for the cardiovascular safety of metformin–sulphonylurea combination therapy [28, 29]. Consistent with the insulin sensitising action of metformin, it is now common practice to add metformin to ongoing insulin therapy, which may reduce exogenous insulin dose requirements, attenuates weight gain associated with exogenous insulin and the potential reductions in hypoglycaemia risk due to reduced exogenous insulin requirements. This approach is now widespread and includes combination with all insulin regimens including once daily, twice daily and basal bolus. Metformin has, in the US Diabetes Prevention Programme, also been shown to reduce the incidence of progression from impaired glucose tolerance to frank type 2 diabetes in overweight and obese patients by 33% compared with an intensive lifestyle regimen reduction of 58%. Younger, more obese individuals demonstrate the most substantial responses to metform therapy.

Adverse effects

Abdominal discomfort and various adverse gastrointestinal effects are the most common tolerability issues related to metformin therapy. These symptoms may remit if the dose is reduced or titration occurs slowly, however, around 10% of patients cannot tolerate metformin at any dose. The most serious and feared adverse event associated with metformin is lactic acidosis. The occurrence is rare (0.03 cases per 1000 patient-years), but the mortality rate is high. The majority of cases of lactic acidosis that have been reported in association with metformin have been due to inappropriate prescription of the drug, primarily in the context of significant renal insufficiency. Metformin increases lactate, particularly in the splanchnic bed, which may be aggravated by any hypoxic condition or in the context of impaired liver function. Hyperlactataemia occurs in cardiogenic shock and other conditions associated with tissue hypoperfusion and thus metformin is often an innocent bystander in cases of lactic acidosis caused by other severe illnesses. However, in the absence of any reliable data to the contrary, metformin should be discontinued immediately in all cases of suspected or proven lactic acidosis, regardless of cause or in any conditions that may result in tissue hypoperfusion. Lactic acidosis is typically characterised by elevated serum lactate (>5 mmol/l), decreased arterial pH and reduced bicarbonate concentrations with a high ion gap (>15 mmol/l). Presentation is often non-specific but frequently includes hyperventilation, malaise and abdominal discomfort. Bicarbonate is the therapy of choice, but evidence of its efficacy is limited.
THE INCRETIN HORMONES

Factors released from the gastrointestinal tract have the potential to lower blood glucose [30] (Figure 1.4). The entero-insular axis is a concept that was developed to describe the regulation of pancreatic islet cell hormone secretion by signals from the gastrointestinal tract [31]. This idea was based on the observation that for equivalent levels of glycaemia, oral glucose stimulates considerably more insulin than intravenous glucose, referred to as the ‘incretin effect’. This incretin effect is not limited to glucose, since an augmented release of insulin is observed in response to oral as compared with parenteral administration of lipids and amino acids [32, 33]. This incretin effect is predominantly based on the insulinotropic effect of two hormones, gastric inhibitory polypeptide (GIP) and glucagon-like peptide-1 (GLP-1) [34, 35], accounting for up to 60% of postprandial insulin secretion in healthy individuals [35].

GLP-1

GLP-1 is a product of the glucagon gene [36]. It is produced from proglucagon in the enteroendocrine L-cells in the distal ileum and colon. Proglucagon is cleaved, not to produce glucagon as in the islets, but to release from its C-terminal part the two glucagon-like peptides GLP-1 and GLP-2, both exhibiting approximately 50% amino acid identity to pancreatic glucagon. GLP-1 has 30 amino acids and is rapidly secreted from the distal gut within minutes of food being ingested via a combination of neural and endocrine stimulatory factors. It is now well established that the pancreatic β-cell expresses the GLP-1 and GIP receptors. These receptors are members of the glucagon/secretin family of G-protein coupled receptors. Activation of the incretin receptors by ligand binding stimulates the generation of cAMP and through the guanine nucleotide exchange factor II pathway insulin exocytosis from the β-cell occurs [37]. The insulinotropic effect of the incretins is dependent on acute elevations in ambient glucose and is only minimally apparent at basal glucose concentrations. GLP-1 contains an NH₂-terminal alanine at position 2, rendering it a substrate for cleavage by the endovascular serine protease enzyme dipeptidyl peptidase (DPP)-4. Both enzymatic action and renal clearance contribute to the short half-life for native GLP-1. Inactivation of GLP-1 by the enzyme DPP-4

Figure 1.4 Summary of the glucoregulatory effects of the incretin system. GLP-1 = glucagon-like peptide-1.
Blood glucose lowering therapies leads to the generation of the metabolite GLP-1(9-36) amide, which does not activate the GLP-1 receptor [38] and may even antagonise the actions of intact GLP-1 [39].

In addition to stimulation of glucose-dependent insulin secretion, GLP-1 has been shown to improve insulin sensitivity, delay gastric emptying, induce satiety with resultant reduction in calorie intake and also suppress glucagon secretion from islet α-cells without having an impact on its protective effect on hypoglycaemia. The effect of GLP-1 on gastric emptying and satiety also offers the potential for weight reduction. GLP-1 also has extrametabolic effects on the cardiovascular, pulmonary and hypothalamic–pituitary systems [41]. However, its most interesting effect is on the suppression of apoptosis and proliferation of β-cells in animal studies. GLP-1 increases β-cell mass in rodent models – treatment for between 2 days and 2 weeks leads to a 1.4- to 6.2-fold increase in β-cell mass [41] with β-cell hyperplasia being responsible for this increase in mass [42]. Should this effect be demonstrated in humans, it would be a key milestone in treatment aimed at reversing the inevitable decline in β-cells seen in type 2 diabetes.

Due to the fact that in vivo GLP-1 only remains active for 1–2 minutes it has to be administered as a continuous infusion. Longer-acting GLP-1 analogues that resist inactivation by the enzyme DPP-4 are now commercially available. Exendin-4, which has 50% homology with human GLP-1, a compound isolated from the saliva of the Gila monster resists inactivation by DPP-4. Exenatide (synthetically produced exendin-4) the first incretin mimetic to become available was a granted a licence in Europe in 2006. It is administered by subcutaneous (SC) injections of 5 µg bd for 4 weeks, increased to 10 µg bd thereafter. This dose titration is to avoid its most common side-effect of nausea, which is prevalent in 36–39% at 5 µg bd and 45–50% with 10 µg bd [43].

Exenatide has been assessed as adjunctive therapy in three trials of similar design, including > 1400 obese patients with type 2 diabetes uncontrolled with metformin [44], sulfonylurea (SU) [45], or both [46]. After 30 weeks, average reductions in HbA1c levels with the high-dose of exenatide (10 µg bd) were approximately 0.8 and 1.0% compared with baseline and placebo, respectively. Similar reductions in HbA1c values were reported in a smaller trial (n = 232) of shorter duration (16 weeks), in which exenatide was evaluated as add-on therapy in patients with type 2 diabetes suboptimally controlled on a thiazolidinedione (TZD) and metformin [47]. At the end of the previous five trials, the average proportions of subjects who achieved HbA1c value of ≤ 7.0%, were 45 and 10% in the exenatide and placebo groups, respectively, an observation that relates both to drug efficacy and baseline HbA1c. In subgroup analysis of subjects with baseline HbA1c >9% compared with <9%; greater reductions were seen with exenatide (5 µg dose, −0.8% vs. −0.4%, respectively; and 10 µg, −1.5% vs. −0.6%)

Exenatide was compared with insulin glargine in 549 patients with type 2 diabetes (baseline HbA1c 8.3%) on a background therapy of SU plus metformin [48]. After 26 weeks, HbA1c was reduced by 1.1% in both groups. In another trial, exenatide was compared with biphasic insulin aspart (formed of 30% short-acting insulin aspart and 70% intermediate-acting insulin) as adjunctive therapy in patients with type 2 diabetes (n = 501) inadequately controlled on metformin plus SU (mean baseline HbA1c 8.6%) [49]. After 52 weeks, no significant differences in HbA1c reductions were found between the exenatide and biphasic insulin aspart groups: 1 and 0.9%, respectively. At 52 weeks, significantly more subjects achieved an HbA1c <7 % in the exenatide group (32%) vs. the biphasic aspart group (24%). In both studies, better postprandial control was achieved with exenatide (difference −0.7 to −1.7 mmol/l).

In the previous two studies, the mean daily doses of insulin glargine and biphasic insulin aspart at the study ends were 26 and 24 units, respectively, suggesting that exenatide efficacy (10 µg bd) may be equivalent to mean daily insulin doses close to that range. However, more studies are needed to examine the benefits and risks of switching from insulin to exenatide therapy. Until these studies become available, such a strategy is not recommended, particularly in patients whose diabetes is not controlled on relatively high-doses of insulin.
For instance, in an exploratory study of 49 subjects with type 2 diabetes having mean baseline HbA1c values of approximately 8.1% while receiving insulin doses > 40 units/day, the substitution of exenatide for insulin resulted in further deterioration of glycemic control in 40% of patients, and lack of improvement in the remaining 60% of patients [50]. Open label long-term extension data has demonstrated a sustained reduction in HbA1c and progressive weight loss (Figures 1.3 and 1.4), with reductions in HbA1c of 1.1% achieved after 12 weeks being maintained after 3 years [51].

In clinical studies, exenatide was associated with progressive and dose-dependent weight loss. After 30 weeks, subjects receiving 10 µg bd exenatide had lost more weight than those receiving placebo (mean 1.6 kg or 2.8 kg) compared with 0.3 and 0.9 kg for placebo. There was no correlation between reported nausea and weight loss. Weight loss was progressive throughout the study period and persisted through the 104 week open label completer analysis. In this study there was progressive reduction in body weight of 1.6, 2.4 and 4.7 kg at weeks 12, 30 and 104, respectively. A similar pattern of weight loss was seen in an 82 week open label completer analysis study (2.9 kg at 30 weeks, 5.3 kg at 82 weeks) [52]. At week 156, patients completing 3 years of exenatide treatment (n = 217) continued to lose body weight (–5.3 ± 0.4 kg; 95% confidence interval [CI]: –6.0 to –4.5 kg; P < 0.0001) [28]. In both insulin comparator trials, weight change favoured exenatide after only 2 weeks.

Significant reductions in Apo B (–5.2 mg/dl) and triglycerides (–73 mg/dl), and increases in high-density lipoprotein-cholesterol (HDL-C) (+4.5 mg/dl) have been seen compared to placebo [52]. Total and low-density lipoprotein-cholesterol (LDL-C) were also reduced (–7.3 mg/dl and –4.4 mg/dl), while LDL-C/HDL-C and TC/HDL-C ratios both fell (–0.37 and –0.73, respectively). Systolic and diastolic blood pressures were also reduced using exenatide for 82 weeks by 6.3 mm.Hg and 4.1 mm.Hg, respectively.

Safety and tolerability of exenatide
The main reported adverse events are gastrointestinal, occurring in a dose-dependent manner in 39% and 48% of subjects receiving 5 µg or 10 µg exenatide, respectively. Symptoms peaking after 8 weeks and declining thereafter and resulting in study withdrawal in only 2% (5 µg) and 4% (10 µg) of subjects, respectively. The etiology of nausea is not fully clear, but may be related to the delay in gastric emptying. Nausea did not seem to be the predominant factor in the weight loss induced by exenatide, as there was no significant correlation between change in body weight and the duration of nausea.

Consistent with the glucose-dependent insulinotropic effect of exenatide, hypoglycemia caused by the drug is generally uncommon and mild-to-moderate in severity. Studies in healthy volunteers suggest that glucagon and other hormonal counter-regulatory responses to hypoglycemia are preserved with short-term administration of exenatide [53]. In clinical trials using metformin alone as background treatment, the frequency of hypoglycemia in the exenatide and placebo groups was similar. However, hypoglycemia was more frequent with exenatide compared with placebo in trials that included an SU as background therapy. The incidence and severity of hypoglycemia with exenatide treatment were similar when compared with insulin glargine and biphasic insulin aspart, which may be due in part to the moderate insulin doses used in these studies. Nocturnal hypoglycaemia was, however, lower with exenatide compared with either glargine or biphasic insulin (–1.6 and –0.9 events per patient-year).

Anti-exenatide antibodies were present in 41% to 49% of subjects receiving exenatide, although the clinical significance is unclear [54]. The antibodies were generally in low titre and were not predictive of glycaemic control or adverse events.

In the post-marketing period, 30 cases of pancreatitis possibly caused by exenatide were reported from the date of the drugs approval through to 31 December 2006 [55], although the frequency of pancreatitis did not appear to be significantly greater than that observed in the background population of patients with type 2 diabetes.
GLP1 – Analogues under development

Liraglutide is another GLP-1 analog with a long duration of action (half-life of around 12 h) owing to its stability against DPP-4, albumin-binding acylated side chain, and self-association, resulting in slow absorption from subcutaneous tissue [56]. It is given by a single daily SC injection [56], and is currently under evaluation in Phase III trials. In the largest randomised trial published to date, Liraglutide Effect and Action in Diabetes 3 (LEAD) [57], 746 patients with early type 2 diabetes were randomly assigned to once daily liraglutide (1.2 mg \( n = 251 \) or 1.8 mg \( n = 247 \)) or glimepiride 8 mg \( n = 248 \) for 52 weeks, with the primary outcome being change in HbA1c. At 52 weeks, HbA1c decreased by 0.51% with glimepiride, compared with 0.84% with liraglutide 1.2 mg (difference -0.33%; 95%CI -0.53 to -0.13, \( P = 0.0014 \)) and 1.14% with liraglutide 1.8 mg (0.62; -0.83 to -0.42, \( P < 0.0001 \)). Five patients in the liraglutide 1.2 mg, and one in 1.8 mg groups discontinued treatment because of vomiting, whereas none in the glimepiride group did so, while subjects receiving liraglutide 1.8 mg od had a reduction in body weight of 3.5 kg as opposed to 0.8 kg weight gain in the glimepiride group.

The effects of a long-acting release (LAR) formulation were assessed in a 15 week placebo-controlled study [58] in which exenatide LAR was given once weekly at doses of 0.8 mg and 2.0 mg suboptimally controlled with metformin and / or diet and exercise with mean duration of diabetes of around 5 years and mean baseline HbA1c 8.5%. From baseline to week 15, exenatide LAR reduced mean HbA1c by -1.4 +/- 0.3% (0.8 mg) and -1.7 +/- 0.3% (2.0 mg), compared with +0.4 +/- 0.3% with placebo LAR (\( P < 0.0001 \) for both). HbA1c of < or =7% was achieved by 36 and 86% of subjects receiving 0.8 and 2.0 mg exenatide LAR, respectively, compared with 0% of subjects receiving placebo LAR. Fasting plasma glucose was reduced by -2.4 +/- 0.9 mmol/l (0.8 mg) and -2.2 +/- 0.5 mmol/l (2.0 mg) compared with +1.0 +/- 0.7 mmol/l with placebo LAR (\( P < 0.001 \) for both). Exenatide LAR reduced self-monitored postprandial hyperglycemia. Subjects receiving 2.0 mg exenatide LAR had body weight reductions (-3.8 +/- 1.4 kg) (\( P < 0.05 \)), whereas body weight was unchanged with both placebo LAR and the 0.8-mg dose. Mild nausea was the most frequent adverse event, with no subjects withdrawing from the study. Thus based on these early results both liraglutide and exenatide LAR appear to be promising therapeutic entities.

DPP-4 INHIBITORS

DPP-4 is the key enzyme responsible for the degradation of GLP-1 and GIP. Hence the inhibition of this enzyme augments endogenous plasma concentrations of GLP-1 and GIP [59]. Although the precise substrates important for DPP-4 action in subjects with type 2 diabetes remains unclear, disruption of GLP-1 and GIP receptors in mice completely eliminates the glucose-lowering properties of DPP-4 inhibitors [60]. Treating diabetic rodents with DPP-4 inhibitors improves islet survival and maintains \( \beta \)-cell mass and islet function [61]. These agents are administered orally and metabolised either by hydrolysis in the liver (vildagliptin) or primary clearance via the kidneys (sitagliptin). These agents are reported to have no impact on satiety or body weight.

In addition to its impact on GLP-1 and GIP, inhibition of DPP-4 is non-specific and may potentially affect other peptides including peptide tyrosine tyrosine (YY), endomorphin, neuropeptide Y, growth hormone releasing hormone, GLP-2, vasoactive intestinal polypeptide as well as paracrine chemokines, stromal cell-derived factor, ecto-ATPase and macrophage-derived chemokine that are involved in regulatory systems [62]. It is also recognised that DPP-4 is a membrane-associated molecule on the surface of T-cells (where it is also known as CD26) and has a function in the immune system by contributing to T-cell activation and proliferation [63]. It has been suggested that GLP-2 acts as an intestinal growth factor [64]. Although DPP-4 inhibition is likely to cause a lesser increase in the concentration of active GLP-2 than that observed for GLP-1, DPP-4 inhibitors may thus also have effects on intestinal proliferation.
Sitagliptin is currently available in the UK at a dose of 100 mg od orally and licensed for use as an add-on therapy to either metformin or a sulphonylurea. Clinical studies have shown it to reduce HbA1c, by around 0.7%, as well as reducing postprandial fasting plasma glucose and proinsulin–insulin ratio [65]. Vildagliptin has also recently been licensed for use in the UK at a dose of 100 mg daily and demonstrates similar effects on HbA1c and glucose homostasis [66].

The two available DPP-4 inhibitors have not been compared directly, but both appeared to lower HbA1c similarly compared with placebo (−0.74% vs. −0.73% for sitagliptin and vildagliptin respectively).

**DPP-4 INHIBITORS IN COMPARISON WITH EXISTING THERAPY**

**Sulphonylureas**
In a non-inferiority trial, sitagliptin was compared with glipizide as add-on therapy in > 1000 patients with inadequate glycemic control on metformin [67]. After 52 weeks, both groups had similar reductions in HbA1c values of approximately 0.7% versus baseline. However, the mean daily dose of glipizide was submaximal (around 10 mg), and withdrawal rates due to lack of efficacy were higher with sitagliptin compared with glipizide: 86 of 588 patients (15%) versus 58 of 584 (10%) patients [67]. On the other hand, sitagliptin was associated with lower rates of hypoglycaemia (5 vs. 32% of patients), and weight loss of 1.5 kg compared with 1.1 kg of weight gain with glipizide [67].

**Metformin**
In a non-inferiority trial, vildagliptin (50 mg bd) was compared with metformin (1000 mg bd) in 780 drug-naïve patients. After 52 weeks, the average reductions in HbA1c values from baseline were significantly greater with metformin compared with vildagliptin: 1.4 and 1.0%, respectively [68]. In another trial of 24-week duration, the placebo-subtracted reductions in HbA1c values with sitagliptin (100 mg once daily), metformin (500 mg bd) and metformin (1000 mg bd) were 0.8, 1.0, and 1.3%, respectively. In these studies there was no significant difference in hypoglycaemia or weight between metformin and DPP-4 inhibitor treated groups, however, GI side-effects were significantly greater with metformin.

**Thiazolidinediones**
In drug-naïve patients with type 2 diabetes, vildagliptin (50 mg bd) and rosiglitazone (8 mg once daily) decreased HbA1c values by 1.1 and 1.3%, respectively, after 24 weeks, meeting the statistical criterion of non-inferiority of vildagliptin relative to rosiglitazone. Patients on rosiglitazone had an average weight gain of 1.6 kg, while vildagliptin had no effect on weight [69]. In another trial including patients with type 2 diabetes inadequately controlled on metformin (mean HbA1c 8.4%), additional treatment with vildagliptin (50 mg bd) was compared with pioglitazone given in submaximal doses (30 mg/day) [70]. After 24 weeks, the reductions in mean HbA1c values were similar in the vildagliptin and pioglitazone groups: 0.9 and 1.0%, respectively. Mean weight gain was significantly greater in the pioglitazone group compared with the vildagliptin group – 1.9 and 0.3 kg, respectively.

**SAFETY OF DPP-4 INHIBITORS**
Both sitagliptin and vildagliptin appear to be well tolerated. Withdrawal rates in patients randomised to either agent being similar to placebo. A recent meta-analysis suggested that the commonest adverse effects reported in slightly higher proportions of patients receiving sitagliptin or vildagliptin were nasopharyngitis (6.4 vs. 6.1% vs. comparator, risk ratio 1.2),
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urinary tract infection (3.2 vs. 2.4% with placebo, risk ratio 1.5) and headache (5.1 vs. 3.9% with placebo, risk ratio 1.4) [66]. Available data suggest that DPP-4 inhibitors may be better tolerated than metformin, glipizide and acarbose [66]. There was no difference in reported mild to moderate hypoglycemia between DPP-4 inhibitors and a comparator group (1.6% vs 1.4%, respectively; risk ratio 1.0). Hypoglycemia did become more evident when DPP-4 inhibitors were used in conjunction with SU, with the proportions of patients reporting hypoglycemia being 12% (27 of 222) and 1.8% (4 of 219) in patients receiving sitagliptin plus glimepiride versus patients receiving glimepiride plus placebo, respectively [71].

ROLE OF INCRETIN THERAPIES IN CLINICAL PRACTICE

There is no doubt that incretin-based drugs represent a useful addition to the existing armamentarium of antidiabetic drugs. These agents have several advantages. First, because of their distinct mechanism of action, they generally exert a beneficial effect on glycemic control, irrespective of the type of background oral agents. Second, by targeting postprandial hyperglycemia more than fasting or pre-meal hyperglycemia, they complement the action of metformin, TZD, and long-acting SU, which act mainly by lowering fasting plasma glucose. A third advantage is the progressive weight loss caused by exenatide, and the weight-neutral effect of the DPP-4 inhibitors. Fourth, the use of incretin-related agents is uncommonly associated with severe hypoglycemia. Moreover, the use of DPP-4 inhibitors is simple, with once or twice-daily oral dosing irrespective of meal intake.

Meanwhile, exenatide and current DPP-4 inhibitors have important limitations. First, it should be emphasized that 50% of patients in clinical trials failed to achieve HbA1c levels < 7.0%. Second, exenatide has to be injected twice daily, and is associated with high rates of nausea, although tolerance to nausea appears to develop over time and a dose escalation protocol for exenatide appears to minimise the gastrointestinal adverse effects. Third, while the short-term (≤ 1 year) safety profile of two DPP-4 inhibitors – sitagliptin and vildagliptin – is reassuring, there are still some unresolved issues related to their safety. For instance, the enzyme DPP-4 plays an important role in the immune system, being a T-cell co-stimulator [72]; this raises concern about possible immune suppression as result of DPP-4 inhibition. In addition to GLP-1 and GIP, DPP-4 inhibits the degradation of other peptides in vitro, such as substance P [50]. Thus, there is a possibility that serum levels of such peptides may rise with the use of DPP-4 inhibitors leading to potential undesired effects. There are also two other enzymes, DPP-8 and DPP-9, structurally related to DPP-4 but with largely unknown functions [72]. Although in-vitro data suggest that DPP-4 inhibitors display high selectivity for DPP-4, no in-vivo data are available.

In individual studies, DPP-4 inhibitors showed no characteristic pattern of adverse effects. However, a recent meta-analysis showed an increased risk of infections, such as urinary tract infection and nasopharyngitis. Although the observed relative risk was small, its implications in clinical practice are unclear and longer term evaluation is required. Potential skin toxicity also remains a consideration with DPP-4 inhibitors with a few serious cases of hypersensitivity reactions being reported possibly related to sitagliptin, including anaphylaxis, angio-oedema and Stevens-Johnson syndrome.

On balance, incretin-based therapies, with modest glucose lowering effects, favorable weight profile, low hypoglycaemia risk and potentially positive effects on cardiovascular risk factors for exenatide, represent a useful alternative to and may offer an advantage over currently available hypoglycaemic agents. Hypoglycemia may still be an issue, especially if incretin therapy is combined with an insulin secretagogue; therefore, when incretin therapy is co-administered with such agents, the dose of the latter should be adjusted to minimise hypoglycemia.

Metformin will remain the drug of choice for initial treatment of type 2 diabetes due to its long-term safety, efficacy and low cost [73]. Meanwhile, based on the available data, and
while longer term efficacy, safety and cost-effectiveness evaluation is awaited, incretin-based therapies may be of particular benefit in specific situations:

**Exenatide / GLP-analogue therapy**

The most recent blood glucose lowering guidelines from the National Institute for Clinical Excellence (NICE) in the UK [74] suggest that such agents may be considered for use in patients with suboptimal glycaemic control, with ongoing metformin/sulphonylurea combination therapy if a person is:

- Obese (a body mass index (BMI) ≥ 35 kg/m²) in those of European descent, with appropriate adjustment for other ethnic groups and other specific psychological or medical problems associated with high body weight.
- Overweight (BMI < 35 kg/m²) and for whom initiation of insulin therapy would have significant occupational implications, or where weight loss would benefit other significant comorbidities such as sleep apnoea.
- Therapy should be only be continued following an appropriate assessment of efficacy and safety, e.g. 1% reduction in HbA1c at 6 months and 5% weight loss after 1 year.

The above approach to the use of these agents, while providing some useful guidance, may be considered as somewhat over prescriptive in nature. Given their high cost and subcutaneous method of administration, it is unlikely that they would gain widespread support for second-line use following metformin monotherapy failure. However, such agents would make a sensible second-line therapy choice for people in who weight loss is a crucial therapeutic priority (e.g. obstructive sleep apnoea and non-alcoholic steatohepatosis).

When considering stipulations around discontinuation of therapy, this is an area where the effects of therapy on both weight and glycaemic control should be assessed on an individual patient basis with the decision to continue treatment or otherwise based on the overall clinical picture, including an evaluation of the potential limitations of alternative therapy options.

The most recent American Diabetes Association / European Association for the Study of Diabetes (ADA / EASD) consensus algorithm for the management of blood glucose in type 2 diabetes [75], suggests that exenatide should only be considered when weight loss is a major consideration and the HbA1c level close to target (<8%). This suggested approach is based on reductions in HbA1c of 0.5–1% seen in clinical trials with exenatide. It is, however, noteworthy that greater reductions in HbA1c have been noted (1–1.5%) in patients with higher baseline HbA1c levels and that these reductions may be maintained for up to 82 weeks of therapy. Thus to define the clinical indication for such agents based on the minimal reported glucose lowering effects set in the context of a population-based glycaemic target approach as opposed to a more individualised approach may lead to significant numbers of patients who would otherwise gain benefit either in terms of weight and glucose reduction being denied treatment.

When deciding between the use of GLP-analogue therapy and insulin, the progression of type 2 diabetes along with the expected improvement in HbA1c as compared with the individualised patient glycaemic are important considerations. In particular if hyperglycaemia is sufficiently pronounced that the addition of GLP-analogue therapy is unlikely to achieve the desired HbA1c target then insulin would be a more appropriate therapy choice.

**DPP-4 inhibitors**

The relatively high cost, limited long-term safety data and modest glucose lowering efficacy means that DPP-4 inhibitors should not generally replace a sulphonylurea as second-line therapy at this time. These agents may, however, be considered as an alternative to a sulphonylurea...
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nylurea in a range of circumstances. These include people for who hypoglycaemia and/or weight gain are of particular concern, although there is insufficient data currently available to define a threshold BMI above which the use of a DPP-4 inhibitor would be particularly appropriate. Rather the potential weight/hypoglycaemia benefits of these agents should be evaluated on an individual patient basis. When considering the use of second-line oral agents in patients with suboptimal glycaemic control on metformin monotherapy, a DPP-4 inhibitor may be more appropriate than a TZD in patients where fracture risk or congestive cardiac failure are a concern or in who further weight gain would exacerbate psychological or medical problems associated with a high body weight. A DPP-4 inhibitor may be considered as add-on therapy to patients with suboptimal glucose control receiving sulphonylurea monotherapy, where the person does not tolerate metformin or it is contraindicated.

If metformin in combination with a sulfonylurea does not adequately control blood glucose (HbA1c ≤ 7.5%) and injection-based therapies such as insulin or GLP-1 analogues are inappropriate then a DPP-4 inhibitor is an appropriate third-line therapy alternative to a TZD based on the considerations outlined above.

The most recent ADA / EASD consensus guidance on the management of blood glucose in type 2 diabetes [75] do not include DPP-4 inhibitors based on their limited clinical data and relative expense. While the absence of long-term data will currently preclude the widespread adoption of this class as a preferred second-line therapy, it is important to remember that these agents have been studied in a wide variety of clinical scenarios over periods of up to 1 year. Furthermore, in an era of ever tighter glycaemic targets there is not only considerable patient morbidity but also cost implications associated with managing hypoglycaemia, weight gain and congestive heart failure risk associated with achieving HbA1c targets of < 7% with more established therapies such as sulphonylureas and TZDs.

The decision to continue DPP-4 inhibitor therapy should be based on an individual patient assessment and not simply guided by the achievement of a prespecified Hba1c reduction, taking into consideration the individualized HbA1c target, comorbid conditions and the limitations of alternative therapy options.

SUMMARY

Type 2 diabetes is a complex and progressive disorder that is difficult to effectively treat in the long term. The majority of patients are obese or overweight and find difficulty is sustaining glycaemic control without multiple oral therapies, with a sizeable proportion requiring exogenous insulin. This characteristic need for therapeutic escalation reflects progressive loss of β-cell function combined with obesity-related insulin resistance. The management of type 2 diabetes has never before been so complex, with a variety of differing classes of hypoglycaemic therapies comprising heterogeneous modes of action, safety and tolerability profiles. These classes include agents that stimulate insulin secretion (sulphonylureas, insulin secretagogues and incretin mimetics), agents that reduce hepatic glucose output (biguanides), and agents that improve insulin sensitivity (thiazolidinediones) The UKPDS (United Kingdom Prospective Diabetes Study) demonstrated the benefits of intensive blood glucose control on microvascular complications, while metformin was demonstrated to improve macrovascular outcomes in obese patients. The STENO-2 study demonstrated that a target driven multifactorial approach based around a sulphonylurea was associated with improved macrovascular and microvascular outcomes. Recent studies using thiazolidinediones have suggested improved cardiovascular outcomes with pioglitazone and benefits around sustained glycaemic control with rosiglitazone, although safety concerns have been raised around potential cardiovascular adverse events with rosiglitazone and an increased fracture risk with the class as a whole. The selection of initial monotherapy is based on both clinical and biochemical patient factors, insulin may be the treatment of choice where non-pharmacological intervention has failed. Oral therapies should be initiated at low dose and titrated
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according to glycaemic response. The average glucose lowering effects of the individual agents is broadly similar (1–2% reduction in HbA1c). Doses are gradually increased according to response, although maximal glucose lowering effects occur at between 50–75% of the recommended maximum daily dose. With an increasing recognition of the benefits of intensive glucose reduction combination therapy is required in the majority of patients.

Considerable advances have been made over the last few years in understanding the endocrine connections that link the gastrointestinal tract and the pancreatic islet. New therapies that enhance the incretin effect will increasingly become more widely available to both clinicians and patients in day-to-day practice. The possibility of a once weekly preparation of some of these agents in the future holds much promise. DPP-4 inhibitors as oral preparations may have advantages over the parenterally administered GLP-1 analogues. However, they are weight neutral and it must be remembered that DPP-4 is a ubiquitous enzyme with the potential to inhibit various other peptides and there is much more to learn about the long-term side-effects of these agents. Having said that, the potential for these agents to improve β-cell mass, durability and function is an exciting prospect for a metabolic condition that inevitably progresses in spite of optimum treatment.

REFERENCES

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