29 Oral Antidiabetic Agents

Clifford J. Bailey[1] & Andrew J. Krentz[2]

[1] School of Life and Health Sciences, Aston University, Birmingham, UK
[2] Formerly, Department of Diabetes and Endocrinology, Southampton University Hospitals NHS Trust, Southampton, UK

Keypoints

- Glycemic control is a fundamental part of the management of type 2 diabetes mellitus. Adequate glycemic control is necessary to address acute symptoms and to prevent, defer or reduce the severity of chronic microvascular and macrovascular complications.
- Treating type 2 diabetes is complicated by the multivariable and progressive natural history of the disease. Insulin resistance, a progressive decline in β-cell function, defects of other gluco-regulatory hormones and nutrient metabolism give rise to a continually changing presentation of the disease that requires therapy to be adjusted accordingly. Patients are often overweight or obese, exhibit substantial co-morbidity and elevated cardiovascular risk, and receive many other medications which further complicate treatment.
- Care plans and treatment programs should be tailored to fit the prevailing circumstances of the patient. Lifestyle management (diet and exercise) should be emphasized from the time of diagnosis and reinforced thereafter. Drug treatment should be undertaken promptly if lifestyle intervention does not achieve adequate glycemic control.
- Choice of drug therapy should ideally address underlying pathophysiology, but any safe means of restraining the escalating hyperglycemia may be appropriate. Combinations of differently acting agents are frequently required to provide additive efficacy, and single tablet, fixed dose combinations are available to facilitate combination therapy. Contraindications and precautions associated with each component must be respected.
- The biguanide metformin is often selected as initial oral antidiabetic drug therapy. It counters insulin resistance and lowers blood glucose through several insulin-dependent and independent mechanisms, notably reducing hepatic glucose production and also increasing glucose uptake by skeletal muscle. It does not stimulate insulin secretion, carries a low risk of frank hypoglycemia and does not cause weight gain. Metformin also exerts several potentially beneficial effects on cardiovascular risk factors independently of glycemic control, with evidence of improved long-term cardiovascular outcomes. Metformin may be conveniently combined with other classes of antidiabetic drugs. Gastrointestinal side effects including diarrhoea limit the use of metformin. The rare but serious adverse effect of lactic acidosis excludes the use of the drug in patients with significant renal insufficiency, significant liver disease or any condition predisposing to hypoxia or hypoperfusion including cardiac or respiratory failure.
- Sulfonylureas (e.g. gliclazide, glimepiride, glibenclamide/glyburide, glipizide) act on the pancreatic β-cells to stimulate insulin secretion. They bind to the transmembranal complex of sulfonylurea receptors SUR1 with ATP-sensitive Kir6.2 potassium efflux channels. This closes the channels, depolarizes the membrane, opens voltage-dependent calcium channels and raises intracellular free calcium concentrations. This in turn activates proteins regulating insulin secretion. The efficacy of sulfonylureas depends on adequate remaining function of the β-cells. Hypoglycemia is the most serious adverse effect, particularly with longer acting sulfonylureas and in the elderly. Caution with hepatic and/or renal insufficiency is warranted in accordance with the metabolism and elimination of individual preparations, and interactions with other protein-bound drugs can occur.
- Meglitinides (repaglinide and nateglinide), also known as prandial insulin releasers, are rapid and short-acting insulin secretagogues taken before meals to boost insulin levels during digestion, thereby reducing prandial hyperglycemia and decreasing risk of interprandial hypoglycemia. They act in a similar manner to sulfonylureas by binding to a "benzamido" site on the SUR1–Kir6.2 complex. They are conveniently used in combination with an agent that reduces insulin resistance.
- Thiazolidinediones (pioglitazone and rosiglitazone) produce a slow-onset glucose-lowering effect, attributed mainly to increased insulin sensitivity. They alter the expression of certain insulin-sensitive genes by stimulating the peroxisome proliferator-activated receptor γ, increasing adipogenesis, and rebalancing the glucose–fatty acid (Randle) cycle. Thiazolidinediones can be used as monotherapy or in combination with other classes of antidiabetic agents. They have low risk of hypoglycemia but often cause weight gain. The potential for fliud retention and an attendant risk of congestive heart failure should be borne in mind, especially in combination with insulin. Thiazolidinediones are not recommended for individuals at high risk of cardiac disease or women with reduced bone density.

Textbook of Diabetes, 4th edition. Edited by R. Holt, C. Cockram, A. Flyvbjerg and B. Goldstein. © 2010 Blackwell Publishing.

- Gliptins (sitagliptin, vildagliptin and saxagliptin) act predominantly as prandial insulin secretagogues by raising the circulating concentrations of endogenous incretin hormones, notably glucagon-like peptide 1 and glucose-dependent insulinotropic polypeptide. Incretin hormones are released from the intestine during a meal and potentiate nutrient-stimulated insulin secretion, but they are rapidly degraded by the enzyme dipeptidyl peptidase 4: gliptins inhibit this enzyme. Gliptins are weight neutral and, as monotherapy, they carry low risk of interprandial hypoglycemia. They are often used in combination with metformin or a thiazolidinedione.
- α-Glucosidase inhibitors (e.g. acarbose) slow the digestion of carbohydrates by competitive inhibition of intestinal α-glucosidase enzymes. This delays glucose absorption and reduces post-prandial glucose excursions without stimulating insulin secretion. These agents must be used in conjunction with meals rich in digestible complex carbohydrate. They do not cause weight gain or hypoglycemia as monotherapy and can be used alongside any other antidiabetic agents.
- In advanced stages of type 2 diabetes, β-cell function is often too severely compromised to support the continued use of oral agents alone. Insulin therapy should be initiated, continuing one or more oral agents where appropriate.

Table 29.1 Aims of appropriate glycemic control in type 2 diabetes. Adapted from Wallace & Matthews [1].

Purpose	Complications
Prevent acute symptoms of hyperglycemia	Dehydration, thirst, polyuria, blurred vision, increased infections
Prevent acute complications	Hyperosmolar non-ketotic state
Prevent, defer or reduce severity of chronic vascular complications	Microvascular: retinopathy, nephropathy, neuropathy
	Macrovascular: coronary, cerebrovascular, peripheral vascular

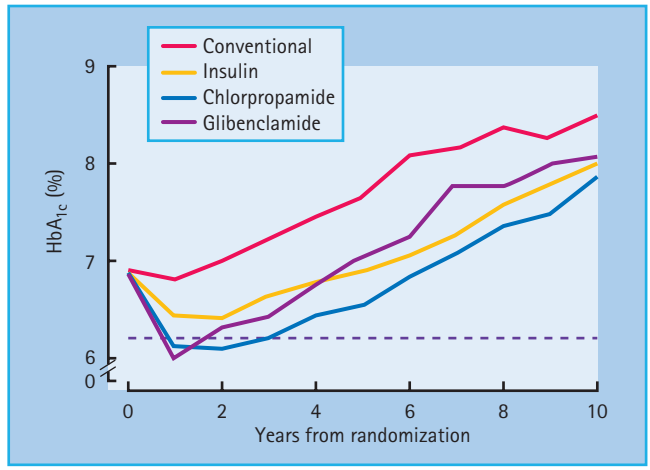

Figure 29.1 The UK Prospective Diabetes Study (UKPDS) shows the progressive rise in HbA_{1c} occurring with time in groups receiving "conventional" (diet) therapy and "intensive" therapy with various antidiabetic drugs (two sulfonylureas – chlorpropamide and glibenclamide – and insulin). Data from Wallace & Matthews [1] and UKPDS [12].

Introduction

Appropriate glycemic control is a fundamental pillar in the management of type 2 diabetes mellitus (T2DM). It is required to prevent and relieve acute symptoms and complications of hyperglycemia; prevent, defer and reduce the severity of microvascular complications; and afford some benefits against macrovascular complications (Table 29.1) (see Chapters 20) [1,2]. Treatment of the hyperglycemia is essential to an individualized care plan that takes account of coexistent diseases and personal circumstances, offers suitable advice on lifestyle and diet, includes other measures to address modifiable cardiovascular risk, selects realistic targets, and facilitates patient education and empowerment, as considered in detail in Part 5. This chapter focuses on the role of oral blood glucose-lowering agents (other antidiabetic therapies are addressed in Chapters 27 and 30) in the treatment of T2DM) [2–5].

Pathophysiologic considerations

The interdependent multiplicity of genetic and environmental factors underlying T2DM (see Chapters 12 and 14) give rise to a highly heterogeneous and progressive natural history [2,6,7]. The pathophysiology typically involves defects of insulin secretion *and* insulin action [8]. Obesity, especially visceral adiposity, and abnormalities of glucagon secretion commonly contribute to the disease process, while cellular disturbances of nutrient metabolism participate both as causes and consequences of glucotoxicity and lipotoxicity [9–11]. An ideal approach to therapy might therefore address the basic endocrine defects, but any other safe means of ameliorating the hyperglycemia and attendant biochemical disruptions should provide clinical benefits.

The progressive nature of T2DM was well-illustrated by the UK Prospective Diabetes Study (UKPDS), a randomized trial of 5102 patients with newly diagnosed T2DM followed for a median of 10 years while receiving either "conventional" (diet) therapy or "intensive" therapy with various oral antidiabetic agents or insulin (Figure 29.1). Note that insulin was introduced earlier than is usual in clinical practice, and insulin was also used as necessary when oral agents were deemed inadequate. Although glycemic control (illustrated by the HbA_{1c} level) deteriorated

Table 29.2 Trials comparing intensive with standard (conventional) glycemic control in type 2 diabetes.

Trial	Number	Duration of follow-up	Age	Duration of diabetes	Baseline HbA_{1c}%	Intensive HbA_{1c}%		Conventional HbA_{1c}%	Relative risk reduction			
									Microvascular		Macrovascular	
									%	*P*	%	*P*
UKPDS	3867[a]	10	53	New	7.1[b]	7.0	vs	7.9	↓ 25%	0.009	↓ 16%[c]	0.052[d]
UKPDS (post-trial follow-up)	2998	8.5	63	10	–		–		↓ 24%	0.001	↓ 15%[c]	0.014
ADVANCE	11,140	5	66	8	7.5	6.5	vs	7.3	↓ 14%	0.01	↓ 6%	0.32[b]
ACCORD[e]	10,251	3.5[e]	62	10	8.3	6.4[e]	vs	7.5	↓ 33%	0.005[f]	↓ 10%	0.16[b]
VADT	1791	5.6	60	11.5	9.4	6.9	vs	8.4	↓ 2.5[g]	0.05	↓ 12%	0.14[b]

ACCORD, Action to Control Cardiovascular Risk in Diabetes; ADVANCE, Action in Diabetes and Vascular Disease: Preterax and Diamicron-MR Controlled Evaluation; UKPDS, UK Prospective Diabetes Study; VADT, Veterans Affairs Diabetes Trial.

[a] Non-obese patients.

[b] After a 3-month dietary run-in.

[c] Myocardial infarction.

[d] Non-significant.

[e] Intensive therapy discontinued at median 3.5 years because of increased deaths in the intensive (257/5128; 5%) versus conventional (203/5123; 4%) group.

[f] Reduction in new or worsening nephropathy. No effect on incidence of progression of retinopathy.

[g] Any increase in albuminuria.

with time irrespective of the treatment, the improvement in glycemic control afforded by intensive therapy (median HbA_{1c} reduced by 0.9% [10 mmol/mol]) was associated with a 12% reduction in overall diabetes-related endpoints and a 25% reduction in microvascular endpoints [12]. An epidemiologic analysis showed that benefits of intensive therapy continued to accrue until glucose levels were returned to the normal range [13]. Moreover, the benefits of earlier "intensive" control were continued during an unrandomized post-trial follow-up (median 8.5 years) during which glycemic differences between the former groups were not maintained [14]. This illustrates the glycemic "legacy" effect in which early intensive glycemic control confers an extended reduction in complications, even when control deteriorates at later stages in the disease process.

Other large randomized trials [15–17] have confirmed fewer microvascular complications amongst those receiving more intensive glycemic management (Table 29.2). One such study, the Action to Control Cardiovascular Risk in Diabetes (ACCORD) study, noted increased mortality during highly intensified (5% mortality, 257/5128) versus standard (4% mortality, 205/5123) glycemic management. This may be ascribed to unique features of the trial design outside of normal practice in an aging population at high cardiovascular risk with a long previous duration of inadequately controlled diabetes given extensive medications and experiencing high rates of hypoglycemia. Indeed, an acceptable HbA_{1c} value does not preclude excessive daily fluctuations in glycemia with hyperglycemic excursions and hypoglycemic troughs, the latter often unrecognized nocturnally (see Chapter 33). Survival of a myocardial event appears to be reduced by hypoglycemia as well as hyperglycemia [18].

Guidelines and algorithms

Factors to consider when selecting a glycemic target for a particular patient are deliberated in detail in Chapter 20, but it is pertinent to reiterate here that the general principle is to safely return glycemia as close to normal as practicable, avoiding hypoglycemia, minimizing potential drug interactions, and observing other necessary cautions and contraindications. An individualized approach is recommended. Current treatment algorithms [19–25] provide a framework for initiating and intensifying therapy, but clinical judgment should be applied to harmonize this with patient circumstances. Thus, a younger, newly diagnosed individual without co-morbidity who is responsive to therapy might be expected to meet a more rigorous target, while an elderly infirm individual with co-morbidity and a long history of problems with diabetes control may require more flexiblity. Management of hyperglycemia should always be part of a comprehensive management program to address coexistent disease and modifiable cardiovascuar risk factors.

It is emphasized that diet, exercise and other lifestyle measures should be introduced at diagnosis and reinforced at every appropriate opportunity thereafter. These measures can provide valuable blood glucose lowering efficacy and may initially enable the desired glycemic target to be achieved (see Chapters 22 and 23); however, even when lifestyle advice is successfully implemented, the progressive natural history of the disease dictates that the majority of patients will later require pharmacologic therapy, and this should be introduced promply if the glycemic target is not met or not maintained.

The main classes of oral antidiabetic drugs and their principal modes of action are listed in Table 29.3. The main tissues through which they exert their glucose-lowering effects are illustrated in Figure 29.2, and the main cautions and contraindications associated with oral antidiabetic agents are listed in Table 29.4. Although there are several different classes from which to choose, many dilemmas continue to impinge on both strategy and individualization of treatment. For example, an increase in fasting glycemia usually accounts for the majority of the hyperglycemia in T2DM: ideally therefore, this should be adequately addressed during therapy [26]. It is also pertinent to note the link between postprandial hyperglycemic excursions and cardiovascular risk, which mandates the need to also address this component of the hyperglycemic day profile [27]. Additionally, consideration should be given to the improvements in glycemic control that can be achieved through the treatment of obesity (see Chapter 14) [28]. By the time of diagnosis, insulin resistance is usually well established and does not usually progress with extended duration of the disease [8]. Nevertheless, the association between insulin resistance and cardiovascular risk warrants the amelioration of insulin resistance as a valued therapeutic strategy. The ongoing deterioration in glycemic control after diagnosis is largely attributed to a further progressive decline in β-cell function [8]. Thus, preserving β-cell function and mass are important considerations in maintaining long-term glycemic control. If β-cell function deteriorates beyond the capacity of oral agents to provide adequate glycemic control, then the introduction of insulin should not be delayed. Incorporating some or all of the above into the treatment process is inevitably a challenge, and the need to explore suitable combinations of therapies to accommodate the changing status of the disease is now accepted practice.

The increasing prevalence of T2DM amongst younger adults and pre-adults adds an extra long-term dimension to risk–benefit

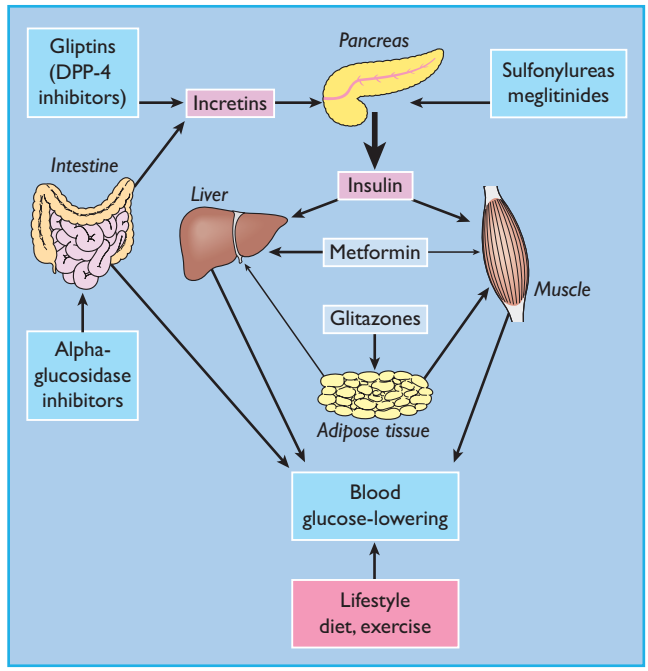

Figure 29.2 Main tissues through which oral antidiabetic agents exert their glucose-lowering effects.

Table 29.3 Classes of oral antidiabetic drugs and their main modes of action.

Class with examples	Main mode of glucose-lowering	Main cellular mechanism of action
Biguanide		
Metformin	Counter insulin resistance (especially decrease hepatic glucose output)	Enhance various insulin dependent and independent actions including AMPK
Sulfonylureas		
Glimepiride, gliclazide, glyburide/glibenclamide, glipizide	Stimulate insulin secretion (typically 6–24 hours)	Bind to SUR1 sulfonylurea receptors on pancreatic β-cells, which closes ATP-sensitive Kir6.2 potassium channels
Meglitinides		
Repaglinide, nateglinide	Stimulate insulin secretion (faster onset and shorter duration of action than sulfonylureas)	Bind to benzamido site on SUR1 receptors on pancreatic β-cells, which closes ATP-sensitive Kir6.2 potassium channels
Gliptins (DPP-4 inhibitors)		
Sitagliptin, vildagliptin, saxagliptin	Increase prandial insulin secretion	Inhibit DPP-4 enzyme, which increases plasma half-life of insulinotropic incretin hormones
Thiazolidinediones (PPAR-γ agonists)		
Pioglitazone, rosiglitazone	Increase insulin sensitivity (especially increase peripheral glucose utilization)	Activate nuclear receptor PPAR-γ mainly in adipose tissue, which affects insulin action and glucose–fatty acid cycle
α-Glucosidase inhibitors		
Acarbose, miglitol, voglibose	Slow rate of carbohydrate digestion	Competitive inhibition of intestinal α-glucosidase enzymes

AMPK, adenosine 5′-monophosphate-activated protein kinase; ATP, adenosine triphosphate; DPP-4, dipeptidyl peptidase 4; PPAR-γ, peroxisome proliferator-activated receptor γ.

Table 29.4 General features of oral antidiabetic treatments for type 2 diabetes including the main cautions and contraindications.

	Metformin	Sulfonylureas	Meglitinides	Thiazolidinediones	Gliptins	α-Glucosidase inhibitors
HbA_{1c}	↓ 1–2%	↓ 1–2%	↓ 0.5–1.5%[h]	↓ 1–1.5%	↓ 0.5–1.5%[h]	↓ 0.5–1%[h]
Body weight	–/↓	↑	↑/–	↑	–	–
Lipids	–/+	–	–	+/–/×	–	–/+
Blood pressure	–	–	–	↓/–	–	–
Tolerability	GI[a]	Hypo[f]	Hypo[i]	Fluid[d]	–	GI[a]
Safety	LA[b]	Hypo[f]	Hypo[i]	Edema Anemia Heart failure[e] Fractures	–	–
Cautions	Renal Liver Hypoxemia[c]	Liver Renal[g]	Liver Renal[g]	CV[e]	–[j]	–

CV, cardiovascular; GI, gastrointestinal; HbA_{1c}, glycated hemoglobin (1% = ~11 mmol/mol); Hypo, hypoglycemia; LA, lactic acidosis.
↑ Increased; ↓ decreased; – neutral; + benefit; × impair.
[a] Gastrointestinal side effects.
[b] Lactic acidosis (rare).
[c] Check for adequate renal and hepatic function, avoid in conditions with heightened risk of hypoxemia.
[d] Fluid retention, anemia, increased risk of heart failure in susceptible patients.
[e] Check for pre-existing cardiovascular disease or developing signs of heart disease: controversy regarding possible early increase in myocardial infarction with rosiglitazone not confirmed in long-term prospective studies.
[f] Risk of hypoglycemia, occasionally severe.
[g] Check liver and/or renal function relevant to mode of metabolism/elimination.
[h] Mostly act to lower post-prandial hyperglycemia – lesser impact on fasting glycemia and on HbA_{1c}.
[i] Lesser risk of severe hypoglycemia than sulfonylurea.
[j] Monitoring of liver function with vildagliptin.

considerations. While initial adequate intervention remains paramount, there is limited experience with oral antidiabetic agents in children and adolescents; metformin has been used safely in controlled pediatric practice from 10 years of age, and sulfonylureas have been used in pediatric presentations of certain forms of maturity-onset diabetes of the young (MODY). Treating T2DM in women who are of childbearing age carries the risk of unplanned pregnancy while receiving oral antidiabetic agents. Treatment with these agents at the time of conception and during the first trimester has not been shown to have any adverse effects on mother or fetus, and judicious use of metformin has been shown to reduce miscarriage and gestational diabetes. Insulin remains the preferred antidiabetic medication in pregnancy, however, having a substantial evidence base for safety and flexibility. A paucity of evidence contraindicates thiazolidinediones and gliptins during pregnancy and lactation.

Elderly patients are more vulnerable to most of the cautions and contraindications to glucose-lowering drugs, and deteriorations in their pathophysiologic status can occur rapidly, necessitating more frequent monitoring (see Chapter 54). Hypoglycemia is a particular concern in this age group. While safety must be judged on an individual drug–patient basis, it is noteworthy that several common medications can impair glycemic control (e.g. glucocorticoids, certain antipsychotics, diuretics and beta-blockers), while others may have their own minor glucose-lowering effect (e.g. aspirin, some angiotensin-converting enzyme [ACE] inhibitors and mineral supplements) (see Chapter 26). The most frequent interactions with glucose-lowering drugs are summarized in Table 29.5.

Terminology within the field of antidiabetic agents may simplify the usage of the different agents. Hypoglycemic agents have the capacity to lower blood glucose below normal to the extent of frank hypoglycemia (e.g. sulfonylureas and insulin). Antihyperglycemic agents can reduce hyperglycemia, but when acting alone they do not have the capability to lower blood glucose below normoglycemia to the extent of frank hypoglycema (e.g. metformin, thiazolidinediones, incretins, gliptins, α-glucosidase inhibitors).

Biguanides

Metformin (dimethylbiguanide) is the only biguanide currently used in most countries (Figure 29.3). The history of biguanides stems from a guanidine-rich herb *Galega officinalis* (goat's rue or French lilac) that was used as a traditional treatment for diabetes in Europe [29]. Guanidine has a glucose-lowering effect, and several guanidine derivatives were adopted for the treatment of

Table 29.5 Drug interactions with oral antidiabetic agents that may affect their glucose-lowering effects.

Antidiabetic agent	Increase glucose lowering	Decrease glucose lowering
Any	Combination with other antidiabetic drugs Minor insulin releasers (e.g. aspirin) Minor insulin sensitivity enhancers, e.g. ACE inhibitors, magnesium or chromium supplements	Agents that impair insulin action (e.g. glucocorticoids, some antipsychotics, minor effects of diuretics, beta-blockers, some β_2-agonists) Impair insulin secretion (e.g. octreotide, some calcium channel blockers)
Metformin	Renal cation secretion competition by cimetidine Minor PK interaction with furosemide and nifedipine	–
Sulfonylureas	Reduce hepatic metabolism (e.g. some antifungals and MAOIs) Displace plasma protein binding (e.g. coumarins, NSAIDs, sulfonamides) Decrease excretion (e.g. probenecid)	K^+–ATP channel openers (e.g. diazoxide) Metabolism secondary to enzyme induction (e.g. rifampicin)
Meglitinides	Reduce hepatic metabolism, gemfibrozil Potentially displace plasma protein binding	Metabolism secondary to enzyme induction (e.g rifampicin, barbiturates, carbamazepine)
Thiazolidinediones	Reduce hepatic metabolism, gemfibrozil Potentially displace plasma protein binding	Metabolism secondary to enzyme induction (e.g rifampicin)
Gliptins	Potential interactions with liver and renal metabolism and plasma protein binding	–
α-Glucosidase inhibitors	Slow gut motility (e.g. cholestyramine)	Potentially with agents that increase gut motility

ACE, angiotensin-converting enzyme; MAOI, mono oxidase inhibitor; NSAID, non-steroidal anti-inflammatory drug; PK, pharmacokinetic.

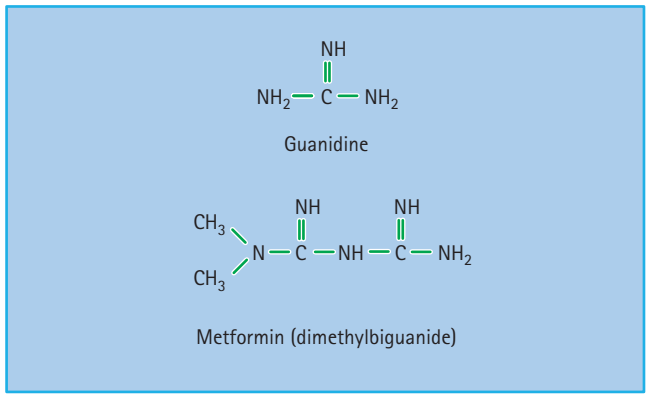

Figure 29.3 Chemical structures of guanidine and metformin.

diabetes in the 1920s [30]. These agents all but disappeared as insulin became available, but three biguanides – metformin, phenformin and buformin – were introduced in the late 1950s. Phenformin and buformin were withdrawn in many countries in the late 1970s because of a high incidence of lactic acidosis. Metformin remained and was introduced into the USA in 1995 [31], and this has since become the most prescribed antidiabetic agent worldwide [32].

Mode of action

Metformin exerts a range of actions that counter insulin resistance and lower blood glucose: the drug also offers some protection against vascular complications independently of its antihyperglycemic effect (Table 29.6) [33,34]. At the cellular

Table 29.6 Diverse metabolic and vascular effects of metformin.

Features associated with diabetes		Effects of metformin
Hyperglycemia	↓	↓ HGP, ↑ peripheral glucose uptake ↑ glucose turnover
Insulin resistance	↓	↑ Receptor–postreceptor insulin signals
Hyperinsulinemia	↓	↓ Fasting and often post-prandial insulin
Obesity	↓/–	↓ or stabilizes body weight
IGT	↓	↓ Progression to type 2 diabetes
Dyslipidemia	↓/–	Modest benefits if abnormal ↓ VLDL-TG, ↓ LDL, ↑ HDL May decrease FA oxidation
Blood pressure	–	No significant effect
Pro-coagulant state	↓	Antithrombotic (↓ fibrinogen, ↓PAI-1, ↓ platelet aggregation)
Endothelial function	↑	↓ Vascular adhesion molecules
Atherosclerosis	↓	↓ MI, ↓ stroke, ↑ vascular reactivity, ↓ cIMT, ↑ life expectancy, anti-atherogenic in animals

↑ Increase; ↓ decrease; – no significant effect; cIMT, carotid intima-media thickness; FA, fatty acid; HDL, high density lipoprotein cholesterol; HGP, hepatic glucose production; IGT, impaired glucose tolerance; LDL, low density lipoprotein cholesterol; MI, myocardial infarction; PAI-1, plasminogen-activator inhibitor-1; VLDL-TG, very low density lipoprotein cholesterol triglyceride.

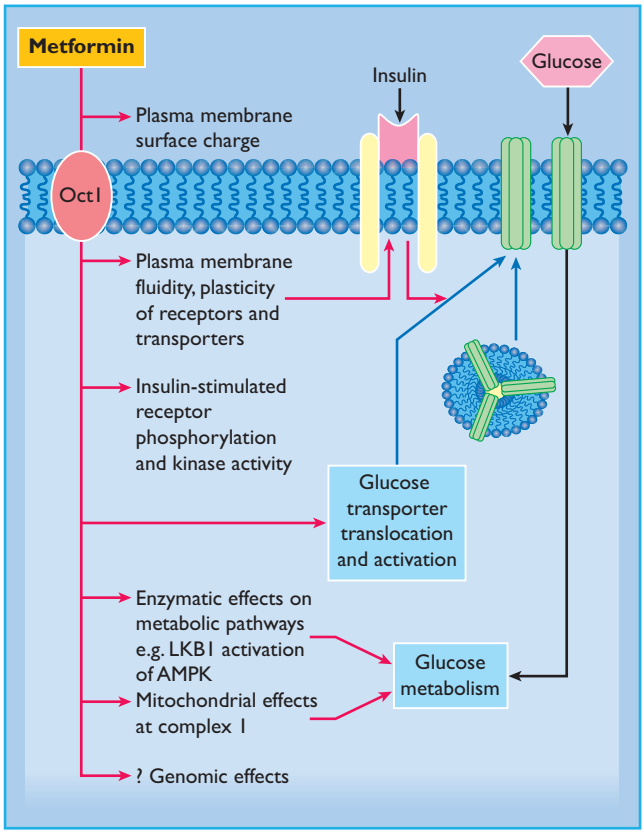

Figure 29.4 Multiple cellular action mechanisms of metformin involve insulin dependent and independent effects. For example, metformin can improve insulin sensitivity via effects on insulin receptor signaling and post-receptor signaling pathways of insulin action. Metformin also appears to influence cellular nutrient metabolism and energy production independently of insulin via activation of adenosine 5′-monophosphate (AMP) activated protein kinase (AMPK). Oct1, organic cation transporter 1; LKB1 protein kinase.

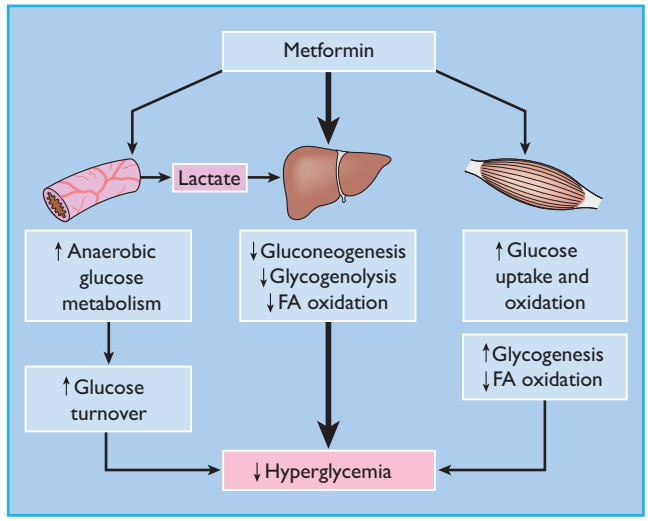

Figure 29.5 Main sites of action of metformin contributing to glucose-lowering effect.

level, metformin exerts insulin-dependent and independent effects on glucose metabolism (Figure 29.4). For example, metformin modestly improves insulin sensitivity probably via post-receptor signaling pathways for insulin, and it also appears to influence nutrient metabolism and energy production independently of insulin via activation of adenosine 5′-monophosphate-activated protein kinase (AMPK) [35].

The glucose-lowering efficacy of metformin requires a presence of at least some insulin because metformin does not mimic or activate the genomic effects of insulin. Also, metformin does not stimulate insulin release; its main glucose-lowering effect appears to be a reduction of hepatic glucose production, but not sufficiently to cause frank hypoglycemia when used as monotherapy. Metformin reduces gluconeogenesis by increasing hepatic insulin sensitivity and by decreasing hepatic extraction of some gluconeogenic substrates such as lactate (Figure 29.5). It also decreases hepatic glycogenolysis. Metformin can enhance insulin-stimulated glucose uptake in skeletal muscle by increasing translocation of insulin-sensitive glucose transporters (GLUT-4) into the cell membrane and increasing activity of glycogen synthase which promotes glycogen synthesis. Independently of insulin, metformin can suppress the oxidation of fatty acids and may reduce triglyceride levels in patients with hypertriglyceridemia. This restricts the supply of energy for hepatic gluconeogenesis and rebalances the glucose–fatty acid (Randle) cycle, allowing greater use of glucose relative to fatty acids as a cellular source of energy. Accumulation of a high cellular concentration of metformin (e.g. in the intestine) can suppress the mitochondrial respiratory chain at complex 1. This may contribute to the blood glucose-lowering effect of the drug, and help to prevent body weight gain by increasing glucose–lactate turnover.

Pharmacokinetics

Metformin is rapidly but incompletely absorbed, shows little binding to plasma proteins and is not metabolized, so it does not interfere with co-administered drugs. Metformin is widely distributed at concentrations similar to plasma (about 10^{-5} mol/L), but much higher concentrations are retained in the walls of the gastrointestinal tract. The plasma half-life ($t_{1/2}$) is about 6 hours with elimination of unchanged drug in the urine, mostly within 12 hours [36]. Although renal clearance is achieved more by tubular secretion than glomerular filtration, metformin is contraindicated for patients with significant impairment of glomerular filtration. Cimetidine is the only drug known to compete for clearance sufficiently to cause a clinically significant increase plasma metformin concentrations.

Indications and contraindications

Because metformin does not cause weight gain it is often preferred for overweight and obese people with T2DM, although it shows similar antihyperglycemic efficacy in normal weight patients [37]. To preclude drug accumulation, patient suitability

should be considered very carefully if there is any evidence of impaired renal function (e.g. if serum creatinine >130 μmol/L or creatinine clearance <60 mL/min or estimated glomerular filtration rate [eGFR] <45 mL/min/1.73 m^2). Further contraindications include significant cardiac or respiratory insufficiency, or any other condition predisposing to hypoxia or reduced tissue perfusion (e.g. hypotension, septicemia), as well as significant liver disease, alcohol abuse or a history of metabolic acidosis. Because the potential for acute deterioration in renal, cardiopulmonary and hepatic function should be taken into account, it is not practicable to identify precise cutoffs for starting or stopping metformin therapy. With this in mind, metformin can be used in the elderly providing renal insufficiency and other exclusions are not present. Ovulation can resume in women with anovulatory polycystic ovarian syndrome (PCOS), which is an unlicensed application of the drug in the absence of diabetes [38].

A standard (so-called immediate release [IR]) tablet or liquid formulation of metformin should be taken with meals or immediately before meals to minimize possible gastrointestinal side effects. Start with 500 or 850 mg once daily, or 500 mg twice daily (divided between the morning and evening meals). The dosage is increased slowly – one tablet at a time – at intervals of about 1–2 weeks until the target level of blood glucose control is attained. If the target is not attained and an additional dose produces no further improvement, return to the previous dose. In the case of monotherapy, consider combination therapy by adding in another agent (e.g. an insulin secretagogue or thiazolidinedione). The maximal effective dosage of metformin is about 2000 mg/day, taken in divided doses with meals, and the maximum is 2550 or 3000 mg/day in different countries.

Slow-release formulations (XR/SR/ER) of metformin are available in most countries; they can be taken once daily in the morning, or if necessary morning and evening. Metformin can also be used in combination with any other class of antidiabetic agent including insulin, and several fixed dose combination tablets are available in which metformin is combined with either a sulfonylurea or thiazolidinedione or dipeptidyl peptidase 4 (DPP-4) inhibitor (see below). Recall that although metformin alone is unlikely to cause serious hypoglycemia, this can occur when metformin is used in combination with an insulin-releasing agent or insulin.

During long-term use of metformin it is advisable to check at least annually for emergence of contraindications, particularly renal (as a minimum, serum creatinine). Metformin can reduce gastrointestinal absorption of vitamin B_{12}, and although this is rarely a cause of frank anemia, an annual hemoglobin measurement is recommended especially for individuals with known or suspected nutritional deficiencies. Metformin should be temporarily stopped when using intravenous radiographic contrast media, or during surgery with general anesthesia or other intercurrent situations in which the exclusion criteria could be invoked. Substitution with insulin may be appropriate at such times.

Efficacy

As monotherapy in patients who are not adequately controlled by lifestyle management, optimally titrated metformin typically reduces fasting plasma glucose by 2–4 mmol/L, corresponding to a decrease in HbA_{1c} by approximately 1–2% (11–22 mmol/mol) [39]. This is largely independent of body weight, age and duration of diabetes provided that some β-cell function is still present. To accommodate the progressive nature of T2DM, it is likely that uptitration of dosage and addition of a second agent will be required to maintain glycemic control in the long term.

Metformin carries minimal risk of significant hypoglycemia or weight gain when used as monotherapy. It may lead to a reduction of basal insulin concentrations, notably in hyperinsulinemic patients, which should help to improve insulin sensitivity. Minor improvements in the blood lipid profile have been observed during metformin therapy, mostly in hyperlipidemic patients: plasma concentrations of triglycerides, fatty acids and low density lipoprotein (LDL) cholesterol tend to fall, whereas high density lipoprotein (HDL) cholesterol tends to rise [37]. These effects appear to be independent of the antihyperglycemic effect, although a lowering of triglyceride and free fatty acids is likely to help improve insulin sensitivity and benefit the glucose–fatty acid cycle.

In the UKPDS, overweight patients who started oral antidiabetic therapy with metformin showed a 39% reduced risk of myocardial infarction compared with conventional treatment ($P = 0.01$) [40]. There was no obvious relationship with metformin dosage, suggesting that patients who can only tolerate a low dosage of metformin may benefit from continuing the drug, even when other agents are required to achieve adequate glycemic control. The decrease in myocardial infarction was not related to the extent of the glucose-lowering effect of metformin, or effects on classic cardiovascular risk factors such as blood pressure or plasma lipids. Reported benefits of metformin on various atherothrombotic risk markers and factors have been reported, including reduced carotid intima-media thickness (cIMT) (Table 29.6), increased fibrinolysis and reduced concentrations of the antithrombolytic factor plasminogen activator inhibitor-1 (PAI-1) [34]. Detracting somewhat from the generally favorable cardiovascular risk reports there is evidence that combination of metformin with a sulfonylurea may initially increase cardiovascular mortality [40,41]. One potentially confounding factor might be greater cardiovascular risk caused by more severe metabolic disease in patients needing treatment with the combination [42]. Evidence from large databases with sulfonylurea plus metformin combination therapy have been reassuring [43,44]. Indeed, recent results from the post-trial follow-up of UKPDS (without continuation of randomized groups) showed that the cardiovascular benefits of metformin were maintained [14].

When metformin is added to the regimens of patients receiving insulin therapy, a reduction of insulin dosage is often required, consistent with the ability of metformin to improve insulin sensitivity. Similarly, addition of insulin in patients already receiving metformin usually requires lesser dosages of insulin and results

in less weight gain. Lesser amounts of insulin are also associated with fewer and less severe episodes of hypoglycemia [44,45]. Although metformin is not indicated for the prevention of diabetes, it is noteworthy that the US Diabetes Prevention Program found metformin to reduce the incidence of new cases of diabetes in overweight and obese subjects with impaired glucose tolerance by 33%, compared with a reduced risk of 58% using an intensive regimen of diet and exercise [46]. The preventive effect of metformin was most evident amongst younger, more obese individuals.

Adverse effects

The main tolerability issue with metformin is abdominal discomfort and other gastrointestinal adverse effects, including diarrhea. These are often transient and can be ameliorated by taking the drug with meals and titrating the dose slowly. Symptoms may remit if the dose is reduced, but around 10% of patients cannot tolerate the drug at any dose. The most serious adverse event associated with metformin is lactic acidosis; it is rare (probably about 0.03 cases per 1000 patient-years), but about half of cases are fatal [31,47,48]. Because the background incidence of lactic acidosis amongst patients with T2DM has not been established, it is possible that some cases previously attributed to metformin were caused by other factors.

Most reported cases of lactic acidosis in patients receiving metformin have been caused by inappropriate prescription, particularly overlooking renal insufficiency. The resulting accumulation of metformin is likely to increase lactate production, and increasing lactate will be aggravated by any hypoxic condition or impaired liver function. Hyperlactatemia occurs in cardiogenic shock and other illnesses that decrease tissue perfusion, so metformin may only be an incidental factor in some cases. Nevertheless, metformin should be stopped immediately in all cases of suspected or proven lactic acidosis, regardless of cause.

Lactic acidosis is typically characterized by a raised blood lactate concentration (e.g. >5 mmol/L), decreased arterial pH and/or bicarbonate concentration with an increased anion gap ($[Na^+] - [Cl^- + HCO_3^-]$ >15 mmol/L). Presenting symptoms are generally non-specific, but often include hyperventilation, malaise and abdominal discomfort. Treatment should be commenced promptly without waiting to determine whether metformin is a cause; bicarbonate remains the usual therapy, but evidence of its efficacy is limited. Hemodialysis to remove excess metformin can be helpful, and may assist restoration of fluid and electrolyte balance during treatment with high-dose intravenous bicarbonate.

Sulfonylureas

Since their introduction in the 1950s, sulfonylureas have been used extensively as insulin secretagogues for the treatment of T2DM. Sulfonylureas were developed as structural variants of sulfonamides after the latter were reported to cause hypoglycemia [49]. Early sulfonylureas such as carbutamide, tolbutamide, acetohexamide, tolazamide and chlorpropamide are often referred to as "first generation." These have been largely superceded by more potent "second-generation" sulfonylureas, notably glibenclamide (glyburide), gliclazide, glipizide and most recently glimepiride (Figure 29.6).

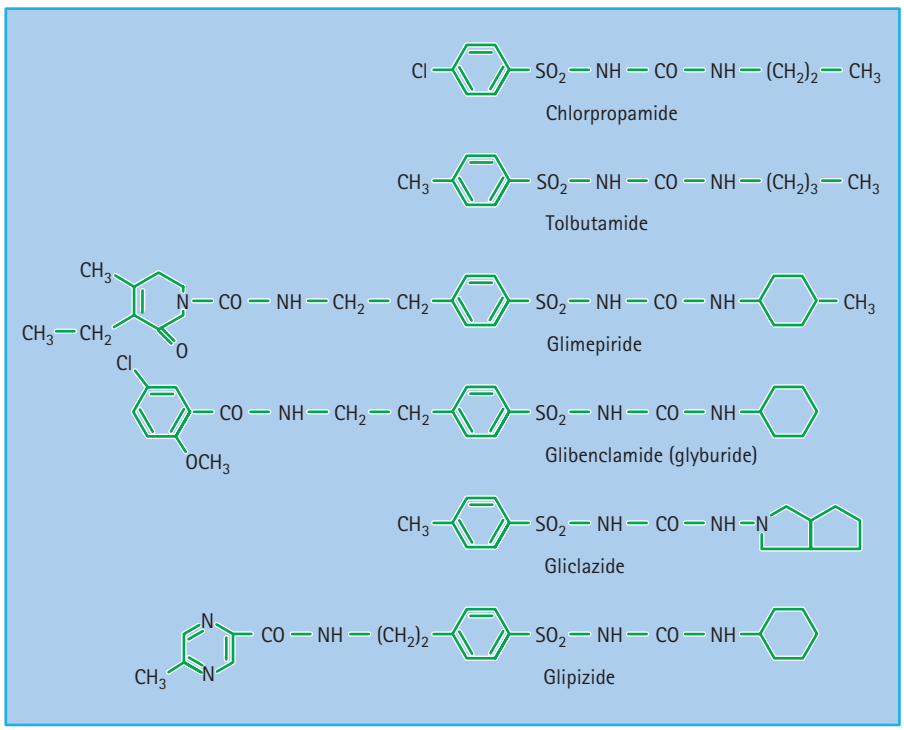

Figure 29.6 Chemical structures of sulfonylureas.

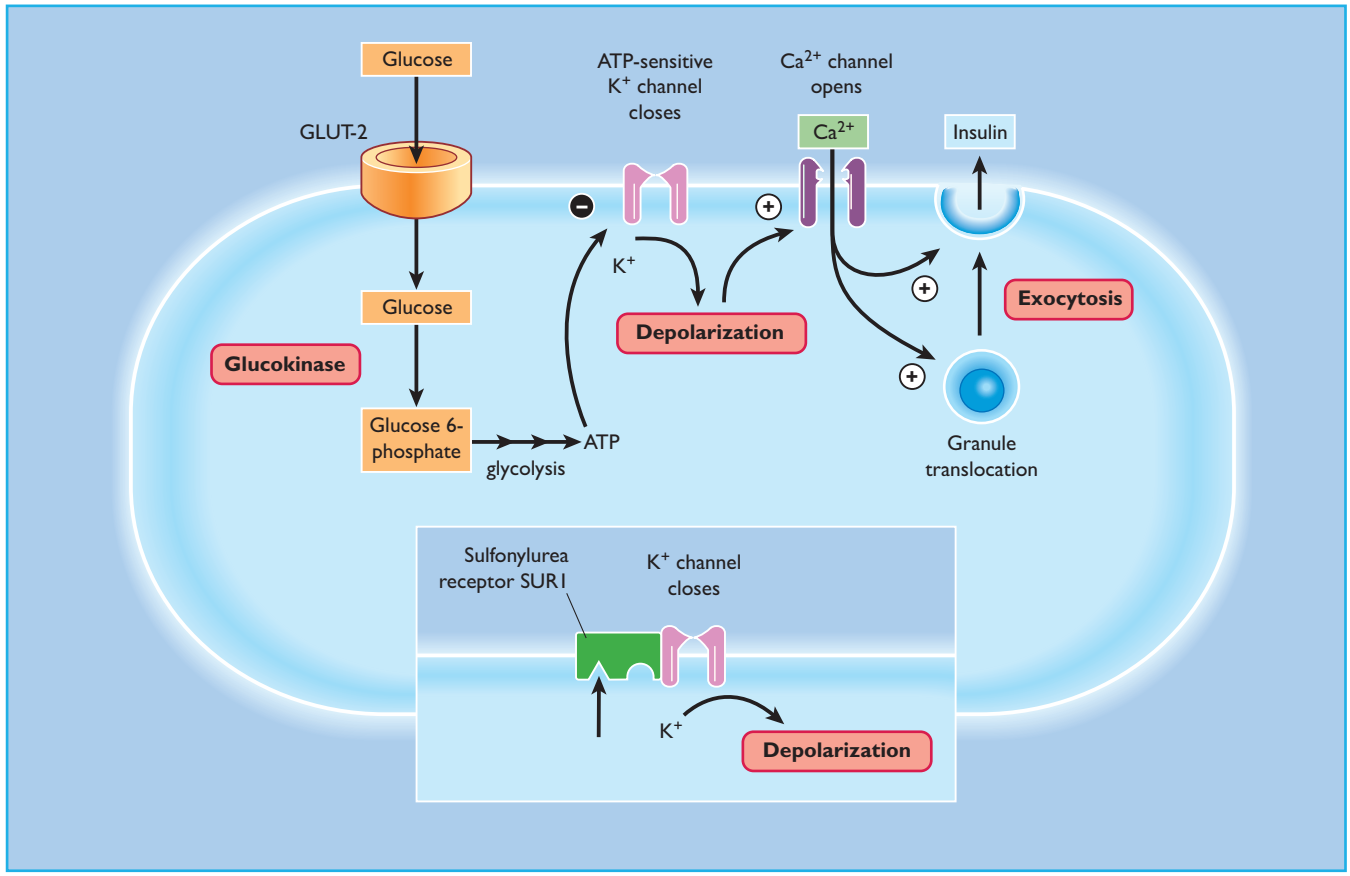

Figure 29.7 Sulfonylureas act on the pancreatic β-cell to stimulate insulin secretion. They bind to the cytosolic surface of the sulfonylurea receptor 1 (SUR1), causing closure of ATP-sensitive Kir6.2 potassium channels, depolarizing the plasma membrane, opening calcium channels, and activating calcium-dependent signaling proteins that control insulin exocytosis.

Mode of action

Sulfonylureas act directly on the β-cells of the islets of Langerhans to stimulate insulin secretion (Figure 29.7). They enter the β-cell and bind to the cytosolic surface of the sulfonylurea receptor 1 (SUR1), which forms part of a transmembrane complex with ATP-sensitive Kir6.2 potassium channels (K^+ATP channels) (Figure 29.8) [50,51]. Binding of a sulfonylurea closes the K^+ATP channel, reducing the efflux of potassium and enabling membrane depolarization. Localized membrane depolarization opens adjacent voltage-dependent L-type calcium channels, increasing calcium influx and raising the cytosolic free calcium concentration. This activates calcium-dependent signaling proteins that control the contractility of micotubules and mictrofilaments that mediate the exocytotic release of insulin granules. Preformed insulin granules adjacent to the plasma membrane are promptly released ("first phase" insulin release), followed by a protracted ("second phase") period of insulin release that begins about 10 minutes later [52]. The "second phase" of insulin release involves translocation of preformed and newly formed insulin granules to the plasma membrane for secretion. Sulfonylureas continue to stimulate insulin release while they are bound to the SUR1 provided that the β-cells are functionally competent. Some desensitization, however, occurs during repeated and protracted stimulation [53]. Because sulfonylureas can stimulate insulin release when glucose concentrations are below the normal threshold for glucose-stimulated insulin release (approximately 5 mmol/L), they are capable of causing hypoglycemia, mainly because of insulin-induced suppression of hepatic glucose production.

There is some evidence that sulfonylureas exert minor glucose-lowering effects independently of increased insulin secretion [54,55]. A small reduction in glucagon concentrations, increased peripheral glucose transport and increased hepatic glucose deposition have been reported, but these effects are not regarded to be of sufficient magnitude to be clinically relevant.

Pharmacokinetics

Sulfonylureas vary considerably in their pharmacokinetic properties (Table 29.7), which in turn affects their clinical suitability for different patients [54,55,56]. They are generally well absorbed, and reach peak plasma concentration in 2–4 hours. Sulfonylureas are highly bound to plasma proteins which can lead to interac-

Table 29.7 Sulfonylureas.

Agent	Dose range (mg/day)	Duration of action (h)	Metabolites	Elimination
Tolbutamide	500–2000	6–10	Inactive	Urine 100%
Glipizide	2.5–20	6–16	Inactive	Urine ~70%
Gliclazide	40–320	12–20	Inactive	Urine ~65%
Gliclazide MR	30–120	18–24	Inactive	Urine ~65%
Glimepiride	1.0–6.0	12–>24	Active	Urine ~60%
Glibenclamide	1.25–15	12–>24	Active	Bile >50%
Chlorpropamide	100–500	24–50	Active	Urine >90%

New patients are not usually started on first generation sulfonylureas (tolbutamide, chlorpropamide).
Glibenclamide is also known as glyburide in some countries.
MR, modified release.

tions with other protein-bound drugs such as salicylates, sulfonamides and warfarin. Also, displacement of protein-bound sulfonylurea can increase the risk of hypoglycemia (Table 29.5). Sulfonylureas are metabolized in the liver to varying extents to a range of active and inactive metabolites that are eliminated along with unchanged drug via the bile and urine. Longer acting sulfonylureas can be given once daily but carry greater risk of hypoglycemia, especially with active metabolites. Sites and rates of metabolism and elimination are also important considerations, especially in older patients and individuals with coexistent liver or kidney disease or taking several other medications.

The formulation of some sulfonylureas has been altered to modify the duration of action [3,4]. For example, a micronized formulation of glibenclamide (glyburide) in the USA increases the rate of gastrointestinal absorption for earlier onset of action. A longer acting ("extended release") formulation of glipizide and a "modified release" (MR) formulation of gliclazide have been introduced for once-daily dosing. Interestingly, the 30 mg preparation of gliclazide MR gives similar efficacy to 80 mg of unmodified gliclazide and reduces risk of severe hypoglycemia [57].

Indications and contraindications

Sulfonylureas are widely used as monotherapy and in combination with metformin or a thiazolidinedione. They can also be used with an α-glucosidase inhibitor, and there are individuals who can benefit from combination of a sulfonylurea with an incretin or DPP-4 inhibitor or insulin. Combination of a sulfonylurea with a different type of antidiabetic agent usually affords approximately additive glucose-lowering efficacy, at least initially, but there is increased risk of hypoglycemia. The additive efficacy of a sulfonylurea with another type of insulin secretagogue is dependent on different modes of action on the β-cell. (Meglinide prandial insulin secretagogues act via the SUR1 complex similarly to sulfonylureas, so they generally offer no extra benefit beyond uptitration of the sulfonylurea, except on rare occasions where the two types of agent are carefully timed to coincide with unusual or unpredictable meal patterns.)

The pharmacologic theory of adding a sulfonylurea (or other insulin secretagogue) to insulin therapy for patients with T2DM is that subcutaneous insulin injections do not mimic the normal endogenous delivery of more insulin to the liver than to the periphery. Thus, where there is residual endogenous β-cell function, a stimulus to increase delivery of endogenous insulin to the liver should assist in reducing hepatic glucose production particularly during digestion of a meal. Hence, daytime sulfonylurea is sometimes given with bedtime insulin, and this can substantially, if only temporarily, reduce the required insulin dose [45,56]. Present guidelines have tended to favor sulfonylureas as alternative first-line oral therapy where metformin is not appropriate or not tolerated. Because sulfonylurea therapy is associated with weight gain, these agents have customarily been preferred for patients who are not overweight.

Begin sulfonylurea therapy with a low dose, preferably with self-monitoring of blood glucose by the patient at least once daily during the first few weeks. This is especially recommended where there are strong concerns about the potential consequences of hypoglycemia (e.g. in elderly patients, those living alone, operating machinery or driving). In general, patients who have responded to some extent (but still inadequately) with lifestyle measures and have less marked fasting hyperglycemia are more likely to incur hypoglycemia with a sulfonylurea. Uptitrate the dosage at 2–4 week intervals as required. Hypoglycemia, or early hypoglycemic symptoms are the main limitation to dose escalation of sulfonylureas. If evidence of hypoglycemia occurs before the glycemic target is achieved, or if a dosage increment produces no further glycemic benefit, it is advisable to return to the previous dose. Adjustment of the administration regimen may assist or an alternative class of insulin secretagogue may be more suitable. Where the sulfonylurea is taken as monotherapy and the glycemic target is not achieved, then addition of an agent to reduce insulin resistance or an α-glucosidase inhibitor is the usual recourse. Note that the maximal blood glucose-lowering effect of a sulfonylurea is usually achieved at a dose that is well below the recommended maximum, indicating that maximum stimulation of insulin secretion has already been achieved.

Efficacy

As monotherapy in patients inadequately controlled by lifestyle measures, sulfonylureas can be expected to reduce fasting plasma glucose by about 2–4 mmol/L, equating to a decrease in HbA_{1c} of 1–2% (11–22 mmol/mol) [3,55,56]. The glucose-lowering effect of sulfonylureas is immediate, and sulfonylureas are particularly effective in the short-term. Efficacy is dependent, however, on sufficient reserve of β-cell function, and this is set against the inevitable decline in β-cell function as the natural history of T2DM proceeds. Thus, it is expected that the dose will need to be escalated to counter the progressive loss of β-cell function, which can reduce the durability of the glucose-lowering efficacy [3,55]. A rapid deterioration of glycemic control during sulfonylurea therapy (sometimes termed "secondary sulfonylurea failure") occurs in approximately 5–10% of patients per annum [55]. While this may possibly vary between compounds it largely reflects the progression of β-cell failure [3,54,56]. Early intervention in patients with a greater reserve of β-cell function usually produces a better and longer response to sulfonylureas, although not without risk of hypoglycemia, whereas late intervention in patients with severely compromised β-cell function is less effective.

Sulfonylureas generally have little effect on blood lipids. Occasionally, their use will cause a small decrease in plasma triglyceride or increase in HDL cholesterol.

Adverse effects

Weight gain, typically in the range of 1–4 kg, is common after initiation of sulfonylurea therapy; it stabilizes by about 6 months [1,3,12]. The weight gain probably reflects the anabolic effects of increased plasma insulin concentrations together with reduced loss of glucose in the urine.

Hypoglycemia is the most common and potentially most serious adverse effect of sulfonylurea therapy. Although it is only rarely life-threatening in patients with T2DM, even mild impairment of neural or motor function can endanger the patient and others, and may predispose to a poor prognosis after a myocardial infarction [3,18]. Patients treated with sulfonylureas should be given instruction on the prevention and recognition of hypoglycemia and the prompt actions required. In the UKPDS, about 20% of sulfonylurea-treated patients reported one or more episodes of hypoglycemic symptoms annually. Other studies have suggested similar rates [12,58]. Severe hypoglycemia (requiring third party assistance) during sulfonylurea therapy occurred in about 1% of patients annually in the UKPDS, and lower rates (approximately 0.2–2.5 episodes per 1000 patient-years) have been reported elsewhere. The mortality risk from sulfonylurea-induced hypoglycemia is reported to be 0.014–0.033 per 1000 patient-years [58]. Longer acting sulfonylureas, irregular meals, other antidiabetic drugs especially insulin, excessive alcohol consumption, already near-normal fasting glycemia, old age and interacting drugs can predispose to increased risk of hypoglycemia (see Chapter 33).

Sulfonylurea-induced hypoglycemia requires prompt admission to hospital. Treat with glucose by continuous intravenous infusion, probably for more than 1 day to guard against the tendency for a recurrence of hypoglycemia where long-acting sulfonylureas are concerned. If accumulation of chlorpropamide is suspected, renal elimination may be enhanced by forced alkaline diuresis. The vasodilator diazoxide and the somatostatin analog octreotide have been used successfully (but with extreme caution) to inhibit insulin secretion in severe sulfonylurea-induced hypoglycemia. Use of glucagon in patients with T2DM should be avoided as this is itself an insulin secretagogue.

Very occasionally, sulfonylureas produce sensitivity reactions, usually transient cutaneous rashes. Erythema multiforme is rare. Fever, jaundice, acute porphyria, photosensitivity and blood dyscrasias are also rare. Chlorpropamide (no longer in common use) was known for its propensilty to cause facial flushing with alcohol and increasing renal sensitivity to antidiuretic hormone, occasionally causing water retention and hyponatremia. Glibenclamide is claimed to have a mild diuretic action.

Although the efficacy of sulfonylureas depends on the stimulation of insulin secretion, this seldom raises plasma insulin concentrations beyond the range of normal (non-diabetic) and subjects with impaired glucose tolerance (IGT). The suggestion emanating from the University Group Diabetes Program study in the 1960s that tolbutamide-induced hyperinsulinemia might have a detrimental effect on the cardiovascular system remains unsubstantiated.

Further studies on the cardiovascular safety of sulfonylureas were prompted by the finding that two isoforms of the sulfonylurea receptor, SUR2A and SUR2B, are expressed in cardiac muscle and vascular smooth muscle, respectively. These isoforms lack the sulfonylurea binding site but they retain the benzamido binding site (Figure 29.8). Therefore, SUR2A/B can only bind those sulfonylureas that contain a benzamido group (glibenclamide, glipizide, glimepiride) [51]. Sulfonylureas without a benzamido group (e.g. tolbutamide, chlorpropamide and gliclazide) show very little interaction with the cardiac and vascular SUR receptors. The effects of the K^+ATP channel opener nicorandil (an anti-anginal drug with cardioprotective properties) are blocked by sulfonylureas that have a benzamido group. Although compounds with a benzamido group could theoretically interfere with ischemic preconditioning and increase vascular contractility at a time when this might be undesirable (e.g. severe myocardial ischemia), there is no clear evidence that therapeutic concentrations of sulfonylureas exert such an effect. Indeed, hyperglycemic states appear to obviate ischemic preconditioning; however, some authorities continue to advocate that use of sulfonylureas is kept to a minimum in patients with overt coronary artery disease [59].

Meglitinides (short-acting prandial insulin releasers)

Meglinide analogs were evaluated as potential antidiabetic agents after an observation in the 1980s that meglitinide – the non-

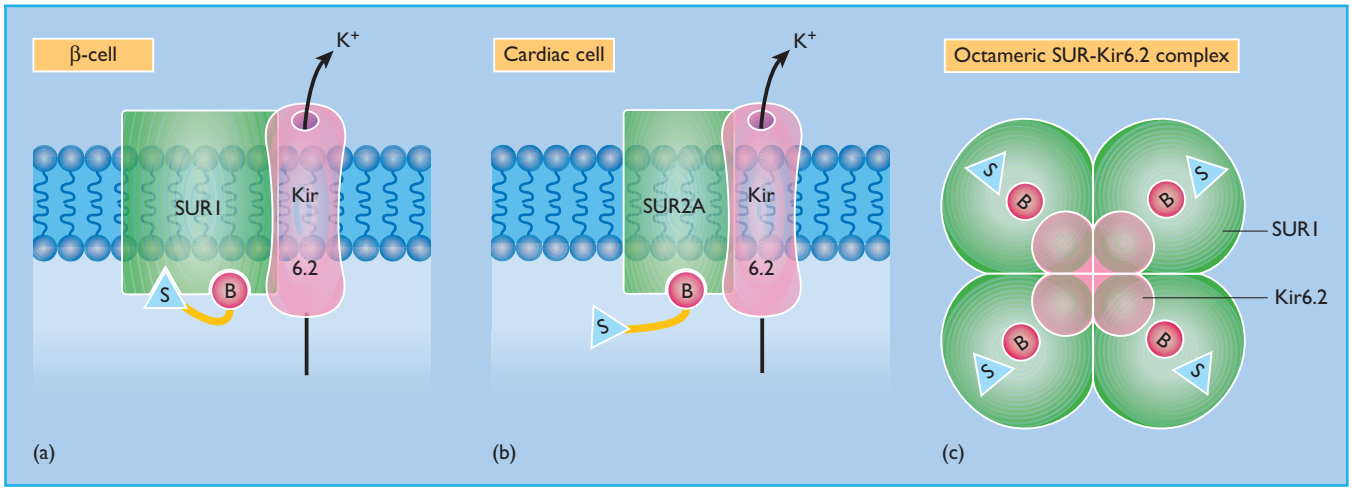

Figure 29.8 This illustrates the transmembrane complex of the SUR1 sulfonylurea receptor and the ATP-sensitive Kir6.2 potassium efflux channel on the pancreatic β-cells (a). Each SUR1 has a cytosolic sulfonylurea (S) binding site and a benzamido (B) binding site. SUR2A on cardiac muscle cells (and SUR2B on vascular smooth muscle cells) does not have a sulfonylurea binding site (b). The SUR1–Kir6.2 complex is a non-covalently bonded octamer comprising 4 × SUR1 and 4 × Kir6.2, illustrated from the cytosolic surface to show the sulfonylurea and benzamido binding sites (c). The Kir6.2 molecules are located at the centre and form the K^+ efflux pore. The Kir6.2 channel has a cytosolic binding region for ADP/ATP.

sulfonylurea moiety of glibenclamide which contains the benzamido group – could stimulate insulin secretion similarly to a sulfonylurea [60]. The pharmacokinetic properties of these compounds favored a rapid but short-lived insulin secretory effect that suited administration with meals to promote prandial insulin release. By generating a prompt increase of insulin to coincide with meal digestion these agents help to restore partially the first phase glucose-induced insulin response that is lost in T2DM. Specifically targeting post-prandial hyperglycemia might also address the vascular risk attributed to prandial glucose excursions, and reduce the risk of interprandial hypoglycemia [61–63]. Two agents, the meglitinide derivative repaglinide and the structurally related phenylalanine derivative nateglinide, were introduced in 1998 and 2001, respectively, as "prandial insulin releasers" (Figure 29.9). Although acting mainly during the prandial and early post-prandial period, their effects extend sufficiently to produce some reduction of fasting hyperglycemia, particularly with repaglinide.

Mode of action

Prandial insulin releasers bind to the benzamido site on the sulfonylurea receptor SUR1 in the plasma membrane of the islet β-cells (Figure 29.8). This site is distinct from the sulfonylurea site, but the response to binding is the same as for sulfonylureas, causing closure of the K^+ATP channel. Thus, there is no therapeutically additive advantage of the two types of agonists, but variations in their binding affinities and duration of action provide opportunities for the specialist to combine a meglitinide and a sulfonylurea to fit with an unusual meal pattern.

Pharmacokinetics

Repaglinide is almost completely and rapidly absorbed with peak plasma concentrations after about 1 hour. It is quickly metabolized in the liver to inactive metabolites, which are mostly excreted in the bile (Table 29.8). Taken about 15 minutes before a meal, repaglinide produces a prompt insulin response which lasts about 3 hours, coinciding with the duration of meal digestion. Nateglinide has a slightly faster onset and shorter duration of action [61–63].

Indications and contraindications

Prandial insulin releasers can be used as monotherapy in patients inadequately controlled by non-pharmacologic measures. They are perhaps most suited for individuals who exhibit post-prandial glycemic excursions while retaining near-normal fasting glycemia. As rapid-acting insulin releasers they can be helpful to individuals with irregular lifestyles with unpredictable or missed meals. The lower risk of hypoglycemia also provides a useful option for some elderly patients, particularly if other agents are contraindicated, although the need for multiple daily dosages may be a disincentive.

Repaglinide is ideally taken 15–30 minutes before a meal. Introduce therapy with a low dose (e.g. 0.5 mg) and monitor glycemic control during titration every 2 weeks up to a maximum of 4 mg before each main meal. When a meal is not consumed, the corresponding dose of repaglinide should be omitted. With appropriate caution and monitoring, repaglinide can be given to patients with moderate renal impairment where some sulfonylureas and metformin are contraindicated.

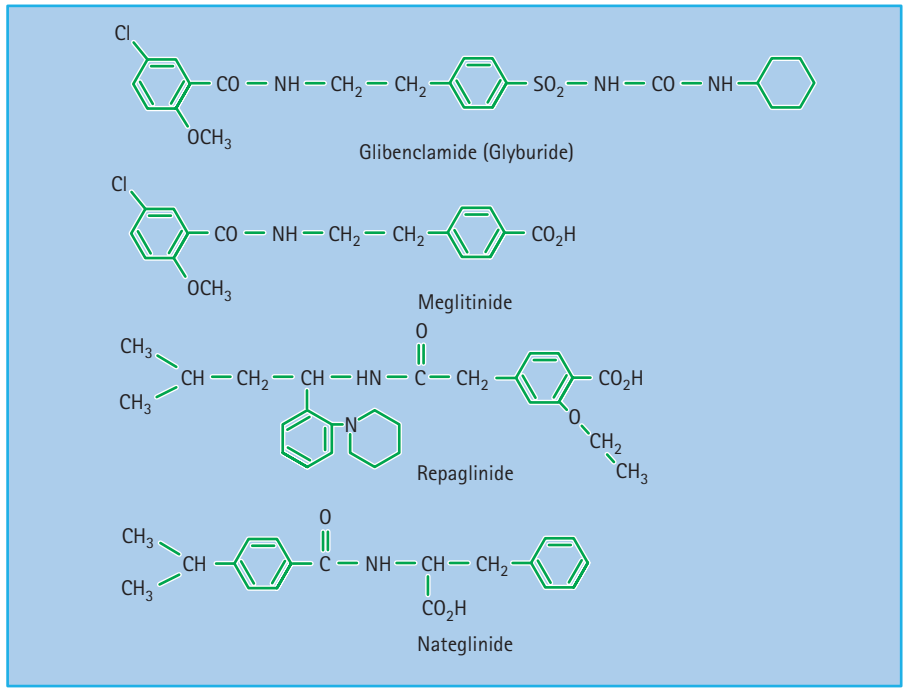

Figure 29.9 Chemical structures of meglitinide, and the prandial insulin releasers repaglinide and nateglinide compared with glibenclamide (glyburide).

Table 29.8 The meglitinides: repaglinide and nateglinide.

Agent	Dose range (mg/meal)	Max daily dose (mg)	Duration of action (h)	Metabolites	Elimination
Repaglinide	0.5–4.0	16	4–6	Inactive	Bile ~90%
Nateglinide	60–180	540	3–5	One slightly active	Urine ~80%

Nateglinide can be used as monotherapy in much the same way as repaglinide, although nateglinide tends to be faster and shorter acting and requires caution in patients with hepatic disease. Note that in some countries, such as the UK, nateglinide is not licensed for use as monotherapy, only for combination therapy.

If the desired glycemic target is not met with a prandial insulin releaser, consider early introduction of combination therapy (e.g. with an agent to reduce insulin resistance). Prandial insulin releasers can also be useful add-ons to monotherapy with metformin or a thiazolidinedione.

Efficacy

Consistent with their use to boost prandial insulin secretion, repaglinide (0.5–4 mg) or nateglinide (60–180 mg) taken before meals produce dose-dependent increases in insulin concentrations and reduce post-prandial hyperglycemia. There is usually a small reduction in fasting hyperglycemia. Reductions in HbA_{1c} are similar to or smaller than with sulfonylureas, as predicted by their shorter duration of action. As add-on to metformin, they can reduce HbA_{1c} by an additional 0.5–1.5% (6–17 mmol/mol).

Adverse effects

Hypoglycemic episodes are fewer and less severe with prandial insulin releasers than with sulfonylureas. Sensitivity reactions, usually transient, are uncommon. Plasma levels of repaglinide may be increased during co-administration with gemfibrozil. Prandial insulin releasers may cause a small increase in body weight when started as initial monotherapy, but body weight is little affected among patients switched from a sulfonylurea or when a prandial insulin releaser is combined with metformin.

Thiazolidinediones

The antidiabetic activity of a thiazolidinedione (ciglitazone) was reported in the early 1980s. In the early 1990s the peroxisome proliferator-activated receptor (PPAR) family was identified as part of the nuclear receptor superfamily 1, and it became evident that thiazolidinediones were potent agonists of PPAR-γ [64]. The PPAR-γ-mediated transcriptional effects of thiazolidinediones were shown to improve whole-body insulin sensitivity, and troglitazone became the first thiazolidinedione to enter routine

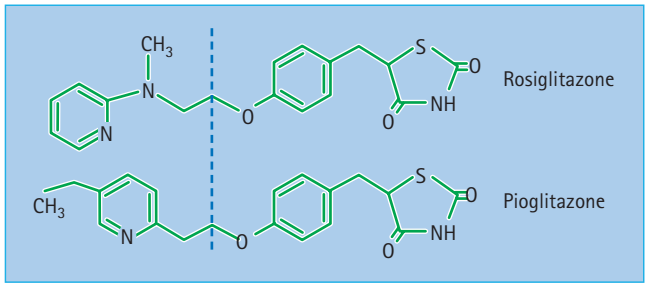

Figure 29.10 Chemical structures of thiazolidinediones rosiglitazone and pioglitazone.

clinical use, introduced in the USA in 1997. The drug, however, was associated with fatal cases of idiosyncratic hepatotoxicity and was withdrawn in 2000. Troglitazone was available for only a few weeks in 1997 in the UK. Two other thiazolidinediones, rosiglitazone and pioglitazone (Figure 29.10), which did not show hepatotoxicity, were introduced in the USA in 1999 and in Europe in 2000 [65]. Fixed-dose combinations of each agent with metformin are also available.

Mode of action

Most of the antidiabetic efficacy of thiazolidinediones appears to be achieved through stimulation of PPAR-γ leading to increased insulin sensitivity [66,67]. PPAR-γ is highly expressed in adipose tissue, and to a lesser extent in muscle and liver. When activated it forms a heterodimeric complex with the retinoid X receptor and binds to a nucleotide sequence (AGGTCAXAGGTCA) termed the peroxisome proliferator response element (PPRE) located in the promoter regions of PPAR-responsive genes. In conjunction with co-activators such as PGC-1, this alters the transcriptional activity of a range of insulin-sensitive and other genes (Table 29.9). Many of these genes participate in lipid and carbohydrate metabolism (Figure 29.11). Stimulation of PPAR-γ by a thiazolidinedione promotes differentiation of pre-adipocytes into mature adipocytes: these new small adipocytes are particularly sensitive to insulin, and show increased uptake of fatty acids with increased lipogenesis. This in turn reduces circulating free fatty acids which rebalances the glucose–fatty acid (Randle) cycle, facilitating glucose utilization and restricting fatty acid availability as an energy source for hepatic gluconeogenesis. By reducing circulating fatty acids, ectopic lipid deposition in muscle and liver is reduced which further contributes to improvements of glucose metabolism.

Thiazolidinediones also increase glucose uptake into adipose tissue and skeletal muscle via increased availability of GLUT 4 glucose transporters. Improvements in insulin sensitivity are likely to be assisted by reduced production of several adipocyte-derived pro-inflammatory cytokines, notably tumor necrosis factor α (TNF-α), which has been implicated in muscle insulin resistance. Thiazolidinediones also increase production of adiponectin, which enhances insulin action and exerts potentially beneficial effects on vascular reactivity [68]. Because PPAR-γ is

Table 29.9 Examples of key genes activated by thiazolidinediones via stimulation of the peroxisome propliferator-activated receptor γ (PPAR-γ). Not all genes appear to be activated in all tissues. The main effects are in adipose tissue.

↑ Lipoprotein lipase
↑ Fatty acid transporter protein (FATP/CD36)
↑ Adipocyte fatty acid binding protein (aP2)
↑ Acyl-CoA synthetase
↑ Malic enzyme
↑ Glycerol kinase (in adipocytes ?)
↑ PEPCK (adipocytes), ↑ perilipin
↑ GLUT-4 (by derepression), ↑ GLUT-2 (islet β-cells)
↓ 11β-hydroxysteroid dehydrogenase-1
↓ Resistin, ↓ RBP 4
↑ Adiponectin (↑ leptin ?)
↓ TNF-α, ↓ IL-6
↓ CRP and some proinflammatory cytokines, ↓ NFκB
↓ PAI-1, ↓ MMP-9
↑ UCP-1 (?)

↑ increase expression; ↓ decrease expression; ? unconfirmed.
CRP, C-reactive protein; GLUT, glucose transporter; IL-6, interleukin 6; NFκB, nuclear factor κB; PAI-1, plasminogen activator inhibitor 1; MMP-9, matrix metalloproteinase 9; PEPCK, phosphoenolpyruvate carboxy kinase; RBP, retinol binding protein; TNF-α, tumor necrosis factor α; UCP-1, uncoupling protein 1.

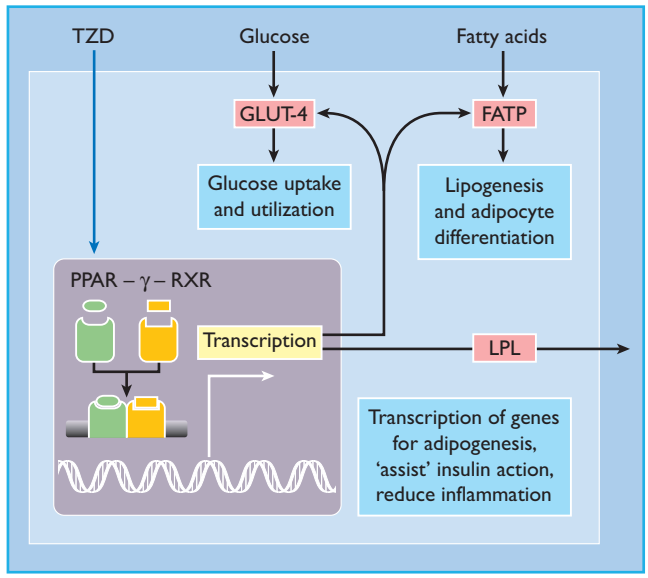

Figure 29.11 Mechanism of action of thiazolidinediones. Most actions of a thiazolidinedione (TZD) are mediated via stimulation of the nuclear peroxisome proliferator-activated receptor γ (PPAR-γ), which is highly expressed in adipose tissue. When stimulated, PPAR-γ forms a heterodimeric complex with the retinoid X receptor (RXR). The complex binds to the peroxisome proliferator response element (PPRE) nucleotide sequence (AGGTCAXAGGTCA) in the promoter regions of certain genes, recruits co-activators, and alters the transcriptional activity of these genes. This modifies nutrient uptake and metabolism, as well as the other functions of the cell.

expressed to a small extent in many tissues, thiazolidinediones can therefore affect responsive genes at these locations, and this has given rise to the tag "pleotropic effects."

Thiazolidinediones, like metformin, are antihyperglycemic agents and require the presence of sufficient insulin to generate their blood glucose-lowering effect. Plasma insulin concentrations are typically lowered by thiazolidinediones, and there is evidence that long-term viability of islet β-cells might be improved [69].

Pharmacokinetics

Absorption of rosiglitazone and pioglitazone is rapid and almost complete, with peak concentrations at 1–2 hours, but slightly delayed when taken with food. Both drugs are metabolized extensively by the liver. Rosiglitazone is metabolized mainly by cytochrome P450 isoform CYP2C8 to inactive or only very weakly active metabolites with a plasma $t_{1/2}$ of 100–160 hours; these are mostly eliminated in the urine. Pioglitazone is metabolized predominantly by CYP2C8 and CYP3A4 to active metabolites that are eliminated in the bile (Table 29.10). Rosiglitazone can interact with gemfibrozil. Pioglitazone does not appear to cause any clinically significant reductions in plasma concentrations of other drugs metabolized by CYP3A4 such as oral contraceptives. Both thiazolidinediones are almost completely bound to plasma proteins, but their concentrations are not sufficient to interfere with other protein-bound drugs.

Indications and contraindications

Thiazolidinediones can be used as monotherapy in non-obese and obese patients with T2DM in whom lifestyle does not afford adequate glycemic control. Various treatment algorithms ascribe different positions for thiazolidinediones, but in general they are used as monotherapy if metformin is inappropriate or not tolerated, and for patients in whom an insulin secretagogue is less favored. They are often used to gain additive efficacy in combination with other antidiabetic drugs, particularly metformin [70]. Because of their slow onset of action it is not straightforward to substitute a thiazolidinedione for either a sulfonylurea or metformin without a temporary deterioration in glycemic control. Combination of a thiazolidinedione with insulin can improve glycemic control while reducing insulin dosages, especially in obese patients, but requires extra caution as peripheral edema is more common [71].

A particular issue with thiazolidinediones is their propensity for fluid retention with increased plasma volume of up to 500 mL, a reduced hematocrit and a decrease in hemoglobin concentration of up to 1 g/dL. Thus, the use of thiazolidinediones is contraindicated in patients with evidence of heart failure. The exclusion criteria, based on cardiac status, vary between countries; for example, New York Heart Association classes I–IV are exclusions in Europe, while III and IV are exclusions in the USA [71]. Appropriate clinical monitoring is important, especially for patients considered at higher risk of cardiac failure and those showing marked initial weight gain. Current controversey has focused on a meta-analysis noting that rosiglitazone increased the risk of myocardial infarction during the first 6–12 months of therapy [72]. While this analysis has received much criticism, the labeling has been tightened to increase awareness of the issue. Despite an increased fluid volume, thiazolidinediones do not increase, and usually slightly decrease, blood pressure.

Although hepatotoxicity has not been a concern with either rosiglitazone or pioglitazone, the troglitazone experience prompted vigilance concerning liver function by measuring serum alanine aminotransferase (ALT) before starting therapy and periodically thereafter. Pre-existing liver disease, development of clinical hepatic dysfunction or elevated ALT levels >2.5 times the upper limit of normal are contraindications to thiazolidinediones. Interestingly, because of the effects of thiazolidinediones on hepatic fat metabolism, recent studies have suggested that this class of drug might even be useful for the treatment of non-alcoholic steatohepatitis.

If there are no contraindications, rosiglitazone and pioglitazone can be used in the elderly. They can also be considered for patients with mild renal impairment, but appreciating the potential for edema. Use of a thiazolidinedione in women with anovulatory PCOS can cause ovulation to resume, but thiazolidinediones should not be continued in pregnancy.

Efficacy

Thiazolidinediones produce a slowly generated antihyperglycemic effect which usually requires 2–3 months to reach maximum effect [65]. This tends to prolong the dose titration process, and because the therapeutic response can vary considerably between individuals, it is appropriate to consider the patient as a non-responder and to switch to another treatment if there is no clinically meaningful effect after 3 months. The two thiazolidinediones have similar blood glucose-lowering effects, reducing HbA_{1c} by around 0.5–1.5% (6–17 mmol/mol). In a long-term monotherapy comparison with metformin or a sulfonylurea (the ADOPT study), rosiglitazone showed a slower onset but a more durable

Table 29.10 The thiazolidinediones: pioglitazone and rosiglitazone.

Agent	Dose range (mg/day)	Duration of action (h)	Metabolites	Elimination
Pioglitazone	15–45	~24	Active	Bile > 60%
Rosiglitazone	4–8	~24	Inactive	Urine ~ 64%

glucose-lowering effect over more than 3 years [69]. Data from clinical trials suggest that the effect of thiazolidinediones may be better in patients with greater β-cell reserve and more overweight individuals, but a clear indicator of the best responders has not been established. Thiazolidinediones do not cause hypoglycemia as monotherapy.

Both thiazolidinediones substantially reduce circulating non-esterified (free) fatty acids, but effects on other components of the plasma lipid profile have been the subject of debate. Rosiglitazone tends to cause a small rise in the total cholesterol concentration, which stabilizes by about 3 months, although this may be mitigated by adequate statin therapy. The effect appears to reflect a rise in both LDL and HDL cholesterol, leaving the LDL:HDL cholesterol ratio and the total:HDL cholesterol ratio little changed or slightly improved. Pioglitazone generally appears to have little effect on total cholesterol, and has frequently reduced triglyceride concentrations in clinical trials. Both thiazolidinediones reduce the proportion of the smaller, more dense (more atherogenic) LDL particles [73].

Weight gain, similar in magnitude to sulfonylurea therapy (typically 1–4 kg) and stabilizing over 6–12 months, is usually observed after initiation of thiazolidinedione therapy. Several studies indicate that the distribution of body fat is altered. The visceral adipose depot is little changed or reduced, while the subcutaneous depot is increased as new small, insulin-sensitive adipocytes are formed [74].

Thiazolidinediones have been reported to exert beneficial effects on a selection of atherothrombotic risk markers, indices of vascular reactivity and components of the "metabolic syndrome" [69,75,76]. For example, thiazolidinediones downregulate PAI-1 expression, decrease urinary albumin excretion to a greater extent than expected for the improvement in glycemic control, reduce cIMT and coronary restenosis, and reduce circulating markers of chronic low-grade inflammation. Thiazolidinediones also reduce the occurrence of new onset diabetes in individuals with IGT or those with a history of gestational diabetes [77,78].

Adverse effects

Despite improvements in several atherothrombotic risk factors, the main concerns over thiazolidinediones focus on the cardiovascular impact of edema, reduced hemoglobin levels and congestive heart disease. Additionally, a meta-analysis has suggested increased risk of myocardial infarction during the initial period of treatment with rosiglitazone, although this has not been confirmed by scrutiny of large treatment databases or by long-term prospective studies [75]. Nevertheless, in a large prospective study, pioglitazone reduced long-term vascular events [76,79,80].

Hypoglycemia may occur several weeks after adding a thiazolidinedione to a sulfonylurea; self-monitoring of blood glucose can be helpful to identify when the dosage of the sulfonylurea should be reduced. It has been suggested that rosiglitazone is initiated at half maximal dosage with a sulfonylurea. Recent studies have also noted an approximate doubling of the risk of a bone fracture – notably at distal sites – amongst postmeopausal women receiving a thiazolidinedione, and possibly a slightly increased risk amongst men [81]. A check on bone density should exclude those at particular risk. Stimulation of PPAR-γ in colonic cells has been reported to both increase and decrease the risk of tumors in animals and cell models; thus, familial polyposis coli is a contraindication to thiazolidinediones on theoretical grounds.

Gliptins

Gliptins are DPP-4 inhibitors that enhance incretin levels. They act as selective inhibitors of the enzyme DPP-4 to enhance endogenous incretin activity by preventing the rapid degradation of the incretin hormones glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide 1 (GLP-1). The history, structure and function of incretin hormones, and the therapeutic role of subcutaneously injected incretin mimetics such as exenatide and liraglutide are covered in Chapter 30. Briefly, incretin hormones are secreted from the intestine in response to meal digestion: one of their key actions is to increase glucose-induced insulin secretion by the pancreatic islet β-cells, thereby reducing prandial glucose excursions [82,83]. GLP-1 also suppresses glucagon secretion from the islet α-cells.

It was noted in the 1980s that the incretin effect is reduced in T2DM, and this was attributed, at least in part, to reduced secretion of GLP-1 [84,85]. By contrast, the biologic actions of GLP-1 remained essentially intact in T2DM, suggesting that administration of extra GLP-1 might be useful therapeutically. This was not a straightforward option because the peptide is rapidly degraded ($t_{1/2}$ < 2 minutes). Studies dating from the early 1990s had shown that degradation was mainly by the enzyme DPP-4. Thus, DPP-4-resistant constructs and analogs of GLP-1 have been developed.

An alternative therapeutic approach is to inhibit the action of DPP-4. The first DPP-4 inhibitors were tested in the late 1990s but were not specific enough for clinical use [85]. Several specific inhibitors have subsequently been developed [86], and sitagliptin (2007) and vildagliptin (2008) were introduced in several countries (Figure 29.12). Another DPP-4 inhibitor, saxagliptin, has recently been introduced (2009) and other DPP-4 inhibitors are currently being developed.

Mode of action

DPP-4 inhibitors act to prevent the aminopeptidase activity of DPP-4, an enzyme found free in the circulation and tethered to endothelia and other epithelial cells in most tissues, especially in the intestinal mucosa [87]. DPP-4 cleaves the N-terminal dipeptide from peptides that have either an alanine or a proline residue penultimate to the N-terminus. The incretins GLP-1 and GIP are prime targets for DPP-4, and DPP-4 inhibitors more than double their circulating concentrations, but this is not as high as the concentrations of subcutaneously administered incretin mimetic [88]. Raised endogenous incretin concentrations enhance nutrient-induced insulin secretion, and animal studies have demonstrated increased insulin biosynthesis and increased β-cell mass

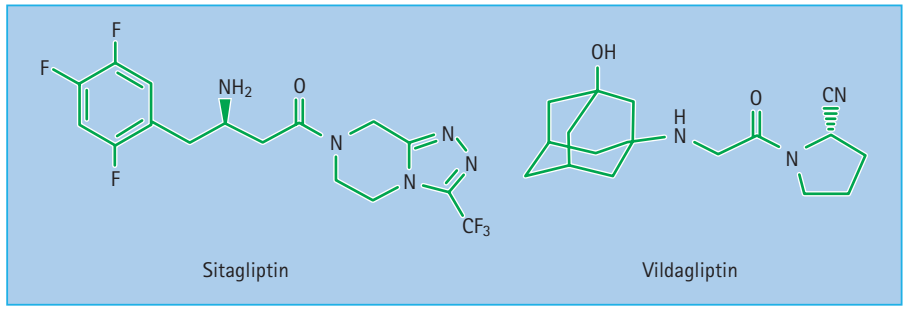

Figure 29.12 Chemical structures of the gliptins (DPP-4 inhibitors) sitagliptin and vildagliptin.

Table 29.11 Effects of the incretin hormones glucagon-like peptide 1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP) on glucose homeostasis.

	GLP-1	GIP
Effects on pancreatic islets		
Increase nutrient-induced insulin secretion	✓	✓
Increase insulin biosynthesis*	✓	✓
Increase β-cell mass*	✓	✓
Suppress glucagon secretion	✓	–
Increase somatostatin secretion	✓	–
Extrapancreatic effects		
Slow gastric emptying	✓	–
Decrease gastric acid secretion	–	✓
Promote satiety and weight reduction	✓	–
Promote lipogenesis	–	✓

✓ yes, – no effect.
* Effect observed in animal studies but not confirmed by clinical studies in type 2 diabetes.

(Table 29.11). Increased GLP-1 concentrations also enhance suppression of glucagon secretion. Because these effects are glucose dependent, there is low risk of inducing significant hypoglycemia. The elevation of GLP-1 levels produced by DPP-4 inhibitors is not generally sufficient to create a measurable satiety effect or sufficient slowing of gastric emptying to cause any nausea, and body weight is usually little changed (Figure 29.13).

Because the incretin-mediated effect of DPP-4 inhibitors potentiates glucose-dependent insulin secretion, the activity period of these agents is mostly prandial. Although they are particularly effective in lowering post-prandial hyperglycemia, there is a substantial carry-over effect to benefit the control of interprandial glycemia [89]. By contrast, DPP-4 inhibitors do not initiate insulin secretion and so they do not increase basal insulin secretion. Also, they only suppress glucagon secretion in the hyperglycemic state, so there is low risk of interprandial "overshoot" into hypoglycemia.

Pharmacokinetics

Sitagliptin and vildagliptin are selective, competitive and reversible inhibitors of DPP-4 (IC50 approximately 18 and 3.5 nmol, respectively). Sitagliptin (piperazine derivative) and vildagliptin (cyanopyrrolidine derivative) are each highly bioavailable (approximately 87% and 85%, respectively), rapidly absorbed (t_{max} 1–4 and <2 hours, respectively), and show relatively low (approximately 38% and 9%, respectively) plasma protein binding. Sitagliptin has a plasma $t_{1/2}$ of 8–14 hours, and a small proportion is metabolized in the liver by CYP3A4 and CYP2C6. Most of a sitagliptin dose (approximately 79%) is eliminated unchanged in the urine through renal tubular secretion via the organic anion transporter OAT3. A single dose of 100 mg sitagliptin achieves near-complete inhibition of DPP-4 activity for about 12 hours and about 80% inhibition up to 24 hours. Vildagliptin has a shorter plasma $t_{1/2}$ of 1.5–4.5 hours: the majority (approximately 69%) undergoes mainly renal metabolism to inactive metabolites with negligible involvement of CYP450 isoforms, and most (approximately 85%) is eliminated in the urine. A dose of 50–100 mg vildagliptin gives almost complete inhibition of DPP-4 for about 12 hours and about 40% inhibition by 24 hours (Table 29.12).

Indications and contraindications

In principle, gliptins can be used as monotherapy in patients with T2DM who have responded inadequately to lifestyle measures, although this is not a licensed indication in all countries where available. Currently, as newly available agents, gliptins tend to be preferred as "add-on" therapy in patients inadequately controlled by metformin or a thiazolidinedione. Theoretically, they could be used with any other class of oral agent or insulin, as their mode of action on the β-cell is different from sulfonylureas and meglitinides, and their ability to reduce glucagon levels could be useful as add-on therapy to insulin even without β-cell function. In practice, however, full efficacy in T2DM requires adequate β-cell reserve. Lack of weight gain makes gliptins suitable for overweight and obese patients, and low risk of hypoglycemia when used as monotherapy (and when used with non-insulin releasing agents) favors their use in patients who have only slightly raised basal glycemia, are close to glycemic target or have unpredictable meal times [89,90].

Sitagliptin is taken once daily (100 mg) in the morning, and vildagliptin is usually twice daily (50 mg). The glucose-dependent mode of action reduces the risk of any significant glucose lowering effect unless there is hyperglycemia, lowering concern over

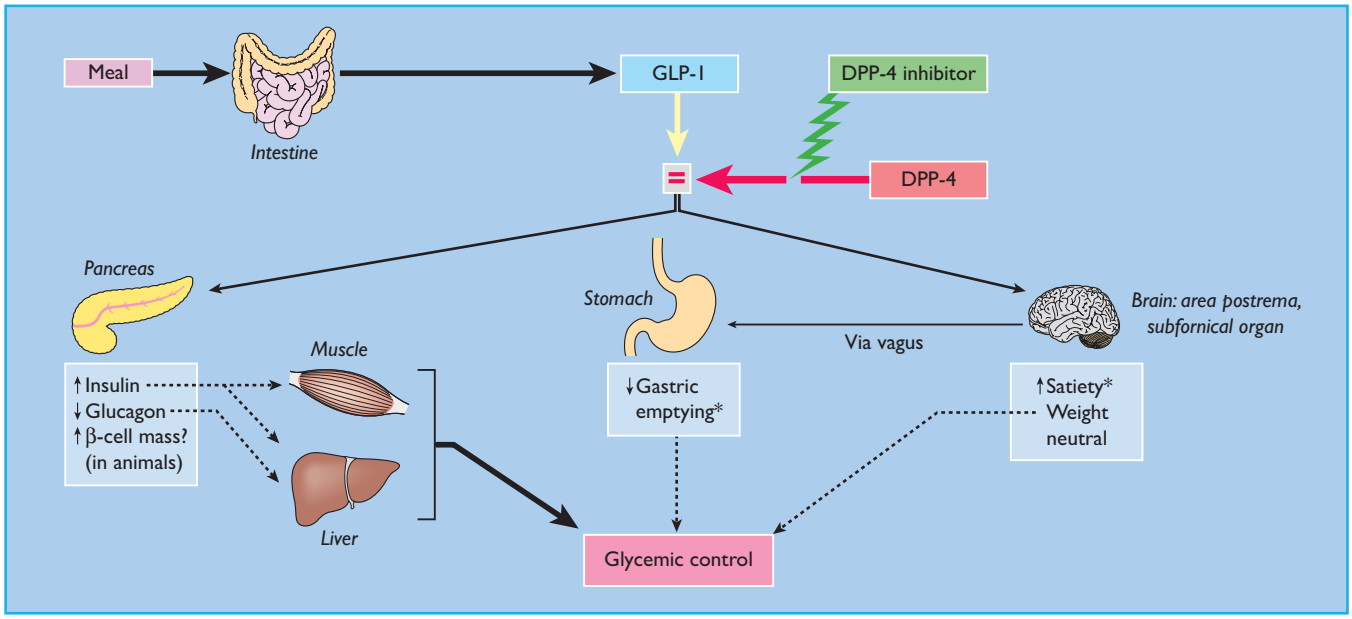

Figure 29.13 Sites of action of gliptins (DPP-4 inhibitors). Incretin hormones such as GLP-1 are released in reponse to a meal. These hormones are normally degraded rapidly by the enzyme DPP-4. Gliptins act as inhibitors of DPP-4, allowing the normal effects of the incretin hormones to be enhanced. The main site of the enhanced incretin effect is on the pancreas to increase nutrient-induced insulin secretion. GLP-1 also reduces glucagon secretion. * Potential effects to slow gastric emptying and increase satiety probably contribute little to the therapeutic efficacy of gliptins.

Table 29.12 Gliptins: sitagliptin and vildagliptin.

Agent	Dose (mg/day)	Duration of action (h)	Metabolites	Elimination
Sitagliptin	100	18–24	Nominal metabolism	Urine ~ 79%*
Vildagliptin	2 × 50	12–24	Inactive	Urine ~ 85%

* Unchanged drug.

missed meals. Thus, there is no dose titration, but it is recommended that fasting and post-prandial glycemia are reviewed after about 2 weeks of therapy, especially when added as a second agent.

Because sitagliptin is mostly eliminated unchanged in the urine, a reduced dose (50 mg once daily) is recommended for patients with moderate renal insufficiency (creatinine clearance ≥30 to <50 mL/min); for patients with severe renal insufficiency (creatinine clearance <30 mL/min) or with end-stage renal disease requiring hemodialysis or peritoneal dialysis, consider a dose of 25 mg once daily. Sitagliptin causes no apparent induction or inhibition of P450 isoforms, which allows its use in patients with mild or moderate impairment of liver function provided renal function is adequate.

In view of the renal metabolism and elimination of vildagliptin, this agent is not recommended in patients with moderate or severe renal impairment (e.g. creatinine clearance <50 mL/min). Some cases of reversibly raised ALT or aspartate aminotransferase (AST) have been observed in patients receiving vildagliptin, therefore a liver function check should be made before starting treatment and periodically thereafter. A marked rise in liver enzymes (e.g. ALT or AST >3× upper limits of normal) or other signs of hepatic impairment contraindicate treatment.

No significant drug interactions have been noted with either gliptin. As clinical experience is limited it is advisable to use these drugs cautiously in patients with heart disease and to stop gliptin therapy in pregnancy.

Efficacy

Sitagliptin

Administration of 100 mg/day sitagliptin as monotherapy or add-on therapy to other antidiabetic agents typically reduced HbA_{1c} (from a baseline of approximately 8% [64 mmol/mol]) by about 0.7–0.8% (8–9 mmol/mol) after 24–52 weeks [89–92]. Individuals with a high baseline HbA_{1c} usually showed reductions in HbA_{1c} of >1% (11 mmol/mol). Fasting plasma glucose concentrations were reduced by about 1.0–1.5 mmol/L, and post-prandial glucose levels measured 2 hours after a standard mixed

meal were usually reduced by about 3 mmol/L. Sitagliptin therapy did not cause a clinically significant increase in the incidence of hypoglycemia, and a sitagliptin + metformin combination was associated with fewer hypoglycemic episodes than a combination of glipizide + metformin despite similar levels of HbA_{1c} [93]. Sitagliptin did not increase body weight compared with placebo in any of the trials.

Vildagliptin

In clinical trials a single daily dose of 50–100 mg/day vildagliptin showed similar efficacy and tolerability to sitagliptin when used as monotherapy or add-on to metformin or a thiazolidinedione [89–91,94]. Although several trials with vildagliptin produced slightly greater reductions in HbA_{1c}, this was mostly associated with a slightly higher average baseline (starting) HbA_{1c} (>8.5% [>69 mmol/mol]). Again there was no effect on hypoglycemia or body weight.

Adverse effects

Clinical experience to date with gliptins has not identified any serious adverse effects. In clinical trials (typically 6–12 months), measures of tolerability and adverse events were generally similar to placebo or comparator. There were some increases in liver enzymes with a 100 mg dose of vildagliptin, but not with the 50 mg dose that is marketed. Nominal increases in reported signs or symptoms of abdominal discomfort suggest that the potential to slow gastric emptying is unlikely to have a clinically significant impact.

Because there are many natural substrates for DPP-4 including bradykinin, enkephalins, neuropeptide Y, peptide YY1–36, gastrin releasing polypeptide, substance P, insulin-like growth factor I, vasostatin 1, the α chains of thyrotropin, luteinizing hormone and chorionic gonadotropin and several chemokines such as monocyte chemotactic protein 1 (MCP-1), gliptins have the potential to influence the hunger–satiety system, gastrointestinal motility, growth, vascular reactivity and immune mechanisms [88]. DPP-4 is also the CD26 T-cell activation antigen, but neither CD26 knockout mice nor the DPP-4-specific inhibitors used in animals or humans have yet shown any significant untoward immune-related effects. The importance of selective DPP-4 inhibition is also noted because inhibition of related enzymes such as DPP-8 and DPP-9 has produced blood dyscrasias and skin lesions in some species, but not in clinical use. Nevertheless, it is advisable to check for any evidence of skin lesions.

α-Glucosidase inhibitors

Studies conducted in the late 1970s noted that inhibitors of intestinal α-glucosidase enzymes could retard the final steps of carbohydrate digestion with consequent delay to the absorption of sugars. By the early 1980s it was demonstrated that this approach could reduce post-prandial hyperglycemia in diabetes [95]. Acarbose, the first α-glucosidase inhibitor, was introduced in the early 1990s. Subsequently, two further agents, miglitol and voglibose, were introduced in some countries (Figure 29.14). In patients

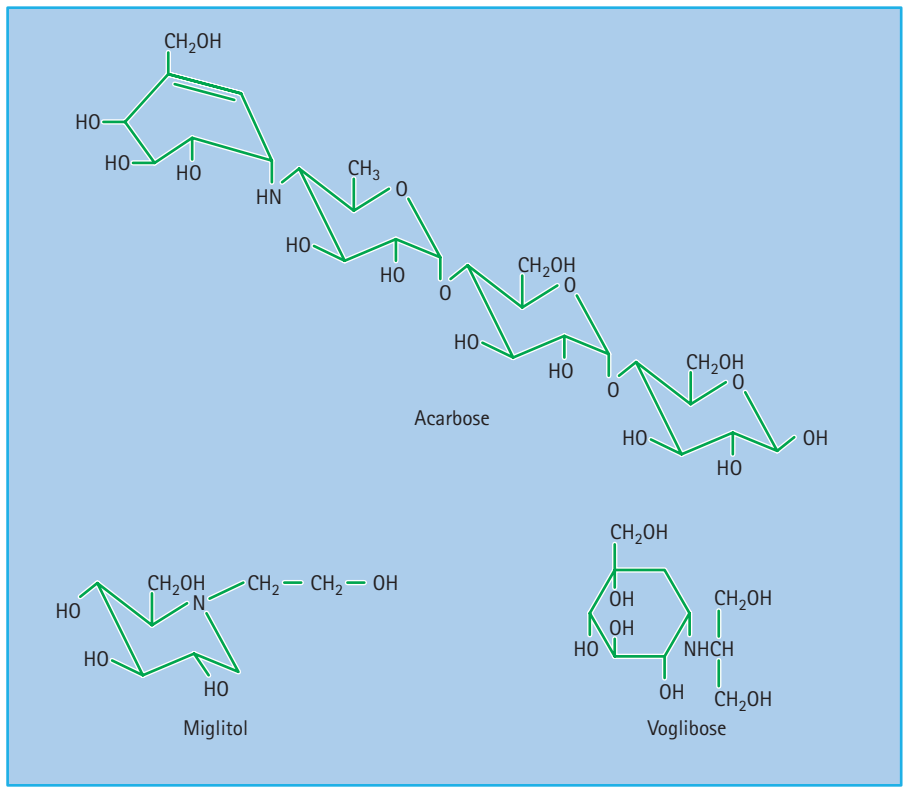

Figure 29.14 Chemical structures of the α-glucosidase inhibitors acarbose, miglitol and volglibose.

who consume meals containing complex carbohydrate, α-glucosidase inhibitors can effectively reduce post-prandial glucose excursions. These agents also have a good safety record but their application has been limited by gastrointestinal side effects.

Mode of action

α-Glucosidase inhibitors competitively inhibit the activity of α-glucosidase enzymes in the brush border of enterocytes lining the intestinal villi (Figure 29.15). They bind to the enzymes with high affinity, preventing the enzymes from cleaving disaccharides and oligosaccharides into monosaccharides. This delays completion of carbohydrate digestion and can defer the process distally along the intestinal tract, leading to a delay in glucose absorption [95]. Different α-glucosidase inhibitors have different affinities for the various α-glucosidase enzymes. This gives slightly different activity profiles (e.g. acarbose has greatest affinity for glycoamylase > sucrase > maltase > dextrinases, whereas miglitol is a stronger inhibitor of sucrase). It is emphasized that α-glucosidase inhibitors can only be effective if the patient is consuming complex digestible carbohydrate. These agents do not significantly affect the absorption of glucose per se. By moving glucose absorption more distally along the intestinal tract, α-glucosidase inhibitors may alter the release of glucose-dependent intestinal hormones such as GIP and GLP-1 which enhance nutrient-induced insulin secretion. Thus, release of GIP, which occurs mainly from the jejunal mucosa, may be reduced by α-glucosidase inhibitors, whereas secretion of GLP-1 (mostly from the ileal mucosa) is increased. α-Glucosidase inhibitors probably reduce post-prandial insulin concentrations through the attenuated rise in post-prandial glucose levels [95].

Pharmacokinetics

Acarbose is degraded by amylases in the small intestine and by intestinal bacteria; less than 2% of the unchanged drug is absorbed along with some of the intestinal degradation products. Absorbed material is mostly eliminated in the urine within 24 hours [95]. Miglitol is almost completely absorbed and eliminated unchanged in the urine.

Indications and contraindications

α-Glucosidase inhibitors can be used as monotherapy, usually for patients with T2DM with post-prandial hyperglycemia but only slightly raised fasting glycemia; however, they are more commonly used as add-on to other therapies, again to target post-prandial hyperglycemia [95]. α-Glucosidase inhibitors can also be used to extend the post-prandial period to reduce interprandial glycemic troughs or hypoglycemia in individuals receiving a sulfonylurea and/or insulin. Acarbose has also been shown to prevent progression of IGT to T2DM [96], although this is not a licensed use.

When starting an α-glucosidase inhibitor the patient should be advised that a diet containing complex digestible carbohydrate is important. α-Glucosidase inhibitors should be taken with meals, starting with a low dose (e.g. 50 mg/day acarbose) and slowly uptitrated over several weeks. Monitoring of post-prandial glycemia is often helpful. Hypoglycemia is unlikely when used as monotherapy, but gastrointestinal symptoms commonly limiting initial tolerability and dose titration. Symptoms tend to be reduced by slow titration and usually subside with time, possibly reflecting some adaptation of the intestinal tract, but tolerability is poor.

α-Glucosidase inhibitors are contraindicated for patients with a history of chronic intestinal disease, and high dosages of acarbose can occasionally increase liver enzyme concentrations; so it is recommended to measure transaminase concentrations periodically in patients receiving a maximum dosage (200 mg acarbose three times daily). Raised liver enzymes should remit as the dosage is reduced, otherwise alternative causes of hepatic dysfunction should be considered.

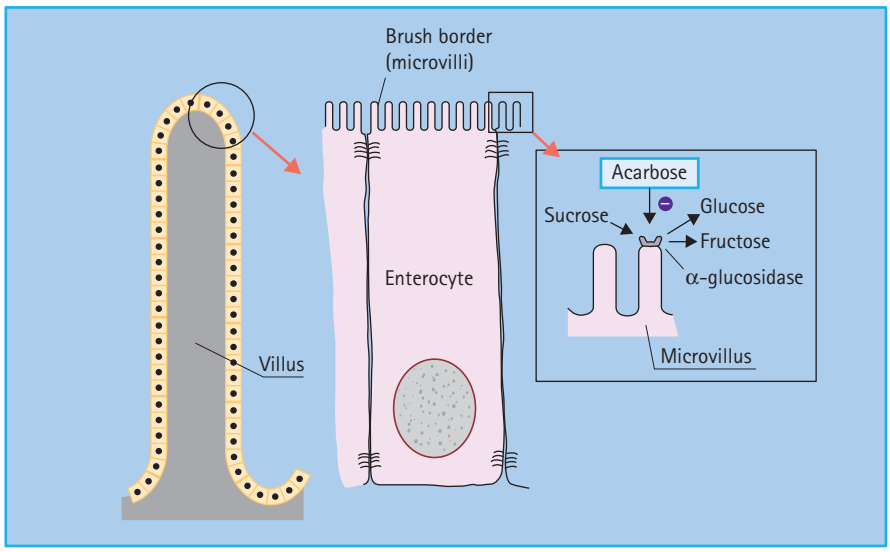

Figure 29.15 Mode of action of α-glucosidase inhibitors. α-Glucosidase inhibitors competitively inhibit the activity of α-glucosidase enzymes in the brush border of enterocytes lining the intestinal villi, preventing these enzymes from cleaving disaccharides and oligosaccharides into monosaccharides. This delays carbohydrate digestion.

Efficacy

Because α-glucosidase inhibitors target post-prandial glucose excursions during meals that contain complex carbohydrate, their effectiveness is entirely dependent on dietary compliance. As monotherapy, these agents can reduce peak post-prandial glucose concentrations by 1–4 mmol/L. The incremental area under the post-prandial plasma glucose curve can be more than halved in some individuals, and there is usually some extended duration of effect to modestly lower basal glycemia up to about 1 mmol/L. The decrease in HbA_{1c} is usually about 0.5–1.0% (6–11 mmol/mol), provided that a high dose of the drug is tolerated and dietary compliance is maintained [97].

Although overall reductions in HbA_{1c} are modest, α-glucosidase inhibitors offer several useful features: they do not cause weight gain or frank hypoglycemia and may reduce inter-prandial episodes of hypoglycemia. When combined with other antidiabetic agents, α-glucosidase inhibitors can reduce post-prandial hyperinsulinemia, and they often lower plasma triglyceride concentrations. Use of an α-glucosidase inhibitor can produce minor alterations to the intestinal absorption of other oral antidiabetic agents when used in combination therapy, but α-glucosidase inhibitors usually provide additive efficacy gains when used in combination with any other class of antidiabetic agent [95]. There is preliminary evidence that acarbose might reduce major cardiac events, including myocardial infarction, but this requires confirmation, and it is unclear if this could be caused by the targeting of post-prandial hyperglycemia or an independent effect of the drug [98].

Adverse effects

Gastrointestinal side effects represent the main problem with α-glucosidase inhibitors. For example, in the STOP-NIDDM trial, 31% of acarbose-treated patients compared with 19% on placebo discontinued treatment early [96]. If the dosage is too high (relative to the amount of complex carbohydrate in the meal), undigested oligosaccharides pass into the large bowel. These are fermented, causing flatulence, abdominal discomfort and sometimes diarrhea, but usually ameliorating with slower titration and time. Hypoglycemia is uncommon and there are no clinically significant drug interations, although use in conjunction with agents affecting gut motility or cholestyramine is not recommended.

Antiobesity therapies

Obesity, especially excess visceral adiposity, predisposes to diabetes, complicates glycemic control and substantially increases the risk of vascular disease (see Chapter 14). The blood glucose-lowering efficacy of lifestyle measures to reduce adiposity in obese T2DM is well appreciated, although it is often very difficult to achieve and maintain significant weight loss in these patients. Interestingly, several studies have suggested that additional glucose-lowering can be attained with pharmacologic antiobesity therapies. Whether this is entirely explained by greater weight loss and improved dietary compliance is unclear because it has been mooted that some antiobesity therapies could have some modest independent glucose-lowering effects.

In conjunction with a mildly hypocaloric and reduced fat diet, the intestinal lipase inhibitor orlistat (120 mg three times daily with meals) can reduce dietary fat absorption by up to 30%. In overweight and obese patients with T2DM this typically increases weight reduction by an extra 2–3 kg, and additional reductions in HbA_{1c} of 0.28–1.1% (3–12 mmol/mol) have been reported [28]. Potential improvements in the glucose–fatty acid cyle might be envisaged. The satiety-inducing serotonin–norepinephrine reuptake inhibitor sibutramine often enables slightly greater reductions of body weight in overweight and obese patients with T2DM, with extra reductions in HbA_{1c} of around 0.6% (7 mmol/mol)*. Sibutramine metabolites might have useful metabolic effects. Antiobesity therapies carry their own contraindications, cautions and side effects, and orlistat could interfere with the absorption and activity of some oral antidiabetic agents, particularly α-glucosidase inhibitors.

Fixed-dose combinations

As the target-driven early and intensified approach to management of hyperglycemia in T2DM gathers momentum, the use of combinations of two or more oral agents with *different* mechanisms of action has become commonplace [99]. To facilitate combination therapy, several fixed dose, single tablet combinations have been made available (Table 29.13). These are designed to provide bioequivalence and thereby similar efficacy, although minor adjustments to formulation may also enable some extra blood glucose-lowering efficacy. Fixed dose combinations can offer convenience, reduce the "pill burden," simplify administration regimens and they may increase patient adherence compared with equivalent combinations of separate tablets. Lower doses of two different types of agents rather than a high dose of one agent may also provide a way to achieve efficacy while circumventing dose-related side effects. Current fixed dose combinations of antidiabetic agents include metformin combined with a sulfonylurea, thiazolidinedione, gliptin or meglitinide, as well as thiazolidinedione–sulfonylurea combinations. Although single tablets could reduce titration flexibility, most of the commonly used dosage combinations have been accommodated. It is reiterated that any form of combination therapy necessitates the same

*The marketing authorization for sibutramine has recently been withdrawn in Europe following the publication of the SCOUT trial. In this trial which included 9,800 overweight or obese individuals at high risk of CVD events, treatment with sibutramine was associated with a 16% increased risk of non-fatal MI, non-fatal stroke, resuscitated cardiac arrest or CVD death. This result was driven by an increased incidence of non-fatal MI and stroke.

Table 29.13 Fixed-dose single-tablet combinations of antidiabetic agents. Adapted from Bailey and Day [99].

Tablet	Components	Strengths (mg)
Glucovance	Metformin +glibenclamide	250:1.25, 500:2.5, 500:5.0
Metaglip	Metformin + glipizide	250:2.5, 500:2.5, 500:5.0
Avandamet	Metformin + rosiglitazone	500:1.0, 500:4.0, 500:2.0, 1000:2.0, 1000:4.0
Competact (Actoplusmet)	Metformin + pioglitazone	500:15, 850:15
Eucreas	Metformin + vildagliptin	850:50, 1000:50
Janumet	Metformin + sitagliptin	500:50, 1000:50
Prandimet	Metformin + repaglinide	500:1, 500:2
Avaglim (Avandaryl)	Rosiglitazone + glimepiride	4:1, 4:2, 4:4, 8:2, 8:4
Tandemact (Duetact)	Pioglitazone + glimepiride	30:, 45:4

Availability of tablets and component strengths differ between countries. Names vary between Europe and USA. Alternative names are given in parentheses.
Glibenclamide = glyburide

cautions and contraindications that apply to each active component.

Conclusions

A minimalistic archetypal algorithm to treat hyperglycemia in T2DM is shown in Figure 29.16. This illustrates a typical stepped approach similar to that advocated in most current guidelines. Guidelines should be interpreted with flexibility, however, to ensure that the care plan, treatment targets and selection of therapies are individualized to suit the circumstances of the patient. The value of lifestyle intervention as initial and ongoing therapy in conjunction with pharmacologic agents should not be underestimated. In view of the progressive natural history of T2DM, the introduction of drug therapy, the need for periodic uptitration of dosage and the use of combination therapy can be expected for most patients (covered in further detail in Chapter 31).

A range of differently acting oral agents is available: metformin and thiazolidinediones counter insulin resistance; sulfonylureas, meglitinides and gliptins increase insulin secretion; and α-glucosidase inhibitors slow carbohydrate digestion. Additionally, injected incretin analogs increase insulin secretion. All of these blood glucose-lowering agents can only provide glycemic control if there is sufficient β-cell reserve. When adequate control is not achieved or not maintained, it is important to proceed to the next stage without delay to avoid periods of hyperglycemia. Insulin should be considered when other therapies do not provide adequate glycemic control or are unsuitable. Integrated management

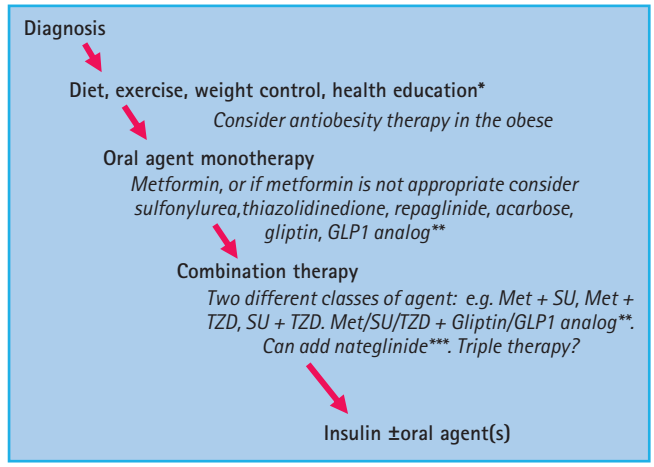

Figure 29.16 Archetypal algorithm used in the treatment of hyperglycemia in type 2 diabetes (except patients presenting with severe hyperglycemia who may require immediate insulin therapy). Start with lifestyle measures (diet and exercise). If the individualized glycemic target for the patient is not achieved quickly using lifestyle measures, then add pharmacologic therapy without delay. The selected monotherapy is uptitrated to achieve the desired glycemic effect. If an uptitration step does not add benefit or is not tolerated revert back a step. When the desired glycemic effect is not achieved or adequate titration is not tolerated, move promptly to the addition of a second agent and uptitrate. If the desired glycemic control is not achieved or maintained consider triple therapy or introduce insulin while maintaining one or two of the existing therapies where appropriate. Respect drug cautions and contraindications at all times, monitor as required, and try to select glycemic targets that are realistic, safely achievable and avoid hypoglycemia. * Lifestyle advice reinforced throughout. ** GLP1 analog given as subcutaneous injection. *** Nateglinide usually only as second agent.

to address cardiovascular risk and co-morbid conditions is essential. Monitoring, therapeutic adjustments for efficacy, safety, avoidance of hypoglycemia and contraindications require constant vigilance, but early, effective and sustained glycemic control is essential to minimize vulnerability to vascular complications later in life.

References

1 Wallace TM, Matthews DR. The drug treatment of type 2 diabetes. In: Pickup JC, Williams G, eds. *Textbook of Diabetes*, 3rd edn. Oxford: Blackwell, 2003: 45.1–45.18.
2 Krentz AJ, Bailey CJ. *Type 2 Diabetes in Practice*, 2nd edn. London: Royal Society of Medicine Press, 2005.
3 Krentz AJ, Bailey CJ. Oral antidiabetic agents: current role in type 2 diabetes mellitus. *Drugs* 2005; **65**:385–411.
4 Krentz AJ, Patel MB, Bailey CJ. New drugs for type 2 diabetes: what is their place in therapy? *Drugs* 2008; **68**:2131–2162.
5 Bailey CJ. Antidiabetic drugs other than insulin. In: Offermans S, Rosenthal W, eds. *Encyclopedia of Molecular Pharmacology*, 2nd edn. Berlin: Springer, 2009: 116–125.

6 Sladek R, Rocheleau G, Rung J, Dina C, Shen L, Serre D, *et al.* A genome-wide association study identifies novel risk loci for type 2 diabetes. *Nature* 2007; **445**:881–885.

7 DeFronzo RA. Pathogenesis of type 2 diabetes mellitus: metabolic and molecular implications for identifying diabetes genes. *Diabetes Rev* 1997; **5**:177–269.

8 Kahn SE. The relative contributions of insulin resistance and beta-cell dysfunction to the pathophysiology of type 2 diabetes. *Diabetologia* 2003; **46**:3–19.

9 Kahn SE, Hull RL, Utzschneider KM. Mechanisms linking obesity to insulin resistance and type 2 diabetes. *Nature* 2006; **444**:840–846.

10 Brownlee M. Biochemistry and molecular cell biology of diabetic complications. *Nature* 2001; **414**:813–820.

11 McGarry JD. Dysregulation of fatty acid metabolism in the etiology of type 2 diabetes. *Diabetes* 2002; **51**:7–17.

12 UK Prospective Study (UKPDS) Group. 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* 1998; **352**:837–853.

13 Stratton IM, Adler AI, Neil HA, Matthews DR, Manley SE, Cull CA, *et al.* Association of glycaemia with macrovascular and microvascular complications of type 2 diabetes (UKPDS 35): prospective observational study. *Br Med J* 2000; **321**:405–412.

14 Holman RR, Paul SK, Bethel MA, Matthews DR, Neil HA. 10-year follow-up of intensive glucose control in type 2 diabetes. *N Engl J Med* 2008; **359**:1577–1589.

15 Action to Control Cardiovascular Risk in Diabetes Study Group. Effects of intensive glucose lowering in type 2 diabetes. *N Engl J Med* 2008; **358**:2545–2559.

16 ADVANCE Collaboratrive Group. Intensive blood glucose and vascular outcomes in patients with type 2 diabetes. *N Engl J Med* 2008; **358**:2560–2572.

17 Duckworth W, Abraira C, Moritz T, Reda D, Emanuele N, Reaven PD, *et al.* Glucose control and vascular complications in veterans with type 2 diabetes. *N Engl J Med* 2009; **360**;129–139.

18 Kosiborod M, Inzucchi SE, Krumholz HM, Xiao L, Jones PG, Fiske S, *et al.* Glucometrics in patients hospitalized with acute myocardial infarction. *Circulation* 2008; **117**:1018–1027.

19 American Diabetes Association. Standards of medical care in diabetes – 2009. *Diabetes Care* 2009; **32**(Suppl 1):13–61.

20 Nathan DM, Buse JB, Davidson MB, Ferrannini E, Holman RR, Sherwin R, *et al.* Management of hyperglycaemia in type 2 diabetes mellitus: a consensus algorithm for the initiation and adjustment of therapy – a consensus statement from the American Diabetes Association and the European Association for the Study of Diabetes. *Diabetologia* 2009; **52**:17–30.

21 International Diabetes Federation Clinical Guidelines Task Force. *Global Guideline for Type 2 Diabetes*. Brussels: International Diabetes Federation, 2005.

22 National Collaborating Centre for Chronic Conditions. *Type 2 diabetes: national clinical guideline for management of primary and secondary care (update)*. London: Royal College of Physicians, 2008.

23 Bailey CJ, Blonde L, Del Prato S, Leiter LA, Nesto R, *et al*. What are the practical implications for treating diabetes in light of recent evidence? Updated recommendations from the Global Partnership for Effective Diabetes Management. *Diabetes Vascular Dis Res* 2009; **6**:283–287.

24 Canadian Diabetes Association Clinical Practice Guidelines Expert Committee. Phamacologic management of type 2 diabetes. *Can J Diabetes* 2003; **27**(Suppl 2):37–42. www.diabetes.ca/cpg2003/downloads/pharmacologic.pdf

25 Matthaei S, Bierwirth R, Fritsche A, Gallwitz B, Haring HU, Joost HG, *et al*. Medical antihyperglycaemic treatment of type 2 diabetes mellitus. Update of the evidence-based guidelines of the German Diabetes Association. *Exp Clin Endocrinol Diabetes* 2009; **117**:522–557.

26 Bonora E, Calcaterra F, Lombardi S, Bonfante N, Formentini G, Bonandonna RC, *et al.* Plasma glucose levels throughout the day and HbA_{1c} interrelationships in type 2 diabetes. *Diabetes Care* 2001; **24**:2023–2029.

27 DECODE study group. Is the current definition for diabetes relevant to mortality risk from all causes and cardiovascular and noncardiovascular diseases. *Diabetes Care* 2003; **26**:688–696.

28 Lloret-Linares C, Greenfield JR, Czernichow S. Effects of weight-reducing agents on glycaemic parameters and progression to type 2 diabetes: a review. *Diabet Med* 2008; **25**:1142–1150.

29 Bailey CJ, Day C. Metformin: its botanical background. *Pract Diabet Int* 2004; **21**:115–117.

30 Bailey CJ. Biguandes and NIDDM. *Diabetes Care* 1992; **15**:755–772.

31 Bailey CJ, Turner RC. Metformin. *N Engl J Med* 1996; **334**:574–579.

32 Bailey CJ, Campbell IW, Chan JCN, Davidson JA, Howlett HCS, Ritz P. *Metformin: The Gold Standard*. Chichester: Wiley, 2007.

33 Bailey CJ. Metformin: effects on micro and macrovascular complications in type 2 diabetes. *Cardiovasc Drugs Ther* 2008; **22**:215–224.

34 Grant PJ. Beneficial effects of metformin on haemostasis and vascular function in man. *Diabetes Metab* 2003; **29**:6S44–52.

35 Zhou G, Myers R, Li Y, Chen Y, Shen X, Fenyk-Melody J, *et al.* Role of AMP-activated protein kinase in the mechanism of action of metformin. *J Clin Invest* 2001; **108**:1167–1174.

36 Scheen AJ. Clinical pharmacokinetics of metformin. *Clin Pharmacokinet* 1996; **30**:359–371.

37 Cusi K, DeFronzo RA. Metformin: a review of its metabolic effects. *Diabetes Rev* 1998; **6**:89–131.

38 Palumbo S, Falbo A, Zullo F, Orio F. Evidence-based and potential benefits of metformin in the polycystic ovary syndrome: a comprehensive review. *Endocr Rev* 2009; **30**:1–50.

39 Natali A, Ferrannini E. Effects of metformin and thiazolidinediones on suppression of hepatic glucose production and stimulation of glucose uptake in type 2 diabetes: a systematic review. *Diabetologia* 2006; **49**:434–441.

40 UK Prospective Diabetes Study Group. Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34). *Lancet* 1998; **352**:854–865.

41 Rao AD, Reynolds K, Kuhadha N, Fonseca VA. Is the combination of sulphonylureas and metformin associated with an increased risk of cardiovascular disease or all-cause mortality? *Diabetes Care* 2008; **31**:1672–1678.

42 Hermann LS, Lindberg G, Lindblad U, Melander A. Efficacy, effectiveness and safety of sulphonylurea-metformin combination therapy in patients with type 2 diabetes. *Diabetes Obes Metab* 2002; **4**:296–304.

43 Johnson JA, Majumdar SR, Simpson SH, Toth EL. Decreased mortality associated with sulfonylurea monotherapy in type 2 diabetes. *Diabetes Care* 2002; **25**:2244–2248.

44 Douek IF, Allen SE, Ewings P, Gale EA, Bingley PJ; Metformin Trial Group. Continuing metformin when starting insulinin patients with type 2 diabetes: a double-blind randomized placebo-controlled trial. *Diabet Med* 2005; **22**:634–640.

45 Yki-Jarvinen H, RyysyL, Nikkila K, Tulokas T, Vanamo R, Heikkilä M. Comparison of bedtime insulin regimens in patients with type 2 diabetes mellitus: a randomized, controlled trial. *Ann Intern Med* 1999; **130**:389–396.

46 Diabetes Prevention Program Research Group. Reduction of the incidence of type 2 diabetes with lifestyle intervention or metformin. *N Engl J Med* 2002; **346**:393–403.

47 Salpeter SR, Greyber E, Pasternak GA, Salpeter EE. Risk of fatal and non-fatal lactic acidosis with metformin use in type 2 diabetes. *Arch Intern Med* 2003; **163**:2594–2602.

48 Lalau J-D, Race J-M. Metformin and lactic acidosis in diabetic humans. *Diabetes Obes Metab* 2000; **2**:131–137.

49 Henquin JC. The fiftieth anniversary of hypoglycaemic suphonamides: how did the mother compound work? *Diabetologia* 1992; **35**:907–912.

50 Ashcroft FM, Gribble FM. ATP-sensitive K^+ channels and insulin secretion: their role in health and disease. *Diabetologia* 1999; **42**:903–919.

51 Gribble FM, Reimann F. Pharmacological modulation of K-ATP channels. *Biochem Soc Trans* 2002; **30**:333–339.

52 Rorsman P, Renstrom E. Insulin granule dynamics in pancreatic beta cells. *Diabetologia* 2003; **46**:1029–1045.

53 Ball AJ, Flatt PR, McClenaghan NH. Desensitization of sulphonylurea- and nutrient-induced insulin secretion following prolonged treatment with glibenclamide. *Eur J Pharmacol* 2000; **408**:327–333.

54 Lebovitz HE. Insulin secretagogues: old and new. *Diabetes Rev* 1999; **7**:139–151.

55 Groop LC. Sulfonylureas in NIDDM. *Diabetes Care* 1992; **15**:1737–1754.

56 Rendell M. The role of sulfonylureas in the management of type 2 diabetes. *Drugs* 2004; **64**:1339–1358.

57 Schernthaner G, Grimaldi A, Di Mario U, Drzewoski J, Kempler P, Kvapil M, *et al.* GUIDE study: double-blind comparison of once-daily gliclazide MR and glimepiride in type 2 diabetic patients. *Eur J Clin Invest* 2004; **34**:535–542.

58 Krentz AJ, Ferner RE, Bailey CJ. Comparative tolerability profiles of oral antidiabetic agents. *Drug Saf* 1994; **11**:223–241.

59 Wilson SH, Kennedy FP, Garratt KN. Optimization of the management of patients with coronary heart disease and type 2 diabetes mellitus. *Drugs Aging* 2001; **18**:325–333.

60 Garrino MG, Schmeer W, Nenquin M, Meissner HP, Henquin JC. Mechanism of the stimulation of insulin release *in vitro* by HB 699, a benzoic acid derivative similar to the non-sulfonylurea moiety of glibenclamide. *Diabetologia* 1985; **28**:697–703.

61 Dornhorst A. Insulotropic meglitinide analogues. *Lancet* 2001; **358**:1709–1715.

62 Davies M. Nateglinide: better post-prandial glucose control. *Prescriber* 2002; **13**:17–27.

63 Blickle JF. Meglitinide analogues: a review of clinical data focused on recent trials. *Diabetes Metab* 2006; **32**:113–120.

64 Day C. Thiazolidinediones: a new class of antidiabetic drugs. *Diabet Med* 1999; **16**:1–14.

65 Yki-Jarvinen H. Thiazolidinediones. *N Engl J Med* 2004; **351**:1106–1118.

66 Staels B, Fruchart J. Therapeutic roles of peroxisome proliferator-activated receptor genes. *Diabetes* 2005; **54**:2460–2470.

67 Semple RK, Chatterjee VK, O'Rahilly S. PPAR gamma and human metabolic disease. *J Clin Invest* 2006; **116**:581–589.

68 Blaschke F, Spanheimer R, Khan M, Law RE. Vascular effects of TZDs: new implications. *Vasc Pharmacol* 2006; **45**:3–18.

69 Kahn SE, Haffner SM, Heise MA, Holman RR, Kravitz BG, Yu D, *et al.* Glycemic durability of rosiglitazone, metformin or glyburide monotherapy. *N Engl J Med* 2006; **355**:2427–2443.

70 Bailey CJ. Treating insulin resistance in type 2 diabetes with metformin and thiazolidinedione. *Diabetes Obes Metab* 2005; **7**:675–691.

71 Nesto RW, Bell D, Bonow RO, Fonseca V, Grundy SM, Horton ES, *et al.* Thiazolidinedione use, fluid retention, and congestive heart failure: a consensus statement from the American Heart Association and the American Diabetes Association. *Circulation* 2003; **108**:2941–2948.

72 Nissen SE, Wolski K. Effect of rosiglitazone on the risk of myocardial infarction and death from cardiovascular casuses. *N Engl J Med* 2007; **356**:2457–2471.

73 Goldberg RB, Kendall DM, Deeg MA, Buse JB, Zagar AJ, Pinaire JA, *et al.* A comparison of lipid and glycemic effects of pioglitazone and rosiglitazone in patients with type 2 diabetes and dyslipidemia. *Diabetes Care* 2005; **28**:1547–1554.

74 Hermansen K, Mortensen LS. Body weight changes associated with antihyperglycaemic agents in type 2 diabetes mellitus. *Drug Saf* 2007; **30**:1127–1142.

75 McGuire DK, Inzucchi SE. New drugs for the treatment of diabetes mellitus. Part 1. thiazolidinedione and their evolving cardiovascular impolications. *Circulation* 2008; **117**:440–449.

76 Dormandy JA, Charbonnel B, Eckland DJ, Erdmann E, Massi-Benedetti M, Moules IK, *et al.* 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* 2005; **366**:1279–1289.

77 DREAM Trial Investigators, Gerstein HC, Yusuf S, Bosch J, Pogue J, Sheridan P, Dinccaq N, *et al.* Effect of rosiglitazone on the frequency of diabetes in patients with impaired glucose tolerance or impaired fasting glucose: a randomized controlled trial. *Lancet* 2006; **368**:1096–1105.

78 Buchanan TA, Xiang AH, Peters RK, Kjos SL, Marroquin A, Goico J, *et al.* Preservation of pancreatic beta-cell function and prevention of type 2 diabetes by pharmacological treatment of insulin resistance in high-risk hispanic women. *Diabetes* 2002; **51**: 2796–2803.

79 Erdmann E, Dormandy JA, Charbonnel B, Massi-Benedetti M, Moules IK, Skene AM; PROactive Investigators. The effect of pioglitazone on recurrent myocardial infarction in 2,445 patients with type 2 diabetes and previous myocardial infarction. Results from the PROactive (PROactive 05) study. *J Am Coll Cardiol* 2007; **49**:1772–1780.

80 Wilcox R, Bousser MG, Betteridge DJ, Schernthaner G, Piraqs V, Kupfer S, *et al.* Effects of pioglitazone in patients with type 2 diabetes with or without previous stroke. Results from PROactive (PROspective pioglitAzone Clinical Trial In macroVascular Events 04). *Stroke* 2007; **38**:865–873.

81 Loke Y, Singh S, Furberg CD. Long-term use of thiazolidinediones and fractures in type 2 diabetes: a meta-analysis. *Can Med Assoc J* 2009; **180**:5–15.

82 Holst JJ. Glucagon-like peptide-1: from extract to agent. The Claude Bernard Lecture, 2005. *Diabetologia* 2006; **49**:253–260.

83 Drucker DJ. The role of gut hormones in glucose homeostasis. *J Clin Invest* 2007; **117**:24–32.

84 Nauck M, Stockmann F, Ebert R, Creutzfeldt W. Reduced incretin effect in type 2 (non-insulin-dependent diabetes. *Diabetologia* 1986; **29**:46–52.

85 Deacon CF. Therapeutic strategies based on glucagon-like peptide 1. *Diabetes* 2004; **53**:2181–2189.

86 Weber AE. Dipeptidyl peptidase IV inhibitors for the treatment of diabetes. *J Med Chem* 2004; **47**:4135–4141.

87 Gorrell MD. Dipeptidyl peptidase IV (DPP-IV) and related enzymes in cell biology and liver disorders. *Clin Sci* 2005; **108**:277–292.

88 Flatt PR, Bailey CJ, Green BD. Dipeptidyl peptidase IV (DPP IV) and related molecules in type 2 diabetes. *Frontiers Biosci* 2008; **13**:3648–3660.

89 Flatt PR, Bailey CJ, Green BD. Recent advances in antidiabetic drug therapies targeting the enteroinsular axis. *Curr Drug Metab* 2009; **10**:125–137.

90 Amori RE, Lau J, Pittas AG. Efficacy and safety of incretin therapy in type 2 diabetes: systematic review and meta-analysis. *JAMA* 2007; **298**:194–206.

91 Green BD, Flatt PR, Bailey CJ. Gliptins: dipeptidyl peptidase-4 (DPP-4) inhibitors to treat type 2 diabetes. *Future Prescriber* 2007; **8**: 7–13.

92 Campbell IW, Day C. Sitagliptin: enhancing incretin action. *Br J Diabetes Vasc Dis* 2007; **7**:134–139.

93 Nauck MA, Meininger G, Sheng D, Terranella L, Stein PP; Sitagliptin Study 024 Group. Efficacy and safety of the dipeptidly peptidase-4 inhibitor, sitagliptin, compared with the sulfonylurea, glipizide, in patients with type 2 diabetes inadequately controlled on metformin alone: a randomized, double-blind, non-inferiority trial. *Diabetes Obes Metab* 2007; **9**:194–205.

94 Croxtall JD, Keam SJ. Vildagliptin: a review of its use in the management of type 2 diabetes mellitus. *Drugs* 2008; **68**:2387–2409.

95 Lebovitz HE. Alpha-glucosidase inhibitors as agents in the treatment of diabetes. *Diabetes Rev* 1998; **6**:132–145.

96 Chiasson JL, Josse RG, Gomis R, Hanefeld M, Karasik A, Laakso M; STOP-NIDDM Trial Research Group. Acarbose for the prevention of diabetes mellitus: the STOP-NIDDM randomised trial. *Lancet* 2002; **359**: 2072–2077.

97 Holman RR, Cull CA, Turner RC. A randomised double-blind trial of acarbose in type 2 diabetes shows improved glycemic control over 3 years (UK Prospective Diabetes Study 44). *Diabetes Care* 1999; **22**:960–964.

98 Chiasson J-L, Josse RG, Gomis R, Hanefeld M, Karasik A, Laakso M; STOP-NIDDM Trial Research Group. Acarbose treatment and the risk of cardiovascular disease and hypertension in patients with impaired glucose tolerance: the STOP-NIDDM trial. *JAMA* 2003; **290**:486–494.

99 Bailey CJ, Day C. Fixed-dose single tablet antidiabetic combinations. *Diabetes Obes Metab* 2009; **11**:527–533.