

Chapter 2

Established classes of glucose-lowering drugs

1. Introduction

Newer drugs for the treatment of type 2 diabetes have to be positioned within an existing framework of more established therapies. There is half a century of clinical experience with biguanides and sulphonylureas. Drugs within these archetypal classes illustrate the potential for clinically important differences between individual compounds. These differences are reflected principally in safety and tolerability rather than appreciable differences in long-term efficacy, although there is some support for the latter.

The UK Prospective Diabetes Study (UKPDS) was completed just as a new class of oral glucose-lowering agents became available – the thiazolidinediones. The launch was inauspicious: severe hepatotoxicity ensured the rapid demise of the first member of the class to enter clinical practice – troglitazone. Issues of weight gain, oedema, risk of bone fractures and cardiac failure in susceptible patients apply to the remaining two drugs – rosiglitazone and pioglitazone. Moreover, new safety concerns have emerged in the past few years. Although they have become well established and widely used, the role of thiazolidinediones is being re-evaluated.

The progressive nature of type 2 diabetes was well demonstrated in the UKPDS. This translates into a need for combinations of glucose-lowering drugs in the majority of patients. In the UKPDS fewer than half of the participants treated with metformin or a sulphonylurea were at the target glycated haemoglobin (HbA_{1c}) level of 7.0% 3 years after diagnosis. Drugs from different classes tend to have additive rather than synergistic effects, and bringing blood glucose concentrations down into the physiological range remains difficult to achieve. All major classes of oral glucose-lowering agents, when used appropriately, reduce glycated haemoglobin concentrations by broadly similar degrees. Some data point to differences between classes but more robust long-term comparisons are required. These observations perhaps point to some fundamental deficits in our understanding of the heterogeneous mechanisms that lead to chronic hyperglycaemia. It is clear that genetic, epigenetic, behavioural and environmental factors conspire to produce a broad range of phenotypes. These factors account for some of the differences in individual responses to oral agents.

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DOI: 10.1007/978-1-908517-77-7_2,

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2. Biguanides

Metformin (dimethylbiguanide) is the only biguanide available in most countries. Phenformin was tarnished by lactic acidosis and was withdrawn from the UK in the late 1970s. Metformin was introduced in the USA in 1995. While metformin carries a much lower risk of lactic acidosis than phenformin, clinicians are required to ensure that appropriate steps are taken to minimise the occurrence of this potentially life-threatening side-effect. Metformin is thought to be the most commonly prescribed oral glucose-lowering agent worldwide. The drug enjoyed a surge in use following the publication of the UKPDS; it is relatively inexpensive compared with newer drugs such as the thiazolidinediones and dipeptidyl peptidase 4 (DPP-4) inhibitors.

2.1 *Mode of action*

Metformin counters defective insulin action, i.e. it has insulin-sensitising properties but does not directly enhance insulin secretion. The drug exerts its effects on glucose metabolism by means of insulin-dependent and insulin-independent intracellular pathways, including the activation of adenosine 5'-monophosphate-activated protein kinase. Metformin appears to offer protection against the vascular complications of diabetes partly through mechanisms that are independent of its antihyperglycaemic properties (Box 2.1).

The full glucose-lowering efficacy of metformin requires the presence of insulin. The main effect is mediated by means of a reduction in hepatic glucose production (Figure 2.1). Metformin reduces gluconeogenesis by increasing hepatic insulin sensitivity, and by decreasing hepatic extraction of gluconeogenic substrates from the circulation; hepatic glycogenolysis is also decreased. To a lesser extent, metformin enhances insulin-stimulated glucose uptake in skeletal muscle cells where it promotes glycogen synthesis. Metformin directly suppresses fatty acid oxidation; this may be of benefit in patients with hypertriglyceridaemia. The actions of metformin on fatty acids permit increased utilisation of glucose as a cellular energy source.

2.2 *Pharmacokinetics*

Metformin is rapidly but incompletely absorbed from the gastrointestinal tract. The drug is not metabolised. There is little binding to plasma proteins. Compared with plasma, higher concentrations are achieved in cells of the gastrointestinal tract. The plasma half-life of metformin is approximately 6 h; urinary elimination is complete within approximately 12 h. Renal clearance occurs principally by tubular secretion. Cimetidine competes for renal clearance and can cause a clinically significant increase in plasma metformin concentrations.

Box 2.1: Metabolic and vascular effects of metformin

Antihyperglycaemic action

- *Suppresses hepatic glucose output*
- *Increases insulin-mediated glucose utilisation*
- *Decreases fatty acid oxidation*
- *Increases splanchnic glucose turnover*

Weight stabilisation or reduction

Improves lipid profile

- *Reduces hypertriglyceridaemia*
- *Lowers plasma fatty acids and LDL-cholesterol; raises HDL-cholesterol in some patients*

No risk of serious hypoglycaemia

Counters insulin resistance

- *Decreases endogenous or exogenous insulin requirements*
- *Reduces basal plasma insulin concentrations*

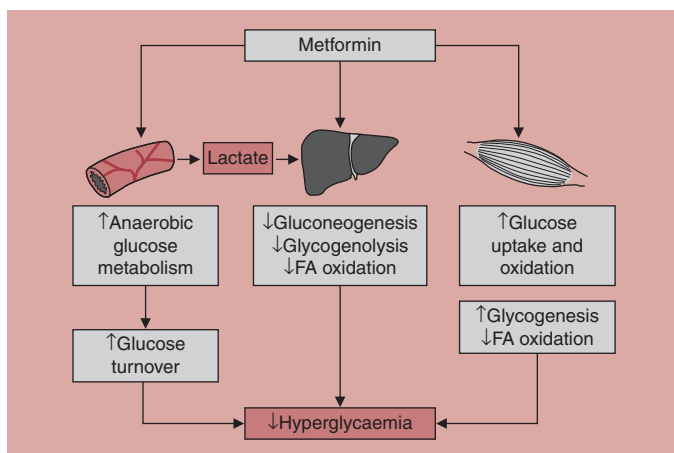
Vascular effects

- *Increased fibrinolysis*
- *Decreases plasminogen activator inhibitor 1 levels*
- *Improved endothelial function*

2.3 Indications and contraindications

Metformin does not cause weight gain and can aid efforts directed at weight loss; this makes it the preferred drug for overweight and obese patients. Metformin appears to have similar antihyperglycaemic efficacy in normal weight patients, although the evidence base is less robust. Because of the risk of drug accumulation the use of metformin in patients with marked impairment of renal function should be avoided. The threshold of glomerular filtration at which risk is deemed unacceptable continues to be debated; this exercise is fraught with uncertainties and the issue remains controversial. In the UK, it is recommended that the dose of metformin be reviewed if the estimated glomerular filtration rate (eGFR) falls below 45 ml/min and avoided if it is less than 30 ml/min. This caution reflects concerns about the most feared adverse event – lactic acidosis. The incidence is low, but mortality is high. The risk of lactic acidosis with metformin has long been the subject of debate. Some prescribers hold the view that the danger has been exaggerated. Further contraindications include significant cardiac or respiratory insufficiency, or any other condition predisposing to major tissue hypoxia, e.g. hypotension, major infection, acute myocardial infarction. Metformin should be avoided in patients with clinically significant liver disease or

Figure 2.1. Main sites of action of metformin contributing to glucose-lowering effect.



FA = Fatty acid.

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alcohol dependency. Advanced age is not a contraindication to metformin in the absence of renal insufficiency and other exclusions. Ovulation can resume in women with polycystic ovary syndrome (PCOS). The use of metformin in PCOS is an unlicensed application in the absence of diabetes.

Unmodified tablet, liquid or powder formulations – so-called immediate release (IR) – should be taken during or immediately after meals in order to minimise gastrointestinal side-effects. Start with 500 or 850 mg once a day, or 500 mg twice a day divided between the morning and evening meals. Increase the dosage slowly – one tablet at a time – at approximately 1–2-week intervals. If glycaemic targets are not attained and an additional dose produces no further improvement, stepping down to the previous dose is sensible. The maximal effective dosage of metformin is approximately 2000 mg/day, although the maximum approved dose in some countries is higher.

Slow-release options (XR/SR/ER) are available in many countries. These can be taken once a day in the morning, or if necessary, morning and evening. Metformin is extensively used in combination with other classes of glucose-lowering agents, including insulin. Fixed-dose combination tablets are available in which metformin is combined with either a sulphonylurea (not available in the UK) or thiazolidinedione (pioglitazone in the UK) or certain DPP-4 inhibitors. Although metformin carries a negligible risk of hypoglycaemia as monotherapy or in combination with

other low-risk drugs such as thiazolidinediones, it will potentiate the actions of insulin-releasing agents and insulin.

During the long-term use of metformin it is advised to check at least annually for the emergence of contraindications, particularly renal function. Metformin can reduce vitamin B₁₂ absorption; this should be borne in mind during long-term therapy in individuals with other nutritional deficiencies. Metformin should be temporarily discontinued when intravenous radiographic contrast media are used because of the risk of an acute deterioration in renal function. Surgery with general anaesthesia carries risks of hypoxia and sepsis; substitution with insulin may be required as a safer option, with metformin being re-introduced when these risks have passed.

2.4 Efficacy

As monotherapy in patients not adequately controlled by lifestyle measures, optimally titrated metformin can be expected to reduce fasting plasma glucose by approximately 2–4 mmol/l; this corresponds to a decrease in HbA_{1c} of approximately 1–2%.

As discussed in Chapter 1, obese patients in the UKPDS who were commenced on metformin had a 39% reduced risk of myocardial infarction compared with conventional treatment ($p = 0.01$). Supporting the observations are studies demonstrating that metformin has beneficial effects on atherothrombotic risk markers (see Box 2.1). Recent results from the post-trial follow-up of UKPDS showed that the cardiovascular benefits of metformin were maintained (Table 2.1). However, a meta-analysis published in 2011 cast some doubt on specific beneficial effects of metformin on macrovascular events and mortality. There have been concerns that combination metformin plus sulphonylurea therapy might be associated with a higher risk of vascular complications than metformin monotherapy. A recent meta-analysis concluded that this combination significantly increased the risk of a cardiovascular event composite endpoint; however, there were no significant effects of this combination therapy on either cardiovascular mortality or all-cause mortality.

Although metformin is not indicated for the prevention of diabetes the US Diabetes Prevention Programme showed that metformin reduced 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; the benefits were most evident in younger, more obese individuals.

2.5 Adverse effects

The main tolerability issue with metformin is abdominal discomfort and other gastrointestinal adverse effects, including diarrhoea. These are often transient side-effects that can be ameliorated by taking the drug with meals and

Table 2.1. UKPDS 10-year follow-up study. Results for metformin compared with conventional treatment at end of UKPDS and after a median 8.5 years post-trial follow-up. Post-trial monitoring results showed continuing benefit of earlier metformin therapy, with maintenance of relative risk reductions – ‘legacy effect’.

Aggregate endpoint	1997	2007
Any diabetes-related endpoint		
Relative risk reduction	32%	21%
p value	0.0023	0.013
Myocardial infarction		
Relative risk reduction	39%	33%
p value	0.01	0.005
All-cause mortality		
Relative risk reduction	36%	27%
p value	0.011	0.002

UKPDS: UK Prospective Diabetes Study.
Reproduced from Holman et al. (2008) and Diabetes Trials Unit, University of Oxford, with permission.

titrating the dose slowly. Symptoms may remit if the dose is reduced, but approximately 10% of patients are unable to tolerate metformin at any dose. The most serious adverse event associated with metformin is lactic acidosis; as already mentioned this is rare, affecting approximately one in 100 000 patients, but its avoidance underpins the aforementioned contraindications to metformin, i.e. clinical situations that can lead to the accumulation of the drug, or produce major tissue hypoxia. Vitamin B₁₂ deficiency is a potential hazard of long-term therapy that could impair peripheral nerve function. Periodic measurement of serum vitamin B₁₂ status is recommended.

3. Sulphonylureas

Since their introduction in the 1950s, sulphonylureas have been used extensively for the treatment of type 2 diabetes. Modern examples include glibenclamide (known as glyburide in the USA and Canada), gliclazide, glipizide and glimepiride; these have largely replaced the first generation of sulphonylureas (Table 2.2). Sulphonylureas are relatively inexpensive. In the UK sulphonylureas and metformin are widely used but account for less than 50% of the total cost of glucose-lowering drugs.

3.1 Mode of action

Sulphonylureas stimulate insulin secretion from islet β cells (Figure 2.2). They bind to the cytosolic surface of the sulphonylurea receptor (SUR) 1, which forms part of a transmembrane complex with ATP-sensitive Kir6.2

potassium channels (K^+ ATP channels). This closes the K^+ ATP channel, reducing potassium efflux with membrane depolarisation resulting in calcium influx that in turn leads to the release of insulin from preformed granules. This generates the initial phase of insulin release which is followed by a more protracted second phase of insulin secretion. Because sulphonylureas will stimulate insulin release even when glucose concentrations are below normal they are capable of causing hypoglycaemia; fasting hypoglycaemia results mainly from the suppression of hepatic glucose production. Drugs with an intrinsically long duration of action, glibenclamide (glyburide) being the prime example, are associated with a higher risk of severe hypoglycaemia compared with shorter-acting sulphonylureas.

3.2 Pharmacokinetics

Sulphonylureas vary in their pharmacokinetic properties. They are all generally well absorbed, reaching peak plasma concentration in approximately 2–4 h. Sulphonylureas are generally highly bound to plasma proteins, which can lead to interactions with drugs such as salicylates, sulphonamides and warfarin. Displacement of protein-bound sulphonylureas can increase the risk of hypoglycaemia. Sulphonylureas are hepatically metabolised to active and inactive metabolites that are eliminated along with the parent drug in bile and urine. The formulation of some sulphonylureas has been altered to modify the duration of action. A micronised formulation of glibenclamide increases the rate of gastrointestinal absorption producing an earlier onset of action. A modified release formulation of gliclazide has been developed to allow once-daily dosing. This formulation is not available in all countries.

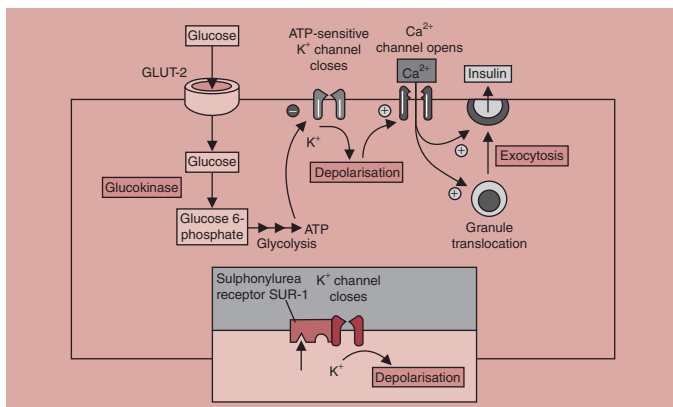
Table 2.2. Sulphonylureas.

Agent	Dose range (mg/day)	Duration of action (h)	Metabolites	Elimination
Tolbutamide	500–2000	6–10	Inactive	Urine 100%
Glipizide	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	1–6	12–>24	Active	Urine ~60%
Glibenclamide	2.5–15	12–>24	Active	Bile >50%
Chlorpropamide	100–500	24–50	Active	Urine >90%

New patients are not usually started on first-generation sulphonylureas (tolbutamide, chlorpropamide). Glibenclamide is also known as glyburide in the USA. Not all drugs or formulations listed are available in every country. Glimepiride is sometimes referred to as a third-generation sulphonylurea.

MR: Modified release.

Figure 2.2. Sulphonylureas act on the pancreatic β cells to stimulate insulin action. They bind to the cytosolic surface of the sulphonylurea receptor 1 (SUR-1), causing closure of ATP-sensitive Kir6.2 potassium channels, depolarising the plasma membrane, opening calcium channels and activating calcium-dependent signalling proteins that control insulin exocytosis.



GLUT-2 = Glucose transporter 2.

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3.3 Indications and contraindications

Sulphonylureas are widely used as monotherapy and in combination with metformin or a thiazolidinedione. They can also be used with an α -glucosidase inhibitor or a DPP-4 inhibitor. Combination therapy with insulin offers little advantage other than a somewhat lower insulin dosage. Combining a sulphonylurea with a different type of oral glucose-lowering agent generally brings an additive effect on glucose lowering, albeit with a higher risk of hypoglycaemia. Meglitinides, which like sulphonylureas act via the SUR-1 complex, generally offer no extra benefit beyond up-titration of the sulphonylurea.

Expert guidelines have tended to favour sulphonylureas as alternative first-line oral therapy when metformin is not appropriate or not tolerated. As sulphonylurea therapy is associated with weight gain, these agents have customarily been preferred for patients who are not overweight. Treatment should begin with a low dose. Up-titrate the dosage at 2–4-week intervals as required. The maximal blood glucose-lowering effect of an unmodified sulphonylurea is usually achieved at a dose well below the recommended maximum. Hypoglycaemia is the main limitation to dose escalation of sulphonylureas. Self-monitoring of blood glucose is recommended during the first few weeks of therapy. If evidence of hypoglycaemia occurs before the

glycaemic target is achieved, or if a dosage increment produces no further glycaemic benefit, it is advisable to return to the previous dose. Additional or alternative therapy should be considered in these situations as appropriate.

3.4 Efficacy

As monotherapy in patients inadequately controlled by lifestyle measures, sulphonylureas can be expected to reduce fasting plasma glucose by approximately 2–4 mmol/l, equating to a decrease in HbA_{1c} of approximately 1–2%. The glucose-lowering effect of sulphonylureas is immediate, although efficacy is dependent on a sufficient reserve of β -cell function. A rapid deterioration of glycaemic control during sulphonylurea therapy occurs in approximately 5–10% of patients per annum. There is some evidence that there are differences between individual sulphonylureas in their capacity to maintain glycaemic control. As a class, the general trend is to a deterioration in control after an initial response, as demonstrated in the UKPDS. No drugs in the class have unequivocally been shown to reduce the progression to diabetes in patients with glucose intolerance. Sulphonylureas generally have little effect on blood lipids. Preliminary pharmacogenetic studies of genetic variants that influence enzymatic hepatic sulphonylurea metabolism and thus pharmacokinetics raise the possibility of identifying individuals more likely to respond well to sulphonylureas.

3.5 Adverse effects

Weight gain of approximately 1–4 kg, is common after the initiation of sulphonylurea therapy, with stabilisation by approximately 6 months. Sulphonylurea-induced weight gain is thought to be a consequence of the anabolic effects of increased plasma insulin concentrations. Hypoglycaemia is the most common and most serious adverse effect of sulphonylurea therapy. Although it is only rarely life threatening in patients with type 2 diabetes, with mild impairment of neural or motor functions. Patients treated with sulphonylureas, and their carers, should be given clear instructions on the prevention, recognition and management of hypoglycaemia. In the UKPDS approximately 20% of sulphonylurea-treated patients reported one or more episodes of symptomatic hypoglycaemia per annum; other studies suggest similar rates. Severe hypoglycaemia, i.e. requiring assistance from another person during sulphonylurea therapy, occurred in approximately 1% of patients annually in the UKPDS. Irregular meals, the concomitant use of other glucose-lowering drugs, excessive alcohol consumption, old age, unplanned or strenuous activity and drug interactions can increase the risk of hypoglycaemia. Patients who have already attained good glycaemic control are at greater risk. Chlorpropamide and glibenclamide (glyburide) are more likely to cause severe prolonged hypoglycaemia compared to newer drugs and their modified

formulations. Severe sulphonylurea-induced hypoglycaemia requires prompt admission to hospital; there is an appreciable risk of fatality and a risk of residual neurological defects in survivors.

The suggestion from the UGDP (University Group Diabetes Program) study in the 1960s that tolbutamide might have a detrimental effect on cardiovascular outcomes remains unsubstantiated. Interest in the cardiovascular safety of sulphonylureas was re-ignited by the finding that two isoforms of the sulphonylurea receptor, SUR-2A and SUR-2B, are expressed in cardiac muscle and vascular smooth muscle, respectively. Whereas these isoforms lack the sulphonylurea binding site, they retain the benzamido binding site. Therefore, SUR-2A/B can only bind those sulphonylureas that contain a benzamido group, i.e. glibenclamide, glipizide and glimepiride. Sulphonylureas without a benzamido group, e.g. tolbutamide, chlorpropamide and gliclazide, show very little interaction with the cardiac and vascular SUR receptors. Theoretically, compounds with a benzamido group could interfere with ischaemic preconditioning and increase vascular contractility under unfavourable conditions, e.g. during myocardial ischaemia. However, there is no clear evidence that therapeutic concentrations of sulphonylureas exert such an effect. This controversy continues, and has been fuelled by reports from non-randomised studies suggesting that some, generally older, sulphonylureas are associated with a worse prognosis after myocardial infarction. Other data refute this assertion.

4. Meglitinides

Meglitinide, the non-sulphonylurea moiety of glibenclamide, which contains the benzamido group, stimulates insulin secretion. The pharmacokinetic properties of compounds developed from this observation provide a rapid and short duration release of insulin. Two agents, the meglitinide derivative repaglinide and the structurally related phenylalanine derivative nateglinide, have been available for a decade or so. Stimulation of first-phase insulin release during the prandial and early postprandial period helps control the rise in blood glucose after meals. The need for multiple daily dosages may detract from the flexibility of these agents, the latter being their main advantage over sulphonylureas. Prandial insulin releasers can be added to metformin or a thiazolidinedione. The meglitinides are relatively expensive compared with generic sulphonylureas.

4.1 Mode of action

Meglitinides bind to the SUR-1 benzamido site of the islet β cells. Whereas this site is distinct from the sulphonylurea site, the response is as for sulphonylureas, i.e. closure of the K^+ ATP channel. It follows that there is generally no therapeutic advantage to combining these agonists. However, variations in binding affinities and duration of action between the classes

may permit combination use of a meglitinide with a sulphonylurea to fit with an unusual meal pattern.

4.2 Pharmacokinetics

Repaglinide is rapidly absorbed with peak plasma concentration attained approximately 1 h after ingestion. Hepatic metabolism produces inactive metabolites, which are predominantly excreted in the bile (Table 2.3). If taken approximately 15 min before a meal, repaglinide produces a prompt insulin response that is complete by approximately 3 h. Nateglinide has a slightly faster onset and shorter duration of action.

4.3 Indications and contraindications

Repaglinide can be used as monotherapy in patients with inadequate glycaemic control after non-pharmacological measures; nateglinide is licensed for combination therapy with metformin in the UK. They can be useful for individuals with irregular lifestyles accompanied by unpredictable or missed meals. The lower risk of hypoglycaemia compared with sulphonylureas may be helpful in elderly patients. Repaglinide is best taken 15–30 min before a meal. Therapy should start with a low dose, e.g. 0.5 mg, unless the individual is transferring from another oral hypoglycaemic agent, in which case the dose should be 1 mg. Self-monitoring of postprandial blood glucose will guide up-titration every 2 weeks; the maximum dose is 4 mg before each main meal. When a meal is not consumed the corresponding dose of repaglinide is omitted. Repaglinide can be used, with caution, in patients with moderate degrees of renal impairment that preclude the use of sulphonylureas and metformin. Nateglinide has a faster onset and shorter duration of action than repaglinide. Caution is required in patients with hepatic disease.

4.4 Efficacy

Repaglinide and nateglinide produce dose-dependent increases in insulin concentrations and reduce postprandial hyperglycaemia. There is usually a

Table 2.3. The meglitinides: repaglinide and nateglinide.

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

lesser improvement in fasting hyperglycaemia. Reductions in HbA_{1c} are similar to or smaller than with sulphonylureas, as predicted by the shorter duration of action of the meglitinides. Added to metformin, they can reduce HbA_{1c} by an additional 0.5–1.5%. In the NAVIGATOR (Nateglinide and Valsartan in Impaired Glucose Tolerance Outcomes Research) trial, nateglinide up to 60 mg three times a day did not achieve a statistically significant reduction in new-onset diabetes in adults aged a mean of approximately 65 years with impaired glucose tolerance; a composite of cardiovascular events were not reduced by the drug.

4.5 Adverse effects

In general, hypoglycaemia is less frequent and less severe with meglitinides than with sulphonylureas. Plasma levels of repaglinide may be increased by gemfibrozil. Prandial insulin releasers cause an increase in body weight when used as initial monotherapy. In the NAVIGATOR trial body weight was approximately 0.4 kg greater in participants treated with nateglinide compared with placebo.

5. Thiazolidinediones

Thiazolidinediones are potent agonists of peroxisome proliferator-activated receptor gamma ($\text{PPAR}\gamma$). The $\text{PPAR}\gamma$ -mediated transcriptional effects of thiazolidinediones on target genes improve whole-body insulin sensitivity. Troglitazone was the first thiazolidinedione to enter clinical use in 1997. However, the drug was associated with cases of fatal hepatotoxicity; it was withdrawn in 2000, having been available for only a few weeks in the UK. Two other thiazolidinediones, rosiglitazone and pioglitazone, which have not shown this hepatotoxicity, were introduced in the USA in 1999 and in Europe in 2000. Fixed-dose combinations of pioglitazone with metformin are available.

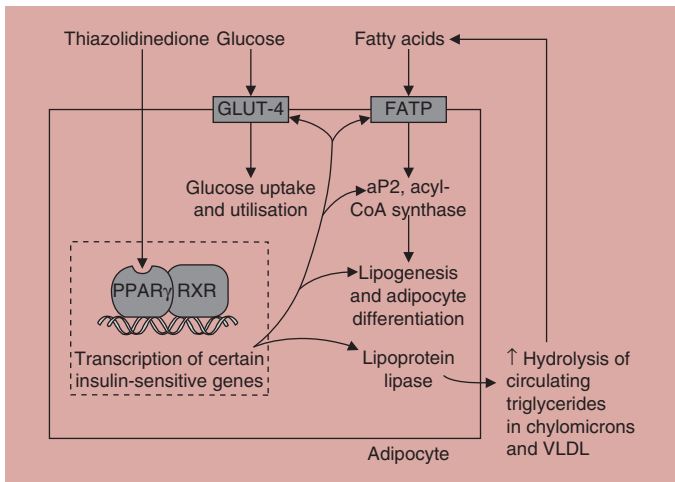
5.1 Mode of action

Most of the glucose-lowering efficacy of thiazolidinediones is thought to be achieved through increased insulin sensitivity in target tissues for insulin, primarily muscle, liver and adipose tissue. $\text{PPAR}\gamma$ is highly expressed in adipocytes, and to a lesser extent in muscle and liver. On activation $\text{PPAR}\gamma$ forms a heterodimeric complex with the retinoid X receptor and binds to a nucleotide sequence termed the peroxisome proliferator response element located in the promoter regions of PPAR -responsive genes. In conjunction with co-activators this alters the transcriptional activity of a range of genes, some of which are insulin sensitive, that participate in lipid and carbohydrate metabolism (Figure 2.3). Stimulation of $\text{PPAR}\gamma$ by thiazolidinediones promotes the differentiation of pre-adipocytes into ma-

ture adipocytes. These new small adipocytes are more sensitive to insulin, as demonstrated by the enhanced uptake of fatty acids and increased rates of lipogenesis. The reduced circulating level of fatty acids re-balances the glucose–fatty acid–Randle cycle, facilitating glucose utilisation in muscle. In the liver, reduced fatty acid availability serves to decrease excessive rates of hepatic gluconeogenesis. Ectopic lipid deposition in muscle and liver is reduced, whereas glucose uptake into adipose tissue and skeletal muscle is increased, by means of cellular insulin-sensitive glucose transporters. The putative contribution to improved insulin sensitivity resulting from the reduced production of adipocyte-derived pro-inflammatory cytokines is less well established. Thiazolidinediones increase the production of adiponectin, an adipocytokine that enhances insulin action and exerts potentially beneficial effects directly on the vasculature.

Thiazolidinediones, like metformin, can be classed as antihyperglycaemic agents – they do not usually cause hypoglycaemia as monotherapy. They require the presence of sufficient insulin to generate a maximal blood glucose-lowering effect. A predictable effect of improved insulin sensitivity is that plasma insulin concentrations are lowered by thiazolidinediones. The secretion of proinsulin and other less potent insulin precursors is reduced. Animal

Figure 2.3. Mechanism of action of a thiazolidinedione on an adipocyte.



aP2 = Adipocyte fatty acid binding protein; CoA = coenzyme A; FATP = fatty acid transporter protein; GLUT-4 = glucose transporter 4; PPAR γ = peroxisome proliferator-activated receptor gamma; RXR = retinoid X receptor; VLDL = very low-density lipoprotein; $\uparrow$ indicates increase.

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Table 2.4. 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%

studies generated hope that the long-term viability of islet β cells might be stabilised or improved. While no firm evidence for such an effect in humans has been found, the glucose-lowering effect of thiazolidinediones has been somewhat more durable than comparator drugs in some studies.

5.2 Pharmacokinetics

The gastrointestinal absorption of rosiglitazone and pioglitazone is rapid and near complete. Peak concentrations are attained at approximately 1–2 h. Both drugs are extensively metabolised by the liver (Table 2.4). Rosiglitazone is metabolised mainly by cytochrome P450 isoform CYP2C8 to metabolites with a plasma half-life of approximately 100–160 h; these are regarded as having no or minor activity and are eliminated in the urine. Pioglitazone is metabolised predominantly by CYP2C8 and CYP3A4 to active metabolites that are eliminated in the bile. Rosiglitazone interacts with the lipid-modifying drug gemfibrozil, causing the level of rosiglitazone to rise. Pioglitazone does not appear to cause any clinically significant reductions in the plasma concentrations of other drugs metabolised by CYP3A4. Rosiglitazone and pioglitazone are almost completely bound to plasma proteins, but at therapeutic concentrations there is no interference with other protein-bound drugs.

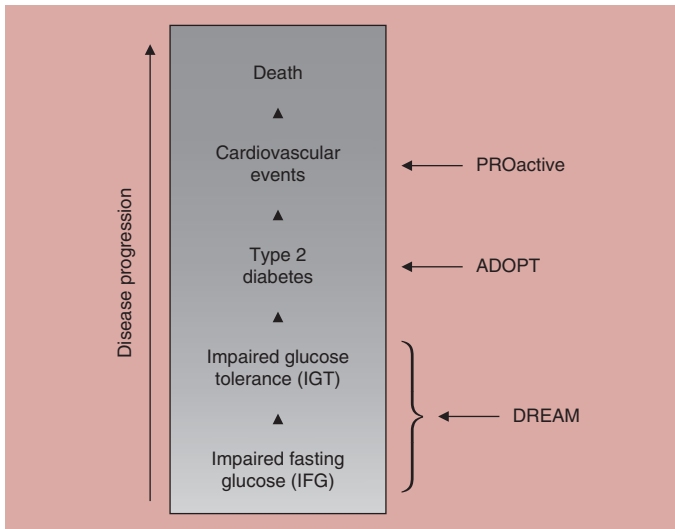
5.3 Indications and contraindications

Current expert guidelines differ in their recommendations on where thiazolidinediones should be placed. Clinical trials have explored their use at several stages of the natural history of type 2 diabetes (Figure 2.4). Thiazolidinediones are used as monotherapy, either as drugs of first choice or if metformin is inappropriate or not tolerated, and for patients in whom an insulin secretagogue is less appropriate. The metabolic syndrome and fatty liver disease are additional factors that might favour a thiazolidinedione over the alternatives. 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 before starting therapy and periodically thereafter. Pre-existing liver disease, the development of clinical hepatic dysfunction or elevated alanine aminotransferase levels more than 2.5 times the upper

limit of the normal range are contraindications to thiazolidinediones. It may seem somewhat counterintuitive that recent studies have suggested that this class of drug might be useful for the treatment of non-alcoholic steatohepatitis; more data are required.

Thiazolidinediones require several weeks to exert a maximal effect on glucose levels. They are often used in combination with other glucose-lowering drugs, particularly metformin. As a result of their slow onset of action, substituting thiazolidinedione for either a sulphonylurea or metformin can result in a temporary deterioration in glycaemic control. Combining pioglitazone with insulin can improve glycaemic control while reducing insulin dosages, especially in obese patients. This approach should, however, be approached with caution: peripheral oedema is more common and concerns about precipitating heart failure are heightened. The propensity of thiazolidinediones to cause fluid retention and to expand plasma volume is a major safety issue. This is associated with minor reductions in blood haemoglobin concentrations. The use of thiazolidinediones is thus contraindicated in patients with heart failure. The precise exclusion

Figure 2.4. Overview of recent studies of thiazolidinediones and the natural history of the development and progression of type 2 diabetes.



ADOPT = A Diabetes Outcome Progression Trial; DREAM = Diabetes Reduction Assessment with Ramipril and Rosiglitazone Medication; PROactive = PROspective pioglitazone Clinical Trial In macro-Vascular Events.

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criteria, based on cardiac status, vary in detail between countries. Appropriate clinical monitoring is important, especially for patients considered at higher risk of cardiac failure and those showing marked initial weight gain.

Hopes were raised that improved insulin sensitivity and positive effects on vascular risk markers would translate into cardioprotection. However, in 2007 a major controversy about the cardiovascular safety of rosiglitazone ignited. A meta-analysis of several clinical trials suggested that rosiglitazone increased the risk of myocardial infarction during the first 6–12 months of therapy. As discussed below, continuing doubts about this issue eventually led to withdrawal of rosiglitazone in Europe and instigation of tight restrictions on use of the drug in the USA.

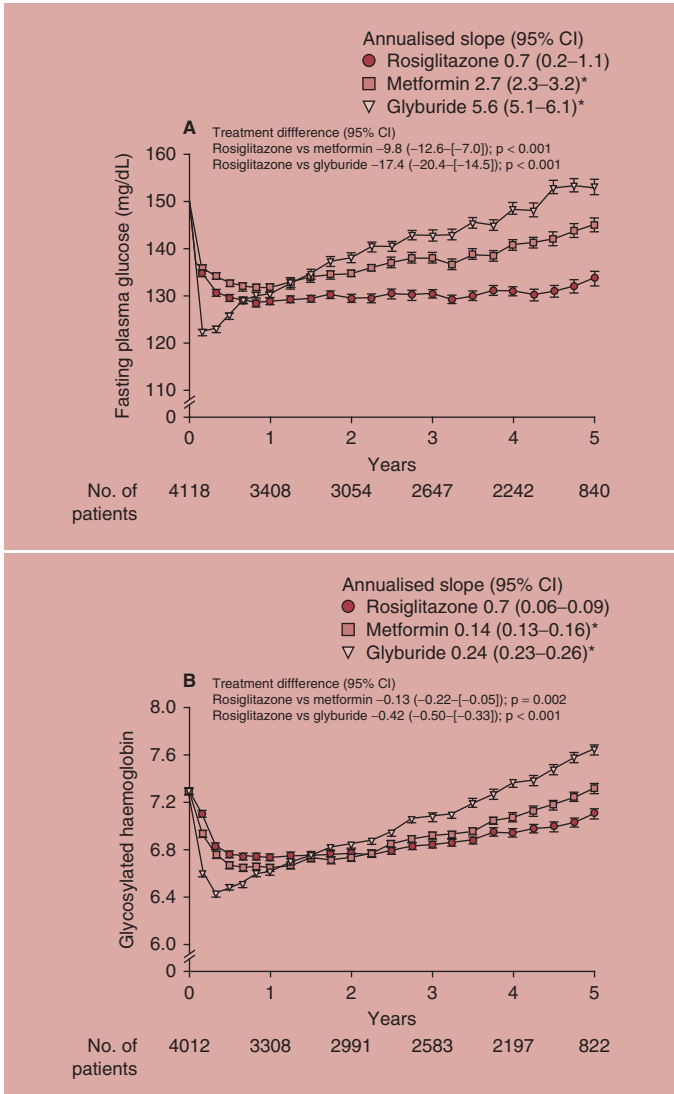
Providing there are no contraindications, thiazolidinediones can be used in the elderly. They can also be considered for patients with mild renal impairment, while appreciating the potential for oedema given the possibility of fluid retention. In women with anovulatory PCOS, thiazolidinedione therapy can cause ovulation to resume; this risk should be explained to the patient. Thiazolidinediones should not be continued during pregnancy.

5.4 Efficacy

Thiazolidinediones produce a slowly generated glucose-lowering effect. An inadequate response may take 2–3 months to confirm. Clinical trials suggest that the effect of thiazolidinediones may be better in patients who are overweight with an adequate reserve of β -cell function. However, clear clinical indicators of the best responders have not been reliably established. A reduction in HbA_{1c} by approximately 0.5–1.5% can be expected when the drugs exert their full effects. In a long-term comparison of monotherapy with metformin or glibenclamide (ADOPT; A Diabetes Outcome Progression Trial), rosiglitazone showed a slower onset but more durable glucose-lowering effect over more than 3 years (Figure 2.5). ADOPT confirmed a gradual loss of glycaemic control with glibenclamide after an initial response. The clinical significance of the difference in HbA_{1c} levels between rosiglitazone and metformin therapy has been questioned by some commentators; a similar percentage of patients treated with rosiglitazone or metformin had an HbA_{1c} level of less than 7.0% at the end of the study. Moreover, the benefit in glucose control needs to be put in the context of adverse effects. Rosiglitazone was associated with weight gain, of nearly 5 kg, contrasting with weight loss in metformin-treated patients. Increased low-density lipoprotein (LDL) cholesterol concentrations, more frequent use of statins, a higher incidence of oedema and a reduction in haematocrit were observed with rosiglitazone. Some evidence of a more sustained glycaemic response, cf. sulphonylureas, has also been shown for pioglitazone.

Thiazolidinediones reduce circulating non-esterified fatty acid concentrations. The effects on other components of the plasma lipid profile

Figure 2.5. Fasting plasma glucose (A) and glycated haemoglobin (B) over time from ADOPT (A Diabetes Outcome Progression Trial).



*Significant difference between rosiglitazone and other treatment groups.

Reproduced from Kahn et al. (2006), with permission.

are variable; this has fed into the recent controversy about the cardiovascular safety profiles of rosiglitazone and pioglitazone. Rosiglitazone tends to cause a small rise in total cholesterol concentration, stabilising by approximately 3 months; this may be obscured by adequate statin therapy. The effect appears to reflect a rise in both LDL-cholesterol and high-density lipoprotein (HDL) cholesterol, leaving the LDL:HDL-cholesterol ratio and the total:HDL-cholesterol ratio little changed or slightly raised. Triglyceride responses vary. Pioglitazone appears to have little effect on total cholesterol, and consistently reduced triglyceride concentrations. Both thiazolidinediones reduce the proportion of small dense atherogenic LDL particles.

Weight gain, similar in magnitude to sulphonylurea therapy, i.e. 1–4 kg stabilising over 6–12 months, is usually observed after the initiation of thiazolidinedione therapy. Several studies have indicated that the distribution of body fat is altered: the visceral adipose depot is little changed or reduced, whereas the subcutaneous depot is increased as new small, insulin-sensitive adipocytes are formed. A proportion of thiazolidinedione-associated weight gain is caused by fluid retention. 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. Thiazolidinedione use is associated with a small decrease in blood pressure.

Thiazolidinediones reduce the occurrence of new-onset diabetes in high-risk individuals with glucose intolerance or those with a history of gestational diabetes. In the DREAM (Diabetes Reduction Assessment with Ramipril and Rosiglitazone Medication) study in subjects with impaired glucose tolerance or fasting hyperglycaemia progression to diabetes was reduced by more than 50% after 3 years, but at the expense of a higher rate of new heart failure in the rosiglitazone (0.5%) compared with placebo (0.1%) arm. The results of a small study using relatively low doses of rosiglitazone in combination with metformin also demonstrated a reduced risk of progression to diabetes. Neither drug is licensed for the prevention of diabetes. Pioglitazone has been shown to reduce the progression of impaired glucose tolerance albeit at the expense of a higher incidence of weight gain and oedema compared to placebo.

Long-term glycaemic control can be achieved with a metformin–sulphonylurea–pioglitazone combination therapy. In an analysis of data from the PROactive (PROspective pioglitAzone Clinical Trial In macroVascular Events) study, when compared with a metformin–sulphonylurea–placebo combination there was a twofold increased likelihood of progression to insulin therapy over a 3-year follow-up period in the placebo group compared with pioglitazone using this combination.

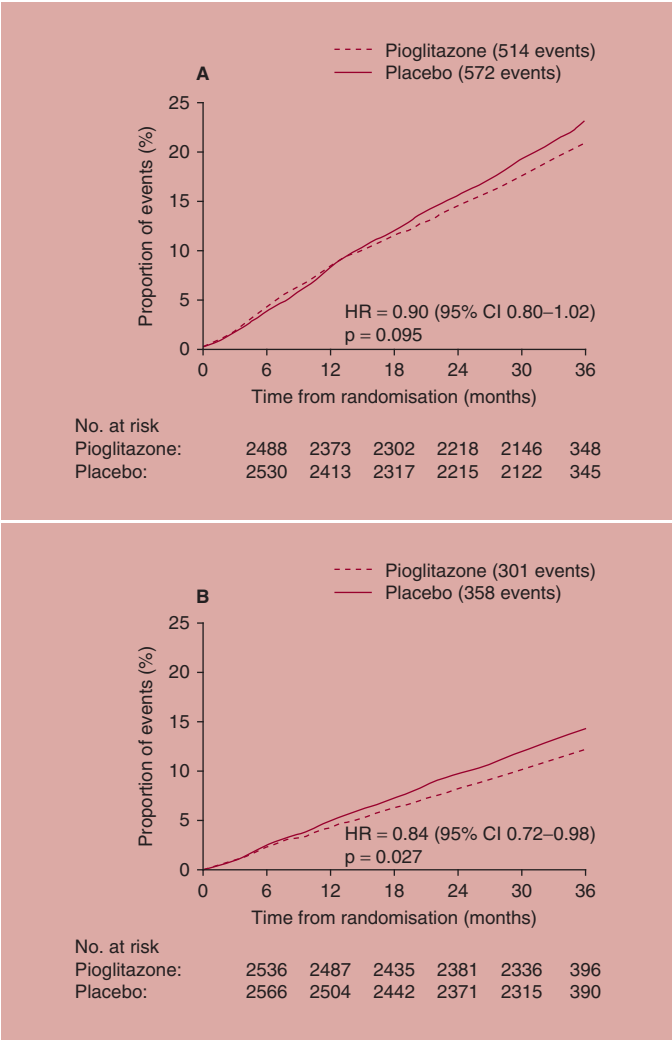
5.5 Adverse effects

Recent safety concerns have centred on cardiovascular safety and bone metabolism. The favourable impact of thiazolidinediones on cardiovascular risk factors raised hopes of reducing the risk of atherothrombotic

events. In PROactive the primary composite endpoint was not significantly reduced, whereas a prespecified composite secondary cardiovascular endpoint (all-cause mortality, non-fatal myocardial infarction and stroke) indicated benefits in high-risk patients with pre-existing cardiovascular disease (Figure 2.6). In the PERISCOPE (Pioglitazone Effect on Regression of Intravascular Sonographic Coronary Obstruction Prospective Evaluation) study, a decrease in atheroma volume was observed in pioglitazone-treated subjects compared with an increase in glimepiride-treated patients using coronary intravascular ultrasound. More patients taking glimepiride developed hypoglycaemia and angina, whereas pioglitazone-treated patients were more likely to develop oedema and gain bodyweight, or sustain skeletal fractures. The evidence for pioglitazone thus suggests vasculoprotective effects, albeit at the cost of an increased incidence of well recognised side-effects.

The European Medicines Agency (EMA) approved the use of pioglitazone and rosiglitazone in 2000, but required post-marketing cardiovascular outcome studies because of concerns over the increased risk of heart failure and other cardiovascular effects. In 2007, publication of the aforementioned meta-analysis of clinical trial data suggested a significant 43% increase in the risk of myocardial infarction ($p=0.03$) along with a non-significant 64% rise in cardiovascular death among patients taking rosiglitazone. Additional meta-analyses proved inconclusive. A warning was added to the US labelling for rosiglitazone in 2007. This stated that the drug was associated with an increased risk of myocardial ischaemic events, such as angina or myocardial infarction, in some patients. It was recommended that the drug be avoided in patients treated with insulin (reflecting a higher risk of myocardial ischaemia in trials in which rosiglitazone was added to insulin) or nitrates. The results of the RECORD (Rosiglitazone Evaluated for Cardiovascular Outcomes) study were more reassuring with respect to cardiovascular safety. The issue of the cardiovascular safety of rosiglitazone had assumed a highly charged political dimension by this point. Pressure was mounting on regulatory authorities that was to lead to decisive action in 2010. Critics pointed to methodological shortcomings in RECORD. This was a non-inferiority trial of over 4000 patients who have inadequate glycaemic control while receiving either metformin or a sulphonylurea. Patients were assigned to add-on rosiglitazone to a combination of metformin plus a sulphonylurea. The primary outcome, cardiovascular hospitalisation or cardiovascular death, was similar between the groups. More patients in the rosiglitazone group required additional therapies to maintain glycaemic control. Skeletal fractures and heart failure were seen more often with rosiglitazone. The ADOPT study also reported an increase in upper limb fractures in women treated with rosiglitazone. Lower limb fractures were increased in the foot but there was no difference in the number of hip fractures. A review of the safety database for pioglitazone has revealed a similar increase in distal bone

Figure 2.6. Kaplan–Meier curve of time to progression to: **(A)** primary composite endpoint (death from any cause, non-fatal myocardial infarction, including silent myocardial infarction, stroke, acute coronary syndrome, leg amputation, coronary revascularisation, or revascularisation of the leg); and **(B)** main secondary endpoint (death from any cause, non-fatal myocardial infarction, excluding silent myocardial infarction, or stroke), from PROactive (PROspective pioglitAzone Clinical Trial In macroVascular Events).



HR = Heart rate.

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fractures in women. Current data suggest that thiazolidinediones may cause bone loss, the effect being most prominent in postmenopausal women. Clinicians must therefore consider the risk of fractures among candidates for thiazolidinedione therapy. Postulated mechanisms leading to bone fragility include the inhibition of osteoblast activity and local adipogenesis. Caution should be exercised in patients considered to be predisposed to osteopenia.

The aforementioned issue of the cardiovascular safety concerns with rosiglitazone reached its conclusion in September 2010. Following the publication of additional studies that lent further support to these concerns the EMA recommended suspension of rosiglitazone. The US Food and Drug Administration (FDA) instituted a strict policy designed to restrict use of the drug but did not demand its withdrawal. These decisions were made in recognition of the availability of pioglitazone as an alternative not tarnished by questions of myocardial safety.

The BARI 2D (Bypass Angioplasty Revascularisation Investigation in Type 2 Diabetes) study included patients with type 2 diabetes and stable ischaemic heart disease. Randomisation was to early coronary revascularisation plus intensive medical therapy or intensive medical therapy alone. In a second randomisation strategy, patients were assigned to either insulin-provision therapy – an insulin secretagogue or insulin – or rosiglitazone. Survival rates were similar between the groups, and the results have been interpreted as reassuring with respect to the safety of rosiglitazone in high-risk cardiac patients. A recently published observational study using data from UK general practice concluded that pioglitazone was superior to rosiglitazone in mortality outcomes. Methodological limitations demand a cautious interpretation of these data. Since mid-2007, prescriptions for rosiglitazone in England have declined; by late 2008 pioglitazone was the most commonly prescribed thiazolidinedione.

In 2011 regulators responded to reports of a small increase in bladder cancer with pioglitazone. The FDA and EMA added warnings to the label with the aim of reducing exposure of high-risk patients to the drug. An association between macular oedema and glitazones has been reported. Familial polyposis coli is a theoretical contraindication to glitazone therapy.

6. Alpha-glucosidase inhibitors

Acarbose was introduced into clinical practice in the early 1990s. Two other agents, miglitol and voglibose, are available in some countries.

6.1 Mode of action

Alpha-glucosidase inhibitors competitively inhibit the activity of α -glucosidase enzymes in the brush border of the enterocytes lining the intestinal villi (Figure 2.7). They bind to the enzymes with high affinity preventing the

cleavage of disaccharides and oligosaccharides to monosaccharides. In patients whose diet includes complex carbohydrates, α -glucosidase inhibitors can reduce postprandial glucose concentrations by retarding the absorption of monosaccharides. Each α -glucosidase inhibitor exhibits somewhat different affinities for the range of α -glucosidase enzymes. By transferring glucose absorption more distally α -glucosidase inhibitors may alter the release of glucose-dependent incretin hormones that enhance nutrient-induced insulin secretion. In practice, α -glucosidase inhibitors reduce postprandial insulin concentrations; this is considered to be secondary to lowering postprandial blood glucose levels.

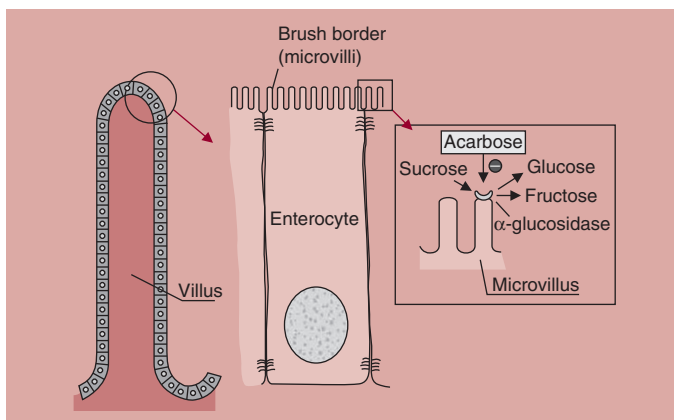
6.2 Pharmacokinetics

Amylases and intestinal bacteria degrade acarbose. Less than 2% of the drug is absorbed together with some intestinal degradation products. Elimination occurs within 24 h, mainly in urine. Miglitol is almost completely absorbed and eliminated unchanged in the urine.

6.3 Indications and contraindications

Alpha-glucosidase inhibitors can be used as monotherapy, being preferred for patients with predominantly postprandial hyperglycaemia. More

Figure 2.7. Mode of action of α -glucosidase inhibitors. Alpha-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.



Redrawn from Bailey and Krentz (2010), with permission.

commonly, α -glucosidase inhibitors are added to other therapies when postprandial hyperglycaemia persists. Acarbose can prevent, or delay, the progression of impaired glucose tolerance to type 2 diabetes in high-risk patients; this is not a licensed indication. Voglibose, in addition to lifestyle modification, reduced the development of type 2 diabetes in a clinical trial of Japanese individuals with impaired glucose tolerance. Alpha-glucosidase inhibitors are contraindicated in patients with a history of chronic intestinal disease. High dosages of acarbose, i.e. 200 mg three times a day, may reversibly increase liver enzyme concentrations.

6.4 Initiation and dose titration

Alpha-glucosidase inhibitors should be taken with meals, starting with a low dose, e.g. 50 mg daily of acarbose, up-titrated over several weeks. Hypoglycaemia is unlikely when α -glucosidase inhibitors are used as monotherapy. Gastrointestinal symptoms, which demand slow dose titration, tend to subside with time. Nonetheless, in practice tolerability is frequently a major issue in UK practice. In contrast, acarbose is more widely used in some other countries; China for example.

6.5 Efficacy

As monotherapy, these agents can reduce peak postprandial glucose concentrations by 1–4 mmol/l. The effects on fasting hyperglycaemia are less impressive, usually less than 1 mmol/l. The decrease in glycated haemoglobin is approximately 0.5–1.0%, if a relatively high dose is tolerated. The theoretical cardiovascular benefits of preferentially reducing postprandial hyperglycaemia found support in the STOP-NIDDM (Study to Prevent Non-Insulin-Dependent Diabetes Mellitus) trial; these observations await confirmation.

6.6 Adverse effects

Alpha-glucosidase inhibitors do not cause weight gain or hypoglycaemia and may lower plasma triglycerides. Combining an α -glucosidase inhibitor with a sulphonylurea may, however, increase the risk of hypoglycaemia compared with sulphonylurea monotherapy. Oral treatment for hypoglycaemia under these circumstances should rely on glucose, not sucrose. In the STOP-NIDDM trial approximately 30% of acarbose-treated patients compared with approximately 20% on placebo discontinued treatment prematurely. If the dosage is too high relative to the amount of complex carbohydrate ingested, oligosaccharides pass undigested into the large bowel. When fermented, flatulence, abdominal discomfort, and sometimes diarrhoea ensue.

7. Fixed dose combinations of orally active drugs

The use of fixed dose combinations of oral glucose-lowering agents with different mechanisms of action has become widely accepted. These are designed to provide bioequivalence and thereby similar efficacy; minor adjustments to the formulation may enable some extra blood glucose-lowering efficacy. Fixed-dose combinations can offer convenience, reduce the treatment burden and simplify daily medication regimens. These may increase patient adherence – a major problem with a long-term condition such as type 2 diabetes, which brings little in the way of symptoms unless hyperglycaemia is marked. Lower doses of two different types of agents rather than a high dose of one agent may provide efficacy while reducing dose-related side effects. Fixed-dose combinations of metformin with several other classes are available. Although single tablets could reduce titration flexibility, most of the commonly used dosage combinations are available. Any combination therapy necessitates the same cautions and contraindications that apply to each active component.

8. Principles of insulin therapy in type 2 diabetes

Clinical experience with insulin is unrivalled among glucose-lowering drug therapies. Clinical trials have demonstrated delayed onset and progression of vascular complications with reduced morbidity and mortality in patients with type 2 diabetes. Many uncertainties about the optimal use of insulin, however, surround its use in clinical practice. Advantages and disadvantages are presented in Box 2.2. In recent decades, developments in insulin manufacture have led to successive refinements, initially with improvements in purity, and then with the mass production of human sequence insulin. These advances have been coupled with advances in injection devices, making the practicalities of self-administration less daunting. However, subcutaneous insulin injection can only partially mimic the exquisitely sensitive response of normal β cells to glucose and other endogenous regulators. Thus fundamental problems with insulin replacement therapy remain unresolved (Box 2.3).

Recent innovations have provided new therapeutic options for type 2 diabetes. Current data and clinical experience indicate that some of these new therapies can replace or delay the need for insulin treatment. The inexorable decline in β -cell function in type 2 diabetes ultimately renders oral agents ineffective. Insulin restores circulating levels of the hormone regardless of the endogenous production or duration of diabetes. Insulin has beneficial effects on insulin sensitivity, vascular function, dyslipidaemia and biomarkers that presage vascular damage. The glucose-lowering effects of insulin are unmatched; no maximum dose exists. Even patients with major metabolic disturbances respond to adequate doses, although in practice arbitrary limits are usually reached. Insulin can be combined with

Box 2.2: Insulin therapy in type 2 diabetes

Advantages

- *Unrivalled glucose lowering*
- *Flexibility in dosage and timing*
- *Rapidly adaptable regimens to suit changing clinical circumstances*
- *Evidence base of microvascular and macrovascular complication reduction*
- *Well-documented tolerability and safety profile*
- *Can be combined with many other glucose-lowering therapies*
- *Strategies to reduce weight gain and the risk of hypoglycaemia have been developed*

Disadvantages

- *Requires injection in standard formulation*
- *Frequent self-monitoring of blood glucose is necessary*
- *Risk of severe hypoglycaemia increases with duration of insulin therapy*
- *Day to day adjustments requires a high level of engagement by the patient*
- *Adequate knowledge about insulin use and safety issues is required*
- *Weight gain is common when insulin is initiated*
- *High doses may be necessary in patients with more severe degrees of insulin resistance*

a range of blood glucose-lowering agents. Insulin analogues (rapid-acting lispro and aspart, long-acting detemir and prolonged duration insulin glargine) are genetically engineered novel molecules. They offer some advantages over human insulin with improved pharmacokinetics (Table 2.5 and Figure 2.8). In practice, however, neither insulin glargine nor insulin detemir always give full 24-h coverage. These analogues approximate the stable, basal, secretion of insulin that normally accounts for approximately 50% of daily production. Insulin analogues can be formulated to provide biphasic pre-mixed options suitable for two or more daily injections. Insulin analogues are more expensive than human sequence insulins.

8.1 Basal insulin analogues

Insulin glargine has additional arginine molecules (B31 arginine and B32 arginine) located at the C-terminus of the B-chain, that confer additional positive charges thereby altering the isoelectric point. In addition, asparagine is replaced by arginine at A21 to confer stability. Glargine was designed to avoid the peak insulin concentration typically observed with conventional longer-acting insulins such as lente. Insulin glargine shows the following action profile: onset at approximately 90 min; prolonged plateau, rather than the peak of action with isophane insulin; duration of approximately 24 h, or longer.

Whereas insulin glargine is soluble at acid pH in the vial, when injected subcutaneously it forms a microprecipitate at the injection site

Box 2.3: Limitations inherent to insulin therapy

- *After subcutaneous injection, absorption delivers insulin into the systemic rather than portal circulation. This results in equivalent plasma insulin concentrations in both compartments; normal physiology maintains a gradient in which portal levels are much higher as a result of first-pass hepatic extraction.*
- *Suboptimal matching of delivery peak and decline of insulin concentrations compared with endogenous secretion results in suboptimal glucose profiles with the risk of hypoglycaemia as a result of continuing insulin action that is inappropriate to plasma glucose.*
- *It is not possible to mimic the endogenous surge of insulin into the portal circulation at the beginning of a meal; this first phase of insulin secretion promptly suppresses hepatic glucose production.*
- *Plasma insulin levels cannot be altered in response to fasting or exercise once an injection has been given; extra carbohydrate may be required.*
- *Controlling fasting plasma glucose concentrations by suppressing hepatic glucose production is difficult without inducing hypoglycaemia during the night. Prolonged duration insulin analogues offer an advantage over isophane insulin as they largely avoid the peak of insulin action that can lead to nocturnal hypoglycaemia. The latter is not always clinically apparent.*
- *Day-to-day variability in the absorption of intermediate duration insulin may be problematical in individual patients. This is reduced with prolonged duration insulin analogues permitting more predictable responses for a given daily dose.*

(because the latter is at a slightly alkaline, physiological pH). The stability of this microprecipitate slows the absorption of insulin into the circulation, which means that a single daily injection can provide a fairly stable level of insulin over a 24-h period, more closely mimicking the basal component of insulin secretion in healthy individuals. Glargine is rapidly converted to metabolites, predominantly M1 (~90-95%), with similar potency. 'Basal' insulin secretion accounts for approximately half of all daily insulin secretion, the rest being secreted in response to meals. The peakless action of glargine has been associated with a reduced incidence of hypoglycaemia, especially nocturnal episodes.

Insulin detemir was introduced in the UK in 2004. This analogue has a C14 fatty acyl group attached to the B-chain (B29 lysine) of the insulin molecule, which binds to albumin, while the B30 threonine has been deleted. Detemir has a more evident peak of action, but it has been reported to produce predictable effects on glycaemic control, with little day-to-day variability. This may be an advantage in some patients when the attainment of glycaemic targets are proving difficult. The duration of action is up to 24 h depending on the dose, with higher doses tending to prolong the duration of action. There are reports of fewer episodes of hypoglycaemia

and less weight gain with detemir compared with other insulins. Higher doses of detemir may be required to achieve equivalent glucose lowering, even though a unit of detemir contains four times as much insulin as other insulins. In some patients insulin detemir causes less local discomfort at injection sites.

The rationale for insulin, and practical steps for its initiation and intensification are discussed in the National Institute for Health and Clinical Excellence (NICE) clinical guideline 87; this guideline also considers the role of insulin glargine and insulin detemir (see Chapter 4). There has been a move away from starting therapy with isophane (neutral protamine Hagedorn; NPH) insulin, as currently advocated by NICE, in favour of insulin glargine and insulin detemir. Clinical trial data suggests benefits of insulin analogues over NPH insulin with respect to frequency of nocturnal hypoglycaemia. The 2009 American Association of Clinical Endocrinologists/American College of Endocrinology consensus panel comes down firmly against NPH insulin citing an inferior pharmacokinetic profile and excessive intra-individual day-to-day variability. Many options for the initiation, optimisation and intensification of insulin therapy have been published; the plurality of approaches reflects the choice of pharmacokinetic options. Insulin regimens are selected and adjusted on a case-by-case basis. Compared with older insulins, modern approaches to insulin therapy can help achieve metabolic targets with lower risks of the well-known adverse effects of therapy,

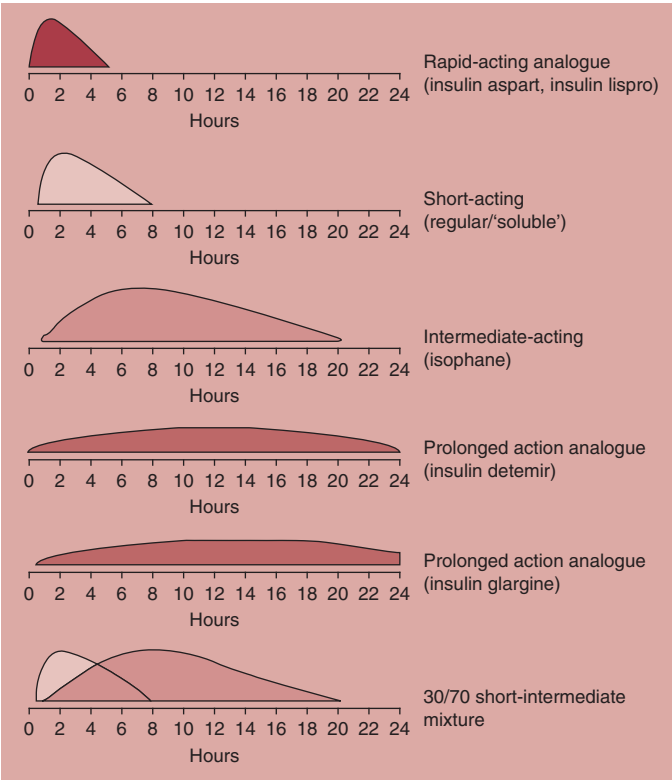
Table 2.5. Timing of metabolic effects for a selection of insulin preparations.

Insulin	Time of glucose-lowering effect (hours)		
	Onset	Peak	Duration
Rapid acting			
Insulin lispro	0–0.15	0.5–1.5	3–5
Insulin aspart	0–0.15	0.5–1.5	3–5
Insulin glulisine	0–0.15	0.5–1.5	3–5
Short acting			
Human soluble	0.25–1	1.5–4	5–9
Intermediate			
NPH (isophane)	0.5–2	3–6	8–14
Prolonged duration			
Insulin glargine	1–6	—	12–26
Insulin detemir	1–4	6–18	8–24

NPH: Neutral protamine Hagedorn.

Times are approximate and may vary between individuals, within individuals from day to day, and with dosage. Higher doses may prolong duration of action. Insulin degludec, a novel ultra-long acting analogue approved in some countries in 2012, has a duration of action of approximately 40 hours. Flexibility of daily dosing time and lower day-to-day variability are reported potential advantages. Ultra-long analogues may permit less than daily dosing.

Figure 2.8. Commonly used insulins in the UK. Action profiles are approximate and may differ between and within individual patients. Intra-individual day-to-day variation can be problematical with isophane (NPH) insulins. Insulin glargine, and in particular insulin detemir, show more predictable plasma levels as a result of less variable absorption. These analogues largely avoid the peak of insulin action observed with isophane insulin permitting the up-titration of doses with less risk of hypoglycaemia.



especially hypoglycaemia and weight gain. However, limitations such as day-to-day variability have not been eliminated.

8.2 Ultra-long insulin analogues

Insulin degludec, which has a duration of action of approximately 40 hours (Table 2.5), was approved in Japan in late 2012. The committee for Medicinal Products for Human Use (CHMP) adopted a positive opinion shortly afterwards. Trials in type 2 diabetes have shown a lower risk of

nocturnal hypoglycaemia compared with other basal analogues at similar levels of glycaemic control.

Despite these advances in basal therapy insulin is often unduly delayed partly due to negative perceptions of patients and physicians. Arguments for the earlier use of insulin include:

1. The attainment and maintenance of glycaemic control is associated with better long-term clinical outcomes.
2. Early intensive insulin therapy in patients with newly diagnosed type 2 diabetes may have favourable effects on β -cell function and can provide protracted glycaemic remission compared with oral glucose-lowering agents.
3. The risk of severe hypoglycaemia, a major barrier to metabolic control, increases as insulin deficiency becomes more pronounced.
4. Strategies for minimising weight gain during the intensification of treatment are now available.
5. The introduction of insulin treatment does not necessarily impair quality of life. Patients often derive symptomatic benefit as hyperglycaemia is brought under control; the concomitant reduction in pill burden is usually welcomed.
6. Modern delivery devices have eased the inconveniences of insulin therapy; innovations such as pulmonary delivery may offer the prospect of greater acceptability.

Clinical judgement and expertise are prerequisites for success. Recent clinical trials have provided some useful information on strategies for initiating insulin in patients with type 2 diabetes (Box 2.4). Translating the results of clinical trials designed and conducted by experts into routine practice within a primary care setting is, however, a formidable challenge. Chapter 4 contains further details of initiating and monitoring insulin therapy.

8.3 Initiating once-daily insulin

A once-daily injection, usually a small dose pre-bed, e.g. 10 U, is added to oral glucose-lowering therapy. The dose is up-titrated according to fasting blood glucose measurements. Algorithms are available that are generally safe and effective. Prolonged duration insulin analogues, insulin glargine and insulin detemir, are often favoured because of their pharmacokinetic advantages. Insulin analogues provide similar glycaemic control to isophane but with a lower risk of minor hypoglycaemia, notably nocturnally. Insulin analogues are more expensive than isophane insulin but are widely used in the UK.

8.4 Preprandial insulin

This approach, which is popular in some countries, targets postprandial hyperglycaemia, but may be associated with greater weight gain and

Box 2.4: Comparison of biphasic, basal, or prandial insulin regimens in patients with type 2 diabetes. Systematic review and meta-analysis of clinical trials using each regimen

- Compared with basal insulin, reductions in HbA_{1c} were greater – 0.45% for each – with biphasic and prandial insulin. Reductions in fasting glucose were less with the latter regimen.
- Larger insulin doses were reported for biphasic and prandial regimens compared with basal insulin.
- No differences in major hypoglycaemic events were observed.
- Minor hypoglycaemic events for prandial and biphasic insulin were reported as either higher than or equivalent to basal insulin.
- Greater weight gain – approaching 2 kg – was seen with prandial compared with basal insulin.

Data from Lasserson et al. (2009)

more frequent hypoglycaemia compared with once-daily basal insulin. The 4-T (Treat to Target in Type 2 Diabetes Trial), which compared three regimens of analogue insulin preparations, demonstrated these limitations. In practice, a balanced approach is required that addresses fasting and postprandial glucose control if glycaemic goals are to be attained.

8.5 Basal-bolus regimens

A once or twice-daily prolonged insulin analogue is combined with pre-meal boluses of a rapid-acting insulin analogue. This approach offers flexibility but demands more frequent self-monitoring of blood glucose.

8.6 Premixed biphasic insulin

This may be initiated twice a day, before breakfast and dinner. Premixed, fixed-dose analogue preparations offer the advantage of immediate injection before, or even just after, a meal. In contrast, human sequence or animal derived biphasic insulin preparations should be injected approximately 30–45 min before meals because of the less rapid increase in plasma insulin concentrations. However, some data suggest this may not be necessary and many patients inject just before meals anyway. A third injection is possible using licensed biphasic preparations. High mix insulin formulations that have a greater proportion of rapid-acting insulin have been explored in clinical trials.

8.7 Continuous subcutaneous insulin infusion

This may be a helpful alternative to multiple daily injections in some patients. A comprehensive insulin pump clinical service is required to deliver safe and effective treatment.

8.8 Combined insulin–oral agent strategies

In the absence of any convincing evidence to date that the natural history of type 2 diabetes can be substantially modified by pharmacotherapy, insulin will remain a major – and inevitable – treatment option. Combining insulin with certain DPP-4 inhibitors, glucagon-like peptide 1 mimetics and perhaps other agents currently in development is expanding, although not all drugs in these classes are licensed for use concurrently with insulin. Reductions in body weight and lower insulin doses may be achieved in some patients. Pioglitazone has a licence for use in combination with insulin. This approach may reduce the dose of insulin required in obese patients who often require very large doses of insulin. Definitions of insulin resistance are not particularly helpful in clinical practice, but the scenario in which several hundreds of units of insulin per day appear to be having little impact has become commonplace in the UK. Strategies to counter this impasse are limited.

Combining insulin with metformin, and to a lesser extent pioglitazone, has become routine practice. Several studies have demonstrated the utility of metformin plus insulin combinations; impressive data from clinical trials that show improved glycaemic control with less weight gain and lower rates of hypoglycaemia are not always reproducible in day-to-day practice. The usual approach is to continue metformin when insulin is started, withdrawing drugs such as sulphonylureas.

8.9 Strategies to counter insulin resistance

Obese patients with inadequately controlled type 2 diabetes and those with additional causes of insulin resistance have higher insulin requirements. The use of U500 insulin reduces the volume of each injection. High-strength insulin must be obtained directly from the manufacturer; it is not licensed in the UK. Although formulated as soluble insulin, the pharmacokinetics of U500 insulin resemble those of isophane insulin. Care should be exercised when using insulin in combination with pioglitazone; the risks of weight gain and fluid retention are increased. Insulin clearance is impaired by complications such as renal impairment or the presence of hepatic cirrhosis. Co-administration of metformin or a GLP-1 agonists may be useful.

8.10 Insulin and cancer risk

A series of reports from retrospective studies raised concerns about a potential association between insulin treatment and cancer. Insulin glargine has come

under particular scrutiny, but the controversy has not been limited to this analogue. Aspects of the data are conflicting and the interpretation of these reports is potentially open to confounding. An increased risk of cancer is a recognised hazard of obesity even in the absence of diabetes. Another potential confounder is the association between type 2 diabetes per se and colon, pancreas and postmenopausal breast cancer. Closely associated metabolic defects, i.e. insulin resistance and glucose intolerance, have also been linked to some forms of cancer. All of these conditions are characterised by hyperinsulinaemia. An alternative hypothesis, based on epidemiological associations between higher HbA_{1c} levels and cancer, proposes that insulin therapy might be protective via reductions in oxidative stress and other mechanisms. Clinical registry data have provided some support for this possibility.

Evidence of a dose–effect association between insulin treatment and cancer risk has been described. In this context it is noteworthy that epidemiological evidence suggests that metformin, which lowers plasma insulin concentrations, may offer protection against certain forms of cancer. To complicate the picture even further, other classes of diabetes drugs, i.e. GLP-1 receptor agonists, pioglitazone and dapagliflozin (See Chapter 4) have been associated with an increased risk of certain forms of cancer. More data are required and, once again, confounding factors are difficult to exclude. It has been hypothesised that the growth of early tumours might be accelerated by insulin, although the cellular mechanisms are uncertain. Reports of increased affinity of insulin glargine for the insulin-like growth factor-1 receptor *in vitro* are of uncertain clinical significance. The major metabolites of glargine bind to this receptor with affinities similar to that of human insulin. Additional support for a potentially causal insulin–cancer link comes from the unsettling history of a rapid-acting insulin analogue – B10Asp. The development of this analogue was terminated when evidence of carcinogenicity emerged in preclinical studies. In this case, mammary tumours in rodents were increased after exposure to high doses. In contrast, it is apposite to note that insulin detemir exhibits lower mitotic activity *in vitro* compared with human insulin. Thus, molecule-specific effects may be important.

Whereas such observations could provide a *prima facie* case for a casual association between insulin treatment and cancer no definitive data are available. The general consensus of expert groups is that the evidence is insufficient to warrant any changes in clinical practice, although the European Association for the Study of Diabetes suggested that alternatives to insulin glargine may be considered. Diabetes UK cautioned that the research claiming a link between certain insulins and some cancers should be regarded as inconclusive; patients were advised to continue medication as prescribed and to discuss any concerns with their healthcare team. The response of the EMA was that a causal association between insulin glargine and cancer could not be confirmed or excluded. The results of a large clinical trial (ORIGIN; Outcome Reduction with an Initial Glargine In-

tervention) published in 2012 provided some reassurance about the safety of glargine in terms of cancer risk. Over a median of 6.2 years follow-up no excess of any form of cancer was observed in subjects with dysglycaemia or type 2 diabetes treated with this insulin analogue.

9. Weight-reducing drugs

The blood glucose-lowering efficacy of lifestyle measures that reduce adiposity in patients with type 2 diabetes is well established. The difficulties faced in achieving and maintaining significant weight loss are, however, readily apparent in daily practice. The history of weight-reducing drugs could perhaps be summarised thus: generally limited efficacy punctuated by periodic safety concerns, compounded by limited tolerability and low concordance rates. The issue of high dropout rates in clinical trials, which can be 30–40%, hampers the interpretation of the efficacy of new agents.

The intestinal lipase inhibitor orlistat 120 mg three times a day with meals can reduce dietary fat absorption by up to 30%. In the context of a reduced fat diet this typically increases weight reduction by an extra 2–3 kg in overweight and obese patients; additional reductions in HbA_{1c} have been reported that are generally lower than those achieved using oral glucose-lowering drugs.

The satiety-inducing serotonin-noradrenaline reuptake inhibitor sibutramine often enables slightly greater reductions of body weight in overweight and obese patients, with extra reductions in HbA_{1c} of approximately 0.5%. Concerns about increases in heart rate and blood pressure in some patients suggested a potential for harm. In 2009, the EMA issued a reminder to prescribers and patients that sibutramine should be used with caution in patients with cardiovascular disease. This was followed in early 2010 by the suspension of marketing authorisation for the drug in the light of an interim analysis of a large post-approval safety trial – the SCOUT (Sibutramine Cardiovascular OUTcomes) study. An excess of cardiovascular events was observed in patients receiving the drug compared with placebo. Of note, the trial included higher-risk patients who would not normally have been candidates for sibutramine. The US Food and Drug Administration took a different line, demanding new warnings about the cardiovascular safety of the drug pending further review of the data.

The first in a new class of agents with beneficial effects on glucose and lipid metabolism, the selective cannabinoid receptor 1 antagonist rimonabant was withdrawn because of concerns about psychological side-effects, including depression with suicidal ideation. In 2012 two new weight-reducing drugs were approved for use in the US. One combines two established drugs: phenteramine + controlled-release topiramate. The other agent – lorcaserin, a serotonin 2C receptor activator – was the first new class of obesity drug to be approved in more than a decade.

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<http://www.springer.com/978-1-908517-64-7>

Drug Therapy for Type 2 Diabetes

Krentz, A.

2012, VII, 102 p. 20 illus. in color., Softcover

ISBN: 978-1-908517-64-7