



## Diabetes mellitus: new drugs for a new epidemic

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### Editor's key points

- Prevalence of diabetes mellitus is increasing rapidly in the 21st century.
- Several new drugs have been introduced, some with novel modes of action.
- Incretin mimetics show promise in managing type 2 diabetes.
- New insulin analogues permit the adoption of the basal-bolus regimen to glucose control.
- Thiazolidinediones (pioglitazone) are now only a third-line treatment.

**Summary.** The prevalence of diabetes mellitus (DM) is increasing rapidly in the 21st century as a result of obesity, an ageing population, lack of exercise, and increased migration of susceptible patients. This costly and chronic disease has been likened recently to the 'Black Death' of the 14th century. Type 2 DM is the more common form and the primary aim of management is to delay the micro- and macrovascular complications by achieving good glycaemic control. This involves changes in lifestyle, such as weight loss and exercise, and drug therapy. Increased knowledge of the pathophysiology of diabetes has contributed to the development of novel treatments: glucagon-like peptide-1 (GLP-1) mimetics, dipeptidyl peptidase-4 (DPP-4) inhibitors, thiazolidinediones (TZDs), and insulin analogues. GLP-1 agonists mimic the effect of this incretin, whereas DPP-4 inhibitors prevent the inactivation of the endogenously released hormone. Both agents offer an effective alternative to the currently available hypoglycaemic drugs but further evaluation is needed to confirm their safety and clinical role. The past decade has seen the rise and fall in the use of the TZDs (glitazones), such that the only glitazone recommended is pioglitazone as a third-line treatment. The association between the use of rosiglitazone and adverse cardiac outcomes is still disputed by some authorities. The advent of new insulin analogues, fast-acting, and basal release formulations, has enabled the adoption of a basal-bolus regimen for the management of blood glucose. This regimen aims to provide a continuous, low basal insulin release between meals with bolus fast-acting insulin to limit hyperglycaemia after meals. Insulin therapy is increasingly used in type 2 DM to enhance glycaemic control. Recently, it has been suggested that the use of the basal-release insulins, particularly insulin glargine may be associated with an increased risk of cancer. Although attention is focused increasingly on newer agents in the treatment of diabetes, metformin and the sulphonylureas are still used in many patients. Metformin, in particular, remains of great value and may have novel anti-cancer properties.

**Keywords:** anaesthesia; diabetes; treatment; surgery

The International Diabetes Federation estimated in 2008 that 246 million adults worldwide had diabetes mellitus (DM) and the prevalence was expected to reach 380 million by 2025.<sup>1</sup> The World Health Organization (WHO) has revised its estimates for the prevalence of DM in the USA in 2025 from 21.9 million to 30.3 (prevalence of 11.2%).<sup>2,3</sup> This increase in DM results from a rise in new patients of type 2 DM, which is a consequence of obesity, an ageing population, lack of exercise, and increased migration of susceptible patients. Indeed, the global pandemic of obesity and type 2 DM has been compared with the 'Black Death' of the 14th century.<sup>4</sup> DM is a costly chronic disease and patients develop micro- and macrovascular complications that often need surgery. Patients with type 2 DM can expect a 10 yr reduction in life expectancy and, globally, 5% of all deaths could be attributed to DM (both types 1 and 2) in 2000 and this increased to 6.8% in 2010.<sup>5,6</sup> Improved glycaemic control has been shown to delay the onset of microvascular complications

(nephropathy, retinopathy, and neuropathy), whereas the beneficial effects on macrovascular complications are less clear. However, the 10 yr follow-up of United Kingdom Prospective Diabetes Study (UKPDS), again emphasized the benefits of long-term glycaemic control on all-cause death, micro- and macrovascular complications in type 2 DM.<sup>7</sup> Increased knowledge of pathophysiology of type 2 DM, particularly insulin signalling and insulin resistance, has contributed to the development of novel treatments. The primary aim of managing type 2 DM is to delay, or even prevent, the complications of the disease by achieving good glycaemic control. In addition to drug therapy, this often involves changes in lifestyle such as diet and exercise.

Patients with DM presenting for surgery are challenging for a number of reasons. They may have vascular, renal, or neurological disease as a consequence of their underlying DM and are more prone to wound infections. Maintaining normal blood glucose concentrations has been shown to reduce perioperative morbidity and mortality, although the

evidence for this derives mainly from studies in patients undergoing cardiac surgery. However, a recent retrospective survey found that perioperative hyperglycaemia was associated with increased length of hospital stay, morbidity, and mortality after non-cardiac general surgery in diabetic and non-diabetic patients.<sup>8</sup> It was notable that the risk of death increased proportionally with the increase in glucose values in non-diabetic patients but not in those with DM. A number of studies have identified substantial gaps in inpatient diabetic care in the UK<sup>9</sup> with prolonged inpatient length of stay being a significant problem in those patients with cardiac or surgical conditions.<sup>10</sup>

The aim of this review is to explore novel agents used in diabetic management in the 21st century.

## Diagnosis

The difficulty in diagnosing DM is the lack of a unique qualitative, biological marker that separates all people with diabetes from non-diabetics.<sup>11</sup> Diabetic retinopathy is one such characteristic but has the obvious disadvantage that it usually becomes evident many years after the onset of DM. Because of the lack of a suitable marker, metabolic abnormalities such as hyperglycaemia provide the most useful diagnostic tests. Different parameters such as fasting plasma glucose (FPG), impaired fasting glucose (IFG), and impaired glucose tolerance (IGT) have all been used. In 1997, an International Expert Committee re-examined the classification and diagnostic criteria from the 1979 National Diabetes Data Group and the 1985 WHO study group and proposed some changes to the diagnostic criteria for DM and impaired glucose regulation.<sup>12</sup> The 1997 guidelines included recommending the use of FPG as part of the diagnostic tests but the cut-off point was reduced from 7.8 to 7.0 mmol l<sup>-1</sup>. Normal FPG was defined as <6.1 mmol l<sup>-1</sup>. The use of glycosylated haemoglobin (HbA<sub>1c</sub>) as a diagnostic test was not recommended owing to the lack of standardized methodology among laboratories. The utility of the oral glucose tolerance test (OGTT) that measures plasma glucose (PG) 2 h after a 75 g oral glucose load was recognized and an abnormal result was accepted as >11.1 mmol l<sup>-1</sup>. However, because of the inconvenience, increased costs, and difficulties in reproducibility, the use of this test for diagnostic purposes was discouraged but the diagnostic category of IGT was retained. This refers to individuals with a normal FPG but a 2 h PG of 7.8–11 mmol l<sup>-1</sup> after a 75 g oral glucose challenge. IFG was defined as FPG between 6.1 and 6.9 mmol l<sup>-1</sup>.

Since 1997, many studies relating to the diagnosis of diabetes have been published and a number of questions have been raised including the use of FPG vs the 2 h PG after OGTT. It has been noted that the category of IGT is associated with cardiovascular disease risk factors and events, whereas IFG is much less strongly associated with cardiovascular events or mortality.<sup>13–15</sup> It was shown that lifestyle changes such as diet and exercise and the use of metformin or acarbose may delay or prevent the progression from IGT to

overt DM. In 2003, a reconstituted International Expert Committee met to evaluate these issues and make appropriate revisions to the previous criteria.<sup>11</sup> The principal recommendations were that the cut-off points of FPG and 2 h PG should remain as in the 1997 report:  $\geq 7.0$  and  $\geq 11.1$  mmol l<sup>-1</sup>, respectively, but that lowering the IFG cut-off point from 6.1 to 5.6 mmol l<sup>-1</sup> would optimize its sensitivity and specificity. The committee noted that measurement of HbA<sub>1c</sub> has numerous advantages including an indication of glucose concentrations over a number of weeks and is a useful monitor of both diagnosis and response to treatment. However, in 2003, it was considered premature to add HbA<sub>1c</sub> to the list of tests used for the definitive diagnosis of DM. Both the FPG and the 2 h PG have advantages and disadvantages; the 2 h PG is a more sensitive assay but the FPG is more reproducible, less costly, and likely to be more convenient.

More recently, since the introduction of a new standardized HbA<sub>1c</sub> assay, the use of HbA<sub>1c</sub> both as a diagnostic tool and as a predictor of perioperative outcomes has been re-examined. Two studies used HbA<sub>1c</sub> values >6.5% (48 mmol mol<sup>-1</sup>) as a single diagnostic marker for DM compared with standard glucose-based methods and concluded that it lacked sensitivity.<sup>16–17</sup> However, HbA<sub>1c</sub> may have a greater role in predicting perioperative outcomes in patients with or without DM undergoing a variety of surgical procedures.<sup>18–20</sup>

## Drug therapy

DM is defined by an absolute (type 1) or relative (type 2) deficiency of insulin. Type 2 DM is characterized by insulin resistance, abnormal hepatic glucose production, and progressive worsening of pancreatic  $\beta$ -cell function over time.<sup>21</sup> Prevention and treatment of DM is a major public health challenge. In the Diabetes Prevention Programme (DPP) 10 yr follow-up study, lifestyle management including diet and exercise led to a 31–58% reduction in the incidence of diabetes.<sup>22–23</sup> Greater understanding of the pathophysiology of DM has contributed to the development of new pharmacological approaches. The currently available classes of anti-diabetic agents are glucagon-like peptide-1 (GLP-1) receptor agonists, dipeptidyl peptidase-IV (DPP-4) inhibitors, thiazolidinediones (TZDs; glitazones), insulin analogues, biguanides, sulphonylureas, meglitinides,  $\alpha$ -glucosidase inhibitors, and synthetic amylin analogues (Table 1). In addition, endocannabinoid antagonists acting at the CB1 receptor show promise for affecting food intake and improving glucose homeostasis. Insulin treatment, particularly with new basal formulations, is used increasingly in type 2 diabetics.

At present, there is little published information on the perioperative management of patients taking the newer agents but guidelines have been agreed by the Joint British Diabetic Societies (*Management of adults with diabetes undergoing surgery and elective procedures: improving standards*) and can be accessed at [www.diabetes.nhs.uk](http://www.diabetes.nhs.uk).

**Table 1** Current drugs available for the treatment of diabetes mellitus. Sodium glucose co-transporter inhibitor—insufficient data at present

New agents—primary treatment
GLP-1 receptor agonists
DPP-4 inhibitors
Thiazolidinediones
Insulin analogues, basal, and short-acting
Current proved agents—primary treatment
Biguanides
Sulphonylureas
New agents—secondary treatment
Meglitimides
$\alpha$ -Glucosidase inhibitors
Synthetic amylin analogues

## Incretins/GLP-1 mimetics

Incretins are gut-derived peptides secreted in response to meals; the incretin effect refers to the augmented release of insulin from oral ingestion of glucose compared with an i.v. glucose challenge. The two major incretins are GLP-1, which is produced by the neuroendocrine L cells of the ileum and colon, and glucose-dependent insulinotropic peptide, which is produced by the K cells of the duodenum and jejunum. Both are released rapidly after a meal and they limit postprandial glucose excursions.<sup>24</sup> Incretins stimulate insulin production from pancreatic  $\beta$  cells and GLP-1 also decreases glucagon secretion, slows gastric emptying, and suppresses appetite. GLP-1 may also reduce  $\beta$ -cell apoptosis and promote  $\beta$ -cell proliferation.<sup>25 26</sup> Patients with diabetes demonstrate a blunted rise in GLP-1 concentrations after food intake.<sup>27</sup> I.V. GLP-1 infusion will increase insulin release and reduce fasting blood glucose concentrations, even in patients with longstanding type 2 DM.<sup>21</sup> One of the major clinical concerns about the use of GLP-1 is its rapid enzymatic degradation by DPP-4. To counteract this, agents that are resistant to DPP-4 degradation such as exenatide and liraglutide have been developed. Another approach is the development of specific DPP-4 inhibitors.

There are two commercially available GLP-1 agonists in the UK—exenatide and liraglutide. Exenatide is derived from the naturally occurring peptide, exendin-4, which was isolated from the salivary secretions of the lizard *Heloderma suspectum* (Gila monster). This lizard eats once a month and the function of exendin-4 is to rapidly increase the production of insulin in response to nutrients entering the gut. Exenatide is a complete agonist at the GLP-1 receptor, is resistant to DPP-4 degradation, and is cleared by the kidneys. It is usually administered twice daily as injections and provides adequate daily replacement of GLP-1. Exenatide is approved for the treatment of type 2 DM in patients receiving concurrent metformin or sulphonylurea treatment, although the dose of sulphonylurea may need to be reduced to avoid hypoglycaemia. Clinical trials have demonstrated

a reduction in both fasting and postprandial glucose concentrations, a 1–2% reduction in HbA<sub>1c</sub> concentrations, and a moderate weight loss of 2–5 kg.<sup>28–30</sup> Side-effects of exenatide include nausea and less commonly, vomiting or diarrhoea, particularly when starting therapy. It is recommended that treatment is initiated with a dose of 5  $\mu$ g twice daily which may be increased to 10  $\mu$ g twice daily approximately 1 month later. A recent study of once-weekly dosing using a sustained release formulation of exenatide showed improvements in glycaemic control, no increased risk of hypoglycaemia, and similar reductions in body weight.<sup>31</sup>

Liraglutide, another incretin mimetic, is administered once daily, is not excreted by the kidneys, is not subjected to DPP-4 degradation, and may be a promising alternative.<sup>32</sup> It provides greater improvements in glycaemic control, induces weight loss, improves obesity-related risk factors, and reduces pre-diabetes. It is also associated with reductions in HbA<sub>1c</sub> and blood pressure.<sup>33–35</sup> Animal studies have shown an increased occurrence of thyroid medullary cancer with high doses of liraglutide but the clinical relevance of this work is unclear. Early clinical trials of liraglutide suggested an increased incidence of pancreatitis.

In summary, incretin therapy appears to offer an effective alternative to the currently available hypoglycaemic agents. Continued evaluation and further long-term studies will confirm its safety and clinical role.<sup>36</sup>

## DPP-4 inhibitors

The effects of endogenous incretins are short-lived because of rapid degradation and inactivation by the enzyme DPP-4. This enzyme is widely expressed throughout the body and circulates in a soluble form. It acts by cleavage of the two NH<sub>2</sub>-terminal amino acids of bioactive peptides, provided the second amino acid is alanine or proline. Cleavage is rapid and endogenous GLP-1 has a short half-life (<2 min). Inhibitors of DPP-4 have been developed to prevent the inactivation of GLP-1 and prolong the activity of the endogenously released hormone.<sup>37</sup> In contrast to GLP-1 receptor agonists, these drugs are available orally and have a longer duration of action, requiring only once daily dosing. The drugs currently available in the UK are sitagliptin, saxagliptin, and vildagliptin as sole agents and also combined with metformin. They are effective at controlling hyperglycaemia, reducing HbA<sub>1c</sub> concentrations by around 1%, improving pancreatic  $\beta$ -cell function, and can be used as monotherapy or in combination with other agents. They are safe and well-tolerated with a low risk of hypoglycaemia, but do not reduce appetite or cause weight loss such as GLP-1 agonists.<sup>38</sup> One potential concern, however, is the ability of DPP-4 to cleave other bioactive peptides, including neuropeptide Y, gastrin-releasing peptide, substance P, and various chemokines.<sup>37</sup> Inhibition of DPP-4 activity may cause adverse events such as increased blood pressure, neurogenic inflammation, and immunological reactions. No severe effects have been reported to date, but further long-term trials are needed.

## Thiazolidinediones

The 21st century has seen the increase and decrease of TZDs. TZDs, like metformin, belong to the class of drugs known as insulin sensitizers. Metformin acts mainly on the muscle and the hepatocyte, while TZDs act predominantly on the adipocyte and the muscle. TZDs enhance insulin sensitivity by increasing the efficiency of glucose transporters, lowering HbA<sub>1c</sub> by 1–2%, and reducing both fasting and postprandial glucose concentrations.<sup>39</sup> They do not cause hypoglycaemia when used as a single agent but can do so when used in combination with other agents. Troglitazone was the first TZD approved to treat type 2 DM in 1997, but was withdrawn from clinical practice in 2000 because of rare idiosyncratic hepatotoxicity, a side-effect not observed with rosiglitazone and pioglitazone. TZDs activate peroxisome proliferator-activated gamma nuclear receptors throughout the body, exerting their main insulin-sensitization in fat and muscles. This in turn results in altered gene transcription in adipocytes, a modulation of fatty acid metabolism and a reduction in circulating free fatty acids by 20–40%.<sup>40 41</sup>

A decrease in circulating free fatty acids is postulated to enhance insulin-receptor signalling in skeletal muscle, resulting in increased insulin sensitivity throughout the whole body. A further benefit may be favourable effects on pancreatic  $\beta$ -cell function by reducing exposure of  $\beta$ -cells to lipotoxicity, which may contribute to  $\beta$ -cell death.<sup>40 42</sup> This proposed improvement in  $\beta$ -cell function may account for the lower risk of monotherapy failure, after 5 yr, for rosiglitazone vs metformin (32% lower) or rosiglitazone vs glyburide (glibenclamide) (63% lower).<sup>43</sup>

TZDs redistribute fat from visceral to subcutaneous deposits, a pattern which is associated with a lower risk of cardiovascular disease.<sup>44</sup> Both rosiglitazone and pioglitazone increase high-density lipoprotein cholesterol (HDL-c) and low-density lipoprotein cholesterol (LDL-c); pioglitazone also decreases triglyceride concentrations.<sup>45</sup> Other benefits associated with the use of TZD include anti-inflammatory effects,<sup>46</sup> improved peripheral and coronary vascular endothelial function, and a modest improvement in hypertension.<sup>47</sup>

New or worsening peripheral oedema is common with the use of TZD with the incidence ranging from 2.5% to 16.2%. The risk is increased with age, drug dose, female sex, impaired renal function, and concomitant insulin use. One of the likely mechanisms for this is increased renal reabsorption of sodium and plasma volume expansion. A greater concern, however, is the potential for worsening of heart failure with these drugs. Although relatively uncommon, the annual increment in heart failure is 0.25–0.45% per year. Thus, these drugs are contraindicated in patients with New York Heart Association class III or IV cardiac status and should be used with caution in those with class II disease.<sup>48</sup>

TZDs have also been associated with an increased incidence of myocardial infarction (MI). A controversial meta-analysis evaluated the cardiovascular effects of rosiglitazone vs placebo or active controls from 42 trials, and concluded that rosiglitazone was associated with a significant

43% increased odds ratio for MI and a trend towards a 64% increased odds ratio for cardiovascular death.<sup>49</sup> However, none of these studies were designed to assess cardiovascular effects and had extremely low cardiovascular event rates. A Food and Drugs Administration (FDA) enquiry had concluded in 2007 that the evidence against rosiglitazone was insufficient to recommend that it be withdrawn.<sup>50</sup>

TZDs, therefore, have a number of effects on the cardiovascular system apart from benefitting glucose metabolism. One important study, the PROactive study (Prospective Pioglitazone Clinical Trial in Macrovascular Events), demonstrated a reduction in the hazard ratio and a reduction in all-cause mortality, non-fatal MI, and stroke in high-risk patients with type 2 DM taking pioglitazone.<sup>51</sup> Furthermore, there may exist differences between the two available agents. In an observational study of almost 30 000 patients with a 1.2 yr follow-up, pioglitazone was associated with a 22% lower rate of MI when compared with rosiglitazone and a 15% decrease in MI and coronary revascularization.<sup>52</sup>

In January 2008, both the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) recommended TZDs as the second-line treatment for type 2 DM after lifestyle intervention and metformin. In 2008, the ACCORD (Action to Control Cardiovascular Risk in Diabetes) trial was terminated early when it was shown that patients in the intensive treatment arm, 91% of whom received rosiglitazone, were at significantly increased risk of death from cardiovascular disease.<sup>53</sup> Further analysis showed that the use of intensive therapy to achieve normal glycosylated haemoglobin values for 3.5 yr increased mortality, attributed mostly to hypoglycaemia, and did not significantly reduce the major cardiovascular events. There was no evidence to show that any one drug class was directly responsible.<sup>54</sup> Nevertheless, in October 2008 both the ADA and the EASD issued guidelines that explicitly advised against the use of rosiglitazone for the treatment of type 2 DM. Current consensus relegates pioglitazone to third-line treatment and states that rosiglitazone is not recommended.<sup>55</sup> However, Woo<sup>56</sup> has re-emphasized the differences in clinical practice guidelines between Canada, America, and Europe and the lack of evidence from long-term studies regarding the association between rosiglitazone and MI. The results of the RECORD study, which was designed to prospectively assess the cardiac outcomes of rosiglitazone, confirmed that the addition of rosiglitazone to glucose-lowering therapy increased the risk of heart failure and of some fractures, mainly in women, although the data were inconclusive about any possible effect on MI. The authors concluded that rosiglitazone is not recommended for patients with a history of heart failure and should be used with caution in women at high risk of fractures, but does not increase the overall cardiovascular morbidity or mortality.<sup>57</sup>

## Insulin therapy

Type 1 DM is caused by autoimmune destruction of the pancreas and patients require insulin from the outset of their illness. In type 2 DM with progressive  $\beta$ -cell failure, individuals

**Table 2** Pharmacokinetics of new insulin analogues

Drug	Onset (min)	Peak (h)	Duration (h)
Rapid-acting			
Lispro	5–15	2	4
Aspart	5–15	2	4
Glulisine	5–15	2	4
Basal			
Glargine	15	Flat	24
Detemir	15	Flat	24
Analogue mixture			
Biphasic insulin			
Lispro	5–15	2–4	18
Biphasic insulin			
Aspart	5–15	2–4	20–24

may require insulin therapy as the disease progresses. Increasingly, insulin is no longer seen as a ‘last resort’ after long-term oral agent combinations have failed, but as a therapeutic tool for earlier use. Starting insulin therapy with low doses in combination with oral agents is effective in achieving glycaemic targets and maintaining HbA<sub>1c</sub> values.<sup>58 59</sup> Furthermore, insulin use can improve insulin resistance<sup>58</sup> and may have cardiovascular benefits. Concerns that insulin therapy would worsen weight gain, obesity, and accelerate coronary artery disease have not been realized.

The goal of insulin therapy is to mimic as closely as possible the physiological pattern of insulin secretion seen in non-diabetic patients. Normally insulin secretion in response to a meal consists of a first- and second-phase response, and type 2 DM is characterized by a defect in first-stage or acute glucose-induced insulin secretion. Insulin therapy should address both basal and post-prandial insulin requirements, the basal-bolus concept.<sup>21</sup> This requires basal insulin to suppress glucose production between meals, and overnight and bolus insulin to limit postprandial hyperglycaemia. Bolus insulin may comprise up to 10–20% of total daily insulin at each meal. When used in this manner, insulin should demonstrate an immediate increase and a sharp peak to effectively control glucose. This has been made feasible by the development of newer fast-acting analogues, such as insulin lispro, insulin aspart, and insulin glulisine (Table 2). Changes in their amino acid structure reduce the tendency to aggregate into dimers thus speeding their absorption after subcutaneous injection. They have a rapid onset of action (typically 5–15 min), peak activity 2 h after injection, and their effect has almost disappeared after 4–5 h. This matches normal mealtime peaks of plasma insulin more closely than human regular insulin, and in turn results in less immediate post-prandial hyperglycaemia and less late post-prandial hypoglycaemia.<sup>58</sup>

New long-acting insulin formulations such as glargine and detemir provide good glycaemic control between meals without the risk of hypoglycaemia. Insulin glargine results from two modifications of human insulin, substitution of

glycine at position A21, and addition of two arginine molecules at the C terminal of the B chain. These substitutions reduce the solubility at physiological pH and stabilize the molecule. It is released very slowly from the injection site and its duration of action is prolonged allowing a relatively constant basal insulin supply for more than 24 h.

There have been recent reports suggesting an increased risk of cancer in patients taking long-acting insulins.<sup>60</sup> Type 2 DM, *per se*, is associated with three leading cancers—colon, pancreas, and breast and is also a risk factor for liver cancer.<sup>61</sup> Cancers linked with type 2 DM are, however, also associated with obesity or insulin resistance, so the cause may be multifactorial. Interestingly, metformin therapy is associated with a reduced cancer risk compared with insulin or sulphonylureas.<sup>62–64</sup> Indeed, cancer mortality was shown to almost double among insulin users when compared with metformin users and use of sulphonylurea was also associated with increased mortality.<sup>63</sup> Insulin is a growth factor for a number of epithelial tumours in cell culture systems and increased insulin concentrations also cause a secondary increase in (IGF-1) (insulin-like growth factor), which is another known tumour growth factor.<sup>60</sup> The newer biosynthetic insulins have increased trophic effects and increase DNA synthesis and cell division in cell culture systems. These effects are mediated by prolonged binding to the insulin receptor or increased cross-reactivity to the IGF-1 receptor.<sup>60</sup> Observational studies in patients foster the debate. In a large observational study, there was a strong correlation between insulin dose and cancer risk, regardless of the insulin type, but when adjusted for dose insulin glargine had a higher risk than human insulin.<sup>65</sup> A Swedish study of more than 100 000 patients found that those patients on insulin glargine alone had a higher risk of breast cancer than those on other insulins (with or without glargine) although the number of patients was relatively small.<sup>66</sup> Further reports from Scotland suggested that patients on insulin glargine alone had a higher risk of breast cancer.<sup>67</sup> These studies have been criticized for possible selection bias and other statistical deficiencies.<sup>68</sup> Two, more recent analyses of the literature<sup>69 70</sup> failed to find an increased risk of cancer in patients on insulin glargine. The authors commented that even if research was to establish an increased risk of cancer among insulin users, this would be unlikely to diminish the favourable benefit–risk ratio for patients requiring insulin therapy.<sup>70</sup> A recent editorial stated that ultimately what matters is good glucose control—when other therapies fail, insulin and the insulin analogues achieve this.<sup>71</sup>

## Established agents

Although the treatment of diabetes in the 21st century has been dominated by interest in the newer agents described above, there is still a major role for well-established drugs, particularly the biguanides and sulphonylureas.

## Biguanides

Metformin and phenformin were introduced for the treatment of diabetes in the 1950s. Phenformin was withdrawn

from clinical use in the 1970s and metformin is the sole agent in clinical use in this class. Metformin improves insulin sensitivity especially in skeletal muscle, decreases hepatic gluconeogenesis, and inhibits glycogenolysis. Other beneficial effects include a reduction in plasma triglyceride and LDL concentrations.<sup>72</sup> Metformin, before the introduction of newer agents, was the only drug that improved glycaemia and was associated with a lack of weight gain and even weight loss in some patients. This makes it an ideal first-line agent particularly in overweight patients. Metformin may also improve other cardiovascular risk factors; the UKPDS group studies suggest that metformin used as monotherapy in obese patients reduced the rate of MI and all-cause mortality.<sup>73</sup> The 10 yr follow-up of UKPDS, again emphasized the benefits of long-term glycaemic control on all causes of death, micro-, and macrovascular complications.<sup>74</sup>

Metformin has a mostly favourable side-effect profile. Because it does not affect insulin secretion, it is not associated with hypoglycaemia when used as monotherapy but can do so when used in combination with sulphonylureas or insulin. Gastrointestinal side-effects such as metallic taste, nausea, abdominal pain, and diarrhoea occur to varying degrees in up to 30% of patients. Most of these are transient and occur when the drug is introduced or the dose increased rapidly.

Lactic acidosis is a potential concern with metformin. However, the evidence for metformin-induced lactic acidosis stems from about 300 case reports.<sup>75</sup> Underlying medical conditions such as chronic renal disease or MI are well-established risk factors for lactic acidosis and attributing lactic acidosis to metformin vs an underlying condition is often difficult. The reported frequency of metformin-induced lactic acidosis is three patients per 100 000 patient-years.<sup>75</sup> Nevertheless, metformin is not recommended in patients with renal disease (creatinine clearance  $<60 \text{ ml min}^{-1}$ , serum creatinine  $>120 \mu\text{mol l}^{-1}$  in women or  $>130 \mu\text{mol l}^{-1}$  in men), hepatic disease, cardiac disease (NYHA class III or IV), chronic pulmonary disease, severe infection, alcohol abuse, history of lactic acidosis, pregnancy, or use of i.v. radiographic contrast medium.<sup>21 72</sup> Despite these concerns, metformin remains one of the mainstays of diabetic management.<sup>76</sup> Stumvoll and colleagues<sup>77</sup> have highlighted the lack of good evidence to support the contraindications to metformin and suggested that this drug can be safely used in elderly patients, those with stable heart failure, moderate renal impairment (emphasizing the need for a reduced dose), and mild liver impairment (which is often owing to fatty liver and which improves with metformin). It has been shown that continuing metformin ingestion does not increase morbidity or mortality after cardiac surgery and may indeed, have beneficial effects. Metformin-treated patients had less post-operative prolonged tracheal intubation, infection, and overall cardiac morbidity.<sup>78</sup> Metformin treatment is associated with a dose-dependent reduction in cancer risk and it has been postulated that it may have a role as a novel anti-cancer drug.<sup>79</sup>

## Sulphonylureas

Sulphonylureas have been used since the 1950s and their efficacy is well-established. However, they are being superseded by newer agents.

Sulphonylureas act mainly by stimulating insulin release from the  $\beta$ -cells of the pancreas and may also improve insulin resistance in peripheral target tissues such as muscle and fat. These drugs reduce concentrations of HbA<sub>1c</sub> by 1–2% and fasting blood glucose concentrations by 3.3–3.9 mmol l<sup>-1</sup>.<sup>80–82</sup> Hypoglycaemia is the most common side-effect and is of particular concern with agents that are metabolized to an active metabolite with significant renal excretion, such as glibenclamide. These should be avoided in patients with renal impairment and in elderly patients. Other well-recognized side-effects include an increase in appetite and weight gain, and sulphonylureas are not the first choice for the management of obese patients.<sup>83</sup>

There has been controversy about the cardiovascular risk associated with the use of sulphonylureas. The University Group Diabetes Programme suggested that use of sulphonylurea was associated with an increased risk for cardiovascular events.<sup>84–86</sup> Two high-profile randomized trials have addressed these concerns. The UKPDS and ADOPT (A Diabetes Outcome Progression Trial) have suggested a reduced cardiovascular risk, which approached statistical significance and a lower incidence of cardiovascular events, using glibenclamide, when compared with rosiglitazone or metformin.<sup>87 43</sup>

## Other agents

### Meglitinides

The glinides, repaglinide, and nateglinide, are secretagogues that stimulate rapid insulin production by the pancreas and reduce both post-prandial blood glucose and HbA<sub>1c</sub> by 0.5–2%.<sup>88</sup> This early insulin release rapidly suppresses hepatic glucose production and reduces the need for additional insulin secretion. The glinides have a faster onset and shorter duration of action than the sulphonylureas.<sup>39</sup> They are associated with a reduced risk of hypoglycaemia, cause less weight gain, and are metabolized and excreted by the liver, and so can be used in patients with impaired renal function.

### $\alpha$ -Glucosidase inhibitors

Alpha-glucosidase inhibitors block the enzyme  $\alpha$ -glucosidase in the brush border of the small intestine, which delays absorption of glucose, thereby decreasing meal-related blood glucose increases.<sup>39</sup> Acarbose is taken before carbohydrate containing meals and should not be used when meals are missed. It does not cause weight gain or hypoglycaemia. Its use is contraindicated in patients with hepatic or renal impairment (serum creatinine  $>180 \mu\text{mol l}^{-1}$ ), inflammatory bowel disease, or a history of bowel obstruction.<sup>86</sup> Side-effects include bloating, flatulence, abdominal cramps, and diarrhoea, which limits their clinical use. Acarbose is probably of greatest use in patients with mild fasting

hyperglycaemia or who are already on combination oral therapy, but require an additional agent. Some studies have suggested that its use is associated with a reduction in cardiovascular events and a favourable effect on lipid metabolism.<sup>89 90</sup>

### Synthetic amylin analogues

Amylin is a peptide neurohormone that is synthesized and secreted by the  $\beta$ -cells of the pancreas with insulin. Patients lacking functional  $\beta$ -cells (i.e. patients with type 1 DM or advanced type 2 DM) are deficient in both insulin and amylin. Amylin secretion, like GLP-1, is stimulated by the presence of food in the gut and its 24 h profile resembles that of insulin with low baseline values and a rapid increase in response to meals. The physiological effects of amylin are also similar to those of GLP-1 but it is not an incretin hormone. Amylin suppresses glucagon secretion, delays gastric-emptying, and acts centrally in the area postrema of the hindbrain to induce satiety. Amylin slows the passage of glucose into the circulation while insulin stimulates cellular uptake of glucose to reduce glucose concentrations.<sup>91 92</sup>

Synthetic analogues of amylin such as pramlintide have been developed. Pramlintide is a stable, bioactive analogue that differs from human amylin by three amino acid substitutions.<sup>93</sup> It is given as a subcutaneous injection two to three times daily and is administered before meals. It has a rapid onset of action and duration of action of 2–4 h. It is currently used in patients with type 1 DM and in those type 2 diabetics using meal time insulin or insulin in combination with a sulphonylurea or metformin.<sup>94</sup> Nausea is a common side-effect. Hypoglycaemia can occur particularly in the first 4 weeks of treatment. Decreasing the dose of pre-meal insulin by 50% when starting therapy avoids this problem. Pramlintide also causes some weight loss,<sup>95 96</sup> reduces HbA<sub>1c</sub> by 0.3–0.6%, and significantly lowers postprandial glucose.<sup>94</sup> The role of pramlintide in the treatment of type 2 DM is unclear but it may be of some benefit to those patients already on insulin regimens.

Finally, as part of the quest for newer agents, research has focused on insulin-independent mechanisms. One of the newest agents is dapagliflozin, an SGLT2 inhibitor. Sodium-glucose co-transporter 2 (SGLT2) is located mainly in the proximal tubule of the nephron. It reabsorbs most of the glucose filtered by the glomerulus. Binding of dapagliflozin inhibits renal glucose reabsorption and promotes urinary glucose excretion. One study of more than 500 patients, who had inadequate diabetic control with metformin alone, found that the addition of dapagliflozin reduced HbA<sub>1c</sub> and FPG, with no increased risk in hypoglycaemia but with an increased incidence of genital infections. The investigators concluded that addition of dapagliflozin to metformin provided a new therapeutic option.<sup>97</sup>

### Conflict of interest

None declared.

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