Management of type 2 diabetes: new and future developments in treatment

Abd A Tahrani, Clifford J Bailey, Stefano Del Prato, Anthony H Barnett

The increasing prevalence, variable pathogenesis, progressive natural history, and complications of type 2 diabetes emphasise the urgent need for new treatment strategies. Long-acting (eg, once weekly) agonists of the glucagon-like-peptide-1 receptor are advanced in development, and they improve prandial insulin secretion, reduce excess glucagon production, and promote satiety. Trials of inhibitors of dipeptidyl peptidase 4, which enhance the effect of endogenous incretin hormones, are also nearing completion. Novel approaches to glycaemic regulation include use of inhibitors of the sodium–glucose cotransporter 2, which increase renal glucose elimination, and inhibitors of 11β-hydroxysteroid dehydrogenase 1, which reduce the glucocorticoid effects in liver and fat. Insulin-releasing glucokinase activators and pancreatic-G-protein-coupled fatty-acid-receptor agonists, glucagon-receptor antagonists, and metabolic inhibitors of hepatic glucose output are being assessed. Early proof of principle has been shown for compounds that enhance and partly mimic insulin action and replicate some effects of bariatric surgery.

Introduction

Type 2 diabetes mellitus is a complex endocrine and metabolic disorder. The interaction between several genetic and environmental factors results in a heterogeneous and progressive disorder with variable degrees of insulin resistance and pancreatic β-cell dysfunction.1 Overweight and obesity are major contributors to the development of insulin resistance and impaired glucose tolerance.1–3 When β cells are no longer able to secrete sufficient insulin to overcome insulin resistance, impaired glucose tolerance progresses to type 2 diabetes.1,3 Abnormalities in other hormones such as reduced secretion of the incretin glucagon-like peptide 1 (GLP-1), hyperglucagonaemia, and raised concentrations of other counter-regulatory hormones also contribute to insulin resistance, reduced insulin secretion, and hyperglycaemia in type 2 diabetes (figure 1).4–7

Insulin resistance usually begins many years before the onset of type 2 diabetes as a result of the interaction of genetic and several environmental factors.1,3,7,10 Key genes, including PPARG, CAPN10, KCNJ11, TCF7L2, HHEXIIIDE, KCNQ1, FTO, and MC4R, act in conjunction with environmental factors, including pregnancy, physical inactivity, quality and quantity of nutrients, puberty and ageing, to promote adiposity, impair β-cell function, and impair insulin action.1,9–11 Overweight and obesity contribute to insulin resistance through several pathways, including an imbalance in the concentrations of hormones (eg, increased leptin, reduced adiponectin, and increased glucagon), increased concentrations of cytokines (eg, tumour necrosis factor α, interleukin 6), suppressors of cytokine signalling (eg, suppressor of cytokine signalling 3), other inflammatory signals (eg, nuclear factor κB), and possibly retinol-binding protein 4.4,1,3,12–15 Crucially, increased release of non-esterified fatty acids, particularly from intra-abdominal adipose tissue in obesity, raises concentrations of intracellular diacylglycerol and fatty acyl-CoA, which reduce insulin postreceptor signalling.1 Concurrent alterations in β-cell function often include a period of compensatory hyperinsulinaemia with abnormal secretory dynamics. When insulin secretion is no longer sufficient to overcome insulin resistance, glucose intolerance progresses to type 2 diabetes. The decline in β-cell function seems to involve chronic hyperglycaemia (glucotoxicity), chronic exposure to non-esterified fatty acids (lipotoxicity), oxidative stress, inflammation, and amyloid formation.9–15 Patients with type 2 diabetes usually have pancreatic β-cell dysfunction that results in increased (or non-suppressed) glucagon secretion in the presence of hyperglycaemia1 and probably reduced prandial GLP-1 secretion.16 Roles have also been suggested for melatonin, through the melatonin receptor 1B, in reducing insulin secretion;1 and circadian genes and transcription factors (circadian locomotor output cycles kaput and brain and muscle aryl hydrocarbon receptor nuclear translocation-like) in insulin secretion and proliferation of islet cells,21 and hypothalamic function.22 Because of the variable and progressive pathophysiological changes associated with type 2 diabetes, differently acting pharmacological compounds are needed at different stages of the disease to complement the benefits of lifestyle changes, which can be effective but difficult to maintain.12,15 Pharmacological compounds, however, have several limitations (table I). Most of the
initial improvements in glycaemia are not sustained because of continued β-cell dysfunction. Additionally, many of these treatments have side-effects—hypoglycaemia, weight gain, gastrointestinal disturbances, peripheral oedema, and potential cardiovascular effects. Therefore, new treatments need to be developed that will sustain glycaemic control, reverse or halt the decline in β-cell function, assist with weight loss, improve insulin action, avoid hypoglycaemia, and have a favourable effect on cardiovascular disease. Herein we review the glucose-lowering treatments that are being developed for patients with type 2 diabetes.

Glucose-lowering treatments in development can be classified as those that target the pancreas or liver, enhance insulin action, act independently of insulin, or address features of the metabolic syndrome. Additionally, metabolic surgery is gaining momentum as a potential treatment for type 2 diabetes.

**Drugs targeting β-cell dysfunction**

**New incretin-based treatments**

Drugs targeting the pancreas can act directly or indirectly on the β cells (secrete insulin, C-peptide, and amylin), α cells (secrete glucagon), or δ cells (secrete somatostatin, which predominantly suppresses glucagon secretion). Since the early 20th century, evidence has suggested that intestinal factors are secreted in response to nutrients to enhance blood-glucose lowering; these factors were named incretins in the 1930s. The higher insulin response to glucose that is administered orally than that administered parenterally is brought about by incretins; this incretin effect probably causes more than 50% of meal-related insulin secretion in healthy individuals.

The two main incretins are glucose-dependent insulinotropic peptide (GIP) and GLP-1. GLP-1, a 30-aminoacid polypeptide secreted from the L cells in the ileum and colon, potentiates glucose-dependent insulin secretion and glucagon suppression, slows gastric emptying, and reduces food intake with a long-term effect to help with weight loss. In studies of animals (but not confirmed in individuals with type 2 diabetes), GLP-1 increases the mass and reduces apoptosis of β cells by increasing expression of several key genes implicated in β-cell differentiation. The results of studies in animals also indicate that GLP-1 might independently promote the accumulation of glycogen in the liver, increase glucose uptake, and lower concentrations of triglycerides. GLP-1 also increases cardiac inotropic and chronotropic activities, reduces the severity of myocardial infarction in

![Figure 1: Typical pathogenic features of hyperglycaemia in type 2 diabetes](image-url)

Adapted from DeFronzo with permission.
rats, and improves left ventricular ejection fraction after infarction in people.\(^4\) Studies of the cardiovascular effect of GLP-1 analogues are in progress, although these are mostly to comply with regulatory safety requirements.

Incretins are rapidly inactivated by dipeptidyl peptidase 4 (DPP-4), which cleaves the active peptide at the alanine residue that is penultimate to the N terminus.\(^1\) DPP-4 is widely expressed, especially by endothelial cells lining vessels that drain from the intestinal mucosa,\(^2\) hence the rapid inactivation and short circulating half-life of incretins (<2 min for GLP-1 and 5–7 min for GIP).\(^2\) To extend the half-life, DPP-4-resistant GLP-1 analogues with GLP-1-receptor (GLP-1R) agonist properties have been developed (exenatide, lixisenatide).\(^3\)

Another strategy has been to increase endogenous GLP-1 by highly specific DPP-4 inhibitors (sitagliptin, vildagliptin, saxagliptin).

Phase 3 clinical trials of some short-acting (lixisenatide) and sustained-release drugs (exenatide once weekly, taspoglutide, albiglutide, and CJC-1134-PC) are in progress.\(^3\) Sustained-release formulations offer the prospect of intermittent administration of once weekly or less frequently.

The durable DPP-4 resistance of these GLP-1 analogues has been achieved by use of different methods of preparation. Sustained release of exenatide, for subcutaneous injection, was achieved through formulation with biodegradable polymeric microspheres of poly(lactide-co-glycolide) or other biodegradable polymeric systems. Sustained-release formulations of GLP-1 receptor agonists are now available, with the potential to improve relative cardiovascular safety.

### Examples

<table>
<thead>
<tr>
<th>Examples</th>
<th>Mechanism(s) of action</th>
<th>Route</th>
<th>Dosing</th>
<th>Cardiovascular safety</th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sulphonylureas(^24,27)</td>
<td>Increase insulin secretion by binding to sulphonylurea receptor 1, resulting in depolarisation and calcium influx that initiates insulin secretion</td>
<td>Oral</td>
<td>Once or twice a day</td>
<td>Conflicting results from database studies, but no adverse outcomes from large prospective interventional studies reported in past 15 years</td>
<td>Long-term safety Low cost</td>
<td>Hypoglycaemia Weight gain Possible need for self-monitoring blood glucose Careful dose titration</td>
</tr>
<tr>
<td>Acarbose(^24,29–31)</td>
<td>Inhibit carbohydrate degradation in gut</td>
<td>Oral</td>
<td>Up to three times a day</td>
<td>Unknown, preliminary evidence of benefits</td>
<td>Weight neutral Low cost</td>
<td>Gastrointestinal side-effects</td>
</tr>
<tr>
<td>β-glucosidase inhibitors(^24,25)</td>
<td>Peroxisome-proliferator-activated-receptor-γ agonants act primarily in the adipose tissue to increase subcutaneous adipogenesis and reduce release of free fatty acids Increase insulin sensitivity in muscle and liver</td>
<td>Oral</td>
<td>Once a day</td>
<td>Oedema and potential to increase risk of heart failure Effects on cardiovascular disease and mortality have been reported Pioglitazone reduced composite endpoint of all-cause mortality, non-fatal myocardial infarction, and stroke in the PROACTIVE trial, whereas rosiglitazone did not show substantial benefit in the RECORD trial</td>
<td>Low risk of hypoglycaemia Might reduce blood pressure Long-term safety not established: risk of weight gain, oedema, heart failure, and fractures</td>
<td></td>
</tr>
<tr>
<td>Exenatide, Lixisenatide(^2,3)</td>
<td>Binds to glucagon-like-peptide-1 receptor, causing increased glucagon-dependent insulin secretion and glucagon suppression, delayed gastric emptying, and appetite suppression</td>
<td>Subcutaneous injection</td>
<td>Once or twice a day</td>
<td>Not known, but slight favourable effect on cardiovascular risk factors such as blood pressure and lipid profile Data from studies in animals suggest potential beneficial effect in myocardial ischaemia and congestive heart failure</td>
<td>Weight loss Low risk of hypoglycaemia (unless combined with sulphonylureas) Possible effect on β-cell survival and decline (data from studies in animals) Long-term safety not known Unconfirmed association with pancreatitis and medullary cell carcinoma Gastrointestinal side-effects Avoid in renal failure</td>
<td>(Continues on next page)</td>
</tr>
</tbody>
</table>

### Notes

- DPP-4: dipeptidyl peptidase 4
- GLP-1: glucagon-like peptide 1
- GIP: glucose-dependent insulinotropic polypeptide

### References

### Table 1: Summary of available drugs that lower blood glucose

<table>
<thead>
<tr>
<th>Examples</th>
<th>Mechanism(s) of action</th>
<th>Route</th>
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<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dipeptidyl-peptidase-4</td>
<td>Sitagliptin</td>
<td>Oral</td>
<td>Once a day</td>
<td>Not known, but no evidence of adverse effects so far</td>
<td>Weight neutral</td>
<td>Long-term safety not known</td>
</tr>
<tr>
<td>inhibitors (2005*)</td>
<td>Vildagliptin</td>
<td></td>
<td></td>
<td></td>
<td>Low risk of hypoglycaemia (unless combined with sulphonylureas)</td>
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<tr>
<td></td>
<td>Saxagliptin</td>
<td></td>
<td></td>
<td></td>
<td>Possible effect on β-cell survival and decline (data from studies in animals)</td>
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<tr>
<td></td>
<td><strong>Amylin analogue</strong></td>
<td><strong>Pramlintide</strong></td>
<td><strong>Subcutaneous injection</strong></td>
<td>Three times a day</td>
<td>Weight loss</td>
<td>Unknown long-term safety</td>
</tr>
<tr>
<td>(2005*)</td>
<td></td>
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<td></td>
<td><strong>Insulin</strong></td>
<td><strong>Rapid acting (aspart, lispro, glulisine)</strong></td>
<td><strong>Subcutaneous injection</strong></td>
<td>Once to four times a day</td>
<td>Historically controversial, but the results of large interventional trials and database studies have not shown adverse effects</td>
<td>More sustained glycaemic improvements compared with other drugs</td>
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<td></td>
<td><strong>Short acting (actrapid, humulin S, insuman rapid)</strong></td>
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<td></td>
<td><strong>Intermediate acting</strong></td>
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<td></td>
<td><strong>Long acting (glargine, detemir)</strong></td>
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<td></td>
<td><strong>Biphasic premixed</strong></td>
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</table>

Drugs such as bromocriptine quick release (dopamine agonist), colesucretam (bile sequestrant), phenformin (biguanide), and voglibose (α-glucosidase inhibitor) are approved for the treatment of hyperglycaemia in type 2 diabetes in some countries. UKPDS=United Kingdom Prospective Diabetes Study. NAVIGATOR=Nateglinide And Valsartan in Impaired Glucose Tolerance Outcomes Research. RECORD=Rosiglitazone Evaluated for Cardiac Outcomes and Regulation of Glycaemia in Diabetes. PROACTIVE=Prospective pioglitAzone Clinical Trial In macro-Vascular Events. *Year the drug class became available for clinical use. †Discontinued in Europe in 2010. ‡Not licensed in the USA, and often administered twice a day. §Not licensed in Europe.

To obviate the problem of subcutaneous delivery of peptide incretins, orally administered non-peptide molecules that bind and stimulate the GLP-1R have been identified. From a library of 48,160 synthetic and natural compounds, S4P and Boc5 bound and activated the GLP-1R and produced similar effects to GLP-1 analogues in studies of animals. Boc5, administered intraperitoneally to diabetic db/db mice, reduced glycated haemoglobin A1c (HbA1c) concentrations, food intake, and weight gain, and improved glucose tolerance. A substituted quinoxaline GLP-1R agonist was discovered in a screen of 250,000 compounds. Chemical modulation resulted in more potent molecules, showing proof of principle for non-peptide GLP-IR agonists. The discovery of orally active insulin-releasing GIP agonists has also been reported.

Linagliptin and alogliptin, both DPP-4 inhibitors, are being assessed in advanced phase 3 trials. In a phase 2 trial, linagliptin greatly improved oral glucose tolerance when given for 12 days. Linagliptin monotherapy improved glycaemic control in drug-naive patients and those who were intolerant to metformin (adjusted mean HbA1c difference was about –0.6%), and linagliptin in combination with sulphonylureas or metformin (adjusted mean change in HbA1c from baseline was about –0.5%) was not associated with increased risk of hypoglycaemia and dose adjustment.
was not needed in renal impairment.\textsuperscript{42} Alogliptin, as monotherapy or in combination with metformin or glibenclamide in type 2 diabetes, improved fasting glycaemia and reduced concentrations of HbA\textsubscript{1c} at 26 weeks (HbA\textsubscript{1c} mean change from baseline was about –0.4% to –0.6%), and was associated with good gastrointestinal tolerability and a low incidence of hypoglycaemia.\textsuperscript{43,44} When used with an unchanged dose of insulin, it improved glycaemic control without increasing hypoglycaemia and without exacerbating weight gain.\textsuperscript{45} Similar features have been described for other DPP-4 inhibitors that are in the early stages of development—eg, melogliptin and R1438.\textsuperscript{46} DPP-4 inhibitors in development seem to have similar glucose-lowering efficacies, but they have different pharmacokinetic properties that could be useful in different subpopulations (eg, linagliptin is almost entirely metabolised and eliminated by the liver, making it potentially useful in renal impairment).

### Non-incretin β-cell stimulants

The phosphorylation of glucose by glucokinase after entry into the β cell affects the rate of glucose metabolism and subsequent ATP production, which closes potassium–ATP channels and initiates insulin secretion (figure 2).\textsuperscript{47} To enhance glucokinase action in β cells, several glucokinase activators have been developed, including piragliatin, compound 14, R1511, AZD1656, AZD6370, compound 6, and ID1101.\textsuperscript{48} Glucokinase activators increased insulin concentrations and reduced glucose concentrations in animal models of diabetes and patients with type 2 diabetes.\textsuperscript{49-51} Glucokinase activators can additionally reduce glucose concentrations through effects on hepatic glucose metabolism. Glucokinase activation is associated with increased concentrations of triglycerides and risk of hypoglycaemia.\textsuperscript{52}

Several G-protein-coupled receptors for fatty acids and their derivatives are expressed by β cells, notably G-protein-coupled receptors 40, 119, and 120. Oral synthetic synthetic...
agonists of these receptors increase β-cell concentrations of cyclic adenosine monophosphate (cAMP) and potentiate glucose-induced insulin secretion with improvements in glucose tolerance in animal models. The same G-protein-coupled receptors are also expressed by intestinal K cells and L cells, enabling an additional insulin-releasing effect through the incretins GIP and GLP-1.

Although reduction of β-cell mass has been reported in type 2 diabetes, no treatment is available to prevent this continuous shrinkage of functional β-cell mass. After islet-cell transplantation in patients with type 1 diabetes, exenatide can reduce the need for insulin or prolong insulin independence, suggesting a positive effect on graft survival and function. Compounds that reduce oxidative stress have been shown to reduce β-cell apoptosis in islets isolated from patients with type 2 diabetes. In preclinical studies, anti-inflammatory drugs such as interleukin-1-receptor antagonists improved insulin secretion, reduced hyperglycaemia, reduced inflammatory infiltrates and fibrosis in the islets, and improved islet vascularisation, suggesting a possible effect on β-cell mass and survival.

**Drugs targeting α-cell dysfunction**

Patients with type 2 diabetes usually have very high fasting glucagon concentrations and impaired suppression of postprandial glucagon secretion (ie, low insulin-to-glucagon ratio). Glucagon suppresses hepatic glycogen synthesis and stimulates glycogenolysis and gluconeogenesis. Thus, excess glucagon prevents normal suppression of hepatic glucose output, contributing to fasting and postprandial hyperglycaemia in type 2 diabetes. Incretin-based treatments (GLP-1R agonists and DPP-4 inhibitors) reduce glucagon secretion in a glucose-dependent manner (ie, only in association with hyperglycaemia), reducing postprandial glucose concentrations without compromising hypoglycaemic counter-regulation.

Another mechanism to counter excess glucagon secretion is to block the glucagon receptor or its signalling after binding with the hormone. Animal models with a null mutation of the glucagon receptor or reduced expression with antisense oligonucleotides show significant reduction in basal glycaemia and improved glucose tolerance, but significant elevations in glucagon and α-cell hyperplasia might also arise. Various peptide and non-peptide glucagon-receptor antagonists have been assessed in animal models, but little evidence exists for chronic efficacy. If the effect of glucagon-receptor antagonists is not maintained, hepatic glucose output might rebound. Maintenance of the glucagon-receptor antagonism, however, might reduce the ability to counteract hypoglycaemia.

**Drugs targeting α-cell and β-cell dysfunction**

One possible approach to counter rebound hyperglycaemia after administration of glucagon-receptor antagonists would be to suppress glucagon secretion with GLP-1. Hybrid peptides have been developed that consist of the native sequence for GLP-1R agonism and part of the glucagon sequence that binds without activating the glucagon receptor. An example is dual-acting peptide for diabetes (DAPD). Pegylated DAPD, designed for an extended duration of action, increased insulin secretion, improved glucose tolerance, and reduced glucose concentrations after a glucagon challenge in db/db mice. However, it also increased glucagon concentrations but did not affect gastrointestinal motility.

Another peptide from the preproglucagon family is oxyntomodulin, which is secreted postprandially from the L cells with GLP-1. Oxyntomodulin is an agonist for both the GLP-1R and glucagon receptor. It induced weight loss, and reduced food intake and glucose in rats with diet-induced obesity. Subcutaneous administration to obese individuals reduced food intake, and increased energy expenditure and weight loss.

**Insulin-action enhancers**

Many patients with type 2 diabetes need a combination of two or more differently acting glucose-lowering drugs.
Insulin is used to compensate for advanced β-cell failure and might also be used to overcome severe insulin resistance. Figure 3 summarises the main pathways that are initiated when insulin binds to its receptor. To circumvent the difficulties of insulin delivery and acknowledge the physiological value of having higher portal than peripheral insulin concentrations, various enterally administered non-peptide approaches have been assessed to activate the insulin receptor or early postreceptor signalling intermediates. These approaches are difficult because many of the postreceptor targets are also part of other regulatory pathways, including some involved in cell differentiation and cell death. Hence, any potential insulin mimetic needs to be sensitive, specific, reversible, and incomplete to avoid disruption to signals shared with other cellular pathways.

In 1999, a non-peptide metabolite (demethyl-asterriquinone, L-783281) was identified in cultures of the fungus *Pseudomassaria* that activates the human insulin-receptor tyrosine kinase. This molecule reduced blood-glucose concentrations in rodent models of diabetes when administered orally. L-783281 interacted selectively with the β subunit of the insulin receptor without displacing insulin. Although L-783281 is probably not suitable for use in people because its hydroxyquinone moiety increases the generation of free radicals when in contact with high-energy electrons, it provides proof of concept that the development of an oral non-peptide insulin-receptor agonist is feasible. A new non-quinone derivative of L-783281 (D-410639) has been developed that potently activates the human insulin receptor and is 128 times less cytotoxic than is L-783281.

Insulin action can be potentiated by prolonging phosphorylation of the β subunit of the insulin receptor after insulin binds to the α subunit. Several classes of compounds can potentiate insulin action, including TLK16998 and signalling intermediates that are activated by C-peptide and insulin-like growth factor 1. TLK16998 is a non-peptide molecule that does not displace insulin from the insulin receptor and has no effect in the absence of insulin, but enhances phosphorylation of the β subunit in the presence of insulin.

**Figure 3:** Potential sites for intervention in intracellular pathways of insulin signalling
Adapted with permission from Bailey. Dashed line with a bar at the end means inhibition. Solid line with an arrowhead means a stimulatory effect.
tyrosine phosphatase 1B reduce dephosphorylation of the β subunit, thereby potentiating insulin action. These inhibitors reduce the concentration of blood glucose in an animal model of hyperglycaemia, and might help weight loss and improve endothelial function. Vanadium salts also reduce phosphatase activity and amplify the effect of insulin sufficiently to improve glycaemic control in animal models of diabetes. Although the therapeutic window is narrow, treatment can be intermittent and lasting, and the prospect of using organic vanadium complexes as insulin potentiators is not unrealistic.

Several other potential treatment targets within the insulin postreceptor signalling pathway could prevent negative feedback to reduce the activity of tyrosine kinases. Compounds that inhibit protein kinase C, κ-B kinase-β, c-Jun N-terminal kinase, and potentiate phosphatidylinositol-3 kinase have shown proof of principle in cell and animal models.

**Drugs targeting non-insulin-dependent pathways**

**Sodium-glucose-cotransporter-2 (SGLT2) inhibitors**

The kidneys contribute to glucose homeostasis through gluconeogenesis, glucose use, and glucose reabsorption from the glomerular filtrate. Renal gluconeogenesis might contribute 20–25% of total glucose production in the fasting state, most of which can be used immediately by the kidney. About 180 L of plasma is normally filtered daily through the kidneys, and represents about 180 g of glucose if the average plasma glucose concentration is 5.5 mmol/L. All of this glucose is normally reabsorbed, mostly through SGLT2, a low-affinity high-capacity transporter, located predominantly in the brush border membrane of the S1 segment of the proximal tubule. The remainder is reabsorbed in the S2 and S3 segments of the renal proximal tubule by a high-affinity low-capacity transporter, SGLT1 (also brings about glucose absorption from the gastrointestinal tract; figure 4).

In type 2 diabetes, renal gluconeogenesis is increased and renal glucose reabsorption might be enhanced because of upregulation of the SGLT2 transport. Although hyperglycaemia often exceeds the renal threshold in type 2 diabetes, inhibition of SGLT2 can increase the glucosuria sufficiently to reduce hyperglycaemia. Patients with familial renal glucosuria (caused by specific mutations of the gene encoding SGLT2) have glucosuria and live healthy lives. Because the inhibition of SGLT2 is insulin-independent and is compensated by glucose reabsorption through SGLT1 at low concentrations of glucose, the risk of hyperglycaemia is low. Also, the glucosuric effect can aid weight loss, and a slight osmotic diuresis might help to reduce blood pressure.

Several SGLT2 inhibitors are undergoing development, including dapagliflozin, canagliflozin, ASP1941, LX4211, and BI10773. Dapagliflozin reduces fasting and postprandial plasma concentrations of glucose and HbA1c, and bodyweight with low risk of hypoglycaemia. It can be used alone or in combination with established glucose-lowering drugs, including insulin. Table 3 summarises the clinical efficacy of dapagliflozin. This inhibitor was similarly effective in reducing HbA1c concentrations in patients with drug-naive and insulin-treated diabetes; the effect on weight loss, however, was often more striking in patients with longer duration of diabetes. Dapagliflozin was associated with increased risk of genital and urinary-tract infections in most studies, but these were typically mild and managed with standard intervention.

**Hepatic targets**

The liver contributes to glucose homeostasis through rapid postprandial clearance of glucose from the portal vein; when blood glucose falls below normal concentrations, glycogen is mobilised and glucose is produced by gluconeogenesis. When the blood glucose concentration increases, hepatic glucose uptake increases proportionally, stimulating glucokinase and glycogen synthesis. Raised blood-glucose concentrations normally increase insulin release and reduce glucagon release, increasing the insulin-to-glucagon ratio, which inactivates glycogen phosphorylase (inhibiting glycogenolysis), activates glycogen synthase (activating glycogen synthesis), and increases the concentrations of fructose-1,6-bisphosphate. The net effect of these events
is to reduce hepatic production of glucose and increase hepatic storage of glucose as glycogen (figure 5).26
Genetically modified animals that lack sufficient glucokinase become hyperglycaemic and die within days, whereas animals that overexpress glucokinase have improved glucose tolerance.27 Similarly, in people, mutations that reduce glucokinase activity cause maturity-onset diabetes of the young (heretogous) or permanent neonatal diabetes (homogous), whereas overactivation of glucokinase can cause hypoglycaemia.28,29 Thus, glucokinase activators, in addition to stimulating insulin secretion, can promote hepatic glucose storage. These combined effects improve glucose tolerance but will require caution to avoid hypoglycaemia (figure 2).
Glucose-6-phosphatase converts glucose-6-phosphate to glucose as a final step in glycolgenolysis and gluconeogenesis (figure 5).30 Hence, inhibition of this enzyme reduces hepatic glucose output and lowers glucose concentrations. Generally used treatments for

<table>
<thead>
<tr>
<th>Baseline treatment</th>
<th>Groups</th>
<th>Duration (weeks)</th>
<th>HbA1c (%)</th>
<th>HbA1c change (%)</th>
<th>Weight change (kg)</th>
<th>Hypoglycaemia</th>
<th>Upper urinary tract infection</th>
</tr>
</thead>
<tbody>
<tr>
<td>List et al102</td>
<td>Drug naive</td>
<td>Dapagliflozin</td>
<td>12</td>
<td>50 mg 7.8 (1.0)</td>
<td>–0.9 (0.1)</td>
<td>–3.4% (–4.1 to –2.6)</td>
<td>Dapagliflozin 50 mg, 7.6 (0.8)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Dapagliflozin</td>
<td></td>
<td>88 (20)</td>
<td>–18 (0.1)</td>
<td>–4.7 (–5.4 to –4.0)</td>
<td>Metformin, 0%</td>
</tr>
<tr>
<td>Wilding et al103</td>
<td>Patients on oral antidiabetes treatments + insulin (but no sulphonylurea)</td>
<td>Dapagliflozin</td>
<td>12</td>
<td>10 mg 8.0 (0.0)</td>
<td>–0.8 (0.0)</td>
<td>–1.1 (–2.0 to –0.2)</td>
<td>Placebo, 9.8 (0.9)</td>
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<tr>
<td></td>
<td></td>
<td>Dapagliflozin</td>
<td></td>
<td>87 (17.5)</td>
<td>–0.3 (0.0)</td>
<td>–0.7 (–1.5 to –0.0)</td>
<td>Placebo, 8.7 (17.9)</td>
</tr>
<tr>
<td>Bailey et al104</td>
<td>Metformin</td>
<td>Dapagliflozin</td>
<td>24</td>
<td>50 mg 7.8 (1.0)</td>
<td>–0.7 (0.1)</td>
<td>–3.4% (–4.1 to –2.6)</td>
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</tr>
<tr>
<td>Wilding et al105</td>
<td>Insulin</td>
<td>Dapagliflozin</td>
<td>40</td>
<td>7.8 (0.8)</td>
<td>–0.6 (0.1)</td>
<td>–1.1% (–1.8 to –0.4)</td>
<td>Dapagliflozin 7.8 (0.8)</td>
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<td></td>
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<td>Dapagliflozin</td>
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<td>87 (17.5)</td>
<td>–0.3 (0.0)</td>
<td>–0.7 (–1.5 to –0.0)</td>
<td>Placebo, 8.7 (17.9)</td>
</tr>
<tr>
<td>Nauck et al106</td>
<td>Metformin</td>
<td>Dapagliflozin</td>
<td>52</td>
<td>10 mg 8.0 (0.0)</td>
<td>–0.5 (0.0)</td>
<td>–1.1% (–1.8 to –0.4)</td>
<td>Dapagliflozin 10 mg, 7.8 (0.8)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Dapagliflozin</td>
<td></td>
<td>87 (17.5)</td>
<td>–0.3 (0.0)</td>
<td>–0.7 (–1.5 to –0.0)</td>
<td>Placebo, 8.7 (17.9)</td>
</tr>
<tr>
<td>Ferrannini et al107</td>
<td>Drug naive</td>
<td>Dapagliflozin</td>
<td>24</td>
<td>50 mg 7.8 (1.0)</td>
<td>–0.9 (0.1)</td>
<td>–3.4% (–4.1 to –2.6)</td>
<td>Dapagliflozin 50 mg, 7.6 (0.8)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Dapagliflozin</td>
<td></td>
<td>88 (20)</td>
<td>–18 (0.1)</td>
<td>–4.7 (–5.4 to –4.0)</td>
<td>Metformin, 0%</td>
</tr>
</tbody>
</table>

Data are mean (SD) or mean (95% CI), unless otherwise indicated. HbA1c = glycated haemoglobin A1c. NA = not available. All doses are per day. *Data based on abstracts presented at the European Association for the Study of Diabetes, Stockholm, 2003, because full-study data were not accessible.

Table 3: Summary of clinical trials of sodium-glucose-cotransporter-2 inhibitor dapagliflozin
diabetes, such as metformin and insulin, can reduce expression of glucose-6-phosphatase. In studies of animals, inhibition of glucose-6-phosphatase rapidly reduced blood-glucose concentrations. However, this strategy has two main limitations. First, since glucose-6-phosphatase catalyses the final step of glycogenolysis and gluconeogenesis, inhibition of this enzyme might precipitate hypoglycaemia because it restrains the main counter-regulatory response triggered by glucagon and catecholamines. Second, the accumulation of glucose-6-phosphate, resulting from glucose-6-phosphatase inhibition, has been implicated in the induction of lipogenic genes that leads to hepatic steatosis.

Fructose-1,6-bisphosphatase is another target in the gluconeogenesis pathway (figure 5). Its activity is increased in animal models of diabetes and insulin resistance, and inhibition of this enzyme in Zucker diabetic rats inhibits gluconeogenesis and reduces blood-glucose concentrations. Unlike the inhibition of glucose-6-phosphatase, inhibition of fructose-1,6-bisphosphatase does not induce hypoglycaemia because of a concomitant increase in glycolysis that does not increase glucose-6-phosphate concentrations. Hence, inhibition of fructose-1,6-bisphosphatase does not cause hepatic steatosis.

Another target is glycogen phosphorylase, which is inhibited by insulin and activated by glucagon and other counter-regulatory hormones. It catalyses glycogenolysis, resulting in increased hepatic glucose output. In animal models of diabetes or insulin resistance, hepatic activity of glycogen phosphorylase is increased; inhibitors that bind and inactivate this enzyme reduce glycaemia in animal models of diabetes. In a clinical study, CP-316819, an inhibitor of glycogen phosphorylase, prevented
hyperglycaemia after a glucagon challenge without affecting fasting glucose concentrations.79 Recently, GP921, which was administered for 28 days to Zucker diabetic fatty rats, raised hepatic concentrations of lipids with increased inflammation, fibrosis, haemorrhage, and necrosis; the necrosis seemed histologically similar to human glycogen storage disease.114

Drugs targeting the metabolic syndrome

GIP antagonists

GIP, like GLP-1, potentiates glucose-dependent insulin secretion,11 but unlike GLP-1, it promotes fat deposition in the adipocytes,110 does not inhibit glucagon secretion, and has little effect on food intake, satiety, gastric emptying, or bodyweight.111 Studies of animal models of diabetes have shown that blocking GIP action increases energy expenditure, and reduces fat deposition and lipotoxicity. This inhibition has a favourable effect on glucose homoeostasis, enhancing muscle glucose uptake, reducing hepatic glucose output, and improving β-cell function.112 Hence, GIP-receptor antagonists are potential treatments for patients with type 2 diabetes. Orally active insulin-releasing GIP agonists have also been reported.11

11β-hydroxysteroid-dehydrogenase-1 inhibitors

11β-hydroxysteroid dehydrogenase 1 predominantly converts low-activity cortisone to the more active cortisol.6 The enzyme is mainly expressed in the liver and adipose tissue, and expression can be induced in fibroblasts, muscles, and other tissues.6,32,33 11β-hydroxysteroid dehydrogenase 2 converts cortisol to cortisone. It is mainly expressed in tissues that also express the mineralocorticoid receptor (especially the kidneys), allowing aldosterone to bind to this receptor.4 The phenotypic and metabolic similarities between metabolic syndrome and Cushing’s syndrome have sparked interest in the therapeutic potential of inhibiting 11β-hydroxysteroid dehydrogenase 1 to reduce cortisol formation in the liver and adipose tissue.4 Knockout of 11β-hydroxysteroid dehydrogenase 1 in rodents reduces insulin resistance, prevents stress-induced obesity, improves glucose tolerance, and enhances insulin-secretory responsiveness.5,32

INCB13739 (200 mg) added on to metformin in patients with type 2 diabetes for 12 weeks reduced HbA1c by 0·6%, fasting plasma glucose concentrations by 1·33 mmol/L, and homoeostasis model assessment–insulin resistance by 24% compared with placebo.32 Reductions were also noted in concentrations of total cholesterol, LDL cholesterol, and triglycerides in patients with hyperlipidaemia, offering possible additional cardiovascular benefits.114

PPAR modulators

Activated peroxisome-proliferator-activated receptors (PPARs) form heterodimers with the retinoid-X receptor to modulate transcription of a wide variety of genes affecting nutrient metabolism and inflammation (figure 6).62 PPAR-γ agonists (eg, pioglitazone) improve insulin sensitivity and are an established treatment for type 2 diabetes,111 whereas PPAR-α agonists (fibrates) are for dyslipidaemia, particularly high triglyceride and low HDL concentrations. The effects of PPAR-γ and PPAR-α agonism are fully retained when used together. Thus, dual PPAR-α and PPAR-γ agonists (glitazars) were developed to achieve a combined effect on lipids and glucose.62,112 Development of previous dual agonists, such as tesaglitazar and muraglitazar, was stopped because of adverse events, but aleglitazar (a newer dual PPAR-α and PPAR-γ agonist) seems to have a better side-effect profile.112,113 Administration of aleglitazar (300–900 μg once a day for 6 weeks) to patients with type 2 diabetes resulted in dose-dependent improvements in fasting and postprandial glucose concentrations, reduced insulin resistance, and improved lipid variables.112 In a 16-week study, patients with type 2 diabetes were randomly assigned to aleglitazar (50–600 μg) or placebo, or to open-label pioglitazone 45 mg once a day.113 Aleglitazar reduced HbA1c in a dose-dependent manner (from –0·36%, 95% CI 0 to –0·70, p=0·048, with 50 μg to –1·35%, –0·99 to –1·70, p<0·0001, with 600 μg).113 The typical side-effects of PPAR-γ agonism, oedema and weight gain, were less severe with doses that were smaller than 300 μg aleglitazar than with pioglitazone.111 The effects of aleglitazar on the incidence of cardiovascular disease and mortality in patients with type 2 diabetes after a recent acute coronary syndrome are being assessed in a phase 3 trial (ALECARDIO).114

Drugs with unknown mechanisms

Dopamine D2-receptor agonists

Bromocriptine is an ergot alkaloid dopamine-D2-receptor agonist that has been available since 1978 to treat patients with prolactinomas and Parkinson’s disease.115 Although bromocriptine quick release has only been licensed since 2010 by the US Food and Drug Administration (FDA) for the treatment of type 2 diabetes as an adjunct to lifestyle changes,116 its effects on glycaemic variables have been noted since 1980.116 Bromocriptine produces its effects without increasing insulin concentrations, possibly by altering the activity of hypothalamic neurons to reduce hepatic gluconeogenesis through a vagally mediated route.116,117 In a randomised trial of 3095 patients, bromocriptine quick release (as monotherapy or in combination with two blood-glucose-lowering drugs, including insulin) reduced the risk of cardiovascular disease compared with placebo (hazard ratio 0·60, 95% CI 0·35–0·96) by 52 weeks.118 Bromocriptine is not licensed in Europe for the treatment of type 2 diabetes.

Bile acid sequestrants

Bile acid sequestrants are well established for the treatment of dyslipidaemia, and reduce the risk of
cardiovascular disease. They also reduce glucose concentrations in patients with type 2 diabetes. The mechanism of action is not known, but is possibly mediated by activation of liver farnesoid receptors. In 2009, the FDA licensed colesevelam to improve glycaemic control in patients with type 2 diabetes as an adjunct to lifestyle changes. Colesevelam reduced HbA1c concentrations by 0.50–0.54% when used in combination with metformin, sulphonylureas, or insulin, without increasing the risk of hypoglycaemia. Despite its favourable effect on the concentrations of LDL and HDL cholesterol, colesevelam increased concentrations of triglycerides by 11–22%. Colesevelam is not licensed in Europe for the treatment of type 2 diabetes.

Metabolic surgery

In 1995, Pories and colleagues described the outcomes of 608 patients who underwent gastric bypass over 14 years and noted that weight control was durable. 83% (121 of 146) of patients with type 2 diabetes maintained normal concentrations of HbA1c and plasma glucose. The gastric bypass also corrected or improved a wide range of obesity-related comorbidities such as hypertension, sleep apnoea, cardiopulmonary failure, arthritis, and infertility. The results of subsequent trials provide confirmation that metabolic surgery can produce sustainable weight loss, improve or resolve obesity-related complications, and reduce mortality. The benefits of bariatric surgery seem to exceed those attributable entirely to weight loss, hence the term metabolic surgery is favoured rather than bariatric surgery.

The several types of metabolic surgery include gastropasty, laparoscopic adjustable gastric banding, sleeve gastrectomy, gastric bypass, and bilipancreatic diversion. The results of a meta-analysis of 621 studies with 135246 patients showed that overall 78.1% of patients with diabetes had resolution, and an additional 8.5% showed improved glycaemic control, with the greatest weight loss and resolution of diabetes in patients who underwent bilipancreatic diversion, followed by gastric bypass, and then laparoscopic adjustable gastric banding. Thus the question of whether metabolic surgery could be used as a primary mode of treatment for type 2 diabetes was asked. In a randomised controlled trial, rates of remission of type 2 diabetes (defined as fasting glucose ≤7.0 mmol/L and HbA1c <6.2%) without pharmacological treatment based on the diabetologist’s discretion; 73% vs 13%, respectively).

Rapid remission of type 2 diabetes after gastric bypass and bilipancreatic diversion is independent of the amount of weight loss. The mechanisms resulting in weight loss and diabetes remission after surgery are multifactorial, but gut hormones might play an important part. Gastric bypass surgery increases postprandial GLP-1 and peptide YY concentrations, and reduces basal ghrelin concentrations; these changes lead to weight loss and improve β-cell function. In studies of animals, gastric bypass prevented the reduction in energy expenditure that is usually noted with medical weight loss. Moreover, diet-induced thermogenesis increased compared with bodyweight-matched controls. A change in taste perception after gastric bypass could also contribute to sustained weight loss and resolution of type 2 diabetes. The number of centres offering metabolic surgery has increased by more than ten times over 8 years in the USA. Evidence suggests that surgery is effective in patients with type 2 diabetes even when they have a body-mass index of less than 35 kg/m², and newer types of metabolic surgery, such as ileal interposition and duodenal-jejunal bypass sleeve, are being developed.

Although the remission of type 2 diabetes after bariatric surgery can be impressive, the definition of remission has varied between studies and the true remission rates might be lower if consistently strict criteria are applied. With the exception of Dixon and colleagues’ study, surgery has not been compared with conventional
treatment in type 2 diabetes in randomised controlled trials. There is no evidence available that suggests that metabolic surgery confers long-term benefits on vascular outcomes in patients with type 2 diabetes. The rapid improvement in glycaemic status after surgery also has to be rationalised against evidence that a rapid and substantial fall in blood-glucose concentration can initially worsen microvascular complications before long-term benefits ensue. Although the risk is low, metabolic surgery is not without mortality, side-effects, and complications. Metabolic surgery seems to be a valuable treatment option for selected patients with type 2 diabetes, but further evidence is needed before it is accepted as a primary mode of treatment. Furthermore, understanding the effects of bariatric surgery will help the development of new targeted treatment for obesity.

Conclusions
Type 2 diabetes is a rapidly increasing epidemic, with a catastrophe of pending vascular complications. Established glucose-lowering treatments (eg, metformin, sulphonylureas, meglitinides, PPAR-γ agonists, α-glucosidase inhibitors, and insulin) and incretin-based treatments (GLP-1 analogues, DPP-4 inhibitors) provide choice, but whether the incretin-based treatments can prevent disease progression is not clear. Potential new treatment targets have been identified and new compounds are in development to reduce blood-glucose concentrations with minimum risk of hypoglycaemia and weight gain, while possibly preserving β-cell mass and increasing durability of efficacy. Additionally, some newer treatments offer the opportunity of once-weekly dosing, which might have a positive effect on patient satisfaction, quality of life, and compliance. Combination of such new treatments will target different aspects of the multifactorial nature of type 2 diabetes. Nonetheless, long-term safety data are lacking for the newer treatments. Hence, the choice of treatment should be individualised and based on the risk-benefit balance, taking into account the potential for hypoglycaemia, and the weight and HbA1c concentration targets that need to be achieved for a particular patient. Despite all these new treatments, metformin is likely to remain a well established first-line pharmacological treatment for patients with type 2 diabetes who are over-weight because of its efficacy, long-term safety, and cardioprotective properties. Metabolic surgery is emerging as an interesting treatment option for patients with type 2 diabetes, but detailed investigation is awaited.

Contributors
AAT did the initial literature review after discussion and drawing up an outline with all the authors. He subsequently wrote the first draft and CJR, SDP, and AHB provided critical review and redrafting of the report, and helped with further literature review.

Conflicts of interest
AAT is a research training fellow supported by the National Institute for Health Research. The views expressed in this report are those of the author(s) and not necessarily those of the National Health Service, National Institute for Health Research, or the Department of Health. AAT has also won research grants from Sanofi-Aventis and Novo Nordisk UK Research Foundation. CJR has attended advisory board meetings of Bristol-Myers Squibb and AstraZeneca; undertaken ad-hoc consultancy for Bristol-Myers Squibb, AstraZeneca, Merck Sharp & Dohme, Novo Nordisk, GlaxoSmithKline, and Takeda; received research grants from AstraZeneca and Sanofi-Aventis; delivered continuing medical educational programmes sponsored by Bristol-Myers Squibb, AstraZeneca, GlaxoSmithKline, Merck Serono, and Merck Sharp & Dohme; and received travel or accommodation reimbursement from GlaxoSmithKline and Bristol-Myers Squibb. SDP has received honoraria for lectures and advisory work and research funding from Merck Sharp & Dohme, Novartis, GlaxoSmithKline, Bristol-Myers Squibb, AstraZeneca, Eli Lilly, Novo Nordisk, Roche, and Sanofi-Aventis. AHB has received honoraria for lectures and advisory work, and research funding from Servier, Merck Sharp & Dohme, Novartis, Takeda, GlaxoSmithKline, Bristol-Myers Squibb, AstraZeneca, Eli Lilly, Novo Nordisk, Roche, Roehringer-Ingelheim, and Sanofi-Aventis.

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