New therapies in the management of type 2 diabetes mellitus

New therapies for type 2 diabetes are many and varied in their approach, with several recent advances now questioned because of an adverse longer-term side-effect profile. This review describes some of the major recent and prospective developments.

Traditional therapies for type 2 diabetes mellitus have concentrated on correcting pancreatic β-cell failure and/or insulin resistance. Despite the many available therapies using a variety of mechanisms of action, type 2 diabetes remains a progressive disease that has a significant impact on patient morbidity and mortality. New approaches to the control of blood glucose are required that are cognisant of the metabolic comorbities of weight gain, hypertension, dyslipidaemia and the progression of diabetes through further reduction in β-cell mass. This article reviews several new agents that may offer novel means of restoring normoglycaemia and maintaining a metabolic balance in patients with type 2 diabetes. Starting with metabolic (bariatric) surgery, therapies are presented in order of their stage of development.

Metabolic (and/or bariatric) surgery or intervention

One approach to treatment not involving pharmacological intervention involves bariatric surgery to restrict calorie intake. Bariatric surgical procedures fall into three broad categories: 'restriction', 'malabsorption' and 'combination' procedures. Restrictive procedures involve reducing the size of the stomach, resulting in early satiety and a reduction in calorie intake. Current restrictive techniques use sleeve gastrectomy, vertical banded gastroplasty and laparoscopic adjustable gastric banding.

Techniques to induce malabsorption use procedures to effectively reduce the functional length of the small intestine. Combination procedures have restrictive and malabsorptive properties and include 'Roux-en-Y' and biliopancreatic diversion procedures.

In the UK, around 86% of diabetic patients are overweight, 52% are obese and 8% are morbidly obese (Daousi et al, 2006). In the context of these figures, even a modest 5% reduction in weight is associated with improved insulin efficacy and less hyperglycaemia. In addition to improved diabetic control, bariatric surgery also improves hypertension, sleep apnoea, dyslipidaemia, wellbeing and usually weight loss (Polymeris, 2012). A meta-analysis of 103 studies, reporting on the remission of clinical or laboratory manifestations of diabetes, revealed that 78.1% of 135 000 patients demonstrated evidence of remission following metabolic surgery (Buchwald et al, 2009). The National Institute for Health and Clinical Excellence (2006) guidance recommends that bariatric surgery be considered for obese patients (body mass index of between 30 and 35 kg/m^2) with type 2 diabetes not achieving treatment targets having tried all non-surgical therapies.

To date, only one randomized controlled trial has prospectively evaluated bariatric surgery as a treatment for type 2 diabetes. Remission of diabetes was significantly higher in those who had undergone surgery (73%), comprising adjustable laparoscopic gastric banding, as compared with patients receiving conventional therapy (13%) with a particular emphasis on weight loss and exercise (Dixon et al, 2008). Aside from the benefits of metabolic surgery it appears cost effective and in some studies has been shown to be cost-saving because of the lifetime costs of type 2 diabetes ($US305 000 if diagnosed at the age of 30 years) (Dixon et al, 2011). On the down side, there is a high initial cost outlay, estimated at around £14 000 in the UK.

Surgery carries a mortality risk which is usually less than 1% and predominantly caused by sepsis, thromboembolic events or anastomotic leaks. Longer term issues include ulcers, gastritis, erosions, fistulae, adhesions, bowel obstruction and hernias. Patients are also liable to nutrient deficiencies, that include iron, folic acid, vitamins B_{12}, C and D, calcium and other vital elements. Without chronic nutrient replacement, pathologies include neuropathies, Wernicke's encephalopathy, anaemia, coagulopathy, osteoporosis, cardiomyopathy and various dermatological pathologies (Polymeris, 2012). Some patients also suffer from gastric dumping and can experience hypoglycaemia. Depression following bariatric surgery is well recognized and many patients will also require cosmetic surgery, particularly to remove excess skin. These complications have to be balanced against the benefits of

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potentially curing type 2 diabetes and reducing the risk from hypertension, atherosclerosis, hypertension, respiratory compromise, renal impairment and a number of neoplastic propensities.

Peroxisome proliferator-activated receptor agonists

Peroxisome proliferator-activated receptor (PPAR) agonists are frequently referred to as the 'glitazones'. They act on a group of nuclear receptors (α, δ and γ) that ultimately influence lipid metabolism and insulin sensitivity. Alpha (α) receptor activity lowers levels of plasma triglycerides and very low-density lipoprotein particles and increases levels of high-density lipoprotein cholesterol. Delta (δ) receptor agonism appears to change a 'fuel preference' from glucose to lipids and gamma (γ) receptor activity influences free fatty acid flux and reduces insulin resistance and blood glucose levels. Dual activity targets both insulin resistance (the inability of tissues to use insulin efficiently for the uptake of glucose), the secretion by adipocytes of insulin-sensitizing hormones, such as adiponectin, and key aspects of the dyslipidaemia that contribute to the high risk of cardiovascular disease in diabetes. Besides augmenting insulin sensitivity, dual PPAR agonists show evidence of attenuating inflammation and having benefits on vascular function and remodelling (Tenenbaum et al, 2005).

Currently pioglitazone (Actos), a γ-receptor agonist of the thiazolidinedione structure, is the only glitazone being marketed in the UK. When used as monotherapy, the effect on lowering glycosylated haemoglobin (HbA_{1c}) is comparable to that of established agents, with a dose-related effect of between 0.5 and 1.5%, and a low risk of hypoglycaemia (Fuchtenbusch et al, 2000). Pioglitazone can be used in combination with the biguanide metformin, sulphonylureas, a combination of both, or with insulin.

However, the risk of heart failure is increased with pioglitazone and it is also associated with a small increased risk of bladder cancer. Rosiglitazone (Avandia) was withdrawn in September 2010 because of evidence of increased cardiovascular events, particularly heart failure and myocardial infarction. An additional concern with this class of drug is possible weight increase, fluid retention leading to oedema and a potential for hepatotoxicity (Yoon et al, 2011). Citiglitazone was not marketed and troglitazone (Rezulin) was withdrawn from the American market in 2000 because of an increased incidence of drug-induced hepatitis. All drugs in this class can increase the risk of osteoporosis in post-menopausal women. Thiazolidinediones should not be used in patients with a history of, or potential for, heart failure. When prescribed, surveillance of liver enzymes in necessary. Their use should also be avoided in patients with a risk of bladder cancer or osteoporosis.

The balanced dual PPAR α/γ agonists aleglitazar, muraglitazar and tesaglitazar are novel agents currently under development. Aleglitazar, which reduces hyperglycaemia and results in falls in HbA_{1c}, demonstrates beneficial cardiovascular effects on high-density lipoprotein, low-density lipoprotein and triglycerides in the absence of overt PPAR-type adverse effects (Henry et al, 2009). Although aleglitazar appears to have a clinical development profile likely to achieve a clinical licence (Dzyakanchuk et al, 2010), the development of muraglitazar has been halted because of an increase in cardiovascular events (myocardial infarction, stroke, transient ischaemic attack and congestive heart failure) when compared to pioglitazone or placebo. Tesaglitazar was also withdrawn in the developmental phase as a result of concerns over an apparent rise in creatinine levels and an associated fall in glomerular filtration rate. There remains considerable anxiety over the development and use of agents influencing the PPARs, because the broader actions of these agents are not yet fully understood.

Dipeptidyl peptidase-4 (DPP-4) inhibitors

Dipeptidyl peptidase-4 (DPP-4) inhibitors are a class of orally active hypoglycaemics, also referred to as 'gliptins', which have a target mode of action similar to that of the type 1 glucagon-like peptide (GLP-1) analogues. These agents act through inhibition of the dipeptidyl peptidase 4 enzyme, which ordinarily inactivates the incretins GLP-1 and glucose-dependent insulinotropic peptide (GIP). The net effect is inhibition of glucagon release and increased insulin secretion with a resultant decrease in blood glucose.

Four drugs in this category are available for clinical use in the UK: sitagliptin (Januvia), vildagliptin (Eucras), saxagliptin (Onglyza) and linagliptin (Trajenta). Aside from gastrointestinal side effects the main concern within this class is a small risk of pancreatitis. They are described specifically and in greater detail in an accompanying article in this symposium (p. 192).

Analogues of glucagon-like peptide-1

GLP-1 and GIP are gut-derived hormones (incretins) that promote lower glucose levels through the combined stimulation of insulin production and suppression of glucagon. The plasma levels of both moieties rise rapidly after eating. By inhibiting gastric emptying, GLP-1 also induces satiety through central neurological feedback mechanisms. Activity of GLP-1 is promoted via the inhibition of DPP-4, an enzyme responsible for the degradation of incretins (Drucker and Nauck, 2006).

Briefly, exenatide (Byetta) and liraglutide (Victoza) are GLP-1 analogues with insulin secretagogue properties and gluco-regulatory effects. They are recommended for use as adjunctive therapy to improve glycaemic control in patients taking metformin, or a combination of metformin and a sulfonylurea. A potential advantage of these drugs is the benefit of associated weight loss and only a

limited risk of hypoglycaemia. Exenatide and liraglutide are administered by subcutaneous injection, daily or twice-daily respectively. More recently, a once-weekly modified release formulation of exenatide (Bydureon) has been approved for clinical use. An additional GLP-1 analogue, lixisenatide (Lyxumia), a once-daily injectable GLP-1 agonist, was granted marketing authorization for use in type 2 diabetes in 2013, both as monotherapy and in combination with metformin (Christensen et al, 2011). Concern is escalating regarding a risk of pancreatitis within this drug class. GLP-1 agonists are described in greater detail in an accompanying article in this symposium (p. 198).

Sodium glucose lithium co-transporter-2 inhibitors

At least two renal mechanisms are active in the regulation of blood glucose – gluconeogenesis and proximal tubule reabsorption. Renal gluconeogenesis serves to maintain levels of glycaemia through the synthesis of new glucose from precursors, including lactate, glycerol and amino acids. In contrast, glucose is reclaimed from the glomerular filtrate, predominantly through reabsorption by the type 2 sodium glucose lithium co-transporter in the proximal tubules of the nephrons (Bailey et al, 2010). Several orally active pharmaceuticals have been developed that inhibit this membrane transporter.

Most inhibitors cause a loss of around 50 g of glucose/day and effect modest reductions in HbA_{1c} of around 0.5–0.8% (Bailey et al, 2010). Inhibitors of the sodium glucose lithium co-transporter also work well in combination with current conventional antidiabetic therapies without promoting an increase in hypoglycaemic episodes (Hardman and Dubrey, 2011). Additional advantages include weight loss (around 2.5 kg over 6 months) and a modest reduction in blood pressure. Anticipated complications associated with this approach to glucose lowering include glycosuria that may be associated with an increased risk of urogenital bacterial and fungal infections. In addition, glycosuria might induce an osmotic diuresis resulting in polyuria and polydipsia.

Dapagliflozin reduces blood glucose levels in an insulin-independent manner and has an efficacy at 52 weeks comparable with that of the sulphonylurea glipizide, but with an associated reduction in weight and fewer reported episodes of hypoglycaemia. Dapaglifozin (Forxiga) was launched for clinical use in the UK in 2013, as an orally active monotherapy or as add-on therapy for type 2 diabetes. Dapaglifozin is not indicated for weight loss or in patients receiving loop diuretics. It is not indicated for concomitant use with pioglitazone and has not been studied with DPP-4 inhibitors or GLP-1 analogues. A possible increase in risk of hepatotoxicity and incidence of breast and bladder cancers resulted in an unfavourable review by the US Food and Drug Administration.

Similar acting molecules currently in the developmental phase include remogliflozin, sergliflozin and canagliflozin. An alternative approach to inactivation of this membrane transporter pump has been the development of antisense oligonucleotides that inhibit the expression of the sodium glucose lithium cotransporter (Hardman and Dubrey, 2011).

Bile acid sequestrant (colesevelam)

Bile acid sequestrants reduce lipids and also decrease glucose in patients with type 2 diabetes (Fonseca et al, 2010). Not licensed for diabetic therapy in Europe, the bile acid sequestrant colesevelam was licensed in the USA as an adjunct to glycaemic control in 2009. When administered twice or four times daily colesevelam in combination with insulin, a sulfonylurea or metformin produces falls in HbA_{1c} of 0.5–0.7% compared with placebo. The exact mechanism of action is unknown but may involve activation of hepatic farnesoid receptors, a bile acid sensor that influences gluconeogenic pathways in the liver and regulates glucocorticoid receptor expression. Their net effect is a reduction in endogenous glucose production, likely through actions on hepatic gluconeogenesis in the transition from the fasted to fed state. Colesevelam also increases levels of the incretin hormones GLP-1 and GIP, both of which influence glucose homeostasis (Handelsman, 2011).

Despite favourable cardiovascular effects on the profile of low and high density lipoprotein cholesterol, colesevelam can cause an increase in triglycerides of around 10–20% (Fonseca et al, 2010). Gastrointestinal side effects with bile acids are relatively common, with constipation predominating. Any risk of hypoglycaemia is low and their effect on weight appears to be neutral.

Amylin analogues

Amylin (islet amyloid polypeptide) is an islet of Langerhans beta cell neuroendocrine hormone, secreted in conjunction with insulin in response to meals. Its co-role in the regulation of post-prandial glucose regulation is through suppression of glucagon secretion and vagus-mediated regulation of gastric emptying.

Pramlintide has been developed as a soluble non-aggregating synthetic analogue of human amylin and was approved for use in type 2 diabetes in the United States in 2005. It has not yet been licensed in the UK. The importance of creating an aqueous form lies in the fact that amylin is highly insoluble, which in a fibrillary amyloid form is inherently toxic to beta cells (Adeghate and Kalasz, 2011). Pramlintide currently requires subcutaneous administration with meals and can be used in type 2 diabetes with insulin or with a combination of insulin, metformin and or a sulfonylurea. Pramlintide is also associated with modest weight reduction of around 1.35 kg over a period of 52 weeks of use. It exerts an additional satiety effect through actions on central hypothalamic receptors that are different from those stimulated

by GLP-1 incretins and may also allow a reduction in insulin dose. In a meta-analysis of five studies, pramlintide had only modest effects on HbA_{1c} with reductions of 0.3–0.62% (Ryan et al, 2005). Nausea is the most frequently reported adverse event, along with the disadvantage of requiring twice to three times daily subcutaneous injections.

Dopamine-2 receptor agonists

The ergot alkaloid dopamine receptor agonist, bromocriptine, is widely used for the treatment of hyperprolactinaemia and Parkinson's disease. In 2009, it was licenced for use in the United States for the treatment of type 2 diabetes, but at a 2–6-fold lower dose than for its neuroendocrine indications. Studies on seasonal metabolic changes in migrating birds, and hibernating vertebrates indicated that their temporary induction of an insulin resistant state mimics the permanent change to insulin resistance seen in human diabetes. The mechanism is considered to be through an action to reset an abnormally elevated hypothalamic drive, for increased plasma glucose, free fatty acids and triglycerides, in insulin-resistant patients.

Administration of a quick release formulation of bromocriptine early in the morning resets dopamine and serotonin levels, improving insulin resistance and other metabolic abnormalities. More specifically, low hypothalamic dopamine levels appear augmented and there is inhibition of excessive CNS sympathetic tone, resulting in a reduction in post-prandial glucose levels (Shivaprasad and Kalra, 2011). Either alone, or in combination, quick release formulations of bromocriptine can reduce HbA_{1c} by 0.6–1.2% (Holt et al, 2010).

11β–hydroxysteroid dehydrogenase inhibitors

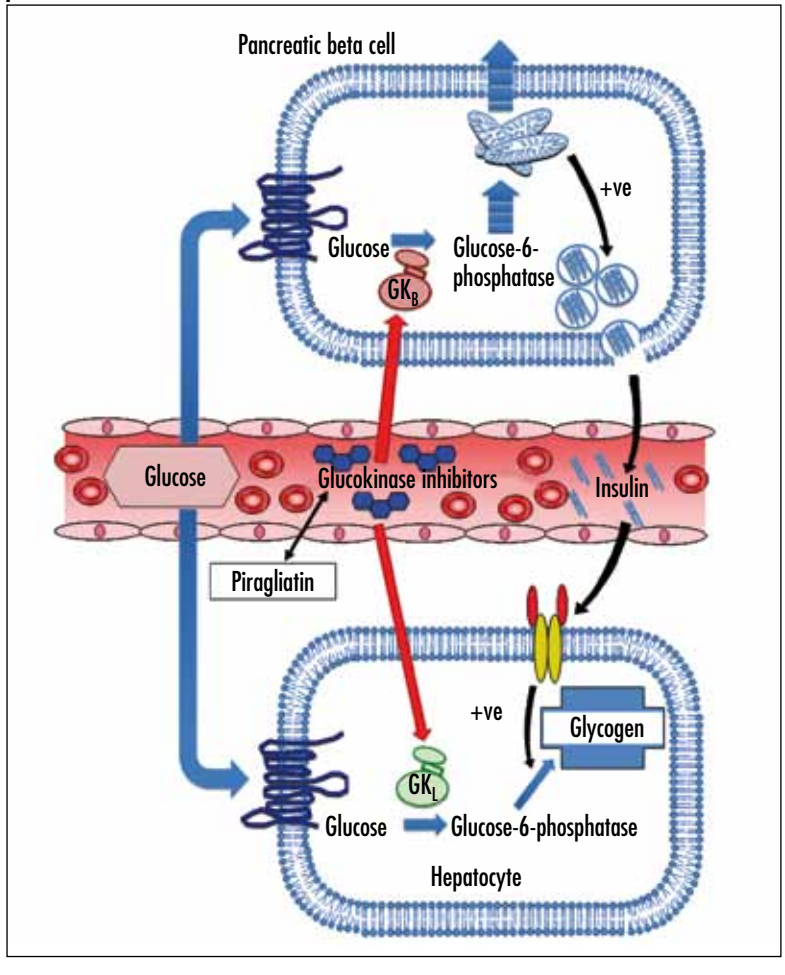
The enzyme 11β-hydroxysteroid dehydrogenase (11β-HSD1) converts inactive glucocorticoids (cortisone) to active metabolites within the liver and adipose tissue. Increased activity of 11β-HSD1 and/or an excess of cortisol is associated with increased risk of obesity, dyslipidaemia and insulin resistance (Wamil and Seckl, 2007). A potential therapeutic target in type 2 diabetes would be to lower 11β-HSD1, thus lowering intracellular cortisol levels, without affecting circulating glucocorticoid concentrations or their response to stress. Several pharmaceutical companies are pursuing small-molecule 11β-HSD1 inhibitors as possible treatments for type 2 diabetes, as well as for the metabolic syndrome and as inhibitors of age-related cognitive decline. One such compound is carbenoxolone, a constituent of liquorice, which has inhibitory effects on 11β-HSD1. Compared to placebo, carbenoxolone reduces the rate of glucose production during episodes of hyperglucagonaemia in diabetic patients (1.9±0.2 mg/kg/min *vs* 1.53±0.3 mg/kg/min; $P<0.05$) (Andrews et al, 2003). However, a potential complication of this approach is the simultaneous inhibition of the enzyme 11β-HSD2 in the distal nephron, which can cause an elevation of cortisol and mineralocorticoid, exacerbating hypertension and hypokalaemia.

Glucokinase activators

Glucokinase, an enzyme responsible for the phosphorylation of glucose to glucose-6-phosphate, plays a pivotal role in the regulation of the synthesis of glycogen from blood glucose (*Figure 1*). It also has a glucose sensor role in pancreatic β-cells and, being the rate-controlling enzyme for hepatic glucose clearance and glycogen synthesis, has a significant impact on glucose homeostasis. Activators of glucokinase stimulate insulin biosynthesis and secretion, so augmenting glucose metabolism and use in the liver (Pal, 2009).

Furthermore, mutations in the gene encoding glucokinase activity can cause both hyperglycaemia and hypoglycaemia. Several heterozygous and homozygous inactivating mutations of glucokinase have been identified as responsible for differing phenotypes of diabetes in children (Gloyn, 2003; Pal, 2009). As such, the pivotal

Figure 1. Hepatic glucose metabolism and the pancreatic beta cell sensor role of the enzyme glucokinase (GK). Glucokinase activators (piragliatin) accelerate glucokinase activity to promote glycogen synthesis in hepatocytes and insulin secretion from pancreatic beta cells.



role of glucokinase was identified as a prime drug target for the development of antidiabetic medicines.

Currently, no compound has been approved for clinical use. At a developmental phase, piragliatin is the first glucokinase activator candidate (*Figure 1*). It has an acute glucose-lowering action in patients with mild type 2 diabetes and appears to cause a dose-dependent effect on β-cell function (Bonadonna et al, 2010). The potential for hypoglycaemia and metabolic accumulation of 'off-products', including lipid-induced non-alcoholic steatohepatitis and glycogen storage issues, requires caution.

Several other enzymes in the gluconeogenesis cascade are also being explored as possible drug targets in the treatment of type 2 diabetes (Tahrani et al, 2011).

Pancreatic G-protein receptor agonists

Pancreatic β-cell dysfunction is the characteristic feature of the progression of type 2 diabetes and there is an increasing need for agents to preserve or improve β-cell functionality. Several pancreatic G-protein-coupled receptors, including GPR-40, GPR-119 and GPR-120, are reported to play a role through glucose-dependent insulin secretion (Chu et al, 2007). Free fatty acids have also been shown to be natural ligands for a number of these receptors (Rayasam et al, 2007), enhancing insulin secretion through increased intracellular calcium signalling.

Agonists to these receptors increase β-cell concentrations of cyclic adenosine monophosphate, modulating glucose homeostasis through enhanced glucose-induced insulin secretion. Responding to the presence of food in the gut, intestinal K-cell- and L-cell-based G-protein-coupled receptors signal the pancreas to increase insulin release, acting through the incretins GLP-1 and GIP, serving to restore euglycaemia after eating.

G-protein receptor agonists have thus been considered reasonable candidates as potential treatments in type 2 diabetes. They would also result in satiety, thus helping prevent an increase in body weight (Wilding, 2012). Several compounds are in a developmental phase.

Products in an experimental and/or unproven stage of development

Despite the broad nature of various novel treatments being investigated and described above there remain several mechanisms yet to be exploited.

For example, otelixizumab, an anti-CD3 monoclonal antibody, stimulates C-peptide levels and reduces insulin requirement in type 1 diabetes (Miller and St Onge, 2011). Similarly, data from studies with teplizumab are also encouraging (Masharani and Becker, 2010).

Potent nuclear PPARγ inhibitors appear to block the action of cyclin-dependent kinase 5, believed to be one of the mechanisms behind the antidiabetic activity of thiazolidenediones (Choi et al, 2011).

The central histamine H3 receptor ligand, proxyfan, significantly improves glucose excursion by increasing plasma insulin levels through a glucose-independent mechanism (Henry et al, 2011).

The compound 5,8-diacetyloxy-2,3-dichloro-1,4-naphtho-quinone selectively provokes insulin receptor activation by binding directly to the receptor kinase domain, triggering its kinase activity. This elevates adipocyte glucose uptake resulting in an overall hypoglycaemic effect (He et al, 2011).

Promising antidiabetic and antioxidant effects have been observed with β-sitosterol, a plant sterol currently used for its cholesterol-lowering properties (Gupta et al, 2011). The mechanism is through β-sitosterol being capable of stimulating insulin release and through inhibition of glucose-6-phosphatase. An additional inhibitory role on alpha-glucosidase (an enzyme in the brush border of the small intestine) reduces the rate of digestion of carbohydrate, a mechanism already used by the licensed antidiabetic product acarbose (Glucobay).

Finally, and despite considerable scepticism from the medical profession, a large number of herbs and supplements are purported to aid glycaemic control in type 2 diabetes. Most are clinically unproven. Nevertheless, the supplements market is estimated to represent sales of around £670 million per year in the UK (NHS Choices, 2011), with many products purchased by patients with diabetes. Readers are referred to a review by Yeh et al (2003).

Hypoglycaemia in type 2 diabetes

Hypoglycaemia in type 2 diabetes is predominantly an issue for patients who use insulin or secretagogues, such as sulphonylureas and the glinides (nateglinide (Starlix) and repaglinide (Prandin)). The latter largely cause hypoglycaemia because of their rapid short duration of action in the post-prandial phase.

More recent therapeutic developments of novel agents suggest a considerably lower risk of hypoglycaemia. Bariatric surgery does offer a risk of hypoglycaemia and caution is still important when combinations of hypoglycaemics are prescribed. National guidelines suggest that when there is concern about hypoglycaemia, add-on therapy to metformin could include a DPP-4 inhibitor or pioglitazone, in preference to a sulphonylurea (National Collaborating Centre for Chronic Conditions, 2008).

Conclusions

Current guidance on diabetes management places focus on individualizing therapy with the emphasis on an alliance between patient and prescriber. Newer therapies follow our increasing understanding of diabetes and provide a greater range of approaches to a bespoke service to lower glucose and address concomitant medical conditions. **BJHM**

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KEY POINTS

- New therapies should ideally address the complications of type 2 diabetes.
- Hypoglycaemia appears less of an issue with the newer therapies.
- In the obese diabetic patient, bariatric (metabolic) surgery looks a likely candidate to compete with the 'front runner' that is currently metformin.
- Ongoing vigilance for serious side effects is important with several of the new developments.