# Type 2 diabetes

*Sudesna Chatterjee, Kamlesh Khunti, Melanie J Davies*

**415 million people live with diabetes worldwide, and an estimated 193 million people have undiagnosed diabetes. Type 2 diabetes accounts for more than 90% of patients with diabetes and leads to microvascular and macrovascular complications that cause profound psychological and physical distress to both patients and carers and put a huge burden on health-care systems. Despite increasing knowledge regarding risk factors for type 2 diabetes and evidence for successful prevention programmes, the incidence and prevalence of the disease continues to rise globally. Early detection through screening programmes and the availability of safe and effective therapies reduces morbidity and mortality by preventing or delaying complications. Increased understanding of specific diabetes phenotypes and genotypes might result in more specific and tailored management of patients with type 2 diabetes, as has been shown in patients with maturity onset diabetes of the young. In this Seminar, we describe recent developments in the diagnosis and management of type 2 diabetes, existing controversies, and future directions of care.**

Published **Online** February 9, 2017 http://dx.doi.org/10.1016/S0140-6736(17)30058-2

**This online publication has been corrected. The corrected version first appeared at thelancet.com on February 21, 2017.**

**Leicester Diabetes Centre, Leicester General Hospital** (S Chatterjee MD, Prof K Khunti PhD, Prof M J Davies MD)**; and Diabetes Research Centre, College of Medicine, Biological Sciences and Psychology** (S Chatterjee, Prof K Khunti, Prof M J Davies)**, University of Leicester, Leicester, UK**

Correspondence to: Prof Melanie J Davies, Leicester Diabetes Centre, Leicester General Hospital, University of Leicester, Leicester LE5 4PW, UK **melanie.davies@uhl-tr.nhs.uk**

## Introduction

Type 2 diabetes is characterised by relative insulin deficiency caused by pancreatic β-cell dysfunction and insulin resistance in target organs. Between 1980 and 2004, the global rise in obesity, sedentary lifestyles, and an ageing population have quadrupled the incidence and prevalence of type 2 diabetes.[1] As the sixth leading cause of disability in 2015,[2] diabetes places considerable socioeconomic pressures on the individual and overwhelming costs to global health economies, estimated at US$825 billion.[3] Cardiovascular disease is the greatest cause of morbidity and mortality associated with type 2 diabetes[4] and needs intensive management of glucose and lipid concentrations as well as blood pressure to minimise risk of complications and disease progression.[5] The benefits of intensive glucose management on microvascular complications, such as retinopathy, nephropathy, and neuropathy, have been shown in several large randomised controlled trials, including the United Kingdom Prospective Diabetes Study (UKPDS),[6] Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation (ADVANCE),[7] and Veterans Association Diabetes Trial (VADT).[8] Evidence that intensive glucose reduction reduces macrovascular outcomes such as cardiovascular disease and stroke is less well established.[9–12] Hypoglycaemia is a major barrier to optimising glucose-lowering therapy, and results of an observational study[13] showed that severe hypoglycaemia was associated with increased mortality at 12 months even in people not receiving insulin.

Quality outcomes for patients are optimised by early detection of type 2 diabetes through screening and intensive patient-centred management. Disease management should be combined with structured education and self-management programmes and psychological support based on the most recent guidelines and supported by a multidisciplinary team (figure 1).[14] As the pathophysiology and underlying mechanisms of diabetes become increasingly understood, treatment can be individualised and targeted appropriately (precision medicine).

Type 2 diabetes is especially challenging in patients younger than 25 years for whom complex phenotypes might necessitate many decades of intensive management to minimise development and progression of microvascular and macrovascular complications. Intensive management of type 2 diabetes in elderly patients (65 years of age or older) must be balanced against management of other comorbidities, cognitive impairment, and hypoglycaemia risk. In this Seminar, we review the existing management strategies, discuss new developments in diagnosis, treatment, and cardiovascular benefits, highlight controversies and uncertainties, and address outstanding research questions.

## Epidemiology and pathophysiology

The global rising tide of obesity, physical inactivity, and energy-dense diets has resulted in an unprecedented increase in the number of patients with type 2 diabetes. In 2015, 415 million people were estimated to have diabetes, more than 90% of whom had type 2 diabetes, with a projected increase to 642 million by 2040.[15] Incidence and prevalence of type 2 diabetes vary according to geographical region, with more than 80% of patients living in low-to-middle-income countries, but the overall trend is an increase in diabetes prevalence in every country since 1980.[1] An additional 318 million people have a preclinical state of impaired glucose regulation,[15] but intensive lifestyle modification,

### Search strategy and selection criteria

We searched Cochrane Library, MEDLINE, and Embase for manuscripts published between Jan 1, 2000, and Dec 31, 2016, using the terms "type 2 diabetes" and "type 2 diabetes mellitus". We largely selected articles published in the past 5 years but did not exclude commonly referenced and highly regarded, older articles. We also searched the reference lists of articles identified by this search strategy and selected those we judged relevant. Reviews are cited to provide readers with more details and more references than this Seminar could accommodate.

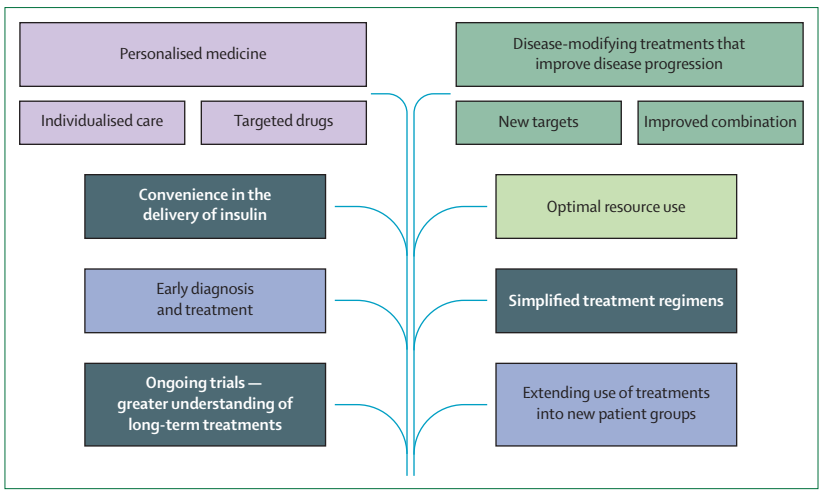


*Figure 1*: **Optimisation of existing strategies for treating type 2 diabetes**

pharmacotherapy, or both can reverse or delay development of type 2 diabetes.[16]

Compared with people who do not have diabetes, patients with type 2 diabetes have a 15% increased risk of all-cause mortality, which is twice as high in young people, and in those who are younger than 55 years of age and have a concentration of glycated haemoglobin ($HbA_{1c}$) of 6·9% (55 mmol/mol) or less, it is twice as high compared with people without diabetes.[17] In a meta-analysis[18] of 698782 people, diabetes was associated with increased risk of coronary heart disease (hazard ratio [HR] 2·00; 95% CI 1·83–2·19), ischaemic stroke (HR 2·27; 1·95–2·65), and other deaths related to vascular disease (HR 1·73; 1·51–1·98). At diagnosis, which can be delayed by up to 12 years, patients with type 2 diabetes can present with established complications such as retinopathy.[19]

Epidemiology of type 2 diabetes is affected by genetic and environmental factors. Genetic factors exert their effect following exposure to an obesogenic environment characterised by sedentary behaviour and excessive sugar and fat consumption. Genome-wide association studies have led to the identification of common variants of glycaemic genetic traits for type 2 diabetes, but these only account for 10% of total trait variance, suggesting that rare variants are important.[20] Transcriptomics, involving whole-genome analysis of gene expression products (mRNA), has shown large numbers of gene associations with type 2 diabetes and obesity by correlating genotype with phenotype.[21] Increased genetic burden, calculated by additive genetic risk scores, is associated with high all-cause mortality risk, especially in non-Hispanic white people who are obese and have type 2 diabetes compared with other ethnic groups, highlighting the importance of environmental and lifestyle modification in the reduction of mortality.[22] Type 1 diabetes genetic risk scores, consisting of nine single nucleotide polymorphisms, have been developed to distinguish between type 1 diabetes and type 2 diabetes in adults aged 20–40 years, as diagnosis can be challenging when based solely on clinical features and autoantibody markers.[23]

An aggressive phenotype has been identified in people (15–30 years of age) diagnosed with young-onset type 2 diabetes, which appears to increase risk of cardiovascular death, macrovascular complications, and neuropathy scores compared with young people with type 1 diabetes diagnosed at a similar age and with equivalent diabetes duration.[24] People of different ethnic origin may have different specific phenotypes that increase predisposition to clusters of cardiovascular disease risk factors, including hypertension, insulin resistance, and dyslipidaemia. In a pooled analysis[25] of three multiethnic studies of more than 2000 adults with diabetes but not cardiovascular disease, optimal management of coexisting risk factors was found to reduce the risk of cardiovascular disease (unadjusted HR 0·46; 95% CI 0·30–0·69).

Type 2 diabetes is characterised by increased hyperinsulinaemia, insulin resistance, and pancreatic β-cell failure, with up to 50% cell loss at diagnosis.[9] β-cell loss occurs more rapidly in young patients (10–17 years of age), which might explain earlier treatment failure in patients who are diagnosed at a young age.[26] The organs involved in type 2 diabetes development include the pancreas (β cells and α cells), liver, skeletal muscle, kidneys, brain, small intestine, and adipose tissue.[27] The incretin effect, changes in the colon and microbiome, immune dysregulation, and inflammation have emerged as important pathophysiological factors[28] and are either established or have the potential to be therapeutic targets (table 1).

Other mechanisms for development of microvascular and macrovascular complications caused by hyperglycaemia are endothelial dysfunction, advanced glycation end-product formation, hypercoagulability, increased platelet reactivity, and sodium-glucose co-transporter-2 (SGLT-2) hyperexpression, all of which are therapeutic targets for modulating disease. For example, fibrinolysis and platelet aggregation are improved by metformin therapy,[30] and results of small experimental studies[31,32] have shown that glucagon-like peptide-1 (GLP-1) receptor agonists have protective effects on the endothelium, which may reverse so-called endothelial resistance and dysfunction and reduce inflammation.

Possibly the most effective therapeutic strategies for patients with type 2 diabetes will target both aspects of the complex interaction between the genotype and phenotype, although more research is needed in these areas to optimise and personalise treatments.

## Prevention of type 2 diabetes

Prevention of type 2 diabetes will bring substantial benefits to the patient, who otherwise could enter many decades of drug therapy and complications. Considerable evidence suggest that type 2 diabetes can be prevented by managing obesity and impaired glucose regulation with diet and exercise interventions and, to a lesser extent, pharmacological therapy with metformin and thiazolidinediones.[33,34]

 Published online February 9, 2017 http://dx.doi.org/10.1016/S0140-6736(17)30058-2

Findings by the US Diabetes Prevention Program (DPP)[16] showed that intensive lifestyle modification (physical activity and low fat diet aimed at weight reduction) reduced the risk of type 2 diabetes in 3234 adults who were either overweight or obese and had impaired glucose tolerance (mean follow-up time 2·8 years; relative risk reduction [RRR] 58%) and was more effective than metformin (RRR 31%) or placebo. This benefit was found in all patient populations irrespective of gender, ethnic origin, or genetic predisposition. Metformin was most effective in women with a medical history of gestational diabetes, whereas lifestyle intervention conferred the greatest benefit in patients older than 60 years. At the 15-year follow-up of DPP (DPPOS),[35] diabetes incidence was found to be reduced by 27% in people who received lifestyle intervention and by 18% in patients treated with metformin. The findings in DPPOS also revealed that normalisation of glucose tolerance reduced the Framingham cardiovascular disease risk score by 2·7% ($p<0·01$) after 10 years in individuals with pre-diabetes.[36]

Despite these positive findings, subsequent meta-analyses of lifestyle interventions have highlighted difficulties in replicating trial results in the real world,[37,38] mainly because of low participation rates, poor coverage through medical insurance schemes, and concerns with cost-effectiveness. However, national policies, such as the UK Diabetes Prevention Programme, are now being delivered to tackle this epidemic cost-effectively.[39]

## Screening and early detection of type 2 diabetes

Individuals who are at risk of type 2 diabetes must be screened to minimise development and progression of microvascular and macrovascular complications. Universal screening is not advocated because results of large randomised controlled trials[40,41] show that intensive management of screened patients does not improve cardiovascular disease risk or other outcomes. Opportunistic screening using validated risk scores, ideally tailored to different countries and subpopulations,[42] is recommended because this approach can identify patients at high risk who can have the diagnosis confirmed by measurements of fasting plasma glucose or $HbA_{1c}$ concentrations or tests for oral glucose tolerance. $HbA_{1c}$ concentration is a stable diagnostic measure that does not require fasting and is equivalent to fasting plasma glucose with respect to predicting the development of retinopathy in cross-sectional associations and is therefore a robust diagnostic measure for type 2 diabetes.[43] However, $HbA_{1c}$ concentration should not be used for diagnosis of type 2 diabetes in children (<18 years old), pregnant women, or people with disorders in red blood cell turnover (eg, anaemia). $HbA_{1c}$ test standardisation is essential, especially in developing countries, and discordance of fasting plasma glucose and $HbA_{1c}$ concentrations is recognised between ethnic groups and with increased age.[44]

Differentiation between type 1 diabetes, type 2 diabetes, and monogenic diabetes or maturity onset diabetes of the young (MODY) can be challenging because type 2 diabetes is increasingly being diagnosed at young ages. The phenotype in people younger than 25 years might not allow a clear distinction between various underlying pathophysiologies. The concentration of C-peptide, a surrogate marker for circulating plasma insulin, is a useful measure because C-peptide is usually undetectable up to 3 years after diagnosis of type 1 diabetes. Diagnosis of MODY requires a high level of clinical suspicion, especially in slim-built patients younger than 25 years who have relatively mild disease and a strong family history of diabetes. Accurate MODY diagnosis also requires genetic tests for mutations of commonly affected genes, such as *HNF-1α*, *HNF-4α*, and *GCK*.[45] Latent autoimmune diabetes in the adult could be mistaken for type 2 diabetes although it is most similar in presentation and natural history to type 1 diabetes and characterised by a short duration of onset of clinical symptoms and rapid progression (about 6 months) to insulin therapy. Classification of diabetes is often challenging, and new β-cell-centric treatment frameworks are recommended.[28]

| | Pathophysiological defect | Glucose-lowering therapy | |
|---|---|---|---|
| | | Existing | Future (phase 1–3 clinical trials) |
| Pancreatic β cell | Loss of cell mass and function; impaired insulin secretion | Sulfonylureas; meglitinides | Imeglimin |
| Pancreatic α cell | Dysregulated glucagon secretion; increased glucagon concentration | GLP-1 receptor agonist | Glucagon-receptor antagonists |
| Incretin | Diminished incretin response | GLP-1 receptor agonist; DPP-IV inhibitors | Oral GLP-1 receptor agonist; once-weekly DPP-IV inhibitors |
| Inflammation | Immune dysregulation | GLP-1 receptor agonist; DPP-IV inhibitors | Immune modulators; anti-inflammatory agents |
| Liver | Increased hepatic glucose output | Metformin; pioglitazone | Glucagon-receptor antagonists |
| Muscle | Reduced peripheral glucose uptake; insulin resistance | Metformin; pioglitazone | Selective PPAR modulators |
| Adipose tissue | Reduced peripheral glucose uptake; insulin resistance | Metformin; pioglitazone | Selective PPAR modulators; FGF21 analogues; fatty acid receptor agonists |
| Kidney | Increased glucose reabsorption caused by upregulation of SGLT-2 receptors | SGLT-2 inhibitors | Combined SGLT-1/-2 inhibitors |
| Brain | Increased appetite; lack of satiety | GLP-1 receptor agonist | GLP-1-glucagon-gastric inhibitory peptide dual or triple agonists |
| Stomach or intestine | Increased rate of glucose absorption | GLP-1 receptor agonist; DPP-IV inhibitors; alpha-glucosidase inhibitors; pramlintide | SGLT-1 inhibitors |
| Colon (microbiome) | Abnormal gut microbiota | Metformin; GLP-1 receptor agonist; DPP-IV inhibitors | Probiotics |

GLP-1=glucagon-like peptide-1; DPP-IV inhibitors=dipeptidyl peptidase-IV inhibitors; GIP=gastric inhibitory peptide; SGLT-1/SGLT-2 inhibitors=sodium glucose co-transporter-1/ sodium glucose co-transporter-2 inhibitors; PPAR=peroxisome proliferator-activated receptor. FGF21=fibroblast growth factor 21.

***Table 1*: Existing and future glucose-lowering therapeutic options by organ or organ system[29]**

| | Patient characteristics | Baseline complications | Intervention | Outcomes in intervention arm | Post-trial follow-up |
|---|---|---|---|---|---|
| United Kingdom Prospective Diabetes Study (UKPDS; N=4209; reported in 1998)[6] | Newly diagnosed type 2 diabetes at study enrolment; mean age 53·3 years; median follow-up 10 years | 50% of patients showed evidence of pre-existing complications including retinopathy and neuropathy | Metformin, sulfonylureas, insulin, blood pressure managment | Microvascular: reduced RRR (25%; p<0·05); macrovascular: no change in RRR (16%; p=0·052) | Legacy effect with significant reduction in myocardial infarction, all-cause mortality and any diabetes-related endpoint in intensively managed patients 10 years post-trial |
| Action in Diabetes and Vascular Disease: Preterax + Diamicron Modified Release Controlled Evaluation (ADVANCE; N=11 140; reported in 2008)[7] | Pre-existing type 2 diabetes; mean duration 10 years; mean age 66·0 years; median follow-up 4·9 years | 32% of patients had macrovascular disease at baseline | Metformin, sulfonylureas, insulin | Microvascular: reduced HR (0·86; 95% CI 0·77–0·97); macrovascular: no change in HR (0·94; 0·84–1·06) | No sustained benefits in microvascular and macrovascular outcomes after median post-trial follow-up of 5·9 years |
| The Action to Control Cardiovascular Risk in Diabetes Study (ACCORD; N=10 250; reported in 2008)[58] | Pre-existing type 2 diabetes; mean duration 8 years; mean age 62·2 years; median follow-up 3·5 years (terminated early due to excess mortality in intensive arm) | 35% of patients had macrovascular disease at baseline | Metformin, sulfonylureas, rosiglitazone, insulin | Microvascular: no change in all-cause mortality; macrovascular: increased all-cause mortality (HR 1·22; 95% CI 1·01–1·46) | Reduction in retinopathy progression 4 years post-trial |
| Veterans Affairs Diabetes Trial (VADT; N=1791; reported in 2009)[8] | Pre-existing type 2 diabetes; mean duration 11·5 years; mean age 60·4 years; median follow-up 5·6 years | 40% of patients had macrovascular disease at baseline | Metformin, sulfonylureas, rosiglitazone, insulin | Microvascular: reduction in progression to albuminuria only (p=0·01); macrovascular: no reduction (HR 0·88; 95% CI 0·74–1·05) | 8·6 fewer major cardiovascular events per 1000 person-years in intensive treatment arm at 10 year follow-up |
| Steno-2 (N=160; reported in 2003)[5] | Pre-existing type 2 diabetes; median duration 5·5–6 years; mean age 55·1 years; median follow-up 7·8 years | Microalbuminuria | Multifactorial cardiovascular disease risk management with drugs and lifestyle modification | Microvascular: reduced HR (eg, nephropathy HR 0·39; 95% CI 0·17–0·87); macrovascular: reduced HR (0·47; 0·24–0·73) | Median gain of 7·9 years in intensive treatment arm at 21·2 years of follow-up |
| EMPA-REG OUTCOME (N=7020; cardiovascular outcome trial reported in 2015)[60] | Pre-existing type 2 diabetes; 57% of patients had a mean duration of diabetes that was longer than 10 years; mean age 63 years; median follow-up 3·1 years | 76% of patients had coronary artery disease at baseline | Empagliflozin *vs* placebo | 14% reduction in primary major adverse cardiovascular event endpoint (cardiovascular death, non-fatal myocardial infarction, non-fatal stroke), 38% reduction in cardiovascular mortality | N/A |
| LEADER (N=9340; cardiovascular outcome trial reported in 2016)[61] | Pre-existing type 2 diabetes; mean duration 13 years; mean age 64 years; median follow-up 3·8 years | 81% of patients had cardiovascular disease at baseline | Liraglutide *vs* placebo | 13% reduction in primary major adverse cardiovascular event endpoint (cardiovascular death, non-fatal myocardial infarction, non-fatal stroke); 22% reduction in cardiovascular mortality; lower rate of nephropathy events in liraglutide group | N/A |

HR=hazard ratio; RRR=relative risk reduction; N/A=non-applicable. MACE=major adverse cardiovascular event.

***Table 2*: Key characteristics of landmark studies in type 2 diabetes**

Early detection of type 2 diabetes enables initiation of patient-centred management to improve glycaemic control and minimise complications. Optimal management consists of lifestyle interventions such as weight reduction,[46] increased physical activity,[47] healthy diet, smoking cessation, moderation of alcohol consumption, and glucose-lowering therapies to reach individualised glycaemic targets. These interventions should be supported by structured education and self-management programmes at the time of diagnosis, combined, as necessary, with psychological support. Structured education improves both biomedical and psychosocial outcomes[47] but relies on reinforcement for ongoing benefit.[49]

In Look AHEAD,[50] a randomised controlled trial of intensive lifestyle modification in more than 5000 patients with type 2 diabetes (median follow-up 9·6 years), no improvement in cardiovascular disease outcomes was found. However, patients receiving intensive lifestyle interventions showed substantial weight loss and associated improvements in waist circumference, HDL cholesterol, and $HbA_{1c}$ concentration as well as increased physical activity within 6 months.[51] Additional benefits included reduced sexual dysfunction and depression in women, improved quality of life, and prevention or delay of chronic kidney disease.[52–54]

## Randomised controlled trials and effects on macrovascular and microvascular complications

Cardiovascular disease is the major macrovascular complication of type 2 diabetes and increases the risk of death three to four times compared with people who do not have cardiovascular disease.[55] Results of large multicentre studies show that macrovascular outcomes are not improved as convincingly as microvascular endpoints with intensive glycaemic control.[56] With the results of

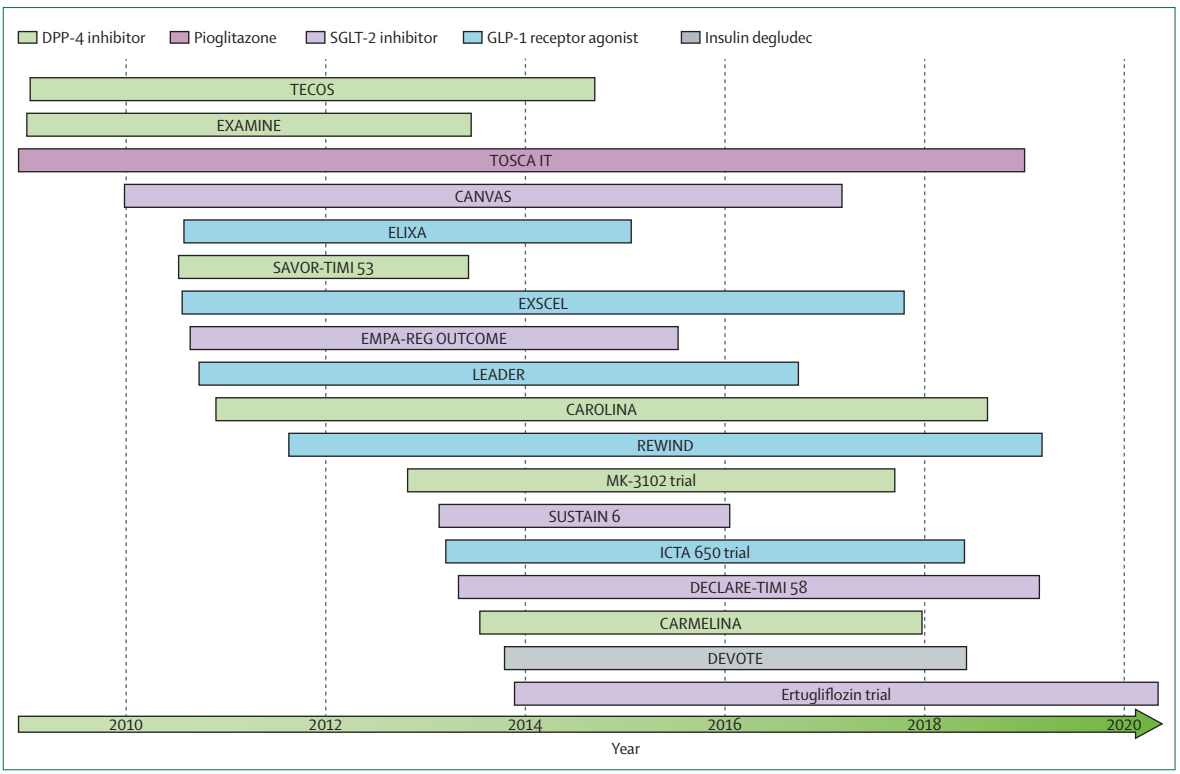


***Figure 2*: Completed and ongoing cardiovascular outcome trials**
DPP-IV=dipeptidyl peptidase-IV; SGLT-2=sodium-glucose co-transporter 2; GLP-1=glucagon-like peptide-1. Adapted from Holman and colleagues (2014).[10]

UKPDS,[6] which included 5102 patients newly diagnosed with type 2 diabetes and randomly allocated to receive either conventional therapy or intensive therapy with metformin, sulfonylureas, and insulin, investigators showed that a decade of intensive glycaemic and blood pressure control improved microvascular outcomes such as retinopathy and albuminuria. Macrovascular outcomes were not improved, although metformin led to a 39% risk reduction for myocardial infarction.[57] Findings of several subsequent randomised controlled trials, including ACCORD,[58] ADVANCE,[7] VADT,[8] and Steno-2,[59] confirmed the benefits of intensive management on microvascular outcomes (table 2). However, the results of meta-analyses[62,63] of these trials showed that intensive glycaemic treatment increased the risk of severe hypoglycaemia and had no effect on all-cause mortality or stroke, with little improvement of macrovascular outcomes such as non-fatal myocardial infarction and coronary heart disease. Further analysis of ACCORD[62] data indicates that increased mortality was associated with high $HbA_{1c}$ concentration.

Findings from follow-up studies[64] of the original trial cohorts have shown that a sustained period of intensive glycaemic control early in type 2 diabetes development reduces complication rates (with main benefits to microvascular outcomes such as nephropathy), even after glycaemic differences between intensive and standard care arms have dissipated. This effect has been described as metabolic memory or glycaemic legacy. For example, follow-up of 8494 participants of the original ADVANCE cohort[65] for an additional 5·4 years showed long-term reduction in end-stage kidney disease (HR 0·54; p<0·01), with no increase in risk of all-cause or cardiovascular death or major cardiovascular events.

Since the 2008 meta-analysis of rosiglitazone studies,[66] after which concerns of adverse cardiovascular outcomes were raised, the US Food and Drug Administration has recommended that all new glucose-lowering therapies are tested in placebo-controlled phase 2 and phase 3 clinical trials with patients who are at high risk of cardiovascular disease and that the analysis should be adjudicated for cardiovascular endpoints by an independent committee (figure 2). A composite endpoint of major adverse cardiovascular events is recommended, and is defined as an aggregate of fatal and non-fatal myocardial infarction and stroke and other cardiovascular deaths. Results of cardiovascular outcome trials of dipeptidyl peptidase-IV (DPP-IV) inhibitors saxagliptin (SAVOR-TIMI 53)[67] and alogliptin (EXAMINE)[68] showed non-inferiority for most major adverse cardiovascular endpoints, although increased rates of admission to hospital for heart failure were noted, and both drugs are contraindicated in patients with pre-existing heart or kidney failure.[69] Cardiovascular safety of sitagliptin was confirmed in the Trial Evaluating Cardiovascular Safety with Sitagliptin (TECOS),[70] with no increased risk of hospital admission from heart failure.

For the **US Food and Drug Administration's Guidance for Industry: Diabetes Mellitus—Evaluating Cardiovascular Risk in New Antidiabetic Therapies to Treat Type 2 Diabetes** see http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm071627.pdf

In the first cardiovascular outcome trial for SGLT-2 inhibitors, EMPA-REG Outcome,[60] empagliflozin was found to reduce the primary composite outcome of death from cardiovascular causes, non-fatal myocardial infarction, or stroke (RRR 14%). Empagliflozin also improved outcomes from death from cardiovascular disease causes (RRR 38%), sudden death (RRR 31%), and admission to hospital for heart failure (RRR 35%), with benefits seen within 3 months of study enrolment. The underlying mechanism remains unclear and has been attributed to a diuretic effect through blood pressure reduction (mean 4·0/1·5 mm Hg) but could also be related to osmotic diuresis and haemodynamic effects.[71] Cardiovascular outcomes are awaited for trials of SGLT-2 inhibitors dapagliflozin (DECLARE)[72] and canagliflozin (CANVAS).[73] The GLP-1 receptor agonist liraglutide (LEADER)[61] and semaglutide (SUSTAIN 6)[74] are superior to placebo for major adverse cardiovascular endpoints. Although cardiovascular safety has been confirmed for lixisenatide (ELIXA),[75] this drug is not superior to placebo.

Results of a meta-analysis[76] of all glucose-lowering treatments and strategies in more than 95 000 patients indicate that weight gain of 1 kg increases risk of heart failure by 7·1% (95% CI 1·0–13·6; p=0·022), with intensive weight loss and basal insulin regimens associated with neutral risk of heart failure and treatment with DPP-IV inhibitors and peroxisome proliferator-activated receptor (PPAR) agonists associated with increased risk of heart failure, although the size of the effect was heterogeneous.

## Management of obesity

60% of patients with type 2 diabetes are obese (body-mass index [BMI] ≥30 kg/m²) and show insulin resistance. Obesity is addressed by lifestyle modification, although pharmacotherapy, very low calorie diets, and bariatric surgery might also be considered. The pancreatic lipase inhibitor orlistat has modest effects on weight (mean weight loss 6·1%), and although long-term data have confirmed its safety, use of orlistat is associated with gastrointestinal side-effects.[77] High doses of the GLP-1 analogue liraglutide (3·0 mg daily) are licensed for obesity management in patients with and without diabetes.[78,79]

In patients with severe obesity (BMI >35 kg/m²), very low calorie diets (≤800 kcal/day) or bariatric surgery can result in substantial weight loss and type 2 diabetes remission. In one small study[80] of 30 patients with type 2 diabetes who discontinued glucose-lowering therapy and followed very low calorie diets for 8 weeks, 40% of patients maintained fasting plasma glucose concentrations less than 7 mmol/L at 6 months, indicating remission, with responders having higher plasma insulin concentrations and shorter diabetes duration at baseline than non-responders. Bariatric surgery, especially Roux-en-Y gastric bypass or sleeve gastrectomy, is more effective than medical treatment for weight reduction and maintenance for at least 5 years, although ongoing glycaemic control monitoring is recommended because of the increased risk of hyperglycaemia.[81]

## Drug therapy for patients with type 2 diabetes

Metformin remains the first-line therapy of choice for patients with type 2 diabetes unless specifically contraindicated, for example in patients with renal impairment. Metformin reduces hepatic glucose output, enhances peripheral tissue sensitivity, and stimulates GLP-1 secretion.[82] Furthermore, metformin effectively lowers $HbA_{1c}$ concentration by about 1–2%, is weight neutral, does not cause hypoglycaemia, and can have modest beneficial effects on blood pressure and lipid profile.[83] Gastrointestinal side-effects are reduced with gradual dose titration, and the risk of lactic acidosis with metformin is rare (less than 1 per 100 000).[84] However, metformin is associated with vitamin B12 deficiency and contraindicated in patients with moderate to severe chronic kidney disease (eGFR <30 mL/min/1·73 m²), although cautious use of metformin, with dose reduction, is permitted in patients with mild-to-moderate chronic kidney disease.[85] Metformin has been found to decrease cardiovascular risk compared with sulfonylurea therapy or placebo.[86]

In 2015, the American Diabetes Association and European Association for the Study of Diabetes updated their treatment algorithm to include all glucose-lowering therapies as possible second-line agents for addition to metformin if glycaemic targets are not reached.[87] Although this update allows personalised treatment plans, the wide range of treatment options means that the best combination depends on a knowledge of the existing evidence base and specific features of each drug class.

Sulfonylureas, such as gliclazide and glimepiride, act on β cells to stimulate insulin secretion and, as a consequence of established efficacy and low cost, are often the first choice for dual therapy. However, these drugs are associated with hypoglycaemia (up to six times increased risk compared with metformin)[88] and weight gain, and concerns remain with respect to an association with adverse cardiovascular disease outcomes.[89] As monotherapy, these drugs do not offer durable control compared with metformin and thiazolidinediones.[90] Their preference as second-line therapy is being challenged by DPP-IV inhibitors, GLP-1 receptor agonists, and SGLT-2 inhibitors. The results of an ongoing comparative effectiveness study[91] of the main oral glucose-lowering therapies (excluding SGLT-2 inhibitors) when added to metformin should confirm the most effective and safe drug combination. Meglitinides (repaglinide, nateglinide) have a similar mechanism of action to sulfonylureas,[92] but are less effective[93] and have a shorter duration of action, are associated with a lower hypoglycaemic risk and can be used as glucose-lowering therapy in patients who need short-acting, meal-related

insulin secretion, such as shift workers, fasting patients, and people with moderate to severe renal failure.[94]

Thiazolidinediones, also known as PPAR γ agonists, (rosiglitazone, pioglitazone) improve insulin sensitivity in target organs. Use of these drugs has been controversial, with the first-in-class troglitazone withdrawn because of liver toxicity.[95] Rosiglitazone is now used infrequently because of adverse cardiovascular outcomes (which have since been disproved).[96] These drugs are associated with durable control[90] and improve $HbA_{1c}$ concentration by up to about 1%. They are not associated with hypoglycaemia unless combined with sulfonylureas or insulin and might cause weight gain of up to 6 kg, mainly because of fluid retention. Pioglitazone can be used dose-unchanged at all stages of chronic kidney disease but is contraindicated in patients with heart failure (New York Heart Association class III or IV).[97] Treatment with pioglitazone is associated with bone fractures[98] and increased safety signals for prostate and pancreatic cancer, although the evidence for the association of pioglitazone with bladder cancer risk is inconclusive.[99,100]

Incretin therapies include subcutaneously injectable GLP-1 receptor agonists and oral DPP-IV inhibitors. GLP-1 agonists trigger GLP-1-like effects, which include increased insulin secretion, reduced glucagon secretion, reduced hepatic glucose output, delayed gastric emptying, and increased satiety.[101] GLP-1 receptor agonists are either long-acting (dulaglutide, albiglutide, liraglutide) or short-acting (exenatide, lixisenatide) drugs that are given once weekly or once or twice daily. This class of drugs is effective, with reductions in $HbA_{1c}$ concentration of about 1% and weight loss of up to 4 kg. The risk of hypoglycaemia is low unless combined with sulfonylureas or insulin,[102] and the main side-effect is nausea and vomiting on initiation, which is reduced by gradual dose titration. The most effective GLP-1 receptor agonists overall appear to be exenatide and liraglutide.[103] The results of a network meta-analysis[104] of long-acting GLP-1 receptor agonists specifically indicate that although they are all effective at lowering $HbA_{1c}$ and fasting plasma glucose concentrations, adverse events such as nausea and effects on weight differ between the drugs. GLP-1 receptor agonists are contraindicated in patients with a history of chronic pancreatitis or pancreatic cancer, although the signal for pancreatic cancer is not increased.[105] Compared with insulin alone, fixed combinations of GLP-1 receptor agonists with long-acting insulin, such as insulin degludec and liraglutide or insulin glargine and lixisenatide, are associated with less hypoglycaemia and weight gain, as well as reduced insulin doses.[106] Findings from head-to-head studies[107] of basal insulin and GLP-1 receptor agonist combinations indicated that the drugs are as effective as basal bolus insulin regimens, possibly because GLP-1 receptor agonists reduce postprandial glucose excursions. DPP-IV inhibitors (sitagliptin, saxagliptin, linagliptin, vildagliptin, alogliptin) potentiate the effects of physiological GLP-1.[101] Taken orally once or twice per day, DPP-IV inhibitors improve $HbA_{1c}$ concentration by up to 0·7%, are weight neutral, and do not cause hypoglycaemia unless combined with sulfonylureas or insulin. DPP-IV inhibitors are well tolerated and safe with dose reduction (eg, sitagliptin) or without dose reduction (linagliptin) in patients with moderate to severe renal impairment.

SGLT-2 inhibitors (dapagliflozin, canagliflozin, empagliflozin) are the latest glucose-lowering agents to become available. These drugs increase urinary glucose excretion by inhibiting SGLT-2 in the renal proximal tubule.[32] Findings from a meta-analysis[108] of dapagliflozin and canagliflozin trials confirmed efficacy with reductions in $HbA_{1c}$ concentrations of about 0·7%. Through a mechanism of glycosuria and urinary calorie loss of up to 320 kcal per day, substantial weight reduction was achieved when, for example, dapagliflozin was compared with glipizide (–3·2 kg *vs* 1·2 kg; p≤0·0001) at 52 weeks.[109] Weight loss was sustained long term (78 weeks) with empagliflozin when compared with placebo (2·2 kg *vs* 0·7 kg; p≤0·01).[110] These drugs do not cause hypoglycaemia unless combined with sulfonylureas or insulin. The main side-effect is urinary or genital tract infection, both of which are more common in women.[111] SGLT-2 inhibitors are less effective in patients with moderate to severe renal impairment (eGFR 30–60 mL/min/1·73 m²), because dose reduction is necessary (canagliflozin and empagliflozin)[111] and should not be used when eGFR is less than 30 mL/min/1·73m². SGLT-2 inhibitors are associated with euglycaemic ketoacidosis, and they should be discontinued during periods of acute illness and treatment in hospital.[112] Bone fractures and peripheral vascular disease are associated with use of canagliflozin.

Insulin therapy is the most effective treatment in terms of overall glycaemic control, with a reduction in $HbA_{1c}$ concentration of 1·5–2%. However, insulin therapy is associated with increased risk of hypoglycaemia, especially in elderly people, and a mean weight gain of 4 kg.[113] Ideally, treatment algorithms should be used to optimise insulin titration and quickly reach glycaemic targets. Poor adherence to insulin therapy is associated with factors such as risk and fear of developing hypoglycaemia or weight gain, practical difficulties of self-injecting and reluctance to do so (pyschological insulin resistance), and lifestyle restrictions.[114] Findings from the 4-T study[115] showed that the greatest efficacy and safety is achieved when basal insulin is added to oral and other subcutaneous therapies, although prandial insulin three times per day is equally effective but leads to more hypoglycaemia. Early insulin is useful for short-term glucose stabilisation because it potentially preserves β-cell function and reduces glucotoxicity.[116]

In head-to-head studies[117,118] of basal human and analogue insulins, no major differences in efficacy were found; however, the risk of nocturnal and symptomatic hypoglycaemia, but not total hypoglycaemia, was reduced

with the insulin analogues glargine and detemir. Detemir and glargine do not differ in efficacy or safety, but use of detemir was associated with less weight gain and higher insulin dose requirements.[119]

Very long-acting insulin analogues (plasma half-life of 42 hours) such as insulin degludec reduce the risk of nocturnal hypoglycaemia because of a relatively peakless profile (figure 3).[121] High-strength formulations, including glargine U300[122] and insulin U500,[123,124] are effective in patients who need high doses because of insulin resistance.

## Challenges in optimisation and maintenance of glycaemic control

Major difficulties in optimising glucose-lowering therapies are clinical inertia and treatment non-adherence. Clinical inertia is the reluctance of health-care professionals to initiate and titrate therapy appropriately to reach glycaemic targets and is associated with lack of knowledge, fear of adverse effects such as hypoglycaemia, and a perception that patients will not accept treatment intensification.[125–127] However, clinical inertia increases a patient's risk of developing complications and needs to be addressed with appropriate strategies such as health-care professional and patient education, electronic reminders, and adherence to guidelines as well as regular monitoring of $HbA_{1c}$ and blood glucose concentration, as appropriate, to achieve targets. Treatment non-adherence places considerable financial burden on health-care economies with billions of US$ wasted on medication that is prescribed but not consumed.[128] Patients can get help to adhere to treatment through structured education and self-management programmes, which have been shown to improve personal responsibility[48] and should be emphasised for all medications, including anti-hypertensive and lipid-lowering therapies.

Iatrogenic hypoglycaemia in people with diabetes has been defined by a 2013 American Diabetes Association and Endocrine Society workgroup as "all episodes of abnormally low plasma glucose that expose the individual to potential harm"[129] and limits long-term treatment intensification and optimisation.[130] The risk of hypoglycaemia increases with diabetes duration and occurs especially with use of sulfonylureas, meglitinides, and insulin. Other glucose-lowering therapies, including metformin, thiazolidinediones, DPP-IV inhibitors, GLP-1 receptor agonists, and SGLT-2 inhibitors, only increase the risk of hypoglycaemia if combined with these agents. Compared with patients receiving placebo or other glucose-lowering drugs, patients receiving sulfonylureas have a three-times increased risk of hypoglycaemia, and this risk increases even further in patients with low $HbA_{1c}$ and high BMI at baseline.[88] Hypoglycaemia can be asymptomatic, symptomatic and mild, or severe.

Severe hypoglycaemia is defined as requiring another person's assistance to administer carbohydrate, glucagon, or other supportive action to aid recovery. Although patients with type 1 diabetes are more likely to have severe hypoglycaemia, the results of an observational uncontrolled study[13] showed that mortality was higher in patients with type 2 diabetes 12 months after a severe hypoglycaemic episode (4·45% *vs* 22·1%), with age and type of diabetes being predictive factors and hypoglycaemia possibly a marker of underlying morbidity. Appropriate choice and dosage of therapeutic agents can minimise hypoglycaemia risk. Recurrent episodes cause hypoglycaemia unawareness by blunting counter-regulatory responses. Incidence of hypoglycaemia, which occurs more frequently in the real

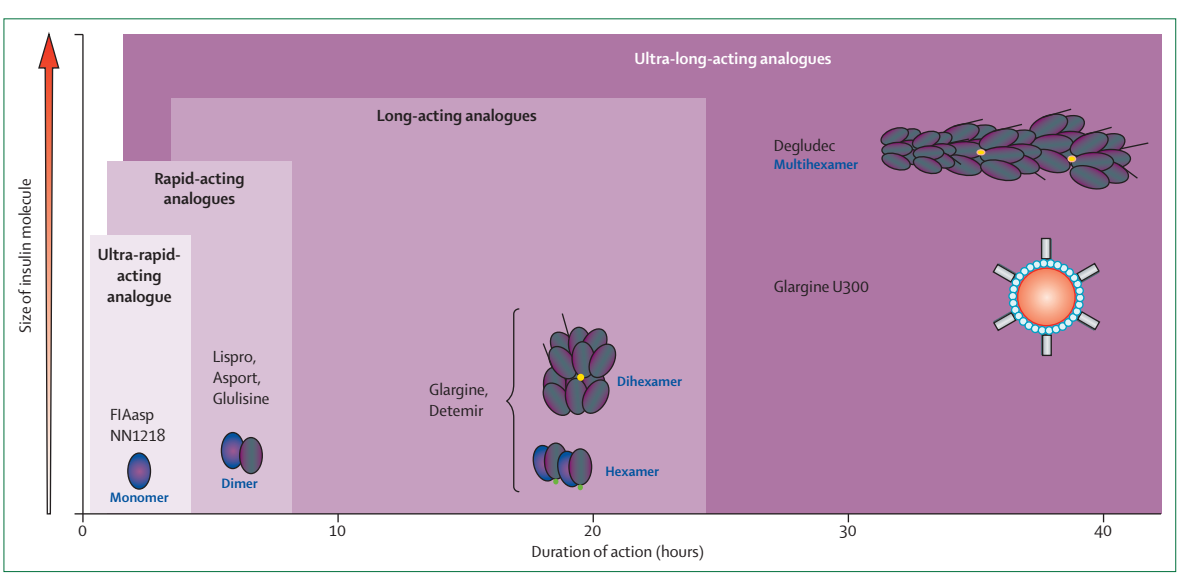


***Figure 3*: Insulin analogue formulations with duration of action**
Reproduced from Gururaj Setty and colleagues (2016),[120] by permission of BMJ Publishing.

world than is reported during clinical trials,[131] is minimised by individualising glycaemic goals and providing structured education and self-management training on early recognition and treatment of symptoms (capillary glucose ≤3·9 mmol/L), considering risk factors, and appropriate home blood glucose monitoring with, if necessary, continuous glucose monitoring for short periods.[132] Severe hypoglycaemia is associated with a four-times increase in risk of motor vehicle accidents,[133] and patients need to learn to check glucose levels before driving and always carry rapid-acting glucose.[134]

Hypoglycaemia is a particular challenge for achieving treatment targets in elderly people (age >65 years) because of under-recognition, risk of falls, polypharmacy, diminished autonomic symptoms, impaired counter-regulatory responses, and cognitive impairment.[135] Hypoglycaemia is the cause of up to a fifth of hospital admissions of patients with diabetes who are older than 80 years.[136] Patients with type 2 diabetes that is tightly controlled ($HbA_{1c}$ <42 mmol/mol [6·0%]), poorly controlled ($HbA_{1c}$ >75 mmol/mol [9·0%]),[137] or associated with renal or cognitive impairment[136] are more likely to be at risk of severe hypoglycaemia. Key strategies include assessment for frailty and cognitive impairment, a choice of therapeutic agents that are not associated with hypoglycaemia titrated to a minimal effective dose, relaxing glycaemic goals as necessary, and aiming for glucose concentration above 7 mmol/L. Because microvascular and macrovascular complications are increased in elderly people, hypoglycaemia should not be used as a justification for suboptimal glycaemic control.[138]

Young patients (age <25 years) with type 2 diabetes often present with a constellation of other dysmetabolic features, including hyperlipidaemia, hypertension, fatty liver, and microalbuminuria, and are at increased risk of macrovascular and microvascular complications and mortality.[26] Diagnosis and differentiation from type 1 diabetes is based on identifying markers of insulin resistance, such as acanthosis nigricans, and results of biochemical tests, including high C-peptide concentrations and absence of autoantibodies. Young patients are often women, from ethnic minorities, or from disadvantaged social groups and need intensive multifactorial management, education, and psychological support from diagnosis.[139] Metformin and insulin are the only drugs available for treatment of patients who are 18 years or younger. New drugs such as DPP-IV inhibitors are being tested in young patients, but recruitment of children to these studies is challenging.[140]

## New technology and therapeutic options for patients with type 2 diabetes

A number of outstanding research questions remain, chief of which is whether a cure for type 2 diabetes is on the horizon. In the short term, diabetes remission is achievable with very low calorie diet[141] or bariatric surgery.[142] Both interventions could potentially cause harm and are difficult to implement on a wide scale. Stem-cell research could pave the way to increasing β-cell mass, thereby delaying type 2 diabetes progression and the need for additional glucose-lowering therapy.[143] Other delivery methods for insulin, including the bionic pancreas, might also contribute to type 2 diabetes management strategies in future years.[144]

As the pathophysiology of type 2 diabetes becomes increasingly understood, targeted therapeutic approaches will be tailored to the individual (precision medicine). Key organs of therapeutic potential include the brain and gut. The effects of stimulating hormones that suppress appetite (neuropeptide Y-Y, leptin, GLP-1) or inhibitors of appetite stimulators (ghrelin) are being explored.[77] Triple agonism of GLP-1, gastric inhibitory polypeptide, and glucagon receptors improves glucose control and inhibits caloric intake in rodent models.[145] However, the effect on the genotype of epigenetic factors including ageing, environment, and lifestyle must be identified and understood before personalised drug formulations can be developed successfully.[29] Improved stratification of cardiovascular risk optimises patient outcomes and can be achieved by adding cardiac biomarkers such as high-sensitivity troponin T and N-terminal prohormone brain natriuretic peptide (NT-proBNP) to existing risk scores,[146] although no data exist to show that addition of expensive biomarkers will improve diabetes outcomes.

Continuous glucose monitoring systems provide detailed and valuable information about the effects of glucose-lowering therapy by providing 24-h monitoring of glycaemic excursions and hypoglycaemia for 7 days. Accessibility and availability of continuous glucose monitoring systems is limited by cost, resources, and training. Flash glucose monitoring is cheaper and easier to use and does not require calibration.[147]

The CSII (insulin pump) is an established insulin delivery device for patients with type 1 diabetes but is not yet advocated for widespread use by patients with type 2 diabetes. Findings from early trials[148] suggest that insulin pumps can improve glucose stabilisation and control and can be enhanced by continuous glucose monitoring systems especially to target postprandial glucose levels.[149] Insulin delivery methods in development include patch devices and inhalers, but the assessment of bioavailability, efficacy, and safety is still pending.

Glucagon receptor antagonists (eg, PF-06291874) are a new class of drugs that show good therapeutic potential and are being assessed in long-duration trials. This class of drugs reduces fasting plasma glucose and mean daily glucose concentrations at 14 days with low risk of hypoglycaemia.[150] Other glucose-lowering therapies being developed include fibroblast growth factor 21 analogues, adiponectin receptor agonists, cellular glucocorticoid inhibitors, selective PPAR modulators, imeglimin, and glucokinase activators.[151]

A further challenge is translating favourable trial outcomes to a real world setting and ensuring that

evidence-based guidelines are followed in clinical practice. Patient adherence to lifestyle and treatment advice remains a significant hurdle in achieving health-care targets and novel cost-effective strategies are necessary to optimise adherence.

## Conclusion

The evidence base for optimal type 2 diabetes management is growing rapidly with the ability to deliver effective multidisciplinary care after early diagnosis and initiate effective glucose-lowering therapies supported by structured education and self-management programmes. Nevertheless, many patients still develop serious and life-threatening microvascular and macrovascular complications. Prevention of type 2 diabetes is possible and should be attempted with widespread national prevention programmes. Once diabetes develops, treatment must be centred on the patient's needs and circumstances, with aggressive management targeted to those who are most likely to benefit from treatment.

**Contributors**

All authors were involved in writing and revision at all stages of manuscript preparation. All authors have seen and approved the final text.

**Declaration of interests**

SC declares speaker fees, educational funding, or both, from Janssen, Eli Lilly, Novo Nordisk, AstraZeneca, and Boehringer Ingelheim, and grants in support of investigator-initiated trials from Boehringer Ingelheim and Janssen. MJD declares personal fees from Novo Nordisk, Sanofi-Aventis, Lilly, Merck Sharp & Dohme, Boehringer Ingelheim, AstraZeneca, Janssen, Mitsubishi Tanabe Pharma Corporation, and Takeda Pharmaceuticals International, and grants from Novo Nordisk, Sanofi-Aventis, Lilly, Boehringer Ingelheim, and Janssen. KK has acted as a consultant and speaker for AstraZeneca, Novartis, Novo Nordisk, Sanofi-Aventis, Lilly, Merck Sharp & Dohme, Janssen, and Boehringer Ingelheim. KK declares grants in support of investigator and investigator initiated trials from AstraZeneca, Novartis, Novo Nordisk, Sanofi-Aventis, Lilly, Boehringer Ingelheim, Merck Sharp & Dohme, and Roche. KK has served on advisory boards for AstraZeneca, Novartis, Novo Nordisk, Sanofi-Aventis, Lilly, Merck Sharp & Dohme, Janssen, and Boehringer Ingelheim.

**Acknowledgments**

We thank the National Institute for Health Research Collaboration for Leadership in Applied Health Research and Care—East Midlands (NIHR CLAHRC—EM), the Leicester Clinical Trials Unit, and the NIHR Leicester-Loughborough Diet, Lifestyle and Physical Activity Biomedical Research Unit, which is a partnership between the University Hospitals of Leicester NHS Trust, Loughborough University, and the University of Leicester.

**References**

1 NCD Risk Factor Collaboration (NCD-RisC). Worldwide trends in diabetes since 1980: a pooled analysis of 751 population-based studies with 4·4 million participants. *Lancet* 2016; **387:** 1513–30.

2 GBD 2015 Disease and Injury Incidence and Prevalence Collaborators. Global, regional, and national incidence, prevalence, and years lived with disability for 310 diseases and injuries, 1990–2015: a systematic analysis for the Global Burden of Disease Study 2015. *Lancet* 2016; **388:** 1545–602.

3 Seuring T, Archangelidi O, Suhrcke M. The economic costs of type 2 diabetes: a global systematic review. *Pharmacoeconomics* 2015; **33:** 811–31.

4 WHO. Non-communicable diseases country profile 2014. July, 2014. http://www.who.int/nmh/publications/ncd-profiles-2014/en/ (accessed Oct 6, 2016).

5 Gaede P, Vedel P, Larsen N, Jensen GV, Parving HH, Pedersen O. Multifactorial intervention and cardiovascular disease in patients with type 2 diabetes. *N Engl J Med* 2003; **348:** 383–93.

6 UK Prospective Diabetes Study (UKPDS) Group. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). *Lancet* 1998; **352:** 837–53.

7 ADVANCE Collaborative Group, Patel A, MacMahon S, et al. Intensive blood glucose control and vascular outcomes in patients with type 2 diabetes. *N Engl J Med* 2008; **358:** 2560–72.

8 Duckworth W, Abraira C, Moritz T, et al. Glucose control and vascular complications in veterans with type 2 diabetes. *N Engl J Med* 2009; **360:** 129–39.

9 Holman RR, Paul SK, Bethel MA, Matthews DR, Neil HA. 10-year follow-up of intensive glucose control in type 2 diabetes. *N Engl J Med* 2008; **359:** 1577–89.

10 Holman RR, Sourij H, Califf RM. Cardiovascular outcome trials of glucose-lowering drugs or strategies in type 2 diabetes. *Lancet* 2014; **383:** 2008–17.

11 Skyler JS, Bergenstal R, Bonow RO, et al. Intensive glycemic control and the prevention of cardiovascular events: implications of the ACCORD, ADVANCE, and VA diabetes trials: a position statement of the American Diabetes Association and a scientific statement of the American College of Cardiology Foundation and the American Heart Association. *Diabetes Care* 2009; **32:** 187–92.

12 Cefalu WT. Glycemic targets and cardiovascular disease. *N Engl J Med* 2008; **358:** 2633–35.

13 Elwen FR, Huskinson A, Clapham L, et al. An observational study of patient characteristics and mortality following hypoglycemia in the community. *BMJ Open Diabetes Res Care* 2015; **3:** e000094.

14 Tricco AC, Ivers NM, Grimshaw JM, et al. Effectiveness of quality improvement strategies on the management of diabetes: a systematic review and meta-analysis. *Lancet* 2012; **379:** 2252–61.

15 International Diabetes Federation. IDF Diabetes Atlas, 7th edn. 2015. http://www.diabetesatlas.org/ (accessed Oct 6, 2016).

16 Knowler WC, Barrett-Connor E, Fowler SE, et al. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. *N Engl J Med* 2002; **346:** 393–403.

17 Tancredi M, Rosengren A, Svensson AM, et al. Excess mortality among persons with type 2 diabetes. *N Engl J Med* 2015; **373:** 1720–32.

18 The Emerging Risk Factors Collaboration. Diabetes mellitus, fasting blood glucose concentration, and risk of vascular disease: a collaborative meta-analysis of 102 prospective studies. *Lancet* 2010; **375:** 2215–22.

19 Harris MI, Klein R, Welborn TA, Knuiman MW. Onset of NIDDM occurs at least 4-7 yr before clinical diagnosis. *Diabetes Care* 1992; **15:** 815–19.

20 Grarup N, Sandholt CH, Hansen T, Pedersen O. Genetic susceptibility to type 2 diabetes and obesity: from genome-wide association studies to rare variants and beyond. *Diabetologia* 2014; **57:** 1528–41.

21 Jenkinson CP, Goring HH, Arya R, Blangero J, Duggirala R, DeFronzo RA. Transcriptomics in type 2 diabetes: Bridging the gap between genotype and phenotype. *Genom Data* 2015; **8:** 25–36.

22 Leong A, Porneala B, Dupuis J, Florez JC, Meigs JB. Type 2 diabetes genetic predisposition, obesity, all-cause mortality risk in the US: a multiethnic analysis. *Diabetes Care* 2016; **39:** 539–46.

23 Oram RA, Patel K, Hill A, et al. A type 1 diabetes genetic risk score can aid discrimination between type 1 and type 2 diabetes in young adults. *Diabetes Care* 2016; **39:** 337–44.

24 Constantino MI, Molyneaux L, Limacher-Gisler F, et al. Long-term complications and mortality in young-onset diabetes: type 2 diabetes is more hazardous and lethal than type 1 diabetes. *Diabetes Care* 2013; **36:** 3863–69.

25 Wong ND, Zhao Y, Patel R, et al. Cardiovascular risk factor targets and cardiovascular disease event risk in diabetes: a pooling project of the Atherosclerosis Risk in Communities Study, Multi-ethnic Study of Atherosclerosis, and Jackson Heart Study. *Diabetes Care* 2016; **39:** 668–76.

26 TODAY Study Group, Zeitler P, Hirst K, et al. A clinical trial to maintain glycemic control in youth with type 2 diabetes. *N Engl J Med* 2012; **366:** 2247–56.

27 Defronzo RA. Banting Lecture. From the triumvirate to the ominous octet: a new paradigm for the treatment of type 2 diabetes mellitus. *Diabetes* 2009; **58:** 773–95.

28 Schwartz SS, Epstein S, Corkey BE, Grant SF, Gavin JR 3rd, Aguilar RB. The time is right for a new classification system for diabetes: rationale and implications of the β-Cell-Centric Classification Schema. *Diabetes Care* 2016; **39:** 179–86.

29 Gruber K. Moving towards a more precise treatment of diabetes. *Lancet Diabetes Endocrinol* 2015; **3:** 171.

30 de Jager J, Kooy A, Schalkwijk C, et al. Long-term effects of metformin on endothelial function in type 2 diabetes: a randomized controlled trial. *J Intern Med* 2014; **275:** 59–70.

31 Ceriello A, Esposito K, Testa R, Bonfigli AR, Marra M, Giugliano D. The possible protective role of glucagon-like peptide 1 on endothelium during the meal and evidence for an "endothelial resistance" to glucagon-like peptide 1 in diabetes. *Diabetes Care* 2011; **34:** 697–702.

32 Wilding JP. The role of the kidneys in glucose homeostasis in type 2 diabetes: clinical implications and therapeutic significance through sodium glucose co-transporter 2 inhibitors. *Metabolism* 2014; **63:** 1228–37.

33 Orozco LJ, Buchleitner AM, Gimenez-Perez G, Roque I Figuls M, Richter B, Mauricio D. Exercise or exercise and diet for preventing type 2 diabetes mellitus. *Cochrane Database Syst Rev* 2008; **3:** CD003054.

34 Merlotti C, Morabito A, Pontiroli AE. Prevention of type 2 diabetes; a systematic review and meta-analysis of different intervention strategies. *Diabetes Obes Metab* 2014; **16:** 719–27.

35 Diabetes Prevention Program Research Group. Long-term effects of lifestyle intervention or metformin on diabetes development and microvascular complications over 15-year follow-up: the Diabetes Prevention Program Outcomes Study. *Lancet Diabetes Endocrinol* 2015; **3:** 866–75.

36 Perreault L, Temprosa M, Mather KJ, et al. Regression from prediabetes to normal glucose regulation is associated with reduction in cardiovascular risk: results from the Diabetes Prevention Program outcomes study. *Diabetes Care* 2014; **37:** 2622–31.

37 Cardona-Morrell M, Rychetnik L, Morrell SL, Espinel PT, Bauman A. Reduction of diabetes risk in routine clinical practice: are physical activity and nutrition interventions feasible and are the outcomes from reference trials replicable? A systematic review and meta-analysis. *BMC Public Health* 2010; **10:** 653.

38 Dunkley AJ, Bodicoat DH, Greaves CJ, et al. Diabetes prevention in the real world: effectiveness of pragmatic lifestyle interventions for the prevention of type 2 diabetes and of the impact of adherence to guideline recommendations: a systematic review and meta-analysis. *Diabetes Care* 2014; **37:** 922–33.

39 Maruthappu M, Sood H, Keogh B. Radically upgrading diabetes prevention in England. *Lancet Diabetes Endocrinol* 2015; **3:** 312–13.

40 Webb DR, Gray LJ, Khunti K, et al. Screening for diabetes using an oral glucose tolerance test within a western multi-ethnic population identifies modifiable cardiovascular risk: the ADDITION-Leicester study. *Diabetologia* 2011; **54:** 2237–46.

41 Simmons RK, Echouffo-Tcheugui JB, Sharp SJ, et al. Screening for type 2 diabetes and population mortality over 10 years (ADDITION-Cambridge): a cluster-randomised controlled trial. *Lancet* 2012; **380:** 1741–48.

42 Khunti K, Mani H, Achana F, Cooper N, Gray LJ, Davies MJ. Systematic review and meta-analysis of response rates and diagnostic yield of screening for type 2 diabetes and those at high risk of diabetes. *PLoS One* 2015; **10:** e0135702.

43 Colagiuri S, Lee CM, Wong TY, Balkau B, Shaw JE, Borch-Johnsen K, DETECT-2 Collaboration Writing Group. Glycemic thresholds for diabetes-specific retinopathy: implications for diagnostic criteria for diabetes. *Diabetes Care* 2011; **34:** 145–50.

44 Welsh KJ, Kirkman MS, Sacks DB. Role of glycated proteins in the diagnosis and management of diabetes: research gaps and future directions. *Diabetes Care* 2016; **39:** 1299–306.

45 Thanabalasingham G, Pal A, Selwood MP, et al. Systematic assessment of etiology in adults with a clinical diagnosis of young-onset type 2 diabetes is a successful strategy for identifying maturity-onset diabetes of the young. *Diabetes Care* 2012; **35:** 1206–12.

46 Norris SL, Zhang X, Avenell A, et al. Long-term non-pharmacologic weight loss interventions for adults with type 2 diabetes. *Cochrane Database Syst Rev* 2005; **2:** CD004095.

47 Thomas DE, Elliott EJ, Naughton GA. Exercise for type 2 diabetes mellitus. *Cochrane Database Syst Rev* 2006; **3:** CD002968.

48 Davies MJ, Heller S, Skinner TC, et al. Effectiveness of the diabetes education and self management for ongoing and newly diagnosed (DESMOND) programme for people with newly diagnosed type 2 diabetes: cluster randomised controlled trial. *BMJ* 2008; **336:** 491–95.

49 Khunti K, Gray LJ, Skinner T, et al. Effectiveness of a diabetes education and self management programme (DESMOND) for people with newly diagnosed type 2 diabetes mellitus: three year follow-up of a cluster randomised controlled trial in primary care. *BMJ* 2012; **344:** e2333.

50 Belalcazar LM, Reboussin DM, Haffner SM, et al. A 1-year lifestyle intervention for weight loss in individuals with type 2 diabetes reduces high C-reactive protein levels and identifies metabolic predictors of change: from the Look AHEAD (Action for Health in Diabetes) study. *Diabetes Care* 2010; **33:** 2297–303.

51 Look AHEAD Research Group, Wing RR, Bolin P, et al. Cardiovascular effects of intensive lifestyle intervention in type 2 diabetes. *N Engl J Med* 2013; **369:** 145–54.

52 Wing RR, Bond DS, Gendrano IN 3rd, et al. Effect of intensive lifestyle intervention on sexual dysfunction in women with type 2 diabetes: results from an ancillary Look AHEAD study. *Diabetes Care* 2013; **36:** 2937–44.

53 Rubin RR, Wadden TA, Bahnson JL, et al. Impact of intensive lifestyle intervention on depression and health-related quality of life in type 2 diabetes: the Look AHEAD Trial. *Diabetes Care* 2014; **37:** 1544–53.

54 Look AHEAD Research Group. Effect of a long-term behavioural weight loss intervention on nephropathy in overweight or obese adults with type 2 diabetes: a secondary analysis of the Look AHEAD randomised clinical trial. *Lancet Diabetes Endocrinol* 2014; **2:** 801–09.

55 Stamler J, Vaccaro O, Neaton JD, Wentworth D. Diabetes, other risk factors, and 12-yr cardiovascular mortality for men screened in the Multiple Risk Factor Intervention Trial. *Diabetes Care* 1993; **16:** 434–44.

56 Fox CS, Golden SH, Anderson C, et al. Update on prevention of cardiovascular disease in adults with type 2 diabetes mellitus in light of recent evidence: a scientific statement from the American Heart Association and the American Diabetes Association. *Diabetes Care* 2015; **38:** 1777–803.

57 UK Prospective Diabetes Study (UKPDS) Group. Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34). *Lancet* 1998; **352:** 854–65.

58 Action to Control Cardiovascular Risk in Diabetes Study Group, Gerstein HC, Miller ME, et al. Effects of intensive glucose lowering in type 2 diabetes. *N Engl J Med* 2008; **358:** 2545–59.

59 Gaede P, Vedel P, Parving HH, Pedersen O. Intensified multifactorial intervention in patients with type 2 diabetes mellitus and microalbuminuria: the Steno type 2 randomised study. *Lancet* 1999; **353:** 617–22.

60 Zinman B, Wanner C, Lachin JM, et al. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. *N Engl J Med* 2015; **74:** 1094.

61 Marso SP, Daniels GH, Brown-Frandsen K, et al. Liraglutide and cardiovascular outcomes in type 2 diabetes. *N Engl J Med* 2016; **375:** 311–22.

62 Control Group, Turnbull FM, Abraira C, et al. Intensive glucose control and macrovascular outcomes in type 2 diabetes. *Diabetologia* 2009; **52:** 2288–98.

63 Ray KK, Seshasai SR, Wijesuriya S, et al. Effect of intensive control of glucose on cardiovascular outcomes and death in patients with diabetes mellitus: a meta-analysis of randomised controlled trials. *Lancet* 2009; **373:** 1765–72.

64 Riddle MC, Ambrosius WT, Brillon DJ, et al. Epidemiologic relationships between A1C and all-cause mortality during a median 3·4-year follow-up of glycemic treatment in the ACCORD trial. *Diabetes Care* 2010; **33:** 983–90.

65 Wong MG, Perkovic V, Chalmers J, et al. Long-term benefits of intensive glucose control for preventing end-stage kidney disease: ADVANCE-ON. *Diabetes Care* 2016; **39:** 694–700.

66 Nissen SE, Wolski K. Effect of rosiglitazone on the risk of myocardial infarction and death from cardiovascular causes. *N Engl J Med* 2007; **356:** 2457–71.

67 Scirica BM, Bhatt DL, Braunwald E, et al. Saxagliptin and cardiovascular outcomes in patients with type 2 diabetes mellitus. *N Engl J Med* 2013; **369:** 1317–26.

68 White WB, Cannon CP, Heller SR, et al. Alogliptin after acute coronary syndrome in patients with type 2 diabetes. *N Engl J Med* 2013; **369:** 1327–35.

69 US Food and Drug Administration. Diabetes medications containing saxagliptin and alogliptin: drug safety communication—risk of heart failure. April 19, 2016. http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm494252.htm (accessed Oct 6, 2016).

70 Green JB, Bethel MA, Armstrong PW, et al. Effect of sitagliptin on cardiovascular outcomes in type 2 diabetes. *N Engl J Med* 2015; **373:** 232–42.

71 Sarafidis PA, Tsapas A. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. *N Engl J Med* 2016; **374:** 1092.

72 AstraZeneca. Multicenter trial to investigate the effect of dapagliflozin on the incidence of cardiovascular events (DECLARE-TIMI58). 2015. https://clinicaltrials.gov/ct2/show/NCT01730534 (accessed Oct 21, 2015).

73 Janssen Research and Development LLC. CANVAS—CANagliflozin cardioVascular Assessment Study. 2015. https://clinicaltrials.gov/ct2/show/NCT01032629 (accessed Oct 21, 2015).

74 Marso SP, Bain SC, Consoli A, et al. Semaglutide and cardiovascular outcomes in patients with type 2 diabetes. *N Engl J Med* 2016; published online Sept 15. DOI:10.1056/NEJMoa1607141.

75 Pfeffer MA, on behalf of ELIXA steering group. The evaluation of lixisenatide in acute coronary syndrome—the results of ELIXA. *ADA Scientific Sessions* 2015; Abstracts: 3-CT-SY28.

76 Udell JA, Cavender MA, Bhatt DL, Chatterjee S, Farkouh ME, Scirica BM. Glucose-lowering drugs or strategies and cardiovascular outcomes in patients with or at risk for type 2 diabetes: a meta-analysis of randomised controlled trials. *Lancet Diabetes Endocrinol* 2015; **3:** 356–66.

77 Bray GA, Fruhbeck G, Ryan DH, Wilding JP. Management of obesity. *Lancet* 2016; **387:** 1947–56.

78 Davies MJ, Bergenstal R, Bode B, et al. Efficacy of liraglutide for weight loss among patients with type 2 diabetes: the SCALE Diabetes Randomized Clinical Trial. *JAMA* 2015; **314:** 687–99.

79 Wadden TA, Hollander P, Klein S, et al. Weight maintenance and additional weight loss with liraglutide after low-calorie-diet-induced weight loss: the SCALE Maintenance randomized study. *Int J Obes (Lond)* 2013; **37:** 1443–51.

80 Steven S, Hollingsworth KG, Al-Mrabeh A, et al. Very-low-calorie diet and 6 months of weight stability in type 2 diabetes: pathophysiologic changes in responders and nonresponders. *Diabetes Care* 2016; **39:** 808–15.

81 Mingrone G, Panunzi S, De Gaetano A, et al. Bariatric surgery versus conventional medical therapy for type 2 diabetes. *N Engl J Med* 2012; **366:** 1577–85.

82 DeFronzo RA, Buse JB, Kim T, et al. Once-daily delayed-release metformin lowers plasma glucose and enhances fasting and postprandial GLP-1 and PYY: results from two randomised trials. *Diabetologia* 2016; **59:** 1645–54.

83 Pernicova I, Korbonits M. Metformin—mode of action and clinical implications for diabetes and cancer. *Nat Rev Endocrinol* 2014; **10:** 143–56.

84 Salpeter SR, Greyber E, Pasternak GA, Salpeter EE. Risk of fatal and nonfatal lactic acidosis with metformin use in type 2 diabetes mellitus. *Cochrane Database Syst Rev* 2010; **4:** CD002967.

85 Inzucchi SE, Lipska KJ, Mayo H, Bailey CJ, McGuire DK. Metformin in patients with type 2 diabetes and kidney disease: a systematic review. *JAMA* 2014; **312:** 2668–75.

86 Hemmingsen B, Schroll JB, Wetterslev J, et al. Sulfonylurea versus metformin monotherapy in patients with type 2 diabetes: a Cochrane systematic review and meta-analysis of randomized clinical trials and trial sequential analysis. *CMAJ Open* 2014; **2:** E162–75.

87 Inzucchi SE, Bergenstal RM, Buse JB, et al. Management of hyperglycaemia in type 2 diabetes: a patient-centered approach. Position statement of the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). *Diabetologia* 2012; **55:** 1577–96.

88 Monami M, Dicembrini I, Kundisova L, Zannoni S, Nreu B, Mannucci E. A meta-analysis of the hypoglycaemic risk in randomized controlled trials with sulphonylureas in patients with type 2 diabetes. *Diabetes Obes Metab* 2014; **16:** 833–40.

89 Abdelmoneim AS, Eurich DT, Light PE, et al. Cardiovascular safety of sulphonylureas: over 40 years of continuous controversy without an answer. *Diabetes Obes Metab* 2015; **17:** 523–32.

90 Kahn SE, Lachin JM, Zinman B, et al. Effects of rosiglitazone, glyburide, and metformin on beta-cell function and insulin sensitivity in ADOPT. *Diabetes* 2011; **60:** 1552–60.

91 Nathan DM, Buse JB, Kahn SE, et al. Rationale and design of the glycemia reduction approaches in diabetes: a comparative effectiveness study (GRADE). *Diabetes Care* 2013; **36:** 2254–61.

92 Fuhlendorff J, Rorsman P, Kofod H, et al. Stimulation of insulin release by repaglinide and glibenclamide involves both common and distinct processes. *Diabetes* 1998; **47:** 345–51.

93 Miwa S, Watada H, Ohmura C, Tanaka Y, Kawamori R. Efficacy and safety of once daily gliclazide (20 mg/day) compared with nateglinide. *Endocr J* 2004; **51:** 393–98.

94 Black C, Donnelly P, McIntyre L, Royle PL, Shepherd JP, Thomas S. Meglitinide analogues for type 2 diabetes mellitus. *Cochrane Database Syst Rev* 2007; **2:** CD004654.

95 Kohlroser J, Mathai J, Reichheld J, Banner BF, Bonkovsky HL. Hepatotoxicity due to troglitazone: report of two cases and review of adverse events reported to the United States Food and Drug Administration. *Am J Gastroenterol* 2000; **95:** 272–76.

96 Mahaffey KW, Hafley G, Dickerson S, et al. Results of a reevaluation of cardiovascular outcomes in the RECORD trial. *Am Heart J* 2013; **166:** 240, 249. e1.

97 Authors/Task Force Members, Ryden L, Grant PJ, et al. ESC Guidelines on diabetes, pre-diabetes, and cardiovascular diseases developed in collaboration with the EASD: the Task Force on diabetes, pre-diabetes, and cardiovascular diseases of the European Society of Cardiology (ESC) and developed in collaboration with the European Association for the Study of Diabetes (EASD). *Eur Heart J* 2013; **34:** 3035–87.

98 Loke YK, Singh S, Furberg CD. Long-term use of thiazolidinediones and fractures in type 2 diabetes: a meta-analysis. *CMAJ* 2009; **180:** 32–39.

99 Lewis JD, Habel LA, Quesenberry CP, et al. Pioglitazone use and risk of bladder cancer and other common cancers in persons with diabetes. *JAMA* 2015; **314:** 265–77.

100 Tuccori M, Filion KB, Yin H, Yu OH, Platt RW, Azoulay L. Pioglitazone use and risk of bladder cancer: population based cohort study. *BMJ* 2016; **352:** i1541.

101 Nauck MA, Meier JJ. The incretin effect in healthy individuals and those with type 2 diabetes: physiology, pathophysiology, and response to therapeutic interventions. *Lancet Diabetes Endocrinol* 2016; **4:** 525–36.

102 Garber A, Henry R, Ratner R, et al. Liraglutide versus glimepiride monotherapy for type 2 diabetes (LEAD-3 Mono): a randomised, 52-week, phase III, double-blind, parallel-treatment trial. *Lancet* 2009; **373:** 473–81.

103 Trujillo JM, Nuffer W, Ellis SL. GLP-1 receptor agonists: a review of head-to-head clinical studies. *Ther Adv Endocrinol Metab* 2015; **6:** 19–28.

104 Zaccardi F, Htike ZZ, Webb DR, Khunti K, Davies MJ. Benefits and harms of once-weekly glucagon-like peptide-1 receptor agonist treatments: a systematic review and network meta-analysis. *Ann Intern Med* 2016; **164:** 102–13.

105 Butler PC, Elashoff M, Elashoff R, Gale EA. A critical analysis of the clinical use of incretin-based therapies: are the GLP-1 therapies safe? *Diabetes Care* 2013; **36:** 2118–25.

106 Eng C, Kramer CK, Zinman B, Retnakaran R. Glucagon-like peptide-1 receptor agonist and basal insulin combination treatment for the management of type 2 diabetes: a systematic review and meta-analysis. *Lancet* 2014; **384:** 2228–34.

107 Heine RJ, Van Gaal LF, Johns D, Mihm MJ, Widel MH, Brodows RG, GWAA Study Group. Exenatide versus insulin glargine in patients with suboptimally controlled type 2 diabetes: a randomized trial. *Ann Intern Med* 2005; **143:** 559–69.

108 Vasilakou D, Karagiannis T, Athanasiadou E, et al. Sodium-glucose cotransporter 2 inhibitors for type 2 diabetes: a systematic review and meta-analysis. *Ann Intern Med* 2013; **159:** 262–74.

109 Nauck MA, Del Prato S, Meier JJ, et al. Dapagliflozin versus glipizide as add-on therapy in patients with type 2 diabetes who have inadequate glycemic control with metformin: a randomized, 52-week, double-blind, active-controlled noninferiority trial. *Diabetes Care* 2011; **34:** 2015–22.

110 Rosenstock J, Jelaska A, Wang F, et al. Empagliflozin as add on to basal insulin for 78 weeks improves glycemic control with weight loss in insulin-treated type 2 diabetes (T2DM). *Can J Diabetes* 2013; **37:** S32.

111 Tahrani AA, Barnett AH, Bailey CJ. SGLT inhibitors in management of diabetes. *Lancet Diabetes Endocrinol* 2013; **1:** 140–51.

112 Peters AL, Buschur EO, Buse JB, Cohan P, Diner JC, Hirsch IB. Euglycemic diabetic ketoacidosis: a potential complication of treatment with sodium-glucose cotransporter 2 inhibition. *Diabetes Care* 2015; **38:** 1687–93.

113 Barnett AH. Complementing insulin therapy to achieve glycemic control. *Adv Ther* 2013; **30:** 557–76.

114 Davies MJ, Gagliardino JJ, Gray LJ, Khunti K, Mohan V, Hughes R. Real-world factors affecting adherence to insulin therapy in patients with type 1 or type 2 diabetes mellitus: a systematic review. *Diabet Med* 2013; **30:** 512–24.

115 Holman RR, Farmer AJ, Davies MJ, et al. Three-year efficacy of complex insulin regimens in type 2 diabetes. *N Engl J Med* 2009; **361:** 1736–47.

116 Weng J, Li Y, Xu W, et al. Effect of intensive insulin therapy on beta-cell function and glycaemic control in patients with newly diagnosed type 2 diabetes: a multicentre randomised parallel-group trial. *Lancet* 2008; **371:** 1753–60.

117 Horvath K, Jeitler K, Berghold A, et al. Long-acting insulin analogues versus NPH insulin (human isophane insulin) for type 2 diabetes mellitus. *Cochrane Database Syst Rev* 2007; **2:** CD005613.

118 Monami M, Marchionni N, Mannucci E. Long-acting insulin analogues versus NPH human insulin in type 2 diabetes: a meta-analysis. *Diabetes Res Clin Pract* 2008; **81:** 184–89.

119 Swinnen SG, Simon AC, Holleman F, Hoekstra JB, Devries JH. Insulin detemir versus insulin glargine for type 2 diabetes mellitus. *Cochrane Database Syst Rev* 2011; **7:** CD006383.

120 Gururaj Setty S, Crasto W, Jarvis J, Khunti J, Davies MJ. New insulins and newer insulin regimens: a review of their role in improving glycaemic control in patients with diabetes. *Postgrad Med J* 2016; **92:** 152–164.

121 Garber AJ, King AB, Del Prato S, et al. Insulin degludec, an ultra-longacting basal insulin, versus insulin glargine in basal-bolus treatment with mealtime insulin aspart in type 2 diabetes (BEGIN Basal-Bolus Type 2): a phase 3, randomised, open-label, treat-to-target non-inferiority trial. *Lancet* 2012; **379:** 1498–507.

122 Steinstraesser A, Schmidt R, Bergmann K, Dahmen R, Becker RH. Investigational new insulin glargine 300 U/ml has the same metabolism as insulin glargine 100 U/ml. *Diabetes Obes Metab* 2014; **16:** 873–76.

123 Crasto W, Jarvis J, Hackett E, et al. Insulin U-500 in severe insulin resistance in type 2 diabetes mellitus. *Postgrad Med J* 2009; **85:** 219–22.

124 Mari A, Rosenstock J, Ma X, Li YG, Jackson JA. Optimized human regular U-500 insulin treatment improves beta-cell function in severely insulin-resistant patients with long-standing type 2 diabetes and high insulin requirements. *Endocr Pract* 2015; **21:** 1344–52.

125 Zafar A, Davies M, Azhar A, Khunti K. Clinical inertia in management of T2DM. *Prim Care Diabetes* 2010; **4:** 203–07.

126 Khunti K, Wolden ML, Thorsted BL, Andersen M, Davies MJ. Clinical inertia in people with type 2 diabetes: a retrospective cohort study of more than 80,000 people. *Diabetes Care* 2013; **36:** 3411–17.

127 Khunti K, Nikolajsen A, Thorsted BL, Andersen M, Davies MJ, Paul SK. Clinical inertia in intensifying therapy among people with type 2 diabetes treated with basal insulin. *Diabetes Obes Metab* 2016; **8:** 401–09.

128 Erickson J. The cost of medication noncompliance. *AAPPO J* 1993; **3:** 33–34, 38–40.

129 Seaquist ER, Anderson J, Childs B, et al. Hypoglycemia and diabetes: a report of a workgroup of the American Diabetes Association and the Endocrine Society. *Diabetes Care* 2013; **36:** 1384–95.

130 Cryer PE. Glycemic goals in diabetes: trade-off between glycemic control and iatrogenic hypoglycemia. *Diabetes* 2014; **63:** 2188–95.

131 Khunti K, Alsifri S, Aronson R, et al. Rates and predictors of hypoglycaemia in 27,585 people from 24 countries with insulin-treated type 1 and type 2 diabetes: the global HAT study. *Diabetes Obes Metab* 2016; **18:** 907–15.

132 International Hypoglycaemia Study Group. Minimizing hypoglycemia in diabetes. *Diabetes Care* 2015; **38:** 1583–91.

133 Redelmeier DA, Kenshole AB, Ray JG. Motor vehicle crashes in diabetic patients with tight glycemic control: a population-based case control analysis. *PLoS Med* 2009; **6:** e1000192.

134 American Diabetes Association. Diabetes and driving. *Diabetes Care* 2014; **37** (suppl 1)**:** S97–S103.

135 Sinclair A, Dunning T, Rodriguez-Manas L. Diabetes in older people: new insights and remaining challenges. *Lancet Diabetes Endocrinol* 2015; **3:** 275–85.

136 Greco D, Pisciotta M, Gambina F, Maggio F. Severe hypoglycaemia leading to hospital admission in type 2 diabetic patients aged 80 years or older. *Exp Clin Endocrinol Diabetes* 2010; **118:** 215–19.

137 Lipska KJ, Ross JS, Miao Y, Shah ND, Lee SJ, Steinman MA. Potential overtreatment of diabetes mellitus in older adults with tight glycemic control. *JAMA Intern Med* 2015; **175:** 356–62.

138 Huang ES, Laiteerapong N, Liu JY, John PM, Moffet HH, Karter AJ. Rates of complications and mortality in older patients with diabetes mellitus: the diabetes and aging study. *JAMA Intern Med* 2014; **174:** 251–58.

139 Copeland KC, Zeitler P, Geffner M, et al. Characteristics of adolescents and youth with recent-onset type 2 diabetes: the TODAY cohort at baseline. *J Clin Endocrinol Metab* 2011; 96: 159–67.

140 Tamborlane WV, Haymond MW, Dunger D, et al. Expanding treatment options for youth with type 2 diabetes: current problems and proposed solutions. A white paper From the NICHD Diabetes Working Group. *Diabetes Care* 2016; **39:** 323–29.

141 Steven S, Taylor R. Restoring normoglycaemia by use of a very low calorie diet in long- and short-duration type 2 diabetes. *Diabet Med* 2015; **32:** 1149–55.

142 Steven S, Carey PE, Small PK, Taylor R. Reversal of type 2 diabetes after bariatric surgery is determined by the degree of achieved weight loss in both short- and long-duration diabetes. *Diabet Med* 2015; **32:** 47–53.

143 Xie Z, Hao H, Tong C, et al. Human umbilical cord-derived mesenchymal stem cells elicit macrophages into an anti-inflammatory phenotype to alleviate insulin resistance in type 2 diabetic rats. *Stem Cells* 2016; **34:** 627–39.

144 Woo VC. New insulins and new aspects in insulin delivery. *Can J Diabetes* 2015; **39:** 335–43.

145 Finan B, Yang B, Ottaway N, et al. A rationally designed monomeric peptide triagonist corrects obesity and diabetes in rodents. *Nat Med* 2015; **21:** 27–36.

146 Gori M, Gupta DK, Claggett B, et al. Natriuretic peptide and high-sensitivity troponin for cardiovascular risk prediction in diabetes: the Atherosclerosis Risk in Communities (ARIC) Study. *Diabetes Care* 2016; **39:** 677–85.

147 Distiller LA, Cranston I, Mazze R. First clinical experience with retrospective flash glucose monitoring (FGM) analysis in South Africa: characterizing glycemic control with ambulatory glucose profile. *J Diabetes Sci Technol* 2016; **10:** 1294–302.

148 Reznik Y, Cohen O, Aronson R, et al. Insulin pump treatment compared with multiple daily injections for treatment of type 2 diabetes (OpT2mise): a randomised open-label controlled trial. *Lancet* 2014; **384:** 1265–72.

149 Cox DJ, Taylor AG, Moncrief M, et al. Continuous glucose monitoring in the self-management of type 2 diabetes: a paradigm shift. *Diabetes Care* 2016; **9:** e71–73.

150 Kazierad DJ, Bergman A, Tan B, et al. Effects of multiple ascending doses of the glucagon receptor antagonist, PF-06291874, in patients with type 2 diabetes mellitus. *Diabetes Obes Metab* 2016; **18:** 795–802.

151 Bailey CJ, Tahrani AA, Barnett AH. Future glucose-lowering drugs for type 2 diabetes. *Lancet Diabetes Endocrinol* 2016; **4:** 350–09.