Advances in the management of diabetes: therapies for type 2 diabetes

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Received 17 March 2020

Revised 28 April 2020

Accepted 29 April 2020

ABSTRACT

The incidence of type 2 diabetes is rapidly rising worldwide leading to an increasing burden of cardiovascular and microvascular complications. The aim of treatment of the condition is to improve quality of life and reduce such complications. To this end, improvement in glucose control remains an important consideration. In recent years, important therapeutic advances have occurred in the management of hyperglycaemia in people with type 2 diabetes. These include the use of dipeptidylpeptidase-4 inhibitors, glucagon-like peptide-1 receptor agonists and sodium glucose transporter-2 inhibitors. The latter two classes appear to have some specific beneficial effects on cardiovascular and renal outcomes, independent of their antihyperglycaemic effects. This review aims to outline the current state of diagnosis and management of diabetes for the general physician, with a particular focus on new therapeutic agents for management of glucose in patients with type 2 diabetes.

INTRODUCTION

In 2017, it was estimated that 451 million adults worldwide had diabetes, equivalent to around 1 adult in 11 living with the condition,¹ and approximately 90% of these patients have type 2 diabetes (T2D).² Alarming, at present rate of increase, this number is expected to rise to 693 million by 2045. Around 5 million deaths worldwide were linked to diabetes in 2017, and the global healthcare expenditure on the condition was estimated to be US\$850 billion.²

In high-income countries, diabetes is the most common cause of blindness in people of working age,³ the most common cause of end-stage kidney disease (ESKD) and non-traumatic amputation.⁴ Cardiovascular (CV) complications are, however, the leading cause of morbidity and mortality, with nearly three out of every four people with the condition dying from CV complications.² Furthermore, the risk of a stroke is increased by four times,⁵ development of liver cirrhosis by three times⁶ and epidemiological data also suggest a significantly increased risk of cancer in patients with diabetes, independent of obesity.⁷ It is also increasingly recognised that heart failure is a major diabetes-related comorbidity.⁸

Multiple factors have driven the global epidemic of T2D, including ageing populations, sedentary lifestyles, obesity and unhealthy diets.² T2D may be preventable with lifestyle change. Meta-analysis suggests a role for lifestyle intervention and/or metformin in preventing the onset of T2M in patients with non-diabetic hyperglycaemia.⁹

Diagnosis of diabetes

Diagnosis of diabetes is based on biochemical evidence of hyperglycaemia, in the presence or absence of symptoms.¹⁰ Symptoms include polyuria, polydipsia, unexplained weight loss, hyperphagia, recurrent orogenital candidiasis or skin abscesses. Diagnostic criteria for diabetes are shown in [table 1](#). In patients who do not have symptoms, at least one additional measurement in the diabetes range is required.

WHO suggests that the use of glycated haemoglobin (HbA_{1c}) in the diagnosis of T2D provides a convenient screening method ([table 1](#)).¹¹ It is important to note, however, that the value of HbA_{1c} is dependent on the lifespan of red blood cells. Therefore, any condition that might increase red cell turnover (such as haemolysis or blood loss) will lead to a falsely lowered HbA_{1c}, and any condition that reduces red cell turnover (such as severe iron deficiency) can lead to a falsely elevated HbA_{1c}.¹² In addition, haemoglobinopathy or interfering haemoglobins may render the HbA_{1c} uninterpretable, and hence glucose tests should be used diagnostically in this circumstance.

Glycaemic control in T2D

The aim of management of diabetes is to improve quality of life and reduce diabetes-related symptoms and complications. Interventions to reduce complications include diabetes education to aid self-management, smoking cessation, improved diet and exercise, and management of blood pressure and lipids.¹³ In addition, systematic annual screening for complications is required. [Table 2](#) lists the regular assessments and interventions which people with diabetes require each year.

There exists an array of conflicting evidence demonstrating the effects of intensive versus standard glycaemic control on diabetes outcomes. A meta-analysis studying 13 randomised controlled trials (RCTs) favoured intensive glucose control at reducing risk of non-fatal myocardial infarction (MI), but showed no significant effect on CV death and all-cause mortality when compared with standard glucose control.¹⁴ This was, however, associated with a doubling in risk of severe hypoglycaemia as well as significant weight gain. With regards to microvascular complications, the meta-analysis only demonstrated a significant 10% reduction in the risk of microalbuminuria. There exists nevertheless stronger evidence that intensive glucose control may reduce the risk of nephropathy (microalbuminuria and macroalbuminuria) and progressive retinopathy in T2D. This does not, however, translate to conclusive evidence that

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To cite: Tsoutsouki J, Wunna W, Chowdhury A, et al. *Postgrad Med J* 2020;**96**:610–618.

Table 1 Diagnostic criteria for diabetes mellitus and abnormal glucose tolerance

	Fasting plasma glucose (mmol/L)		2 hours plasma glucose (mmol/L)	Random plasma glucose (mmol/L)	Glycated haemoglobin (%)
Normal	≤6.0	–	<7.8	<7.8	<6.0 (<42 mmol/mol)
Impaired fasting glucose	6.1–6.9	and	<7.8	–	–
Impaired glucose tolerance	<7.0	and	7.8–11.0	–	Pre-diabetes: 6.0–6.4 (42–47 mmol/mol)
Diabetes mellitus	≥7.0	or	≥11.1	≥11.1	≥6.5 (≥48 mmol/mol)

intensive glucose lowering treatment reduces the risk of ESKD, blindness or amputation in patients with T2D.¹⁵ Meta-analysis of observational studies also suggests a 'J-shaped' relationship between HbA_{1c} and all-cause mortality in patients with T2D, whereby very low HbA_{1c} levels appear to be associated with an increased risk of all-cause mortality.¹⁶

The Action to Control Cardiovascular Risk in Diabetes (ACCORD) study was an RCT specifically designed to look at the effect of intensive glycaemic control (HbA_{1c} <6% vs 7%–7.9%) on macrovascular (cardiovascular disease (CVD) morbidity, all-cause mortality) and microvascular complications in patients with T2D.¹⁷ The intensive glycaemic control arm had to be prematurely discontinued after a median of 3.7 years follow-up due to concerning evidence that it led to a 22% increase in all-cause mortality rate (HR 1.22, CI 1.01 to 1.46, *p*=0.04). The ACCORD trial did have its limitations as all the participants belonged to a higher risk group with average diabetes duration of about 10 years, and were either older or with already established or high-risk CVD, compared with previous studies. Also, the tailoring of medication in order to achieve the target HbA_{1c} was not carefully selected, leading to high rates of hypoglycaemia which might have contributed to these higher mortality rates.

With this in mind, many international guidelines suggest *individualisation* of glycaemic targets. The 2018 European Association for the Study of Diabetes and the American Diabetes Association guidelines currently suggest an HbA_{1c} target

of around 53 mmol/mol (7.0%) or less, but individualised based on patient characteristics and risk of adverse effects of therapy.¹⁸ Similarly, the UK National Institute of Health and Clinical Excellence guidelines recommend that HbA_{1c} targets should be relaxed in patients who are at high risk of the consequences of hypoglycaemia, such as the older, frailer and those with a longer duration of diabetes, or presence of severe comorbidities and/or established vascular complications.^{19 20}

PHARMACOLOGICAL MANAGEMENT OF GLUCOSE IN T2D

The number of therapeutic agents available for the management of hyperglycaemia in T2D has grown significantly in the last two decades. In 2008, the US Food and Drug Advisory Committee mandated that all new antihyperglycaemic therapies should undergo testing to establish their CV safety, using cardiovascular outcome trials (CVOTs).²¹ This was in response to concerns around the use of rosiglitazone which, while an effective antihyperglycaemic agent, appeared to increase CV events in certain patients.²² CVOTs are large, multicentre, double-blind, randomised control trials, most of which use three-point major adverse cardiovascular events (3p-MACE) as their primary endpoint (non-fatal stroke, non-fatal MI and CV death), with some also adding hospitalisation for unstable angina to these three outcomes (4p-MACE). Hospitalisation for heart failure (hHf), being a common complication of T2D and contributing to its high mortality, is also included, usually as a secondary end point. More recently, there has been a shift of focus of trials specifically examining renal outcomes.

Table 3 presents an overview of newer and older glucose lowering medications, and table 4 outlines the latest CVOTs published using newer glucose lowering medications.

Older agents

Metformin

Metformin is the first line antihyperglycaemic for the management of T2D in the absence of contraindications.²³ It inhibits gluconeogenesis and increases insulin-mediated glucose utilisation peripherally.²⁴ It has good glycaemic efficacy (10–15 mmol/mol (1.0%–1.5%) HbA_{1c} reduction) and excellent long-term safety profile.²⁵ It does not cause hypoglycaemia and favours weight reduction (approximately 1.1 kg).²⁶ The most common side effect is gastrointestinal upset, which may be mitigated by slow titration and taking the drug with meals.²⁷ It is contraindicated in patients with estimated glomerular filtration rate (eGFR) <30 mL/min/1.73 m², active liver disease, unstable heart failure or history of lactic acidosis while on metformin. There is weak evidence associating metformin use in these subgroups to lactic acidosis.²⁸

Table 2 Annual assessment and interventions in patients with type 2 diabetes

Assessment	Intervention
Diet and lifestyle	Referral for structured diabetes education and dietary management
Smoking status	Referral for smoking cessation
Foot assessment	If high risk for ulceration, referral for podiatry
Digital retinal screen	Referral for retinopathy management to ophthalmology
Blood pressure (BP)	Treat if persistently above 140/80 mm Hg (or 130/80 mm Hg with renal or cardiovascular disease)
Lipids	Statin therapy in all with CHD risk >10%, or type 1 diabetes >10 years
Renal assessment (urine albumin/creatinine ratio (ACR) and estimated GFR)	ACE inhibitors or angiotensin receptor blockers if ACR elevated, aiming for BP <130/80 mm Hg
Glycaemic control (HbA _{1c})	Decide on target and optimise therapy

GFR, glomerular filtration rate.

Table 3 An overview of antidiabetic medications

Class	Mechanism of action	Clinical characteristics	Side effects	Contraindications/cautions
Biguanide: <i>Metformin</i>	Decrease hepatic gluconeogenesis and intestinal glucose absorption Increase insulin-mediated glucose utilisation peripherally	Reduce LDL/increase HDL cholesterol Low risk of hypoglycaemic Weight neutral Cost effective	Gastrointestinal symptoms (nausea, diarrhoea, flatulence) Metformin-associated lactic acidosis (rare)	Chronic kidney disease (CKD; eGFR <30 mL/min) Severe liver failure Previous lactic acidosis on metformin
Sulfonylureas: <i>Gliclazide</i> Prandial glucose regulators: <i>Repaglinide</i>	Increase insulin secretion by beta-cells	Low cost	Hypoglycaemic Weight gain	Obesity Severe cardiovascular comorbidity
Thiazolidinediones: <i>Pioglitazone</i>	Increase insulin sensitivity by activating PPAR γ	Reduce LDL and triglycerides Increase HDL No risk of hypoglycaemia	Fluid retention Weight gain Increased risk of heart failure Postmenopausal fracture	Congestive heart failure Liver failure History of bladder cancer Osteopaenia/osteoporosis
GLP-1 RA: <i>Albiglutide</i> <i>Dulaglutide</i> <i>Exenatide</i> <i>Liraglutide</i> <i>Semaglutide</i>	Mimic incretin effect: increase insulin secretion, decrease glucagon secretion, delay gastric emptying	No risk of hypoglycaemia Weight loss	Gastrointestinal upset Association with pancreatitis	Chronic pancreatitis or family history of pancreatic cancer
DPP-4i: <i>Alogliptin</i> <i>Linagliptin</i> <i>Saxagliptin</i> <i>Sitagliptin</i> <i>Vildagliptin</i>	Increase endogenous insulin and suppress glucagon.	No risk of hypoglycaemia Weight neutrality	Gastrointestinal upset Slight increased risk of pancreatitis	Personal history of pancreatitis
SGLT-2i: <i>Canagliflozin</i> <i>Dapagliflozin</i> <i>Empagliflozin</i>	Reversible inhibition of SGLT2 receptors in the kidney leading to glycosuria and reduced glucose absorption	Weight loss Reduces blood pressure Cardiovascular and renal protection	Urogenital infections Euglycaemic diabetic ketoacidosis Fournier's gangrene (rare)	Recurrent urinary tract infections CKD

DPP-4i, dipeptidylpeptidase-4 inhibitor; eGFR, estimated glomerular filtration rate; GLP-1 RA, glucagon-like peptide-1 receptor agonist; HDL, high-density lipoprotein; LDL, low-density lipoprotein; PPAR γ , peroxisome proliferator activated receptor- γ ; SGLT-2i, sodium glucose transporter-2 inhibitor.

Metformin reduces all-cause mortality and hHF.²⁹ There is some epidemiological evidence that it may reduce the risk of cancer.^{30 31}

Sulfonylureas

Sulfonylureas stimulate pancreatic beta-cells to release insulin. Their use is favoured by their low cost and potent glucose-lowering properties (10–15 mmol/mol (1%–1.5%) HbA_{1c} reduction).³² Weight gain associated with their use is a significant undesired risk factor, and sulfonylureas may also lose efficacy as a result of beta-cell failure.³³ Hypoglycaemia, which can be severe in certain groups such as the elderly or renally impaired, is the main factor limiting their use, as it is much more frequent compared with incretin-based therapies or metformin.^{34 35} As sulfonylurea metabolites are renally excreted, the risk of hypoglycaemia is significantly higher in patients with chronic kidney disease (CKD), although less problematic with shorter acting sulfonylureas with mostly inactive metabolites, such as glimepiride and gliclazide.³⁶ Sulfonylureas may cause severe, prolonged hypoglycaemia, especially in the elderly with the presence of cognitive decline or meal inconsistency.³⁷ Newer sulfonylureas may have a slightly more favourable CV profile, compared with older agents.³⁸

Thiazolidinediones

Thiazolidinediones (glitazones) act via peroxisome proliferator-activated receptor- γ receptors in muscle, adipose tissue and liver to increase insulin sensitivity. They have similar glycaemic effectiveness to metformin,³⁹ but their use is limited due to adverse effects, including weight gain and fluid retention, which can exacerbate heart failure (and hence are contraindicated),⁴⁰ and

increased postmenopausal fractures in women.⁴¹ An increased risk of bladder cancer was associated with pioglitazone use in T2D,⁴² although this association was not confirmed at 10-year follow-up.⁴³

Rosiglitazone increases baseline LDL levels,⁴⁴ and was associated with a 43% increase in MI in a meta-analysis,²⁵ although this was not confirmed in a subsequent RCT.⁴⁵ Rosiglitazone has been discontinued in Europe following concerns over its safety profile.

Newer agents

Glucagon-like peptide-1 receptor analogues (GLP-1 RA)

GLP-1, a natural peptide involved in glucose homeostasis, is secreted by the L-cells of the small intestine in response to glucose ingestion. It stimulates pancreatic β -cell insulin secretion, inhibits glucagon release from α -cells and has a direct effect on delaying gastric emptying and inducing satiety.⁴⁶ This is known as the incretin effect, which is disrupted in T2D.⁴⁷ Native GLP-1 has a short half-life as it is degraded by the enzyme, dipeptidyl-peptidase-4 (DPP-4).⁴⁸

GLP1-RAs stimulate glucose-dependent insulin secretion. They are resistant to DPP-4 degradation and are administered subcutaneously. They achieve significant reductions in HbA_{1c} without the risk of hypoglycaemia. GLP1-RAs favour weight loss and improvements in lipids and blood pressure. They can be initiated in patients with eGFR as low as 15 mL/min/1.73 m².

Gastrointestinal upset is a common adverse effect, and frequent reason for discontinuation. Early studies suggested an association with pancreatitis and pancreatic cancer, but this unconfirmed in recent meta-analysis.⁴⁹ In SUSTAIN-6, semaglutide was linked to higher rates of retinopathy compared with

Table 4 A summary of cardiovascular (CV) outcomes trials with antihyperglycaemic medications in type 2 diabetes (T2DM)

Class	Drug	CVOT and total patients (n)	Median follow-up (years)	Patient characteristics (all T2DM)	Outcomes
SGLT-2i	Empagliflozin	EMPA-REG Outcome (2015) n=7020	3.1	Established CVD (99%) eGFR >30 History of: MI>50% Multivessel CVD 5% HF 10%	Lower 3p-MACE HR 0.86 (0.79 to 0.9) Lower CV-related deaths HR 0.62 (0.49 to 0.77) Lower death from any cause HR 0.68 (0.57 to 0.82) Lower hHF HR 0.65 (0.50 to 0.85) No significant difference in: MI, stroke
	Canagliflozin	CANVAS Program (2017) n=10 142	2.4	Either: 1. >30 years old +established CVD (65.6%) 2. >50 years+2 or more CV risk factors eGFR >30	Lower 3p-MACE HR 0.86 (0.75 to 0.97) Lower albuminuria progression HR 0.73 (0.67 to 0.79) Lower composite outcome of 40% eGFR reduction, RRT need, death from renal causes HR 0.60 (0.47 to 0.77) No significant difference in CV death, death from any cause
		CREDENCE (2019) n=4401	2.62	Albuminuric CKD	Lower renal-specific composite of ESRD, doubling of creatinine, death from renal causes HR 0.66 (0.53 to 0.81) Lower ESRD HR 0.68 (0.54 to 0.86) Lower CV death, MI, stroke HR 0.80 (0.67 to 0.95) Lower hHF HR 0.61 (0.47 to 0.80)
	Dapagliflozin	DECLARE-TIMI 58 (2019) n=17 160	4.2	Either: 1. Established CVD (40.6%) 2. Multiple CV risk factors (59.4%)	No significant difference in 3p-MACE HR 0.93 (0.84 to 1.03) Lower hHF HR 0.73 (0.61 to 0.88) Reduced renal events HR 0.76 (0.67 to 0.87) No significant difference in CV death, death from any cause
DPP-4i	Saxagliptin	SAVOR-TIMI 53 (2013) n=16 492	2.1	History or multiple risk factors for CVD	No significant difference in 3p-MACE HR 1.0 (0.89 to 1.12) No significant difference in all-cause mortality, CV death, MI, stroke, hospitalisation for angina Significant increase in hHF HR 1.27 (1.07 to 1.51)
	Alogliptin	EXAMINE (2013) n=5380	1.5	ACS (AMI or UA requiring hospitalisation) within 15–90 days before randomisation	No significant difference in 3p-MACE HR 0.96 (≤1.16) No significant difference in all-cause mortality, CV death Contributed to a non-significant 19% increase in hHF
	Sitagliptin	TECOS (2015) n=14 671	3.0	Established CVD	No significant difference in 4p-MACE HR 0.98 (0.88 to 1.09) No significant difference in hHF HR 1.0 (0.83 to 1.20)
	Linagliptin	CARMELINA (2018) n=6979	2.2	High CV risk (history of vascular disease and UACR >200 mg/g), and High renal risk (reduced eGFR and microalbuminuria or macroalbuminuria). ESRD patients excluded	No significant difference in 3p-MACE HR 1.02 (0.89 to 1.17) No significant difference for hHF HR 0.90 (0.74 to 1.08)
		CAROLINA (2019) n=6042	6.3	High CV risk	Non inferior to glimepiride in 3p-MACE HR 0.98 (0.84 to 1.14); p<0.001 for non-inferiority
GLP-1 RA	Exenatide	EXSCEL (2017) n=14 752	3.2	73.1% with established CVD	No significant difference in 3p-MACE HR 0.91 (0.83 to 1.00) No significant difference in CV death, fatal or non-fatal MI, fatal or non-fatal stroke, hHF, ACS hospitalisation
	Lixisenatide	ELIXA (2015) n=6068	2.1	History of ACS	No significant difference in 4p-MACE HR 1.02 (95% CI 0.89 to 1.17) No significant difference in CV death, hHF
	Liraglutide	LEADER (2016) n=9340	3.8	Either: 1. ≥50 years with established CVD 2. ≥60 years with at least one CV risk factor	Lower 3p-MACE HR 0.87 (0.78 to 0.97) Lower CV-related deaths HR 0.78 (0.66 to 0.93) Lower all-cause mortality HR 0.85 (0.74 to 0.97) No significant difference in hHF, non-fatal MI, non-fatal stroke
	Semaglutide	SUSTAIN-6 (2016) n=3297	2.1	83% with established CVD, CKD or both 17% with CV risk factors	Lower 3p-MACE HR 0.74 (0.58 to 0.95) Lower rate of non-fatal MI HR 0.74 (0.51 to 1.08) Lower rate of non-fatal stroke HR 0.61 (0.38 to 0.99) No significant difference in CV deaths, hHF
	Dulaglutide	REWIND (2019) n=9622	5.4	≥50 years old 31% with established CVD 69% with CV risk factors	Lower 3p-MACE HR 0.88 (0.79 to 0.99) Lower rate of non-fatal stroke HR 0.76 (0.6 to 0.95) No significant difference in non-fatal MI, all-cause mortality
	Albiglutide	HARMONY (2018) n=9400	1.6	≥40 years old Established CVD	Lower 3p-MACE HR 0.78 (0.65 to 0.90) Lower rate of fatal or non-fatal MI HR 0.75 (0.61 to 0.90)

ACS, acute coronary syndrome; CARMELINA, Cardiovascular Safety and Renal Microvascular Outcome Study With Linagliptin; CAROLINA, Cardiovascular Outcome study of LINagliptin versus glimepiride in patients with type 2 diabetes; CKD, chronic kidney disease; CREDENCE, Canagliflozin and Renal Endpoints in Diabetes with Established Nephropathy Clinical Evaluation; CVD, cardiovascular disease; CVOT, cardiovascular outcomes trials; DECLARE-TIMI, Dapagliflozin Effect on Cardiovascular Events–Thrombolysis in Myocardial Infarction; DPP-4i, dipeptidylpeptidase-4 inhibitor; eGFR, estimated glomerular filtration rate; EMPA-REG, The Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients–Removing Excess Glucose; ESRD, end-stage renal disease; EXAMINE, Examination of Cardiovascular Outcomes with Alogliptin versus Standard of Care; GLP-1 RA, glucagon-like peptide-1 receptor agonist; HF, heart failure; hHF, hospitalisation for heart failure; MI, myocardial infarction; 3p-MACE, three-point major adverse cardiovascular event (composite of cardiovascular death, non-fatal myocardial infarction, non-fatal stroke); 4p-MACE, four-point major adverse cardiovascular event (composite of cardiovascular death, non-fatal myocardial infarction, non-fatal stroke, or hospitalisation for unstable angina); RRT, renal replacement therapy; SAVOR-TIMI, Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus–Thrombolysis in Myocardial Infarction; SGLT-2i, sodium glucose transporter-2 inhibitor; TECOS, Trial to Evaluate Cardiovascular Outcomes After Treatment With Sitagliptin.

placebo, thought to be due to rapid HbA_{1c} reductions in patients with pre-existing retinopathy.⁵⁰

GLP1-RAs have differing structures and duration of action and the CVOTs involving these agents varied in size and patient characteristics, making the findings inconsistent. A meta-analysis of the seven largest trials (ELIXA,⁵¹ EXSCAL,⁵² LEADER,⁵³ SUSTAIN-6,⁵⁰ REWIND,⁵⁴ PIONEER-6,⁵⁵ HARMONY⁵⁶) studying 56 004 patients showed a 12% reduction in the 3p-MACE associated with GLP1-RAs, without heterogeneity across patient subgroups.⁴⁹ This observation was due to reduced rates of CV death (12%), fatal or nonfatal stroke (16%) and fatal or nonfatal MI (9%). There was also a reduction in all-cause mortality (12%) and hHF (9%), predominantly seen with albiglutide.⁵⁶ There is some heterogeneity between agents—exenatide and lixisenatide have not demonstrated improved CV outcomes.^{51–52} A composite renal outcome was reduced by 17% for all GLP1-RA, mainly due to a reduction in new macroalbuminuria.

Liraglutide (LEADER) was the first GLP1-RA to prove superiority with a 13% decrease in 3p-MACE, attributed to a 22% decrease in CV deaths after 3.8 years of follow-up.⁵³ There was no significant effect on the hHF and non-fatal rates of MI and stroke. All cause mortality decreased by 15%. Liraglutide's benefits were observed in a high CV risk cohort (81.3% had established CV disease, HbA_{1c} averaged 8.7% and a significant number had CKD stage 3 or greater), with mean diabetes duration of 12.8 years; therefore, it is uncertain whether these results could be extrapolated into lower CV risk patients.

Dulaglutide was superior to placebo in achieving a 3p-MACE (HR 0.88; 0.79 to 0.99) over 5.4 years due to the significant benefit against non-fatal stroke (HR 0.76; 0.6 to 0.95). In contrast to other studies, REWIND was the longest trial studying GLP1-RAs with only 31% of participants with established CVD and otherwise all had a low baseline HbA_{1c}.⁵⁴

Semaglutide (SUSTAIN-6) led to a 26% reduction in the 3p-MACE after 2.1 years of follow-up, attributed to a 26% reduction in non-fatal MI and a 39% decrease in the rate of non-fatal stroke. Semaglutide did not affect hHF outcomes or CV-related deaths. Comparable to the LEADER trial, the participants also had high CV risk.⁵⁰ Semaglutide led to a significant 76% increase in retinopathy complications (HR 1.76 (1.11 to 2.78), not seen in other trials. This could be attributed to the large and rapid HbA_{1c} improvement observed (−0.7% and −1.0% with Semaglutide 0.5 mg and 1.0 mg, respectively), not seen with most other GLP1-RAs. The significant HbA_{1c} improvement might also be responsible for the CV benefit observed. More recently, oral semaglutide studied in PIONEER-6 only showed non-inferiority to placebo in 3p-MACE.⁵⁵

Finally, albiglutide (HARMONY outcomes) reduced the 3p-MACE relative risk by 22% over a median of 1.6 years. All participants had established CVD, cerebrovascular disease, heart failure or peripheral arterial disease. Alike SUSTAIN-6 and LEADER, the participants had a high baseline HbA_{1c} (median 8.7%). The CV effects were irrespective of the small glucose-lowering effect (−0.52%)⁵⁶; therefore, challenging the possibility that the cardioprotective effects of GLP-1 RAs are solely linked to glucose-lowering efficacy. This study did not look at retinopathy outcomes, which would help infer whether the increased retinopathy events in SUSTAIN-6 (Semaglutide) were an undesirable effect of the drug or were due to the relative rapid reduction in HbA_{1c}.

DPP-4 inhibitors (DPP-4i)

DPP-4i (gliptins) increase the bioavailability of native GLP-1. They improve glycaemic control by increasing endogenous insulin and

suppressing glucagon. They demonstrate modestly improved glycaemic control, but smaller HbA_{1c} improvements compared with GLP1-RAs (8–10 mmol/mol (0.8–1.0%)). They are weight neutral with a low risk of hypoglycaemia, and few side effects.⁵⁷ A slight increase in risk of pancreatitis has been linked to their use.⁵⁸

All CVOTs studying DPP-4i (TECOS (sitagliptin),⁵⁹ EXAMINE (alogliptin),⁶⁰ SAVOR-TIMI53 (saxagliptin),⁶¹ VIVID (vildagliptin in ventricular dysfunction diabetes),⁶² CARMELINA (linagliptin))⁶³ have demonstrated CV safety, but no evidence of CV protection. Sitagliptin (TECOS) was not inferior to placebo in terms of four-point MACE outcomes, which included hospitalisations for unstable angina, and hospitalisations with heart failure in patients with established CVD.⁵⁹

Saxagliptin and alogliptin may exacerbate heart failure. Saxagliptin contributed to a significant 27% increase in hHF,⁶¹ and alogliptin was associated with a non-significant 19% increase in hHF.⁶⁰ Meta-analysis confirmed an increased risk of hHF by 25%.⁶⁴ Alogliptin was studied in a high CV risk population that were recently hospitalised with ACS. This might have been a confounding factor contributing to the higher rates of heart failure observed. EXAMINE, however, provides reassuring data that alogliptin does not increase CV morbidity or mortality over 18 months in patients with a recent ACS.

Linagliptin (CAROLINA) had comparable 3p-MACE rates to the sulfonylurea glimepiride in 6033 adults with T2D over a median of 6 years. Lower incidence of hypoglycaemia and weight gain was noted with linagliptin.⁶⁵ In patients with CKD, linagliptin can be given at a standard dose irrespective of the renal function. To date, CARMELINA is the only trial evaluating kidney outcomes of DPP-4i in patients with T2D at high cardiorenal risk. Linagliptin did not cause renal disease progression, irrespective of the level of renal impairment, but did demonstrate lower rates of albuminuria progression (HR 0.86) compared with placebo.⁶⁶

Sodium glucose transporter-2 inhibitors (SGLT-2i)

SGLT-2i (gliflozins) inhibit SGLT-2 in the proximal convoluted tubule, hence promoting glycosuria. This improves glycaemic control and leads to weight loss of up to 5 kg.⁶⁷ They have comparable glycaemic efficacy to conventional treatments.⁶⁸ As their action depends on GFR, their glucose-lowering effect decreases with worsening renal function. Both dapagliflozin and canagliflozin are comparable to glimepiride in glycaemic lowering when added to metformin.^{69–70} Canagliflozin and empagliflozin produce greater HbA_{1c} reductions than sitagliptin irrespective of their dose, when added to metformin.^{71–72} The risk of hypoglycaemia in the absence of insulin or sulfonylureas is low.⁶⁷

Enhanced natriuresis and glycosuria-driven osmotic diuresis, with subsequent inhibition of the renin-angiotensin system, contributes to blood pressure reduction. Other improvements also noted are reduced arterial stiffness, intravascular volume contraction and intrarenal haemodynamic alterations.⁷³ They are generally associated with an all-cause mortality reduction, irrespective of the HbA_{1c}, body weight, blood pressure and serum uric acid reductions seen in studies, therefore linking it to the diuretic and natriuretic properties of the drugs.⁶⁸ Current guidelines advise initiation of SGLT-2i in T2D only when eGFR is >60 mL/min/1.73 m² and discontinuation once below 45 mL/min/1.73 m². Their most common side effect is urinary tract infection, or genital mycotic infections. SGLT-2i have been associated with a slightly increased risk of euglycaemic diabetic ketoacidosis⁷⁴ and Fournier's gangrene.⁷⁵ An increased risk of amputation was seen with canagliflozin in the CANVAS trial,⁷⁶ which was not reproduced in a subsequent study.

Nevertheless, it is prudent to stop canagliflozin if a significant lower limb complication arises and avoid in patients at high risk.

A recent meta-analysis of three large CVOTs studying the effects of empagliflozin (EMPA-REG),⁷⁷ canagliflozin (CANVAS-PROGRAM)⁷⁶ and dapagliflozin (DECLARE-TIMI 58)⁷⁸ on CV and renal outcomes demonstrated benefits in all endpoints, the extent of which depended on the patient characteristics in which they were used. SGLT-2i, as a group, led to an 11% reduction in the 3p-MACE, an effect entirely confined to patients with underlying atherosclerotic CVD (HR 0.86 (0.80 to 0.93) vs HR 1.00 (0.87 to 1.16)). MI risk was reduced by 15% and CV death by 20% (38% for empagliflozin, 13% for canagliflozin). SGLT-2i had no effect on stroke in both subgroups.⁷⁹

In DECLARE-TIMI 58,⁷⁸ dapagliflozin did not lead to a significant 3p-MACE (HR 0.93 (0.84 to 1.03)) or CV death reduction, but only 40.6% of the participants had established CVD, as opposed to 100% and 65.6% in EMPA-REG and CANVAS, respectively. In their respective studies, both empagliflozin and canagliflozin led to a 14% reduction of the 3p-MACE. Meta-analysis showed that in patients with atherosclerotic CVD, empagliflozin had a more pronounced effect on CV death than canagliflozin or dapagliflozin. Whether this is attributed to the underlying patient characteristics or specific drug differences is undetermined.

In the same meta-analysis, a significant reduction of 23% was seen in the risk for the composite of CV death and hHF, irrespective of underlying CV characteristics. hHF was reduced by 31% in both subgroups (35% for empagliflozin, 33% for canagliflozin and 27% for dapagliflozin). Interestingly, patients with worse renal function had greater reductions in hHF.

SGLT-2i also caused a robust 45% reduction in the composite renal outcomes, which were more pronounced in patients with better renal function at baseline.⁷⁹ This comprised reductions in

albuminuria progression, worsening renal function, advancement of ESRF and death from a renal cause. Macroalbuminuria rates were significantly reduced by 38% for empagliflozin,⁸⁰ 42% for canagliflozin⁸¹ and 29% for dapagliflozin,⁸² in their respective studies.

The CREDENCE study⁸³ looked at cardiorenal outcomes in two groups of patients with T2D and albuminuric CKD—50.4% had a history of CVD. All participants were already on ACE inhibitors. At median follow-up of 2.62 years, canagliflozin was associated with a 34% reduction in the renal specific composite (doubling of serum creatinine (HR 0.60), ESKD (HR 0.68), renal or CV death (HR 0.72)), without heterogeneity across the primary and secondary prevention groups. Urinary albumin creatinine ratio (ACR) was 31% lower in the canagliflozin group. This was in addition to a 20% relative risk decline in all three components of the 3p-MACE, and 39% reductions in hHF, studied as secondary outcomes. Canagliflozin is, therefore, the only antihyperglycaemic drug to show effectiveness in reducing cardiorenal outcomes in primary prevention groups with T2D and CKD. It also demonstrates cardiorenal efficacy across all stages of CKD, highest in the eGFR groups of 45–60 mL/min/1.73 m² and urinary ACR >1000 mg/mL.

CONCLUSIONS

The management of patients with diabetes involves a multidisciplinary team approach, with the patient at the centre of their care, and indeed new guidelines emphasise the need to tailor the approach to the needs of the patient. New therapeutics for T2D enables us to approach each patient as an individual, and personalise therapy according to their preferences, complications and comorbidities. The positive benefits of newer therapies on other conditions such as weight, blood pressure, CVD and renal disease, plus the lack of hypoglycaemia with these drugs, suggest

Main messages

- Therapeutic options for the management of glucose in people with type 2 diabetes (T2D) have grown in recent years. Large cardiovascular outcomes trials have given an insight into the effects of these drugs on non-glucose-related outcomes.
- Glucagon-like-peptide-1 receptor agonists (GLP-1 RA) are injectable agents that have the positive benefit of improving glucose control and reducing weight. They frequently, however, cause gastrointestinal side effects. Some GLP-1 RAs have shown positive benefits in reduction of cardiovascular outcomes.
- Sodium glucose transporter-2 inhibitors (SGLT-2i) are oral agents that improve glucose and weight by inducing glycosuria. They may cause urogenital infections and occasionally euglycaemic ketoacidosis. Large randomised trials of SGLT-2i have shown benefits in cardiovascular outcomes, especially heart failure and stroke. In addition, renal outcome studies suggest a reduction in the risk of progressive renal disease.

Current research questions

- Do GLP-1 RAs have a role in the prevention of cardiovascular disease (CVD) in people with or without T2D?
- Do SGLT2-i agents have a role in the prevention of CVD or renal disease in people with or without T2D?
- Do GLP-1 RAs or SGLT-2i agents have a role in the prevention of T2D in people at high risk for developing the condition?

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Self assessment questions

1. A 56-year-old man with type 2 diabetes was seen in a diabetes clinic for review. His diabetes clinician suggested that his glucose control was poor, and that he needed another agent in addition to metformin. His body mass index was 27 kg/m² and he had evidence of proteinuria. His estimated glomerular filtration rate was >60 mL/min/1.73 m². Which of the following agents is the most appropriate to prescribe?
 - a. Di-peptidylpeptidase-4 inhibitor (eg, sitagliptin).
 - b. Insulin.
 - c. Pioglitazone.
 - d. Sodium glucose transporter-2 inhibitor (eg, canagliflozin).
 - e. Sulfonylurea (eg, gliclazide).
2. A 46-year-old woman with type 2 diabetes was seen by her practice nurse with poor glycaemic control. She was treated with metformin and sitagliptin at maximum tolerated doses. She had a history of myocardial infarction. Her body mass index was 37 kg/m². Which of the following agents is most appropriate to prescribe?
 - a. Add insulin.
 - b. Add pioglitazone.
 - c. Add sodium glucose transporter-2 inhibitor (eg, canagliflozin).
 - d. Add sulfonylurea (eg, gliclazide).
 - e. Stop sitagliptin and add glucagon-like peptide-1 receptor antagonist (eg, liraglutide).
3. An 82-year-old man with type 2 diabetes was admitted to hospital following a fall. He had type 2 diabetes and a history of cognitive impairment. His glycated haemoglobin was noted to be 68 mmol/mol (8.5%), treated with metformin. He had no symptoms related to his diabetes. Which of the following is the correct therapeutic option?
 - a. Glucagon-like peptide-1 receptor antagonist (eg, liraglutide).
 - b. Insulin.
 - c. No additional treatment needed.
 - d. Sodium glucose transporter-2 inhibitor (eg, canagliflozin).
 - e. Sulfonylurea (eg, gliclazide).
4. A 45-year-old man with type 2 diabetes was seen by his general practitioner, complaining of nausea, abdominal pain and vomiting. His diabetes medications included metformin, sitagliptin and empagliflozin, the latter of which was started 3 months earlier. On examination, blood pressure was 96/54 mm Hg, pulse 109 and he was afebrile. Capillary blood glucose was 10.5 mmol/L. Which of the following tests should be immediately undertaken?
 - a. Chest X-ray.
 - b. ECG.
 - c. N-terminal pro-BNP (brain natriuretic peptide).
 - d. Plasma ketones.
 - e. Pulse oximetry.
5. A 76-year-old man was seen for diabetes review. He had type 2 diabetes for 12 years, and stable chronic kidney disease stage 3b. He was treated with metformin 500 mg two times a day, linagliptin 5 mg one time a day and gliclazide 80 mg two times a day. His glycated haemoglobin was 50 mmol/mol (6.7%). Which of the following is most appropriate?
 - a. Add glucagon-like peptide-1 receptor antagonist (eg, liraglutide).
 - b. Add sodium glucose transporter-2 inhibitor (eg, canagliflozin).
 - c. No change required.
 - d. Reduce and consider stopping gliclazide.
 - e. Stop metformin.

that these agents should be higher in the therapeutic pathway for many patients with these comorbidities. In particular, GLP-1 RAs and SGLT-2i may be prescribed more frequently in patients to prevent weight gain, renal or CVD. Non-specialists need to be aware of the effects and adverse effects of these agents as they are likely to be prescribed more frequently in the future.

Contributors JT wrote the main sections on glucose control and older/newer agents. AC and WW contributed sections, referenced, reviewed and revised the manuscript. TAC conceived the idea, wrote and rewrote various sections including the self-assessment questions and is the guarantor.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient consent for publication Not required.

Provenance and peer review Commissioned; externally peer reviewed.

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Answers

1. (d)
2. (e)
3. (c)
4. (d)
5. (d)