New type 2 diabetes drugs and their cardiovascular effects

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Recent cardiovascular outcome trials have shown that drugs in the new glucose-lowering medication classes, the GLP-1 receptor agonists, the DPP-4 inhibitors and the SGLT-2 inhibitors, are safe to use in patients with type 2 diabetes and can, to varying degrees, improve various cardiovascular risk factors.

Key points

- **Cardiovascular disease is the leading cause of death, morbidity and hospitalisation in people with type 2 diabetes.**
- **Several new classes of antidiabetic agents can improve various cardiovascular risk factors, including weight, blood pressure and lipid profile, in addition to lowering blood glucose levels. They rarely cause hypoglycaemia.**
- **Cardiovascular outcome studies to date support the safety of three dipeptidyl peptidase-4 (DPP-4) inhibitors (alogliptin, saxagliptin and sitagliptin), one glucagon-like peptide-1 (GLP-1) receptor agonist (lixisenatide) and one sodium–glucose cotransporter-2 (SGLT-2) inhibitor (empagliflozin) in people with type 2 diabetes who have, or are at high risk of, cardiovascular disease.**
- **Specific cardiovascular benefits of DPP-4 inhibitors and GLP-1 receptor agonists over standard diabetes therapy have not yet been demonstrated.**
- **There remains some concern about DPP-4 inhibitors and heart failure risk despite the reassuring findings with sitagliptin in the TECOS trial.**
- **One study has shown that the use of the SGLT-2 inhibitor empagliflozin in patients with type 2 diabetes and established cardiovascular disease improves cardiovascular and all-cause mortality and heart failure outcomes.**

Cardiovascular disease is the major cause of morbidity, hospitalisation and mortality in people with type 2 diabetes.[1] Epidemiological and Mendelian genetic studies have suggested that glycaemia is an important predictor of cardiovascular disease. Several studies have shown improved quality of life and a reduction in symptoms and microvascular complications (retinopathy, nephropathy and neuropathy) through targeting stricter glycaemic control over three to five years, but it has been much more difficult to demonstrate better cardiovascular outcomes.

Longer-term follow up of participants in the original UK Prospective Diabetes Study (UKPDS) and Veterans Affairs Diabetes Trial (VADT) have shown improvements in cardiovascular outcomes with intensive glucose lowering that have not been shown in the short-term studies.[2,3] Improved cardiovascular outcomes may not have been seen in these studies due to their own shorter duration of follow up; however, a possible explanation for this may be potential adverse cardiovascular effects of some therapies used in these studies. This issue was first raised over 40 years ago when the University Group Diabetes Program (UGDP) study findings suggested an increased cardiovascular risk in people with type 2 diabetes treated with the sulfonylurea tolbutamide.[4] Further concern occurred when the use of the thiazolidinedione rosiglitazone was found to be associated with an increased risk of myocardial infarction and cardiac death.[5] As a result of this concern, the TGA issued a boxed warning for rosiglitazone in 2010. Various drug regulatory bodies around the world, including the US Food and Drug Administration, now require strict guidelines to be met by new antidiabetic agents to ensure that they are not associated with an unacceptable increase in cardiovascular risk.[6]

Several new classes of glucose-lowering medications have been developed for the treatment of type 2 diabetes. These new drug classes are the glucagon-like peptide-1 (GLP-1) receptor agonists, dipeptidyl peptidase-4 (DPP-4) inhibitors and sodium–glucose cotransporter-2 (SGLT-2) inhibitors. This article will discuss the drugs that are available within Australia.

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All the available drugs in these classes have demonstrated efficacy in lowering glycated haemoglobin (HbA_{1c}) and their risk of causing hypoglycaemia is low. Minimising hypoglycaemia is of particular importance as the Action to Control Cardiovascular Risk in Diabetes (ACCORD) study demonstrated a clear association between hypoglycaemic events and increased cardiovascular mortality.[7] The exact mechanism by which this increased cardiovascular mortality occurs is uncertain but is thought to involve the effects of inflammation and sympathoadrenal responses on vascular endothelium, cardiomyocytes and platelets.[8]

Recent trials have demonstrated that these newer antidiabetic agents can, to varying degrees, improve cardiovascular risk factors, including weight, blood pressure and dyslipidaemia (Tables 1 and 2). Animal models and short-term human trials may suggest other potentially favourable cardiovascular effects, but ultimately long-term follow up of large numbers of people with type 2 diabetes in trials specifically designed to evaluate cardiovascular outcomes is required to demonstrate the cardiovascular effects of these agents.

Glucagon-like peptide-1 receptor agonists

GLP-1 receptor agonists mimic the action of endogenous GLP-1. Preparations (solutions for injection) of exenatide for twice-daily and weekly use, dulaglutide for weekly use and lixisenatide and liraglutide for daily use are TGA approved for the treatment of type 2 diabetes in Australia. However, the twice-daily preparation of exenatide is the only one of these to be listed on the PBS. Semaglutide, a once-weekly preparation, is still in clinical trials. These drugs improve glycaemic control through multiple actions, including glucose-dependent stimulation of insulin secretion, decreased hunger and increased satiety, delayed gastric emptying and suppression of endogenous glucagon secretion.

GLP-1 receptor agonists are associated with weight loss, a reduction in waist circumference and visceral fat. Liraglutide has been demonstrated to cause an average loss of 8.4 kg in total body weight and a 8.2 cm reduction in waist circumference.[9] High-dose liraglutide was approved in the USA in late 2014 as an antiobesity agent for use in overweight patients with at least one weight-related comorbidity such as hypertension, diabetes or dyslipidaemia.

GLP-1 receptor agonists also reduce systolic and diastolic blood pressures by a mean of 4 to 5 mmHg and 1 to 2.6 mmHg, respectively.[10,11] Lipid profiles are also improved by liraglutide, generally in proportion to glycaemic control, with an increase in HDL-cholesterol levels and a reduction in non-HDL-cholesterol and triglycerides levels.[10,11] There is also an observed increase in heart rate of two to three beats per minute with liraglutide; the clinical consequences, if any, of this phenomenon are unknown, but this increase in heart rate appears to be a class effect.[12]

Interestingly, GLP-1 receptors have been found in cardiomyocytes and the vascular endothelium, suggesting they may have direct effects on cardiovascular health.[9] Animal models of acute myocardial ischaemia have shown improved myocardial functional recovery with use of GLP-1 receptor agonists. In small short-term human studies, infusions of GLP-1 can improve endothelial function, including flow-mediated vasodilatation, and left ventricular function after myocardial infarction, and attenuate myocardial stunning.[13-15] Acute administration of the GLP-1 receptor agonist exenatide can reduce reperfusion injury (even in normoglycaemic patients, suggesting a nonglucose-mediated mechanism of action) and myocardial infarct size in patients undergoing percutaneous interventions.[13] GLP-1 receptors are also present within the sinoatrial node but it is uncertain whether this mediates the observed increase in heart rate.[16,17]

The results of the first GLP-1 receptor agonist cardiovascular outcome trial were presented at the American Diabetes Association meeting in June 2015 and published in December 2015.[18] This study, the ELIXA (Evaluation of Lixisenatide in Acute Coronary Syndrome) trial, compared lixisenatide with placebo in more than 6000 patients with type 2 diabetes. The trial demonstrated cardiovascular safety with no increase in major adverse cardiovascular events (MACE), the primary endpoint being a composite of cardiovascular death, nonfatal myocardial infarction, nonfatal stroke and unstable angina when compared with placebo. Further cardiovascular outcome trials using GLP-1 receptor agonists will report over the next few years (Table 2).

Dipeptidyl peptidase-4 inhibitors

Dipeptidyl peptidase-4 (DPP-4) inhibitors block the breakdown of GLP-1, gastric inhibitory peptide and several other peptides. Vildagliptin, linagliptin, sitagliptin, saxagliptin and alogliptin (listed in order of TGA approval) are available for use within Australia and are all listed on the PBS. These oral agents are generally weight neutral and have not been demonstrated to significantly lower blood pressure. They do, however, improve lipid profiles by slightly lowering total cholesterol levels.[19]

Three large prospective cardiovascular outcome trials have been published recently: the SAVOR-TIMI 53 (Saxagliptin and Cardiovascular Outcomes in Patients with Type 2 Diabetes Mellitus), EXAMINE (Alogliptin after Acute Coronary Syndrome in Patients with Type 2 Diabetes) and TECOS (Effect of Sitagliptin on Cardiovascular Outcomes in Type 2 Diabetes) trials.[20-23] The results are awaited of a trial looking at linagliptin, CARMELINA (Cardiovascular and Renal Microvascular Outcome Study with Linagliptin in Patients with Type 2 Diabetes Mellitus).

Table 1. New drug classes for type 2 diabetes: effects on cardiovascular risk factors and outcomes

Diabetes medication class	Class effects on cardiovascular risk factors			Effect on cardiovascular outcomes*
	Weight	Blood pressure	Lipid profile	
GLP-1 receptor agonists	Reduction	Reduction	Improved	Neutral† One trial (ELIXA)[18]
DPP-4 inhibitors	Neutral	Neutral	Improved	Neutral† Three trials (EXAMINE, SAVOR-TIMI, TECOS)[20-23]
SGLT-2 inhibitors	Reduction	Reduction	Mixed	Improved One trial (EMPA–REG OUTCOME)[30]

Abbreviations: DPP-4 = dipeptidyl peptidase-4; GLP-1 = glucagon-like peptide-1; SGLT-2 = sodium–glucose cotransporter-2.
* On evidence of reported cardiovascular outcome trials; see Table 2 for trial details.
† Cardiovascular safety demonstrated, with no increase in major adverse cardiovascular events.

SAVOR-TIMI 53 compared saxagliptin with placebo in over 16,000 patients with type 2 diabetes who had a history or were at high risk for cardiovascular disease.[20] It found that saxagliptin had a neutral effect with regard to its primary MACE (a composite of cardiovascular death, nonfatal myocardial infarction or nonfatal ischaemic stroke). No significant difference was also seen with regard to various secondary endpoints including unstable angina and coronary revascularisation, and death from any cause. There was, however, an unexpected increase in congestive cardiac failure requiring hospitalisation with saxagliptin, a 3.5% incidence versus 2.8% when compared with placebo.

The EXAMINE trial evaluated the safety of alogliptin compared with placebo in over 5000 patients with type 2 diabetes who had recently been admitted to hospital for an acute coronary syndrome.[21,22] This too found a neutral effect with regard to its primary endpoint of a composite of CV death, nonfatal myocardial infarction or nonfatal stroke. The secondary endpoint, which included urgent revascularisation due to unstable angina in addition to primary outcomes, was not significantly different between alogliptin and placebo. Death from any cause was also similar within the two groups. There were numerically more episodes of hospitalisation for heart failure in the alogliptin group but this did not reach statistical significance.

The TECOS trial studied sitagliptin in over 14,500 people with type 2 diabetes who had established cardiovascular disease, and had a longer period of follow up than the other two trials.[23] It showed a neutral cardiovascular outcome regarding its primary MACE outcome (a composite of cardiovascular death, nonfatal myocardial infarction, nonfatal stroke or hospitalisation for unstable angina). With regard to secondary outcomes, there was no increase in death from any cause and, reassuringly, no suggestion of increased heart failure hospitalisations.

The reasons behind the different heart failure outcomes in the studies are unclear but could include different effects of agents within the same class or differences in study populations.

Sodium–glucose cotransporter-2 inhibitors

The SGLT-2 inhibitors dapagliflozin, canagliflozin and empagliflozin (listed in order of TGA approval) are available within Australia for the treatment of type 2 diabetes; however, only dapagliflozin and empagliflozin are listed on the PBS. These oral agents lower plasma glucose concentrations by increasing the renal excretion of glucose, and this effect is independent of insulin concentration and peripheral insulin resistance. They block the reuptake of glucose within the proximal tubule by inhibiting the glucose transporter SGLT-2, resulting in urinary loss of up to 80 mg glucose, equating to around 300 kcal per day (1255 kJ per day).

It has been shown that dapagliflozin has beneficial effects on cardiovascular risk factors, improving weight and blood pressure.[24-29] Reductions in mean systolic and diastolic blood pressures in the order of 2.1 to 7.2 mmHg and 1.8 to 2.5 mmHg, respectively, have been shown. A meta-analysis of dapagliflozin showed between 2.2 and 4.5 kg of weight loss was achieved over 26 weeks and maintained over 12 to 24 months.[24] This is due to loss of calories from the excretion of excess glucose within the urine. When dapagliflozin is used in combination with insulin, a reduction in weight is also seen, with approximately 3.3 kg lost.[27]

SGLT-2 inhibitors have not demonstrated a substantial effect on lipid profile. Small increases in total and LDL-cholesterol levels are generally offset by elevations in HDL-cholesterol levels and reduction in triglyceride levels, which are probably due to the improvement in blood glucose level and associated weight loss.[28,29]

The first long-term cardiovascular safety study for this class, the EMPA-REG OUTCOME (Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes) trial, was published in late 2015.[30] This randomised controlled double-blinded trial compared empagliflozin 10 mg and 25 mg with placebo in 7020 patients with type 2 diabetes who had established cardiovascular disease. Study medication (empagliflozin or placebo) was given in addition to standard care, with primary outcomes being a composite three-point MACE (cardiovascular death, nonfatal myocardial infarction or nonfatal stroke). The pooled empagliflozin group showed a significant reduction in the combined three-point MACE outcome of 14%. Further analysis showed a reduction in cardiovascular death in the empagliflozin group by 38% when compared with standard therapy. Secondary endpoints also had favourable outcomes, including hospitalisation for heart failure, which was reduced by 35%, and death from any cause,

Table 2. New drug classes for type 2 diabetes: cardiovascular outcome trials

Diabetes medication class	Cardiovascular outcome trial	
	Reported results	**Awaited results**
GLP-1 receptor agonists	• ELIXA: Evaluation of Lixisenatide in Acute Coronary Syndrome Lixisenatide; 2015[18]	• LEADER: Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results Liraglutide; 2016 • SUSTAIN 6: Trial to Evaluate Cardiovascular and Other Long-term Outcomes with Semaglutide in Subjects with Type 2 Diabetes Semaglutide; 2016 • EXSCEL: Exenatide Study of Cardiovascular Events Lowering Trial Exenatide LAR; 2018 • REWIND: Researching Cardiovascular Events with a Weekly Incretin in Diabetes Dulaglutide; 2018
DPP-4 inhibitors	• SAVOR-TIMI 53: Saxagliptin and Cardiovascular Outcomes in Patients with Type 2 Diabetes Mellitus Saxagliptin; 2013[20] • EXAMINE: Alogliptin after Acute Coronary Syndrome in Patients with Type 2 Diabetes Alogliptin; 2013[21] • TECOS: Effect of Sitagliptin on Cardiovascular Outcomes in Type 2 Diabetes Sitagliptin; 2015[23]	• CARMELINA: Cardiovascular and Renal Microvascular Outcome Study With Linagliptin in Patients With Type 2 Diabetes Mellitus Linagliptin; 2018
SGLT-2 inhibitors	• EMPA-REG OUTCOME: Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes Empagliflozin; 2015[30]	• CANVAS: Canagliflozin Cardiovascular Assessment Study Canagliflozin; 2017 • DECLARE-TIMI 58: Multicenter Trial to Evaluate the Effect of Dapagliflozin on the Incidence of Cardiovascular Events Dapagliflozin; 2019

Abbreviations: DPP-4 = dipeptidyl peptidase-4; GLP-1 = glucagon-like peptide-1; SGLT-2 = sodium–glucose cotransporter-2.

which was reduced by 32% (both when compared with placebo). Stroke outcomes did not improve, stroke occurring in 3.5% of patients in the pooled empagliflozin group and in 3.0% of patients in the placebo group; this difference, however, was not statistically significant. It was interesting to observe the favourable cardiovascular outcomes occurring with both the 10 mg and 25 mg doses of empagliflozin, and that these benefits were seen within months of commencing treatment.

It is hoped that the outcomes of the EMPA-REG OUTCOME trial are due to a class effect, and the outcomes of the CANVAS (Canagliflozin Cardiovascular Assessment Study) and DECLARE-TIMI 28 (Multicenter Trial to Evaluate the Effect of Dapagliflozin on the Incidence of Cardiovascular Events) trials are eagerly awaited.

Conclusion

Cardiovascular disease is the leading cause of death, morbidity and hospitalisation in people with type 2 diabetes. The new classes of antidiabetic agents, the GLP-1 receptor agonists, DPP-4 inhibitors and SGLT-2 inhibitors, can improve various cardiovascular risk factors, including weight, blood pressure and lipid profile, in addition to lowering blood glucose.

Cardiovascular outcome studies to date support the safety of three different DPP-4 inhibitors (alogliptin, saxagliptin and sitagliptin; EXAMINE, SAVOR-TIMI 53 and TECOS, respectively), one GLP-1 receptor agonist (lixisenatide; ELIXA) and one SGLT-2 inhibitor (empagliflozin; EMPA-REG OUTCOME) in people with type 2 diabetes who have or are at high risk of cardiovascular disease. Specific cardiovascular benefits of DPP-4 inhibitors and GLP-1 receptor agonists over standard diabetes therapy have not yet been demonstrated. There is some residual concern about DPP-4 inhibitors and heart failure risk despite the reassuring findings with sitagliptin in the TECOS trial. Studies to date have shown the use of the SGLT-2 inhibitor empagliflozin in individuals with cardiovascular disease improves cardiovascular and all-cause mortality and heart failure outcomes. Agents in these new drug classes rarely cause hypoglycaemia. **ET**

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A list of references is included in the website version of this article (www.endocrinologytoday.com.au).

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