The health burden of type 2 diabetes mellitus (T2DM) is increasing worldwide, with a substantial portion of this burden being due to the development of cardiovascular (CV) disease. Multiple individual randomised clinical trials of intensive versus conventional glucose control, based on the use of traditional oral hypoglycaemic agents, have failed to convincingly show that intensive glucose control significantly reduces CV disease outcomes. In recent times, two new approaches to lowering glucose levels have become available. One targets the “incretin effect” which involves the modulation of peptide hormones that normally regulate glucose levels when nutrients are given orally. The other approach is based on inhibiting the sodium-glucose co-transporter 2 (SGLT-2) in the tubules of the kidney to promote glycosuria. Incretin-based therapies, especially glucagon-like peptide-1 receptor analogues, reduce glucose levels, with a low risk of hypoglycaemia, by increasing insulin secretion, inhibiting glucagon release and increasing satiety. Clinical and experimental studies have also shown favourable effects on CV disease risk factors such as dyslipidaemia, blood pressure, and improvements in endothelial function and cardiac contractility. Similarly, SGLT-2 inhibitors reduce glucose levels with a low risk for hypoglycaemia and have positive effects on multiple CV disease risk factors. Whether the beneficial effects of these novel glucose lowering approaches on surrogate markers of CV disease risk translates to an improvement in CV events remains unknown. Several CV outcome trials are currently being performed to show that at a minimum, these novel glucose lowering agents are safe, but also have positive CV benefits.

Keywords
Type 2 diabetes • Cardiovascular • Glucose • GLP-1 • DPP-4 • SGLT-2

Introduction
Type 2 diabetes mellitus (T2DM) is an independent cardiovascular (CV) disease risk factor and people with diabetes have a two- to four-fold increased risk for developing CV disease compared to those without diabetes. This increased risk persists even after accounting for traditional risk factors such as smoking, hypertension, obesity, and dyslipidaemia [1]. The increasing incidence and prevalence of T2DM, affecting almost 382 million people worldwide, the progressive natural history of the disease and the potential for multi-system complications to develop, emphasise...
the urgent need for effective treatment and preventative strategies [2].

Many studies have demonstrated a relationship between chronic hyperglycaemia and the development of CV disease. However, strategies that reduce chronic hyperglycaemia, based on the use of traditional glucose lowering agents such as insulin, sulfonylureas and metformin, have not clearly reduced CV events in individual intervention studies such as the United Kingdom Prospective Diabetes Study (UKPDS), the Veterans Affairs Diabetes Trial (VADT), the Action to Control Cardiovascular Risks in Diabetes (ADVANCE) study and the Action to Control Cardiovascular Risks in Diabetes (ACCORD) study [3–6]. Similarly, the Outcome Reduction with an Initial Glargine Intervention (ORIGIN) study showed that normalising fasting sugar levels with the early initiation of insulin therapy, even in the setting of impaired glucose tolerance, had no additional benefit on the incidence of CV mortality and morbidity compared with conventional glucose control strategies [7]. The demonstration of the benefits of glucose lowering on CV events in T2DM are confined to meta-analysis of data from individual trials and the results of one long-term follow-up observational study (UKPDS-80) of patients with newly diagnosed diabetes that were originally randomised to intensive glucose control in an interventional study [8–10]. Results from this follow-up study suggest that early strict glucose control generates a “legacy-effect” that takes many years before eventually being translated into protection from CV events [9,10].

Investigating the relationship between intensive glycaemic control and CV outcomes has been hampered by the inability to safely intensify glucose lowering strategies with a low risk of hypoglycaemia and the avoidance of other side-effects such as weight gain. Recently, two new classes of glucose lowering medications have been released onto the Australian market that may help to further delineate the relationship between glucose lowering and CV disease and possibly even offer CV benefits over and beyond glucose lowering. One class of medication targets the so called “incretin effect”, whilst the other inhibits a sodium-glucose transporter in the renal tubules to induce glycosuria. Both classes of medication lower glucose levels with a low risk of hypoglycaemia and have beneficial effects on blood pressure (BP), body weight and possibly other deleterious risk factors and metabolic pathways implicated in the development of CV disease. Here we briefly review the evidence as to whether more contemporary pharmacological agents for lowering glucose levels offer CV disease protection beyond their glucose lowering effects.

**Newer Glucose Lowering Therapies**

Two new approaches to lowering glucose levels are now available. One targets the “incretin effect” which involves the modulation of peptide hormones that normally regulate glucose levels when nutrients are given orally. The other approach is based on inhibiting the sodium-glucose co-transporter 2 (SGLT-2) in the tubules of the kidney to promote glycosuria. Medications that target the “incretin effect” are usually classified into the Glucagon Like Peptide-1 (GLP-1) receptor analogues and Dipeptidyl Peptidase-4 (DPP-4) inhibitors. The incretins are a family of gut hormones that lower blood glucose levels via the so-called “incretin effect”. This phenomenon accounts for the two- to three-fold increase in plasma insulin concentrations observed after the oral ingestion compared to the intravenous administration of an equivalent glucose load. The two principal incretin peptide hormones, GLP-1 secreted by intestinal L cells, and glucose-dependent insulinotropic polypeptide (GIP) secreted by intestinal K cells, are released after nutrients enter the small intestine. A key function of the incretins is to enhance the glucose sensing and insulin secretory capacity of the pancreas during postprandial hyperglycaemia.

Additionally, activating the GLP-1 receptor has other beneficial effects such as inhibition of glucagon release from the pancreas, a slowing of gastric emptying, and increased satiety [11]. Normally GLP-1 has a very short half-life and is quickly degraded by the dipeptidyl peptidase 4 (DPP-4) enzyme. Two pharmacological approaches have been taken to target the “incretin-system” to develop new glucose lowering medications. One approach has been to develop GLP-1 receptor analogues that are resistant to degradation by the DPP-4 enzyme, hence enhancing their half-life. The other approach has been to develop inhibitors of the DPP-4 enzyme, with the aim of increasing plasma levels of native GLP-1 by inhibiting its degradation. Of note, the modification of native GIP, to date, has not been shown to have any therapeutic potential for the treatment of T2DM [12,13].

**Incretin Based Therapy: Glucagon Like Peptide-1 (GLP-1) Receptor Analogues**

The currently GLP-1 receptor analogues that have been developed for clinical use are shown in Table 1. However, only two of these GLP-1 receptor analogues are available on the Australian market, Exenatide and Liraglutide. GLP-1 receptors, apart from being found on pancreatic beta-cells, are also widely distributed in various cell types including: cardiac myocytes, endothelial cells, vascular smooth muscle cells and in regions of the CNS. This wide range of receptor expression may have potential beneficial implications for incretin based therapy over and above that related to glucose lowering.

Exenatide is the synthetic version of a naturally occurring 39-amino acid peptide found in the saliva of the Gila monster lizard (Exendin-4). A meta-analysis of studies reported a greater decline of the HbA1c in the exenatide group compared with placebo (weighted mean difference in change in HbA1c -1.01%, 95% CI -1.18 to -0.84), as well as a higher proportion of these patients being more likely to achieve glycaemic goals of HbA1c ≤ 7% compared with placebo [14,15]. In clinical practice, most patients are given a trial of exenatide, 5 mcg bid for a month with a dose escalation to 10 mcg bid if nausea and vomiting are not major side-effects.
Furthermore, a long-acting once weekly subcutaneous exenatide (LAR), approved by the Therapeutics Goods Association (TGA) and expected to be available soon, has been found to provide more potent glycaemic control (1.9% vs. 1.5% HbA1c reduction) compared to twice daily exenatide [16]. Apart from favourable effects on reduction of HbA1c, significant improvement in weight (approximately a 3-5 kg reduction from baseline, which was sustained for up to three years); lipid profiles (total cholesterol, LDL, TAG), and hepatic aminotransferases have also been reported [16].

Liraglutide (Table 1) is available for use as monotherapy, as an adjunct to diet and exercise or in combination with oral agents in T2DM. The Liraglutide Effects and Action in Diabetes (LEAD) program [17] has demonstrated that liraglutide, both as monotherapy and in combination with other anti-diabetic drugs, is associated with substantial improvements in HbA1c (by up to 2.5% from baseline in patients with poor initial glycaemic control i.e. HbA1c >10%), fasting and postprandial glucose levels, weight loss and improved beta-cell function. A meta-analysis of the LEAD trials has also shown significant reductions in systolic blood pressure (up to 2.6 mmHg) [17]. Liraglutide is administered as a once daily injection via a prefilled pen-injection device with the starting dose being 0.6 mg daily. The dose should be increased to

![Table 1 Glucagon like peptide-1 receptor analogues currently developed for the treatment of Hyperglycaemia.](image)

**Abbreviations:** CI: Contraindication, CrCl: Creatinine clearance, CV: Cardiovascular, FDA: US Food And Drug Administration, GIT: Gastrointestinal, PBS: Pharmaceutical Benefits Scheme, SC: Subcutaneous, SBP: Systolic blood pressure, TGA: Therapeutic Goods Administration, *: Restrictions apply for issuing a PBS script.
1.2 mg after one week if nausea and vomiting are not major side-effects. The dose can then be increased to 1.8 mg to achieve maximum efficacy.

The side effects of GLP-1 receptor analogues are predominantly gastrointestinal with nausea being the most common. There have been concerns regarding an increased risk of pancreatitis, pancreatic cancer and medullary C-cell thyroid carcinoma of the thyroid with the use of GLP-1 receptor analogues. Reassuringly, after review of currently available data, the US Food and Drug Administration and the European Medicines Agency have agreed that there is insufficient evidence to confirm an increased risk of cancer and pancreatitis with the use of GLP-1 receptor analogues, however GLP-1 receptor analogues should be contraindicated in patients with a history of the above conditions [18]. There have also been case reports of acute renal failure in patients taking GLP-1 receptor analogues (when used if glomerular filtration rate (GFR) is <30 ml/min) (Table 1) [19].

**Incretin Based Therapy: Dipeptidyl Peptidase 4 Inhibitors (DPP-4 inhibitors)**

There are now five DPP-4 inhibitors listed on the PBS in Australia (Table 2). In clinical trials, use of the DPP-4 inhibitors result in a mean decrease in HbA1c ranging between 0.5% and 1%, depending on the baseline degree of hyperglycaemia [20]. There have been no major head-to-head trials comparing the glucose lowering effects of the different DPP-4 inhibitors, and currently glucose-lowering efficacy is considered to be similar for all the medications in this class. Generally, the DPP-4 inhibitors are very well tolerated (Table 2) but concerns about increased rates of pancreatitis and pancreatic cancer have been raised, as discussed below.

In clinical trials, the most commonly reported adverse effects associated with DPP-4 inhibitor therapy included nasopharyngitis, upper respiratory tract infection, urinary tract infection and headache. These side-effects are generally not observed in clinical practice. However, some studies have also reported a slightly increased risk of acute pancreatitis in patients using sitagliptin, saxagliptin and alogliptin. In retrospective cohort studies, the incidence of acute pancreatitis in sitagliptin users was 5.6 cases per 1000 patient years compared to the risk of acute pancreatitis in the diabetic group, non-diabetic group and patients using exenatide [21]. There have also been reports of increased risk of pancreatic cancer and neuroendocrine tumours in sitagliptin users [21]. In a similar fashion to concerns surrounding the use of GLP-1 receptor analogues, there is currently insufficient evidence to establish a direct link between the DPP-4 inhibitors and the above adverse outcomes [22]. To date, there have been two long-term randomised clinical trials that have been performed involving the use of DPP-4 inhibitors which have not shown any increased risk for pancreatitis or pancreatic cancer in participants randomised to DPP-4 inhibitors compared to placebo [23,24]. However, a history of pancreatitis or pancreatic cancer should be considered as a contraindication to using DPP-4 inhibitors.

**Sodium Glucose Co-transporter 2 (SGLT-2) Inhibitors:**

Currently there are three SGLT-2 inhibitors that have been developed for clinical use (Table 3). Two members of the SGLT-2 inhibitors class, Canagliflozin and Dapagliflozin, are now available in the Australian market and are listed by the PBS. SGLT-2 inhibitors are a new class of glucose lowering medications that increase urinary glucose excretion. Given their mode of action, they are expected to be used to complement insulin and non-insulin dependent therapies in T2DM. The kidneys are known to play an integral role in glucose homeostasis, accounting for more than 10% of glucose utilisation and up to 20% of all glucose production via gluconeogenesis [25]. The insulin resistance of T2DM augments the above, resulting in increases in overall glucose production from the liver and kidneys, as well as increasing renal glucose re-absorption [26]. There is also the possibility of volume depletion in people taking SGLT-2 inhibitors. In patients at risk for volume depletion, volume status should be monitored carefully if a SGLT-2 inhibitor is started. Furthermore, it is not recommended that SGLT-2 inhibitors are used in patients on loop diuretics or who are already volume depleted.

The main disadvantage of their mode of action is that their effectiveness for lowering glucose levels is dependent on renal function and hence they are not recommended for patients with impaired renal function. Potential side-effects include increased rates of urinary tract infections and genital tract infections.

SGLT-2 inhibitors have been shown to reduce fasting plasma glucose and HbA1c levels (Table 3). When used as monotherapy, clinical trials have demonstrated reductions in fasting glucose levels of up to 0.8-3.6 mmol/L [27,28]. When used in combination (i.e. with metformin), an additional reduction of up to 1.8 mmol/L was observed [29]. Furthermore, in a head-to-head comparison of canagliflozin versus sitagliptin (a DPP-4 inhibitor) in patients with T2DM, who do not have adequate glycaemia control on metformin plus a sulfonylurea, the addition of canagliflozin was associated with a greater HbA1c reduction compared with the addition of sitagliptin, (-1.03% vs. -0.66%, a difference of 0.37%, 95% CI -0.50 to -0.25) [30].

**Potential CV Benefits of New Glucose Lowering Agents**

**GLP-1 Receptor Analogues: CV Disease Risk Factor Modification**

Most clinical studies of GLP-1 receptor analogues have shown that the lipid profile improves for patients taking this class of medication [31]. The exact mechanism by which these therapies cause alterations in the lipid profile is unknown, however potential explanations include: changes in the expression of hepatic enzymes responsible for lipid oxidation and lipid biosynthesis, and decreased secretion of intestinal
Table 2  Dipeptidyl peptidase-4 (DPP-4) inhibitors currently developed for the treatment of hyperglycaemia.

<table>
<thead>
<tr>
<th>Name</th>
<th>Route</th>
<th>Dosing</th>
<th>Strength of Preparation</th>
<th>Advantages</th>
<th>Disadvantages</th>
<th>Approval (TGA/PBS/FDA)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sitagliptin</strong></td>
<td>Oral</td>
<td>Once daily</td>
<td>100 mg, 50 mg, 25 mg</td>
<td>HbA1c reduction of 1.1% (Baseline 8.4%). Low risk hypoglycaemia. Weight neutral. No drug interactions</td>
<td>Dose adjustment in renal impairment required. Possible link to pancreatitis. Caution with CCF. Long term CV safety unknown, trial in progress (TECOS) CI in CKD and ESRD due to limited data. Not recommended in hepatic impairment or LFTs&gt;2.5x upper limit of normal. Caution with CCF. Possible link to pancreatitis. Expensive. No CV outcome trial in progress CI in CKD and ESRD due to limited data. Possible link to pancreatitis. Drug interactions involving Cytochrome P450 3A4/5. Caution with CCF. CV outcome trial completed (SAVOR-TIMI 53) Possible link to pancreatitis. Caution with CCF. Long term CV safety unknown, trials in progress (CAROLINA)</td>
<td>All PBS'</td>
</tr>
<tr>
<td><strong>Vildagliptin</strong></td>
<td>Oral</td>
<td>Twice daily</td>
<td>50 mg</td>
<td>HbA1c reduction of 1.1% (Baseline 8.4%). Low risk hypoglycaemia. Weight neutral. No drug interactions</td>
<td>Dose adjustment in renal impairment required. Possible link to pancreatitis. Caution with CCF. Long term CV safety unknown, trial in progress (TECOS) CI in CKD and ESRD due to limited data. Not recommended in hepatic impairment or LFTs&gt;2.5x upper limit of normal. Caution with CCF. Possible link to pancreatitis. Expensive. No CV outcome trial in progress CI in CKD and ESRD due to limited data. Possible link to pancreatitis. Drug interactions involving Cytochrome P450 3A4/5. Caution with CCF. CV outcome trial completed (SAVOR-TIMI 53) Possible link to pancreatitis. Caution with CCF. Long term CV safety unknown, trials in progress (CAROLINA)</td>
<td>All PBS'</td>
</tr>
<tr>
<td><strong>Saxagliptin</strong></td>
<td>Oral</td>
<td>Once daily</td>
<td>5 mg</td>
<td>HbA1c reduction of 0.8% (Baseline 8.1%). Low risk hypoglycaemia. Weight neutral</td>
<td>Dose adjustment in renal impairment required. Possible link to pancreatitis. Caution with CCF. Long term CV safety unknown, trial in progress (TECOS) CI in CKD and ESRD due to limited data. Not recommended in hepatic impairment or LFTs&gt;2.5x upper limit of normal. Caution with CCF. Possible link to pancreatitis. Expensive. No CV outcome trial in progress CI in CKD and ESRD due to limited data. Possible link to pancreatitis. Drug interactions involving Cytochrome P450 3A4/5. Caution with CCF. CV outcome trial completed (SAVOR-TIMI 53) Possible link to pancreatitis. Caution with CCF. Long term CV safety unknown, trials in progress (CAROLINA)</td>
<td>All PBS'</td>
</tr>
<tr>
<td><strong>Linagliptin</strong></td>
<td>Oral</td>
<td>Once daily</td>
<td>5 mg</td>
<td>HbA1c reduction of 0.64% (Baseline 8.1%). No drug interactions. Low risk hypoglycaemia. No dose adjustment. Required in renal impairment. Weight neutral</td>
<td>Dose adjustment in renal impairment required. Possible link to pancreatitis. Caution with CCF. Long term CV safety unknown, trials in progress (CAROLINA)</td>
<td>All PBS'</td>
</tr>
<tr>
<td><strong>Alogliptin</strong></td>
<td>Oral</td>
<td>Once daily</td>
<td>6.25 mg, 12.5 mg, 25 mg</td>
<td>HbA1c reduction of 0.8% (Baseline 8%). No drug interactions. Low risk hypoglycaemia. Weight neutral</td>
<td>Dose adjustment in renal impairment. CI in severe hepatic impairment (Child-Pugh score&gt;9). Possible link to pancreatitis. Caution with CCF. CV outcome trial completed (EXAMINE)</td>
<td>All PBS'</td>
</tr>
</tbody>
</table>

**Table 2** Dipeptidyl peptidase-4 (DPP-4) inhibitors currently developed for the treatment of hyperglycaemia.

**Route**
- Oral

**Dosing**
- Once daily
- Twice daily

**Strength of Preparation**
- 100 mg, 50 mg, 25 mg
- 50 mg
- 5 mg
- 6.25 mg, 12.5 mg, 25 mg

**Advantages**
- HbA1c reduction of 1.1% (Baseline 8.4%). Low risk hypoglycaemia. Weight neutral. No drug interactions
- HbA1c reduction of 1.1% (Baseline 8.4%). Low risk hypoglycaemia. Weight neutral. No drug interactions
- HbA1c reduction of 0.8% (Baseline 8.1%). Low risk hypoglycaemia. Weight neutral
- HbA1c reduction of 0.64% (Baseline 8.1%). No drug interactions. Low risk hypoglycaemia. No dose adjustment. Required in renal impairment. Weight neutral
- HbA1c reduction of 0.8% (Baseline 8%). No drug interactions. Low risk hypoglycaemia. Weight neutral

**Disadvantages**
- Dose adjustment in renal impairment required. Possible link to pancreatitis. Caution with CCF. Long term CV safety unknown, trial in progress (TECOS) CI in CKD and ESRD due to limited data. Not recommended in hepatic impairment or LFTs>2.5x upper limit of normal. Caution with CCF. Possible link to pancreatitis. Expensive. No CV outcome trial in progress CI in CKD and ESRD due to limited data. Possible link to pancreatitis. Drug interactions involving Cytochrome P450 3A4/5. Caution with CCF. CV outcome trial completed (SAVOR-TIMI 53) Possible link to pancreatitis. Caution with CCF. Long term CV safety unknown, trials in progress (CAROLINA)
- Dose adjustment in renal impairment required. Possible link to pancreatitis. Caution with CCF. Long term CV safety unknown, trial in progress (TECOS) CI in CKD and ESRD due to limited data. Not recommended in hepatic impairment or LFTs>2.5x upper limit of normal. Caution with CCF. Possible link to pancreatitis. Expensive. No CV outcome trial in progress CI in CKD and ESRD due to limited data. Possible link to pancreatitis. Drug interactions involving Cytochrome P450 3A4/5. Caution with CCF. CV outcome trial completed (SAVOR-TIMI 53) Possible link to pancreatitis. Caution with CCF. Long term CV safety unknown, trials in progress (CAROLINA)
- Dose adjustment in renal impairment. CI in severe hepatic impairment (Child-Pugh score>9). Possible link to pancreatitis. Caution with CCF. CV outcome trial completed (EXAMINE)

**Approval (TGA/PBS/FDA)**
- All PBS'
- All PBS'
- All PBS'
- All PBS'
- All PBS'

**Abbreviations:** CCF: Congestive cardiac failure, CI: Contraindication, CKD: Chronic kidney disease, CV: Cardiovascular, ESRD: End stage renal disease, FDA: US Food And Drug Administration, LFTs: Liver function tests, PBS: Pharmaceutical Benefits Scheme, TGA: Therapeutic Goods Administration.

*Restrictions apply for issuing a PBS script.

tri-glyceride-rich lipoproteins. A clinical study has shown that administration of twice a day exenatide resulted in reductions in triglycerides (-11% from baseline, 95% CI -16 to -4) and total cholesterol levels (-0.10 from baseline, 95% CI -0.22 to 0.02). Additionally, a potential reduction in these parameters was seen with the administration of once weekly exenatide compared with twice daily doses (Triglycerides: -15% from baseline, 95% CI -20 to -9; Total cholesterol: -0.31 from baseline, 95% CI -0.42 to -0.19) [32]. Furthermore, 1.2 mg of liraglutide, when used as add-on therapy to metformin and TZDs resulted in significant reductions in: free fatty acids (-0.03 ± 0.02 mmol/L; p < 0.05), triglycerides (-0.38 ± 0.10 mmol/L; p < 0.05),
total \((0.21 \pm 0.9 \text{ mmol/L; } p < 0.05)\) and LDL cholesterol \((-0.28 \pm 0.07 \text{ mmol/L; } p < 0.05)\), compared to placebo [33].

Systolic and diastolic blood pressures have also been shown to improve in several GLP-1 receptor analogues based studies. In a meta-analysis of six trials, exenatide was associated with a reduction of 2 to 4 mmHg in systolic blood pressure when compared to placebo or insulin therapy, an effect seen in patients with a high baseline blood pressure as opposed to a normal baseline [34]. Potential explanations for this reduction may result from inhibition of sodium absorption in the proximal tubule resulting in a naturet effect, or the central effects of GLP-1 receptor agonists on the adrenal-medullary catecholamine neurons.

Additionally, GLP-1 receptor analogues such as exenatide and liraglutide are known to result in a decrease in weight [34]. A meta-analysis of 21 trials confirmed a small but statistically significant reduction in body weight from baseline as a result of GLP-1 therapy \((-1.22 \text{ kg, 95\% CI } -1.51 \text{ to } -0.93)\) [34]. The mechanism by which weight loss is achieved may potentially be explained by the GLP-1 analogues’ ability to decrease gastric emptying as well as induce a feeling of satiety. Overall, this effect of GLP-1 analogues on weight reduction could be considered beneficial, but large ongoing clinical trials will need to determine as to whether this translates into a reduction in CV morbidity and mortality in patients with diabetes.

### GLP-1 Receptor Analogues: Effects on Atherogenesis and Myocardial Infarction

Vascular dysfunction has strong associations with diabetes and insulin resistance, initiating early atherosclerosis. Endothelial dysfunction is characterised by the expression of cell adhesion molecules and chemokines. This facilitates the adhesion and migration of inflammatory cells such as CD4-positive lymphocytes and monocytes to the vessel wall. GLP-1 receptor analogues have been shown to inhibit lymphocyte chemotaxis [31] and improve endothelial-dependent vasodilation. Studies have also shown decreased atherosclerosis and decreased plaque macrophages with GLP-1 receptor analogue use.

The effects of incretin-based therapies in humans with established coronary artery disease have been limited. Clinical and experimental studies have, however, shown favourable outcomes of using GLP-1 receptor analogues. While percutaneous coronary intervention or thrombolysis are still the preferred acute management strategy for acute myocardial infarction, reperfusion injury can occur after opening the blocked vessel. This in turn can cause additional damage to the already ischaemic myocardium, and has been shown to contribute to 50% of the final infarct size in animals [35]. An experiment performed in pigs with 72 hours of treatment with exenatide, following 75 minutes of ischaemia, resulted in significantly decreased infarct size and improved recovery.

### Table 3 Sodium Glucose Transporter-2 (SGLT-2) inhibitors currently developed for the treatment of hyperglycaemia.

<table>
<thead>
<tr>
<th>Route</th>
<th>Dosing</th>
<th>Strength of Preparation</th>
<th>Advantages</th>
<th>Disadvantages</th>
<th>Approval (TGA/PBS/FDA)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Canagliflozin (Invokana)</td>
<td>OralOnce daily</td>
<td>100 mg, 300 mg</td>
<td>Similar glucose lowering potential to Metformin. Low risk of hypoglycaemia BP reductions. Promotes weight loss</td>
<td>CI if CrCl&lt; 60 mL/min or moderate hepatic impairment. Increased risk of vulvovaginal candidiasis and genital infections. Increase in urinary tract infections. Long term CV safety unknown, trial in progress (CANTAS)</td>
<td>All PBS*</td>
</tr>
<tr>
<td>Dapagliflozin (Forxiga)</td>
<td>OralOnce daily</td>
<td>10 mg</td>
<td>As above</td>
<td>As above. Unclear risk of breast cancer and Bladder cancer (9 cases). Long term CV safety unknown, trial in progress (DECLARE-TIMI-58)</td>
<td>All PBS*</td>
</tr>
<tr>
<td>Empagliflozin (?)</td>
<td>OralOnce daily</td>
<td>10 mg, 25 mg</td>
<td>As above</td>
<td>As above. Long term CV safety unknown. Trial in progress (EMPA-REG Outcome)</td>
<td>None</td>
</tr>
</tbody>
</table>

of both systolic and diastolic function [35]. Moreover, in a non-randomised study of 10 patients with acute myocardial infarction and severe left ventricular systolic dysfunction (Left ventricular ejection fraction (LVEF) < 40%), a 72 hour continuous infusion of a GLP-1 receptor analogue (started shortly after successful PCI) was associated with significant improvements in LVEF (from 29 ± 2% to 39 ± 2%, p < 0.01) and both global wall function (1.94 ± 0.11 to 1.63 ± 0.09, p < 0.01) and regional wall function (2.53 ± 0.08 to 2.02 ± 0.11, p < 0.01), compared to the 11 control patients (i.e. patients of similar presentation who received comparable medical and interventional therapy without GLP-1 receptor analogue treatment) [36]. This study also revealed that the benefits of the GLP-1 receptor analogues were independent of infarct location or history of diabetes.

**GLP-1 Receptor Analogues: Can They Improve Heart Failure?**

Diabetes is known to be an independent risk factor for heart failure [37,38]. Factors that contribute to this include: the increased risk of developing coronary artery disease resulting in ischaemic cardiomyopathy, and ventricular dysfunction that can occur in the absence of coronary artery disease and hypertension, known as diabetic cardiomyopathy. GLP-1 receptors are present in the heart and are known to increase myocardial glucose uptake. Studies on heart-failure prone rats have shown that continuous use of a GLP-1 receptor analogues over a nine month period increases myocardial glucose uptake, enhances left ventricular function and results in greater survival rates [39]. The above study also suggested an association with decreased myocyte apoptosis, suggesting anti-apoptotic effects of GLP-1 receptor analogues. These results were also replicated in studies using 48-h continuous GLP-1 receptor analogue infusions on dogs with dilated cardiomyopathy secondary to rapid pacing [40]. In vitro studies have further shown that GLP-1 receptor analogues appear to protect cardiomyocytes against apoptosis [41].

Limited human studies of GLP-1 based therapies have shown potential benefits in heart failure patients. A new study of 12 patients with NYHA class III/IV heart failure, with a continuous infusion of a GLP-1 receptor analogue for 12 weeks, exhibited improvements in maximal oxygen consumption (VO₂ max) and the 6-minute walk tests compared to nine patients with heart failure on standard therapy [42]. In addition, a continuous 48-h GLP-1 receptor analogue infusion in dogs with pacing induced dilated cardiomyopathy, resulted in increased cardiac contractility (the rate of increase in LV pressure in accordance to the left ventricular contractile force, commonly indexed as dP/dt, increased by 98%), stroke volume and cardiac output [40].

**GLP-1 Receptor Analogues: Effects on Heart Rate (HR)**

The wide physiological distribution of GLP-1 receptors results in multiple mechanisms of metabolic control, involving both centrally and peripheral neuro-humoral pathways [43]. Diabetes is known to be associated with autonomic imbalance (i.e. from parasympathetic withdrawal and sympathetic dominance), which may result in patients with T2DM being more sensitive to drugs that alter the autonomic control of HR. Some clinical studies have shown that use of GLP-1 receptor analogues have resulted in increases in HR, which in turn has raised the issue as to whether this effect will be translated into adverse CV outcomes [34]. This increase in HR with the use of GLP-1 receptor analogues has not been a universal finding, as a double-blinded randomised pilot study performed to assess the effect of exenatide on HR and blood pressure in subjects with T2DM reported no change in HR for GLP-1 receptor analogues treated-subjects over a 12 week period [43]. Furthermore, such observations have been consistent with larger longer-term trials that did not reveal any apparent CV safety concerns with the use of GLP-1 receptor analogues [44]. Due to inconsistent findings of the above clinical trials, further studies are warranted to examine the effects of GLP-1 receptor analogues on HR and to assess whether an increase in HR will negate any potential CV benefits of these agents.

**GLP-1 Receptor Analogues: CV Disease Outcome Studies**

As discussed above, apart from the several studies that have demonstrated a modification in CV risk factors, improvement in markers of endothelial function and improvement in CV outcomes after ischaemic and reperfusion injury with the use of GLP-1 analogues, meta-analysis have been conducted to further highlight potential for GLP-1 receptor analogues to reduce CV disease risk. A meta-analysis of 15 studies conducted by Marso, et al [45], based on the liraglutide clinical development program (LEAD), showed that the use of liraglutide was associated with a non-significant reduction in major CV events compared to placebo (Hazard ratio 0.73, 95% CI 0.38 to 1.41). In addition a meta-analysis of 12 controlled trials of exenatide use versus placebo also reported a non-significant reduction in major CV events (Hazard ratio 0.7, 95% CI 0.38-1.31) [46].

Of interest, the US Food and Drug Administration (FDA) has mandated that certain requirements are met to establish a lack of CV toxicity for new glucose lowering medications. For initial approval, clinical trials must rule out a possible > 1.8 fold (the upper 95% CI of the estimated risk) in major CV events. If the premarketing application data shows the 95% CI of the estimated risk to be between 1.3 and 1.8, then a post-marketing trial is generally considered necessary to definitively show the upper bound of the 95% CI is < 1.3 [47]. The major CV safety trials that are currently being undertaken for the GLP-1 receptor analogues are summarised in (Table 4).

**DPP-4 Inhibitors: Potential for Vascular Protection?**

Multiple experimental and clinical studies have resulted in considerable speculation that DPP-4 inhibitors may exert beneficial effects on the CV system. These benefits are
Table 4  Glucagon like peptide-1 receptor analogue CV Safety outcome trials.

<table>
<thead>
<tr>
<th>Trial Name</th>
<th>Drug</th>
<th>Number of patients</th>
<th>Primary End Point</th>
<th>Expected Duration (Years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>LEADER</td>
<td>Liraglutide</td>
<td>9340</td>
<td>MACE</td>
<td>5</td>
</tr>
<tr>
<td>EXSCEL</td>
<td>Exenatide</td>
<td>9,500</td>
<td>MACE</td>
<td>7.5</td>
</tr>
<tr>
<td>EXSCEL</td>
<td>Exenatide LAR</td>
<td>12,000</td>
<td>MACE</td>
<td>5.5</td>
</tr>
<tr>
<td>SUSTAIN 6</td>
<td>Semaglutide</td>
<td>3,260</td>
<td>MACE</td>
<td>2.8</td>
</tr>
<tr>
<td>ELIXA</td>
<td>Lixisenatide</td>
<td>6,000</td>
<td>MACE</td>
<td>3.9</td>
</tr>
<tr>
<td>REWIND</td>
<td>Dulaglutide</td>
<td>9,622</td>
<td>MACE</td>
<td>6.5</td>
</tr>
</tbody>
</table>

Abbreviations: ELIXA: Evaluation of Cardiovascular Outcomes in patients with Type 2 Diabetes After Acute Coronary syndrome, EXSCEL: Exenatide Study of Cardiovascular Event Lowering Trial, GLP-1: Glucagon-like peptide, LEADER: Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results, MACE: Major adverse cardiovascular events, REWIND: Researching Cardiovascular Events With a Weekly Incretin in Diabetes, SUSTAIN 6: Trial to Evaluate Cardiovascular and Other Long-term outcomes With Semaglutide in subjects with Type 2 diabetes.

thought to be mediated through their hypolipidaemic action, improvements in endothelial dysfunction and their direct myocardial protective effects (i.e. prevention of apoptosis of cardiomyocytes and increased myocardial insulin sensitivity) [48]. Similarly, a meta-analysis of 18 randomised control trials on 8,544 subjects showed that DPP-4 inhibitor use was associated with a lower risk of adverse CV effects (RR 0.48, 95% CI 0.31 to 0.75, p = 0.001), and a lower risk of non-fatal myocardial infarction (RR 0.40, 95% CI 0.18 to 0.88, p = 0.01) [49]. However, it should be noted that this meta-analysis was based on short-term studies involving DPP-4 inhibitors that mainly focused on the glucose ability of the DPP-4 inhibitors and not their effects on CV outcomes.

DPP-4 Inhibitors: CV Disease Outcome Studies

Subsequently, to the performance of the above meta-analysis, two phase CV outcome trials based on the use of the DPP-4 inhibitors saxagliptin and alogliptin have been published. The Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus Thrombolysis in Myocardial Infarction 53 trial [SAVOR-TIMI 53] showed significant reductions in fasting plasma glucose levels, significantly lower HbA1c levels at one year (7.6% vs. 7.9%, p < 0.001) and an improved albumin-to-creatinine ratio for saxagliptin compared with placebo treated participants [50]. Despite this, the CV event rate in the saxagliptin and placebo treated participants was not significantly different after two years. The primary CV end-point of death, non-fatal myocardial infarction and non-fatal ischaemic stroke occurred in 613 patients in the saxagliptin group (7.3%), compared to 609 patients in the placebo group (7.2%) (Hazard ratio 1.00; 95% CI, 0.89 to 1.12; p = 0.99). An unexpected increase in hospitalisations for heart failure was observed in the participants randomised to saxagliptin treatment, as discussed below.

Similarly, the Examination of Cardiovascular Outcomes with Alogliptin versus Standard of Care (EXAMINE) trial performed in 5380 participants, revealed that rates of major adverse CV events were similar in the alogliptin and placebo treated arms of the trial [51]. Participants randomised to alogliptin treatment improved baseline HbA1c levels (-0.33% vs. 0.03%, p < 0.001) but had similar rates of the study primary CV end-point (death from cardiovascular causes, nonfatal myocardial infarction, or non-fatal stroke) (11.3% vs. 11.8%, Hazard ratio 0.96; one sided repeated CI bound, 1.16) after a median follow up of 18 months compared to those randomised to placebo. Further analysis of the study results also failed to show any significant difference in a secondary CV end point (primary end-point with the addition of urgent revascularisation) for alogliptin (12.7%) compared to placebo (13.4%) treated participants (Hazard ratio 0.95; one-sided repeated CI bound, 1.14). Other, long-term CV outcome trails of the DPP-4 inhibitors are currently underway to further define the effects of this class of medication on the CV system in people with T2DM (Table 5).

DPP-4 Inhibitors: Do They Cause Heart Failure?

An unexpected finding of an increased rate of hospitalisation for heart failure was reported in SAVIOR-TIMI study for saxagliptin (3.5%) compared with placebo (2.8%) treated participants over 2.1 years (hazard ratio 1.27, 95% CI 1.07 to 1.51, p = 0.007). In the EXAMINE study, preliminary results suggest a non-significant trend towards an increase in hospitalisation for heart failure with alogliptin (12.8%) compared with placebo (12.4%) treated participants over a two year period (hazard ratio 1.07; 95% CI 0.94 to 1.11; p = 0.657) [24,52]. No echocardiography information was collected in participants in the above study and currently no mechanism of linking DDP-4 inhibitor use with precipitating heart failure symptoms has been proven. However, one suggested link is an increase in vasoactive substances that occurs in the presence of DPP-4 inhibitors. The breakdown of neuropeptide Y and substance P is impaired by
DPP-4 inhibitors, especially in the presence of ACE inhibition. Neuropeptide Y normally has vaso-constrictive properties and substance P has been shown to induce adverse myocardial remodelling in an experimental model. Therefore the modulation of these peptides by DPP-4 inhibitors could theoretically put patients at risk for the development of heart failure [33].

Currently there is no consensus regarding the use of DDP-4 inhibitors in patients with heart failure. Possibly it is prudent to counsel patients started on DPP-4 inhibitors about the symptoms and signs of heart failure and monitor them closely for the development of heart failure for the first six months after starting treatment, as cases of heart failure appeared to occur in the first few months of the SAVOR-TIMI-53 trial.

**SGLT-2 Inhibitors: Potential for Vascular Protection?**

SGLT-2 inhibitors have shown moderate weight loss in patients with T2DM. Mechanisms by which this could occur include: calorie loss from loss of glucose in the urine and from the osmotic diuretic effect of glycosuria. Weight reductions of up to 1-4 kg have been observed with both monotherapy and combination treatments [27,29]. A trial of dapagliflozin and metformin, lasting 24 weeks, revealed early and continued weight loss, reductions of at least 5% of body weight, throughout the treatment period [54].

Reductions in systolic blood pressure of up to 3-9 mmHg have also been observed, likely secondary to the mild osmotic diuresis induced by this class of medication. Dapagliflozin has been shown to increase daily urine production by up to 450 mL/day. Furthermore, an overall reduction in weight and increase in sodium ion excretion may contribute to blood pressure reductions [29]. Despite slight changes in systolic blood pressure, trials have not been able to show reductions in diastolic blood pressure.

Some trials have reported small beneficial changes in total cholesterol and high density lipoprotein cholesterol (HDL-C). A multi-centre, double blinded phase 3 trial using dapagliflozin in patients with T2DM who were receiving metformin (>1500 mg per day) and had inadequate glycaemic control, revealed mean increases in HDL-C (1.8% - 4.4% from baseline) and decreases in triglycerides (-2.4% to -6.2% from baseline), compared to placebo [29]. This study showed no apparent changes in fasting lipid profiles. Furthermore, a 52 week randomised phase 3 study done on canagliflozin (as add on therapy in patients using metformin and sulfonylurea), showed a mean increase in HDL-C (mean % change of 7.6%, 95% CI: 4.6 to 9.3), with also an increase in LDL-C (mean % change of 11.7%, 95% CI: 1.7 to 11.2) [55]. Overall, this resulted in no significant change in the total cholesterol to HDL-C ratio [55]. Thus, these minor changes in lipid parameters may not have any impact in clinical practice, especially as also many patients with T2DM are already taking lipid modifying agents.

Furthermore, SGLT-2 inhibitors are reported to have small reductions (approximately 0.05 mmol/L) in uric acid levels [56]. This is thought to occur via the increased secretion of uric acid alongside the secretion of glucose. This may have potential CV benefits considering that elevated serum uric acid levels are emerging as an independent risk factor for CV disease [57].

**SGLT-2 Inhibitors: CV Disease Outcome Studies**

The CV effects of long-term SGLT-2 inhibition are unknown, however trials are in progress to assess the effects of SGLT-2 inhibitors on CV outcomes (Table 6). A randomised-placebo controlled trial on the drug canagliflozin, Canagliflozin Cardiovascular Assessment Study (CANVAS), is currently underway, designed to evaluate drug-profile safety as well as the effects of canagliflozin on the risk of CV disease. The primary end point for this study will be the incidence of major cardiovascular events including cardiovascular death, non-fatal myocardial infarction and non-fatal stroke. The study is planned to run for nine years with results estimated to be released in June 2018.

**Table 5** Dipeptidyl peptidase-4 inhibitor CV safety outcome trials.

<table>
<thead>
<tr>
<th>Trial Name</th>
<th>Drug</th>
<th>Number of patients</th>
<th>Primary End Point</th>
<th>Expected Duration (Years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TECOS</td>
<td>Sitagliptin</td>
<td>14,000</td>
<td>MACE + USA</td>
<td>6</td>
</tr>
<tr>
<td>SAVOR-TIMI 53</td>
<td>Saxagliptin</td>
<td>16,492</td>
<td>MACE</td>
<td>2.1 (completed)</td>
</tr>
<tr>
<td>EXAMINE</td>
<td>Alogliptin</td>
<td>5,380</td>
<td>MACE</td>
<td>3.3 (completed)</td>
</tr>
<tr>
<td>CAROLINA</td>
<td>Linagliptin</td>
<td>6,000</td>
<td>MACE + USA</td>
<td>7.6</td>
</tr>
</tbody>
</table>

Abbreviations: CAROLINA: Cardiovascular Outcome Study of Linagliptin Versus Glimepiride in Patients With Type 2 Diabetes, DPP-4: Dipeptidyl peptidase-4, EXAMINE: Cardiovascular Outcomes Study of Alogliptin in Subjects With Type 2 Diabetes and Acute Coronary Syndrome, MACE: Major adverse cardiovascular events, SAVOR-TIMI 53: Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus, TECOS: Sitagliptin Cardiovascular Outcome study, USA: Unstable angina.
Table 6 Sodium Glucose Transporter-2 inhibitor CV safety outcome trials.

<table>
<thead>
<tr>
<th>Trial Name</th>
<th>Drug</th>
<th>Number of patients</th>
<th>Primary End Point</th>
<th>Expected Duration (Years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>DECLARE-TIMI-58</td>
<td>Dapagliflozin</td>
<td>Recruiting patients</td>
<td>MACE</td>
<td>7</td>
</tr>
<tr>
<td>CANVAS</td>
<td>Canagliflozin</td>
<td>4,500</td>
<td>MACE</td>
<td>9</td>
</tr>
<tr>
<td>EMPA-REG Outcome</td>
<td>Empagliflozin</td>
<td>7,000</td>
<td>MACE</td>
<td>8</td>
</tr>
</tbody>
</table>


Data from short-term glycaemic focused clinical studies involving dapagliflozin, submitted to the US FDA, reports a hazard ratio of 0.67 (95% CI 0.42-1.08) for a composite end-point comprised of vascular death, non-fatal stroke, and myocardial infarction and hospitalised angina [58]. A specific CV outcomes study of dapagliflozin, the Multicentre Trial to Evaluate the Effect of Dapagliflozin on the Incidence of Cardiovascular Events (DECLARE-TIMI-58 study), is aiming to enrol over 17,000 patients with T2DM diabetes and established CV disease or at least two cardiovascular risk factors, has commenced in Europe. Furthermore, a new study done on empagliflozin in normotensive type 1 diabetics, has been shown to decrease arterial stiffness, which is a surrogate marker for renal and CV outcomes [59].

Conclusion

Many studies have demonstrated a relationship between chronic hyperglycaemia and the development of CV disease. Use of traditional glucose lowering drugs has shown that intensive glucose control reduces microvascular outcomes and potentially has benefits on CV outcomes in newly diagnosed T2DM diabetes. Studies currently undertaken or underway on the novel compounds; GLP-1 receptor analogues, DPP-4 inhibitors and SGLT-2 inhibitors, primarily done to assess drug safety profiles, are showing potential pleiotropic benefits on CV disease risk factors that are beyond their glucose lowering capacity. These benefits are enabled by the ability of these new agents to modulate different stages of the CV continuum, with potential direct and indirect effects on the vascular endothelium and atherogenesis, heart failure, blood pressure, lipids and body weight. So far, two randomised placebo controlled trials that have run for two to three years have shown that the DPP-4 inhibitors, saxagliptin and alogliptin are generally safe in terms of their CV profile but do not offer any particular CV benefits. A possible relationship between increased rates of hospitalisation for heart failure and saxagliptin use has emerged from one of these trials. Longer follow up studies of DPP-4 inhibitors, GLP-1 receptor analogues and SGLT-2 inhibitors will help define whether these new glucose lowering medications have CV benefits over and above their ability to lower glucose levels. These studies are still needed to better understand benefits and potential risks of these agents in the long term.

Conflict of Interest Statement

Richard MacIisaac, Glenn Ward and David O’Neal have participated in clinical trials involving the use of saxagliptin, lixisenatide and liraglutide. Richard MacIisaac has received honoraria for lectures from Eli lily, Novo Nordisk, Sanofi Aventis, Astra Zeneca, Merck Sharp & Dohme and Norvartis over the last two years. He has received research grants from Novo Nordisk in 2011. He attended one advisory board meeting for Boehringer-Ingelheim in 2013.

References


