Antihyperglycemic Medications and Cardiovascular Risk Reduction

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Cardiovascular disease (CVD) remains a leading cause of death in patients with type 2 diabetes (T2D). In addition to glycemic control, a major focus of diabetes treatment involves cardiovascular (CV) risk reduction. In 2008, the US Food and Drug Administration (FDA) instituted a new requirement that new drugs developed and studied for the treatment of T2D must undergo CV safety testing. Since the advent of this new policy, canagliflozin, empagliflozin, liraglutide and semaglutide have demonstrated superior CV event reduction – via a composite of reduction in CV death, nonfatal myocardial infarction (MI), and nonfatal stroke – compared with placebo in patients with T2D and existing CVD, or at high risk of CVD. Multiple studies are underway to evaluate the CV outcomes of other antihyperglycemic agents. In a time when there are numerous drugs in the T2D armamentarium, positive CV outcomes data influence drug selection and aids practitioners in making more individualised therapeutic recommendations for their patients.

Cardiovascular disease (CVD) is a common cause of morbidity and mortality in patients with type 2 diabetes (T2D). Patients with T2D have approximately twice the risk of developing CVD compared with the non-diabetic population, independent of other traditional CVD risk factors.[1] Although the rate of death from CVD in patients with T2D is declining, it still exceeds that of the non-diabetic population.[2] Improved glycaemia in patients with T2D may improve CVD and CVD-related death; however, it is still unclear whether optimal glycaemic control reduces the incidence of either of these.[3] In several studies published during the past 10 years, improved glycaemic control and/ or addition of an antihyperglycaemic agent to a patient with T2D were associated with negative or neutral impact on cardiovascular (CV) outcomes. The Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial demonstrated an increased risk of CV events and mortality in patients who received an intensive glucose-lowering intervention.[4] The Rosiglitazone Evaluated for CV Outcomes in Oral Agent Combination Therapy for Type 2 Diabetes (RECORD) trial showed that the addition of rosiglitazone to therapy in patients with T2D increased the incidence of heart failure (HF).[5] While the RECORD study was in progress, a meta-analysis of 42 trials involving patients with T2D who received rosiglitazone revealed an increased risk of myocardial infarction (MI) and CV-related death in patients who received the drug.[6]

Despite the increased incidence of CVD and excess mortality attributed CVD-related deaths in the T2D population, it was not until these phase 4 studies unmasked a potential link between antihyperglycaemic agents and CV risk that the US Food and Drug Administration (FDA) required that new drug therapies for T2D undergo assessment of CV safety.[7] The European Medicines Agency (EMA) followed with a similar requirement in 2012.[8] In order to meet the FDA requirements, antihyperglycaemic CV outcomes trials in patients with T2D must include patients with advanced CVD, elderly patients and patients with renal dysfunction. These studies must track and include at least 24 months' CV safety data. Trials can be designed as non-inferiority or superiority and there are specific statistical requirements defining each trial type.[7]

Since this requirement to evaluate the CV safety of antihyperglycaemic agents was enacted, four studies have demonstrated that specific antihyperglycaemic agents (canagliflozin, empagliflozin, liraglutide and semaglutide) have beneficial effects on CV outcomes. Numerous other CV outcomes studies are ongoing with aspirations to demonstrate the same. In this review, we present the studies that have demonstrated a beneficial association between antihyperglycaemic agent use and CVD risk lowering, the ongoing CV outcomes trials with approved and investigational antihyperglycaemic agents, and reflect on the implications of these data for clinical practice.

Positive cardiovascular outcome studies

Positive CV risk-lowering findings in major clinical trials for antihyperglycaemic agents over the last two years have been essential to modifying the approach to glycaemic management and CV risk reduction therapy for patients with T2D. Sodium-glucose cotransporter-2 (SGLT2) inhibitors

Table 1: Positive cardiovascular outcome trials

Drug	Trial	N	Patient population	Follow-up median (years)	Primary outcome	Other outcomes
Empagliflozin	EMPA-REG (NCT26378978)	7,020	T2D with established CVD	3.1	MACE: 10.5% (E) vs. 12.1% (P); p<0.001	Death: 8.3% (E) vs. 5.7% (P); p<0.001 CV Death: 5.9% (E) vs. 3.7% (P); p<0.001 Hospitalisation for HF or CV death: 8.5% (E) vs. 5.7% (P); p<0.001
Liraglutide	LEADER (NCT27295427)	9,340	T2D with high risk of CVD or established CVD	3.8	MACE: 13.0% (L) vs. 14.9% (P); p=0.01	Death: 8.2% (L) vs. 9.6% (P); p=0.02 CV Death: 4.7% (L) vs. 6.0% (P); p=0.007 Nephropathy: 5.7% (L) vs. 7.2% (P); p=0.003
Semaglutide	SUSTAIN-6 (NCT27633186)	2,735	T2D with high risk of CVD or established CVD	2.1	MACE: 6.6% (S) vs. 8.9% (P); p=0.02	Nonfatal stroke: 1.6% (S) vs. 2.7% (P); p=0.04 Retinopathy: 3.0% (S) vs. 1.8% (P); p=0.02 Nephropathy: 3.8% (S) vs. 6.1% (P); p=0.005
Canagliflozin	CANVAS (NCT01032629)	10,142	T2D with high risk of CVD or established CVD	2.4	MACE: 26.9 (C) vs. 31.5 (P) per 1,000 patient years, p=0.02 for superiority	Progression to albuminuria: 89.4 (C) vs. 128.7 (P) per 1,000 patient years (HR=0.73; 95% CI 0.67 to 0.79) Risk of amputation: 6.3 (C) vs. 3.4 (P) per 1,000 Patient years (HR=1.97; 95% CI 1.41 to 2.75)

C = canagliflozin; CI = confidence interval; CV = cardiovascular; CVD = cardiovascular disease; E = emplagliflozin; HF = heart failure; HR = hazard ratio; L = liraglutide; MACE = major adverse cardiovascular event; P = placebo; S = semaglutide; T2D = type 2 diabetes.

(empagliflozin and canagliflozin) and glucagon-like peptide-1 receptor agonists (GLP-1 RA) (liraglutide and semaglutide) are the two major antihyperglycaemic classes to have demonstrated these positive CV findings to date (see *Table 1*).

Empagliflozin was the first of these four antihyperglycaemic agents to demonstrate positive CV outcomes in the Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes (EMPA-REG OUTCOME) trial.[9] The EMPA-REG OUTCOME trial included 7,020 patients with T2D and established CVD. At baseline, patients had a mean age of 63 years, glycosylated haemoglobin (A1C) of 8.1%, and more than half of patients had been diagnosed with T2D for more than 10 years. Approximately 75% of patients had coronary artery disease (CAD) and nearly 50% had a history of MI. Patients were randomised to receive empagliflozin 10 mg or 25 m g or placebo once daily. The primary composite major adverse cardiovascular event (MACE) included CV death, nonfatal MI, or nonfatal stroke. The study resulted in significant findings between the pooled empagliflozin- (10 mg and 25 mg) and the placebo-treated patients. The primary CV composite outcome occurred in 10.5% and 12.1% of the empagliflozin- and placebo-treated patients, respectively, over a median of 3.1 years (p=0.04). This results in a number needed to treat (NNT) of 65 patients with T2D and CVD over 3 years to prevent one additional major CV event. There was no difference between the rates of MI or stroke between groups. However, patients treated with empagliflozin had a significantly lower rate of CV death (3.7% versus 5.9%), all-cause death (5.7% versus 8.3%), and hospitalisation for heart failure (HHF) (5.7% versus 8.5%) compared to those treated with placebo (p<0.001). These results support the rationale to optimise antihyperglycaemic therapy with empagliflozin in addition to first-line antihyperglycaemic therapy (e.g., metformin) in order to decrease the CV risk of patients with established CVD.

Liraglutide was the next agent to demonstrate positive CV outcomes in the Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results (LEADER) trial.[10] The LEADER trial included 9,340 patients with T2D who were at least 50 years of age with established CVD or greater than 60 years of age with major CVD risk factors. Major CVD risk factors included: microalbuminuria or proteinuria, hypertension (HTN) and left ventricular hypertrophy (LVH), left ventricular systolic or diastolic

dysfunction, or an ankle-brachial index (ABI) of <0.9. At baseline, enrolled patients had a mean age of 64 years, A1C of 8.7%, and duration of diabetes of 13 years. Nearly all patients (81%) had established CVD with prior MI and prior revascularisation being the most common diagnoses. Patients were randomised to receive 1.8 mg of liraglutide or placebo once daily as a subcutaneous injection. The primary composite MACE was the same as EMPA-REG OUTCOME included CV death, nonfatal MI or nonfatal stroke. The study resulted in a significantly lower frequency of the composite outcome in the liraglutide-treated patients versus placebo. The primary CV composite outcome occurred in 13.0% and 14.9% of the liraglutide and placebo treated patients, respectively, over a median of 3.8 years (p=0.01). This results in a NNT of 67 patients with T2D and CVD or CVD risk factors over 3 years to prevent one additional major CV event. There was no difference between the rates of nonfatal MI, nonfatal stroke, or HHF between groups. Patients in the liraglutide group had statistically significantly lower rates of CV death (4.7% versus 6.0%; p=0.007) and all-cause death (8.2% versus 9.6%; p=0.02) compared to those receiving placebo. While there was a non-significant higher rate of pancreatitis in the placebo group compared to the liraglutide group (23 versus 18; p=0.44), there was a signal toward increased risk of pancreatic cancer in the liraglutide-treated patients. There were 13 patients in the liraglutide group and five patients in the placebo group who developed a pancreatic carcinoma during the trial (p=0.06). All 18 patients with pancreatic cancer passed away and it was discovered that another four patients in the placebo group (of a total of nine) passed away from 'malignancy related to pancreatic cancer'. The study authors concluded that due to small number of cases of pancreatic cancer, the association between liraglutide and pancreatic cancer risk in this study cohort could not be confirmed or excluded. In summary, these study results support the rationale to optimise antihyperglycaemic therapy with liraglutide in addition to first-line antihyperglycaemic therapy (e.g. metformin) in order to decrease the CV risk of patients aged 60 or greater with established CVD or patients 50 years of age or older with known CV risk factors.

Semaglutide was the third of these four antihyperglycaemic agents to demonstrate positive CV outcomes in the Trial to Evaluate Cardiovascular and Other Long-term Outcomes with Semaglutide in Subjects with Type 2 Diabetes (SUSTAIN-6).[11] The SUSTAIN-6 trial included 2,735 patients with T2D who were at least 50 years of age, with established CVD, HF or chronic kidney disease (CKD) stage 3 to 5, or who were 60 years of age

or greater with major CV risk factors. Just as in the LEADER trial, major CVD risk factors included: microalbuminuria or proteinuria, HTN and LVH, left ventricular systolic or diastolic dysfunction or an ABI of <0.9. At baseline, the mean patient age was 65 years, A1C was 8.7% and duration of diabetes was 14 years. Nearly all patients (92.8%) had HTN, 60.5% had ischaemic heart disease, 28.5% had moderate to severe renal impairment (estimated glomerular filtration rate [eGFR] <60 ml/min/1.73m²), and 23.6% had HF. Patients were randomised to receive a once-weekly subcutaneous injection of 0.5 mg or 1 mg of semaglutide or placebo. The primary composite MACE included CV death, nonfatal MI or nonfatal stroke. The study resulted in significant findings between the pooled semaglutide (0.5 mg and 1 mg) and the placebo-treated patients. The primary CV composite outcome occurred in 6.6% and 8.9% of the semaglutide- and placebo-treated patients, respectively, over a median of 2.1 years (p<0.001). This results in a NNT of 31 patients with T2D and CVD or CVD risk factors over 3 years to prevent one additional major CV event. No difference was noted between the rates of nonfatal MI between groups, but patients treated with semaglutide experienced a significantly lower rate of nonfatal stroke (1.6% versus 2.7%; p=0.04) and revascularisation (5.0% versus 7.6%; p=0.003) compared to those treated with placebo. Diabetic retinopathy occurred more frequently in semaglutide-treated patients compared to those who received placebo (3.0% versus 1.8%; hazard ratio [HR]=1.76; 95% confidence interval [CI], 1.11 to 2.78; p=0.02). The number needed to harm (NNH) is 58 patients over 3 years to see one additional case of diabetic retinopathy. It should be noted, however, that 83.5% of patients who developed a retinopathy-related complication during the study had pre-existing retinopathy at baseline. These study findings support the rationale to optimise antihyperglycaemic therapy with semaglutide in addition to first-line antihyperglycaemic therapy (e.g., metformin) in order to decrease the CV risk of patients with established CVD with or without CKD who do not have evidence of diabetic retinopathy.

Most recently, canagliflozin has become the fourth antihyperglycaemic agent to demonstrate positive CV outcomes, albeit at an increased risk of limb or digit amputation. The CANagliflozin cardioVascular Assessment Study (CANVAS) trial evaluated the risk for MACE in patients with T2D and high CVD risk or existing CVD who received either canagliflozin 100 mg or 300 mg daily) or placebo. Data from CANVAS were combined with data from the Study of the Effects of Canagliflozin on Renal Endpoints in Adult Subjects with Type 2 Diabetes Mellitus [CANVAS-R] in a pre-specified integrated analysis of CV safety outcomes. Patients enrolled in CANVAS-R received canagliflozin 100 mg daily or placebo. The CANVAS programme (CANVAS and CANVAS-R) included 10,142 patients with T2D and at high risk for or existing CVD. Patients enrolled had a mean age of 63.3 years, baseline A1C of 8.2%, and duration of diabetes of 13.5 years.[12] A majority of patients (65.6%) had existing CVD. The primary composite MACE included CV death, nonfatal MI or nonfatal stroke. The CANVAS program resulted in significant findings between the canagliflozin and the placebo-treated patients. The primary CV composite outcome occurred in 26.9 and 31.5 participants per 1,000 patient-years in the canagliflozin and placebo treated patients, respectively, over a median of 2.4 years (p=0.02 for superiority). This results in a number needed to treat (NNT) of 179 patients over 3 years to prevent one additional major CV event. Progression to albuminuria was less frequent in the canagliflozin-treated patients compared with those in the placebo group (89.4 versus 128.7 events per 1,000 patient-years; HR=0.73; 95% CI, 0.67 to 0.79). Serious adverse events were less frequent in the canagliflozin group compared to placebo (104.3 versus 120.0 patients with an event per 1,000 patient-years; HR=0.93; 95% CI, 0.87 to 1.00). However, there was a significantly higher risk of amputation in the canagliflozin group compared to placebo

(6.3 versus 3.4 participants with amputation per 1,000 patient-years; HR=1.97; 95% CI, 1.41 to 2.75). This corresponds to a number needed to harm (NNH) of 277 patients over 3 years to see one additional amputation. Most affected patients (71%) had a toe or metatarsal amputation and risk of amputation was highest among those with a history of amputation or concomitant peripheral vascular disease (PVD). Study authors acknowledge that the increased risk of amputation is a new finding and caution should be exercised when using canagliflozin in patients at risk for amputation. The US prescribing information for canagliflozin has been updated to include a new black box warning regarding the risk of amputation. Overall, these study findings support the rationale to optimise antihyperglycaemic therapy with canagliflozin in addition to first line antihyperglycaemic therapy (e.g. metformin) in order to decrease the CV risk of patients at high risk for or with established CVD. Healthcare providers should screen patients for risk factors for amputation (e.g., PVD) prior to prescribing canagliflozin. Patients and healthcare providers will need to weigh the CV benefit against the risk of amputation when considering canagliflozin for the treatment of T2D.

In addition to these individual drug studies, the Comparative Effectiveness of Cardiovascular Outcomes in New Users of SGLT-2 Inhibitors (CVD-REAL) trial was a large, real-world study that retrospectively evaluated the risk for HHF, all-cause mortality, and the combined endpoint of HHF or all-cause mortality in patients with T2D (with and without CVD) who were new users of an approved SGLT2 inhibitor (canagliflozin, dapagliflozin and empagliflozin) compared to patients with T2D who were new users of any other antihyperglycaemic agent.[13] Safety outcomes were not assessed. Data was collected via medical claims, primary care or hospital records, and national registries for nearly 310,000 patients with T2D across six countries. Patients newly initiated on an SGLT2 inhibitor were propensity score-matched with patients newly initiated on any other antihyperglycaemic agent (including fixed-dose combinations). After matching, the mean age was 57 years and 13% had CVD. Baseline A1C was not reported. Most new users of SGLT2 inhibitors received either canagliflozin (51%) or dapagliflozin (46%). Insulin was the most common index antihyperglycaemic agent (34%) for patients not on an SGLT2 inhibitor, followed by dipeptidyl peptidase-4 (DPP-4) inhibitors (18%). Data analysis demonstrated that SGLT2 inhibitors reduce risk of HHF by 39% and all-cause mortality by 51%. The study authors concluded that these data confirmed the positive outcomes demonstrate in EMPA-REG OUTCOME and further support that CV benefit may be a class effect with SGLT2 inhibitors.

Ongoing or unpublished cardiovascular outcome studies

In addition to EMPA-REG OUTCOME, LEADER, SUSTAIN-6 and the CANVAS programme, multiple other studies evaluating the CV outcomes of individual antihyperglycaemic agents or classes of agents are currently ongoing or recently completed but not yet published (see *Table 2*). Cardiovascular outcomes trials of GLP-1 RAs, DPP-4 inhibitors, and SGLT2 inhibitors have either recently been completed or are scheduled to be completed within the next two years and will provide additional evidence that will undoubtedly influence antihyperglycaemic selection for patients with T2D and established CVD or at high risk of CVD.

There are five GLP-1 RA studies either recently completed or due to be completed. The studies are diverse in their methods and outcomes; if the CV trial data are consistently favourable, this will strengthen the case that beneficial CV effect is a class effect. However, if the trial data are neutral or negative, this could complicate the role in therapy of GLP-1 RAs. A Study to Evaluate Cardiovascular Outcomes in Patients with Type 2 Diabetes

Table 2: Summary of ongoing or unpublished cardiovascular outcome trials

Drug	Trial	N	Intervention	Comments	Completion date
Exenatide in DUROS	FREEDOM-CVO (NCT01455896)	4,000	Exenatide in DUROS 60 mcg daily versus placebo	Drug not yet FDA or EMA approved	March 2016
Liraglutide	MAGNA VICTORIA (NCT01761318)	50	Liraglutide 0.6–1.8 mg daily versus placebo		March 2016
Exenatide once-weekly	EXSCEL (NCT01144338)	14,000	Exenatide 2 mg weekly versus placebo		September 2017
Dulaglutide	REWIND (NCT01394952)	9,622	Dulaglutide 1.5 mg weekly versus placebo		July 2018
Albiglutide	HARMONY Outcomes (NCT02465515)	9,400	Albiglutide 30 mg or 50 mg weekly versus placebo		May 2019
Dapagliflozin	DECLARE-TIMI58 (NCT01730534)	17,276	Dapagliflozin 10 mg daily versus placebo		April 2019
Ertugliflozin	VERTIS CV (NCT01986881)	8,000	Ertugliflozin 5 mg or 15 mg daily versus placebo	Drug not yet FDA or EMA approved	October 2019
Linagliptin	CAROLINA (NCT01243424)	6,115	Linagliptin 5 mg daily versus glimepiride 1–4 mg daily		February 2019
	CARMELINA (NCT01897532)	8,300	Linagliptin 5 mg daily versus placebo		January 2018

CV = cardiovascular; DPP-4 = dipeptidyl peptidase 4; EMA = European Medicines Agency; FDA = United States Food and Drug Administration; SFU = sulfonylurea.

Treated with ITCA 650 (FREEDOM-CVO) was completed in March 2016 and evaluated time to first occurrence of a composite endpoint of CV death, nonfatal MI, nonfatal stroke, or hospitalization for unstable angina for patients treated with investigational exenatide in DUROS® (Intarcia Therapeutics; ITCA 650) 60mcg daily.[14] The drug ITCA 650 is a continuous subcutaneous delivery of exenatide via the DUROS device placed under the skin of the patient's abdomen twice yearly during an in-office procedure. Also completed in March 2016, the Effect of Liraglutide on Cardiovascular Endpoints in Diabetes Mellitus Type 2 Patients (MAGNA VICTORIA) aims to add data supporting the demonstrated CV benefit of liraglutide.[15] The MAGNA VICTORIA investigators hypothesised that liraglutide improves CV function and has included targeted outcome measures that include stroke volume, ejection fraction and cardiac output. While both studies were completed in early 2016, results have not yet been published. The Exenatide Study of Cardiovascular Event Lowering (EXSCEL), the largest GLP-1 receptor agonist trial to date, recently reported out top-line results indicating that EXSCEL met its primary safety endpoint of non-inferiority for MACE.[16,17] Although there were fewer CV events in the exenatide arm of the trial, superior MACE reduction was not achieved. Further evaluation of trial data is ongoing and more data are to be presented at the European Association for the Study of Diabetes (EASD) annual meeting in September 2017.[17] Researching Cardiovascular Events with a Weekly Incretin in Diabetes (REWIND) and A Long Term, Randomised, Double Blind, Placebo-controlled Study to Determine the Effect of Albiglutide, When Added to Standard Blood Glucose Lowering Therapies, on Major Cardiovascular Events in Patients With Type 2 Diabetes Mellitus (HARMONY Outcomes) trials are ongoing and are evaluating the time to first occurrence of a composite of CV death, nonfatal MI or nonfatal stroke in patients treated with dulaglutide and albiglutide, respectively.[18,19] The other two trials are expected to be completed within the next 2 years.

Two ongoing trials of SGLT2 inhibitors also seek to evaluate CV outcomes. The Multicenter Trial to Evaluate the Effect of Dapagliflozin on the Incidence of Cardiovascular Events (DECLARE-TIMI58) and Cardiovascular Outcomes Following Ertugliflozin Treatment in Type 2 Diabetes Mellitus Participants With Vascular Disease (VERTIS CV) Study are each evaluating an SGLT2 inhibitor and time to first occurrence of CV death, nonfatal MI or nonfatal stroke.[20,21] DECLARE-TIMI58 is set to enroll over 17,000 patients and will be one of the largest CV outcomes trials to date. Ertugliflozin is not yet approved for use but the FDA and EMA both accepted new drug approval (NDA) filings for this agent in March 2017.

There are two ongoing CV outcomes studies of the DPP-4 inhibitor linagliptin. The Cardiovascular and Renal Microvascular Outcome Study with Linagliptin in Patients with Type 2 Diabetes Mellitus (CARMELINA) study is investigating the long-term impact of linagliptin versus placebo on CV morbidity and mortality (primary outcomes) and renal function (secondary outcomes) in patients with T2D at high risk of CV events.[22] CARMELINA is a 48-month trial – two years longer than most other CV outcomes trials – with CV endpoints of time-to-first-occurrence of a composite of CV death, nonfatal MI, nonfatal stroke and hospitalisation for unstable angina. The secondary renal endpoints include renal death, end-stage renal disease (ESRD), or a sustained decrease in eGFR of 50% or more. The Cardiovascular Outcome Study of Linagliptin Versus Glimepiride in Patients with Type 2 Diabetes (CAROLINA) trial is a comparison of CV outcomes a DPP-4 inhibitor (linagliptin) versus a sulfonylurea (glimepiride).[23] CAROLINA is the largest trial of its kind comparing two oral antihypergylcemic agents head-to-head regarding their effects on CV outcomes. Given the concern for increased risk of HHF in the Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus – Thrombolysis in Myocardial Infarction 53 (SAVOR-TIMI 53) trial, it will be important for the study investigators of these two linagliptin trials to report out on any HF-related findings.[24]

Implications for practice

Results of the published studies are influencing diabetes management guidelines; data from EMPA-REG OUTCOME and LEADER guided drug therapy recommendations in the 2017 American Diabetes Association Standards of Medical Care in Diabetes and the Canadian Pharmacologic Management of Type 2 Diabetes: November 2016 Interim Update. Both guidelines endorse the use of empagliflozin or liraglutide in patients with established CVD to reduce their risk of CV mortality.[25–27] The positive CV outcomes data for semaglutide will likely be included in the next guideline update. It is unclear how the

positive CV outcomes data for canagliflozin will be incorporated into updated guidelines and, ultimately, into practice given the increased risk of amputations and new black box warning related to this.

The mechanism(s) behind the CV benefit of empagliflozin, liraglutide, semaglutide and canagliflozin have not been clearly established. All four drugs have multiple beneficial effects on the body, such as glucose lowering, blood pressure (BP) lowering, and weight loss. It has been hypothesised that improvements in glycaemic control, BP and weight are linked with positive CV outcomes. However, the effects of empagliflozin, liraglutide, semaglutide and canagliflozin on these parameters in their respective CV outcomes trials were relatively modest. Across the three CV outcomes trials for the four drugs, A1C was reduced 0.24% to 0.7%, systolic BP was reduced 1 to 4 mmHg, and weight was reduced 2 to 4 kg compared with placebo.[9–11] While reduction in each surrogate marker is beneficial to the patient, the small magnitude of change does not explain the CV benefit.[28–30] The beneficial CV effects of empagliflozin are possibly related to in the body's use of ketones as a fuel source.[31] Empagliflozin may improve cardiac contractility and efficiency via preferential use of ketone bodies that produce energy more efficiently than glucose or free fatty acids.[31] Because canagliflozin has the same mechanism of action as empagliflozin, this hypothesis is likely true for canagliflozin as well. The beneficial effects of liraglutide and semaglutide are possibly related to atherosclerosis prevention, though the definitive mechanism by which this occurs is unclear.[10,28,32]

Until more data are available, it is unknown whether the beneficial CV effects of these drugs represent a class effect (for SGLT-2 inhibitors and GLP-1 receptor agonists) or if the CV benefit is unique to the individual agents. Another unknown is whether these CV benefits extend to a lower CV risk population, such as primary prevention patients. Caution must be exercised to not extrapolate the results of EMPA-REG OUTCOME, LEADER, SUSTAIN-6 and the CANVAS programme to all patients with T2D. However, both SGLT-2 inhibitors and GLP-1 receptor agonists are guideline-supported add-on therapies irrespective of a patient's CV risk.[26]

Conclusion

Canagliflozin, empagliflozin, liraglutide and semaglutide have all demonstrated CV benefit in patients with T2D and existing CVD and/or high risk of CVD. Given the risk of amputation, canagliflozin is the least preferred agent of the four despite its positive CV benefit. Preference should be given to the use of empagliflozin, liraglutide and semaglutide as add-on to first-line therapy in patients with T2D and CVD or at high CVD risk who require additional medication for glucose lowering. Caution should be exercised regarding potential adverse effects; not every patient is a candidate for these hyperglycaemic agents. Multiple other CV outcomes studies are underway and will provide more insights into additional agents that also have favourable CV effects, mechanisms of CV benefit, whether CV benefits are a class effect and whether lower-risk patients derive CV benefit from these agents. ❑

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