Series: Cardiovascular outcome trials for diabetes drugs
Canagliflozin and the CANVAS Program, dapagliflozin and DECLARE-TIMI 58, ertugliflozin and VERTIS CV

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Abstract

EMPA-REG OUTCOME was a landmark trial with the sodium-glucose co-transporter-2 (SGLT2) inhibitor empagliflozin, which demonstrated significant reductions in major adverse cardiovascular events (MACE, a composite of cardiovascular death, non-fatal myocardial infarction and non-fatal stroke) driven by reductions in cardiovascular deaths and accompanied by an early reduction in hospitalisation for heart failure. This was followed by cardiovascular outcome trials with canagliflozin, dapagliflozin and ertugliflozin. The CANVAS Program was an integrated analysis of the CANVAS and CANVAS-R trials with canagliflozin. It demonstrated a significant reduction in MACE, but not in any of the components, and there was an unexpected increase in amputations and fractures with canagliflozin. The DECLARE-TIMI 58 trial with dapagliflozin had two co-primary endpoints. A composite endpoint of cardiovascular death or hospitalisation for heart failure was significantly reduced, but there was no significant difference in MACE comparing dapagliflozin with placebo. Analysis of patients with a prior myocardial infarction, however, demonstrated significant reductions in MACE. The VERTIS CV trial with ertugliflozin was disappointing as there was no difference in MACE comparing ertugliflozin and placebo. In all four trials a reduction in hospitalisation for heart failure was observed in patients with type 2 diabetes, regardless of whether they had existing atherosclerotic cardiovascular disease or increased cardiovascular risk. Prespecified renal outcomes were reduced with empagliflozin, canagliflozin and dapagliflozin, and these drugs are now commonly used in the management of people with type 2 diabetes. It is hard to envisage an ongoing role for ertugliflozin in routine clinical management as the evidence for its cardiovascular benefit is not convincing.

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Key words: diabetes, cardiovascular outcome trial, canagliflozin, dapagliflozin, ertugliflozin

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Introduction

Licensing requirements for new antidiabetic drugs changed in the USA and EU following the rosiglitazone controversy and there was a much greater requirement to demonstrate cardiovascular safety. Between 2015 and 2020 four dedicated cardiovascular outcome trials were completed with sodium-glucose co-transporter-2 (SGLT2) inhibitors in patients with type 2 diabetes.[1–4] EMPA-REG OUTCOME (Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients) was the first of these,[1] and was reviewed earlier in this series.[5] EMPA-REG OUTCOME can truly be described as a landmark trial as not only did it satisfy the safety requirements for empagliflozin, but it demonstrated remarkable cardiovascular benefits, including significant reductions in major adverse cardiovascular events (MACE, a composite of cardiovascular death, non-fatal myocardial infarction and non-fatal stroke) powered by an early reduction in cardiovascular deaths. Secondary outcomes of hospitalisation for heart failure and a renal composite outcome were also significantly reduced.[1]

This review describes results from the other three cardiovascular safety trials with SGLT2 inhibitors in patients with type 2 diabetes; the CANVAS Program with canagliflozin,[2] DECLARE-TIMI 58 with dapagliflozin[3] and VERTIS CV with ertugliflozin.[4] The review describes the primary endpoint and important secondary outcomes from the principal publications, making comparisons with the results of EMPA-REG OUTCOME, and directs attention to important subsequent publications of data from subgroups and/or post hoc analyses.

The CANVAS Program

The CANVAS Program comprised two sister trials and data from the two trials were integrated to assess cardiovascular safety and

efficacy. The rationale, design and baseline characteristics from CANVAS (Canagliflozin Cardiovascular Assessment Study) was published in 2013,[6] and the rationale, design, and baseline characteristics of CANVAS-R (Canagliflozin Cardiovascular Assessment Study-Renal) was published in 2017.[7] Prior to the completion of the trials, the CANVAS Program collaborative group described how the integrated statistical analysis would be performed to optimise the analysis strategy.[8]

The principal results from the CANVAS Program were presented in 2017 at the meeting of the American Diabetes Association (ADA) and published simultaneously in the *New England Journal of Medicine*.[2] The key features of the trial and baseline characteristics of subjects are described in Table 1. The CANVAS Program recruited a mixture of subjects with established atherosclerotic cardiovascular disease (66%) and subjects over 50 years of age with two or more risk factors for cardiovascular disease (34%), whereas EMPA-REG OUTCOME recruited only patients with established atherosclerotic cardiovascular disease. Two doses of canagliflozin were included (100 mg and 300 mg) and the results of both doses of canagliflozin and both CANVAS trials were pooled for analysis.

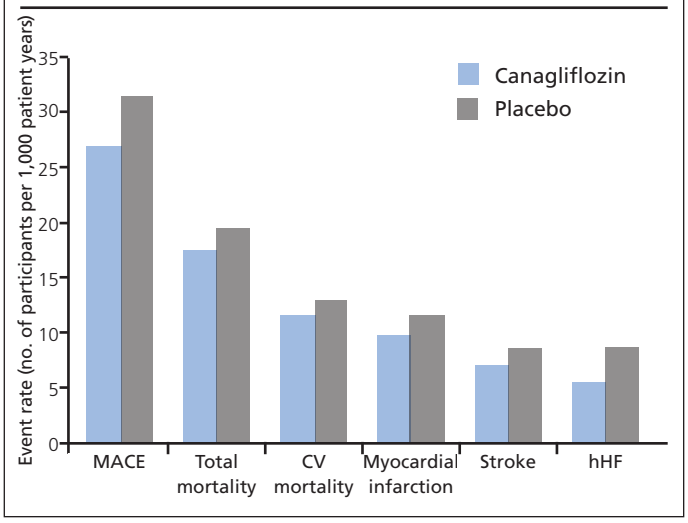
In the CANVAS Program there was a significant reduction in MACE with canagliflozin, demonstrating superiority versus placebo (Figure 1, Box 1). Statistical hypothesis testing was scheduled to proceed sequentially, and there was no significant difference in the next sequential outcome which was all-cause mortality. Any further statistical analysis of CANVAS is therefore deemed to be exploratory. There were no nominal differences in any of the components of the composite MACE outcome, but there were reductions in hospitalisation for heart failure, the progression of albuminuria and a renal composite outcome (40% reduction in estimated glomerular filtration rate (eGFR), the need for renal replacement therapy or death from renal causes).

Unexpectedly, there was a significantly increased rate of amputation of the toes, feet or legs with canagliflozin, which was particularly seen in subjects with a history of amputation or peripheral vascular disease. The rate of all fractures was also significantly higher with canagliflozin than placebo, and this appeared to be higher with canagliflozin than placebo in the CANVAS trial but not in CANVAS-R. As might be anticipated, rates of genital fungal infections with canagliflozin were significantly increased in women and men. Diabetic ketoacidosis was rare with only 18 episodes, and although it was twice as common in the canagliflozin group, this was not statistically significant.

Other results from the CANVAS Program

The effect of canagliflozin on amputation risk in the CANVAS Program was calculated for amputations of different types and aetiologies and different canagliflozin doses.[9] The increased risk of amputation was similar for ischaemic and infective aetiologies and for 100 mg and 300 mg doses. The risk of amputation was associated with a baseline history of previous amputation and other established risk factors for amputation. Disappointingly, no specific aetiological mechanism or at-risk subgroup for canagliflozin was identified.

Figure 1. Event rates (number of participants/1,000 patient-years) comparing canagliflozin and placebo for major adverse cardiovascular events (MACE), total mortality, cardiovascular mortality (CV mortality), non-fatal myocardial infarction, non-fatal stroke and hospitalisation for heart failure (hHF).



Box 1 Results of the CANVAS Program[2]

Principal result

- Significant reduction in MACE and hospitalisation for heart failure[2]

Other results from the CANVAS Program

- The increased risk of amputation was similar for ischaemic and infective causes, and was associated with a history of previous amputation and other established risk factors for amputation.[9]
- The increase in fracture risk was not explained by interactions with participant characteristics, dose effects, duration of follow-up, metabolic effects, adverse events related to falls or adverse events possibly causing falls.[10]
- In a pre-specified exploratory analysis, canagliflozin treatment was associated with a reduced risk of sustained loss of kidney function, attenuated eGFR decline and a reduction in albuminuria,[25] supporting a possible renoprotective effect of this drug that was later confirmed in CREDENCE.[11]
- Canagliflozin reduced the risk of cardiovascular death or hospitalisation for heart failure across a broad range of different patient subgroups, but benefits appeared greater in those with a history of heart failure at baseline.[26]

Further analysis of fractures in the CANVAS Program was also disappointing as the differences in fracture risk between CANVAS and CANVAS-R was not explained by differences in baseline characteristics, interactions of randomised treatment with participant characteristics, dose effects, duration of follow-up, metabolic effects, adverse events related to falls or adverse events possibly causing falls.[10] The investigators concluded that this was a chance finding without providing any evidence for this conclusion, other than the fact that there was no increase in fractures (or amputations) in the CREDENCE renal outcome trial with canagliflozin.[11] They conceded that an unidentified mechanism related to falls remained a possibility. The results of

CREDENCE were not available when the post hoc analysis of amputations was performed, but it would have stretched credibility to suggest that the increase in amputations and fractures were both chance findings!

DECLARE-TIMI 58

Papers on the design and rationale for DECLARE-TIMI 58 (Dapagliflozin Effect on Cardiovascular Events-Thrombolysis in Myocardial Infarction 58) and on the baseline patient characteristics were published in 2018.[12,13] Key features of the trial and baseline characteristics of subjects are described in Table 1. Like the CANVAS Program, DECLARE-TIMI 58 recruited a mixture of subjects with established atherosclerotic cardiovascular disease (41%) and subjects over 55 years of age with one or more risk factors for cardiovascular disease (59%). For the statistical analysis, the first analysis was for non-inferiority of dapagliflozin to placebo for MACE. If non-inferiority was confirmed, then two co-primary outcomes were tested for superiority, which were MACE and a composite of cardiovascular death or hospitalisation for heart failure. MACE is the primary endpoint in cardiovascular trials when studying drugs that reduce events in patients with atherosclerosis (eg, statins), and the composite of cardiovascular death or hospitalisation for heart failure is the preferred primary endpoint when studying drugs that reduce events in patients with heart failure (eg, ACE inhibitors, beta blockers, etc).

The principal results from DECLARE-TIMI 58 were presented in 2018 at the meeting of the American Heart Association (AHA) and published simultaneously in the *New England Journal of Medicine*.[3] In DECLARE-TIMI 58 there was a significant reduction in the co-primary composite endpoint of cardiovascular death or hospitalisation for heart failure with dapagliflozin, but no significant reduction in the co-primary MACE endpoint (Figure 2, Box 2). There were no significant differences in death from any cause, death from cardiovascular causes, myocardial infarction or stroke. There were statistically significant differences in the rate of hospitalisation for heart failure and in the pre-defined renal composite outcome which in DECLARE-TIMI 58 was a ≥40% reduction in eGFR to <60 mL/min/1.73 m^2, new end-stage renal disease or death from renal or cardiovascular causes.

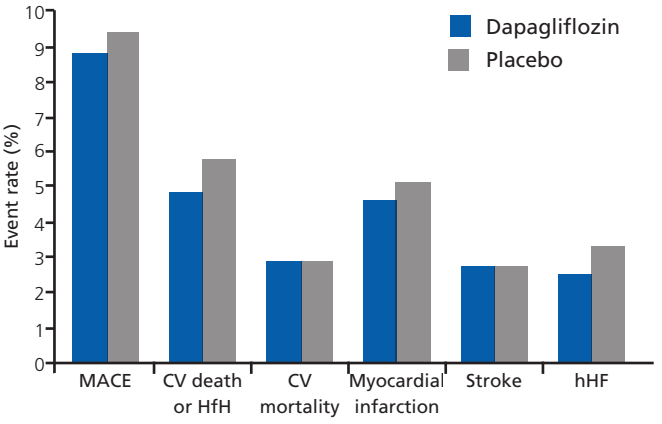
Again, as expected there was a significant increase in genital infections with dapagliflozin, and rates of diabetic ketoacidosis were doubled, which in DECLARE-TIMI 58 was a statistically significant difference. There was no difference in the rates of amputation or fracture.

Other results from DECLARE-TIMI 58

The biggest differences between DECLARE-TIMI 58 and EMPA-REG OUTCOME were the inclusion of a large number of patients without established atherosclerotic cardiovascular disease in DECLARE-TIMI 58, and the absence of a reduction in MACE in the results. Perhaps anticipating these findings, the DECLARE-TIMI 58 investigators pre-specified subjects with a prior myocardial infarction as a subgroup of interest.[14]

A statistically significant reduction in MACE was observed comparing dapagliflozin and placebo in the 3,584 subjects with a previous myocardial infarction, but there was no difference in subjects without a previous myocardial infarction, including in patients with established atherosclerotic disease but without a prior myocardial infarction.

Figure 2. Event rates (%) comparing dapagliflozin and placebo for major adverse cardiovascular events (MACE), cardiovascular death or hospitalisation for heart failure (CV death or HFH), cardiovascular mortality (CV mortality), myocardial infarction, stroke and hospitalisation for heart failure (hHF)



Box 2 Results of the DECLARE-TIMI 58 trial[3]

Principal result
- Significant reduction in the composite of cardiovascular death and hospitalisation for heart failure[3]
- No significant difference in MACE[3]

Other results from DECLARE-TIMI 58
- A statistically significant reduction in MACE was observed comparing dapagliflozin and placebo in the 3,584 subjects with a previous myocardial infarction, but there was no difference in subjects without a previous myocardial infarction.[14]
- Of 17,160 patients, 671 (3.9%) had heart failure with a reduced ejection fraction (HFrEF), 1,316 (7.7%) had heart failure without known reduced ejection fraction and 15,173 (88.4%) had no history of heart failure at baseline. Dapagliflozin reduced cardiovascular death/hospitalisation for heart failure more in patients with HFrEF than in those without HFrEF.[27]
- A pre-specified secondary cardiorenal composite defined as a sustained decline of at least 40% in estimated glomerular filtration rate (eGFR) to <60 mL/min/1.73 m^2, end-stage renal disease (defined as dialysis for at least 90 days, kidney transplantation or confirmed sustained eGFR <15 mL/min/1.73 m^2) or death from renal or cardiovascular causes was reduced, as was a pre-specified renal specific composite outcome which was the same but excluded death from cardiovascular causes.[28]
- Acute kidney injury was less common with dapagliflozin, and there was no increase in adverse events suggestive of volume depletion irrespective of blood pressure or diuretic use including the use of loop diuretics.[29]

VERTIS CV

A paper describing the design and baseline characteristics of VERTIS CV (Evaluation of Ertugliflozin Efficacy and Safety Cardiovascular

Outcomes Trial) was published in 2018.[15] This explained that, following the publication of the results of EMPA-REG OUTCOME, it was decided to double the number of subjects in VERTIS CV with the aim of testing for superiority for cardiovascular and renal outcomes. The principal VERTIS CV results were presented in 2020 at the virtual meeting of the ADA and the results were accompanied with an updated systematic review and meta-analysis of cardiovascular and renal outcomes of SGLT2 inhibitors in patients with type 2 diabetes. The print publication of VERTIS CV in the *New England Journal of Medicine* followed later in 2020[4] and the meta-analysis was published soon after in *JAMA Cardiology*.[16] Key features of the trial and baseline characteristics of subjects are described in Table 1. Like EMPA-REG OUTCOME, all the subjects in VERTIS CV had established atherosclerotic heart disease, and the main difference in VERTIS CV was a higher rate of investigator reported heart failure at baseline (24% in VERTIS CV versus 10% in EMPA-REG OUTCOME).

Surprisingly, in VERTIS CV there was no significant difference in MACE, so non-inferiority was established but not superiority (Figure 3, Box 3). There was also no difference in the composite of death from cardiovascular causes or hospitalisation for heart failure, no difference in death from cardiovascular causes, and no difference in the pre-specified renal composite outcome, which for VERTIS CV was doubling of serum creatinine levels, the need for renal replacement therapy or death from renal causes. A reduction was observed in the rate of hospitalisation for heart failure with ertugliflozin, which again can be considered exploratory because of the hierarchal statistical testing sequence.

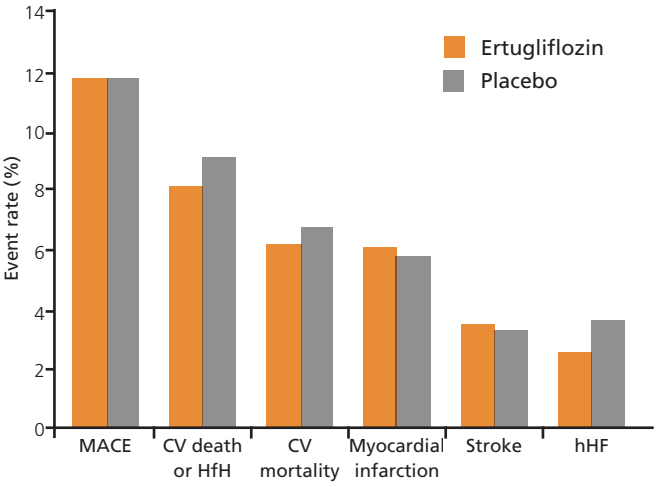
In VERTIS CV genital mycotic infections were significantly increased in women and men in the ertugliflozin group. Numerical increases were seen in diabetic ketoacidosis and amputations, but these were not statistically significant.

Results of the meta-analysis and other results from VERTIS CV

VERTIS CV failed to demonstrate reductions in MACE or the secondary renal composite outcome, and an early publication after the principal publication reported the results of a pre-specified exploratory analysis of renal outcomes.[17] The analysis replaced doubling of serum creatinine with a sustained 40% decrease from baseline in eGFR, and on this analysis a significant reduction in the renal composite outcome was observed. As had been seen in other SGLT2 inhibitor outcome trials, there was an attenuation of the decline in eGFR with ertugliflozin, and there was a decrease in the albumin to creatinine ratio.

The meta-analysis included data from the four cardiovascular outcome trials plus CREDENCE.[16] The authors reported that there was no significant heterogeneity across the trials in the reduction in MACE or the reduction in kidney outcomes, and that the risk reduction for hospitalisation for heart failure was consistent across the trials. Regardless of the statistical analysis, it is striking that there was absolutely no effect of ertugliflozin on MACE (hazard ratio 0.99, 95% confidence intervals 0.88 to 1.12). Significant heterogeneity of associations with outcomes was noted for cardiovascular death, and only EMPA-REG OUTCOME was associated with a reduction in cardiovascular death.

Figure 3. Event rates (%) comparing ertugliflozin and placebo for major adverse cardiovascular events (MACE), cardiovascular death or hospitalisation for heart failure (CV death or HFH), cardiovascular mortality (CV mortality), fatal or non-fatal myocardial infarction, fatal or non-fatal stroke, and hospitalisation for heart failure (hHF)



Box 3 Results of the VERTIS CV trial

Principal result
- No significant difference in MACE

Other results from VERTIS CV
- An analysis replacing doubling of serum creatinine with a sustained 40% decrease from baseline in estimated glomerular filtration rate (eGFR) showed a statistically significant reduction in the renal composite outcome, with an attenuation of the decline in eGFR, and a decrease in the albumin to creatinine ratio.[17]
- Ertugliflozin reduced the risk for first and total hospitalisation for heart failure (HHF) and total HHF/cardiovascular death, adding further support for the use of SGLT2 inhibitors in primary and secondary prevention of HHF.[30]

Discussion

EMPA-REG OUTCOME was a landmark study which rapidly increased the use of empagliflozin in diabetic patients with established atherosclerotic cardiovascular disease. By comparison, the results of the CANVAS Program were less dramatic. Although the pattern of benefit was broadly similar to EMPA-REG OUTCOME, several individual outcomes were not significantly reduced. Part of this difference can be explained by the inclusion of lower risk subjects who did not have established atherosclerotic cardiovascular disease, and the CANVAS Program may have been statistically underpowered for some of the comparisons. Renal benefits of canagliflozin were demonstrated in the CANVAS Program and subsequently confirmed in the dedicated CREDENCE trial of people with diabetic kidney disease. Reductions in hospitalisation for heart failure were also seen as a secondary outcome in the CANVAS Program, but to date there are no plans for a dedicated heart failure outcome trial with

Table 1 Key features of EMPA-REG OUTCOME,[1] the CANVAS Program,[2,6,7] DECLARE-TIMI 58[3,12,13] and VERTIS CV[4]

	EMPA-REG OUTCOME[1]	CANVAS Program[2,6,7]	DECLARE-TIMI 58[3,12,13]	VERTIS CV[4,15]
SGLT2 inhibitor	Empagliflozin 10 mg and 25 mg	Canagliflozin 100 mg to 300 mg	Dapagliflozin 10 mg	Ertugliflozin 5 mg and 15 mg
Subjects	7,020	10,142	17,160	8,246
Follow-up	Median observation 3.1 years	Mean 3.6 years	Median 4.2 years	Mean 3.5 years
Age	63 years	63 years	64 years	64 years
Duration of diabetes	57% duration over 10 years	14 years	11 years	13 years
Baseline HbA_{1c}	8.1% (65 mmol/mol)	8.2% (66 mmol/mol)	8.3% (67 mmol/mol)	8.2% (66 mmol/mol)
Baseline CVD	99% ASCVD 76% CAD 46% prior MI 23% stroke 10% HF	66% ASCVD 56% CAD 19% stroke/cvd 14% HF 34% CV risk	40% ASCVD 33% CAD 21% prior MI 7% stroke/cvd 10% HF 60% CV risk	100% ASCVD 76% CAD 48% Prior MI 23% stroke/cvd 24% HF
Baseline diabetes treatments	74% metformin 42% sulfonylurea 48% insulin 11% DPP-4 inhibitor 3% GLP-1 RA	77% metformin 43% sulfonylurea 50% insulin 12% DPP-4 inhibitor 4% GLP-1 RA	82% metformin 43% sulfonylurea 40% insulin 17% DPP-4 inhibitor 4% GLP-1 RA	77% metformin 41% sulfonylurea 47% insulin 11% DPP-4 inhibitor 3% GLP-1 RA

ASCVD, atherosclerotic cardiovascular disease; CAD, coronary artery disease; CV risk, subjects without established cardiovascular disease but at increased risk of developing cardiovascular disease; HF, heart failure; MI, myocardial infarction; stroke/CVD, stroke or cerebrovascular disease.

canagliflozin. Although not replicated in CREDENCE or in several real-world databases, the increase in amputations and fractures is worrying and lacks a credible explanation.

As the third published cardiovascular trial with an SGLT2 inhibitor trial, the results of DECLARE-TIMI 58 were also broadly similar to EMPA-REG OUTCOME. A reduction in heart failure events was seen in a wider population of people with type 2 diabetes in DECLARE-TIM 58, with reductions in patients who were at increased cardiovascular risk but did not have established cardiovascular disease. A dedicated outcome trial of dapagliflozin in patients with well characterised heart failure with a reduced left ventricular ejection fraction (DAPA-HF) subsequently demonstrated clear benefits with reductions in heart failure events in subjects with and without diabetes.[18] Trials with empagliflozin have shown reductions in heart failure events in patients with and without diabetes who have heart failure with a reduced ejection fraction (EMPEROR-Reduced)[19] and patients with a preserved ejection fraction (EMPEROR-Preserved).[20] A trial of dapagliflozin in patients with heart failure and a preserved ejection fraction (DELIVER) is expected to complete in 2022.[21] The licences of dapagliflozin and empagliflozin have been updated to allow prescribing in patients with heart failure in addition to use in patients with diabetes.

In DECLARE-TIMI 58 reductions in the renal composite outcome were also seen in a wider group of patients than in EMPA-REG OUTCOME. A subsequent dedicated outcome trial of dapagliflozin in patient with chronic kidney disease with and without diabetes (DAPA-CKD) demonstrated clear reductions in renal outcomes.[22] Another change in the licence for dapagliflozin broadens the indication for use in this group of patients, and canagliflozin has a similar licence for use in patients with kidney disease, but only for diabetic patients. A dedicated renal trial with empagliflozin (EMPA-KIDNEY) including patients with and without diabetes is expected to complete in 2022.[23]

There was general expectation that the results of VERTIS CV would be broadly similar to the results of EMPA-REG OUTCOME as the study population was very similar. The lack of a clear benefit in reducing the major study endpoints was a surprise, with only reductions in hospitalisation for heart failure and a revised renal composite outcome. There are no current plans for dedicated trails of ertugliflozin in patients with heart failure or chronic kidney disease. None of the four dedicated cardiovascular trials studied possible mechanisms of benefit, and there are many possible explanations for the reductions in cardiovascular and renal outcomes that are observed with SGLT2 inhibitors. As ertugliflozin has similar effects to dapagliflozin and empagliflozin on HbA_{1c}, body weight and blood pressure, as presented by the VERTIS CV investigators at the virtual ADA meeting, the benefits are unlikely to be mediated by changes in HbA_{1c}, body weight or blood pressure.[24] For diabetic patients with established atherosclerosis, empagliflozin is a better treatment option than ertugliflozin based on the results of EMPA-REG OUTCOME and, for patients who are at increased cardiovascular risk, dapagliflozin is a better treatment option based on the results of DECLARE-TIMI 58.

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Key messages

- In the CANVAS Program, canagliflozin reduced major adverse cardiovascular events in patients with type 2 diabetes but at the expense of an increase in amputations and fractures
- In DECLARE-TIMI 58 there was a reduction in heart failure events in a broad spectrum of patients with type 2 diabetes, but reductions in major adverse cardiovascular events were only observed in patients with a previous myocardial infarction
- The results of the VERTIS CV cardiovascular outcome trial with ertugliflozin were disappointing as there was no significant reduction in major adverse cardiovascular events or the chosen renal composite outcome

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