CURRENT TOPICS

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

MILES FISHER

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. Pre-specified 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.

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

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. EMPA-REG OUTCOME (Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients) was the first of these, and was reviewed earlier in this series. 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.

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, DECLARE-TIMI 58 with dapagliflozin and VERTIS CV with ertugliflozin. 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

Address for correspondence: Professor Miles Fisher
Department of Diabetes, Endocrinology & Clinical Pharmacology,
Glasgow Royal Infirmary, 84 Castle Street, Glasgow G4 0SF, UK
E-mail: miles.fisher@ggc.scot.nhs.uk
https://doi.org/10.15277/bjd.2021.320

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significant reduction in MACE and hospitalisation for heart failure.

Canagliflozin reduced the risk of cardiovascular death or hospitalisation for heart failure (hHF).

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

Principal result
- Significant reduction in MACE and hospitalisation for heart failure

Other results from the CANVAS Program
- The increased risk of amputation was similar for ischaemic and infective aetiologies, and was associated with a history of previous amputation and other established risk factors for amputation.
- 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.
- 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, supporting a possible renoprotective effect of this drug that was later confirmed in CREDENCE.
- 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.

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. 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. They conceded that an unidentified mechanism related to falls remained a possibility. The results of
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 previous myocardial infarction, but there was no difference in subjects without a previous myocardial infarction.14

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 m², 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.

VERTIS CV
A paper describing the design and baseline characteristics of VERTIS CV (Evaluation of Ertugliflozin Efficacy and Safety Cardiovascular Disease in Established Atherosclerotic Cardiovascular Disease) was published simultaneously in the New England Journal of Medicine.3

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 m², 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.

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

Box 2 Results of the DECLARE-TIMI 58 trial

Principal result
- Significant reduction in the composite of cardiovascular death and hospitalisation for heart failure3
- No significant difference in MACE4

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.22
- 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 m², end-stage renal disease (defined as dialysis for at least 90 days, kidney transplantation or confirmed sustained eGFR <15 mL/min/1.73 m²) 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

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Outcomes Trial) was published in 2018. 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 and the meta-analysis was published soon after in JAMA Cardiology. 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 hierarchical 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. The analysis replaced 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. Other results from VERTIS CV

- No significant difference in MACE
- 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.

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 CREDEENCE 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
canagliflozin. Although not replicated in CREDEENCE 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-TIMI 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. 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) and patients with a preserved ejection fraction (EMPEROR-Preserved). A trial of dapagliflozin in patients with heart failure and a preserved ejection fraction (DELIVER) is expected to complete in 2022. The licences of dapagliflozin in patients with heart failure and a preserved ejection fraction (EMPEROR-Reduced) and patients with a preserved ejection fraction (EMPEROR-Preserved) have shown reductions in heart failure events in patients with and without diabetes who have heart failure with a reduced ejection fraction (EMPEROR-Reduced) and patients with a preserved ejection fraction (EMPEROR-Preserved). A trial of dapagliflozin in patients with heart failure and a preserved ejection fraction (DELIVER) is expected to complete in 2022.

Table 1: Key features of EMPA-REG OUTCOME,1 the CANVAS Program,2,6,7 DECLARE-TIMI 588,12,13 and VERTIS CV4

|                  | EMPA-REG OUTCOME1 | CANVAS Program2,6,7 | DECLARE-TIMI 588,12,13 | VERTIS CV48,15 |
|------------------|-------------------|---------------------|------------------------|---------------|
| 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 HbA1c   | 8.1% (65 mmol/mol) | 8.2% (66 mmol/mol)  | 8.3% (67 mmol/mol)     | 8.2% (66 mmol/mol) |
| Baseline CVD     | 99% ASCVD         | 66% ASCVD           | 40% ASCVD              | 100% ASCVD    |
|                  | 76% CAD           | 56% CAD             | 33% CAD                | 76% CAD       |
|                  | 46% prior MI      | 19% stroke/cvd      | 21% prior MI           | 48% Prior MI  |
|                  | 23% stroke        | 14% HF              | 7% stroke/cvd          | 23% stroke/cvd|
|                  | 10% HF            | 34% CV risk         | 10% HF                 | 24% HF        |
| Baseline diabetes treatments | 74% metformin | 77% metformin | 82% metformin | 77% metformin |
|                  | 42% sulfonylurea  | 43% sulfonylurea    | 43% sulfonylurea       | 41% sulfonylurea|
|                  | 48% insulin       | 50% insulin         | 40% insulin            | 47% insulin   |
|                  | 11% DPP-4 inhibitor | 12% DPP-4 inhibitor | 17% DPP-4 inhibitor    | 11% DPP-4 inhibitor |
|                  | 3% GLP-1 RA       | 4% GLP-1 RA         | 4% GLP-1 RA            | 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.

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 trials of etrogliflozin 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 etrogiloflozin has similar effects to dapagliflozin and empagliflozin on HbA1c, 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 HbA1c, body weight or blood pressure. For diabetic patients with established atherosclerosis, empagliflozin is a better treatment option than etrogliflozin 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.

Conflict of interest: The author has received personal fees from AstraZeneca, Boehringer Ingelheim, Eli Lilly, Lexicon, MSD, NAPP, Novo Nordisk and Sanofi outside the submitted work.

Funding: None.
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 etrugliflozin were disappointing as there was no significant reduction in major adverse cardiovascular events or the chosen renal composite outcome.

References

1. Zinman B, Wanner C, Lachin JM, et al, for the EMPA-REG OUTCOME Investigators. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. N Engl J Med 2015;373:2117–28. https://doi.org/10.1056/NEJMoA1504720
2. Neal B, Perkovic V, Mahaffey KW, et al, for the CANVAS Program Collaborative Group. Canagliflozin and cardiovascular outcomes in type 2 diabetes. N Engl J Med 2017;377:644–57. https://doi.org/10.1056/NEJMoA1611925
3. Wiviott SD, Bonaca MP, Mosenzon O, et al, for the DECLARE-TIMI 58 Investigators. Dapagliflozin and cardiovascular outcomes in type 2 diabetes. N Engl J Med 2019;380:347–57. https://doi.org/10.1056/NEJMoA1812389
4. Cannon CP, Pratley R, Daggoo-Jack S, et al, for the VERTIS CV Investigators. Cardiovascular outcomes with etrugliflozin in type 2 diabetes. N Engl J Med 2020;383:1425–35. https://doi.org/10.1056/NEJMoA2004967
5. Fisher M. Empagliflozin and EMPA-REG OUTCOMES. Br J Diabetol 2020;20:138–41. https://doi.org/10.15277/bjdi.2020.254
6. Neal B, Perkovic V, de Zeeuw D, et al. Rationale, design, and baseline characteristics of the Canagliflozin Cardiovascular Assessment Study (CANVAS)—a randomized placebo-controlled trial. Am Heart J 2013;166:217–23. https://doi.org/10.1016/j.amheart.2013.05.007
7. Neal B, Perkovic V, Mathews DR, et al. Rationale, design and baseline characteristics of the CANagliflozin Cardiovascular Assessment Study—Renal (CANVAS-R): a randomized, placebo-controlled trial. Diabetes Obes Metab 2017;19:387–93. https://doi.org/10.1111/dom.12829
8. Neal B, Perkovic V, Mathews DR, et al. Optimizing the analysis strategy for the CANVAS Program: a prespecified plan for the integrated analyses of the CANVAS and CANVAS-R trials. Diabetes Obes Metab 2017;19:926–35. https://doi.org/10.1111/dom.12924
9. Mathews DR, Li Q, Perkovic V, et al. Effects of canagliflozin on amputation risk in type 2 diabetes: the CANVAS Program. Diabetologia 2019;62:926–38. https://doi.org/10.1007/s00125-019-4899-8
10. Zhou Z, Jardine M, Perkovic V, et al. Canagliflozin and fracture risk in individuals with type 2 diabetes: results from the CANVAS Program. Diabetologia 2019;62:1854–67. https://doi.org/10.1007/s00125-019-4955-5
11. Perkovic V, Jardine MJ, Neal B, et al, for the CREDENCE Trial Investigators. Canagliflozin and renal outcomes in type 2 diabetes and nephropathy. N Engl J Med 2019;380:2295–306. https://doi.org/10.1056/NEJMoA181744
12. Wiviott SD, Raz I, Bonaca MP, et al. The design and rationale for the Dapagliflozin Effect on Cardiovascular Events (DECLARE-TIMI 58) Trial. Am Heart J 2018;200:83–9. https://doi.org/10.1016/j.ahj.2018.01.012
13. Raz I, Mosenzon O, Bonaca MP, et al. DECLARE-TIMI 58: Participants’ baseline characteristics. Diabetes Obes Metab 2018;20:1102–10. https://doi.org/10.1111/dom.13217
14. Furtado RM, Bonaca MP, Raz I, et al. Dapagliflozin and cardiovascular outcomes in patients with type 2 diabetes mellitus and previous myocardial infarction: subanalysis from the DECLARE-TIMI 58 Trial. Circulation 2019;139:2516–27. https://doi.org/10.1161/CIRCULATIONAHA.119.039996
15. Cannon CP, McGuire DK, Pratley R, et al. Design and baseline characteristics of the eValuation of ERugliflozin efficacy and Safety Cardiovascular outcomes trial (VERTIS-CV). Am Heart J 2018;206:11–23. https://doi.org/10.1016/j.ahj.2018.08.016
16. McGuire DK, Shih WJ, Cosentino F, et al. Association of SGLT2 inhibitors with cardiovascular and kidney outcomes in patients with type 2 diabetes. A meta-analysis. JAMA Cardiol 2021;6:148–58. https://doi.org/10.1001/jamacardio.2020.4511
17. Cherney DZI, Charbonnel B, Cosentino F, et al. Effects of ertugliflozin on kidney composite outcomes, renal function and albuminuria in patients with type 2 diabetes mellitus: an analysis from the randomised VERTIS CV trial. Diabetologia 2021;64:1256–67. https://doi.org/10.1007/s00125-021-05407-5
18. McMurray JVF, Solomon SD, Inzucchi SE, et al, for the DAPA-HF Trial Committees and Investigators. Dapagliflozin in patients with heart failure and reduced ejection fraction. N Engl J Med 2019;381:1995–2008. https://doi.org/10.1056/NEJMoA1911303
19. Parker M, Anker SD, Butler J, et al, for the EMPEROR-Reduced Trial Investigators. Cardiovascular and renal outcomes with empagliflozin in heart failure. N Engl J Med 2020;383:1413–24. https://doi.org/10.1056/NEJMoA2022190
20. Anker SD, Butler J, Filipatos G, et al, for the EMPEROR-Preserved Trial Investigators. Empagliflozin in heart failure with a preserved ejection fraction. N Engl J Med 2021;385:1451–61. https://doi.org/10.1056/NEJMoA2107038
21. Solomon SD, de Boer RA, DeMets D, et al. Dapagliflozin in heart failure with preserved and mildly reduced ejection fraction: rationale and design of the DELIVER trial. Eur J Heart Fail 2021;23:1217–25. https://doi.org/10.1002/ejhf.2249
22. Heerspink HJ, Stefansson BV, Correa-Rotter R, et al. Dapagliflozin in patients with chronic kidney disease. N Engl J Med 2020;383:1436–46. https://doi.org/10.1056/NEJMoA2024816
23. Herrington WC, Preis D, Haynes R, et al. The potential for improving cardiac-renal outcomes by sodium-glucose co-transporter-2 inhibition in people with chronic kidney disease: a rationale for the EMPA-KIDNEY study. Clin J Am Soc Nephrol 2021;16:749–61. https://doi.org/10.1089/cjasn.2020.0369
24. Cowie MR, Fisher M. SGLT2 inhibitors: mechanisms of cardiovascular benefit beyond glycaemic control. Nat Rev Cardiol 2020;17:761–72. https://doi.org/10.1038/s41591-020-0406-8
25. Perkovic V, de Zeeuw D, Mahaffey KW, et al. Canagliflozin and renal outcomes in type 2 diabetes: results from the CANVAS Program randomised clinical trials. Lancet Diabetes Endocrinol 2018;6:691–704. https://doi.org/10.1016/S2213-8587(18)30144-1
26. Radhomin K, Figtine G, Perkovic V, et al. Canagliflozin and heart failure in type 2 diabetes mellitus: results from the CANVAS Program. Circulation 2018;138:458–68. https://doi.org/10.1161/CIRCULATIONAHA.118.034222
27. Kato ET, Silverman MG, Mosenzon O, et al. Effect of dapagliflozin on heart failure and mortality in type 2 diabetes mellitus. Circulation 2019;139:2528–36. https://doi.org/10.1161/CIRCULATIONAHA.119.040130
28. Mosenzon O, Wiviott SD, Cahn A, et al. Effects of dapagliflozin on development and progression of kidney disease in patients with type 2 diabetes: an analysis from the DECLARE-TIMI 58 randomised trial. Lancet Diabetes Endocrinol 2019;7:606–17. https://doi.org/10.1016/S2213-8587(19)30180-9
29. Cahn A, Raz I, Bonaca M, et al. Safety of dapagliflozin in a broad population of patients with type 2 diabetes: analyses from the DECLARE-TIMI 58 study. Diabetes Obes Metab 2020;22:1357–68. https://doi.org/10.1111/dob.14041
30. Cosentino F, Cannon CP, Cherney DZI, et al. Efficacy of ertugliflozin on heart failure-related events in patients with type 2 diabetes mellitus and established atherosclerotic cardiovascular disease results of the VERTIS CV trial. Circulation 2020;142:2205–15. https://doi.org/10.1161/CIRCULATIONAHA.120.050255

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