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# Cardiovascular outcome trials of GLP-1RAs and SGLT-2 inhibitors: a concise review from the clinicians' perspective

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## Abstract

Prevention of cardiovascular disease (CVD) is one of the main objectives in the management of people with type 2 diabetes (T2DM). New glucose-lowering therapies such as glucagon-like peptide-1 receptor agonists (GLP-1RAs) and sodium-glucose cotransporter-2 (SGLT-2) inhibitors have demonstrated not only cardiovascular safety but also cardiovascular benefits. In line with emerging evidence from the cardiovascular outcome trials (CVOTs), major international guidelines advocate GLP-1RAs and SGLT-2 inhibitors with proven cardiovascular benefits as a first add-on or monotherapy in individuals with T2DM and established CVD or CVD risk factors. Based on subsequent cardiorenal outcomes and heart failure trials, the licensed indications of some SGLT-2 inhibitors have been extended beyond glycaemic management. SGLT-2 inhibitors have now been approved for the management of chronic heart failure and chronic kidney disease, both irrespective of diabetes status. This review aims to summarise the CVOTs of GLP-1RAs and SGLT-2 inhibitors from the clinician's perspective.

**Keywords:** CVOT, cardiovascular disease, type 2 diabetes, GLP-1RA, SGLT-2 inhibitor

## INTRODUCTION

Diabetes is associated with a heightened threat of cardiovascular disease (CVD). It is thought that approximately one-third of those with type 2 diabetes (T2DM) have comorbid CVD, namely atherosclerosis, angina, heart failure (HF), myocardial infarction (MI), and stroke [1]. CVD is also a major cause of death in T2DM, contributing to approximately 50% of all-cause mortality[1]. Prevention of CVD is one of the major objectives in the management of T2DM. Multifactorial risk factor intervention can reduce T2DM-related CV morbidity and mortality by as much as 50%[2], and this has led to a move away from the traditional 'glucocentric approach' in the management of T2DM[3]. Following the launch of US Food and Drugs Administration (FDA) guidance towards the end of 2008, cardiovascular outcome trials (CVOTs) and confirmation of CV safety are necessary for FDA approval of novel glucose-lowering drugs[4]. In line with the emerging evidence from the CVOTs, there has been a major shift in the management of T2DM. Glucose-lowering therapies, which have established cardiovascular benefits, are recommended regardless of metformin use and glycaemic status[3,5]. In this concise review, we aim to summarise the CVOT results of glucagon-like peptide-1 receptor agonists (GLP-1RAs) and sodium-glucose cotransporter-2 (SGLT-2) inhibitors from the perspective of practising clinicians.

## DIABETES CVOTS

In the past fifteen years, CVOTs have been conducted to demonstrate the CV safety of new glucose-lowering therapies. These CVOTs recruited people with T2DM and either established CVD or with CV risk factors and aimed to show a hazard ratio (HR) for major CV events of less than 1.8, an arbitrary safety margin. Most CVOTs used a primary composite endpoint of major adverse CV events (MACE) comprising the first occurrence of CV mortality, non-fatal myocardial infarction (MI), or non-fatal stroke [designated the '3-point MACE' (3P-MACE)]. Some CVOTs also included an additional CV event creating a 4-point MACE (4P-MACE) primary composite: for example, hospitalisation for unstable angina in the ELIXA lixisenatide trial[6]. Although the main objective of CVOTs was to examine CV safety, some CVOTs of GLP-1RAs, and SGLT-2 inhibitors demonstrated not only safety but also CV protection.

### Cardiovascular benefits of GLP-1RAs

Currently, six GLP-1RA injectable formulations and one oral formulation (semaglutide once daily) are approved in Europe and the United States (US). These are based on the exendin-4 molecule, which was originally isolated from the Gila Monster lizard [exenatide (twice daily [BD]), exenatide (once weekly [QW]) and lixisenatide (once daily[OD])] or human GLP-1 [liraglutide (OD), dulaglutide (QW) and semaglutide (QW)]. A further preparation (albiglutide) was launched in 2018 but was quickly withdrawn for commercial reasons. To date, there have been a total of nine randomised CVOTs investigating the use of GLP-1RAs: ELIXA (lixisenatide)[6], LEADER (liraglutide)[7], SUSTAIN-6 (injectable semaglutide)[8], EXSCEL (weekly exenatide)[9], HARMONY OUTCOMES (albiglutide)[10], REWIND (dulaglutide)[11], PIONEER-6 (oral semaglutide)[12], AMPLITUDE-O (efpeglenatide)[13] and FREEDOM-CVO (continuous subcutaneous infusion of exenatide)[14] were published between 2015 and 2021. To date, efpeglenatide is not a licensed treatment. An overview of GLP-1RA CVOTs is summarised in Table 1.

All of the above-mentioned CVOTS demonstrated CV safety (meeting the 3P-MACE or 4P-MACE non-inferiority criteria) in individuals with T2DM and established CVD or with CV risk factors. In addition, significant risk reductions (superior to placebo) in 3P-MACE/ 4P-MACE were observed in five of the subcutaneously administered (daily or weekly) GLP-1RAs: liraglutide, semaglutide, albiglutide, dulaglutide and efpeglenatide. The HRs for 3P-MACE/4P-MACE were 0.87 [95% confidence intervals (CI) 0.78-0.97; $P$ = 0.01] in LEADER (liraglutide)[7]; 0.74 (95%CI: 0.58-0.95; $P$ = 0.02) in SUSTAIN-6 (semaglutide)[8]; 0.78 (95%CI: 0.68-0.90 $P$ = 0.0006) in HARMONY OUTCOMES (albiglutide)[10]; 0.88 (95%CI: 0.79-0.99; $P$ =

**Table 1. Overview of Cardiovascular outcome trials of GLP-1RAs**

| Study | Inclusion Criteria | Established CVD (%) | 3P/4P-MACE HR (95%CI) | CV death HR (95%CI) | Non-fatal MI HR (95%CI) | Non-fatal stroke HR (95%CI) | All-cause mortality HR (95%CI) | Other benefits |
|---|---|---|---|---|---|---|---|---|
| ELIXA *Lixisenatide*[6] | ●→ ACS within 180 days | 100% | 1.02 (0.89-1.17) *P* = 0.81 | 0.98 (0.78-1.22) | 1.03 (0.87-1.22) | 1.12 (0.79-1.58) | 0.94 (0.78-1.13) | HHF 0.96 (0.75-1.23) *P* = 0.75 |
| LEADER *Liraglutide*[7] | ●→ Age > 50 years with ≥ 1 CVD OR ●→ Age > 60 years with ≥ 1 CV risk factor | 81.3% | 0.87 (0.78-0.97) *P* < 0.001, *P* = 0.01* | 0.78 (0.66-0.93) *P* = 0.007 | 0.88 (0.75-1.03) | 0.89 (0.72-1.11) | 0.85 (0.74-0.97) *P* = 0.02 | Nephropathy 0.78 (0.67-0.92) *P* = 0.003 |
| SUSTAIN-6 *Semaglutide (injectable)*[8] | ●→ Age ≥ 50 years with established CVD or CHF or CKD ≥ stage 3 OR ●→ Age ≥ 60 years with ≥ 1 CV risk factors | 83% | 0.74 (0.58-0.95) *P* < 0.001, *P* = 0.02* | 0.98 (0.65-1.48) | 0.74 (0.51-1.08) *P* = 0.12 | 0.61 (0.38-0.99) *P* = 0.04 | 1.05 (0.74-1.5) | Nephropathy 0.64 (0.46-0.88) *P* = 0.005 |
| EXSCEL *Exenatide (QW)*[9] | ●→ Any level of CV risk | 73.1% | 0.91 (0.83-1.00) *P* < 0.001, *P* = 0.06* | 0.88 (0.76-1.02) | 0.97 (0.85-1.10) | 0.85 (0.70-1.03) | 0.86 (0.77-0.97) | HHF 0.94 (0.78-1.13) |
| HARMONY *Albiglutide*[10] | ●→ Age ≥ 40 years with established CVD | 100% | 0.78 (0.68-0.9) *P* < 0.0001, *P* = 0.0006* | 0.93 (0.73-1.19) | 0.75 (0.61-0.9) ** *P* = 0.003 | 0.86 (0.66-1.14) | 0.95 (0.79-1.16) | |
| REWIND *Dulaglutide*[11] | ●→ Age ≥ 50 years with vascular disease ●→ Age ≥ 55 years with ≥1 cardio-renal condition ●→ Age ≥ 60 years with ≥ 2 CV risk factors | 31.5% | 0.88 (0.79-0.99) *P* = 0.026 | 0.91 (0.78-1.06) | 0.96 (0.79-1.16) | 0.76 (0.61-0.95) *P* = 0.017 | 0.90 (0.8-1.01) *P* = 0.067 | Renal benefits |
| PIONEER-6 *Oral Semaglutide*[12] | ●→ ≥ 50 years old with established CVD or CKD or ●→ ≥ 60 years with CV risk factors | 84.7% | 0.79 (0.57-1.11) *P* < 0.001, *P* = 0.17* | 0.49 (0.27-0.92) | 1.18 (0.73-1.90) | 0.74 (0.35-1.57) | 0.51 (0.31-0.84) | HHF 0.86 (0.48-1.55) |
| AMPLITUDE-O *Efpeglenatide*[13] | ●→ Age ≥ 18 years with CVD ●→ Age ≥ 50 years (male) or ≥ 55 years (female) with kidney disease and CV risk factors | 89.6% | 0.73 (0.58-0.92) *P* < 0.001, *P* = 0.007* | 0.72 (0.50-1.03) | 0.78 (0.55-1.10) | 0.80 (0.48-1.31) | 0.73 (0.59-0.91) *P* = 0.004 *** | Renal composite outcome 0.68 (0.57-0.79) *P* < 0.001 |

*P values are for non-inferiority and superiority; **Fatal and non-fatal MI; *** MACE or death from non-CV cause; ACS: Acute Coronary Syndrome; HHF: Hospitalisation for Heart Failure; CVD: Cardiovascular Disease; CKD: Chronic Kidney Disease.

0.026) in REWIND (dulaglutide)[11] and 0.73 (95%CI: 0.58-0.92; *P* = 0.007) in AMPLITUDE-O (efpeglenatide)[13] respectively. The impact of GLP-1RAs on individual components of the 3P/4P-MACE was not consistent across these trials. Liraglutide and oral semaglutide achieved a significant reduction in CV mortality (relative risk reductions [RRR] of 22% and 51%, respectively), while injectable dulaglutide and semaglutide demonstrated a favourable outcome on non-fatal stroke and albiglutide demonstrated a significantly reduced risk of MI.

### Renal benefits of GLP-1RAs

Unlike SGLT-2 inhibitors, the kidney protective effect of GLP-1RAs has not been fully evaluated. Exploratory analyses of renal outcomes from the CVOTs of GLP-1RAs suggest a reno-protective effect[15]. However, these studies were not designed to assess hard endpoints such as a decline in eGFR, end-stage renal disease (ESRD) or kidney-related mortality. A meta-analysis reported that GLP-1RAs achieved a 17% RRR in the broad kidney consisting of new occurrence of macroalbuminuria, doubling of serum creatinine or decline in estimated glomerular filtration rate (eGFR) of 40% or more, renal replacement therapy (RRT) and renal death (HR 0.83; 95%CI: 0.78 -0.89; $P < 0.0001$), this occurring over a median follow-up of 3.2 years[16]. Supportive of this analysis, the recently published AMPLITUDE-O trial demonstrated a 32% RRR in a composite renal outcome with efpeglenatide against placebo[13]. The exploratory analysis of this trial also illustrated the CV and renal safety of efpeglenatide, and this was independent of the concomitant administration of SGLT-2 inhibitors[17].

### Cardiovascular benefits of SGLT-2 inhibitors

To date, there have been four published CVOTs of SGLT-2 inhibitors: CANVAS and CANVAS-R (canagliflozin)[18], DECLARE-TIMI 58 (dapagliflozin)[19], EMPA-REG OUTCOME (empagliflozin)[20] and VERTIS CV (ertugliflozin)[21], which all demonstrated CV safety. The EMPA-REG OUTCOME trial was the first CVOT of an SGLT-2 inhibitor not only to illustrate CV safety but also to reduce CV outcomes (3P-MACE) compared to placebo in people with T2DM and documented CVD. The impressive findings of a 14% RRR in the primary composite endpoint (HR 0.86; 95%CI: 0.74- 0.99; $P = 0.04$), a 38% RRR in CV death (HR 0.62 ; 95%CI: 0.49- 0.77; $P < 0.001$) and a 32% RRR in all-cause mortality (a pre-specified secondary outcome) were seen with empagliflozin[20]. However, no significant benefits in non-fatal MI or non-fatal stroke were noted[20]. Two years later, the CANVAS program was presented in 2017, reporting a lower risk of CV events in people receiving canagliflozin in a cohort with T2DM and established CVD or an elevated risk of CVD (HR 0.86; 95%CI: 0.75- 0.97; $P < 0.001$ for non-inferiority; $P = 0.02$ for superiority)[18]. Canagliflozin, however, did not result in any significant differences for each component of the 3P-MACE (CV death, non-fatal MI, non-fatal stroke) or for mortality from any cause. Of concern, an increased risk of toe or metatarsal amputation and risk of bony fracture was observed with canagliflozin (HR 1.97; 95%CI: 1.41-2.75 and HR 0.80; 95%CI: 0.49-1.29, respectively).

In contrast, the DECLARE-TIMI 58 (dapagliflozin CVOT) did not demonstrate a superior CV benefit. In the co-primary event analysis, dapagliflozin did not significantly reduce the 3P-MACE endpoint (HR 0.93; 95%CI: 0.84-1.03; $P = 0.17$), or CV death. However, dapagliflozin did result in a lower rate of CV death or hospitalisation for heart failure (HHF) (HR 0.83; 95%CI: 0.73- 0.95; $P = 0.005$), a finding reflected by a lower rate of hospitalisation for heart failure (HR 0.73; 95%CI:, 0.61 to 0.88), not by CV death (HR 0.98 ; 95%CI: 0.82- 1.17)[19]. (The impact of the SGLT-2 inhibitor class on heart failure is discussed in the next section). Similarly, the ertugliflozin CVOT in the VERTIS-CV trail did not show a benefit in 3P-MACE (HR 0.97; 95.6%CI: 0.85-1.11) nor in each component of the 3P-MACE[21]. Of interest, VERTIS-CV included an additional primary endpoint (CV death or HHF); however, ertugliflozin also failed to show superiority (HR 0.88; 95%CI: 0.75-1.03; $P = 0.11$) for this endpoint[22].

It is essential to be aware that the study designs and baseline CV status of trial populations differ between the SGLT-2 inhibitor CVOTs. The proportions of trial participants with known CVD were 99%, 65%, 41%, and 100% in EMPA-REG OUTCOME, CANVAS trial program, DECLARE-TIMI 58, and VERTIS CV, respectively. It has been speculated that differences in CV outcomes between empagliflozin/ canagliflozin and dapagliflozin were due to heterogeneity of trial design rather than drug-specific effects. With the recent findings from VERTIS CV, which had comparable baseline CV status to EMPA-REG OUTCOME, it is possible that the CV benefit of SGLT-2 inhibitors might not be applicable to all agents within the class, but

further research is needed to establish this. Of interest, Suzuki et al. demonstrated that there was no significant difference in the risk of developing heart failure, angina, MI, stroke, and atrial fibrillation in 25,315 patients with T2DM who were taking SGLT-2 inhibitors[23]. SGLT-2 inhibitors included in this study were empagliflozin, dapagliflozin, canagliflozin, ipragliflozin, tofogliflozin, and luseogliflozin. Of note, the latter three are not approved by the FDA[23]. An overview of SGLT-2 inhibitor CVOTs is shown in Table 2.

### Heart failure benefits of SGLT-2 inhibitors

A consistent finding from all SGLT-2 inhibitor CVOTs was a reduction in HHF in people with T2DM. Empagliflozin produced a 35% RRR in HHF, canagliflozin a 33% RRR, dapagliflozin a 27% RRR, and ertugliflozin a 30% RRR respectively. Following these findings, dedicated heart failure outcome trials of dapagliflozin (DAPA-HF[24] and DELIVER[25]) and empagliflozin (EMPEROR-Reduced[26] and EMPEROR-Preserved[27]) have been performed in people with or without comorbid T2D. The heart failure trials of SGLT-2 inhibitors are summarised in Table 3.

The DAPA-HF trial investigated dapagliflozin versus placebo, added to standard of care therapy in people with reduced ejection fraction (rEF) on echocardiogram (41.8% had already an established diagnosis of T2DM). The primary outcome of the trial was a composite of CV death or worsening heart failure (hospitalization or an emergency room urgent visit resulting in intravenous diuretic therapy). Dapagliflozin resulted in a 26% RRR in the composite heart failure outcome (HR 0.74; 95%CI: 0.65- 0.85; $P < 0.001$), an 18% RRR in CV mortality (HR 0.82; 95%CI: 0.69- 0.98) and a 17% RRR in all-cause mortality (HR 0.83; 95%CI: 0.71- 0.97). The impact of dapagliflozin on HF was consistent irrespective of the presence or absence of T2DM[24]. The EMPEROR-Reduced study of empagliflozin in people with rEF illustrated similar findings; empagliflozin produced a 25% RRR in the composite heart failure outcome (HR 0.75; 95%CI: 0.65 - 0.86; $P < 0.001$) and a 30% RRR in HHF (HR 0.70; 95%CI: 0.58 - 0.85; $P < 0.001$). Results in those with T2DM had similar HF benefits: a RRR of 31% in HHF for all trial subjects and 33% in the subgroup of people with T2DM[26]. Based on these data, dapagliflozin and empagliflozin gained approval for the management of chronic heart failure with rEF, irrespective of diabetes mellitus.

Following this impressive evidence from heart failure rEF outcome trials, two trials (EMPEROR-Preserved; Empagliflozin) and (DELIVER; Dapagliflozin) were performed in people with chronic heart failure and preserved ejection fraction (pEF). In early 2022, the FDA extended the licensed indication of empagliflozin for the treatment of heart failure with pEF[28] based on findings from the EMPEROR-Preserved trial. Similar to the EMPEROR-Reduced trial observations, empagliflozin produced a significant reduction in the composite heart failure outcome (HR 0.79; 95%CI: 0.69 - 0.90; $P < 0.001$) in people with chronic heart failure with pEF. This effect was largely due to the reduction in risk of HHF in the empagliflozin cohort (RRR of 27%; HR 0.73; 95%CI: 0.61 - 0.88; $P < 0.001$)[27]. The recently published DELIVER trial confirmed the benefit of SGLT2-inhibitors for the treatment of heart failure with pEF[25]. It investigated dapagliflozin (10 mg) in individuals with pEF ($n = 6,263$) and reported an 18% RRR in the composite heart failure outcome (HR 0.82; 95%CI: 0.73 - 0.92; $P < 0.001$); this effect was mainly related to a reduction in worsening of heart failure rather than CV mortality.

### Renal benefits of SGLT-2 inhibitors

There are consistent reports of reno-protection afforded by SGLT-2 inhibitors in the CVOTs [Table 2]. A secondary analysis of all four SGLT-2 inhibitor CVOTs (empagliflozin, canagliflozin, dapagliflozin, and ertugliflozin) demonstrated a RRR (> 35%) in renal function decline and a slowing of progression of albuminuria. These findings were confirmed by dedicated renal outcome studies, CREDENCE, and DAPA-CKD [Table 4].

**Table 2. Overview of Cardiovascular outcome trials of SGLT-2 inhibitors**

| | Inclusion Criteria | Established CVD (%) | 3P/4P-MACE HR (95%CI) | CV death HR (95%CI) | Non-fatal MI HR (95%CI) | Non-fatal stroke HR (95%CI) | All-cause mortality HR (95%CI) | Other benefits |
|---|---|---|---|---|---|---|---|---|
| EMPA-REG OUTCOME *Empagliflozin*[20] | ●→ Age ≥ 18 years with established CVD | 99% | 0.86 (0.74-0.99) $P < 0.001$; $P = 0.04^{*}$ | 0.62 (0.49-0.77) $P < 0.001$ | 0.87 (0.70-1.09) | 1.24 (0.92-1.67) | 0.68 (0.57-0.82) $P = 0.001$ | HHF 0.65 (0.50-0.85) Renal benefits |
| CANVAS *Canagliflozin*[18] | ●→ Age ≥ 30 years with symptomatic ASCVD OR ●→ Age ≥ 50 years with ≥ 2 CV risk factor | 65% | 0.86 (0.75-0.97) $P < 0.001$; $P = 0.02^{*}$ | 0.87 (0.72-1.06) | 0.85 (0.69-1.05) | 0.90 (0.71-1.15) | 0.87 (0.74-1.01) | HHF 0.67 (0.52-0.87) Renal outcome 0.60 (0.47-0.77) |
| DECLARE TIMI-58 *Dapagliflozin*[19] | ●→ Age ≥ 40 years with established CVD or ≥ 1 CV risk factors | 41% | 0.93 (0.84-1.03) | 0.98 (0.82-1.17) | 0.89 (0.77-1.01)[#] | 1.01 (0.84-1.21) | 0.93 (0.82-1.04) | HHF 0.73 (0.61-0.88) Renal outcome 0.53 (0.43-0.66) |
| VERTIS-CV *Ertugliflozin*[21] | ●→Age ≥ 40 years with ASCVD | 100% | 0.97 (0.85-1.11) | 0.92 (0.77-1.11) | 1.04 (0.86-1.27) | 1.00 (0.76-1.32) | 0.93 (0.80-1.08) | HHF 0.70 (0.54-0.90) Renal outcome 0.81 (0.63-1.04) |

CVD: Cardiovascular Disease; ASCVD: Atherosclerotic CVD; HHF: Hospitalisation for Heart Failure; CKD: Chronic Kidney Disease; [*] *P* values are for non-inferiority and superiority; [#] Both fatal and non-fatal MI included; [^] Both fatal and non-fatal stroke included.

**Table 3. Overview of Heart Failure outcome trials of SGLT-2 inhibitors**

| Study | Inclusion Criteria | T2D (%) | P' Composite Outcome HR (95%CI) | HHF HR (95%CI) | CV death HR (95%CI) | All-cause mortality HR (95%CI) | Renal Benefit |
|---|---|---|---|---|---|---|---|
| DAPA-HF[#] *Dapagliflozin*[24] | ●→ Age ≥ 18 years with NYHA II-IV and EF ≤ 40% ($n$ = 4,744) | 42% | 0.74 (0.65-0.85) $P < 0.001$ | 0.70 (0.59-0.83) | 0.82 (0.69-0.98) | 0.83 (0.71-0.97) | |
| EMPORER-Reduced[##] *Empagliflozin*[26] | ●→ Age ≥ 18 years with NYHA II-IV and EF ≤ 40% ($n$ = 3,730) | 50% | 0.75 (0.65-0.86) $P < 0.001$ | 0.70 (0.58-0.85) | 0.91 (0.76-1.09) | 1.00 (0.87-1.15) | eGFR decline 1.36 (1.06-1.66) $P < 0.001$ |
| EMPORER-Preserved[#] *Empagliflozin*[27] | ●→ Age ≥ 40 years with established CVD or ≥ 1 CV risk factors ($n$ = 5,988) | 49% | 0.79 (0.69-0.90) $P < 0.001$ | 0.73 (0.61-0.88) | 0.91 (0.76-1.09) | 1.00 (0.87-1.15) | eGFR decline 1.36 (1.06-1.66) $P < 0.001$ |
| DELIVER[##] *Dapagliflozin*[25] | ●→ Age ≥ 40 years with ASCVD ($n$ = 6,263) | 48% | 0.82 (0.73-0.92) $P < 0.001$ | 0.79 (0.69-0.91) | 0.88 (0.74-1.05) | 0.94 (0.83-1.07) | |

HHF: Hospitalisation for Heart Failure; CKD: Chronic Kidney Disease; [#]Primary composite outcomes: worsening HF or CV death; [##]Primary composite outcomes: HHF or CV death

**Table 4. Overview of Cardiorenal outcome trials of SGLT-2 inhibitors**

| Study | Inclusion Criteria | T2D (%) | Primary Outcome HR (95%CI) | Renal Composite Outcome HR (95%CI) | ESRD HR (95%CI) | All-cause mortality HR (95%CI) | 3P-MACE | HHF |
|---|---|---|---|---|---|---|---|---|
| CREDENCE[#] *Canagliflozin*[29] | ●→ Age ≥ 18 years T2DM and albuminuric CKD ($n$ = 4,401) | 100% | 0.70 (0.59-0.82) $P$ < 0.001 | 0.66 (0.53-0.81) $P$ < 0.001 | 0.68 (0.54-0.86) $P$ = 0.002 | 0.83 (0.68-1.02) | 0.80 (0.67-0.95) $P$ = 0.01 | 0.61 (0.47-0.80) $P$ < 0.001 |
| DAPA-CKD[##] *Dapagliflozin*[30] | ●→ eGFR 25-75 with UACR 200-5,000 ($n$ = 4,304) | 68% | 0.61 (0.51-0.72) $P$ < 0.001 | 0.56 (0.45-0.68) $P$ < 0.001 | 0.64 (0.50-0.82) | 0.69 (0.53-0.88) $P$ = 0.004 | | 0.71 (0.55-0.92) $P$ = 0.009 |

HHF: Hospitalisation for Heart Failure; CKD: Chronic Kidney Disease; UACR: Urine Albumin Creatinine Ratio; #Primary outcome: a composite of ESRD (Dialysis, transplantation or a sustained eGFR < 15 ml/min/1.73 $m^2$), a doubling of serum creatinine level or death from renal or CV causes; ##Primary outcome: a composite of sustained decline in eGFR < 50%, ESRD, or death from renal or CV cause.

CREDENCE was the first dedicated renal outcome study for an SGLT-2 inhibitor and investigated canagliflozin (100 mg) in individuals with chronic kidney disease (CKD) and T2DM. A 30% RRR in the primary outcome [a composite of ESRD (dialysis, transplantation, or a sustained eGFR of ≤ 15 mL per minute per 1.73 $m^2$), doubling of the serum creatinine level, or death from renal or CV causes], a 34% RRR in renal specific outcomes and a 32% RRR in ESRD were observed[29]. Based on the CREDENCE study findings, canagliflozin has been approved with an extended indication to treat CKD in people with T2DM.

The DAPA-CKD study examined dapagliflozin and placebo in people with CKD (defined as a urinary albumin-to-creatinine ratio (UACR) of 200-5,000 mg/g, and eGFR of 25-75 mL/min per 1.73$m^2$) with or without T2DM in addition to the standard medical care. Dapagliflozin significantly reduced the composite cardiorenal outcome (a sustained decline in the eGFR > 50%, ESRD or death from renal or CV causes)[30,31]. The renal benefit was greater in people with T2DM, higher HbA1c, and higher UACR[30]. More importantly, DAPA-CKD demonstrated that dapagliflozin significantly lowered mortality. Following the DAPA-CKD study, dapagliflozin was the first SGLT-2 inhibitor approved for the treatment of CKD in people with or without T2DM.

## Clinical implications

Recent years have seen the updating of major international guidelines to reflect evidence from CVOTs of glucose-lowering therapies, including GLP-1RAs and SGLT-2 inhibitors. The European Association for the Study of Diabetes/American Diabetes Association (EASD/ADA)[3], European Society of Cardiology (ESC)[5], American College of Cardiology (ACC)[32] and Kidney Disease Improving Global Outcomes (KDIGO)[33] guidelines recommend specific classes of therapy for people with renal disease and/or CVD. These guidelines are generally aligned in recommending SGLT-2 inhibitors or GLP-1RA with established CV benefit, as a first add-on to metformin or as monotherapy for individuals with T2DM and established CVD or high risk of CVD. The EASD/ADA guidelines advocate the use of a GLP-1RA or SGLT-2 inhibitor for people with HF, CKD, established CVD, or multiple CV risk factors, irrespective of the use of metformin[3]. The combined use of SGLT-2 inhibitors and GLP-1RA is promoted if the target HbA1c levels (which should be individualised) are not achieved[3]. ESC guidelines recommend canagliflozin, dapagliflozin, or empagliflozin in people with T2DM and CVD or with high CVD risk to reduce CV events and empagliflozin to reduce mortality. Regarding GLP-1RAs, dulaglutide, liraglutide and semaglutide are advocated to reduce CV events, while liraglutide is recommended to reduce the risk of death[5]. The KDIGO guidelines recommend an SGLT-2 inhibitor with proven renal benefit (canagliflozin, dapagliflozin, and

empagliflozin) for people with T2DM and CKD if eGFR ≥ 20 mL/min per 1.73m$^2$. Once an SGLT-2 inhibitor is commenced, it is reasonable to continue even if the renal function declines (i.e., eGFR falls below 20 mL/min per 1.73m$^2$ ) unless it is poorly tolerated or RRT is initiated[33].

When SGLT inhibitors were first launched, there were concerns about the safety profile regarding adverse events such as acute kidney injury, volume depletion, hypotension, amputation, and fractures. However, long-term prospective studies did not support these concerns and have not demonstrated a significantly increased risk[34,35]. Dedicated renal outcome studies subsequently confirmed a reno-protective effect. The CREDENCE study did not confirm an increased risk of amputation with canagliflozin as reported by the CANVAS program. In fact, people with T2DM and peripheral arterial disease (PAD) benefit more from SGLT-2 inhibitors, compared with those without PAD[36]. Regarding GLP-1RAs, the adverse events of interest included medullary thyroid cancer, pancreatitis, and pancreatic cancer but data from the CVOTs did not indicate that there is an increased risk of these outcomes[37]. Worsening of diabetic retinopathy events observed in the SUSTAIN-6 trial (only) is thought to be related to the magnitude and rapidity of glucose reduction in people with higher baseline HbA1c and pre-existing retinopathy[38].

## CONCLUSIONS

There is unequivocal evidence for CV benefits of SGLT-2 inhibitors and GLP-1RAs from CVOTs, and this has led to major changes in the management of hyperglycaemia in people with T2DM). Both GLP-1RAs and SLGT-2 inhibitors have illustrated a role beyond the glucose-lowering effect. They both have demonstrated a beneficiary effect on CV risk factors such as weight and blood pressure[39,40]. With regard to lipid metabolism, GLP-1RAs were associated with slight reductions in total cholesterol, triglycerides, and LDL cholesterol but no significant impact on HDL cholesterol[41], whereas SGLT-2 inhibitors were associated with a reduction in triglycerides and an increase in HDL cholesterol and LDL cholesterol[42]. International guidelines recommend these agents for people with T2DM and established CVD/ or multiple CV risk factors, independent of HbA1c level and metformin use. However, there is clinical inertia that has slowed the adoption of SGLT-2 inhibitors and GLP-1RAs into routine clinical practice[43]. The effective translation of CVOT evidence and modern guidelines into routine clinical practice will need educational tools, implementation programmes and raising awareness amongst healthcare professionals of the potential benefit for patients.

## DECLARATIONS

### Authors' contributions

Made substantial contributions to the conception and design of the review article: Min T, Bain SC
Drafting the work or revising it critically for important intellectual content and final approval of the version to be published: Min T, Bain SC, Crockett E, Pavlou A

### Availability of data and materials

Not applicable.

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### Conflicts of interest

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### Ethical approval and consent to participate

Not applicable.

### Consent for publication

Not applicable.

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