

Review

Open Access



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

Thinzar Min<sup>1,2</sup>, Elin Crockett<sup>3</sup>, Andreas Pavlou<sup>3</sup>, Stephen C Bain<sup>1,3</sup>

<sup>1</sup>Diabetes Research Group, Swansea University Medical School, Swansea SA2 8PP, UK.

<sup>2</sup>Department of Diabetes and Endocrinology, Neath Port Talbot Hospital, Swansea Bay University Health Board, Swansea SA12 7BX, UK.

<sup>3</sup>Department of Diabetes and Endocrinology, Singleton Hospital, Swansea Bay University Health Board, Swansea SA2 8QA, UK.

**Correspondence to:** Dr. Thinzar Min, Diabetes Research Group, Swansea University Medical School, Grove Building, Singleton Campus, Swansea University, Swansea SA2 8PP, UK. E-mail: Thinzar.Min@swansea.ac.uk

**How to cite this article:** Min T, Crockett E, Pavlou A, Bain SC. Cardiovascular outcome trials of GLP-1RAs and SGLT-2 inhibitors: a concise review from the clinicians' perspective. *Metab Target Organ Damage* 2023;3:6.  
<https://dx.doi.org/10.20517/mtod.2023.09>

**Received:** 17 Feb 2023 **First Decision:** 7 Apr 2023 **Revised:** 24 Apr 2023 **Accepted:** 9 May 2023 **Published:** 16 May 2023

**Academic Editors:** Stefano Ballestri, Amedeo Lonardo **Copy Editor:** Yanbing Bai **Production Editor:** Yanbing Bai

## 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



© The Author(s) 2023. **Open Access** This article is licensed under a Creative Commons Attribution 4.0 International License (<https://creativecommons.org/licenses/by/4.0/>), which permits unrestricted use, sharing, adaptation, distribution and reproduction in any medium or format, for any purpose, even commercially, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons license, and indicate if changes were made.



## 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<sup>[1]</sup>. CVD is also a major cause of death in T2DM, contributing to approximately 50% of all-cause mortality<sup>[1]</sup>. 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%<sup>[2]</sup>, and this has led to a move away from the traditional 'gluco-centric approach' in the management of T2DM<sup>[3]</sup>. 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<sup>[4]</sup>. 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<sup>[3,5]</sup>. 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<sup>[6]</sup>. 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)<sup>[6]</sup>, LEADER (liraglutide)<sup>[7]</sup>, SUSTAIN-6 (injectable semaglutide)<sup>[8]</sup>, EXSCEL (weekly exenatide)<sup>[9]</sup>, HARMONY OUTCOMES (albiglutide)<sup>[10]</sup>, REWIND (dulaglutide)<sup>[11]</sup>, PIONEER-6 (oral semaglutide)<sup>[12]</sup>, AMPLITUDE-O (efpeglenatide)<sup>[13]</sup> and FREEDOM-CVO (continuous subcutaneous infusion of exenatide)<sup>[14]</sup> 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)<sup>[7]</sup>; 0.74 (95%CI: 0.58-0.95;  $P = 0.02$ ) in SUSTAIN-6 (semaglutide)<sup>[8]</sup>; 0.78 (95%CI: 0.68-0.90  $P = 0.0006$ ) in HARMONY OUTCOMES (albiglutide)<sup>[10]</sup>; 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 <i>Lixisenatide</i> <sup>[6]</sup>	●→ ACS within 180 days	100%	1.02 (0.89-1.17) <i>P</i> = 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) <i>P</i> = 0.75
LEADER <i>Liraglutide</i> <sup>[7]</sup>	●→ Age > 50 years with ≥ 1 CVD OR ●→ Age > 60 years with ≥ 1 CV risk factor	81.3%	0.87 (0.78-0.97) <i>P</i> < 0.001, <i>P</i> = 0.01	0.78 (0.66-0.93) <i>P</i> = 0.007	0.88 (0.75-1.03)	0.89 (0.72-1.11)	0.85 (0.74-0.97) <i>P</i> = 0.02	Nephropathy 0.78 (0.67-0.92) <i>P</i> = 0.003
SUSTAIN-6 <i>Semaglutide (injectable)</i> <sup>[8]</sup>	●→ 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) <i>P</i> < 0.001, <i>P</i> = 0.02	0.98 (0.65-1.48)	0.74 (0.51-1.08) <i>P</i> = 0.12	0.61 (0.38-0.99) <i>P</i> = 0.04	1.05 (0.74-1.5)	Nephropathy 0.64 (0.46-0.88) <i>P</i> = 0.005
EXSCEL <i>Exenatide (QW)</i> <sup>[9]</sup>	●→ Any level of CV risk	73.1%	0.91 (0.83-1.00) <i>P</i> < 0.001, <i>P</i> = 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 <i>Albiglutide</i> <sup>[10]</sup>	●→ Age ≥ 40 years with established CVD	100%	0.78 (0.68-0.9) <i>P</i> < 0.0001, <i>P</i> = 0.0006	0.93 (0.73-1.19)	0.75 (0.61-0.9) <i>P</i> = 0.003	0.86 (0.66-1.14)	0.95 (0.79-1.16)	
REWIND <i>Dulaglutide</i> <sup>[11]</sup>	●→ 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) <i>P</i> = 0.026	0.91 (0.78-1.06)	0.96 (0.79-1.16)	0.76 (0.61-0.95) <i>P</i> = 0.017	0.90 (0.8-1.01) <i>P</i> = 0.067	Renal benefits
PIONEER-6 Oral <i>Semaglutide</i> <sup>[12]</sup>	●→ ≥ 50 years old with established CVD or CKD or ●→ ≥ 60 years with CV risk factors	84.7%	0.79 (0.57-1.11) <i>P</i> < 0.001, <i>P</i> = 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 <i>Efpeglenatide</i> <sup>[13]</sup>	●→ 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) <i>P</i> < 0.001, <i>P</i> = 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) <i>P</i> = 0.004	Renal composite outcome 0.68 (0.57-0.79) <i>P</i> < 0.001

<sup>\*</sup> *P* values are for non-inferiority and superiority; <sup>\*\*</sup> Fatal and non-fatal MI; <sup>\*\*\*</sup> 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)<sup>[11]</sup> and 0.73 (95%CI: 0.58-0.92; *P* = 0.007) in AMPLITUDE-O (efpeglenatide)<sup>[13]</sup> 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<sup>[15]</sup>. 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<sup>[16]</sup>. Supportive of this analysis, the recently published AMPLITUDE-O trial demonstrated a 32% RRR in a composite renal outcome with efpeglenatide against placebo<sup>[13]</sup>. 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<sup>[17]</sup>.

### Cardiovascular benefits of SGLT-2 inhibitors

To date, there have been four published CVOTs of SGLT-2 inhibitors: CANVAS and CANVAS-R (canagliflozin)<sup>[18]</sup>, DECLARE-TIMI 58 (dapagliflozin)<sup>[19]</sup>, EMPA-REG OUTCOME (empagliflozin)<sup>[20]</sup> and VERTIS CV (ertugliflozin)<sup>[21]</sup>, 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<sup>[20]</sup>. However, no significant benefits in non-fatal MI or non-fatal stroke were noted<sup>[20]</sup>. 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)<sup>[18]</sup>. 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)<sup>[19]</sup>. (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<sup>[21]</sup>. 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<sup>[22]</sup>.

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<sup>[23]</sup>. 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<sup>[23]</sup>. 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<sup>[24]</sup> and DELIVER<sup>[25]</sup>) and empagliflozin (EMPEROR-Reduced<sup>[26]</sup> and EMPEROR-Preserved<sup>[27]</sup>) 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<sup>[24]</sup>. 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<sup>[26]</sup>. 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<sup>[28]</sup> 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;  $P < 0.001$ )<sup>[27]</sup>. The recently published DELIVER trial confirmed the benefit of SGLT2-inhibitors for the treatment of heart failure with pEF<sup>[25]</sup>. 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 <sup>[20]</sup>	●→ 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 <sup>[18]</sup>	●→ 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 <sup>[19]</sup>	●→ 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) <sup>#</sup>	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 <sup>[21]</sup>	●→ 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; <sup>#</sup> Both fatal and non-fatal MI included; <sup>##</sup> 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 <sup>#</sup> Dapagliflozin <sup>[24]</sup>	●→ 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)	
EMPOWER-Reduced <sup>##</sup> Empagliflozin <sup>[26]</sup>	●→ 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
EMPOWER-Preserved <sup>#</sup> Empagliflozin <sup>[27]</sup>	●→ 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 <sup>##</sup> Dapagliflozin <sup>[25]</sup>	●→ 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; <sup>#</sup>Primary composite outcomes: worsening HF or CV death; <sup>##</sup>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
CREDESCENCE <sup>#</sup> Canagliflozin <sup>f</sup>	●→ 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 <sup>##</sup> Dapagliflozin <sup>f</sup>	●→ 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; <sup>#</sup>Primary outcome: a composite of ESRD (Dialysis, transplantation or a sustained eGFR < 15 ml/min/1.73 m<sup>2</sup>), a doubling of serum creatinine level or death from renal or CV causes; <sup>##</sup>Primary outcome: a composite of sustained decline in eGFR < 50%, ESRD, or death from renal or CV cause.

CREDESCENCE 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<sup>2</sup>), 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<sup>[29]</sup>. Based on the CREDESCENCE 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 1.73m<sup>2</sup>) 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)<sup>[30,31]</sup>. The renal benefit was greater in people with T2DM, higher HbA1c, and higher UACR<sup>[30]</sup>. 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)<sup>[3]</sup>, European Society of Cardiology (ESC)<sup>[5]</sup>, American College of Cardiology (ACC)<sup>[32]</sup> and Kidney Disease Improving Global Outcomes (KDIGO)<sup>[33]</sup> 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<sup>[3]</sup>. The combined use of SGLT-2 inhibitors and GLP-1RA is promoted if the target HbA1c levels (which should be individualised) are not achieved<sup>[3]</sup>. 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<sup>[5]</sup>. The KDIGO guidelines recommend an SGLT-2 inhibitor with proven renal benefit (canagliflozin, dapagliflozin, and

empagliflozin) for people with T2DM and CKD if eGFR  $\geq 20$  mL/min per  $1.73\text{m}^2$ . 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  $1.73\text{m}^2$ ) unless it is poorly tolerated or RRT is initiated<sup>[33]</sup>.

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<sup>[34,35]</sup>. 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<sup>[36]</sup>. 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<sup>[37]</sup>. 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<sup>[38]</sup>.

## 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 SGLT-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<sup>[39,40]</sup>. 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<sup>[41]</sup>, whereas SGLT-2 inhibitors were associated with a reduction in triglycerides and an increase in HDL cholesterol and LDL cholesterol<sup>[42]</sup>. 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<sup>[43]</sup>. 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.

### Financial support and sponsorship

None.

### Conflicts of interest

E Crockett and A Pavlou have nothing to disclose. SC Bain reports grants and personal fees from AstraZeneca, Novo Nordisk, and Sanofi-Aventis; personal fees from Boehringer Ingelheim, Eli Lilly, and Merck Sharp & Dohme; grants from Medscape; expert advice provided to All-Wales Medicines Strategy Group and National Institute for Health and Care Excellence UK; and partnership in Glycosmedia. T Min



reports personal fees and travel grants from AstraZeneca, Boehringer Ingelheim, Napp and Abbott Diabetes Care.

#### Ethical approval and consent to participate

Not applicable.

#### Consent for publication

Not applicable.

#### Copyright

© The Author(s) 2023.

## REFERENCES

1. Einarson TR, Acs A, Ludwig C, Panton UH. Prevalence of cardiovascular disease in type 2 diabetes: a systematic literature review of scientific evidence from across the world in 2007-2017. *Cardiovasc Diabetol* 2018;17:83. [DOI](#) [PubMed](#) [PMC](#)
2. Gaede P, Vedel P, Larsen N, Jensen GV, Parving HH, Pedersen O. Multifactorial intervention and cardiovascular disease in patients with type 2 diabetes. *N Engl J Med* 2003;348:383-93. [DOI](#) [PubMed](#)
3. Davies MJ, Aroda VR, Collins BS, et al. Management of hyperglycemia in type 2 diabetes, 2022. a consensus report by the american diabetes association (ADA) and the european association for the study of diabetes (EASD). *Diabetes Care* 2022;45:2753-86. [DOI](#) [PubMed](#) [PMC](#)
4. FDA. Type 2 Diabetes Mellitus: Evaluating the Safety of New Drugs for Improving Glycemic Control Guidance for Industry. Available from: <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/type-2-diabetes-mellitus-evaluating-safety-new-drugs-improving-glycemic-control-guidance-industry> [Last accessed on 13 May 2023].
5. Cosentino F, Grant PJ, Aboyans V, et al; ESC Scientific Document Group. 2019 ESC Guidelines on diabetes, pre-diabetes, and cardiovascular diseases developed in collaboration with the EASD. *Eur Heart J* 2020;41:255-323. [DOI](#) [PubMed](#)
6. Pfeffer MA, Claggett B, Diaz R, et al; ELIXA Investigators. Lixisenatide in patients with type 2 diabetes and acute coronary syndrome. *N Engl J Med* 2015;373:2247-57. [DOI](#)
7. Marso SP, Daniels GH, Brown-Frandsen K, et al; LEADER Steering Committee; LEADER Trial Investigators. Liraglutide and cardiovascular outcomes in type 2 diabetes. *N Engl J Med* 2016;375:311-22. [DOI](#) [PubMed](#) [PMC](#)
8. Marso SP, Bain SC, Consoli A, et al; SUSTAIN-6 Investigators. Semaglutide and cardiovascular outcomes in patients with type 2 diabetes. *N Engl J Med* 2016;375:1834-44. [DOI](#) [PubMed](#)
9. Holman RR, Bethel MA, Mentz RJ, et al; EXSCEL Study Group. Effects of once-Weekly exenatide on cardiovascular outcomes in type 2 diabetes. *N Engl J Med* 2017;377:1228-39. [DOI](#) [PubMed](#) [PMC](#)
10. Hernandez AF, Green JB, Janmohamed S, et al; Harmony Outcomes committees and investigators. Albiglutide and cardiovascular outcomes in patients with type 2 diabetes and cardiovascular disease (Harmony Outcomes): a double-blind, randomised placebo-controlled trial. *Lancet* 2018;392:1519-29. [DOI](#)
11. Gerstein HC, Colhoun HM, Dagenais GR, et al; REWIND Investigators. Dulaglutide and cardiovascular outcomes in type 2 diabetes (REWIND): a double-blind, randomised placebo-controlled trial. *Lancet* 2019;394:121-30. [DOI](#) [PubMed](#)
12. Husain M, Birkenfeld AL, Donsmark M, et al; PIONEER 6 Investigators. Oral semaglutide and cardiovascular outcomes in patients with type 2 diabetes. *N Engl J Med* 2019;381:841-51. [DOI](#) [PubMed](#)
13. Gerstein HC, Sattar N, Rosenstock J, et al; AMPLITUDE-O Trial Investigators. Cardiovascular and renal outcomes with efpeglenatide in type 2 diabetes. *N Engl J Med* 2021;385:896-907. [DOI](#)
14. Ruff CT, Baron M, Im K, O'Donoghue ML, Fiedorek FT, Sabatine MS. Subcutaneous infusion of exenatide and cardiovascular outcomes in type 2 diabetes: a non-inferiority randomized controlled trial. *Nat Med* 2022;28:89-95. [DOI](#) [PubMed](#)
15. Yin WL, Bain SC, Min T. The effect of glucagon-like peptide-1 receptor agonists on renal outcomes in type 2 diabetes. *Diabetes Ther* 2020;11:835-44. [DOI](#) [PubMed](#) [PMC](#)
16. Kristensen SL, Rørth R, Jhund PS, et al. Cardiovascular, mortality, and kidney outcomes with GLP-1 receptor agonists in patients with type 2 diabetes: a systematic review and meta-analysis of cardiovascular outcome trials. *Lancet Diabetes Endocrinol* 2019;7:776-85. [DOI](#)
17. Lam CSP, Ramasundarahettige C, Branch KRH, et al. Efpeglenatide and clinical outcomes with and without concomitant sodium-glucose cotransporter-2 inhibition use in type 2 diabetes: exploratory analysis of the AMPLITUDE-O trial. *Circulation* 2022;145:565-74. [DOI](#)
18. Neal B, Perkovic V, Mahaffey KW, et al; CANVAS Program Collaborative Group. Canagliflozin and cardiovascular and renal events in type 2 diabetes. *N Engl J Med* 2017;377:644-57. [DOI](#) [PubMed](#)
19. Wiviott SD, Raz I, Bonaca MP, et al; DECLARE-TIMI 58 Investigators. Dapagliflozin and cardiovascular outcomes in type 2 diabetes. *N Engl J Med* 2019;380:347-57. [DOI](#) [PubMed](#)

20. Zinman B, Wanner C, Lachin JM, et al; EMPA-REG OUTCOME Investigators. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. *N Engl J Med* 2015;373:2117-28. DOI
21. Cannon CP, Pratley R, Dagogo-Jack S, et al; VERTIS CV Investigators. Cardiovascular outcomes with ertugliflozin in type 2 diabetes. *N Engl J Med* 2020;383:1425-35. DOI
22. 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. *Circulation* 2020;142:2205-15. DOI
23. Suzuki Y, Kaneko H, Okada A, et al. Comparison of cardiovascular outcomes between SGLT2 inhibitors in diabetes mellitus. *Cardiovasc Diabetol* 2022;21:67. DOI PubMed PMC
24. McMurray JJV, Solomon SD, Inzucchi SE, et al; DAPA-HF Trial Committees and Investigators. Dapagliflozin in patients with heart failure and reduced ejection fraction. *N Engl J Med* 2019;381:1995-2008. DOI
25. Solomon SD, McMurray JJV, Claggett B, et al; DELIVER Trial Committees and Investigators. Dapagliflozin in heart failure with mildly reduced or preserved ejection fraction. *N Engl J Med* 2022;387:1089-98. DOI
26. Packer M, Anker SD, Butler J, et al; EMPEROR-Reduced Trial Investigators. Cardiovascular and renal outcomes with empagliflozin in heart failure. *N Engl J Med* 2020;383:1413-24. DOI
27. Anker SD, Butler J, Filippatos G, et al; EMPEROR-Preserved Trial Investigators. Empagliflozin in heart failure with a preserved ejection fraction. *N Engl J Med* 2021;385:1451-61. DOI
28. FDA. FDA approves treatment for wider range of patients with heart failure. Available from: <https://www.fda.gov/news-events/press-announcements/fda-approves-treatment-wider-range-patients-heart-failure> [Last accessed on 11 May 2023].
29. Perkovic V, Jardine MJ, Neal B, et al; CREDENCE Trial Investigators. Canagliflozin and renal outcomes in type 2 diabetes and nephropathy. *N Engl J Med* 2019;380:2295-306. DOI
30. Heerspink HJL, Jongs N, Chertow GM, et al; DAPA-CKD Trial Committees and Investigators. Effect of dapagliflozin on the rate of decline in kidney function in patients with chronic kidney disease with and without type 2 diabetes: a prespecified analysis from the DAPA-CKD trial. *Lancet Diabetes Endocrinol* 2021;9:743-54. DOI
31. Jongs N, Greene T, Chertow GM, et al; DAPA-CKD Trial Committees and Investigators. Effect of dapagliflozin on urinary albumin excretion in patients with chronic kidney disease with and without type 2 diabetes: a prespecified analysis from the DAPA-CKD trial. *Lancet Diabetes Endocrinol* 2021;9:755-66. DOI
32. Das SR, Everett BM, Birtcher KK, et al. 2020 expert consensus decision pathway on novel therapies for cardiovascular risk reduction in patients with type 2 diabetes: a report of the American college of cardiology solution set oversight committee. *J Am Coll Cardiol* 2020;76:1117-45. DOI PubMed PMC
33. Kidney Disease: improving global outcomes (KDIGO) diabetes work group. KDIGO 2022 clinical practice guideline for diabetes management in chronic kidney disease. *Kidney Int* 2022;102:S1-S127. DOI PubMed
34. Mascolo A, Di Napoli R, Balzano N, et al. Safety profile of sodium glucose co-transporter 2 (SGLT2) inhibitors: a brief summary. *Front Cardiovasc Med* 2022;9:1010693. DOI PubMed PMC
35. Toyama T, Neuen BL, Jun M, et al. Effect of SGLT2 inhibitors on cardiovascular, renal and safety outcomes in patients with type 2 diabetes mellitus and chronic kidney disease: A systematic review and meta-analysis. *Diabetes Obes Metab* 2019;21:1237-50. DOI
36. Barraclough JY, Yu J, Figtree GA, et al. Cardiovascular and renal outcomes with canagliflozin in patients with peripheral arterial disease: Data from the CANVAS Program and CREDENCE trial. *Diabetes Obes Metab* 2022;24:1072-83. DOI PubMed
37. Htike ZZ, Zaccardi F, Papamargaritis D, Webb DR, Khunti K, Davies MJ. Efficacy and safety of glucagon-like peptide-1 receptor agonists in type 2 diabetes: a systematic review and mixed-treatment comparison analysis. *Diabetes Obes Metab* 2017;19:524-36. DOI PubMed
38. Vilsbøll T, Bain SC, Leiter LA, et al. Semaglutide, reduction in glycated haemoglobin and the risk of diabetic retinopathy. *Diabetes Obes Metab* 2018;20:889-97. DOI PubMed PMC
39. Marx N, Husain M, Lehrke M, Verma S, Sattar N. GLP-1 receptor agonists for the reduction of atherosclerotic cardiovascular risk in patients with type 2 diabetes. *Circulation* 2022;146:1882-94. DOI PubMed
40. Majewski C, Bakris GL. Blood pressure reduction: an added benefit of sodium-glucose cotransporter 2 inhibitors in patients with type 2 diabetes. *Diabetes Care* 2015;38:429-30. DOI PubMed PMC
41. Sun F, Wu S, Wang J, et al. Effect of glucagon-like peptide-1 receptor agonists on lipid profiles among type 2 diabetes: a systematic review and network meta-analysis. *Clin Ther* 2015;37:225-241.e8. DOI
42. Lazarte J, Kanagalingam T, Hegele RA. Lipid effects of sodium-glucose cotransporter 2 inhibitors. *Curr Opin Lipidol* 2021;32:183-90. DOI PubMed
43. Schernthaner G, Shehadeh N, Ametov AS, et al. Worldwide inertia to the use of cardiorenal protective glucose-lowering drugs (SGLT2i and GLP-1 RA) in high-risk patients with type 2 diabetes. *Cardiovasc Diabetol* 2020;19:185. DOI PubMed PMC