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Review

SGLT-2 Inhibitor Renal Outcome Modification in Type-2 Diabetes: Evidence from Studies in Patients with High or Low Renal Risk

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Short Running Title: **Strength of evidence for renal outcome modification with SGLT2 inhibitors in T2D**

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Abstract

Data from three completed cardiovascular outcome trials (CVOTs), EMPA-REG OUTCOME, CANVAS Program and DECLARE-TIMI 58, add to the evidence supporting the potential renoprotective effects of sodium-glucose linked transporter-2 (SGLT2) inhibitors in patients with type-2 diabetes (T2D). Despite recommendations in recent guidelines, it is difficult to support a view that definitive evidence for renoprotection exists from these SGLT2 inhibitor CVOT results. To date, the only dedicated trial to report definitive data on the renal impact of SGLT2 inhibition is CREDENCE. Notably, the total number of patient relevant renal endpoint events (dialysis, transplant or renal death) observed in CREDENCE was significantly higher than the total for all three CVOTs collectively (183 events/4,401 patients vs. 69 events/34,322 patients, respectively), which demonstrates the increased statistical power of CREDENCE for these renal endpoints. Treatment with canagliflozin was associated with a 30% relative risk reduction (RRR) in the primary composite endpoint of end-stage kidney disease, doubling of serum creatinine, or death from renal or cardiovascular causes and a 34% RRR for the renal-specific elements of this primary endpoint (P <0.001). Canagliflozin has therefore become the first US approved SGLT2 inhibitor to include an indication for renal risk reduction, in addition to T2D glycemic control and cardiovascular (CV) risk reduction. While confirmatory of the exploratory data from CVOTs, CREDENCE provides the first robust data on the effects of canagliflozin on patient relevant renal endpoints. Extrapolation to a

conclusion of a SGLT2 inhibitor class effect cannot be made until additional renal trials with other SGLT2 inhibitors are reported.

Keywords: SGLT-2 inhibitors, CVOT, CKD, DKD, T2D, renoprotection, MARE

Introduction

Given the controversy that certain anti-diabetic drugs, notably the thiazolidinedione rosiglitazone, might increase the risk of cardiovascular (CV) death, the US Food and Drug Administration (FDA) mandated for all new anti-diabetic drugs to undergo proof of cardiovascular (CV) safety through large-scale cardiovascular outcome trials (CVOTs).[1,2] Since 2008, a number of CVOTs aimed at validating cardiovascular safety using the FDA specified major adverse cardiology events (MACE: a composite of cardiovascular death, nonfatal myocardial infarction, and nonfatal stroke) as the primary endpoint have been performed.[2] The EMPA-REG OUTCOME study published in 2015 was the first completed CVOT with a sodium-glucose linked transporter-2 (SGLT2) inhibitor.[3] The study unexpectedly showed that a glucose-lowering agent, empagliflozin, could reduce 3-point MACE, as well as cardiovascular mortality, hospitalisation for heart failure (HHF) and overall mortality when given in addition to standard care in T2D patients at high CV risk.[3] CVOTs with other SGLT2 inhibitors have also been completed and in keeping with the promising results from the EMPA-REG OUTCOME study also show reduction of CV events, particularly HHF.[4,5]

Besides the surprising cardioprotective benefits of empagliflozin, a beneficial effect was also discovered from analysis of the secondary composite microvascular outcome, which was driven entirely by its renal component with respect to mitigating albuminuria and slowing deterioration of kidney function.[6] This potential renoprotective effect created much excitement within the scientific community, and consequently, the renal microvascular component of the secondary outcome was further explored in a post-hoc sensitivity analysis.[6] Secondary or exploratory analyses of major adverse renal events (MARE) for other SGLT2 inhibitors in CVOTs have also been completed or are ongoing, providing valuable insights into the potential of this drug class to offer renoprotection.[7,8]

This review provides a critical reappraisal of the various renal outcomes reported from CVOTs to date. Whilst the CVOT secondary analyses prompted interesting hypotheses about the effect of SGLT2 inhibitors on renal outcomes in T2D patients, conclusive evidence required trials based on patient relevant renal endpoints, such as progression to end stage renal disease (ESRD) or death due to renal causes,[9] requiring studies in T2D patients with more advanced baseline kidney disease.

Of note, in all the SGLT2 inhibitor trials reporting MARE, none required either a biopsy or stringent exclusion of other potential causes of kidney disease. In the absence of clinical features suggestive of other aetiologies, there is a presumption that the underlying kidney disease is diabetic nephropathy but because other causes of chronic kidney disease (CKD) cannot be ruled out conclusively, diabetic kidney disease (DKD) is the term used in this review; this approach also mirrors current clincial practice. In addition, the first dedicated trial based on patient relevant renal endpoints, CREDENCE, has recently been published and is also discussed herein.

General limitations of SGLT2 inhibitor CVOTs

The CV safety of empagliflozin, canagliflozin and dapagliflozin has been evaluated in three large, placebo-controlled CVOTs, respectively named EMPA-REG OUTCOME, CANVAS Program and DECLARE-TIMI 58.[3-5] The CANVAS Program consisted of an integrated analysis of two double-blind, randomised trials (CANVAS and CANVAS-R) that assessed canagliflozin versus placebo in participants with T2D who were at high risk of cardiovascular events. Another CVOT, VERTIS-CV, evaluating the SGLT2 inhibitor ertugliflozin has recently been completed but results had not yet been published at the time of this review.[10] To date, the four completed CVOTs have enrolled 42,322 patients with T2D. All four CVOTs are multicentre, multinational studies and are described in detail elsewhere.[3-6,10-12]

Whilst these trials all had the common aim of reporting cardiovascular benefits associated with SGLT2 inhibition, it should be noted that there were potentially important differences in study design between them (**Table 1**). Due to the differences in study design and baseline characteristics of the study populations, reported trial outcomes cannot be extrapolated to the general T2D patient population.[13] This is exemplified by the fact that only 1% of the US adult T2D population would have met the eligibility criteria for all four CVOTs.[14]

In addition to CV endpoints, renal endpoints, including the impact on albuminuria and renal function, were included only as secondary or exploratory outcomes in all trials (**Table 1**). Therefore, renal outcomes with SGLT2 inhibitors needed to be confirmed in trials specifically powered to assess patient relevant renal endpoints, as in the case of canagliflozin in the CREDENCE trial.[11]

Given the new evidence derived from CREDENCE and the CVOTs, the 2018 American Diabetes Association (ADA) and the European Association for the Study of

Diabetes (EASD) guidelines recommend that patients with T2D and clinical cardiovascular disease (CVD) with inadequate glucose control despite treatment with metformin should receive an SGLT2 inhibitor or GLP-1 receptor agonist.[15] More recently, in the 2019 European Society of Cardiology (ESC) and the EASD guidelines, SGLT2 inhibitors are recommended as first-line treatment, before metformin in T2D patients who are at very high/high CV risk: (1) to lower glucose; (2) to reduce risk of death (empagliflozin only) in patients with CVD; (3) to lower risk of HF hospitalisation; and (4) to reduce progression of DKD.[16] However, the use of SGLT2 inhibitors or glucagon-like peptide-1 (GLP-1) receptor agonists as monotherapy remains off-label in most countries since there are no studies to date on the use of these compounds as monotherapy in any CVOT. In most of the SGLT2 inhibitor CVOTs, metformin was used as background therapy in 74-82% of patients and CV outcomes in patients with and without metformin therapy were quite different when the subgroup analyses data were reported.[3-5]

Baseline renal risk of study participants in SGLT2 inhibitor CVOTs

Figure 1 shows the very different baseline renal risk of patients included in the DECLARE-TIMI 58, EMPA-REG OUTCOME, CANVAS Program and CREDENCE studies. Since the primary aim of the CVOTs was assessment of CV safety, and although some patients in the analysis populations of the three completed SGLT2 inhibitor trials showed prevalent kidney disease at baseline (e.g. 32% of patients in the EMPA-REG OUTCOME trial had prevalent DKD), overall the CVOTs populations did not match the high renal risk of patients in CREDENCE nor the high degree of renal progression required for inclusion of patients in the landmark RENAAL (Angiotensin II Antagonist Losartan) study and the Irbesartan Diabetic Nephropathy Trial (IDNT).[17] Differences in design, study populations and renal outcomes among the three reported CVOTs prevent reliable comparison of between-study outcomes.

In EMPA-REG OUTCOME, potential study participants were excluded with an eGFR < 30 ml/min/1.73m^2 but there were no exclusion criteria for albuminuria or other aetiologies of kidney disease.[3] In addition, subjects were not required to be on a maximum tolerated dose of an angiotensin converting enzyme (ACE) inhibitor or angiotensin-II receptor blocker (ARB), currently the primary treatment for the prevention and treatment of DKD; however, nearly all participants at baseline were reported to be taking a renin-angiotensin-aldosterone system (RAAS) blocker (notably, 80.7% were on an ACE inhibitor or ARB as part of standard-of-care).[3]

Of the 7,020 participants enrolled in EMPA-REG, there were 5,199 patients with an eGFR of ≥ 60mL/min/1.73 m^2,[3,6] of which 64% had normoalbuminuria (UACR < 30 mg/g), 27% had microalbuminuria and 8% had macroalbuminuria; two participants had missing data for eGFR.[6] There were 1,819 patients with an eGFR < 60mL/min/1.73 m^2, [3] of which 47% had normoalbuminuria, 34% had microalbuminuria and 18% had macroalbuminuria.[6]

Like EMPA-REG OUTCOME, subjects for both CANVAS and CANVAS-R were not required to be on a maximum tolerated dose of an ACE inhibitor or ARB, although nearly all were reported to be on a RAAS blocker at baseline (80.2%).[4] Of the 10,142 participants recruited, there were 8,101 patients with an eGFR of ≥ 60mL/min/1.73

m^2 at baseline, of which 73% had normoalbuminuria.[18] Notably, 2,039 (20.1%) of participants had an eGFR < 60mL/min/1.73 m^2 at baseline, of which 55% had normoalbuminuria.[18]

The DECLARE-TIMI 58 population was at lower risk of MARE than EMPA-REG OUTCOME and CANVAS Program populations (**Figure 1; Table 1**), which themselves had overall lower renal risk populations compared with the landmark ARB trials, RENAAL and IDNT. The study population in DECLARE-TIMI 58 did not have substantially reduced eGFR at baseline (mean eGFR was 85.2 ml/min/1.73 m^2) because patients with creatinine clearance < 60mL/min/1.73 m^2 were excluded. Most participants had preserved renal function at baseline and notably, 69.1% had normoalbuminuria, i.e. only 30% had baseline DKD.[5,7] Of the 17,160 participants enrolled, 15,894 (93%) had an eGFR of ≥ 60 mL/min/1·73 m^2 and 1,265 (7%) had an eGFR of < 60 mL/min/1·73 m^2 at baseline.[7] Similarly, the majority (approximately 85%) of study patients were taking an ACE inhibitor/ARB at baseline, however there was no specific directive to ensure optimal treatment.[5]

Renal endpoints and outcomes in SGLT2 inhibitor CVOTs

Although the CVOTs under consideration in this manuscript had MACE as the primary endpoint, the regulators asked different questions of the sponsors which affected the renal recruitment criteria. Overall, the main renal endpoint definitions in CVOTs prior to CREDENCE are heterogeneous making direct comparisons between trials difficult, and outcome measures were based on surrogate endpoints, such as creatinine doubling and progression of albuminuria (**Table 2**).[3] Furthermore, renal composite endpoints were used to provide evidence of SGLT2 inhibitor efficacy in slowing the loss of renal function and delaying progression to ESRD.[19]

Efforts to identify optimal endpoints for evaluating DKD treatments, as well as efforts to standardise the reporting of the data, are important for expediting the development of new anti-diabetic treatments for DKD. For future trials, uniformly agreed definitions for renal endpoints would make meta-analyses easier and would facilitate the comparison of different studies.[9] New major renal events (MARE) definitions have been developed, which include major morbidity and mortality events (e.g. development of new-onset DKD, reaching ESRD, starting RRT or receiving a kidney transplant, and mortality from renal cause).[9] Results from future trials that adopt the use of MARE as a primary outcome and add intermediate endpoints and surrogate endpoints where appropriate would be more comparable and patient relevant.[9] Indeed CREDENCE, a post-hoc analysis of the composite endpoint of RRT, transplantation or death was assessed with a view to providing patient relevant clinical trial data.[8]

Figure 2 shows the composite renal outcome rates and composite renal outcome relative risk reductions (RRRs) in CVOTs**.**

BOX 1 provides a summary of key issues with renal endpoints and outcomes pertaining to the design of EMPA-REG OUTCOME, CANVAS Program and DECLARE-TIMI 58 CVOTs.

EMPA-REG OUTCOME

In analyses of the renal endpoints, it was concluded that empagliflozin improved renal outcomes defined by reduced risk of incident or worsening DKD, reduced progression to macroalbuminuria, reduced incidence of renal-replacement therapy and reduced occurrence of doubling of serum creatinine compared with placebo (**Table 2; Box 1**).

It is however important to note that renal endpoints were redefined during the main EMPA-REG OUTCOME trial and that key aspects of the endpoints were either defined after trial completion (although reportedly before database lock) or were not defined prospectively.[20] No renal related endpoints were included in plans to control the overall Type-1 error rate because, as the sponsor explicitly stated, the endpoints "are of exploratory nature and no correction for multiple hypothesis testing was made."[21] In the final protocol, the secondary safety outcome was a composite microvascular outcome that included the first occurrence of any of the following: the initiation of retinal photocoagulation, vitreous haemorrhage, diabetes-related blindness, or new or worsening DKD. The first renal microvascular outcome was incident or worsening DKD, defined as progression to macroalbuminuria (UACR > 300 mg/g), doubling of serum creatinine with an eGFR (MDRD) ≤ 45 mL/min/1.73m^2, initiation of continuous renal replacement therapy, or death due to renal disease.[3,6]

EMPA-REG OUTCOME was not a dedicated renal outcomes trial and renal endpoints were not adjudicated during the study. However, the results for MARE were validated in a post-hoc sensitivity analysis in a subgroup analysis of patients with prevalent DKD at study entry defined as eGFR (Modification of Diet in Renal

Disease (MDRD) Study equation) < 60 ml/min/1.73 m^2 and/or macroalbuminuria (UACR > 300mg/g) at baseline.[6] The first renal outcome of this post-hoc subgroup study was a four-point composite of new onset or worsening of DKD (defined as progression to macroalbuminuria, doubling of serum creatinine level associated with an eGFR ≤ 45 mL/min/1.73 m^2, initiation of RRT and renal death). A total of 6,185 patients entered this pre-specified subgroup analysis. The incident or worsening DKD endpoint occurred in 388 of 2061 (18.8%) placebo and 525 of 4124 (12.7%) empaglifozin treated patients which resulted in a relative risk reduction of 39% in patients that received empaglifozin (Hazard Ratio (HR): 0.61; 95% CI: 0.53, 0.7; P <0.001).[6] As defined, the new onset macroalbuminuria component could capture small, transient and/or reversible changes in albuminuria of uncertain clinical significance.[21] In fact, there was no difference in albuminuria between the placebo and empagliflozin arms following discontinuation of study drug. It has been postulated that SGLT-2 inhibitors exert a haemodynamic effect rather than a direct effect on the underlying disease process, however the exact mechanism remains to be elucidated.[22] In the recent randomised, double-blind RED trial, the renal haemodynamic effects of an SGLT-2 inhibitor were shown to be caused by post-glomerular vasodilatation rather than pre-glomerular vasoconstriction in metformin-treated T2D patients.[23]

In EMPA-REG OUTCOME, there was no significant between-group differences in the rate of incident albuminuria for patients with normoalbuminuria at baseline (51.5 and 51.2% with empagliflozin and placebo, respectively; P =0.25).[6] However, overall progression to macroalbuminuria was reduced by 38% (P <0.001), suggesting a different effect of the SGLT-2 inhibitor on patients with different levels of urinary albumin excretion.[6] Efficacy claims of “sustained normo- or microalbuminuria in patients with baseline macroalbuminuria” are difficult to maintain.[24] To date, regulatory agencies have not accepted on-treatment effects on albuminuria as a surrogate for clinical outcomes in diabetic nephropathy, in part because therapies can have acute and reversible pharmacologic effects on albuminuria that may differ from their long-term effects on the irreversible loss of renal function and underlying disease progression.[25,26] It is also important to note that persons with a reduction in eGFR without elevations in urinary albumin may or may not show benefit from SGLT-2 inhibitor treatment, however further trials will be required to determine this.

CANVAS Program

Analysis of renal endpoints showed that canagliflozin reduced the occurrence of progression to albuminuria and increased the occurrence of regression of albuminuria (**Table 2; Box 1**). A renal adjudication committee was responsible for adjudicating the following endpoint events: ESRD (i.e. need for RRT), doubling of serum creatinine and 40% reduction of eGFR.[4] However, as with EMPA-REG OUTCOME, the CANVAS Program was not designed to formally examine renal outcomes and the total number of renal events was small. The decrease in HR for composite renal outcome was driven primarily by the surrogate endpoints of renal function rather than patient relevant MARE namely, ESRD, renal transplantation or renal death.

Canagliflozin reduced the time to first occurrence of all adjudicated renal composite endpoints relative to placebo with the upper bound of the 95% CI excluding 1.0.[4] The composite outcome of sustained 40% reduction in eGFR, renal death and RRT occurred less frequently in the canagliflozin group compared with the placebo group (5.54 vs. 9.03/1,000 patient-years, respectively) corresponding to a HR of 0.60 (95% CI: 0.47, 0.77).[4] Furthermore, lower HRs were also observed in the canagliflozin group when progression to macroalbuminuria (HR: 0.57; 95% CI: 0.50, 0.66) or CV death (HR: 0.77; 95% CI: 0.66, 0.89) were included in this composite.[4]

The CANVAS Investigators introduced alternative renal endpoints in their analyses, i.e. a 40% decline in eGFR and eGFR slope, which might be more practical in trials of shorter duration.[4,27] However, since these endpoints are less applicable at higher baseline renal function (e.g. as typically the case in CVOTs), effects on these endpoints might not translate into true improvement in MARE. For each of these outcomes, substituting the 40% reduction in eGFR component with doubling of serum creatinine resulted in fewer events but similar canagliflozin treatment effect estimates.[4] The results of the composite endpoints were mainly driven by sustained 40% reduction in eGFR and doubling of serum creatinine.[4]

DECLARE-TIMI 58

In addition to the FDA-mandated primary safety endpoint (non-inferiority for 3-point MACE) and the primary efficacy endpoint superiority for 3-point MACE, a new co-primary composite efficacy endpoint of HHF and CV death was added, due to new insights from previously reported SGLT2 inhibitor CVOTs.[5] However, because the study failed to meet the primary efficacy endpoint of superiority for 3-point MACE, the pre-specified adjudicated secondary cardio-renal composite outcome defaulted to an exploratory endpoint. This cardio-renal exploratory endpoint was defined as a sustained decline of at least 40% in estimated eGFR to < 60 mL/min/1·73m², ESRD (defined as dialysis for ≥ 90 days, kidney transplantation, or confirmed sustained eGFR < 15mL/min/1·73 m²), or death from renal or cardiovascular causes.[5] A second, renal-specific composite outcome was the same but excluded death from CV causes and this occurred in 1.5% versus 2.8% of patients in the dapagliflozin and placebo treatment groups, respectively (HR 0.53; 95% CI: 0.43-0.66).[5] Hence, the exploratory outcome analysis showed a 47% RRR with dapagliflozin in the composite renal outcome.[5] Despite the good HR reported for the renal composite endpoint, it was mainly driven by a reduction in doubling of serum creatinine.[7]

Overall, the authors from DECLARE-TIMI 58 concluded that dapagliflozin was able to prevent renal function deterioration and clinically important renal endpoints compared with placebo in T2D patients with and without established atherosclerotic CVD and preserved renal function.[5] Based on the Phase 3 DECLARE-TIMI 58 trial results, the European Commission has recently approved a label update for dapagliflozin to include both CV and renal data. However, owing to the fact that this trial included a population with near normal renal function at baseline (93% eGFR > 60mL/min/1.73m^2), only a small number of renal events was actually reported (**Table 1; Box 1**).[5] Of the 17,160 patients enrolled in this study, only 11 vs. 27 ESRD or renal death events were reported for the dapagliflozin and placebo groups, respectively (HR: 0.41; P =0.012).[7] The inclusion of sustained eGFR changes only (i.e. with two consecutive tests ≥ 30 days apart) was an important parameter in the renal endpoint definition.

Supporting the DECLARE-TIMI 58 cardio-renal outcomes, results from a pre-specified sub-analysis, recently presented at the 2019 ESC conference, showed that dapagliflozin's effect on CV death/HHF and MACE was consistent across baseline renal function and albuminuria status (P =0.29 for CV death/HHF and P =0.62 for 3-point MACE), [28] although numerically greatest (42% RRR) in patients with reduced eGFR and albuminuria.[28] Similarly in a recent meta-analysis which included EMPA-REG OUTCOME, CANVAS Program, DECLARE-TIMI 58 and CREDENCE data, renoprotection was consistent irrespective of baseline albuminuria (P_{trend} = 0.66) with benefit identified at all levels of kidney function, including for patients with a baseline eGFR 30-40 mL/min/1.73m^2 (Relative Risk 0.70: 95% CI 0.54-0.91; P =0.008).[29] Despite the results of this meta-analysis being driven predominantly by canagliflozin in the single CREDENCE study, renoprotection with the other SGLT2 inhibitors, empagliflozin and dapagliflozin, seems consistent.[29]

Renal endpoints and outcomes in CREDENCE

As previously mentioned, CREDENCE is the first and only completed clinical trial to investigate a SGLT2 inhibitor primarily for renal protection in patients with T2DM and CKD.[12] Baseline eGFR and UACR for CREDENCE was 56.2 mL/min/1.73 m^2 and 927 mg/g, respectively.[12] **Figure 2** shows the composite renal outcome rates and composite renal outcome relative risk reductions (RRRs) in CREDENCE versus the SGLT2 inhibitor CVOTs**.**

CREDENCE included 4,400 patients and was stopped early due to a signal of clear efficacy in the prevention of the composite renal and cardiovascular primary endpoint, [12] doubling of serum creatinine, ESRD, renal death and CV death; both ESRD and renal death were robustly defined. In addition, unlike the SGLT2 inhibitor CVOTs, all renal endpoints were assessed by a blinded adjudication committee.[12] The relative risk of the primary outcome was 30% lower for patients taking 100mg of canagliflozin (a dose that had no effect upon lowering of HbA1C) compared with placebo (HR: 0.70; 95% CI: 0.59, 0.82; *P* =0.00001).[12,16] There was also 34% RRR for the renal-specific elements of the primary endpoint, excluding CV death, for those taking canagliflozin (HR: 0.66; 95% CI: 0.53, 0.81; *P* <0.001) (**Table 2**).[12] By 42 months, eGFR had dropped by a mean of -1.85 mg/mL/min/1.73m^2 per year in the canagliflozin group and a mean of -4.59 mg/mL/min/1.73m^2 per year in the placebo group, which translates to a 60% reduction in eGFR slope decline.[8]

The renal results observed in the overall study population were consistent across the primary and secondary prevention groups, across all 15 subgroups tested, regardless of prior CVD history. Specifically, canagliflozin reduced the risk of ESRD by 32% (HR: 0.69; 95% CI: 0.51 to 0.95; *P* =0.89) and 33% (HR: 0.67; 95% CI: 0.47, 0.96; *P* =0.89) in the primary (≥ 50 years of age with ≥ 2 risk factors for CV events but with no prior CV event) and the secondary (≥ 30 years of age with a prior CV event) prevention groups, respectively.[30] The number needed to treat with canagliflozin was 22 to prevent one primary composite outcome event (doubling of serum creatinine, ESRD, renal death, or CV death) over 2.5 years.[12] To prevent one primary composite outcome event over 2.5 years in patients with eGFR (> 30 to < 45 ml/min/1.73m^2) the number needed to treat with canagliflozin was 16.[12,31]

A signal of potential increased risk of distal fracture and lower limb amputation was noted in the CANVAS Program [12] but was not seen in CREDENCE or in a cohort study of 79,964 T2D patients.[16,32]

Based on the exploratory/secondary renal endpoints of the CVOTs plus the dedicated CREDENCE trial, empagliflozin, canagliflozin or dapagliflozin are now recommended as treatment to reduce progression of DKD.[16] CREDENCE also demonstrated that canagliflozin may be used with benefit down to an eGFR of 30 mL/min/1.73m^2.[12,16] Hence the ESC/EASD 2019 guidelines state that "treatment with an SGLT2 inhibitor is associated with a lower risk of renal endpoints and should be considered for T2D patients if eGFR is 30 to < 90 mL/min/1.73 m^2."[16]

Strength of evidence for renal outcome modification in T2DM with SGLT2 inhibitors

Ideally, before adoption of the SGLT2 inhibitor CVOT results to support indications for renoprotection in guidelines, confirmatory results from other dedicated renal outcome trials in addition to CREDENCE are needed.[33] Such studies must include patients who are at substantially higher risk of renal events than those enrolled in the published CVOTs, to ensure that a sufficient number of sustained renal events is accrued, that there is appropriate follow-up, and that the study design uses the US Food and Drug Association (FDA)-approved and generally-accepted renal endpoints, appropriate measurements and adjudication.[34] Notably, longer duration of follow-up (e.g., ≥3 years) in kidney trials many be more important for renal outcomes than cardiovascular outcomes.

Despite consistency of RRR for MARE across the SGLT2 inhibitor CVOTs (EMPA-REG OUTCOME, CANVAS Program and DECLARE-TIMI 58), the rate of sustained renal events was extremely low at just 69 events per 34,322 participants.[29] In contrast, the total number of sustained RRT events from CREDENCE was 183 events per 4,401 participants.[12] Excluding CREDENCE data, the strength of evidence for renoprotection with SGLT2 inhibitors in patients with CKD has also been assessed in a second recent systematic review and meta-analysis.[35] The results for MARE were found to be less robust than for MACE, due to the relatively small number of renal events.[35] The systematic review states that the “effect on the renal composite outcome was no longer clear in a sensitivity analysis excluding the DECLARE-TIMI 58 trial,” because most of the renal events used in the meta-analysis were from this trial.[35]

Nevertheless, it is noteworthy that there were 765, 533, 1,184 and 758 persons with baseline macroalbuminuria in EMPA-REG OUTCOME, CANVAS Program, DECLARE-TIMI 58 and VERTIS-CV, respectively, for a total of 3240 persons, which is comparable to the 3,873 with macroalbuminuria in CREDENCE, although the prevalence of macroalbuminuria was lower in the CVOTs and eGFR was certainly lower in CREDENCE.

Taken together it is clear that the renoprotective effects reported in the SGLT2 inhibitor CVOTs are substantially less robust than those observed in CREDENCE. As highlighted in the recent ESC/EASD guidelines, whether the renoprotection demonstrated in CREDENCE is a SGLT2 inhibitor class effect or specific to canagliflozin remains to be determined by further additional trials with the other SGLT2 inhibitors in patients with more advanced CKD.[16]

Ongoing and future studies

Based on the results from the landmark CREDENCE renal outcomes trial, canagliflozin has recently been approved by the FDA to reduce the risk of (i) end-stage kidney disease; (ii) worsening of kidney function; and (iii) cardiovascular death/hospitalisation for heart failure in people with T2D and CKD. Canagliflozin is therefore the first SGLT2 inhibitor to include indications for T2D glycemic control, CV risk reduction and renal risk reduction.[36]

Several trials are underway to further investigate the cardiovascular and renal benefits of the other SGLT2 inhibitors. The Study of Heart and Kidney Protection With Empagliflozin (EMPA-KIDNEY; NCT03594110), will evaluate approximately 5,000 patients with established CKD, with and without T2DM, to determine the effect of empagliflozin on time to clinically relevant kidney disease progression or CV death.[37] The findings of this trial will build on results of the EMPA-REG OUTCOME trial, with new data on the effects of empagliflozin in a broad range of people, with or without T2D.

The DAPA-CKD (Study to Evaluate the Effect of Dapagliflozin on Renal Outcomes and Cardiovascular Mortality in Patients With Chronic Kidney Disease; NCT03036150), evaluating the effect of dapagliflozin on renal outcomes and cardiovascular mortality in patients with chronic kidney disease is already fully recruited with patients now under follow-up. The primary endpoint will be time to the first occurrence of any of the components of the composite: ≥50% sustained decline in eGFR or reaching ESRD, CV death or renal death.[37]

The recently completed VERTIS-CV CVOT (NCT01986881) is evaluating ertugliflozin in 8,238 patients with established atherosclerotic CVD and includes a secondary composite outcome of renal death, dialysis/transplant or doubling of baseline serum creatinine.[10,37]

Outcomes have recently been reported for the DAPA-HF trial (Study to Evaluate the Effect of Dapagliflozin on the Incidence of Worsening Heart Failure or Cardiovascular Death in Patients With Chronic Heart Failure; NCT03036124).[38,39] DAPA-HF primarily investigated the effect of dapagliflozin on a composite of worsening heart failure (hospitalisation or an urgent visit resulting in intravenous therapy for heart failure) or cardiovascular death in patients with chronic heart failure with reduced ejection fraction (HR: 0.74; 95% CI: 0.65, 0.85; P <0.001).[39] A secondary outcome measure will include time to the first occurrence of any of the components of a renal composite (≥50% sustained decline in eGFR, ESRD, or renal death).[37,38]

Two Phase 3 trials are currently recruiting subjects to investigate the safety and efficacy of empagliflozin versus placebo added to guideline-directed therapy in patients with heart failure. The two EMPEROR (EMPagliflozin outcomE tRial in Patients With chrOnic heaRt Failure) trials will include patients with heart failure due to either reduced ejection fraction (EMPEROR-Reduced; NCT03057977) or with preserved ejection fraction (EMPEROR-Preserved; NCT03057951).[37] Secondary endpoints in both trials will include change/slope in eGFR from baseline, and time to first occurrence of chronic dialysis or renal transplant and sustained reduction of eGFR.[37]

Conclusions

Insights into the potential role of the SGLT2 inhibitor class of drugs in the prevention and treatment of DKD have been provided by CVOTs and CREDENCE.[4,6,7,12] The overall renoprotective effect, although a secondary outcome in the CVOTs, does seem to be consistent for empagliflozin, canagliflozin and dapagliflozin with no evidence of heterogeneity.[29] In a recent meta-analysis, SGLT2 inhibition reduced ESRD (0·65, 0·53–0·81, p<0·0001), and acute kidney injury (0·75, 0·66–0·85, p<0·0001), with consistent benefits across studies (EMPA-REG OUTCOME, CANVAS Program and CREDENCE, and DECLARE–TIMI 58).[29] Irrespective of baseline albuminuria and use of RAAS blockade, renoprotection was also consistent across the studies.[29] However, concurrent with the latest 2019 ESC/ EASD guidelines, Neuen et al. (2019) highlighted that the consistency of RRR in renal outcomes being a class effect among the SGLT2 inhibitors remains uncertain because of the different characteristics of participants in the included SGLT2 inhibitor CVOTs as well as the fact that only the CREDENCE trial was specifically powered for renal outcomes.[16,29]

Thus, from the CVOT data alone, it would be inappropriate to conclude that SGLT2 inhibitors provide a clear favourable effect on patient relevant clinical outcomes in DKD and also that any such effect would be a class effect.[16] The only definitive prospective clinical trial that has demonstrated a clear, highly clinically significant effect on major renal outcomes in participants with CKD has been CREDENCE. Until the ongoing dedicated renal trials for empagliflozin and dapagliflozin report conclusions on the renoprotective efficacy of these compounds in DKD and on class effects cannot be made with complete confidence.

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Table 1. Key differences between the study design of SGLT2 inhibitor CVOTs and CREDENCE.

Trial Name	EMPA-REG OUTCOME	CANVAS Program	DECLARE-TIMI 58	VERTIS-CV	CREDENCE
Comparisons	1:1:1 ratio: empagliflozin 10 mg, empagliflozin 25 mg, placebo	CANVAS 1:1:1 ratio: canagliflozin 300 mg, canagliflozin 100 mg, placebo; CANVAS-R 1:1 ratio: canagliflozin 100 mg (optional increase to 300 mg), placebo	1:1 ratio: dapagliflozin 10mg, placebo	1:1:1 ratio: ertugliflozin 5mg, ertugliflozin 15 mg, placebo	1:1 ratio: canagliflozin 100mg, placebo
Number of patients in primary analysis	7,020	10,142	17,160	8,238	4,401
Main inclusion criteria:					
• CVD	established CVD	age ≥ 30 years and established CVD or age ≥ 50 years with ≥ 2 CVD risk factors	high CVD risk or established CVD	established vascular complications	no criteria
• Renal	no criteria	micro- or macroalbuminuria	no criteria	no criteria	stage 2 or 3 CKD or macroalbuminuria
• eGFR	≥30 mL/min/1.73m^2	>30 mL/min/1.73m^2	CCr ≥60 ml/min	≥45 to ≤60 mL/min/1.73m^2	≥30 to <90 mL/min/1.73m^2
• HbA1c	≥7.0% to ≤9.0%	≥7.0% to ≤10.5%	≥6.5% to ≤12.0%	≥7.0% to ≤10.5%	≥6.5% to ≤12.0%

• UACR	no criteria	no criteria	no criteria	no criteria	>300 to 5,000 mg/g
Primary endpoint	3P-MACE	3P-MACE	3P-MACE; CV composite of CV death or HHF	3P-MACE	renal composite of ESRD, SCr doubling, renal/CV death
Secondary CV endpoint	4P-MACE (composite of the primary outcome plus hospitalisation for unstable angina)	all-cause mortality, CV death, composite of death from CV causes and HHF	no criteria	CV death or HHF; CV death	composite of CV death and HHF; CV death; all-cause death; CV composite of CV death, nonfatal MI, nonfatal stroke, HHF and hospitalisation for unstable angina
Secondary/exploratory renal endpoint	progression to macroalbuminuria, SCr doubling, initiation of RRT or death from renal disease	renal composite endpoint: 40% reduction in eGFR, need for RRT, or death from renal causes; albuminuria progression/regression	renal composite endpoint: 40% reduction in eGFR, new ESRD, or death from CV and/or renal causes	renal composite of renal death, dialysis/ transplant, or doubling of SCr from baseline	renal composite endpoint of ESRD, SCr doubling, and renal death; composite endpoint of ESRD and renal/CV death; individual components of the composite endpoints
Median follow-up (years)	3.1	2.4	4.2	ongoing	2.6

Patients with established CVD	99%	65.6%	40.6%	99.9%	50.4%
Baseline renal characteristics					
• mean eGFR	eGFR: 74.0 ml/min/1.73 m^2 (25.9% < 60 and 74.1% >60 ml/min/1.73m^2);	76.5 ml/min/1.73 m^2 (20.1% < 60 and 79.9% >60 ml/min/1.73m^2)	85.2 ml/min/1.73 m^2 (45% between 60 and 90 ml/min/1.73 m^2 and 7.0% < 60 ml/min/1.73 m^2)	76.0 ml/min/1.73 m^2 (22% < 60 and 78% >60 ml/min/1.73m^2)	56.2 ml/min/1.73 m^2 (60% < 60 and 40% >60 ml/min/1.73m^2)
• median UACR	78 mg/g	12.3 mg/g	13.1 mg/g	ns	927.0 mg/g
• microabuminuria	28.5%	22.6%	23.9%	30.2%	11%
• macroalbuminuria	10.9%	7.6%	6.9%	9.2%	88%
Reference(s)	[3,6]	[4]	[5,7]	[10]	[11,12]

CCr: creatinine clearance rate; CKD: chronic kidney disease; CV: cardiovascular; CVD: cardiovascular disease; eGFR: estimated glomerular filtration rate; ESRD: end stage renal disease; HbA1c: glycated haemoglobin; HHF: hospitalisation for heart failure; 3-P MACE: 3 point major adverse cardiovascular event = CV death, nonfatal MI, or nonfatal stroke; ns: not specified; RRT: renal replacement therapy; SCr: serum creatinine; SGLT2: sodium glucose linked transporter-2; T2D: type-2 diabetes; UACR: Urine albumin-to-creatinine ratio.

Table 2. Summary of key renal outcome measures across SGLT2 inhibitor CVOTs and CREDENCE.

Trial	EMPA-REG N = 7,020 [3,6]	CANVAS N = 10,142 [4,8]	DECLARE-TIMI 58 N = 17,160 [5,7]	CREDENCE N = 4,401 [12]
Cardiovascular Endpoint:	HR (95% CI; *P*-value)			
3-point MACE	0.86 (0.74-0.99; *P* <0.001 for noninferiority and *P* =0.04 for superiority)	0.86 (0.75-0.97; *P* <0.001 for noninferiority and *P* =0.02 for superiority)	0.93 (0.84-1.03; *P* =0.17)	0.80 (0.67-0.95; *P* =0.01)
Renal Endpoint:	HR (95% CI; *P*-value)			
Cardiorenal composite			0.76 (0.67-0.87; *P* <0.0001)	0.70 (0.59-0.82; *P* =0.00001)
Renal-specific composite[†]	0.54 (0.40-0.75; *P* <0.001)	0.60 (0.47-0.77)	0.53 (0.43-0.66; *P* <0.0001)	0.66 (0.53-0.81; P<0.001)
Doubling of serum creatinine	0.56 (0.39-0.79; *P* <0.001)			0.60 (0.48-0.76; *P* <0.001)
40% eGFR reduction			0.54 (*0.43-0.67; P* <0.0001)	

ESRD (initiation of dialysis)	0.45 (0.21-0.97; *P* = 0.04)		0.31 (0.13-0.79; *P* =0.013)	0.68 (0.54-0.86; *P* =0.002)
Dialysis, kidney transplant or death				0.72 (0.54-0.97; *P* = NA[§])
Progression of albuminuria[‡]	0.62 (0.54-0.72)	0.73 (0.67-0.79; *NR*)	0.84 (0.79-0.89)	NA

[†]Described as the composite risk of doubling of serum creatinine level accompanied by an estimated glomercular filtration rate (eGFR) of ≤ 45 ml/min/1.73 m^2, initiation of renal replacement therapy, or death from renal disease in the EMPA-REG OUTCOME trial; as the composite risk of 40% reduction in eGFR, renal replacement therapy, or renal death in the CANVAS Program; as the composite risk of > 40% decrease in eGFR to < 60 ml/min/1.73 m^2, ESRD, or death from renal cause in the DECLARE-TIMI 58 trial; and as the composite outcome of end-stage kidney disease, doubling of serum creatinine level, or renal or cardiovascular death in the CREDENCE trial.

[‡]Described as progression to macroalbuminuria in the EMPA-REG OUTCOME trial; as > 30% increase in albuminuria, change from either normoalbuminuria to micro-/macroalbuminuria or micro- to macroalbuminuria in the CANVAS Program; and as the composite risk of normo- to micro- or macroalbuminuria in the DECLARE-TIMI 58 trial.

[§]NA: not applicable since P-values were only reported in CREDENCE for outcomes that were included in the hierarchical-testing strategy.

SGLT2: sodium-glucose linked transporter-2; CVOTs: cardiovascular outcome trials; HR: hazard ratio; CI: confidence interval; CV: cardiovascular; ESRD: end stage renal disease; eGRF: estimated glomerular filtration rate; NA: not applicable; NR: not reported.

Box 1. Key renal endpoint and outcome considerations with regard to the EMPA-REG OUTCOME, CANVAS Program and DECLARE-TIMI 58 study designs

a. In EMPA-REG OUTCOME, the “new or worsening nephropathy” component of the microvascular composite outcome was largely driven by cases of new onset macroalbuminuria, which accounted for over 85% of events.[21]

b. In CANVAS, the annual eGFR decline was slower with canagliflozin (slope difference between groups 1.2mL/min/1.73m^2/year; 95% CI: 1.0, 1.4).[8] This effect is similar to that observed with RAAS blockers. An initial, functional ‘dip’ in eGFR is associated with long-term nephroprotection and is reversible upon discontinuation of the drug.[40]

c. Post-hoc analyses of data from the CANVAS Program have shown that the beneficial effects of canagliflozin on CV and renal outcomes were not influenced by baseline renal function in people with T2DM and a history or high risk of CVD down to eGFR levels of 30 mL/min/1.73.m^2.[18] This finding led to the suggestion that the use of canagliflozin might be appropriate for patients with eGFR levels that are below the previously recommended level in view of the potential CV and renal benefits of therapy.[41]

d. As with the other CVOTs, despite an impressive HR reduction in the exploratory composite renal endpoint in DECLARE-TIMI 58, it was driven by the components of eGFR decrease to < 60 mL/min/1.73.m^2 and CV death.[7] Of note, the patient relevant renal endpoints of ESRD, renal death and ESRD or renal death were comparatively rare events in this study.[7,42]

Figure 1. Baseline renal risk in study populations of SGLT2 inhibitor CVOTs and CREDENCE. Adapted from [11].

Figure 2. Composite renal outcome rates and composite renal outcome relative risk reductions (RRRs) in SGLT2 inhibitor CVOTs and CREDENCE. Adapted from [43].

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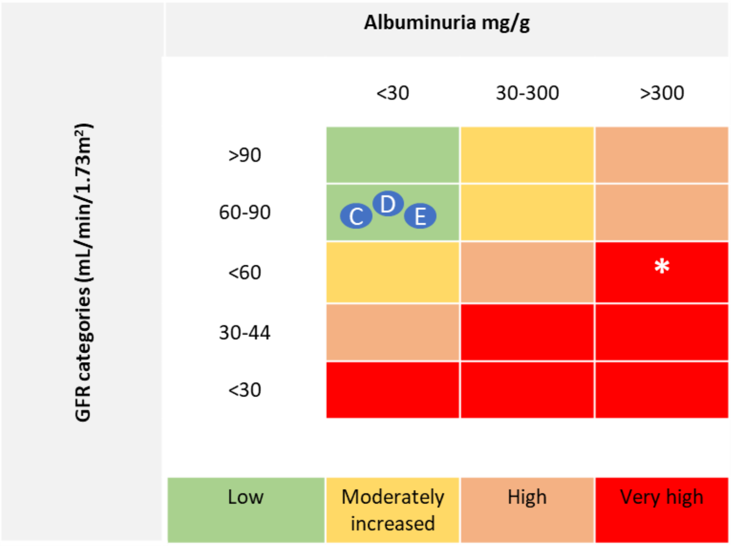
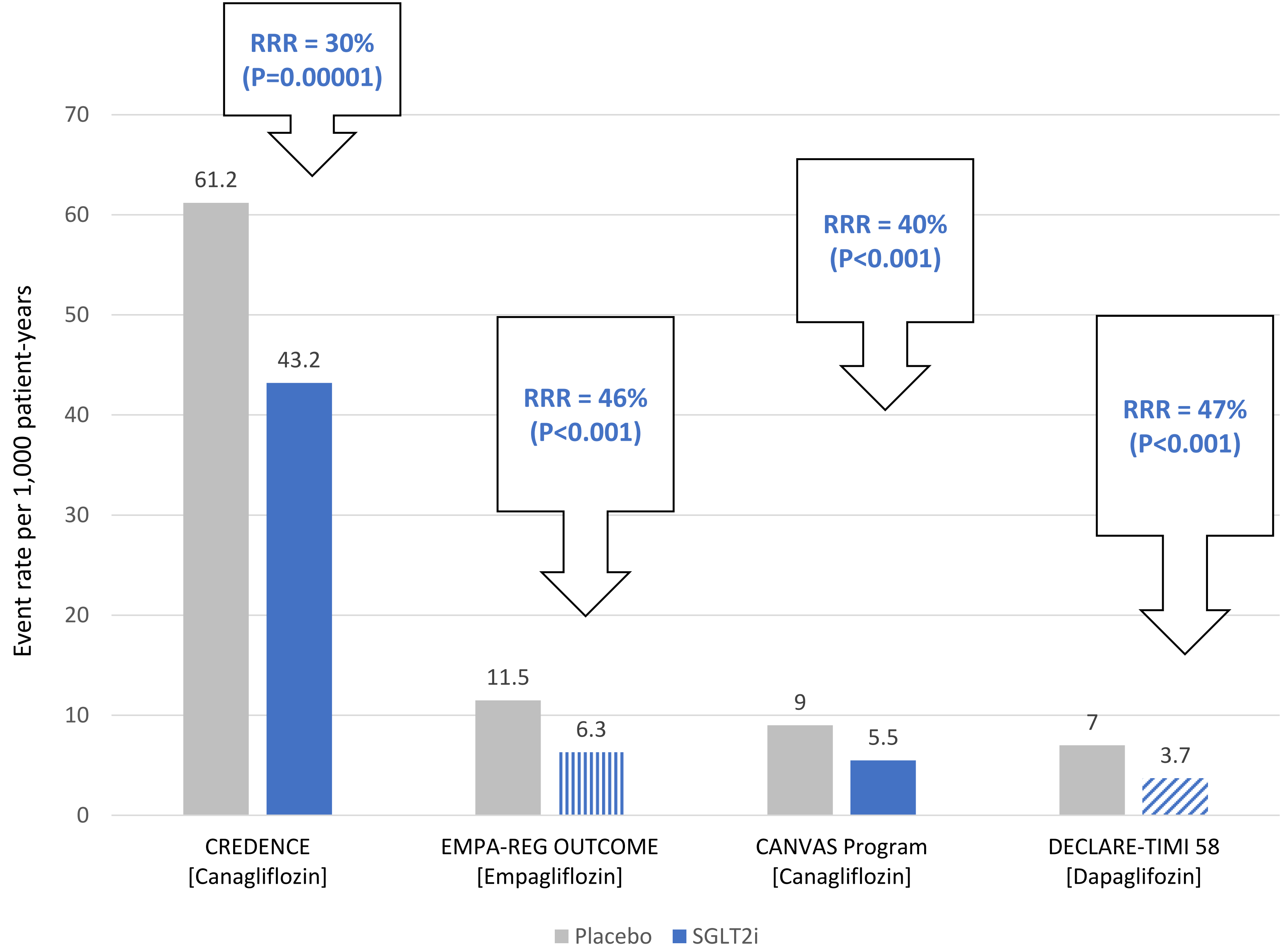
Figure 1.



Trial Name	DECLARE-TIMI 58	CANVAS Program	EMPA-REG OUTCOME	CREDENCE
	D	C	E	*
mean eGFR (mL/min/1.73m^2)	85	76.5	74	56
eGFR <60	1,265 (7.4%)	2,037 (20.1%)	1,819 (25.9%)	2,631 (59.8%)
eGFR ≥60	15,894 (92.6%)	8,101 (79.9%)	5,199 (74.1%)	1,769 (40.2%)
median UACR (mg/g)	13.1	12.3	18	927
<30 n (%)	11,644 (69.1%)	7,007 (69.8%)	4,171 (60.0%)	31 (0.7%)
30-300 n (%)	4,029 (23.9%)	2,266 (22.6%)	2,013 (29.0%)	496 (11.3%)
>300 n (%)	1,169 (7.0%)	760 (7.6%)	769 (11.0%)	3,874 (88.0%)

Empaglilozin: EMPA-REG OUTCOME; Canagliflozin: CANVAS Program, and CREDENCE; Dapagliflozin: DECLARE-TIMI 58.

SGLT2: sodium-glucose linked transporter-2; CVOTs: cardiovascular outcome trials; eGRF: estimated glomerular filtration rate; UACR: urine albumin-to-creatinine ratio.



Due to the heterogeneity of populations and endpoints, any comparison between studies and SGLT-2 inhibitors should be made with caution.