

Sodium-glucose cotransporter 2 inhibitor effects on cardiovascular outcomes in chronic kidney disease

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ABSTRACT

Sodium-glucose cotransporter 2 (SGLT2) inhibitors reduce cardiovascular events, specifically those related to heart failure in patients with type 2 diabetes. Reductions in major adverse cardiovascular event (MACE) outcomes are also observed, but confined largely to patients who have prior cardiovascular disease. Cardiovascular outcome benefits extend to patients with type 2 diabetes and reduced estimated glomerular filtration (eGFR) rate down to 30 mL/min/1.73 m² and to patients with heart failure but without diabetes. Ongoing trials are exploring whether patients with chronic kidney disease (CKD) but without diabetes will gain similar benefits from this class of agents. Although some safety concerns have emerged, it seems likely that SGLT2 inhibitors will be used more widely in CKD patients to reduce their cardiovascular risk.

Keywords: cardiovascular disease, chronic kidney disease, heart failure, type 2 diabetes, SGLT2 inhibitors

INTRODUCTION

In patients with chronic kidney disease (CKD), a higher risk of cardiovascular disease is associated with lower estimated glomerular filtration rate (eGFR) and higher levels of urinary albumin excretion [1]. The presence of type 2 diabetes does not substantially impact on these associations. The relative risk of cardiovascular death is similar throughout the range of eGFR and urinary albumin excretion rates in patients with and without diabetes even though the absolute risks are higher in those with both CKD and diabetes [1]. Therefore, in patients with diabetes, the presence of CKD identifies those who are at high risk of adverse cardiovascular outcomes and who should be targeted for interventions that reduce this risk. Efforts to improve outcomes for CKD patients (both with and without diabetes) have focused on the development and implementation of interventional strategies that not only reduce the risk of progression of kidney disease, but also prevent the associated adverse cardiovascular outcomes. Here we focus on new

data supporting the use of sodium-glucose cotransporter 2 (SGLT2) inhibitors to improve cardiovascular outcomes in patients with type 2 diabetes and CKD and consider whether these benefits might extend to patients with CKD but without diabetes.

THE NEED FOR CARDIOVASCULAR OUTCOMES TRIALS OF NEW MEDICATIONS FOR TYPE 2 DIABETES

The cardiovascular benefits of SGLT2 inhibitors became apparent as a result of company-sponsored cardiovascular outcome trials (CVOTs) required by regulatory authorities. These trials have been recommended for all new therapies introduced to treat type 2 diabetes mellitus by the US Food and Drugs Administration (since 2008) and European Medicines Agency (since 2012) and followed concerns surrounding the potential for new therapies to increase cardiovascular risk [2]. For example, a meta-analysis of 42 clinical trials published in 2007 suggested that rosiglitazone use was associated with an elevated risk of myocardial infarction (MI) [3]. There was also concern that in some trials, more intensive glucose control appeared to be associated with an increased mortality when compared with standard care, a finding contrary to the expectation of the investigators [4]. In addition to conducting large-scale cardiovascular outcome studies, the current regulatory guidance recommends that sponsors establish independent cardiovascular endpoints committees for diabetes mellitus trials to prospectively adjudicate all cardiovascular events occurring across the Phases II and III registration programme. These trials should encompass major adverse cardiac events (MACEs), including cardiovascular death, non-fatal MI and non-fatal stroke. Although regulatory authorities have not mandated reporting of heart failure, the close relationship between diabetes and heart failure and concerns surrounding increased fluid retention associated with thiazolidinediones in the Rosiglitazone Evaluated for Cardiac Outcomes and Regulation of Glycaemia in Diabetes (RECORD) and Prospective Pioglitazone Clinical

Trial In Macrovascular Events studies (PROactive) [5, 6] have led investigators to evaluate heart failure in CVOTs as a pre-specified secondary endpoint.

CARDIOVASCULAR EFFECTS OF SGLT2 INHIBITORS IN TYPE 2 DIABETES BASED ON DATA FROM CVOTs

Three CVOTs involving three SGLT2 inhibitors have been published to date, the Empagliflozin and Cardiovascular Outcome Event Trial (EMPA-REG OUTCOME) [7], Canagliflozin Cardiovascular Assessment Study (CANVAS) [8] and Dapagliflozin Effect on Cardiovascular Events–Thrombolysis in Myocardial Infarction 58 (DECLARE–TIMI 58) [9]. These studies randomized patients with type 2 diabetes with either a prior cardiovascular event or with cardiovascular risk factors to empagliflozin, canagliflozin and dapagliflozin or placebo, respectively. The proportion of patients who had experienced a prior cardiovascular event differed between these studies, ranging from 100% in EMPA-REG OUTCOME through 65.6% in CANVAS and 40.6% in DECLARE–TIMI 58 (Table 1). Although designed to confirm safety, all three studies demonstrated a reduction in cardiovascular events, particularly heart failure, in patients randomized to active drug.

What can we learn from these trials about clinical outcome benefits in ‘high-risk’ patients who have both type 2 diabetes and CKD? As with most cardiovascular trials, exclusion criteria limited enrolment of patients with more severely impaired kidney function. Patients with an eGFR <30 mL/min/1.73 m² were excluded from EMPA-REG and CANVAS, while a creatinine clearance (by Cockcroft–Gault) of 60 mL/min was the lower cut-off for kidney function in the DECLARE–TIMI 58 trial. Because of these inclusion/exclusion criteria, patients with Stages 4 and 5 CKD were not recruited into these studies. However, all three CVOTs did include patients who fulfil criteria for Stage 3 CKD (on the basis of a sustained reduction in eGFR between 30 and 60 mL/min/1.73 m²) and Stages 1 and 2 CKD (on the basis of an eGFR between 60 and 90 mL/min/1.73 m² with persistent albuminuria).

Post hoc analyses of the three CVOTs have provided valuable insights into the likely benefits of SGLT2 inhibitors on cardiovascular outcomes in patients with Stages 1–3 CKD. In the

EMPA-REG OUTCOME trial, 7020 individuals with type 2 diabetes mellitus [haemoglobin A1c (HbA1c) of 7–10%], who had a prior cardiovascular event reflecting underlying coronary, peripheral or cerebrovascular disease were enrolled. These patients were randomized to receive empagliflozin (either 10 or 20 mg) or placebo in addition to standard care [7]. Of these patients, 2250 individuals had prevalent CKD {defined as an eGFR <60 mL/min/1.73 m² and/or macroalbuminuria [urine albumin:creatinine ratio (UACR) >300 mg/g] at baseline} [10]. Event rates were numerically higher in patients recruited with an eGFR <60 mL/min/1.73 m² than in patients with an eGFR ≥60 mL/min/1.73 m² and in those with macroalbuminuria as compared with those with no albuminuria at baseline as would be expected.

In patients with CKD at baseline, empagliflozin (both doses combined for analysis) reduced all-cause mortality by 24% {hazard ratio [HR] 0.76 [95% confidence interval (CI) 0.59–0.99]}, cardiovascular death by 29% [HR 0.71 (95% CI 0.52–0.98)] and hospitalization for heart failure by 39% [HR 0.61 (95% CI 0.42–0.87)] compared with placebo. Reductions in the risk of cardiovascular events including 3-point MACE (all-cause mortality, non-fatal MI and non-fatal stroke) with empagliflozin were broadly consistent in patients with an eGFR <60 mL/min/1.73 m² compared with those with an eGFR >60 mL/min/1.73 m², suggesting that the cardiovascular benefits of the drug were not attenuated in Stage 3 CKD. Risk reductions were also consistent across the range of UACR from >33.9 mg/mmol to <3.39 mg/mmol (>300–<30 mg/g) at baseline. The adverse event profile of empagliflozin was similar in patients in all eGFR subgroups.

The CANVAS Programme included two multicentre, double-blind, placebo-controlled, randomized trials, CANVAS and CANVAS-R, the results of which were combined for analysis [8]. In these two trials, 10 142 participants with type 2 diabetes (HbA1c ≥7.0% and ≤10.5%), who were either ≥30 years old with established atherosclerotic vascular disease or ≥50 years old with two or more cardiovascular risk factors (65% primary prevention), were randomized to canagliflozin (100 or 300 mg) or placebo (Table 1). The mean follow-up duration was 188.2 weeks. At baseline, 2039 (20.1%) participants had an eGFR <60 mL/min/1.73 m², with characteristics similar to the participants in the EMPA-REG trial [11]. In participants

Table 1. Details of CKD patients studied in SGLT2 inhibitor trials with main cardiovascular outcomes (compared with non-CKD patient subgroups where possible)

Characteristics	EMPA-REG OUTCOME	CANVAS	DECLARE–TIMI 58	CRENDENCE
Drug	Empagliflozin	Canagliflozin	Dapagliflozin	Canagliflozin
Median follow-up time (years)	3.1	2.4	4.2	2.62
Trial participants, <i>n</i>	7020	10 142	17 160	4401
Patients with established ASCVD, <i>n</i> (%)	7020 (100)	6656 (65.6)	6974 (40.6)	2220 (50.4)
Patients with history of heart failure, <i>n</i> (%)	706 (10.1)	1461 (14.4)	1724 (10.0)	652 (14.8)
Patients with eGFR <60 mL/min/1.73 m ² , <i>n</i> (%)	1819 (25.9)	2039 (20.1)	1265 (7.4)	2631 (59.8)
Patients with elevated UACR, <i>n</i> (%)	2035 (29%)	3026 (29.8)	5198 (30.3)	4401(100)
Relevant CV event	CV death, MI, stroke	CV death, MI, stroke	CV death, heart failure	CV death, MI, stroke
CKD patient group, HR (95% CI)	0.88 ^a (0.69–1.13)	0.70 (0.55–0.99)	NA	0.80 (0.67–0.95)
Non-CKD subgroup, HR (95% CI)	0.84 (0.70–1.01)	0.92 (0.79–1.07)		All patients had CKD
P-value (heterogeneity)	0.76	0.08	0.29	NA

^aCKD subgroup defined as eGFR <60 mL/min/1.73 m² (or on the basis of albuminuria). CV, cardiovascular; NA, not available.

randomized to both canagliflozin and placebo, event rates for all outcomes except for fatal/non-fatal stroke were numerically higher in patients with eGFR <60 mL/min/1.73 m² than in patients with eGFR ≥ 60 mL/min/1.73 m² at baseline. With respect to the primary composite outcome (cardiovascular death, non-fatal MI and non-fatal stroke), the risk reduction in patients randomized to canagliflozin (both doses combined) was similar in participants with an eGFR < 60 mL/min/1.73 m² [HR 0.70 (95% CI 0.55–0.90)] compared with those with an eGFR >60 mL/min/1.73 m² [HR 0.92 (95% CI 0.79–1.07); *p* for heterogeneity = 0.08]. Relative effects on most cardiovascular outcomes were similar across eGFR subgroups, with possible heterogeneity suggested only for the outcome of fatal/non-fatal stroke, with possibly greater benefit at lower eGFRs (*p* for heterogeneity = 0.01), as were results for almost all safety outcomes. There was an increased risk of amputation in the canagliflozin-treated patients, but this was not exacerbated by the presence of CKD [12].

The DECLARE study (dapagliflozin and cardiovascular outcomes in type 2 diabetes), the most recently published CVOT involving SGLT2 inhibitors, randomized 17 160 with type 2 diabetes (HbA1c 6.5–12.0%) and established atherosclerotic cardiovascular disease (ASCVD) (*n* = 6874) or multiple risk factors for ASCVD (*n* = 10 186; 40.6% secondary prevention) to a single dose of dapagliflozin (10 mg) or placebo [9] (Table 1). Detailed cardiovascular outcome data for patients with CKD enrolled in this trial are now emerging from *post hoc* analyses. With the exclusion criterion of a Cockcroft–Gault eGFR of <60 mL/min/1.73 m² at baseline, 1265 participants (7.4% of the total) had an eGFR <60 mL/min/1.73 m² based on the Chronic Kidney Disease Epidemiological Collaboration equation [13]. In the study population overall, dapagliflozin reduced cardiovascular death or hospitalization for heart failure compared with placebo [4.9% versus 5.8%; HR 0.83 (95% CI 0.73–0.95); *p* = 0.005], one of the two primary endpoints, mainly due to a lower rate of hospitalization for heart failure [HR 0.73 (95% CI 0.61–0.88)]. In a *post hoc* analysis, 5367 (31.3%) participants were identified with CKD based on either an eGFR <60 mL/min/1.73 m² or a UACR >3.39 mg/mmol (30 mg/g). Patients with CKD were stratified according to whether they had reduced eGFR, albuminuria or both. Cardiovascular event rates were higher in patients with CKD than in those without, with the highest risk for CV death, hospitalization for heart failure and MACEs observed in patients with both a low eGFR and albuminuria [14]. Once again, the relative risk reduction for these cardiovascular endpoints in patients randomized to dapagliflozin was generally consistent across the subgroups, although, as expected, the greatest absolute reduction was observed in those at highest risk based on level of eGFR and urinary albumin excretion.

A recent meta-analysis of the three CVOTs described above including 34 322 patients with type 2 diabetes (of whom 60.2% had established ASCVD at baseline) demonstrated that SGLT2 inhibitors reduced MACEs by 11% [HR 0.89 (95% CI 0.83–0.96); *p* = 0.0014] [15]. This benefit was apparent in patients with a history of ASCVD [HR 0.86 (95% CI 0.80–0.93)] and not in those without [HR 1.00 (95% CI 0.87–1.16); *p* for interaction = 0.0501]. These data suggest that SGLT2s reduced MACE outcomes (i.e. outcomes driven by ASCVD), but this

benefit is confined largely to patients with prior ASCVD events. In addition, there was a 23% reduction in the risk of cardiovascular death or hospitalization for heart failure [HR 0.77 (95% CI 0.71–0.84); *p* < 0.0001], with no significant difference between patients with and without baseline ASCVD (*p* for interaction = 0.41) nor with or without a history of heart failure (*P* for interaction = 0.51). A greater reduction of 31% was seen in the risk of hospitalization for heart failure [HR 0.69 (95% CI 0.61–0.79); *p* < 0.0001], again observed regardless of prior cardiovascular history. Of the patients included in this meta-analysis, 14.2% had an eGFR <60 mL/min/1.73 m². The reduction of MACEs by SGLT2 inhibitors was not different across three eGFR subgroups (≤ 60 , 60–90 and ≥ 90 mL/min/1.73 m²). However, the reduction in hospitalization for heart failure was 40, 31 and 12%, respectively (*P* for interaction = 0.0073), suggesting a greater relative benefit in patients with more severely impaired kidney function at baseline.

Thus data from the EMPA-REG, CANVAS and DECLARE-TIMI 58 studies show broadly consistent associations between eGFR, UACR and enhanced cardiovascular risk in patients with type 2 diabetes. All three trials demonstrate that reductions in cardiovascular events in participants randomized to SGLT2 inhibitors are not attenuated by concomitant Stages 1–3 CKD, and reductions in heart failure on SGLT2 inhibitors may be accentuated in CKD patients (Table 1).

CARDIOVASCULAR BENEFITS OF SGLT2 INHIBITORS IN PATIENTS WITH TYPE 2 DIABETES AND CKD (THE CREDENCE STUDY)

The Canagliflozin and Renal Outcomes in Type 2 Diabetes and Nephropathy (CREDENCE) trial, which recruited patients with type 2 diabetes and albuminuric CKD (eGFR 30–90 mL/min/1.73 m² and UACR 300–5000 mg/g), examined the impact of canagliflozin 100 mg daily or placebo for both renal and cardiovascular endpoints [16]. The inclusion criteria required that all patients were on a stable (maximum tolerated) dose of either an angiotensin-converting enzyme inhibitor or an angiotensin receptor blocker for at least 4 weeks prior to randomization. Patients randomized to canagliflozin had a lower risk of a composite of cardiovascular death or hospitalization due to heart failure [HR 0.69 (95% CI 0.57–0.83); *p* < 0.001]; a lower risk of a composite of cardiovascular death, MI or stroke [HR 0.80 (95% CI 0.67–0.95); *p* = 0.01] and a lower risk of hospitalization for heart failure [HR 0.61 (95% CI 0.47–0.80); *p* < 0.001] [17]. However, no significant risk reduction in cardiovascular death [HR 0.78 (95% CI 0.61–1.00); *p* = 0.05] was observed. Unlike previous studies, benefits for both MACEs and heart failure events were observed whether or not patients had a prior cardiovascular event at baseline [18]. Furthermore, the cardioprotective benefits of canagliflozin were not diminished in CKD patients who had a baseline HbA1c $<7.0\%$ (53 mmol/mol) at baseline, suggesting that poor diabetic control was not a prerequisite for cardiovascular risk reduction [19].

The cardiovascular benefits of canagliflozin observed in the CREDENCE trial are broadly consistent with prior data from the EMPA-REG, CANVAS and DECLARE-TIMI 58 CVOTs,

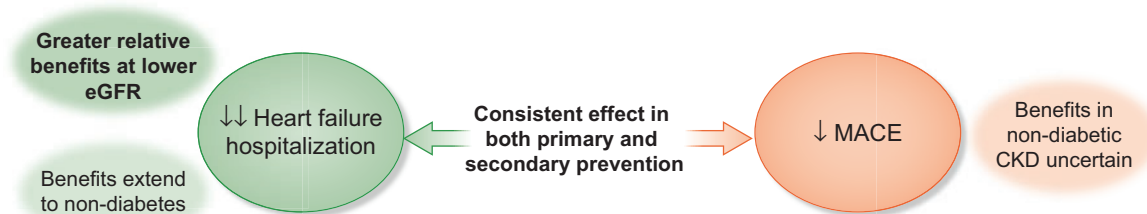


FIGURE 1: Summary of cardiovascular benefits of SGLT2 inhibitors in CKD.

with baseline eGFR and albuminuria being the most powerful indicators of cardiovascular risk across all four studies. Such consistency suggests a class effect of SGLT2 inhibitors on cardiovascular outcomes across both non-CKD and CKD patients [20].

CARDIOVASCULAR BENEFITS OF SGLT2 INHIBITORS BEYOND DIABETES

Recent data from a heart failure study indicate that the cardiovascular benefits of SGLT2 inhibitors extend beyond patients with type 2 diabetes. The Dapagliflozin in Patients with Heart Failure and Reduced Ejection Fraction (DAPA-HF study) recruited 4744 patients with New York Heart Association Class II, III or IV heart failure and an ejection fraction $\leq 40\%$ and randomly assigned these individuals to either dapagliflozin 10 mg or placebo in addition to conventional evidence-based therapy [21]. The primary outcome was a composite of worsening heart failure or cardiovascular death observed over a median of 18.2 months. Of the 4744 patients, 41.8% had a diagnosis of type 2 diabetes mellitus and 40.6% had an eGFR between 30 and 60 mL/min/1.73 m². The primary outcome was reduced by 24% [HR 0.74 (95% CI 0.65–0.85); $p < 0.001$] in patients randomized to dapagliflozin compared with placebo. The benefit was similar across patients with a baseline eGFR < 60 mL/min/1.73 m² [HR 0.72 (95% CI 0.59–0.86)] and eGFR ≥ 60 mL/min/1.73 m² [HR 0.76 (95% CI 0.63–0.92)]. Importantly, there was no difference in the HR when comparing patients with type 2 diabetes at baseline [0.75 (95% CI 0.63–0.90)] and those without [0.73 (95% CI 0.60–0.88)], suggesting that the cardiovascular benefits of dapagliflozin are not dependent on the presence of type 2 diabetes.

ONGOING STUDIES OF SGLT2 INHIBITORS IN CKD

The ongoing Dapagliflozin and Prevention of Adverse outcomes in CKD (DAPA-CKD) study and The Study of Heart and Kidney Protection With Empagliflozin (EMPA-KIDNEY) explore the benefits of dapagliflozin and Empagliflozin, respectively, in patients with CKD both with and without a background history of diabetes. The DAPA-CKD study will recruit ~4000 patients with CKD [eGFR 25–75 mL/min/1.73 m² and a UACR 22.6–565 mg/mmol (200–5000 mg/g)] with and without a diagnosis of type 2 diabetes at baseline [22]. The EMPA-KIDNEY investigators plan to recruit 5000 patients with CKD [eGFR 20–45 mL/min/1.73 m² or eGFR 45–90 mL/min/1.73 m²

and a UACR > 22.6 mg/mmol (200 mg/g)] with and without diabetes (both types 1 and 2 diabetes) [23]. These ongoing trials should further advance our knowledge of the cardiovascular benefits of SGLT2 inhibitors in the clinical setting of CKD, both in the presence and absence of diabetes.

CONCLUSION

The available data from completed trials demonstrate that the SGLT2 inhibitors reduce the risk of cardiovascular events, particularly heart failure outcomes in patients with CKD with albuminuria and an eGFR between 30 and 60 mL/min/1.73 m² (Figure 1). In the context of heart failure, these benefits extend to CKD patients who do not have type 2 diabetes. Ongoing trials will further explore the cardiovascular benefits of these agents in patients with lower levels of eGFR and in those without diabetes. Assuming no unexpected safety signals emerge from these studies, it seems likely that SGLT2 inhibitors could become standard therapy along with angiotensin-converting enzyme inhibitors/angiotensin receptor blockers and statins to reduce cardiovascular risk in patients with CKD.

CONFLICT OF INTEREST STATEMENT

O.S. declares no conflicts of interest. N.S. has consulted for Amgen, Boehringer Ingelheim, Ely Lilly, Novo Nordisk, Napp, Pfizer and Sanofi and received grant support from Boehringer Ingelheim. D.C.W. has received consultancy fees from Amgen, AstraZeneca, Bayer, Boehringer Ingelheim, Merck Sharp and Dohme, Mundipharma, Napp, Reata and Vifor Fresenius.

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Received: 7.12.2019; Editorial decision: 10.12.2019