Systematic Review

The Effects of SGLT2 Inhibitors on Cardiovascular and Renal Outcomes in Diabetic Patients: A Systematic Review and Meta-Analysis

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Keywords

SGLT2i meta-analysis · Cardiovascular outcomes · Renal outcomes

Abstract

Background: Previous meta-analyses demonstrated the benefits of sodium-glucose cotransporter 2 inhibitors (SGLT2i) primarily on patients with established atherosclerotic cardiovascular disease (ASCVD), but with questionable efficacy on patients at risk of ASCVD. Additionally, evidence of beneficial cardiorenal outcomes in patients with estimated glomerular filtration rate (eGFR) <60 mL/min/1.73 m² with the CV outcomes trials remains unclear. Canagliflozin, one of the SGLT2i, has recently been studied in a large randomized controlled trial in diabetic patients with chronic kidney disease. Thus, there is a need to understand the combined outcomes on the population targeted for treatment with SGLT2i as a whole, regardless of ASCVD status. This meta-analysis will therefore assess the efficacy of SGLT2i in cardiovascular and renal outcomes in general, and in patients with eGFR under 60 mL/min/1.73 m² in particular. **Methods:** We searched PubMed and Cochrane databases for randomized, placebo-controlled studies involving SGLT2i. We examined composite cardiovascular outcomes of death from cardiovascular causes, nonfatal myocardial infarctions, nonfatal stroke, and heart failure hospitalizations. Renal composite outcomes and progression of albuminuria were also analyzed. Pooled relative risks (RR) and their 95% confidence intervals (CI) were calculated using a fixed-effects model. **Results:** The search yielded a total of 252 articles. Four studies were ultimately included in the meta-analysis after exclusion of other irrelevant studies. The

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pooled RR (95% CI) for the composite cardiovascular outcome was 0.93 (0.87–0.99) with a number needed to treat (NNT) of 167 in the general study population and 0.89 (0.77–1.02) in patients with eGFR <60 mL/min/1.73 m². The pooled RR for all-cause mortality was 0.9 (0.84–0.97) with NNT = 143. The pooled RR for death from cardiovascular causes alone was 0.89 (0.81–0.99) in the general population and 0.82 (0.62–1.07) in patients with eGFR <60 mL/min/1.73 m². The pooled RR for heart failure hospitalizations was 0.71 (0.63–0.79) with NNT = 91. With respect to renal outcomes, the pooled RR for the composite renal outcome was 0.63 (0.56–0.71) with NNT = 67; this was true even in patients with eGFR <60 mL/min/1.73 m² 0.67 (0.59–0.76). Lastly, the pooled RR for progression of albuminuria was 0.80 (0.76–0.84). **Conclusion:** SGLT2i are associated with significantly lower major adverse cardiovascular events, heart failure hospitalizations, and all-cause mortality. The evidence is strongest in reducing heart failure hospitalizations. However, the evidence is weaker when it comes to the population subset with eGFR <60 mL/min/1.73 m². SGLT2i are also associated with significantly lower adverse renal events, with these effects apparent even in the population with eGFR <60 mL/min/1.73 m².

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Introduction

Type 2 diabetes mellitus (T2DM) is a major risk factor for the development of cardiovascular (CV) and renal disease and is a key determinant of hospitalizations, morbidity, and mortality [1, 2]. Until recently, the pharmacotherapy of T2DM was characterized by limited direct beneficial CV or renal effects, with a range of deleterious side effects. These include proliferative retinopathy with insulin [3], edema, and heart failure hospitalizations (HHF) with thiazolidinediones [4] and hypoglycemia and CV disease-related deaths with sulfonylureas [5, 6]. In response, the 2008 United States Food and Drug Administration (FDA) anti-diabetic drug guidelines required CV outcomes trials (CVOTs) for novel antihyperglycemic medications to provide data on safety and ensure that new drugs for the treatment of T2DM would not increase the risk for myocardial infarction (MI), stroke, or CV death [7].

Sodium-glucose cotransporter 2 (SGLT2) inhibitors were developed for the management of T2DM through inhibition of proximal tubule reabsorption of the filtered glucose load [8]. In addition, SGLT2 inhibitors (SGLT2i) enhance natriuresis, cause intravascular volume contraction and alter intra-renal hemodynamics, which likely contribute to beneficial effects on blood pressure, body weight, and albuminuria [9]. These pleiotropic effects have translated into reductions in adverse CV and renal events in large CVOTs [10–13]. On this basis, the FDA has approved 4 SGLT2i for clinical use: canagliflozin (Invokana), dapagliflozin (Farxiga), empagliflozin (Jardiance), and ertugliflozin (Steglatro). A fifth combined SGLT1 and 2 inhibitor, sotagliflozin (Zynquista), is in clinical development.

Three SGLT2i (canagliflozin, empagliflozin, dapagliflozin) have been studied in large CVOTs [10–12]. More recently, canagliflozin has been studied in a large randomized controlled trial in diabetic patients with chronic kidney disease (CKD) [13]. Secondary analyses of renal outcomes in previous CVOTs also suggested improvement in renal outcomes with SGLT2i use [11, 12, 14]. A previous meta-analysis incorporating the three CVOTs found that SGLT2i significantly decreased the risk of major adverse CV events (MACE) in patients with established atherosclerotic CV disease (ASCVD) [15]. However, these results were not significant in subjects at risk for, but without established ASCVD [15]. In the Dapagliflozin and Cardiovascular Outcomes in Type 2 Diabetes (DECLARE-TIMI 58) trial, which included a significant number of subjects without established ASCVD, dapagliflozin did not show a significantly lower rate of MACE compared to placebo [12]. The Canagliflozin and Cardiovascular and

Renal Events in Type 2 Diabetes (CANVAS) trial also demonstrated no significant difference in MACE compared to placebo [11]. DECLARE-TIMI 58 and CANVAS had relatively low event rates compared to the Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes (EMPA-REG OUTCOME) trial, which may have led to the differences in the results reported between these trials [10–12]. The CVOTs also differed with respect to cut-off limits for inclusion by estimated glomerular filtration rate (eGFR), resulting in varying baseline eGFR and therefore divergent baseline ASCVD risk.

Current North American and European guidelines recommend SGLT2i as second-line therapy after metformin not only for patients with ASCVD, but also in those with heart failure (HF) and CKD [16, 17]. With the advent of new trial data [13], there is a need to look at the combined outcomes on the population targeted for treatment with SGLT2i as a whole, regardless of ASCVD status. In addition, the quality of evidence for cardiorenal beneficial outcomes in patients with eGFR <60 mL/min/1.73 m² is still unclear, and a large population sample analysis is needed to estimate the true benefit. This meta-analysis sought to assess the efficacy of SGLT2 inhibitors on CV and renal outcomes overall, and specifically in patients with eGFR under 60 mL/min/1.73 m².

Materials and Methods

Eligibility Criteria

We included all randomized, placebo-controlled studies involving SGLT2i. The trials had to study CV endpoints such as CV death and MACE. Other prospective and nonrandomized studies were all excluded.

Search Methods for Identification of Studies

We did not restrict the search by language, date, publication status, or any other trial characteristics. We searched the following electronic databases: Cochrane Central Register of Controlled Trials in the Cochrane Library and PubMed until July 6, 2019. References within the primary selected studies reviewed in full text were screened, but no gray literature was included/screened. The search strategy is found in the supplementary material in detail.

Selection of Studies

Two authors (K.B.L. and F.G.) independently screened each title and abstract. If necessary, the full text was also reviewed. All screened studies were assessed for inclusion in accordance with the eligibility criteria. Disagreements were resolved by consensus between the two screening authors, and a third author (P.R.) was consulted when agreement could not be met. Studies with inherent high risk of bias on review based on risk of bias criteria below were excluded. We used a modified Oxford Centre for Evidence-based Medicine's Levels of Evidence for quality rating of the studies included [18] (online suppl. Table 1; for all online suppl. material, see www.karger.com/doi/10.1159/000503919).

Data Abstraction

The authors (K.B.L., F.G. and A.Y.K.) independently abstracted study data including date of publication, study design, and number of samples. Inclusion/exclusion criteria as well as CV and renal outcomes were recorded. If any study data were not readily available from the published literature, efforts were made to contact the study investigators or sponsors to obtain the additional data where feasible.

Outcomes

We examined the composite CV outcome of death from CV causes, nonfatal MI and nonfatal stroke, as well as HHF. Renal composite outcomes varied by trial, but generally included doubling of serum creatinine or 40% reduction in eGFR, initiation of renal replacement therapy, or death due to renal disease. We also analyzed progression of albuminuria, defined as more than a 30% increase in albuminuria and a change from either normo-albuminuria to microalbuminuria or macroalbuminuria, or from microalbuminuria to macroalbuminuria. Pooled relative risks (RR) and their 95% confidence intervals (CI) were calculated using a fixed-effects model.

Risk of Bias

Two authors (K.B.L. and F.G.) independently assessed the risk of systematic errors (bias) in the included studies using the Cochrane Collaboration's risk-of-bias tool for randomized studies [19]. This tool checks random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other potential biases [19]. See online supplementary Figure 2 for the risk of bias summary. We were unable to perform a funnel plot to test for publication bias due to the small number of studies in our analysis.

Data Synthesis

We calculated pooled RR and 95% CI estimates using RevMan version 5.3 [20]. Studies were weighted according to their sample size to produce the final pooled odds ratios. We considered a *p* value less than 0.05 statistically significant.

Assessment of Heterogeneity

Heterogeneity was assessed using I^2 with low, moderate, and high levels of heterogeneity corresponding to I^2 values of 25, 50, and 75%, respectively [21].

Results

The final search yielded a total of 252 articles. After removal of duplicates, 225 were individually screened. A total of 17 studies were identified, but 13 were excluded due to their sub-analysis/post hoc analytic nature, with outcomes not included in our inclusion criteria. The final 4 studies were included in the meta-analysis. Online supplementary Figure 1 depicts the PRISMA diagram [22] and online supplementary Table 1 the summary of studies included in the meta-analysis. The study population covered in this meta-analysis are predominantly patients with type 2 diabetes with $\text{eGFR} \geq 30 \text{ mL/min/1.73 m}^2$, and either have established CV disease or had risk factors for CV disease. At least 40% of the study population had established CV disease in every study. The mean eGFR in the studies ranged from 56 to $85 \text{ mL/min/1.73 m}^2$. Close to 20% had $\text{eGFR} < 60 \text{ mL/min/1.73 m}^2$. This is the population where we did the predefined subgroup analysis of the outcomes.

All included studies had low risk of bias (online suppl. Fig. 2). The pooled RR (95% CI) for the composite CV outcome for the general study population was 0.93 (0.87–0.99), with heterogeneity of 56% and number needed to treat (NNT) of 167. The pooled RR for the composite CV outcome in patients with $\text{eGFR} < 60 \text{ mL/min/1.73 m}^2$ was 0.89 (0.77–1.02) with heterogeneity of 0% (Fig. 1, 2). The pooled RR for all-cause mortality was 0.9 (0.84–0.97) with heterogeneity of 79% (online suppl. Fig. 3) and $\text{NNT} = 143$. The pooled RR for death from CV causes alone was 0.89 (0.81–0.99) with heterogeneity of 82% and $\text{NNT} = 250$, while the pooled RR for death from CV causes alone in patients with $\text{eGFR} < 60 \text{ mL/min/1.73 m}^2$ was 0.82 (0.62–1.07) with heterogeneity of 0% $\text{NNT} = 65$ (online suppl. Fig. 4, 5). The pooled RR for HHF was 0.71 (0.63–0.79) with heterogeneity of 0% and $\text{NNT} = 91$ (online suppl. Fig. 6).

With respect to renal outcomes, the pooled RR for the composite renal outcome of doubling of serum creatinine or 40% decrease in eGFR , initiation of renal replacement therapy, or death due to renal disease was 0.63 (0.56–0.71), with heterogeneity of 41% and $\text{NNT} = 67$, while the pooled RR for the composite renal outcome in patients with $\text{eGFR} < 60 \text{ mL/min/1.73 m}^2$ was 0.67 (0.59–0.76) with 0% heterogeneity $\text{NNT} = 37$ (Fig. 3, 4). Lastly, the pooled RR for progression of albuminuria was 0.80 (0.76–0.84) with heterogeneity of 88% $\text{NNT} = 27$ (online suppl. Fig. 7).

Fig. 1. Forest plot for composite cardiovascular outcome in patients with type 2 diabetes with either established cardiovascular disease or cardiovascular risk factors.

Fig. 2. Forest plot for the composite cardiovascular outcome in patients with eGFR <60 mL/min/1.73 m² with type 2 diabetes with either established cardiovascular disease or cardiovascular risk factors.

Fig. 3. Forest plot for the composite renal outcome in patients with type 2 diabetes with either established cardiovascular disease or cardiovascular risk factors.

Fig. 4. Forest plot for the composite renal outcome in patients with eGFR <60 mL/min/1.73 m² with type 2 diabetes with either established cardiovascular disease or cardiovascular risk factors.

Discussion/Conclusion

To our knowledge, this is the first meta-analysis to summarize data from all four recent large randomized controlled trials involving SGLT2i, along with a sub-analysis in patients with eGFR <60 mL/min/1.73 m². The Empagliflozin and Progression of Kidney Disease in Type 2 Diabetes (EMPA-REG OUTCOME) and Canagliflozin and Cardiovascular and Renal Events in Type 2 Diabetes (CANVAS) trials demonstrated a reduction in MACE outcomes with the use of SGLT2i versus placebo (hazard ratio [HR] = 0.86, $p = 0.04$ and 0.86, $p = 0.08$, respectively) [10–11]. However, DECLARE-TIMI 58, the largest of the three CVOTs, found no significant difference in MACE reduction between the treatment and placebo groups (HR = 0.93, $p = 0.17$), leading to some uncertainty with regard to initially perceived CV benefit, especially in patients without established ASCVD [12]. Conversely, the Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation (CREDENCE) trial found a significant reduction in MACE (HR = 0.80, $p = 0.01$).

The inconsistent results with MACE can be attributed to the differences in baseline CV and renal risk due to varying inclusion criteria [23]. The mean baseline eGFRs were 85.2, 76.5, 74, and 56.2 mL/min and prior ASCVD rates were 40.6, 65.6, 99.2, and 50.4% for DECLARE, CANVAS, EMPA-REG, and CREDENCE, respectively. Thus, the DECLARE-TIMI 58 trial population was at significantly lower baseline cardiorenal risk; this may explain the fewer observed MACE outcomes in treatment and placebo arms. By including data from the recent CREDENCE trial and examining all patients treated with SGLT2i regardless of baseline ASCVD status, our meta-analysis found an overall significant reduction not only in MACE outcomes, but also in CV death, HHF, all-cause mortality, and progression of renal disease.

A previous meta-analysis by Zelniker et al. [15] found that patients using SGLT2i had an overall 11% RR reduction (RRR) of MACE outcomes. Those with established ASCVD were seen to have a 14% RRR, whereas no clinical benefit in MACE was seen in patients with multiple risk factors for ASCVD [15]. Despite this finding, there remains a role for SGLT2i in patients without ASCVD due to significant reductions in HHF and progression of kidney disease. After including data from the CREDENCE trial, our meta-analysis found an overall 7% RRR in MACE outcomes and 11% reduction in CV death alone. All-cause mortality was also found to be significantly lower with an RR of 0.9 ([0.84–0.97] $p = 0.006$) in our analysis of all four trials. The pooled outcome estimates of the outcomes in this meta-analysis were statistically significant but lower than prior estimates in subjects with established ASCVD. This was

expected, as we included all patients in the analysis regardless of baseline ASCVD status. We believe these pooled data accurately reflect the real-world experience regarding the use of SGLT2i, given that these agents are prescribed to patients both at risk for as well as those with established ASCVD, and across a spectrum of baseline eGFR values.

Although SGLT2i have modest HbA1c reduction, the observed effects likely stem from mechanisms independent of improved blood glycemic control. The EMPA-REG OUTCOME and CANVAS trials found that SGLT2i reduced progression of albuminuria [11, 14]. The mechanisms behind this observation are likely due to the effects of SGLT2i on tubule-glomerular feedback and the resultant decrease in intraglomerular pressure [24]. Microalbuminuria is a known risk factor for mortality and progression of CV and renal diseases [25–28], and reductions in proteinuria by SGLT2i may serve as a partial explanation of the observed clinical effects [24]. The osmotic and diuretic effects of SGLT2i further reduce effective plasma volume and systolic and diastolic pressures, improving cardiorenal hemodynamics [24] and potentially leading to better HF outcomes.

All four clinical trials found significant reductions in HHF in patients utilizing SGLT2i. Currently, HF is the leading cause of rehospitalization within 30 days in patients aged 64 years and older [29]; furthermore, patients admitted for HF are 23.2% more likely to be readmitted within 30 days [30]. Each potentially avoidable HF admission incurs an estimated cost of USD 14,631 resulting in significant economic burden [31]. Our analysis found a 29% RRR in HF admissions in patients utilizing SGLT2i with an NNT of just 91. Further potential economic benefit can be extended to renal outcomes as SGLT2i were effective in reducing the composite outcome of end-stage renal disease (ESRD) progression, serum creatinine doubling, and renal death by 37 and 35% in patients with eGFR >60 and <60 mL/min/1.73 m², respectively. ESRD patients account for 7% of the Medicare budget estimated at nearly USD 34 billion [32]. SGLT2i have significant potential in reducing not only morbidity and mortality caused by CV and renal disease, but also providing substantial economic benefit to the leading causes of US healthcare expenditure.

We found that SGLT2i reduced MACE outcomes by 11% in patients with eGFR <60 mL/min/1.73 m². This result was not statistically significant but showed trends towards significance, likely due to the analysis being potentially underpowered (HR = 0.89 [0.77–1.02] *p* = 0.09). Note that CREDENCE did not report on CV events specifically in the group of patients with eGFR <60 mL/min/1.73 m², so we were only able to analyze 725 events for this population subset. This is an important question to be pursued in future studies and trial designs as the CV effects of SGLT2i vary by renal function, with noted greater reductions in HHF in patients with more severe kidney disease at baseline [33]. One can also argue on the fact that the main mechanism of action for the SGLT2i is dependent on filtered glucose load which is in turn dependent on GFR [34]. Another mechanism is the induction of tubuloglomerular feedback potentially decreasing hyperfiltration and subsequent progression of kidney injury [34]. Thus in patients with CKD where there is a lower number of potential functioning nephrons with a lower GFR, there can be an expected lower drop in glucose levels and lower reduction in glomerular hyperfiltration potentially affecting efficacy in patients with CKD. However, SGLT2i are also associated with non-glucose-dependent beneficial effects such as blood pressure reduction, weight reduction, intrarenal and systemic hemodynamic effects, and potentially decreased inflammatory and fibrotic responses [34]. These potential alternative mechanisms seem to translate to better clinical outcomes in early studies in HF even in patients with low eGFRs as mentioned above [33]. Clearly there is more to these pleiotropic effects of SGLT2i that needs to be clearly elucidated in future animal models as well as in clinical trials.

Our analysis found significantly reduced adverse renal composite outcomes both in the general study population 0.63 (0.56–0.71) and in patients with eGFR <60 mL/min/1.73 m²

0.67 (0.59–0.76). Furthermore, we also found significantly reduced progression of albuminuria 0.80 (0.76–0.84), which is itself a known CV risk factor [35]. Clearly, there will be significant real-world overlap in the use of SGLT2i in patients with both CKD and those at risk of or with ASCVD to decrease adverse cardiorenal outcomes. It remains to be seen if decreased adverse renal outcomes in the subset of patients with moderate to severe CKD (eGFR <60 mL/min/1.63 m²) translate to subsequent decreased CV events, but the hypothesis appears plausible.

Limitations

This analysis was primarily limited by the differences in the design and inclusion criteria of the SGLT2i studies. There was significant heterogeneity in the analysis: up to 80–90% in all-cause mortality and CV death. Likely due to varying inclusion and exclusion criteria, the trials differed with respect to the baseline CVD risk and eGFR of their study populations, thus limiting the generalizability of these trial data to the real-world population. We also have to note that these were all large randomized controlled trials done in a strict controlled environment which may not necessarily reflect real-world conditions. Although there is an almost uniform use of angiotensin-converting enzyme inhibitors (ACEi) and angiotensin receptor blockers (ARBs) among the studies (80–100% rates of use), there is minimal evidence regarding the concomitant use of SGLT2i with other medications such as ACEi/ARBs and diuretics. Volume depletion and natriuresis from SGLT2i can stimulate the renin angiotensin aldosterone system in the early phase which is then potentially counteracted by ACEi/ARBs suggesting a potential synergistic response [36]. In relation to concomitant diuretic use as well as from other medications, the evidence is scarce, and trials are ongoing to look at its potential clinical impact such as the ongoing Renal and Cardiovascular Effects of sodium-glucose cotransporter 2 (SGLT2) inhibition in combination with loop Diuretics in diabetic patients with Chronic Heart Failure (RECEDE-CHF) trial [37]. SGLT2i use with other potential synergistic or even antagonistic medications might contribute to some of the variability in the studies.

The follow-up time for DECLARE-TIMI 58 was longer than that of the other studies, and thus may have created unknown differences in cardiorenal outcomes than if follow-up time was uniform across all four studies. Moreover, the definitions of the composite end points differed slightly among the trials. In addition, CREDENCE did not report composite CV outcomes in the subgroup of patients with eGFR <60 mL/min/1.73 m² with the total events analyzed in this eGFR subset amounting to only 725 events. However, the HR of the individual studies in this regard were strikingly similar. Although the total number of studies included was limited, a significant number of events (over 1,000) was available for analysis from the 4 large randomized trials for the other outcomes. There were not enough data on outcomes in patients with eGFR between 30 and 45 mL/min/1.73 m², and we could not study stroke or MI as individual outcomes because CREDENCE did not report them. African-American patients were underrepresented in all four trials (<10% of study populations), and effect estimates from this meta-analysis might not necessarily be applicable to that patient group.

Conclusion

Among patients with type 2 diabetes and established CV disease or at risk for CV disease, SGLT2i are associated with significantly lower MACE, HHF, and all-cause mortality. The evidence is strongest with regard to reducing HHF. The evidence is weaker when it comes to the population subset with eGFR <60 mL/min/1.73 m², though it exhibited trends towards significance. SGLT2i are also associated with significantly lower adverse renal events, with the effects apparent even in the population with eGFR <60 mL/min/1.73 m².

Statement of Ethics

Ethical approval was not required or obtained as the research study was a meta-analysis and no individual subjects were enrolled or studied.

Disclosure Statement

The authors have no conflicts of interest to declare.

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Author Contributions

Kevin B. Lo, MD, Fahad Gul, MD, Pradhun Ram, MD, Aaron Y. Kluger, MPH, Kristen M. Tecson, PhD, Peter A. McCullough, MD, MPH, and Janani Rangaswami, MD, were all involved in the initial study conceptualization and planning. Kevin Lo, Fahad Gul, Pradhun Ram, Aaron Kluger went through the studies and extracted the data. Kevin B. Lo, Aaron Kluger, Kristen M. Tecson were involved with the analysis of the data. All authors were involved with the writing of the preliminary, prefinal, and final versions of the manuscript. Dr. McCullough and Dr. Rangaswami also served supervisory roles which are not limited to writing and editing essential parts of the discussion, methodology, and revision of the figures.

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