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

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ABSTRACT

Aim

The use of sodium glucose co-transporter 2 (SGLT2) inhibitors in individuals with type 2 diabetes mellitus (T2DM) and chronic kidney disease (CKD) has been limited, primarily because glycemic efficacy is dependent on kidney function. We performed a systematic review and meta-analysis to assess the efficacy and safety of SGLT2 inhibitors in individuals with T2DM and CKD, defined as estimated glomerular filtration rate (eGFR) <60 mL/min/1.73m².

Materials and methods

We searched MEDLINE, EMBASE and the Cochrane Library to August 7, 2018, as well as the websites of the United States, European, and Japanese regulatory authorities to July 27, 2018 for data from randomized controlled trials of SGLT2 inhibitors that included reporting of effects on biomarkers, cardiovascular, renal, or safety outcomes in individuals with T2DM and CKD. Random effects models and inverse variance weighting were used to calculate relative risks with 95% confidence intervals.

Results

Data were obtained from 27 studies with up to 7,363 individuals contributing. In patients with T2DM and CKD, SGLT2 inhibitors lowered glycated hemoglobin (–0.29%, 95% CI –0.39 to –0.19), as well as blood pressure, body weight, and albuminuria. SGLT2 inhibition reduced the risk of cardiovascular death, nonfatal myocardial infarction or nonfatal stroke (RR 0.81, 95% CI 0.70-0.94) and heart failure (RR 0.61, 95% CI 0.48-0.78), with a borderline effect on all-cause mortality (HR 0.86, 95% CI 0.73-1.01). These agents also attenuated the annual decline in eGFR slope (placebo-subtracted difference of 1.35 mL/1.73m²/year, 95% CI 0.78-1.93) and reduced the risk of the composite renal outcome (HR 0.71, 95% CI 0.53-0.95).
There was no evidence of additional risks with SGLT2 inhibition in CKD beyond those already known for the class, although heterogeneity was observed across individual agents for some safety outcomes.

**Conclusion**

Despite modest reductions in glycated hemoglobin, SGLT2 inhibitors reduced the risk of cardiovascular and renal outcomes in individuals with T2DM and CKD, with no evidence of additional safety concerns. Current restrictions on the use of SGLT2 inhibitors in patients with CKD may warrant review, given the evidence for cardio-renal protection in this population.
INTRODUCTION

Sodium glucose co-transporter 2 (SGLT2) inhibitors are approved for use in type 2 diabetes mellitus (T2DM) and act by blocking glucose and sodium reuptake in the proximal renal tubule, thereby promoting glycosuria. In addition, SGLT2 inhibitors enhance natriuresis, cause intravascular volume contraction, and alter intra-renal hemodynamics, which likely contribute to beneficial effects on blood pressure, body weight, and albuminuria. These pleiotropic effects have translated into reductions in cardiovascular events and preservation of kidney function in large cardiovascular outcome trials, and as a consequence, this class of agent is now recommended as second line therapy after metformin for individuals with T2DM and established cardiovascular disease in the latest North American and European clinical practice guidelines.

Because of their renal-based mechanism of action, and the potential that the balance of benefits and risks may be different in people with chronic kidney disease (CKD), SGLT2 inhibitors are currently not approved for use in people with an estimated glomerular filtration rate (eGFR) of <45 mL/min/1.73m² for empagliflozin and canagliflozin, and <60 mL/min/1.73m² for dapagliflozin and ertugliflozin. The glucose lowering effect of SGLT2 inhibitors depends on glomerular filtration and is progressively attenuated as kidney function declines. In contrast, other non-glycemic effects such as reductions in blood pressure and albuminuria appear similar across different levels of kidney function, raising questions about the effects on cardiovascular, renal, and safety outcomes in people with reduced eGFR.
Approximately 40% of individuals with T2DM develop CKD during their lifetime,\textsuperscript{15,16} representing one of the highest risk groups for cardiovascular complications and progression to end-stage kidney disease.\textsuperscript{17} Because of this, it is important to understand whether the benefits of SGLT2 inhibition might extend to those with T2DM and CKD, and whether the risk of adverse events, in particular renal safety, are similar or different for individuals with CKD.

There have been two previous meta-analyses on the effects of SGLT2 inhibition in individuals with reduced kidney function. Both studies largely focused on intermediate markers of efficacy such as glycated hemoglobin (HbA1c), body weight, and albuminuria. These studies did not quantitatively synthesize the three large cardiovascular outcome trials published to date, nor did they report the effect of SGLT2 inhibitors on specific safety outcomes of interest, such as fractures, amputations, and diabetic ketoacidosis.

We therefore undertook a systematic review and meta-analysis of randomized controlled trials to better understand the role of this class of agent for cardio-renal protection in individuals with T2DM and CKD, defined as an eGFR <60 mL/min/1.73m\textsuperscript{2}.

**METHODS**

This study is a systematic review and meta-analysis assessing the class and individual drug effects of SGLT2 inhibitors versus placebo or active control in individuals with T2DM and CKD. It was conducted and reported in accordance with the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines.\textsuperscript{18}
Data sources and searches

We searched the following data sources up to August 7, 2018 to identify relevant randomized controlled trials: MEDLINE via Ovid (from Jan 1 1946), EMBASE (from Jan 1 1947), and the Cochrane Central Register of Controlled Trials (no date restriction). The text words and medical subject headings comprised terms relating to “sodium-glucose transporter 2”, “clinical trial”, and the individual drug names (Supplementary Table 1). The search was limited to data from randomized controlled trials but without language restriction. We also searched the websites of the United States (US) Food and Drugs Administration, European Medicines Agency, and the Japanese Pharmaceuticals and Medical Devices Agency up to July 27, 2018 to identify any relevant data from regulatory reports. Reference lists of identified trials, review articles, and reports were also hand searched to identify any additional data.

Two authors (BLN and TT) independently screened the titles and abstracts of all identified articles and reviewed all full texts of potentially relevant studies and reports for inclusion. Any uncertainty or disagreements were settled by consultation with a third author (VP).

Study selection

We included all studies or regulatory documents reporting individual randomized controlled trial data of any SGLT2 inhibitor versus placebo or active control in human adults with T2DM when studies reported data for participants with CKD, defined as eGFR <60 mL/min/1.73m². Individual trial data were supplemented or substituted outcome by outcome with information from pooled analyses when the pooled...
analyses provided a greater quantity of data and was clearly identified as not overlapping with another report. Duplicate reports and those not reporting outcomes of interest were excluded. We did not exclude studies based on length of follow-up. Where there were multiple reports of a single study, the report with longest follow-up was included, and if different reports of the same trial provided data for different outcomes then the complete non-overlapping data were extracted from each report. In cases where two or more studies provided data for a relevant outcome with similar numbers of participants, we included the study with the largest number of total patient-years.

**Data extraction and quality assessment**

Two authors independently extracted all data using a standardized electronic spreadsheet (BLN and TT). Attempts were made to contact individual study authors or study sponsors wherever possible with additional data used to supplement or substitute published reports, if these provided more comprehensive or complete data. Risk of bias was independently assessed by two authors (BLN and TT) using the Cochrane Risk of Bias Tool\(^1\) and assessed in the following domains: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome assessment, incomplete outcome data, and selective reporting. A third author adjudicated any discrepancies in the risk of bias assessment (MJ).

We extracted data for four broad sets of outcomes: (1) biomarkers, and (2) cardiovascular, (3) renal, and (4) safety outcomes. The biomarkers of interest were:
change from baseline in HbA1c, fasting glucose, systolic and diastolic blood pressure, body weight, albuminuria, and serum potassium. The main cardiovascular outcome was a composite of cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke. Other cardiovascular outcomes were cardiovascular death, fatal or nonfatal myocardial infarction, fatal or nonfatal stroke, as well as hospitalized or fatal heart failure. All-cause mortality was also reported. The renal outcomes of interest were: annual mean difference in kidney function between treatment and control (eGFR slope), and a composite of doubling of serum creatinine, end-stage kidney disease, or renal death. Because of the recognized non-linear association of eGFR effects and time resulting from the acute renal hemodynamic effect of SGLT2 inhibitors, we only included data that reported long-term eGFR slope after the first month of treatment (i.e. chronic eGFR slope). Safety outcomes of interest were: urinary tract infection, genital infection, hypovolemia, hypoglycemia, amputation, bone fracture, ketoacidosis, renal related adverse events, acute kidney injury, and hyperkalemia. The definition of many of these safety outcomes, particularly hypovolemia and renal related adverse events, was dependent on the reports and therefore difficult to establish, so that direct comparability of definitions for most safety outcomes could not be assured.

Data synthesis and analysis

Analyses were done by individual SGLT2 inhibitor and for all agents collectively, versus active or placebo control. If outcome data were available for different eGFR categories (e.g. <45 mL/min/1.73m² and 45-60 mL/min/1.73m²) but not eGFR <60 mL/min/1.73m², then the eGFR subgroups were merged using the methods described below to obtain a best estimate for the eGFR <60 mL/min/1.73m² group.
To synthesize the effect of SGLT2 inhibitors on biomarkers, we calculated the differences in treatment effect and standard error from data provided in each study pooled by the generic inverse variance method with a random-effects model. We calculated the effects of treatment on continuous biomarker outcomes as the mean difference and standard error from baseline across the entire follow-up period, or to end of follow-up, as reported in each individual study. The exception was for albuminuria, reported as urinary albumin:creatinine ratio (UACR), where we separately calculated both (1) the percentage change in the geometric mean of treatment versus control and (2) the absolute change in albuminuria depending on how UACR was reported in each individual study. We were primarily interested in the former, because of the substantial impact of baseline values on subsequent albuminuria reduction and the highly skewed distribution of this variable in most studies. In studies with more than two intervention arms (e.g. different SGLT2 inhibitor doses), the effects on the continuous outcome for the different doses were combined by weighting with sample size, to obtain a mean overall difference for SGLT2 inhibitor versus placebo. Where data were presented in figures in the absence of numerical values, image extraction software was used to extract the required data points (WebPlotDigitizer version 4.1, Ankit Rohatgi, Austin, TX, https://automeris.io/WebPlotDigitizer/).

For cardiovascular, renal, and safety outcomes, we sought, in order of preference, to use hazard ratios and 95% confidence intervals, or the incidence rate ratio and 95% confidence interval (based upon events/participant years), or the risk ratio (based upon events/participant numbers). This approach was used to optimize our ability to accurately detect treatment effects of SGLT2 inhibitors, particularly for canagliflozin,
where the integrated analysis and reporting of two parallel companion trials, CANVAS and CANVAS-R, with different lengths of follow-up precluded use of risk ratios (Ref CANVAS Program design paper). If required, hazard ratio estimates combining two or more subgroups (e.g. male and female genital infections) were merged using the fixed effects model. When calculating risk ratios in studies comparing different SGLT2 inhibitor doses, the number of events and participants were combined across active treatment arms and compared to control to obtain an estimate for SGLT2 inhibitor versus placebo or active control. The same was done when data were provided for eGFR subgroups but not individuals with CKD overall. Wherever possible, trial level data were used. To ensure maximum use of available data, when an outcome was reported in both individual trials and pooled analyses we included summary estimates and uncertainty intervals only when these included more data than could be obtained from individual trials, as long as there was no overlap in included participants. As was the case with continuous outcomes, image extraction software was used to retrieve data presented in figures without corresponding numerical data.

Summary estimates of relative risk ratios were obtained using a random effects model. The percentage of variability across pooled estimates attributable to heterogeneity beyond chance was estimated using the $I^2$ statistic and also by calculating the $P$ value for heterogeneity. An $I^2$ statistic of 0–25% was considered to reflect a low likelihood, 26–75% a moderate likelihood, and 76–100% a high likelihood of differences beyond chance. A $P$ value for heterogeneity of <0.05 was also considered likely to reflect a high likelihood of differences beyond chance. Statistical analyses were performed using R Version 3.4.4 (R Foundation for Statistical Computing, Vienna, Austria) with
the package 'meta' Version 4.9-1 as a statistical software.

**Role of the funding source**

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. BN, TT, and VP had full access to all the data in the study. The corresponding author had final responsibility for the decision to submit for publication.

**RESULTS**

The literature search yielded 2557 articles of which 734 were reviewed in full text (Figure 1). One large cardiovascular outcome trial for dapagliflozin was identified after the systematic literature search. In total, 27 studies contributed data on biomarkers, cardiovascular, renal, or safety outcomes, with substantial contributions from three large cardiovascular outcome trials of empagliflozin, canagliflozin and dapagliflozin. Of the 27 studies, 18 were individual trials, 8 were pooled analyses, and one was a regulatory report for ertugliflozin (Figure 1 and Supplementary Table 2). The 8 pooled analyses combined data from 41 individual trials where results were not available for the CKD population. Thus, in total, data from 59 trials contributed data to the meta-analysis: 18 studies where individual trial data were available for the CKD population, as well as 41 trials which were included through the 8 pooled analyses and one regulatory report (Supplementary Table 3).

Of the 59 trials that contributed data to this analysis, 19 assessed the effects of empagliflozin, 19 assessed dapagliflozin, 7 assessed ertugliflozin, 6 assessed ipragliflozin, and 5 assessed canagliflozin, while luseogliflozin, sotagliflozin and
ofogliflozin were assessed in one trial each. The CANagliflozin cardioVascular Assessment Study (CANVAS) Program, which comprised two parallel trials with identical inclusion criteria, was considered as one study. There were data available on up to 6,589 individuals for analyses of biomarkers, 6,376 for analyses of cardiovascular outcomes, 7,363 for analyses of all-cause mortality, 5,863 for analyses of renal outcomes, and 6,160 for analyses of safety outcomes. SGLT2 inhibitors were compared against placebo in all cases, with the exception of one regulatory report for ertugliflozin, which pooled data on all-cause mortality across 7 trials (n=566), two of which were against active control. Study duration ranged from 7 days to a median of 4.2 years, with mean participant age between 63.5 and 68.5 years. Mean eGFR ranged from 38.0 to 53.5 mL/min/1.73m² (Supplementary Table 2). The median and mean UACR ranged from 12.8 to 76.0 mg/g and 209.8 to 567.9 mg/g respectively. The risk of bias was generally low overall; most trials described adequate random sequence generation and in all studies blinding of participants and personnel occurred along with low risk of selective reporting (Supplementary Figure 1). Funnel plots and Begg’s tests for the main composite outcome of cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke, as well as all-cause mortality are displayed in Supplementary Figure 2. The relatively small number of studies for these outcomes limited the assessment of publication bias. Results for effects on biomarkers, cardiovascular, renal, and safety outcomes by individual study are also presented in the supplementary appendix (Supplementary Figures 3–7).

Biomarker outcomes
Data on a range of biomarkers were available for up to 7 SGLT2 inhibitors across 4 to 14 studies. Overall, SGLT2 inhibitors reduced HbA1c, fasting glucose, systolic and
diastolic blood pressure, and body weight, with no significant effect on serum potassium (Figure 1). These agents also reduced albuminuria, whether reported as percentage or absolute change (Figure 1 and Supplementary Figure 4, respectively). There was significant evidence of heterogeneity across SGLT2 inhibitors for the effect on HbA1c ($I^2=65\%$, $P$-heterogeneity <0.01), moderate evidence of heterogeneity for fasting glucose ($I^2=52\%$, $P=0.05$) but no evidence of heterogeneity of effects for the other biomarkers (all $I^2\leq 12\%$, all $P\geq 0.34$; Figure 2). The difference in the effect on HbA1c across individual agents was substantively attenuated by excluding the tofogliflozin study ($I^2=39\%$, $P=0.15$), in which a particularly large reduction in HbA1c was observed. The effect of SGLT2 inhibitors on HbA1c was consistent in analyses stratified by the duration of follow up ($\geq 26$ weeks vs. <26 weeks, and $\geq 24$ weeks vs. <24 weeks; $P=0.50$ and 0.13, respectively).

Cardiovascular outcomes

Data on the main cardiovascular composite outcome of cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke were available for canagliflozin, dapagliflozin and empagliflozin with 756 events recorded across 7 trials. For the analyses of other cardiovascular outcomes, there were 352 cardiovascular deaths, 335 fatal or nonfatal myocardial infarctions, 200 fatal or nonfatal strokes, 279 hospitalized or fatal heart failure events, and 593 all-cause deaths. Cardiovascular outcome data were available for the same 3 SGLT2 inhibitors, except for stroke and all-cause mortality where limited additional data was available for ertugliflozin, ipragliflozin and luseogliflozin. For all outcomes, effect estimates were dominated by three large trial reports for empagliflozin, canagliflozin, and dapagliflozin.$^{3,4}$
Overall, SGLT2 inhibitors reduced the risk of the composite cardiovascular outcome (RR 0.81, 95% CI 0.70-0.94), hospitalized or fatal heart failure (RR 0.61, 95% CI 0.48-0.78), and myocardial infarction (RR 0.77, 95% CI 0.60-0.99), with no clear effect on stroke or cardiovascular death (Figure 3). The point estimate favored SGLT2 inhibitors for all-cause mortality (RR 0.86, 95% CI 0.73-1.01) but the effect did not reach statistical significance. There was a low likelihood of difference in effect between individual agents for most cardiovascular outcomes (Figure 3), aside from stroke, where there was a moderate likelihood of difference between the individual agents ($I^2=51\%, P=0.11$; Figure 3).

We conducted sensitivity analyses comparing data from the three cardiovascular outcome trials vs. other SGLT2 inhibitor trials. There was no clear evidence of heterogeneity between the two trial categories for any of the cardiovascular outcomes (all $I^2<50\%$ and $P>0.15$). The exclusion of non-cardiovascular outcome trial data did not materially change overall effect estimates for most cardiovascular outcomes. For myocardial infarction, the treatment effect became non-significant when analyzing data from only the three cardiovascular outcome trials (RR 0.81, 95% CI 0.62-1.07).

Renal outcomes

Based on two trials, SGLT2 inhibitors slowed the annual decline in eGFR slope with a difference between treatment and control of 1.35 mL/min/1.73m² per year (95% CI 0.78-1.93; Figure 4) and a moderate likelihood of differences beyond chance between canagliflozin and empagliflozin ($I^2=62\%, P=0.11$). SGLT2 inhibitors also reduced the risk of the composite renal outcome of doubling of serum creatinine, end-stage kidney disease, or renal death (RR 0.71, 95% CI 0.53-0.95; Figure 4), with no evidence of
heterogeneity by individual agents ($I^2=0\%, \ P=0.93$). We conducted a sensitivity analysis excluding the DECLARE-TIMI 58 trial, which used 40% decline in eGFR in place of doubling of serum creatinine as a component of the composite outcome. Following this, the treatment effect became non-significant (RR 0.77, 95% CI 0.54-1.07).

Safety outcomes

The risks of adverse outcomes with SGLT2 inhibitors are displayed in Figure 5. There was an overall increased risk of genital infections with SGLT2 inhibition (RR 2.86, 95% CI 2.00-4.10). While there was no overall increased risk of other safety outcomes, including for amputations and fractures, there was at least a moderate likelihood of differences between agents arising beyond chance for a number of outcomes, including hypoglycemia, hypovolemia, and amputation (all $I^2\geq57\%$, all $P\leq0.04$). In each case, empagliflozin was associated with a lesser risk compared to the other agents (Figure 5). SGLT2 inhibitors did not increase the risk of renal related adverse events, acute kidney injury, or hyperkalemia (Figure 4).

DISCUSSION

The available data suggest that SGLT2 inhibitors reduce the risk of cardiovascular outcomes and heart failure events in individuals with T2DM and CKD. The data also suggest that SGLT2 inhibitors might have broader benefits on a range of other cardiovascular outcomes as well as all-cause mortality. While data for renal outcomes was perhaps less robust, there was evidence that SGLT2 inhibitors slow the annual loss in kidney function, as measured by eGFR slope, and might also reduce the risk of the renal composite outcome. The absence of any additional safety concerns when
used in individuals with CKD is also reassuring. Taken together, these data suggest that SGLT2 inhibitors are likely to have an important role in the prevention of cardiovascular and renal complications amongst individuals with T2DM and CKD.

This class of agent exerts multiple beneficial metabolic effects (lowering HbA1c, blood pressure and body weight) that might contribute to cardiovascular risk reduction. However, the reduction in HbA1c for individuals with CKD was modest in comparison to that previously reported for the general T2DM population.\textsuperscript{3,4,83} This was consistent with the known mechanism of action of these agents, for which glycemic efficacy is proportional to filtered glucose load.\textsuperscript{1} The observed heterogeneity of the effect on HbA1c across SGLT2 inhibitors may be related to differences in mean baseline HbA1c or kidney function across contributing trials. Nevertheless, given only small improvements in HbA1c and the inconsistent evidence for glucose lowering in the prevention of macrovascular complications in T2DM,\textsuperscript{84,85} these results suggest that improved glycemic control is not driving the observed reduction in cardiovascular events in this population.

Augmented natriuresis and intravascular volume contraction, the putative mechanisms for blood pressure lowering with this class of agents,\textsuperscript{1} would also be anticipated to be attenuated in CKD but there is no corresponding attenuation of the antihypertensive effect. It might be that individuals with CKD are more sensitive to small changes in renal salt handling and changes in intravascular volume,\textsuperscript{86,87} or that hemodynamic effects may be enhanced by concurrent use of diuretic therapies,\textsuperscript{88} which were more prevalent in individuals with CKD in two large contributing trials.\textsuperscript{14,89} Regardless of the explanation, the preserved effects on natriuresis and blood pressure implicate
sodium retention and intravascular volume expansion as a key pathway to cardiovascular complications, especially heart failure. The resulting reductions in cardiac preload and afterload with SGLT2 inhibitors are likely to be particularly beneficial in diabetic kidney disease, which is characterized by glomerular and systemic hemodynamic dysregulation that in turn contributes to higher rates of subclinical or overt cardiac dysfunction in this population. Other direct cellular and metabolic effects might also play a role; SGLT2 inhibitors shift metabolism from carbohydrates towards lipolysis, thus promoting mild ketogenesis, which may provide an alternative energy substrate to myocardial cells in the setting of ischemic stress.

A key physiological concept underpinning the renoprotective effect of this class of agents is that they alter glomerular hemodynamics and reduce hyperfiltration, a critical process in the pathogenesis of diabetic kidney disease. This is supported by head-to-head studies with other glucose lowering agents that show SGLT2 inhibitors preserve kidney function, independent of glycemic control. SGLT2 inhibition in the proximal tubule increases distal sodium delivery, which in turn stimulates tubuloglomerular feedback to promote afferent arteriolar vasoconstriction and thus reduce intraglomerular pressure. Clinically, this is reflected in an acute decrease in eGFR, similar to that observed with renin-angiotensin system blockade. These results highlight the importance of perturbations in glomerular hemodynamics in the development of renal (and cardiovascular) complications in diabetes, while also suggesting that effect of these agents in reducing hyperfiltration (as measured by reductions in albuminuria and slower annual loss of kidney function) are maintained in individuals with CKD. The evidence for renoprotection in patients with CKD in this analysis is perhaps less robust than for cardiovascular outcomes, as the effect on
the renal composite outcome was not consistent in sensitivity analysis excluding the DECLARE TIMI 58 trial. Nevertheless, the Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation (CREDENCE) trial will provide definitive information on the effects of SGLT2 inhibition on renal outcomes in people with CKD in 4401 participants with stage 2 or 3 CKD and macroalbuminuria, approximately 60% of whom have an eGFR <60 mL/min/1.73m². The trial has been terminated early based on advice from the Data Monitoring Committee that pre-specified efficacy criteria had been achieved at a scheduled interim analysis.

Given what is known about the safety profile of this class of agents, the results of this meta-analysis suggest the risks of harms in CKD are no different to the general T2DM population, with no additional concerns regarding renal safety. SGLT2 inhibitors increase the risk of genital infections but not urinary tract infections. The risk of several safety outcomes, including hypovolemia, hypoglycemia, and – most importantly – amputations, appeared more favorable with empagliflozin compared to the other SGLT2 inhibitors. The reasons for the observed heterogeneity across individual agents for these outcomes were not entirely clear. While there was no increased risk of fracture for any one agent or overall, the CANVAS Program demonstrated an increased risk with canagliflozin in the overall trial population. Given this effect was not modified by baseline kidney function, our analysis is likely to be underpowered and cannot definitively exclude a risk of fracture with canagliflozin in CKD. Diabetic ketoacidosis, a rare but potentially life threatening adverse effect of this class of agent, occurred very infrequently and a robust assessment of this risk in this population was not possible.
This study benefits from the robust, systematic methodology that was used, providing a comprehensive assessment of the effects of SGLT2 inhibition on a wide range of biomarkers, cardiovascular, renal, and safety outcomes in individuals with T2DM and CKD. In particular, the inclusion of continuous outcome data in the form of eGFR slope provided additional power to explore the renoprotective effect of these agents in CKD. The main limitation of this review relates to the relative paucity of data on safety outcomes for agents other than canagliflozin and empagliflozin. We combined different SGLT2 inhibitor doses (e.g. dapagliflozin 5 and 10mg), merged trials with varying lengths of follow up, and used data from pooled analyses rather than individual trials if needed to ensure the most comprehensive assessment of published data. It was difficult to fully account for variations in duration of follow up across individual studies because of the use of pooled data, but sensitivity analyses suggested that differences in trial length did not substantially affect our results. Even with the use of pooled data, there were relatively few events for some less common safety outcomes. As a consequence it is likely that this analysis was underpowered to detect harms, and these results should be interpreted cautiously in the context of results from the cardiovascular outcome trials in the broader T2DM population. Urinary albumin excretion is another important manifestation of CKD, but whether the effects of SGLT2 inhibition vary across different levels of albuminuria also remains to be determined.

Dedicated trials of SGLT2 inhibitors in individuals with CKD are expected to resolve these issues by providing definitive information about effects on cardiovascular, renal, and safety outcomes for this high-risk population. In addition to the CREDENCE trial,
there are CKD outcome trials underway for dapagliflozin (DAPA-CKD), empagliflozin (EMPA-KIDNEY), and sotogliflozin (SCORED). Because of the unique renal hemodynamic effects of this class of agents, both DAPA-CKD and EMPA-KIDNEY plan to recruit participants with and without diabetes and will provide important data on potential renal benefits in both populations.

In conclusion, SGLT2 inhibitors reduced the risk of cardiovascular and renal outcomes in individuals with T2DM and CKD, with no strong evidence of safety concerns beyond their known risk profile. Taken together, this comprehensive analysis of all currently available data suggests that eGFR-based restrictions on the use of SGLT2 inhibitors in individuals with T2DM and CKD may warrant review, given the evidence for cardio-renal protection in this population.

**Contributors**

BLN, TT, TN, MJ, MJJ, and VP contributed to the design of the study. TT and BN performed the literature search and screening for eligible studies. BLN, TT, TO, and HJH extracted the data. TT created the figures and tables. All authors contributed to the interpretation and presentation of the data. BN, TT, and VP wrote the first draft of the manuscript and all authors contributed to subsequent drafts and approved the final version for submission. BLN, TT, and VP had full access to all the data in the study and take responsibility for the integrity of the data and accuracy of the data analysis. TT and BLN contributed equally to the manuscript.

**Declaration of interests**
BLN has received travel support from Janssen and is funded by a John Chalmers PhD Scholarship from The George Institute for Global Health and a University Postgraduate Award from UNSW Sydney. TO is supported by a John Chalmers Postdoctoral Fellowship from The George Institute for Global Health. MJ supported by a Scientia Fellowship from UNSW Sydney, Australia. MJJ is supported by a Medical Research Future Fund Next Generation Clinical Researchers Program Career Development Fellowship, is responsible for research projects that have received unrestricted funding from Gambro, Baxter, CSL, Amgen, Eli Lilly, and Merck, has served on advisory boards sponsored by Akebia, Baxter and Boehringer Ingelheim, spoken at scientific meetings sponsored by Janssen, Amgen and Roche; with any consultancy, honoraria or travel support paid to her institution. MGW has received honorarium for scientific lectures from AstraZeneca, Amgen and Baxter, and is supported by Diabetes Australia Research Trust Millennium Grant. BN reports receiving research support from the Australian National Health and Medical Research Council Principal Research Fellowship and from Janssen, Roche, Servier, and Merck Schering Plough; and serving on advisory boards and/or involvement in CME programs for Abbott, Janssen, Novartis, Pfizer, Roche, and Servier, with any consultancy, honoraria, or travel support paid to his institution. H.J.L.H. has served as a consultant for Abbvie Astellas, AstraZeneca, Boehringer Ingelheim, Fresenius, Janssen, and Merck and has received grant support from AstraZeneca and Boehringer Ingelheim; he has a policy that all honoraria are paid to his institution. TW is a national lead investigator on a renal outcome study of a sodium-glucose cotransporter-2 (SGLT2) inhibitor (canagliflozin). V.P. reports receiving research support from the Australian National Health and Medical Research Council (Senior Research Fellowship and Program Grant); serving on Steering Committees for
AbbVie, Boehringer Ingelheim, GlaxoSmithKline, Janssen and Pfizer; and serving on advisory boards and/or speaking at scientific meetings for AbbVie, Astellas, AstraZeneca, Bayer, Baxter, Bristol-Myers Squibb, Boehringer Ingelheim, Durect, Eli Lilly, Gilead, GlaxoSmithKline, Janssen, Merck, Novartis, Novo Nordisk, Pfizer, Pharmalink, Relypsa, Roche, Sanofi, Servier and Vitae with all honoraria paid to his employer. MJJ, HLH, and BN and VP are members of the steering committee of a renal outcome study of a sodium-glucose cotransporter-2 (SGLT2) inhibitor (canagliflozin), with VP serving as chair of the steering committee. The George Institute for Global Health (which funds BLN and TO) provides contract research services to Janssen for trials of SGLT2 inhibitors. Other authors report no declarations of interest.

Acknowledgements

This work was not specifically funded but it was supported in part by programme grant funding provided by the National Health and Medical Research Council of Australia.
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FIGURE LEGEND

Figure 1. Identification of eligible studies

Figure 2. Effects of SGLT2 inhibitors on biomarkers in individuals with type 2 diabetes and chronic kidney disease (estimated glomerular filtration rate <60 mL/min/1.73m²).

Abbreviations: HbA1c, glycated haemoglobin; CI, confidence interval.

Figure 3. Effects of SGLT2 inhibitors on cardiovascular outcomes and all-cause mortality in individuals with type 2 diabetes and chronic kidney disease (estimated glomerular filtration rate <60 mL/min/1.73m²).

Abbreviations: n, number of cases with events; N, group size; HR, hazard ratio; RR, risk ratio; CI, confidence interval; NA, not available.

Figure 4. Effects of SGLT2 inhibitors on cardiovascular and renal outcomes in individuals with type 2 diabetes and chronic kidney disease (estimated glomerular filtration rate <60 mL/min/1.73m²).

Abbreviations: n, number of cases with events; N, group size; HR, hazard ratio; RR, risk ratio; CI, confidence interval; ESKD, end-stage kidney disease.

† Week 6 (CANVAS) or 13 (CANVAS-R) to last available measurement was used.
‡ Week 4 to the last value on treatment was used.
§ ESKD and renal death were only reported in CANVAS Program and EMPA-REG OUTCOME.
Figure 5. Effects of SGLT2 inhibitors on safety outcomes in individuals with type 2 diabetes and chronic kidney disease (estimated glomerular filtration rate <60 mL/min/1.73m²).

Abbreviations: n, number of cases with events; N, group size; HR, hazard ratio; RR, risk ratio; NA, not available.