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ORIGINAL ARTICLE

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

Materials and methods: We searched MEDLINE, EMBASE and the Cochrane Library until 7 August 2018 and websites of the US, European and Japanese regulatory authorities until 27 July 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 7363 participants involved. In patients with T2DM and CKD, SGLT2 inhibitors lowered glycated haemoglobin (−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), without a clear 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/1.73 m^2/y; 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: Currently available data suggest that, despite only modest reductions in glycated haemoglobin, SGLT2 inhibitors reduce the risk of cardiovascular and renal outcomes in patients with T2DM and CKD, without clear evidence of additional safety concerns.

KEYWORDS

chronic kidney disease, clinical outcomes, meta-analysis, SGLT2 inhibitors, systematic review, type 2 diabetes

*Tadashi Toyama and Brendon L. Neuen contributed equally to this study.

1 | 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 re-uptake in the proximal renal tubule, thereby promoting glycosuria.[1] In addition, SGLT2 inhibitors enhance natriuresis, cause intravascular volume contraction and alter intra-renal haemodynamics, which probably contribute to beneficial effects on blood pressure, body weight and albuminuria.[1] These pleiotropic effects have translated into reductions in cardiovascular events and preservation of kidney function in large cardiovascular outcome trials[2–6] 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.[7–10]

Because of their renal-based mechanism of action, and the potential that the balance of benefits and risks may differ among individuals with chronic kidney disease (CKD), SGLT2 inhibitors are currently not approved for use in individuals with an estimated glomerular filtration rate (eGFR) <45 mL/min/1.73 m^2 for empagliflozin and canagliflozin, and <60 mL/min/1.73 m^2 for dapagliflozin and ertugliflozin.[11,12] The glucose-lowering effect of SGLT2 inhibitors depends on glomerular filtration and is progressively attenuated as kidney function declines.[13,14] In contrast, other non-glycaemic effects, such as reductions in blood pressure and albuminuria, appear similar across different levels of kidney function,[13–15] raising questions about the effects on cardiovascular, renal and safety outcomes in indviduals with reduced eGFR.

Approximately 40% of individuals with T2DM develop CKD during their lifetime,[16,17] representing one of the highest risk groups for cardiovascular complications and progression to end-stage kidney disease.[18] 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.

Previous meta-analyses have assessed the effects of SGLT2 inhibition in individuals with reduced kidney function.[19–21] These studies largely focused on intermediate markers of efficacy such as glycated haemoglobin (HbA1c), body weight and albuminuria, and most did not quantitatively synthesize the three large cardiovascular outcome trials published to date. In addition, these studies did not report on specific safety outcomes of interest in patients with CKD, 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 eGFR <60 mL/min/1.73 m^2.

2 | METHODS

This study is a systematic review and meta-analysis assessing the class and individual drug effects of SGLT2 inhibitors as compared to 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.[22]

2.1 | Data sources and searches

We searched the following data sources until 7 August 2018 to identify relevant randomized controlled trials: MEDLINE via Ovid (from 1 January 1946), EMBASE (from 1 January 1947) and the Cochrane Central Register of Controlled Trials (without date restriction). The text words and medical subject headings comprised terms relating to "sodium-glucose transporter 2," "clinical trial" and the individual drug names (Supporting Information Table S1). The search was limited to data from randomized controlled trials, without language restriction. We also searched websites of the US Food and Drug Administration, the European Medicines Agency and the Japanese Pharmaceuticals and Medical Devices Agency until 27 July 2018 to identify 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 (B. L. N. and T. T.) 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 (V. P.).

2.2 | Study selection

We included all studies or regulatory documents that reported individual randomized controlled trial data on any SGLT2 inhibitor vs placebo or active control in adult humans with T2DM when studies reported data for participants with CKD, defined as eGFR <60 mL/min/1.73 m^2. Individual trial data were supplemented or substituted, outcome by outcome, with information from pooled analyses when the pooled analyses provided more data and were 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 the longest follow-up period was included, and if different reports of the same trial provided data for different outcomes, 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.

2.3 | Data extraction and quality assessment

Two authors (B. L. N. and T. T.) independently extracted all data using a standardized electronic spreadsheet. Attempts were made to contact individual study authors or study sponsors wherever possible for additional data, to supplement or substitute for published reports if responses to these contacts provided more comprehensive or complete data.

Risk of bias was independently assessed by two authors (B. L. N. and T. T.) using the Cochrane Risk of Bias Tool[23] and was 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 (M. J.) adjudicated any discrepancies in the risk of bias assessment.

Data were extracted for four broad sets of outcomes: biomarkers and cardiovascular, renal and 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 hospitalised or fatal heart failure. All-cause mortality was also reported. 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. If studies reported 40% decline in eGFR instead of doubling of serum creatinine as a component of the renal composite outcome, this outcome was included in the main analysis but excluded in sensitivity analyses. Because of the recognized non-linear association of eGFR effects and time resulting from the acute renal haemodynamic effect of SGLT2 inhibitors, only data that reported long-term eGFR slope after the first month of treatment, that is, chronic eGFR slope, were included. Safety outcomes of interest were: urinary tract infection, genital infection, hypovolaemia, hypoglycaemia, amputation, bone fracture, ketoacidosis, renal-related adverse events, acute kidney injury and hyperkalaemia. The definition of many of these safety outcomes, particularly hypovolaemia and renal-related adverse events, was dependent on the reports and, therefore, was difficult to establish; thus, direct comparability of definitions for most safety outcomes could not be assured.

2.4 | Data synthesis and analysis

Analyses were done by individual SGLT2 inhibitor and for all agents collectively, vs active or placebo control. If outcome data were available for different eGFR categories (eg, <45 mL/min/1.73 m^2 and 45-60 mL/min/1.73 m^2) but not eGFR <60 mL/min/1.73 m^2, the eGFR subgroups were merged using the methods described below to obtain a best estimate for the eGFR <60 mL/min/1.73 m^2 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 the ratio of the geometric mean of post-randomization UACR measures with treatment vs control and the absolute change in albuminuria depending on the way 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 (eg, 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 vs 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, Texas; https://automeris.io/WebPlotDigitizer/).

For cardiovascular, renal and safety outcomes, we sought to use, in order of preference, 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.[24] If required, hazard ratio estimates combining two or more subgroups (eg, 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 vs placebo or active control. The same was done when data were provided for eGFR subgroups but not for 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, ensuring 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.

Risk ratios expressed as relative risks (RR), which were obtained using a random effects model, were used as the summary measure of association across studies. As the outcomes evaluated could be considered rare outcomes, reported hazards, rate and risk ratios were assumed to approximate the same measure of relative risk following Cornfield's rare disease outcome assumption.[25] 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. I^2 statistics of 0-25%, 26-75%, and 76-100% were considered to reflect a low, moderate, and high likelihood of differences beyond chance, respectively. A *P* value for heterogeneity of <0.05 was also considered to probably 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.

3 | RESULTS

The literature search yielded 2557 articles, of which 734 were reviewed in full text (Figure 1). One large cardiovascular outcome trial

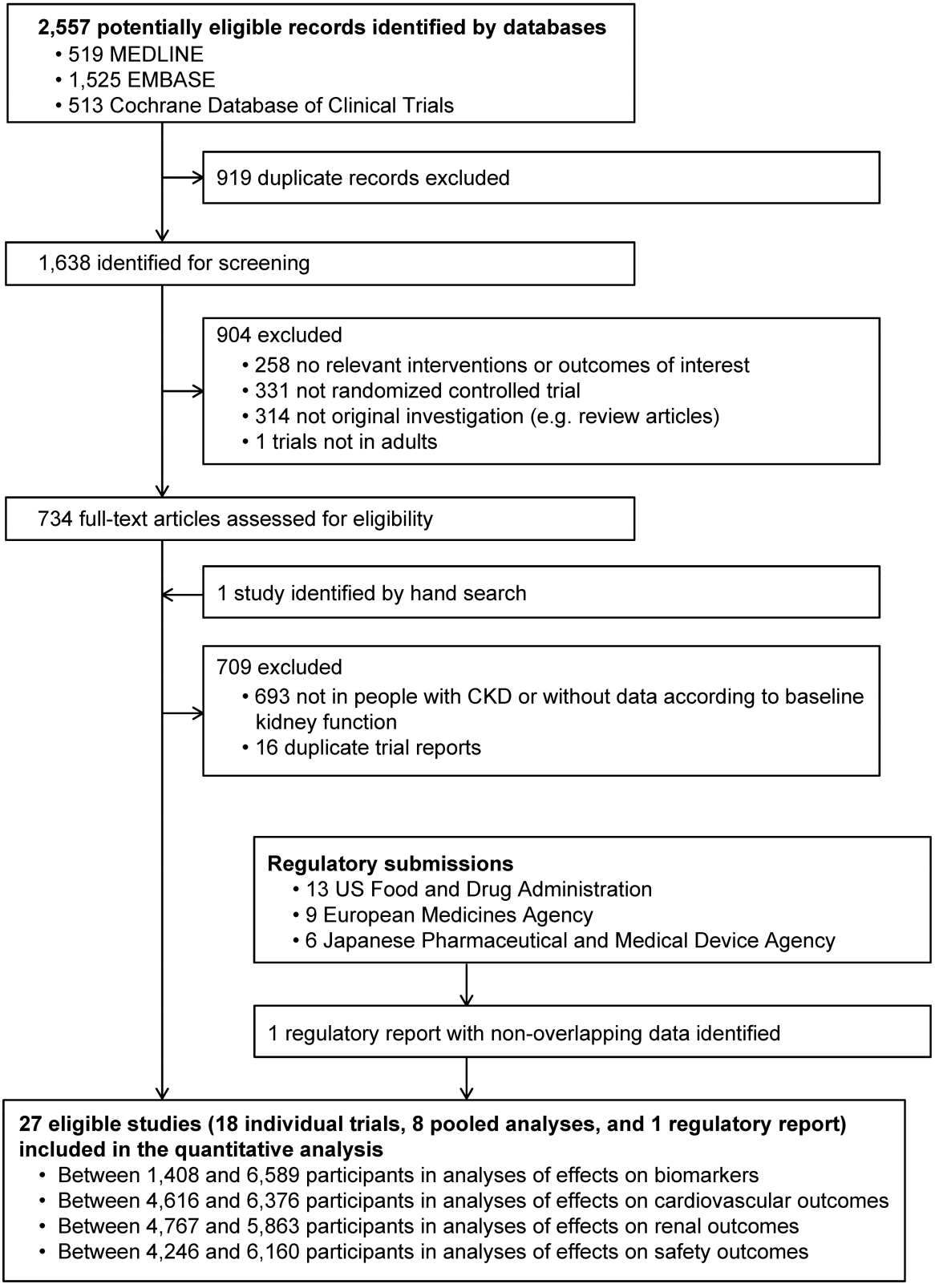

FIGURE 1 Identification of eligible studies

for dapagliflozin was identified after the systematic literature search.[6] In total, 27 studies yeilded data on biomarkers or on cardiovascular, renal or safety outcomes, with substantial contributions from three large cardiovascular outcome trials of empagliflozin, canagliflozin and dapagliflozin.[2,3,6] Of the 27 studies, 18 were individual trials,[2,3,6,26–40] eight were pooled analyses[13,14,41–46] and one was a regulatory report for ertugliflozin[47] (Figure 1 and Supporting Information Table S2). The eight pooled analyses and one regulatory report combined data from 41 individual trials from which results were not individually available for the CKD population. Thus, in total, data from 59 trials contributed data to the meta-analysis: 18 studies from which individual trial data were available for the CKD population, as well as 41 trials which were

included through the eight pooled analyses and one regulatory report (Supporting Information Table S3).[48–88]

Of the 59 trials from which data were used for this analysis, 19 assessed the effects of empagliflozin, 19 assessed effects of dapagliflozin, seven assessed effects of ertugliflozin, six assessed effects of ipragliflozin and five assessed effects of canagliflozin, while luseogliflozin, sotagliflozin and tofogliflozin 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.[3] Data were available for up to 6589 individuals for analyses of biomarkers, 6376 for analyses of cardiovascular outcomes, 7363 for analyses of all-cause mortality, 5863 for analyses of renal outcomes and 6160 for analyses of safety outcomes. SGLT2 inhibitors were compared to placebo in all cases, with the exception of one regulatory report for ertugliflozin, which pooled data on all-cause mortality across seven 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/1.73 m^2 (Supporting Information Table S2). Median and mean UACR ranged from 12.8 to 76.0 mg/g and 209.8 to 567.9 mg/g, respectively. Risk of bias varied across studies (Supporting Information Table S1). The domain in which the largest proportion of studies was judged as high risk was incomplete outcome data (70%). The majority of trials reporting effects on HbA1c and other continuous biomarkers was potentially biased by incomplete handling of missing repeated measures (S1). Inappropriate imputation methods were not relevant for dichotomous outcomes. Most trials described adequate random sequence generation and blinding of participants, personnel and outcome assessment, with low risk of selective reporting overall (Supporting Information Figure S1). Tests for publication bias were not performed because of the small number of studies reporting the effect of SGLT2 inhibitors on the main composite of cardiovascular and renal outcomes, as well as all-cause mortality. Results for effects on biomarkers and on cardiovascular, renal and safety outcomes by individual study are also presented online (Supporting Information Figures S3–S6).

3.1 | Biomarker outcomes

Data on a range of biomarkers were available for up to seven SGLT2 inhibitors across four 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 Supporting Information Figure S2, 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*-heterogeneity = 0.05), but no evidence of heterogeneity of effects for the other biomarkers (all $I^2 \leq 12\%$; all *P*-heterogeneity ≥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*-heterogeneity = 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 (≥26 vs <26 weeks; I^2 = 0%; *P*-heterogeneity = 0.50).

3.2 | 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 seven 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 hospitalised or fatal heart failure events and 593 all-cause deaths. Cardiovascular outcome data were available for the same three SGLT2 inhibitors, with the exception of stroke and all-cause mortality where limited additional data were available for ertugliflozin, ipragliflozin and luseogliflozin. For all outcomes, effect estimates were dominated by three large trial reports for empagliflozin, canagliflozin and dapagliflozin.[2,3,6]

Overall, SGLT2 inhibitors reduced the risk of the composite cardiovascular outcome (RR, 0.81; 95% CI, 0.70-0.94), hospitalised 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). While the point estimate favoured SGLT2 inhibitors for all-cause mortality, the confidence interval spanned unity (RR, 0.86; 95% CI, 0.73-1.01). 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*-heterogeneity = 0.11) (Figure 3).

We conducted sensitivity analyses comparing data from the three cardiovascular outcome trials with that from 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%; all *P*-heterogeneity >0.15). 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 analysing data from only the three cardiovascular outcome trials (RR, 0.81; 95% CI, 0.62-1.07).

3.3 | Renal outcomes

Based on two trials, SGLT2 inhibitors slowed the annual decline in eGFR slope, with a placebo-subtracted difference of 1.35 mL/min/1.73 m^2 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*-heterogeneity = 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 9;5% CI, 0.53-0.95; Figure 4), with no evidence of heterogeneity by individual agents (I^2 = 0%; *P*-heterogeneity = 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).

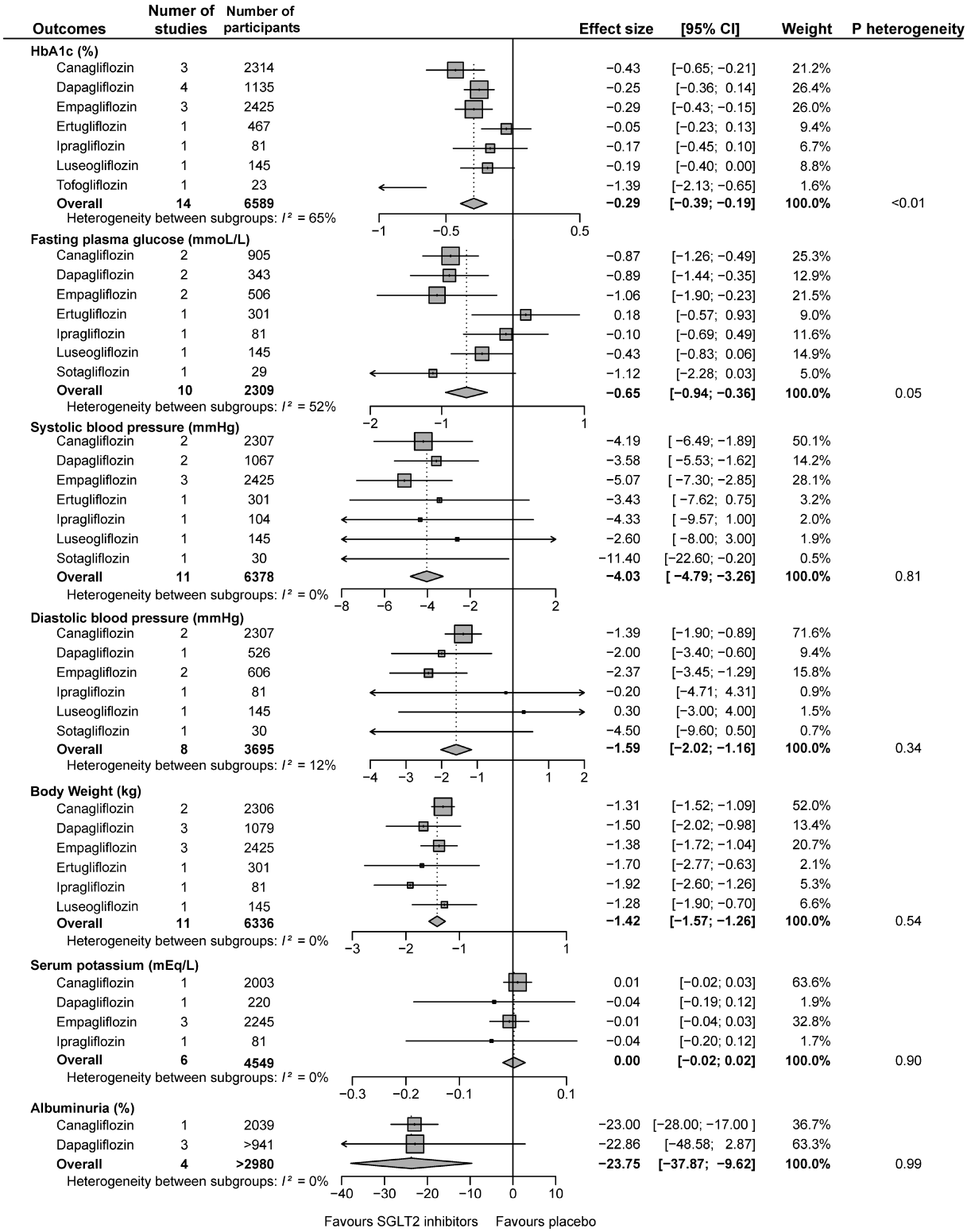

FIGURE 2 Effects of SGLT2 inhibitors on biomarkers in individuals with type 2 diabetes and chronic kidney disease (estimated glomerular filtration rate < 60 mL/min/1.73 m^2). Abbreviations: CI, confidence interval; HbA1c, glycated haemoglobin

3.4 | 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 amputations and fractures, there was at least a moderate likelihood of difference between agents arising beyond chance for a number of outcomes, including hypoglycaemia, hypovolaemia and amputation (all $I^2 \geq 57\%$; all *P*-heterogeneity ≤0.04). 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 hyperkalaemia (Figure 4).

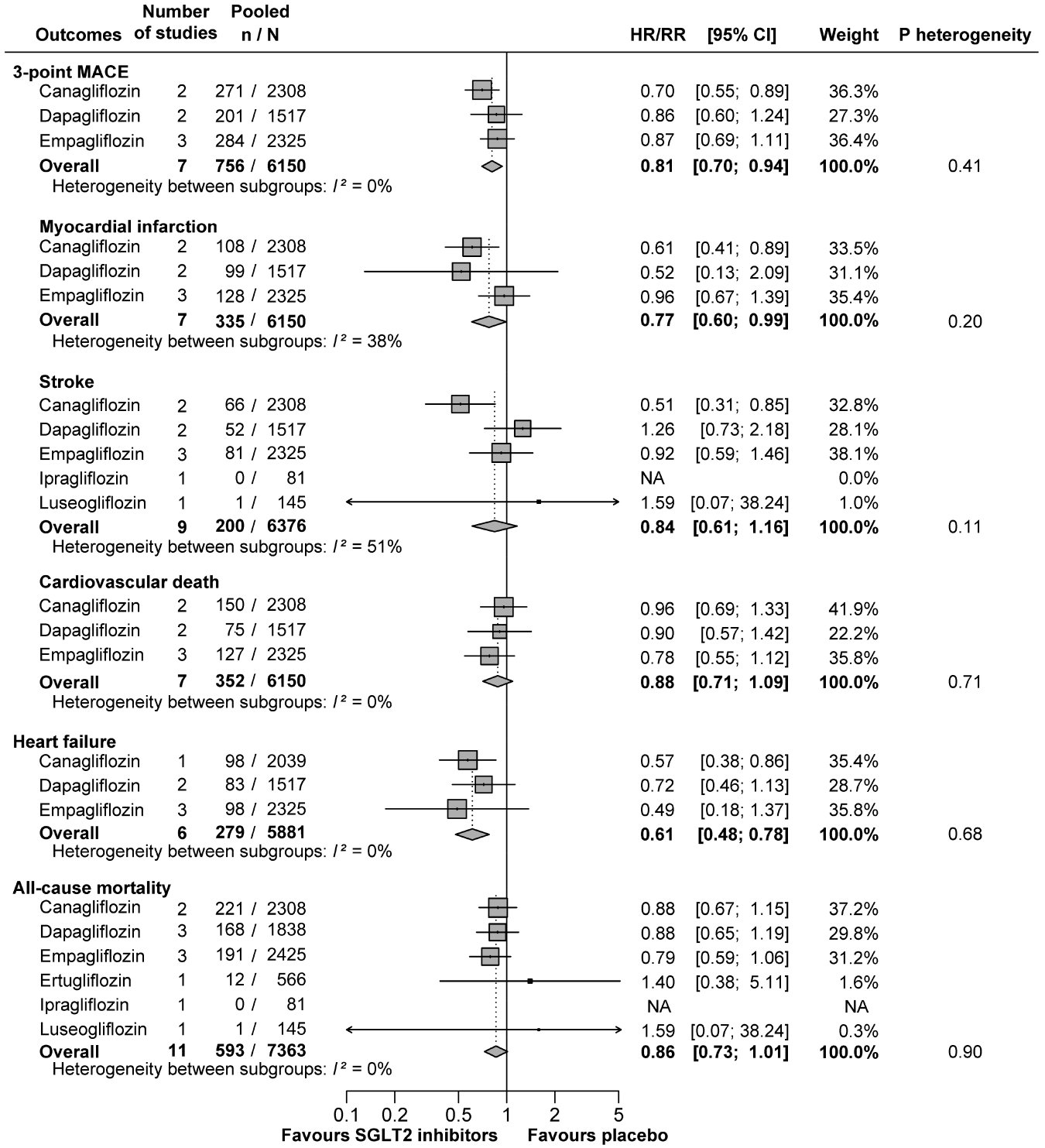

FIGURE 3 Effects of SGLT2 inhibitors on cardiovascular outcomes and all-cause mortality in individuals with type 2 diabetes and chronic kidney disease (estimated glomerular filtration rate < 60 mL/min/1.73m^2). Abbreviations: CI, confidence interval; HR, hazard ratio; n, number of cases with events; N, group size; NA, not available; RR, risk ratio

4 | DISCUSSION

Available data suggest that SGLT2 inhibitors reduce the risk of major adverse cardiovascular events and heart failure in individuals with T2DM and CKD. The strength of evidence for these outcomes is buttressed by the quality of the three large cardiovascular outcome trials from which these data were largely derived. The data also suggest that SGLT2 inhibitors might have broader benefits to a range of other cardiovascular outcomes as well as all-cause mortality. 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, although none of the included trials was explicitly designed to provide definitive information on the renoprotective effect of SGLT2 inhibitors in CKD. The absence of additional

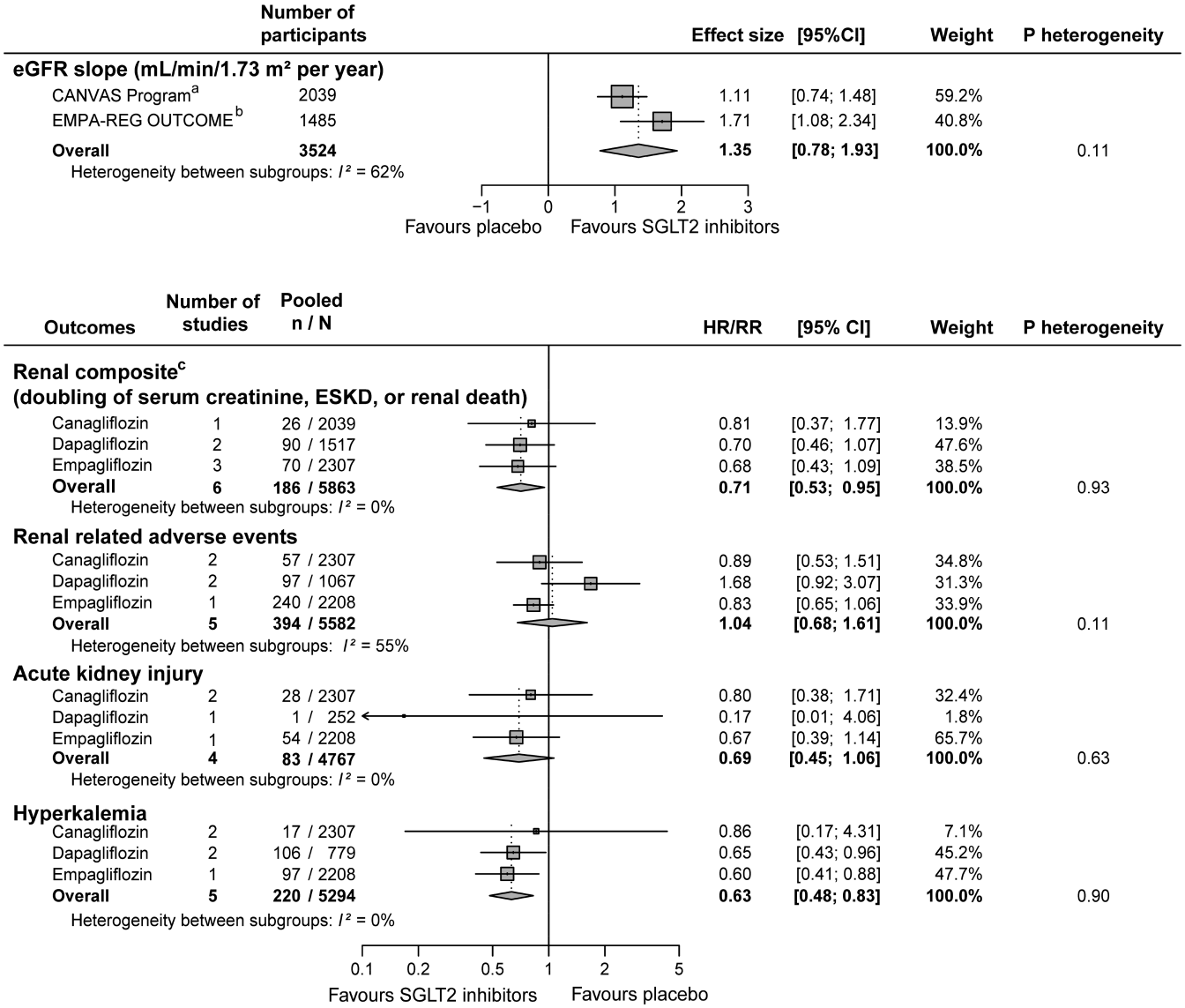

FIGURE 4 Effects of SGLT2 inhibitors on cardiovascular and renal outcomes in individuals with type 2 diabetes and chronic kidney disease (estimated glomerular filtration rate < 60 mL/min/1.73 m^2). Abbreviations: CI, confidence interval; ESKD, end-stage kidney disease; HR, hazard ratio; n, number of cases with events; N, group size; RR, risk ratio. a, Week 6 (CANVAS) or 13 (CANVAS-R) to last available measurement was used. b, Week 4 to the last value on treatment was used. c, For the DECLARE-TIMI 58 trial, 40% decrease in eGFR was substituted for doubling of serum creatinine in the renal composite outcome

safety concerns when used in individuals with CKD is also promising. Taken together, these data suggest that SGLT2 inhibitors are likely to have an important role in the prevention of cardiovascular and renal complications among individuals with T2DM and CKD.

This class of agent exerts multiple beneficial metabolic effects, that is, 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.[2,3,89] This was consistent with the known mechanism of action of these agents, for which glycaemic efficacy is proportional to filtered glucose load.[1] The observed heterogeneity of the effect on HbA1c and fasting glucose across SGLT2 inhibitors may be related to differences in mean baseline HbA1c or kidney function across included trials. Alternatively, observed differences in glycaemic efficacy may be related to bias in the statistical methods used to handle missing repeated measurements across the contributing studies; some of these approaches have been shown to be particularly problematic, including in the context of trials concerning SGLT2 inhibitors.[90] Nevertheless, given only small and variable improvements in HbA1c, as well as the inconsistent evidence of glucose lowering in the prevention of macrovascular complications in T2DM,[91,92] these results suggest that improved glycaemic 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,[1] would also be anticipated to be attenuated in CKD, but there appears to be 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

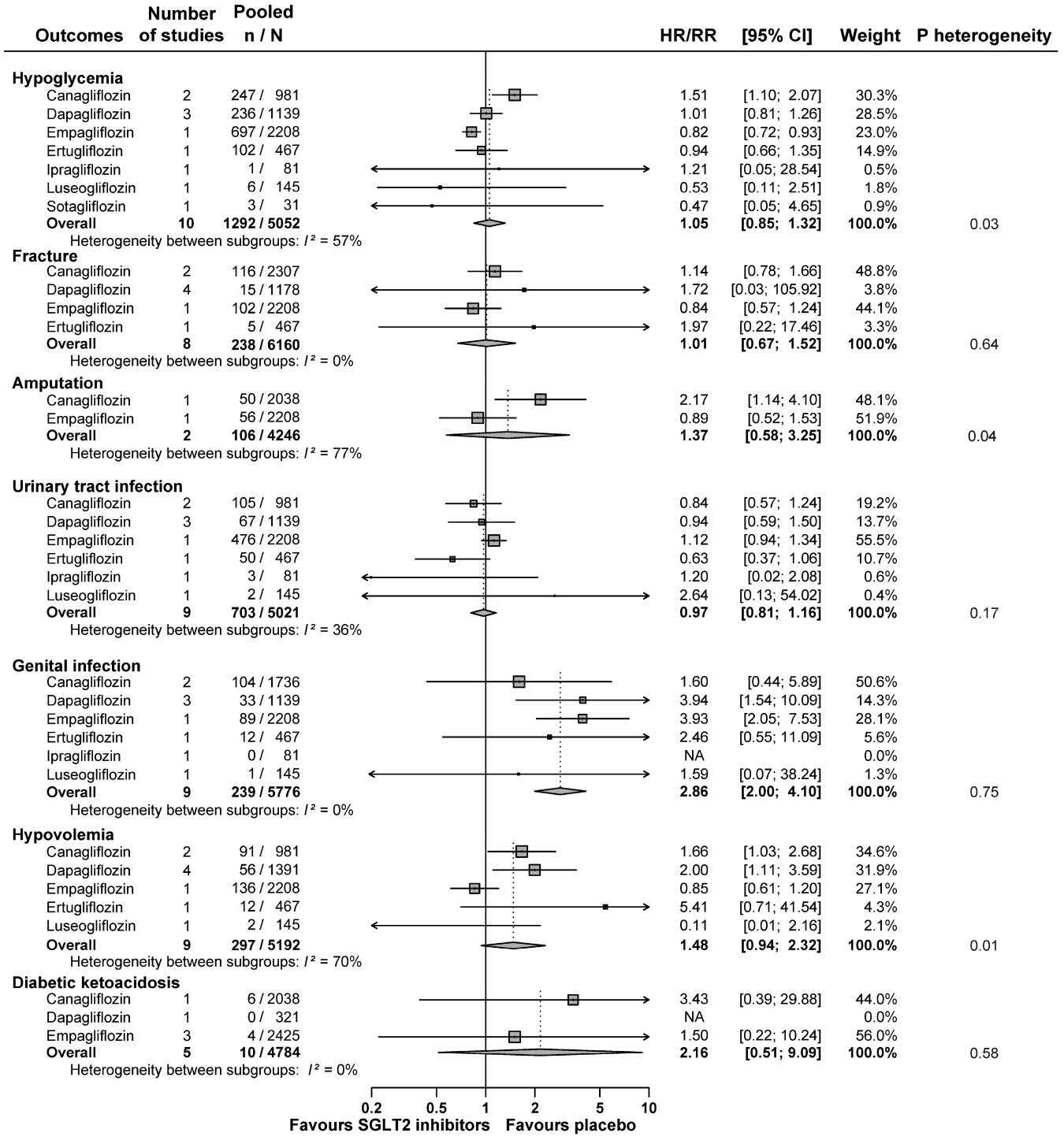

FIGURE 5 Effects of SGLT2 inhibitors on safety outcomes in individuals with type 2 diabetes and chronic kidney disease (estimated glomerular filtration rate < 60 mL/min/1.73 m^2). Abbreviations: HR, hazard ratio; n, number of cases with events; N, group size; NA, not available; RR, risk ratio

intravascular volume,[93,94] or that haemodynamic effects may be enhanced by concurrent use of diuretic therapies,[95] which were more prevalent in individuals with CKD in two large included trials.[15,96] 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.[97] 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 haemodynamic dysregulation that in turn contributes to higher rates of subclinical or overt cardiac dysfunction in this population.[98] Other direct cellular and metabolic effects might also play a role.[99] 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 ischaemic stress.[100]

A key physiological concept underpinning the probable renoprotective effect of this class of agents is that they reduce hyperfiltration, a critical process in the pathogenesis of diabetic kidney disease.[101] This is supported by head-to-head studies with other glucose-lowering agents that show that SGLT2 inhibitors preserve kidney function, independent of glycaemic control.[102] 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.[93] 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 haemodynamics in the development of renal, and cardiovascular, complications in diabetes, while also suggesting that the 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 strength of evidence for renoprotection in patients with CKD in this analysis was less robust than that for cardiovascular outcomes, because of the relatively small number of renal events. Additionally, the effect on the renal composite outcome was no longer clear in sensitivity analysis, excluding the DECLARE TIMI 58 trial. The Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation (CREDENCE) trial will provide definitive information concerning the effects of SGLT2 inhibition on renal outcomes in individuals with CKD. The CREDENCE trial enrolled 4401 participants with stage 2 or 3 CKD and macroalbuminuria, approximately 60% of whom with eGFR <60 mL/min/1.73 m^2.[103] The trial was terminated early based on advice from the Data Monitoring Committee that pre-specified efficacy criteria had been achieved at a scheduled interim analysis.[104]

Given what is known about the safety profile of this class of agents,[105] the results of this meta-analysis suggest that the risks of harm in CKD are probably no different than those of the general T2DM population, with no clear evidence of additional concerns regarding renal safety. SGLT2 inhibitors increase the risk of genital infections but not of urinary tract infections. The risk of some safety outcomes, including hypovolaemia, hypoglycaemia and amputations, appeared more favourable with use of empagliflozin compared to use of the other SGLT2 inhibitors. Reasons for the observed heterogeneity across individual agents for these outcomes were not entirely clear. While there was no increased risk of fracture with any one agent or overall, the CANVAS Program demonstrated an increased risk with canagliflozin in the overall trial population.[4] Given that this effect was not modified by baseline kidney function,[14] our analysis is probably 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. The imprecision of summary effect estimates for some adverse outcomes underscores the ongoing need for dedicated renal endpoint trials to provide definitive information concerning safety.

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 and on 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 was that data were derived, for the most part, from subgroup analyses of three large randomized trials, none of which were dedicated renal endpoint trials. We combined different SGLT2 inhibitor doses (eg, dapagliflozin 5 and 10 mg), 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 a range of 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 probable that this analysis was underpowered to detect harms, and these results should be interpreted cautiously in the context of results from cardiovascular outcome trials in the broader T2DM population. Additionally, studies included in this analysis involved relatively few participants with more advanced CKD (eg, eGFR <45 mL/min/1.73 m^2). Therefore, whether the renoprotective effects of SGLT2 inhibitors persist at very low levels of eGFR remains an open question. 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 concerning 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 announced or already underway for dapagliflozin (DAPA-CKD), empagliflozin (EMPA-KIDNEY) and sotagliflozin (SCORED).[106,107] Because of the unique renal haemodynamic 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.[106,107]

In conclusion, currently available data suggest that SGLT2 inhibitors reduce the risk of cardiovascular and renal outcomes in patients with T2DM and CKD, without clear evidence of additional safety concerns; however, the robustness of these findings requires confirmation in upcoming dedicated CKD outcome trials.

CONFLICTS OF INTEREST

B. L. N. has received travel support from Janssen and is funded by a John Chalmers PhD Scholarship from The George Institute for Global Health, a University Postgraduate Award from UNSW Sydney and a Clarendon Scholarship from the University of Oxford. T. T. is supported by the Japan Society for the Promotion of Science Program for Fostering Globally Talented Researchers. T. O. is supported by a John Chalmers Postdoctoral Fellowship from The George Institute for Global Health. M. J. is supported by a Scientia Fellowship from UNSW Sydney, Australia. M. J. J. 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; has spoken at scientific meetings sponsored by Janssen, Amgen and Roche, with any consultancy, honoraria or travel support paid to her institution. M. G. W. has received honorarium for scientific lectures from AstraZeneca, Amgen and Baxter, and is supported by a Diabetes Australia Research Trust Millennium Grant. B. N. has received research support from the Australian National Health and Medical Research Council Principal Research Fellowship and from Janssen, Roche, Servier, and Merck Schering Plough; and is serving on advisory boards and/or has 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, with all honoraria paid to his institution. T. W. is a national lead investigator of a renal outcome study of a sodium-glucose cotransporter-2 (SGLT2) inhibitor (canagliflozin). V. P. is receiving research support from the Australian National Health and Medical Research Council (Senior Research Fellowship and Program Grant); is serving on Steering Committees for AbbVie, Boehringer Ingelheim, GlaxoSmithKline, Janssen and Pfizer; and is 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. M. J. J., H. L. H., B. N. and V. P. are members of the steering committee of a renal outcome study of a sodium-glucose cotransporter-2 (SGLT2) inhibitor (canagliflozin), with V. P. serving as chair of the steering committee. The George Institute for Global Health, which funds B. L. N. and T. O., provides contract research services to Janssen for trials of SGLT2 inhibitors. The other authors report no declarations of interest.

Author contributions

B. L. N, T. T., T. N., M. J., M. J. J. and V. P. contributed to the design of the study. T. T. and B. N. performed the literature search and screening for eligible studies. B. L. N., T. T., T. O. and H. J. H. extracted the data. T. T. created the Figures and Tables. All authors contributed to the interpretation and presentation of the data. B. N., T. T. and V. P. wrote the first draft of the manuscript and all authors contributed to subsequent drafts and approved the final version for submission. B. L. N., T. T. and V. P. 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. T. T. and B. L. N. contributed equally to the manuscript.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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