Sodium–glucose cotransporter 2 inhibitors and risk of adverse renal outcomes among type 2 diabetes patients: a network and cumulative meta-analysis of randomized controlled trials

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ABSTRACT

Aim: The renal safety of sodium–glucose cotransporter 2 (SGLT2) inhibitors in patients with type 2 diabetes mellitus (T2DM) remains uncertain. This meta-analysis aimed to compare the effects of each SGLT2 inhibitor on adverse renal outcomes in patients with T2DM.

Methods: PubMed, EMBASE, CENTRAL, and ClinicalTrials.gov were searched up to May 24 2016 without language or date restrictions. Randomized trials that reporting at least one renal-related adverse outcome in T2DM patients treated with SGLT2 inhibitors were included. Pairwise and network meta-analyses were carried out to calculate the odds ratio (OR) with 95% confidence interval (CI) and a cumulative meta-analysis was performed to assess the robustness of evidence.

Results: In total, we extracted 1,334 composite renal events among 39,741 patients from 58 trials and 511 acute renal impairment/failure events among 36,716 patients from 53 trials. Dapagliflozin was significantly associated with a greater risk of composite renal events than placebo (OR, 1.64; 95% CI, 1.26 to 2.13). Empagliflozin seemed to confer a lower risk than placebo (OR, 0.63, 95% CI, 0.54 to 0.72), canagliflozin (OR, 0.48; 95% CI, 0.29 to 0.82), and dapagliflozin (OR 0.38, 95% CI, 0.28 to 0.51). With regard to acute renal impairment/failure, only empagliflozin was significantly associated with a lower risk than placebo (OR, 0.72, 95% CI, 0.60 to 0.86). Our cumulative meta-analysis indicated the robustness of our significant findings.

Conclusions: Our meta-analysis indicated that dapagliflozin may increase the risk of adverse renal events while empagliflozin may have a protective effect among T2DM patients. Further data from large well-conducted RCTs and real-world setting are

warranted.

KEYWORDS

SGLT2 inhibitor, renal outcomes, type 2 diabetes, meta-analysis

INTRODUCTION

The sodium glucose cotransporter 2 (SGLT2) is located in the proximal tubule of the kidney and accounts for 90% of reabsorption of filtered glucose in the kidney[1]. SGLT2 inhibitors with highly potent in selectively inhibiting SGLT2 [2], have been approved for treating type 2 diabetes mellitus (T2DM). Unlike other glucose-lowering agents, SGLT2 inhibitors exert insulin-independent hypoglycemia effects by selectively inhibiting renal glucose reabsorption and thereby increasing urinary glucose excretion [3]. Many clinical trials have demonstrated that SGLT2 inhibitors have beneficial effects on glycemic control, body weight loss, and blood pressure reduction without causing hypoglycemia [4-6].

Because of the mechanisms of action of SGLT2 inhibitors in the kidney, there is a concern that they may induce renal impairment. Intravascular volume depletion can be caused by osmotic diuresis in patients receiving SGLT2 inhibitors [7]. Subsequently, transient hypotensive episodes secondary to volume reduction are likely to result in acute kidney injury [8]. An early and dose-dependent increase in serum creatinine or blood urea nitrogen (BUN) levels and a decrease in estimated glomerular filtration rate (eGFR) were observed after the use of SGLT2 inhibitors, especially in patients with chronic kidney disease (CKD) [9, 10]. On June 14th, 2016, the U.S. Food and Drug Administration (FDA) strengthened an existing warning about the risk of acute kidney injury for canagliflozin and dapagliflozin [11]. The risk of adverse renal events was increased with the use of dapagliflozin or canagliflozin as compared to placebo [4, 12]. However, some trials showed that the early abnormal renal parameters returned toward baseline in patients receiving SGLT2 inhibitors over time [13]. Some evidence indicated

that SGLT2 inhibitors might offer renoprotection in patients with T2DM [14]. Recently, one large randomized trial (EMPA-REG OUTCOME trial) with up to 5 years of follow-up showed that patients taking empagliflozin were less likely to experience acute renal failure (including acute kidney injury) than those taking placebo [15].

Regarding possible adverse effects of SGLT2 inhibitors on renal outcomes, the evidence from individual randomized trials has been inconsistent. We therefore conducted a comprehensive pairwise and network meta-analyses to synthesize both direct and indirect evidence from all available randomized controlled trials (RCTs) to compare the effects of individual SGLT2 inhibitors on adverse renal outcomes in patients with T2DM. We also used cumulative meta-analysis to determine when the evidence became robust.

METHODS

The report of this review was performed according to the PRISMA extension statement for reporting of systematic reviews incorporating network meta-analyses of health care interventions [16] .

Search strategy

The electronic databases of PubMed, Embase, and Cochrane Central Register of Controlled Trials (CENTRAL) were searched to identify eligible RCTs using relevant search terms described in **Table S1**. We identified articles published up to May 24, 2016, without restrictions on language, year of publication, or publication status. An additional manual search of the references of included trials, relevant meta-analyses, and ClinicalTrials.gov was carried out to identify other published and unpublished trials.

Study selection

We included RCTs that compared SGLT2 inhibitors to placebo or other active antidiabetic treatments in adults with T2DM. We required follow-up periods of at least 12 weeks and reporting of at least one renal-related adverse outcome (e.g., increased creatinine or BUN level, decreased eGFR, renal impairment, or renal failure) in published articles. In addition, the trials with the results presented on ClinicalTrials.gov were also considered. The primary outcomes included composite renal events (including increased creatinine or BUN level, decreased eGFR, renal impairment, and renal failure) and acute renal impairment/failure events reported by each investigator as an adverse event (or serious adverse event) using pre-specified lists from the Medical Dictionary for Regulatory Activities (MedDRA) or laboratory values (e.g. serum creatinine, BUN, or eGFR). Conference abstracts were excluded due to lack of detailed information assessing the trials' characteristics, definition of outcomes, and trial quality.

Data extraction and quality assessment

A standardized data extraction form was developed as follows: first author (publication year), study characteristics (country of origin and funding), patient characteristics (inclusion criteria, background treatments, ethnicity, mean age, proportion of male, pre-existing CKD, and pre-existing cardiovascular disease), interventions (type of SGLT2 inhibitor and control), and renal-related adverse events (incidence of any specified adverse renal outcome).

If multiple reports were retrieved on the same population, only the most complete and/or more recently reported data were used. If adverse renal outcomes were not reported in

the publication, data from the “Serious Adverse Events” section on the ClinicalTrials.gov were extracted. In addition, if trials with the results presented on ClinicalTrials.gov, but without reporting adverse renal events, the number of events was assumed to be zero. If two different comparison groups of non-overlapping patients (i.e., A *vs.* B and C *vs.* D) were included in the same report, each group was considered separately. If three arms (i.e., A *vs.* B *vs.* A+B) were evaluated in the trials, only two arms (A *vs.* B) were included. When placebo was switched to an active comparator in extended-period trials, only the period with placebo was documented. Two reviewers (HT and DL) independently performed study selection and data extraction, and any disagreements were resolved by consensus or referral to a third reviewer (YS).

We used the Cochrane risk-of-bias tool to qualitatively assess the quality of RCTs [17]. Two authors (HT and DL) independently reviewed and judged each RCT as having low, high, or unclear risk of bias based on the following criteria: random sequence generation (selection bias), allocation concealment (selection bias), blinding (performance bias and detection bias), incomplete outcome data (attrition bias), and selective reporting (reporting bias).

Statistical analysis

Pairwise and network meta-analyses with their odds ratios (ORs) and 95% confidence intervals (CIs) were performed to calculate comparative effect sizes.

For pairwise meta-analyses, ORs were calculated based on Peto’s method for direct comparisons between SGLT2 inhibitors and control due to low event rates [18]. An I^2 statistic was used to evaluate heterogeneity within meta-analyses, with <25%, 25%- 75%,

and >75% indicating low, moderate, and high level of statistical heterogeneity, respectively. In addition, several subgroup analyses were carried out to explore the source of heterogeneity: (1) type of control group (placebo vs active treatment); (2) length of trial duration (≤ 26 weeks vs 26-104 weeks vs ⩾104 weeks); (3) age (< 60 years vs ⩾60 years); (4) pre-existing cardiovascular disease (yes vs no); and (5) pre-existing chronic kidney disease (yes vs no).

For indirect and mixed comparisons, a network meta-analysis with a random-effects model was used to compare interventions. The network meta-analysis was performed with STATA version 14.0 using the “mvmeta” command and programmed STATA routines [19, 20]. For zero-event RCT, a 0.5 zero-cell correction was applied [21]. To rank the SGLT2 inhibitors for a specified outcome, we estimated the relative ranking probabilities of each treatment using surface under the cumulative ranking curve (SUCRA) probabilities and mean ranks. For adverse renal outcomes, higher SUCRA probability and lower mean rank indicate a safer intervention [22]. The heterogeneity variance (tau) estimated by a restricted maximum likelihood method was employed to quantify between-study heterogeneity for each outcome [23].

To check for possible inconsistency, a loop inconsistency–specific approach was introduced to evaluate the difference between direct and indirect estimates for a specific comparison [24]. To check the assumption of consistency in the entire network, a design-by-treatment interaction model using the χ^2 test was applied [25]. To test the robustness of the findings, we assessed the modulating effects of different trial and participant characteristics on primary outcomes of sensitivity analyses restricted to trials

involving patients without CKD, white patients, SGLT2 inhibitor combination therapy, or excluding the largest trial (EMPA-REG OUTCOME Trial), separately. In addition, a cumulative pairwise meta-analysis was performed to test the stability of our significant findings with the accumulation of data over time [26]. Finally, a comparison-adjusted funnel plot was used to assess small-study effects within a network of interventions, with symmetry around the summary effect line indicating the absence of small-study effects [27].

RESULTS

Study selection and study characteristics

Of 1,874 citations retrieved through electronic search and 8 eligible RCTs identified from ClinicalTrials.gov, finally, 58 eligible RCTs were included in this meta-analysis (**Figure 1**). The **Table S2** summarized the characteristics of the 58 trials, in which a total of 38,079 patients were randomly assigned to groups receiving either SGLT2 inhibitors (canagliflozin, dapagliflozin, empagliflozin, or luseogliflozin) or control treatments (placebo or other active anti-diabetic medications). Sample sizes of individual trials ranged from 71 to 7,020 participants, and the periods of follow-up ranged from 12 to 260 weeks. One trial provided two independent datasets for two different comparisons (empagliflozin versus metformin and empagliflozin versus sitagliptin), which we considered separately [28]. Combined data from two trials were presented on ClinicalTrials.gov and were included as one independent trial [29, 30]. Networks of eligible comparisons for the primary outcomes are presented in the **Figure 2**, showing

predominantly pairwise comparisons of SGLT2 inhibitors with placebo and absence of pairwise comparison between any two SGLT2 inhibitors.

Risk of bias within studies

The risk of bias for the 58 RCTs was summarized as follows: 37 RCTs reported adequate random-sequence generation, 35 RCTs reported adequate allocation concealment; masking conditions were high in three RCTs, of which two were open-label in extended periods and the other set one arm with open label; and 24 RCTs reported events of adverse renal outcome. All of the trials were funded by industry. More information is presented in the **Figure S1.**

Meta-analysis

The analyses of composite renal events included data from 58 trials reporting 1,334 events among 39,741 patients. The results of pairwise meta-analysis are presented in **Table S3**. Canagliflozin (OR, 1.69; 95%CI, 1.06 to 2.72) and dapagliflozin (OR, 1.70; 95%CI, 1.34 to 2.16) were significantly associated with greater risk of composite renal events as compared with control group, respectively. Empagliflozin was significantly associated with lower risk of composite renal events than control group (OR, 0.62; 95%CI, 0.54 to 0.72). Subgroup analysis by type of control showed that canagliflozin posed higher risk of composite renal events than other active treatments (OR, 2.57; 95%CI, 1.10 to 6.04), dapagliflozin significantly increased the risk as compared with placebo (OR, 1.71; 95%CI, 1.32 to 2.21), while empagliflozin significantly decreased the risk as compared with placebo (OR, 0.62; 95%CI, 0.54 to 0.72). An increased risk of composite renal events was observed in trials with duration from 26 to 104 weeks for

canagliflozin (OR, 1.71; 95%CI, 1.00 to 2.92) and dapagliflozin (OR, 2.06; 95%CI, 1.56 to 2.71), respectively, while a decreased risk for empagliflozin in those with durations more than 104 weeks (OR, 0.62; 95%CI, 0.53 to 0.72). It should be noted that in the patients without pre-existing CKD, canagliflozin and dapagliflozin were associated with increased risk of composite renal events, with an OR of 2.05 (95%CI, 1.17 to 3.59) and 1.80 (95%CI, 1.40 to 2.30) respectively, while empagliflozin was associated with decreased risk (OR, 0.62; 95%CI, 0.53 to 0.72). Statistical heterogeneity within the pairwise meta-analysis was low to moderate, with an I^2 statistic from 0 to 51.9%. Our network meta-analysis showed that dapagliflozin was significantly associated with a higher risk of composite renal events (OR, 1.64; 95%CI, 1.26 to 2.13), while empagliflozin was significantly associated with a lower risk than placebo (OR, 0.63; 95%CI, 0.54 to 0.72). In particular, empaglilflozin was significantly associated with fewer events than dapagliflozin (OR, 0.38; 95%CI, 0.28 to 0.51) and canagliflozin (OR, 0.48; 95%CI, 0.29 to 0.82) (**Figure 3A**). We generated hierarchies of treatment effects based on the SUCRA probabilities. Empagliflozin posed the lowest risk for composite renal events, whereas dapagliflozin conferred the highest risk among these three SGLT2 inhibitors. The network meta-analysis had low statistical heterogeneity (tau≈0). We detected no inconsistency in the loop of comparisons between direct and indirect evidence (all 95%CIs across zero). In addition, no global inconsistency was detected within any network (P=0.76). Detailed information was presented in the **Tables S4-S6.**

A total of 511 events of acute renal impairment/failure were reported in 53 trials with 36,716 patients. Pairwise meta-analysis showed that canagliflozin (OR, 1.82; 95%CI, 0.28 to 11.77) and dapagliflizin (OR, 1.93; 95%CI, 0.42 to 8.83) had a tendency to

increase the risk of acute renal impairment/failure events as compared with control group, respectively. However, empagliflozin posed a significantly lower risk of acute renal impairment/failure than control group (OR, 0.72; 95%CI, 0.59 to 0.87). Subgroup analysis by type of control showed that only empagliflozin significantly reduced the risk of acute renal impairment/failure as compare with either placebo (OR, 0.73; 95%CI, 0.60 to 0.88) or active treatments (OR, 0.07; 95%CI, 0.01 to 0.74) (**Table S7**). Low to moderate evidence of statistical heterogeneity was detected, with the I^2 statistic from 0 to 66.8%. The results from our network meta-analysis with a low level of statistical heterogeneity (tau≈0) showed that only empagliflozin was significantly associated with lower risk of acute impairment/failure events than placebo (OR, 0.72; 95%CI, 0.60 to 0.86). Neither canagliflozin (OR, 0.67; 95%CI, 0.25 to 1.80) nor dapagliflozin (OR, 0.75; 95%CI, 0.33 to 1.74) was significantly associated with acute renal impairment/failure (**Figure 3B**). According to the SUCRA probabilities, empagliflozin conferred the lowest risk of acute renal impairment/failure, whereas dapagliflozin had the highest risk among these three SGLT2 inhibitors. In addition, no loop inconsistency in the loop of comparisons (all 95%CIs across zero) or global inconsistency within any network was detected (P = 0.72). Detailed information was presented in the **Tables S4-S6**.

Sensitivity and cumulative meta-analyses

The main results did not appreciably change in the sensitivity analysis after being restricted to trials involving patients without CKD, white patients, and SGLT2 inhibitor combination therapy. However, the significantly protective effect of empagliflozin against acute renal impairment/failure seemed to be largely driven by the largest trial (EMPA-REG OUTCOME trial) [15]. When this trial was removed, there was no

significant difference between empagliflozin and placebo in risk of acute renal impairment/failure events (OR, 0.55; 95%CI, 0.21 to 1.42). The rankings of SGLT2 inhibitors for adverse renal outcomes in the sensitivity analyses were relatively stable (**Table 1**).

In addition, a cumulative meta-analysis by publication year of trials showed that dapagliflozin was significantly associated with a higher risk of composite renal events than placebo since 2014 when a trial was published by Leiter LA et al in 2014 (cumulative OR, 1.74; 95%CI, 1.21 to 2.50) and the effect size was robust in the following years (**Figure 4A**). In consistent with the sensitivity analysis, the cumulative meta-analysis also showed that the significantly lower risk of acute renal impairment/failure from empagliflozin versus placebo was largely driven by the EMPA-REG OUTCOME trial (**Figure 4B**). Further, the comparison-adjusted funnel plot revealed no small-study effects, which indicated the absence of any over-estimate or under-estimate of the effect of SGLT2 inhibitors (**Figure S2)**.

DISCUSSION

Our comprehensive meta-analysis of 58 RCTs involving 39,741 patients showed that dapagliflozin was consistently associated with a significantly higher risk of composite renal events than placebo. Conversely, empagliflozin was significantly associated with a lower risk of composite renal events and acute renal impairment/failure than placebo. However, the significance of the effect on acute renal outcomes by empagliflozin was largely driven by one single study, the EMPA-REG OUTCOME trial.

Our findings clearly show that, compared to placebo, dapagliflozin was significantly associated with an increased risk of composite renal events. Moreover, the cumulative meta-analysis showed that sufficient evidence had emerged by 2014. Some previous trials also reported that dapagliflozin was associated with an increased incidence of renal impairment or failure and creatinine increase or eGFR decrease in T2DM patients, especially in elderly patients or those with extant renal impairment [9, 10, 31]. Evidence showed that elevated serum creatinine or lowered eGFR returned to baseline levels more frequently in patients treated with dapagliflozin than with a comparator after a few months of therapy or when therapy was discontinued [32-35]. These findings indicated that abnormal changes in eGFR or creatinine during dapagliflozin therapy might reflect a temporary and reversible change in renal function, possibly caused by hemodynamic changes related to osmotic diuresis, reduction in blood pressure, or altered intrarenal hemodynamics [10, 14, 34, 36]. Our subgroup analysis found that an increased risk of composite renal events was observed in the studies with follow-up durations from 26 to 104 weeks, but not in those with either less than 26 weeks or more than 104 weeks. Nevertheless, one pooled analysis of 12 trials showed that in patients with normal or mildly impaired renal function, dapagliflozin was not associated with elevated risk of acute renal toxicity or deterioration of renal function [34]. Our meta-analysis (7 events from 9391 patients) also found no sign of significantly increased risk of dapagliflozin on acute renal impairment/failure.

There are suggestive evidence that renal function was reduced by other SGLT2 inhibitors, indicating a class effect [14, 37]. Canagliflozin was associated with early abnormal changes in serum creatinine, BUN levels, or eGFR [14]. Our pairwise

meta-analysis also showed that canagliflozin was significantly associated with elevated risk of composite renal events, despite a nonsignificantly increased risk was observed from network meta-analysis. Empagliflozin also showed a similar pattern of short term decrease in renal function, but with a significantly improvement after the discontinuation of empagliflozin [38]. However, our meta-analysis showed that empagliflozin was associated with decreased risk of adverse renal outcomes. Furthermore, in June 2016, the U.S FDA strengthened an existing warning about the risk of acute kidney injury for canagliflozin and dapagliflozin [11]. Given some suggestive evidence of the harmful effects of dapagliflozin or canagliflozin on renal function, monitoring of long-term renal function is necessary for these two drugs in T2DM patients, especially those with renal impairment.

It is interesting to find that only empagliflozin was significantly associated with lower risk of both composite renal events and acute renal impairment/failure events than placebo, suggesting its possible renoprotective effects in patients with T2DM. However, the precise mechanisms underlying the renal benefit of empagliflozin are still unclear. Some evidence showed that SGLT2 inhibitors might reduce proximal tubular hypertrophy, inflammation, and fibrosis, and ameliorate the hyperfiltration that accompanies hyperglycemia [39]. SGLT2 inhibitors might reduce albuminuria, a marker of glomerular damage in patients with CKD [9, 37, 40]. However, it is important to note that EMPA-REG OUTCOME trial contributed substantially to the summary estimate of acute renal impairment/failure events (about 95% weight of the summary estimate), and when this trial was removed, there was no significant difference between empagliflozin and placebo [15]. The renal benefit from empagliflozin was largely driven the EMPA-REG

OUTCOME trial. Further, data from well-conducted RCTs and real-world setting with renal events as primary outcomes are warranted to confirm our findings.

A key issue is whether the renal benefit from empagliflozin applies to other drugs in class of SGLT2 inhibitors. However, our findings suggest that dapagliflozin and canagliflozin may have a harm effect on renal function. The disparate effects of the various SGLT2 inhibitors on renal impairment/failure are probably due to data availability of adverse renal events. Adverse renal events associated with dapagliflozin were usually reported as adverse events in the peer-reviewed journals, while most data on the other two SGLT2 inhibitors were extracted from ClinicalTrials.gov, with renal events being considered serious adverse events. In addition, patients with chronic comorbid disease (e.g., coronary heart disease) might affect renal outcomes[41]. Emapagliflozin was associated with a significant reduction in risk of renal outcomes in EMPA-REG OUTCOME Trial, which included T2DM patients at high cardiovascular risk. However, we did not find a similar trend in other SGLT2 inhibitors. Notably, there is some evidence indicating pharmacokinetics or pharmacodynamics differences and variabilities in various SGLT2 inhibitors. The likelihood of renal-related adverse events may depend on whether and to what extent the drug is cleared from the body through kidney excretion [42]. It is reported that about 75% of dapagliflozine is eliminated by the renal pathway, while the other two SGLT2 inhibitors appear to be less subject to renal clearance (33% of canagliflozin and 54% of empagliflozin) [43-45]. Nevertheless, additional data are required to explore different renal effects by these SGLT2 inhibitors. Several large ongoing prospective RCTs including Canagliflozin and Renal Events in Diabetes with Estimated Nephropathy Clinical Evaluation (CREDENCE; NCT02065791), CANagliflozin

cardiovascular Assessment Study-renal outcomes (CANVAS-R; NCT01989754), and Multicenter Trial to Evaluate the Effect of Dapagliflozin on the Incidence of Cardiovascular Events (DECLARE-TIMI58; NCT01730534), will not only provide enough statistical power to determine the renal safety of SGLT2 inhibitors, but also solve the issue of whether or not the renal benefit is a class effect or a specific drug effect.

In contrast to the null finding from one previous published meta-analysis [46], our meta-analysis showed that dapagliflozin had harmful effects on renal function, while empagliflozin had renoprotecive effects. Compared to that study, our meta-analysis has several advantages: (1) our research question was more specific on adverse renal outcomes; (2) this is the first network meta-analysis to comprehensively assess the comparative effects of SGLT2 inhibitors on adverse renal outcomes; (3) we systematically identified eligible RCTs that presented at least one adverse renal outcome. Additional data from Clinicaltrials.gov were also checked to identify unpublished studies; and (4) multiple sensitivity analyses and cumulative meta-analysis were performed to test the robustness of the findings.

However, some limitations of our study merit consideration. First, we focused on all or acute adverse renal outcomes as reported by trials. The adverse renal events (including an increase of creatinine or BUN, or a decrease of eGFR) was defined by the investigators as an adverse event (or a serious adverse event), which did not allow a clear separation between chronic and acute renal outcomes and identifying each outcome. Second, majority of the trials (especially canagliflozin and empagliflozin) are less likely to report adverse renal outcomes in their full publications due to unknown reasons, although additional data were obtained from the ClinicalTrials.gov to minimize

the risk of reporting bias. Third, variation in background treatments and patient characteristics across RCTs might contribute to heterogeneity, although we found low statistical heterogeneity and no inconsistency in our network model. Finally, adverse renal outcomes for SGLT2 inhibitors other than empagliflozin and dapagliflozin remain uncertain due to lack of sufficient RCT data.

In conclusion, there has been an increased risk harm effects on renal function in patients taking dapagliflozin while empagliflozin appeared to have renal protective effects. These results call for future safety monitoring of SGLT2 inhibitors in RCTs and real-world settings.

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Disclosure Statement

The authors have nothing to disclose.

Contributor Statements

HT and YS had the idea for the study and led the study design. HT and DL identified and selected trials and extracted data. HT, DL, JZ, TW, and YS performed all data analyses, checked for statistical consistency, and interpreted results. HT, YL, SZ, and YS contributed to data interpretation. HT drafted the report, and all other authors (DL, JZ, YL, TW, SZ, and YS) critically reviewed the report. All authors read and approved the final manuscript.

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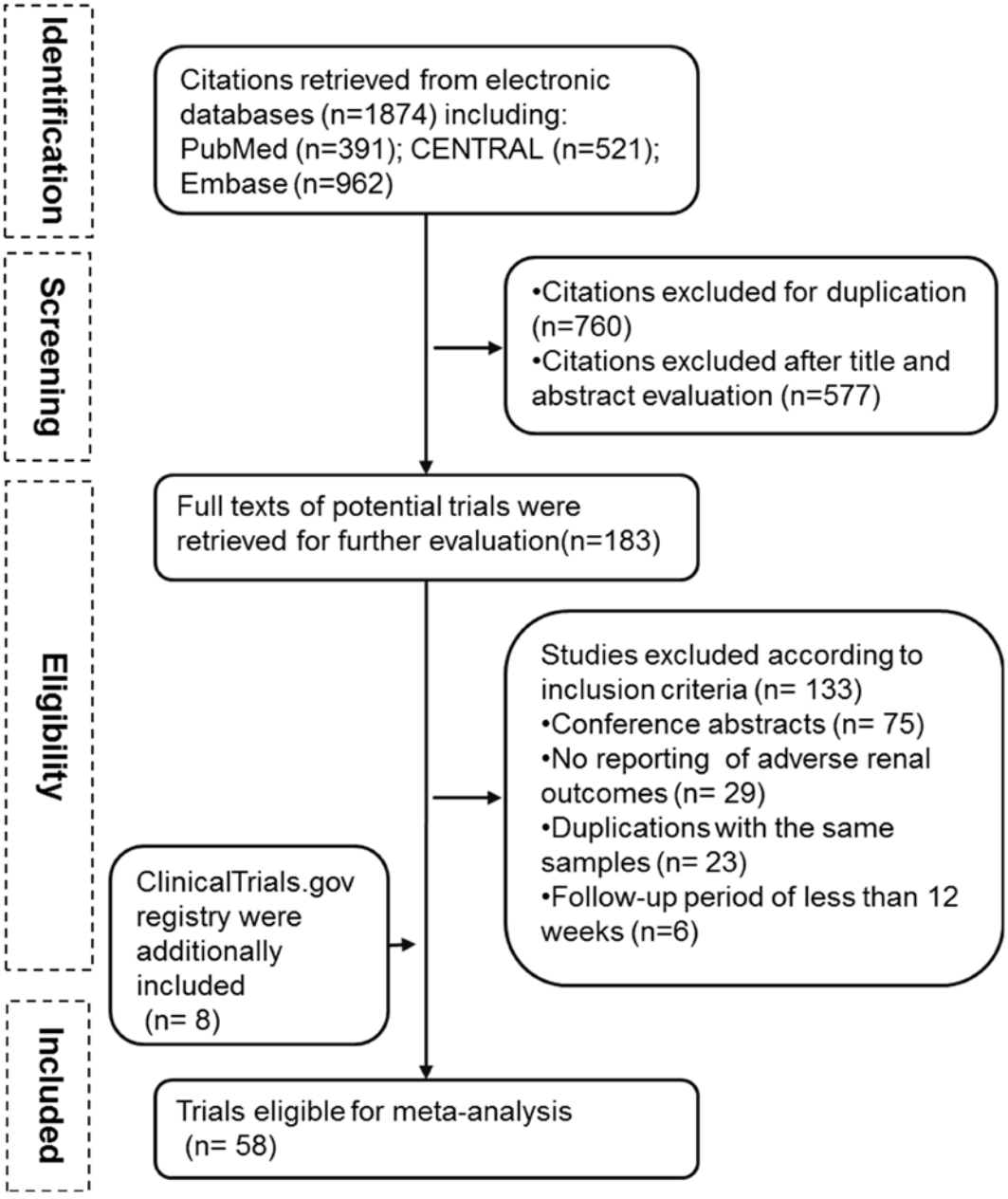
Table 1 Sensitivity analyses for the odds ratios of SGLT2 inhibitor versus placebo on adverse renal outcomes.

Treatments	Overall analysis	SUCRA rank	Non-CKD patients	SUCRA rank	White patients	SUCRA rank	Exclude EMPA-REG OUTCOME Trial	SUCRA rank	Combination therapy	SUCRA rank
Composite renal events										
Canagliflozin	1.29 (0.78,2.15)	4	1.44 (0.77,2.67)	3	1.34 (0.80,2.24)	3	1.27 (0.75,2.15)	4	1.24 (0.73,2.09)	4
Dapagliflozin	1.64 (1.26,2.13)	5	1.76 (1.34,2.31)	4	1.68 (1.29,2.20)	4	1.60 (1.12,2.29)	5	1.70 (1.30,2.23)	5
Empagliflozin	0.38 (0.28,0.51)	1	0.62 (0.54,0.72)	1	0.63 (0.55,0.73)	1	0.47 (0.23,0.96)	1	0.63 (0.55,0.72)	1
Luseogliflozin	0.67 (0.22,2.06)	2	NA	NA	NA	NA	0.67 (0.22,2.10)	2	0.67 (0.22,2.06)	2
Active treatments	1.01 (0.58,1.75)	3	1.08 (0.62,1.89)	2	0.97 (0.55,1.72)	2	0.96 (0.53,1.73)	3	1.02 (0.57,1.82)	3
Heterogeneity (tau)[1]	≈0 Low		≈0 Low		≈0 Low		=0.1 Low		≈0 Low	
Acute renal impairment/failure events										
Canagliflozin	0.67 (0.26,1.73)	2	0.62 (0.22,1.76)	2	0.69 (0.25,1.91)	2	0.85 (0.26,2.76)	2	0.62 (0.21,1.79)	2
Dapagliflozin	0.75 (0.33,1.74)	3	0.86 (0.35,2.09)	3	0.80 (0.33,1.93)	3	0.87 (0.32,2.35)	3	0.75 (0.31,1.85)	3
Empagliflozin	0.72 (0.60,0.86)	1	0.72 (0.59,0.86)	1	0.73 (0.61,0.88)	1	0.55 (0.21,1.42)	1	0.72 (0.60,0.87)	1
Active treatments	1.42 (0.52,3.89)	4	1.43 (0.52,3.96)	4	1.17 (0.37,3.69)	4	1.37 (0.43,4.32)	4	1.10 (0.32,3.73)	4
Heterogeneity (tau)[1]	≈0 Low		≈0 Low		≈0 Low		≈0 Low		≈0 Low	

[1] Degree of between-study heterogeneity. NA, not applicable; CKD, chronic kidney disease; SUCRA, surface under the cumulative ranking curve.

Figure 1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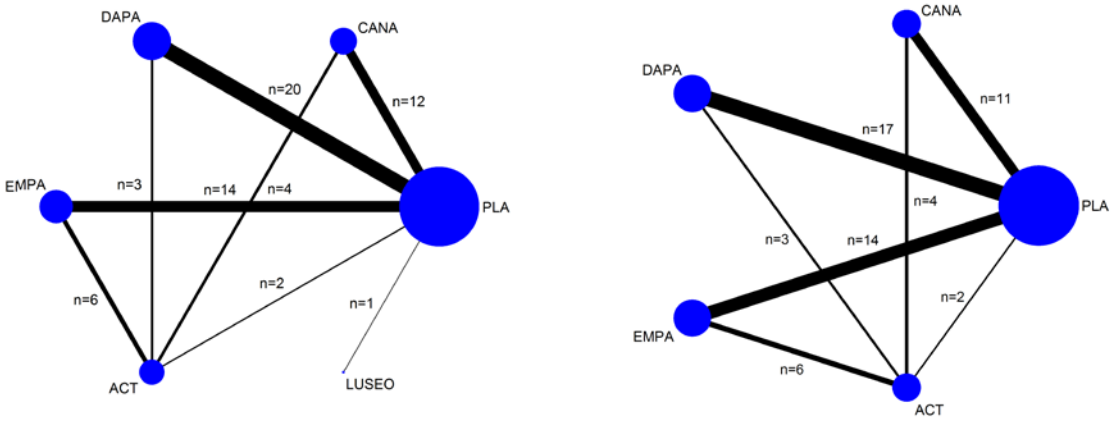
Screening
Eligibility
Included
Citations retrieved from electronic databases (n=1874) including: PubMed (n=391); CENTRAL (n=521); Embase (n=962)
•Citations excluded for duplication (n=760)
•Citations excluded after title and abstract evaluation (n=577)
Full texts of potential trials were retrieved for further evaluation(n=183)
Studies excluded according to inclusion criteria (n= 133)
•Conference abstracts (n= 75)
•No reporting of adverse renal outcomes (n= 29)
•Duplications with the same samples (n= 23)
•Follow-up period of less than 12 weeks (n=6)
ClinicalTrials.gov registry were additionally included (n= 8)
Trials eligible for meta-analysis (n= 58)

Figure 2


DAPA
CANA
n=20
n=12
EMPA
n=3
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n=4
PLA
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n=1
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ACT

Figure 3

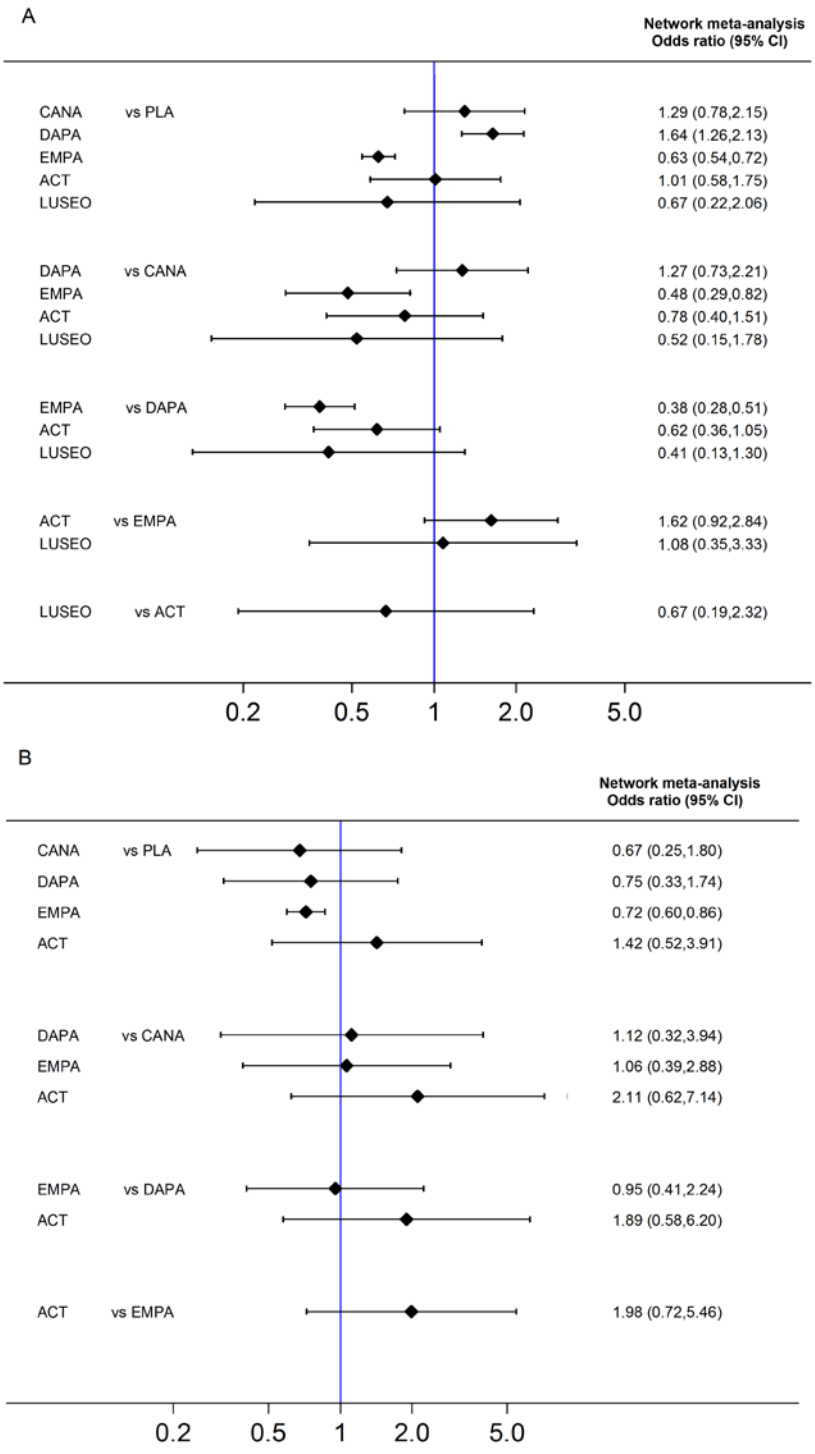
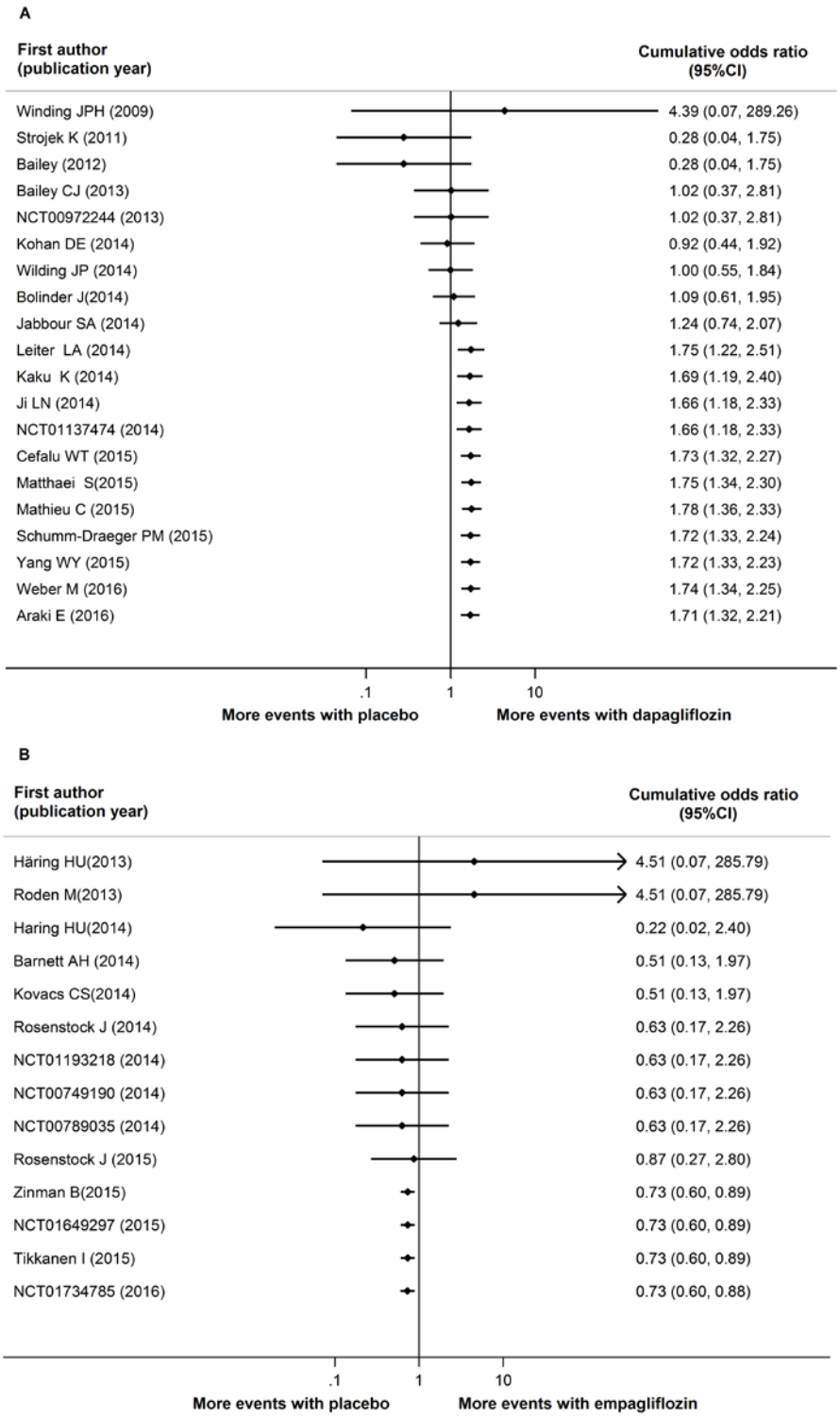

A
Network meta-analysis
Odds ratio (95% CI)
CANA vs PLA 1.29 (0.78,2.15)
DAPA 1.64 (1.26,2.13)
EMPA 0.63 (0.54,0.72)
ACT 1.01 (0.58,1.75)
LUSEO 0.67 (0.22,2.06)
DAPA vs CANA 1.27 (0.73,2.21)
EMPA 0.48 (0.29,0.82)
ACT 0.78 (0.40,1.51)
LUSEO 0.52 (0.15,1.78)
EMPA vs DAPA 0.38 (0.28,0.51)
ACT 0.62 (0.36,1.05)
LUSEO 0.41 (0.13,1.30)
ACT vs EMPA 1.62 (0.92,2.84)
LUSEO 1.08 (0.35,3.33)
LUSEO vs ACT 0.67 (0.19,2.32)
0.2
0.5
1
2.0
5.0
B
Network meta-analysis
Odds ratio (95% CI)
CANA vs PLA 0.67 (0.25,1.80)
DAPA 0.75 (0.33,1.74)
EMPA 0.72 (0.60,0.86)
ACT 1.42 (0.52,3.91)
DAPA vs CANA 1.12 (0.32,3.94)
EMPA 1.06 (0.39,2.88)
ACT 2.11 (0.62,7.14)
EMPA vs DAPA 0.95 (0.41,2.24)
ACT 1.89 (0.58,6.20)
ACT vs EMPA 1.98 (0.72,5.46)
0.2
0.5
1
2.0
5.0

Figure 4


A
First author (publication year)
Cumulative odds ratio (95%CI)
Winding JPH (2009) 4.39 (0.07, 289.26)
Strojek K (2011) 0.28 (0.04, 1.75)
Bailey (2012) 0.28 (0.04, 1.75)
Bailey CJ (2013) 1.02 (0.37, 2.81)
NCT00972244 (2013) 1.02 (0.37, 2.81)
Kohan DE (2014) 0.92 (0.44, 1.92)
Wilding JP (2014) 1.00 (0.55, 1.84)
Bolinder J(2014) 1.09 (0.61, 1.95)
Jabbour SA (2014) 1.24 (0.74, 2.07)
Leiter LA (2014) 1.75 (1.22, 2.51)
Kaku K (2014) 1.69 (1.19, 2.40)
Ji LN (2014) 1.66 (1.18, 2.33)
NCT01137474 (2014) 1.66 (1.18, 2.33)
Cefalu WT (2015) 1.73 (1.32, 2.27)
Matthaei S(2015) 1.75 (1.34, 2.30)
Mathieu C (2015) 1.78 (1.36, 2.33)
Schumm-Draeger PM (2015) 1.72 (1.33, 2.24)
Yang WY (2015) 1.72 (1.33, 2.23)
Weber M (2016) 1.74 (1.34, 2.25)
Araki E (2016) 1.71 (1.32, 2.21)
.1
1
10
More events with placebo
More events with dapagliflozin
B
First author (publication year)
Cumulative odds ratio (95%CI)
Häring HU(2013) 4.51 (0.07, 285.79)
Roden M(2013) 4.51 (0.07, 285.79)
Haring HU(2014) 0.22 (0.02, 2.40)
Barnett AH (2014) 0.51 (0.13, 1.97)
Kovacs CS(2014) 0.51 (0.13, 1.97)
Rosenstock J (2014) 0.63 (0.17, 2.26)
NCT01193218 (2014) 0.63 (0.17, 2.26)
NCT00749190 (2014) 0.63 (0.17, 2.26)
NCT00789035 (2014) 0.63 (0.17, 2.26)
Rosenstock J (2015) 0.87 (0.27, 2.80)
Zinman B(2015) 0.73 (0.60, 0.89)
NCT01649297 (2015) 0.73 (0.60, 0.89)
Tikkanen I (2015) 0.73 (0.60, 0.89)
NCT01734785 (2016) 0.73 (0.60, 0.88)
.1
1
10
More events with placebo
More events with empagliflozin

SUPPORTING INFORMATION

References

Table S1 Search Strategy

Search data: May-24, 2016

Data source	Search terms
PubMed	#1 Sodium glucose co-transporter #2 SGLT2 OR SGLT-2 OR SGLT 2 #3 Tofogliflozin OR Apleway OR Deberza OR CSG452 #4 Empagliflozin OR Jardiance #5 dapagliflozin OR Farxiga OR Forxiga #6 Canagliflozin OR Invokana #7 Sotagliflozin OR LX4211 #8 luseogliflozin OR Lusefi #9 Ipragliflozin OR Suglat #10 remogliflozin OR BHV091009 #11 sergliflozin OR GW869682X #12 ertugliflozin OR MK-8835 OR PF-04971729 #13 OR#1- #12 #14 random* #15 "Randomized Controlled Trial"[Publication Type] #16 RCT or RCTs #17 #14 OR #16 #18 #13 AND #17
CENTRAL	TITLE-ABSTRACT- KEYWORDS（Sodium Glucose co-transporter OR SGLT2 OR SGLT-2 OR SGLT 2 OR Tofogliflozin OR Empagliflozin OR dapagliflozin OR Canagliflozin OR Sotagliflozin OR luseogliflozin OR Ipragliflozin OR remogliflozin OR sergliflozin OR ertugliflozin）
Embase	(TITLE-ABSTRACT-INDEX TERM (Sodium Glucose co-transporter OR SGLT2 OR SGLT-2 OR SGLT 2 OR Tofogliflozin OR Empagliflozin OR dapagliflozin OR Canagliflozin OR Sotagliflozin OR luseogliflozin OR Ipragliflozin OR remogliflozin OR sergliflozin OR ertugliflozin) AND TITLE-ABSTRACT-INDEX TERM (RCT* OR random*))
ClinicalTrials.gov	Tofogliflozin OR Empagliflozin OR dapagliflozin OR Canagliflozin OR Sotagliflozin OR luseogliflozin OR Ipragliflozin OR remogliflozin OR sergliflozin OR ertugliflozin

Table S2 Characteristics of included Studies

Author (year)	NCT	N	Interventions	Background therapy	Mean Age (year)	Male (%)	Race (Primary)	Pre-existing CKD	Pre-existing CVD	Outcomes reported	Data source of outcome	Follow-up (weeks)
Leiter LA (2015)[1]	NCT00968812	1450	Canagliflozin vs glimepiride	MET	56.2	52.0	White	No	No	GFR decreased and renal failure (leading to discontinuation)	Publications	104
Stenlof K (2013)[2]	NCT01081834	584	Canagliflozin vs placebo	Naïve treatment	55.4	44.2	White	No	No	Acute renal failure based on prespecified SAE item from MedDRA	Clinitrial trial registration	26
Yale JF (2014)[3]	NCT01064414	269	Canagliflozin vs placebo	SU or INS	68.5	60.6	White	Yes	No	Decreased renal function (e.g. specific terms of renal impairment and blood creatinine increased)	Publications	52
Wilding JPH (2013)[4]	NCT01106625	469	Canagliflozin vs placebo	MET + SU	56.8	51.0	White	No	No	Not reported[3]	Clinitrial trial registration	52
Bode B (2015)[5]	NCT01106651	714	Canagliflozin vs placebo	OAD	63.6	55.5	White	No	No	Renal impairment	Clinitrial trial registration	104
Forst T (2014)[6]	NCT01106690	342	Canagliflozin vs placebo	MET+PIOG	57.4	63.2	White	No	No	Not reported[3]	Clinitrial trial registration	26
Inagaki N (2015)[7]	NCT01413204	272	Canagliflozin vs placebo	Naïve treatment	58	70.5	Asian	No	No	Not reported[3]	Clinitrial trial registration	24
Rosenstock J (2016)[8]	NCT01809327	1186	Canagliflozin vs placebo	MET	54.9	48.0	White	No	No	Renal-related AEs (e.g. blood Cr increased, GFR decreased, and renal impairment) based on AE reports, and safety laboratory tests.	Publications	30
Neal B (2015)[9]	NCT01032629	1972	Canagliflozin vs placebo	INS+OAD	62.7	66.0	White	No	No	Renal-related adverse events based on prespecified AE items from MedDRA	Publications	52
Qiu R (2014)[10]	NCT01340664	279	Canagliflozin vs placebo	MET	57.4	46.6	White	No	No	GFR decreased (lead ing to discontinuation) based on AE reports, and safety laboratory tests	Publications	18
NCT01381900 (2014)[11]	NCT01381900	676	Canagliflozin vs placebo	MET+SU	56.3	53.6	Asian	No	No	Not reported[3]	Clinitrial trial registration	18
Rosenstock J (2012)[12]	NCT00642278	451	Canagliflozin vs placebo	MET	52.9	52.0	White	No	No	Not reported[3]	Clinitrial trial registration	12

Inagaki N(2013)[13]	NCT01022112	383	Canagliflozin vs placebo	Naïve treatment	57.4	68.1	Asian	No	No	Not reported[3]	Clinitrial trial registration	12
Schernthaner G (2013)[14]	NCT01137812	755	Canagliflozin vs sita	MET+SU	56.7	55.9	White	No	No	Not reported[3]	Clinitrial trial registration	52
Lavalle-González FJ(2013)[15]	NCT01106677	1284	Canagliflozin vs sita vs placebo	MET	55.4	47.1	White	No	No	Not reported[3]	Clinitrial trial registration	26
Henry RR (2012)[16]	NCT00859898	638	Dapagliflozin + MET vs Dapagliflozin vs MET	Naïve treatment	51.6	48.2	White	No	No	Not reported[3]	Clinitrial trial registration	24
Rosenstock J (2015)[17]	NCT01606007	534	Dapagliflozin + SAXA vs SAXA vs Dapagliflozin	MET	54	50.2	White	No	No	GFR decrease based on laboratory values	Publications	24
Nauck MA (2011)[18]	NCT00660907	814	Dapagliflozin vs glipizide	MET	58	55.3	White	No	No	Renal impairment/failure (e.g. calculated Cr renal clearance decreased, renal impairment, blood Cr increased, eGFR,and acute renal failure) based on prespecified AE item from MedDRA and laboratory values	Publications	52
Cefalu WT (2015)[19]	NCT01031680	922	Dapagliflozin vs placebo	OAD	62.9	68.3	White	No	Yes	Renal impairment/failure (e.g. decreased renal Cr clearance, renal impairment, acute renal failure, increased blood Cr, decreased GFR) based on prespecified renal impairment/failure AE items from MedDRA	Publications	52
Leiter LA (2014)[20]	NCT01042977	962	Dapagliflozin vs placebo	Standard care	63.8	66.9	White	No	Yes	Renal impairment/failure (e.g. renal impairment, renal failure, and acute renal failure) based on prespecified AE item from MedDRA	Publications	52
Bailey CJ (2012)[21]	NCT00736879	282	Dapagliflozin vs placebo	Naïve treatment	53	50.0	White	No	No	Not reported[3]	Clinitrial trial registration	24
Bailey CJ (2013)[22]	NCT00528879	546	Dapagliflozin vs placebo	MET	53.9	53.5	White	No	No	Renal impairment/failure (e.g. increases in serum Cr >1.5 timesthe baseline value or attaining an absolute value of 221 umol/l) (defined by a prespecified list)	Publications	102
Strojek K (2011)[23]	NCT00680745	592	Dapagliflozin vs placebo	Glimepiride	59.8	48.1	White	No	No	Renal impairment/failure based on prespecified AE item from MedDRA and laboratory	Publications	24

										values		
Wilding JP (2014)[24]	NCT00673231	807	Dapagliflozin vs placebo	INS ± OAD	59.3	47.8	White	No	No	Renal impairment/failure based on prespecified AE item from MedDRA and laboratory values	Publications	104
Kaku K (2014)[25]	NCT01294423	261	Dapagliflozin vs placebo	Naïve treatment	58.9	59.4	Japan	Yes	No	Renal impairment based on laboratory values, calculated Cr clearance, and eGFR	Publications	24
Jabbour SA (2014)[26]	NCT00984867	447	Dapagliflozin vs placebo	SIT ±MET	54.9	54.8	White	No	No	Renal impairment (e.g., decreased renal Cr clearance)	Publications	48
Bolinder J (2014)[27]	NCT00855166	180	Dapagliflozin vs placebo	MET	60.7	55.6	White	No	No	Renal impairment/failure based on prespecified AE items from MedDRA	Publications	104
Matthaei S (2015)[28]	NCT01392677	216	Dapagliflozin vs placebo	MET+SU	61	49.1	White	No	No	renal impairment/failure (e.g. renal Cr clearance) based on prespecified AE items from MedDRA	Publications	52
Mathieu C (2015)[29]	NCT01646320	320	Dapagliflozin vs placebo	SAXA+MET	55.1	45.6	White	No	No	GFR decreased	Publications	52
Kohan DE (2014)[30]	NCT00663260	252	Dapagliflozin vs placebo	Standard care	67	65.1	White	Yes	No	Renal impairment or failure based on adverse event or laboratory abnormalities	Publications	104
Schumm-Draeger PM (2015)[31]	NCT01217892	399	Dapagliflozin vs placebo	MET	58.5	44.9	White	No	No	Renal impairment/failure-based on prespecified AE item from MedDRA	Publications	16
Ji LN (2014)[32]	NCT01095653	393	Dapagliflozin vs placebo	Naïve treatment	51.4	64.9	Asian	No	No	Renal impairment based on prespecified AE item from MedDRA	Publications	24
Weber M (2016)[33]	NCT01195662	449	Dapagliflozin vs placebo	OAD	56.5	55.0	White	No	No	Renal function based on prespecified AE item from MedDRA	Publications	12
Yang WY (2015)[34]	NCT01095666	444	Dapagliflozin vs placebo	MET	53.8	80.3	Asian	No	No	AE related to renal function based on prespecified AE item from MedDRA	Publications	24
Winding JP (2009)[35]	NCT00357370	71	Dapagliflozin vs placebo	INS+OAD	56.7	59.1	White	No	No	Renal failure based on treatment-emergent adverse events, vital signs, and laboratory measurements	Publications	12
NCT01137474 (2014)[36]	NCT01137474	944	Dapagliflozin vs placebo	OAD ± INS	NR	56.0	White	No	No	Not reported[3]	Clinitrial trial registration	12
NCT00972244 (2013)[37]	NCT00972244	279	Dapagliflozin vs placebo	Naïve treatment	57.3	57.3	Asian	No	No	Not reported[3]	Clinitrial trial registration	12

Araki E (2016)[38]	NCT02157298	182	Dapagliflozin vs placebo	INS±DPP4I	58	70.9	Asian	No	No	GFR decreased based on prespecified AE item from MedDRA	Publications	16
Lewin A (2015); & DeFronzo RA (2015)[39, 40][1]	NCT01422876	1341	Empagliflozin + LINA vs Empagliflozin vs LINA	±MET	55.4	53.8	White	No	No	Acute renal failue based on prespecified SAE item from MedDRA	Clinitrial trial registration	52
Ridderstrale M (2014)[41]	NCT01167881	1545	Empagliflozin vs glimepiride	MET	55.9	55.2	White	No	No	Renal failure, acute renal failure based on prespecified SAE item from MedDRA	Clinitrial trial registration	104
Ferrannini E (2013)-Study1[42][2]	NCT00881530	271	Empagliflozin vs metformin	Naïve treatment	57.9	49.4	White	No	No	Not reported[3]	Clinitrial trial registration	90
Ferrannini E (2013)-Study2[42][2]	NCT00881530	388	Empagliflozin vs SIT	MET	58.9	51.5	White	No	No	Not reported[3]	Clinitrial trial registration	90
Araki E (2015)[43]	NCT01368081	336	Empagliflozin vs metformin	SU	61.3	72.0	NR	No	No	Not reported[3]	Clinitrial trial registration	52
NCT00789035 (2014)[44]	NCT00789035	406	Empagliflozin vs metformin vs placebo	Naïve treatment	57.5	52.0	NR	No	No	Not reported[3]	Clinitrial trial registration	12
Barnett AH (2014)[45]	NCT01164501	741	Empagliflozin vs placebo	OAD	62.6	61.0	White	Yes	No	Renal impairment/failure (e.g . acute renal failure) based on prespecified SAE item from MedDRA	Clinitrial trial registration	52
Haring HU (2013)[46]	NCT01159600 / NCT01289990	669	Empagliflozin vs placebo	MET+SU	57.1	51.0	Asian	No	No	Not reported[3]	Clinitrial trial registration	76
Haring HU (2014)[47]	NCT01159600 / NCT01289990	638	Empagliflozin vs placebo	MET	55.7	57.0	White	No	No	Renal failure and acute renal failure based on prespecified SAE item from MedDRA	Clinitrial trial registration	76
Kovacs CS (2014)[48]	NCT01210001 / NCT01289990	499	Empagliflozin vs placebo	PIOG+-MET	54.5	48.4	Asian	No	No	Not reported[3]	Clinitrial trial registration	76
Rosenstock J (2014) [49]	NCT01306214	563	Empagliflozin vs placebo	INS	56.7	45.0	White	No	No	Renal impairment and acute renal failure based on prespecified SAE item from MedDRA	Clinitrial trial registration	52

Rosenstock J (2015)[50]	NCT01011868	494	Empagliflozin vs placebo	INS ± OAD	58.8	55.9	White	No	No	Renal failure and acute renal failure based on prespecified SAE item from MedDRA	Clinitrial trial registration	78
Zinman B (2015)[51]	NCT01131676	7020	Empagliflozin vs placebo	Standard care	63.2	71.0	White	No	Yes	Incident or worsening nephropathy and acute renal impairment/failure based on prespecified AE items from MedDRA	Publications	160
NCT01649297 (2015)[52]	NCT01649297	965	Empagliflozin vs placebo	MET	58.2	53.9	NR	No	No	Not reported[3]	Clinitrial trial registration	16
NCT01734785 (2016)[53]	NCT01734785	332	Empagliflozin vs placebo	LINA	55.2	59.6	NR	No	No	Acute renal failure based on prespecified SAE item from MedDRA	Clinitrial trial registration	24
NCT01193218 (2014)[54]	NCT01193218	547	Empagliflozin vs placebo	Naïve tre atment	57.5	74.9	Asian	No	No	Not reported[3]	Clinitrial trial registration	12
Tikkanen I (2015)[55]	NCT01370005	823	Empagliflozin vs placebo	OAD± INS	60.2	60.1	White	No	No	Not reported[3]	Clinitrial trial registration	12
Roden M (2013)[56]	NCT01177813 / NCT01289990	899	Empagliflozin vs SITA vs placebo	Naïve treatment	55	61.0	Asian	No	No	Acute renal failure based on prespecified SAE item from MedDRA	Clinitrial trial registration	76
NCT00749190 (2014)[57]	NCT00749190	495	Empagliflozin vs SITA vs placebo	MET	58.3	49.5	White	No	No	Not reported[3]	Clinitrial trial registration	12
Haneda M (2016)[58]	JapicCTI-111543	145	Luseogliflozin vs placebo	OAD	68	76.6	Asian	Yes	No	AE related to renal function (e.g. blood Cr increased and GFR decreased) based on prespecified AE item from MedDRA	Publications	24

Abbreviation: NR,not reported; CKD, chronic kidney disease; GFR, glomerular filtration rate; EMPA, empagliflozin; DAPA, dapagliflozin; CANA, canagliflozin; PLA, placebo; MET, metformin; SIT, sitagliptin; SAXA, saxagliptin; LINA, linagliptin; SU, sulfonylureas; OAD, oral antidiabetic drugs; INS, insulin; PIOG, pioglitazone; MedDRA, medical dictionary for regulatory activities; AE, adverse event; SAE, serious adverse event; Cr, creatinine.

[1]the data of these two trials presented on the clinicaltrials.gov together.

[2]the report with two independent datasets for RCT, which were considered separately.

[3]the incidence of adverse renal events was assumed to be zero

Figure S1 Risk of bias assessments

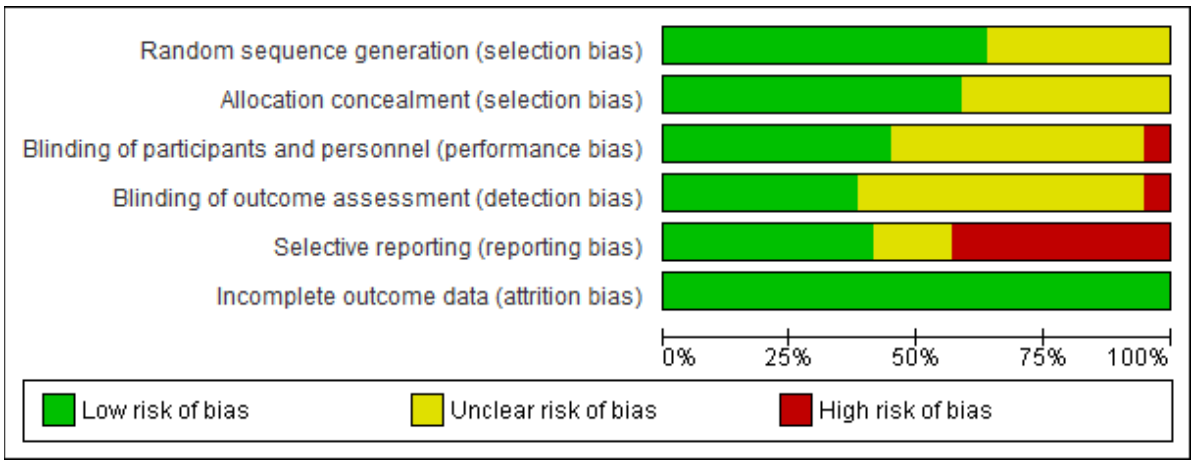


Table S3 Pairwise meta-analysis results of individual SGLT2 inhibitors on composite renal events

Group/Subgroup		n	SGLT2 inhibitor (events/ patients)	Control (events/ patients)	Peto odds ratio (95%CI)	Heterogeneity (I^2 %)
Canagliflozin						
	Overall	15	62/7669	18/3678	1.69 (1.06, 2.72)	0
Control	Placebo	12	41/5114	15/2215	1.41 (0.80, 2.48)	0
	Other active treatments	4	21/2555	3/1463	2.57 (1.10, 6.04)	18.9
Duration	≥ 104 weeks	2	12/1445	4/719	1.45 (0.51, 4.13)	0
	26-104 weeks	5	48/2626	14/1551	1.71 (1.00, 2.92)	37.8
	≤ 26 weeks	8	2/3598	0/1408	4.46 (0.23, 84.77)	0
Mean age	< 60 years	12	23/5731	3/2661	2.69 (1.18, 6.10)	0
	≥ 60 years	3	39/1939	15/1017	1.35 (0.76, 2.40)	0
CVD	Preexisting CVD	0	-	-	-	-
	Non-preexisting CVD	15	62/7669	18/3678	1.69 (1.06, 2.72)	0
CKD	Preexisting CKD	1	17/179	8/90	1.07 (0.45, 2.57)	-
	Non-preexisting CKD	14	45/7490	10/3588	2.05 (1.17, 3.59)	0
Dapagliflozin						
	Overall	23	208/6528	97/6528	1.70 (1.34, 2.16)	11.1
Control	Placebo	20	184/5724	82/3299	1.71 (1.32, 2.21)	14.1
	Other active treatments	3	24/804	15/792	1.63 (0.86, 3.09)	37.9
Duration	≥ 104 weeks	3	28/869	11/372	1.13 (0.56, 2.29)	0
	26-104 weeks	7	149/2250	70/1984	2.06 (1.56, 2.71)	0
	≤ 26 weeks	13	31/3409	16/1735	0.88 (0.47, 1.65)	12.9
Mean age	< 60 years	18	92/5219	40/2863	1.37 (0.95, 1.99)	5.3
	≥ 60 years	5	116/1309	57/1228	1.98 (1.45, 2.70)	7.6
CVD	Preexisting CVD	2	101/942	50/945	2.09 (1.50, 2.92)	0
	Non-preexisting CVD	21	107/5586	47/3146	1.37 (0.97, 1.92)	3.2
CKD	Preexisting CKD	2	16/342	9/171	0.88 (0.38, 2.07)	0
	Non-preexisting CKD	21	192/6186	88/3920	1.80 (1.40, 2.30)	9.8
Empagliflozin						
	Overall	19	536/12783	399/6030	0.62 (0.54, 0.72)	33.3
Control	Placebo	14	535/10199	396/4585	0.62 (0.54, 0.72)	44.2
	Other active treatments	6	1/2584	3/1445	0.24 (0.03, 1.83)	8.7
Duration	≥ 104 weeks	2	526/5452	389/3113	0.62 (0.53, 0.72)	0
	26-104 weeks	11	10/4593	9/2167	0.69 (0.27, 1.74)	51.9
	≤ 26 weeks	6	0/2738	1/750	0.05 (0.00, 3.15)	-
Mean age	< 60 years	15	6/6852	6/3044	0.54 (0.17, 1.79)	49.3
	≥ 60 years	4	530/5931	393/2986	0.62 (0.54, 0.72)	0
CVD	Preexisting CVD	1	525/4687	388/2333	0.62 (0.53, 0.72)	-
	Non-preexisting CVD	18	11/8096	11/3697	0.64 (0.27, 1.51)	41.6
CKD	Preexisting CKD	1	5/419	5/319	0.76 (0.21, 2.65)	-
	Non-preexisting CKD	18	531/12364	394/5711	0.62 (0.53, 0.72)	41.1

Luseogliflozin						
	Placebo	1	8/95	6/50	0.67 (0.21, 2.11)	-

Abbreviation: CI, confidence interval; CVD, cardiovascular disease; CKD, chronic kidney disease; -, not applicable

Table S4 Assessment of loop inconsistency in networks

Loop	Inconsistency factor	95% confidence interval	P-value	Loop heterogeneity tau2
Composite renal events				
PLA-CANA-ACT	0.968	0.00-3.73	0.492	0.000
PLA-EMPA-ACT	0.385	0.00-3.23	0.791	0.000
PLA-DAPA-ACT	0.386	0.00-2.97	0.769	0.000
Acute renal impairment/failure events				
PLA-DAPA-ACT	1.336	0.00-4.71	0.437	0.000
PLA-EMPA-ACT	0.833	0.00-3.71	0.570	0.000
PLA-CANA-ACT	0.774	0.00-4.07	0.645	0.000

Abbreviation: CANA, canagliflozin; DAPA, dapagliflozin; EMPA, empagliflozin; PLA, placebo; ACT, active treatments.

Table S5 Assessment of global inconsistency in networks using the 'design-by-treatment' interaction model.

Network outcome	Chi square	P value for test of global inconsistency
Composite renal events	3.41	0.76
Acute renal impairment/failure	3.65	0.72

Table S6 The results of the surface under the cumulative ranking curve (SUCRA) and mean ranks.

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	Composite renal events		Acute renal impairment/failure	
Treatment	**SUCRA**	**MeanRank**	**SUCRA**	**MeanRank**
Placebo	52.1	3	30.7	4
Canagliflozin	27.0	5	69.5	2
Dapagliflozin	6.0	6	62.0	3
Empagliflozin	90.0	1	72.9	1
Luseogliflozin	74.6	2	-	-
Other Active treatments	50.3	4	15.0	5

Abbreviation: SUCRA, surface under the cumulative ranking curve

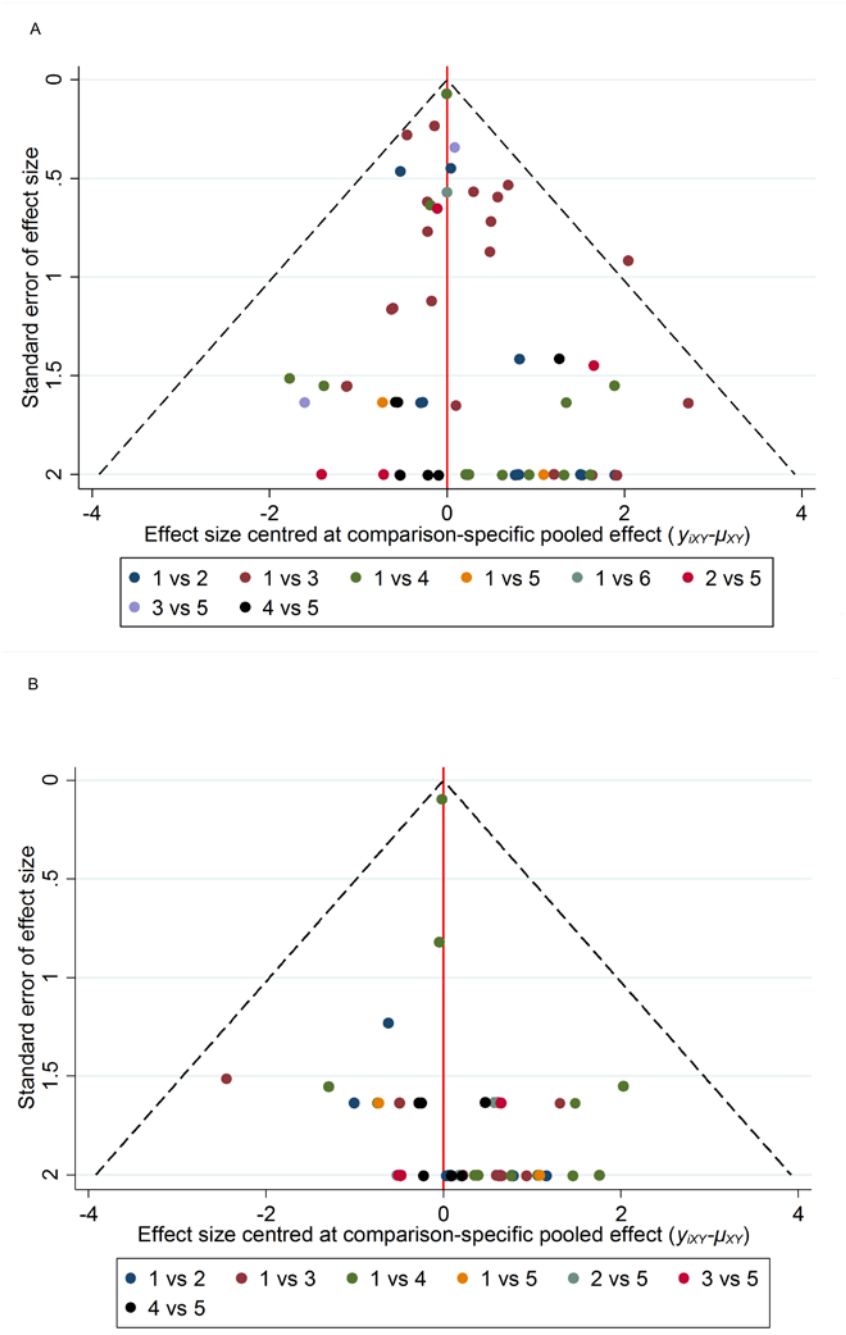
Table S7 Pairwise meta-analysis results of individual SGLT2 inhibitors on acute renal impairment/failure events

Group/Subgroup		n	SGLT2 inhibitor (events/ patients)	Control (events/ patients)	Peto odds ratio (95%CI)	Heterogeneity (I^2)
Canagliflozin						
	Overall	14	4/5912	1/2751	1.82 (0.28, 11.77)	0
Control	Placebo	11	3/3832	1/1525	1.46 (0.18, 11.7)	0
	Other active treatments	4	1/2555	0/1463	4.47 (0.07, 286.7)	-
Duration	≥ 104 weeks	2	1/1445	0/719	4.47 (0.07, 286.7)	-
	26-104 weeks	4	2/1344	1/861	1.01 (0.09, 11.17)	-
	≤ 26 weeks	8	1/3598	0/1408	4.44 (0.07, 287.7)	-
Mean age	< 60 years	12	2/5731	0/2661	4.45 (0.23, 84.77)	0
	≥ 60 years	2	2/656	1/327	1.01 (0.09, 11.17)	-
CVD	Preexisting CVD	0	-	-	-	-
	Non-preexisting CVD	14	4/5912	1/2751	1.82 (0.28, 11.8)	0
CKD	Preexisting CKD	1	2/179	1/90	1.01 (0.09, 11.17)	-
	Non-preexisting CKD	13	2/6208	0/2898	4.45 (0.23, 84.77)	0
Dapagliflozin						
	Overall	20	5/5760	2/3631	1.93 (0.42, 8.83)	39.8
Control	Placebo	17	4/5116	2/2999	1.52 (0.29, 7.92)	50.9
	Other active treatments	3	1/804	0/792	7.43 (0.15, 374.2)	-
Duration	≥ 104 weeks	3	0/869	1/372	0.05 (0.00, 3.18)	-
	26-104 weeks	7	5/2250	1/1984	3.40 (0.66, 17.42)	6.6
	≤ 26 weeks	10	0/2801	0/1435	-	-
Mean age	< 60 years	15	2/4611	0/2563	5.57 (0.29, 107.7)	0
	≥ 60 years	5	3/1309	2/1228	1.32 (0.22, 7.77)	66.2
CVD	Preexisting CVD	2	3/942	1/945	2.73 (0.38, 19.43)	66.8
	Non-preexisting CVD	18	2/4978	1/2846	1.14 (0.10, 12.7)	39.9
CKD	Preexisting CKD	2	0/342	1/171	0.05 (0.00, 3.18)	-
	Non-preexisting CKD	18	5/5578	1/3620	3.40 (0.66, 17.42)	6.6
Empagliflozin						
	Overall	19	298/12783	201/6030	0.72 (0.59, 0.87)	24.5
Control	Placebo	14	298/10199	198/4585	0.73 (0.60, 0.88)	24.9
	Other active treatments	6	0/2584	3/1445	0.07 (0.01, 0.74)	0
Duration	≥ 104 weeks	2	291/5452	193/3113	0.73 (0.60, 0.88)	0
	26-104 weeks	11	7/4593	7/2167	0.58 (0.20, 1.74)	36.7
	≤ 26 weeks	6	0/2738	1/750	0.05 (0.00, 3.15)	-
Mean age	< 60 years	15	4/6852	6/3044	0.33 (0.09, 1.22)	33.5
	≥ 60 years	4	294/5931	195/2986	0.73 (0.60, 0.89)	0
CVD	Preexisting CVD	1	291/4687	192/2333	0.73 (0.60, 0.89)	-

	Non-preexisting CVD	18	7/8096	9/3697	0.46 (0.17, 1.26)	28.2
CKD	Preexisting CKD	1	3/419	3/319	0.76 (0.15, 3.83)	-
	Non-preexisting CKD	18	295/12364	198/5711	0.72 (0.59, 0.87)	32.9

Abbreviation: CI, confidence interval; CVD, cardiovascular disease; CKD, chronic kidney disease; -, not applicable

Figure S2 Comparison-adjusted funnel plot for the network meta-analysis of SGLT2 inhibitors on composite renal events (A) and acute renal impairment/failure events (B). The red line represents the null hypothesis that the study-specific effect sizes do not differ from the respective comparison-specific pooled effect estimates. The two black dashed lines represent a 95% CI for the difference between study-specific effect sizes and comparison-specific summary estimates. y_{ixy} is the noted effect size in study i that compares x with y. μ_{xy} is the comparison specific summary estimate for x versus y. 1, placebo; 2, canagliflozin; 3, dapagliflozin; 4, empagliflozin; 5, active treatments;6, luseogliflozin.



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