The Renoprotective Effects of SGLT2 Inhibitors versus Placebo in Patients with Type 2 Diabetes with or without Prevalent Kidney Disease: A Systematic Review and Meta-analysis

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Aims: We undertook a systematic review and meta-analysis to assess the efficacy and safety of Sodium-Glucose cotransporter 2 inhibitors (SGLT2is) on kidney outcomes in patients with type 2 diabetes mellitus (T2DM) with or without prevalent kidney disease.

Materials and Methods: PubMed, Web of science, Embase and the Cochrane Library were systematically searched for randomized controlled trials (RCTs) to assess the efficacy and safety of SGLT2is treatment versus placebo in T2DM. The weighted mean difference (WMD) and its 95% confidence interval (CI) were applied for continuous variables, and the risk ratio (RR) and its 95%CI were used for dichotomous outcomes. Patients were categorized according to whether baseline mean estimated glomerular filtration rate (eGFR) was less or more than 60 ml/min/1.73 m^2.

Results: 25 eligible studies with 43721 participants were included. There was an initial and small decrease of eGFR in early treatment period (WMD, -4.63; 95%CI, -6.08 to -3.19 mL/min/1.73 m^2), which was noted at 1-6

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weeks and gradually narrowed over time, with a protection from eGFR decline in the long term (WMD, 3.82; 95% CI, 2.80 to 4.85 mL/min/1.73 m^2). SGLT2is significantly delayed albuminuria progression (RR, 0.71; 95%CI, 0.66 to 0.76) and promoted albuminuria regression (RR,1.71; 95%CI, 1.54 to 1.90), improved the composite of e40% decrease in eGFR, the need for renal-replacement, or death from renal causes (RR,0.57; 95%CI, 0.49 to 0.66), and reduced all-cause mortality (RR,0.84; 95%CI, 0.75 to 0.94),while they significantly increased the risk of genital infection (RR,3.43; 95%CI, 2.87 to 4.10) versus placebo in T2DM. Meta-regression analyses showed that the eGFR-preservation effects were not significantly associated with patients' basic characteristics (age, BMI, HbA1c, and eGFR level), but influenced by drug administration (treatment duration, type and dosage of SGLT2is). Subgroup analyses showed that the relative effects on renal outcomes of SGLT2is versus placebo were similar across eGFR subgroups (P heterogeneity > 0.05).

Conclusions: SGLT2is slowed eGFR decline, lowered albuminuria progression, improved adverse renal endpoints and reduced all-cause mortality, but increased risk of genital infections versus placebo in T2DM. The indication of consistent renal benefits across categories of baseline eGFR levels may allow additional individuals to benefit from SGLT2is therapy.

Introduction

Diabetic nephropathy has become the most significant cause of end-stage renal disease (ESRD) worldwide and more than 40% of diabetic patients has progressed to an advanced stage because of insufficiency in management.[1] As the rate of diabetes increases, diabetic nephropathy and associated adverse events have become a growing public health concern.[2] To delay the deterioration in kidney function requires intensive glycemic and blood pressure control. However, the general antihyperglycemic therapy, including the use of metformin, sulfonylureas and thiazolidinediones, remains controversial regarding its efficiency and tolerability

in preventing the incidence and progression of chronic kidney disease (CKD).[3] Therefore, there is a persistent desire for a new, effective and well-tolerated therapy to prevent and delay kidney disease progression in diabetic patients.

SGLT2 is a high-capacity and low-affinity protein abundantly expressing in the initial proximal renal tubules, which plays a significant role in the reabsorption of glucose through co-transport with sodium. SGLT2is, by blocking glucose reabsorption in the kidney, represent a novel approach to reduce hyperglycemia independent of insulin secretion and action.[4, 5] Additional benefits beyond glycemic control such as weight loss and reduction in blood pressure, may also play important role in delaying deterioration of kidney function.[6] Recently, more and more clinical trials as well as overviews have evaluated renal effects of SGLT2is and indicated the possibility to delay kidney disease progression in T2DM patients. In particular, a meta-analysis[7] which studied renal outcomes of SGLT2is in type 2 diabetes reported that SGLT2is treatment prevented eGFR decline and albuminuria progression. However, they studied the renal outcomes without considering baseline kidney function which varies in included studies, and didn't give an analysis about the renal-related adverse outcomes such as albuminuria progression, ESRD, renal-related death and so on. Heterogeneity in that analysis was considerably high and forest plots didn't show significant difference between SGLT2is and controls. Lacking of meta regression or subgroup analysis by possible co-founders, such as drug dosage or participants' basic characteristics, stopped them from getting more accurate conclusions.

With this systematic review and meta-analysis, we aim to synthesize all available clinical trial information for SGLT2is administration in T2DM patients, and evaluate the efficacy and safety of SGLT2is treatment on kidney outcomes.

Materials and Methods

Data Sources and Search Strategy

We performed this systematic review and meta-analysis based on a prespecified protocol (PROSPERO registration No CRD42018112873), and report our methods and results according to the PRISMA guidelines[8]. We searched PubMed, web of science, Embase and the Cochrane Library from inception to November, 2018, as well as grey literature sources, without language restrictions. Two reviewers (Ch. Wang, Y. Zhou) independently screened titles and abstracts of all records, full texts of potentially eligible studies. The detailed search strategy is available in Table S1. Any disagreements were resolved by consensus with a third reviewer (Y. Wang).

Inclusion and exclusion criteria

Eligible trials were listed and assessed independently by 2 reviewers (Ch Wang, Y. Zhou) using predefined inclusion criteria. Studies were included if they met the following criteria: (1) randomized controlled design; (2) type 2 diabetic patients with or without prevalent kidney disease (defined as an eGFR < 60 ml/min/m^2 as calculated by the MDRD formula); (3) patients 18 years or older; (4) the intervention group received SGLT2is including dapagliflozin, canagliflozin or empagliflozin; (5) the comparison group received placebo; (6) reported at least one outcome of interest. There were no restrictions on length of follow-up.

The exclusion criteria were as follows: (1) animal studies; (2) non-randomized design; (3) patients with diabetes other than Type 2 or patients with underlying debilitating conditions (4) articles that provided inadequate information of interest or primary data.

Outcomes of Interest

All studies reporting at least one of the following outcome measures: absolute changes in eGFR from baseline, risk of albuminuria progression (change from either normoalbuminuria to microalbuminuria or

macroalbuminuria, or from microalbuminuria to macroalbuminuria) and regression (opposed to albuminuria progression), renal composite (a composition of sustained 40% reduction in eGFR, ESRD which need for renal-replacement therapy and death from renal causes), all-cause mortality, and genital infections. Change in eGFR from baseline was considered as the primary outcome, while the others were considered the secondary outcomes of interest.

Study selection and data extraction

Two independent authors (ZL.Kong, Y. Zhou) screened the search results and selected studies in strict accordance with the inclusion and exclusion criteria. Two authors (ZL.Kong, Y. Zhou) used predefined forms to extract data from each included study: trial characteristics (first author, publication year, sample size, duration of therapy, type and dose of drug), participants' baseline [age, gender, body mass index (BMI), HbA1c, and eGFR level], and outcomes of interest mentioned above. When data items were not available, requests for the information were sent to the corresponding authors. Any resulting disagreements were resolved by discussion with a third author (WS Lv).

Quality assessment

The quality of eligible study was assessed using the Cochrane Collaboration's risk-of-bias assessment tool,[9] which included random sequence generation (selection bias), allocation concealment (selection bias), blinding of participants and personal (performance bias), blinding of outcome assessment (detection bias), incomplete outcome data (attrition bias), selective reporting(reporting bias) and other potential sources of bias. The judgment for each entry involves answering a question, with 'Yes' indicating low risk of bias, 'No' indicating high risk of bias, and unclear indicating lack of information or uncertainty about the possibility of bias. Disagreements between authors were resolved with consensus.

Data synthesis and statistical analysis

For each outcome measure of interest, the MD and its 95% CI were applied for continuous variables while RR and its 95% CI were used for dichotomous outcomes. Considering the differences in baseline participants characteristics and drug administration, a random effects model was selected for analyses. A P-value < 0.05 for any test or model was considered statistically significant. The degree of between-study variability attributable to heterogeneity beyond chance was calculated using the I^2 statistic and Q statistic.[10] Outcomes with I^2 levels from 0% to 40% were considered minimally heterogeneous, while I^2 >50% was considered an indication of statistically significant heterogeneity among included studies.

In order to keep baseline comparable and further explore the relationship between baseline renal function and renal effects, we performed separate or subgroup analyses based on basal eGFR levels (eGFR ≥ or < 60 ml/min/1.73m^2). Considering previously reported time-related renal effects, we also predefined subgroup analyses based on treatment duration in eGFR group for further study. Prespecified univariable meta-regression analyses were also performed to evaluate if efficacy outcomes are associated with participants' baseline characteristics (age, BMI, HbA1c, or eGFR level) as well as drug administration (type and dosage of SGLT2is, treatment duration). Forest plots were used for graphic representation of the data. Funnel plots and Egger test were used for assessing publication bias. If necessary, trim and fill method was used to identify and correct for funnel plot asymmetry arising from publication bias.

Risk of bias assessment were performed by the Review Manager statistical software package (Version 5.3) and the meta-analyses and regression-analyses were performed by the STATA statistical software package (Version 12.0).

RESULTS

Search results and study characteristics

The combined search of the PubMed, Embase, Web of science, and Cochrane Library of Controlled Trials databases identified 1905 citations. We excluded 1282 articles because of a duplication of studies, and 501 articles following a review of the title and abstract; 122 were retrieved for a detailed evaluation, and 25 RCTs[11-35] with 43721 patients satisfying the inclusion criteria were finally analyzed in a meta-analysis published. The process used to select studies for the meta-analysis is given in Figure S1.

Characteristics of the 25 eligible studies are presented in Table S1. Most of the included studies had a parallel-group design, from which 3 different SGLT2 inhibitors (canagliflozin, dapagliflozin and empagliflozin) were studied. All of the 25 included studies were placebo controlled, from which 2 trials[26, 28] were also compared with active comparators (Metformin XR, Sitagliptin). Participants were inadequately controlled on background antidiabetic drugs such as insulin, metformin, sulfonylureas, or thiazolidinediones, with HbA1c between 7.0% and 11.0% at baseline. Follow-up duration ranged from less than 6 weeks to more than 4 years, from which EMPA-REG OUTCOME, CANVAS Program and DECLARE TIMI-58 trial which conducted in large groups of population were with an expected average follow-up of more than 3 years.

Quality of the included trials

A summary of study quality is presented in Figure S2. In accordance with the Cochrane Collaboration's tool for assessing risk of bias, "High risk of bias" indicates possible bias that weakens confidence in the results, and an overall "low risk of bias" classification was assigned to studies that had been scored as low risk for all key domains indicating that any possible bias is unlikely to alter results. For a domain to be classified as "unclear risk of bias," there must have been insufficient information to allow judgment of either low risk or high risk. The risk of bias for most studies was assessed as low, and all data were derived from randomized studies.

Efficacy outcomes

15 trials[12, 13, 16-18, 20, 22, 24, 25, 28-33] with participants' mean eGFR ≥ 60ml/min/1.73m^2 and 6 trials[12, 14, 15, 21, 32, 35] enrolling participants with mean eGFR < 60ml/min/1.73m^2 reported effects of SGLT2is on absolute changes in eGFR. Similar time-dependent preservation in eGFR were observed consistent with the overall trial population findings. Compared with placebo, initial decrease in eGFR was observed with SGLT2is treatment, which was noted at 1-6 weeks (WMD, -5.02 [95%CI, -7.60 to -2.44] mL/min/1.73 m^2 in subgroup of eGFR < 60ml/min/1.73m^2; WMD, -4.45 [95%CI, -6.20 to -2.71] mL/min/1.73m^2 in subgroup of eGFR ≥ 60ml/min/1.73m^2; WMD, -4.63[95%CI, -6.08 to -3.19] mL/min/1.73 m^2 in overall participants) and gradually narrowed over time. Until week 72-104, SGLT2is showed no inferiority and even superiority in preserving eGFR versus placebo (WMD,0.07 [95% CI, -1.56 to 1.69] mL/min/1.73 m^2; WMD,1.74 [95% CI, 0.58 to 2.90] mL/min/1.73 m^2; WMD,1.17 [95% CI, 0.23 to 2.12] mL/min/1.73 m^2), and the superiority became more significant after 4 years (WMD, 3.10 [95% CI, 1.88 to 4.32] mL/min/1.73 m^2; WMD, 4.63 [95% CI, 3.84 to 5.42] mL/min/1.73 m^2; WMD, 3.82 [95% CI, 2.80 to 4.85] mL/min/1.73 m^2). Heterogeneity between studies within each subgroup was low, while heterogeneity between subgroups was considerably significant (P<0.00001 for subgroup difference; Figure 1), indicating treatment duration was the source of heterogeneity.

6 studies[12, 14, 21, 24, 32, 35] reported effects of SGLT2is on albuminuria progression and 6 studies[12, 14, 18, 21, 24, 35] reported on albuminuria regression. Compared with placebo, more patients with SGLT2is treatment shifted to a lower albuminuria level (RR,1.71; 95%CI, 1.54 to 1.90) and fewer progressed to a higher level (RR,0.71; 95% CI, 0.66 to 0.76). We did not observe significant difference between different eGFR subgroups either in albuminuria progression (P=0.333 for subgroup difference) or in albuminuria regression (P=0.678 for subgroup

difference), indicating similar advantages for patients in different stages of renal function. Low heterogeneity between included studies indicated a robust result in this group (Figure 2).

3 studies[24, 32, 34] reported effects of SGLT2is on renal composite which is a composite of a sustained 40% reduction in eGFR, ESRD which need for renal-replacement therapy and death from renal causes. Compared with placebo, the reduction in composite renal endpoints with SGLT2is treatment was present across all baseline eGFR levels (RR,0.57; 95%CI, 0.49 to 0.66),with a 32% renal composites reduction in patients whose mean eGFR < 60 mL/min /1·73 m² (RR,0.68; 95%CI, 0.52 to 0.89) and a 48% reduction in patients whose mean eGFR ≥ 60 mL/min /1·73 m² (RR,0.52; 95%CI, 0.43 to 0.63).It seems that the improvements in renal composites tend to be greater in those with preserved renal function, but the statistically insignificant difference between subgroups (P=0.673 for subgroup difference; Figure 3) indicated consistent renoprotective benefits regardless of baseline renal function levels.

13 studies[11, 12, 14, 16, 21, 22, 28, 29, 32-36] reported effects of SGLT2is on risk of all-cause mortality. Compared with placebo, SGLT2is therapy significantly reduced the risk of all-cause mortality versus placebo in T2DM (RR,0.84; 95%CI, 0.75 to 0.94). Similarly, we did not observe significant difference between subgroups stratified by baseline eGFR levels (P=0.85 for subgroup difference; Figure 4), indicating the relative reductions in risk of all-cause mortality with SGLT2is were independent of baseline eGFR levels.

Safety outcomes

SGLT2is increased urinary glucose excretion with a corresponding reduction in blood glucose levels, which increased the possibility of genital infections events.[37] We did the meta-analysis on the frequency of genital infections with SGLT2is treatment to further evaluate drug safety. Compared with placebo, elevated rates of genital infections were presented across all baseline eGFR levels with SGLT2is treatment (RR,3.43; 95%CI,

2.87 to 4.10). Subgroup analysis showed that patients with more severe kidney disease tend to experience lower rates of genital infections, particularly with 2.44-fold in patients whose eGFR < 60 mL/min /1·73 m² (RR,2.44; 95%CI, 1.72 to 3.46) and 3.77-fold in patients whose eGFR ≥ 60 mL/min /1·73 m² (RR,3.77; 95%CI, 3.10 to 4.58) respectively, which may account for the reduction in urinary glucose excretion with increasing renal impairment. However, differences between subgroups were calculated not statistically significant (P=0.19 for subgroup difference; Figure 5), indicating the adverse event profile in patients with more advanced kidney disease was still consistent with the overall trial population.

Meta-regression analysis

Meta-regression analyses conducted in eGFR group showed a significant association between eGFR-preservation effects and SGLT2is treatment duration (Coef. = 0.032, 95% CI, 0.024 to 0.040, P=0.000) which is consistent with the results of subgroup analyses, suggesting a persistent preservation of renal function with long-term SGLT2is treatment. We also detected a significant association between renoprotective effects and type of SGLT2is (empagliflozin preferred; Coef. = 1.750, 95% CI, 0.546 to 2.953, P=0.005) as well as drug dosage (larger dose preferred; Coef. = -2.007, 95% CI, -3.598 to -0.417, P=0.015). Meanwhile, the eGFR-preservation effects were not observed associated with patients' baseline characteristics (age, BMI, HbA1c and eGFR level; Table 1; Figure S3).

Assessment of publication bias

Funnel plots did not reveal asymmetry in any other outcomes except for eGFR group (Egger's test: P < 0.005 for eGFR change, P = 0.285 for albuminuria progression, P = 0.796 for albuminuria regression, P = 0.424 for all-cause mortality, P = 0.445 for genital infection). Given the small number of studies included reporting the composite renal endpoints, we did not present the evaluation of publication bias in this group. We used the

trim and fill method to identify and correct for funnel plot asymmetry arising from publication bias, from which we found the estimated value of combined effect did not change significantly before and after trim and fill, indicating the publication bias has little effect on overall outcomes and the result is relatively robust (Figure S5-S7).

DISCUSSION

This large quantitative review indicated that SGLT2 inhibitors produced a time-dependent preservation of eGFR, lowered albuminuria progression, improved adverse renal endpoints and reduced all-cause mortality, regardless of baseline renal function levels in type 2 diabetes. Patients' basic characteristics (age, BMI, HbA1c and eGFR level) were not significantly associated with the preservation of eGFR, while SGLT2is administration (type, dosage, treatment duration) made an influence on the overall outcomes. However, caution may be warranted for incidence of genital infections, for approximate 3.43-fold risk was observed in patients treated with SGLT2is compared with placebo. Overall, administering SGLT2is is a feasible and promising way to prevent and delay kidney disease progression for T2DM patients.

SGLT2is induced an initial and small reduction in eGFR during early treatment period, which was noted at 1-6 weeks and gradually narrowed over time, finally with a long-term protection from eGFR decline. Recent studies[38] exploring effects of SGLT2is on inflammatory and kidney injury markers have observed no correlations between early changes of renal function indicators and changes of kidney injury markers (KIM-1, IL-6 et al.), and further pointed out that the early transient changes of eGFR were not associated with an excess risk of renal adverse events. We considered the initial drop of eGFR was attributed to the amelioration of volume overload related to an osmotic diuresis which is consistent with an increased incidence of adverse events potentially indicative of volume depletion which also start early after initiating therapy,[30] as well as

tubuloglomerular feedback[39] with increased sodium delivery to the juxtaglomerular apparatus. SGLT2is increase sodium delivery to the macula densa, and the increased sodium delivery is sensed as an increase in circulating volume at the level of the juxtaglomerular apparatus, thus leading to a constriction of afferent renal arterioles, a reduction in intraglomerular pressure and a reversible reduction in single nephron GFR.[18]

Microalbuminuria was considered as a biomarker of renal function as well as cardiovascular risk, with reduction suggesting an overall favorable effect on cardiovascular risk and possibly progression to ESRD.[40] Our analyses showed that SGLT2is significantly delayed albuminuria progression and promoted albuminuria regression versus placebo. Beside continuous glucose excretion and the resulting metabolic effects, SGLT2is could also exert intrarenal anti-inflammatory effects mediated by inhibition of glucose entry into tubular cells, which have indeed been linked with albuminuria reduction.[41] The restore of the charge or size selectivity of the glomerular basement membrane may also play a helpful role.[42]

SGLT2is also significantly reduced the risk of renal adverse endpoints (composite of a sustained 40% reduction in eGFR, ESRD and renal death), as well as reduced the risk of all-cause mortality in T2DM patients. Overall, besides the general blood pressure-lowering and weight-loss effects, the renoprotective effects could also be attributed to the reduction in glomerular hyperfiltration mediated through increased natriuresis and tubuloglomerular feedback[43] as well as the beneficial energy utilization which leads to the anti-inflammatory and antifibrotic benefits.[44, 45]The improvement in renal hypoxia associated with reduction of the oxygen-consuming transport workload may help to improve tubular cell integrity and potentially tubular albumin reabsorption.[38, 46]

Adverse events such as urinary tract infection, acute renal failure, hyperkalemia, fractures, lower limb amputations and hypoglycemia were previously reported to occur at lower or similar rates with SGLT2is versus

placebo, while greater percentages of patients treated with SGLT2is than placebo had events consistent with genital infections[47]. Compared with placebo, approximate 3.43-fold genital infection risk was observed in patients treated with SGLT2is in this comprehensive analysis. Similar with the efficacy outcomes, the adverse event profile in patients with more advanced kidney disease was still consistent with the overall trial population.

As individuals with CKD are among the highest risk group for progression to ESRD, it is important to understand whether the benefits of SGLT2is for renal outcomes are similar to those in people with normal renal function. Prior studies suggested that SGLT2is were to exhibit reduced hypoglycemic efficacy and increased toxicity in patients with more advanced CKD and are generally contraindicated in those with an eGFR of less than 45 mL/min/1.73 m^2.[48] However, whether the renopotective effects are consistent with patients with different eGFR levels is still incompletely understood. A pooled analysis of 11 RCTs[49] have pointed that regardless of the decreased HbA1c-lowering effects of dapagliflozin as renal function declines, the pharmacodynamic changes such as blood pressure, albuminuria, and body weight were not significantly dependent on renal function. Another subgroup analysis with patients' baseline eGFR < 60 ml/min/1.73m^2 of the EMPA-REG OUTCOME study[50] indicated the beneficial outcomes of empagliflozin were no difference from those with normal baseline kidney function, and the adverse event profile was also proved similar. Our analyses further confirmed that the improved clinical renal outcomes with SGLT2is were consistent across categories of baseline eGFR levels in T2DM, indicating that the effects of SGLT2is on renal function may be to some degree uncoupled from their glycemic effects. What' more, the indication of consistent renal benefits in patients with lower versus higher eGFR levels made us reconsider current eGFR-based limitations on the use of SGLT2is, which may allow additional individuals to benefit from SGLT2is therapy. However, cautious should

to paid to use SGLT2is in patients with an eGFR <30 ml/min/1.73 m^2, due to very few data available at this advanced stage of CKD.

To our knowledge, the current study represents the largest systematic review of SGLT2is administration on kidney disease progression as well as all-cause mortality in type 2 diabetes. This study, which gave an in-depth analysis on the time-dependent renal efficacy outcomes as well as composite kidney adverse events, provides strong evidence for the clinical applications of SGLT2is in T2DM. What' more, the indication of consistent renal benefits in patients with different eGFR levels made us reconsider current eGFR-based limitations on the use of SGLT2is, which may allow additional individuals to benefit from SGLT2is therapy. The study has some potential limitations. First, we only analyzed three common types of SGLT2is (Empagliflozin, Dapagliflozin and Canagliflozin), without studying else type of SGLT2is such as tofogliflozin, luseogliflozin and ipragliflozin. Second, the main studying endpoints in some included trials are metabolic parameters and cardiovascular disease rather than kidney outcomes, therefore the publication bias will probably inaccurately reflect the effect of SGLT2is on renal endpoints. Next, heterogeneity among the eligible RCTs were existed probably due to differences in the baseline characters of participants, sample size or combined treatment. For this reason, we selected random effects model in all analyses, performed meta-regression as well as subgroup analyses to find sources of heterogeneity and further explore the relationship between possible confounders and outcomes of interest. Third, asymmetric funnel plots in primary outcome (eGFR) indicated existence of publication bias, but next conducted trim and fill method to correct for funnel plot asymmetry arising from publication bias furtherly showed a robust result. Additionlly, the relatively small number of participants with eGFR < 30ml/min/1.73m^2 precludes our ability to draw definite conclusions about renal effects of SGLT2is in patients at this advanced stage of CKD.

In conclusion, SGLT2is slowed eGFR decline, lowered albuminuria progression, improved adverse renal endpoints and reduced all-cause mortality, but increased genital infection risk versus placebo in T2DM with or without prevalent kidney disease. The renoprotective effects were not significantly influenced by patients' baseline characteristics, but associated with choices of drug administration (treatment duration, drug variety and drug dosage). The indication of consistent renal benefits across categories of baseline eGFR levels for T2DM patients may allow additional individuals to benefit from SGLT2is therapy.

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Conflict of interest

No potential conflicts of interest relevant to this article were reported.

Author contributions

YG Wang and Chen Wang did the study design. Y Zhou and ZL Kong did the literature search. Y Zhou and Chen Wang contributed to the data acquisition. Y Zhou and WS Lv contributed to data interpretation and statistical analysis. X Wang and Z Geng contributed to supervision or mentorship. Y Zhou and Chen Wang wrote the first draft of the report. YG Wang and ZL Kong edited the report and all authors contributed to revision of the report. All authors reviewed the manuscript, approved the final draft and agreed to submit it for publication.

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Table 1. Meta-regression analysis of demographic and clinical variables on renal function among type 2 diabetes

Characteristics	Coefficient, 95% CI	P-value	tau^2	Adj R-squared (%)
Age (years)	0.005 (-0.163,0.172)	0.955	5.077	-2.83
BMI (kg/m^2)	-0.221 (-0.635,0.194)	0.287	5.416	0.10
HbAlc (%)	1.733 (-1.490,4.957)	0.283	4.950	-0.25
eGFR (ml/min/1.73 m^2)	0.005 (-0.039, 0.049)	0.817	5.066	-2.60
Treatment duration (years)	0.032 (0.024,0.040)	0.000	1.106	77.60
Daily dosage (mg/d)	-2.007 (-3.598, -0.417)	0.015	4.280	13.33
Type of SGLT2 inhibitor	1.750 (0.546, 2.953)	0.005	3.899	21.04%

All above are univariate meta-regression analyses except for type of SGLT2is, in which dapagliflozin and empagliflozin were both compared with canagliflozin which was used as a reference.

Proportion of between-study variance explained with Knapp-Hartung modification; BMI, body mass index; eGFR, estimated glomerular filtration rate.

LEGENDS TO FIGURES

Figure 1. Forest plot for absolute change in eGFR in patients with (A) baseline eGFR more than 60 ml/min/1.73 m^2, (B) baseline eGFR less than 60 ml/min/1.73 m^2. The left favours SGLT2is and the right favours placebo. Abbreviations: CI, confidence interval; MD, mean difference.

Figure 2. Forest plot for incidence of (A) albuminuria progression, (B) albuminuria regression. The left favours SGLT2is and the right favours placebo. Abbreviations: CI, confidence interval; RR, risk ratio.

Figure 3. Forest plot for incidence of renal composite (a composite of a sustained 40% reduction in eGFR, the need for renal-replacement therapy and death from renal causes). The left favours SGLT2is and the right favours placebo. Abbreviations: CI, confidence interval; RR, risk ratio.

Figure 4. Forest plot for incidence of all-cause mortality. The left favours SGLT2is and the right favours placebo. Abbreviations: CI, confidence interval; RR, risk ratio.

Figure 5. Forest plot for incidence of genital infection. The left favours SGLT2is and the right favours placebo. Abbreviations: CI, confidence interval; RR, risk ratio.

SUPPLEMENTARY MATERIAL

Table S1. Search strategy

Table S2. Characteristics of Trials Included in the Present Analysis

Figure S1. Study flow diagram. Abbreviation: RCTs, randomized clinical trials.

Figure S2. (A) Risk of bias summary of included trials; (B) Risk of bias graph.

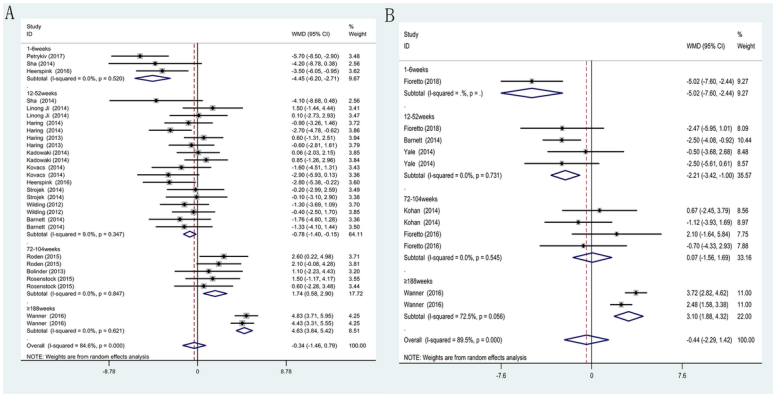
Figure S3. Meta-regression bubble plots of the association between mean changes in eGFR and (A) Age, (B) Body mass index, (C) HbA1c (D) eGFR, (E) type of SGLT2 inhibitors, (F) dosage of SGLT2 inhibitors, (G) SGLT2 inhibitors treatment duration. The size of each circle is inversely proportional to the variance of change.

Figure S4. Trim and fill method to correct for funnel plot asymmetry arising from publication bias for absolute changes in eGFR in (A) patients with baseline eGFR more than 60 ml/min/1.73 m^2, (B) patients with baseline eGFR less than 60 ml/min/1.73 m^2, (C) overall patients

Figure S5. Funnel plot of (A) albuminuria progression, (B) albuminuria regression events for SGLT2 inhibitors versus placebo. No evidence of publication bias was detected in this meta-analysis (Egger's test: P=0.285; P=0.796).

Figure S8. Funnel plot of all-cause mortality events for SGLT2 inhibitors versus placebo. No evidence of publication bias was detected in this meta-analysis (Egger's test: P = 0.424).

Figure S7. Funnel plot of genital infection events for SGLT2 inhibitors versus placebo. No evidence of publication bias was detected in this meta-analysis (Egger's test: P = 0.445).



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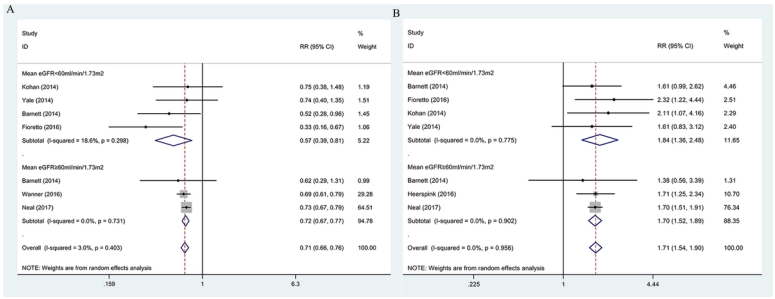

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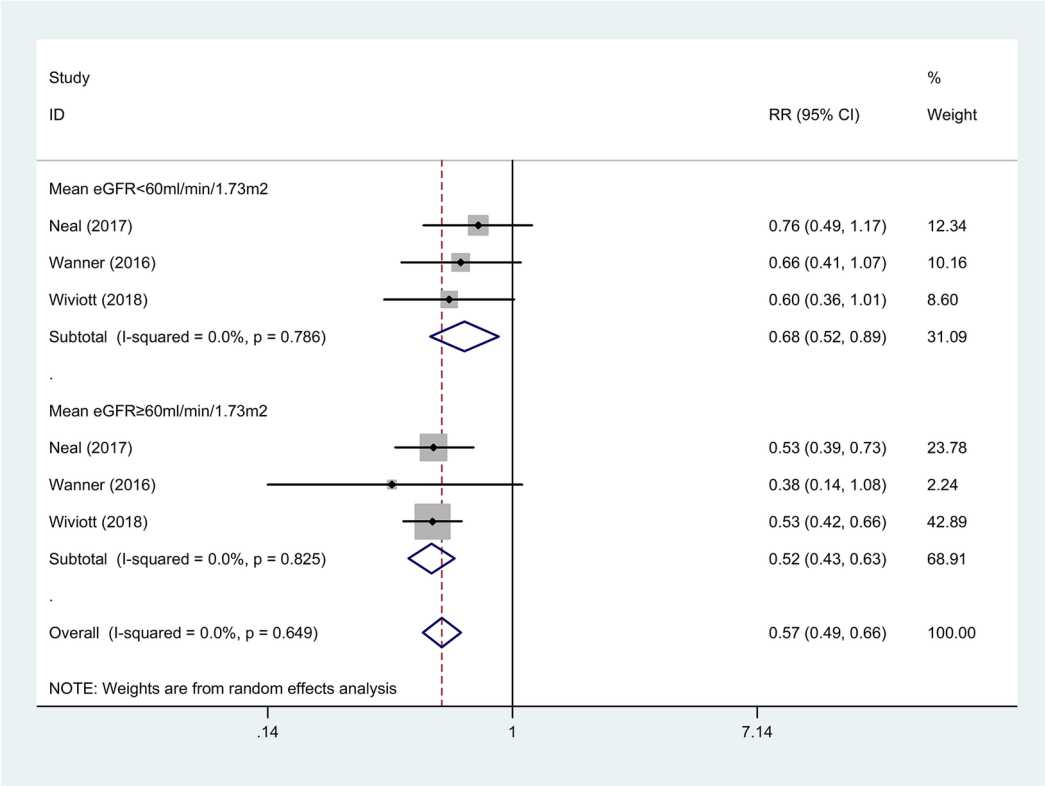

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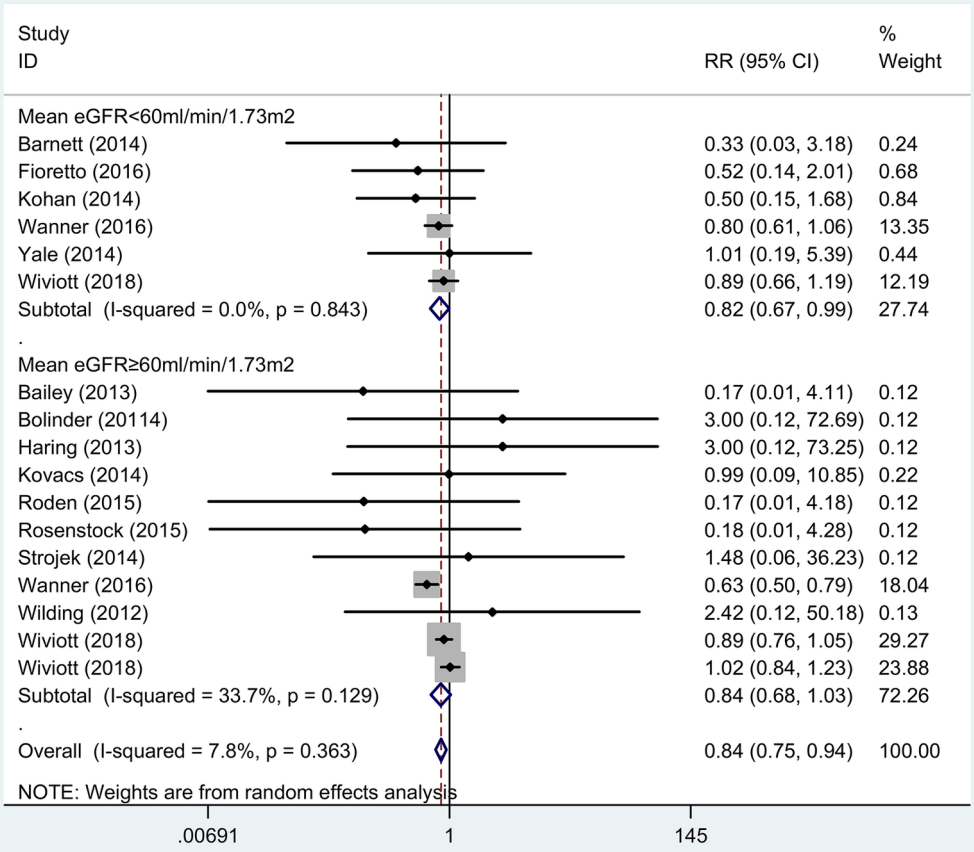

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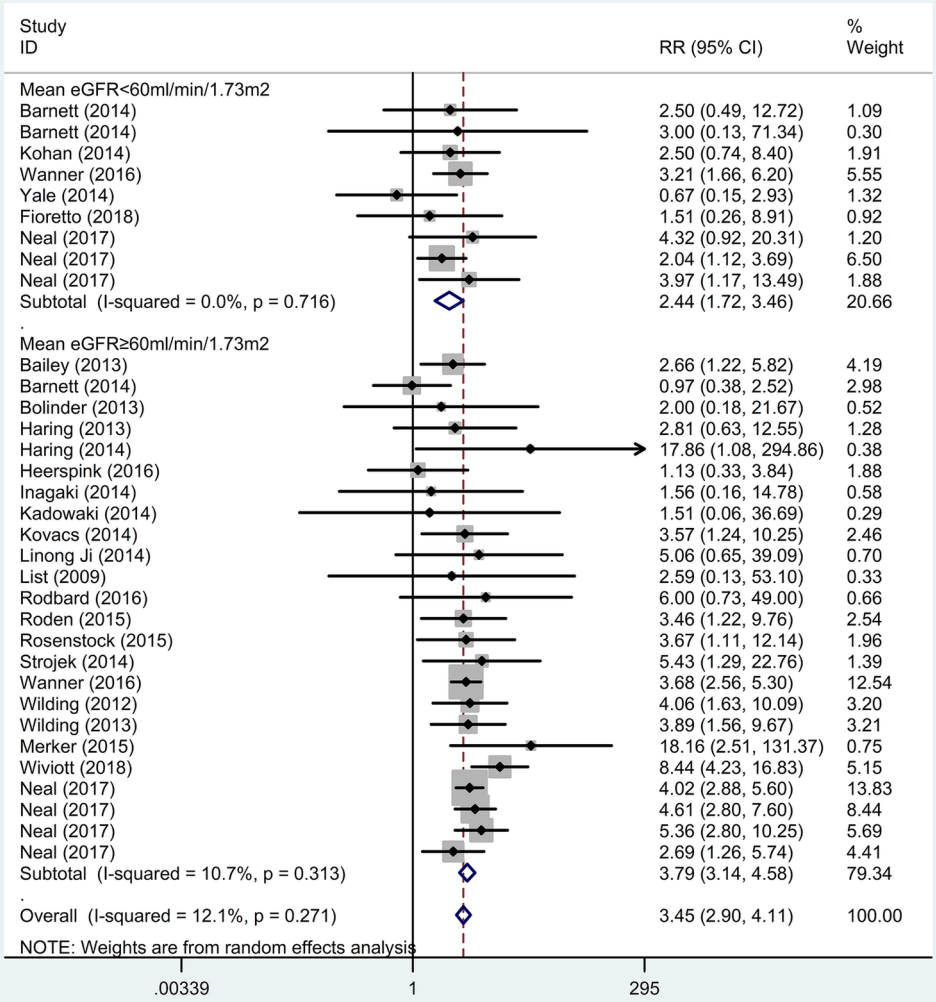

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