




BMJ Open Cardiovascular and renal efficacy and safety of sodium-glucose cotransporter-2 inhibitors in patients without diabetes: a systematic review and meta-analysis of randomised placebo-controlled trials

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ABSTRACT

Objectives To assess the cardiovascular and renal efficacy and safety of sodium-glucose cotransporter-2 (SGLT2) inhibitors in patients without diabetes.

Methods We searched PubMed, MEDLINE, Embase and Cochrane Library for publications up to 17 August 2022. Certainty of evidence was assessed using the Grading of Recommendations, Assessment, Development and Evaluation approach. Random-effects meta-analyses were performed to pool effect measures across studies. Risk ratios (RRs) with 95% CIs are expressed for composite cardiovascular outcome of cardiovascular death or hospitalisation for heart failure, cardiovascular death, hospitalisation for heart failure, all-cause mortality and composite renal outcome of $\geq 50\%$ reduction in estimated glomerular filtration rate (eGFR), end-stage kidney disease or renal death. Annual rate of change in eGFR is expressed as the mean difference with 95% CI.

Results We identified four trials with 8927 patients with heart failure or chronic kidney disease (CKD). Compared with placebo, SGLT2 inhibitors showed favourable effects on the composite cardiovascular outcome (RR: 0.79, 95% CI: 0.71 to 0.87; moderate certainty), cardiovascular death (0.85, 0.74 to 0.99; moderate certainty), hospitalisation for heart failure (0.72, 0.62 to 0.82; moderate certainty), the composite renal outcome (0.64, 0.48 to 0.85; low certainty) and the annual rate of change in eGFR (mean difference: 0.99, 0.59 to 1.39 mL/min/1.73 m²/year; moderate certainty), while there was no significant difference in all-cause mortality (0.88, 0.77 to 1.01; very low certainty). Moderate certainty evidence indicated that SGLT2 inhibitors reduced the risk of serious adverse events and acute renal failure. Low certainty evidence suggested that SGLT2 inhibitors increased the risk of urinary tract infection and genital infection, while there were no differences in discontinuation due to adverse events, amputation, fracture, hypoglycaemia, ketoacidosis or volume depletion.

Conclusions Evidence of low to moderate certainty suggests that SGLT2 inhibitors provide cardiorenal benefits

STRENGTHS AND LIMITATIONS OF THIS STUDY

- ⇒ Extraction of non-diabetic data from currently available randomised clinical trials (RCTs), this systematic review and meta-analysis enrolled 8927 patients with heart failure or chronic kidney disease, and over 3500 events of cardiovascular and renal outcomes.
- ⇒ Six different types of efficacy outcomes and 10 safety outcomes were analysed to evaluate the cardiorenal protective effects and drug safety of sodium-glucose cotransporter-2 inhibitors.
- ⇒ The Grading of Recommendations, Assessment, Development and Evaluation approach was used to appraise the body of the evidence.
- ⇒ Only four RCTs were included, and most of the trials had a relatively short study duration, which limited the power of the analyses of endpoints such as all-cause mortality.
- ⇒ Focusing on long-term clinical outcomes of chronic conditions, studies with acute conditions or follow-up duration less than 1 year were not included.

but have increased risk for urinary tract infection and genital infection in patients without diabetes and with heart failure or CKD.

PROSPERO registration number CRD42021239807.

INTRODUCTION

Sodium-glucose cotransporter-2 (SGLT2) inhibitors were initially developed and approved as glucose-lowering drugs with the unique mechanism of inducing glycosuria in patients with type 2 diabetes.¹ Recent large randomised clinical trials (RCTs) have reported that SGLT2 inhibitors improved cardiovascular (CV) and renal outcomes, most notably reducing the risks of heart failure and kidney failure among patients with diabetes with high CV risk.^{2–3} Post hoc analyses of these trials suggested that the

favourable CV and renal effects of SGLT2 inhibitors could not be completely explained by the modest improvement in metabolic profiles.^{4–6} These beneficial effects appeared to be maintained at decreased levels of renal function with attenuated glycosuric effects and seemed to be independent of their glucose-lowering effects.^{7,8} Therefore, SGLT2 inhibitors were proposed to provide additional cardioprotective and renoprotective effects beyond the mechanisms of promoting glycosuria.^{9–11}

RCTs comparing SGLT2 inhibitors with placebo, in which one-third to half of the participants did not have pre-existing diabetes, reported that SGLT2 inhibitors reduced the risk of CV and renal events, and the CV and renal benefits were similar among participants with and without diabetes.^{12–14} These encouraging effects in reducing CV and renal risks may not be directly linked to glucose-lowering effects, suggesting that the benefits of SGLT2 inhibitors might also be extended to individuals without diabetes. Following the results from the Dapagliflozin and Prevention of Adverse Outcomes in Chronic Kidney Disease (DAPA-CKD) trial,¹⁴ the US Food and Drug Administration recently approved the use of dapagliflozin to reduce the risk of kidney function decline, kidney failure, CV death and heart failure in adults with chronic kidney disease (CKD) regardless of their diabetes status.¹⁵

To date, effective interventions to improve cardiorenal outcomes in patients without diabetes mellitus have been scarce, and there is an urgent need to identify therapeutic agents that may provide organ-protective effects.^{16,17} It is not known whether the routine use of SGLT2 inhibitors would provide additional cardiorenal benefits in patients without diabetes. Given the great promise in providing remarkable cardiorenal benefits that are independent of glycaemic control, we hypothesised that SGLT2 inhibitors could have cardiorenal protective effects in patients without diabetes mellitus in addition to the background standard of care for heart failure or CKD. In this systematic review and meta-analysis, we synthesised results from RCTs to evaluate the effects of SGLT2 inhibitors versus placebo on CV and renal outcomes in patients without diabetes with heart failure or CKD. We also assessed the safety outcomes of treatment with SGLT2 inhibitors compared with placebo.

METHODS

Data sources and search strategies

We conducted electronic literature searches in PubMed, MEDLINE, Embase and Cochrane Library from inception until 17 August 2022. The search terms included Medical Subject Headings and text words that were relevant to SGLT2 inhibitors, CV outcomes, renal outcomes and RCTs. We hand-searched the reference lists of all identified publications to identify additional studies. There was no restriction on the language of publication. The searches were rerun prior to the final analyses, and any further studies identified were retrieved for inclusion.

Additional details of study protocol and search strategies are provided in online supplemental appendices 1 and 2. The study protocol for this review was registered in the International Prospective Register of Systematic Reviews (PROSPERO, registration number CRD42021239807). This study was reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis guidelines.¹⁸

Study selection

We included randomised, parallel-group designed clinical trials comparing SGLT2 inhibitors with placebo that enrolled adult participants older than 18 years without pre-existing diabetes. The included studies reported at least one prespecified CV or renal outcome. We excluded review articles, articles with irrelevant study designs, study protocols and RCTs assessing active comparisons or with a study duration of less than 1 year. We also excluded articles that enrolled solely patients with diabetes. Studies reporting outcomes from subgroups without diabetes were also included.

Data extraction and certainty/quality of evidence assessment

Two reviewers (W-CT and H-YW) independently extracted the following data: details of the study design, year of publication, study duration, generic name and dose of SGLT2 inhibitors, patient characteristics (age, sex and ethnicity), systolic blood pressure, estimated glomerular filtration rate (eGFR), glycated haemoglobin (HbA1c), underlying diseases, outcome events and adverse events. Two investigators (W-CT and H-YW) independently evaluated the methodological quality of the eligible trials by using the Cochrane Collaboration's tool for assessing the risk of bias.¹⁹ The certainty of evidence was assessed independently using the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) approach.²⁰ Disagreements between the two authors were resolved by discussion or consultation.

Outcomes

Our outcomes of interest were (1) the composite CV outcome of CV death or hospitalisation for heart failure; (2) CV death; (3) hospitalisation for heart failure; (4) all-cause mortality; (5) the composite renal outcome of 50% or greater reduction in eGFR, end-stage kidney disease (ESKD) or renal death; and (6) the annual rate of change in eGFR (mL/min/1.73 m²/year). The prespecified outcome major adverse cardiovascular events (defined as a composite of CV death, non-fatal myocardial infarction and non-fatal stroke), individually or in combination, were not available and were not included in this study even though multiple attempts through various modes of communication (email, industry and social media) were made to achieve relevant data. For safety outcomes, we assessed adverse events, including any serious adverse event, discontinuation of the study drug due to adverse events, hypoglycaemia, ketoacidosis, amputation,

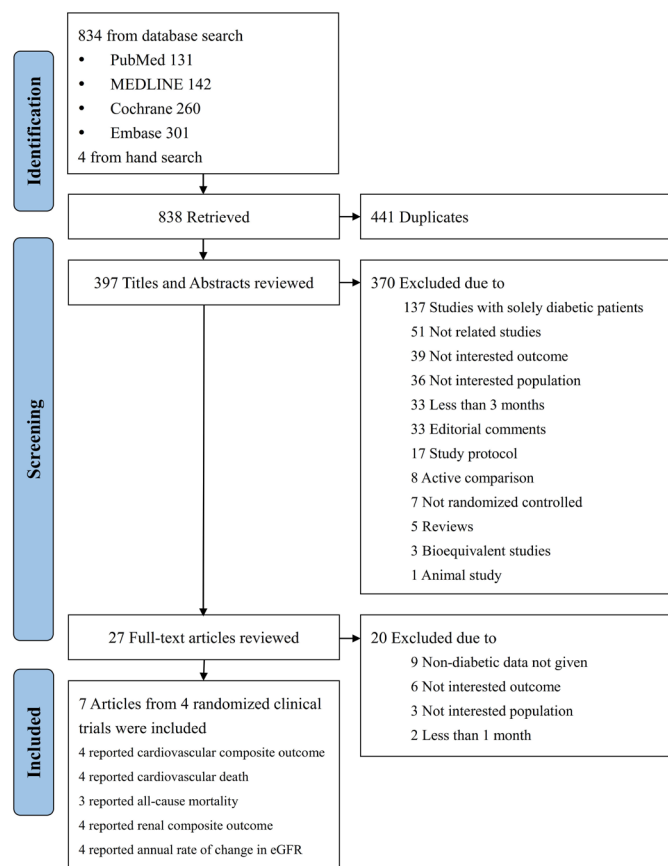


Figure 1 Summary of study identification and selection. eGFR, estimated glomerular filtration rate.

fracture, volume depletion, acute renal failure, urinary tract infection and genital infection.

Data synthesis and analysis

Analyses were conducted with R software (V.4.0.5, R Foundation for Statistical Computing, Vienna, Austria).²¹ Tables of the GRADE summary of findings were developed with GRADEpro GDT (Guideline Development Tool), showing the certainty of the evidence for each outcome across studies.²² The pooled estimates of effect measures and 95% CIs of comparisons between the use of SGLT2 inhibitors and placebo were calculated using both the fixed-effect model and the DerSimonian and Laird random-effects model.²³ The effect size of binary outcomes, including the composite CV outcome, CV death, hospitalisation for heart failure, all-cause mortality and the composite renal outcome, is expressed as risk ratios (RRs) with 95% CIs. Therapy with SGLT2 inhibitors would provide a better protective effect if the RR was significantly less than 1, and vice versa. The continuous outcome, the annual rate of change in eGFR, is expressed as the mean difference (MD) with 95% CI. Therapy with SGLT2 inhibitors would provide a better renoprotective effect if the MD was significantly greater than zero (ie, a lower rate of decline in eGFR), and vice versa. For the data needed to pool the annual rate of change in eGFR, we used imputation methods to reconstruct the missing

values as recommended in the Cochrane Handbook (online supplemental appendix 3).²³ Since the included studies in our systematic review enrolled populations with different types of chronic diseases, the between-study variance could be substantial, and the use of a fixed-effect model might not properly summarise the effect measures.²⁴ Therefore, the random-effects model was used as the primary analytical model to calculate the pooled estimates for the effect measures of the included studies. The between-study heterogeneity was assessed by the I^2 statistic and the Cochrane Q-test.²³ There were no study-level covariates available to explore the potential sources of heterogeneity, and we did not perform subgroup analyses or meta-regression in this study. To assess publication bias, we performed the funnel plot and Egger's test.²⁵ For study outcomes with fewer than three included studies, Egger's test could not be performed. Two-sided p values <0.05 were considered statistically significant.

Patient and public involvement

Patients or the public were not involved in this study.

RESULTS

As shown in figure 1, a total of 838 articles were identified by the literature search. Of these, 27 articles were reviewed in full text, and 7 articles from four trials were included.

Study characteristics

There were four RCTs from seven eligible articles^{26–29} that enrolled a total of 8927 participants without diabetes. All studies were multicentre, double-blind, placebo-controlled, randomised trials. The clinical and methodological characteristics of each study are summarised in table 1.

Three studies enrolled patients with chronic heart failure, and one study focused on those with CKD. All studies were designed to compare SGLT2 inhibitors with placebo as an adjunct to the standard of care. The status of diabetes at baseline was one of the stratification variables in all four trials. The length of follow-up ranged from 1.3 to 2.4 years. In terms of the SGLT2 inhibitors, dapagliflozin was prescribed in two studies, and empagliflozin was prescribed in another two studies. All regimens were administered at a dosage of 10 mg once daily. The mean age of the participants in the studies ranged from 56 to 73 years, with females accounting for 33%. Regarding ethnicity, 70% of the participants were white, one-fifth were Asian and 5% were black. Overall, the majority of the participants (85%) had a history of chronic heart failure. The mean HbA1C of the participants in the studies ranged from 5.6% to 5.8%. Half of the participants (51%) had eGFR levels less than 60 mL/min/1.73 m². As a standard of care, 45% of the participants received angiotensin-converting enzyme inhibitors, 35% received angiotensin receptor blockers and 76% received diuretics.

Table 1 Characteristics of the non-diabetic study participants from the included studies

Source	Petrie et al 2020 (DAPA-HF) ²⁶	Anker et al 2021 (EMPEROR-Reduced) ²⁸	Wheeler et al 2021 (DAPA-CKD) ²⁹	Filippatos et al 2022 (EMPEROR-Preserved) ³⁰
Inclusion criteria	Chronic HFpEF, NYHA class II–IV with LVEF ≤40% and elevated NT-proBNP	Chronic HFpEF, NYHA class II–IV with LVEF ≤40% and elevated NT-proBNP	Chronic HFpEF, NYHA class II–IV with LVEF ≤40% and elevated NT-proBNP	Chronic HFpEF, NYHA class II–IV with LVEF >40% and elevated NT-proBNP
Received standard of care	Yes	Yes	Yes	Yes
Diabetes as a stratification variable in the trial	Yes	Yes	Yes	Yes
Follow-up (years)	1.5	1.3	2.4	2.2
Total number of participants without diabetes	2605	1874	1398	3050
Type of intervention	Dapagliflozin 10 mg once daily	Empagliflozin 10 mg once daily	Dapagliflozin 10 mg once daily	Empagliflozin 10 mg once daily
Number of participants in each group	1298	936	938	701
Age (years)	66±12	68±12	66±12	56±15
Women, n (%)	324 (25)	227 (24)	238 (25)	245 (35)
Race, n (%)				
White	918 (71)	679 (73)	665 (71)	376 (54)
Black	50 (4)	66 (7)	71 (8)	26 (4)
Asian	311 (24)	154 (17)	160 (17)	267 (38)
Other	19 (2)	37 (4)	42 (5)	32 (5)
History of heart failure, n (%)	1295 (100)	936 (100)	937 (100)	3050 (100)
Systolic blood pressure (mm Hg)	121±16	122±16	120±15	133±17
Haemoglobin A1c (%)	5.7±0.4	5.8±0.4	5.7±0.4	5.6±0.4
eGFR (mL/min/1.73 m ²)	68±19	63±21	63±21	42±12
eGFR <60 mL/min/1.73 m ² , n (%)	480 (37)	434 (46)	426 (45)	650 (93)
ACE inhibitor, n (%)	737 (57)	451 (48)	425 (45)	238 (34)
ARB, n (%)	357 (28)	213 (23)	227 (24)	452 (64)
Diuretic, n (%)	1191 (92)	779 (83)	809 (86)	207 (30)
Data are the mean±SD or n (%).				
*Characteristics of overall non-diabetic group data are presented for the EMPEROR-Preserved trial as no data for each intervention group can be extracted.				
ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; CKD, chronic kidney disease; DAPA-CKD, Dapagliflozin and Prevention of Adverse Outcomes in Chronic Kidney Disease; DAPA-HF, Dapagliflozin and Prevention of Adverse Outcomes in Heart Failure; eGFR, estimated glomerular filtration rate; EMPEROR-Preserved, Empagliflozin Outcome Trial in Patients With Chronic Heart Failure and a Reduced Ejection Fraction; HFpEF, heart failure with preserved ejection fraction; HFREF, heart failure with reduced ejection fraction; LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; SGLT2, sodium-glucose cotransporter-2; UACR, urinary albumin-to-creatinine ratio (with albumin measured in milligrams and creatinine measured in grams).				

Assessment of risk of bias and body of evidence

The risk of bias of the included studies is summarised in online supplemental figures S1 and S2. All four studies were deemed to be at low risk of bias in all domains.

For efficacy outcomes, certainty of evidence was rated 'moderate' for composite CV outcome, CV death, hospitalisation for heart failure and annual rate of change in eGFR, 'low' for composite renal outcome and 'very low' for all-cause mortality (online supplemental table S1). For safety outcomes, certainty of evidence was rated 'moderate' for any serious adverse event and acute renal failure, and 'low' for amputation, fracture, volume depletion, urinary tract infection and genital infection (online supplemental table S2).

Effects of SGLT2 inhibitors on CV and renal outcomes

There were a total of 3512 CV and renal events in the four RCTs, including 1184 composite CV outcomes, 646 CV deaths, 727 hospitalisations for heart failure, 723 deaths and 232 composite renal outcomes. Figure 2 shows the pooled estimates of CV and renal outcomes. The composite renal outcome generally included renal death, ESKD and a sustained reduction in eGFR of 50% or greater in the DAPA-HF trial²⁶ and DAPA-CKD trial²⁹ and 40% or greater in the EMPEROR-Reduced trial²⁸ and EMPEROR-Preserved trial³⁰; the composite renal outcome did not include renal-related death in the EMPEROR-Reduced trial²⁸ and EMPEROR-Preserved trial³⁰ (online supplemental table S3). Between-study heterogeneity was not present in the CV and renal outcomes (figure 2A–F). The funnel plots and Egger's test indicated no significant publication bias for the study outcomes except for all-cause mortality that had funnel plot asymmetry (Egger's test, $p=0.01$) (online supplemental figure S3).

Compared with placebo, SGLT2 inhibitors significantly reduced the risk of the composite CV outcome (RR: 0.79, 95% CI: 0.71 to 0.87, $p<0.001$; figure 2A; moderate certainty evidence, online supplemental table S1), CV death (RR: 0.85, 95% CI: 0.74 to 0.99, $p=0.04$; figure 2B; moderate certainty evidence, online supplemental table S1), hospitalisation for heart failure (RR: 0.72, 95% CI: 0.62 to 0.82, $p<0.001$; figure 2C; moderate certainty evidence, online supplemental table S1), the composite renal outcome (RR: 0.64, 95% CI: 0.48 to 0.85, $p=0.002$; figure 2E; low certainty evidence, online supplemental table S1) and the annual rate of change in eGFR (MD: 0.99, 95% CI: 0.59 to 1.39 mL/min/1.73 m²/year, $p<0.001$; figure 2F; moderate certainty evidence, online supplemental table S1). SGLT2 inhibitors did not reduce the risk of all-cause mortality (RR: 0.88, 95% CI: 0.77 to 1.01, $p=0.07$; figure 2D; very low certainty evidence, online supplemental table S1) compared with placebo.

Safety profile of therapy with SGLT2 inhibitors

Table 2 summarises the adverse events reported in the included studies.

Figure 3 displays the pooled estimates for the safety outcomes. All four trials^{26 28–30} reported data on adverse

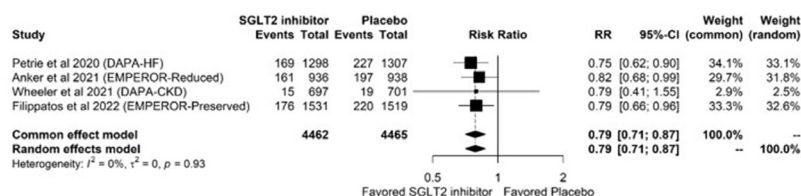
events, including any serious adverse event, discontinuation of the study drug due to adverse events, hypoglycaemia, ketoacidosis, amputation, volume depletion and acute renal failure. Three trials^{26 28 29} reported the risk of fracture. Three trials^{28–30} reported the risk of urinary tract infection and genital infection. Three trials^{26 28 29} reported that there was no event of hypoglycaemia in either group and one trial³⁰ reported two hypoglycaemic events in each group. All four trials reported that there was no event of ketoacidosis in either group. Heterogeneity between studies was not present in any of the safety outcomes (figure 3A–H). No evidence of publication bias was detected in the funnel plots and Egger's test for the safety outcomes (online supplemental figure S4).

Of the 8917 participants, 3509 (39%) experienced serious adverse events: 38% in the SGLT2 inhibitor group and 41% in the placebo group. Compared with participants in the placebo group, those in the SGLT2 inhibitor group had a lower risk of any serious adverse event (RR: 0.91, 95% CI: 0.87 to 0.96, $p<0.001$; figure 3A; moderate certainty evidence, online supplemental table S2), and acute renal failure (RR: 0.82, 95% CI: 0.71 to 0.94, $p=0.006$; figure 3F; moderate certainty evidence, online supplemental table S2). Compared with placebo, SGLT2 inhibitors significantly increased the risk of urinary tract infection (RR: 1.29, 95% CI: 1.05 to 1.58, $p=0.02$; figure 3G; low certainty evidence, online supplemental table S2) and genital infection (RR: 2.44, 95% CI: 1.14 to 5.25, $p=0.02$; figure 3H; low certainty evidence, online supplemental table S2). There were no between-group differences in discontinuation of the study drug due to adverse events (RR: 1.05, 95% CI: 0.94 to 1.18, $p=0.38$; figure 3B; low certainty evidence, online supplemental table S2), amputation (RR: 0.48, 95% CI: 0.13 to 1.74, $p=0.26$; figure 3C; low certainty evidence, online supplemental table S2), fracture (RR: 1.22, 95% CI: 0.87 to 1.72, $p=0.25$; figure 3D; low certainty evidence, online supplemental table S2) or volume depletion (RR: 1.21, 95% CI: 0.99 to 1.48, $p=0.07$; figure 3E; low certainty evidence, online supplemental table S2).

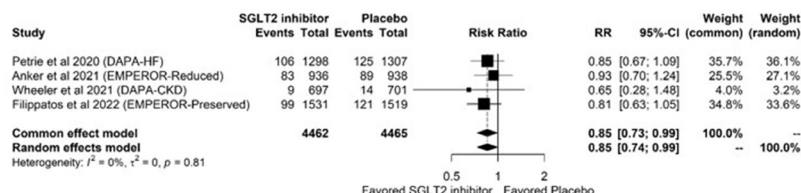
DISCUSSION

In this systematic review and meta-analysis comparing SGLT2 inhibitors with placebo in patients without diabetes with chronic heart failure or CKD, we found that SGLT2 inhibitors provided cardiorenal protective effects with additional adverse effects. A total of 8927 participants were analysed, and all received medical standards of care. The majority of the participants had pre-existing chronic heart failure and half of them had CKD. Compared with placebo, the pooled treatment effects showed that SGLT2 inhibitors reduced the risk of the composite CV outcome of CV death or hospitalisation for heart failure by 21%, CV death by 15%, hospitalisation for heart failure by 28% and decreased the risk of the composite renal outcome of $\geq 50\%$ reduction in eGFR, ESKD or renal death by 36%. SGLT2 inhibitors also postponed the decline in eGFR by

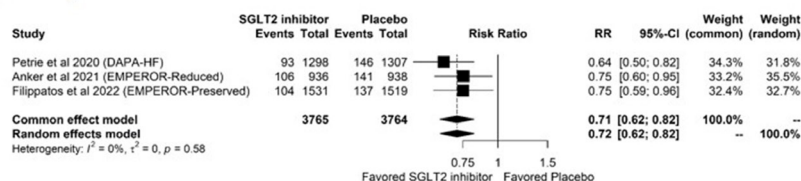
A Composite cardiovascular outcome of cardiovascular death or hospitalization for heart failure



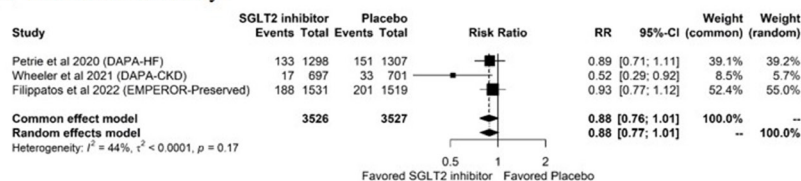
B Cardiovascular death



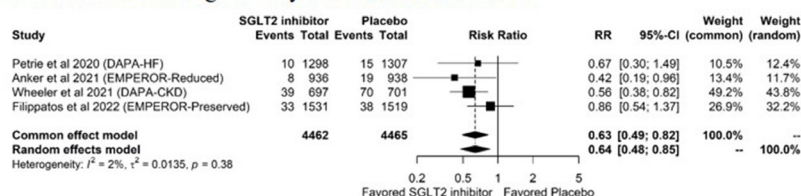
C Hospitalization for heart failure



D All-cause mortality



E Composite renal outcome of 50% or greater reduction in estimated glomerular filtration rate, end-stage kidney disease, or renal death



F Annual rate of change in estimated glomerular filtration rate (ml/min/1.73 m²/year)

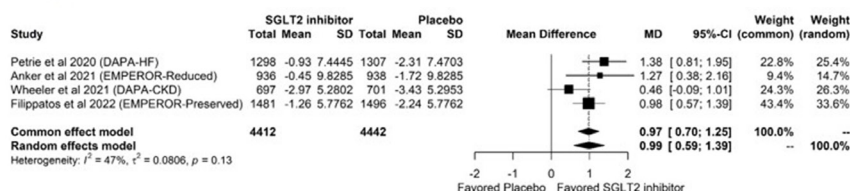


Figure 2 Pooled estimates of the efficacy outcomes comparing SGLT2 inhibitors with placebo. (A) Composite cardiovascular outcome of cardiovascular death or hospitalisation for heart failure, (B) cardiovascular death, (C) hospitalisation for heart failure, (D) all-cause mortality, (E) composite renal outcome of 50% or greater reduction in eGFR, end-stage kidney disease or renal death and (F) annual rate of change in eGFR (mL/min/1.73 m²/year) for comparisons between SGLT2 inhibitors and placebo. DAPA-CKD, Dapagliflozin and Prevention of Adverse Outcomes in Chronic Kidney Disease; DAPA-HF, Dapagliflozin and Prevention of Adverse Outcomes in Heart Failure; eGFR, estimated glomerular filtration rate; EMPEROR-Preserved, Empagliflozin Outcome Trial in Patients With Chronic Heart Failure With Preserved Ejection Fraction; EMPEROR-Reduced, Empagliflozin Outcome Trial in Patients with Chronic Heart Failure and a Reduced Ejection Fraction; MD, mean difference; RR, risk ratio; SGLT2, sodium-glucose cotransporter-2.

Table 2 Adverse events reported in the included studies

Source	Overall	Petrie <i>et al</i> 2020 (DAPA-HF) ²⁶		Anker <i>et al</i> 2021 (EMPEROR-Reduced) ²⁸		Wheeler <i>et al</i> 2021 (DAPA-CKD) ²⁹		Filippatos <i>et al</i> 2022 (EMPEROR-Preserved) ³⁰		
Type of intervention	SGLT2 inhibitor (n=4458)	Placebo (n=4459)	Dapagliflozin (n=1295)	Placebo (n=1305)	Empagliflozin (n=936)	Placebo (n=937)	Dapagliflozin (n=696)	Placebo (n=699)	Empagliflozin (n=1531)	Placebo (n=1518)
Any serious adverse event*	1677 (38)	1832 (41)	448 (35)	481 (36)	375 (40)	439 (47)	150 (22)	167 (24)	704 (46)	745 (49)
Discontinuation of the study drug due to adverse events	532 (12)	503 (11)	68 (5)	59 (5)	147 (16)	152 (16)	36 (5)	29 (4)	281 (18)	263 (17)
Hypoglycaemia	2 (<1)	2 (<1)	0	0	0	0	0	0	2 (<1)	2 (<1)
Ketoacidosis	0	0	0	0	0	0	0	0	0	0
Amputation	3 (<1)	7 (<1)	1 (<1)	3 (<1)	1 (<1)	1 (<1)	0	1 (<1)	1 (<1)	2 (<1)
Fracture	72 (2)	59 (2)	27 (2)	25 (2)	25 (3)	16 (2)	20 (3)	18 (3)	NA	NA
Volume depletion	418 (9)	347 (8)	94 (7)	79 (6)	94 (10)	100 (11)	35 (5)	19 (3)	195 (13)	149 (10)
Acute renal failure	306 (7)	374 (8)	34 (5)	40 (6)	77 (8)	94 (10)	62 (5)	78 (6)	133 (9)	162 (11)
Urinary tract infection	194 (4)	150 (3)	NA	NA	39 (4)	34 (4)	6 (<1)	4 (<1)	149 (10)	112 (7)
Genital infection	43 (1)	16 (<1)	NA	NA	13 (1)	8 (<1)	0	0	30 (2)	8 (<1)

Data are n (%).

*The original definition in each trial included any adverse event that required hospitalisation, resulted in death, and so on.

DAPA-CKD, Dapagliflozin and Prevention of Adverse Outcomes in Chronic Kidney Disease; DAPA-HF, Dapagliflozin and Prevention of Adverse Outcomes in Heart Failure; EMPEROR-Preserved, Empagliflozin Outcome Trial in Patients With Chronic Heart Failure With Preserved Ejection Fraction; EMPEROR-Reduced, Empagliflozin Outcome Trial in Patients with Chronic Heart Failure and a Reduced Ejection Fraction; NA, not available; SGLT2, sodium-glucose cotransporter-2.

Data are n (%).

*The original definition in each trial included any adverse event that required hospitalisation, resulted in death, and so on.

DAPA-CKD, Dapagliflozin and Prevention of Adverse Outcomes in Chronic Kidney Disease; DAPA-HF, Dapagliflozin and Prevention of Adverse Outcomes in Heart Failure; EMPEROR-Preserved, Empagliflozin Outcome Trial in Patients With Chronic Heart Failure With Preserved Ejection Fraction; EMPEROR-Reduced, Empagliflozin Outcome Trial in Patients With Chronic Heart Failure and a Reduced Ejection Fraction; NA, not available; SGLT2, sodium-glucose cotransporter-2.

0.99 mL/min/1.73 m² per year. Compared with those who received placebo, patients treated with SGLT2 inhibitors had a lower risk of serious adverse events and acute renal failure but did show an increased risk of urinary tract infection and genital infection. Adopting the GRADE approach, low to moderate certainty evidence demonstrated that SGLT2 inhibitors should be considered in individuals without diabetes and with chronic heart failure or CKD to prevent the deleterious effects of CV and renal diseases. However, evidence of low certainty suggested that SGLT2 inhibitors might cause clinically important adverse events such as urinary tract infection and genital infection, which could jeopardise tolerability of long-term treatment with SGLT2 inhibitors.

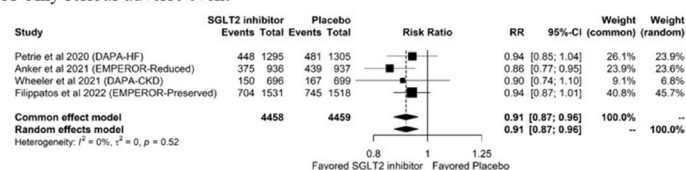
Strengths of this study

To the best of our knowledge, this is one of the largest systematic review and meta-analysis comparing SGLT2 inhibitors with placebo in terms of cardiorenal protective effects and safety among patients without diabetes. Following a standard study protocol and using a comprehensive search strategy, this systematic review enrolled four large-scale RCTs with more than 8900 patients and over 3500 events of CV and renal outcomes. Six different types of efficacy outcomes were analysed to evaluate the cardiorenal protective effects of SGLT2 inhibitors, and most of the pooled treatment effects showed significant protective effects. The safety of SGLT2 inhibitors was also demonstrated after evaluating ten different types of safety outcomes. Quality appraisals used the GRADE approach. Accordingly, our data favourably provide comprehensive evidence of the cardiorenal protective effects and drug safety of SGLT2 inhibitors in patients without diabetes and with heart failure or CKD.

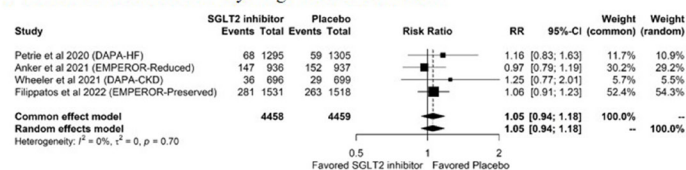
Results in relation to other studies and reviews

Despite substantial evidence of the beneficial effects of SGLT2 inhibitors on important clinical outcomes in patients with type 2 diabetes,^{31 32} few studies have attempted to focus on populations without diabetes. Recently, several large-scale RCTs have enrolled both patients with and without diabetes to evaluate the clinical benefits of SGLT2 inhibitors.^{12–14} The Dapagliflozin and Prevention of Adverse Outcomes in Heart Failure (DAPA-HF) trial, which included individuals without diabetes accounting for 55% of the enrollees, evaluated the effects of dapagliflozin in 4744 participants with chronic heart failure.¹² After a median follow-up of 18.2 months, dapagliflozin reduced the risk of the primary outcome of CV death or worsening heart failure by 26% (HR: 0.74, 95% CI: 0.65 to 0.85), with similar benefits in patients with and without diabetes (p value for interaction=0.83).¹² The DAPA-CKD trial enrolled a total of 4304 participants with CKD, among which one-third were individuals without diabetes.¹⁴ After a median follow-up of 2.4 years, dapagliflozin reduced the risk of the primary outcome of ≥50% sustained eGFR decline, ESKD or death from renal or CV causes by 39% (HR: 0.61, 95% CI: 0.51 to 0.72),

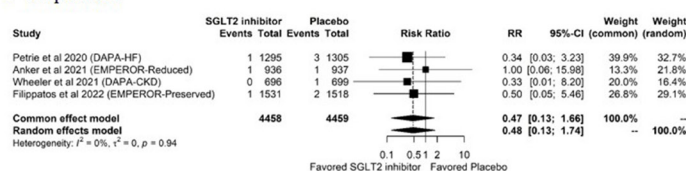
A Any serious adverse event



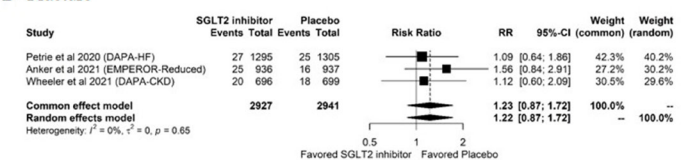
B Discontinuation of the study drug due to adverse event



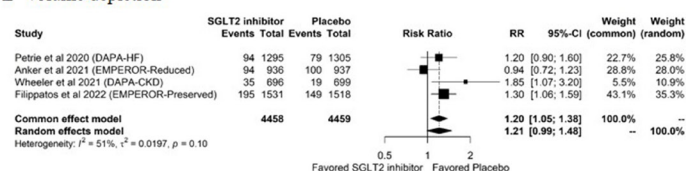
C Amputation



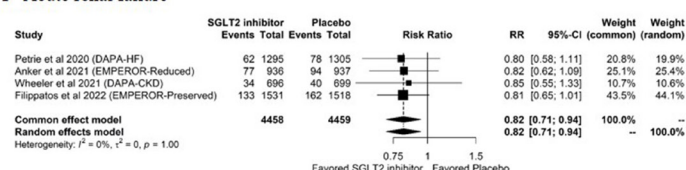
D Fracture



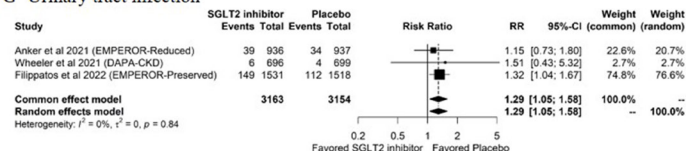
E Volume depletion



F Acute renal failure



G Urinary tract infection



H Genital infection

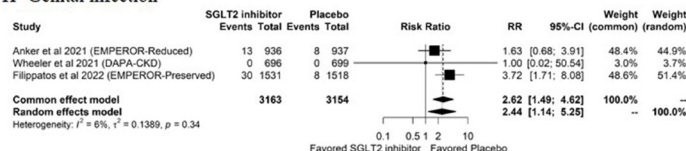


Figure 3 Pooled estimates of the safety outcomes comparing SGLT2 inhibitors with placebo. (A) Any serious adverse event, (B) discontinuation of the study drug due to adverse events, (C) amputation, (D) fracture, (E) volume depletion, (F) acute renal failure, (G) urinary tract infection and (H) genital infection, for comparisons between SGLT2 inhibitors and placebo. DAPA-CKD, Dapagliflozin and Prevention of Adverse Outcomes in Chronic Kidney Disease; DAPA-HF, Dapagliflozin and Prevention of Adverse Outcomes in Heart Failure; EMPEROR-Preserved, Empagliflozin Outcome Trial in Patients With Chronic Heart Failure With Preserved Ejection Fraction; EMPEROR-Reduced, Empagliflozin Outcome Trial in Patients with Chronic Heart Failure and a Reduced Ejection Fraction; RR, risk ratio; SGLT2, sodium-glucose cotransporter-2.

with similar benefits in patients with and without diabetes (p value for interaction=0.24).¹⁴ Evidence of the clinical benefits of SGLT2 inhibitors in the population without diabetes was obtained from subgroup analyses of these trials, which were generally underpowered. In a systematic review, Teo *et al* reported better cardiac outcomes in patients without diabetes who received SGLT2 inhibitors than in those who received placebo,³³ but the landmark DAPA-CKD trial was not included in this review. In a meta-analysis of the DAPA-HF and the Empagliflozin Outcome Trial in Patients with Chronic Heart Failure and a Reduced Ejection Fraction (EMPEROR-Reduced) trials, Zannad *et al* reported that treatment with SGLT2 inhibitors reduced the risk of the composite outcome of hospitalisation for heart failure or CV death by 25% (HR: 0.75, 95% CI: 0.65 to 0.87) in patients without diabetes.³⁴ In a recent systematic review and meta-analysis reported by Salah *et al*, initiation of SGLT2 inhibitors in patients hospitalised for acute heart failure reduced the risk of rehospitalisation for heart failure by 48%, while the effect on adverse events remained uncertain as the findings from included studies were limited due to few events.³⁵ After extracting information on participants without diabetes from the four latest large-scale trials, our findings were consistent with those of individual trials and previous systematic reviews. Our data not only supported the CV and renal efficacy but also uncovered the adverse effect of SGLT2 inhibitors in patients without diabetes with heart failure or CKD.

The mechanisms underlying the organ-protective effects of SGLT2 inhibitors in these populations are not yet completely understood but may be beyond their metabolic effects of enhancing glycosuria. Within a few years, there has been an increasing number of proposed pathways for the systemic organ-protective effects of SGLT2 inhibitors, which are related to preventing sodium and water retention,³⁶ favourable metabolic adaptations for energy production,^{37 38} restored myocardial sodium and calcium balance by the inhibition of sodium-hydrogen exchanger 1,³⁹ reduced tissue sodium content,⁴⁰ attenuations of tubuloglomerular feedback and subsequent intraglomerular hypertension leading to renoprotection,^{41 42} activation of the depressor arm of the renal-angiotensin-aldosterone system evoking vasodilatory, antioxidant, anti-inflammatory and sympathoinhibitory effects,¹¹ suppression of inflammation and fibrosis,⁴³ induction of erythropoiesis⁴⁴ and adaptive reprogramming of stressed cells via the activation of sirtuin 1, which promotes homeostasis and survival.⁹

By evaluating a total of 10 safety outcomes, the results of our study showed that treatment with SGLT2 inhibitors elicited some adverse events though had lower risk for any serious adverse events and acute renal failure in the population without diabetes. It is also important to note that there were no events of hypoglycaemia or ketoacidosis in the included trials, except for EMPEROR-Preserved trial reported by Filippatos *et al*³⁰ that showed a similar hypoglycaemic event in both groups. Compared with those in the placebo group, participants in the

SGLT2 inhibitors group experienced an increased risk of urinary tract infection by 29% (RR: 1.29, 95% CI: 1.05 to 1.58, p=0.02; [figure 3G](#); low certainty evidence, online supplemental table S2) and a 2.44-fold higher risk of genital infection (RR: 2.44, 95% CI: 1.14 to 5.25, p=0.02; [figure 3H](#); low certainty evidence, online supplemental table S2). However, there was a lower risk of any serious adverse events by 9% (RR: 0.91, 95% CI: 0.87 to 0.96, p<0.001; [figure 3A](#); moderate certainty evidence, online supplemental table S2), and acute renal failure by 18% (RR: 0.82, 95% CI: 0.71 to 0.94, p=0.006; [figure 3F](#); moderate certainty evidence, online supplemental table S2) among participants who received SGLT2 inhibitors than among those who received placebo, while the risks of other adverse events including discontinuation of the study drug due to adverse events, amputation, fracture and volume depletion were similar among participants in the SGLT2 inhibitor and placebo groups ([figure 3B–E](#)). The increased risk of clinically important adverse events such as urinary tract infection and genital infection observed in our study must be balanced with the cardiorenal benefits of SGLT2 inhibitors, especially in the context of long-term use.

Limitations

Our study has several limitations. First, subgroup analysis and meta-regression of the study outcomes were not performed in this study because there were no study-level covariates available. Although there was no significant between-study heterogeneity for all efficacy and safety outcomes, whether the cardiorenal benefits differ among different stages of heart failure or CKD deserves further study. Second, our study included patients without diabetes with chronic heart failure or CKD. Therefore, the organ-protective effects of SGLT2 inhibitors that we observed are restricted to these populations. Ongoing trials such as EMPA-Kidney⁴⁵ should contribute to expanding the population that benefits from SGLT2 inhibition if they meet their primary endpoints. Third, the number of included RCTs was small, and most of the trials had a relatively short study duration, which limited the power of the analyses of endpoints such as all-cause mortality. However, the power to detect a true benefit might be increased by the inclusion of over 8900 patients with heart or kidney disease and by the collection of more than 3500 events of cardiorenal outcomes in this study. Fourth, the included studies were not designed to enrol solely patients without diabetes. Because participants were stratified by status of diabetes at randomisation in all included trials, the baseline characteristics of the participants were similar among the SGLT2 inhibitor and placebo groups. As a result, it was reasonable to extract data from participants without diabetes in these trials. Finally, the SGLT2 inhibitors prescribed in the included trials were dapagliflozin or empagliflozin. Whether other SGLT2 inhibitors provide similar cardioprotective or renoprotective effects in patients without diabetes deserves further study.

CONCLUSIONS

Our analyses showed that treatment with SGLT2 inhibitors provided additional cardiorenal benefits in patients without diabetes who had received standard of care for heart failure or CKD. However, there were safety concerns, such as urinary tract infection and genital infection, regarding the use of SGLT2 inhibitors. With the evidence of low to moderate certainty, our study confers substantial evidence supporting the routine use of SGLT2 inhibitors in individuals without diabetes and with chronic heart failure or CKD to reduce CV and renal morbidities and mortalities, but the integrity of such strategy might be compromised due to an increased risk of adverse events.

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Contributors W-CT, S-PH, Y-LC, Y-KT, Y-SP and H-YW conceived and designed the study. W-CT and H-YW independently collected, screened and extracted the data. W-CT and H-YW independently evaluated risk of bias and quality of evidence. W-CT, S-PH, Y-SP and H-YW resolved disagreement through discussion. W-CT, J-YY, M-FP, M-JK, Y-KT and W-CT performed the analyses or interpretation of data. W-CT, Y-LC, Y-SP and H-YW conducted the drafting of the work. All authors critically revised the manuscript for important intellectual content and final approval of the version to be published. W-CT and H-YW had grants for the study. Y-KT, K-YH and K-LC supervised the study. H-YW and Y-SP had full access to all of the data in the study, took responsibility for the conduct of the study, the integrity of the data and the accuracy of the data analysis, and controlled the decision to publish. H-YW and Y-SP contributed equally as corresponding authors to this work.

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Supplemental Information

Tsai WC, Peng YS, Wu HY, *et al.* Cardiovascular and Renal Efficacy and Safety of Sodium-Glucose Cotransporter-2 Inhibitors in Patients without Diabetes: A Systematic Review and Meta-Analysis of Randomized Placebo-controlled Trials

Appendix 1. Study Protocol

Appendix 2. Search Strategies

Appendix 3. Imputations for Missing Data

References. References for Study Protocol and Imputation Methods

Figure S1. Summary of Risk of Bias of the Included Studies

Figure S2. Risk of Bias Graph of the Included Studies

Figure S3. Funnel Plots and Egger's Test for the Assessment of Publication Bias for Efficacy Outcomes

Figure S4. Funnel Plots and Egger's Test for the Assessment of Publication Bias for Safety Outcomes

Table S1. GRADE Evidence Profile for Efficacy Outcomes Comparing Sodium-Glucose Cotransporter-2 Inhibitors with Placebo

Table S2. GRADE Evidence Profile for Safety Outcomes Comparing Sodium-Glucose Cotransporter-2 Inhibitors with Placebo

Table S3. Comparisons of the Definitions of Composite Renal Outcomes Across the Included Studies

Appendix 1. Study Protocol

The study protocol for this review was registered in the International Prospective Register of Systematic Reviews (PROSPERO, registration number CRD42021239807) before the analyses were initiated (on April 1, 2021).

Objective

To synthesize the results of all available randomized placebo-controlled trials that compare the effects of sodium-glucose cotransporter-2 (SGLT2) inhibitors versus placebo on cardiovascular and renal efficacy and safety in patients without diabetes.

Review question

- Is the use of SGLT2 inhibitors beneficial in patients without diabetes in terms of cardiovascular and renal outcomes?
- What are the possible side effects of SGLT2 inhibitors?

Condition or domain being studied

Cardiovascular and renal outcomes among patients without preexisting diabetes who use SGLT2 inhibitors irrespective of the presence of chronic kidney disease (CKD) or heart failure status.

Participants/population

Inclusion:

- Eligible studies should have included adult participants older than 18 years without preexisting diabetes regardless of their CKD or heart failure status who were randomized to use SGLT2 inhibitors or placebo and should have assessed cardiovascular or renal outcomes.

Exclusion:

- Studies that do not have a randomized, placebo-controlled design will be excluded.
- Studies assessing active comparisons will be excluded.
- Crossover, cohort or phase I/II studies will be excluded.
- Studies enrolling solely diabetic subjects will be excluded.
- Studies with durations of less than 1 year will be excluded.

Intervention(s) and exposure(s)

Inclusion:

- Studies testing any of the SGLT2 inhibitors (including but not limited to empagliflozin, canagliflozin, and dapagliflozin) will be eligible.
- Studies evaluating the drug as a single intervention in addition to standard care with or without glucose-lowering medication will be eligible.

Exclusion:

- Studies evaluating the drug as a dual intervention will be excluded.

Comparator(s)/control

Inclusion criteria: Placebo-controlled.

Exclusion criteria: Active comparator or no control group.

Types of studies to be included

Inclusion: Randomized, placebo-controlled trials.

Exclusion: Crossover, cohort, phase I/II studies or studies with a duration of less than 1 year.

Context

- Studies that compared the effects of SGLT2 inhibitors versus a placebo in patients without preexisting diabetes and assessed cardiovascular and renal outcomes will be included.
- Eligible studies should have reported at least one of the cardiovascular or renal outcomes of interest.
- Studies reporting outcomes from subgroup analyses will also be included.

Main outcome(s)

- The cardiovascular outcomes of interest include hospitalization for heart failure, cardiovascular death, myocardial infarction, stroke, major adverse cardiovascular events (MACE), and all-cause mortality, and the renal outcomes of interest include annual rate of change in estimated glomerular filtration rate (eGFR) (mL/min/1.73 m²/year), doubling of serum creatinine, 50% reduction in eGFR, end-stage kidney disease (ESKD), and renal death.
- The main outcomes include the composite cardiovascular outcome of cardiovascular death and hospitalization for heart failure, MACE (defined as a composite of cardiovascular death, nonfatal myocardial infarction, and nonfatal stroke), and the composite renal outcome defined as a 50% reduction in eGFR, ESKD, or renal death.
- We will also individually analyze the abovementioned cardiovascular and renal outcomes to examine the consistency of the evidence.

Measures of effect

Risk ratios (RRs) will be used for binary outcomes, and mean differences (MDs) will be used for continuous outcomes.

Additional outcome(s)

Adverse events include hypoglycemia, acute kidney injury, diabetic ketoacidosis, genital tract infection, urinary tract infection, volume depletion, amputation, fracture, discontinuation of the study

drug due to adverse events and other notable adverse effects reported in the included studies.

Measures of effect

Risk ratios (RR) will be used for binary outcomes.

Data extraction (selection and coding)

The selection of studies for inclusion will be conducted using Endnote software. Two investigators (Wan-Chuan Tsai and Hon-Yen Wu) will perform the initial title and abstract screening to identify appropriate studies. For studies with appropriate titles or abstracts, further full text assessment will be undertaken. Disagreements between the two authors will be resolved by discussion. If a disagreement persists, two other senior investigators (Yu-Sen Peng and Shih-Ping Hsu) will be consulted to reach a consensus.

Two reviewers (Wan-Chuan Tsai and Hon-Yen Wu) will independently perform the data extraction. The following information will be extracted and entered into databases using an Excel spreadsheet: details of the study design, location and published year of study, study duration, name and dose of SGLT2 inhibitors, patient characteristics (age, sex, and ethnicity), systolic blood pressure level (mm Hg), eGFR (mL/min/1.73 m²), HbA1c (%), diabetes status, cardiovascular disease and heart failure status, outcome events, and possible adverse events. When relevant information regarding the design or outcomes is unclear, or when doubt exists about duplicate publications, the original authors will be contacted for clarifications.

Risk of bias (quality) assessment

The methodological quality of the eligible trials will be evaluated independently by two investigators (Wan-Chuan Tsai and Hon-Yen Wu) using the Cochrane Collaboration's tool for assessing the risk of bias.¹

Certainty of the evidence assessment

The certainty of the evidence for each outcome across studies will be assessed independently by two investigators (Wan-Chuan Tsai and Hon-Yen Wu) using the GRADE (Grading of Recommendations, Assessment, Development and Evaluation) approach.² Ratings of evidence certainty include considerations of risk of bias, inconsistency, indirectness, imprecision, and publication bias. The GRADE approach classifies evidence into high, moderate, low, or very low certainty. To develop tables of the GRADE summary of findings, we will use GRADEpro GDT, showing the plausible benefits or harms of each outcome and the certainty of the evidence.³

Strategy for data synthesis

A descriptive analysis of the systematic review findings will be conducted. The effect measures from studies with the same main outcome of interest will be pooled by meta-analysis. The pooled estimates

of effect measures and 95% confidence intervals (CIs) will be calculated using both the fixed-effect model and the DerSimonian and Laird random-effects model.⁴ To make an appropriate choice between the fixed-effect and random-effects models, the recommendations of Borenstein will be followed.⁵ The effect sizes of binary outcomes (composite or individual cardiovascular and renal outcomes) will be expressed as risk ratios (RRs) with 95% CIs. The effect size of the continuous outcome (annual rate of change in eGFR; mL/min/1.73 m²/year) will be expressed as the mean difference (MD) with 95% CI. Heterogeneity of treatment effects across studies will be assessed by the I-squared (I²) statistic and the Cochrane Q-test.⁴ If the heterogeneity of the treatment effects across studies is statistically significant, we will perform additional analyses, including subgroup analyses and meta-regression with mixed-effects models to explore the sources of heterogeneity across studies. Furthermore, sensitivity analyses will be conducted to explore the robustness of the findings to make key decisions during the review process. Publication bias will be examined using the funnel plot method and Egger's regression asymmetry test.⁶ A two-sided $P \leq 0.05$ will be considered statistically significant. Statistical analyses will be performed with R software (version 4.0.5, R Foundation for Statistical Computing, Vienna, Austria).⁷

Analysis of subgroups or subsets

Variables potentially associated with the cardiovascular and renal outcomes of interest based on the literature review will serve as covariates in additional analyses, including age (≤ 65 vs > 65 years), sex (men vs women), ethnicity (white, black or Asian), eGFR (< 60 vs ≥ 60 mL/min/1.73 m²), cardiovascular disease (yes vs no) and heart failure status (yes vs no).

Appendix 2. Search Strategies

We will search the following electronic databases:

1. PubMed
2. MEDLINE
3. Cochrane Library
4. Embase

We will search the reference lists of all identified publications for additional studies, including relevant meta-analyses and systematic reviews. There is no restriction on the language of publication. The searches will be rerun prior to the final analyses and any further studies identified will be included.

(1) PubMed (NCBI interface):

("Sodium-Glucose Transporter 2 Inhibitors" [Mesh] OR Empagliflozin OR "Canagliflozin/adverse effects" [Majr] OR "Canagliflozin/therapeutic use" [Majr] OR Dapagliflozin OR Ertugliflozin OR Luseogliflozin OR Ipragliflozin OR Sotagliflozin OR Tofogliflozin OR Bexagliflozin OR Remogliflozin OR henagliflozin OR licogliflozin) AND (Mortality [Mesh] OR Death [Mesh] OR "Cardiovascular Diseases"[Mesh] OR "Myocardial Infarction"[Mesh] OR "Coronary Artery Disease"[Mesh] OR Stroke [Mesh] OR "Heart Failure"[Mesh] OR Hospitalization [Mesh] OR "Renal Insufficiency, Chronic"[Mesh] OR "Kidney Failure, Chronic"[Mesh]) AND ("Randomized Controlled Trial" [Publication Type]) NOT (Review OR "Meta-Analysis" OR Editorial OR "Clinical Trials, Phase I as Topic"[Mesh] OR "Clinical Trials, Phase II as Topic"[Mesh] OR "Cross-Over Studies"[Mesh:NoExp] OR "Cohort Studies"[Mesh] OR "Pharmacokinetics"[Mesh] OR rationale[Title] OR design[Title] OR "Cost-Benefit Analysis"[Mesh:NoExp]) NOT (diabet*[Title] NOT ("non diabet*[Title] or "without diabet*[Title]))

(2) MEDLINE (Ovid interface):

1. exp Sodium-Glucose Transporter 2 Inhibitors/
2. (Empagliflozin: or Canagliflozin: or Dapagliflozin: or Ertugliflozin: or Luseogliflozin: or Ipragliflozin: or Sotagliflozin: or Tofogliflozin: or Bexagliflozin: or Remogliflozin: or henagliflozin: or licogliflozin:).tw.
3. 1 or 2
4. (Mortality: or death: or "Cardiovascular Diseases:" or "Myocardial Infarction:" or "Coronary Artery Disease:" or Stroke: or "Heart Failure:" or Hospitalization: or "Renal Insufficiency, Chronic:" or "Kidney Failure, Chronic:").tw.
5. exp Randomized Controlled Trial/
6. 3 and 4 and 5
7. (Review or "Meta-Analysis" or Editorial).tw.
8. ("Cross-Over Studies" or "Clinical Trials, Phase I" or "Clinical Trials, Phase II" or

pharmacokinetics or "Cohort").tw.

9. (rationale or design or cost).ti.
10. 7 or 8 or 9
11. 6 not 10
12. (Diabet*).ti.
13. ("non diabet*").ti.
14. ("without diabet*").ti.
15. 13 or 14
16. 11 not (12 not 15)

(3) Cochrane Library (Wiley interface):

1. MeSH descriptor: [Sodium-Glucose Transporter 2 Inhibitors] explode all trees
2. ("Sodium-Glucose Transporter 2 Inhibitors" OR Empagliflozin OR Canagliflozin OR Dapagliflozin OR Ertugliflozin OR Luseogliflozin OR Ipragliflozin OR Sotagliflozin OR Tofogliflozin OR Bexagliflozin OR Remogliflozin OR henagliflozin OR licogliflozin):ti,ab,kw
3. #1 OR #2
4. (Mortality OR Death OR "Cardiovascular Diseases" OR "Myocardial Infarction" OR "Coronary Artery Disease" OR Stroke OR "Heart Failure" OR Hospitalization OR "Renal Insufficiency, Chronic" OR "Kidney Failure, Chronic"):ti,ab,kw
5. ("Randomized Controlled Trial"):ti,ab,kw
6. #3 AND #4 AND #5
7. (Review OR "Meta-Analysis" OR Editorial):ti,ab,kw
8. ("Cross-Over Studies" OR "Clinical Trials, Phase I" OR "Clinical Trials, Phase II" OR pharmacokinetics OR "Cohort"):ti,ab,kw
9. (rationale OR design OR cost):ti
10. #7 OR #8 OR #9
11. #6 NOT #10
12. (Diabet*):ti
13. (non-diabet* OR without diabet*):ti
14. #11 NOT (#12 NOT #13)

(4) Embase (Elsevier interface):

('Sodium-Glucose Transporter 2 Inhibitors' OR 'Empagliflozin' OR 'Canagliflozin' OR 'Dapagliflozin' OR 'Ertugliflozin' OR 'Luseogliflozin' OR 'Ipragliflozin' OR 'Sotagliflozin' OR 'Tofogliflozin' OR 'Bexagliflozin' OR 'Remogliflozin' OR 'henagliflozin' OR 'licogliflozin') AND ('Mortality' OR 'Death' OR 'Cardiovascular Diseases' OR 'Myocardial Infarction' OR 'Coronary Artery Disease' OR 'Stroke' OR 'Heart Failure' OR 'Hospitalization' OR 'Renal Insufficiency, Chronic' OR 'Kidney Failure, Chronic') AND ('Randomized Controlled Trial') NOT ('Review' OR 'Meta-Analysis' OR 'Editorial')

OR 'Clinical Trials, Phase I as Topic' OR 'Clinical Trials, Phase II as Topic' OR 'Cross-Over Studies'
OR 'Cohort Studies' OR 'Pharmacokinetics' OR 'rationale':ti OR 'design':ti OR 'Cost-Benefit
Analysis') NOT ('diabet*':ti NOT ('non diabet*':ti or 'without diabet*':ti))

Appendix 3. Imputations for Missing Data

For the data needed to pool the outcome of the annual rate of change in the estimated glomerular filtration rate (eGFR), we used imputation methods to reconstruct the missing values as recommended in the Cochrane Handbook.⁴

First, we obtained the change in eGFR from 14 to 720 days in Figure 4 of the study reported by Jhund *et al*⁸ as the data of the annual rate of change in eGFR of the nondiabetic participants in the Dapagliflozin and Prevention of Adverse Outcomes in Heart Failure (DAPA-HF) trial. The confidence interval (CI) for the mean in each study group was used to calculate the standard deviation (SD). The SD for each group was obtained by dividing the width of the confidence interval by 3.92 and then multiplying by the square root of the sample size (N) in that group using the following formula: [SD = \sqrt{N} (upper limit of CI - lower limit of CI)/3.92].

Second, we obtained the standard error (SE) from the CI for the mean difference between two intervention groups in the study reported by Anker *et al*⁹ using the following formula: [SE = (upper limit of CI - lower limit of CI)/3.92]. We then calculated the SD for each group from that SE using the following formula: [SD = $\frac{SE}{\sqrt{\frac{1}{N_1} + \frac{1}{N_2}}}$], where N1 = sample size of the experimental group and N2 = sample size of the control group.

Third, we obtained the SE from the CI for the mean difference between two intervention groups in the study reported by Filippatos *et al*¹⁰ using the following formula: [SE = (upper limit of CI - lower limit of CI)/3.92]. We then calculated the SD for each group from that SE using the following formula: [SD = $\frac{SE}{\sqrt{\frac{1}{N_1} + \frac{1}{N_2}}}$], where N1 = sample size of the experimental group and N2 = sample size of the control group.

References. References for Study Protocol and Imputation Methods

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10. Filippatos G, Butler J, Farmakis D, et al. Empagliflozin for Heart Failure With Preserved Left Ventricular Ejection Fraction With and Without Diabetes. *Circulation* 2022;101161CIRCULATIONAHA122059785. doi: 10.1161/CIRCULATIONAHA.122.059785
11. Petrie MC, Verma S, Docherty KF, et al. Effect of Dapagliflozin on Worsening Heart Failure and Cardiovascular Death in Patients With Heart Failure With and Without Diabetes. *Jama* 2020;323(14):1353-68. doi: 10.1001/jama.2020.1906 [published Online First: 2020/03/29]

12. Wheeler DC, Stefánsson BV, Jongs N, et al. Effects of dapagliflozin on major adverse kidney and cardiovascular events in patients with diabetic and non-diabetic chronic kidney disease: a prespecified analysis from the DAPA-CKD trial. *The lancet Diabetes & endocrinology* 2021;9(1):22-31. doi: 10.1016/S2213-8587(20)30369-7

Figure S1. Summary of Risk of Bias of the Included Studies

The green symbols represent a low risk of bias. The figure was generated using Review Manager Version 5.4.

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Anker et al 2021	+	+	+	+	+	+	+
Filippatos et al 2022	+	+	+	+	+	+	+
Petrie et al 2020	+	+	+	+	+	+	+
Wheeler et al 2021	+	+	+	+	+	+	+

Figure S2. Risk of Bias Graph of the Included Studies

Each domain of bias is presented as percentages across all included studies. The figure was generated using Review Manager Version 5.4.

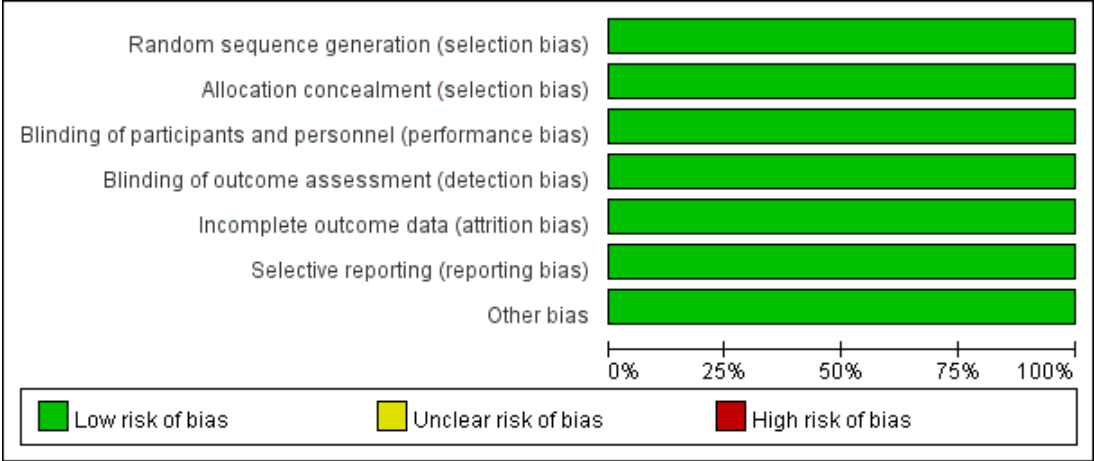
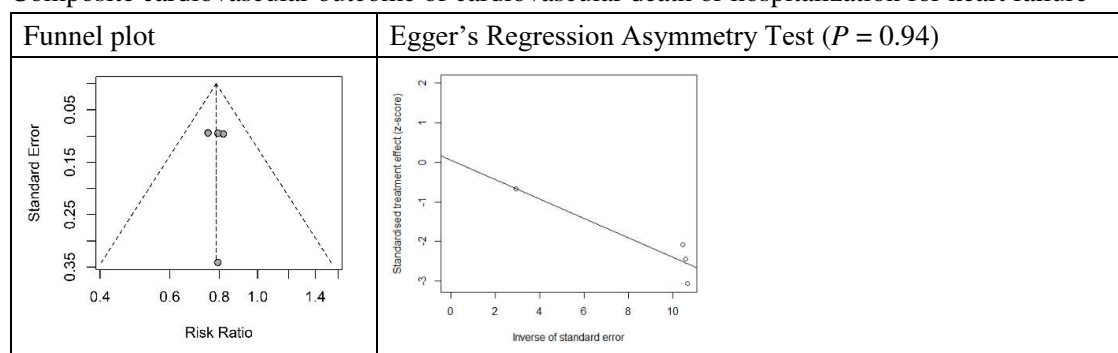


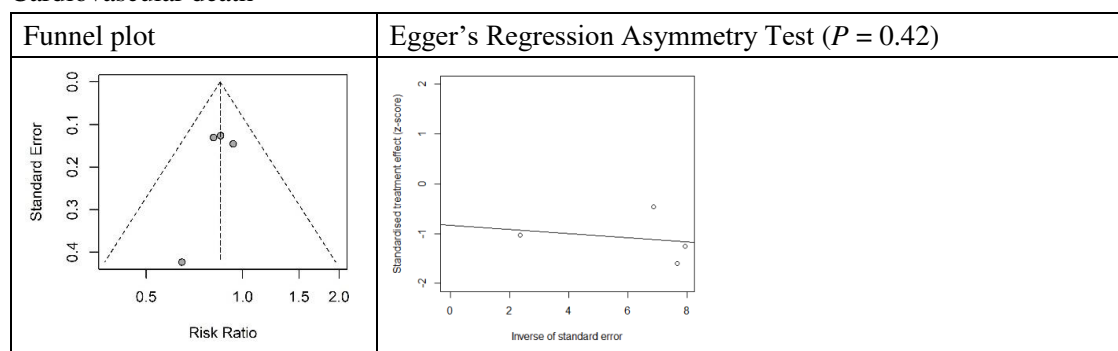
Figure S3. Funnel Plots and Egger's Test for the Assessment of Publication Bias for Efficacy Outcomes

(A) Composite cardiovascular outcome of cardiovascular death or hospitalization for heart failure, (B) cardiovascular death, (C) hospitalization for heart failure, (D) all-cause mortality, (E) composite renal outcome of 50% or greater reduction in estimated glomerular filtration rate (eGFR), end-stage kidney disease, or renal death and (F) annual rate of change in eGFR (mL/min/1.73 m²/year) for comparisons between sodium-glucose cotransporter-2 inhibitors and placebo.

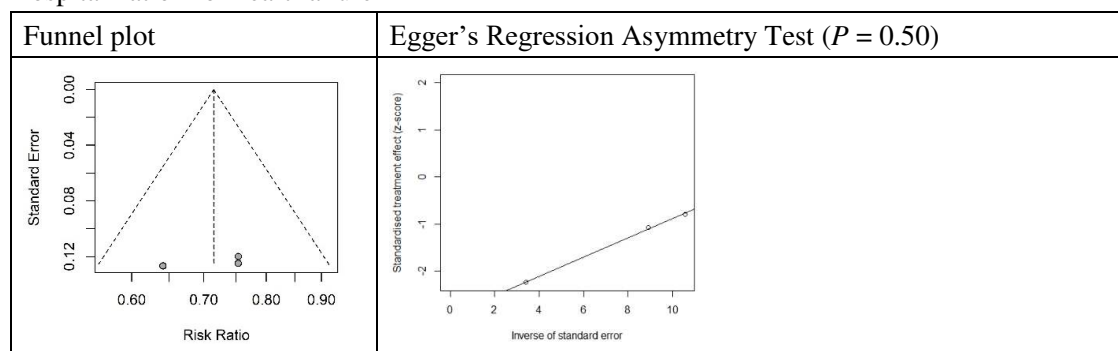
(A) Composite cardiovascular outcome of cardiovascular death or hospitalization for heart failure



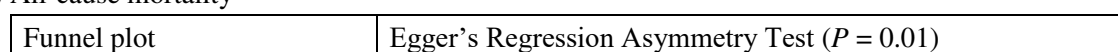
(B) Cardiovascular death

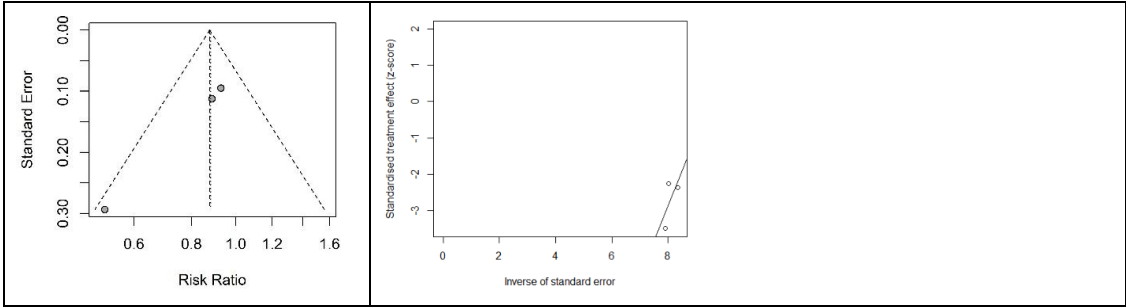


(C) Hospitalization for heart failure

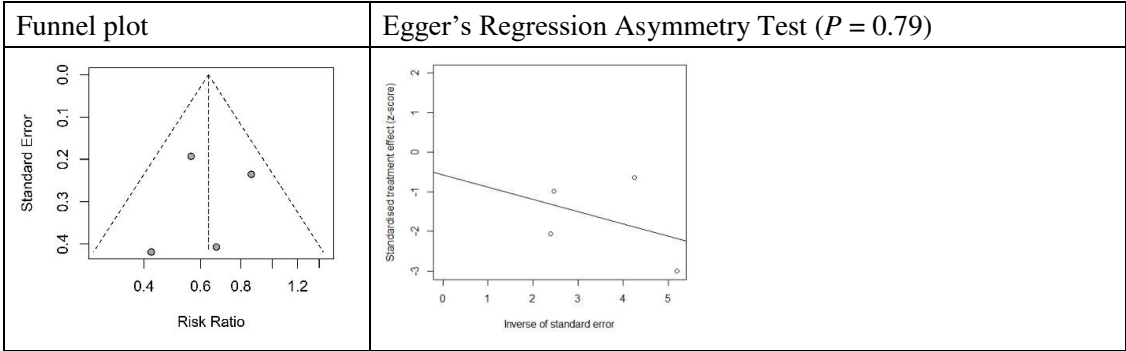


(D) All-cause mortality





(E) Composite renal outcome of 50% or greater reduction in eGFR, end-stage kidney disease, or renal death



(F) Annual rate of change in eGFR (mL/min/1.73 m²/year)

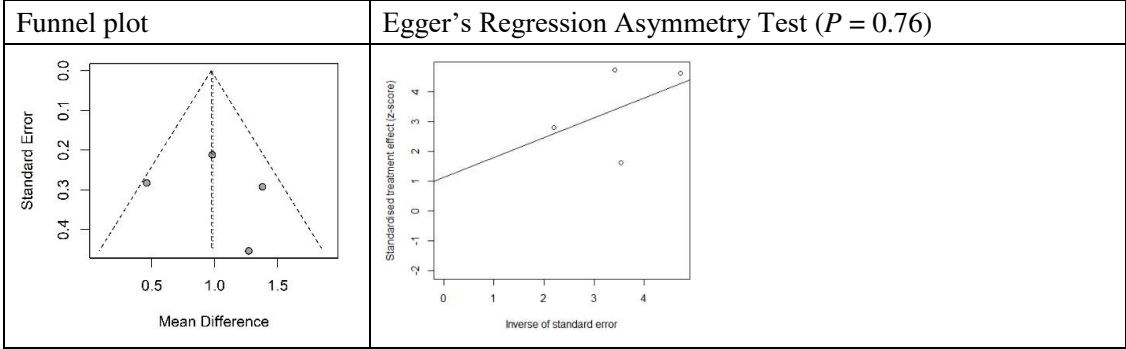
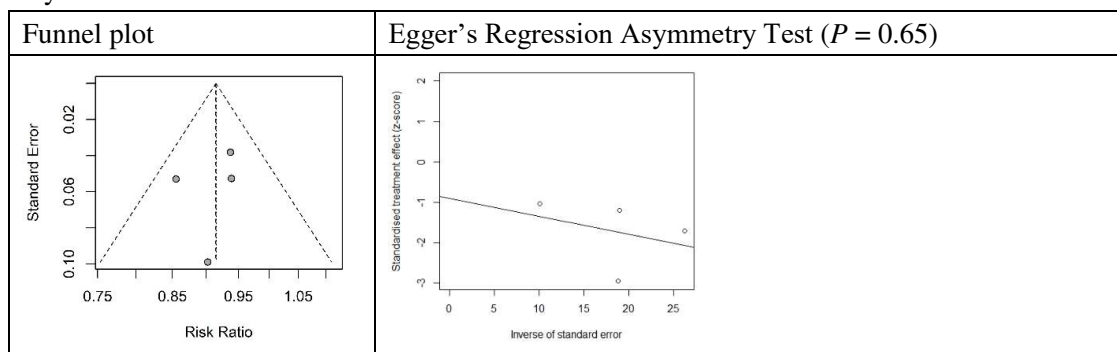


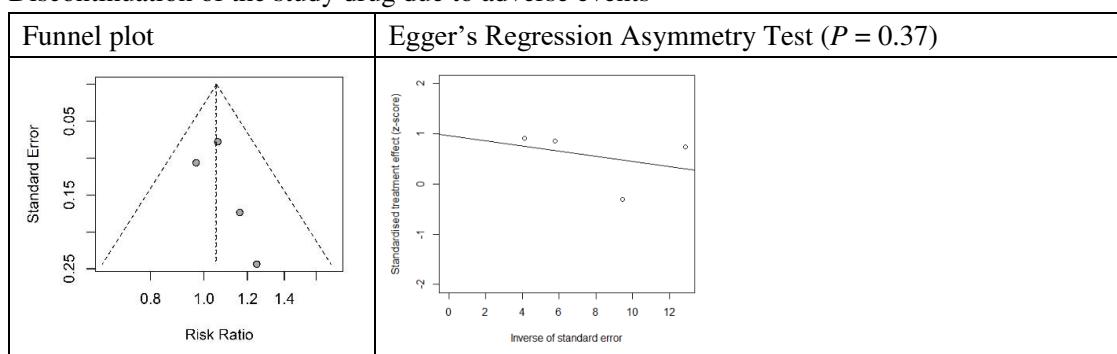
Figure S4. Funnel Plots and Egger's Test for the Assessment of Publication Bias for Safety Outcomes

(A) Any serious adverse event, (B) discontinuation of the study drug due to adverse events, (C) amputation, (D) fracture, (E) volume depletion, (F) acute renal failure, (G) urinary tract infection and (H) genital infection, for comparisons between sodium-glucose cotransporter-2 inhibitors and placebo.

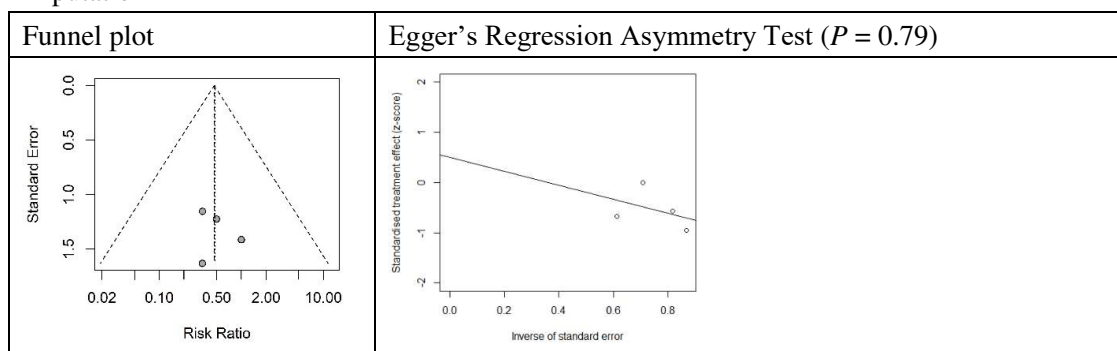
(A) Any serious adverse event



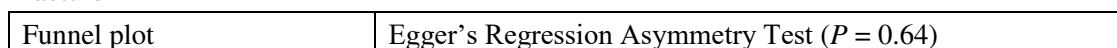
(B) Discontinuation of the study drug due to adverse events

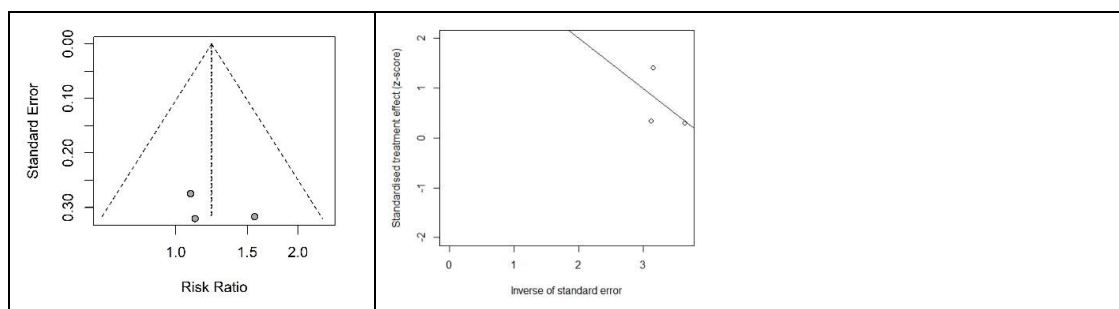


(C) Amputation

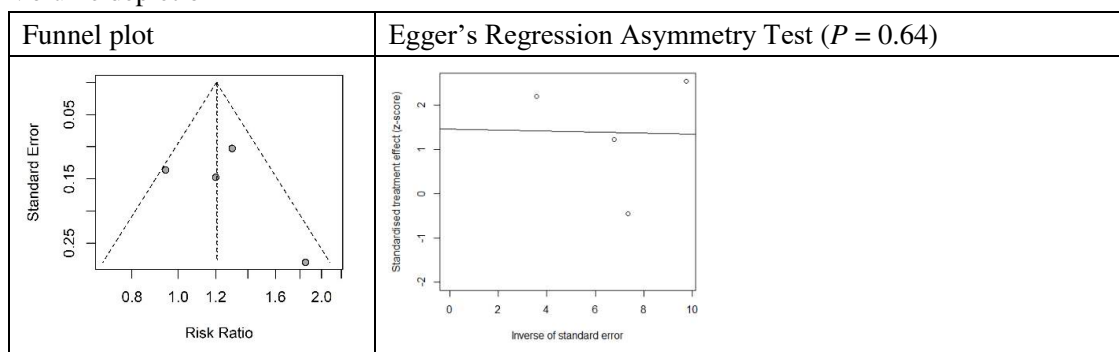


(D) Fracture

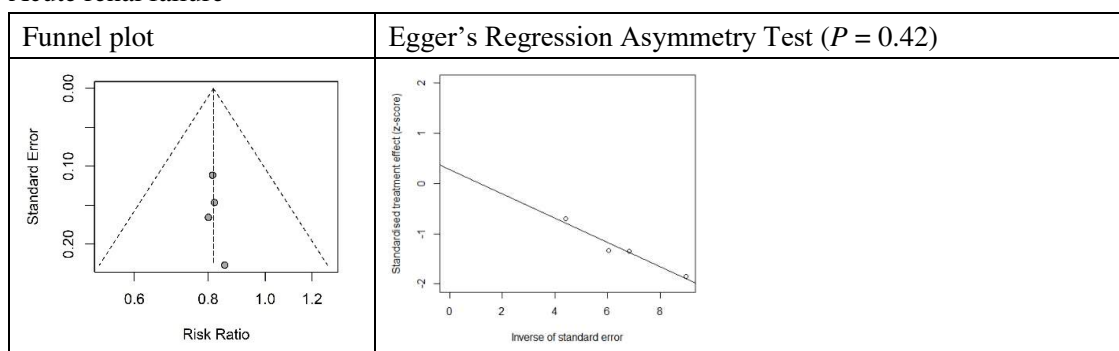




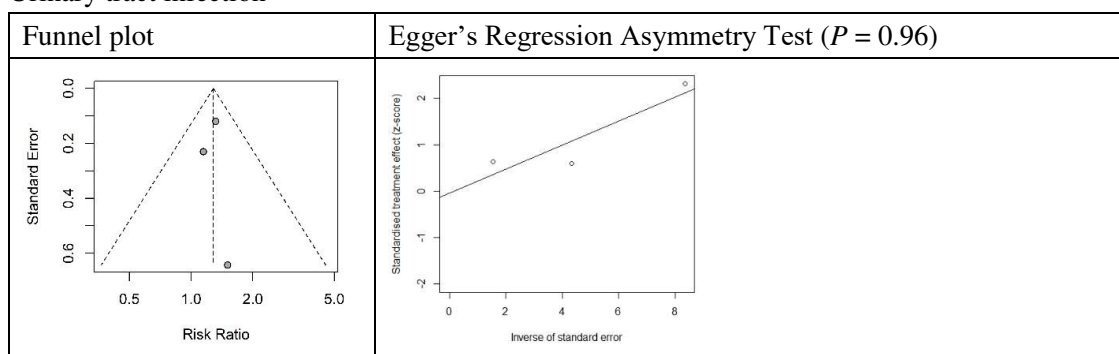
(E) Volume depletion



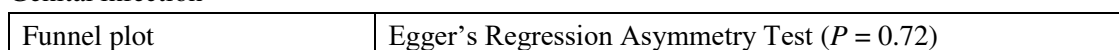
(F) Acute renal failure



(G) Urinary tract infection



(H) Genital infection



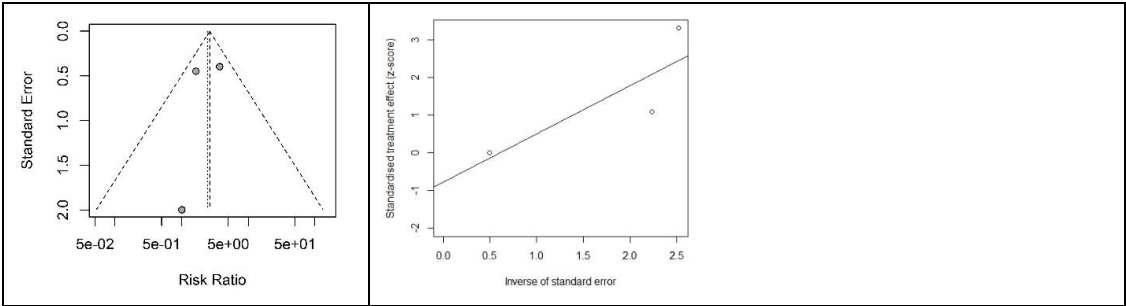


Table S1. GRADE Evidence Profile for Efficacy Outcomes Comparing Sodium-Glucose Cotransporter-2 Inhibitors with Placebo







Question: Is the use of SGLT2 inhibitors compared to placebo beneficial in patients without diabetes in terms of cardiovascular and renal outcomes?

Population: Patient without diabetes

Setting: Long-term prevention and control of clinical outcomes in chronic conditions

Intervention: SGLT2 inhibitors

Comparison: Placebo

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	SGLT2 inhibitors	Placebo	Relative (95% CI)	Absolute (95% CI)		
Composite cardiovascular outcome of cardiovascular death or hospitalization for heart failure (follow-up: range 1.3 years to 2.4 years)												
4	randomised trials	not serious	not serious	serious ^a	not serious	none	521/4462 (11.7%)	663/4465 (14.8%)	RR 0.79 (0.71 to 0.87)	31 fewer per 1,000 (from 43 fewer to 19 fewer)	 Moderate	CRITICAL
Cardiovascular death (follow-up: range 1.3 years to 2.4 years)												
4	randomised trials	not serious	not serious	serious ^a	not serious	none	297/4462 (6.7%)	349/4465 (7.8%)	RR 0.85 (0.74 to 0.99)	12 fewer per 1,000 (from 20 fewer to 1 fewer)	 Moderate	CRITICAL
Hospitalization for heart failure (follow-up: range 1.3 years to 2.4 years)												
3	randomised trials	not serious	not serious	serious ^a	not serious	none	303/3765 (8.0%)	424/3764 (11.3%)	RR 0.72 (0.62 to 0.82)	32 fewer per 1,000 (from 43 fewer to 20 fewer)	 Moderate	IMPORTANT
All-cause mortality (follow-up: range 1.3 years to 2.4 years)												
3	randomised trials	not serious	not serious	serious ^a	serious ^b	publication bias strongly suspected ^c	338/3526 (9.6%)	385/3527 (10.9%)	RR 0.88 (0.77 to 1.01)	13 fewer per 1,000 (from 25 fewer to 1 more)	 Very low	CRITICAL
Composite renal outcome of 50% or greater reduction in estimated glomerular filtration rate, end-stage kidney disease, or renal death (follow-up: range 1.3 years to 2.4 years)												
4	randomised trials	not serious	not serious	serious ^a	serious ^d	none	90/4462 (2.0%)	142/4465 (3.2%)	RR 0.64 (0.48 to 0.85)	11 fewer per 1,000 (from 17 fewer to 5 fewer)	 Low	CRITICAL
Annual rate of change in estimated glomerular filtration rate (mL/min/1.73 m2/year) (follow-up: range 1.3 years to 2.4 years)												
4	randomised trials	not serious	not serious	serious ^a	not serious	none	4412	4442	-	MD 0.99 mL/min/1.73 m2/year higher (0.59 higher to 1.39 higher)	 Moderate	CRITICAL

CI: confidence interval; MD: mean difference; RR: risk ratio

Explanations

- a. Downgraded because the included studies were restricted to patients with chronic heart failure or chronic kidney disease.
- b. Downgraded because the confidence interval for the effect on all-cause mortality include harm.
- c. Downgraded because of funnel plot asymmetry (Egger's test, *P* = .01).
- d. Downgraded because of few events.

Table S2. GRADE Evidence Profile for Safety Outcomes Comparing Sodium-Glucose Cotransporter-2 Inhibitors with Placebo

Question: What are the possible side effects of SGLT2 inhibitors?
Population: Patient without diabetes
Setting: Safety issues in long-term treatment with SGLT2 inhibitors
Intervention: SGLT2 inhibitors
Comparison: Placebo

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	SGLT2 inhibitors	Placebo	Relative (95% CI)	Absolute (95% CI)		
Any serious adverse event (follow-up: range 1.3 years to 2.4 years)												
4	randomised trials	not serious	not serious	serious ^a	not serious	none	1677/4458 (37.6%)	1832/4459 (41.1%)	RR 0.91 (0.87 to 0.96)	37 fewer per 1,000 (from 53 fewer to 16 fewer)	⊕⊕⊕○ Moderate	IMPORTANT
Amputation (follow-up: range 1.3 years to 2.4 years)												
4	randomised trials	not serious	not serious	serious ^a	serious ^b	none	3/4458 (0.1%)	7/4459 (0.2%)	RR 0.48 (0.13 to 1.74)	1 fewer per 1,000 (from 1 fewer to 1 more)	⊕⊕○○○ Low	CRITICAL
Fracture (follow-up: range 1.3 years to 2.4 years)												
3	randomised trials	not serious	not serious	serious ^a	serious ^b	none	72/2927 (2.5%)	59/2941 (2.0%)	RR 1.22 (0.87 to 1.72)	4 more per 1,000 (from 3 fewer to 14 more)	⊕⊕○○○ Low	CRITICAL
Volume depletion (follow-up: range 1.3 years to 2.4 years)												
4	randomised trials	not serious	not serious	serious ^a	serious ^c	none	418/4458 (9.4%)	347/4459 (7.8%)	RR 1.21 (0.99 to 1.48)	16 more per 1,000 (from 1 fewer to 37 more)	⊕⊕○○○ Low	IMPORTANT
Acute renal failure (follow-up: range 1.3 years to 2.4 years)												
4	randomised trials	not serious	not serious	serious ^a	not serious	none	306/4458 (6.9%)	374/4459 (8.4%)	RR 0.82 (0.71 to 0.94)	15 fewer per 1,000 (from 24 fewer to 5 fewer)	⊕⊕⊕○ Moderate	IMPORTANT
Urinary tract infection (follow-up: range 1.3 years to 2.4 years)												
3	randomised trials	not serious	not serious	serious ^a	serious ^d	none	194/3163 (6.1%)	150/3154 (4.8%)	RR 1.29 (1.05 to 1.58)	14 more per 1,000 (from 2 more to 28 more)	⊕⊕○○○ Low	IMPORTANT
Genital infection (follow-up: range 1.3 years to 2.4 years)												
3	randomised trials	not serious	not serious	serious ^a	serious ^d	none	43/3161 (1.4%)	16/3154 (0.5%)	RR 2.44 (1.14 to 5.25)	7 more per 1,000 (from 1 more to 22 more)	⊕⊕○○○ Low	IMPORTANT

Note. In accordance with Cochrane’s recommendations, 7 main outcomes that are essential for decision-making are presented. CI: confidence interval; RR: risk ratio

Explanations

- a. Downgraded because the included studies were restricted to patients with chronic heart failure or chronic kidney disease
- b. Downgraded due to few events and the confidence intervals include appreciable benefit or harm.
- c. Downgraded because the confidence intervals include appreciable benefit or harm.
- d. Downgraded due to few events and wide confidence intervals.

Table S3. Comparisons of the Definitions for Composite Renal Outcomes Across the Included Studies

Study	Prespecified composite renal outcome	Percentage of reduction in eGFR	Repeat assessment and confirmation of changes in kidney function and initiation of dialysis	Included renal death
Petrie <i>et al</i> 2020 (DAPA-HF) ¹¹	Time to first occurrence of 50% or greater reduction in eGFR sustained for at least 28 days, kidney failure, or death from kidney-related causes. <ul style="list-style-type: none"> Kidney failure was defined as eGFR less than 15 mL/min/1.73 m² sustained for at least 28 days, chronic dialysis treatment sustained for at least 28 days, or kidney transplant. 	50%	Yes	Yes
Anker <i>et al</i> 2021 (EMPEROR-Reduced) ^{9*}	Time to first event of chronic dialysis, renal transplant or sustained reduction of $\geq 40\%$ eGFR or for patients with eGFR ≥ 30 mL/min/1.73 m ² at baseline: sustained eGFR < 15 mL/min/1.73 m ² ; for patients with eGFR < 30 mL/min/1.73 m ² at baseline: sustained eGFR < 10 mL/min/1.73 m ² . <ul style="list-style-type: none"> An eGFR reduction is considered sustained if it is determined by two or more consecutive postbaseline central laboratory measurements separated by at least 30 days (first to last of the consecutive eGFR values). Dialysis is regarded as chronic if the frequency of dialysis is twice or more per week for at least 90 days. 	40%	Yes	No
Wheeler <i>et al</i> 2021 (DAPA-CKD) ¹²	A composite of a sustained decline of 50% or more in eGFR (confirmed by a second serum creatinine after at least 28 days), onset of end-stage kidney disease (defined as maintenance dialysis for more than 28 days, kidney transplantation, or eGFR < 15 mL/min per 1.73 m ² confirmed by a second measurement after at least 28 days), or death from kidney causes.	50%	Yes	Yes
Filippatos <i>et al</i> 2022 (EMPEROR-Preserved) ¹⁰	Time to first occurrence of chronic dialysis, renal transplantation, sustained reduction of $\geq 40\%$ in eGFR or sustained eGFR < 15 mL/min per 1.73 m ² for patients with baseline eGFR ≥ 30 mL/min per 1.73 m ² or < 10 mL/min per 1.73 m ² for patients with baseline eGFR < 30 mL/min per 1.73 m ² .	40%	Yes	No

*The definition in original study protocol was provided for detail.

Note. All studies used the CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration Creatinine) equation for estimating GFR. eGFR, estimated glomerular filtration rate.