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

Tsai W-C, *et al. BMJ Open* 2022; 12:e060655. doi: 10.1136/bmjopen-2021-060655

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 m^2/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 m^2), 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 m^2/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 (I^2) 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 m^2), 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" "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= $\frac{SE}{\sqrt{\frac{1}{N1}+\frac{1}{N2}}}$], 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= $\frac{SE}{\sqrt{\frac{1}{N1}+\frac{1}{N2}}}$], where N1 = sample size of the experimental group and N2 = sample size of the control group.

References. References for Study Protocol and Imputation Methods

1. Higgins JPT, Savović J, Page MJ, Elbers RG, Sterne JAC. Chapter 8: Assessing risk of bias in a randomized trial. In: Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA (editors). Cochrane Handbook for Systematic Reviews of Interventions version 6.3 (updated February 2022). Cochrane, 2022. Available from www.training.cochrane.org/handbook.
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5. Borenstein M, Hedges LV, Higgins JPT, et al. Introduction to Meta-Analysis: John Wiley & Sons, Ltd. 2009.
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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
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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.

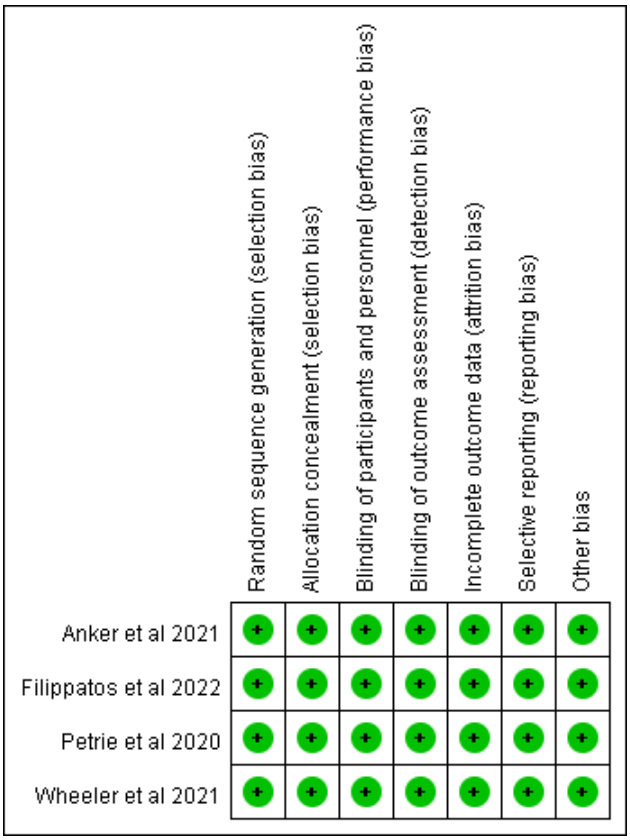


Figure S2. Risk of Bias Graph of the Included Studies

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

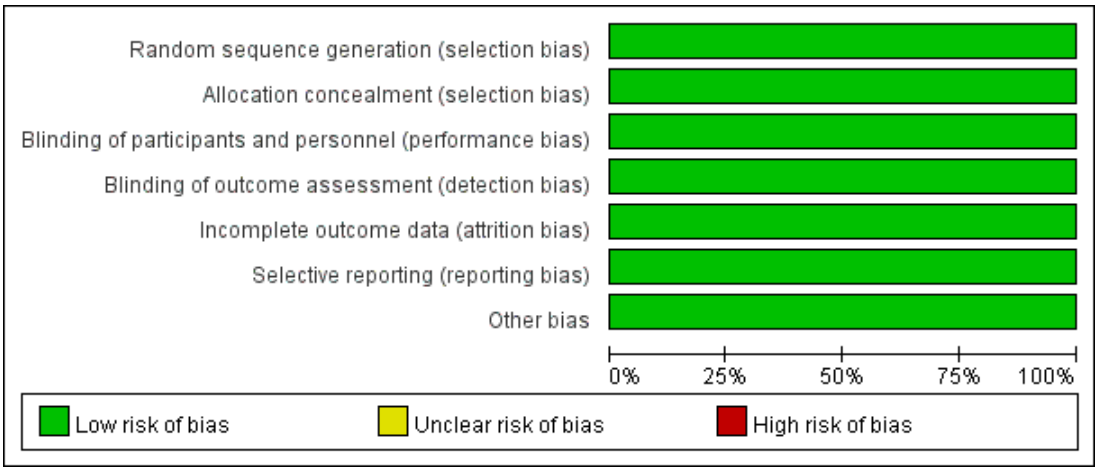
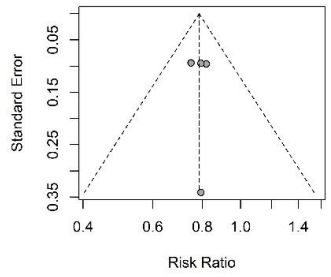
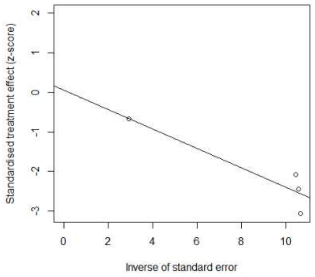


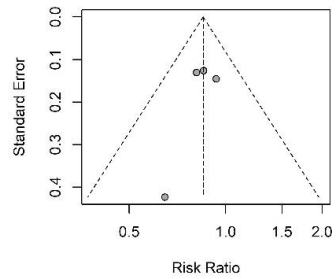
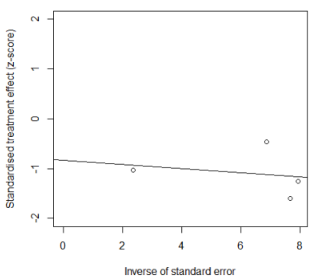
Figure S3. Funnel Plots and Egger's Test for the Assessment of Publication Bias for Efficacy Outcomes

(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 m^2/year) for comparisons between sodium-glucose cotransporter-2 inhibitors and placebo.

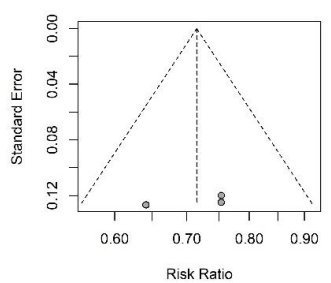
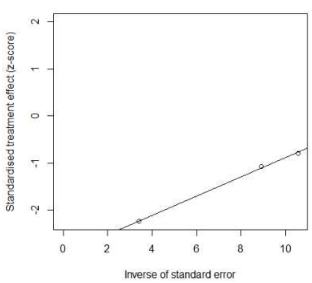
(A) Composite cardiovascular outcome of cardiovascular death or hospitalization for heart failure

Funnel plot	Egger's Regression Asymmetry Test (P = 0.94)
	

(B) Cardiovascular death

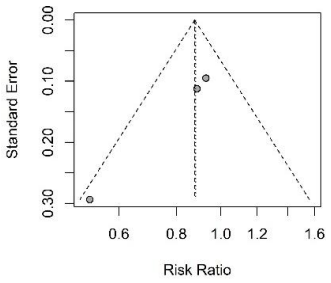
Funnel plot	Egger's Regression Asymmetry Test (P = 0.42)
	

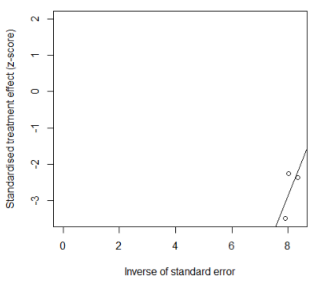
(C) Hospitalization for heart failure

Funnel plot	Egger's Regression Asymmetry Test (P = 0.50)
	

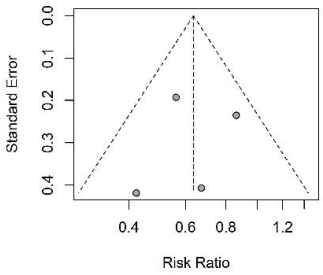
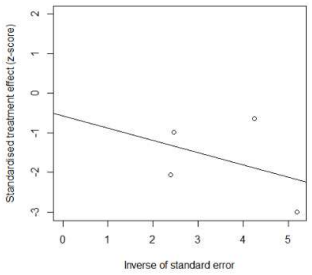
(D) All-cause mortality

Funnel plot	Egger's Regression Asymmetry Test (P = 0.01)





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

Funnel plot	Egger's Regression Asymmetry Test (P = 0.79)
	

(F) Annual rate of change in eGFR (mL/min/1.73 m^2/year)

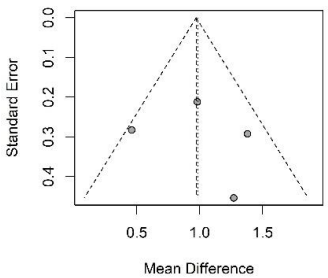
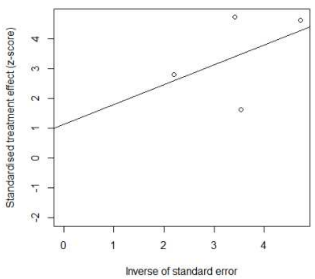
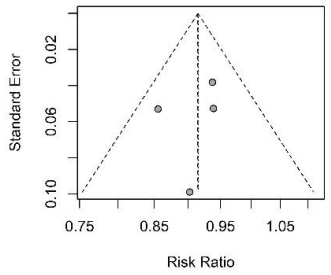
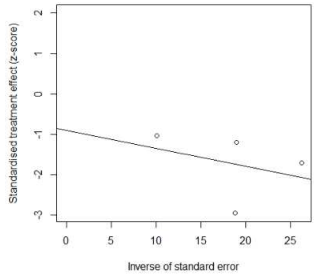
Funnel plot	Egger's Regression Asymmetry Test (P = 0.76)
	

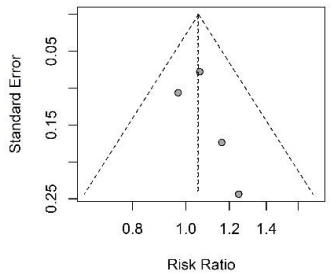
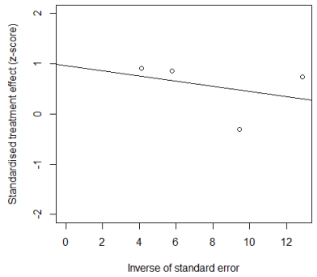
Figure S4. Funnel Plots and Egger's Test for the Assessment of Publication Bias for Safety Outcomes

(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.

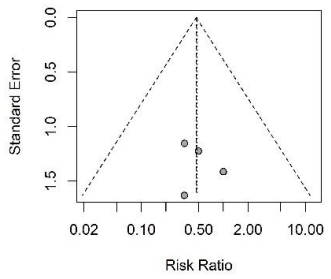
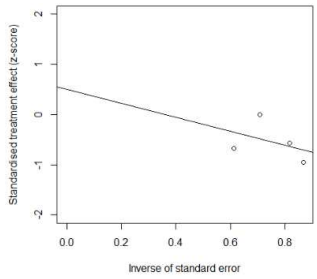
(A) Any serious adverse event

Funnel plot	Egger's Regression Asymmetry Test (P = 0.65)
	

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

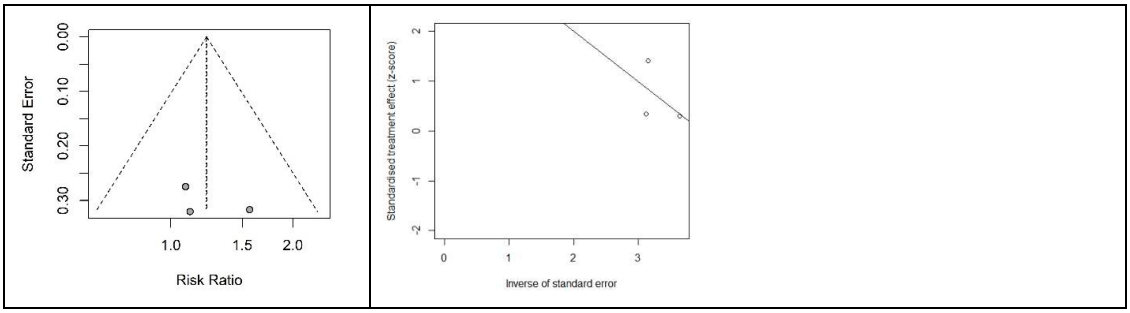
Funnel plot	Egger's Regression Asymmetry Test (P = 0.37)
	

(C) Amputation

Funnel plot	Egger's Regression Asymmetry Test (P = 0.79)
	

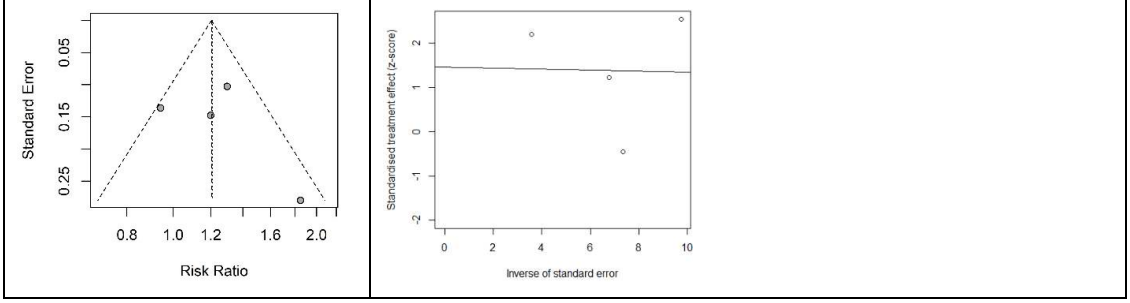
(D) Fracture

Funnel plot	Egger's Regression Asymmetry Test (P = 0.64)



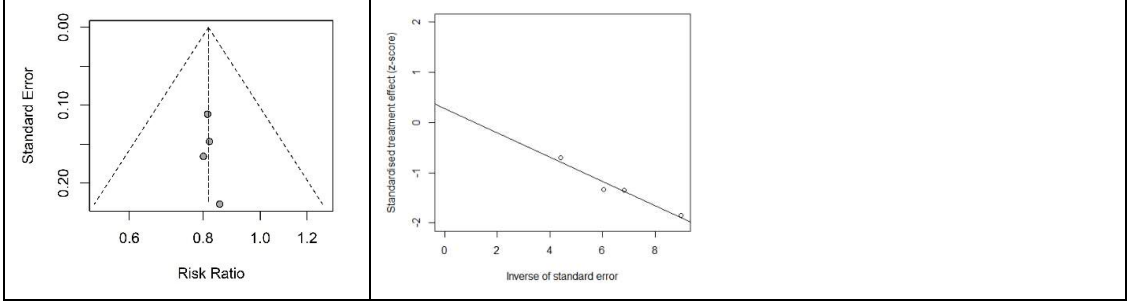
(E) Volume depletion

Funnel plot	Egger's Regression Asymmetry Test (P = 0.64)



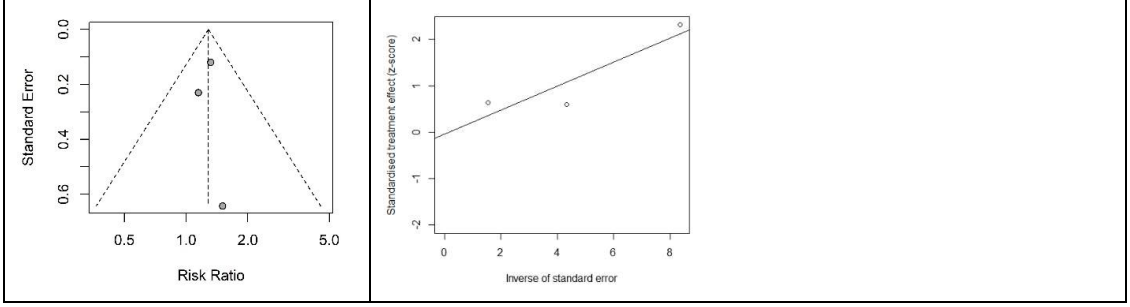
(F) Acute renal failure

Funnel plot	Egger's Regression Asymmetry Test (P = 0.42)



(G) Urinary tract infection

Funnel plot	Egger's Regression Asymmetry Test (P = 0.96)



(H) Genital infection

Funnel plot	Egger's Regression Asymmetry Test (P = 0.72)

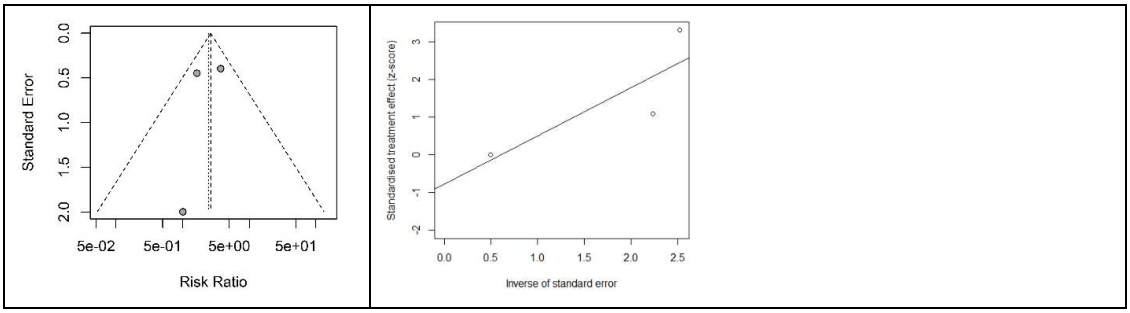

Standard Error
0.0
0.5
1.0
1.5
2.0
5e-02
5e-01
5e+00
5e+01
Risk Ratio
Standardised treatment effect (z-score)
-2
-1
0
1
2
3
0.0
0.5
1.0
1.5
2.0
2.5
Inverse of standard error

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 *et al* 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. • Kidney failure was defined as eGFR less than 15 mL/min/1.73 m^2 sustained for at least 28 days, chronic dialysis treatment sustained for at least 28 days, or kidney transplant.	50%	Yes	Yes
Anker *et al* 2021 (EMPEROR-Reduced)[9]*	Time to first event of chronic dialysis, renal transplant or sustained reduction of ≥ 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. • 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 *et al* 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 m² confirmed by a second measurement after at least 28 days), or death from kidney causes.	50%	Yes	Yes
Filippatos *et al* 2022 (EMPEROR-Preserved)[10]	Time to first occurrence of chronic dialysis, renal transplantation, sustained reduction of ≥ 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.