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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

Wan-Chuan Tsai ,[1,2] Shih-Ping Hsu,[1,3,4] Yen-Ling Chiu,[1,3,5] Ju-Yeh Yang ,[1,2,3] Mei-Fen Pai,[1,3] Mei-Ju Ko,[6,7] Yu-Kang Tu,[8] Kuan-Yu Hung,[3] Kuo-Liong Chien ,[3,8] Yu-Sen Peng,[1,3,9,10] Hon-Yen Wu[1,3,8,11]

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Correspondence to
Dr Hon-Yen Wu; honyenwu@ntu.edu.tw and Dr Yu-Sen Peng; taan70@yahoo.com.tw

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 ≥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 m^2/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 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.

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.

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

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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 m^2/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,

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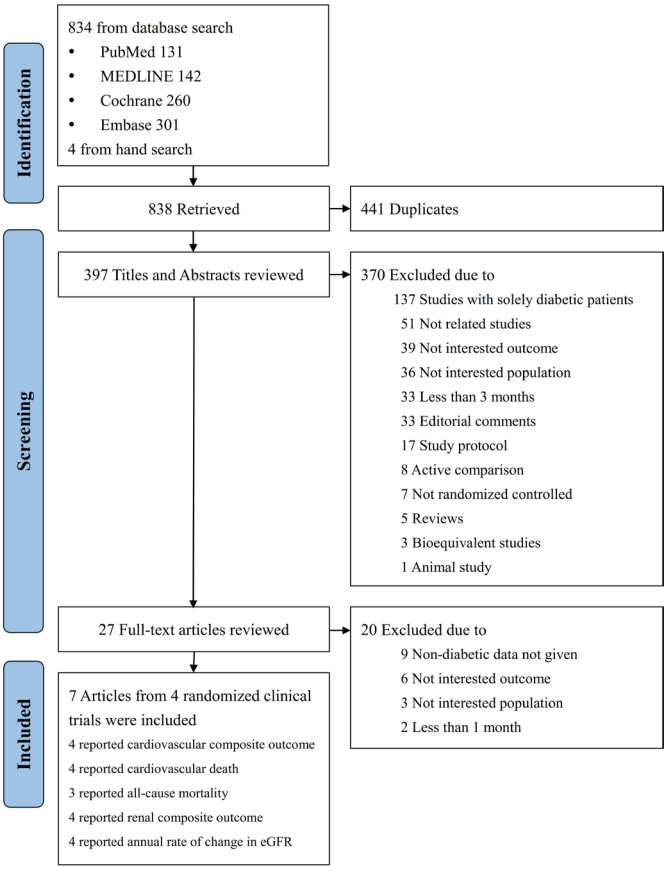

Figure 1 Summary of study identification and selection. eGFR, estimated glomerular filtration rate.

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 m^2. As a standard of care, 45% of the participants received angiotensin-converting enzyme inhibitors, 35% received angiotensin receptor blockers and 76% received diuretics.

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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 HFrEF, NYHA class II–IV with LVEF ≤40% and elevated NT-proBNP		Chronic HFrEF, NYHA class II–IV with LVEF ≤40% and elevated NT-proBNP		CKD, eGFR 25–75 mL/min/1.73 m^2 and UACR 200–5000 mg/g		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**	**Placebo**	**Empagliflozin 10 mg once daily**	**Placebo**	**Dapagliflozin 10 mg once daily**	**Placebo**	**Empagliflozin 10 mg once daily**	**Placebo**
Number of participants in each group	1298	1307	936	938	697	701	1531	1519
Age (years)	66±12	66±12	68±12	66±12	57±15	56±15	73±10	
Women, n (%)	324 (25)	308 (24)	227 (24)	238 (25)	215 (31)	245 (35)	1420 (47)	
Race, n (%)								
White	918 (71)	926 (71)	679 (73)	665 (71)	373 (54)	376 (54)	2334 (77)	
Black	50 (4)	48 (4)	66 (7)	71 (8)	28 (4)	26 (4)	117 (4)	
Asian	311 (24)	314 (24)	154 (17)	160 (17)	268 (38)	267 (38)	431 (14)	
Other	19 (2)	19 (2)	37 (4)	42 (5)	28 (4)	32 (5)	167 (6)	
History of heart failure, n (%)	1295 (100)	1305 (100)	936 (100)	937 (100)	58 (8)	49 (7)	3050 (100)	
Systolic blood pressure (mm Hg)	121±16	120±16	122±16	120±15	132±16	133±17	130±15	
Haemoglobin A1c (%)	5.7±0.4	5.8±0.4	5.8±0.4	5.7±0.4	5.6±0.4	5.6±0.4	5.7±0.4	
eGFR (mL/min/1.73 m^2)	68±19	68±19	63±21	63±21	42±12	42±12	62±19	
eGFR <60 mL/min/1.73 m^2, n (%)	480 (37)	464 (36)	434 (46)	426 (45)	642 (92)	650 (93)	1478 (49)	
ACE inhibitor, n (%)	737 (57)	752 (58)	451 (48)	425 (45)	222 (32)	238 (34)	1229 (40)	
ARB, n (%)	357 (28)	335 (26)	213 (23)	227 (24)	460 (66)	452 (64)	1093 (36)	
Diuretic, n (%)	1191 (92)	1214 (93)	779 (83)	809 (86)	210 (30)	207 (30)	2358 (77)	

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 With Preserved Ejection Fraction; EMPEROR-Reduced, 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).

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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 trial[26] and DAPA-CKD trial[29] and 40% or greater in the EMPEROR-Reduced trial[28] and EMPEROR-Preserved trial[30]; the composite renal outcome did not include renal-related death in the EMPEROR-Reduced trial[28] and EMPEROR-Preserved trial[30] (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 m^2/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 trial[30] 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 ≥50% reduction in eGFR, ESKD or renal death by 36%. SGLT2 inhibitors also postponed the decline in eGFR by

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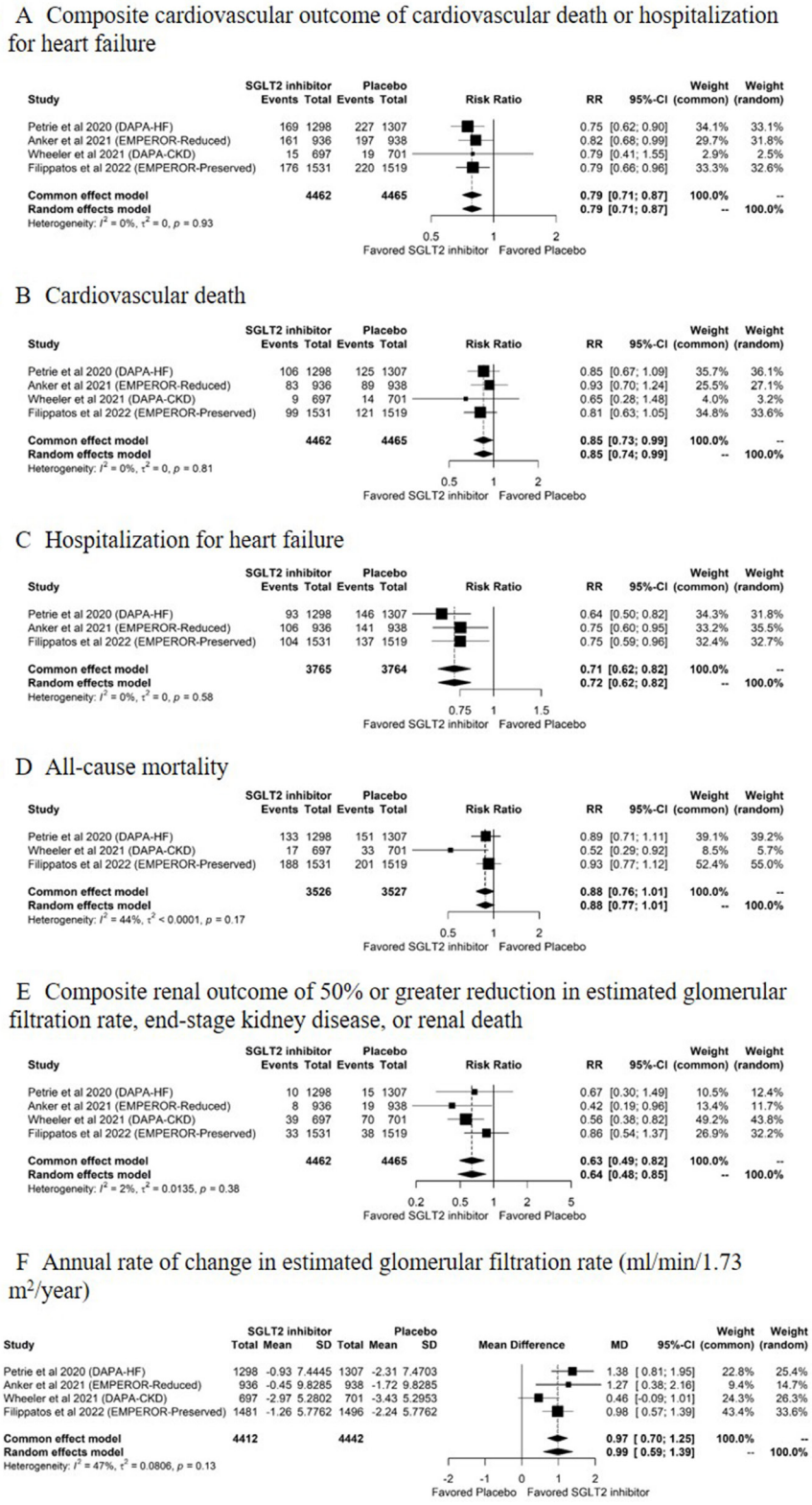

Figure 2 Pooled estimates of the efficacy outcomes comparing SGLT2 inhibitors with placebo. (A) Composite cardiovascular outcome of cardiovascular death or hospitalisation for heart failure, (B) cardiovascular death, (C) hospitalisation for heart failure, (D) all-cause mortality, (E) composite renal 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 m^2/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.

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Table 2 Adverse events reported in the included studies

Source	Overall		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]	
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.

0.99 mL/min/1.73 m^2 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),

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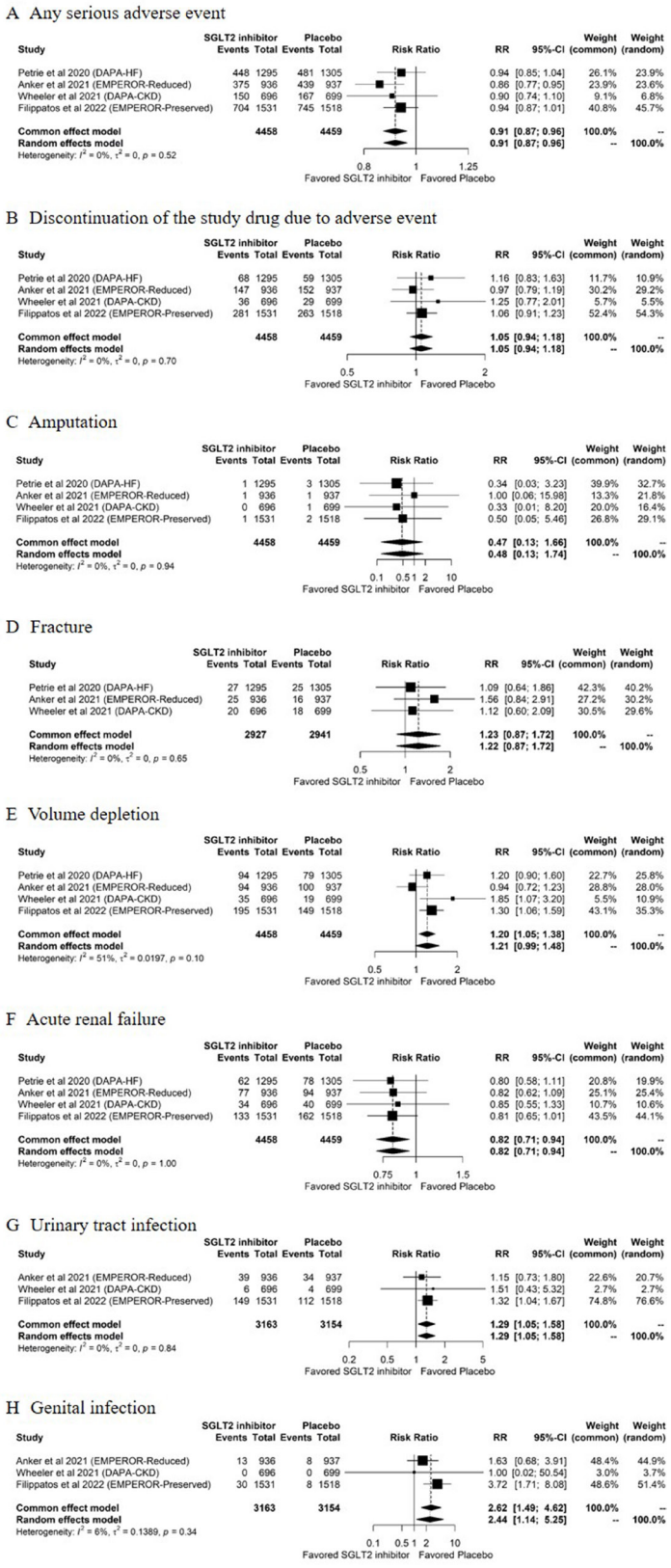

Figure 3 Pooled estimates of the safety outcomes comparing SGLT2 inhibitors with placebo. (A) Any serious adverse event, (B) discontinuation of the study drug due to adverse events, (C) amputation, (D) fracture, (E) volume depletion, (F) acute renal failure, (G) urinary tract infection and (H) genital 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.

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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 erythropoiesis[44] 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-Kidney[45] 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.

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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.

Author affiliations
[1]Division of Nephrology, Department of Internal Medicine, Far Eastern Memorial Hospital, New Taipei City, Taiwan
[2]Center for General Education, Lee-Ming Institute of Technology, New Taipei City, Taiwan
[3]Department of Internal Medicine, National Taiwan University Hospital and College of Medicine, Taipei City, Taiwan
[4]School of Life Science, National Taiwan Normal University, Taipei City, Taiwan
[5]Graduate Program in Biomedical Informatics, Yuan Ze University, Taoyuan City, Taiwan
[6]Department of Dermatology, National Taiwan University Hospital and College of Medicine, Taipei City, Taiwan
[7]Department of Dermatology, Taipei City Hospital, Taipei City, Taiwan
[8]Institute of Epidemiology and Preventive Medicine, College of Public Health, National Taiwan University, Taipei City, Taiwan
[9]Department of Applied Cosmetology, Lee-Ming Institute of Technology, New Taipei City, Taiwan
[10]Department of Electrical Engineering, Yuan Ze University, Taoyuan City, Taiwan
[11]School of Medicine, College of Medicine, National Yang Ming Chiao Tung University, Taipei City, Taiwan

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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ORCID iDs
Wan-Chuan Tsai http://orcid.org/0000-0002-6728-5851
Ju-Yeh Yang http://orcid.org/0000-0003-3034-021X
Kuo-Liong Chien http://orcid.org/0000-0003-4979-8351

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