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The effect of empagliflozin on cardiovascular outcomes in patients with chronic kidney disease; a systematic review and meta-analysis

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ABSTRACT

Introduction: Chronic kidney disease (CKD) is among the fastest causes of mortality worldwide, associated with cardiovascular disease and diabetes. This study aimed to evaluate the impact of empagliflozin use on cardiovascular outcomes in patients with CKD.

Materials and Methods: This systematic review and meta-analysis was conducted according to PRISMA guidelines. Electronic databases, including PubMed, Scopus, Web of Science, Cochrane, and the Google Scholar search engine, were searched until June 5, 2023. Data were analyzed using STATA software version 14. A P< 0.05 indicated the significance of statistical tests.

Results: Eight clinical trial studies with a total sample of 39620 participants were evaluated in this meta-analysis. Compared with placebo, empagliflozin administration in CKD patients lowered the risk of cardiovascular death or first heart failure hospitalization by 28% (OR: 0.72; 95% CI: 0.66, 0.80), cardiovascular death by 25% (OR: 0.75; 95% CI: 0.63, 0.88), first heart failure hospitalization by 30% (OR: 0.70; 95% CI: 0.63, 0.77), total (first and recurrent) heart failure hospitalizations by 28% (OR: 0.72; 95% CI: 0.65, 0.81), and all-cause mortality by 20% (OR: 0.80; 95% CI: 0.69, 0.93). However, it demonstrated no significant effect on reducing the risk of composite kidney outcome (OR: 0.75; 95% CI: 0.55, 1.02). In addition, long-term empagliflozin use (over 105 weeks) caused a drastic reduction in cardiovascular death risk in these patients. The lowering effect of empagliflozin on cardiovascular risk decreased as the patient's age increased.

Conclusion: Empagliflozin declined the risk of cardiovascular death or first heart failure hospitalization, cardiovascular death, first heart failure hospitalization, total (first and recurrent) heart failure hospitalization, and all-cause mortality in CKD patients.

Registration: This study has been compiled based on the PRISMA checklist, and its protocol was registered on the PROSPERO (ID: CRD42023438798).

Meta-analysis

Implication for health policy/practice/research/medical education:
Chronic kidney disease (CKD) is one of the main causes of cardiovascular and diabetes-related mortality. Management of diabetes and cardiovascular diseases in patients with chronic kidney failure is very important. Evaluation of the empagliflozin use on cardiovascular outcomes in patients with CKD indicated a decline in the risk of cardiovascular death or first heart failure hospitalization, cardiovascular death, first heart failure hospitalization, total (first and recurrent) heart failure hospitalization, and all-cause mortality in CKD patients.

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Introduction

Chronic kidney disease (CKD) is a comorbidity usually associated with heart failure and type 2 diabetes, affecting more than 10 percent of the population in many countries. Nearly 40% of patients with heart failure concomitantly suffer from kidney dysfunction (1). In type 2 diabetic patients with an already high risk of cardiovascular diseases, diabetic renal disease further increases the risk of cardiovascular diseases and mortality (2). Diabetes-attributed CKD is a global cause of kidney failure,

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necessitating dialysis modally or renal transplantation (3). Chronic kidney disease is detected to become the fifth cause of global mortality by 2040, while in countries with longer life expectancy, it may become the second cause of mortality before the end of the century (4,5). CKD treatment poses a huge burden on healthcare systems in terms of resources and costs (6,7). Thus, from health and economic perspectives, it is essential to improve the clinical outcomes in patients with CKD and type 2 diabetes (8). The administration of sodium-glucose transporter 2 (SGLT2) inhibitors in diabetic patients caused a 32% decrease in the risk of all-cause mortality and heart failure-related hospitalization and also reduced their systolic blood pressure levels (9,10). Past studies have indicated that SGLT2 inhibitors, such as empagliflozin and dapagliflozin, decrease cardiovascular mortality, heart failure, and hospitalization in type 2 diabetic patients with or without CKD (11-14). In addition, empagliflozin slows the onset and progression of chronic renal failure in patients with type 2 diabetes (15). The glucose-lowering effects of SGLT2is reduced with declined estimated glomerular filtration rate. However, it is still unclear whether or not the cardiac benefits of SGLT2is are independent of renal function (16). Given the inconsistencies in previous studies, the present systematic review and meta-analysis aimed to assess the impact of empagliflozin administration on cardiovascular outcomes in CKD patients.

Materials and Methods

Study design

This systematic review and meta-analysis assessed the impact of empagliflozin use on the cardiovascular outcomes of CKD patients. This study was written according to Preferred Reporting Items for Systematic-review and Meta-analysis (PRISMA) guidelines (17), and its protocol was registered on the PROSPERO website (CRD42023438798).

Search strategy

Electronic databases, including PubMed, Scopus, Web of Science, Cochrane, and the Google Scholar search engine, were searched without time restriction until June 5, 2023. The following keywords were utilized in this study: "Empagliflozin," "sodium-glucose transporter 2 inhibitors," "SGLT-2 inhibitors," "chronic kidney disease," and "cardiovascular outcomes." Additionally, MeSH keywords and their combinations using Boolean operators (AND, OR) were utilized to retrieve the relevant articles. Two authors performed a manual search by screening the reference lists of the initially identified articles. The search strategy used in the PubMed database was as follows: ((Empagliflozin OR Sodium-Glucose Transporter 2 Inhibitors OR SGLT-2 Inhibitors) AND (Cardiovascular outcomes)) AND (Chronic Kidney Disease) (See Supplementary file 1 for more details).

PICO components

- Population: studies choosing CKD patients as their statistical population.
- Intervention: empagliflozin use.
- Comparison: placebo.
- Outcomes: the impact of empagliflozin use on the risk of the following outcomes: cardiovascular death or first heart failure hospitalization, cardiovascular death, first heart failure hospitalization, total (first and recurrent) heart failure, all-cause mortality, and composite kidney outcome.

Inclusion criteria

Clinical trial studies evaluating the effect of empagliflozin use on cardiovascular outcomes in chronic renal failure cases.

Exclusion criteria

Studies whose full texts were unavailable; case-report studies; studies exploring the effect of empagliflozin on cardiovascular outcomes of non-CKD patients; low-quality studies; studies lacking sufficient data for analysis; duplicates; studies that evaluated the effectiveness of other types of SGLT2 inhibitors (other than empagliflozin) on cardiovascular outcomes in chronic renal failure cases and studies failing to report data quantitatively.

Quality appraisal

Two authors independently assessed the quality of the studies using the Cochrane Institute checklist for clinical trials (18). This checklist contains seven questions, each assessing one type of major bias in clinical trial studies, with three response items ("low risk," "high risk," and "unclear risk"). Studies with desirable quality were included in the present meta-analysis.

Data extraction

After developing a data extraction checklist, two authors independently extracted data from the identified articles. The checklist contained the author's name, publication year of the study, average age, dose and duration of empagliflozin use, type of the study, and sample size, among others.

Data analysis

The relationship between empagliflozin use and the risk of cardiovascular outcomes in chronic renal failure patients was assessed using the OR index. Accordingly, the logarithmic OR was calculated in each study and employed to pool the results of the included trials. The heterogeneity within studies was measured using the I^2 index. Moreover, the fixed-effects model was utilized in case of low heterogeneity, and the random-effects model was chosen in case of high heterogeneity. Data were examined in STATA software version 14.0, and a $P < 0.05$ indicated the statistical significance of the tests.

Results

A total of 958 articles were retrieved from the database search. After eliminating 352 duplicates, 606 articles were screened by abstract, and 31 were discarded due to the unavailability of their full texts. Of the 575 remaining articles, 83 irrelevant studies were excluded. Additionally, 484 out of 494 remaining articles were omitted due to other exclusion criteria. Eventually, eight high-quality studies entered the meta-analysis process (Figure 1).

This systematic review and meta-analysis included eight clinical trial studies with a total sample of 39 620 participants. The publication years of the trials ranged from 2018 to 2023, although no time restriction was applied to the literature search (Table 1).

As shown in Figure 2, compared to placebo, empagliflozin use in CKD patients decreased the risk of cardiovascular death or first heart failure hospitalization by 28%, and this relationship was statistically significant (OR: 0.72; 95% CI: 0.66, 0.80).

Empagliflozin use resulted in a 25% lower risk of cardiovascular death in CKD patients compared to placebo, and the observed association was statistically significant (OR: 0.75; 95% CI: 0.63, 0.88) (Figure 3).

As shown in Figure 4, empagliflozin achieved a 30% reduction in risk of first heart failure hospitalization in CKD patients compared to placebo, and this finding was statistically significant (OR: 0.70; 95% CI: 0.63, 0.77).

Patients with CKD using empagliflozin experienced a 28% lower risk of total (first and recurrent) heart failure hospitalizations than the control group receiving placebo (OR: 0.72; 95% CI: 0.65, 0.81) (Figure 5).

Moreover, empagliflozin, compared to placebo, diminished all-cause mortality risk in CKD patients by 20% (OR: 0.80; 95% CI: 0.69, 0.93) (Figure 6).

When compared with placebo, empagliflozin revealed no significant effect on reducing composite kidney outcome risk in chronic renal failure patients (OR: 0.75; 95% CI: 0.55, 1.02) (Figure 7).

A sub-group analysis by the duration of empagliflozin use was conducted to evaluate the association between empagliflozin treatment and cardiovascular death risk in CKD patients. Cardiovascular death risk showed no reduction in patients receiving empagliflozin for less than or equal to 52 weeks (OR: 0.65; 95% CI: 0.34, 1.22). Similarly, 53 to 105 weeks of treatment with empagliflozin did not reduce the cardiovascular death risk in these patients (OR: 0.80; 95% CI: 0.59, 1.08). However, cardiovascular death risk significantly dropped in patients receiving empagliflozin for more than 105 weeks (OR: 0.75; 95% CI: 0.57, 0.98). These results suggest that long-

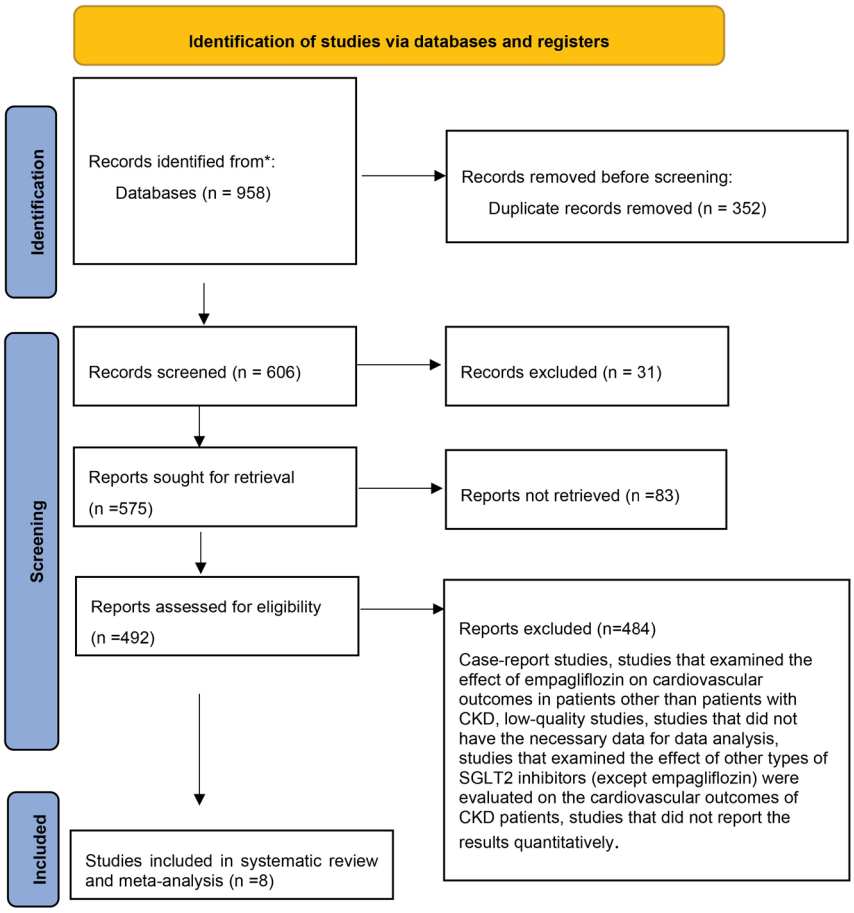

Figure 1. The process of entering the studies into the systematic review and meta-analysis.

Table 1. Studies included in the meta-analysis

Author, year of publication	Type of study	Source	Sample size in empagliflozin group	Mean age in empagliflozin group (y)	Sample size in placebo group	Mean age in placebo group (y)	Compared with	Dosage (mg)	Duration of use (wk)
Butler et al, 2023 (19)	Multicenter, double-blind, randomized, parallel-group, placebo-controlled trials	EMPEROR-Reduced and EMPEROR-Preserved	9718	>18	NR	NR	Placebo	NR	124 weeks
Zannad et al, 2021 (20)	Double-blind, placebo-controlled, parallel-group, event-driven randomized trial	EMPEROR-Reduced	981	70.4	997	70.1	Placebo	10	52 Weeks
Wanner et al, 2018 (21)	Randomized controlled trial	EMPA-REG	1498	66.2	752	66	Placebo	10 or 25	164 weeks
Herrington et al, 2023 (22)	Randomized controlled trial	EMPA-KIDNEY	3304	63.9	3305	63.8	Placebo	10	2 Year
Sharma et al, 2023 (23)	Double-blind, placebo-controlled trial	EMPEROR-Preserved	1615	74.2	1583	74.2	Placebo	10	26.2 months
Inzucchi et al, 2020(24)	Randomized Controlled Trial	EMPA-REG Outcome	1228	NR	599	NR	Placebo	10 or 25	12 weeks
Ruggenenti et al, 2022 (25)	Double-blind, placebo-controlled, multinational trial	EMPA-REG Outcome	4687	63.2	2333	63.2	Placebo	10 or 25	1.9 Year
Levin et al, 2020 (26)	Randomized, double-blind, placebo-controlled, multinational trial	EMPA-REG Outcome	4687	63.01	2333	63.5	Placebo	10 or 25	September 2010 to April 2013

NR: Not report; EMPEROR-Reduced: Empagliflozin Outcome Trial in Patients with Chronic Heart Failure with Reduced Ejection Fraction; EMPEROR-Preserved: Empagliflozin Outcome Trial in Patients with Chronic Heart Failure with Preserved Ejection Fraction; EMPA-REG OUTCOME: Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients; EMPA-KIDNEY: EMPAgliflozin once daily to assess cardio-renal outcomes in patients with chronic KIDNEY disease.

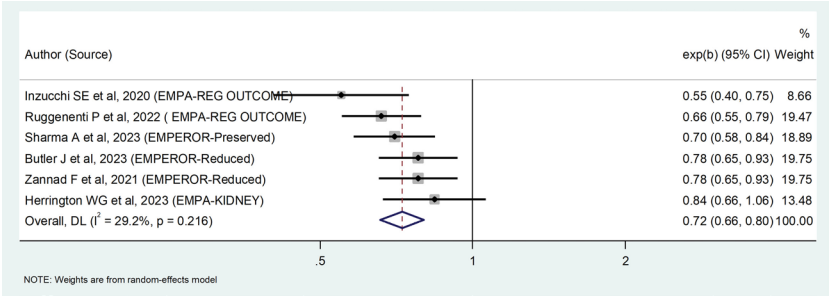

Figure 2. The relationship between empagliflozin and cardiovascular death or first heart failure hospitalization (with 95% confidence interval).

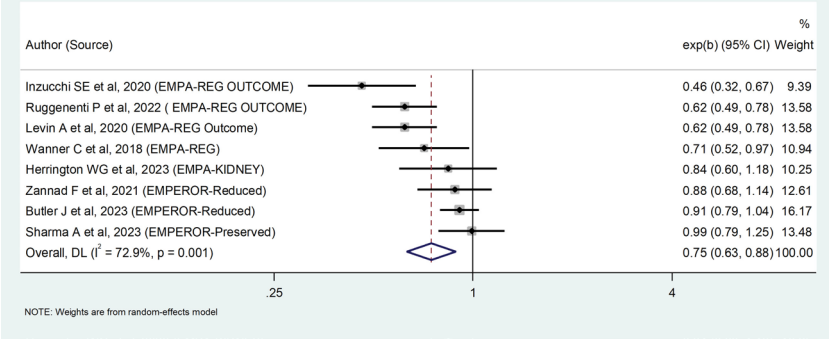

Figure 3. The relationship between empagliflozin and cardiovascular death (with 95% confidence interval).

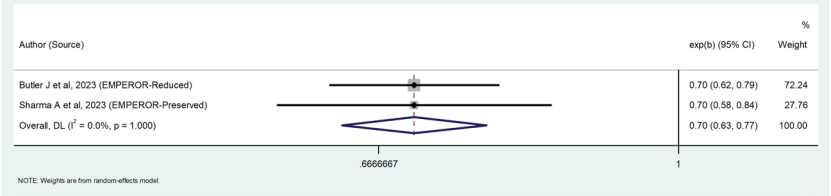

Figure 4. The relationship between empagliflozin and first heart failure hospitalization (with 95% confidence interval).

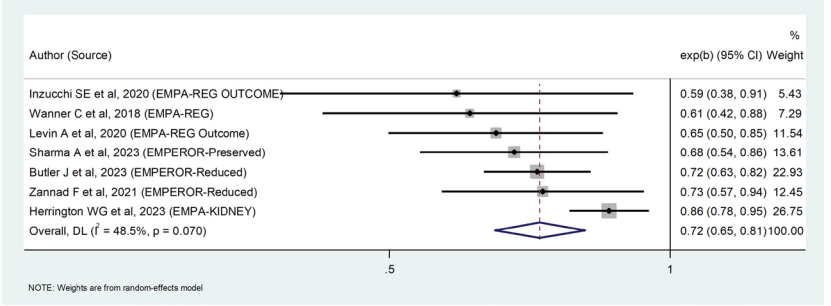

Figure 5. The relationship between empagliflozin and total (first and recurrent) heart failure hospitalizations (with 95% confidence interval).

term empagliflozin use can cause a significant reduction in the cardiovascular death rate of CKD patients (Figure 8).

In a sub-group analysis by age, empagliflozin use contributed to a 34% reduction in cardiovascular death risk in CKD patients aged from 60 to 69 years (OR: 0.66; 95% CI: 0.58, 0.76), while this relationship was statistically non-significant in the age group of 70-79 years (OR: 0.94; 95% CI: 0.79, 1.12). These findings indicated the decreased effectiveness of empagliflozin in mitigating the cardiovascular death risk as the patient's age increases (Figure 9).

The publication bias plot was not statistically significant ($P = 0.175$), suggesting that the literature search phase was fully completed and the published studies were reviewed regardless of their results being positively or negatively reported; therefore, no publication bias was present (Figure 10).

Discussion

The meta-analysis results demonstrated that empagliflozin lowered the risk of cardiac outcomes, hospitalization, and mortality compared to placebo. However, it did not affect kidney outcomes in diabetic patients with CKD. In a meta-analysis by Zelniker et al on three clinical trials, the

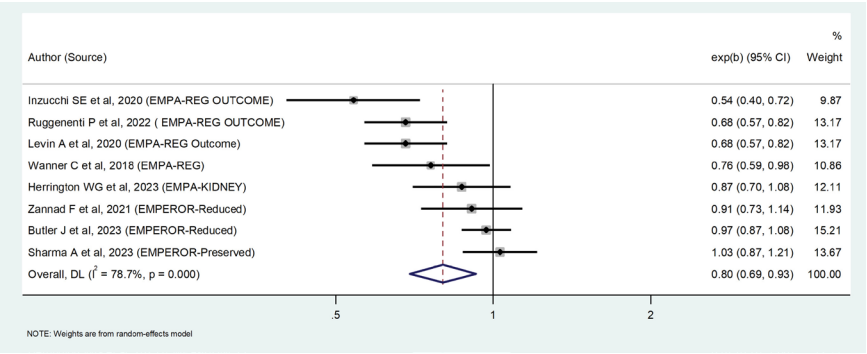

Figure 6. The relationship between empagliflozin and all-cause mortality (with 95% confidence interval).

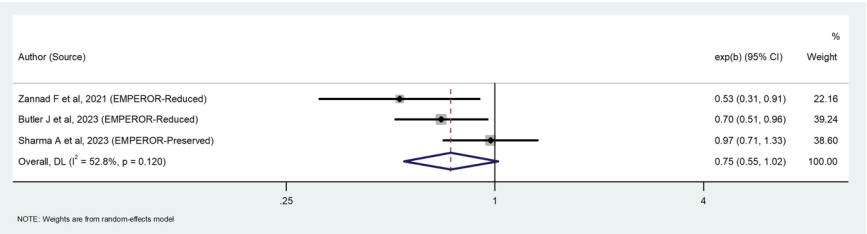

Figure 7. The relationship between empagliflozin and composite kidney outcome (with 95% confidence interval).

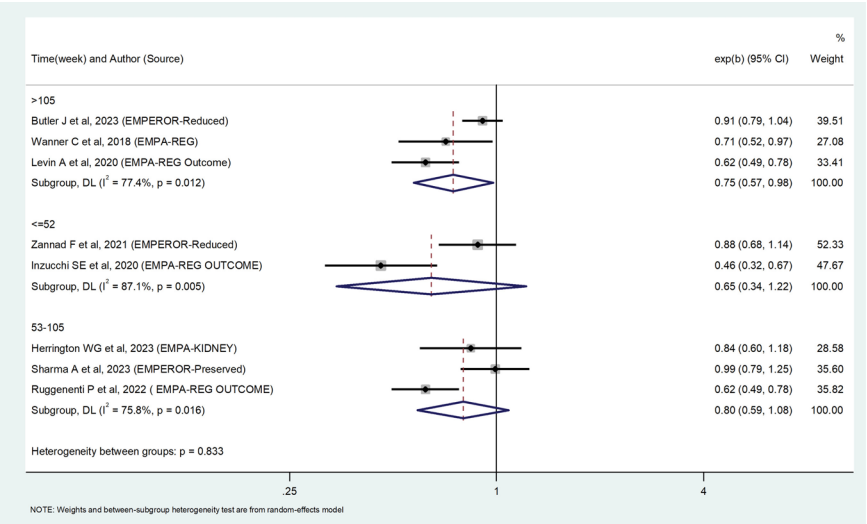

Figure 8. The relationship between empagliflozin and cardiovascular death by duration of use (with 95% confidence interval).

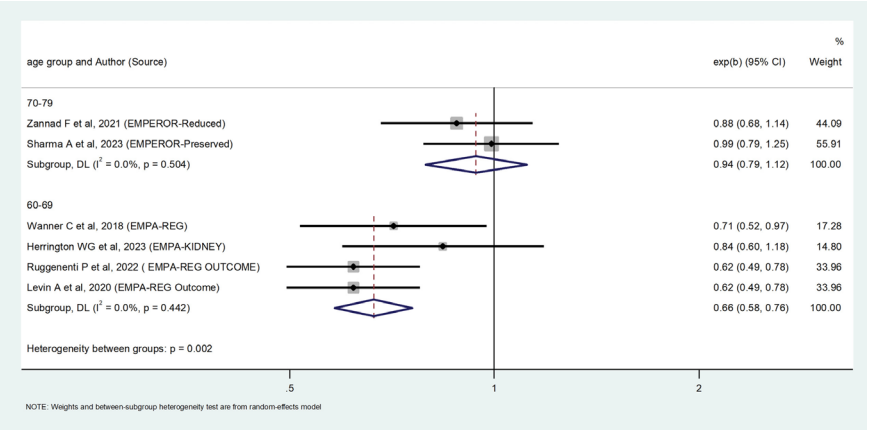

Figure 9. The relationship between empagliflozin and cardiovascular death by age groups (with 95% confidence interval).

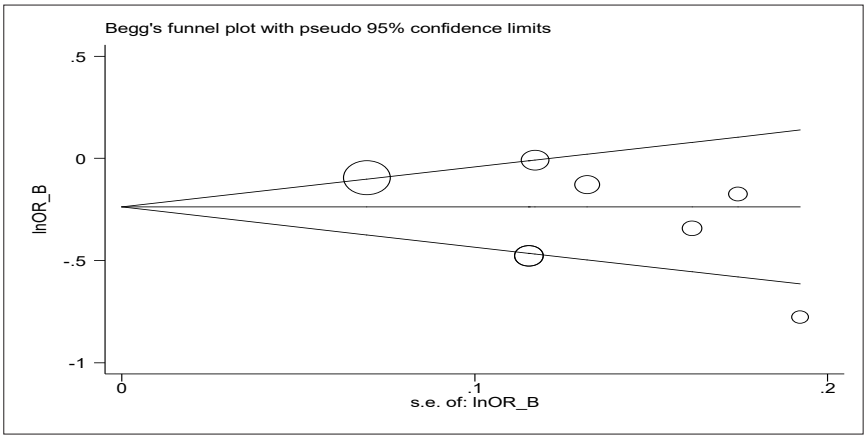

Figure 10. Publication bias.

use of SGLT2 inhibitors in type 2 diabetic patients reduced the major adverse cardiovascular events up to 11% (HR 0.89; 95%: CI 0.83–0.96), risk of cardiovascular death or hospitalization due to heart failure by 23% (0.77; 0.71–0.84), and the risk of renal disease progression by 45% (0.55; 0.48–0.64) (9). Another meta-analysis by Maddaloni et also revealed that SGLT2 is compared to placebo, was associated with a significant reduction in the risk of renal events, heart failure events, cardiovascular death (HR 0.82; 95% CI: 0.74-0.92), and all-cause mortality (HR 0.84; 95% CI: 0.75-0.93) (27). In contrast to meta-analyses conducted by Zelniker et al and Maddaloni et al, which demonstrated an improvement in both cardiac and renal outcomes of patients, we found an improvement only in cardiac outcomes and not in renal outcomes. However, it should be noted that the above two meta-analyses included diabetic patients, while ours targeted diabetic patients with CKD.

Malik et al conducted a meta-analysis in 2020 on 6527 patients with type 2 diabetes and CKD and concluded that SGLT-2 inhibitors led to a lower risk of myocardial infarction (22%) (HR 0.78; 95% CI: 0.62, 0.97), hospitalization due to heart failure (39%) (HR 0.61; 95% CI: 0.47, 0.77), and major adverse cardiac events (20%). However, they found no reduction in the risk of cardiovascular mortality (28). Our meta-analysis indicated that in addition to improving cardiac status and reducing hospitalization due to heart failure, empagliflozin also lessened cardiovascular deaths and all-cause death, which contradicts the results of Malik et al. The observed discrepancy in results may be due to the different designs of each study. For instance, Malik et al assessed the effect of SGLT-2 inhibitors on cardiovascular death in patients, whereas our study only examined the effect of empagliflozin on cardiovascular death in patients.

In a 2016 meta-analysis on type 2 diabetic patients, Salsali et al determined that empagliflozin, compared to placebo, mitigated the risk of cardiovascular death (HR: 0.61; 95% CI: 0.49, 0.76), all-cause mortality (HR: 0.68; 95% CI 0.57, 0.81), and hospitalization due to heart failure (HR: 0.63; 95% CI 0.48, 0.81) (29). According to a meta-analysis by Pan et al on seven studies involving 5150 patients with heart failure, empagliflozin use resulted in a significant risk reduction in cardiovascular death or hospitalization due to heart failure (RR: 0.77; 95% CI: 0.68–0.87) and hospitalization due to heart failure (RR: 0.71; 95% CI: 0.61–0.82) (30). Another meta-analysis

by Arnott et al aiming to evaluate the efficacy of SGLT2 in preventing cardiovascular events in type 2 diabetic patients indicated a reduction in cardiovascular death risk by 17% (HR: 0.83; 95% CI: 0.75–0.92), hospitalization for cardiac failure by 32% (HR: 0.68; 95% CI: 0.60–0.76), and all-cause mortality by 15% (HR: 0.85; 95% CI: 0.79–0.92) (31). Toyama et al carried out a meta-analysis in 2019, including 7363 patients with type 2 diabetes and CKD, and reported the effectiveness of SGLT2 inhibitors in lowering the risk of cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke (RR: 0.81, 95% CI: 0.70-0.94), and heart failure (RR: 0.61: 95% CI: 0.48-0.78) (32). The results of these meta-analyses were in line with and corroborated those of our study.

Limitations of the study

The present study faced some limitations: 1) Given that the comparison and placebo groups were the same in all reviewed articles, we could not compare empagliflozin with other types of SGLT2 inhibitors regarding its effect on cardiovascular outcomes of CKD patients. 2) Empagliflozin dose for CKD patients ranged from 10 to 25 mg across included studies, which did not allow us to perform sub-group analysis by dose of empagliflozin. Therefore, we could not determine whether higher doses of empagliflozin were more effective than lower doses in reducing the risk of cardiovascular death and hospitalization due to heart failure. 3) In included studies, data for clinical trials were not from a specific country. Thus, we were unable to conduct a sub-group analysis by country. 4) Most reviewed trials failed to provide gender-stratified results, which precluded us from comparing the effect of empagliflozin on cardiovascular outcomes between male and female CKD patients. Hopefully, future studies can address these limitations.

Conclusion

Compared with the placebo, empagliflozin mitigated the risk of cardiovascular death or first heart failure hospitalization, cardiovascular death, first heart failure hospitalization, total (first and recurrent) heart failure hospitalizations, and all-cause mortality in CKD patients. However, empagliflozin treatment did not affect composite kidney outcome risk. Moreover, this meta-analysis demonstrated that the lowering effect of empagliflozin on cardiovascular death reduced with an increase in patients' age. Thus, empagliflozin is recommended for inclusion in the list of prescribed medications for CKD patients suffering from cardiovascular diseases. A decrease in cardiac mortality and length of heart failure hospitalization contributes to reduced hospital costs and enhanced life expectancy of patients.

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Authors' Contribution

Conceptualization: Majid Foroutan, Maliheh Yarmohammadi.
Data curation: Majid Foroutan, Maliheh Yarmohammadi.
Formal analysis: Majid Foroutan, Maliheh Yarmohammadi.
Investigation: Maliheh Yarmohammadi.
Methodology: Majid Foroutan, Maliheh Yarmohammadi.
Project administration: Maliheh Yarmohammadi.
Resources: Majid Foroutan, Maliheh Yarmohammadi.
Software: Majid Foroutan.
Supervision: Maliheh Yarmohammadi.
Validation: Majid Foroutan.
Visualization: Majid Foroutan, Maliheh Yarmohammadi.
Writing–original draft: Majid Foroutan, Maliheh Yarmohammadi.
Writing–review & editing: Majid Foroutan, Maliheh Yarmohammadi.

Conflicts of interest

The authors declare that they have no competing interests.

Ethical issues

This study has been compiled based on the PRISMA checklist, and its protocol was registered on the PROSPERO (International Prospective Register of Systematic Reviews) website with (ID: CRD42023438798). Besides, ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by the author.

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Nil.

Supplementary files

Supplementary file 1 contains the search strategies conducted in databases.

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