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Long-term surrogate cardiovascular outcomes of SGLT2 inhibitor empagliflozin in chronic heart failure: a systematic review and meta-analysis

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Abstract

The sodium–glucose cotransporter-2 (SGLT2) inhibitor empagliflozin (EMPA) has been demonstrated to reduce the risk of cardiovascular mortality or hospitalization for heart failure (HF) in patients. Nevertheless, data concerning the long-term cardiovascular effects in clinically important subgroups are scarce. A prespecified meta-analysis of randomized controlled trials (RCTs) was conducted to assess the long-term effects of EMPA on cardiovascular outcomes in HF patients, regardless of HF type and glycemic status. The assessment included parameters related to left ventricular (LV) remodeling, including the LV volume, the LV mass index (LVMI), the ejection fraction, the systolic blood pressure, and biomarkers. Moreover, the effects of the treatment on exercise capacity and quality of life (QoL) were analyzed. Furthermore, these cardiovascular parameters were evaluated in prespecified subgroups of HF patients, including type of HF, type 2 diabetes status, and duration of therapy. The quantitative meta-analysis was synthesized and analyzed via the statistical software Stata 17.0. The meta-analysis revealed that EMPA administration significantly contributed to a reduction in systolic blood pressure (SBP) (MD = 4.93 mmHg, 95% CI=[-9.67, -0.19]; $P < 0.0001$) and left ventricular end-diastolic volume (LVEDV) (MD=-18.03 mL, 95% CI=[-25.4, -10.67], $P < 0.0001$). Furthermore, left ventricular end-systolic volume (LVESV) (MD=-16.09 mL, 95% CI=[-26.94, -5.25]; $P < 0.0001$) and N-terminal pro-B-type NP (NT-proBNP) (SMD=-0.54, 95% CI=[-0.94, -0.13]; $P = 0.01$) significantly decreased. These decreases were accompanied by improvements in the 6-minute walk distance (6MWD, SMD = 0.78, 95% CI=[-0.22, -1.79], $P = 0.13$) and KCCQ score (MD = 1.98, 0.97–2.99; $P < 0.0001$). The results of the subgroup analysis indicated that EMPA administration was associated with more pronounced benefits in terms of cardiac remodeling, function and exercise capacity for specific populations, including (1) HF with a reduced ejection fraction (HFrEF); (2) the absence of diabetes; and (3) treatment for no less than 6 months. Additionally, EMPA may lead to an increased risk of cardiovascular adverse events (AEs) but is less effective for improving the QoL in HF patients with preserved EF (HFpEF) populations.

Keywords Empagliflozin, Heart failure, Meta-analysis, Subgroup analysis

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Introduction

Despite advances in pharmacological treatment, heart failure (HF) remains a significant cause of mortality and hospitalization worldwide [1]. Patients with HF present with either a reduced ejection fraction (HFrEF, patients with an ejection fraction of no more than 40%) or a preserved ejection fraction and suffer from overactivation of the endogenous neurohormonal system [2, 3]. However, therapeutic options for HF patients, particularly those with a preserved ejection fraction (HFpEF), are currently limited [4, 5].

Since the beginning of the 21st century, sodium–glucose cotransporter 2 (SGLT2) inhibitors are a novel class of oral antihyperglycemic agents. And the mechanism of redution of HF includes more importantly other mechanisms reducing the development and progression of HF in patients wiht type 2 diabetes (T2DM) by inhibiting renal reabsorption of glucose and increasing urinary glucose excretion [6, 7]. These findings prompted a series of clinical trials on cardiovascular safety and efficacy, which verified that SGLT2 inhibitors benefit cardiovascular outcomes in patients with or without T2DM [8]. However, the effects of these inhibitors vary among individual drugs.

The European Union and the United States of America have recently approved empagliflozin (EMPA) for the treatment of all adults with symptomatic chronic heart failure (CHF). This approval is based on the drug's ability to reduce the risk of cardiovascular events, including hospitalizations for HF and cardiovascular death, regardless of the left ventricular ejection fraction (LVEF) [9, 10]. Furthermore, clinical trials and recent meta-analyses have corroborated the cardiovascular efficacy of EMPA in patients with HF, irrespective of whether they have a reported history of T2DM. The SUGAR-DM-HF trial revealed that EMPA administration contributed to reduced left ventricular volumes in HF patients with T2DM [11]. In addition, Santos-Gallego CG et al. [12] reported that in nondiabetic patients with HF, EMPA significantly improved cardiac structure, functional capacity, and quality of life (QoL), irrespective of glycemic status. Therefore, these findings indicate that EMPA may reduce the incidence of hospitalization and mortality due to HF via a favorable reverse cardiac remodeling process. However, quantitative analysis of the parameters of cardiac remodeling, including cardiac structure and function, is lacking. Hence, to investigate the effects on cardiovascular outcomes and safety in HF populations, a systematic review of the literature and a meta-analysis of cardiac parameters in randomized controlled trials of EMPA administration for HF with subgroup analysis were conducted, thereby providing evidence-based outcomes.

Methods

This meta-analysis was conducted in accordance with the standard guidelines and in alignment with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [13, 14]. Two reviewers independently carried out the literature searches, eligibility assessment, data extraction, and meta-analyses (including subgroup analyses). No restriction of language was imposed, and the ethics approval declaration was waved for the meta-analysis, which was based on previously published studies. The study protocol was registered in PROSPERO (www.crd.york.ac.uk/PROSPERO, CRD42024570205).

Data sources and searches

The PubMed, Medline, Cochrane Library and EMBASE databases were searched from inception to 30 April, 2024, using the terminology "sodium–glucose cotransporter-2 inhibitors" OR "SGLT2 inhibitors" OR "SGLT2i" OR "empagliflozin" OR "EMPA"; a second search was based on the term "heart failure"; and the third search included "randomized controlled trial". Meanwhile, the reference lists of the systematic reviews were screened to identify additional eligible citations.

Eligibility criteria

The following inclusion criteria were applied in this systematic review and meta-analysis: (1) a RCT in humans; (2) HF patients with or without diabetes who were treated with EMPA and compared with either a placebo or a control group; and (3) patients with at least one report of cardiovascular outcomes. This study focused on the long-term efficacy and safety of EMPA. Consequently, RCTs were included those pooled HF populations treated with EMPA for a long-term period of at least 3 months, regardless of LVEF. Trials that enrolled patients with acute HF were excluded. The assessment of all the articles was independently conducted by two reviewers, and any disagreements were resolved by discussion.

Outcomes

The cardiovascular outcomes were described, including parameters of cardiac structure (LV volume and left ventricular mass index) and function, blood pressure, and biomarkers of HF, in addition to the 6MWD, which presents the exercise capacity of these patients, and health status (evaluated by the Kansas City Cardiomyopathy Questionnaire (KCCQ) score). The pooled studies revealed the occurrence of serious adverse events (AEs), which were classified as either cardiovascular or noncardiovascular.

Data extraction

The data relating to demographic characteristics (first author, publication year), number of populations, duration of follow-up, LVEF levels, CV outcomes, non-CV outcomes, and serious adverse events were extracted by two authors working independently via a predefined, standardized protocol and data extraction instrument. Any discrepancies were resolved by consensus following discussion among the authors.

Risk of bias and recommendation

The risk of bias was evaluated in accordance with the revised Cochrane risk of bias tool [15]. The evaluation tool consists of five domains: (1) the randomization process; (2) deviations from intended interventions; (3) missing outcome data; (4) measurement of the outcome; and (5) selection of the reported results. Each domain may be judged as exhibiting either a low risk (of bias), a moderate risk (with some concerns), or a high risk. Furthermore, quality of evidence for the pooled studies was evaluated. The domains of evaluation included statistical inconsistency, publication bias, risk of bias, indirectness, and statistical imprecision. The quality of the citations is rated as high, moderate, low or very low [16].

Statistical analysis

All meta-analyses and subgroup analyses were conducted via Stata 17.0 software, and a P value of less than 0.05 was considered statistically significant. Pooled hazard ratios (HRs) with 95% confidence intervals (CIs) for dichotomous variables were calculated, and mean differences (MDs) or standardized mean differences (SMDs) with 95% CIs were calculated for continuous variables. The presence of statistical heterogeneity was identified via the I^2 statistic. A sensitivity analysis was conducted to decrease the degree of heterogeneity. When the I^2 statistic exceeded 50%, a random-effect model was employed for subsequent analyses. Conversely, a fixed-effect model was used when the I^2 value was less than 50%. To identify publication bias, we examined asymmetry via Begg's and Egger's tests. To test the therapeutic differences of EMPA in different HF populations, we conducted subgroup analyses based on type of HF (HFpEF or HFrEF), glycemic status, and therapeutic duration. The data presented in the figures (without detailed data) were extracted via Engauge Digitizer software (See Table 1).

Variables in the subgroup analysis

Additionally, we investigated EMPA treatment for HF populations with different characteristics. The characteristics we focused on included the following:

1) EMPA helps to improve the cardiovascular outcomes regardless of LVEF, while there lacks a comparable meta-analysis for HF populations of different types treated with EMPA. The pooled patietns were then stratified into 2 groups: (1) HFrEF; (2) HFpEF.
2) EMPA improve cardiovascular outcomes in HF patients with or without diabetes, while there lacks a comparable meta-analysis for HF with or without diabetes populations treated with EMPA. The pooled patietns were then stratified into 2 groups as: (1) with diabetes; (2) without diabetes.
3) Though EMPA treatment helps to improve cardiovascular outcomes, there lacks a synthesized analysis for the therapeutic duration of EMPA for cardiovascular improvements. The pooled patietns were then stratified into 2 groups as: 1) 3–6 months; 2) ≥ 6 months (a longer-term evaluation).

Results

Study selection and basic characteristics

The process of literature screening is shown in Fig. 1. The initial electronic searches yielded 5284 potentially relevant references. Following the removal of duplicates and screening of titles, 29 articles were selected for full-text screening. Of these, 17 articles described rare cardiovascular parameters, whereas one study [17] was excluded because of short-term administration. Voors AA et al. [18] conducted a multinational randomized trial to explore the effect of EMPA on cardiovascular outcomes in patients with acute heart failure. Eventually, nine trials [11, 12, 19–25] were included in this meta-analysis. One of these studies was a crossover RCT with a follow-up period of six weeks, and one study [19] included five treatment arms, which included EMPA, licogliflozin (2.5 mg, 10 mg, and 50 mg), and a placebo. To ensure homogeneity in the intervention, the EMPA and placebo arms of this RCT were used. The number of patients in the intervention group ranged from 30 to 2997, with a minimum duration of 12 weeks and a maximum duration of 26.2 months (see Table S1 for details).

Change in SBP

A meta-analysis of SBP changes indicated that EMPA administration was associated with a statistically significant reduction in SBP from baseline by 1.19 mmHg (MD=-1.19 mmHg, 95% CI=[-8.56, -0.66], $P=0.001$).

Evaluation of left ventricular remodeling

Compared with placebo, EMPA significantly reduced the changes in left ventricular end-diastolic volume (LVEDV) and left ventricular end-systolic volume (LVESV) from baseline by 18.05 mL (MD=-18.05 mL, 95% CI=[-25.3, -10.80]; $P<0.0001$) (Figs. 2) and 16.05 mL (95% CI=[-27.59, -5.50]; $P=0.006$) (Fig. 3).

Table 1 Included studies

Study	Year	Diabetes	EMPA	Age Mean (SD)	Female sex (%)	Placebo	Age Mean (SD)	Female sex (%)	Duration	LVEF	Cardivascular outcomes	AEs or SAEs
de Boer RA, et al. RCT [19]	2019	100.0%	*N* = 30 10-25 mg once daily	68.5(3.0)	33.3%	*N* = 33	71.0 (3.75)	42.4%	12 weeks	NA	1) Blood pressure (BP), including SBP and DBP; 2) NT-proBNP; 3) Cardiac parameters; 4) NYHA class.	Yes
Packer M, et al.(EMPEROR-Reduced), RCT [20]	2020	NA	*N* = 1863 10 mg once daily	67.2 (10.8)	23.5%	*N* = 1867	66.5 (11.2)	24.4%	16 months	≤ 40%	1) Cardiovascular worsening (including CV death and hospitalization for HF); 2) NT-proBNP; 3) Systolic BP; 4) Change in quality-of-life score on KCCQ.	Yes
Nassif ME, et al. (EMBRACE-HF), RCT [21]	2020	52.0%	*N* = 33 10 mg once daily	69.5(12.0)	36.4%	*N* = 32	62.9 (13.3)	37.5%	12 weeks	>40% (mean 44%)	1) Change in PA diastolic pressure from baseline to end of treatment; 2) KCCQ; 3) NT-proBNP; 4) 6-min walking distance (6MWD); 5) Systolic BP.	NR
Anker SD, et al. (EMPEROR-Preserved), RCT [22]	2021	NA	*N* = 2997 10 mg once daily	71.8 (9.3)	44.6%	*N* = 2991	71.9 (9.6)	44.7%	26.2 months	> 40%	1) Cardiovascular worsening (including CV death and hospitalization for HF); 2) NT-proBNP; 3) Change in quality-of-life score on KCCQ.	Yes
Omar M, et al. (Empire HF), RCT [23]	2021	12.6%	*N* = 95 10 mg once daily	65.0 (10.0)	17.0%	*N* = 95	63.0 (12.0)	13.0%	12 weeks	≤ 40%	Cardiac parameters: 1) Left ventricular end-systolic and end-diastolic volume indexes (LVESV and LVEDV); 2) Left atrial volume index (LAVi); 3) LVEF (adjusted for age, sex, type 2 diabetes, and atrial fibrillation); 4) Changes in LVMI; 5) Global longitudinal strain; 6) Relative wall thickness; 7) PCWP; 8) Cardiac index.	NR
Lee MMY, et al. (SUGAR-DM-HF), RCT [11]	2021	100.0%	*N* = 52 10 mg once daily	68.2 (11.7)	34.6%	*N* = 53	69.2(10.6)	18.9%	36 weeks	≤ 40%	Cardiac parameters : 1) Change in LV end-systolic volume index (LVESVi); 2) LV end-diastolic volume index (LVEDVi); 3) LV global longitudinal strain; 4) LVEF; 5) KCCQ-TSS 6) 6MWD 7) NT-proBNP	NA

Table 1 (continued)

Study	Year	Diabetes	EMPA	Age Mean (SD)	Female sex (%)	Placebo	Age Mean (SD)	Female sex (%)	Duration	LVEF	Cardivascular outcomes	AEs or SAEs
Abraham WT, et al. (EMPERIAL-Reduced), RCT [24]	2021	59.9%	*N* = 156 10 mg once daily	69.0 (3.63)	22.4%	*N* = 156	70.0 (3.63)	28.8%	12 weeks	≤ 40%	1) 6MWD; 2) KCCQ-TSS; 3) CHQ-SAS dyspnea score; 4) NT-proBNP.	Yes
Abraham WT, et al. (EMPERIAL-Preserved). RCT [24]	2021	40.6%	*N* = 157 10 mg once daily	74.0 (2.75)	44.6%	*N* = 158	75.0 (6.5)	41.8%	12 weeks	> 40%	1) 6MWD; 2) KCCQ-TSS; 3) CHQ-SAS dyspnea score; 4) NT-proBNP.	Yes
Santos-Gallego CG, et al. RCT [12]	2021	0.0%	*N* = 84 10 mg once daily	64.2(10.9)	36.0%	*N* = 84	59.9(13.1)	35.7%	6 months	≤ 40%	Cardiac parameters: 1) LV end-systolic and -diastolic volume (LVESV and LVEDV); 2) LV mass; 3) LVEF; 4) 6MWD; 5) KCCQ.	Yes
Pietschner R, et al. RCT [25]	2021	24.5%	*N* = 36	69.0 (8.1)	19.4%	*N* = 17	67.4(8.7)	5.9%	12 weeks	38.8% (8.6%)	1) BP 2) 24-hour ambulatory BP	NA
Filippatos G, et al. RCT* [27]	2022	100.0%	*N* = 1466	NR	NR	*N* = 1472	NA	NA	52 weeks	NA	1) KCCQ-TSS; 2) CHQ-SAS dyspnea score; 3) NT-proBNP. 4) BP	Yes
Filippatos G, et al. RCT* [27]	2022	0.0%	*N* = 1531	NR	NR	*N* = 1472	NA	NA	52 weeks	NA	1) KCCQ-TSS; 2) CHQ-SAS dyspnea score; 3) NT-proBNP. 4) BP	Yes

* A study mentioned the populations with or without diabetes based on the trial conducted by Anker SD

EMPA = empagliflozin; SD = standard deviation; LVEF = left ventricular ejection fraction; LVEDV = left ventricular end-diastolic volume; LVESV = left ventricular end-systolic volume; SBP = systolic blood pressure; NT-proBNP = N-terminal pro brain natriuretic peptide; 6MWD = 6 min walking distance; KCCQ = Kansas City Cardiomyopathy Questionnaire; HFrEF = heart failure with reduced EF; HFpEF = heart failure with preserved EF; AE = adverse events; NA = not available

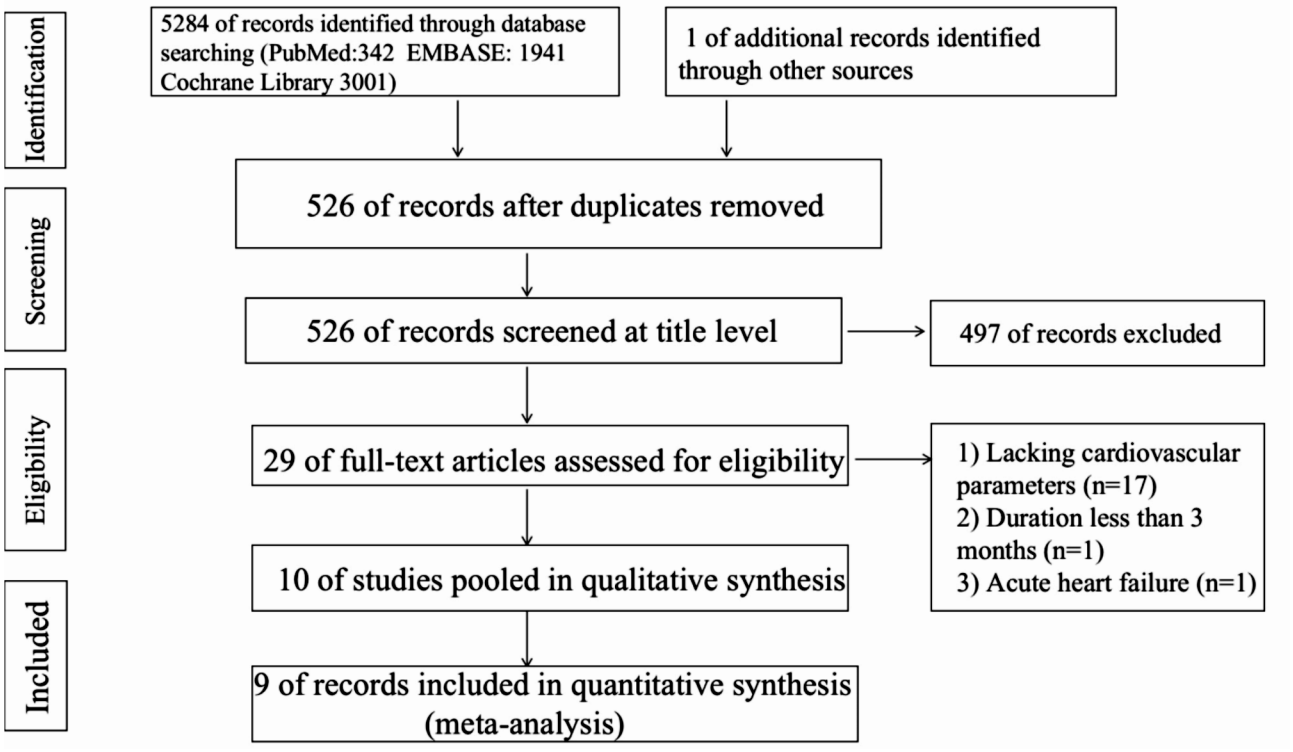

Fig. 1 Flowchart of meta-analysis

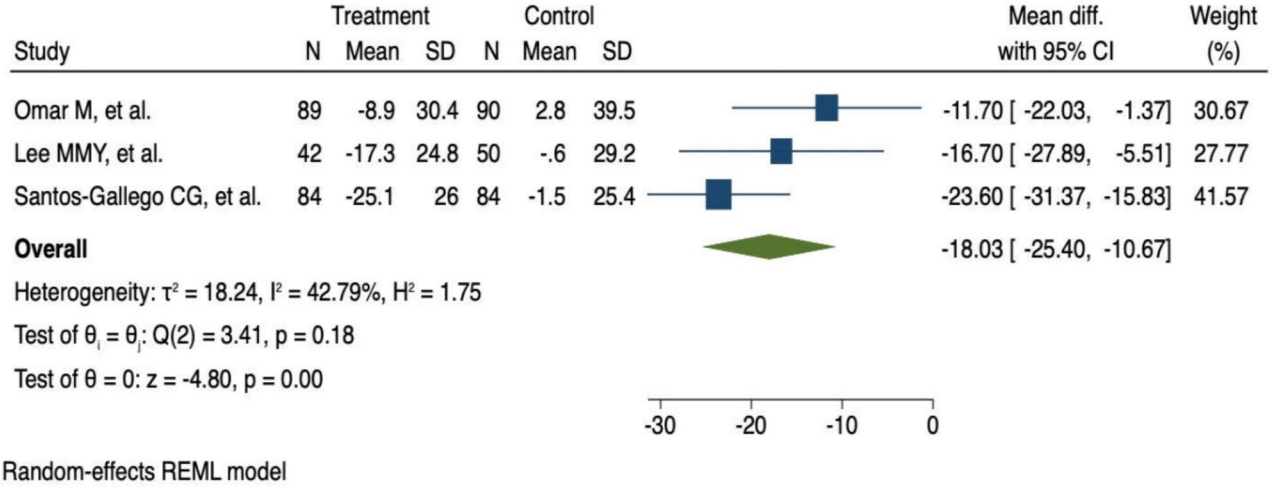

Fig. 2 The forest map of LVEDV

No notable differences were observed in the changes in the LVMI (MD= -1.30, 95% CI=[-3.85, 1.25]; $P=0.32$) or LVEF (MD=2.52%, 95% CI=[-0.86, 5.89]; $P=0.14$). Conversely, we observed that EMPA reduced N-terminal pro-B-type NP (NT-proBNP) levels more effectively than placebo (SMD=-0.50, 95% CI=[-0.74, -0.26]; $P<0.0001$), thereby reversing left ventricular remodeling following EMPA treatment.

6MWD

Four studies [11, 12, 21, 24] reported changes in the 6MWD after treatment with EMPA or placebo. Meta-analysis revealed that EMPA administration significantly improved the 6MWD in HF patients (MD=27.50 m, 95% CI=[9.02, 45.97], $P=0.004$).

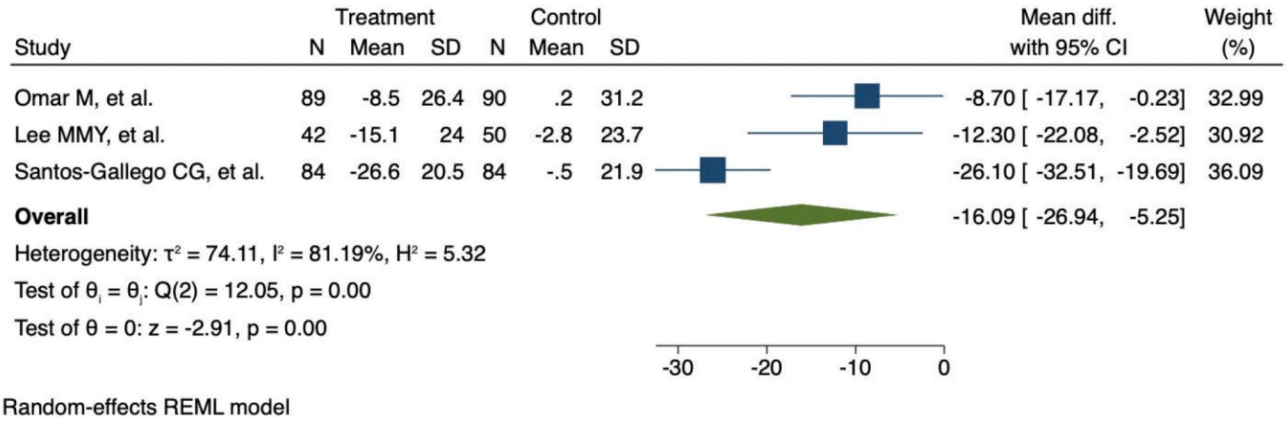

Fig. 3 The forest map of LVESV

Changes in quality-of-life (QoL) scores on the KCCQ

Accordingly, the KCCQ has been approved by the FDA as a clinical outcome assessment tool and is recommended as a performance measure for quantifying QoL [26]. The KCCQ is an effective tool for measuring the impact of HF patients' lives, with scores ranging from 0 to 100. A higher score indicates a better quality of life. Therefore, a meta-analysis was conducted to evaluate the impact of EMPA on QoL in HF patients, with the objective of observing changes in the QoL score on the KCCQ from baseline. In total, 6 RCTs [11, 12, 20–22, 24] reported a change in QoL in terms of KCCQ score, and the meta-analysis revealed marked heterogeneity among the studies (I^2=91.2%). The random effects model revealed that EMPA significantly improved the QoL score on the KCCQ by 2.72 (MD=2.72, 95% CI=[1.27, 4.12]; P<0.0001).

Subgroup analysis

1) **Type of HF (HFrEF or HFpEF)**

A total of five RCTs [11, 12, 20, 23, 24] included populations with HFrEF, whereas three studies [21, 22, 24] included HFpEF patients. Two studies [19, 25] demonstrated the efficacy of EMPA in participants with any type of HF, irrespective of LVEF. In order to investigate a comparable meta-analysis for HF populations of different types treated with EMPA, subgroup analysis of cardiovascular parameters in HFrEF and HFpEF were conducted. When grouped according to LVEF (40%), the results demonstrated that EMPA administration to HFrEF patients increased the 6MWD (MD=34.33 m, P< 0.0001) and QoL (KCCQ scores: MD=5.00, 95% CI=[0.92, 9.07]; P=0.016) scores. Moreover, in the LV volume notably decreased (LVEDV: MD=-18.05 mL, 95% CI=[-25.3, -10.80]; P<0.0001; LVESV: MD=-16.05 mL, 95% CI=[-27.59, -4.50]; P = 0.006). The NT-proBNP levels (SMD=-0.31, 95% CI=[-0.37, -0.25]; P<0.0001) and SBP (MD=-2.35 mmHg, 95% CI=[-6.12, 1.43]; P=0.22) were significantly reduced. In patients with HFpEF, EMPA was associated with less pronounced improvements in the 6MWD (MD=20.83 m, 95% CI=[-10.62, 52.29]; P = 0.194) and KCCQ score (MD=1.33, 95% CI=[1.31, 1.35]; P<0.0001). A subgroup analysis of the 6MWD is shown in Figure S1, whereas the KCCQ scores are shown in Figure S2. NT-proBNP levels were found to decrease (SMD=-0.85, 95% CI=[-1.73, 0.03]; P = 0.058), but data concerning left ventricular remodeling in EMPA-treated HFpEF patients are lacking.

2) **Patients with or without diabetes**

Subsequently, we conducted a subgroup analysis for a comparable meta-analysis for HF with (the study enrolled only HF patients with diabetes) or without T2DM (the study enrolled only HF patients without diabetes) populations treated with EMPA. Filippatos G et al. [27] investigated the efficacy of EMPA in diabetic and nondiabetic HF patients in the EMPEROR trial. And Lee MMY and collegues conducted a RCT demonstrating EMPA treatment for HF populations with T2DM. These results demonstrated that EMPA treatment significantly contributed to greater improvements in the LV volume, LV function, SBP control, 6MWD, and QoL in HF patients without diabetes.

3) **Therapeutic duration**

As there still lacks a synthesized analysis for the therapeutic duration of EMPA improveing cardiovascular outcomes, the cardiovascular parameters of the meta-analysis and subgroup analysis were conducted based on the duration of EMPA therapy, and defined as: 1) 3–6 months and 2)≥6 months (a longer-term evaluation). Furthermore, in patients with HF, a significant reduction in the LV volume was observed when EMPA was administered for ≥6 months (LVEDV: MD=-21.31

mL, 95% CI=[-27.67, -14.96]; $P<0.0001$; LVESV: MD=-21.95 mL, 95% CI=[-27.32, -16.59]; $P<0.0001$). LVMI was notably ameliorated (MD=-0.11, 95% CI=[-0.13, -0.09]; $P<0.0001$), in addition to a large reduction in NT-proBNP levels (SMD=-0.23, 95% CI=[-0.39, -0.08]; $P<0.0001$). Additionally, long-term EMPA treatment contributed to a significant improvement in the KCCQ score, suggesting a better QoL (KCCQ score: MD=1.33, 95% CI=[1.31, 1.35]; $P<0.0001$).

Quality assessment and publication bias

The assessment of the risk of bias in the included studies is shown in Table S1, indicating that the pooled studies were of high quality. Begg's and Egger's tests revealed no significant publication bias across pooled studies ($P=0.227$ for Begg's test and $P=0.548$ for Egger's test).

Safety

Overall, the incidences of cardiovascular and noncardiovascular AEs were compared between the two groups. Additionally, the results of the analysis of serious AEs are presented (log odds ratio=-0.06, 95% CI=-0.41, 0.29; $P=0.75$) (see Table S2 for details).

Discussion

This study involved a total of nine RCTs, with a total of 5503 patients in the EMPA group and 5486 patients in the control group. The evidence presented is of high quality and provides support for the cardiovascular benefits of EMPA in populations with varying clinical characteristics, including types of HF, duration of treatment, and the presence of combined diabetes.

The meta-analysis demonstrated that EMPA administration resulted in a statistically significant reduction in SBP from baseline ($P=0.02$). The LV volume (end-diastolic or end-systolic) was previously identified as a surrogate marker for adverse ventricular remodeling in HF patients and is strongly correlated with the impact of a particular drug therapy on patient survival [28, 29]. The role of NT-proBNP in the diagnosis and risk stratification of HF has been extensively demonstrated, and this biomarker is a critical tool to screen populations for HF [30]. The results of our meta-analysis indicated that EMPA treatment had a favorable impact on decreasing NT-proBNP levels in both the HFrEF and HFpEF populations, and it significantly changed the LVEDV ($P<0.0001$) and LVESV ($P<0.0001$). These findings suggest that EMPA administration represents a promising approach for improving LV remodeling in HF patients.

In light of the provided data, we evaluated the benefits of EMPA by assessing the changes in the 6MWD and KCCQ scores (the 6MWD represents exercise capacity, and the KCCQ score commonly represents QoL) across different HF groups. The results of the meta-analysis and subgroup analysis indicated that EMPA administration was more beneficial for patients with HFrEF than for those with HFpEF. This difference was evidenced by greater improvements in the 6MWD (HFrEF: MD=34.33 m vs. HFpEF: MD=20.83 m) and KCCQ scores (HFrEF: MD=5.21 vs. HFpEF: MD=1.43). These findings demonstrated that EMPA therapy may be more effective in enhancing exercise capacity and QoL in patients with HFrEF than in those with HFpEF. Notably, EMPA has been shown to significantly decrease the levels of both BP and NT-proBNP in HFpEF patients, a degree of reduction that has been found to be even more pronounced than that in patients with HFrEF. This phenomenon is likely attributable to the distinctive characteristics of cardiac remodeling. Therefore, EMPA administration may improve cardiac remodeling in HF patients, irrespective of the specific type.

Glycemic status has been demonstrated to influence cardiometabolic remodeling. Notably, disorders of glycemic control are observed with considerable frequency in patients with chronic HF [31, 32], a phenomenon that is, to some extent, attributable to the severity of hemodynamic abnormalities. In a clinical trial conducted by Lee MMY et al. [11], EMPA was administered to patients with HF and diabetes. The results revealed an improvement in LV remodeling (LVEDV, LVESV, LVMI, LVEF, and NT-proBNP). Notably, the 6MWD and KCCQ scores were reduced, indicating an unanticipated outcome of EMPA monotherapy for patients with HF and T2DM. A double-blind, placebo-controlled trial [12] was conducted to assess the effect of EMPA in nondiabetic HF patients. The results demonstrated that EMPA administration to nondiabetic HF patients significantly improved the LV volume, LVMI, LV systolic function, functional capacity, and QoL. These observations provide robust evidence that EMPA plays a role in HF patients, irrespective of glycemic status. These findings also suggest that additional or replacement therapy may be needed to improve exercise capacity and QoL in diabetic HF patients.

Based on the therapeutic duration of EMPA administration, we categorized the pooled trials into two groups: 1) 3 ~ 6 months and 2) ≥6 months (a longer-term trial level). The results of this analysis showed that EMPA administered over a period of 3 months contributed to a significant reduction in both SBP and the NT-proBNP levels. Furthermore, a longer-term trial of EMPA resulted in a more pronounced reversal of the LVEDV, LVESV and LVMI, with statistically significant differences ($P<0.0001$), in addition to a greater improvement in LVEF (MD=3.40%). Notably, longer-term EMPA treatment greatly improved QoL, as evaluated by KCCQ scores ($P<0.0001$).

Furthermore, safety profiles of EMPA-related AEs were evaluated in this study, which revealed that EMPA

is relatively safe for HF patients compared with placebo, except for a greater risk of urinary tract infections (log OR=0.34, $P<0.0001$). This finding may be related to the mechanism of SGLT2 inhibitors. In addition, patients with HFpEF are at increased risk of experiencing serious AEs ($P=0.01$), particularly cardiovascular events ($P<0.0001$).

Conclusion

The meta-analysis revealed that longer-term administration of EMPA (≥6 months) is an appropriate therapeutic option for HF patients to improve LV remodeling, exercise capacity and QoL. These improvements occurred regardless of the presence of diabetes or reductions in the LVEF. Importantly, (1) glycemic status has been demonstrated to influence the efficacy of this agent for HF patients; (2) despite the absence of renal dysfunctions in a previous trial [33], we identified an elevated risk of urinary tract infections; (3) EMPA has been shown to potentially increase the risk of cardiovascular AEs but does not significantly improve the QoL of HFpEF patients; (4) further clinical trials are needed to provide data concerning LV remodeling in EMPA-treated HFpEF patients, and additional therapy should be considered for HFpEF patients.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12872-024-04316-w.

Supplementary Material 1

Author contributions

Author contributions were as follows: Qingkai Yan and Xinrao Chen: study design, literature search, systematic review and data collection, statistical analysis, interpretation of results, and writing of the manuscript. Changqing Yu and Yuehui Yin: principal investigator, study design, assessment of all results, rewriting and checking typographical and grammatical errors. The corresponding authors confirmed all contributing authors gave permission to be named in this manuscript.

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Data availability

Data available on request from the authors: the data that support the findings of this study are available from the corresponding author upon reasonable request.

Declarations

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

Human ethics and consent to participate

Not applicable.

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