Am J Transl Res 2026;18(3):2287-2296
www.ajtr.org /ISSN:1943-8141/AJTR0170756

Review Article

Impact of SGLT-2 inhibitors on long-term prognosis in patients with heart failure with preserved ejection fraction: a systematic review and meta-analysis of randomized controlled trials

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Received December 15, 2025; Accepted February 7, 2026; Epub March 15, 2026; Published March 30, 2026

Abstract: Objectives: This study aimed to assess the effect of Sodium-Glucose Cotransporter-2 (SGLT-2) inhibitor (SGLT-2i) on long-term (≥1 year) mortality, heart failure (HF)-related hospital admissions, and safety in patients suffering from heart failure with preserved ejection fraction (HFpEF), via a systematic review and meta-analysis of recent high-quality randomized controlled trials (RCTs), and further provide the updated evidence to inform clinical management strategies. Methods: A systematic literature search was conducted in PubMed, Embase, the Cochrane Library, and ClinicalTrials.gov. Pooled risk ratios (RR) with 95% confidence intervals (CI) were calculated using either a random-effects or fixed-effect model, selected based on heterogeneity as measured by Q test and the I^2 statistic. Study quality was assessed using the Cochrane RoB 2.0 tool. Data analysis was conducted with RevMan 5.4.1 and Stata 17.0. Results: A total of six international multicenter RCTs published between 2020 and 2025, enrolling 16,543 participants, were included in the meta-analysis. The findings showed that treatment with SGLT-2i significantly reduced the risk of heart failure hospitalizations when compared to placebo ($P<0.05$). A significant reduction in all-cause mortality was also observed in the SGLT-2 inhibitor group. Rates of adverse events were similar between the SGLT-2 inhibitor and placebo arms. Besides, funnel plot analysis showed no significant publication bias. Conclusion: In patients with HFpEF, SGLT-2 inhibitor therapy safely reduces the risk of heart failure hospitalization and mortality. These findings support the use of SGLT-2 inhibitors as a valuable treatment strategy in this population.

Keywords: SGLT-2 inhibitors, heart failure with preserved ejection fraction, long-term prognosis, mortality, hospitalization for heart failure

Introduction

Globally, heart failure (HF) with preserved ejection fraction (HFpEF) represents the most prevalent HF subtype, accounting for more than half of all cases [1]. The global incidence of HFpEF is increasing, primarily due to demographic aging, rising obesity rates, and the expanding burden of diabetes mellitus [2]. The underlying pathophysiology of HFpEF is notably complex and heterogeneous, characterized by impaired myocardial relaxation, increased ventricular stiffness, and a state of chronic systemic inflammation. Although current therapeutic strategies provide symptomatic relief, they have not consistently demonstrated significant reductions in all-cause mortality or hospitalizations related to HF [3]. Therefore, the development of effective treatment approaches for HFpEF remains a major unmet need and a critical priority in cardiovascular research worldwide.

In recent years, the management of HF has been transformed by the emergence of sodium-glucose cotransporter 2 (SGLT-2) inhibitors (SGLT-2i) [4]. Initially developed as antihyperglycemic agents (e.g., empagliflozin, dapagliflozin), SGLT-2i have become foundational therapies for heart failure with reduced ejection fraction (HFrEF), with robust evidence supporting their ability to reduce both all-cause mortality and HF-related hospitalizations [5, 6]. This success has prompted investigation into their efficacy in HFpEF. Large-scale clinical trials, including EMPEROR-Preserved (2021) and DELIVER (2022), have demonstrated that SGLT-2i

https://doi.org/10.62347/LKZD8562

are associated with approximately a 20% reduction in the composite risk of cardiovascular death or HF hospitalization [7]. Nevertheless, uncertainties remain regarding long-term (>1 year) outcomes, largely due to variability in trial follow-up durations (median 16-24 months), differences in patient populations (e.g., presence or absence of diabetes), and inconsistencies in endpoint definitions across studies [8, 9].

Consequently, this study aims to evaluate the long-term impact of SGLT-2i on outcomes in HFpEF. We perform a meta-analysis of high-quality randomized controlled trials (RCTs) published to synthesize global evidence. Confirmation of a sustained benefit on all-cause mortality or HF hospitalization would establish SGLT-2i as a foundational therapy for HFpEF, potentially influencing treatment guidelines. Conversely, limited benefits would necessitate research into combination or precision treatments. In either case, our findings offer critical evidence to help clinicians optimize long-term HFpEF management and improve patient outcomes.

Information and methodology

Research design

Adhering to the Preferred Reporting Items for Systematic Reviews and Meta-Analyzes (PRISMA 2020) guidelines, this investigation adopted a prospective systematic review and meta-analysis design. It comprehensively integrated high-quality randomized controlled trials (RCTs) undertaken worldwide until August 2025, aiming at evaluating the impact of SGLT-2i on the long-term (≥1 year) prognosis of HFpEF patients. The study has been registered on the PROSPERO platform (CRD420261277554).

Inclusion and exclusion criteria

Inclusion criteria comprised: (1) RCTs on HFpEF conducted across multiple centers or internationally, comparing SGLT-2i (monotherapy or add-on) versus placebo/standard care (non-SGLT-2i therapy); (2) Adult HFpEF patients (≥18 years), with a diagnosis confirmed by left ventricular ejection fraction (LVEF) ≥50% and elevated N-terminal pro-B-type Natriuretic Peptide (NT-proBNP)/B-type Natriuretic Peptide (BNP) (measured in clinical stability rather than during acute decompensation); (3) The SGLT-2i group received SGLT-2i (e.g., empagliflozin, dapagliflozin, sotagliflozin), while the control group received either a placebo or standard HF therapy (e.g., renin-angiotensin system inhibitors, beta-blockers); (4) Reporting of ≥1 long-term (≥12 months follow-up) hard endpoint, such as all-cause death, HF hospitalization (readmissions due to HF relapse), and adverse events; (5) A minimum of 12 months to allow for meaningful evaluation of long-term prognostic effects.

Exclusion criteria were: (1) Non-RCTs or non-quasi-experimental studies; (2) Duplicate reports or subgroup analyzes of the same primary study; (3) Sample size <10 patients (to minimize the risk of underpowered statistical analyzes); (4) Severe hepatorenal dysfunction (estimated glomerular filtration rate [eGFR] <20 mL/min/1.73 m^2) or concurrent malignancy, which could confound the interpretation of the primary outcomes.

Search strategy

The literature search was completed in August 2025, covering PubMed, Embase, Cochrane Library and ClinicalTrials.gov databases. The combination of search terms was 'SGLT-2 inhibitor OR Sodium-Glucose Cotransporter-2 inhibitor OR SGLT-2i' AND 'heart failure with preserved ejection fraction OR HFpEF AND Placebo OR randomized controlled trial. The PubMed search query is provided as an illustration: ((((((SGLT-2 inhibitor) or (Sodium-Glucose Cotransporter-2 inhibitor) or (SGLT-2i)) AND (heart failure)) AND (heart failure with preserved ejection fraction)) OR (HFpEF)) AND (Placebo).

Literature screening and data extraction

The literature was processed independently by two investigators (Peijian Shi and Tanqi Chen) using EndNote X20. Initial deduplication was followed by a title and abstract screening to eliminate clearly irrelevant records. The remaining articles underwent full-text review, and those meeting the criteria were selected for final inclusion. The screening procedure was documented using a PRISMA flow diagram. Any disagreements were resolved by a third researcher (C). A standardized data extraction form was developed in Excel. Two investigators independently collected the following details.

Core publication details: first author, year of publication, country/region, study design (dou-

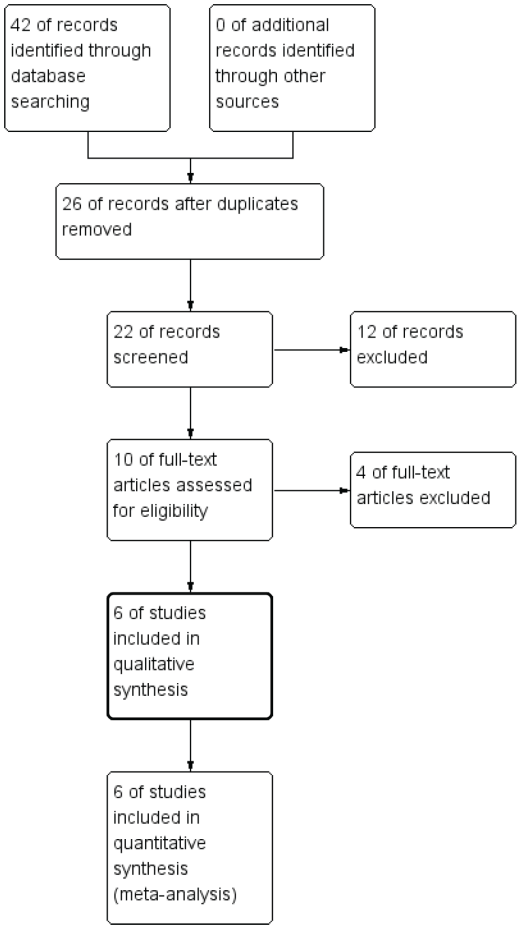

Figure 1. PRISMA literature screening flowchart. Showing the complete process from database retrieval to final inclusion in the study.

ble-blind/open-label), and follow-up duration; Participant characteristics: sample size (SGLT-2i group/placebo group) and baseline data (age, sex, LVEF, NT-proBNP, diabetes prevalence, New York Heart Association [NYHA] cardiac function classification); Treatment protocols: SGLT-2i agent, dosing, treatment period; comparator placebo details; Outcome measures: mortality rate, frequency of HF hospitalizations, adverse reactions, and follow-up time.

Literature quality evaluation

A quality assessment of the included RCTs was conducted with the Cochrane Risk of Bias tool (RoB 2.0). The evaluation dimensions included randomization, allocation concealment, blinding (of participants, intervention providers, and outcome assessors), data completeness, selective reporting, and other potential biases.

Statistical analysis

Data analysis was conducted with RevMan 5.4.1 (Cochrane Collaboration) and Stata 17.0. Odds ratios (OR) with corresponding 95% confidence intervals (CI) calculated. Dichotomous variables were pooled via the Mantel-Haenszel method. The extent of heterogeneity among studies was quantified with the I^2 statistic and Q test: a fixed-effect model was chosen for low heterogeneity ($I^2 \leq 50\%$), while a random-effects model was employed for significant heterogeneity ($I^2 > 50\%$). Funnel plots were generated to assess potential bias. Results were deemed significant at $P<0.05$.

Results

Literature screening results

A total of 386 literature pieces were obtained in the initial review. After removing duplicates with EndNote X20, 42 remained. Through title and abstract screening, 16 studies that did not conform to the topic (such as non-HFPEF, non-RCT) were excluded. A full-text review was conducted on the remaining 26 articles. Those with a sample size of less than 10 cases (2 articles), a follow-up period of less than 12 months (12 articles), and duplicate reports (4 articles) were excluded. Eventually, 6 RCTs that met the criteria were included. The literature search identified six relevant RCTs [10-15] focusing on SGLT-2i therapy for HFpEF, all published from 2020 to 2025 (**Figure 1**).

Characteristics of literature

This analysis included 16,543 participants from the 6 selected studies. The SGLT-2i group (n=9,645) was administered one of five medications (Empagliflozin, Sotagliflozin, Ertugliflozin, Dapagliflozin, or Canagliflozin), and the placebo group (n=6,898) received a matching control. **Table 1** details the information on the selected literature. All the studies used monotherapy and there was no combination therapy (**Table 1**).

Impact of SGLT-2i on HF hospitalization in HFpEF patients

Each of the incorporated studies reported on the effect of SGLT-2i on HF hospitalization among HFpEF patients. Due to considerable heterogeneity across the literature ($I^2=68\%$), a

Table 1. Data from the literature

	SGLT-2i group				Placebo group				Median follow-up time (months)	Outcome measures
	Treatment	n	Age	Male/Female	Treatment	n	Age	Male/Female		
Abraham WT 2021 [10]	Empagliflozin	157	74.0 (68.0, 79.0)	87/70	Placebo	158	75.0 (68.0, 79.0)	92/66	13	②③
Anker SD 2021 [11]	Empagliflozin	2997	71.8±9.3	1659/1338	Placebo	2991	71.9±9.6	1653/1338	26.2	①②③
Bhatt DL 2021 [12]	Sotagliflozin	608	69 (63-76)	410/198	Placebo	614	70 (64-76)	400/214	14.2	①③
Cosentino F 2020 [13]	Ertugliflozin	5499	-	3516/1983	Placebo	2747	-	1862/885	36	③
Nassif ME 2021 [14]	Dapagliflozin	162	69 (64, 77)	70/92	Placebo	162	71 (63, 78)	70/92	18	②③
Spertus JA 2022 [15]	Canagliflozin	222	62.9±13.19	118/104	Placebo	226	64.0±13.45	129/97	20	①②③

Note: ① frequency of HF hospitalizations, ② adverse reactions, ③ mortality rate. Sodium-Glucose Cotransporter-2 inhibitor (SGLT-2i).

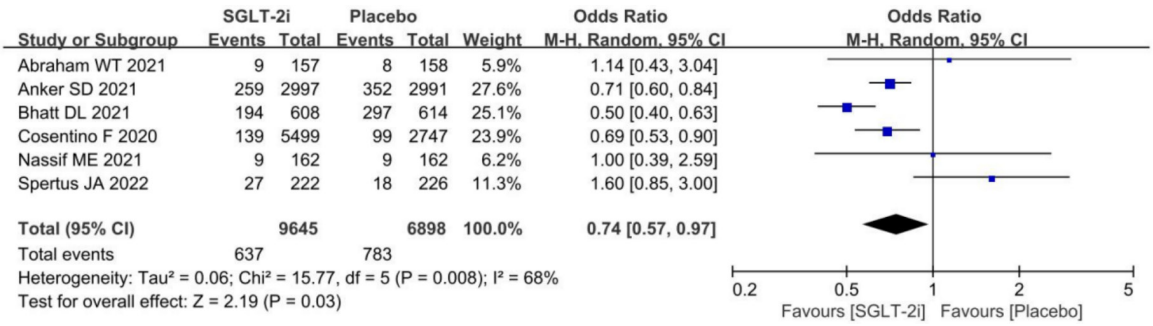

Figure 2. Forest plot of the impact of SGLT-2i on the risk of HF hospitalization in patients with HFpEF (Random effects model). Sodium-Glucose Cotransporter-2 inhibitor (SGLT-2i), Confidence interval (CI).

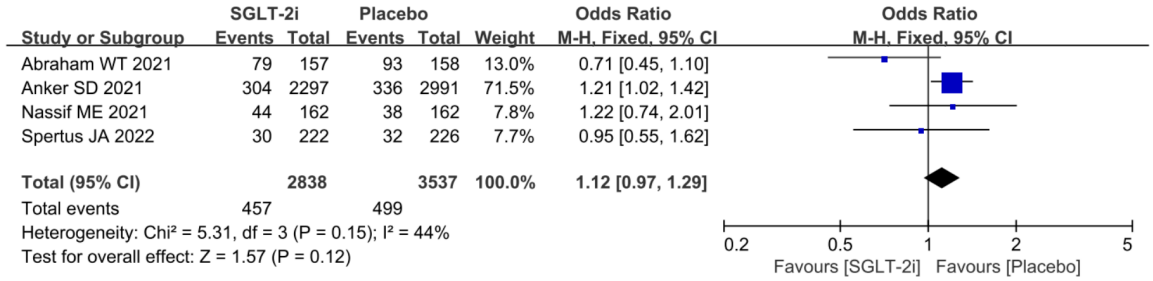

Figure 3. Forest plot of the safety impact of SGLT-2i on patients with HFpEF (fixed effects model). Sodium-Glucose Cotransporter-2 inhibitor (SGLT-2i), Confidence interval (CI).

random-effects model was employed. The analysis revealed that SGLT-2i therapy significantly lowered the risk of HF rehospitalization relative to placebo (P=0.03; OR=0.74, 95% CI: 0.57-0.97). Thus, SGLT-2i is favorable for prognostic health in this population (**Figure 2**).

Effect of SGLT-2i on prognostic safety in the HFpEF population

Four studies reported adverse reactions in HFpEF patients. Heterogeneity among the studies was low (I^2=44%), allowing for a fixed-effects meta-analysis. The results demonstrated no significant difference in the incidence of adverse events between the SGLT-2i and control groups (P=0.12). This suggests that SGLT-2i therapy is not associated with an elevated risk of adverse prognosis in HFpEF patients (**Figure 3**).

Influence of SGLT-2i on prognostic survival in HFpEF patients

Finally, the impact of SGLT-2i on survival outcomes was evaluated across all studies. Heterogeneity among studies was not substantial (I^2=47%). SGLT-2i use significantly reduced mortality relative to placebo (P=0.001, OR= 0.78, 95% CI: 0.67-0.90), supporting its role in decreasing mortality risk in the HFpEF population (**Figure 4**).

Quality assessment of literature

After evaluation, the evaluated studies demonstrated a low-to-moderate risk of bias, indicating their high reference value. Two studies (Spertus JA 2022, Bhatt DL 2021) were assessed as having a “moderate risk of bias”, whereas the remaining four studies were categorized as “low risk of bias”. The core drivers of moderate bias risk were concentrated in the following domains: The CHIEF-HF trial conducted by Spertus JA (2022) explicitly employed an open-label design without placebo matching, meaning both participants and investigators were unmasked to treatment group assignments. While outcome assessors were blinded (with HF hospitalization and mortality events adjudicated by independent third parties), the open-label design introduces potential biases: investigators may exhibit differential recording of adverse events (e.g., over vigilance for adverse events in the SGLT-2i arm), or partici-

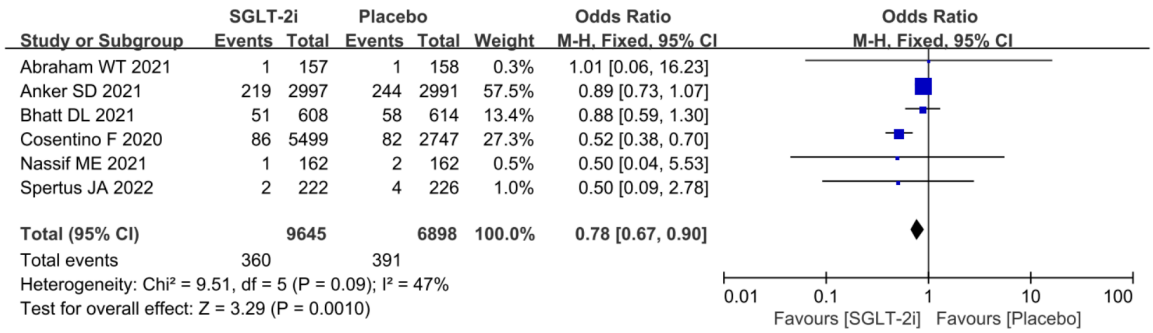

Figure 4. Forest plot of the effect of SGLT-2i on mortality in patients with HFpEF (fixed effects model). Sodium-Glucose Cotransporter-2 inhibitor (SGLT-2i), Confidence interval (CI).

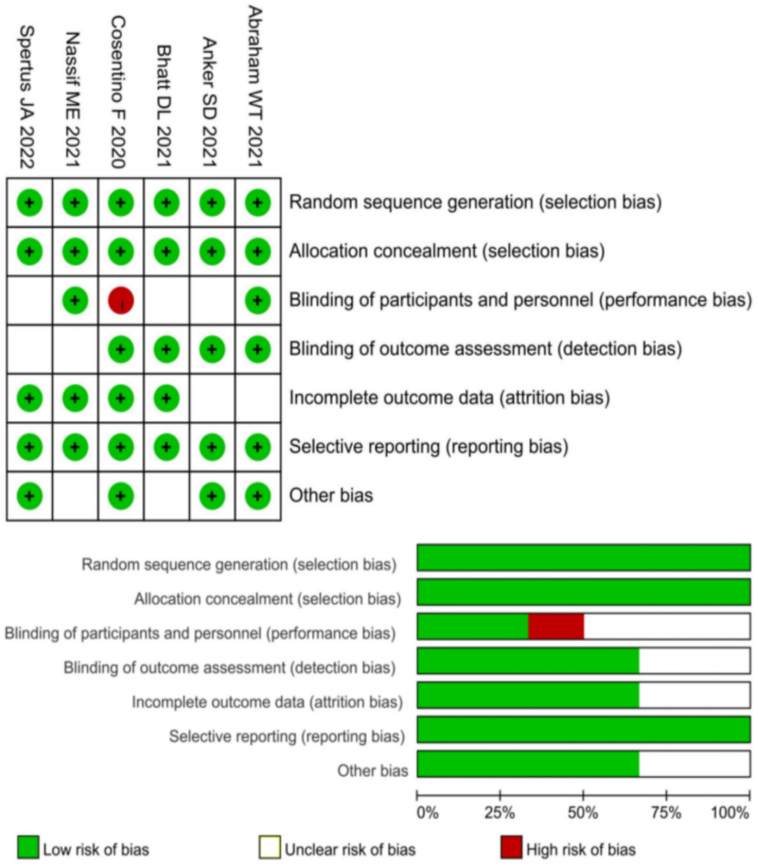

Figure 5. Bias risk assessment map included in RCTs (Cochrane RoB 2.0 tool). Randomized controlled trials (RCTs).

pants may modify their lifestyle behaviors (e.g., increased physical activity, dietary adjustments) upon awareness of their group allocation, which could confound outcome assessment. Consequently, this trial was rated as having a "moderate risk of bias" in the "blinding of participants and personnel" domain. Notably, despite their moderate bias risk, neither of the two studies compromised key bias domains relevant to core outcomes (HF hospitalization and mortality), such as random sequence generation or selective reporting. Furthermore, sensitivity analyses (excluding heterogeneous studies) confirmed the robustness of the results. The remaining four studies were all low risk of bias. Collectively, the methodological design of all included studies was generally rigorous with high data credibility, providing solid evidential support for the conclusions of this meta-analysis (**Figure 5**).

Publication bias

To evaluate publication bias regarding HF hospitalization, a funnel plot was generated. The initial plot showed two studies (Bhatt DL 2021 and Spertus JA 2022) falling outside the CI (**Figure 6**). A subsequent sensitivity analysis excluding these outliers revealed a consistent reduction in HF hospitalization risk with SGLT-2i versus placebo (P<0.05, OR=0.74, 95% CI=0.65-0.84), with a more substantial difference than the primary analysis (**Figure 7**).

Discussion

The introduction of SGLT-2i has transformed the management of HFrEF [16]; however, the long-term role in HFpEF remains uncertain. By

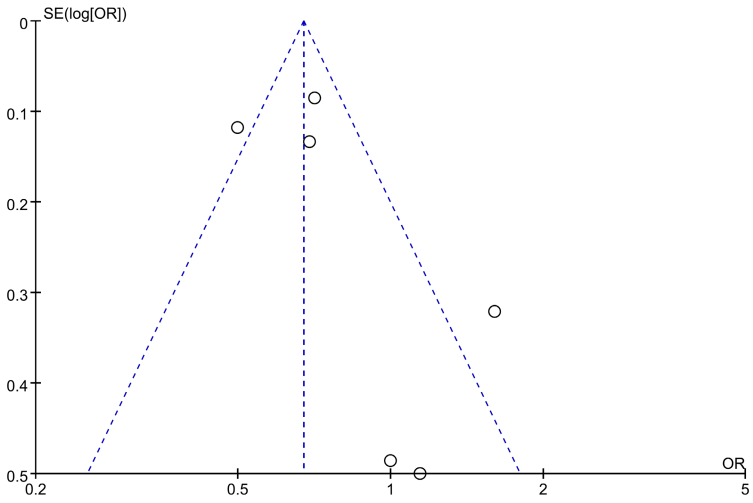

Figure 6. Publication bias funnel plot of HF hospitalization outcomes. heart failure (HF).

systematically reviewing six rigorously conducted RCTs published between 2020 and 2025, this analysis demonstrates that SGLT-2i therapy is associated with significant reductions in heart failure hospitalizations and mortality among patients with HFpEF, without notable safety concerns. These findings underscore the therapeutic potential of SGLT-2i in HFpEF and provide contemporary evidence to support clinical decision-making.

The analysis reveals that the reduction in risk of heart failure rehospitalization is one of the most prominent clinical benefits of SGLT-2i in patients with HFpEF. Notably, although impaired myocardial contractility is not the primary pathophysiological feature of HFpEF, the beneficial effects of SGLT-2i on heart failure outcomes are likely mediated through multiple mechanisms that collectively reduce cardiac preload and afterload: (1) SGLT-2i inhibits glucose reabsorption in the proximal renal tubule, leading to osmotic diuresis. The resulting reduction in intravascular volume decreases cardiac preload and alleviates pulmonary congestion [17]. This effect is particularly relevant in HFpEF, which is frequently associated with volume overload and pulmonary hypertension [18]. (2) SGLT-2i reduces left ventricular filling pressures by decreasing arterial stiffness and improving vascular compliance. This mechanism is supported by a small sub-analysis showing that three months of empagliflozin therapy significantly lowered the E/e' ratio - a noninvasive echocardiographic index reflecting improved diastolic function [19]. An additional contributing mechanism involves the optimization of myocardial energy metabolism, whereby SGLT-2i promotes the utilization of ketone bodies and free fatty acid oxidation, thereby reducing cardiomyocyte apoptosis [20]. This metabolic modulation, previously shown to be beneficial in HFrEF, may also counteract the mitochondrial dysfunction and energetic deficit characteristic of HFpEF [21].

Additionally, safety analyses confirmed comparable adverse event rates between SGLT-2i and placebo in patients with HFpEF, with no statistically significant differences observed. Nevertheless, several potential risks warrant careful consideration: (1) SGLT-2i may increase the risk of genitourinary infections due to elevated local glucose concentrations in the urogenital tract resulting from enhanced urinary glucose excretion [17]. (2) Although the incidence is low, cases of diabetic ketoacidosis (DKA) have been reported. This serious adverse event is mechanistically associated with SGLT-2i-induced reduction in renal glucose reabsorption and increased glucagon secretion. Patients receiving insulin therapy or those with limited carbohydrate intake are at higher risk [22]. (3) While SGLT-2i monotherapy carries a low inherent risk of hypoglycemia owing to its insulin-independent mechanism of action, the concomitant use of SGLT-2i with sulfonylureas or insulin may increase this risk, necessitating close monitoring.

Finally, our analysis associates SGLT-2i use with reduced all-cause mortality in individuals with HFpEF, potentially mediated through multiple pathways: (1) Attenuation of ventricular remodeling: Preclinical studies indicate that SGLT-2i can inhibit myocardial fibrosis and reduce left ventricular mass index [23]. (2) Anti-inflammatory and antioxidant effects: SGLT-2i mitigates systemic inflammation by suppressing activation of the NLRP3 inflammasome and reducing reactive oxygen species production [24]. These effects are particularly relevant in HFpEF, a condition often characterized by chronic, low-grade systemic inflammation. (3)

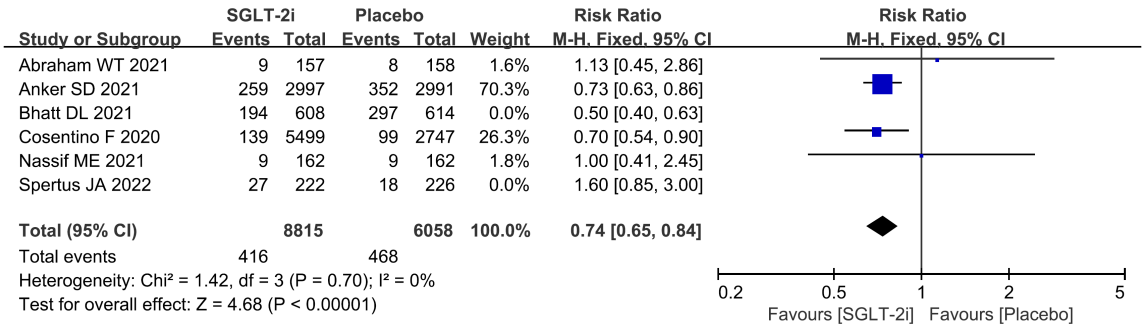

Figure 7. Forest plot for sensitivity analysis of HF hospitalization outcomes (excluding studies with high heterogeneity). Sodium-Glucose Cotransporter-2 inhibitor (SGLT-2i), Confidence interval (CI).

Renoprotective effects: SGLT-2i are known to slow the progression of diabetic nephropathy. This renoprotective property is critically important, as worsening renal function independently predicts mortality in patients with HFpEF [25].

Notably, the observed heterogeneity in hospitalization for heart failure across studies may be attributed to variations in patient age and follow-up duration. Differences in the molecular structures of SGLT-2i may also contribute to variations in efficacy. For validation, a further analysis was conducted after removing the highly heterogeneous literature. This sensitivity analysis produced congruent findings, thereby substantiating the credibility of the initial analysis.

The study findings support the prioritization of SGLT-2i in the long-term care of HFpEF patients, a strategy expected to lead to an improved prognosis. Notwithstanding adjustments via random-effects models and subgroup analyzes to reduce bias, the validity of the findings may be compromised by underlying differences among the RCTs. These include a wide spectrum of follow-up periods (16-36 months), the specific type of SGLT-2i administered (e.g., empagliflozin, dapagliflozin), and differing patient profiles at baseline (e.g., the prevalence of diabetes mellitus). For safety analysis, only four studies provided complete safety data. Data supporting the long-term risks (exceeding five years) of urogenital infections and other adverse events are lacking. Finally, the comprehensive benefits of SGLT-2i might also be undervalued when softer indicators like quality of life and medical resource consumption are omitted from analysis.

Conclusion

Based on a meta-analysis of six high-quality RCTs, SGLT-2i therapy is significantly associated with reduced risks of HF rehospitalization and all-cause mortality in patients with HFpEF, with a favorable safety profile. Although moderate heterogeneity was observed across studies, consistent effect estimates - further supported by subgroup analyses and extended follow-up data - underscore the robustness of these benefits, particularly among high-risk patient subgroups. Nevertheless, future large-scale, multinational RCTs with prolonged follow-up periods are warranted to confirm these findings, elucidate the mechanisms underlying differential treatment responses, and evaluate the efficacy and safety of SGLT-2i-based combination therapies.

Disclosure of conflict of interest

None.

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