Effect of SGLT2 inhibitors on heart failure outcomes in patients with and without diabetes: A systematic review and meta-analysis of randomized controlled trials

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Abstract. Heart failure (HF) is a debilitating condition with high morbidity and mortality rates worldwide. Sodium-glucose cotransporter 2 inhibitors (SGLT2i) exhibit cardiovascular (CV) and renal protective effects beyond glucose lowering, and may serve a role in managing HF across numerous patient populations, including non-diabetics. Therefore, the present systematic review and meta-analysis aimed to evaluate the efficacy of SGLT2i in reducing HF hospitalizations, CV mortality and adverse events in patients with and without type 2 diabetes mellitus. Following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses 2020 guidelines, comprehensive literature searches were conducted across PubMed, Scopus, Web of Science and Cochrane Central databases up to May 2025. Randomized controlled trials (RCTs; phases II-IV) enrolling adults with HF, irrespective of ejection fraction or diabetes status, comparing SGLT2i with placebo or standard-of-care were included in the present study. Outcomes analyzed encompassed HF hospitalizations, CV and all-cause mortality, adverse events and patient-reported quality of life measures. Meta-analysis was performed with RevMan 5.4 using a random-effects model. Data from 28 RCTs, including numerous high-quality trials, consistently demonstrated that SGLT2i significantly reduced the risk of first and total hospitalization for HF by 24% [odds ratio (OR)=0.76; 95% CI: 0.64-0.91; P=0.002; I^2=0%] and 33% (OR=0.67; 95% CI: 0.63-0.72; P<0.00001; I^2=33%), respectively. In addition, the use of SGLT2i decreased all-cause and CV-associated mortality by 28% (OR=0.72; 95% CI: 0.61-0.86; P=0.0002; I^2=88%) and 24% (OR=0.76; 95% CI: 0.70-0.83; P<0.00001; I^2=57%), respectively. Furthermore, adverse events occurred in 22% (OR=0.78; 95% CI: 0.59-1.02; P=0.07; I^2=97%), regardless of the diabetic status of the patients. Publication bias was significant (P<0.05) in studies addressing total hospitalization, while studies evaluating all-cause mortality, CV-associated mortality and adverse events did not exhibit significant publication bias (P≥0.05). The majority of studies were found to have a low risk of bias, with only a small number of studies exhibiting a high risk of bias. Low-to-high certainty of evidence was observed. Overall, SGLT2i were indicated to be effective in reducing hospitalization for HF and improving survival in a broad spectrum of patients, including those without diabetes. The multifactorial mechanisms of SGLT2i are likely to contribute to these benefits, supporting their emerging role in HF management.

Introduction

Heart failure (HF) occurs when the heart loses its ability to pump sufficient amounts of blood to the body. HF represents a pervasive global public health challenge, affecting >64 million individuals worldwide, and exhibits a growing prevalence due to the aging population (1,2). The prevalence of HF exhibited a notable increase from 641.14/100,000 individuals in 1990 to 676.68/100,000 individuals in 2021, with men (760.78/100,000) showing an increased incidence rate compared with women (604/100,000) (3). HF may be caused by numerous different conditions, including right ventricular dysfunction, left ventricular (LV) dysfunction, pericardial disease, valvular heart disease and obstructive lesions in the great vessels or heart (4). Despite notable improvements in pharmacological (nesiritide, ularitide, inotropic agents, serelaxin, angiotensin II type 1 receptor, rolofylline) and non-pharmacological (ventilator support, ultrafiltration) treatment strategies (5), HF continues to be associated with high morbidity, frequent hospitalizations, impaired quality of life and substantial mortality rates [32% deaths in patients who had HF with LV ejection fraction (LVEF) <40%] (6). This burden is magnified in the context of type 2 diabetes mellitus (T2DM), a frequent comorbidity that not only accelerates HF progression but also

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complicates management strategies (7). Importantly, the pathophysiological association between hyperglycemia, oxidative stress, insulin resistance, myocardial fibrosis and inflammation, contributes to both functional and structural deterioration of the heart (8). Thus, targeting the overlapping mechanisms of diabetes and HF has been of great interest. Among recent and emerging therapies, sodium-glucose cotransporter 2 inhibitors (SGLT2i), which were initially developed for glycemic control, demonstrate promise as potent agents conferring cardiovascular (CV) and renal protection, beyond the glucose-lowering effect they exhibit (9,10). Notable CV outcome trials in patients with T2DM first demonstrated a reduction in hospitalizations related to HF and CV mortality, establishing the foundation for dedicated HF trials that excluded diabetes status as an inclusion criterion (11,12).

Subsequently, high-quality randomized controlled trials (RCTs) across the spectrum of HF phenotypes, ranging from reduced to preserved ejection fraction and including non-diabetic individuals, have consistently demonstrated that SGLT2i reduce HF hospitalizations, improve functional capacity and enhance health-related quality of life (13). RCTs, such as the 'Dapagliflozin and Prevention of Adverse Outcomes in HF' trial (DAPA-HF) and the empagliflozin outcome trial in patients with preserved ejection fraction (EMPEROR-preserved), have highlighted the efficacy of SGLT2i in reducing HF-related hospitalizations and CV mortality, extending their use to non-diabetic populations (14,15). These patient-centered benefits, as evidenced by the Kansas City Cardiomyopathy Questionnaire (KCCQ) and New York Heart Association functional classification scores, underscore the broader importance of SGLT2i in HF management (16).

Beyond their glucose-lowering effects, SGLT2i exhibit pleiotropic benefits, including natriuresis, blood pressure reduction, improved ventricular loading conditions and potential direct myocardial effects (17). Previous meta-analyses have supported the favorable effect of SGLT2i on HF outcomes; however, they tended to include a limited number of studies with heterogeneous populations (18,19). Therefore, questions remain regarding the consistency and magnitude of SGLT2i benefits across diabetic and non-diabetic patients, and whether the observed outcomes are uniformly applicable across a number of patient populations and HF phenotypes. Moreover, as evidence continues to accumulate from both CV outcome trials and HF-specific RCTs, an updated and more focused analysis with additional variables is warranted. Therefore, the present systematic review and meta-analysis aimed to collect evidence from RCTs to evaluate the effect of SGLT2i on HF outcomes in adults with and without T2DM. The primary objective was to determine whether SGLT2i reduces the risk of hospitalization for HF across this population. Secondary objectives included assessing the impact of SGLT2i on CV mortality, all-cause mortality and adverse events.

Materials and methods

Data sources and search. Comprehensive literature searches were performed in PubMed, Scopus, Web of Science and Cochrane Central, from database inception to May 2025, applying combinations of vocabulary and key words related to SGLT2i, empagliflozin, canagliflozin, dapagliflozin and HF. These search terms were combined using Boolean operators and the detailed search strategy is described in Table SI. The present systematic review and meta-analysis was designed following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines (20).

Eligibility criteria and outcomes. Eligible studies included phase II-IV RCTs enrolling adult patients (aged ≥18 years) diagnosed with HF, irrespective of ejection fraction category or diabetes status. Studies must have compared any SGLT2i with a placebo or standard-of-care treatment and reported at least one of the following outcomes: i) Hospitalization for HF (primary outcome); ii) CV mortality; iii) all-cause mortality; iv) ejection fraction; v) myocardial infraction; or vi) health-related quality of life assessed according to the KCCQ. Studies that exclusively enrolled pediatric populations, animal models or healthy volunteers were excluded. Additionally, trials lacking extractable outcome data or those without stratification by diabetes status were also excluded.

Study selection process. Independent screening processes were carried out by two authors using the PRISMA flow chart. In the first phase, 1,870 studies were retrieved through a search in different electronic databases and 250 duplicate studies were removed using the EndNote X9 referencing software (Clarivate; www.endnote.com). In the second phase, 1,620 studies were screened by checking their titles and abstracts, and 1,553 studies were excluded due to being irrelevant, or being reviews or letters to editors, leaving 67 studies eligible for full-text assessment. During the full-text assessment, 39 studies were excluded due to non-availability of the full text, not reporting the required outcomes or not having used SGLT2i. The study selection process is illustrated in Fig. 1. Finally, 28 studies were selected for qualitative and quantitative analysis. Discrepancies were resolved through consensus or consultation with a third author.

Data extraction. Data were extracted from each eligible study by two independent authors, using a predefined data collection form. Extracted information included study characteristics (author, year of publication, country, trial phase and sample size), participant demographics (age, sex, diabetes status and baseline LVEF), intervention and comparator details (agent, dosage, administration route and treatment duration), follow-up periods and reported effect estimates [hazard ratios (HRs), risk ratios and mean differences with 95% CIs].

Methodological quality and risk of bias assessment. Risk of bias was assessed at the study level using the Cochrane Risk of Bias 2.0 tool (https://methods.cochrane.org/bias/resources/rob-2-revised-cochrane-risk-bias-tool-randomized-trials), with judgments made in the domains of randomization, deviations from intended interventions, missing outcome data, measurement of outcomes and selective reporting. Outcomes were reported in the form of visualization judgments associated with each risk of bias item and presented as percentages using the web-based application Risk of Bias VISualization (21). This entire process was performed by two independent authors and any discrepancies were resolved with the consultation of a third senior author.

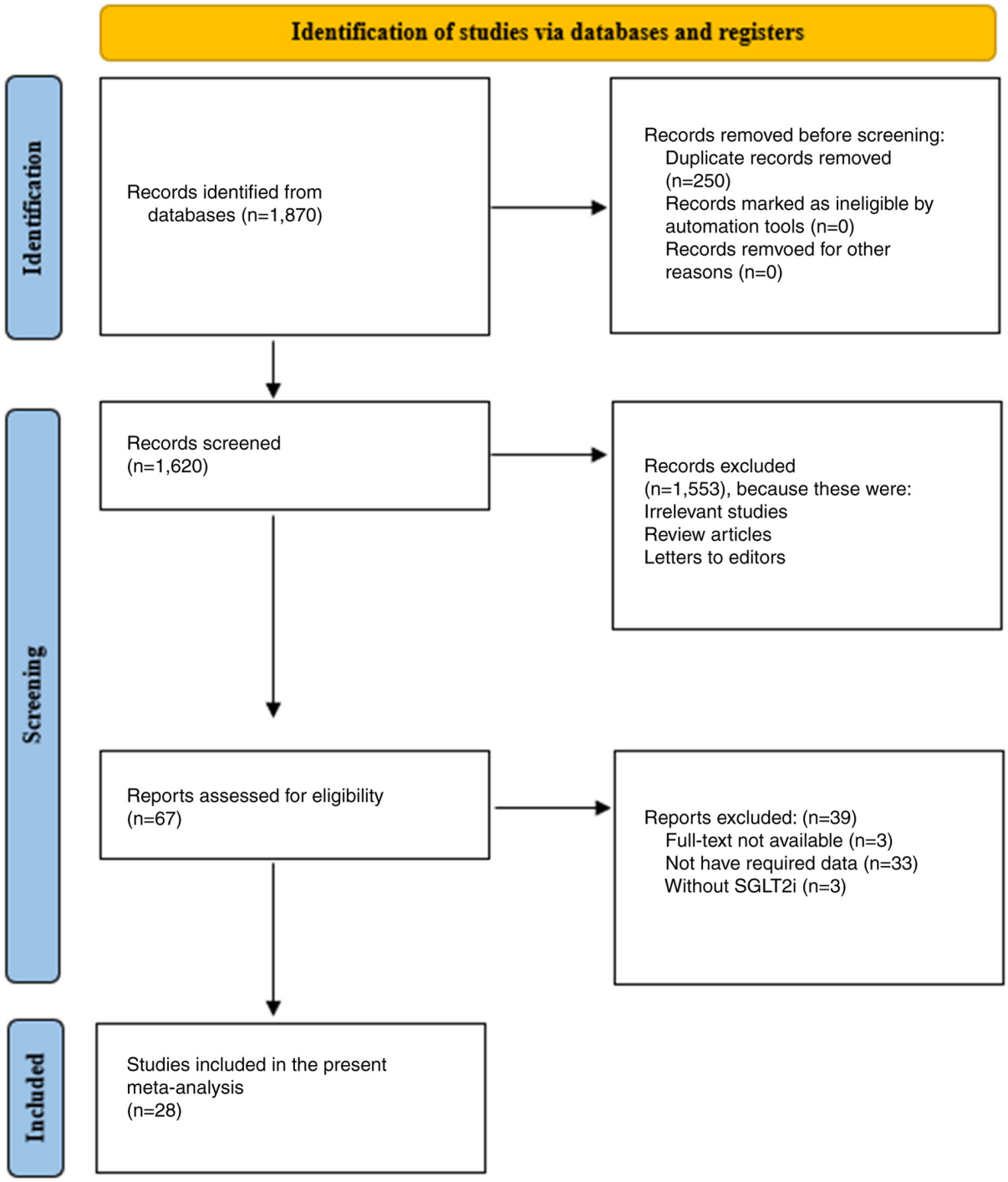

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow chart for the selection of studies. SGLT2i, sodium-glucose cotransporter 2 inhibitors.

Meta-analysis. For qualitative data, narrative synthesis was performed, with key characteristics of studies and patients presented as tables. Quantitative data were analyzed using RevMan 5.4 (https://www.cochrane.org/learn/courses-and-resources/software) for the construction of forest plots using a random-effects model. The association between HF clinical outcomes and SGLT2i was measured using a χ^2 test and $P<0.05$ was considered to indicate a statistically significant difference. Heterogeneity among studies was calculated using the I^2 statistic, with a heterogeneity of <25, 26-75 and >75% being considered as low, moderate and high, respectively. Funnel plots were constructed for publication bias. If the distribution of studies was symmetrical and a clear funnel shape was observed, low publication bias was found among the studies, while an asymmetrical distribution of studies without a clear funnel shape indicated a higher publication bias. The funnel plot asymmetry was evaluated using Egger's linear regression test through RStudio software (version 4.0.2; Posit Software, PBC) for Windows.

Certainty of evidence. Certainty of evidence was evaluated using the Grading of Recommendations Assessment,

Table I. Summary of general characteristics of the included studies.

Study characteristics				Participant characteristics						
First author, year	Country	Trial phase	Sample size, N	Age, years	Sex, M:F	Diabetic status	Comorbidities	BMI, kg/m^2	Baseline LVEF	(Refs.)
Zinman *et al*, 2015	Multinational (42 countries from North America, Australia, New Zealand, Latin America, Europe, Africa and Asia)	NA	Intervention group, 468,7; control group, 233,3	Intervention group, 63.2; control group, 63.1	Intervention group, 333,6:135,1; control group, 168,0:653	Diabetic patients	NA	Intervention group, 30.6; control group, 30.7	NA	(41)
Fitchett *et al*, 2016	Multinational (42 countries)	EMPA-REG OUTCOME trial	Intervention group, 468,7; control group, 233,3	Intervention group, 63.1; control group, 63.1	505,4:196,6	Diabetic patients	NA	30.6	NA	(34)
Neal *et al*, 2017	Multinational (30 countries)	NA	Intervention group, 579,5; control group, 434,7	Intervention group, 63.2; control group, 63.4	Intervention group, 375,9:203,6; control group, 275,0:159,7	Diabetes (chronic)	Hypertension	Intervention group, 31.9; control group, 32.0	NA	(38)
Wanner *et al*, 2018	Multinational (countries from Europe, North America, Asia, Africa, Latin America, Australia and New Zealand)	NA	Intervention group, 464,7; control group, 222,7	61.0	Intervention group, 330,2:134,5; control group, 167,1:556	Diabetic patients	Kidney diseases	30.8	NA	(40)
Mahaffey *et al*, 2018	Multinational (North America, South/Central America, Europe and the rest of the world)	CANVAS program	101,42	62.7-63.8[a]	650,9:363,3	Diabetic patients	Hypertension	31.7-32.5[b]	NA	(37)
Kato *et al*, 2019	Multinational (countries from North America, Latin America, Europe and the Asia Pacific)	DECLARE-TIMI 58 trial	171,60	63-65[a]	108,11:634,9	Diabetic patients	Hypertension	31.1-31.6[b]	<45% (n=671), >45% (n=808)	(36)

Table I. Continued.

Study characteristics				Participant characteristics						
First author, year	Country	Trial phase	Sample size, N	Age, years	Sex, M:F	Diabetic status	Comorbidities	BMI, kg/m^2	Baseline LVEF	(Refs.)
McMurray *et al*, 2019	Multinational (countries from North and South America, Europe and the Asia Pacific)	Phase 3	Intervention group, 237,3; control group, 237,1	Intervention group, 66.2; control group, 66.5	Intervention group, 180,9:564; control group, 1,826:545	With or without diabetes	NA	Intervention group, 28.2; control group, 28.1	<40%	(48)
Wiviott *et al*, 2019	Multinational (North America, Latin America, Europe and Asia Pacific)	DECLARE-TIMI 58 trial/phase 3	Intervention group, 858,2; control group, 857,8	Intervention group, 63.9; control group, 64.0	Intervention group, 541,1:317,1; control group, 5,327:3,251	Diabetic patients	NA	Intervention group, 32.1; control group, 32.0	NA	(31)
Perkovic *et al*, 2019	Australia	NA	Intervention group, 220,2; control group, 219,9	Intervention group, 62.9; control group, 63.2	Intervention group, 144,0:762; control group, 146,7:732	Diabetic patients	Hypertension	Intervention group, 31.4; control group, 31.3	NA	(28)
Cannon *et al*, 2020	Multinational (countries from North and South America, Asia, Europe, South Africa, New Zealand and Australia)	NA	Intervention group, 549,9; control group, 274,7	64.4	Intervention group, 386,6:163,3; control group, 1,903:844	Diabetic patients	Coronary artery disease, cerebrovascular disease, peripheral arterial disease and MI	Intervention group, 31.9; control group, 32.0	NA	(33)
Heerspink *et al*, 2020	The Netherlands	NA	Intervention group, 215,2; control group, 215,2	Intervention group, 61.8; control group, 61.9	Intervention group, 144,3:709; control group, 143,6:716	With or without diabetes	Kidney diseases	Intervention group, 29.4; control group, 29.6	NA	(30)
Kosiborod *et al*, 2020	Multinational (countries from the Asia Pacific, Europe, North and South America)	DAPA-HF trial	444,3	66.3	345,2:991	With or without diabetes	Hypertension	NA	6.8%	(46)
Inzucchi *et al*, 2020	Multinational (countries from Europe, Asia, Latin America, North America and Africa)	EMPA-REG OUTCOME trial	Intervention group, 468,7; control group, 233,3	62.5-63.4[a]	495,1:198,4	Diabetic patients	NA	NA	NA	(35)

Table I. Continued.

Study characteristics				Participant characteristics						
First author, year	Country	Trial phase	Sample size, N	Age, years	Sex, M:F	Diabetic status	Comorbidities	BMI, kg/m^2	Baseline LVEF	(Refs.)
Verma *et al*, 2020	Canada	EMPA-REG OUTCOME trial	702,0	61.4-65.5[a]	NA	Diabetic patients	Hypertension	30.0-31.0[b]	NA	(29)
Ohkuma *et al*, 2020	Multinational	CANVAS program	101,28	62.8-64.0[a]	650,1:362,7	Diabetic patients	Hypertension	<25.0 or >30.0	NA	(39)
Bhatt *et al*, 2021	Multinational (countries from North America, Latin America, western Europe, eastern Europe and the rest of the world)	NA	Intervention group, 608; control group, 614	Intervention group, 69.0; control group, 70.0	Intervention group, 410:198; control group, 400:214	Diabetic patients	NA	NA	<50%: Intervention group (n=481) and control group (n=485)	(32)
McMurray *et al*, 2021	Multinational (Europe, Asia Pacific, South and North America)	NA	430,4	61.4-65.3[a]	287,9:142,5	With or without diabetes	CKD, hypertension, angina, MI and stroke	NA	NA	(49)
Nassif *et al*, 2021	USA	NA	Intervention group, 162; control group, 162	Intervention group, 69.0; control group, 71.0	Intervention group, 70:92; control group, 70:92	With or without diabetes	NA	Intervention group, 35.1; control group, 34.6	Intervention group, 60%; control group, 60%	(23)
Anker *et al*, 2021	Multinational (countries from Latin and North America, Europe and Asia)	EMPEROR-preserved trial	Intervention group, 299,7; control group, 299,1	Intervention group, 71.8; control group, 71.9	Intervention group; 165,9:133,8; control group, 165,3:133,8	With or without diabetes	NA	Intervention group, 29.77; control group, 29.90	Intervention group: ≤50% (n=995), ≤60% (n=1,028), >60% (n=974); control group: ≤50% (n=988), ≤60% (n=1,030) and >60% (n=973)	(42)
Anker *et al*, 2021	Multinational (countries from Latin and North America, Asia and Europe)	EMPEROR-reduced trial	Intervention group, 299,7; control group, 299,1	66.3-67.6[a]	Intervention group, 165,9:133,8; control group, 165,3:133,8	With or without diabetes	Hypertension	27.0-28.8[b]	≤40%	(43)

Table I. Continued.

Study characteristics				Participant characteristics						
First author, year	Country	Trial phase	Sample size, N	Age, years	Sex, M:F	Diabetic status	Comorbidities	BMI, kg/m^2	Baseline LVEF	(Refs.)
Spertus *et al*, 2022	USA	CHIEF-HF	Intervention group, 222; control group, 226	Intervention group, 62.9; control group, 64.0	Intervention group, 118:104; control group, 129:97	With or without diabetes	NA	NA	NA	(24)
Kosiborod *et al*, 2022	Multinational (countries from Asia, North America and Europe)	EMPULSE trial	Intervention group, 265; control group, 265	66.5-69.5[a]	349:177	With or without diabetes	Hypertension	27.4-32.6[b]	NA	(45)
Solomon *et al*, 2022	Multinational (countries from Asia, Europe, Saudi Arabia, Latin and North America)	NA	Intervention group, 313,1; control group, 313,2	Intervention group, 71.8; control group, 71.5	Intervention group, 176,7:136,4; control group, 174,9:138,3	With or without diabetes	Hypertension	NA	Intervention group, 54%; control group, 54.3%	(50)
Herrington *et al*, 2023	UK	NA	Intervention group, 330,4; control group, 330,5	Intervention group, 63.9; control group, 63.8	Intervention group, 220,7:109,7; control group, 221,0:109,5	With or without diabetes	NA	Intervention group, 29.7; control group, 29.8	NA	(26)
Hernandez *et al*, 2024	Multinational (22 countries from North and Latin America, Europe and Asia)	NA	Intervention group, 326,0; control group, 326,2	Intervention group, 63.6; control group, 63.7	Intervention group, 244,8:812; control group, 244,9:813	With or without diabetes	Hypertension and peripheral arterial disease	Intervention group, 28.1; control group, 28.1	<45% in 78.4% of patients	(44)
McMurray *et al*, 2024	Western Europe, North America and the rest of the world	The DETERMINE randomized clinical trials	DETERMINE-reduced intervention group, 156; control group, 157. DETERMINE-preserved intervention group, 253; control group, 251	DETERMINE-reduced intervention group, 69.0; control group, 69.0. DETERMINE-preserved intervention group, 73.0; control group, 73.0	DETERMINE-reduced intervention group, 111:45; control group, 122:35. DETERMINE-preserved intervention group, 162:91; control group, 158:93	With or without diabetes	NA	DETERMINE-reduced intervention group, 28.0; control group, 29.0. DETERMINE-preserved intervention group, 29.0; control group, 28.0	DETERMINE-reduced intervention group, 30%; control group, 29%. DETERMINE-preserved intervention group, 50%; control group, 53%	(47)

Table I. Continued.

Study characteristics				Participant characteristics						
First author, year	Country	Trial phase	Sample size, N	Age, years	Sex, M:F	Diabetic status	Comorbidities	BMI, kg/m^2	Baseline LVEF	(Refs.)
Vaduganathan *et al*, 2024	USA	CANVAS program and CREDENCE	145,43	62-65.5[a]	941,8:512,5	Diabetic patients	Kidney diseases and hypertension	NA	NA	(25)
Petrie *et al*, 2025	UK	EMPACT-MI trial	652,2	63.0-64.0[a]	489,2:163,0	With or without diabetes	Hypertension and COPD	27.0-29.0[b]	<45%	(27)

[a]Range of age; [b]range of BMI. MI, myocardial infarction; M, male; F, female; COPD, chronic obstructive pulmonary disease; NA, not available; LVEF, left ventricular ejection fraction; CKD, chronic kidney disease.

Development and Evaluation framework (22), a reproducible and structured framework used for the assessment of outcomes derived from the included studies. The level of certainty ranges from low to high after considering specific criteria, such as the risk of bias, result inconsistency and publication bias.

Results

General characteristics of studies. Numerous included studies were performed in multiple countries from Latin America, North America, South America, Europe and Asia. However, a limited number of studies were also performed in a single country, such as the USA (23-25), the UK (26,27), Australia (28), Canada (29) and the Netherlands (30). The majority of the studies were part of trials or programs, as described in Table I. Sample sizes varied notably and the majority of the studies used large sample sizes ranging from 8,582 to 8,578 individuals in the intervention and placebo groups (31), with the lowest sample size of 162 individuals in both the intervention and placebo groups (23). Overall, studies included middle-aged and elderly individuals, between 61 and 73 years of age, with predominant male representation (Table I). Furthermore, the majority of the studies included patients with diabetes only (25,28,29,31-41), while a reasonable number of studies analyzed both diabetic and non-diabetic patients (23,24,26,27,30,42-50). BMI also markedly ranged from average (<25 kg/m^2) to obese (35.1 kg/m^2) (23,39). Among the comorbidities, hypertension and kidney-associated diseases were the most prevalent (Table I). In addition, a number of studies focused on patients with an LVEF of <45 or <40% (23,27,32,36,42-44,47,48,50), while one study focused on the preserved or reduced range of ejection fraction and one study gave chronic kidney disease (CKD) stage information (49), as described in Table I.

Characteristics of intervention and control groups. Among SGLT2i, the most commonly used agents were empagliflozin (26,27,29,34,35,40-45), dapagliflozin (23,30,31,36,46-50) and canagliflozin (24,25,28,37-39), while other less frequently used agents included ertugliflozin and sotagliflozin (32,33). Most agents were administered orally once daily; however, a wide range was observed in the dosages administered, depending on the agent. Empagliflozin was administered at a dose of 10 or 25 mg, dapagliflozin at 10 mg and canagliflozin at either 100 or 300 mg, as described in Table II. Variation was also observed in the treatment durations, ranging from 14 days (33,38,40,41,44) to 2.6 years (34). Across all included studies, a standard-of-care was used as a comparison group, ensuring consistency in comparative evaluation (Table II).

Outcomes. Overall, the majority of the studies reported a significant reduction in hospitalization for HF and CV-associated mortality with the use of SGLT2i, with HR values ranging from 0.51 to 2.64, indicating consistent benefits. Similarly, these agents also demonstrated favorable outcomes in reducing all-cause mortality, although a number of studies reported a neutral impact in reducing these CV-mortality outcomes (33,50). In addition, myocardial infarction rates (in studies that reported them) also demonstrated a non-significant difference (31,33,38,41) between the SGLT2i and

Table II. Summary of intervention and control characteristics.

First author, year	Intervention and control characteristics					
	Agent	Dosage	Administration route	Treatment duration	Control	(Refs.)
Zinman *et al*, 2015	Empagliflozin	10 or 25 mg daily	Oral	14 days	Placebo	(41)
Fitchett *et al*, 2016	Empagliflozin	10 or 25 mg daily	Oral	2.6 years	Placebo	(34)
Neal *et al*, 2017	Canagliflozin	100 or 300 mg daily	Oral	14 days	Placebo	(38)
Wanner *et al*, 2018	Empagliflozin	10 or 25 mg daily	Oral	14 days	Placebo	(40)
Mahaffey *et al*, 2018	Canagliflozin	NA	NA	NA	Placebo	(37)
Kato *et al*, 2019	Dapagliflozin	NA	NA	NA	Placebo	(36)
McMurray *et al*, 2019	Dapagliflozin	10 mg daily	Oral	NA	Placebo	(48)
Wiviott *et al*, 2019	Dapagliflozin	10 mg daily	Oral	NA	Placebo	(31)
Perkovic *et al*, 2019	Canagliflozin	100 mg daily	Oral	NA	Placebo	(28)
Cannon *et al*, 2020	Ertugliflozin	5 or 15 mg daily	Oral	14 days	Placebo	(33)
Heerspink *et al*, 2020	Dapagliflozin	10 mg daily	Oral	2.4 years	Placebo	(30)
Kosiborod *et al*, 2020	Dapagliflozin	10 mg daily	Oral	NA	Placebo	(46)
Inzucchi *et al*, 2020	Empagliflozin	10 or 25 mg daily	Oral	12 weeks	Placebo	(35)
Verma *et al*, 2020	Empagliflozin	10 or 25 mg daily	Oral	NA	Placebo	(29)
Ohkuma *et al*, 2020	Canagliflozin	100 or 300 mg daily	Oral	NA	Placebo	(39)
Bhatt *et al*, 2021	Sotagliflozin	200 mg daily	Oral	NA	Placebo	(32)
McMurray *et al*, 2021	Dapagliflozin	10 mg daily	Oral	NA	Placebo	(49)
Nassif *et al*, 2021	Dapagliflozin	NA	NA	12 weeks	Placebo	(23)
Anker *et al*, 2021	Empagliflozin	10 mg daily	Oral	NA	Placebo	(42)
Anker *et al*, 2021	Empagliflozin	10 mg daily	Oral	NA	Placebo	(43)
Spertus *et al*, 2022	Canagliflozin	100 mg	Oral	12 weeks	Placebo	(24)
Kosiborod *et al*, 2022	Empagliflozin	10 mg daily	Oral	90 days	Placebo	(45)
Solomon *et al*, 2022	Dapagliflozin	10 mg daily	Oral	NA	Placebo	(50)
Herrington *et al*, 2023	Empagliflozin	10 mg daily	Oral	NA	Placebo	(26)
Hernandez *et al*, 2024	Empagliflozin	10 mg daily	Oral	14 days	Placebo	(44)
McMurray *et al*, 2024	Dapagliflozin	NA	NA	NA	Placebo	(47)
Vaduganathan *et al*, 2024	Canagliflozin	100 or 300 mg daily	Oral	NA	Placebo	(25)
Petrie *et al*, 2025	Empagliflozin	10 mg daily	Oral	NA	Placebo	(27)

NA, not available.

placebo groups. However, quality of life was improved after the administration of SGLT2i agents, as observed through improved scores based on the KCCQ (Table III). A wide range was observed in the follow-up duration of these trials, with most studies having reported >1 year of follow-up (26-28,30, 33,34,36,38,41,42,44,47,48) and one study following up for <1 year (32). The most commonly occurring adverse events associated with SGLT2i were genital mycotic infections, urinary tract infections, volume depletion/hypotension, acute kidney injury (AKI), lower limb amputation, severe hypoglycemia, ketoacidosis and hypovolemia (Table III). Overall, these results consistently supported the efficacy and safety of SGLT2i in improving HF-associated outcomes in patients with or without diabetes.

Hospitalization for HF. Among patients with HF who had diabetes and were treated with empagliflozin, the risk of first hospitalization for HF was significantly reduced by 24% (OR=0.76; 95% CI: 0.64-0.91; P=0.002; I^2=0%; Fig. 2). In addition, the risk of hospitalization for total HF was reduced by 34% (OR=0.66; 95% CI: 0.60-0.71; P<0.00001; I^2=0%), when patients were treated with empagliflozin. Similarly, a significant reduction of 27% (OR=0.73; 95% CI: 0.64-0.83; P<0.00001) was observed when patients were treated with dapagliflozin, with moderate heterogeneity (I^2=44%). In addition, other SGLT2i, such as ertugliflozin and sotagliflozin, also resulted in a significant reduction of 41% in the risk of hospitalization for HF (OR=0.59; 95% CI: 0.43-0.81; P=0.001), with a notable heterogeneity (I^2=70%). Overall, the pooled effect size

Table III. Summary of outcomes associated with the application of sodium-glucose cotransporter 2 inhibitors.

	Outcomes								
First author, year	Hospitalization for total HF	CV mortality	All-cause mortality	Myocardia infraction	QoL (KCCQ)	Follow-up	Adverse events	Conclusion	(Refs.)
Zinman *et al*, 2015	0.65 (95% CI: 0.50-0.85)	0.62 (95% CI: 0.49-0.77)	0.68 (95% CI: 0.57-0.82)	0.87 (95% CI: 0.70-1.09)	NA	206 weeks	UTI	Empagliflozin was found effective in reducing primary CV outcomes	(41)
Fitchett *et al*, 2016	0.65 (95% CI: 0.50-0.85)	0.66 (95% CI: 0.55-0.79)	0.68 (95% CI: 0.57-0.82)	NA	NA	3.1 years	Adverse events occurred in both groups, like hypoglycemia	Empagliflozin effectively reduced HF hospitalization and CV mortality	(34)
Neal *et al*, 2017	NA	0.87 (95% CI: 0.72-1.06)	0.87 (95% CI: 0.74-1.01)	0.86 (95% CI: 0.75-0.97)	NA	188.2 weeks	Volume depletion, kidney problems, diuresis	Canagliflozin successfully lowered the risk of CV events	(38)
Wanner *et al*, 2018	0.61 (95% CI: 0.42-0.87)	0.71 (95% CI: 0.52-0.98)	0.76 (95% CI: 0.59-0.99)	NA	NA	NA	Acute renal failure, bone fracture, lower limb amputation and hyperkalemia	Empagliflozin improved clinical outcomes	(40)
Mahaffey *et al*, 2018	2.64 (95% CI: 1.90-3.65)	2.51 (95% CI: 1.99-3.16)	1.86 (95% CI: 1.57-2.22)	NA	NA	NA	Amputations, genital infections, fractures, volume depletion and renal adverse events	Canagliflozin reduced CV outcomes	(37)
Kato *et al*, 2019	0.64 (95% CI: 0.43-0.95)	0.55 (95% CI: 0.34-0.90)	0.59 (95% CI: 0.40-0.88)	NA	NA	4.2 years	Major hypoglycemia, amputation, diabetic ketoacidosis, fracture, acute renal failure, genital infection, urinary tract infection	Dapagliflozin reduced CV outcomes	(36)
McMurray *et al*, 2019	0.70 (95% CI: 0.59-0.83)	0.82 (95% CI: 0.69-0.98)	0.83 (95% CI: 0.71-0.97)	NA	NA	18.2 months	Renal dysfunction, hypoglycemia and volume depletion	Dapagliflozin reduced HF in patients with and without diabetes	(48)
Wiviott *et al*, 2019	0.73 (95% CI: 0.61-0.88)	0.83 (95% CI: 0.73-0.95)	0.93 (95% CI: 0.82-1.04)	0.89 (95% CI: 0.77-1.01)	NA	4.2 years	Renal failure and ketoacidosis	Dapagliflozin did not result in a higher or lower rate of MACE than placebo but did result in a lower rate of CV mortality or hospitalization for HF	(31)
Perkovic *et al*, 2019	0.61 (95% CI: 0.47-0.80)	0.78 (95% CI: 0.61-1.00)	0.83 (95% CI: 0.68-1.02)	NA	NA	2.62 years	Amputation, fracture, renal cell carcinoma, bladder and breast cancer, acute pancreatitis	Canagliflozin was found to be effective in reducing cardiovascular events and kidney failure events	(28)

Table III. Continued.

First author, year	Outcomes								(Refs.)
	Hospitalization for total HF	CV mortality	All-cause mortality	Myocardia infraction	QoL (KCCQ)	Follow-up	Adverse events	Conclusion	
Cannon *et al*, 2020	0.70 (95% CI: 0.54-0.90)	0.92 (95.8% CI: 0.77-1.11)	0.93 (95% CI: 0.80-1.08)	1.04 (95% CI: 0.86-1.27)	NA	3.5 years	Amputation, UTI, genital mycotic infection, hypovolemia, AKI and diabetic ketoacidosis	Ertugliflozin was non-inferior to placebo with respect to MACE	(33)
Heerspink *et al*, 2020	NA	0.71 (95% CI: 0.55-0.92	NA	NA	NA	2.4 years	Amputation, fracture, renal failure and volume depletion	Dapagliflozin markedly reduced CV outcomes	(30)
Kosiborod *et al*, 2020	NA	0.70 (95% CI: 0.57-0.86)	NA	NA	2.8-point improvement (intervention)	12 months	NA	Dapagliflozin reduced CV mortality and worsening HF across the range of baseline KCCQ	(46)
Inzucchi *et al*, 2020	1.91 (95% CI: 0.96-3.79)	4.00 (95% CI: 2.26-7.11)	NA	NA	NA	NA	Non-fatal myocardial infarction, non-fatal stroke	Empagliflozin effectively improved CV outcomes	(35)
Verma *et al*, 2020	0.53 (95% CI: 0.28-1.01)	0.75 (95% CI: 0.48-1.18)	0.68 (95% CI: 0.48-0.97)	NA	NA	NA	UTI, volume depletion and acute renal failure	Empagliflozin reduced CV outcomes	(29)
Ohkuma *et al*, 2020	0.67 (95% CI: 0.52-0.87)	0.87 (95% CI: 0.72-1.06)	NA	NA	NA	NA	Amputation, fractures, infection, serious hyperkalemia, diabetic ketoacidosis	Canagliflozin improved CV outcomes	(39)
Bhatt *et al*, 2021	0.64 (95% CI: 0.49-0.83)	0.84 (95% CI: 0.58-1.22)	0.82 (95% CI: 0.59-1.14)	NA	4.10 (95% CI: 1.3-7.00)	9 months	Diarrhea, severe hypoglycemia, hypotension and AKI	Sotagliflozin therapy markedly lowered CV mortality and hospitalizations	(32)
McMurray *et al*, 2021	0.51 (95% CI: 0.34-0.76)	0.68 (95% CI: 0.44-1.05)	0.56 (95% CI: 0.34-0.93)	NA	NA	2.4 years	Amputation, fracture, renal adverse events, major hypoglycemia, volume depletion	Dapagliflozin reduced the risk of CV mortality and HF hospitalization	(49)
Nassif *et al*, 2021	NA	NA	Intervention group (0.6%) and control group (1.2%)	NA	5.8 points (95% CI: 2.3-9.2)	12 weeks	AKI, volume depletion and hypoglycemic events, lower limb amputation	Dapagliflozin markedly improved patient-reported symptoms	(23)
Anker *et al*, 2021	0.73 (95% CI: 0.61-0.88)	0.91 (95% CI: 0.76-1.09)	1.00 (95% CI: 0.87-1.15)	NA	HR=1.32 (95% CI: 0.45-2.19)	26.2 months	Uncomplicated genital infections, UTI and hypotension were reported more frequently in the intervention group	Empagliflozin reduced the combined risk of CV mortality or hospitalization for HF	(42)

Table III. Continued.

First author, year	Outcomes								(Refs.)
	Hospitalization for total HF	CV mortality	All-cause mortality	Myocardia infraction	QoL (KCCQ)	Follow-up	Adverse events	Conclusion	
Anker *et al*, 2021	0.70 (95% CI: 0.58-0.85)	0.75 (95% CI: 0.65-0.86)	NA	NA	Difference in change: 1.75 (95% CI: 0.5-3.0)	NA	Hypotension, volume depletion, hypoglycemic events, ketoacidosis and lower limp amputation	Empagliflozin markedly improved CV and renal outcomes	(43)
Spertus *et al*, 2022	NA	NA	NA	NA	KCCQ TSS change: 4.3 points (95% CI: 0.8-7.8) higher in the intervention group	12 weeks	Infections, hypotension, increased urination	Canagliflozin markedly improves symptom burden in HF, regardless of ejection fraction or diabetes status	(24)
Kosiborod *et al*, 2022	NA	NA	NA	NA	Corrected difference: 1.36 win ratio (95% CI: 1.09-1.68)	90 days	NA	Empagliflozin markedly improved symptoms, physical limitations and QoL	(45)
Solomon *et al*, 2022	0.82 (95% CI: 0.73-0.92)	0.88 (95% CI: 0.74-1.05)	0.94 (95% CI: 0.83-1.07)	NA	Corrected difference: 2.4 points (95% CI: 1.5-3.4)	2.3 years	Amputation, hypergly cemic events, ketoacidosis and volume depletion	Dapagliflozin reduced the risk of worsening HF or CV mortality	(50)
Herrington *et al*, 2023	NA	0.84 (95% CI: 0.60-1.19)	0.87 (95% CI: 0.70-1.08)	NA	NA	2 years	UTI, genital infection, hyperkalemia, AKI, liver injury, lower limb amputation, fractures and severe hypoglycemia	Empagliflozin was found to be effective for reducing risk of progression of kidney diseases and cardiovascular deaths	(26)
Hernandez *et al*, 2024	First inter-vention group (118/3,260) and control group (153/3, 262); total inter vention group (148/3, 260) and control group (207/3,262)	Intervention group (280/3,260) and control group (338/3,262)	Intervention group (20/3,260) and control group (30/3,262)	NA	NA	17.9 months	Intervention group, cardiac failure and cardiogenic shock; control group, cardiac failure, cardiogenic shock and acute pulmonary edema	Empagliflozin reduced the risk of HF	(44)

Table III. Continued.

First author, year	Outcomes								(Refs.)
	Hospitalization for total HF	CV mortality	All-cause mortality	Myocardia infraction	QoL (KCCQ)	Follow-up	Adverse events	Conclusion	
McMurray *et al*, 2024	NA	NA	NA	NA	KCCQ-TSS corrected difference after 16 weeks: 4.2 (95% CI:1.0-8.2) favoring dapagliflozin; KCCQ-PLS: 4.2 (95% CI: 0.0-8.3)	16 weeks	Adverse events occurred in both groups	Dapagliflozin improved the KCCQ-TSS in patients with HF with reduced ejection fraction, but did not improve KCCQ-PLS	(47)
Vaduganathan *et al*, 2024	Intervention group (304) and control group (368)	NA	NA	NA	NA	2.5 years	NA	Canagliflozin reduced the total burden of HF hospitalizations	(25)
Petrie *et al*, 2025	First HR=0.77 (95% CI: 0.60-0.98); total HR=0.67 (95% CI: 0.50-0.89)	NA	HR=0.96 (95% CI: 0.78-1.19)	NA	NA	17.9 months	AKI, hypotension, volume depletion, hypoglycemia, hepatic injury and ketoacidosis	Empagliflozin reduced first and total HF hospitalizations	(27)

HR, hazard ratio; NA, not available; HF, heart failure; KCCQ, Kansas City Cardiomyopathy Questionnaire; TSS, total symptom score; PLS, physical limitation score; UTI, urinary tract infection; AKI, acute kidney incidence; MACE, major adverse cardiac events; QoL, quality of life; CV, cardiovascular.

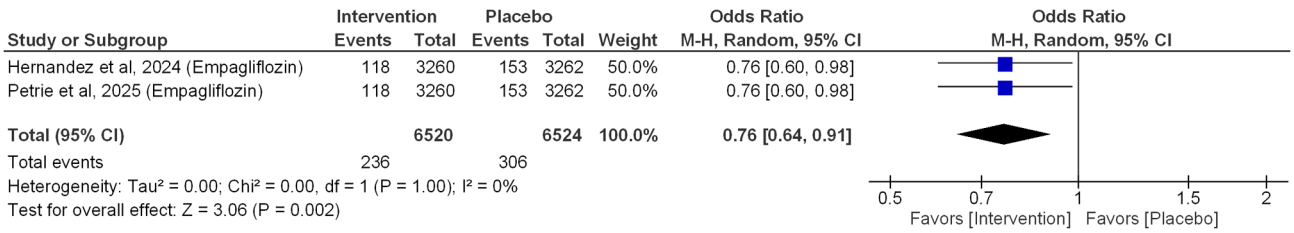

Figure 2. Forest plot outlining the effect of sodium-glucose cotransporter 2 inhibitors compared with a placebo on the composite of first heart failure hospitalizations in the overall cohort of patients with or without diabetes mellitus. M-H, Mantel-Haenszel; df, degrees of freedom.

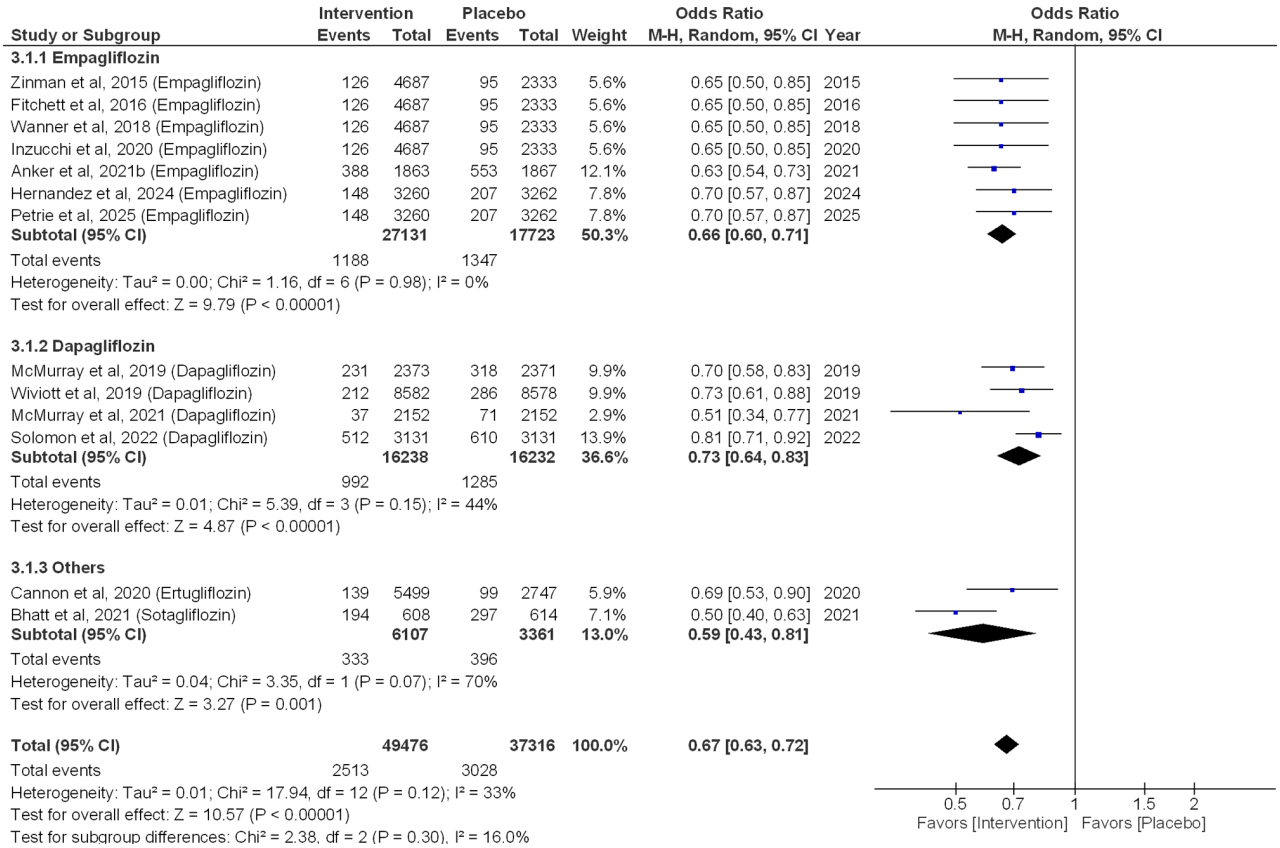

Figure 3. Forest plot outlining the effect of sodium-glucose cotransporter 2 inhibitors compared with a placebo on the composite of total heart failure hospitalizations in the overall cohort of patients with or without diabetes mellitus. M-H, Mantel-Haenszel; df, degrees of freedom.

(OR=0.67; 95% CI: 0.63-0.72; P<0.00001; I^2=33%) indicated that SGT2i effectively reduced the risk of hospitalization for HF by 33%, as shown in Fig. 3.

All-cause mortality and CV mortality. Among patients with HF who had diabetes, empagliflozin significantly reduced the risk of all-cause mortality by 47% (OR=0.53; 95% CI: 0.36-0.78; P=0.001; I^2=93%; Fig. 4). Dapagliflozin also resulted in a significant reduction in all-cause mortality by 9% (OR=0.91; 95% CI: 0.84-0.99; P=0.03; I^2=0%). Other SGLT2i, such as sotagliflozin, ertugliflozin and canagliflozin, also led to a significant reduction in all-cause mortality by 12% (OR=0.88; 95% CI: 0.78-0.99; P=0.04, I^2=0%). Overall, a 28% reduction was observed in all-cause mortality when patients were treated with SGLT2i (OR=0.72; 95% CI: 0.61-0.86; P=0.0002; I^2=88%), as illustrated in Fig. 4.

Similarly, regarding CV mortality, the risk was reduced by 31% (OR=0.69; 95% CI: 0.62-0.76; P<0.00001; I^2=40%) when patients were treated with empagliflozin. Patients treated with dapagliflozin exhibited a significant 14% reduction in CV-associated mortality (OR=0.86; 95% CI: 0.76-0.97; P=0.01; I^2=33%). Similarly, patients treated with other SGLT2i (sotagliflozin, ertugliflozin and canagliflozin) exhibited a non-significant 13% reduction (OR=0.87; 95% CI: 0.75-1.00; P=0.05; I^2=0%). Overall, the pooled effect size (OR=0.76; 95% CI: 0.70-0.83; P<0.00001; I^2=57%) indicated that SGLT2i effectively reduced the risk of CV-associated mortality by 24%, as shown in Fig. 5.

Adverse events. Within the empagliflozin treatment group, a non-significant 52% reduction in the risk of adverse events was demonstrated (OR=0.48; 95% CI: 0.23-1.01; P=0.05; I^2=99%). Dapagliflozin (OR=0.93; 95% CI: 0.83-1.03; P=0.14;

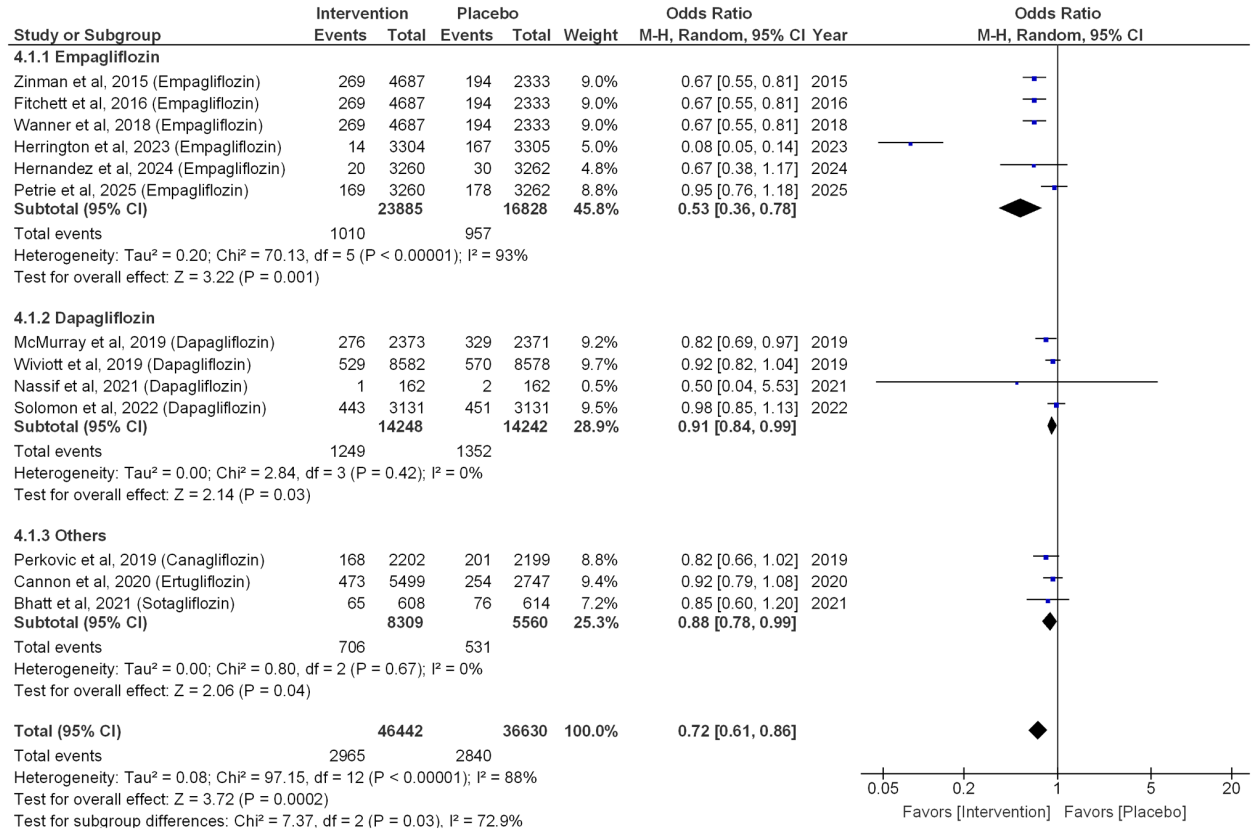

Figure 4. Forest plot outlining all-cause mortality when both diabetic and non-diabetic patients were treated with sodium-glucose cotransporter 2 inhibitors compared with a placebo. M-H, Mantel-Haenszel; df, degrees of freedom.

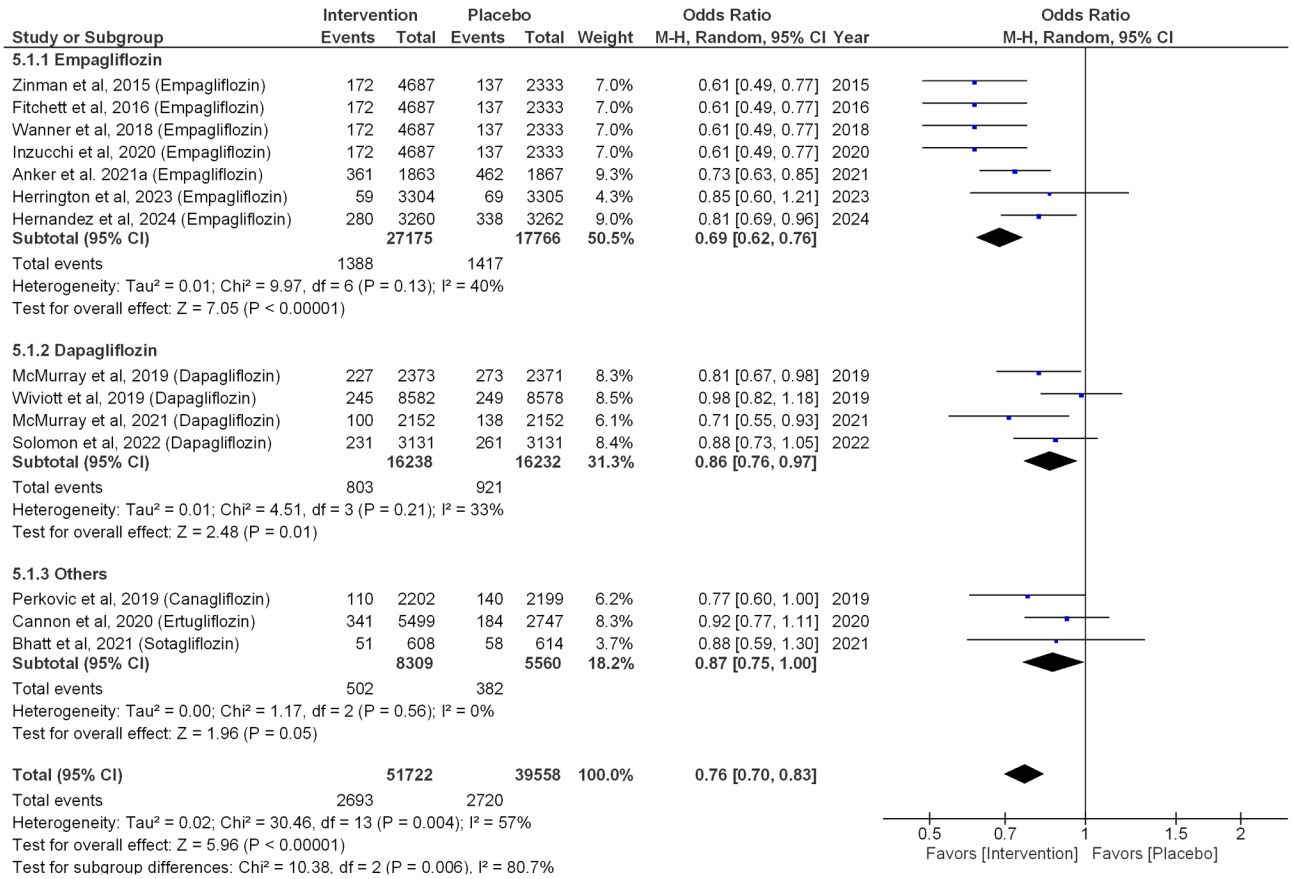

Figure 5. Forest plot outlining cardiovascular-associated mortality when both diabetic and non-diabetic patients were treated with sodium-glucose cotransporter 2 inhibitors compared with a placebo. M-H, Mantel-Haenszel; df, degrees of freedom.

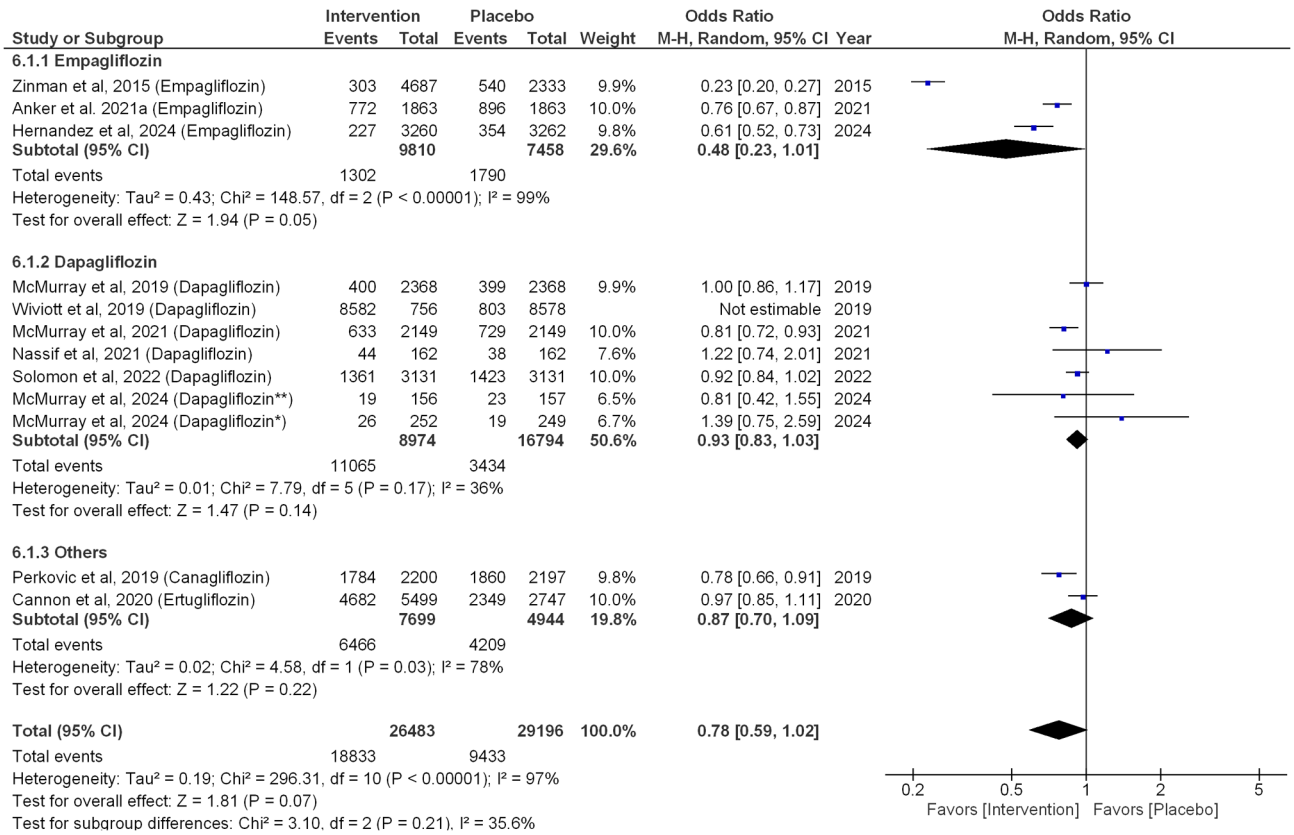

Figure 6. Forest plot outlining the adverse events in diabetic and non-diabetic patients when treated with sodium-glucose cotransporter 2 inhibitors compared with a placebo. *Preserved ejection fraction and **reduced ejection fraction. M-H, Mantel-Haenszel; df, degrees of freedom.

I^2=36%) and other SGLT2i, such as ertugliflozin and ertugliflozin (OR=0.87; 95% CI: 0.70-1.09; P=0.22; I^2=78%), did not significantly reduce the risk of adverse events compared with that in the placebo group. Overall, the pooled effect size for adverse events (OR=0.78; 95% CI: 0.59-1.02; P=0.07; I^2=97%), indicated that SGLT2i non-significantly reduced the risk of adverse events by 22% compared with that in the placebo group (Fig. 6).

Methodological quality assessment. Overall, the majority of included studies exhibited a low risk of bias in the randomization process, deviations from intended interventions, missing outcome data, measurement of the outcome and reporting results domains. However, a total of 4 studies exhibited a high risk of bias in the randomization domain (31,36,45,46), while 5 studies exhibited some concerns in the randomization domain (25,34,37,44,49), as illustrated in Fig. 7.

Publication bias. The Egger's regression test for publication bias regarding the first hospitalization for HF was not performed due to the presence of <10 studies. However, for total hospitalization for HF (t=-2.21; P=0.048), the distribution of studies appeared relatively asymmetrical around the effect size line, suggesting a high publication bias (Fig. 8A). On the other hand, the distribution of studies for all-cause mortality (t=-2.10; P=0.058), CV-associated mortality (t=-0.72; P=0.479) and adverse events (t=-0.01; P=0.988) appeared relatively symmetrical around the effect size line, suggesting a low publication bias (Fig. 8B-D).

Source of heterogeneity. However, despite efforts to further investigate potential sources of heterogeneity, the available data did not allow more conclusive results to be drawn, as the included studies did not provide sufficient association data to evaluate the sources of heterogeneity (such as the impact of age and sex of patients, drug type, comorbidities, diabetes status and follow-up durations on the outcomes). As a result, the sources of heterogeneity could not be examined further despite a number of studies providing basic demographic information, including age and sex.

Certainty of evidence. Outcomes, including the impact of SGLT2i on hospitalization for HF (first and total), mortality (all-cause and CV-associated) and adverse events in patients with or without diabetes, were assessed in the domain of risk of bias, inconsistency, indirectness, imprecision and publication bias. Total hospitalization for HF, all-cause mortality and adverse events were assessed in these domains and rated with low certainty due to the presence of high heterogeneity and publication bias, while, CV-associated mortality had moderate certainty due to moderate heterogeneity. Furthermore, a high certainty was present for the first hospitalization for HF, which may be due to the limited number of studies, as publication bias test could not be assessed (Table IV).

Discussion

Encompassing data from 28 studies, the present comprehensive meta-analysis provided robust evidence regarding the clinical

Figure 7. Methodological quality assessment of included randomized controlled trials.

benefits of SGLT2i across diabetic and non-diabetic populations with HF. The outcomes of the present meta-analysis indicated that SGLT2i were significantly associated with a relative risk reduction in the composite endpoint of first and total hospitalizations for HF in patients with and without diabetes by 24 and 33%, respectively. Similarly, pooled analysis

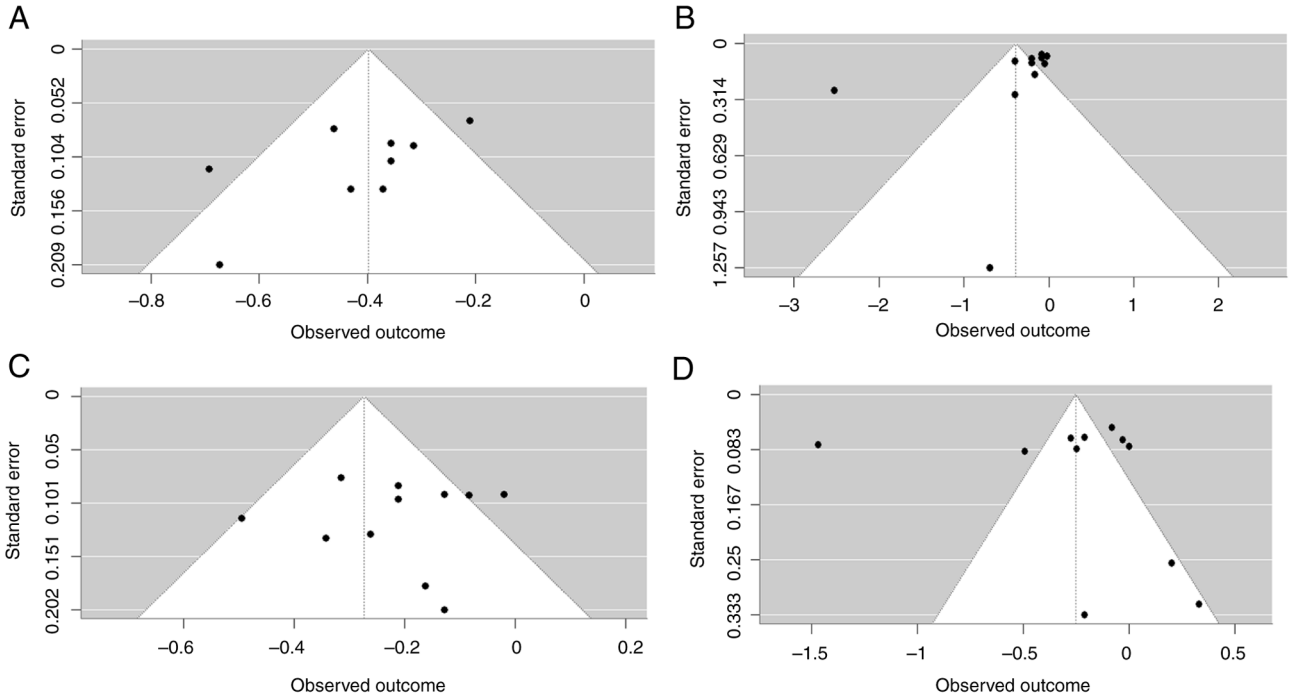

Figure 8. Publication bias among the included studies. (A) Total hospitalization for heart failure, (B) all-cause mortality, (C) cardiovascular-associated mortality and (D) adverse events associated with the administration of sodium-glucose cotransporter 2 inhibitors.

for all-cause mortality and CV-associated mortality also demonstrated a significantly reduced risk in patients treated with SGLT2i by 28 and 24%, respectively. In addition, the risk of adverse events was reduced by 22% in the SGLT2i-treated intervention group compared with that in the placebo group; however, this result was not significant. Furthermore, the majority of studies exhibited a low risk of bias, except for a small number of studies, which exhibited a high risk of bias or some concerns in the randomization process. This was due to these studies not mentioning or explaining the process used for randomization. For example, these studies (31,36,45,46) did not use a computer-generated randomization process or any other standard procedure, like random number generators, flip coin method, or block randomization. This may have influenced the reliability of the pooled estimates, thereby underestimating the true effect of treatment. However, most overall outcomes were found without any publication bias, except for total hospitalizations, which likely reflects an over-representation of studies reporting significant reductions in total hospitalizations, while studies with non-significant outcomes may remain unpublished or less accessible. Due to this reason, positive findings may skew the pooled effect estimate, indicating treatment to be more effective than the true effect estimates if non-significant outcomes were included. Therefore, the total hospitalization outcome in particular should be interpreted with caution.

The present findings align with those of a previous meta-analysis, which included 15 studies and observed a 29% (HR=0.71; 95% CI: 0.67-0.77) reduction in the risk of first hospitalization for HF in patients with diabetes treated with SGLT2i. Similarly, CV-associated mortality was also reduced by 14% (HR=0.86; 95% CI: 0.79-0.93) (51). The main difference between the present study and this previous meta-analysis was the larger number of studies being included in the present analysis, making it more reliable. In addition, another difference was the inclusion of both diabetic and non-diabetic patients in the present study. Similarly, another previous meta-analysis included 8 studies, observing a reduced relative risk in CV-associated mortality and HF hospitalizations by 20% (52). The main difference between this study and the present meta-analysis is both the number of studies included in the analysis and the parameters examined, such as adverse events, and all-cause mortality. Greene *et al* (53) demonstrated that diabetic and non-diabetic patients with HF exhibit an annual mortality rate of 8-10%, even in the presence of sTable symptoms. In addition, nearly one in four patients either succumb to the disease or are re-hospitalized within 30 days of a previous hospitalization for HF. These findings provide support for the use of SGLT2i in reducing both hospitalization for HF and CV mortality in this population. Although absolute event rates varied across the trials, from ~35 per 1,000 patient-years in the EMPA-REG OUTCOME (41), CANVAS (38) and EMPEROR-preserved trials to >120 per 1,000 patient-years in the SOLOIST-WHF trial, low heterogeneity in the treatment effects suggests the applicability of these findings across a wide risk spectrum (32).

The benefits of SGLT2i are likely multifactorial and may include favorable effects on cardiac remodeling. In addition, in patients with diabetes, SGLT2i were found to be effective in reducing both first and total hospitalizations for HF and in reducing all-cause and CV-associated mortality. Diabetes has been shown to significantly elevate the HF risk by ~2-fold in men and 5-fold in women (54). The observed benefits in these patients appear to be largely independent of glycemic control, as the outcomes did associate with the changes in HbA1c across the trial (55). Instead, these effects may be attributable to cardiorenal (55) and systemic hemodynamic mechanisms (56).

Table IV. Summary of the certainty of evidence.

Outcomes	Number of studies	RoB	Inconsistency	Indirectness	Imprecision	Publication bias	Effect size (OR)	Certainty of evidence
First hospitalization for HF	Empagliflozin (n=2)	Low to some concerns	Not serious (I^2=0%)	Not serious	Not serious	Not assessed	0.76 (95% CI: 0.64-0.91)	High ΘΘΘ
Total hospitalization for HF	Empagliflozin (n=7), dapagliflozin (n=4) and others (n=2)	Low to high	Partially serious (I^2=33%)	Not serious	Not serious	Present	0.67 (95% CI: 0.63-0.72)	Low Θ
All-cause mortality	Empagliflozin (n=6), dapagliflozin (n=4) and others (n=3)	Low to high	Serious (I^2=88%)	Not serious	Not serious	Absent	0.72 (95% CI: 0.61-0.86)	Low Θ
CV-associated mortality	Empagliflozin (n=7), dapagliflozin (n=4) and others (n=3)	Low to high	Serious (I^2=57%)	Not serious	Not serious	Absent	0.76 (95% CI: 0.70-0.83)	Moderate ΘΘΘ
Adverse events	Empagliflozin (n=3), dapagliflozin (n=7) and others (n=2)	Low to high	Serious (I^2=97%)	Not serious	Not serious	Absent	0.78 (95% CI: 0.59-1.02)	Low Θ

OR, odds ratio; RoB, risk of bias; HF, heart failure; CV, cardiovascular; Θ, level of certainty.

Within this bidirectional pathophysiologic relationship, use of SGLT2i emerges as a safe and effective therapeutic strategy.

Furthermore, a 22% reduction in adverse events was observed in the SGLT2i-treated groups in the present study, which is consistent with another recent meta-analysis showing that SGLT2i markedly reduced the risk of kidney disease progression and AKI across a broad spectrum of renal functions (diabetic kidney disease or nephropathy, ischemic and hypertensive kidney disease), irrespective of T2DM status (57). SGLT2i can improve CV-associated outcomes by blocking glucose and sodium reabsorption in the proximal renal tubules, causing increased urinary excretion of both glucose and sodium, which reduces preload and afterload through natriuresis and diuresis, lowering interstitial fluid volume without notable electrolyte loss or disturbance (58). This reduction in sodium reabsorption also reduces renal oxygen demand and improves tubuloglomerular feedback by reabsorption in the proximal tubule, increasing sodium delivery to the macula densa and contributing to improved heart function (59). In addition, SGLT2i also enhances myocardial energy efficiency, and reduces fibrosis by downregulating pro-inflammatory pathways (IL-6, TNF-alpha), cardiac inflammation and oxidative stress whilst improving endothelial function, collectively leading to reduced hospitalization and mortality rates in both populations exhibiting HF with reduced ejection fraction and HF with preserved ejection fraction (60). SGLT2i improve glycemic control and reduce glucotoxicity in diabetic patients, while in non-diabetic patients, the mechanisms are primarily hemodynamic and metabolic, independent of glucose lowering (61,62).

Low-to-high heterogeneity was observed in the present meta-analysis, which can be attributed to a number of reasons. For example, baseline LVEF and presence of comorbidities, such as CKD, are critical modifiers of the treatment response. In the present study, these factors were not considered due to the unavailability of uniform data for performing subgroup analysis. These factors suggest that the response of patients with reduced and preserved ejection fraction towards treatment may be different, with studies indicating greater relative benefits in HF with reduced ejection fraction (51,63). Similarly, CKD severity can also markedly affect both the efficacy and safety of SGLT2i, as renal function impacts drug pharmacodynamics and the associated metabolic responses (64).

The findings of the present meta-analysis may have important clinical implications for the management of HF in patients with or without diabetes, as a significant reduction in the risk of hospitalizations for HF, mortality and adverse events was observed in the SGLT2i-treated groups. These outcomes strongly suggest the routine incorporation of SGLT2i into HF treatment protocols for both diabetic and non-diabetic patients.

The present study exhibits a number of strengths, such as the inclusion of a large number of RCTs with diverse populations from across the globe, enhancing the generalizability of the present findings across both diabetic and non-diabetic patients with HF. In addition, the present study also focused on key outcomes, such as first and total hospitalizations for HF, all-cause mortality, CV mortality and adverse events associated with the administration of SGLT2i. Another strength may lie in the inclusion of studies with a low risk of bias. However, certain limitations should be considered

during interpretation of the results. Firstly, high heterogeneity was observed among the studies, which can affect the generalizability of the outcomes. This may have been due to the included population, as in certain studies only diabetic patients were considered, while in other studies, both diabetic and non-diabetic patients were included. The heterogeneity may have also been impacted by the exclusion of non-English studies. Another limitation may be the administration of varying SGLT2i with different dosages and follow-up durations, which were found to be non-consistent across all studies. Secondly, a meta-analysis could not be performed regarding the impact of LVEF and comorbidities such as CKD, due to the unavailability of consistent data, which may have influenced the outcomes of the present study. Thirdly, subgroup analysis between diabetic and non-diabetic patients could not be performed, as HR values were presented as composite measures that combined different clinical outcomes (such as HF hospitalization and mortality), making them unsuitable for pooling in a meaningful or methodologically sound subgroup analysis. In addition, the reporting across studies lacked sufficient consistency in outcome definitions (assessment tools used for assessment of clinical outcomes, like hospitalization) and stratification, further limiting the feasibility of combining these data. Therefore, incorporating composite HRs that merge numerous endpoints would affect or compromise the clarity and validity of the present findings. Future studies are required to elucidate the general understanding of the cardioprotective mechanisms and long-term safety of SGLT2i.

In conclusion, the findings of the present meta-analysis provided marked evidence that SGLT2i significantly reduce the risk of first and total hospitalizations for HF, all-cause mortality and CV mortality in both diabetic and non-diabetic patients with HF. However, a non-significant reduction in adverse events was observed. The consistent benefits demonstrated across a wide range of clinical outcomes and populations highlight the therapeutic importance of SGLT2i as a treatment in HF management, supporting their clinical relevance and routine use in improving outcomes. Future meta-analyses should aim to focus on broader HF populations, including those with preserved ejection fraction and numerous comorbidities. In addition, the mechanism behind the cardioprotective impact of SGLT2i in non-diabetic patients should be examined.

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Availability of data and materials

The data generated in the present study may be requested from the corresponding author.

Authors' contributions

DAB and NHA conceptualized and designed the present study, contributed to data analysis, interpretation and curation, created graphs, contributed to the interpretation of results and served a key role in writing the manuscript. DAB and NHA confirm the authenticity of all the raw data. Both authors have read and approved the final version of the manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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