Meta-Analysis on the Safety and Efficacy of Sodium Glucose Cotransporters 2 Inhibitors in Patients With Heart Failure With and Without Diabetes

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Heart failure (HF) is the most common cardiovascular cause of hospitalization in patients over 60 years, affecting about 64.3 million patients worldwide. Few studies have investigated the role of sodium glucose cotransporter inhibitors (SGLT2Is) in patients with HF without and without diabetes. Thus, we conducted our meta-analysis to further investigate the role of SGLT2I role in patients with HF without and without diabetes. PubMed, Scopus, Web of Science, and Embase were searched. All clinical trials that compared the effect of SGLT2Is versus placebo on patients with HF were included. Dichotomous data were extracted, pooled as risk ratio (RR) with 95% confidence interval (CI), and analyzed using RevMan version 5.3 for windows using the Mantel-Haenszel method. A total of 13 randomized clinical trials were included for analysis, with a total number of 75,287 patients. SGLT2Is significantly lowered the risk of hospitalization for HF in patients with (RR = 0.68, 95% CI 0.63 to 0.74) and without diabetes (RR = 0.75, 95% CI 0.62 to 0.89). Furthermore, they lowered the mortality risk in both patients with diabetes with statistical significance (RR = 0.87, 95% CI 0.77 to 0.99), yet without statistical significance in patients without diabetes (RR = 0.93, 95% CI 0.70 to 1.23). Further analyses for serious adverse events were conducted, and SGLT2I showed a significant lower risk in patients with diabetes (RR = 0.94, 95% CI 0.90 to 0.98) and without diabetes (RR = 0.72, 95% CI 0.38 to 1.39). in patients with diabetes, SGLT2Is significantly reduced cardiovascular mortality, HHF, and serious adverse events. However, in patients without, despite showing a significant reduction in HHF, SGLT2I reduced cardiovascular mortality or serious adverse events but without statistical significance. **(Am J Cardiol 2022;187:1−7)**

Affecting 64.3 million patients worldwide, heart failure (HF) is the most common cardiovascular cause of hospitalization in patients over 60 years.[1,2] It has a poor prognosis, with a 30-day readmission rate for all-cause mortality of 19% in the United States.[1,3] Loop diuretics are strongly suggested to reduce edema and congestion, which are key predictors for HF prognosis.[4,5] Furthermore, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, and β blockers are strongly advised to increase survival and decrease hospitalizations for HF.[5] However, recently, Food and Drug Administration-approved angiotensin receptor neprilysin inhibitors, such as sacubitril/valsartan, has substituted angiotensin-converting enzyme inhibitors and angiotensin receptor blockers in their conjunction usage with the standard HF treatments because of its efficacy in managing patients with HF, especially those with not only reduced but also preserved ejection fraction.[6] In addition, sodium glucose cotransporter inhibitors (SGLT2Is) have been introduced because of its effects in HF prevention and reduction of cardiovascular mortality and hospitalization.[6,7] Because they act in the kidneys by inhibiting glucose and sodium reabsorption in the proximal tubules,[8,9] the increased electrolyte-free water clearance and plasma osmolality help remove the interstitial fluid. However, the reduction of interstitial fluid-to-blood volume in patients with HF is still unknown. Several studies supported using SGLT2Is in patients with HF without as well.[10,11] Thus, in our meta-analysis, we aimed to further investigate the differential efficacy of SGLT2I on patients with and without diabetes.

Methods

This study was reported according to the Cochrane Handbook for Systematic Reviews of Interventions and Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines[12,13] and was registered with doi: 10.17605/OSF.IO/QBVGA.

We searched PubMed, Scopus, Web of Science, and Embase until September 1, 2022, using the following Medical Subject Headings terms: (Sodium-Glucose Transporter

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See page 5 for disclosure information.

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2 Inhibitors OR Sodium-Glucose Transporter 2 Inhibitor OR SGLT 2 Inhibitors OR Gliflozins OR Gliflozin OR SLC5A2 Protein OR Canagliflozin Hemihydrate OR Invokana OR Canagliflozin Anhydrous OR 1-Glucopyranosyl-4-methyl-3-5-4-fluorophenyl-2-thienylmethylbenzene OR Dapagliflozin OR Farxiga OR Forxiga OR empagliflozin OR Jardiance) AND (Cardiac Failure OR Heart Decompensation OR Right-Sided Heart Failure OR Myocardial Failure OR Congestive Heart Failure OR Left-Sided Heart Failure). The Medical Subject Headings database was used. No language or publication period restrictions were used. In addition, the references of included studies were scanned to identify any missed articles that may be relevant to our research question.

All clinical trials that compared SGLT2Is (empagliflozin, dapagliflozin, canagliflozin, ertugliflozin, sotagliflozin) versus placebo in patients with HF (with or without diabetes) and were published in the English language in a peer-reviewed journal were included. Articles in a non-English language, abstracts, and designs other than clinical trials were excluded. A total of 2 independent authors applied the selection criteria in 2 stages (title and abstract screening and full-text screening) to determine the included studies. A third author resolved any disagreement to reach a consensus.

A total of 2 independent authors extracted the following data: (1) characteristics of study design; (2) characteristics of patients; (3) risk of bias domains; and (4) the outcomes, including hospitalization for HF (HHF), urgent HF visit, stroke, total mortality, cardiovascular mortality, myocardial infarction (MI), serious adverse event, and adverse event leading to drug discontinuation. No missing data necessitated contacting the corresponding authors of each article included.

Cochrane risk of bias assessment tool, described in chapter 8.5 of the Cochrane handbook, was used.[13] It can detect 5 types of bias: selection, performance, detection, attrition, and reporting. The included articles were classified as low, high, or unclear risk of bias in each domain. Publication bias was assessed using the Egger test for funnel plot asymmetry.[14]

RevMan version 5.3 for windows was used. Dichotomous data were extracted and pooled as risk ratio (RR) with 95% confidence interval (CI) using Mantel-Haenszel method. The chi-square test assessed heterogeneity, and the I^2 test determined the magnitude. According to the Cochrane handbook,[13] heterogeneity was significant if the chi-square value was below 0.1. The I^2 test was interpreted as follows: not important (0% to 40%), moderate heterogeneity (30% to 60%), and substantial heterogeneity (50% to 90%). In the case of significant heterogeneity, the random-effects model was used. Otherwise, the fixed-effects model was used.

Results

Our study was conducted according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines (Supplementary Figure 1) Supplementary Table 1. Our search retrieved 1,643 unique articles. After the title and abstract screening, 123 articles were retrieved and assessed for eligibility. Finally, 13 randomized controlled trials[10,11,15–25] were included for analysis, with a total of 75,287 patients (41,054 in the SGLT2Is group and 34,233 in the placebo group). Baseline and summary of included studies are reported in Table 1.

All included studies had a low risk of bias regarding random sequence generation, allocation concealment, blinding of outcome assessment, and selective reporting, except for EMPEROR-Preserved[11] and VERTIS CV trials,[17] which were unclear regarding allocation concealment and

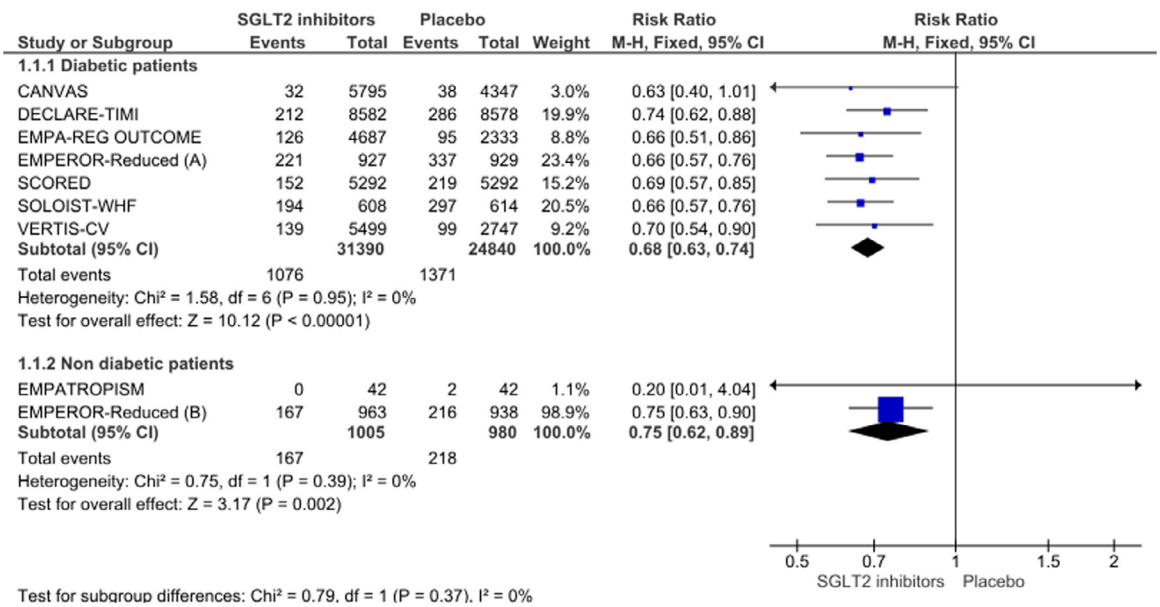

Figure 1. Analysis for hospitalization for heart failure. M-H = Mantel-Haenszel.

Table 1
Baseline characteristics and summary of included studies

Study ID	Groups	Sample size	Age mean (SD), years	Diabetes, n(%)		HbA1c, mean(SD) (%)	BMI (kg/m^2), mean(SD)	Sex, n(%)		LVEF, mean(SD)	HFpEF; n(%)	HFrEF n(%)	NT-proBNP,, pg/ml, median (interquartile range)	eGFR, mean(SD), mL/min/1.73 m	Change in quality of life,KCCQ-12, mean (SD)	Heart failure medications, n (%)			
				Diabetic	Non-Diabetic			Male	Female							ACE inhibitor ARB		ARNI	Mineralocorticoid receptor antagonist
EMPATROPISM	Empagliflozin	42	64.2 (10.9)	NA	42 (100)	5.8 (0.3)	29.3 (6)	27 (64.2)	15 (35.8)	36.2 (8.2)	NA	42 (100)	NA	80 (21)	21±18	16 (38)		21 (50)	13 (31)
	Placebo	42	59 (13.1)	NA	42 (100)	5.8 (0.3)	84.1 (21.6)	27 (64.2)	15 (35.8)	36.5 (8)	NA	42 (100)	NA	83 (23)	1.9±15	19 (45)		15 (36)	15 (36)
EMPEROR-Preserved	Empagliflozin	2997	71.8 (9.3)	1466 (48.9)	1531 (51.1)	NA	29.77 (5.8)	1659 (55.4)	1338 (44.6)	54.3 (8.8)	2997 (100)	NA	994 (501−1740)	60.6 (19.8)	NA	2428 (81.1)			(1119)37.3
	Placebo	2991	71.9 (9.6)	1472 (49.2)	1519 (50.8)	NA	29.90 (5.9)	1653 (55.3)	1338 (44.7)	54.3 (8.8)	2991 (100)	NA	946 (498−1725)	60.6 (19.9)	NA	(2404)80.4			1125 (37.6)
EMPEROR-Reduced	Empagliflozin	1863	67.6 (11.6)	927 (50)	936 (50)	5.8 (0.4)	27.2 (5.3)	1426 (76.5)	437 (23.5)	27.9 (6.0)	NA	1863 (100)	1887 (1077-3429)	62.7 (21.1)	5.8 (0.4)	876 (46.5)	451 (24.2)	340 (18.2)	1306 (70.1)
	Placebo	1867	66.3 (12.0)	929 (50)	938 (50)	5.7 (0.4)	27.0 (5.2)	1411 (75.6)	456 (24.4)	27.2 (6.0)	NA	1867 (100)	1926 (1153-3525)	63.0 (21.0)	4.1 (0.4)	836 (44.8)	457 (24.5)	387 (20.7)	1355 (72.6)
SOLOIST-WHF	Sotagliflozin	608	69 (63−76)*	608 (100)	NA	NA	30.4 (26.3−34.3)*	410 (67.4)	198 (32.6)	35 (28−47)*	494 (40.5)	725 (59.5)	1816.8 (854.7−3658.5)	49.2 (39.5−61.2)*	17.7	254 (41.8)	245 (40.3)	93 (15.3)	403 (66.3)
	Placebo	614	70 (64−76)*	614 (100)	NA	NA	31.1 (27.3−34.5)*	400 (65.1)	214 (34.9)	35 (28−45)*			1741.0 (842.5−3582.2)	50.5 (40.5−64.6)*	13.6	241 (39.3)	270 (44.0)	112 (18.2)	385 (62.7)
SCORED	Sotagliflozin	5292	69 (63−74)*	5292 (100)	NA	8.3 (7.6−9.3)*	31.9 (28.1−36.2)*	2945 (55.7)	2347 (44.3)	60 (51−64)*	843 (15.9)	795 (15)	196.0 (75.1−564.6)	44.4 (37.0−51.3)*	NA	2009 (38.0)	261.9 (49.5)	66 (1.2)	810 (15.3)
	Placebo	5292	69 (63−74)*	5292 (100)	NA	8.3 (7.6−9.4)*	31.7 (28.0−36.1)*	2885 (54.5)	2407 (45.5)	60 (51−65)*	824 (15.6)	819 (15.5)	198.1 (74.6−560.7)	44.7 (37.0−51.5)*	NA	2039 (38.5)	2562 (48.4)	65 (1.2)	776 (14.7)
VERTIS CV	Ertugliflozin	5493	64.4 (8.1)	5493 (100)	NA	8.2 (1.0)	31.9 (5.4)	3866 (70.3)	1633 (29.7)	NA	NA	NA	NA	76.1±20.9	NA	NA	NA	NA	NA
	Placebo	2474	64.4 (8.0)	2474 (100)	NA	8.2 (0.9)	32.0 (5.5)	1903 (69.3)	844 (30.7)	NA	NA	NA	NA	75.7±20.8	NA	NA	NA	NA	NA
Empire HF Renal	Empagliflozin	60	68 (10)	9 (15)	NA	5.8 (5.4-5.9)*	29 (4.4)	47 (78)	13 (22)	31 (7)	NA	NA	586 (349−1068)	70 (18)	NA	33 (55)		40 (67)	22 (37)
	Placebo	60	67 (10)	6 (10)	NA	5.7 (5.7-5.9)*	30 (5)	52 (87)	8 (13)	31 (7.5)	NA	NA	623 (375−1098)	73 (18)	NA	36 (60)		43 (72)	23 (38)
CANVAS Program	Canagliflozin	5795	63.2 (8.3)	13.5 (7.7)	NA	8.2 (0.9)	31.9 (5.9)	3759 (64.9)	2036 (35.1)	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
	Placebo	4347	63.4 (8.2)	13.7 (7.8)	NA	8.2 (0.9)	32.0 (6.0)	2750 (63.3)	1597 (36.7)	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
DAPA-HF	Dapagliflozin	2373	66.2 (11.0)	993 (41.8)	NA	≥6.5	28.2 (6.0)	1809 (76.2)	564 (23.8)	31.2 (6.7)	NA	NA	1428 (857−2655)*	66.0 (19.6)	NA	1332 (56.1)	675 (28.4)	1696 (71.5)	250 (10.5)
	Placebo	2371	66.5 (10.8)	990 (41.8)	NA	≥6.5	28.1 (5.9)	1826 (77)	545 (23.0)	30.9 (6.9)	NA	NA	1446 (857−2641)*	65.5 (19.3)	NA	1329 (56.1)	632 (26.7)	1674 (70.6)	258 (10.9)
DECLARE−TIMI	Dapagliflozin	8582	63.9 (6.8)	8582 (100)	NA	8.3 (1.2)	32.1 (6.0)	5411 (63.05)	3171 (36.9)	NA	NA	NA	NA	85.4 (15.8)	NA	6977 (81.3)	NA	NA	NA
	Placebo	8578	64.0 (6.8)	8578 (100)	NA	8.3 (1.2)	32.0 (6.1)	5327 (62.1)	3251 (37.9)	NA	NA	NA	NA	85.1 (16.0)	NA	6973 (81.3)	NA	NA	NA
DEFINE-HF	Dapagliflozin	131	62.2 (11)	81 (61.8)	NA	7.0 (1.8)	30.7 (27.3, 35.9)*	95 (72.5)	36 (27.5)	27.2 (8.0)	NA	NA	1136 (668, 2465)*	66.9 (21.1)	NA	76 (58.0)		76 (58.0)	47 (35.9)
	Placebo	132	60.4 (12)	85 (64.4)	NA	7.3 (2.0)	30.6 (27.6, 36.4)*	98 (74.2)	34 (25.8)	25.7 (8.2)	NA	NA	1136 (545, 2049)*	71.2 (23.1)	NA	80 (60.6)		84 (63.6)	38 (28.8)
EMPA-REG OUTCOME	Empagliflozin	4687	<65 yr=2596 ≥65yr=2091	4687 (100)	NA	<8.5%=3212 ≥8.5%=1475	<30=2279 ≥30=2408	3336	1351	NA	NA	NA	NA	≥90=1050 60 to <90=2425 <60=1212	NA	3798 (81)		NA	NA
	Placebo	2333	<65 yr=1297 ≥65yr=1036	2333 (100)	NA	<8.5%=1607 ≥8.5%=726	<30=1120 ≥30=1213	1680	653	NA	NA	NA	NA	≥90=488 60 to <90=1238 <60=607	NA	1868 (80)		NA	NA
DELIVER	Dapagliflozin	3131	71.8 (9.6)	1401 (44.7)	1730 (55.3)	NA	29.8 (6.2)	1767 (56.4)	1364 (43.6)	54.0 (8.6)	2064 (65.9)	1067 (34.1)	In Atrial Fibrillation/ Flutter 1408 (956, 2256) In other patients 729 (472, 1299)	61 (19)	70 (23)	1144 (36.5)	1133 (36.2)	165 (5.3)	1340 (42.8)
	Placebo	3132	71.5 (9.5)	1405 (44.9)	1727 (55.1)	NA	29.9 (6.1)	1749 (55.8)	1383 (44.2)	54.3 (8.9)	2083 (66.5)	1049 (33.5)	In Atrial Fibrillation/Flutter 1387 (965.5, 2180.5) In other patients 704 (467, 1265)	61 (19)	70 (22)	1151 (36.7)	1139 (36.4)	136 (4.3)	1327 (42.4)

ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; ARNI = angiotensin Receptor Neprilysin Inhibitor; BMI = body mass index; eGFR = estimated glomerular filtration rate; HbA1 = hemoglobin A 1 C; HFpEF = heart failure with preserved ejection fraction; HFrEF = heart failure with reduced ejection; LVEF = left ventricular ejection fraction; NA = not available; NT-proBNP = N-terminal pro-B-type natriuretic peptide; SD = standard deviation.

* Data reported in median and Interquartile range

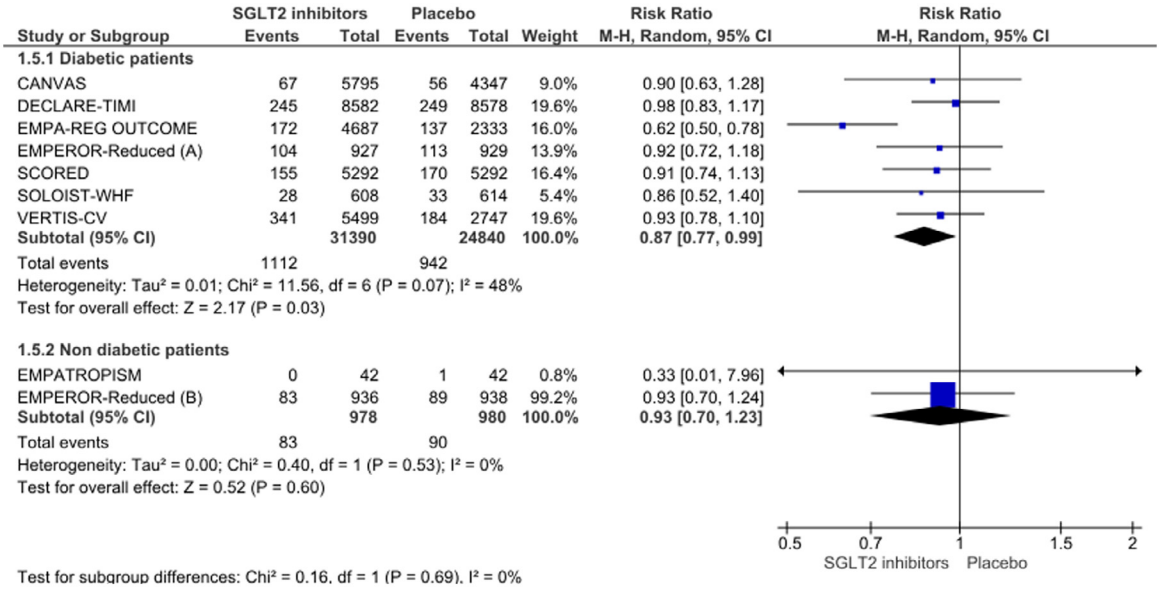

Figure 2. Analysis for cardiovascular mortality. M-H = Mantel-Haenszel.

selective reporting, respectively. All included articles had a low risk regarding the participants' blinding, except for EMPEROR-Reduced,[24] SCORED,[21] and VERTIS-CV[17] trials. Outcome data were adequately reported in all trials, except for Empire-HF-Renal[20] and SOLOIST-WHF[23] trials. All included studies had a high risk of bias regarding other potential biases, except for DAPA-HF,[22] DECLARE-TIMI,[15] EMPIRE HF Renal,[20] and SCORED.[21] A summary of the risk of bias assessment domains of the included studies is shown in Supplementary Figure 2.

Regarding HHF patients with diabetes, the pooled effect estimates for 7 studies showed a statistically significant lower risk in SGLT2Is than placebo (RR 0.68, 95% CI 0.63 to 0.74, p <0.00001); the pooled studies were homogenous (p = 0.95, I^2 = 0%) (Figure 1). For patients without diabetes, the pooled effect estimates for HHF in 2 studies showed a statistically significant lower risk in SGLT2Is than placebo (RR 0.75, 95% CI 0.62 to 0.89, p = 0.002); the pooled studies were homogenous (p = 0.39, I^2 = 0%) (Figure 1). Cardiovascular mortality in patients with diabetes (the pooled effect estimates for 7 studies) showed a statistically significant lower risk in SGLT2Is than placebo (RR 0.87, 95% CI 0.77 to 0.99, p = 0.03, I^2 = 48%). The heterogeneity was resolved by excluding EMPA-REG OUTCOME[17] trial because the pooled studies were homogenous (p = 0.99; I^2 = 0%) (Figure 2). For patients without diabetes, the pooled effect estimates for cardiovascular mortality in 2 studies showed lower risk in SGLT2Is than placebo but without statistical significance (RR 0.93, 95% CI 0.70 to 1.23, p = 0.60). The pooled studies were homogenous (p = 0.53, I^2 = 0%) (Figure 2). The pooled effect estimates for the outcome of urgent HF visit for 6 studies showed a statistically significant lower risk in SGLT2Is than placebo (RR 0.62, 95% CI 0.52 to 0.74, p <0.00001). The pooled studies were homogenous (p = 0.52, I^2 = 0%) (Figure 3). Regarding MI, the pooled effect estimates for 7 studies showed lower risk in SGLT2Is than placebo but without statistical significance (RR 0.92, 95% CI 0.87 to 1.01, p <0.00001). The pooled studies were homogenous (p = 0.41, I^2 = 1%) (Supplementary Figure 3). The pooled effect estimates for the outcome of stroke in 6 studies showed equal risk between SGLT2Is and placebo but without statistical significance (RR 1.05, 95% CI 0.93 to 1.18, p = 0.46). The pooled studies were homogenous (p = 0.72, I^2 = 0%) (Supplementary Figure 4). Total mortality (the pooled effects estimate for 12 studies) showed a statistically significant

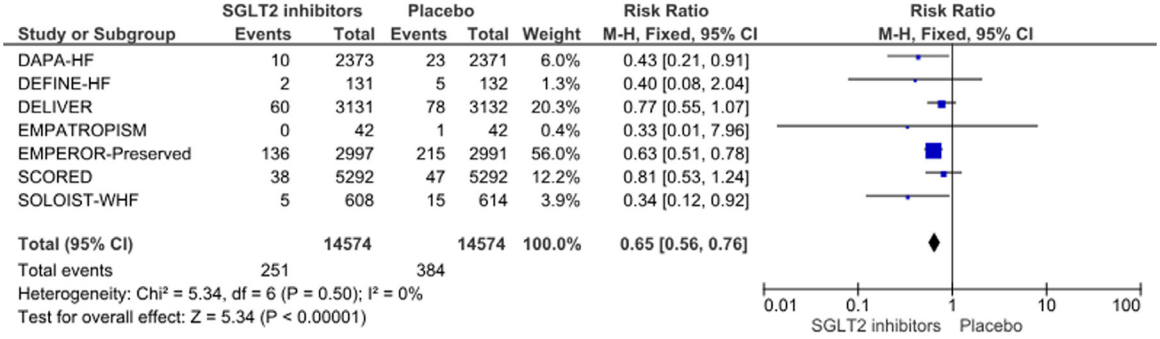

Figure 3. Analysis for urgent heart failure. M-H = Mantel-Haenszel.

lower risk in SGLT2Is than placebo (RR 0.91, 95% CI 0.87 to 0.96, p = 0.0002). The pooled studies were homogenous (p = 0.16, I^2 = 30%) (Suuplementary Figure 5). No publication bias was found; the funnel plot observed a symmetric pattern among studies (Supplementary Figures 4 and 6).

Regarding serious adverse events, for patients with diabetes, the pooled effect estimates for 6 studies showed a statistically significant lower risk in SGLT2Is than placebo (RR 0.94, 95% CI 0.90 to 0.98, p = 0.004). The pooled studies were heterogenous (p = 0.06; I^2 = 53%). The heterogeneity was resolved after excluding SOLOIST-WHF[22] trial because pooled studies were homogenous (p = 0.33, I^2 = 14%) (Supplementary Figure 6). For patients without diabetes, the pooled effect estimates for serious adverse events in 2 studies showed a lower risk in SGLT2Is than placebo but without statistical significance (RR 0.72, 95% CI 0.38 to 1.39, p = 0.33). The pooled studies were homogenous (p = 0.20, I^2 = 39%) (Supplementary Figure 7). The adverse events leading to discontinuation (the pooled effect estimates for 6 studies in patients with diabetes) showed no differences between SGLT2Is than placebo (RR 1.04, 95% CI 0.93 to 1.16, p = 0.53). The pooled studies were heterogenous (p = 0.02, I^2 = 63%). The heterogeneity resolved after excluding EMPA-REG OUTCOME[17] trial because pooled studies were homogenous (p = 0.65; I^2 = 0%) (Supplementary Figure 8). For patients without, the pooled effect estimates for adverse events leading to discontinuation in 2 studies showed no differences between SGLT2Is than placebo (RR 0.97, 95% CI 0.79 to 1.20, p = 0.79); the pooled studies were homogenous (p = 0.49; I^2 = 0%); (Supplementary Figure 7).

Discussion

To the best of our knowledge, this study is the most recent and the largest study that assessed the safety and efficacy of SGLT2Is in patients without diabetes with HF. The study pooled data from 13 trials (75,287 patients). Patients were stratified into diabetics and non-diabetics. Regarding efficacy analysis, SGLT2Is effectively decreased the HHF risk in patients with and without. Regarding urgent HF visits and total mortality, the results favored SGLT2Is over placebo, but we could not stratify the patients according to their diabetic status because of a lack of data.

In patients with diabetes, SGLT2Is exhibited a trend toward reducing cardiovascular mortality, which can be further explained by the SGLT2Is mechanism of action on increasing electrolyte-free water clearance and plasma osmolality, removing extra interstitial fluid, which further decrease the circulatory overload on the failing heart. In contrast, patients without diabetes did not show a significant reduction, which can be explained by the lack of deteriorating amount of glucose presented in the circulation, causing volume overload. Furthermore, the present study revealed that SGLT2Is did not decrease stroke and MI risk in patients with HF, which is, at the moment, scientifically sound and away from the mechanism of action of SGLT2Is because the underlying mechanism of MI and stroke is dependent mainly on elevation of low-density lipoproteins and the atherosclerotic progression of blood vessels causing vascular ischemia. We could not stratify the patients according to their diabetic status because of a lack of data.

Regarding safety, the SGLT2I group had a decreased risk of major adverse events in patients with diabetes, but the results were insignificant in patients without diabetes. Adverse events leading to discontinuation were similar in patients with and without diabetes. The percentage of patients with acute renal failure in the EMPA-REG OUTCOME[19] trial was not equal in both groups, affecting the homogeneity of the included studies. Also, the SOLOIST-WHF[23] trial affected the homogeneity because of its insufficient statistical power. It was terminated early before reaching the planned sample size. Butler et al[26] pooled data from 17,000 patients with HF. They did not stratify the patients according to their diabetic status. They found that SGLT2Is reduced the risk of death, cardiovascular mortality, and HHF. Also, they found insignificant results in serious adverse events or adverse events leading to discontinuation. Their data were scarce and heterogeneous.

Several studies[27–31] suggest that SGLT2Is effectively reduce the risk of cardiovascular mortality, HHF, and a composite of cardiovascular mortality/HHF in patients with HF with reduced ejection fraction and HF with preserved ejection fraction, regardless of their diabetic status. The results of the present study revealed that SGLT2Is reduced the HHF risk in patients with and without diabetes but had no effect on the risk of cardiovascular death in those without diabetes. A previous network meta-analysis[32] demonstrated that SGLT2Is improve the metabolic profile of patients without diabetes, but their results were questioned because of the lack of data and statistical power.

Our study limitations include the increased heterogeneity in some of our analyses, which were solved by sensitivity analysis, and the different types of SGLT2Is prescribed, thus calling for a network meta-analysis to further investigate the best SGLT2I agent to use in patients with HF. In addition, there are limited published data on patients without diabetes.

In conclusions, in patients with diabetes, SGLT2Is significantly reduced cardiovascular mortality, HHF, and serious adverse events. However, in patients without, despite showing a significant reduction in HHF, SGLT2I reduced cardiovascular mortality or serious adverse events but without statistical significance. We suggest that the effects of SGLT2Is in patients without diabetes require further studies to be consolidated.

Author Contributions

Ahmed K. Awad, Mohamed Shih, Amir N. Attia, and Heba Aboeldahab performed the screening and data extraction, Mohammed Tarek Hasan did the analysis, and Mohammed Tarek Hasan and Ahmed K. Awad wrote the primary draft, which was further edited and modified by Ahmed Bendary and Mohamed Bendary. all authors reviewed and agreed to the final version of the manuscript. All authors have participated in the work and have reviewed and agree with the content of the article.

Disclosures

The authors have no conflicts of interest to declare.

Availability of data and materials

All data are available and attached.

Human Ethics and Consent to Participate Statement

This study was not applied on human beings and thus requires no ethical approval.

Consent for Publication

All authors reviewed and agreed on the final version of the manuscript.

Supplementary materials

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.amjcard.2022.10.027.

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