Original Article
Cardiovascular benefits of SGLT2 inhibitors in patients with heart failure: a meta-analysis of small and large randomized controlled trials

Saeed Shoar[1], Ahmed Ali Shah[2], Waleed Ikram[3], Najam Farooq[2], Agnes Udoh[4], Elsa Tabibzadeh[5], Soheila Khavandi[6], Siamak Khavandi[7]

[1]Department of Clinical Research, ScientificWriting Corp, Houston, TX, USA; [2]School of Medicine, Quaid-e-Azam Medical College, Bahawalpur, Pakistan; [3]School of Medicine, Lahore Medical and Dental College, Lahore, Pakistan; [4]School of Medicine, Madonna University, Okija, Nigeria; [5]Department of Anesthesiology and Critical Care, Tabriz University of Medical Sciences, Tabriz, Iran; [6]Department of Cardiology, Tabriz University of Medical Sciences, Tabriz, Iran; [7]Department of Ophthalmology, Tabriz University of Medical Sciences, Tabriz, Iran

Abstract: Background: Sodium-glucose cotransporter 2 (SGLT2) inhibitors have shown promise in improving cardiovascular outcome in patients with heart failure (HF) and diabetes mellitus (DM). Although these benefits have been confirmed by several meta-analyses, small studies have not been included into these pooled analyses. Aim: Publication of recent RCTs prompted us to perform this updated meta-analysis to examine the consistency of favorable cardiovascular outcomes of SGLT2 inhibitors in HF patients by inclusion of clinical trials with small sample size. Methods: We conducted a systematic review of the literature in PubMed/Medline and ClinicalTrials.gov to identify all RCTs investigating the benefits of SGLT2 inhibitors in patients with HF. The primary endpoint of this meta-analysis was to compare the cardiovascular death (CVD) and hospitalization for HF (HHF) between patients who received an SGLT2 inhibitor and those who received a placebo or a non-SGLT2 inhibitor. We used a risk difference (RD) and log hazard ratio (HR) to pool the reported difference across the included RCTs. Results: A total of 12 RCTs encompassing 59,825 patients at different stages of HF and DM were included, 32,448 patients in the SGLT2 inhibitor group and 27,377 patients in the control group. A pooled analysis of RCTs, regardless of HF severity or DM status, showed a significantly reduced RD for CVD (RD =-0.01, 95% CI [-0.01, 0.00], P=0.01) and HHF (RD =-0.02, 95% CI [-0.03, -0.01], P=0.0005) in patients who received a SGLT2 inhibitor compared to those who did not. A sub-group analysis showed a significantly reduced RD for CVD (RD =-0.01, 95% CI [-0.02, 0.00], P=0.03) and HHF (RD =-0.02, 95% CI [-0.03, 0.00], P=0.01) in patients with DM who received SGLT2 inhibitors regardless of the severity of HF. Also, regardless of DM status, RD for HHF favored the use of SGLT2 inhibitor than the control medication (RD =-0.05, 95% CI [-0.06, -0.03], P<0.00001). Conclusion: SGLT2 inhibitors have shown a promise in reducing CVD and HHF in patients with HF, regardless of ejection fraction or diabetes status.

Keywords: SGLT2 inhibitor, heart failure, diabetes mellitus, cardiovascular mortality, hospitalization for heart failure

Introduction

Sodium-glucose cotransporter 2 (SGLT2) inhibitors have received endorsement by the professional cardiology and endocrinology societies for their use in reducing the risk of hospitalization for heart failure (HHF) and cardiovascular death (CVD) in diabetic patients with atherosclerotic complications [1-3]. There is growing evidence from randomized clinical trials (RCTs) of such a beneficial effect in patients with dia-

betes mellitus (DM) regardless of the degree of left ventricular ejection fraction (EF) [4, 5]. Further RCTs have started to show that SGLT2 inhibitors reduce CVD and HHF rate in patients with established cardiovascular diseases regardless of the DM status [6-9].

Previous meta-analyses have stratified the data in the literature on cardiovascular benefits of SGLT2 inhibitors according to the HF status, DM, and kidney function [10-12]. However, their

level of certainty is low for patients without DM due to the mixing of data in diabetics and non-diabetics in the original studies. Moreover, these meta-analyses excluded small RCTs [7, 13, 14] from their pooled analyses. Recent publication of the results of the cardiovascular benefits of the empagliflozin in non-diabetic patients with HF [14] and the results of SCORED trial [15] prompted us to perform this meta-analysis to update the results of previous studies and to determine, with a high degree of confidence, if the favorable effects of SGLT2 inhibitors can be extended to HF patients without DM.

Methods and materials

Study design

We performed a systematic review of literature according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses [16]. Our aim was to identify all the RCTs comparing the rate of HHF and CVD between adult patients receiving an SGLT2 inhibitor or placebo/non-SGLT2 inhibitor as an add-on treatment to the guideline-directed pharmacotherapy for cardio-metabolic conditions.

Literature review

We queried Medline/PubMed and ClinicalTrials.gov using a combination of these search terms: "SGLT2 inhibitor", "Sodium-glucose cotransporter 2 inhibitor", "randomized clinical trial", and "heart failure". Title/abstract of retrieved articles was reviewed for locating a relevant article and full-text of the relevant articles were obtained for eligibility review. Any conflict was resolved through discussion with another investigator.

Outcome measure

The primary outcome of the present study was to compare the pooled data on HHF and CVD in patients who received an SGLT2 inhibitor and those who did not. The secondary outcome was to examine the primary endpoints in the two subgroups of patients, without HF and without DM.

Data collection

Data on the variables of interest were collected from individual trials. Attempts were made to obtain data from each study based on our analytical endpoint. For example, if a study had stratified the overall data based on an underlying condition such as HF or DM, data for that subgroup analysis was also extracted for the purpose of subgroup meta-analysis. For data pertinent to the CANagliflozin cardioVascular Assessment Study (CANVAS) and CANVAS-Renal RCTs, the pooled CANVAS Program Collaborative Group data were utilized [4].

Statistical analysis

We used Review Manager (Version 5.3. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014) for this meta-analysis. Mantel-Haenszel statistical method was used to calculate the risk difference (RD) in CVD and HF hospitalization in SGLT2 inhibitor group compared to the control group. An RD was used to examine this relationship due to the grouping of data from large RCTs and smaller studies, which did not provide a hazard ratio (HR) and the corresponding 95% confidence interval (95% CI). When feasible, a pooled HR was estimated by a generic inverse variance method using a log HR and standard error (SE). Besides an overall analysis of cardiovascular benefits of SGLT2 inhibitors in HF patients, a subgroup analysis was also performed to investigate these outcome measures in those without a reduced EF. Another subgroup analysis was performed to estimate such benefits in studies regardless of DM status and in non-diabetic patients.

The heterogeneity was assessed through Cochran I^2 statistic as the percentage of variation across the studies, which can be explained by the heterogeneity rather than the chance [17]:

$$I^2 = 100\% \times (Q\text{-df})/Q$$

An $I^2 < 25\%$, 25% to 75%, and >75% were considered low, moderate, and high, respectively. A fixed-effect model was used when the heterogeneity was low and a random-effect model when it was medium or high. A two-sided P<0.05 considered statistically significant.

Publication bias was assessed by visual inspection of the funnel plot, when the number of studies included into the meta-analysis was >10. An Egger test was used to depict the funnel plot of effect estimates versus sample size
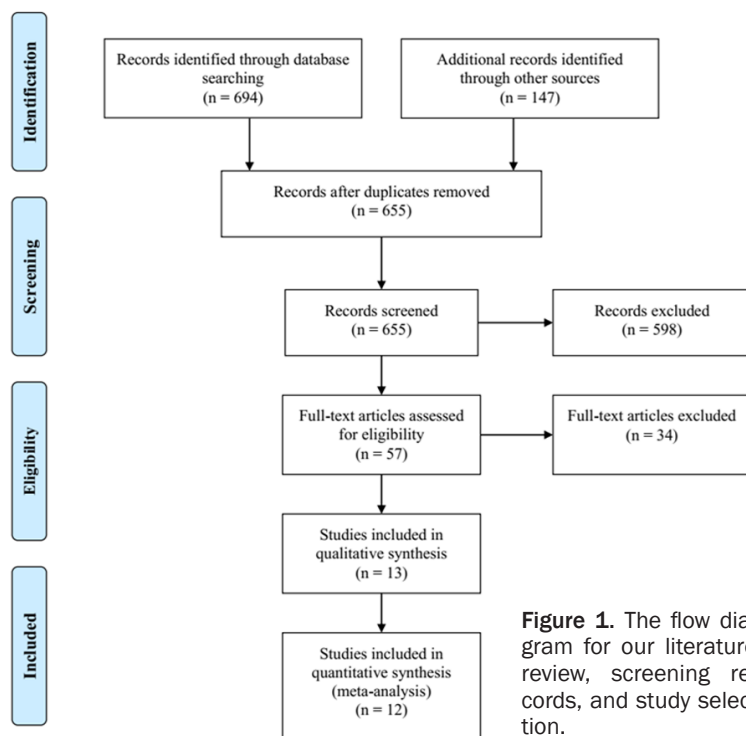
Figure 1. The flow diagram for our literature review, screening records, and study selection.

[18]. An asymmetrical plot was interpreted as a small-study publication bias.

Results

A total of 12 RCTs encompassing 59,825 patients with different HF class and DM severity were included in our meta-analysis [4-9, 13-15, 19-22]. This provided us with 32,448 patients in the SGLT2 inhibitor group and 27,377 patients in the control group. **Figure 1** depicts the flow of our literature review and study selection.

The majority of the study population were men and older than 60 years of age. Four of the trials had only enrolled patients with DM [6, 7, 9, 14]. The characteristics of the study population including HF class and DM status in each trial are summarized in **Table 1**. Additionally, **Table 2** presents the results of the quality assessment of the included clinical trials.

A meta-analysis of RCTs, regardless of HF severity or DM status, showed a significantly reduced RD for CVD (RD =-0.01, 95% CI [-0.01, 0.00], P=0.01) and HHF (RD =-0.02, 95% CI [-0.03, -0.01], P=0.0005) in patients who received an SGLT2 inhibitor compared to those who did not (**Figure 2**). A sub-group meta-analy-

sis of RCTs in patients with DM regardless of the HF class or EF at baseline also showed a significantly reduced RD for CVD (RD=-0.01, 95% CI [-0.02, 0.00], P=0.03) and HHF (RD= -0.02, 95% CI [-0.03, 0.00], P=0.01) for those receiving SGLT2 inhibitors compared to those who did not (**Figure 2**). Interestingly, while the RD for CVD (RD=0.02, 95% CI [-0.04, 0.01], P=0.17) was comparable between those who received SGLT2 inhibitor and those who did not regardless of the DM status, the RD for HHF was in the favor of those receiving the SGLT2 inhibitor (RD=-0.05, 95% CI [-0.06, -0.03], P<0.00001) (**Figure 2**).

Using a generic inverse variance method to pool the HR and SE, similar outcome measures were observed for CVD and HHF in favor of patients receiving SGLT 2 inhibitor compared to those who did not receive SGLT 2 inhibitor (**Figure 3**).

A pooled sub-group analysis of two studies in non-diabetic patients with HF [14, 23] showed a non-significant reduction in CVD in those receiving an SGLT2 inhibitor (RD=-0.02, 95% CI [-0.04, 0.01], P=0.17) (**Figure 4**). However, the reduction in HHF was substantially significant in patients receiving SGLT2 inhibitor compared to those who did not receive SGLT 2 inhibitor (RD=-0.04, 95% CI [-0.06, -0.02], P=0.002).

The funnel plot for the publication bias was inspected for all studies included in the pooled analysis for overall CVD and HHF (**Figure 5**). As shown in the figure, there was an asymmetry in the plot favoring the publication of studies reporting the cardiovascular benefits of SGLT2 inhibitor at the cost of nonpublication of studies with no favorable effect.

Discussion

This meta-analysis pools the data of 12 RCTs on CVD and HHF in patients receiving different SGLT2 inhibitors. Besides comprehensiveness by including data from small studies and recent

Table 1. Characteristics of clinical trials with published results on the outcome of patients with heart failure receiving sodium-glucose co-transporter type 2 inhibitor

Clinical Trial	NCT	Medication	Characteristics of the study population						Baseline Study Criteria				
			SGLT-2 inhibitor group			Placebo/control group							
			N	Age	M:F (%)	N	Age	M:F (%)	EF	NYHA	HF (%)	DM (%)	F/u (med)
SCORED	NCT03315143	Sotagliflozin	5,292	69 (63-74)	55.7:44.3	5,292	69 (63-74)	54.5:45.5	≤40%	N/A	31	100	16 months
EMPA-TROPISM (ATRU-4)	NCT 03485222	Empagliflozin	42	64.2±10.9	63:36	42	59.9±13.1	64:36	<50	II-III	100	0	6 months
VERTIS CV	NCT01986881	Ertugliflozin	5,499	64.4±8.1	70.3:29.7	2,747	64.4±8.0	69.3:30.7	N/A	N/A	23.7	100	3.5 years
EMPEROR-Reduced*	NCT03057977	Empagliflozin	1,863	67.2±10.8	76.5:23.5	1,867	66.5±11.2	75.6:24.4	≤40%	II-IV	100	49.7	16 months
CREDENCE*	NCT02065791	Canagliflozin	2,202	62.9±9.17	65.4:34.6	2,199	63.2±9.23	66.7:33.3	N/A	I-III	N/A	100	2.62 years
DAPA-HF* *Overall*	NCT03036124	Dapagliflozin	2,373	66.2±11	76.2:23.8	2,371	66.5±10.8	77:23	≤40%	II-IV	100	45.1	27.8 months
DM+			1075	66.3±9.9	77.7:22.3	1064	66.7±9.8	77.7:22.3	≤40%	II-IV	100	100	27.8 months
DM-			1298	66±11.8	75:25	1307	66.4±11.5	76.4:23.6	≤40%	II-IV	100	0	27.8 months
REFORM*	NCT02397421	Dapagliflozin	28	N/A	N/A	28	N/A	N/A	≤45%	I-III	100	100	1 year
DECLARE-TIMI58 *Overall*	NCT01730534	Dapagliflozin	8,582	63.9±6.8	63.1:36.9	8,578	64±6.8	62.1:37.9	≤45%	I-III	11.6	100	4.2 years
HFrEF			318	N/A	N/A	353	N/A	N/A	≤45%	I-III	100	100	4.2 years
DAPA-HDL*	NCT02327039	Dapagliflozin	15	65.7±5.9	66.7:33.3	15	61.0±7.2	66.7:33.3	≤40%	I-II	0	100	12 weeks
DEFINE-HF*	NCT 02653482	Dapagliflozin	131	62.2±11.0	72.5:27.5	132	60.4±12.0	74.2:25.8	≤40%	II-III	100	63.1	13 weeks
CANVAS*	NCT01032629	Canagliflozin	2888	62.5±8.1	66:34	1442	62.3±7.94	66.3:33.7	N/A	N/A	14.4	100	N/A
CANVAS-R*	NCT01989754	Canagliflozin	2907	63.9±8.4	63.8:36.2	2905	64±8.3	61.8:38.2	N/A	N/A	14.4	100	78 weeks
EMPA-REG OUTCOME*	NCT01131676	Empagliflozin	46872	63.1±8.6	71.2:28.8	2333	63.2±8.8	72:28	N/A	N/A	N/A	100	3.1 years

NCT: National clinical trial number; *HF*: Heart failure; *M:F*: Male to female ratio; *EF*: Ejection fraction; *NYHA*: New York Heart Association functional class; *DM*: Diabetes mellitus; *F/U*: Follow-up; *Med*: Median; *: Sodium-glucose cotransporter type 2 inhibitor (SGLT2i) included canagliflozin, dapagliflozin, or empagliflozin while oral or injectable glucose lowering medications were other drugs besides these); *N/A*: Not available.

Table 2. Cochrane tools for quality assessment of clinical trials

Clinical trial	Random Sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
SCORED	+	+	+	+	+	+	?
EMPA-TROPISM (ATRU-4)	+	+	+	+	+	+	?
VERTIS CV	+	+	+	+	+	+	?
EMPEROR-Reduced*	+	+	+	+	+	+	?
CREDENCE*	+	+	+	+	+	+	?
DAPA-HF*	+	+	+	+	+	+	?
DAPA-HDL*	+	+	+	+	+	+	?
DEFINE-HF*	+	+	+	+	+	+	?
CANVAS*	+	+	+	+	+	+	?
CANVAS-R*	+	+	+	+	+	+	?
EMPA-REG OUTCOME*	+	+	+	+	+	+	?

+: Yes; -: No; ?: Unknown.

Cardiovascular benefits of SGLT2 inhibitors in patients with heart failure

A

Study or Subgroup	SGLT2 Inhibitor Events	Total	Placebo/Control Events	Total	Weight	Risk Difference M-H, Random, 95% CI
CANVAS Program Integrated Data	116	10000	128	10000	19.1%	-0.00 [-0.00, 0.00]
CREDENCE	110	2202	140	2199	8.8%	-0.01 [-0.03, -0.00]
DAPA HF	227	2373	273	2371	6.5%	-0.02 [-0.04, -0.00]
DECLARE TIMI-58	245	8582	249	8578	17.3%	-0.00 [-0.01, 0.00]
DEFINE-HF	1	131	1	132	4.9%	0.00 [-0.02, 0.02]
EMPA-REG OUTCOME	172	4687	137	2333	11.0%	-0.02 [-0.03, -0.01]
EMPA-TROPISM	0	40	1	40	0.6%	-0.03 [-0.09, 0.04]
EMPEROR-Reduced	187	1863	202	1867	5.5%	-0.01 [-0.03, 0.01]
REFORM	0	28	3	28	0.2%	-0.11 [-0.23, 0.02]
SCORED	155	5292	170	5292	15.6%	-0.00 [-0.01, 0.00]
VERTIS CV	341	5499	184	2747	10.7%	-0.00 [-0.02, 0.01]
Total (95% CI)		40697		35587	100.0%	-0.01 [-0.01, -0.00]
Total events	1554		1488			

Heterogeneity: Tau² = 0.00; Chi² = 28.69, df = 10 (P = 0.001); I² = 65%
Test for overall effect: Z = 2.53 (P = 0.01)

Risk Difference M-H, Random, 95% CI — scale -1, -0.5, 0, 0.5, 1 — Placebo/Control SGLT2 Inhibitor

B

Study or Subgroup	SGLT2 Inhibitor Events	Total	Placebo/Control Events	Total	Weight	Risk Difference M-H, Random, 95% CI
CANVAS Program Integrated Data	116	10000	128	10000	23.9%	-0.00 [-0.00, 0.00]
CREDENCE	110	2202	140	2199	15.5%	-0.01 [-0.03, -0.00]
DECLARE TIMI-58	25	318	47	353	3.2%	-0.05 [-0.10, -0.01]
EMPA-REG OUTCOME	172	4687	137	2333	17.8%	-0.02 [-0.03, -0.01]
REFORM	0	28	3	28	0.5%	-0.11 [-0.23, 0.02]
SCORED	155	5292	170	5292	21.6%	-0.00 [-0.01, 0.00]
VERTIS CV	341	5499	184	2747	17.5%	-0.00 [-0.02, 0.01]
Total (95% CI)		28026		22952	100.0%	-0.01 [-0.02, -0.00]
Total events	919		809			

Heterogeneity: Tau² = 0.00; Chi² = 29.03, df = 6 (P < 0.0001); I² = 79%
Test for overall effect: Z = 2.23 (P = 0.03)

Risk Difference M-H, Random, 95% CI — scale -1, -0.5, 0, 0.5, 1 — Placebo/Control SGLT2 Inhibitor

C

Study or Subgroup	SGLT2 Inhibitor Events	Total	Placebo/Control Events	Total	Weight	Risk Difference M-H, Fixed, 95% CI
DAPA HF	106	1298	126	1307	97.0%	-0.01 [-0.04, 0.01]
DEFINE-HF	1	131	1	132		Not estimable
EMPA-TROPISM	0	40	1	40	3.0%	-0.03 [-0.09, 0.04]
EMPEROR-Reduced	187	1863	202	1867		Not estimable
Total (95% CI)		1338		1347	100.0%	-0.02 [-0.04, 0.01]
Total events	106		127			

Heterogeneity: Chi² = 0.09, df = 1 (P = 0.77); I² = 0%
Test for overall effect: Z = 1.38 (P = 0.17)

Risk Difference M-H, Fixed, 95% CI — scale -1, -0.5, 0, 0.5, 1 — Placebo/Control SGLT2 Inhibitor

D

Study or Subgroup	SGLT2 Inhibitor Events	Total	Placebo/Control Events	Total	Weight	Risk Difference M-H, Random, 95% CI
CANVAS Program Integrated Data	55	10000	87	10000	14.0%	-0.00 [-0.01, -0.00]
CREDENCE	89	2202	141	2199	11.4%	-0.02 [-0.04, -0.01]
DAPA HF	231	2373	318	2371	9.8%	-0.04 [-0.05, -0.02]
DECLARE TIMI-58	212	8582	286	8578	13.6%	-0.01 [-0.01, -0.00]
DEFINE-HF	10	131	8	132	2.3%	0.02 [-0.05, 0.08]
EMPA-REG OUTCOME	126	4687	95	2333	12.6%	-0.01 [-0.02, -0.00]
EMPA-TROPISM	0	40	2	40	1.5%	-0.05 [-0.13, 0.03]
EMPEROR-Reduced	246	1863	342	1867	8.1%	-0.05 [-0.07, -0.03]
REFORM	1	28	1	28	1.0%	0.00 [-0.10, 0.10]
SCORED	245	5292	360	5292	12.7%	-0.02 [-0.03, -0.01]
VERTIS CV	139	5499	99	2747	12.9%	-0.01 [-0.02, -0.00]
Total (95% CI)		40697		35587	100.0%	-0.02 [-0.03, -0.01]
Total events	1354		1739			

Heterogeneity: Tau² = 0.00; Chi² = 117.13, df = 10 (P < 0.00001); I² = 91%
Test for overall effect: Z = 3.51 (P = 0.0005)

Risk Difference M-H, Random, 95% CI — scale -1, -0.5, 0, 0.5, 1 — Placebo/Control SGLT2 Inhibitor

E

Study or Subgroup	SGLT2 Inhibitor Events	Total	Placebo/Control Events	Total	Weight	Risk Difference M-H, Random, 95% CI
CANVAS Program Integrated Data	55	10000	87	10000	20.7%	-0.00 [-0.01, -0.00]
CREDENCE	89	2202	141	2199	16.9%	-0.02 [-0.04, -0.01]
DECLARE TIMI-58	41	318	63	353	4.2%	-0.05 [-0.10, 0.00]
EMPA-REG OUTCOME	126	4687	95	2333	18.7%	-0.01 [-0.02, -0.00]
REFORM	1	28	1	28	1.5%	0.00 [-0.10, 0.10]
SCORED	245	5292	360	5292	18.9%	-0.02 [-0.03, -0.01]
VERTIS CV	139	5499	99	2747	19.1%	-0.01 [-0.02, -0.00]
Total (95% CI)		28026		22952	100.0%	-0.02 [-0.03, -0.00]
Total events	696		846			

Heterogeneity: Tau² = 0.00; Chi² = 65.97, df = 6 (P < 0.00001); I² = 91%
Test for overall effect: Z = 2.43 (P = 0.01)

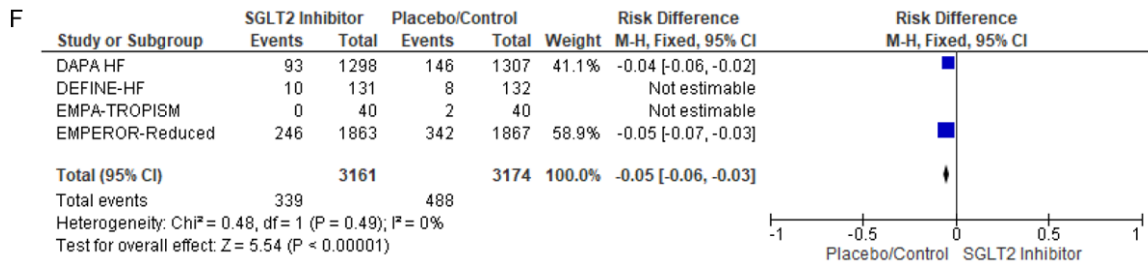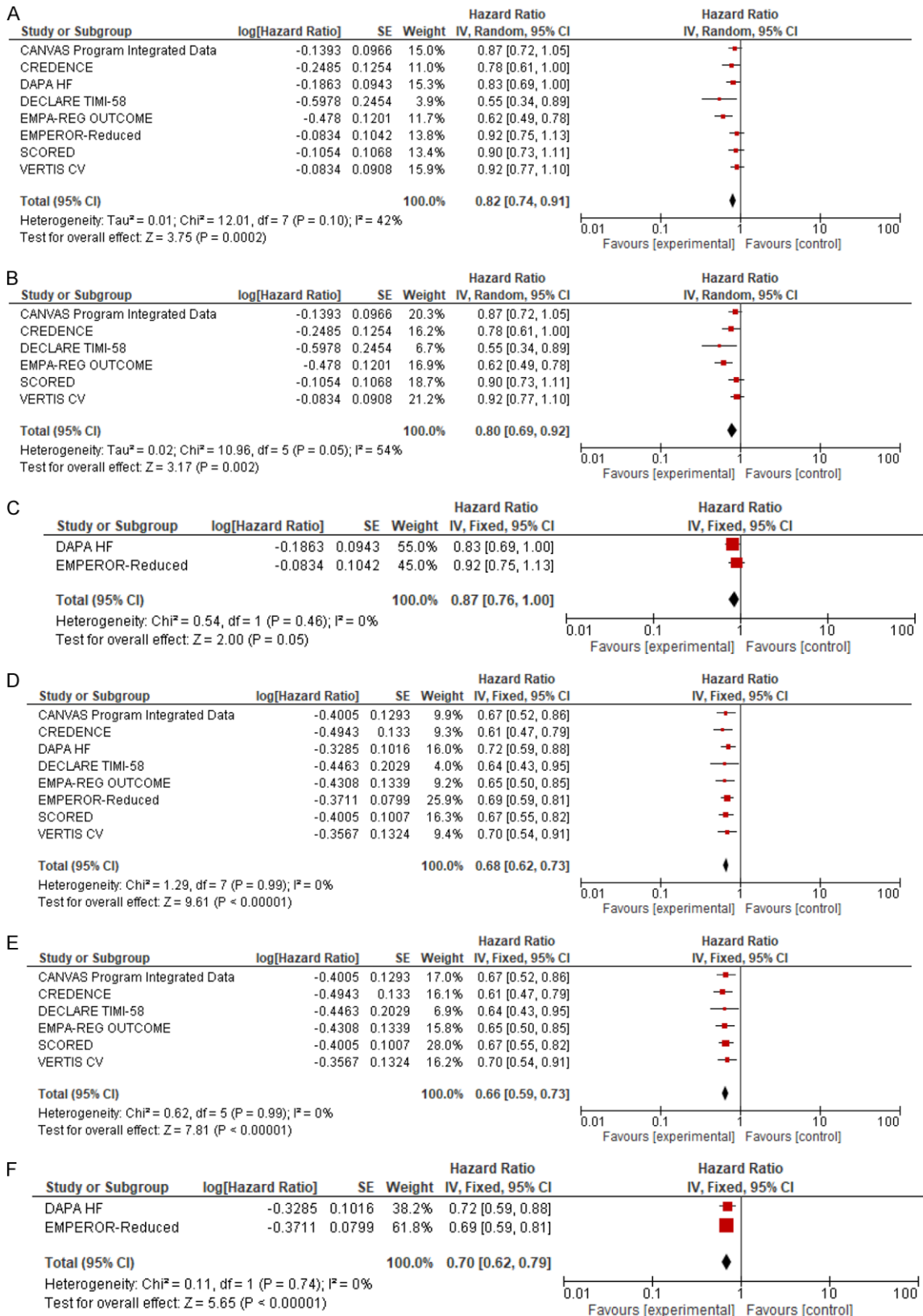Risk Difference M-H, Random, 95% CI — scale -1, -0.5, 0, 0.5, 1 — Placebo/Control SGLT2 Inhibitor

Figure 2. Forest plot comparing the relative risk of major outcome measures in patients receiving sodium-glucose co-transporter type 2 inhibitor versus placebo/other treatments in DM patients with HF, stratified based on DM and HF severity. From above to below: Cardiovascular death, in general (A), in DM patients regardless of baseline HF severity (B), in HF patients regardless of DM status (C). Hospitalization for heart failure, in general (D), in DM patients regardless of baseline HF severity (E), and in HF patients regardless of DM status (F).

trials, this meta-analysis uses different metrics to pool the clinical data including risk difference and log hazard ratio. Our pooled analysis confirms the favorable cardiovascular benefits of SGLT2 inhibitors in reducing the risk of CVD and HHF in HF patients regardless of the severity of EF reduction and in patients with DM regardless of the severity of DM. However, while these benefits extend to non-diabetic patients in terms of HHF reduction, their benefit in reducing CVD is uncertain for non-diabetic patients with HF currently.

Our pooled analysis confirms, with a high degree of certainty, the findings of other meta-analyses on the cardiorenal benefits of SGLT2 inhibitors in diabetic patients regardless of HF status [10, 12]. Moreover, our results are aligned in the same direction with previous pooled analysis in the fact that the cardiovascular benefits of SGLT2 inhibitors are seen regardless of the proportion of patients with DM. However, previous meta-analyses have not included data from small RCTs [7, 13, 14, 19], which could lead to a publication bias. Nonetheless, these previous meta-analyses included <10 studies. This can be especially problematic considering our equivocal findings for the beneficial effects of SGLT2 inhibitors for CVD mortality in non-diabetic patients with HF, even after inclusion of the results of a recent RCT with exclusive data in nondiabetic patients with HF [14], which has not been included in any of the previous meta-analyses.

SGLT-2 inhibitors have a glucose-lowering effect which is independent from stimulating insulin release from β cells and is mainly mediated through the inhibition of renal tubular reabsorption of the filtered glucose [24]. An

increasing number of SGLT2 inhibitors have been approved by the Food and Drug Administration (FDA) for the treatment of DM. Besides their anti-diabetic effects, the cardiovascular and renal protective benefits of this drug class in DM population have been consistently shown in placebo-controlled RCTs [10-12, 25]. Of note, these trials have been conducted in patients with history of DM for ≥10 years and established cardiovascular disease. However, it is not clear at this time if SGLT2 inhibitors might confer their cardiovascular benefit in patients without DM or recently diagnosed diabetic patients.

The glycosuric and natriuretic functions of SGLT2 inhibitors probably contributed to the cardiovascular and renal protective effects. Excess excretion of the plasma glucose and sodium results in a significant reduction in the intravascular overload and arterial blood pressure. Further, improvement in endothelial function and vascular wall stiffness, reduction in the myocardial stretch and excess work, and amelioration of albuminuria and glomerular filtration rate loss through enhanced tubuloglomerular feedback may also contribute to the salutary effects of this drug class [26]. We believe that our analysis, especially through a step-by-step subgroup analysis of the only two RCTs in nondiabetic patients, can guide the ongoing work on detailed mechanisms of the effects of SGLT2 inhibitors.

Based on our analysis, we suggest that SGLT2 inhibitors reduce the risk of CVD in DM patients by 1% regardless of the type and severity of HF. The SGLT2 inhibitors double the benefit, i.e. a reduction of 2%, in HF patients without DM. On the other hand, HHF is reduced by 2% in

A

Study or Subgroup	log[Hazard Ratio]	SE	Weight	Hazard Ratio IV, Random, 95% CI
CANVAS Program Integrated Data	-0.1393	0.0966	15.0%	0.87 [0.72, 1.05]
CREDENCE	-0.2485	0.1254	11.0%	0.78 [0.61, 1.00]
DAPA HF	-0.1863	0.0943	15.3%	0.83 [0.69, 1.00]
DECLARE TIMI-58	-0.5978	0.2454	3.9%	0.55 [0.34, 0.89]
EMPA-REG OUTCOME	-0.478	0.1201	11.7%	0.62 [0.49, 0.78]
EMPEROR-Reduced	-0.0834	0.1042	13.8%	0.92 [0.75, 1.13]
SCORED	-0.1054	0.1068	13.4%	0.90 [0.73, 1.11]
VERTIS CV	-0.0834	0.0908	15.9%	0.92 [0.77, 1.10]
Total (95% CI)			**100.0%**	**0.82 [0.74, 0.91]**

Heterogeneity: Tau² = 0.01; Chi² = 12.01, df = 7 (P = 0.10); I² = 42%
Test for overall effect: Z = 3.75 (P = 0.0002)

B

Study or Subgroup	log[Hazard Ratio]	SE	Weight	Hazard Ratio IV, Random, 95% CI
CANVAS Program Integrated Data	-0.1393	0.0966	20.3%	0.87 [0.72, 1.05]
CREDENCE	-0.2485	0.1254	16.2%	0.78 [0.61, 1.00]
DECLARE TIMI-58	-0.5978	0.2454	6.7%	0.55 [0.34, 0.89]
EMPA-REG OUTCOME	-0.478	0.1201	16.9%	0.62 [0.49, 0.78]
SCORED	-0.1054	0.1068	18.7%	0.90 [0.73, 1.11]
VERTIS CV	-0.0834	0.0908	21.2%	0.92 [0.77, 1.10]
Total (95% CI)			**100.0%**	**0.80 [0.69, 0.92]**

Heterogeneity: Tau² = 0.02; Chi² = 10.96, df = 5 (P = 0.05); I² = 54%
Test for overall effect: Z = 3.17 (P = 0.002)

C

Study or Subgroup	log[Hazard Ratio]	SE	Weight	Hazard Ratio IV, Fixed, 95% CI
DAPA HF	-0.1863	0.0943	55.0%	0.83 [0.69, 1.00]
EMPEROR-Reduced	-0.0834	0.1042	45.0%	0.92 [0.75, 1.13]
Total (95% CI)			**100.0%**	**0.87 [0.76, 1.00]**

Heterogeneity: Chi² = 0.54, df = 1 (P = 0.46); I² = 0%
Test for overall effect: Z = 2.00 (P = 0.05)

D

Study or Subgroup	log[Hazard Ratio]	SE	Weight	Hazard Ratio IV, Fixed, 95% CI
CANVAS Program Integrated Data	-0.4005	0.1293	9.9%	0.67 [0.52, 0.86]
CREDENCE	-0.4943	0.133	9.3%	0.61 [0.47, 0.79]
DAPA HF	-0.3285	0.1016	16.0%	0.72 [0.59, 0.88]
DECLARE TIMI-58	-0.4463	0.2029	4.0%	0.64 [0.43, 0.95]
EMPA-REG OUTCOME	-0.4308	0.1339	9.2%	0.65 [0.50, 0.85]
EMPEROR-Reduced	-0.3711	0.0799	25.9%	0.69 [0.59, 0.81]
SCORED	-0.4005	0.1007	16.3%	0.67 [0.55, 0.82]
VERTIS CV	-0.3567	0.1324	9.4%	0.70 [0.54, 0.91]
Total (95% CI)			**100.0%**	**0.68 [0.62, 0.73]**

Heterogeneity: Chi² = 1.29, df = 7 (P = 0.99); I² = 0%
Test for overall effect: Z = 9.61 (P < 0.00001)

E

Study or Subgroup	log[Hazard Ratio]	SE	Weight	Hazard Ratio IV, Fixed, 95% CI
CANVAS Program Integrated Data	-0.4005	0.1293	17.0%	0.67 [0.52, 0.86]
CREDENCE	-0.4943	0.133	16.1%	0.61 [0.47, 0.79]
DECLARE TIMI-58	-0.4463	0.2029	6.9%	0.64 [0.43, 0.95]
EMPA-REG OUTCOME	-0.4308	0.1339	15.8%	0.65 [0.50, 0.85]
SCORED	-0.4005	0.1007	28.0%	0.67 [0.55, 0.82]
VERTIS CV	-0.3567	0.1324	16.2%	0.70 [0.54, 0.91]
Total (95% CI)			**100.0%**	**0.66 [0.59, 0.73]**

Heterogeneity: Chi² = 0.62, df = 5 (P = 0.99); I² = 0%
Test for overall effect: Z = 7.81 (P < 0.00001)

F

Study or Subgroup	log[Hazard Ratio]	SE	Weight	Hazard Ratio IV, Fixed, 95% CI
DAPA HF	-0.3285	0.1016	38.2%	0.72 [0.59, 0.88]
EMPEROR-Reduced	-0.3711	0.0799	61.8%	0.69 [0.59, 0.81]
Total (95% CI)			**100.0%**	**0.70 [0.62, 0.79]**

Heterogeneity: Chi² = 0.11, df = 1 (P = 0.74); I² = 0%
Test for overall effect: Z = 5.65 (P < 0.00001)

Figure 3. Forest plot comparing the log hazard ratio of major outcome measures in patients receiving sodium-glucose co-transporter type 2 inhibitor versus placebo/other treatments, stratified based on DM status and HF severity. From above to below: 1. Cardiovascular death, in general (A), in DM patients regardless of baseline HF severity (B),

and in HF patients regardless of DM status (C). 2. Hospitalization for heart failure, in general (D), in DM patients regardless of baseline HF severity (E), and in HF patients regardless of DM status (F).
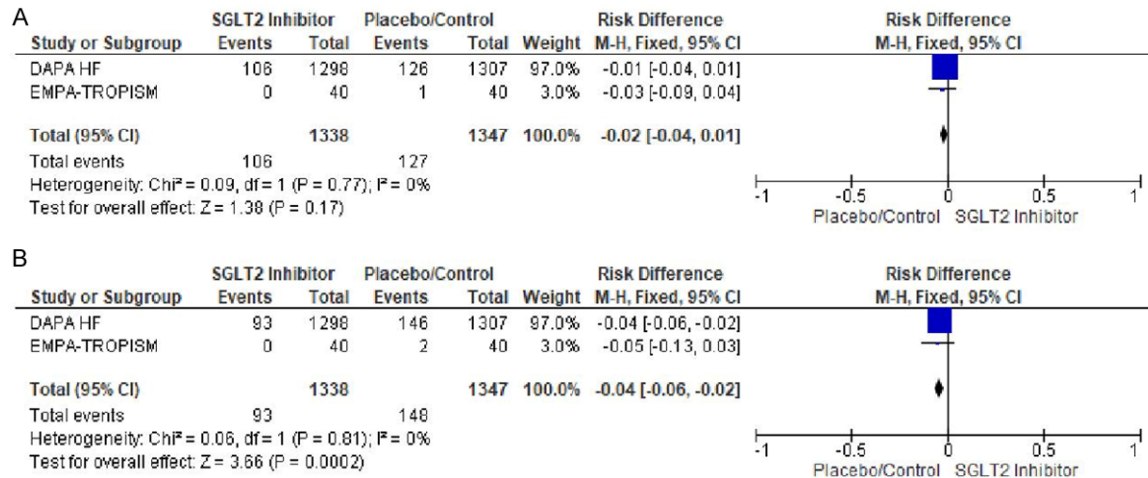

Figure 4. A subgroup analysis of studies with nondiabetic patients with heart failure receiving an SGLT2 inhibitor compared to placebo/control. Above: Cardiovascular death; Below: Hospitalization for heart failure.
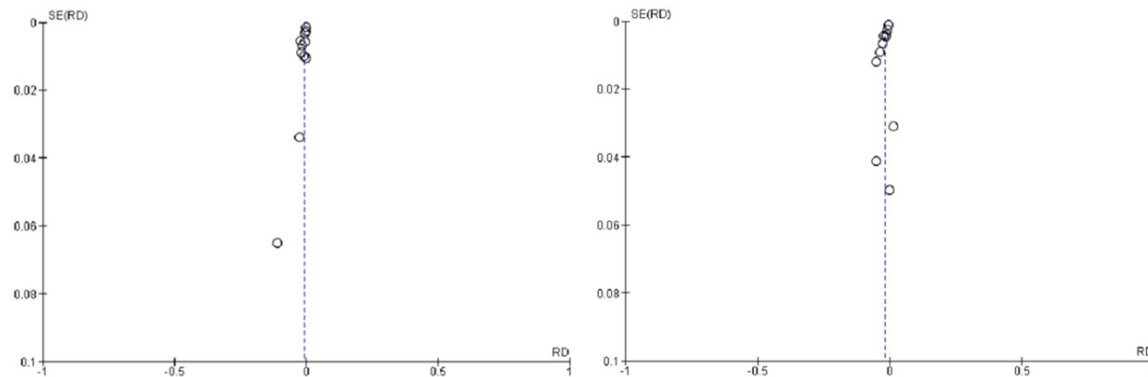

Figure 5. Funnel plots depicting the study precision against the study effect size for evaluation of the publication bias. Left: Cardiovascular death; Right: Hospitalization for heart failure.

patients with DM and HF, this benefit doubles to 5% in HF patients without DM (**Figure 2**). While this might be interpreted as twice the benefit in patients without DM, in terms of reduction in CVD and HHF, the statistical significance and the level of confidence for this interpretation is low due to the limited number of studies in non-diabetic HF patients.

There was a moderate level of heterogeneity across the included studies, for both outcome measures, which diminished the confidence in relation to HF severity and DM status. Other factors might have also contributed to the observed heterogeneity such as different population characteristics, variable selectivity of different drugs in the SGLT2 inhibitor classes, and different duration of follow-up [24, 26]. The outcome trials included in our analysis used SGLT2 inhibitors with different selectivity for their target, with canagliflozin having the least selectivity and empagliflozin having the greatest one [24, 27]. Additionally, these trials had a mix of patients with HF and DM, especial in relation to the severity of HF and control of DM, with only few dedicated trials designed to study the effect of dapagliflozin in patients with HF [6].

Future RCTs in HF patients receiving SGLT2 inhibitors are required to provide stratified

analyses based on different HF classes, EF reduction, DM status, and glycemic control. Additionally, future studies may provide information on cost-benefit in different groups of patients with HF and DM status.

Conclusion

SGLT2 inhibitors have shown benefits in reducing CVD and HHF in patients with HF and DM. Such benefits have also been shown in patients without DM. However, evidence of benefit in nondiabetic patients with HF remains unclear. We hope this will be confirmed in future trials. We think that the cost-benefit of the use of SGLT2 inhibitors must be shown prior to routine use of this drug class in HF patients with and without DM can be recommended.

Disclosure of conflict of interest

None.

Address correspondence to: Dr. Saeed Shoar, Department of Clinical Research, ScientificWriting Corp, 3403 Garth Road, Houston, TX 77521, USA. Tel: 929-351-9063; E-mail: saeedshoar@scientific-writing.org

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