



Commentary: Sodium Glucose Cotransporter 2 Inhibitors Reduce the Risk of Heart Failure Hospitalization in Patients With Type 2 Diabetes Mellitus: A Systematic Review and Meta-Analysis of Randomized Controlled Trials

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A Commentary on

Sodium Glucose Cotransporter 2 Inhibitors Reduce the Risk of Heart Failure Hospitalization in Patients With Type 2 Diabetes Mellitus: A Systematic Review and Meta-Analysis of Randomized Controlled Trials

By Zhang A, Luo X, Meng H, et al. Front Endocrinol (Lausanne) (2020) 11:604250. doi: 10.3389/fendo.2020.604250

INTRODUCTION

We read with interest a meta-analysis (1) recently published in "Frontiers in Endocrinology" conducted by Zhang et al. In this study (1), Zhang and colleagues included eight randomized controlled trials (RCTs) comparing sodium-glucose cotransporter 2 inhibitors (SGLT2is) with placebo in patients with type 2 diabetes (T2D), and performed a meta-analysis to produce a pooled risk ratio (RR) and 95% confidence interval (CI) of SGLT2is versus placebo in reducing four cardiovascular endpoints.

The authors in this study (1) concluded that SGLT2is would be an ideal choice for T2D patients with heart failure (HF) because they found that SGLT2is significantly reduced hospitalization for heart failure (HHF), major adverse cardiovascular events (MACE, a composite of cardiovascular death, myocardial infarction, or stroke), and cardiovascular death (CVD) versus placebo in T2D patients. On the other hand, they concluded that SGLT2is did not significantly affect all-cause death (ACD) because they produced the nonsignificant 95% CI of RR (SGLT2is versus placebo: RR 0.77, 95% CI 0.59-1.01) for ACD. In my opinion, these two conclusions are not rigorous. First, they cannot conclude that SGLT2is are an ideal choice for T2D patients with HF until they assess the

efficacy of SGLT2is in this T2D subgroup of concomitant HF and identify the obvious effectiveness. Second, using RR as drug effect is not accurate enough; all the original studies included in the meta-analysis (1) used hazard ratio (HR) as drug effect and RR only contains the status of the occurrence of events, but fails to contain the time when events happen. HR, on the other hand, contains both.

Thus, to validate and further extend the findings in the metaanalysis by Zhang et al. (1), we implemented this further quantitative synthesis study by carrying out a meta-analysis stratified by the status of HF based on the data of HRs and 95% CIs as reported in the original studies. Moreover, we additionally incorporated the recently published SOLOIST-WHF trial (2), in addition to the eight RCTs included in the study by Zhang et al. (1), because this trial (2) contributed to the relevant data of the T2D subgroup of concomitant HF.

FINDINGS DERIVED FROM OUR META-ANALYSIS

Figure 1 shows the results of fixed-effects meta-analysis of the effects of SGLT2is on HHF, MACE, CVD, and ACD in T2D patients, stratified by the status of HF. Compared with placebo, SGLT2is significantly reduced HHF in T2D patients with HF (HR 0.66, 95% CI 0.58-0.74, P <0.001) and in T2D patients without HF (HR 0.68, 95% CI 0.60-0.78, P < 0.001), with the nonsignificant subgroup effect (P_{subgroup} =0.677) (Figure 1A). SGLT2is did not significantly affect MACE in T2D patients with HF (HR 0.95, 95% CI 0.84-1.09, P =0.492) but significantly reduced MACE in T2D patients without HF (HR 0.89, 95% CI 0.83-0.96, P =0.002), with the nonsignificant subgroup effect (P_{subgroup} =0.377) (Figure 1B). SGLT2is produced a reduced trend in the risk of CVD in T2D patients with HF (HR 0.88, 95% CI 0.76-1.01, P =0.070) and significantly reduced CVD in T2D patients without HF (HR 0.81, 95% CI 0.72-0.92, P =0.001), with the nonsignificant subgroup effect (P_{subgroup} =0.452) (Figure 1C). SGLT2is significantly reduced ACD in T2D patients with HF (HR 0.82, 95% CI 0.71-0.95, P =0.007) and in T2D patients without HF (HR 0.87, 95% CI 0.79-0.95, P =0.002), with the nonsignificant subgroup effect (P_{subgroup} =0.509) (Figure 1D).

Due to substantial heterogeneity observed in fixed-effects meta-analyses of CVD and ACD, an additional meta-analysis using a random-effects model was conducted for the two outcomes to assess the robustness of pooled analysis results. **Figure S1** (random-effects model for CVD) shows that SGLT2is significantly reduced CVD (Overall HR 0.83, 95% CI 0.74-0.94, P <0.001) in T2D patients regardless of whether they were with/without HF ($P_{subgroup} = 0.452$). **Figure S2** (random-effects model for ACD) shows that SGLT2is significantly reduced ACD (Overall HR 0.84, 95% CI 0.77-0.92, P <0.001) in T2D patients regardless of whether they were with/without HF (P_subgroup =0.509). The results revealed by random-effects model were consistent with those shown by the fixed-effects model. All the data extracted from included studies and analyzed in the present meta-analysis are given in **Supplementary Material 1**.

DISCUSSION

Based on the HRs and 95% CIs derived from nine RCTs, consisting of eight RCTs included in the meta-analysis by Zhang et al. (1) and the SOLOIST-WHF trial (2), we conducted a further meta-analysis to evaluate the efficacy of SGLT2is on four cardiovascular outcomes (HHF, MACE, CVD, and ACD) in the two T2D subgroups of T2D patients with HF and T2D patients without HF. Accordingly, we identified that SGLT2is versus placebo significantly reduced HHF (HR 0.66, 95% CI 0.58-0.74) and ACD (HR 0.82, 95% CI 0.71-0.95) and showed a decreased trend in the risk of CVD (HR 0.88, 95% CI 0.76-1.01) but did not significantly affect MACE (HR 0.95, 95% CI 0.84-1.09) in T2D patients with HF, while SGLT2is significantly reduced the four endpoints in T2D patients without HF. These findings support that SGLT2is should be used in T2D patients with HF as well as in T2D patients without HF to prevent the occurrence of these mortality and cardiovascular outcomes.

Two prior meta-analyses (3, 4), including three to five RCTs revealed that SGLT2is versus placebo significantly reduced the composite outcome of CVD or HHF in T2D patients regardless of whether they were with/without HF, but failed to assess the two individual outcomes according to the status of HF. Our present meta-analysis, including nine RCTs, further demonstrates the efficacy of SGLT2is on three individual outcomes (i.e., HHF, CVD, and ACD) in T2D patients independent of the status of HF.

Moreover, a meta-analysis (4) from our research team also confirmed that SGLT2is significantly reduced HF and renal failure composite outcomes in T2D patients regardless of whether they were with/without HF and regardless of whether they were had chronic kidney disease (CKD). A meta-analysis (5) based on the two trials of DAPA-HF (6) and EMPEROR-Reduced (7) conducted in HF patients identified the effectiveness of SGLT2is in reducing HF composite outcome among HF patients independent of T2D and CKD status. The DAPA-CKD trial (8) revealed that dapagliflozin produced similar benefits on the renal and cardiovascular composite endpoint for CKD patients regardless of T2D status. According to the above findings from previous studies (4-8), SGLT2is should be recommended in T2D patients with/without CKD, in HF patients with/without T2D/CKD, and in CKD patients with/without T2D to prevent cardiovascular, renal, and mortality events.

In the present meta-analysis, we conducted subgroup analyses stratified by the presence of HF or not, but failed to carry out more specific subgroup analyses stratified by HF with reduced ejection fraction (HFrEF), HF with mid-range ejection fraction (HFmrEF), or HF with preserved ejection fraction (HFpEF). Further studies performing these analyses would be clinically meaningful.

The findings revealed by the present meta-analysis suggest that SGLT2is should be used in T2D patients with/without HF, while those revealed by previous meta-analyses and large randomized trials suggest that SGLT2is should be also recommended in T2D

Study		Treatment	Placebo				%	Subgroup		Treatment	Placebo			96
,	Treatment	(n)	(n)			HR (95% CI)	Weight	Study	Treatment	(n)	(n)		HR (95% CI)	Weight
T2D with HF								T2D						
EMPA-REG OUTCOME			244		-+	- 0.75 (0.48, 1.19)		T2D with HF				_		
CANVAS Program	Canagliflozin		658		-+	0.51 (0.33, 0.78)		CANVAS Program	Canagliflozin		658	-•;	- 0.80 (0.61, 1.05)	
DECLARE-TIMI 58	Dapagliflozin		872			0.73 (0.55, 0.96)		DECLARE-TIMI 58	Dapagliflozin	852	872		1.01 (0.81, 1.27)	7.76
CREDENCE	Canagliflozin		323		•	- 0.76 (0.47, 1.22)		CREDENCE	Canagliflozin	329	323		0.93 (0.63, 1.37)	2.60
VERTIS CV	Ertugliflozin		672			0.63 (0.44, 0.90)		VERTIS CV	Ertugliflozin	1286	672		 1.05 (0.82, 1.35) 	6.31
Kosiborod 2017	Dapagliflozin		149 —	*		- 0.14 (0.02, 1.15)		Kosiborod 2017	Dapagliflozin	171	149		0.87 (0.30, 2.53)	0.35
EMPEROR-Reduced	Empagliflozin		929			0.65 (0.50, 0.85)		Subtotal (I-squared				Å	> 0.95 (0.84, 1.09)	
SOLOIST-WHF	Sotagliflozin		614		-	0.64 (0.49, 0.83)		Subtotal (I-squaret	1 - 0.070, p - 0.	045)		Y	0.55 (0.04, 1.05)	22.55
Subtotal (I-squared =	0.0%, p = 0.672)				- Y-	0.66 (0.58, 0.74)	54.20							
T2D 11								T2D without HF						
T2D without HF EMPA–REG OUTCOME	Former all film all a	4005	2089			0.59 (0.43, 0.82)	0.10	CANVAS Program	Canagliflozin	4992	3689		0.87 (0.76, 1.01)	19.40
			2089 3689					DECLARE-TIMI 58	Dapagliflozin	7730	7706	-	0.92 (0.82, 1.02)	32.93
CANVAS Program DECLARE-TIMI 58	Canagliflozin Dapagliflozin		3689 7706		_	0.79 (0.57, 1.09) 0.73 (0.58, 0.92)		CREDENCE	Canagliflozin	1873	1876	+	0.76 (0.62, 0.93)	9.54
CREDENCE	Canagliflozin		1876			0.73 (0.58, 0.92) 0.54 (0.39, 0.75)		VERTIS CV	Ertugliflozin		2075		0.95 (0.81, 1.11)	
VERTIS CV	Ertugliflozin		2075			 0.34 (0.39, 0.73) 0.79 (0.54, 1.15) 		Subtotal (I-squared	-		20/5		0.89 (0.83, 0.96)	
Subtotal (I-squared =	-		2075			0.68 (0.60, 0.78)		Subtotal (I-squaret	1 = 12.7%, p = 0	J.529)		Y	0.09 (0.05, 0.90)	//.0/
Subtotal (i-squared -	5.0%, p = 0.550)				Υ	0.00 (0.00, 0.78)	45.00							
Heterogeneity betwee	a groups: p = 0.6	577						Heterogeneity betw	/een groups: p	= 0.377				
Overall (I-squared = 0.					6	0.67 (0.61, 0.73)	100.00	Overall (I-squared	= 0.0%, p = 0.5	70)		\Diamond	0.91 (0.85, 0.96)	100.00
oreian (r squarea - s	(, , , , , , , , , , , , , , , , , , ,				Ť.	0107 (010 1) 017 07								
C Cardiov	ascular de	eath		SGLT2is r	educe risk	SGLT2is increase ri	isk	D All-ca	ause dea	ath		SGLT2is reduce risk	SGLT2is increase risk	
ouraior		eath Treatment	Placebo	SGLT2is r	educe risk	SGLT2is increase ri	%	D All-ca	ause dea	ath Treatment		SGL12Is reduce risk	SGLT2is increase risk	%
Subgroup			Placebo (n)	SGLT2is r	educe risk	SGLT2is increase ri HR (95% Cl)		7 11 0	ause dea Treatment			SGL12Is reduce risk	SGLT2is increase risk HR (95% CI)	% Weigh
C Cardiov Subgroup Study T2D with HF		Treatment		SGLT2is r	educe risk		%	Subgroup Study		Treatment	Placebo	SGL12IS reduce risk		% Weigh
Subgroup Study		Treatment (n)		SGLT2is r	educe risk		% Weight	Subgroup Study T2D with HF	Treatment	Treatment (n)	Placebo	SGL 12Is reduce risk	HR (95% CI)	
Sudgroup Study F2D with HF EMPA-REG OUTCOME	Treatment	Treatment (n) 462	(n)	SGLT2is r	educe risk	HR (95% CI)	% Weight 3.48	Subgroup Study T2D with HF EMPA–REG OUTCOME	Treatment	Treatment (n) n 462	Placebo (n) 244	SGL 12is reduce risk	HR (95% CI)	3.33
F2D with HF EMPA-REG OUTCOME CANVAS Program	Treatment Empagliflozin Canagliflozin	Treatment (n) 462 803	(n) 244	SGLT2is r	educe risk	HR (95% Cl) 0.71 (0.43, 1.16) 0.72 (0.51, 1.02)	% Weight 3.48 7.14	Subgroup Study T2D with HF EMPA–REG OUTCOME CANVAS Program	Treatment Empagliflozin Canagliflozin	Treatment (n) n 462 i 803	Placebo (n) 244 658	SGL I Zis reduce risk	HR (95% CI)	3.33 5.83
Subgroup Study T2D with HF EMPA-REG OUTCOME CANVAS Program DECLARE-TIMI 58	Treatment Empagliflozin Canagliflozin Dapagliflozin	Treatment (n) 462 803 852	(n) 244	SGLT2is r	educe risk	HR (95% CI) 0.71 (0.43, 1.16) 0.72 (0.51, 1.02) 1.01 (0.73, 1.39)	% Weight 3.48 7.14 8.27	Subgroup Study T2D with HF EMPA-REG OUTCOME CANVAS Program DECLARE-TIMI 58	Treatment Empagliflozin Canagliflozin Dapagliflozin	Treatment (n) n 462 n 803 n 852	Placebo (n) 244 658 872	SGL I Zis reduce risk	HR (95% CI)	3.33 5.83 9.36
T2D with HF EMPA-REG OUTCOME CANVAS Program DECLARE-TIMI 58 CREDENCE	Treatment Empagliflozin Canagliflozin Dapagliflozin Canagliflozin	Treatment (n) 462 803 852 329	(n) 244	SGLT2Is r	educe risk	HR (95% Cl) 0.71 (0.43, 1.16) 0.72 (0.51, 1.02) 1.01 (0.73, 1.39) 1.02 (0.63, 1.65)	% Weight 3.48 7.14 8.27 3.70	Subgroup Study T2D with HF EMPA-REG OUTCOME CANVAS Program DECLARE-TIMI 58 CREDENCE	Treatment Empagliflozin Canagliflozin Dapagliflozin Canagliflozin	Treatment (n) n 462 i 803 n 852 i 329	Placebo (n) 244 658 872 323	Sul Lis reduce risk	HR (95% CI)	3.33 5.83 9.36 3.34
T2D with HF EMPA-REG OUTCOME CANVAS Program DECLARE-TIMI 58 CREDENCE EMPEROR-Reduced	Treatment Empagliflozin Canagliflozin Dapagliflozin Canagliflozin Empagliflozin	Treatment (n) 462 803 852 329 927	(n) 244 658 872 323 929	SGLT2Is r	educe risk	HR (95% Cl) 0.71 (0.43, 1.16) 0.72 (0.51, 1.02) 1.01 (0.73, 1.39) 1.02 (0.63, 1.65) 0.92 (0.71, 1.20)	% Weight 3.48 7.14 8.27 3.70 12.45	Subgroup Study T2D with HF EMPA-REG OUTCOME CANVAS Program DECLARE-TIMI 58	Treatment Empagliflozin Canagliflozin Dapagliflozin	Treatment (n) n 462 i 803 n 852 i 329	Placebo (n) 244 658 872	Sol 1 Zis reduce risk	HR (95% CI)	3.33 5.83 9.36 3.34
T2D with HF EMPA-REG OUTCOME CANVAS Program DECLARE-TIMI 58 CREDENCE EMPEROR-Reduced SOLOISTWHF	Treatment Empagliflozin Canagliflozin Dapagliflozin Canagliflozin Sotagliflozin	Treatment (n) 462 803 852 329 927	(n) 244	SGLT28r	educe risk	HR (95% Cl) 0.71 (0.43, 1.16) 0.72 (0.51, 1.02) 1.01 (0.73, 1.39) 1.02 (0.63, 1.65) 0.92 (0.71, 1.20) 0.84 (0.58, 1.22)	% Weight 3.48 7.14 8.27 3.70 12.45 6.20	Subgroup Study T2D with HF EMPA-REG OUTCOME CANVAS Program DECLARE-TIMI 58 CREDENCE	Treatment Empagliflozir Canagliflozin Dapagliflozin Canagliflozin Sotagliflozin	Treatment (n) n 462 i 803 n 852 i 329	Placebo (n) 244 658 872 323	Sol 12/s reduce risk	HR (95% CI)	3.33 5.83 9.36 3.34 5.37
CANNAS PROFESSIONAL CONTENTS OF CONTENTS O	Treatment Empagliflozin Canagliflozin Dapagliflozin Canagliflozin Sotagliflozin	Treatment (n) 462 803 852 329 927	(n) 244 658 872 323 929	SGLT2Is r	educe risk	HR (95% Cl) 0.71 (0.43, 1.16) 0.72 (0.51, 1.02) 1.01 (0.73, 1.39) 1.02 (0.63, 1.65) 0.92 (0.71, 1.20)	% Weight 3.48 7.14 8.27 3.70 12.45 6.20	Subgroup Study T2D with HF EMPA-REG OUTCOME CANVAS Program DECLARE-TIMI 58 CREDENCE SOLOIST-WHF	Treatment Empagliflozir Canagliflozin Dapagliflozin Canagliflozin Sotagliflozin	Treatment (n) n 462 i 803 n 852 i 329	Placebo (n) 244 658 872 323	Sol 12/s reduce risk	HR (95% C) 0.79 (0.52, 1.20 0.70 (0.51, 0.96 0.87 (0.68, 1.12 0.94 (0.62, 1.43 0.94 (0.62, 1.43 0.82 (0.59, 1.14	3.33 5.83 9.36 3.34 5.37
Subgroup Study T2D with HF EMPA-REG OUTCOME CANVAS Program DECLARE-TIMI 58 CREDENCE EMPEROR-Reduced SOLOISTWHF Subtotal (I-squared = 0	Treatment Empagliflozin Canagliflozin Dapagliflozin Canagliflozin Sotagliflozin	Treatment (n) 462 803 852 329 927	(n) 244 658 872 323 929	SGLT28r	educe risk	HR (95% Cl) 0.71 (0.43, 1.16) 0.72 (0.51, 1.02) 1.01 (0.73, 1.39) 1.02 (0.63, 1.65) 0.92 (0.71, 1.20) 0.84 (0.58, 1.22)	% Weight 3.48 7.14 8.27 3.70 12.45 6.20	Subgroup Study T2D with HF EMPA-REG OUTCOME CANVAS Program DECLARE-TIMI 58 CREDENCE SOLOIST-WHF	Treatment Empagliflozir Canagliflozin Dapagliflozin Canagliflozin Sotagliflozin	Treatment (n) n 462 i 803 n 852 i 329	Placebo (n) 244 658 872 323	Sol 12/s reduce risk	HR (95% C) 0.79 (0.52, 1.20 0.70 (0.51, 0.96 0.87 (0.68, 1.12 0.94 (0.62, 1.43 0.94 (0.62, 1.43 0.82 (0.59, 1.14	3.33 5.83 9.36 3.34 5.37
T2D with HF EMPA-REG OUTCOME CANVAS Program DECLARE-TIMI 58 CREDENCE EMPEROR-Reduced SIGLOISTWHF Subtotal (I-squared = 0 T2D without HF	Treatment Empagliflozin Canagliflozin Dapagliflozin Canagliflozin Sotagliflozin 30%, p = 0.664)	Treatment (n) 462 803 852 329 927 608	(n) 244 658 872 323 929 614	SGLT28r	educe risk	HR (95% CI) 0.71 (0.43, 1.16) 0.72 (0.51, 1.02) 1.01 (0.73, 1.39) 1.02 (0.63, 1.65) 0.92 (0.71, 1.20) 0.84 (0.58, 1.22) 0.88 (0.76, 1.01)	% Weight 3.48 7.14 8.27 3.70 12.45 6.20 41.24	Subgroup Study T2D with HF EMPA-REG OUTCOME CANVAS Program DECLARE-TIMI 58 CREDENCE SOLOIST-WHF Subtotal (I-squared = C T2D without HF	Treatment Empagliflozin Canagliflozin Dapagliflozin Canagliflozin Sotagliflozin Sotagliflozin	Treatment (n) n 462 h 803 h 852 h 329 608	Placebo (n) 244 658 872 323	Sul 12is reduce risk	HR (95% CI) 0.79 (0.52, 1.20 0.70 (0.51, 0.96 0.87 (0.68, 1.12 0.94 (0.62, 1.43 0.82 (0.59, 1.14 0.82 (0.71, 0.95	3.33 5.83 9.36 3.34 5.37 27.24
T2D with HF EMPA-REG OUTCOME CANVAS Program DECLARE-TIMI 58 CREDENCE EMPEROR-Reduced SOLOIST-WHF Subtotal (I-squared = 0 T2D without HF EMPA-REG OUTCOME	Treatment Empagliflozin Canagliflozin Dapagliflozin Canagliflozin Sotagliflozin 0%, p = 0.664) Empagliflozin	Treatment (n) 462 803 852 329 927 608 4225	(n) 244	SGLT2Is r	educe risk	HR (95% Cl) 0.71 (0.43, 1.16) 0.72 (0.51, 1.02) 1.01 (0.73, 1.39) 1.02 (0.63, 1.65) 0.92 (0.71, 1.20) 0.84 (0.58, 1.22) 0.88 (0.76, 1.01) 0.60 (0.47, 0.77)	% Weight 3.48 7.14 8.27 3.70 12.45 6.20 41.24 14.07	Subgroup Study T2D with HF EMPA-REG OUTCOME CANVAS Program DECLARE-TIM IS8 CREDENCE SOLOIST-WHF Subtotal (I-squared = (I T2D without HF EMPA-REG OUTCOME	Treatment Empagliflozin Canagliflozin Dapagliflozin Canagliflozin Sotagliflozin Sotagliflozin Canagliflozin Empagliflozin	Treatment (n) 462 803 852 608 n 4225	Placebo (n) 244 658 872 323 614 2089	Sol 1 2/s reduce risk	HR (95% CI) 0.79 (0.52, 1.20 0.70 (0.51, 0.96 0.87 (0.68, 1.12 0.94 (0.62, 1.43 0.94 (0.62, 1.43 0.82 (0.59, 1.14 0.82 (0.71, 0.95 0.66 (0.51, 0.81)	3.33 5.83 9.36 3.34 5.37 27.24
Canvas and a construction of the construction	Treatment Empagliflozin Canagliflozin Canagliflozin Canagliflozin Sotagliflozin 0%, p = 0.664) Empagliflozin Canagliflozin	Treatment (n) 462 803 852 329 927 608 4225 4992	(n) 244	SGLT2Is r	educe risk	HR (95% C)) 0.71 (0.43, 1.16) 0.72 (0.51, 1.02) 1.01 (0.73, 1.39) 1.02 (0.63, 1.65) 0.92 (0.71, 1.20) 0.84 (0.58, 1.22) 0.88 (0.76, 1.01) 0.60 (0.47, 0.77) 0.95 (0.76, 1.20)	% Weight 3.48 7.14 8.27 3.70 12.45 6.20 41.24 14.07 16.44	Subgroup Study T2D with HF EMPA-REG OUTCOME CANVAS Program DECLARE-TIMI 58 CREDENCE SOLOIST-WHF Subtotal (I-squared = (T2D without HF EMPA-REG OUTCOME CANVAS Program	Treatment Empagliflozi Canagliflozin Dapagliflozin Canagliflozin Sotagliflozin Sotagliflozin Empagliflozin Canagliflozin	Treatment (n) 462 803 852 608 608	Placebo (n) 244 658 872 323 614 2089 3689	Sul 12is reduce risk	HR (95% C) 0.79 (0.52, 1.20 0.70 (0.51, 0.96 0.87 (0.68, 1.12 0.94 (0.62, 1.43 0.94 (0.62, 1.43 0.82 (0.59, 1.14 0.82 (0.71, 0.95 0.66 (0.51, 0.81 0.93 (0.78, 1.11)	3.33 5.83 9.36 3.34 5.37 27.24 10.90 18.73
CLARENCE Study T2D with HF EMPA-REG OUTCOME CANVAS Program DECLARE-TIMI 58 ERDENCE EMPEROR-Reduced SOLOIST-WHF Subtotal (I-squared = 0 T2D without HF EMPA-REG OUTCOME CANVAS Program DECLARE-TIMI 58	Treatment Empagliflozin Canagliflozin Dapagliflozin Canagliflozin Sotagliflozin 0%, p = 0.664) Empagliflozin	Treatment (n) 462 803 852 329 927 608 4225 4992	(n) 244	SGLT28 r	educe risk	HR (95% C)) 0.71 (0.43, 1.16) 0.72 (0.51, 1.02) 1.01 (0.73, 1.39) 1.02 (0.63, 1.65) 0.92 (0.71, 1.20) 0.84 (0.58, 1.22) 0.88 (0.76, 1.01) 0.60 (0.47, 0.77) 0.95 (0.76, 1.20) 0.97 (0.78, 1.20)	% Weight 3.48 7.14 8.27 3.70 12.45 6.20 41.24 14.07	Subgroup Study T2D with HF EMPA-REG OUTCOME CANVAS Program DECLARE-TIMI 58 CREDENCE SOLOIST-WHF Subtotal (I-squared = (T2D without HF EMPA-REG OUTCOME CANVAS Program DECLARE-TIMI 58	Treatment Empagliflozin Dapagliflozin Canagliflozin Sotagliflozin Sotagliflozin J.0%, p = 0.806) Empagliflozin Canagliflozin Dapagliflozin	Treatment (n) 462 803 803 852 329 608 4092 4992 7730	Placebo (n) 244 658 872 323 614 2089 3689 7706	Sol 12/s reduce risk	HR (95% C)	3.33 5.83 9.36 3.34 5.37 27.24 10.90 18.73 32.93
CLARENCE Study T2D with HF EMPA-REG OUTCOME CANVAS Program DECLARE-TIMI 58 ERDENCE EMPEROR-Reduced SOLOIST-WHF Subtotal (I-squared = 0 T2D without HF EMPA-REG OUTCOME CANVAS Program DECLARE-TIMI 58	Treatment Empagliflozin Canagliflozin Canagliflozin Canagliflozin Sotagliflozin 0%, p = 0.664) Empagliflozin Canagliflozin	Treatment (n) 462 803 852 329 927 608 4225 4992 7730	(n) 244	SGLT28r	educe risk	HR (95% C)) 0.71 (0.43, 1.16) 0.72 (0.51, 1.02) 1.01 (0.73, 1.39) 1.02 (0.63, 1.65) 0.92 (0.71, 1.20) 0.84 (0.58, 1.22) 0.88 (0.76, 1.01) 0.60 (0.47, 0.77) 0.95 (0.76, 1.20) 0.97 (0.78, 1.20)	% Weight 3.48 7.14 8.27 3.70 12.45 6.20 41.24 14.07 16.44	Subgroup Study T2D with HF EMPA-REG OUTCOME CANVAS Program DECLARE-TIMI 58 CREDENCE SOLOISTWHF Subtotal (I-squared = (T2D without HF EMPA-REG OUTCOME CANVAS Program DECLARE-TIMI 58 CREDENCE	Treatment Empagliflozin Canagliflozin Dapagliflozin Sotagliflozin Sotagliflozin Sotagliflozin Canagliflozin Dapagliflozin Dapagliflozin Canagliflozin	Treatment (n) 462 803 852 833 608 608 4992 1730 1873	Placebo (n) 244 658 872 323 614 2089 3689	Sol 12/s reduce risk	HR (95% C) 0.79 (0.52, 1.20 0.70 (0.51, 0.96 0.87 (0.68, 1.12 0.94 (0.62, 1.43 0.94 (0.62, 1.43 0.94 (0.62, 1.43 0.82 (0.71, 0.95 0.66 (0.51, 0.81 0.93 (0.78, 1.11 0.94 (0.82, 1.07 0.79 (0.62, 1.00 0.79 (0.62, 1.00	3.33 5.83 9.36 3.34 5.37 27.24 10.90 18.73 32.93 10.20
CELARE OF COMPARENCE OF COMPAR	Treatment Empagliflozin Canagliflozin Canagliflozin Canagliflozin Sotagliflozin 0%, p = 0.664) Empagliflozin Canagliflozin Dapagliflozin Canagliflozin	Treatment (n) 462 803 852 329 927 608 4225 4992 7730	(n) 244	SGLT28 r	educe risk	HR (95% C)) 0.71 (0.43, 1.16) 0.72 (0.51, 1.02) 1.01 (0.73, 1.39) 1.02 (0.63, 1.65) 0.92 (0.71, 1.20) 0.84 (0.58, 1.22) 0.88 (0.76, 1.01) 0.60 (0.47, 0.77) 0.95 (0.76, 1.20) 0.97 (0.78, 1.20) 0.70 (0.52, 0.94)	% Weight 3.48 7.14 8.27 3.70 12.45 6.20 41.24 14.07 16.44 18.48	Subgroup Study T2D with HF EMPA-REG OUTCOME CANVAS Program DECLARE-TIMI 58 CREDENCE SOLOIST-WHF Subtotal (I-squared = (T2D without HF EMPA-REG OUTCOME CANVAS Program DECLARE-TIMI 58	Treatment Empagliflozin Canagliflozin Dapagliflozin Sotagliflozin Sotagliflozin Sotagliflozin Canagliflozin Dapagliflozin Dapagliflozin Canagliflozin	Treatment (n) 462 803 852 833 608 608 4992 1730 1873	Placebo (n) 244 658 872 323 614 2089 3689 7706	Sol 12/s reduce risk	HR (95% C)	3.33 5.83 9.36 3.34 5.37 27.24 10.90 18.73 32.93 10.20
Canada and a construction of the construction	Treatment Empagliflozin Dapagliflozin Canagliflozin O%, p = 0.664) Empagliflozin Oangliflozin Dapagliflozin Dapagliflozin 3.1%, p = 0.011)	Treatment (n) 462 803 852 329 927 608 4225 4992 7730 1873	(n) 244	SGLT28r	educe risk	HR (95% C)) 0.71 (0.43, 1.16) 0.72 (0.51, 1.02) 1.01 (0.73, 1.39) 1.02 (0.63, 1.65) 0.92 (0.71, 1.20) 0.84 (0.58, 1.22) 0.88 (0.76, 1.01) 0.60 (0.47, 0.77) 0.95 (0.76, 1.20) 0.97 (0.78, 1.20) 0.70 (0.52, 0.94)	% Weight 3.48 7.14 8.27 3.70 12.45 6.20 41.24 14.07 16.44 18.48 9.78	Subgroup Study T2D with HF EMPA-REG OUTCOME CANVAS Program DECLARE-TIMI 58 CREDENCE SOLOISTWHF Subtotal (I-squared = (T2D without HF EMPA-REG OUTCOME CANVAS Program DECLARE-TIMI 58 CREDENCE	Treatment Empagliflozi Canagliflozin Sotagliflozin Sotagliflozin Sotagliflozin Sotagliflozin Canagliflozin Dapagliflozin Canagliflozis 52.3%, p = 0.047	Treatment (n) 462 803 1852 329 608 608 1873 1873	Placebo (n) 244 658 872 323 614 2089 3689 7706	Sol 1 2/s reduce risk	HR (95% C) 0.79 (0.52, 1.20 0.70 (0.51, 0.96 0.87 (0.68, 1.12 0.94 (0.62, 1.43 0.94 (0.62, 1.43 0.94 (0.62, 1.43 0.82 (0.71, 0.95 0.66 (0.51, 0.81 0.93 (0.78, 1.11 0.94 (0.82, 1.07 0.79 (0.62, 1.00 0.79 (0.62, 1.00	3.33 5.83 9.36 3.34 5.37 27.24 10.90 18.73 32.93 10.20
T2D with HF EMPA-REG OUTCOME CANVAS Program DECLARE-TIMI 58 CREDENCE EMPEROR-Reduced SOLOISTWHF	Treatment Empagliflozin Dapagliflozin Canagliflozin Sotagliflozin O%, p = 0.664) Empagliflozin Canagliflozin Dapagliflozin Canagliflozin 3.1%, p = 0.011) groups: p = 0.45	Treatment (n) 462 803 852 329 927 608 4225 4992 7730 1873	(n) 244	SGLT28 r	educe risk	HR (95% C) 0.71 (0.43, 1.16) 0.72 (0.51, 1.02) 1.01 (0.73, 1.39) 1.02 (0.63, 1.65) 0.92 (0.71, 1.20) 0.84 (0.58, 1.22) 0.88 (0.76, 1.01) 0.60 (0.47, 0.77) 0.95 (0.76, 1.20) 0.97 (0.78, 1.20) 0.70 (0.52, 0.94) 0.81 (0.72, 0.92)	% Weight 3.48 7.14 8.27 3.70 12.45 6.20 41.24 14.07 16.44 18.48 9.78	Subgroup Study T2D with HF EMPA-REG OUTCOME CANVAS Program DECLARE-TIMI 58 CREDENCE Subtotal (I-squared = C T2D without HF EMPA-REG OUTCOME CANVAS Program DECLARE-TIMI 58 CREDENCE Subtotal (I-squared = C	Treatment Empagliflozi Canagliflozi Sotagliflozi Sotagliflozi Sotagliflozi Canagliflozi Canagliflozi Canagliflozi Canagliflozi S2.3%, p = 0.047 9 groups: p = 0.5	Treatment (n) 462 803 1852 329 608 608 1873 1873	Placebo (n) 244 658 872 323 614 2089 3689 7706	Sul 12/s reduce risk	HR (95% C) 0.79 (0.52, 1.20 0.70 (0.51, 0.96 0.87 (0.68, 1.12 0.94 (0.62, 1.43 0.94 (0.62, 1.43 0.94 (0.62, 1.43 0.82 (0.71, 0.95 0.66 (0.51, 0.81 0.93 (0.78, 1.11 0.94 (0.82, 1.07 0.79 (0.62, 1.00 0.79 (0.62, 1.00	3.33 5.83 9.36 3.34 5.37 27.24 10.90 18.73 32.93 10.20 72.76
22 with HF 22 with HF 22 with HF 22 with HF 24 WAS Program 25 CLARE-TIMI 58 26 CLARE-TIMI 58 27 WHF 20 Without HF 20 Without HF	Treatment Empagliflozin Dapagliflozin Canagliflozin Sotagliflozin O%, p = 0.664) Empagliflozin Canagliflozin Dapagliflozin Canagliflozin 3.1%, p = 0.011) groups: p = 0.45	Treatment (n) 462 803 852 329 927 608 4225 4992 7730 1873	(n) 244	SGLT28 r	educe risk	HR (95% C) 0.71 (0.43, 1.16) 0.72 (0.51, 1.02) 1.01 (0.73, 1.39) 1.02 (0.63, 1.65) 0.92 (0.71, 1.20) 0.84 (0.58, 1.22) 0.88 (0.76, 1.01) 0.60 (0.47, 0.77) 0.95 (0.76, 1.20) 0.97 (0.78, 1.20) 0.70 (0.52, 0.94) 0.81 (0.72, 0.92)	% Weight 3.48 7.14 8.27 3.70 12.45 6.20 41.24 14.07 16.44 18.48 9.78 58.76	Subgroup Study T2D with HF EMPA-REG OUTCOME CANVAS Program DECLARE-TIMI 58 CREDENCE SUDIOIST-WHF Subtotal (I-squared = C T2D without HF EMPA-REG OUTCOME CANVAS Program DECLARE-TIMI 58 CREDENCE Subtotal (I-squared = C Heterogeneity between	Treatment Empagliflozi Canagliflozi Sotagliflozi Sotagliflozi Sotagliflozi Canagliflozi Canagliflozi Canagliflozi Canagliflozi S2.3%, p = 0.047 9 groups: p = 0.5	Treatment (n) 462 803 1852 329 608 608 1873 1873	Placebo (n) 244 658 872 323 614 2089 3689 7706		HR (95% CI)	3.33 5.83 9.36 3.34 5.37 27.24 10.90 18.73 32.93 10.20 72.76

FIGURE 1 | Fixed-effects meta-analysis of the effects of SGLT2 is on hospitalization for heart failure (A), major adverse cardiovascular events (B), cardiovascular death (C), and all-cause death (D) in T2D patients, stratified by the status of HF. SGLT2 is = sodium-glucose cotransporter 2 inhibitors. T2D, type 2 diabetes; HF, heart failure; HR, hazard ratio; CI, confidence interval.

patients with/without CKD, in HF patients with/without T2D/ CKD, and in CKD patients with/without T2D to prevent cardiovascular, renal, and mortality events. Writing – Original Draft Preparation: MQ. Writing – Review and Editing: H-RZ and L-LD. All authors contributed to the article and approved the submitted version.

AUTHOR CONTRIBUTIONS

Conceptualization: MQ. Data Collection: MQ, L-LD, and H-RZ. Formal Analysis: L-LD and H-RZ. Validation: MQ, and Z-LZ.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fendo.2021. 664502/full#supplementary-material

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Supplementary Figure 1 | Random-effects meta-analysis of the effect of SGLT2is on cardiovascular death in T2D patients, stratified by the status of HF.

Supplementary Figure 2 | Random-effects meta-analysis of the effect of SGLT2is on all-cause death in T2D patients, stratified by the status of HF.

Supplementary Material 1 | Data extracted from included studies.

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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