



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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Edited by:

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Reviewed by:

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Specialty section:

This article was submitted to Clinical Diabetes, a section of the journal Frontiers in Endocrinology

Received: 05 February 2021 Accepted: 12 March 2021 Published: 26 March 2021

Citation:

Qiu M, Ding L-L, Zhan Z-L and Zhou H-R (2021) 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. Front. Endocrinol. 12:664502. doi: 10.3389/fendo.2021.664502 Mei Qiu^{1*†}, Liang-Liang Ding^{2†}, Ze-Lin Zhan³ and Hai-Rong Zhou^{1*}

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Keywords: SGLT2 inhibitors (gliflozins), type 2 diabetes (clinical domain), heart failure - pharmacological treatment - systolic dysfunction, cardiovascular death, all-cause death

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

bubgroup		Treatment	Placebo				%	Subgroup		Treatment	Placebo				%
itudy	Treatment	(n)	(n)			HR (95% CI)	Weight	Study	Treatment	(n)	(n)			HR (95% CI)	Weight
2D with HF								T2D with HE							
MPA-REG OUTCOME	Empagliflozin	462	244			- 0.75 (0.48, 1.19)	4.10	CANIVAS Brogram	Canadiflatin	000	450			0.90 (0.61 1.05)	5 22
ANVAS Program	Canagliflozin	803	658			0.51 (0.33, 0.78)	4.56	CANVAS Program	Canagiinozin	803	000		T	0.80 (0.61, 1.05)	5.32
ECLARE-TIMI 58	Dapaglifiozin	852	8/2			0.73 (0.55, 0.96)	10.88	DECLARE-TIMI 58	Dapagliflozin	852	872	1	•	1.01 (0.81, 1.27)	7.76
REDENCE	Canagliflozin	329	323			- 0.76 (0.47, 1.22)	3.71	CREDENCE	Canagliflozin	329	323		-	0.93 (0.63, 1.37)	2.60
ERTIS CV	Ertuglifiozin	1286	6/2			0.63 (0.44, 0.90)	6.59	VERTIS CV	Ertugliflozin	1286	672	+	•	1.05 (0.82, 1.35)	6.31
osiborod 2017	Dapaglifiozin	1/1	149 —	•		- 0.14 (0.02, 1.15)	0.21	Kosiborod 2017	Dapagliflozin	171	149 —	•		- 0.87 (0.30, 2.53)	0.35
MPEROR-Reduced	Empagliflozin	927	929			0.65 (0.50, 0.85)	11.99	Subtotal (I_square	1-0.0% n-0	540)		1	\$	0.95 (0.84, 1.09)	22.33
JLOIST-WHF	Sotagliflozin	608	614		-	0.64 (0.49, 0.83)	12.16	Subtotal (I-Square	a = 0.070, p = 0.	545)			1	0.55 (0.04, 1.05)	22.55
ubtotal (I-squared =	0.0%, p = 0.672)				Y	0.66 (0.58, 0.74)	54.20	700 11 115							
D with a st UF								T2D without HF							
	F	4225	2000			0.50 (0.42, 0.02)	0.10	CANVAS Program	Canagliflozin	4992	3689	-+		0.87 (0.76, 1.01)	19.40
ANIVAS Program	Canaglific=in	4000	2009			0.39 (0.43, 0.82)	0.10	DECLARE-TIMI 58	Dapagliflozin	7730	7706		⊢	0.92 (0.82, 1.02)	32.93
	Danagiinozin	4992	2009 7706			0.79 (0.57, 1.09)	0.03	CREDENCE	Canagliflozin	1873	1876		1	0.76 (0.62, 0.93)	9.54
SEDENCE	Capaglification	1072	1076			0.75 (0.58, 0.92)	13.00	VERTIS CV	Frtualiflozin	4213	2075		•	0.95 (0.81, 1.11)	15.80
	Canagimozin	18/3	18/0			0.54 (0.39, 0.75)	7.90	Cubertal (Lanuare	- 10.70/ - /	1213	2075			0.00 (0.07, 1.11)	77.00
ubtotal (Leguarod -	0.00% m = 0.250)	4215	2075			0.79 (0.54, 1.15)	3.91	Subtotal (I-square	a = 12.7%, p = 0	1.329)		Y	1	0.89 (0.83, 0.96)	//.0/
ubtotal (I-squareu =	9.0%, p = 0.550)				Υ	0.08 (0.00, 0.78)	43.00								
atorogonaitu batucau	n arauna n - 0 (Heterogeneity betv	veen groups: p	= 0.377		1			
vorall (L squared – 0	0% p = 0.650	377			×	0.67 (0.61 0.72)	100.00	Overall (I-squared	= 0.0%, p = 0.5	70)		Ó	>	0.91 (0.85, 0.96)	100.0
verali (i—squared = 0.	.0%, p = 0.659)				- Y I	0.07 (0.01, 0.75)	100.00					1			
Cardiov	ascular de	eath	0.02	SGLT2is	1 reduce risk	1.23 SGLT2is increase ri	isk	D All-c	ause dea	ith	0.30 SGL	2is reduce risk	1 SGLT2is incr	2.56 ease risk	
	ascular de	eath Treatment	0.02 Расеbo	SGLT2is	1 reduce risk	1.23 SGLT2is increase ri	isk %	D All-C.	ause dea	ith Treatment	I 0.30 SGL ⁻ Placebo	2is reduce risk	1 SGLT2is incr	1 2.56 ease risk	%
bgroup Jdy	ascular de Treatment	eath Treatment (n)	I 0.02 Placebo in)	SGLT2is	1 reduce risk	1.23 SGLT2is increase ri HR (95% CI)	isk % Weight	D All-C Subgroup Study	ause dea	I th Treatment (n)	0.30 SGL ⁻ Placebo (n)	2is reduce risk	1 SGLT2is incr	2.56 ease risk HR (95% CI)	% Weigl
bgroup udy D with HF	ascular de Treatment	eath Treatment (n)	I 0.02 Placebo (n)	SGLT2is	1 reduce risk	1.23 SGLT2is increase ri HR (95% CI)	isk % Weight	D All-C Subgroup Study T2D with HF	ause dea	t h Treatment (n)	0.30 SGL [*] Placebo (n)	2is reduce risk	1 SGLT2is incr	I 2.56 ease risk HR (95% CI)	% Weigl
Cardiov bgroup udy D with HF IPA-REG OUTCOME	ascular de Treatment Empagliflozin	eath Treatment (n) 462	Placebo (n) 244	SGLT2is	1 reduce risk	1.23 SGLT2is increase ri HR (95% CI) 0.71 (0.43, 1.16)	% Weight 3.48	D All-C Subgroup Study T2D with HF EMPA_BEG OLITICOME	ause dea Treatment	th Treatment (n)	0.30 SGL [*] Placebo (n)	2is reduce risk	1 SGLT2is incr	1 2.56 ease risk HR (95% CI)	% Weigh
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Cardiova bgroup dy D with HF IPA-REG OUTCOME NVAS Program CLARE-TIMI 58	ascular de Treatment Empagliflozin Canagliflozin Dapagliflozin	2021 Treatment (n) 462 803 852	I 0.02 Placebo (n) 244	SGLT2is	1 reduce risk	1.23 SGLT2is increase ri HR (95% Cl) 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	D All-c Subgroup Study T2D with HF EMPA-REG OUTCOME CANVAS Program	ause dea Treatment Empagliflozin Canagliflozin	th Treatment (n) 1 462 803	0.30 SGL ⁻ Placebo (n) 244 — 658 —	2is reduce risk	1 SGLT2is incr	1 2.56 ease risk HR (95% CI) 0.79 (0.52, 1.20) 0.70 (0.51, 0.96)	% Weig 3.33 5.83
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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.

FUNDING

This work is supported by the Shenzhen Key Medical Discipline Construction Fund (SZXK063).

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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