



# **Commentary: Cardiovascular Outcome in Patients Treated With SGLT2 Inhibitors for Heart Failure: A Meta-Analysis**

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#### Specialty section:

This article was submitted to Cardiovascular Therapeutics, a section of the journal Frontiers in Cardiovascular Medicine

> Received: 16 September 2021 Accepted: 27 September 2021 Published: 26 October 2021

#### Citation:

Qiu M and Zhao L-M (2021) Commentary: Cardiovascular Outcome in Patients Treated With SGLT2 Inhibitors for Heart Failure: A Meta-Analysis. Front. Cardiovasc. Med. 8:778284. doi: 10.3389/fcvm.2021.778284 Keywords: SGLT2 inhibitors (gliflozins), heart failure, NYHA class, region, race, HFPEF, HFrEF-heart failure with reduced ejection fraction

#### A Commentary on

# Cardiovascular Outcome in Patients Treated With SGLT2 Inhibitors for Heart Failure: A Meta-Analysis

by Gager, G. M, Gelbenegger, G., Jilma, B., von Lewinski, D., Sourij, H., Eyileten, C., Filipiak, K., Postula, M., Siller-Matula, J. M. (2021). Front. Cardiovasc. Med. 8:691907. doi: 10.3389/fcvm.2021.691907

## INTRODUCTION

In the meta-analysis of Gager et al. (1) recently published in the journal *Frontiers in Cardiovascular Medicine*, the authors identified that sodium-glucose co-transporter-2 (SGLT2) inhibitors could reduce heart failure (HF) events and all-cause mortality in patients with HF and that the benefit of this drug class on the primary endpoint (i.e., a composite of hospitalization for HF HHF) or cardiovascular mortality (CVM) was consistent across relevant HF subgroups defined by the following clinically important factors: the status of type 2 diabetes at baseline, type of HF (according to left ventricular ejection fraction, LVEF), cause of HF, specific SGLT2 inhibitors, gender, age, estimated glomerular filtration rate (eGFR), body mass index, and concomitant medications. However, Gager et al. (1) failed to evaluate the effect of SGLT2 inhibitors in several subgroups defined by three other clinically important factors: race, region, and baseline New York Heart Association (NYHA) class. Hence, we aimed to conduct another meta-analysis to examine whether these factors affect the efficacy of gliflozins in patients with HF or not.

Moreover, Gager et al. in their meta-analysis (1), failed to include the latest EMPEROR-Preserved trial (2) assessing empagliflozin in patients with HF with an LVEF of > 40%. Since that trial (2) provided the new data in the subgroup of HF with mildly reduced LVEF (HFmrEF) and the subgroup of HF with preserved LVEF (HFpEF), we repeated the subgroup analysis according to LVEF by adding these new data, although this subgroup analysis had been performed in the meta-analysis of Gager et al. (1).

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## METHODS AND FINDINGS

We only included in this meta-analysis large cardiovascular outcome trials (CVOTs) that compared the HF outcomes of

SGLT2 inhibitors with those of placebo in patients with HF. The only endpoint of interest for this meta-analysis was the composite HF outcome, which was defined as a composite of HHF or CVM. Embase and PubMed were searched (from inception to August

A		rd Batio	Weight	В			
Study		95% CI	(%)			Hazard Ratio	Weigh
Region: Asia				Study		with 95% CI	(%)
DAPA-HF		.49, 0.87]	6.71	Race: Asian			
EMPEROR-Reduced		.38, 0.79]	4.50	DAPA-HF		0.64 [ 0.48, 0.86]	9.38
SOLOIST-WHF		.23, 1.57]	0.68	EMPEROR-Reduced		0.57 [ 0.41, 0.79]	8.27
EMPEROR-Preserved		.41, 0.85]	4.27	EMPEROR-Preserved		0.65 [ 0.46, 0.92]	7.47
Heterogeneity: $t^2 = 0.00$ , $I^2 = 0.00\%$ , $H^2 = 1.00$ Test of $\theta_i = \theta_i$ : Q(3) = 0.53, p = 0.91	0.60[0.	.50, 0.73]		Heterogeneity: $\tau^2 = 0.00$ , $I^2 = 0.00\%$ , $H^2 = 1.00$	-	0.62 [ 0.52, 0.74]	
Test of $\theta_i = \theta_j$ . $Q(3) = 0.53$ , $p = 0.91$				Test of $\theta_i = \theta_i$ : Q(2) = 0.38, p = 0.83		0.02[ 0.02, 0.74]	
Region: Europe				$1031010_1 = 0_1$ . $0(2) = 0.000$ , $p = 0.000$			
DAPA-HF		.69, 1.02]		Race: Black			
EMPEROR-Reduced		.74, 1.19]	9.47				
SOLOIST-WHF		.50, 0.95]	5.52	DAPA-HF		0.62 [ 0.37, 1.04]	
EMPEROR-Preserved Heterogeneity: $\tau^2 = 0.00$ , $I^2 = 0.00\%$ , $H^2 = 1.00$		.65, 0.98]	11.56	EMPEROR-Reduced		0.46 [ 0.28, 0.75]	
Test of $\theta_i = \theta_i$ : Q(3) = 2.50, p = 0.47	0.83 [ 0.	.74, 0.93]		SOLOIST-WHF		1.12 [ 0.51, 2.45]	1.93
1000000 = 0.0000000000000000000000000000				EMPEROR-Preserved		0.73 [ 0.42, 1.26]	3.69
Region: Latin America				Heterogeneity: $\tau^2 = 0.02$ , $I^2 = 15.52\%$ , $H^2 = 1.18$		0.64 [ 0.47, 0.87]	
DAPA-HF		.47, 0.88]	5.75	Test of $\theta_i = \theta_i$ : Q(3) = 3.91, p = 0.27			
EMPEROR-Reduced		.57, 0.93]	8.96				
SOLOIST-WHF EMPEBOB-Preserved		.43, 0.95]	3.77 7.86	Race: White			
EMPEROR–Preserved Heterogeneity: $\tau^2 = 0.00$ , $I^2 = 0.00\%$ , $H^2 = 1.00$		0.67, 1.13]	1.66	DAPA-HF		0.78 [ 0.66, 0.92]	16 40
Test of $\theta_i = \theta_i$ : Q(3) = 2.82, p = 0.42	- 0.74[0.						
				EMPEROR-Reduced		0.88 [ 0.75, 1.04]	
Region: North America				SOLOIST-WHF		0.63 [ 0.49, 0.81]	
DAPA-HF		.51, 1.04]	4.69	EMPEROR-Preserved		0.81 [ 0.69, 0.95]	16.90
EMPEROR-Reduced		.48, 1.00]	4.23 3.77	Heterogeneity: $\tau^2 = 0.00$ , $I^2 = 23.61\%$ , $H^2 = 1.31$	•	0.79 [ 0.72, 0.88]	
SOLOIST-WHF EMPEBOB-Preserved		.43, 0.95]	3.77 5.34	Test of $\theta_i = \theta_j$ : Q(3) = 4.88, p = 0.18			
Heterogeneity: $\tau^2 = 0.00$ , $I^2 = 0.00\%$ , $H^2 = 1.00$		.58, 0.84]	5.54				
Test of $\theta_i = \theta_i$ : Q(3) = 0.28, p = 0.96	0.701 0.			Overall	•	0.72 [ 0.64, 0.80]	
,,				Heterogeneity: $\tau^2 = 0.01$ , $I^2 = 43.44\%$ , $H^2 = 1.77$			
Overall	• 0.74 [ 0.	.68, 0.80]		Test of $\theta_i = \theta_i$ : Q(10) = 16.61, p = 0.08			
Heterogeneity: τ <sup>2</sup> = 0.00, I <sup>2</sup> = 13.33%, H <sup>2</sup> = 1.15				$1000 \text{ f}_{i} = 0$ , $Q(10) = 10.01$ , $p = 0.00$			
Test of $\theta_i = \theta_j$ : Q(15) = 14.97, p = 0.45				Test of group differences: $Q_b(2) = 6.26$ , $p = 0.04$	1		
Test of $\theta_i = \theta_j$ : Q(15) = 14.97, p = 0.45					1/2 1	2	
Test of $\theta_i = \theta_i$ : Q(15) = 14.97, p = 0.45 Test of group differences: Q <sub>0</sub> (3) = 8.84, p = 0.03 Bandom-effects REML model	1/4 1/2 1 Favours SGLT2 inhibitors Favours placebo						
Test of $\theta_i = \theta_i$ : Q(15) = 14.97, p = 0.45 Test of group differences: Q <sub>0</sub> (3) = 8.84, p = 0.03 Random-effects REML model	1/4 1/2 1 Favours SGLT2 inhibitors Favours placebo			Random-effects REML model	1/2 1		
Test of $\theta_i=\theta_i.~Q(15)=14.97,~p=0.45$ Test of group differences: $Q_{\rm b}(3)=8.84,~p=0.03$	Favours SGLT2 inhibitors Favours placebo	rd Patio	Weight	F	1/2 1	urs placebo	Weigh
Test of $\theta_i = \theta_i$ : Q(15) = 14.97, $p = 0.45$ Test of group differences: Q <sub>6</sub> (3) = 8.84, $p = 0.03$ Random–effects REML model	Favours SGLT2 Inhibitors Favours placebo		Weight	Random-effects REML model	1/2 1		
Test of $\theta_i = \theta_i$ : Q(15) = 14.97, $p = 0.45$ Test of group differences: Q <sub>6</sub> (3) = 8.84, $p = 0.03$ Random–effects REML model	Favours SGLT2 Inhibitors Favours placebo	rd Ratio 95% Cl	Weight (%)	Random-effects REML model F D Study	1/2 1	urs placebo Hazard Ratio	
Test of 0, = 0; Q(15) = 14.97, p = 0.45 Test of group differences: Q <sub>6</sub> (3) = 8.84, p = 0.03 Random-effects REML model C Study	Favours SGLT2 Inhibitors Favours placebo		•	Random-effects REML model F D Study LVEF at baseline: >40% to <50%	1/2 1	urs placebo Hazard Ratio with 95% Cl	Weigh (%)
Test of $\theta_i = \theta_i$ : Q(15) = 14.97, $p = 0.45$ Test of group differences: Q <sub>6</sub> (3) = 8.84, $p = 0.03$ Random-effects REML model C Study Baseline NYHA class: Class II	Favours SGLT2 inhibitors Favours placebo Hazarr With 9	95% CI	(%)	Random-effects REML model         F           D         Study           LVEF at baseline: >40% to <50%	avours SGLT2 inhibitors Favo	Hazard Ratio with 95% Cl 0.74 [ 0.40, 1.38]	(%)
Test of 0, = 0; Q(15) = 14.97, p = 0.45 Test of group differences: Q <sub>6</sub> (3) = 8.84, p = 0.03 Random-effects REML model C Study Baseline NYHA class: Class II DAPA-HF	Favours SGLT2 inhibitors Favours placebo	95% CI	(%)	Random-effects REML model         F           D         Study           LVEF at baseline: >40% to <50%	1/2 1	Hazard Ratio with 95% Cl 0.74 [ 0.40, 1.38] 0.71 [ 0.57, 0.88]	(%)
Test of 0, = 0; Q(15) = 14.97, p = 0.45 Test of group differences: Q <sub>6</sub> (3) = 8.84, p = 0.03 Random-effects REML model C Study Baseline NYHA class: Class II DAPA-HF	Favours SGLT2 inhibitors Favours placebo	95% CI	(%)	Build for the second	avours SGLT2 inhibitors Favo	Hazard Ratio with 95% Cl 0.74 [ 0.40, 1.38]	(%)
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Test of 0, = 0; Q(15) = 14.97, p = 0.45 Test of group differences: Q <sub>6</sub> (3) = 8.84, p = 0.03 Random-effects REML model C Study Baseline NYHA class: Class II DAPA-HF EMPEROR-Reduced SOLOIST-WHF	Favours SGLT2 inhibitors         Favours placebo           Hazan         with 9           0.63 [ 0.         0.71 [ 0.           0.58 [ 0.         0.58 [ 0.	95% CI 0.52, 0.76] 0.60, 0.85] 0.40, 0.84]	(%) 15.37 15.97 5.74	Build for the second	avours SGLT2 inhibitors Favo	Hazard Ratio with 95% Cl 0.74 [ 0.40, 1.38] 0.71 [ 0.57, 0.88]	(%)
Test of 0, = 0; Q(15) = 14.97, p = 0.45 Test of group differences: Q <sub>6</sub> (3) = 8.84, p = 0.03 Random-effects REML model C Study Baseline NYHA class: Class II DAPA-HF EMPEROR-Reduced SOLOIST-WHF EMPEROR-Preserved	Favours SGLT2 inhibitors         Favours placebo           Hazan         with 9           0.63 [ 0.         0.71 [ 0.           0.58 [ 0.         0.58 [ 0.	95% CI 0.52, 0.76] 0.60, 0.85]	(%) 15.37 15.97 5.74	Build for the second	avours SGLT2 inhibitors Favo	Hazard Ratio with 95% Cl 0.74 [ 0.40, 1.38] 0.71 [ 0.57, 0.88]	(%)
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Test of $0, = 0$ ; Q(15) = 14.97, $p = 0.45$ Test of group differences: Q <sub>6</sub> (3) = 8.84, $p = 0.03$ Random-effects REML model C Study Baseline NYHA class: Class II DAPA-HF EMPEROR-Reduced SOLOIST-WHF EMPEROR-Preserved Heterogeneity: $t^2 = 0.00, l^2 = 5.02\%, H^2 = 1.05$	Favours SGLT2 inhibitors         Favours placebo           Hazan         with 9           0.63 [ 0.         0.71 [ 0.           0.58 [ 0.         0.58 [ 0.           0.57 [ 0.         0.57 [ 0.	95% Cl 0.52, 0.76] 0.60, 0.85] 0.40, 0.84] 0.64, 0.87]	(%) 15.37 15.97 5.74	Random-effects REML model       F         D       Study         LVEF at baseline: >40% to <50%	avours SGLT2 inhibitors Favo	Hazard Ratio with 95% CI 0.74 [ 0.40, 1.38] 0.71 [ 0.57, 0.88] 0.71 [ 0.58, 0.88] 0.70 [ 0.59, 0.84]	(%) 1.7( 11.8; 16.1(
Test of $0, = 0$ ; Q(15) = 14.97, $p = 0.45$ Test of group differences: Q <sub>6</sub> (3) = 8.84, $p = 0.03$ Random-effects REML model C Study Baseline NYHA class: Class II DAPA-HF EMPEROR-Reduced SOLOIST-WHF EMPEROR-Preserved Heterogeneity: $t^2 = 0.00, l^2 = 5.02\%, H^2 = 1.05$	Favours SGLT2 inhibitors         Favours placebo           Hazan         with 9           0.63 [ 0.         0.71 [ 0.           0.58 [ 0.         0.58 [ 0.           0.57 [ 0.         0.57 [ 0.	95% Cl 0.52, 0.76] 0.60, 0.85] 0.40, 0.84] 0.64, 0.87]	(%) 15.37 15.97 5.74	$\label{eq:response} \begin{array}{l} \mbox{F} \\ \mbox{Barbon effects REML model} \\ \mbox{D} \\ \mbox{Study} \\ \mbox{LVEF at baseline: >40% to <50%} \\ \mbox{SOLOIST-WHF} \\ \mbox{EMPEROR-Preserved} \\ \mbox{Heterogeneity: } t^2 = 0.00, t^2 = 0.00\%, tt^2 = 1.00 \\ \mbox{Test of } \theta_i = \theta_i; O(1) = 0.02, p = 0.90 \\ \mbox{LVEF at baseline: $\leq 40\% \\ \mbox{DAPA-HF: LVEF $> Median \\ \mbox{DAPA-HF: LVEF $> Median \\ \mbox{DAPA-HF: LVEF $> Median \\ \end{tabular} \end{array}$	avours SGLT2 inhibitors Favo	Hazard Ratio with 95% Cl 0.74 [ 0.40, 1.38] 0.71 [ 0.57, 0.88] 0.71 [ 0.58, 0.88] 0.70 [ 0.59, 0.84] 0.81 [ 0.66, 1.00]	(%) 1.76 11.83 16.16 12.43
Test of $0, = 0$ ; Q(15) = 14.97, $p = 0.45$ Test of group differences: Q <sub>6</sub> (3) = 8.84, $p = 0.03$ Random-effects REML model C Study Baseline NYHA class: Class II DAPA-HF EMPEROR-Reduced SOLOIST-WHF EMPEROR-Preserved Heterogeneity: $t^2 = 0.00, l^2 = 5.02\%, H^2 = 1.05$	Favours SGLT2 inhibitors         Favours placebo           Hazan         with 9           0.63 [ 0.         0.71 [ 0.           0.58 [ 0.         0.58 [ 0.           0.57 [ 0.         0.57 [ 0.	95% Cl 0.52, 0.76] 0.60, 0.85] 0.40, 0.84] 0.64, 0.87]	(%) 15.37 15.97 5.74	Random-effects REML model       F         D       Study         LVEF at baseline: >40% to <50%	avours SGLT2 inhibitors Favo	Hazard Ratio with 95% Cl 0.74 [ 0.40, 1.38] 0.71 [ 0.57, 0.88] 0.71 [ 0.58, 0.88] 0.70 [ 0.59, 0.84] 0.81 [ 0.66, 1.00] 0.67 [ 0.57, 0.78]	(%) 1.7( 11.8; 16.1( 12.4; 18.0)
Test of $\theta_i = \theta_i$ : Q(15) = 14.97, p = 0.45 Test of group differences: Q <sub>4</sub> (3) = 8.84, p = 0.03 Random-effects REML model C Study Baseline NYHA class: Class II DAPA-HF EMPEROR-Reduced SOLOIST-WHF EMPEROR-Preserved Heterogeneily: $t^2 = 0.00$ , $l^2 = 5.02\%$ , $H^2 = 1.05$ Test of $\theta_i = \theta_i$ : Q(3) = 3.02, p = 0.39	Favours SGLT2 inhibitors         Favours placebo           Hazan         with 9           0.63 [ 0.         0.71 [ 0.           0.58 [ 0.         0.58 [ 0.           0.57 [ 0.         0.57 [ 0.	95% Cl 0.52, 0.76] 0.60, 0.85] 0.40, 0.84] 0.64, 0.87]	(%) 15.37 15.97 5.74	Random-effects REML model       F         D       Study         LVEF at baseline: >40% to <50%	avours SGLT2 inhibitors Favo	Hazard Ratio with 95% Cl 0.74 [ 0.40, 1.38] 0.71 [ 0.57, 0.88] 0.71 [ 0.58, 0.88] 0.70 [ 0.59, 0.84] 0.81 [ 0.66, 1.00] 0.67 [ 0.57, 0.78] 0.99 [ 0.75, 1.30]	(%) 1.7( 11.8; 16.1( 12.4; 18.0) 8.1(
Test of $\theta_i = \theta_i$ : Q(15) = 14.97, p = 0.45 Test of group differences: Q <sub>4</sub> (3) = 8.84, p = 0.03 Random-effects REML model C Study Baseline NYHA class: Class II DAPA-HF EMPEROR-Reduced SOLOIST-WHF EMPEROR-Preserved Heterogeneity: $t^2 = 0.00$ , $t^2 = 5.02\%$ , $H^2 = 1.05$ Test of $\theta_i = \theta_i$ : Q(3) = 3.02, p = 0.39 Baseline NYHA class: Class III or IV	Favours SGLT2 inhibitors         Favours placebo           Hazar         with 9           0.63 [ 0.         0.71 [ 0.           0.58 [ 0.         0.69 [ 0.	95% Cl 1.52, 0.76] 1.60, 0.85] 1.40, 0.84] 1.64, 0.87] 1.63, 0.76]	(%) 15.37 15.97 5.74 18.31	$\label{eq:result} \begin{array}{l} \mbox{F} \\ \mbox{Baseline: >40% to <50%} \\ \mbox{SoLOIST-WHF} \\ \mbox{EMPEROR-Preserved} \\ \mbox{Heterogeneity: } \ell = 0.00, l^2 = 0.00\%, H^2 = 1.00 \\ \mbox{Test of } \theta_i = \theta_i \cdot \mathbf{Q}(1) = 0.02, p = 0.90 \\ \\ EVEF at baseline: $ $ $ $ $ $ $ $ $ $ $ $ $ $ $ $ $ $ $$	Favours SGLT2 inhibitors Favo	Hazard Ratio with 95% CI 0.74 [ 0.40, 1.38] 0.71 [ 0.57, 0.88] 0.71 [ 0.58, 0.88] 0.71 [ 0.58, 0.88] 0.71 [ 0.59, 0.84] 0.81 [ 0.66, 1.00] 0.67 [ 0.57, 0.78] 0.69 [ 0.51, 0.93]	(%) 1.7( 11.8; 16.1( 12.4; 18.0) 8.1(
Test of $\theta_i = \theta_i$ : Q(15) = 14.97, p = 0.45 Test of group differences: Q <sub>4</sub> (3) = 8.84, p = 0.03 Random-effects REML model C Study Baseline NYHA class: Class II DAPA-HF EMPEROR-Reduced SOLOIST-WHF EMPEROR-Preserved Heterogeneity: $t^2 = 0.00$ , $l^2 = 5.02\%$ , $H^2 = 1.05$ Test of $\theta_i = \theta_i$ : Q(3) = 3.02, p = 0.39 Baseline NYHA class: Class III or IV DAPA-HF	Favours SGLT2 inhibitors Favours placebo Hazar with 9 0.63 [ 0. 0.71 [ 0. 0.58 [ 0. 0.58 [ 0. 0.69 [ 0. 0.69 [ 0.	95% CI 1.52, 0.76] 1.60, 0.85] 1.40, 0.84] 1.64, 0.87] 1.63, 0.76]	(%) 15.37 15.97 5.74 18.31	Random-effects REML model       F         D       Study         LVEF at baseline: >40% to <50%	Favours SGLT2 inhibitors Favo	Hazard Ratio with 95% Cl 0.74 [ 0.40, 1.38] 0.71 [ 0.57, 0.88] 0.71 [ 0.58, 0.88] 0.70 [ 0.59, 0.84] 0.81 [ 0.66, 1.00] 0.67 [ 0.57, 0.78] 0.99 [ 0.75, 1.30]	(%) 1.7( 11.8; 16.1( 12.4; 18.0) 8.1(
Test of $\theta_i = \theta_i$ : Q(15) = 14.97, p = 0.45 Test of group differences: Q <sub>4</sub> (3) = 8.84, p = 0.03 Random-effects REML model C Study Baseline NYHA class: Class II DAPA-HF EMPEROR-Reduced SOLOIST-WHF EMPEROR-Preserved Heterogeneity: $t^2 = 0.00$ , $l^2 = 5.02\%$ , $H^2 = 1.05$ Test of $\theta_i = \theta_i$ : Q(3) = 3.02, p = 0.39 Baseline NYHA class: Class III or IV DAPA-HF	Favours SGLT2 inhibitors Favours placebo Hazar with 9 0.63 [ 0. 0.71 [ 0. 0.58 [ 0. 0.58 [ 0. 0.69 [ 0. 0.69 [ 0.	95% Cl 1.52, 0.76] 1.60, 0.85] 1.40, 0.84] 1.64, 0.87] 1.63, 0.76]	(%) 15.37 15.97 5.74 18.31	$\label{eq:response} \begin{array}{l} \mbox{F} \\ \mbox{Baseline: >40% to <50%} \\ \mbox{SoLOIST-WHF} \\ \mbox{EMPEROR-Preserved} \\ \mbox{Heterogeneity: } \ell = 0.00, l^2 = 0.00\%, H^2 = 1.00 \\ \mbox{Test of } \theta_i = \theta_i \cdot \mathbf{Q}(1) = 0.02, p = 0.90 \\ \\ EVEF at baseline: $ $ $ $ $ $ $ $ $ $ $ $ $ $ $ $ $ $ $$	Favours SGLT2 inhibitors Favo	Hazard Ratio with 95% CI 0.74 [ 0.40, 1.38] 0.71 [ 0.57, 0.88] 0.71 [ 0.58, 0.88] 0.71 [ 0.58, 0.88] 0.71 [ 0.59, 0.84] 0.81 [ 0.66, 1.00] 0.67 [ 0.57, 0.78] 0.69 [ 0.51, 0.93]	(%) 1.7( 11.8; 16.1( 12.4; 18.0) 8.1(
Test of $\theta_i = \theta_i$ : Q(15) = 14.97, p = 0.45 Test of group differences: Q <sub>4</sub> (3) = 8.84, p = 0.03 Random-effects REML model C Study Baseline NYHA class: Class II DAPA-HF EMPEROR-Reduced SOLOIST-WHF EMPEROR-Preserved Heterogeneity: $\hat{t} = 0.00, \hat{t}^2 = 5.02\%, \hat{H}^2 = 1.05$ Test of $\theta_i = \theta_i$ : Q(3) = 3.02, p = 0.39 Baseline NYHA class: Class III or IV DAPA-HF EMPEROR-Reduced	Favours SGLT2 inhibitors         Favours placebo           Hazar         0.63 [ 0.           0.71 [ 0.         0.71 [ 0.           0.58 [ 0.         0.75 [ 0.           0.69 [ 0.         0.69 [ 0.           0.90 [ 0.         0.83 [ 0.	95% CI 1.52, 0.76] 1.60, 0.85] 1.40, 0.84] 1.64, 0.87] 1.63, 0.76] 1.74, 1.09] 1.66, 1.04]	(%) 15.37 15.97 5.74 18.31 14.45 11.89	$\label{eq:response} \begin{array}{l} \mbox{F} \\ \begin{tabular}{lllllllllllllllllllllllllllllllllll$	Favours SGLT2 inhibitors Favo	Hazard Ratio with 95% CI 0.74 [ 0.40, 1.38] 0.71 [ 0.57, 0.88] 0.71 [ 0.58, 0.88] 0.71 [ 0.58, 0.88] 0.71 [ 0.59, 0.84] 0.81 [ 0.66, 1.00] 0.67 [ 0.57, 0.78] 0.69 [ 0.51, 0.93]	(%) 1.7( 11.8; 16.1( 12.4; 18.0) 8.1(
Test of $\theta_i = 0$ ; Q(15) = 14.97, p = 0.45 Test of group differences: Q <sub>6</sub> (3) = 8.84, p = 0.03 Random-effects REML model C Study Baseline NYHA class: Class II DAPA-HF EMPEROR-Reduced SOLOIST-WHF EMPEROR-Preserved Heterogeneity: $\hat{t} = 0.00$ , $I^2 = 5.02\%$ , $H^2 = 1.05$ Test of $\theta_i = \theta_i$ ; Q(3) = 3.02, p = 0.39 Baseline NYHA class: Class III or IV DAPA-HF EMPEROR-Reduced SOLOIST-WHF	Favours SGLT2 inhibitors         Favours placebo           Hazar         0.63 [ 0.           0.71 [ 0.         0.71 [ 0.           0.58 [ 0.         0.75 [ 0.           0.69 [ 0.         0.69 [ 0.           0.03 [ 0.         0.83 [ 0.           0.03 [ 0.         0.83 [ 0.	95% CI 1.52, 0.76] 1.60, 0.85] 1.40, 0.84] 1.64, 0.87] 1.63, 0.76] 1.74, 1.09] 1.66, 1.04] 1.60, 1.16]	(%) 15.37 15.97 5.74 18.31 14.45 11.89 6.95	Random-effects REML model <b>D</b> Study <b>LVEF at baseline:</b> >40% to <50% SOLOIST-WHF EMPEROR-Preserved Heterogeneity: $t^2 = 0.00$ , $t^2 = 0.00\%$ , $H^2 = 1.00$ Test of $0_1 = 0$ ; $Q(1) = 0.02$ , $p = 0.90$ <b>LVEF at baseline:</b> $\le 40\%$ DAPA-HF: LVEF $\le$ Median DAPA-HF: LVEF $\le$ Median EMPEROR-Reduced: LVEF $\le 30\%$ EMPEROR-Reduced: LVEF $\le 30\%$ SOLOIST-WHF Heterogeneity: $t^2 = 0.01$ , $t^2 = 44.23\%$ , $H^2 = 1.79$ Test of $0_1 = 0$ ; $Q(4) = 7.29$ , $p = 0.12$	Favours SGLT2 inhibitors Favo	Hazard Ratio with 95% CI 0.74 [ 0.40, 1.38] 0.71 [ 0.57, 0.88] 0.71 [ 0.58, 0.88] 0.71 [ 0.58, 0.88] 0.71 [ 0.59, 0.84] 0.81 [ 0.66, 1.00] 0.67 [ 0.57, 0.78] 0.69 [ 0.51, 0.93]	(%) 1.7( 11.8; 16.1( 12.4; 18.0) 8.1(
Test of $\theta_i = \theta_i$ : Q(15) = 14.97, p = 0.45 Test of group differences: Q <sub>4</sub> (3) = 8.84, p = 0.03 Random-effects REML model C Study Baseline NYHA class: Class II DAPA-HF EMPEROR-Reduced SOLOIST-WHF EMPEROR-Preserved Heterogeneity: $\hat{t} = 0.00, \hat{t}^2 = 5.02\%, \hat{H}^2 = 1.05$ Test of $\theta_i = \theta_i$ : Q(3) = 3.02, p = 0.39 Baseline NYHA class: Class III or IV DAPA-HF EMPEROR-Reduced SOLOIST-WHF	Favours SGLT2 inhibitors         Favours placebo           Hazar         0.63 [ 0.           0.71 [ 0.         0.71 [ 0.           0.58 [ 0.         0.75 [ 0.           0.69 [ 0.         0.69 [ 0.           0.03 [ 0.         0.83 [ 0.           0.03 [ 0.         0.83 [ 0.	95% CI 1.52, 0.76] 1.60, 0.85] 1.40, 0.84] 1.64, 0.87] 1.63, 0.76] 1.74, 1.09] 1.66, 1.04]	(%) 15.37 15.97 5.74 18.31 14.45 11.89 6.95	Random-effects REML model <b>D</b> Study <b>LVEF at baseline:</b> >40% to <50% SOLDIST-WHF EMPEROR-Preserved Heterogeneity: $t^2 = 0.00$ , $t^2 = 0.00\%$ , $H^2 = 1.00$ Test of $\theta_i = \theta_i$ : Q(1) = 0.02, p = 0.90 <b>LVEF at baseline:</b> ≤40% DAPA-HF: LVEF ≤ Median DAPA-HF: LVEF ≤ Median DAPA-HF: LVEF ≤ Median EMPEROR-Reduced: LVEF ≤30% EMPEROR-Reduced: LVEF ≤30% SOLDIST-WHF Heterogeneity: $t^2 = 0.01$ , $t^2 = 44.23\%$ , $H^2 = 1.79$ Test of $\theta_i = \theta_i$ : Q(4) = 7.29, p = 0.12 <b>LVEF at baseline:</b> ≥50%	Favours SGLT2 inhibitors Favo	Hazard Ratio with 95% CI 0.74 [ 0.40, 1.38] 0.71 [ 0.57, 0.88] 0.71 [ 0.58, 0.88] 0.71 [ 0.58, 0.88] 0.71 [ 0.59, 0.84] 0.81 [ 0.66, 1.00] 0.67 [ 0.57, 0.78] 0.69 [ 0.51, 0.93] 0.75 [ 0.66, 0.85]	(%) 1.74 11.8 16.14 12.4 18.09 8.14 7.09
Test of $\theta_i = \theta_i$ : Q(15) = 14.97, p = 0.45 Test of group differences: Q <sub>6</sub> (3) = 8.84, p = 0.03 Random-effects REML model C Study Baseline NYHA class: Class II DAPA-HF EMPEROR-Reduced SOLOIST-WHF EMPEROR-Preserved Heterogeneity: $\hat{t} = 0.00$ , $\hat{t}^2 = 5.02\%$ , $\hat{H}^2 = 1.05$ Test of $\theta_i = \theta_i$ : Q(3) = 3.02, p = 0.39 Baseline NYHA class: Class III or IV DAPA-HF EMPEROR-Reduced SOLOIST-WHF EMPEROR-Reduced SOLOIST-WHF	Favours SGLT2 inhibitors         Favours placebo           Hazar         0.63 [ 0.           0.71 [ 0.         0.71 [ 0.           0.58 [ 0.         0.75 [ 0.           0.69 [ 0.         0.69 [ 0.           0.83 [ 0.         0.83 [ 0.           0.83 [ 0.         0.83 [ 0.           0.83 [ 0.         0.88 [ 0.	95% CI 1.52, 0.76] 1.60, 0.85] 1.40, 0.84] 1.64, 0.87] 1.63, 0.76] 1.74, 1.09] 1.66, 1.04] 1.60, 1.16] 1.68, 1.09]	(%) 15.37 15.97 5.74 18.31 14.45 11.89 6.95	Random-effects REML model <b>D</b> Study <b>LVEF at baseline:</b> >40% to <50% SOLDISTWHF EMPEROR-Preserved Heterogeneity: $t^2 = 0.00$ , $t^2 = 0.00\%$ , $H^2 = 1.00$ Test of $\theta_i = \theta_i$ (Q(1) = 0.02, p = 0.90 <b>LVEF at baseline:</b> ≤40% DAPA-HF: LVEF ≤Median DAPA-HF: LVEF ≤Median DAPA-HF: LVEF ≤Median DAPA-HF: LVEF ≤Median DAPA-HF: LVEF ≤Median DAPA-HF: LVEF ≤Median EMPEROR-Reduced: LVEF ≤30% SOLDIST-WHF Heterogeneity: $t^2 = 0.01$ , $t^2 = 44.23\%$ , $H^2 = 1.79$ Test of $\theta_i = \theta_i$ (Q(4) = 7.29, p = 0.12 <b>LVEF at baseline:</b> ≥50% SOLDIST-WHF	Favours SGLT2 inhibitors Favo	Hazard Ratio with 95% CI 0.74 [ 0.40, 1.38] 0.71 [ 0.57, 0.88] 0.71 [ 0.58, 0.88] 0.71 [ 0.59, 0.84] 0.81 [ 0.66, 1.00] 0.67 [ 0.57, 0.78] 0.99 [ 0.75, 1.30] 0.99 [ 0.51, 0.93] 0.75 [ 0.66, 0.85]	(%) 1.7( 11.83 16.1( 12.43 18.09 8.14 7.09 2.2 <sup>-1</sup>
Test of $\theta_i = 0$ ; Q(15) = 14.97, p = 0.45 Test of group differences: Q <sub>6</sub> (3) = 8.84, p = 0.03 Random-effects REML model C Study Baseline NYHA class: Class II DAPA-HF EMPEROR-Reduced SOLOIST-WHF EMPEROR-Preserved Heterogeneity: $t^2 = 0.00$ , $t^2 = 5.02\%$ , $H^2 = 1.05$ Test of $\theta_i = 0$ ; Q(3) = 3.02, p = 0.39 Baseline NYHA class: Class III or IV DAPA-HF EMPEROR-Reduced SOLOIST-WHF EMPEROR-Reduced SOLOIST-WHF EMPEROR-Preserved Heterogeneity: $t^2 = 0.00$ , $t^2 = 0.00\%$ , $H^2 = 1.00$	Favours SGLT2 inhibitors         Favours placebo           Hazar         0.63 [ 0.           0.71 [ 0.         0.71 [ 0.           0.58 [ 0.         0.75 [ 0.           0.69 [ 0.         0.69 [ 0.           0.83 [ 0.         0.83 [ 0.           0.83 [ 0.         0.83 [ 0.           0.83 [ 0.         0.88 [ 0.	95% CI 1.52, 0.76] 1.60, 0.85] 1.40, 0.84] 1.64, 0.87] 1.63, 0.76] 1.74, 1.09] 1.66, 1.04] 1.60, 1.16]	(%) 15.37 15.97 5.74 18.31 14.45 11.89 6.95	Random-effects REML model       F         D       Study         LVEF at baseline: >40% to <50%	Favours SGLT2 inhibitors Favo	Hazard Ratio with 95% Cl 0.74 [ 0.40, 1.38] 0.71 [ 0.57, 0.88] 0.71 [ 0.58, 0.88] 0.71 [ 0.58, 0.88] 0.81 [ 0.66, 1.00] 0.67 [ 0.57, 0.78] 0.99 [ 0.75, 1.30] 0.69 [ 0.51, 0.93] 0.75 [ 0.66, 0.85] 0.80 [ 0.64, 0.99]	(%) 1.7( 11.83 16.1( 12.43 18.09 8.14 7.09 2.2 <sup>2</sup> 11.74
Test of $\theta_i = 0$ ; Q(15) = 14.97, p = 0.45 Test of group differences: Q <sub>6</sub> (3) = 8.84, p = 0.03 Random-effects REML model C Study Baseline NYHA class: Class II DAPA-HF EMPEROR-Reduced SOLOIST-WHF EMPEROR-Preserved Heterogeneity: $t^2 = 0.00$ , $t^2 = 5.02\%$ , $H^2 = 1.05$ Test of $\theta_i = 0$ ; Q(3) = 3.02, p = 0.39 Baseline NYHA class: Class III or IV DAPA-HF EMPEROR-Reduced SOLOIST-WHF EMPEROR-Reduced SOLOIST-WHF EMPEROR-Preserved Heterogeneity: $t^2 = 0.00$ , $t^2 = 0.00\%$ , $H^2 = 1.00$	Favours SGLT2 inhibitors         Favours placebo           Hazar         0.63 [ 0.           0.71 [ 0.         0.71 [ 0.           0.58 [ 0.         0.75 [ 0.           0.69 [ 0.         0.69 [ 0.           0.83 [ 0.         0.83 [ 0.           0.83 [ 0.         0.83 [ 0.           0.83 [ 0.         0.88 [ 0.	95% CI 1.52, 0.76] 1.60, 0.85] 1.40, 0.84] 1.64, 0.87] 1.63, 0.76] 1.74, 1.09] 1.66, 1.04] 1.60, 1.16] 1.68, 1.09]	(%) 15.37 15.97 5.74 18.31 14.45 11.89 6.95	Random-effects REML model       F         D       Study         LVEF at baseline: >40% to <50%	Favours SGLT2 inhibitors Favo	Hazard Ratio with 95% Cl 0.74 [ 0.40, 1.38] 0.71 [ 0.57, 0.88] 0.71 [ 0.57, 0.88] 0.70 [ 0.59, 0.84] 0.81 [ 0.66, 1.00] 0.67 [ 0.57, 0.78] 0.99 [ 0.75, 1.30] 0.69 [ 0.51, 0.93] 0.75 [ 0.66, 0.85] 0.66 [ 0.38, 1.15] 0.80 [ 0.64, 0.99] 0.87 [ 0.69, 1.10]	(%) 1.7( 11.83 16.1( 12.43 18.09 8.14 7.09 2.2 <sup>2</sup> 11.74
Test of $\theta_i = \theta_i$ : Q(15) = 14.97, p = 0.45 Test of group differences: Q <sub>6</sub> (3) = 8.84, p = 0.03 Random-effects REML model C Study Baseline NYHA class: Class II DAPA-HF EMPEROR-Reduced SOLOIST-WHF EMPEROR-Preserved Heterogeneity: $t^2 = 0.00$ , $t^2 = 5.02\%$ , $H^2 = 1.05$ Test of $\theta_i = \theta_i$ : Q(3) = 3.02, p = 0.39 Baseline NYHA class: Class III or IV DAPA-HF EMPEROR-Reduced SOLOIST-WHF EMPEROR-Reduced SOLOIST-WHF EMPEROR-Preserved Heterogeneity: $t^2 = 0.00$ , $t^2 = 0.00\%$ , $H^2 = 1.00$	Favours SGLT2 inhibitors         Favours placebo           Hazar         0.63 [ 0.           0.71 [ 0.         0.71 [ 0.           0.58 [ 0.         0.75 [ 0.           0.69 [ 0.         0.69 [ 0.           0.83 [ 0.         0.83 [ 0.           0.83 [ 0.         0.83 [ 0.           0.83 [ 0.         0.88 [ 0.	95% CI 1.52, 0.76] 1.60, 0.85] 1.40, 0.84] 1.64, 0.87] 1.63, 0.76] 1.74, 1.09] 1.66, 1.04] 1.60, 1.16] 1.68, 1.09]	(%) 15.37 15.97 5.74 18.31 14.45 11.89 6.95	Random-effects REML model       F         D       Study         LVEF at baseline: >40% to <50%	Favours SGLT2 inhibitors Favo	Hazard Ratio with 95% Cl 0.74 [ 0.40, 1.38] 0.71 [ 0.57, 0.88] 0.71 [ 0.58, 0.88] 0.71 [ 0.58, 0.88] 0.81 [ 0.66, 1.00] 0.67 [ 0.57, 0.78] 0.99 [ 0.75, 1.30] 0.69 [ 0.51, 0.93] 0.75 [ 0.66, 0.85] 0.80 [ 0.64, 0.99]	(%) 1.7( 11.83 16.1( 12.43 18.09 8.14 7.09 2.27 11.7(
Test of $\theta_i = \theta_i: Q(15) = 14.97, p = 0.45$ Test of group differences: $Q_n(3) = 8.84, p = 0.03$ Random-effects REML model C Study Baseline NYHA class: Class II DAPA-HF EMPEROR-Reduced SOLOIST-WHF EMPEROR-Preserved Heterogeneity: $\hat{\tau} = 0.00, \hat{1}^2 = 5.02\%, \hat{H}^2 = 1.05$ Test of $\theta_i = \theta_i: Q(3) = 3.02, p = 0.39$ Baseline NYHA class: Class III or IV DAPA-HF EMPEROR-Reduced SOLOIST-WHF EMPEROR-Reduced SOLOIST-WHF EMPEROR-Reduced SOLOIST-WHF EMPEROR-Reduced SOLOIST-WHF	Favours SGLT2 inhibitors         Favours placebo           Hazar         0.63 [ 0.           0.71 [ 0.         0.71 [ 0.           0.58 [ 0.         0.75 [ 0.           0.69 [ 0.         0.69 [ 0.           0.83 [ 0.         0.83 [ 0.           0.88 [ 0.         0.88 [ 0.	95% CI 1.52, 0.76] 1.60, 0.85] 1.40, 0.84] 1.64, 0.87] 1.63, 0.76] 1.74, 1.09] 1.66, 1.04] 1.60, 1.16] 1.68, 1.09] 1.77, 0.97]	(%) 15.37 15.97 5.74 18.31 14.45 11.89 6.95	Random-effects REML model       F         D       Study         LVEF at baseline: >40% to <50%	Favours SGLT2 inhibitors Favo	Hazard Ratio with 95% Cl 0.74 [ 0.40, 1.38] 0.71 [ 0.57, 0.88] 0.71 [ 0.57, 0.88] 0.70 [ 0.59, 0.84] 0.81 [ 0.66, 1.00] 0.67 [ 0.57, 0.78] 0.99 [ 0.75, 1.30] 0.69 [ 0.51, 0.93] 0.75 [ 0.66, 0.85] 0.66 [ 0.38, 1.15] 0.80 [ 0.64, 0.99] 0.87 [ 0.69, 1.10]	(%) 1.7( 11.83 16.1( 12.43 18.09 8.14 7.09 2.27 11.7(
Test of $\theta_i = \theta_i: Q(15) = 14.97, p = 0.45$ Test of group differences: $Q_u(3) = 8.84, p = 0.03$ Random-effects REML model <b>C</b> Study Baseline NYHA class: Class II DAPA-HF EMPEROR-Reduced SOLOIST-WHF EMPEROR-Preserved Heterogeneity: $\hat{t} = 0.00, I^2 = 5.02\%, H^2 = 1.05$ Test of $\theta_i = \theta_i: Q(3) = 3.02, p = 0.39$ Baseline NYHA class: Class III or IV DAPA-HF EMPEROR-Reduced SOLOIST-WHF EMPEROR-Preserved Heterogeneity: $\hat{t} = 0.00, I^2 = 0.00\%, H^2 = 1.00$ Test of $\theta_i = \theta_i: Q(3) = 0.34, p = 0.95$	Favours SGLT2 inhibitors         Favours placebo           Hazar         0.63 [ 0.           0.71 [ 0.         0.71 [ 0.           0.58 [ 0.         0.75 [ 0.           0.69 [ 0.         0.69 [ 0.           0.83 [ 0.         0.83 [ 0.           0.88 [ 0.         0.88 [ 0.	95% CI 1.52, 0.76] 1.60, 0.85] 1.40, 0.84] 1.64, 0.87] 1.63, 0.76] 1.74, 1.09] 1.66, 1.04] 1.60, 1.16] 1.68, 1.09]	(%) 15.37 15.97 5.74 18.31 14.45 11.89 6.95	Random-effects REML model       F         Study       LVEF at baseline: >40% to <50%	Favours SGLT2 inhibitors Favo	Hazard Ratio with 95% Cl 0.74 [ 0.40, 1.38] 0.71 [ 0.57, 0.88] 0.71 [ 0.57, 0.88] 0.70 [ 0.59, 0.84] 0.81 [ 0.66, 1.00] 0.67 [ 0.57, 0.78] 0.99 [ 0.75, 1.30] 0.69 [ 0.51, 0.93] 0.75 [ 0.66, 0.85] 0.66 [ 0.38, 1.15] 0.80 [ 0.64, 0.99] 0.87 [ 0.69, 1.10]	(%) 1.7( 11.83 16.1( 12.43 18.09 8.14 7.09 2.27 11.7(
Test of $\theta_i = \theta_i: Q(15) = 14.97, p = 0.45$ Test of group differences: $Q_u(3) = 8.84, p = 0.03$ Random-effects REML model <b>C</b> Study Baseline NYHA class: Class II DAPA-HF EMPEROR-Reduced SOLOIST-WHF EMPEROR-Preserved Heterogeneity: $\hat{t} = 0.00, I^2 = 5.02\%, H^2 = 1.05$ Test of $\theta_i = \theta_i: Q(3) = 3.02, p = 0.39$ Baseline NYHA class: Class III or IV DAPA-HF EMPEROR-Reduced SOLOIST-WHF EMPEROR-Preserved Heterogeneity: $\hat{t} = 0.00, I^2 = 0.00\%, H^2 = 1.00$ Test of $\theta_i = \theta_i: Q(3) = 0.34, p = 0.95$	Favours SGLT2 inhibitors         Favours placebo           Hazar         0.63 [ 0.           0.71 [ 0.         0.71 [ 0.           0.58 [ 0.         0.75 [ 0.           0.69 [ 0.         0.69 [ 0.           0.83 [ 0.         0.83 [ 0.           0.88 [ 0.         0.88 [ 0.	95% CI 1.52, 0.76] 1.60, 0.85] 1.40, 0.84] 1.64, 0.87] 1.63, 0.76] 1.74, 1.09] 1.66, 1.04] 1.60, 1.16] 1.68, 1.09] 1.77, 0.97]	(%) 15.37 15.97 5.74 18.31 14.45 11.89 6.95	Random-effects REML model       F         D       Study         LVEF at baseline: >40% to <50%	Favours SGLT2 inhibitors Favo	Hazard Ratio with 95% Cl 0.74 [ 0.40, 1.38] 0.71 [ 0.57, 0.88] 0.71 [ 0.57, 0.88] 0.71 [ 0.59, 0.84] 0.81 [ 0.66, 1.00] 0.67 [ 0.57, 0.78] 0.99 [ 0.75, 1.30] 0.69 [ 0.57, 0.78] 0.75 [ 0.66, 0.85] 0.75 [ 0.66, 0.85] 0.80 [ 0.64, 0.99] 0.87 [ 0.89, 1.10] 0.82 [ 0.70, 0.95]	(%) 1.7( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8(
Test of $\theta_i = \theta_i$ : Q(15) = 14.97, p = 0.45 Test of group differences: Q <sub>6</sub> (3) = 8.84, p = 0.03 Random-effects REML model C Study Baseline NYHA class: Class II DAPA-HF EMPEROR-Reduced SOLOIST-WHF EMPEROR-Preserved Heterogeneity: $\hat{\tau} = 0.00$ , $I^2 = 5.02\%$ , $H^2 = 1.05$ Test of $\theta_i = \theta_i$ : Q(3) = 3.02, p = 0.39 Baseline NYHA class: Class III or IV DAPA-HF EMPEROR-Reduced SOLOIST-WHF EMPEROR-Reduced SOLOIST-WHF EMPEROR-Preserved Heterogeneity: $\hat{\tau} = 0.00, I^2 = 0.00\%$ , $H^2 = 1.00$ Test of $\theta_i = \theta_i$ : Q(3) = 0.34, p = 0.95 Overall Heterogeneity: $\hat{\tau} = 0.01$ , $I^2 = 38.84\%$ , $H^2 = 1.64$	Favours SGLT2 inhibitors         Favours placebo           Hazar         0.63 [ 0.           0.71 [ 0.         0.71 [ 0.           0.58 [ 0.         0.75 [ 0.           0.69 [ 0.         0.69 [ 0.           0.83 [ 0.         0.83 [ 0.           0.88 [ 0.         0.88 [ 0.	95% CI 1.52, 0.76] 1.60, 0.85] 1.40, 0.84] 1.64, 0.87] 1.63, 0.76] 1.74, 1.09] 1.66, 1.04] 1.60, 1.16] 1.68, 1.09] 1.77, 0.97]	(%) 15.37 15.97 5.74 18.31 14.45 11.89 6.95	Random-effects REML model       F         D       Study         UVEF at baseline: >40% to <50%	Favours SOLT2 inhibitors Favo	Hazard Ratio with 95% Cl 0.74 [ 0.40, 1.38] 0.71 [ 0.57, 0.88] 0.71 [ 0.57, 0.88] 0.70 [ 0.59, 0.84] 0.81 [ 0.66, 1.00] 0.67 [ 0.57, 0.78] 0.99 [ 0.75, 1.30] 0.69 [ 0.51, 0.93] 0.75 [ 0.66, 0.85] 0.66 [ 0.38, 1.15] 0.80 [ 0.64, 0.99] 0.87 [ 0.69, 1.10]	(%) 1.7( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8(
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Test of $\theta_i = \theta_i$ : Q(15) = 14.97, p = 0.45 Test of group differences: Q <sub>6</sub> (3) = 8.84, p = 0.03 Random-effects REML model C Study Baseline NYHA class: Class II DAPA-HF EMPEROR-Reduced SOLOIST-WHF EMPEROR-Preserved Heterogeneity: $t^2 = 0.00$ , $t^2 = 5.02\%$ , $H^2 = 1.05$ Test of $\theta_i = \theta_i$ : Q(3) = 3.02, p = 0.39 Baseline NYHA class: Class III or IV DAPA-HF EMPEROR-Reduced SOLOIST-WHF EMPEROR-Reduced SOLOIST-WHF EMPEROR-Reduced SOLOIST-WHF EMPEROR-Preserved Heterogeneity: $t^2 = 0.00$ , $t^2 = 0.00\%$ , $H^2 = 1.00$ Test of $\theta_i = \theta_i$ : Q(3) = 0.34, p = 0.95 Overall Heterogeneity: $t^2 = 0.01$ , $t^2 = 38.84\%$ , $H^2 = 1.64$ Test of $\theta_i = \theta_i$ : Q(7) = 11.51, p = 0.12	Favours SGLT2 inhibitors         Favours placebo           Hazar         0.63 [ 0.           0.71 [ 0.         0.71 [ 0.           0.58 [ 0.         0.75 [ 0.           0.69 [ 0.         0.69 [ 0.           0.83 [ 0.         0.83 [ 0.           0.88 [ 0.         0.88 [ 0.	95% CI 1.52, 0.76] 1.60, 0.85] 1.40, 0.84] 1.64, 0.87] 1.63, 0.76] 1.74, 1.09] 1.66, 1.04] 1.60, 1.16] 1.68, 1.09] 1.77, 0.97]	(%) 15.37 15.97 5.74 18.31 14.45 11.89 6.95	Random-effects REML model       F         D       Study         UVEF at baseline: >40% to <50%	Favours SOLT2 inhibitors Favo	Hazard Ratio with 95% Cl 0.74 [ 0.40, 1.38] 0.71 [ 0.57, 0.88] 0.71 [ 0.57, 0.88] 0.71 [ 0.59, 0.84] 0.81 [ 0.66, 1.00] 0.67 [ 0.57, 0.78] 0.99 [ 0.75, 1.30] 0.69 [ 0.57, 0.78] 0.75 [ 0.66, 0.85] 0.75 [ 0.66, 0.85] 0.80 [ 0.64, 0.99] 0.87 [ 0.89, 1.10] 0.82 [ 0.70, 0.95]	(%) 1.7( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8( 11.8(
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FIGURE 1 | Forest plots illustrating the effect of SGLT2 inhibitors on composite HF outcome in patients with HF by four important factors. (A) Effects of SGLT2 inhibitors on composite HF outcome in HF patients by Regions. (B) Effects of SGLT2 inhibitors on composite HF outcome in HF patients by Race. (C) Effects of SGLT2 inhibitors on composite HF outcome in HF patients by Baseline NYHA class. (D) Effects of SGLT2 inhibitors on composite HF outcome in HF patients by LVEF at baseline. SGLT2, sodium-glucose co-transporter-2; HF, heart failure; CI, confidence interval; NYHA, New York Heart Association; LVEF, left ventricular ejection fraction; Composite HF outcome: defined as a composite of hospitalization for HF or cardiovascular mortality.

31st, 2021), using the following retrieval terms: "heart failure," "HFpEF," "HF with reduced LVEF (HFrEF)," "SGLT2 inhibitors," "empagliflozin," "canagliflozin," "ertugliflozin," "dapagliflozin," "sotagliflozin," and "randomized controlled trial." Finally, we included four CVOTs (2-5) focusing on assessing gliflozins in patients with HF. We extracted trial-level survival data (i.e., hazard ratios, HRs, and 95% confidence intervals, CIs) in various subgroups of interest from included trials, and, based on them, performed a random-effects meta-analysis. Subgroup analyses were conducted according to the following four factors: region (Asia, Latin America, North America, and Europe), race (White, Asian, and Black), baseline NYHA class (Class II and Class III or IV), and LVEF at baseline (LVEF  $\leq$  40%, i.e., HFrEF, LVEF > 40 to <50%, i.e., HFmrEF, and LVEF > 50%, i.e., HFpEF). Subgroup differences were examined by Cochran's Q test, with P < 0.05 indicating statistical significance. We completed data analyses using Stata (version 16.0).

Compared with placebo, SGLT2 inhibitors reduced the composite HF outcome by 40% in patients with HF enrolled in Asia (HR.6, 95% CI 0.50-0.73), 17% in those enrolled in Europe (HR 0.83, 95% CI 0.74-0.93), 26% in those enrolled in Latin America (HR 0.74, 95% CI 0.64-0.85), and 30% in those enrolled in North America (HR 0.7, 95% CI 0.58-0.84); and yielded more reductions in those enrolled in Asia than in the other three continents ( $P_{subgroup} = 0.03$ ; Figure 1A). SGLT2 inhibitors yielded more reductions in that outcome in Asian patients (38% reduction, HR 0.62, 95% CI 0.52-0.74) and Black patients (36% reduction, HR 0.64, 95% CI 0.47-0.87) than in White patients (21% reduction, HR 0.79, 95% CI 0.72-0.88), with a significant subgroup difference  $(P_{subgroup} = 0.04; Figure 1B)$ . SGLT2 inhibitors yielded more reductions in that outcome in patients with NYHA class II (31% reduction, HR 0.69, 95% CI 0.63-0.76) than NYHA classes III-IV (14% reduction, HR 0.86, 95% CI 0.77-0.97), with a significant subgroup difference ( $P_{subgroup} < 0.01$ ; Figure 1C). SGLT2 inhibitors reduced that outcome by 24% (HR 0.76, 95% CI 0.69-0.82) whether in patients with HFmrEF, patients with HFrEF patients, or patients with HFpEF patients ( $P_{subgroup} =$ 0.53; Figure 1D).

## DISCUSSION

The meta-analysis of Gager et al. (1) confirmed the consistent efficacy of SGLT2 inhibitors on the composite HF outcome (i.e.,

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a composite of HHF/CVM) in various HF subgroups defined by several important factors, such as baseline diabetes status, type of SGLT2 inhibitors, and baseline level of eGFR. However, Gager et al. (1) failed to perform subgroup analyses according to three other important factors: region, race, and baseline NYHA class. Thus, their findings (1) could not guide whether SGLT2 inhibitors should be used in patients with HF patients living in a specific region, those with a specific race, or those with a specific NYHA class. Furthermore, Gager et al. (1) also failed to include the latest CVOT of gliflozins, namely, EMPEROR-Preserved (2).

Conversely, we included all the published CVOTs focusing on comparing gliflozins with placebo in patients with HF, including the latest one (2). More importantly, our meta-analysis focused on subgroup analyses according to region, race, baseline NYHA class, and baseline LVEF. Accordingly, it revealed that SGLT2 inhibitors vs. placebo significantly reduced the composite HF outcome regardless of these four factors, while SGLT2 inhibitors might yield more reductions in that outcome in patients with HF living in Asia, Asian and Black patients with HF, and HF patients with NYHA class II. These findings suggest that as for preventing HF events, SGLT2 inhibitors should be recommended in patients with HF regardless of region, race, baseline NYHA class, and baseline LVEF, and especially in Asian and Black patients with HF and those with NYHA class II. Moreover, the ongoing DELIVER trial (NCT03619213) will further determine the efficacy of SGLT2 inhibitor dapagliflozin in patients with HFpEF or HFmrEF. Due to the limited number of patients with NYHA classes III-IV among included trials, further clinical trials for such a specific population may be beneficial.

In summary, based on the findings from the meta-analysis of Gager et al. (1) and ours, SGLT2 inhibitors should be recommended in a broad population of patients with HF patients, those with diabetes or not, those with reduced eGFR or not, and those with preserved/reduced LVEF. Moreover, SGLT2 inhibitors should be more recommended in Asian and Black patients with HF and patients with HF and with NYHA class II because of the greater benefits of this drug class in these HF subpopulations.

## AUTHOR CONTRIBUTIONS

MQ: design. MQ and L-MZ: conduct/data collection, analysis, and writing manuscript. All authors contributed to the article and approved the submitted version.

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