# Sodium-glucose cotransporter-2 inhibitors in heart failure: an updated meta-analysis

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# Abstract

**Aims** We aimed to examine efficacy and safety outcomes of sodium-glucose cotransporter-2 inhibitor (SGLT2i) for the treatment of heart failure (HF), especially in patients with heart failure with preserved ejection fraction (HFpEF).

**Methods and results** PubMed, Web of Science, and Cochrane Library were searched to identify randomized controlled trials comparing SGLT2i vs. placebo in HF patients. A total of 10 studies with 23 852 HF patients were eventually included. Compared with placebo, SGLT2i is associated with a lower incidence of composite of first hospitalization for heart failure (HHF) or cardio-vascular death (CV death) [hazard ratio (HR) = 0.76 95% confidence interval (CI) = 0.71-0.81], which is consistent regardless of the diabetes status, type of gliflozines used, and follow-up duration. SGLT2i can reduce the risk of total HHF or CV death (HR = 0.74, 95%CI = 0.68-0.81), first HHF (HR = 0.69, 95%CI = 0.64-0.75), CV death (HR = 0.88, 95%CI = 0.80-0.96), any death (HR = 0.90, 95%CI = 0.83-0.97), and any serious events (HR = 0.90, 95%CI = 0.87-0.93) in HF patients, at the cost of increased risk of urinary tract infections (risk ratio = 1.17, 95%CI = 1.03-1.33). In HFpEF patients, SGLT2i is associated with a significant reduction of composite of first HHF or CV death (HR = 0.81, 95%CI = 0.73-0.91), first HHF (HR = 0.71, 95%CI = 0.62-0.82), and total HHF or CV death (HR = 0.61, 95%CI = 0.43-0.86).

**Conclusions** Sodium-glucose cotransporter-2 inhibitor contributed to better efficacy outcomes in overall HF patients and showed an inspiring breakthrough in the treatment of HFpEF.

Keywords Heart failure; Sodium-glucose cotransporter-2 inhibitors; Heart failure with preserved ejection fraction; Meta-analysis

Received: 25 September 2021; Revised: 10 February 2022; Accepted: 7 March 2022 \*Correspondence to: Yi Li and Yaling Han, Department of Cardiology, General Hospital of Northern Theater Command, 83 Wenhua Road, Shenyang 110016, China. Email: doctorliyi@126.com; hanyaling@163.net

# Introduction

Heart failure (HF), as the end-stage manifestation of most heart diseases, is an increasing public health concern worldwide.<sup>1</sup> Among studies<sup>2–4</sup> using standardized criteria and reporting long-term data, the mortality after the incidence of HF is almost 50% in 5 years. Meanwhile, diabetes mellitus and HF interact and coexist frequently. HF accounts for 14.1% of the first cardiovascular events in patients with diabetes mellitus, and 49.4% of hospitalized patients with acute HF have known or previously undiagnosed diabetes.<sup>5,6</sup> Therefore, hypoglycaemic drugs that can improve cardiovascular prognosis need to be developed urgently. Of note, HFpEF, which accounts for approximately 50% of all HF patients, tends to have more comorbidities than HFrEF, and no convincing treatment is available to reduce mortality and morbidity currently.<sup>7,8</sup>

Sodium-glucose cotransporter-2 inhibitor (SGLT2i), as new robustly effective hypoglycaemic therapy, unexpectedly showed profound cardiovascular benefits in cardiovascular outcomes trials mandated by the US Food and Drug Administration. In several large-scale randomized controlled trials (RCTs),<sup>9–18</sup> SGLT2i significantly improved prognosis in HF patients with or without diabetes. However, previous RCTs and meta-analyses<sup>19–22</sup> of SGLT2i did not specifically distinguish first hospitalization for heart failure (HHF) and total HHF and still had controversies on efficacy and safety outcomes such as cardiovascular death, any death, and acute

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kidney injury. The therapeutic role of SGLT2i in HFpEF also remains unclear. The recently published EMPEROR-Preserved study showed a breakthrough that may change the current treatment of HFpEF. Herein, we present an updated meta-analysis of SGLT2i focusing on new data on HF patients with left ventricular ejection fraction (LVEF) > 40% and systematically review and synthesize these data in two ways: (i) all HF patients without LVEF restriction and (ii) HF patients with restricting only to HFpEF.

### Methods

This meta-analysis was completed according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines.<sup>23</sup>

#### Data sources and search strategy

A comprehensive search was conducted in PubMed, Web of Science, and Cochrane Library on 29 August 2021. The following keywords and their MeSH terms were used for the search: (sodium-glucose cotransporter-2 inhibitor OR SGLT2 inhibitor OR canagliflozin OR dapagliflozin OR empagliflozin OR ertugliflozin OR sotagliflozin OR ipragliflozin OR remogliflozin OR sergliflozin OR tofogliflozin) AND (heart failure OR cardiac failure OR HF). The detailed search strategy is presented in the supporting information. Additional studies were selected by manually screening the references of articles identified by the search. No restrictions were placed on the publication date or language.

#### Study selection and eligibility criteria

After duplicates were removed, the titles and abstracts of retrieved literature were reviewed to exclude uncorrelated studies and the full texts of the remaining articles.

Inclusion criteria included the following: (i) compared SGLT2i vs. placebo in HF patients regardless of the LVEF, diabetes status, and follow-up duration; (ii) RCTs or their subgroup analyses and post hoc analyses; and (iii) reported at least one of the predefined efficacy and safety outcomes. Exclusion criteria included the following: (i) observational or nonrandomized studies and (ii) studies that did not provide enough data to analyse the outcomes of interest.

# Outcomes of interest, data extraction, and quality assessment

The predefined primary efficacy outcome was composite of first hospitalization for HF (HHF) or cardiovascular death (CV

death). Other efficacy outcomes were (i) composite of total (first and recurrent) HHF and CV death; (ii) first HHF; (iii) CV death; (iv) any death; (v) major adverse cardiovascular events defined as composite of cardiovascular death, non-fatal myocardial infarction, and non-fatal stroke; and (vi) Kansas City Cardiomyopathy Questionnaire (KCCQ). The primary safety outcome was any serious adverse events (SAE). Other safety outcomes included acute kidney injury (AKI), urinary tract infections, hypoglycaemia, amputation, volume depletion, and bone fracture.

The characteristics, baseline demographics, outcome data, and safety data of eligible studies were extracted onto a predesigned excel spreadsheet. Quality assessment of included RCTs was conducted using Cochrane Handbook for Systematic Reviews of Interventions (version 5.1.0).<sup>24</sup>

All the processes of study selection, data extraction, and quality assessment were carried out by two reviewers (Y. Cao and P. Li) independently, and discrepancies were identified by the third reviewer (Y. Li).

#### **Statistical analysis**

Pooled hazard ratios (HRs) and 95% confidence intervals (CIs) were calculated for estimates of efficacy outcomes using the generic inverse-variance method. Total HHF was reported as a rate ratio among the including studies. Safety outcomes were usually reported as dichotomous data, which would be used to calculate risk ratios (RRs) by Mantel-Haenszel fixed effects model. The heterogeneity between studies was assessed using  $l^2$  statistic. Studies with an  $l^2$  statistic > 50% were considered to have substantial heterogeneity, and the random effects model would be used to analyse. Otherwise, the fixed effects model would be used. Considering the heterogeneity of the follow-up duration, we further calculated the incidence rate ratios (IRR) and incidence rate differences (IRD) to verify the robustness of the results.<sup>25</sup>The results were considered statistically significant when P value < 0.05. Publication bias was examined using a funnel graph. Subgroup analyses were conducted based on the diabetes status, type of gliflozines used, and follow-up duration. Sensitivity analyses were performed by sequential trials removal. Review Manager 5.3 and Stata 16.0 were used for all statistical analyses.

### Results

# Literature search and characteristics of identified studies

Ten RCTs were finally included in our meta-analysis. Of these, four trials (DAPA-HF, EMPEROR-Reduced, SOLOIST-WHF, and EMPEROR-Preserved) were HF-specific, and five trials (CAN-

VAS, EMPA-REG OUTCOME, CREDENCE, DECLARE-TIMI 58, and VERTIS-CV) reported cardiovascular outcomes in subgroup analyses or post hoc analyses. The authors of the SCROED trial presented a pooled analysis of the SOLOIST-WHF and SCORED trials at the American Heart Association 2020 conference. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow chart summarized the search and study selection process and was shown in *Figure 1*.

A total of 23 825 HF patients were eventually included in our meta-analysis. The median follow-up time ranges from 0.75 to 4.2 years. The EMPA-REG OUTCOME, CREDENCE, CANVAS, DECLARE-TIMI 58, VERTIS-CV, and SCORED trials included only DM patients. The DAPA-HF, EMPEROR-Reduced, SOLOIST-WHF, and EMPEROR-Preserved trials included only HF patients. *Table 1* showed the baseline characteristics of the included studies.

# Cardiovascular outcomes for the overall heart failure patients

Compared with placebo, SGLT2i can significantly reduce the risk of composite of first HHF or CV death (HR = 0.76,

95%CI = 0.71–0.81, P < 0.01; Figure 2A), composite of total HHF or CV death (RR = 0.74, 95%CI = 0.68–0.81, P < 0.01; *Figure 2B*), first HHF (HR = 0.69, 95%CI = 0.64-0.75, P < 0.01; Figure 2C), CV death (HR = 0.88, 95%CI = 0.80-0.96, P < 0.01; Figure 2D), and any death (HR = 0.90, 95%CI = 0.83–0.97, P < 0.01; Figure 2E). However, no significant difference in major adverse cardiovascular event (HR = 0.95, 95%CI = 0.83-1.09, P = 0.48; Figure 2F) was observed between placebo and SGLT2i. It should be noted that the improvement of KCCQ (mean difference = 1.62, 95%CI = 1.28–1.97, P < 0.01; Figure 2G) was also statistically significant. The result of primary outcome was consistent regardless of the diabetes status, type of gliflozines used, and follow-up duration (Supporting Information, Figure S1). For CV death or first HHF and CV death, IRR and IRD methods gave similar estimates of effect in favour of the intervention (Figure S2 and Table S1). IRR suggested a 25% reduction in the incidence of the CV death or first HHF (IRR = 0.75, 95%CI = 0.70-0.80, P < 0.01), while IRD implied that the intervention reduced the risk of CV death or first HHF by 3% per patient-year (IRD -0.03/patient-year, 95%CI -0.04 to -0.03, P < 0.01). Sensitivity analyses also showed consistent results.

#### Figure 1 Study flowchart of the article identification, inclusion, and exclusion.



Table 1 Characteris	tics of studies inclu	uded in the me	eta-analysis							
	EMPA-REG OUT	TCOME 2015	CANVAS	2017	CREDENC	E 2019	DECLARE-TIMI	58 2019	DAPA-H	F 2019
Drug	Empagliflozin	Placebo	Canagliflozin	Placebo	Canagliflozin	Placebo	Dapagliflozin	Placebo	Dapagliflozin	Placebo
Total number	462	244	803	658	329	323	852	872	2373	2371
Age, years	64.5 (8.8)	64.5 (8.9)	64.1 (8.3)	63.4 (8.3)	64.8 (8.1)	65.5 (8.1)	NA	AN	66.2 (11.0)	66.5 (10.8)
Female, %	142 (30.7)	69 (28.3)	346 (43.1)	302 (45.9)	124 (37.7)	133 (41.2)	NA	AN	564 (23.8)	545 (23.0)
BMI, kg/m <sup>2</sup>	31.9 (5.6)	32.3 (5.4)	33.1 (5.9)	33.2 (5.9)	32.9 (6.2)	32.5 (6.1)	NA	AN	28.2 (6.0)	28.1 (5.9)
DM, %	462 (100)	244 (100)	803 (100)	658 (100)	329 (100)	323 (100)	NA	AN	993 (41.8)	990 (41.8)
HbA1c, %	8.11 (0.87)	8.01 (0.82)	8.4 (1.0)	8.4(1.0)	8.4(1.3)	8.4 (1.4)	NA	AN	NA	NA
NT-proBNP, pg/mL	NA	NA	NA	AN	NA	NA	NA	ΝA	1428 (857–2655)	1446 (857–2641)
eGFR,	68.4 (20.2)	69.3 (20.7)	72.7 (19.5)	73.3 (19.8)	56.7 (18.8)	57.3 (19.1)	NA	AN	66.0 (19.6)	65.5 (19.3)
mL/min/1.73 m <sup>2</sup>										
Follow up (years) NYHA	3.1		3.6	10	2.(	10	4.2			ſ
_	NA	NA	NA	NA	NA	NA	NA	AN	1606 (67.7)	1597 (67.4)
=	NA	NA	NA	AN	NA	NA	NA	AN	747 (31.5)	751 (31.7)
2	NA	NA	NA	NA	NA	NA	NA	NA	20 (0.8)	23 (1.0)
BMI, body mass ind Data are reported a:	ex; DM, diabetes n 5 <i>n</i> (%), mean (SD)	nellitus; eGFR, e	estimated glomer terquartile range	rular filtration ).	rate; HbA1c, ha	emoglobin A1	c; NA, not availab	ole; NT-proB	NP, NT-proB-type nat	riuretic peptide.

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Table 1 (continued)										
	EMPEROR-Rec	duced 2020	SCORED 2	020	VERTIS-C	V 2020	SOLOIST-V	NHF 2021	EMPEROR-Pre-	erved 2021
Drug	Empagliflozin	Placebo	Sotagliflozin	Placebo	Ertugliflozin	Placebo	Sotagliflozin	Placebo	Empagliflozin	Placebo
Total number	1863	1867	NA	NA	1286	672	608	614	2997	2991
Age, years	67.2 (10.8)	66.5 (11.2)	NA	AN	64.2 (7.9)	64.7 (7.8)	69 (63–76)	70 (64–76)	71.8 (9.3)	71.9 (9.6)
Female, %	437 (23.5)	456 (24.4)	NA	AN	395 (30.7)	229 (34.1)	198 (32.6)	214 (34.9)	1338 (44.6)	1338 (44.7)
BMI, kg/m <sup>2</sup>	28.0 (5.5)	27.8 (5.3)	NA	AN	32.5 (5.5)	32.7 (5.2)	30.4 (26.3-34.3)	31.1 (27.3–34.5)	29.77 (5.8)	29.90 (5.9)
DM, %	927 (49.8)	929 (49.8)	NA	AN	1286 (100)	672 (100)	608 (100)	614 (100)	1466 (48.9)	1472 (49.2)
HbA1c, %	NA	AN	NA	NA	8.3 (0.9)	8.3 (0.9)	7.1 (6.4–8.3)	7.2 (6.4–8.2)	NA	NA
NT-proBNP, pg/mL	1887	1926	NA	NA	NA	NA	1816.8	1741.0	994	946
	(1077–3429)	(1153–3525)					(854.7–3658.5)	(842.5–3582.2)	(501–1740)	(498–1725)
eGFR,	61.8 (21.7)	62.2 (21.5)	NA	NA	NA	AN	49.2 (39.5-61.2)	50.5 (40.5-64.6)	60.6 (19.8)	60.6 (19.9)
mL/min/1.73 m <sup>2</sup>										
Follow up (years)		~	1.3			10	0	.7	2.2	
NYHA										
=	1399 (75.1)	1401 (75.0)	NA	ΝA	838 (65.2)	451 (67.1)	NA	NA	2432 (81.1)	2451 (81.9)
=	455 (24.4)	455 (24.4)	NA	NA	102 (7.9)	37 (5.5)	NA	NA	552 (18.4)	531 (17.8)
≥	9 (0.5)	11 (0.6)	NA	NA	1 (0.1)	0	NA	NA	10 (0.3)	8 (0.3)
BMI, body mass inde Data are reported as	ex; DM, diabetes r n (%), mean (SD)	nellitus; eGFR, e ), or median (int	stimated glome erquartile range	'ular filtrati ).	on rate; HbA1c,	haemoglobin	A1c; NA, not availa	ble; NT-proBNP, NT- <sub>F</sub>	oroB-type natriure	tic peptide.

terval; CV death, cardiovascular death; HHF, hospitalization for heart failure; KCCQ, Kansas City Cardiomyopathy Questionnaire; MACE, major adverse cardiovascular events; SGLT2i, sodium-glucose cotransporter-2 inhibitor.

#### (A) CV death or first HHF

Study of Subgroup	log[Hazard Ratio]	SE Weight	IV, Fixed, 95% C	I Year	IV, Fixed, 95% CI
EMPA-REG OUTCOME 2015	-0.32850407 0.187614	468 2.8%	0.72 [0.50, 1.04]	2015	
CANVAS 2017	-0.49429632 0.138343	325 5.2%	0.61 [0.47, 0.80]	2017	
DECLARE-1101 58 2019 DAPA-HE 2019	-0.23572233 0.115136	377 7.0% 875 24.6%	0.79 [0.63, 0.99]	2019	+
CREDENCE 2019	-0.21072103 0.187614	468 2.8%	0.81 [0.56, 1.17]	2019	
EMPEROR-Reduced 2020	-0.28768207 0.069826	ð11 20.5%	0.75 [0.65, 0.86]	2020	-
VERTIS CV 2020	-0.16251893 0.126886	6.2%	0.85 [0.66, 1.09]	2020	
EMPEROR-Preserved 2021	-0.23572233 0.06651	113 22.6%	0.79 [0.69, 0.90]	2021	
30E0131-WHF 2021	-0.34249031 0.11526	592 7.5%	0.71 [0.57, 0.69]	2021	
Total (95% CI)		100.0%	0.76 [0.71, 0.81]		•
Heterogeneity: Chi2 = 4.37, df = 8	(P = 0.82); I <sup>2</sup> = 0%				
Test for overall effect: Z = 8.79 (P	< 0.00001)			0.1	Favours SGLT2i Favours Placebo
3) CV death or total	HHE				
			Risk Rat	io	Risk Ratio
DAPA-HF 2019	-0.28768207	0.08155546	33.7% 0.75 [0.64	0.881 2019	- IV, Fixed, 95% CI
EMPEROR-Reduced 2020	-0.27443685	0.08056277	34.5% 0.76 [0.65	0.89] 2020	
SOLOIST-WHF and SCORED pooled (	>50) 2021 -0.46203546	0.17627635	7.2% 0.63 [0.45	, 0.89] 2021	
SOLOIST-WHF and SCORED pooled ( SOLOIST-WHF and SCORED pooled (	<40) 2021 -0.24846136	0.22062292	20.0% 0.78 [0.63	, 0.94] 2021	
T-4-1 (05% CI)			400.0% 0.74.00.00	0.041	•
Heterogeneity: Chi <sup>2</sup> = 1.98, df = 4 (P = 1	0.74);  2 = 0%		100.0% 0.74 [0.68,	0.01]	
Test for overall effect: Z = 6.28 (P < 0.0	0001)				0.1 0.2 0.5 1 2 5 Favours SGLT2i Favours Placebo
C) first HHF					
			Hazard Ratio		Hazard Ratio
Study or Subgroup	log[Hazard Ratio]	SE Weight	IV, Fixed, 95% C	I Year	IV, Fixed, 95% CI
EMPA-REG OUTCOME 2015	-0.28768207 0.235528	326 3.1%	0.75 [0.47, 1.19]	2015	
CANVAS 2017	-0.67334455 0.21677	714 3.7%	0.51 [0.33, 0.78]	2017	— <u> </u>
DECLARE-TIMI 58 2019	-0.31471074 0.139739	916 8.9%	0.73 [0.56, 0.96]	2019	
CREDENCE 2019	-0.27443685 0.241473	332 3.0%	0.76 [0.47, 1.22]	2019	
DAPA-HE 2019	-0.3566/494 0.0869	109 23.1%	0.70 [0.59, 0.83]	2019	
VERTIS CV (<45) 2020	-0.37100308 0.06180	r∺o ∠0.1% 532 2.6º/	0.09 [0.39, 0.81]	2020	
VERTIS CV (>45) 2020	-0.35667494 0.20062	116 1 Q%	0.70 [0.30, 1.00]	2020	— <u> </u>
EMPEROR-Preserved 2021	-0.34249031 0.07967	384 27.5%	0,71 [0.61. 0.83]	2021	-
					.
Total (95% CI)		100.0%	0.69 [0.64, 0.75]		•
Heterogeneity: Chi <sup>2</sup> = 2.81, df = 8	(P = 0.95); I <sup>2</sup> = 0%			0.1	
Test for overall effect: Z = 8.71 (P	< 0.00001)			0.1	Favours SGLT2i Favours Placebo
N CV death					
			Hazard Ratio		Hazard Ratio
Study or Subgroup	log[Hazard Ratio]	SE Weight	IV, Fixed, 95% C	I Year	IV, Fixed, 95% CI
EMPA-REG OUTCOME 2015	-0.34249031 0.250464	145 3.3%	0.71 [0.43, 1.16]	2015	
CANVAS 2017	-0.32850407 0.17770	)75 6.6%	0.72 [0.51, 1.02]	2017	
DECLARE-TIMI 58 2019	0.00995033 0.162935	542 7.9%	1.01 [0.73, 1.39]	2019	
EMPEROR-Reduced 2020	-0.19040094 0.090942 _0.08338161 0.10024	100 25.2%	0.02 [0.09, 0.98]	2019	
VERTIS CV (\$45) 2020	-0.00330101 0.10030	334 20.1%	0.92 [0.70, 1.12]	2020	
VERTIS CV (>45) 2020	0.07696104 0.260625	532 3.1%	1.08 [0.65, 1.80]	2020	<del>_</del>
SOLOIST-WHF 2021	-0.17435339 0.190410	033 5.7%	0.84 [0.58, 1.22]	2021	+-
EMPEROR-Preserved 2021	-0.09431068 0.092085	591 24.6%	0.91 [0.76, 1.09]	2021	
T / 1/059/ 00					
rotal (95% CI)	(D = 0.90); 12 = 00(	100.0%	ປ.88 [ປ.80, 0.96]	-	
Test for overall effect: 7 = 2 99 /P	(r - 0.8∠); I = 0% = 0.004)			0.1	0.2 0.5 1 2 5
rest for overall effect. Z = 2.00 (F	- 0.004)				Favours SGLT2i Favours Placebo
E) Any death					
Study or Subgroup			Hazard Ratio	Veer	Hazard Ratio
	or[Hazard Patio]	SE Woight	IV Eixed 95% C		IV Eixed 95% CI
EMPA-REG OUTCOME 2015	log[Hazard Ratio]	SE Weight	IV, Fixed, 95% C	2015	IV, Fixed, 95% Cl
EMPA-REG OUTCOME 2015 CANVAS 2017	log[Hazard Ratio] -0.23572233 0.21328 -0.35667494 0.161149	SE Weight 377 3.2% 346 5.6%	IV, Fixed, 95% C 0.79 [0.52, 1.20] 0.70 [0.51, 0.96]	2015 2017	IV, Fixed, 95% CI
EMPA-REG OUTCOME 2015 CANVAS 2017 DECLARE-TIMI 58 2019	log[Hazard Ratio] -0.23572233 0.21328 -0.35667494 0.161148 -0.13926207 0.128872	SE         Weight           377         3.2%           346         5.6%           283         8.7%	<ul> <li>IV, Fixed, 95% C</li> <li>0.79 [0.52, 1.20]</li> <li>0.70 [0.51, 0.96]</li> <li>0.87 [0.68, 1.12]</li> </ul>	2015 2017 2019	IV, Fixed, 95% CI
EMPA-REG OUTCOME 2015 CANVAS 2017 DECLARE-TIMI 58 2019 CREDENCE 2019	log[Hazard Ratio]           -0.23572233         0.21328           -0.35667494         0.161145           -0.13926207         0.128872           -0.07257069         0.212326	SE         Weight           377         3.2%           346         5.6%           283         8.7%           373         3.2%	<ul> <li>IV, Fixed, 95% C</li> <li>0.79 [0.52, 1.20]</li> <li>0.70 [0.51, 0.96]</li> <li>0.87 [0.68, 1.12]</li> <li>0.93 [0.61, 1.41]</li> </ul>	2015 2017 2019 2019	IV, Fixed, 95% Cl
EMPA-REG OUTCOME 2015 CANVAS 2017 DECLARE-TIMI 58 2019 CREDENCE 2019 DAPA-HF 2019	log[Hazard Ratio]           -0.23572233         0.21328           -0.35667494         0.161149           -0.13926207         0.128872           -0.07257069         0.212326           -0.18632958         0.07952	SE         Weight           377         3.2%           946         5.6%           283         8.7%           373         3.2%           257         22.9%	<ul> <li>IV, Fixed, 95% C</li> <li>0.79 [0.52, 1.20]</li> <li>0.70 [0.51, 0.96]</li> <li>0.87 [0.68, 1.12]</li> <li>0.93 [0.61, 1.41]</li> <li>0.83 [0.71, 0.97]</li> </ul>	2015 2017 2019 2019 2019 2019	IV, Fixed, 95% Cl
EMPA-REG OUTCOME 2015 CANVAS 2017 DECLARE-TIMI 58 2019 CREDENCE 2019 DAPA-HF 2019 VERTIS CV (≤45) 2020 VERTIS CV (≤45) 2020	log[Hazard Ratio] -0.23572233 0.21326 -0.35667494 0.161144 -0.13926207 0.12887 -0.07257069 0.212326 -0.18632958 0.07952 -0.040822 0.237800 0.000822 0.237800	SE         Weight           377         3.2%           946         5.6%           283         8.7%           373         3.2%           257         22.9%           088         2.6%	<ul> <li>IV, Fixed, 95% C</li> <li>0.79 [0.52, 1.20]</li> <li>0.70 [0.51, 0.96]</li> <li>0.87 [0.68, 1.12]</li> <li>0.93 [0.61, 1.41]</li> <li>0.83 [0.71, 0.97]</li> <li>0.96 [0.60, 1.53]</li> <li>1.01 [0.65, 4.53]</li> </ul>	2015 2017 2019 2019 2019 2019 2019 2020 2020	IV, Fixed, 95% Cl
EMPA-REG OUTCOME 2015 CANVAS 2017 DECLARE-TIMI 58 2019 CREDENCE 2019 DAPA-HF 2019 VERTIS CV (≤45) 2020 VERTIS CV (<45) 2020 VERTIS CV (<45) 2020	log[Hazard Ratio] -0.23572233 0.21322 -0.35667494 0.161143 -0.13926207 0.128877 -0.07257069 0.213222 -0.18632958 0.07955 -0.040822 0.237800 0.00995033 0.221800 -0.08338181 0.02185	SE         Weight           377         3.2%           346         5.6%           283         8.7%           373         3.2%           257         22.9%           388         2.6%           382         2.9%           328         17.4%	V, Fixed, 95% C 0.79 [0.52, 1.20] 0.70 [0.51, 0.96] 0.87 [0.68, 1.12] 0.93 [0.61, 1.41] 0.83 [0.71, 0.97] 0.96 [0.60, 1.53] 1.01 [0.65, 1.56] 0.92 [0.77, 140]	2015 2017 2019 2019 2019 2020 2020 2020 2020	IV, Fixed, 95% Cl
EMPA-REG OUTCOME 2015 CANVAS 2017 DECLARE-TIMI 58 2019 CREDENCE 2019 DAPA-HF 2019 VERTIS CV (<45) 2020 VERTIS CV (<45) 2020 EMPEROR-Reduced 2020 EMPEROR-Reduced 2021	log[Hazard Ratio]           -0.23572233         0.21322           -0.35667494         0.6161145           -0.13926207         0.12827           -0.07257069         0.212322           -0.16632958         0.07955           -0.040622         0.237800           0.00995033         0.221803           -0.0338161         0.091165	SE         Weight           377         3.2%           946         5.6%           283         8.7%           573         3.2%           257         22.9%           382         2.9%           328         1.7.4%           711         28.4%	<ul> <li>IV, Fixed, 95% C</li> <li>0.79 [0.52, 1.20]</li> <li>0.70 [0.51, 0.96]</li> <li>0.87 [0.68, 1.12]</li> <li>0.93 [0.61, 1.41]</li> <li>0.83 [0.71, 0.97]</li> <li>0.96 [0.60, 1.53]</li> <li>1.01 [0.65, 1.56]</li> <li>0.92 [0.77, 1.10]</li> <li>1.00 [0.87, 1.15]</li> </ul>	2015 2017 2019 2019 2019 2020 2020 2020 2020 2020	IV, Fixed, 95% Cl
EMPA-REG OUTCOME 2015 CANVAS 2017 DECLARE-TIMI 56 2019 CREDENCE 2019 DAPA-HF 2019 VERTIS CV (≈45) 2020 VERTIS CV (≈45) 2020 EMPEROR-Reduced 2020 EMPEROR-Preserved 2021 SOLOIST-WHF 2021	log[Hazard Ratio]           -0.2357223         0.2132           -0.3567494         0.16114           -0.13926207         0.12887           -0.07257069         0.21232           -0.1663258         0.7955           -0.040822         0.23780           0.09338161         0.901165           0.07303         0.21094           0.18452904         0.16145	SE         Weight           377         3.2%           346         5.6%           283         8.7%           373         3.2%           257         22.9%           382         2.6%           382         2.9%           328         17.4%           711         28.4%           163         5.1%	<ul> <li>IV, Fixed, 95% C</li> <li>0.79 [0.52, 1.20]</li> <li>0.70 [0.51, 0.96]</li> <li>0.87 [0.68, 1.12]</li> <li>0.93 [0.61, 1.41]</li> <li>0.83 [0.71, 0.97]</li> <li>0.96 [0.60, 1.53]</li> <li>1.01 [0.65, 1.56]</li> <li>0.92 [0.77, 1.10]</li> <li>1.00 [0.87, 1.15]</li> <li>0.82 [0.59, 1.14]</li> </ul>	2015 2017 2019 2019 2019 2020 2020 2020 2020 2020	IV, Fixed, 95% Cl
EMPA-REG OUTCOME 2015 CANVAS 2017 DECLARE-TIMI 58 2019 CREDENCE 2019 DAPA-HF 2019 VERTIS CV (≤45) 2020 VERTIS CV (≤45) 2020 VERTIS CV (>45) 2020 EMPEROR-Reduced 2020 EMPEROR-Reduced 2021 SOLOIST-WHF 2021	log[Hazard Ratio]           -0.2357233         0.2132           -0.366744         0.161144           -0.13926207         0.12887           -0.07257069         0.21232           -0.1663258         0.07955           -0.040822         0.237800           -0.00995033         0.221800           -0.038161         0.901166           -0.038161         0.901166           -0.1845209         0.71300           -0.18455094         0.1618107	SE         Weight           377         3.2%           946         5.6%           9283         8.7%           9373         3.2%           9257         22.9%           928         2.6%           928         17.4%           928         17.4%           163         5.1%	<ul> <li>IV, Fixed, 95% C</li> <li>0.79 [0.52, 1.20]</li> <li>0.70 [0.51, 0.96]</li> <li>0.87 [0.68, 1.12]</li> <li>0.93 [0.61, 1.41]</li> <li>0.83 [0.71, 0.97]</li> <li>0.96 [0.60, 1.53]</li> <li>1.01 [0.65, 1.56]</li> <li>0.92 [0.77, 1.10]</li> <li>1.00 [0.87, 1.15]</li> <li>0.82 [0.59, 1.14]</li> </ul>	2015 2017 2019 2019 2019 2020 2020 2020 2020 2021 2021	IV, Fixed, 95% Cl
EMPA-REG OUTCOME 2015 CANVAS 2017 DECLARE-TIMI 56 2019 CREDENCE 2019 DAPA-HF 2019 VERTIS CV (<45) 2020 VERTIS CV (<45) 2020 VERTIS CV (<45) 2020 EMPEROR-Reduced 2020 EMPEROR-Preserved 2021 SOLOIST-WHF 2021 Total (95% CI)	log[Hazard Ratio]           -0.2357223         0.2132           -0.356744         0.18114           -0.13926207         0.12887           -0.07257069         0.21232           -0.18632958         0.07952           -0.040622         0.237800           0.0093503         0.221803           -0.040622         0.237800           -0.0933161         0.09116           0.071303         0.21804           -0.18845094         0.168107	SE         Weight           377         3.2%           946         5.6%           9283         8.7%           9273         3.2%           9257         22.9%           928         2.6%           928         17.4%           928         5.1%           100.0%         100.0%	IV, Fixed, 95% C           0.79 [0.52, 1.20]           0.70 [0.51, 0.96]           0.87 [0.68, 1.12]           0.33 [0.61, 1.41]           0.86 [0.60, 1.53]           0.96 [0.60, 1.53]           0.92 [0.77, 1.10]           1.00 [0.87, 1.15]           0.82 [0.59, 1.14]           0.90 [0.83, 0.97]	2015 2017 2019 2019 2019 2020 2020 2020 2020 2021 2021	IV, Fixed, 95% Cl
EMPA-REG OUTCOME 2015 CANVAS 2017 DECLARE-TIMI 56 2019 OREDENCE 2019 DAPA-HF 2019 VERTIS CV (=45) 2020 EMPEROR-Reduced 2020 EMPEROR-Reduced 2021 SOLOIST-WHF 2021 Total (95% CI) Heterogeneity. Chi <sup>2</sup> = 6.81, df = 9 Test for overall effect. 7 = 2 90 /2	log[Hazard Ratio] -0.23572233 0.21322 -0.3566744 0.161144 -0.13926207 0.12887 -0.07257069 0.212324 -0.16632958 0.07955 -0.040822 0.237600 -0.09338161 0.091165 0.095103 0.22160 -0.0338161 0.091165 0.071307 -0.19845094 0.16810 (P = 0.66); I <sup>2</sup> = 0% = 0.004	SE         Weight           377         3.2%           946         5.6%           823         8.7%           573         3.2%           257         22.9%           3088         2.6%           328         17.4%           11         28.4%           163         5.1%           100.0%         100.0%	IV, Fixed, 95% C           0.79 [0.52, 1.20]           0.70 [0.51, 0.96]           0.83 [0.61, 1.41]           0.83 [0.61, 1.41]           0.83 [0.71, 0.97]           0.96 [0.60, 1.53]           1.01 [0.65, 1.56]           0.92 [0.77, 1.10]           0.82 [0.59, 1.14]           0.90 [0.83, 0.97]	2015 2017 2019 2019 2019 2020 2020 2020 2020 2021 2021	IV, Fixed, 95% Cl
EMPA-REG OUTCOME 2015 CANVAS 2017 DECLARE-TIMI 58 2019 CREDENCE 2019 DAPA-HF 2019 VERTIS CV (≤45) 2020 VERTIS CV (≤45) 2020 EMPEROR-Reduced 2021 SOLOIST-WHF 2021 SOLOIST-WHF 2021 Heterogeneity: Chi <sup>2</sup> = 6.81, df = 9 i Test for overall effect: Z = 2.89 ( <i>P</i>	log[Hazard Ratio]           -0.2357223         0.2132           -0.3567244         0.16114           -0.13926207         0.12887           -0.07257069         0.21232           -0.1663258         0.07955           -0.040822         0.23780           0.09338161         0.901163           0.0338161         0.901163           0.01845294         0.1618107           (P = 0.66); I <sup>2</sup> = 0%         =           = 0.004)         -	SE         Weight           377         3.2%           946         5.6%           823         8.7%           673         3.2%           257         22.9%           928         2.6%           928         17.4%           711         28.4%           163         5.1%           100.0%         300	<ul> <li>W. Fixed, 95% C</li> <li>0.79 (0.52, 1.20)</li> <li>0.70 (0.51, 0.66)</li> <li>0.87 (0.68, 1.12)</li> <li>0.93 (0.61, 1.41)</li> <li>0.83 (0.71, 0.97)</li> <li>0.96 (0.60, 1.53)</li> <li>1.01 (0.65, 1.56)</li> <li>0.92 (0.77, 1.10)</li> <li>1.02 (0.59, 1.14)</li> <li>0.82 (0.59, 1.14)</li> <li>0.80 [0.83, 0.97]</li> </ul>	2015 2017 2019 2019 2019 2020 2020 2020 2020 2021 2021	IV, Fixed, 95% Cl
EMPA-REG OUTCOME 2015 CANVAS 2017 DECLARE-TIMI 58 2019 CREDENCE 2019 DAPA-HF 2019 VERTIS CV (≪45) 2020 VERTIS CV (≪45) 2020 VERTIS CV (≪45) 2020 EMPEROR-Reduced 2020 EMPEROR-Reduced 2020 EMPEROR-Reduced 2021 SOLOIST-WHF 2021 Total (95% CI) Heterogeneity: Chi <sup>2</sup> = 6.81, df = 9 Test for overall effect: Z = 2.89 (P E) MACE	log[Hazard Ratio] 0.23572233 0.21324 0.3566744 0.161144 0.13926207 0.12887 0.07257069 0.21324 0.079557069 0.21324 0.040822 0.237800 0.00985033 0.221600 0.00985033 0.22160 0.009161 0.07130 0.07130 0.07130 (P = 0.66); I <sup>a</sup> = 0% = 0.004)	SE         Weight           377         3.2%           283         8.7%           373         3.2%           267         22.9%           928         17.4%           112         28.4%           163         5.1%           100.0%	IV. Fixed, 95% C 10, 779 (0.52, 1.20) 0.79 (0.52, 1.20) 0.70 (0.51, 0.96) 0.87 (0.68, 1.12) 0.93 (0.61, 1.41) 0.83 (0.71, 0.97) 0.96 (0.60, 0.153) 1.01 (0.65, 1.66) 0.92 (0.77, 1.10) 0.02 (0.77, 1.15) 0.82 (0.59, 1.14) 0.90 [0.83, 0.97]	2015 2017 2019 2019 2019 2020 2020 2020 2020 2020	IV, Fixed, 95% Cl
EMPA-REG OUTCOME 2015 CANVAS 2017 DECLARE-TIMI 58 2019 CREDENCE 2019 DAPA-HF 2019 VERTIS CV (=45) 2020 VERTIS CV (=45) 2020 EMPEROR-Reduced 2020 EMPEROR-Reduced 2020 EMPEROR-Reduced 2021 SOLOIST-WHF 2021 Total (95% CI) Heterogeneity: Chi <sup>2</sup> = 6.81, df = 9 Test for overall effect: Z = 2.89 ( <i>P</i> C) MACCE	log[Hazard Ratio]           -0.2357233         0.2132           -0.3567244         0.16114           -0.1326207         0.12887           -0.13652958         0.07957           -0.040822         0.23780           -0.040822         0.23780           -0.0333         0.21603           -0.16845958         0.07953           -0.0333         0.21603           -0.19845094         0.16810*           (P = 0.66); I <sup>2</sup> = 0%         =           = 0.004)	SE Weight 377 3.2% 446 5.6% 283 8.7% 373 3.2% 257 22.9% 382 2.9% 382 2.9% 382 2.9% 382 2.9% 382 2.9% 382 17.4% 11 28.4% 100.0%	<ul> <li>IV. Fixed, 95% C</li> <li>O.79 (0.52, 1.20)</li> <li>O.70 (0.52, 1.20)</li> <li>O.70 (0.51, 0.96)</li> <li>O.87 (0.68, 1.12)</li> <li>O.93 (0.61, 1.41)</li> <li>O.96 (0.60, 1.53)</li> <li>I.01 (0.65, 1.56)</li> <li>O.92 (0.77, 1.10)</li> <li>O.82 (0.59, 1.14)</li> <li>O.90 [0.83, 0.97]</li> <li>Hazard Ratio</li> </ul>	2015 2017 2019 2019 2019 2020 2020 2020 2020 2020	IV, Fixed, 95% Cl
EMPA-REG OUTCOME 2015 CANVAS 2017 DECLARE-TIMI 56 2019 DECLARE-TIMI 56 2019 DECLARE-TIMI 56 2019 DAPA-HF 2019 VERTIS CV (≈45) 2020 VERTIS CV (≈45) 2020 EMPEROR-Reduced 2021 SOLOIST-WHF 2021 Total (95% CI) Heterogeneity: Chi <sup>9</sup> = 6.81, df = 9 i Test for overall effect: Z = 2.89 ( <i>P</i> <b>C) MACE</b> Study or Subgroup log[N	log[Hazard Ratio]           -0.23572233         0.21322           -0.35672494         0.16114           -0.13926207         0.12887           -0.07257069         0.21324           -0.16823958         0.07955           -0.040822         0.23780           0.0995033         0.221602           -0.08338161         0.091165           0.0338161         0.091165           0.03385094         0.168107           (P = 0.66); I <sup>2</sup> = 0%         =           = 0.004)         SEE	SE         Weight           377         3.2%           446         5.6%           373         3.2%           283         8.7%           373         3.2%           257         22.9%           382         2.9%           328         17.4%           163         5.1%           100.0%         100.0%	IV. Fixed, 95% C           0.79 [0.52, 1.20]           0.79 [0.52, 1.20]           0.70 [0.51, 0.66]           0.87 [0.68, 1.22]           0.30 [0.61, 1.41]           0.68 [0.71, 0.97]           0.96 [0.60, 1.53]           1.01 [0.65, 1.56]           0.92 [0.77, 1.10]           0.90 [0.63, 0.97]           0.90 [0.83, 0.97]           Hazard Ratio           V. Fixed, 95% C1 V.           0.90 [0.40, 95% C1 V.	2015 2017 2019 2019 2019 2020 2020 2020 2020 2020	IV, Fixed, 95% Cl
EMPA-REG OUTCOME 2015 CANVAS 2017 DECLARE-TIMI 58 2019 CREDENCE 2019 DAPA-HE 2019 VERTIS CV (≤45) 2020 VERTIS CV (≤45) 2020 VERTIS CV (≤45) 2020 EMPEROR-Reduced 2020 EMPEROR-Reduced 2020 EMPEROR-Reduced 2021 SOLOIST-WHF 2021 Total (95% CI) Heterogeneily: Chi <sup>2</sup> = 6.81, df = 9 Test for overall effect: Z = 2.89 (P CANVAS 2017 DECL ABE-TIMI 58 2019 DECL ABE-TIMI 58 2019	log[Hazard Ratio]           -0.23572233         0.21322           -0.35672494         0.161144           -0.13926207         0.12887           -0.07257069         0.21322           -0.16632958         0.07955           -0.040822         0.237800           -0.00338161         0.098163           -0.03338161         0.09116           -0.19845094         0.168107           (P = 0.66); I <sup>a</sup> = 0%         =           = 0.004)         SE           -0.22314355         0.13874169           -0.009096033         0.148770	SE         Weight           377         3.2%           946         5.6%           823         8.7%           373         3.2%           926         22.9%           928         17.4%           100.0%         100.0%           Weight         1           24.5%         1           34.6%         1	<ul> <li>IV. Fixed, 95% C</li> <li>O.79 (0.52, 1.20)</li> <li>O.79 (0.52, 1.20)</li> <li>O.70 (0.51, 0.66)</li> <li>O.87 (0.68, 1.12)</li> <li>O.93 (0.61, 1.41)</li> <li>O.96 (0.60, 1.53)</li> <li>I (0.66, 1.56)</li> <li>O.92 (0.77, 1.10)</li> <li>I (0.06, 1.66)</li> <li>O.92 (0.77, 1.10)</li> <li>I (0.06, 1.63)</li> <li>O.90 (0.83, 0.97)</li> <li>Hazard Ratio</li> <li>V. Fixed, 95% CI V</li> <li>O.80 (0.61, 1.05)</li> <li>O.80 (0.61, 1.05)</li> <li>I (0.16, 0.61, 1.05)</li> <li>I (0.16, 0.61, 1.05)</li> <li>I (0.16, 0.61, 1.05)</li> </ul>	2015 2017 2019 2019 2019 2020 2020 2020 2020 2020	IV, Fixed, 95% CI
EMPA-REG         OUTCOME 2015           CANVAS 2017         CANVAS 2017           DECLARE-TIMI 58 2019         DECLARE-TIMI 58 2019           DECLARE-TIMI 58 2019         VERTIS CV (=45) 2020           VERTIS CV (=45) 2020         EMPEROR-Reduced 2020           EMPEROR-Reduced 2020         SOLOIST-WHF 2021           Total (95% CI)         Heterogeneity: Chi <sup>2</sup> = 6.81, df = 9           Test for overall effect: Z = 2.89 (P         D           MACCE         Study or Subgroup         log[]           CANVAS 2017         DECLARE-TIMI 58 2019           DERDERCE-2019         2019	log[Hazard Ratio]           -0.2357233         0.21322           -0.3567244         0.161144           -0.1326207         0.12887           -0.07257089         0.21232           -0.040822         0.23780           -0.040822         0.23780           -0.040822         0.23780           -0.0333         0.21803           -0.0333         0.21803           -0.0338161         0.09116           -0.18845094         0.168107           (P = 0.66); P = 0%         =           = 0.004)         SE           -0.22314355         0.13874169           0.02939503         0.1168707           -0.099431068         0.1168707           -0.099431068         0.119274950	SE         Weight           377         3.2%           346         5.6%           283         8.7%           373         3.2%           257         22.9%           088         2.6%           328         17.4%           100.0%           Weight         1           24.5%         1           34.6%         1           12.4%         1	<ul> <li>IV. Fixed, 95% C</li> <li>O.79 (0.52, 1.20)</li> <li>O.70 (0.52, 1.20)</li> <li>O.70 (0.51, 0.66)</li> <li>O.87 (0.68, 1.12)</li> <li>O.93 (0.61, 1.41)</li> <li>O.96 (0.60, 1.53)</li> <li>I.01 (0.65, 1.56)</li> <li>O.92 (0.77, 1.10)</li> <li>I.00 (0.87, 1.15)</li> <li>O.82 (0.59, 1.14)</li> <li>O.90 (0.83, 0.97)</li> <li>Hazard Ratio</li> <li>V. Fixed, 95% C I V</li> <li>O.80 (0.61, 1.05)</li> <li>I.01 (0.80, 1.27)</li> <li>O.91 (0.62, 1.26)</li> <li>O.91 (0.62, 1.24)</li> </ul>	2015 2017 2019 2019 2019 2020 2020 2020 2020 2021 2021	IV, Fixed, 95% Cl
EMPA-REG OUTCOME 2015 CANVAS 2017 DECLARE-TIMI 56 2019 CREDENCE 2019 DAPA-HE 2019 VERTIS CV (≈45) 2020 VERTIS CV (≈45) 2020 EMPEROR-Reduced 2021 SOLOIST-WHF 2021 Total (95% CI) Heterogeneity: Chi <sup>9</sup> = 6.81, df = 9 i Test for overall effect: Z = 2.89 ( <i>P</i> <b>C) MACE</b> Study or Subgroup log[N CANVAS 2017 DECLARE-TIMI 56 2019 CREDENCE 2019 VERTIS CV 2020	log[Hazard Ratio]           -0.2357233         0.2132           -0.3567249         0.6114           -0.1326207         0.12887           -0.07257069         0.21324           -0.16632958         0.07955           -0.04822         0.23600           -0.00338161         0.09116           0.01945094         0.61141           (-0.00338161         0.09116           0.003380161         0.09116           0.01945094         0.168107           (P = 0.66); I <sup>2</sup> = 0%         = 0.004)           Hazard Ratio]         SE           -0.22314355         0.13874169           0.00995033         0.1168707           -0.09431068         0.19743822           -0.0431068         0.19743822	SE         Weight           37         3.2%           946         5.6%           928         8.7%           37         3.2%           926         5.6%           927         22.9%           9382         2.9%           928         17.4%           100.0%         100.0%           Veight         1           24.5%         1           24.5%         1           24.6%         1           24.6%         1           28.7%         12.1%	IV. Fixed, 95% C           0.79 [0.52, 1.20)           0.79 [0.52, 1.20)           0.70 [0.51, 0.66]           0.87 [0.68, 1.12]           0.93 [0.61, 1.41]           0.80 [0.60, 1.53]           1.01 [0.65, 1.56]           0.92 [0.77, 1.10]           1.00 [0.87, 1.15]           0.82 [0.59, 1.14]           0.90 [0.83, 0.97]           V. Fixed, 95% C1 Y           0.80 [0.61, 0.51]           0.80 [0.61, 0.62]           0.90 [0.82, 0.34]           0.80 [0.61, 0.61, 0.62]           0.91 [0.62, 1.34]           0.91 [0.62, 1.34]	2015 2017 2019 2019 2019 2020 2020 2020 2020 2021 2021	IV, Fixed, 95% CI
EMPAREC OUTCOME 2015           CANVAS 2017           DECLARE-TIMI 68 2019           DECLARE-TIMI 68 2019           DRA-HF 2019           VERTIS CV (=45) 2020           VERTIS CV (=45) 2020           EMPEROR-Reduced 2020           EMPEROR-Reserved 2021           SOLOIST-WHF 2021           Total (95% CI)           Heterogeneity: Chi <sup>2</sup> = 6.81, df = 9 i           Test for overall effect: Z = 2.89 (P           FMACE           Study or Subgroup         log[th           CANVAS 2017         DECLARE-TIMI 58 2019           CREDENCE 2019         VERTIS CV 2020	Log[Hazard Ratio]           -0.23572233         0.21322           -0.3567244         0.161144           -0.13926207         0.12887           -0.07257069         0.21322           -0.16632958         0.07955           -0.040822         0.237800           -0.009338161         0.099163           -0.03338161         0.091163           -0.19845094         0.168107           (P = 0.66); I <sup>a</sup> = 0%         =           = 0.004)         SE           -0.22314355         0.13874169           -0.009431068         0.119743892           0.00945030         0.1188770	SE         Weight           37         3.2%           446         5.6%           828         8.7%           37         3.2%           457         3.2.9%           468         2.6%           471         28.4%           163         5.1%           100.0%         10.0%           24.5%         12.1%           28.7%         28.7%	<ul> <li>IV. Fixed, 95% C</li> <li>O79 (0.52, 1.20)</li> <li>O79 (0.52, 1.20)</li> <li>O70 (0.51, 0.66)</li> <li>O87 (0.68, 1.12)</li> <li>O93 (0.61, 1.41)</li> <li>O.81 (0.71, 0.97)</li> <li>O96 (0.60, 1.53)</li> <li>I (10 (0.65, 1.56)</li> <li>O (0.87, 1.16)</li> <li>O (0.87, 1.15)</li> <li>O (0.87, 1.15)</li> <li>O (0.83, 0.97)</li> <li>Hazard Ratio</li> <li>V, Fixed, 95% CI Y</li> <li>O.80 (0.61, 1.62)</li> <li>O.80 (0.61, 1.62)</li> <li>O.80 (0.61, 1.65)</li> <li>O.80 (0.61, 1.65)</li> <li>O.80 (0.61, 1.65)</li> <li>O.80 (0.61, 1.65)</li> <li>O.91 (0.62, 1.34)</li> <li>O.91 (0.62, 1.34)</li> <li>I.05 (0.82, 1.35)</li> </ul>	2015 2017 2019 2019 2019 2020 2020 2020 2020 2021 2021	IV, Fixed, 95% Cl
EMPA.REG         OUTCOME 2015           CANVAS 2017         CANVAS 2017           DECLARE-TIMI 58 2019         DECLARE-TIMI 58 2019           DEAPA.HF 2019         VERTIS CV (=45) 2020           VERTIS CV (=45) 2020         EMPEROR-Reduced 2021           SOLOIST-WHF 2021         Total (95% CI)           Heterogeneity: ChP = 6.81, df = 9         Test for overall effect: Z = 2.89 (P <b>Study or Subgroup</b> log[H           CANVAS 2017         DECLARE-TIMI 58 2019           CREDENCE 2019         VERTIS CV 2020           Total (95% CI)         Total (95% CI)	log[Hazard Ratio]           -0.2357233         0.2132           -0.3567244         0.16114           -0.13926207         0.12887           -0.0725709         0.21322           -0.040822         0.23760           -0.040822         0.23760           -0.040822         0.23760           -0.040822         0.23760           -0.0333         0.21803           -0.0338161         0.09116           -0.18845094         0.168107           (P = 0.66); P = 0%         =           = 0.004)         SE           -0.22314355         0.13874169           0.0995033         0.118707           0.0993036         0.118707           0.09431068         0.19743822           0.04879016         0.12822165	SE         Weight           37         3.2%           946         5.6%           938         8.7%           73         3.2%           823         8.7%           73         3.2%           823         8.7%           73         3.2%           823         8.7%           826         17.4%           100.0%         100.0%           Weight         12.4%           12.4%         12.4%           12.4%         12.4%	IV. Fixed, 95% C           0.79 [0.52, 1.20]           0.79 [0.52, 1.20]           0.76 [0.51, 0.66]           0.87 [0.68, 1.12]           0.93 [0.61, 1.41]           0.96 [0.60, 1.53]           1.01 [0.65, 1.56]           0.92 [0.77, 1.10]           0.90 [0.63, 1.15]           0.82 [0.59, 1.14]           0.90 [0.83, 0.97]           Hazard Ratio           V. Fixed, 95% Cl Y           0.80 [0.61, 1.65]           1.01 [0.80, 1.27]           0.91 [0.62, 1.36]           0.91 [0.62, 1.312]           1.05 [0.82, 1.35]           1.05 [0.82, 1.36]	2015 2017 2019 2019 2019 2020 2020 2020 2021 2021	IV, Fixed, 95% Cl
EMPA-REG OUTCOME 2015           CANVAS 2017           DECLARE-TIMI 56 2019           DECLARE-TIMI 56 2019           DRA-HF 2019           VERTIS CV (=           VERTIS CV (=           SQL015           EMPEROR-Reduced 2020           EMPEROR-Reduced 2021           SQL015           Total (95% CI)           Heterogeneity: Chi <sup>2</sup> = 6.81, df = 9 i           Test for overall effect: Z = 2.89 (P <b>C MACE</b> Study or Subgroup           DECLARE-TIMI 56 2019           CREAVAS 2017           DECLARE-TIMI 56 2019           CREATE-TIMI 56 2019           VERTIS CV 2020           Total (95% CI)           Heterogeneity: Chi <sup>2</sup> = 2.46, df = 3	log[Hazard Ratio]           -0.2357233         0.2132           -0.35672434         0.16114           -0.1326207         0.12887           -0.07257069         0.21322           -0.16832958         0.07955           -0.04822         0.237800           -0.003306161         0.099163           -0.018432042         0.237800           -0.003306161         0.091163           -0.019845094         0.168107           (P = 0.66); I <sup>2</sup> = 0%         = 0.004)           Hazard Ratio]         SE           -0.09431068         0.11874707           -0.09431068         0.11874392           0.04879016         0.12822165	SE         Weight           37         3.2%           346         5.6%           573         3.2%           573         3.2%           573         3.2%           574         22.9%           322         2.9%           328         17.4%           100.0%         100.0%           Weight         1           24.5%         1           34.6%         1           12.1%         2           28.7%         1	IV. Fixed, 95% C           0.79 [0.52, 1.20)           0.79 [0.52, 1.20)           0.70 [0.51, 0.66]           0.87 [0.68, 1.12]           0.93 [0.61, 1.41]           0.81 [0.61, 1.41]           0.82 [0.71, 0.97]           0.96 [0.60, 1.53]           1.01 [0.65, 1.56]           0.92 [0.77, 1.10]           0.90 [0.83, 0.97]           0.82 [0.59, 1.14]           0.90 [0.83, 0.97]           0.80 [0.61, 1.05]           0.80 [0.61, 1.05]           0.80 [0.61, 1.05]           0.10 [0.80, 1.27]           0.91 [0.62, 1.34]           1.05 [0.82, 1.35]           1.05 [0.82, 1.36]           0.30 [0.62, 1.34]           1.05 [0.82, 1.36]	2015 2017 2019 2019 2020 2020 2020 2020 2020 2020	IV, Fixed, 95% Cl
EMPA-REG OUTCOME 2015           CANVAS 2017           DECLARE-TIMI 58 2019           DECLARE-TIMI 58 2019           DRA-HE 2019           VERTIS CV (=45) 2020           VERTIS CV (=45) 2020           EMPEROR-Reduced 2020           EMPEROR-Reduced 2021           SOLOIST-WHF 2021           Total (95% CI)           Heterogeneity: Chi <sup>2</sup> = 6.81, df = 9           Fest for overall effect: Z = 2.89 (P           Study or subgroup         log[*           CANVAS 2017         DECLARE-TIMI 58 2019           CAREDENCE 2019         VERTIS CV 2020           Total (95% CI)         Heterogeneity: Chi <sup>2</sup> = 2.46, df = 3           Test for overall effect: Z = 0.71 (P	log[Hazard Ratio]           -0.23572233         0.21322           -0.3567244         0.161144           -0.13926207         0.12887           -0.07257069         0.21322           -0.16832958         0.07955           -0.040822         0.237800           -0.009338161         0.099163           -0.013264094         0.161145           -0.040822         0.237800           -0.008338161         0.099163           -0.019845094         0.168107           (P = 0.66); I <sup>a</sup> = 0%         =           = 0.004)         SE           +0.22314355         0.13874169           0.00995033         0.1168707           0.09431068         0.119743892           0.04879016         0.12822165           (P = 0.48); I <sup>a</sup> = 0%         =           = 0.48)         =	SE         Weight           37         3.2%           46         5.6%           83         8.7%           3.2%         567           22.9%         22.9%           382         2.9%           328         17.4%           100.0%         1           24.5%         1           24.5%         1           12.1%         1           28.7%         1           100.0%         0	IV. Fixed, 95% C           0.79 [0.52, 1.20]           0.79 [0.52, 1.20]           0.70 [0.51, 0.66]           0.87 [0.68, 1.12]           0.80 [0.61, 1.41]           0.81 [0.61, 1.41]           0.82 [0.77, 1.62]           0.92 [0.67, 1.16]           0.92 [0.77, 1.10]           1.00 [0.87, 1.15]           0.82 [0.59, 1.14]           0.80 [0.83, 0.97]           Hazard Ratio           V. Fixed, 95% CI Y           0.80 [0.61, 1.05]           0.10 [10.61, 1.26]           0.10 [10.62, 1.34]           1.05 [0.82, 1.35]           1.05 [0.82, 1.36]           1.95 [0.83, 1.09]	2015 2017 2019 2019 2019 2020 2020 2020 2020 2020	IV, Fixed, 95% Cl
EMPA-REG OUTCOME 2015 CANVAS 2017 DECLARE-TIMI 58 2019 CREDENCE 2019 DAPA-HF 2019 VERTIS CV (≤45) 2020 VERTIS CV (≤45) 2020 EMPEROR-Reduced 2020 EMPEROR-Reduced 2020 EMPEROR-Reduced 2021 SOLOIST-WHF 2021 Total (95% CI) Heterogeneity: Chi <sup>2</sup> = 6.81, df = 9 Test for overall effect: Z = 2.89 ( <i>P</i> CANVAS 2017 DECLARE-TIMI 58 2019 CREDENCE 2019 VERTIS CV 2020 Total (95% CI) Heterogeneity: Chi <sup>2</sup> = 2.46, df = 3 Test for overall effect: Z = 0.71 ( <i>P</i> CANCE	$\begin{array}{c} \mbox{log[Hazard Ratio]} \\ -0.2357233 & 0.2132t \\ -0.356744 & 0.16114t \\ -0.13926207 & 0.12887t \\ -0.07257069 & 0.21232t \\ -0.040822 & 0.3780t \\ -0.040822 & 0.33780t \\ -0.040822 & 0.33780t \\ -0.0933161 & 0.09116t \\ 0.00945033 & 0.22160t \\ -0.0333161 & 0.09116t \\ 0.07130t \\ -0.19845094 & 0.16810t \\ \hline \end{tabular} \\ (P = 0.66); I^{p} = 0\% \\ = 0.004 \end{pmatrix} \\ \hline \begin{array}{c} \mbox{tabular} \\ tabula$	SE         Weight           37         3.2%           346         5.6%           383         8.7%           573         3.2%           567         2.2.9%           382         2.7%           382         17.4%           100.0%         100.0%           100.0%         100.0%	IV. Fixed, 95% C           0.79 [0.52, 1.20]           0.79 [0.52, 1.20]           0.76 [0.53, 0.66]           0.87 [0.68, 1.12]           0.93 [0.61, 1.41]           0.96 [0.60, 1.53]           1.01 [0.65, 1.56]           0.92 [0.77, 1.10]           0.90 [0.63, 0.97]           0.90 [0.63, 0.97]           Hazard Ratio           V. Fixed, 95% Cl Y           0.80 [0.61, 1.65]           1.01 [0.80, 1.27]           0.91 [0.62, 1.34]           1.05 [0.82, 1.35]           2.95 [0.83, 1.09]	2015 2017 2019 2019 2019 2020 2020 2020 2020 2020	IV, Fixed, 95% CI
EMPA-REG OUTCOME 2015           CANVAS 2017           DECLARE-TIMI 56 2019           DECLARE-TIMI 56 2019           DAPA-HF 2019           VERTIS CV (=45) 2020           EMPEROR-Reduced 2020           EMPEROR-Reduced 2020           SOLORT-WHF 2021           Total (95% CI)           Heterogeneity: ChiF = 6.81, df = 9.           Test for overall effect: Z = 2.89 (P           CANVAS 2017           DECLARE-TIMI 58 2019           CREDENCE 2019           VERTIS CV (>2020           Total (95% CI)           Heterogeneity: ChiF = 2.46, df = 3           Test for overall effect: Z = 0.71 (P           G)         KCCQ	log[Hazard Ratio]           -0.2357233         0.2132           -0.3567249         0.6114           -0.1326207         0.12887           -0.07257069         0.21324           -0.16832958         0.07955           -0.04822         0.237600           -0.008338161         0.091163           -0.01845094         0.161410           (P = 0.66); P = 0%         0.071300           = 0.004)         SE           -0.00431058         0.13874169           0.009495033         0.1168107           (P = 0.46); P = 0%         0.003431058           = 0.004)         SE           -0.00431058         0.13874169           0.009431058         0.11827169           0.00493016         0.12822165           (P = 0.48); P = 0%         = 0.48)           SGLT21         Placebo	SE Weight 37 3.2% 346 5.6% 388 8.7% 573 3.2% 577 3.2.2% 577 22.9% 582 2.6% 100.0% Weight P 24.5% 100.0% 12.1% 100.0% 0	IV. Fixed, 95% C           0.79 [0.52, 1.20]           0.79 [0.52, 1.20]           0.79 [0.52, 1.20]           0.30 [0.61, 1.41]           0.30 [0.61, 1.41]           0.30 [0.60, 1.53]           1.01 [0.65, 1.56]           0.92 [0.77, 1.10]           1.00 [0.87, 1.15]           0.82 [0.59, 1.14]           0.90 [0.83, 0.97]           Hazard Ratio           V. Fixed, 95% CI ¥           0.80 [0.61, 1.65]           2.0.91 [0.62, 1.34]           1.01 [0.80, 1.27]           0.91 [0.62, 1.34]           1.05 [0.82, 1.35]           0.30 [0.61, 1.06]           2.0.91 [0.62, 1.34]           1.05 [0.82, 1.35]           0.30 [0.81, 1.09]	2015 2017 2019 2019 2019 2020 2020 2020 2020 2020	IV, Fixed, 95% Cl
EMPA.REG OUTCOME 2015 CANVAS 2017           DECLARE-TIMI 58 2019           DECLARE-TIMI 58 2019           DRA-HE 2019           VERTIS CV (=45) 2020           VERTIS CV (=45) 2020           EMPEROR-Reduced 2020           EMPEROR-Reduced 2021           SOLOIST-WHF 2021           Total (95% CI)           Heterogeneity: Chi <sup>P</sup> = 6.81, df = 9 i           Test for overall effect: Z = 2.89 (P           FUNDAS 2017           DECLARE-TIMI 58 2019           CARVAS 2017           DECLARE-TIMI 58 2019           CREDENCE 2019           VERTIS CV 2020           Total (95% CI)           Heterogeneity: Chi <sup>P</sup> = 2.46, df = 3           Test for overall effect: Z = 0.71 (P           G) KCCQ           Study or Subgroup	log[Hazard Ratio]           -0.2357233         0.2132           -0.3567249         0.16114           -0.1326207         0.12887           -0.07257069         0.21322           -0.16632958         0.07955           -0.040822         0.237800           -0.00338161         0.098163           -0.01845094         0.16114           -0.00338161         0.098163           -0.019845094         0.168107           (P = 0.66); I <sup>a</sup> = 0%         =           = 0.004)         SE           -0.023214355         0.13874169           0.00945033         0.1168707           -0.09431068         0.19743892           0.04879016         0.12822165           (P = 0.48); P = 0%           = 0.48)         SGLT21           Placebo         SD Total Mean         SD 1	SE         Weight           37         3.2%           346         5.6%           383         8.7%           573         3.2%           828         8.7%           577         22.9%           382         2.6%           382         2.8%           111         28.4%           100.0%         1           24.5%         1           34.6%         1           12.1%         2           100.0%         C           100.0%         C	IV. Fixed, 95% C           0.79 [0.52, 1.20]           0.79 [0.52, 1.20]           0.76 [0.52, 1.20]           0.30 [0.61, 1.41]           0.81 [0.68, 1.12]           0.96 [0.60, 1.53]           1.01 [0.65, 1.56]           0.92 [0.77, 1.10]           0.92 [0.77, 1.10]           0.90 [0.83, 0.97]           Hazard Ratio           V, Fixed, 95% Cl N           0.80 [0.61, 1.21]           0.91 [0.62, 1.34]           1.01 [0.80, 1.27]           0.91 [0.62, 1.34]           1.01 [0.80, 1.27]           0.91 [0.62, 1.34]           1.05 [0.82, 1.35]           1.05 [0.82, 1.35]           1.05 [0.83, 1.09]	2015 2017 2019 2019 2019 2020 2020 2020 2020 2020	IV, Fixed, 95% Cl
EMPA-REG         OUTCOME 2015           CANVAS 2017         CANVAS 2017           DECLARE-TIMI 58 2019         DECLARE-TIMI 58 2019           DAPA-HF 2019         VERTIS CV (=45) 2020           VERTIS CV (=45) 2020         EMPEROR-Reduced 2020           EMPEROR-Reduced 2020         EMPEROR-Reduced 2021           SOLOIST-WHF 2021         Total (95% CI)           Heterogeneity: ChiP = 6.81, df = 9         Test for overall effect: Z = 2.89 (P           CANVAS 2017         DECLARE-TIMI 58 2019           CREDENCE 2019         VERTIS CV 2020           Total (95% CI)         Heterogeneity: ChiP = 2.46, df = 3           Heterogeneity: ChiP = 2.46, df = 3         Test for overall effect: Z = 0.71 (P           Study or Subgroup         Maar           VERTIS CV 2020         Total (95% CI)           Heterogeneity: ChiP = 2.46, df = 3         CANVAS 2017           DESt for overall effect: Z = 0.71 (P         Study or Subgroup         Maar           Study or Subgroup         Maar         Maar           DAPA-HF 2010         Maar         Maar	log[Hazard Ratio]           -0.2357233         0.2132           -0.3567244         0.81144           -0.13926207         0.12887           -0.07627069         0.21324           -0.18632958         0.07952           -0.040622         0.237800           -0.040622         0.237800           -0.040622         0.237800           -0.040823         0.221802           -0.04338161         0.091165           -0.19845094         0.168107           -0.0404         0.61163107           -0.0404         0.61163107           -0.22314355         0.13874169           0.00939053         0.1168707           -0.09431068         0.119743892           0.04879016         0.12822165           (/P = 0.48);  ² = 0%         =           = 0.48)         >           SGLT2i         Placebo           1<50	SE         Weight           37         3.2%           346         5.6%           383         8.7%           363         8.7%           373         3.2%           577         3.2%           587         3.2%           388         8.7%           382         2.9%           322         8.7.4%           100.0%         1           24.5%         1           12.4%         10           12.1%         1           100.0%         0           501         5.1%           100.0%         0	IV., Fixed, 95% C           0.79 [0.52, 1.20]           0.79 [0.52, 1.20]           0.76 [0.52, 1.20]           0.76 [0.53, 0.66]           0.87 [0.68, 1.12]           0.93 [0.61, 1.41]           0.96 [0.60, 1.53]           1.01 [0.65, 1.56]           0.92 [0.77, 1.10]           0.92 [0.77, 1.10]           0.82 [0.59, 1.14]           0.90 [0.83, 0.97]           Hazard Ratio           V., Fixed, 95% C I Y           0.80 [0.61, 1.05]           1.01 [0.80, 1.27]           0.91 [0.62, 1.34]           1.05 [0.82, 1.35]           2.95 [0.83, 1.09]           Mean Difference:           IV, Randrom, 95%           V. IV, Randrom, 95%	Cear     Cear	IV, Fixed, 95% CI
EMPA-REG         OUTCOME 2015           CANVAS 2017         CANVAS 2017           DECLARE-TIMI 56 2019         DECLARE-TIMI 56 2019           DAPA-HF 2019         VERTIS CV (=45) 2020           VERTIS CV (=45) 2020         EMPEROR-Reduced 2021           SOLOIST-WHF 2021         Total (95% CI)           Helerogeneity. ChiP = 6.81, df = 9.         Test for overall effect: Z = 2.89 (P <b>SNLdy or Subgroup</b> log[I           CANVAS 2017         DECLARE-TIMI 58 2019           CREDENCE 2019         VERTIS CV (=220)           Total (95% CI)         Heterogeneity. ChiP = 2.46, df = 3           Test for overall effect: Z = 0.71 (P         S)           MACE         Study or Subgroup         Mag           DECLARE-TIMI 58 2019         CREDENCE 2019           DECLARE-TIMI 58 2019         CREDENCE 2019           DECLARE-TIMI 58 2019         CREDENCE 2019           DAPA-HF 2019         6.1           EMPEROR-Reduced 2020         5.5           EMPEROR-Reduced 2020         6.1           EMPEROR-Reduced 2020         6.5	log[Hazard Ratio]           -0.2357233         0.2132           -0.3567249         0.6114           -0.3567249         0.6114           -0.13925207         0.12887           -0.07257059         0.21322           -0.16632958         0.07955           -0.04022         0.237000           -0.08338161         0.091163           -0.01345594         0.168107           (P = 0.66); P = 0%         0.001303           = 0.004)         SE           -0.02431055         0.13874169           0.009495033         0.1168107           (P = 0.46); P = 0%         0.00431088           = 0.004)         SE           -0.00431088         0.19743982           0.0489016         0.12822165           (P = 0.48); P = 0%         = 0.48)           SGLT2!         Placebo           186         237         3.3<1922	SE         Weight           37         3.2%           346         5.6%           38         8.7%           373         3.2%           577         3.2%           577         3.2%           577         3.2%           577         3.2%           587         3.2%           100.0%         100.0%           100.0%         12.1%           128.7%         100.0%           100.0%         100.0%	IV. Fixed, 95% Cf           0.79 [0.52, 1.20]           0.79 [0.52, 1.20]           0.76 [0.52, 1.20]           0.87 [0.68, 1.12]           0.30 [0.61, 1.41]           0.83 [0.61, 1.41]           0.83 [0.61, 1.41]           0.87 [0.68, 1.12]           0.96 [0.60, 1.53]           1.01 [0.65, 1.56]           0.92 [0.77, 1.10]           0.00 [0.7, 1.15]           0.82 [0.59, 1.14]           0.90 [0.83, 0.97]           Hazard Ratio           V. Fixed, 95% Cf U           0.80 [0.61, 1.65]           1.05 [0.82, 1.34]           1.05 [0.82, 1.35]           0.95 [0.83, 1.09]           Mean Difference:           IV. Random, 95%           2.80 [1.72, 38, 1.34 1.2]           1.38 [13.1 3.1	2015 2017 2019 2019 2019 2019 2020 2020 2020 2020	IV, Fixed, 95% Cl
EMPAREC OUTCOME 2015           CANVAS 2017           DECLARE-TIMI 68 2019           DECLARE-TIMI 68 2019           DRA-HE 2019           VERTIS CV (=45) 2020           VERTIS CV (=45) 2020           EMPEROR-Reduced 2020           EMPEROR-Reduced 2021           SOLOIST-WHF 2021           Total (95% CI)           Heterogeneity: ChiP = 6.81, df = 9 i           Test for overall effect: Z = 2.89 (P)           CANVAS 2017           DECLARE-TIMI 58 2019           CARVAS 2017           DECLARE-TIMI 58 2019           CARVAS 2017           DECLARE-TIMI 58 2019           CARVAS 2017           DECLARE-TIMI 58 2019           CheeDENCE 2019           VERTIS CV 2020           Total (95% CI)           Heterogeneity: ChiP = 2.46, df = 3           Test for overall effect: Z = 0.71 (P           Study or Subgroup         Mear           DAPAHF 2019         6.1           EMPEROR-Reduced 2020         6.5           EMPEROR-Reduced 2020         4.51	log[Hazard Ratio]           -0.2357233         0.2132           -0.3667244         0.16114           -0.1326207         0.12887           -0.07257069         0.21322           -0.16632958         0.07955           -0.040822         0.237800           -0.0040822         0.237800           -0.00338161         0.098163           -0.00338161         0.09116           -0.19845094         0.168107           (P = 0.66); I <sup>2</sup> = 0%         0.074305           = 0.004)         SE           -0.023314355         0.13874169           0.00945033         0.1168707           -0.09431068         0.119743922           0.04879016         0.12822165           (P = 0.48); P = 0%         0.48;           = 0.48;         Placebo           SGLT2!         Placebo           I         SD         Total           I         6.2373         3.3         19.2           I         0.41863         4.1         0.4         19.3         4.1	SE         Weight           37         3.2%           346         5.6%           353         3.2%           373         3.2%           373         3.2%           373         3.2%           373         3.2%           373         3.2%           373         3.2%           374         3.2           382         2.6%           346         5.1%           100.0%         100.0%           12.1%         28.7%           12.1%         28.7%           12.4%         100.0%           00.0%         0           00.0%         0           00.0%         0	IV. Fixed, 95% C           0.79 [0.52, 1.20]           0.79 [0.52, 1.20]           0.76 [0.52, 1.20]           0.30 [0.61, 1.41]           0.81 [0.68, 1.22]           0.92 [0.67, 1.61]           0.96 [0.60, 1.53]           1.01 [0.65, 1.56]           0.92 [0.77, 1.10]           0.90 [0.83, 0.97]           0.80 [0.67, 1.61]           0.80 [0.67, 1.05]           0.80 [0.61, 1.64]           1.01 [0.80, 1.27]           0.91 [0.62, 1.34]           1.05 [0.82, 1.35]           0.95 [0.83, 1.09]           Mean Difference:           V, Random, 95%           1.70 [1.67, 1.7]           1.33 [1.31, 1.3]	2015 2017 2019 2019 2019 2020 2020 2020 2020 2020	IV, Fixed, 95% Cl
EMPA.REG OUTCOME 2015           CANVAS 2017           DECLARE-TIMI 56 2019           DERA-RE 2019           DPA-HF 2019           VERTIS CV (=45) 2020           VERTIS CV (=45) 2020           EMPEROR-Reduced 2020           EMPEROR-Reduced 2021           SOLOIST-WHF 2021           Total (95% CI)           Heterogeneity: Chi <sup>p</sup> = 6.81, df = 9           Test for overall effect: Z = 2.89 (P <b>C</b> ANVAS 2017           DECLARE-TIMI 58 2019           CREDENCE 2019           VERTIS CV (2020           Total (95% CI)           Heterogeneity: Chi <sup>p</sup> = 2.46, df = 3           Test for overall effect: Z = 0.71 (P <b>G</b> MACE           Study or Subgroup           VERTIS CV 2020           Total (95% CI)           Heterogeneity: Chi <sup>p</sup> = 2.46, df = 3           DAPA-HF 2019 <b>G</b> MACE           Study or Subgroup <b>G</b> ANVAS 2017           DECLARE-TIMI 58 2019           CREDENCE 2019           VERTIS CV 2020           Total (95% CI)           MEREOR-Reduced 2020 <b>S</b> & E           DMPENOR-Reduced 2020 <b>S</b> & E           D	log[Hazard Ratio]           -0.2357233         0.2132           -0.3567243         0.8114           -0.1326207         0.12887           -0.07657069         0.21322           -0.076257069         0.21323           -0.076257069         0.21323           -0.04022         0.237800           -0.04022         0.237800           -0.00338161         0.099163           -0.019845094         0.168107           -0.0043         0.071303           -0.0043         0.168107           -0.0043         0.168707           -0.09431068         0.119743822           0.04879016         0.12822165           (P = 0.48); I <sup>2</sup> = 0%         = 0.48)           SGLT21         Placebo           1<5D Total Mean SD 1	SE         Weight           37         3.2%           346         5.6%           38.8         8.7%           32         2.9%           322         2.9%           322         17.4%           100.0%         1           24.5%         1           12.4%         1           12.4%         1           12.1%         1           12.1%         1           100.0%         0           50.10%         1           34.6%         1           24.5%         1           100.0%         0           50.10%         0           50.10%         0           50.10%         0           50.10%         0           50.10%         0           50.10%         0           50.10%         0           50.10%         0           50.10%         0           50.10%         0           50.10%         0           50.10%         0           50.10%         0           50.10%         0           50.10%         0	IV., Fixed, 95% C           0.79 [0.52, 1.20]           0.79 [0.52, 1.20]           0.76 [0.52, 1.20]           0.76 [0.68, 1.12]           0.93 [0.61, 1.41]           0.96 [0.60, 1.53]           1.01 [0.65, 1.56]           0.92 [0.77, 1.10]           0.92 [0.77, 1.10]           0.90 [0.83, 0.97]           Hazard Ratio           V., Fixed, 95% C I Y           0.80 [0.61, 1.65]           1.01 [0.80, 1.27]           0.91 [0.62, 1.34]           1.05 [0.82, 1.35]           0.95 [0.83, 1.09]           Mean Difference:           IV, Randrom, 95%           2.80 [1.72, 38           1.70 [1.67, 1.7]           1.33 [1.31, 1.3]           1.62 [1.28, 1.9]	Cear         2015           2017         2019           2019         2019           2012         2019           2020         2020           2020         2020           2021         2020           2020         2020           2021         2021           0.1         017           019         0020           0020         0.1           017         019           0020         0.1           0.1         0.1           CI Year         8] 2019           3] 2020         5] 2021           7]         .	IV, Fixed, 95% Cl

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# Safety outcomes for the overall heart failure patients

The results showed that SGLT2i use was associated with a reduction of SAE (RR = 0.90, 95%CI = 0.87–0.93, P < 0.01; *Figure 3A*) and an increase of urinary tract infections (RR = 1.17, 95%CI = 1.03–1.33, P = 0.02; *Figure 3C*). Other safety outcomes were not statistically significant between placebo and SGLT2i including AKI (RR = 0.89, 95%CI = 0.78–1.01, P = 0.07; *Figure 3B*), hypoglycaemia (RR = 0.95, 95%CI = 0.80–1.14, P = 0.58; *Figure 3D*), amputation (RR = 1.27, 95%CI = 0.79–2.03, P = 0.32; *Figure 3E*), volume depletion (RR = 1.08, 95%C I = 0.95–1.23, P = 0.23; *Figure 3F*), and bone fracture (RR = 1.04, 95%C I = 0.88–1.23, P = 0.64; *Figure 3G*).

# Efficacy and safety outcomes for heart failure with preserved ejection fraction patients

The recently published EMPEROR-Preserved study<sup>18</sup> showed exhilarating results in HFpEF patients. We combined data from the DECLARE-TIMI 58, VERTIS-CV, SCORED, SOLOIST-WHF, and EMPEROR-Preserved studies to estimate efficacy and safety outcomes. HFpEF patients were predefined as having an EF cut point of >45% in the first two studies, >40% in the last study, and >50% in SCORED and SOLOIST-WHF studies. The results showed a significant reduction in the composite of first HHF or CV death (HR = 0.81, 95%CI = 0.73-0.91, P < 0.01; Figure 4A), first HHF (HR = 0.71, 95%CI = 0.62–0.82, P < 0.01; Figure 4B), and total HHF or CV death (HR = 0.61, 95%CI = 0.43–0.86, P < 0.01; Figure 4E) with SGLT2i use. However, there was no statistical significance in CV death (HR = 0.99, 95%CI = 0.84-1.15, P = 0.86; Figure 4C) and any death (HR = 1.00, 95%CI = 0.89-1.13, P = 0.95; Figure 4D).

#### Quality assessment and publication bias

Of these included RCTs, four trials (CREDENCE, EMPA-REG OUTCOME, EMPEROR-Reduced, and VERTIS-CV) did not explicitly elucidate the blinding of outcomes assessment in their predesign plans and were considered as unclear risk. The data that produced primary efficacy or safety outcomes were not analysed in accordance with a prespecified analysis plan in three trials (DECLARE-TIMI 58, VERTIS CV, and SCORED) due to loss of funding or change of outcomes. However, these changes were made without knowledge of any blinded or unblinded comparative data, and the statistical method has also changed accordingly. So we tend to determine the three trials as low risk in other bias (*Figure S3*). Visual analyses of funnel plots did not suggest any risk of publication bias (*Figure S4*).

# Discussion

In this updated meta-analysis, we included a total of 10 RCT studies with 23 825 patients. In the overall HF cohort, SGLT2i significantly reduced the risk of composite of first HHF or CV death, composite of total HHF or CV death, first HHF, CV death, and any death by 24%, 26%, 31%, 12%, and 10%, respectively. In several recently published results of large-scale clinical trials, 10,11,14 cardiovascular death and all-cause death tended not to be statistically significant. Nonetheless, our meta-analysis suggests the improvement effect to be statistically significant after combining them. As we all know, HF is characterized by repeated hospitalizations, and the risk of death and successive rehospitalization rises sharply when a patient is firstly admitted to the hospital for decompensated HF.<sup>26</sup> Therefore, distinguishing the first and total rehospitalization for HF is essential for evaluating the effect of new therapy and the prognosis of HF patients clinically. Fortunately, SGLT2i performed well in both outcomes. This is one of the main points highlighted in this article. Symptom control is considered as one of important characteristics of HF management programme, greatly affecting the long-term compliance of chronic HF patients to certain drugs.<sup>8</sup> The effect of SGLT2i on the benefit of quality of life represented by KCCQ in HF patients is inspiring, which indicated that SGLT2i improved not only the long-term prognosis but also clinical symptoms and activity ability. Although the benefit is affirmative, it is noteworthy that the extent of the benefit in our conclusion is exploratory because of the different follow-up durations in various studies. The result of PRESERVED-HF study recently released at the Heart Failure Society of America Annual Scientific Meeting 2021 showed that SGLT2i can improve KCCQ clinical summary score at 12 weeks in HF patients with LVEF  $\geq$  45%, which further validated our conclusion.

In terms of safety outcomes, the SGLT2i group was able to reduce the risk of SAE by 10% and increase the risk of urinary tract infections by 17%. Given that the unique mechanism of SGLT2i is the inhibition of filtered glucose reabsorption in renal proximal convoluted tubule,<sup>27</sup> the increased occurrence of urinary tract infections may be an inevitable result, and this is a risk that we must be aware of in our clinical practice. The remaining safety outcomes were not statistically significant. Although the improvement effect of SGLT2i on AKI was not statistically significant, several studies showed its protective effects on chronic kidney disease by glycaemic control, slowing down the decline of eGFR and other underlying mechanisms.<sup>9,15,18,28</sup> This suggests that SGLT2i can be recommended more often for HF patients in combination with chronic kidney disease or diabetes.

This meta-analysis was the first to include the EMPEROR-Preserved study, which has made a groundbreaking contribution to promoting the use of SGLT2 inhibitors in patients with HFpEF. Our results showed that the risk

#### Figure 3 Forest plot of safety outcomes of sodium-glucose cotransporter-2 inhibitor vs. placebo in overall heart failure patients. AKI, acute kidney injury; SAE, serious adverse events.

(A) SAE				Data Datia	Bata Batia	
Study or Subgroup	log[Rate Ratio]	SE	Weight	IV, Fixed, 95% CI Year	IV, Fixed, 95% CI	
EMPA-REG OUTCOME 2015	-0.09431068	0.11942481	2.4%	0.91 [0.72, 1.15] 2015		
CANVAS 2017	-0.19845094	0.08571007	4.6%	0.82 [0.69, 0.97] 2017		
CREDENCE 2019	-0.10536052	0.03821495	23.0%	0.90 [0.84, 0.97] 2019		
EMPEROR-Reduced 2020	-0.15082289	0.03992459	21.0%	0.86 [0.80, 0.93] 2020	-	
EMPEROR-Preserved 2021	-0.07257069	0.02671836	47.0%	0.93 [0.88, 0.98] 2021	-	
T-1-1 (05% OI)			400.00/	0.00.00.07.0.001	A	
Hotorogonoity: Chi2 = 4.02 df	- E (D - 0 EE): 12 - (	10/	100.0%	0.90 [0.87, 0.93]		
Test for overall effect: $Z = 5.68$	= 0.00001	J /0			0.1 0.2 0.5 1 2 5	10
	(				Favours SGL12i Favours Placebo	
(B) AKI				Rate Ratio	Rate Ratio	
Study or Subgroup	log[Rate Ratio]	SE	Weight	IV, Fixed, 95% CI Year	IV, Fixed, 95% CI	
CANVAS 2017	-1.30933332	1.21996862	0.3%	0.27 [0.02, 2.95] 2017	· · · · · · · · · · · · · · · · · · ·	
CREDENCE 2019	-0.28768207	0.31478868	4.2%	0.75 [0.40, 1.39] 2019		
DAPA-HF 2019 EMPEROR Brooppied 2021	-0.69314718	0.25239604	6.5%	0.50 [0.30, 0.82] 2019	· · · · · · · · · · · · · · · · · · ·	
SOLOIST-WHF 2021	-0.0618754	0.26816807	5.8%	0.94 [0.56, 1.59] 2021	- <b>-</b>	
Total (95% CI)			100.0%	0.89 [0.78, 1.01]	<b>1</b> .	
Heterogeneity: Chi <sup>2</sup> = 7.11, df	$= 4 (P = 0.13); I^2 =$	44%			0.01 0.1 1 10	100
Test for overall effect: Z = 1.80	J(P = 0.07)				Favours SGLT2i Favours Placebo	
(C) Urinary track ir	nfections					
Study or Subgroup	log[Rate Ratio]	SF	Weight	Rate Ratio	Rate Ratio	
DAPA-HF 2019	-0.43078292	0.38411552	2.9%	0.65 [0.31, 1.38] 2019		
EMPEROR-Reduced 2020	0.09531018	0.14793481	19.8%	1.10 [0.82, 1.47] 2020	+	
EMPEROR-Preserved 2021	0.19885086	0.08103244	66.0%	1.22 [1.04, 1.43] 2021	j – 1 – 1 – 1 – 1 – 1 – 1 – 1 – 1 – 1 –	
SOLOIST-WHF 2021	0.17395331	0.19676657	11.2%	1.19 [0.81, 1.75] 2021	-	
Total (95% CI)			100.0%	1 17 [1 03 1 33]	•	
Heterogeneity: Chi <sup>2</sup> = 2.79, df	= 3 (P = 0.43); I <sup>2</sup> =	0%	1001070			
Test for overall effect: Z = 2.38	3 (P = 0.02)				0.01 0.1 1 10 Eavours SGLT2i Eavours Placebo	100
	_					
(D) Hypoglycaenna	4			Rate Ratio	Rate Ratio	
Study or Subgroup	log[Rate Ratio]	SE	Weight	IV, Fixed, 95% CI Year	IV, Fixed, 95% CI	
EMPA-REG OUTCOME 2015	-0.11653382	0.13076314	47.3%	0.89 [0.69, 1.15] 2015	• =	
DAPA-HF 2019	0	0.70601593	1.6%	1.00 [0.25, 3.99] 2019		
SOLOIST-WHE 2021	-0.040822 0.43178242	0.27010307	11.1%	0.96 [0.57, 1.63] 2020	·	
EMPEROR-Preserved 2021	-0.08338161	0.16045578	31.4%	0.92 [0.67, 1.26] 2021	+	
Total (95% CI)	- 4 (0 - 0 60); 12 - 1	20/	100.0%	0.95 [0.80, 1.14]		
Test for overall effect: $Z = 0.55$	= 4 (P = 0.60); P = 0.60); P = 0.60); P = 0.68)	J%			0.01 0.1 1 10	100
	,, 0.00)				Favours SGLT2i Favours Placebo	
(E) Amputation				Innered Dettin	Userand Datis	
Study or Subaroup Loal	Hazard Ratiol	SF W	leiaht l	V. Fixed, 95% CI Year	IV. Fixed, 95% CI	
CANVAS 2017	0.84156719 0.4	4132522 2	29.5%	2.32 [0.98, 5.51] 2017		
CREDENCE 2019	-0.10536052 0.4	0740189 3	34.7%	0.90 [0.41, 2.00] 2019		
DAPA-HF 2019	0.07696104 0.4	0098414 3	85.8%	1.08 [0.49, 2.37] 2019		
T-4-1 (05% CI)			0.0%	07 0 70 0 001		
Hotorogonoity: Chi2 = 2.74 d	f = 2 (D = 0.25); 12	- 270/	JU.U%	1.27 [0.79, 2.03]		
Test for overall effect: $7 = 1$	P = 0.32	- 21 /0			0.1 0.2 0.5 1 2 5	10
	, ,				Favours SGL12i Favours Placebo	
(F) Volume depleti	on			Hannah Datia	Userand Datis	
Study or Subgroup	log[Hazard Ratio]	SE	Weight	IV. Fixed, 95% CI Year	IV. Fixed, 95% Cl	
CANVAS 2017	0.52472853	0.4717044	1.9%	1.69 [0.67, 4.26] 2017		
DAPA-HF 2019	0.06765865	0.0993396	42.4%	1.07 [0.88, 1.30] 2019		
CREDENCE 2019	-0.15082289	0.30709108	4.4%	0.86 [0.47, 1.57] 2019		
EMPEROR-Reduced 2020	0.09531018	0.10448694	38.3%	1.10 [0.90, 1.35] 2020	<b>_</b>	
30E0131-WHI 2021	0.00703003	0.173100	10.076	1.07 [0.75, 1.52] 2021		
Total (95% CI)			100.0%	1.08 [0.95, 1.23]	🛉	
Heterogeneity: Chi <sup>2</sup> = 1.49, df	= 4 (P = 0.83);   <sup>2</sup> = 0	0%			0.1 0.2 0.5 1 2 5	10
l est for overall effect: Z = 1.19	P = 0.23				Favours SGLT2i Favours Placebo	
(G) Bone fracture						
Churchu an Curk married	lear Det : Detf. 1	05	Matula	Rate Ratio	Rate Ratio	
CANIVAS 2017	o 16551444	0.26020020	weight	1 18 [0 70 2 00] 2017	IV, Fixed, 95% Cl	
DAPA-HE 2019	0.10551444	0.20920038	10.2%	0.98 [0.66, 1.45] 2010	- <b>i</b>	
CREDENCE 2019	-1.10866262	0.58565476	2.2%	0.33 [0.10, 1.04] 2019		
EMPEROR-Reduced 2020	0.06765865	0.21161607	16.5%	1.07 [0.71, 1.62] 2020	<u>+</u>	
EMPEROR-Preserved 2021	0.05826891	0.12338555	48.7%	1.06 [0.83, 1.35] 2021		
SOLOIST-WHF 2021	0.30010459	0.43873282	3.8%	1.35 [0.57, 3.19] 2021		
Total (95% CI)			100.0%	1.04 [0.88, 1.23]	•	
Heterogeneity: Chi <sup>2</sup> = 4.55, df	= 5 (P = 0.47); l <sup>2</sup> =	0%				100
Test for overall effect: Z = 0.4	7 (P = 0.64)				Favours SGLT2i Favours Placebo	100

Figure 4 Forest plot of efficacy outcomes of sodium-glucose cotransporter-2 inhibitor vs. placebo in patients with heart failure with preserved ejection fraction. CI, confidence interval; CV death, cardiovascular death; HHF, hospitalization for heart failure; SGLT2i, sodium-glucose cotransporter-2 inhibitor.

(A) CV death or first	HHF		Hazard Ratio	Hazard Ratio
Study or Subgroup	log[Hazard Ratio] SE	Weight	IV, Fixed, 95% CI Year	IV. Fixed, 95% CI
DECLARE-TIMI 58 2019	-0.12783337 0.14532506	16.0%	0.88 [0.66, 1.17] 2019	
VERTIS CV 2020	-0.08338161 0.21055375	7.6%	0.92 [0.61, 1.39] 2020	
EMPEROR-Preserved 2021	-0.23572233 0.06651113	76.4%	0.79 [0.69, 0.90] 2021	
Total (95% CI)		100.0%	0.81 [0.73, 0.91]	•
Heterogeneity: Chi <sup>2</sup> = 0.83, df	= 2 (P = 0.66); I <sup>2</sup> = 0%			
Test for overall effect: Z = 3.56	( <i>P</i> = 0.0004)			0.1 0.2 0.5 1 2 5 10 Favours SGLT2i Favours Placebo
(B) first HHF			Hazard Ratio	Hazard Ratio
Study or Subgroup	log[Hazard Ratio] SE	Weight	IV, Fixed, 95% CI Year	IV, Fixed, 95% Cl
DECLARE-TIMI 58 2019	-0.32850407 0.18761468	14.4%	0.72 [0.50, 1.04] 2019	
VERTIS CV 2020	-0.35667494 0.29989116	5.6%	0.70 [0.39, 1.26] 2020	<u> </u>
EMPEROR-Preserved 2021	-0.34249031 0.07967384	79.9%	0.71 [0.61, 0.83] 2021	
Total (95% CI)		100.0%	0.71 [0.62, 0.82]	•
Heterogeneity: Chi <sup>2</sup> = 0.01, df	= 2 (P = 1.00); I <sup>2</sup> = 0%			
Test for overall effect: Z = 4.79	( <i>P</i> < 0.00001)			Favours SGLT2i Favours Placebo
(C) CV death			Hazard Ratio	Hazard Ratio
Study or Subgroup	log[Hazard Ratio] SE	Weight	IV, Fixed, 95% CI Year	IV, Fixed, 95% Cl
DECLARE-TIMI 58 2019	0.3435897 0.21047565	14.5%	1.41 [0.93, 2.13] 2019	
VERTIS CV 2020	0.07696104 0.26062532	9.5%	1.08 [0.65, 1.80] 2020	
EMPEROR-Preserved 2021	-0.09431068 0.09208591	76.0%	0.91 [0.76, 1.09] 2021	
Total (95% CI)		100.0%	0.99 [0.84, 1.15]	◆
Heterogeneity: Chi <sup>2</sup> = 3.77, df	$= 2 (P = 0.15); I^2 = 47\%$			
Test for overall effect: Z = 0.18	( <i>P</i> = 0.86)			0.1 0.2 0.5 1 2 5 10 Favours SGLT2i Favours Placebo
(D) Any death			Hazard Patio	Hazard Patio
Study or Subgroup	log[Hozard Patio] SE	Woight	IV Eived 05% CI Veer	
DECLARE TIMES 2010	0.01090262 0.15422404	46.0%	1 02 IO 75 1 201 2010	IV. FIXed, 95% CI
DECLARE-TIMI 58 2019	0.01980263 0.15422494	10.2%	1.02 [0.75, 1.38] 2019	
VERTIS CV 2020	0.00995033 0.22180382	7.8%	1.01 [0.65, 1.56] 2020	🛓
EMPEROR-Preserved 2021	0 0.07130711	75.9%	1.00 [0.87, 1.15] 2021	<b>—</b>
Total (95% CI)		100.0%	1.00 [0.89, 1.13]	•
Heterogeneity: Chi <sup>2</sup> = 0.01, df	$= 2 (P = 0.99);  ^{2} = 0\%$			
Test for overall effect: Z = 0.06	( <i>P</i> = 0.95)			0.1 0.2 0.5 1 2 5 10 Favours SGLT2i Favours Placebo
(E) CV death or tota	I HHF	н	azard Ratio	Hazard Ratio
Study or Subgroup log	[Hazard Ratio] SE We	eight IV	, Fixed, 95% CI Year	IV. Fixed, 95% CI
SCORED 2020	-0.41551544 0.29989116 3	5.8% 0	.66 [0.37, 1.19] 2020	
SOLOIST-WHF 2021	-0.54472718 0.22416666 6	4.2% 0	.58 [0.37, 0.90] 2021	
Total (95% CI)	10	0.0% 0.	.61 [0.43, 0.86]	◆
Heterogeneity: Chi <sup>2</sup> = 0.12 d	$f = 1 (P = 0.73)$ : $I^2 = 0\%$			
Test for overall effect: 7 = 2.7	(B = 0.006)		C	0.1 0.2 0.5 1 2 5 10
1000 101 010101 01000 E - 2.1	o., 0.000,			Favours SGLT2i Favours Placebo

of composite of first HHF or CV death, first HHF, and total HHF or CV death were reduced by 19%, 29%, and 39%, respectively, suggesting the effects of SGLT2i on HF events do not vary meaningfully with the HF phenotype. At present, the treatment of HFpEF is mainly to use diuretics to reduce symptoms of congestion.<sup>8</sup> From this point of view, SGLT2i, which has a milder natriuretic effect and will not bring related side effects due to the activation of the sympathetic nervous system or renin-angiotensin system compared with traditional loop diuretics,<sup>29,30</sup> may become a good additional choice for HFpEF patients in the future. It should be noted that the therapeutic effect is different between HFpEF patients with LVEF > 60% and HFrEF patients, which has been demonstrated by the results of PARAGON-HF study and EMPEROR-Preserved study.<sup>18,31</sup> This may be partly due to the apparently lower incidence of cardiovascular events (e.g. hospitalization for HF and cardiovascular death) in HFpEF patients (e.g. EMPEROR-Preserved) than in HFrEF patients (e.g. EMPEROR-Reduced and DAPA-HF). Meanwhile, the difference

in drug response to SGLT2i in patients with HF is relatively smaller than that of ARNI. Compared with the latter's no beneficial effect in the PARAGON-HF study, SGLT2i could reduce the risk of first HF hospitalization even in patients with LVEF > 62.5%, although there was no statistical difference. This broad-spectrum effect may be explained by the multiple mechanisms of SGLT2i, which can reduce cardiac overload by osmotic diuresis, suppress inflammation by activation of adenosine monophosphate-activated protein kinase, and ameliorate myocardial energy metabolism by hypoglycaemic effect. As we know, hypertension, diabetes, and chronic inflammation are all major risk factors for HFpEF.<sup>32</sup> We still need more studies focusing on specific subpopulations of HF to provide evidence for the use of SGLT2i. In addition to the ongoing DELIVER study (NCT01297257), several smaller RCTs are evaluating the effects of SGLT-2i on left ventricular systolic and diastolic function, pulmonary capillary wedge pressure, haemodynamics, biomarkers, and health status in HFpEF patients (NCT04739215, NCT04475042, NCT04730947, NCT03030222, and NCT03416270). We hope that future research can bring more evidence.

In the recently published ESC guidelines for the treatment of acute and chronic HF,<sup>8</sup> SGLT2i was recommended as a new pillar of management of patients with HFrEF (I, A) on the basis of the previous triple therapy (ACEI/ARNI,  $\beta$ -blockers, and MRA). Meanwhile, the US Food and Drug Administration also approved SGLT2i as a treatment for patients with HFrEF. We believe that SGLT2i will also be used in HFpEF patients in near future. But as a new hypoglycaemic drug, the widespread clinical use of SGLT2i in the treatment of HF patients still needs more collaboration between cardiologists and endocrinologists.

It is important to recognize that our study has some limitations. Firstly, the target population, dosage of SGLT2i used, and duration of follow up exist differences between the 10 included RCTs. Although the primary efficacy outcome remained consistent in the subgroup analysis, this difference could still affect the study's evidence level to some extent. Secondly, baseline information was not available in the DECLARE-TIMI 58 and SCORED trials, which makes it difficult to determine whether the ameliorative effect of SGLT2i on HF is influenced by the background therapy or severity of HF. Finally, the sample size of the HFpEF population is relatively small for pooling data, and more evidence focusing on HFpEF patients is needed.

# Conclusion

Sodium-glucose cotransporter-2 inhibitor is associated with lower risk of hospitalization for HF and mortality in patients with HF compared with placebo, regardless of the diabetes status, types of gliflozines used, and follow-up duration. The effect of SGLT2i in HFpEF patients tended to be beneficial in terms of the composite of first HHF or CV death, first HHF, and total HHF or CV death, at a cost of increased risk of urinary tract infections. In a nutshell, its story continues to unfold, and its safety needs further validation.

# **Conflict of interest**

All authors declare that they have no conflict of interest.

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# **Supporting information**

Additional supporting information may be found online in the Supporting Information section at the end of the article.

**Figure S1.** Subgroup analysis based on diabetes status, type of gliflozines used, and follow-up duration.

**Figure S2.** Forest plot of efficacy outcomes calculated by IRD and IRR IRR, the incidence rate ratio obtained using Mantel— Haenszel procedure to estimate a fixed effects model; IRD, the incidence rate difference obtained using a Mantel— Haenszel procedure to estimate a fixed-effects model and an inverse-variance method to estimate a random-effects model; CV death, cardiovascular death; HHF, hospitalization for heart failure.

Figure S3. Quality assessment of the enrolled trials. Figure S4. Funnel plots in the meta-analysis. SAE, serious adverse events; HHF, hospitalization for heart failure. Table S1. Summary outcomes by different measures.

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