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

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

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

#### Introduction

Sodium-glucose cotransporter 2 (SGLT2) inhibitors have received endorsement by the professional cardiology and endocrinology societies for their use in reducing the risk of hospitalization for heart failure (HHF) and cardiovascular death (CVD) in diabetic patients with atherosclerotic complications [1-3]. There is growing evidence from randomized clinical trials (RCTs) of such a beneficial effect in patients with diabetes mellitus (DM) regardless of the degree of left ventricular ejection fraction (EF) [4, 5]. Further RCTs have started to show that SGLT2 inhibitors reduce CVD and HHF rate in patients with established cardiovascular diseases regardless of the DM status [6-9].

Previous meta-analyses have stratified the data in the literature on cardiovascular benefits of SGLT2 inhibitors according to the HF status, DM, and kidney function [10-12]. However, their level of certainty is low for patients without DM due to the mixing of data in diabetics and nondiabetics in the original studies. Moreover, these meta-analyses excluded small RCTs [7, 13, 14] from their pooled analyses. Recent publication of the results of the cardiovascular benefits of the empagliflozin in non-diabetic patients with HF [14] and the results of SCORED trial [15] prompted us to perform this metaanalysis to update the results of previous studies and to determine, with a high degree of confidence, if the favorable effects of SGLT2 inhibitors can be extended to HF patients without DM.

#### Methods and materials

#### Study design

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

#### Literature review

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

# Outcome measure

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

# Data collection

Data on the variables of interest were collected from individual trials. Attempts were made to

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

#### Statistical analysis

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

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

# l<sup>2</sup>=100% × (Q-df)/Q

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

Publication bias was assessed by visual inspection of the funnel plot, when the number of studies included into the meta-analysis was >10. An Egger test was used to depict the funnel plot of effect estimates versus sample size



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

# Results

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

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

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

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

Using a generic inverse variance method to pool the HR and SE, similar outcome mea-

sures were observed for CVD and HHF in favor of patients receiving SGLT 2 inhibitor compared to those who did not receive SGLT 2 inhibitor (Figure 3).

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

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

# Discussion

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

Characteristics of the study population **Baseline Study Criteria** SGLT-2 inhibitor group **Clinical Trial** NCT Medication Placebo/control group Ν M:F (%) Ν M:F (%) EF NYHA HF (%) F/u (med) Age Age DM (%) 69 (63-74) 55.7:44.3 5,292 69 (63-74) SCORED NCT03315143 Sotagliflozin 5,292 54.5:45.5 ≤40% N/A 31 100 16 months EMPA-TROPISM (ATRU-4) NCT 03485222 Empagliflozin 42 64.2±10.9 63:36 42 59.9±13.1 64:36 <50 ||-||| 100 0 6 months VERTIS CV NCT01986881 Ertugliflozin 5,499 64.4±8.1 70.3:29.7 2,747 64.4±8.0 69.3:30.7 N/A N/A 23.7 100 3.5 years EMPEROR-Reduced\* 1,863 67.2±10.8 76.5:23.5 1,867 66.5±11.2 75.6:24.4 II-IV 49.7 NCT03057977 Empagliflozin ≤40% 100 16 months CREDENCE<sup>3</sup> NCT02065791 Canagliflozin 2,202 62.9±9.17 65.4:34.6 2.199 63.2±9.23 66.7:33.3 N/A |-||| N/A 100 2.62 years DAPA-HF\* Overall NCT03036124 Dapagliflozin 2,373 66.2±11 76.2:23.8 2,371 66.5±10.8 77:23 ≤40% II-IV 100 45.1 27.8 months DM+ 1075 66.3±9.9 77.7:22.3 1064 66.7±9.8 77.7:22.3 ≤40% II-IV 100 100 27.8 months DM-1298 66±11.8 75:25 1307 66.4±11.5 76.4:23.6 ≤40% II-IV 100 0 27.8 months **REFORM\*** 28 N/A N/A 28 N/A N/A |-||| NCT02397421 Dapagliflozin ≤45% 100 100 1 year DECLARE-TIMI58 Overall NCT01730534 Dapagliflozin 8,582 63.9±6.8 63.1:36.9 8,578 64±6.8 62.1:37.9 ≤45% |-||| 11.6 100 4.2 years HFrEF 318 N/A N/A 353 N/A N/A ≤45% |-||| 100 100 4.2 years DAPA-HDL\* 65.7±5.9 66.7:33.3 |-|| 0 100 NCT02327039 Dapagliflozin 15 15 61.0±7.2 66.7:33.3 ≤40% 12 weeks 62.2±11.0 72.5:27.5 DEFINE-HF NCT 02653482 Dapagliflozin 131 132 60.4±12.0 74.2:25.8 ≤40% ||-||| 100 63.1 13 weeks CANVAS\* NCT01032629 2888 62.5±8.1 66:34 1442 62.3±7.94 100 Canagliflozin 66.3:33.7 N/A N/A 14.4 N/A CANVAS-R\* NCT01989754 Canagliflozin 2907 63.9±8.4 63.8:36.2 2905 64±8.3 61.8:38.2 N/A N/A 14.4 100 78 weeks EMPA-REG OUTCOME\* NCT01131676 Empagliflozin 46872 63.1±8.6 71.2:28.8 2333 63.2±8.8 72:28 N/A N/A N/A 100 3.1 years

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

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

#### Table 2. Cochrane tools for quality assessment of clinical trials

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

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

A	SGLT2 In	hibitor	Placebo/	Control		Risk Difference	Risk Difference
Study of Subgroup	Events	10000	Events	10000	vveight	M-H, Kandom, 95% Cl	M-H, Kandom, 95% Cl
CANVAS Program Integrated Data	110	10000	128	10000	19.1%	-0.00 [-0.00, 0.00]	1
DAPA HE	227	2202	772	2199	0.070 6.5%	-0.01 [-0.03, -0.00]	-
DECLARE TIMI-58	245	8582	249	8578	17.3%	-0.00 [-0.01, 0.00]	•
DEFINE-HF	1	131	1	132	4.9%	0.00 [-0.02, 0.02]	+
EMPA-REG OUTCOME	172	4687	137	2333	11.0%	-0.02 [-0.03, -0.01]	•
EMPA-TROPISM	0	40	1	40	0.6%	-0.03 [-0.09, 0.04]	-+
EMPEROR-Reduced	187	1863	202	1867	5.5%	-0.01 [-0.03, 0.01]	4
REFORM	0	28	3	28	0.2%	-0.11 [-0.23, 0.02]	
VERTIS CV	155	5292	170	5292	15.6%	-0.00 [-0.01, 0.00]	1
VERTIS CV	341	0499	104	2/4/	10.7%	-0.00 [-0.02, 0.01]	
Total (95% CI)		40697		35587	100.0%	-0.01 [-0.01, -0.00]	
Total events	1554		1488				
Heterogeneity: Tau <sup>2</sup> = 0.00; Chi <sup>2</sup> =	28.69, df = 10	(P = 0.0)	01); I² = 65	%			
Test for overall effect: Z = 2.53 (P =	= 0.01)						Placebo/Control SGLT2 Inhibitor
P	SGI T2 In	hibitor	Diacebo/	Control		Risk Difference	Pick Difference
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	M-H, Random, 95% Cl
CANVAS Program Integrated Data	a 116	10000	128	10000	23.9%	-0.00 [-0.00, 0.00]	•
CREDENCE	110	2202	140	2199	15.5%	-0.01 [-0.03, -0.00]	1
DECLARE TIMI-58	25	318	47	353	3.2%	-0.05 [-0.10, -0.01]	-
EMPA-REG UUTCOME	172	4687	137	2333	17.8%	-0.02 [-0.03, -0.01]	
SCORED	155	28 5292	3 170	28 5292	21.6%	-0.11[-0.23, 0.02] -0.00[-0.01_0.00]	
VERTIS CV	341	5499	184	2747	17.5%	-0.00 [-0.02, 0.01]	
	041	0400	104	21.41	11.0 %	0.00 [ 0.02, 0.01]	
Total (95% CI)	04.0	28026	000	22952	100.0%	-0.01 [-0.02, -0.00]	
Hotarogeneity: Tauž - 0.00: Chiž -	- 20 02 df - 6	/P ~ 0 00	809 01\:IZ = 70	06			
Test for overall effect: Z = 2.23 (P =	= 0.03)	(F < 0.00	01), 1 = 78	70			-1 -0.5 0 0.5 1
	,						Placebo/Control SGL12 Inhibitor
C Study or Sub-	LT2 Inhibito	r Pla	cebo/Con	trol	laiabe I	Risk Difference	Risk Difference
Study or Subgroup EV	/ents 10	tal EV	ents		eight i	M-H, FIXED, 95% CI	M-H, FIXed, 95% CI
	106 12	98	126	1307 9	97.0%	-0.01 [-0.04, 0.01]	
	1 1	31	1	132	2.00	NOT estimable	
EMPEROR Roduced	U 107 10	40 60	202	40	3.0%	-0.03 [-0.09, 0.04]	
EMPEROR-Reduced	187 18	03	202	1867		NULESUMADIE	
Total (95% CI)	13	38		1347 1	00.0%	-0.02 [-0.04, 0.01]	•
Total (95% CI) Total events	<b>13</b> 106	38	127	1347 1	00.0%	-0.02 [-0.04, 0.01]	•
Total (95% CI) Total events Heterogeneity: Chi² = 0.09, (	<b>13</b> 106 df=1 (P=0.	38 77); I <sup>2</sup> =	127 0%	1347 1	00.0%	-0.02 [-0.04, 0.01]	
Total (95% CI) Total events Heterogeneity: Chi <sup>z</sup> = 0.09, Test for overall effect: Z = 1.	<b>13</b> 106 df = 1 (P = 0. 38 (P = 0.17)	38 77); I² =	127 0%	1347 10	00.0%	-0.02 [-0.04, 0.01] ⊢ -1	-0.5 0 0.5 Placebo/Control SGLT2 Inhibitor
Total (95% CI) Total events Heterogeneity: Chi <sup>2</sup> = 0.09, Test for overall effect: Z = 1.	13 106 df = 1 (P = 0. 38 (P = 0.17)	38 77); I <sup>2</sup> = )	127 0%	1347 1(	00.0%	-0.02 [-0.04, 0.01] -1 Dick Difference	-0.5 0 0.5 Placebo/Control SGLT2 Inhibitor
Total (95% CI) Total events Heterogeneity: Chi <sup>2</sup> = 0.09, Test for overall effect: Z = 1. D	13 106 df = 1 (P = 0. 38 (P = 0.17) SGLT2 Int Events	38 77); I <sup>2</sup> = ) hibitor Total	127 0% Placebo/	1347 10 Control	00.0%	-0.02 [-0.04, 0.01] -1 Risk Difference M.H. Random 95% CI	-0.5 0 0.5 Placebo/Control SGLT2 Inhibitor Risk Difference M.H. Bardom 95% Cl
Total (95% CI) Total events Heterogeneity: Chi <sup>2</sup> = 0.09, Test for overall effect: Z = 1. D Study or Subgroup CANVAS Program Integrated Data	13 106 df = 1 (P = 0. 38 (P = 0.17) SGLT2 Int Events	38 77); I <sup>2</sup> = ) hibitor Total	127 0% Placebo// Events 87	1347 10 Control Total	Weight	-0.02 [-0.04, 0.01] -1 Risk Difference <u>M-H, Random, 95% CI</u>	-0.5 0 0.5 Placebo/Control SGLT2 Inhibitor Risk Difference M-H, Random, 95% Cl
Total (95% CI) Total events Heterogeneity: Chi <sup>2</sup> = 0.09, Test for overall effect: Z = 1.: D <u>Study or Subgroup</u> CANVAS Program Integrated Data CREDENCE	13 106 df = 1 (P = 0. 38 (P = 0.17) <u>SGLT2 Ini</u> <u>Events</u> 55 89	38 77); I <sup>2</sup> = ) hibitor Total 10000 2202	127 0% Placebo// Events 87 141	1347 10 Control Total 10000 2199	Weight 14.0%	-0.02 [-0.04, 0.01] -1 Risk Difference <u>M-H, Random, 95% CI</u> -0.00 [-0.01, -0.00] -0.02 [-0.04 -0.01]	-0.5 0 0.5 Placebo/Control SGLT2 Inhibitor Risk Difference M-H, Random, 95% Cl
Total (95% CI) Total events Heterogeneity: Chi <sup>2</sup> = 0.09, Test for overall effect: Z = 1.3 <u>Study or Subgroup</u> CANVAS Program Integrated Data CREDENCE DAPA HF	13 106 df = 1 (P = 0. 38 (P = 0.17) <b>SGLT2 Ini</b> <u>Events</u> 55 89 231	38 77); I <sup>2</sup> = hibitor Total 10000 2202 2373	127 0% Placebo// Events 87 141 318	Control Total 10000 2199 2371	Weight 14.0% 11.4% 9.8%	-0.02 [-0.04, 0.01] -1 Risk Difference <u>M-H, Random, 95% CI</u> -0.00 [-0.01, -0.00] -0.02 [-0.04, -0.01] -0.04 [-0.05, -0.02]	-0.5 0 0.5 Placebo/Control SGLT2 Inhibitor Risk Difference M-H, Random, 95% Cl
Total (95% CI) Total events Heterogeneity: Chi <sup>2</sup> = 0.09, Test for overall effect: Z = 1.2 <u>Study or Subgroup</u> CANVAS Program Integrated Data CREDENCE DAPA HF DECLARE TIMI-58	13 106 df = 1 (P = 0. 38 (P = 0.17) <u>SGLT2 Inl</u> <u>Events</u> 55 89 231 212	<b>38</b> 77);   <sup>2</sup> = hibitor Total 10000 2202 2373 8582	127 0% Placebo// Events 87 141 318 286	Control Total 10000 2199 2371 8578	Weight 14.0% 11.4% 9.8% 13.6%	-0.02 [-0.04, 0.01] -1 Risk Difference <u>M-H, Random, 95% CI</u> -0.00 [-0.01, -0.00] -0.02 [-0.04, -0.01] -0.04 [-0.05, -0.02] -0.01 [-0.01, -0.00]	-0.5 0 0.5 Placebo/Control SGLT2 Inhibitor Risk Difference M-H, Random, 95% Cl
Total (95% CI) Total events Heterogeneity: Chi <sup>2</sup> = 0.09, Test for overall effect: Z = 1. D Study or Subgroup CANVAS Program Integrated Data CREDENCE DAPA HF DECLARE TIMI-58 DEFINE-HF	13 106 df = 1 (P = 0. 38 (P = 0.17) <u>SGLT2 Inl</u> <u>Events</u> 1 55 89 231 212 10	<b>38</b> 77); I <sup>#</sup> = hibitor Total 10000 2202 2373 8582 131	127 0% Placebo/ Events 87 141 318 286 8	<b>Control</b> Total 10000 2199 2371 8578 132	Weight 14.0% 11.4% 9.8% 13.6% 2.3%	-0.02 [-0.04, 0.01] -1 Risk Difference M-H, Random, 95% CI -0.00 [-0.01, -0.00] -0.02 [-0.04, -0.01] -0.04 [-0.01, -0.00] -0.01 [-0.01, -0.00] 0.02 [-0.05, 0.08]	-0.5 0 0.5 Placebo/Control SGLT2 Inhibitor Risk Difference M-H, Random, 95% Cl
Total (95% CI) Total events Heterogeneity: Chi <sup>2</sup> = 0.09, Test for overall effect: Z = 1. D Study or Subgroup CANVAS Program Integrated Data CREDENCE DAPA HF DECLARE TIMI-58 DEFINE-HF EMPA-REG OUTCOME	13 106 df = 1 (P = 0. 38 (P = 0.17) SGLT2 Ini Events 55 89 231 212 10 126	<b>38</b> 77); I <sup>#</sup> = hibitor Total 10000 2202 2373 8582 131 4687	127 0% Placebo/ Events 87 141 318 286 8 95	<b>Control</b> Total 10000 2199 2371 8578 132 2333	Weight 14.0% 11.4% 9.8% 13.6% 2.3% 12.6%	-0.02 [-0.04, 0.01] -1 Risk Difference M-H, Random, 95% CI -0.00 [-0.01, -0.00] -0.02 [-0.04, -0.01] -0.04 [-0.05, -0.02] -0.01 [-0.01, -0.00] 0.02 [-0.05, -0.08] -0.01 [-0.02, -0.00]	-0.5 0 0.5 Placebo/Control SGLT2 Inhibitor Risk Difference M-H, Random, 95% Cl
Total (95% CI) Total events Heterogeneity: Chi <sup>2</sup> = 0.09, · Test for overall effect: Z = 1.: D Study or Subgroup CANVAS Program Integrated Data CREDENCE DAPA HF DECLARE TIMI-58 DEFINE-HF EMPA-REG OUTCOME EMPA-TROPISM	13 106 df = 1 (P = 0. 38 (P = 0.17) <u>SGLT2 Inl</u> <u>Events</u> 5 89 231 212 10 126 0 0	<b>38</b> 77);   <sup>2</sup> = hibitor Total 10000 2020 2373 8582 131 4687 40	127 0% Placebo// Events 87 141 318 286 8 95 2	<b>Control</b> Total 10000 2199 2371 132 2333 40	Weight 14.0% 11.4% 9.8% 13.6% 2.3% 12.6% 1.5%	-0.02 [-0.04, 0.01] -1 Risk Difference <u>M-H, Random, 95% CI</u> -0.00 [-0.01, -0.00] -0.02 [-0.04, -0.01] -0.04 [-0.05, -0.02] -0.01 [-0.02, -0.00] -0.05 [-0.13, 0.03] -0.05 [-0.13, 0.03]	-0.5 0 0.5 Placebo/Control SGLT2 Inhibitor Risk Difference M-H, Random, 95% Cl
Total (95% CI) Total events Heterogeneity: Chi <sup>2</sup> = 0.09, Test for overall effect: Z = 1.2 D Study or Subgroup CANVAS Program Integrated Data CREDENCE DAPA HF DECLARE TIMI-58 DEFINE-HF EMPA-REG OUTCOME EMPA-TROPISM EMPEROR-Reduced	13 106 df = 1 (P = 0. 38 (P = 0.17) sGLT2 Inl Events 5 5 89 231 212 10 126 0 246	<b>38</b> <b>ibitor</b> <b>Total</b> 10000 2202 2373 8582 131 4687 40 1863	127 0% Placebo// Events 87 141 318 286 8 95 2 342	<b>Control</b> <b>Total</b> 10000 2199 2371 8578 1322 2333 40 1867	Weight 14.0% 11.4% 9.8% 13.6% 2.3% 12.6% 1.5% 8.1%	-0.02 [-0.04, 0.01] Risk Difference M-H, Random, 95% CI -0.00 [-0.01, -0.00] -0.02 [-0.04, -0.01] -0.04 [-0.05, -0.02] -0.01 [-0.01, -0.00] 0.02 [-0.05, 0.08] -0.01 [-0.02, -0.00] -0.05 [-0.13, 0.03] -0.05 [-0.13, 0.03] -0.05 [-0.07, -0.03]	-0.5 0 0.5 Placebo/Control SGLT2 Inhibitor Risk Difference M-H, Random, 95% Cl
Total (95% CI) Total events Heterogeneitly: Chi <sup>2</sup> = 0.09, Test for overall effect: Z = 1.3 D Study or Subgroup CANVAS Program Integrated Data CREDENCE DAPA HF DECLARE TIMI-58 DEFINE-HF EMPA-REG OUTCOME EMPA-REOPISM EMPEROR-Reduced REFORM SCODED	13 106 df = 1 (P = 0. 38 (P = 0.17) <b>SGLT2 Ini</b> <u>Events</u> 55 89 231 212 10 126 0 246 1 245	38 77);   <sup>2</sup> = hibitor Total 10000 2202 2373 8582 131 4687 40 1863 28 28	127 0% Placebo// Events 87 141 318 286 8 95 2 2 342 1 260	<b>Control</b> <b>Total</b> 10000 2199 2371 8578 132 2333 40 1867 28 5202	Weight 14.0% 11.4% 9.8% 13.6% 2.3% 12.6% 8.1% 1.5% 8.1%	-0.02 [-0.04, 0.01] Risk Difference M-H, Random, 95% CI -0.00 [-0.01, -0.00] -0.02 [-0.04, -0.01] -0.04 [-0.05, -0.02] -0.01 [-0.02, -0.00] -0.01 [-0.02, -0.00] -0.05 [-0.13, 0.03] -0.05 [-0.13, 0.03] 0.005 [-0.10, 0.10] -0.00 [-0.10, 0.10]	-0.5 0 0.5 Placebo/Control SGLT2 Inhibitor Risk Difference M-H, Random, 95% Cl
Total (95% CI) Total events Heterogeneitly: Chi <sup>2</sup> = 0.09, Test for overall effect: Z = 1.3 D Study or Subgroup CANVAS Program Integrated Data CREDENCE DAPA HF DECLARE TIMI-58 DEFINE-HF EMPA-REG OUTCOME EMPA-REG OUTCOME EMPA-REGOUT	13 106 df = 1 (P = 0. 38 (P = 0.17) <b>SGLT2 Ini</b> <b>Events</b> 55 89 231 212 10 126 0 246 1 245 139	38 77);   <sup>2</sup> = hibitor Total 10000 2202 2373 8582 131 4687 40 1863 28 5292 5499	127 0% Placebo// Events 87 141 318 286 8 95 2 342 342 1 360 99	Control Total 10000 2199 2371 8578 132 2333 400 1867 28 5292 2747	Weight 14.0% 11.4% 9.8% 13.6% 2.3% 12.6% 8.1% 1.5% 8.1% 12.7% 12.7%	-0.02 [-0.04, 0.01] Risk Difference M-H, Random, 95% CI -0.00 [-0.01, -0.00] -0.02 [-0.04, -0.01] -0.04 [-0.05, -0.02] -0.01 [-0.02, -0.00] -0.05 [-0.13, 0.03] -0.05 [-0.13, 0.03] 0.00 [-0.10, 0.10] -0.02 [-0.03, -0.01] -0.01 [-0.02, -0.01] -0.01 [-0.02, -0.01]	-0.5 0 0.5 Placebo/Control SGLT2 Inhibitor Risk Difference M-H, Random, 95% Cl
Total (95% CI) Total events Heterogeneitly: Chi <sup>2</sup> = 0.09, Test for overall effect: Z = 1.3 D Study or Subgroup CANVAS Program Integrated Data CREDENCE DAPA HF DECLARE TIMI-58 DEFINE-HF EMPA-REG OUTCOME EMPA-REOPISM EMPEROR-Reduced REFORM SCORED VERTIS CV	13 106 df = 1 (P = 0. 38 (P = 0.17) <b>SGLT2 Ini</b> <u>Events</u> 5 5 89 231 212 10 126 0 246 1 245 139	38 77);   <sup>2</sup> = hibitor Total 10000 2202 2373 8582 131 4683 28 5292 5499 5499	127 0% Placebo// Events 87 141 318 286 8 95 2 342 1 360 99	Control Total 10000 2199 2371 8578 132 2333 40 1867 28 5292 2747	Weight 14.0% 11.4% 9.8% 13.6% 2.3% 12.6% 8.1% 1.0% 12.7% 12.9%	-0.02 [-0.04, 0.01] Risk Difference M-H, Random, 95% C1 -0.00 [-0.01, -0.00] -0.02 [-0.04, -0.01] -0.04 [-0.05, -0.02] -0.01 [-0.02, -0.00] 0.02 [-0.05, 0.08] -0.05 [-0.07, -0.03] 0.00 [-0.03, 0.01] -0.01 [-0.02, -0.00] 0.00 [-0.03, -0.01] -0.01 [-0.02, -0.00] 0.00 [-0.02, -0.00]	-0.5 0 0.5 Placebo/Control SGLT2 Inhibitor Risk Difference M-H, Random, 95% Cl
Total (95% CI) Total events Heterogeneitly: Chi <sup>2</sup> = 0.09, Test for overall effect: Z = 1.3 D Study or Subgroup CANVAS Program Integrated Data CREDENCE DAPA HF DECLARE TIMI-58 DEFINE-HF EMPA-REG OUTCOME EMPA-REG OUTCOME EMPA-REOPISM EMPEROR-Reduced REFORM SCORED VERTIS CV Total (95% CI) Total (95% CI)	13 106 df = 1 (P = 0. 38 (P = 0.17) <b>SGLT2 Ini</b> <b>Events</b> 55 89 231 212 106 126 0 246 1 245 139	38 77);   <sup>2</sup> = hibitor Total 10000 2202 2373 8582 131 4687 400 1863 28 5292 5499 40697	127 0% Placebo// Events 87 141 318 286 8 95 2 342 1 360 99	Control Total 10000 2371 8578 132 2333 40 1867 28 5292 2747 35587	Weight 14.0% 11.4% 9.8% 13.6% 2.3% 12.6% 1.5% 8.1% 1.0% 12.7% 12.9%	-0.02 [-0.04, 0.01] Risk Difference M-H, Random, 95% C1 -0.00 [-0.01, -0.00] -0.02 [-0.04, -0.01] -0.04 [-0.05, -0.02] -0.01 [-0.02, -0.00] 0.02 [-0.02, -0.03] -0.05 [-0.03, -0.01] -0.01 [-0.02, -0.00] -0.01 [-0.02, -0.00] -0.02 [-0.03, -0.01]	-0.5 0 0.5 Placebo/Control SGLT2 Inhibitor Risk Difference M-H, Random, 95% Cl
Total (95% CI) Total events Heterogeneity: Chi <sup>2</sup> = 0.09, Test for overall effect: Z = 1.3 D Study or Subgroup CANVAS Program Integrated Data CREDENCE DAPA HF DECLARE TIMI-58 DEFINE-HF EMPA-REG OUTCOME EMPA-REG OUTCOME EMPA-REG OUTCOME EMPA-REGOR-Reduced REFORM SCORED VERTIS CV Total events Heterogeneity: Tau <sup>2</sup> = 0.00° Chi <sup>2</sup> =	13 106 df = 1 (P = 0. 38 (P = 0.17) <b>SGLT2 Ini</b> Events 55 89 231 212 10 126 0 246 1 245 139 1354 117 13 df = 1	38 77); I <sup>a</sup> = hibitor Total 10000 2202 2373 8582 131 4687 400 1863 28 5292 5499 40697	127 0% Placebo// Events 87 141 318 286 8 95 2 2 342 1 360 99 1739	Control Total 10000 2199 2371 8578 132 2333 400 1867 28 5292 2747 35587	Weight 14.0% 11.4% 9.8% 13.6% 2.3% 12.6% 8.1% 1.0% 12.7% 12.9% 100.0%	-0.02 [-0.04, 0.01] Risk Difference M-H, Random, 95% CI -0.00 [-0.01, -0.00] -0.02 [-0.04, -0.01] -0.04 [-0.05, -0.02] -0.01 [-0.01, -0.00] -0.05 [-0.13, 0.03] -0.05 [-0.07, -0.03] 0.00 [-0.07, -0.03] -0.02 [-0.03, -0.01] -0.02 [-0.03, -0.01]	-0.5 0 0.5 Placebo/Control SGLT2 Inhibitor Risk Difference M-H, Random, 95% Cl
Total (95% CI) Total events Heterogeneity: Chi <sup>2</sup> = 0.09, Test for overall effect: Z = 1.3 D Study or Subgroup CANVAS Program Integrated Data CREDENCE DAPA HF DECLARE TIMI-58 DEFINE-HF EMPA-REG OUTCOME EMPA-REG OUTCOME EMPA-REGOR-Reduced REFORM SCORED VERTIS CV Total events Heterogeneity: Tau <sup>2</sup> = 0.00; Chi <sup>2</sup> = Test for overall effect: Z = 3.51 (P =	13 106 df = 1 (P = 0. 38 (P = 0.17) <b>SGLT2 Ini</b> <b>Events</b> 55 89 231 212 10 126 0 246 1 245 139 1354 117.13, df = 1 = 0.0005)	38 77); I <sup>a</sup> = hibitor Total 10000 22073 8582 131 4687 400 1863 28 5292 5499 40697 10 (P < 0.)	127 0% Placebo// Events 87 141 318 286 8 95 2 342 1 360 99 1739 00001); P:	Control Total 10000 2199 2371 8578 132 2333 400 1867 28 5292 2747 35587 35587	Weight 14.0% 11.4% 9.8% 13.6% 2.3% 12.6% 1.5% 8.1% 1.0% 12.7% 12.9%	-0.02 [-0.04, 0.01] -1 Risk Difference M-H, Random, 95% CI -0.00 [-0.01, -0.00] -0.02 [-0.04, -0.01] -0.04 [-0.05, -0.02] -0.01 [-0.01, -0.00] -0.05 [-0.13, 0.03] -0.05 [-0.07, -0.03] 0.00 [-0.07, -0.03] -0.02 [-0.03, -0.01] -0.02 [-0.03, -0.01]	-0.5 0 0.5 Placebo/Control SGLT2 Inhibitor Risk Difference M-H, Random, 95% Cl
Total (95% CI) Total events Heterogeneity: Chi <sup>2</sup> = 0.09, Test for overall effect: Z = 1.3 D Study or Subgroup CANVAS Program Integrated Data CREDENCE DAPA HF DECLARE TIMI-58 DEFINE-HF EMPA-REG OUTCOME EMPA-REG OUTCOME EMPA-REGOR-Reduced REFORM SCORED VERTIS CV Total events Heterogeneity: Tau <sup>2</sup> = 0.00; Chi <sup>2</sup> = Test for overall effect: Z = 3.51 (P =	13 106 df = 1 (P = 0. 38 (P = 0.17) <u>SGLT2 Ini</u> <u>Events</u> 55 89 231 212 10 126 0 246 1 245 139 1354 117.13, df = 1 = 0.0005)	38 77); I <sup>a</sup> = hibitor Total 10000 2202 2373 8582 131 4687 400 1863 28 5292 5499 40697 0 (P < 0.1)	127 0% Placebo// Events 87 141 318 286 8 95 2 342 1 360 99 1739 00001); I <sup>a</sup> :	Control Total 10000 2199 2371 8578 132 2333 400 1867 28 5292 2747 35587 35587	Weight 14.0% 11.4% 9.8% 13.6% 2.3% 12.6% 1.5% 8.1% 1.0% 12.7% 12.9%	-0.02 [-0.04, 0.01] -1 Risk Difference M-H, Random, 95% CI -0.00 [-0.01, -0.00] -0.02 [-0.04, -0.01] -0.04 [-0.05, -0.02] -0.01 [-0.01, -0.00] -0.05 [-0.13, 0.03] -0.05 [-0.07, -0.03] 0.00 [-0.07, -0.03] -0.02 [-0.03, -0.01] -0.02 [-0.03, -0.01]	-0.5 0 0.5 Placebo/Control SGLT2 Inhibitor Risk Difference M-H, Random, 95% Cl -1 -0.5 0 0.5 1 Placebo/Control SGLT2 Inhibitor
Total (95% CI) Total events Heterogeneity: Chi <sup>2</sup> = 0.09, Test for overall effect: Z = 1.3 D Study or Subgroup CANVAS Program Integrated Data CREDENCE DAPA HF DECLARE TIMI-58 DEFINE-HF EMPA-REG OUTCOME EMPA-REG OUTCO	13 106 df = 1 (P = 0. 38 (P = 0.17) <b>SGLT2 Ini</b> Events 55 89 231 212 10 126 0 246 1 245 139 1354 117.13, df = 1 = 0.0005) <b>SGLT2 Ini</b>	38 77);   <sup>2</sup> = hibitor Total 10000 22073 8582 131 4683 28 5292 5499 40697 0 (P < 0. hibitor	127 0% Placebo// Events 87 141 318 286 8 95 2 342 1 360 99 1739 00001); P:	Control Total 10000 21371 8578 132 2333 40 1867 28 5292 2747 35587 = 91%	Weight 14.0% 11.4% 9.8% 13.6% 2.3% 12.6% 1.5% 8.1% 1.0% 12.7% 12.9%	-0.02 [-0.04, 0.01] Risk Difference <u>M-H, Random, 95% CI</u> -0.00 [-0.01, -0.00] -0.02 [-0.04, -0.01] -0.04 [-0.05, -0.02] -0.01 [-0.01, -0.00] -0.05 [-0.13, 0.03] -0.05 [-0.13, 0.03] -0.05 [-0.07, -0.03] 0.00 [-0.07, -0.03] -0.02 [-0.03, -0.01] -0.02 [-0.03, -0.01] Risk Difference	-0.5 0 0.5 Placebo/Control SGLT2 Inhibitor Risk Difference M-H, Random, 95% Cl -1 -0.5 0 0.5 1 Placebo/Control SGLT2 Inhibitor Risk Difference Risk Difference
Total (95% CI) Total events Heterogeneity: Chi <sup>2</sup> = 0.09, Test for overall effect: Z = 1.3 D Study or Subgroup CANVAS Program Integrated Data CREDENCE DAPA HF DECLARE TIMI-58 DEFINE-HF EMPA-REG OUTCOME EMPA-REG OUTCOME EMPA-REGOR-Reduced REFORM SCORED VERTIS CV Total events Heterogeneity: Tau <sup>2</sup> = 0.00; Chi <sup>2</sup> = Test for overall effect: Z = 3.51 (P = E Study or Subgroup	13 106 df = 1 (P = 0. 38 (P = 0.17) SGLT2 Ini Events 55 89 231 212 10 126 0 246 1 245 139 1354 117.13, df = 1 = 0.0005) SGLT2 Ini Events 26 27 27 27 27 27 27 27 27 27 27	38 77); I <sup>P</sup> = hibitor Total 10000 2202 2373 8582 131 4687 40 1863 28 5292 5499 40697 10 (P < 0.) hibitor Total	127 0% Placebo/ Events 87 141 318 286 8 95 2 342 1 360 99 1739 00001); P Placebo/ Events	Control Total 10000 2199 2371 8578 1322 2333 40 1867 28 5292 2747 35587 = 91% Control Total	Weight 14.0% 11.4% 9.8% 13.6% 2.3% 12.6% 1.0% 12.7% 12.9% 100.0%	-0.02 [-0.04, 0.01] Risk Difference M-H, Random, 95% CI -0.00 [-0.01, -0.00] -0.02 [-0.04, -0.01] -0.04 [-0.05, -0.02] -0.01 [-0.01, -0.00] -0.05 [-0.07, -0.03] -0.05 [-0.07, -0.03] -0.05 [-0.07, -0.01] -0.02 [-0.03, -0.01] -0.02 [-0.03, -0.01] Risk Difference M-H, Random, 95% CI	-0.5 0 0.5 Placebo/Control SGLT2 Inhibitor Risk Difference M-H, Random, 95% Cl -1 -0.5 0 0.5 1 Placebo/Control SGLT2 Inhibitor Risk Difference M-H, Random, 95% Cl
Total (95% CI) Total events Heterogeneity: Chi <sup>2</sup> = 0.09, Test for overall effect: Z = 1.3 D Study or Subgroup CANVAS Program Integrated Data CREDENCE DAPA HF DECLARE TIMI-58 DEFINE-HF EMPA-REG OUTCOME EMPAREOR-Reduced REFORM SCORED VERTIS CV Total events Heterogeneity: Tau <sup>2</sup> = 0.00; Chi <sup>2</sup> = Test for overall effect: Z = 3.51 (P = E Study or Subgroup CANVAS Program Integrated Data CREDENCE	13 106 df = 1 (P = 0. 38 (P = 0.17) <u>SGLT2 Inl</u> <u>Events</u> 5 5 89 231 212 10 126 0 246 1 245 139 1354 117.13, df = 1 2.00005) <u>SGLT2 In</u> <u>Events</u> a <u>55</u> 89 231 212 245 39 1354 1255 39 246 245 39 255 245 39 245 39 255 245 39 25 25 25 25 25 25 25 25 25 25	38 77);   <sup>P</sup> = hibitor Total 10000 2202 2373 8582 131 4687 40 1863 28 5292 5499 40697 10 (P < 0.) hibitor Total 10000 2202	127 0% Placebo// Events 87 141 318 286 8 95 2 342 1 360 99 1739 00001); F : Placebo/ Events 87 141	Control Total 10000 2199 2371 8578 1322 2333 40 1867 28 5292 2747 35587 = 91% Control Total 10000 2199	Weight 14.0% 14.0% 13.6% 2.3% 12.6% 1.5% 8.1% 1.2.6% 1.0% 12.7% 12.9% 100.0% Weight 20.7% 16.9%	-0.02 [-0.04, 0.01] Risk Difference M-H, Random, 95% CI -0.00 [-0.01, -0.00] -0.02 [-0.04, -0.01] -0.04 [-0.05, -0.02] -0.01 [-0.01, -0.00] -0.05 [-0.07, -0.03] -0.05 [-0.07, -0.03] -0.05 [-0.07, -0.03] -0.02 [-0.03, -0.01] -0.02 [-0.03, -0.01] -0.02 [-0.03, -0.01] Risk Difference M-H, Random, 95% CI -0.00 [-0.01, -0.00] -0.02 [-0.04, -0.01]	-0.5 0 0.5 Placebo/Control SGLT2 Inhibitor Risk Difference M-H, Random, 95% Cl -1 -0.5 0 0.5 1 Placebo/Control SGLT2 Inhibitor Risk Difference M-H, Random, 95% Cl
Total (95% CI) Total events Heterogeneity: Chi <sup>2</sup> = 0.09, Test for overall effect: Z = 1.2 D Study or Subgroup CANVAS Program Integrated Data CREDENCE DAPA HF DECLARE TIMI-58 DEFINE-HF EMPA-REG OUTCOME EMPA-TROPISM EMPEROR-Reduced REFORM SCORED VERTIS CV Total events Heterogeneity: Tau <sup>2</sup> = 0.00; Chi <sup>2</sup> = Test for overall effect: Z = 3.51 (P = E Study or Subgroup CANVAS Program Integrated Data CREDENCE	13 106 df = 1 (P = 0. 38 (P = 0.17) <b>SGLT2 Inl Events</b> 1 55 89 231 212 10 126 0 246 1 245 139 1354 117.13, df = 1 = 0.0005) <b>SGLT2 In</b> <b>Events</b> a 55 89 41	38 77);  P = hibitor Total 10000 2202 2373 8582 1311 4687 40 1863 288 5292 5499 40697 0 (P < 0.) hibitor Total 10000 2202 3118	127 0% Placebo// Events 87 141 318 286 8 95 2 342 342 342 342 342 342 342 342 342 3	Control Total 10000 2199 2371 8578 1322 2333 40 1867 28 5292 2747 35587 = 91% Control Total 10000 2199 3533	Weight 14.0% 11.4% 9.8% 13.6% 2.3% 1.5% 8.1% 1.5% 8.1% 1.2.7% 12.9% 100.0% Weight 20.7% 16.9% 4.2%	-0.02 [-0.04, 0.01] Risk Difference M-H, Random, 95% CI -0.00 [-0.01, -0.00] -0.02 [-0.04, -0.01] -0.04 [-0.05, -0.02] -0.01 [-0.01, -0.00] -0.05 [-0.13, 0.03] -0.05 [-0.07, -0.03] -0.05 [-0.07, -0.03] -0.02 [-0.03, -0.01] -0.02 [-0.03, -0.01] -0.02 [-0.03, -0.01] -0.02 [-0.03, -0.01] -0.02 [-0.03, -0.01] -0.02 [-0.01, -0.00] -0.02 [-0.01, -0.00] -0.02 [-0.01, -0.01] -0.02 [-0.01, -0.01] -0.05 [-0.10, 0.01]	-0.5 0 0.5 Placebo/Control SGLT2 Inhibitor Risk Difference M-H, Random, 95% Cl -1 -0.5 0 0.5 1 Placebo/Control SGLT2 Inhibitor Risk Difference M-H, Random, 95% Cl
Total (95% CI) Total events Heterogeneity: Chi <sup>2</sup> = 0.09, Test for overall effect: Z = 1.2 D Study or Subgroup CANVAS Program Integrated Data CREDENCE DAPA HF DECLARE TIMI-58 DEFINE-HF EMPA-REG OUTCOME EMPA-REG OUTCOME EMPA-REGOUTCOME EMPA-REGRA SCORED VERTIS CV Total (95% CI) Total events Heterogeneity: Tau <sup>2</sup> = 0.00; Chi <sup>2</sup> = Test for overall effect: Z = 3.51 (P = E Study or Subgroup CANVAS Program Integrated Data CREDENCE DECLARE TIMI-58 EMPA-REG OUTCOME	13 106 df = 1 (P = 0. 38 (P = 0.17) SGLT2 Inl Events 5 5 89 231 212 10 126 0 246 1 245 139 1354 117.13, df = 1 = 0.0005) SGLT2 In Events a 55 89 41 126	38 77);   <sup>P</sup> = hibitor Total 10000 2202 2373 8582 131 4683 28 5292 5499 40697 10 (P < 0.1) hibitor Total 10000 2202 318 4687	127 0% Placebo// Events 87 141 318 286 8 95 2 342 1 360 99 1739 00001); P 9 9 1739 000001); P 9 9 1739 000001); P 1 141 6 3 99	Control Total 10000 2199 2371 8578 132 2333 40 1867 2333 40 1867 28 5292 2747 35587 = 91% Control Total 10000 2199 353 2333	Weight 14.0% 11.4% 9.8% 13.6% 2.3% 12.6% 1.5% 8.1% 12.7% 12.9% 100.0% Weight 20.7% 16.9% 4.2% 18.7%	-0.02 [-0.04, 0.01] Risk Difference M-H, Random, 95% CI -0.00 [-0.01, -0.00] -0.02 [-0.04, -0.01] -0.04 [-0.05, -0.02] -0.01 [-0.02, -0.00] -0.05 [-0.13, 0.03] -0.05 [-0.13, 0.03] -0.05 [-0.07, -0.03] 0.00 [-0.10, -0.00] -0.02 [-0.03, -0.01] -0.02 [-0.03, -0.01] -0.02 [-0.04, -0.01] -0.02 [-0.04, -0.01] -0.02 [-0.04, -0.01] -0.05 [-0.04, -0.01]	-0.5 0 0.5 Placebo/Control SGLT2 Inhibitor Risk Difference M-H, Random, 95% Cl -1 -0.5 0 0.5 1 Placebo/Control SGLT2 Inhibitor Risk Difference M-H, Random, 95% Cl
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Total (95% CI)         Total events         Heterogeneity: Chi <sup>2</sup> = 0.09, .         Test for overall effect: Z = 1.3         D         Study or Subgroup         CANVAS Program Integrated Data         CREDENCE         DAPA HF         DECLARE TIMI-58         DEFINE-HF         EMPA-REG OUTCOME         EMPA-REGOUTCOME         E         Study or Subgroup         CANVAS Program Integrated Data         CREDENCE         DECLARE TIMI-58         EMPA-REGOUTCOME         REFORM         SCORED	13 106 df = 1 (P = 0. 38 (P = 0.17) SGLT2 Ini Events 55 89 231 212 106 126 0 246 1 245 139 1354 117.13, df = 1 events a 55 89 231 212 106 126 0 246 1 245 139	38 77);   <sup>P</sup> = hibitor Total 10000 2202 2373 8582 131 4683 28 5292 5499 40097 10 (P < 0.) hibitor Total 10000 2202 318 4687 288 5292	127 0% Placebo/ Events 87 141 318 286 8 95 2 342 1 360 99 1739 900001); P= Placebol Events 87 141 360 99	Control Total 10000 2199 2371 8578 1322 2333 40 1867 28 5292 2747 35587 = 91% Control Total 10000 2199 353 2333 28 5292	Weight 14.0% 11.4% 9.8% 13.6% 2.3% 12.6% 1.5% 8.1% 12.9% 12.9% 12.9% 12.9% 12.9% 12.9% 12.9% 12.9% 100.0%	-0.02 [-0.04, 0.01] Risk Difference <u>M-H, Random, 95% C1</u> -0.00 [-0.01, -0.00] -0.02 [-0.04, -0.01] -0.04 [-0.05, -0.02] -0.01 [-0.01, -0.00] -0.05 [-0.13, 0.03] -0.05 [-0.13, 0.03] -0.05 [-0.13, 0.01] -0.02 [-0.03, -0.01] -0.02 [-0.03, -0.01] -0.02 [-0.03, -0.01] -0.02 [-0.03, -0.01] -0.02 [-0.01, -0.00] -0.02 [-0.01, -0.00] -0.05 [-0.10, 0.00] -0.05 [-0.10, 0.00] -0.01 [-0.02, -0.00] -0.01 [-0.02, -0.00] -0.01 [-0.02, -0.00] -0.01 [-0.02, -0.00] -0.01 [-0.02, -0.00] -0.01 [-0.02, -0.01] -0.01 [-0.02, -0.00] -0.01 [-0.	-0.5 0 0.5 Placebo/Control SGLT2 Inhibitor Risk Difference M-H, Random, 95% Cl -1 -0.5 0 0.5 1 Placebo/Control SGLT2 Inhibitor Risk Difference M-H, Random, 95% Cl -1 -1 -1 -0.5 0 0.5 1 Placebo/Control SGLT2 Inhibitor
Total (95% CI)         Total events         Heterogeneity: Chi <sup>2</sup> = 0.09, .         Test for overall effect: Z = 1.3         D         Study or Subgroup         CANVAS Program Integrated Data         CREDENCE         DAPA HF         DECLARE TIMI-58         DEFINE-HF         EMPA-REG OUTCOME         EMPA-REG OUTCOME         EMPA-ROPISM         EMPEROR-Reduced         REFORM         SCORED         VERTIS CV         Total (95% CI)         Total events         Heterogeneity: Tau <sup>2</sup> = 0.00; Chi <sup>2</sup> =         Test for overall effect: Z = 3.51 (P =         E         Study or Subgroup         CANVAS Program Integrated Dat         CREDENCE         DECLARE TIMI-58         EMPA-REG OUTCOME         REFORM         SCORED         VERTIS CV	13 106 df = 1 (P = 0. 38 (P = 0.17) SGLT2 Ini Events 55 89 231 212 10 126 0 246 1 245 139 1354 117.13, df = 1 events a 55 89 231 212 10 126 139 1354 117.13, df = 1 Events a 55 89 231 212 10 126 139 1354 117.13, df = 1 245 139	38 hibitor Total 10000 2202 2373 8582 131 4687 40 1863 288 5292 5499 40697 10 (P < 0.) hibitor Total 10000 2202 318 4687 28 5292 5499 40697	127 0% Placebo/ Events 87 141 318 286 8 95 2 342 1 360 99 1739 00001); P- 000001); P- 000001); P- 1360 87 141 1360 99 99	Control Total 10000 2199 2371 8578 132 2333 40 1867 28 5292 2747 35587 = 91% Control Total 10000 2199 353 2333 28 5292 2747	Weight 14.0% 11.4% 9.8% 13.6% 2.3% 12.6% 1.0% 12.7% 12.9% 12.9% 100.0% <b>Weight</b> 20.7% 16.9% 16.9% 18.7% 15.5% 18.7% 19.1%	-0.02 [-0.04, 0.01] Risk Difference <u>M-H, Random, 95% C1</u> -0.00 [-0.01, -0.00] -0.02 [-0.04, -0.01] -0.04 [-0.05, -0.02] -0.01 [-0.01, -0.00] -0.05 [-0.13, 0.03] -0.05 [-0.07, -0.03] 0.05 [-0.07, -0.03] -0.02 [-0.03, -0.01] -0.02 [-0.03, -0.01] -0.02 [-0.03, -0.01] -0.02 [-0.03, -0.01] -0.02 [-0.03, -0.01] -0.02 [-0.03, -0.01] -0.02 [-0.01, -0.00] -0.05 [-0.10, 0.00] -0.05 [-0.10, 0.00] -0.05 [-0.10, 0.00] -0.01 [-0.02, -0.00] 0.00 [-0.10, 0.10] -0.01 [-0.02, -0.00]	-0.5 0 0.5 Placebo/Control SGLT2 Inhibitor Risk Difference M-H, Random, 95% Cl -1 -0.5 0 0.5 1 Placebo/Control SGLT2 Inhibitor Risk Difference M-H, Random, 95% Cl
Total (95% CI)         Total events         Heterogeneity: Chi <sup>2</sup> = 0.09, .         Test for overall effect: Z = 1.3         D         Study or Subgroup         CANVAS Program Integrated Data         CREDENCE         DAPA HF         DECLARE TIMI-58         DEFINE-HF         EMPA-REG OUTCOME         EMPA-REG OUTCOME         EMPA-REG OUTCOME         EMPEROR-Reduced         REFORM         SCORED         VERTIS CV         Total (95% CI)         Total events         Heterogeneity: Tau <sup>2</sup> = 0.00; Chi <sup>2</sup> =         Test for overall effect: Z = 3.51 (P =         E         Study or Subgroup         CANVAS Program Integrated Dat         CREDENCE         DECLARE TIMI-58         EMPA-REG OUTCOME         REFORM         SCORED         VERTIS CV         Total (95% CI)	13 106 df = 1 (P = 0. 38 (P = 0.17) <u>SGLT2 Inl</u> <u>Events</u> 5 5 89 231 212 10 126 0 246 1 245 139 1354 117.13, df = 1 245 139 <u>SGLT2 In</u> <u>Events</u> a 55 89 231 212 10 126 0 246 1 245 139 <u>SGLT2 In</u> <u>Events</u> a 55 89 231 212 10 126 0 246 1 245 139 <u>SGLT2 In</u> 245 139 <u>SGLT2 In</u> <u>Events</u> 1 245 139 <u>SGLT2 In</u> <u>Events</u> 3 <u>SGLT2 In</u> <u>Events</u> <u>SGLT2 In</u> <u>Events</u> <u>SGLT2 In</u> <u>SGLT2 In</u> <u>SGLT3 In</u> <u>SGL</u>	38 hibitor Total 10000 2202 2373 8582 131 4687 40 1863 28 5292 5499 40697 10 (P < 0.) hibitor Total 10000 2202 318 4687 28 5292 5499 200 2202 318 4687 28 5292 318 4687 28 5292 318 4687 28 5499 200 200 200 200 200 200 200 2	127 0% Placebo// Events 87 141 318 286 895 2 342 1 360 99 1739 90 00001); P Placebo/ Events 87 141 63 95 1 360 99	Control Total 10000 2199 2371 8578 1322 2333 40 1867 28 5292 2747 35587 = 91% Control Total 10000 2199 353 2333 28 5292 2747 22333 2333 2333 28 5292 2747 22352	Weight 14.0% 11.4% 9.8% 13.6% 2.3% 12.6% 1.5% 8.1% 1.0% 12.7% 12.9% 100.0% Weight 20.7% 16.9% 4.2% 18.7% 1.5% 19.1% 100.0%	-0.02 [-0.04, 0.01] Risk Difference M-H, Random, 95% CI -0.00 [-0.01, -0.00] -0.02 [-0.04, -0.01] -0.04 [-0.05, -0.02] -0.01 [-0.01, -0.00] -0.05 [-0.13, 0.03] -0.05 [-0.07, -0.03] 0.05 [-0.07, -0.03] -0.02 [-0.03, -0.01] -0.02 [-0.03, -0.01] -0.02 [-0.03, -0.01] -0.02 [-0.03, -0.01] -0.05 [-0.10, 0.00] -0.05 [-0.10, 0.00] -0.05 [-0.10, 0.00] -0.05 [-0.10, 0.00] -0.05 [-0.10, 0.00] -0.05 [-0.10, 0.00] -0.01 [-0.02, -0.00] 0.00 [-0.10, 0.10] -0.01 [-0.02, -0.00] -0.01 [-0.02, -0.	-0.5 0 0.5 Placebo/Control SGLT2 Inhibitor Risk Difference M-H, Random, 95% Cl -1 -0.5 0 0.5 1 Placebo/Control SGLT2 Inhibitor Risk Difference M-H, Random, 95% Cl
Total (95% CI)         Total events         Heterogeneity: Chi <sup>2</sup> = 0.09, .         Test for overall effect: Z = 1.3         D         Study or Subgroup         CANVAS Program Integrated Data         CREDENCE         DAPA HF         DECLARE TIMI-58         DEFINE-HF         EMPA-REG OUTCOME         EMPA-REG OUTCOME         EMPA-REG OUTCOME         EMPEROR-Reduced         REFORM         SCORED         VERTIS CV         Total (95% CI)         Total events         Heterogeneity: Tau <sup>2</sup> = 0.00; Chi <sup>2</sup> =         Test for overall effect: Z = 3.51 (P =         E         Study or Subgroup         CANVAS Program Integrated Dat         CREDENCE         DECLARE TIMI-58         EMPA-REG OUTCOME         REFORM         SCORED         VERTIS CV         Total (95% CI)         Total (95% CI)         Total (95% CI)         Total (95% CI)         Total events	13 106 df = 1 (P = 0. 38 (P = 0.17) <u>SGLT2 Inl</u> <u>Events</u> 5 5 89 231 212 10 126 0 246 1 245 139 1354 117.13, df = 1 2455 139 <u>SGLT2 In</u> <u>Events</u> a <u>55</u> 89 41 126 0 246 139 <u>SGLT2 In</u> <u>Events</u> 3 <u>55</u> 89 41 126 9 <u>6</u> 5 89 41 126 9 <u>6</u> 5 89 9 1354 1354 117.13, df = 1 245 139 <u>55</u> 89 41 126 9 <u>55</u> 89 41 126 9 <u>55</u> 89 9 1354 117.13, df = 1 <u>55</u> 89 <u>55</u> 89 <u>55</u> 89 <u>55</u> 89 <u>55</u> 89 <u>55</u> 89 <u>55</u> 89 <u>55</u> 89 <u>55</u> 89 <u>55</u> 89 <u>55</u> 89 <u>55</u> 89 <u>55</u> 89 <u>55</u> 89 <u>55</u> 89 <u>55</u> 89 <u>55</u> 89 <u>55</u> 89 <u>55</u> 89 <u>55</u> 89 <u>55</u> 89 <u>55</u> 89 <u>55</u> 89 <u>55</u> 89 <u>55</u> 89 <u>55</u> 89 <u>55</u> 89 <u>55</u> 89 <u>55</u> 89 <u>55</u> 89 <u>55</u> 89 <u>55</u> 89 <u>55</u> 89 <u>55</u> 89 <u>55</u> 89 <u>61</u> <u>55</u> 89 <u>61</u> <u>55</u> 89 <u>61</u> <u>55</u> 89 <u>61</u> <u>55</u> 89 <u>61</u> <u>55</u> 89 <u>61</u> <u>55</u> 89 <u>61</u> <u>55</u> 89 <u>61</u> <u>61</u> <u>55</u> 89 <u>61</u> <u>61</u> <u>55</u> 89 <u>61</u> <u>61</u> <u>56</u> <u>66</u> <u>696</u> 60 60 60 60 60 60 60 60 60 60	38 77);   <sup>2</sup> = hibitor 10000 2202 2373 8582 131 4687 40 1863 28 5292 5499 40697 10 (P < 0.) hibitor Total 10000 2202 318 4687 28 5499 28026	127 0% Placebo// Events 87 141 318 286 895 2 342 1 360 99 1739 900001); I <sup>+</sup> Placebo/ Events 87 141 63 95 1 360 99 87 141 360 99 87 141 133 87 141 133 87 141 133 87 141 133 87 141 133 87 141 133 87 141 133 87 141 133 87 141 133 87 141 133 87 141 133 87 141 133 87 141 133 141 141	Control Total 10000 2199 2371 8578 1322 2333 40 1867 28 5292 2747 35587 = 91% Control Total 10000 2199 353 2333 28 5292 2747 22952	Weight 14.0% 11.4% 9.8% 13.6% 2.3% 12.6% 1.5% 8.1% 1.0% 12.7% 12.9% 100.0% Weight 20.7% 16.9% 1.5%	-0.02 [-0.04, 0.01] Risk Difference M-H, Random, 95% CI -0.00 [-0.01, -0.00] -0.02 [-0.04, -0.01] -0.04 [-0.05, -0.02] -0.01 [-0.01, -0.00] -0.05 [-0.13, 0.03] -0.05 [-0.07, -0.03] -0.05 [-0.07, -0.03] -0.02 [-0.03, -0.01] -0.02 [-0.03, -0.01] -0.02 [-0.03, -0.01] -0.02 [-0.03, -0.01] -0.05 [-0.10, 0.00] -0.05 [-0.10, 0.00] -0.05 [-0.10, 0.00] -0.05 [-0.10, 0.00] -0.01 [-0.02, -0.00] -0.02 [-0.03, -0.01] -0.01 [-0.02, -0.00] -0.02 [-0.03, -0.00] -0.02 [-0.03, -0.00]	-0.5 0 0.5 Placebo/Control SGLT2 Inhibitor Risk Difference M-H, Random, 95% Cl -1 -0.5 0 0.5 1 Placebo/Control SGLT2 Inhibitor Risk Difference M-H, Random, 95% Cl
Total (95% CI) Total events Heterogeneity: Chi <sup>2</sup> = 0.09, Test for overall effect: Z = 1. D Study or Subgroup CANVAS Program Integrated Data CREDENCE DAPA HF DECLARE TIMI-58 DEFINE-HF EMPA-REG OUTCOME EMPA-TROPISM EMPEROR-Reduced REFORM SCORED VERTIS CV Total (95% CI) Total events Heterogeneity: Tau <sup>2</sup> = 0.00; Chi <sup>2</sup> = Test for overall effect: Z = 3.51 (P = E Study or Subgroup CANVAS Program Integrated Data CREDENCE DECLARE TIMI-58 EMPA-REG OUTCOME REFORM SCORED VERTIS CV Total (95% CI) Total events Heterogeneity: Tau <sup>2</sup> = 0.00; Chi <sup>2</sup> =	13 106 df = 1 (P = 0. 38 (P = 0.17) <u>SGLT2 Inl</u> <u>Events</u> 10 126 0 246 0 246 1 245 139 1354 117.13, df = 1 2.45 3 3 <u>SGLT2 Inl</u> <u>Events</u> 3 <u>SGLT2 Inl</u> <u>Events</u> 4 1 126 0 246 1 245 139 1354 117.13, df = 1 2.45 139 <u>SGLT2 Inl</u> <u>Events</u> 3 <u>SGLT2 Inl</u> <u>SGLT2 Inl</u> <u>Events</u> 3 <u>SGLT2 Inl</u> <u>SGLT2 Inl</u> <u>SG</u>	38 77);   <sup>P</sup> = hibitor 10000 2202 2373 8582 131 4687 40 1863 28 5292 5499 40697 10 (P < 0.0 10000 2202 318 4687 28 5292 5499 28026 (P < 0.00	127 0% Placebo// Events 87 141 318 286 95 2 342 1 360 99 1739 900001); F 99 00001); F 1 360 99 1739 00001); F 1 360 99 87 141 63 95 13 95 141 163 87 141 163 87 141 163 87 141 163 87 141 173 99 99 846 100099	Control Total 10000 2199 2371 8578 1322 2333 40 1867 28 5292 2747 35587 = 91% Control Total 10000 2199 3533 28 5292 2747 22952 2747 22952	Weight 14.0% 14.0% 11.4% 9.8% 13.6% 2.3% 12.6% 1.5% 8.1% 1.2.7% 12.9% 100.0% Weight 20.7% 16.9% 18.7% 18.7% 18.9% 19.1% 100.0%	-0.02 [-0.04, 0.01] Risk Difference M-H, Random, 95% CI -0.00 [-0.01, -0.00] -0.02 [-0.04, -0.01] -0.04 [-0.05, -0.02] -0.01 [-0.01, -0.00] -0.05 [-0.13, 0.03] -0.05 [-0.07, -0.03] -0.05 [-0.07, -0.03] -0.02 [-0.03, -0.01] -0.02 [-0.03, -0.01] -0.02 [-0.03, -0.01] -0.02 [-0.03, -0.01] -0.00 [-0.10, -0.00] -0.00 [-0.10, -0.00] -0.00 [-0.10, -0.00] -0.00 [-0.10, -0.00] -0.01 [-0.02, -0.00] -0.01 [-0.02, -0.00] -0.01 [-0.02, -0.00] -0.01 [-0.02, -0.00] -0.01 [-0.02, -0.00] -0.02 [-0.03, -0.00]	-0.5 0 0.5 Placebo/Control SGLT2 Inhibitor Risk Difference M-H, Random, 95% Cl -1 -0.5 0 0.5 1 Placebo/Control SGLT2 Inhibitor Risk Difference M-H, Random, 95% Cl -1 -0.5 0 0.5 1

F



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

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

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

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

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

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

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

А					Hazard Ratio	Hazard	Ratio	
St	udy or Subgroup	log[Hazard Ratio]	SE	Weight	IV, Random, 95% CI	IV, Randor	n, 95% Cl	
C/	ANVAS Program Integrated Data	-0.1393	0.0966	15.0%	0.87 [0.72, 1.05]	-		
CH		-0.2485	0.1254	11.0%	0.78 [0.61, 1.00]	-		
	SPA HF	-0.1863	0.0943	15.3%	0.83 [0.69, 1.00]			
		-0.3976	0.2404	3.970	0.00 [0.04, 0.09]	-		
EN	MPEROR-Reduced	-0.478	0.1201	13.8%	0.02 [0.45, 0.76]	_		
80	CORED	-0.0034	0.1042	13.4%	0.92 [0.73, 1.13]	-		
VE	ERTIS CV	-0.0834	0.0908	15.9%	0.92 [0.77, 1.10]	-		
To	otal (95% CI)			100.0%	0.82 [0.74, 0.91]	•		
He	eterogeneity: Tau <sup>2</sup> = 0.01; Chi <sup>2</sup> = 12	2.01, df = 7 (P = 0.10)	; I <sup>2</sup> = 429	б		0.01 0.1 1	10	100
Te	est for overall effect: $Z = 3.75$ (P = 0.	.0002)				Favours [experimental]	Favours [control]	
_								
В					Hazard Ratio	Hazard	Ratio	
St	udy or Subgroup	log[Hazard Ratio]	SE	Weight	IV, Random, 95% CI	IV, Randoi	n, 95% Cl	
C/	ANVAS Program Integrated Data	-0.1393	0.0966	20.3%	0.87 [0.72, 1.05]	-		
CF		-0.2485	0.1254	16.2%	0.78 [0.61, 1.00]			
	ECLARE HMI-58	-0.59/8	0.2454	0.7%	0.55 [0.34, 0.89]			
E 1		-0.4/8	0.1201	10.9%	0.02 [0.49, 0.78]			
		-0.1034	0.1008	18.7%	0.90 [0.73, 1.11]			
ΥE		-0.0634	0.0306	21.270	0.82 [0.77, 1.10]	7		
То	otal (95% CI)			100.0%	0.80 [0.69, 0.92]	•		
He	eterogeneity: Tau <sup>2</sup> = 0.02; Chi <sup>2</sup> = 10	).96. df = 5 (P = 0.05)	: I² = 549	6			t	
Te	est for overall effect: Z = 3.17 (P = 0.	.002)				U.U1 0.1 1	10 Favoure (control)	100
		,				Favours (experimental)	Favours [control]	
C					Hazard Ratio	Hazard	Ratio	
C	Study or Subgroup	[Hazard Ratio]	SE V	Noight	W Fixed 05% Cl	IV Fixed	05% CI	
			0040	55 ON	0.00.00.00.1.001	IV, I ACU	, 55/0 CI	
	DAFA HF	-0.1863 0.	0943	35.0%	0.83 [0.89, 1.00]			
	EMPEROR-Reduced	-0.0834 0.	1042	45.0%	0.92 [0.75, 1.13]			
	Total (95% CI)			100.0%	0 97 [0 76 1 00]	▲		
	Hotore acresity Ohi2 - 0.51	-16 - 4 (D - 0 40), IZ	- 001	100.0%	0.07 [0.70, 1.00]	•		
	Heterogeneity: Chir = 0.54, 0	at = 1 (P = 0.46); P:	= 0%		0	.01 0.1 1	10	100
	Test for overall effect: $Z = 2.0$	UU (P = 0.05)				Favours [experimental]	Favours [control]	
_								
D	Shudu an Subarray	la affilia a a d Dati	-1	05 141-1-	Hazard Ratio	Hazard	Ratio	
D _	Study or Subgroup	log[Hazard Rati	0]	SE Weig	Hazard Ratio	Hazard IV, Fixed	Ratio , 95% Cl	
D -	Study or Subgroup CANVAS Program Integrated Data	log[Hazard Rati	o]	<u>SE Weig</u> 93 9.9	Hazard Ratio ht IV, Fixed, 95% CI % 0.67 [0.52, 0.86]	Hazard IV, Fixed	Ratio 95% Cl	
D _	Study or Subgroup CANVAS Program Integrated Data CREDENCE	log[Hazard Rati a -0.400 -0.494	0] 05 0.12 43 0.1	<u>SE Weig</u> 93 9.9 33 9.3	Hazard Ratio ht IV, Fixed, 95% CI % 0.67 [0.52, 0.86] % 0.61 [0.47, 0.79] % 0.21 [0.50 0.00]	Hazard IV, Fixed 	Ratio , 95% Cl	
D -	Study or Subgroup CANVAS Program Integrated Data CREDENCE DAPA HF DECLARE TIML 50	log[Hazard Rati a -0.400 -0.494 -0.326 0.444	o] 05 0.12 43 0.1 35 0.10	<u>SE Weig</u> 93 9.9 33 9.3 16 16.0	Hazard Ratio           ht         IV, Fixed, 95% CI           %         0.67 [0.52, 0.86]           %         0.61 [0.47, 0.79]           %         0.72 [0.59, 0.88]           %         0.72 [0.40, 0.20]	Hazard IV, Fixed 	Ratio 95% Cl	
D -	Study or Subgroup CANVAS Program Integrated Data CREDENCE DAPA HF DECLARE TIMI-58 EMDA BEG OUTCOME	log[Hazard Rati a -0.400 -0.494 -0.326 -0.446 0.446	0] 0 05 0.12 43 0.1 35 0.10 63 0.20	SE Weig 93 9.9 33 9.3 16 16.0 29 4.0	Hazard Ratio ht IV, Fixed, 95% CI % 0.67 [0.52, 0.86] % 0.61 [0.47, 0.79] % 0.72 [0.59, 0.88] % 0.64 [0.43, 0.95] % 0.64 [0.40, 0.95]	Hazard IV, Fixed 	Ratio ,95% Cl	
D -	Study or Subgroup CANVAS Program Integrated Data CREDENCE DAPA HF DECLARE TIMI-58 EMPE-RC9 OUTCOME EMPERCIP_Reduced	log[Hazard Rati a -0.400 -0.494 -0.324 -0.446 -0.430 -0.430	o] 05 0.12 43 0.1 35 0.10 33 0.20 08 0.13 11 0.07	SE         Weig           93         9.9           33         9.3           16         16.0           29         4.0           39         9.2           99         25.9	Hazard Ratio           ht         IV, Fixed, 95% CI           %         0.67 [0.52, 0.86]           %         0.61 [0.47, 0.79]           %         0.72 [0.59, 0.88]           %         0.64 [0.43, 0.95]           %         0.65 [0.50, 0.86]           %         0.65 [0.50, 0.65]	Hazard IV, Fixed 	Ratio 95% Cl	
D	Study or Subgroup CANVAS Program Integrated Data CREDENCE DAPA HF DECLARE TIMI-58 EMPA-REG OUTCOME EMPEROR-Reduced SCORED	log[Hazard Rati a -0.400 -0.494 -0.322 -0.446 -0.430 -0.430 -0.471 -0.401	o]	SE         Weig           93         9.9           33         9.3           16         16.0           29         4.0           39         9.2           99         25.9           07         16.3	Hazard Ratio           ht         IV, Fixed, 95% CI           %         0.67 [0.52, 0.86]           %         0.61 [0.47, 0.79]           %         0.72 [0.59, 0.88]           %         0.64 [0.43, 0.95]           %         0.65 [0.50, 0.85]           %         0.69 [0.59, 0.81]           %         0.67 [0.55, 0.81]	Hazard IV, Fixed 	Ratio 95% Cl	
D _	Study or Subgroup CANVAS Program Integrated Data CREDENCE DAPA HF DECLARE TIMI-58 EMPA-REG OUTCOME EMPEROR-Reduced SCORED VERTIS CV	log[Hazard Rati a -0.400 -0.494 -0.322 -0.446 -0.430 -0.371 -0.400 -0.361	o]	SE         Weig           93         9.9           33         9.3           16         16.0           29         4.0           39         9.2           99         25.9           07         16.3           24         9	Hazard Ratio           ht         IV, Fixed, 95% CI           %         0.67 [0.52, 0.86]           %         0.61 [0.47, 0.79]           %         0.72 [0.59, 0.88]           %         0.65 [0.50, 0.85]           %         0.65 [0.50, 0.85]           %         0.66 [0.59, 0.81]           %         0.67 [0.54, 0.91]	Hazard IV, Fixed      	Ratio 95% Cl	
D _	Study or Subgroup CANVAS Program Integrated Data CREDENCE DAPA HF DECLARE TIMI-58 EMPA-REG OUTCOME EMPEROR-Reduced SCORED VERTIS CV	log[Hazard Rati a -0.400 -0.494 -0.326 -0.444 -0.430 -0.430 -0.371 -0.400 -0.356	o] 5 0.12 43 0.1 35 0.10 33 0.20 08 0.13 11 0.07 05 0.10 37 0.13	SE         Weig           93         9.9           33         9.3           16         16.0           29         4.0           39         9.2           99         25.9           07         16.3           24         9.4	Hazard Ratio           IN, Fixed, 95% CI           %         0.67 [0.52, 0.86]           %         0.61 [0.47, 0.79]           %         0.72 [0.59, 0.88]           %         0.65 [0.50, 0.85]           %         0.65 [0.50, 0.85]           %         0.65 [0.50, 0.85]           %         0.67 [0.55, 0.82]           %         0.70 [0.54, 0.91]	Hazard IV, Fixed       	Ratio 95% Cl	
D -	Study or Subgroup CANVAS Program Integrated Data CREDENCE DAPA HF DECLARE TIMI-58 EMPA-REG OUTCOME EMPEROR-Reduced SCORED VERTIS CV Total (95% CI)	log[Hazard Rati a -0.400 -0.494 -0.326 -0.444 -0.430 -0.430 -0.371 -0.400 -0.356	0]	SE         Weig           93         9.9           33         9.3           16         16.0           29         4.0           39         9.2           99         25.9           07         16.3           24         9.4           100.0         0	Hazard Ratio           ht         IV, Fixed, 95% CI           %         0.67 [0.52, 0.86]           %         0.67 [0.52, 0.86]           %         0.61 [0.47, 0.79]           %         0.72 [0.59, 0.88]           %         0.64 [0.43, 0.95]           %         0.65 [0.50, 0.85]           %         0.69 [0.59, 0.81]           %         0.67 [0.55, 0.82]           %         0.70 [0.54, 0.91]	Hazard IV, Fixed 	Ratio 95% Cl	
D -	Study or Subgroup CANVAS Program Integrated Data CREDENCE DAPA HF DECLARE TIMI-58 EMPEROR-REGUCTOME EMPEROR-Reduced SCORED VERTIS CV Total (95% CI) Heterogeneity: Chi <sup>2</sup> = 1.29, df = 7	log[Hazard Rati a -0.400 -0.490 -0.320 -0.440 -0.430 -0.371 -0.400 -0.350 (P = 0.99); P = 0%	o] 5 05 0.12 43 0.1 35 0.10 33 0.20 38 0.13 11 0.07 35 0.10 37 0.13	SE         Weig           93         9.9           33         9.3           16         16.0           29         4.0           39         9.2           99         25.9           007         16.3           24         9.4           100.0	Hazard Ratio           IV, Fixed, 95% CI           %         0.67 [0.52, 0.86]           %         0.61 [0.47, 0.79]           %         0.62 [0.59, 0.88]           %         0.64 [0.43, 0.95]           %         0.65 [0.50, 0.85]           %         0.65 [0.55, 0.82]           %         0.70 [0.54, 0.91]           %         0.68 [0.62, 0.73]	Hazard IV, Fixed 	Ratio 95% CI	
D _	Study or Subgroup CANVAS Program Integrated Data CREDENCE DAPA HF DECLARE TIMI-58 EMPA-REG OUTCOME EMPEROR-Reduced SCORED VERTIS CV Total (95% CI) Heterogeneity: Chi <sup>2</sup> = 1.29, df = 7 Test for overall effect. Z = 9.61 (P	log[Hazard Rati           a         -0.400           -0.494         -0.326           -0.446         -0.430           -0.371         -0.430           -0.356         -0.356           (P = 0.99); I <sup>a</sup> = 0%         < 0.00001)	o] 50.12 43 0.1 35 0.10 33 0.20 38 0.13 11 0.07 35 0.10 37 0.13	SE         Weig           93         9.9           33         9.3           16         16.0           29         4.0           39         9.2           99         25.9           07         16.3           24         9.4           100.0	Hazard Ratio           ht         IV, Fixed, 95% CI           %         0.67 [0.52, 0.86]           %         0.61 [0.47, 0.79]           %         0.64 [0.43, 0.95]           %         0.65 [0.50, 0.85]           %         0.65 [0.50, 0.85]           %         0.67 [0.55, 0.82]           %         0.70 [0.54, 0.91]           %         0.68 [0.62, 0.73]	Hazard IV, Fixed + + + + + + + + + + + + + + + + + + +	Ratio 95% CI	100
D _	Study or Subgroup CANVAS Program Integrated Data CREDENCE DAPA HF DECLARE TIMI-58 EMPA-REG OUTCOME EMPEROR-Reduced SCORED VERTIS CV Total (95% CI) Heterogeneity: Chi <sup>2</sup> = 1.29, df = 7 Test for overall effect: Z = 9.61 (P	log[Hazard Rati a -0.400 -0.494 -0.322 -0.446 -0.430 -0.430 -0.400 -0.356 (P = 0.99);  P = 0% < 0.00001)	o] 3 5 0.12 43 0.1 35 0.10 33 0.20 33 0.20 38 0.13 11 0.07 35 0.10 37 0.13	SE         Weig           93         9.9           33         9.3           16         16.0           29         4.0           39         9.2           99         25.9           07         16.3           24         9.4           100.0	Hazard Ratio           ht         IV, Fixed, 95% CI           %         0.67 [0.52, 0.86]           %         0.61 [0.47, 0.79]           %         0.62 [0.59, 0.88]           %         0.65 [0.50, 0.85]           %         0.66 [0.59, 0.88]           %         0.67 [0.55, 0.82]           %         0.67 [0.55, 0.82]           %         0.68 [0.62, 0.73]	Hazard IV, Fixed + + + + + + + + + + + 0.01 0.1 1 Favours [experimental]	Ratio .95% CI 10 Favours [control]	100
P_	Study or Subgroup CANVAS Program Integrated Data CREDENCE DAPA HF DECLARE TIMI-58 EMPA-REG OUTCOME EMPEROR-Reduced SCORED VERTIS CV Total (95% CI) Heterogeneity: Chi <sup>2</sup> = 1.29, df = 7 Test for overall effect: Z = 9.61 (P	log[Hazard Rati a -0.400 -0.494 -0.322 -0.440 -0.430 -0.371 -0.400 -0.356 (P = 0.99); I <sup>a</sup> = 0%	o] 3 5 0.12 43 0.1 35 0.10 33 0.20 33 0.20 33 0.20 34 0.13 11 0.07 35 0.10 37 0.13	SE         Weig           93         9,9           33         9,3           16         16,0           29         4,0           39         9,2           99         25,9           07         16,3           24         9,4           100.0         100.0	Hazard Ratio IV, Fixed, 95% CI 0.67 [0.52, 0.86] 0.61 [0.47, 0.79] 0.72 [0.59, 0.88] 0.64 [0.43, 0.95] 0.65 [0.50, 0.85] 0.65 [0.50, 0.85] 0.69 [0.59, 0.81] 0.67 [0.55, 0.82] 0.70 [0.54, 0.91] 0.68 [0.62, 0.73] Hazard Ratio	Hazard IV, Fixed + + + + + + + + + + 0.01 0.1 1 Favours [experimental]	Ratio 95% CI 10 Favours [control] Ratio	100
E	Study or Subgroup CANVAS Program Integrated Data CREDENCE DAPA HF DECLARE TIMI-58 EMPA-REG OUTCOME EMPEROR-Reduced SCORED VERTIS CV Total (95% CI) Heterogeneity: Chi <sup>2</sup> = 1.29, df = 7 Test for overall effect: Z = 9.61 (P	log[Hazard Rati a -0.400 -0.494 -0.322 -0.446 -0.430 -0.371 -0.400 -0.356 (P = 0.99); I <sup>≠</sup> = 0% < 0.00001)	o] 05 0.12 43 0.1 35 0.10 33 0.20 08 0.13 11 0.07 05 0.10 37 0.13 o]	SE         Weig           93         9,9           33         9,3           16         16,0           29         4,0           39         9,2           97         16,3           29         25,9           07         16,3           24         9,4           100,0            SE         Weig	Hazard Ratio IV, Fixed, 95% CI 0.67 [0.52, 0.86] 0.61 [0.47, 0.79] 0.64 [0.43, 0.95] 0.65 [0.50, 0.85] 0.65 [0.50, 0.85] 0.69 [0.59, 0.81] 0.67 [0.55, 0.82] 0.70 [0.54, 0.91] 0.68 [0.62, 0.73] Hazard Ratio IV, Fixed, 95% CI	Hazard IV, Fixed + + + + + + + + + + + + + + + + + + +	Ratio 95% CI 10 Favours [control] Ratio 95% CI	100
E_	Study or Subgroup CANVAS Program Integrated Data CREDENCE DAPA HF DECLARE TIMI-58 EMPA-REG OUTCOME EMPEROR-Reduced SCORED VERTIS CV Total (95% CI) Heterogeneity: Chi <sup>2</sup> = 1.29, df = 7 Test for overall effect: Z = 9.61 (P Study or Subgroup CANVAS Program Integrated Data	log[Hazard Rati           a         -0.400           -0.494         -0.324           -0.446         -0.430           -0.371         -0.400           -0.356         -0.356           (P = 0.99); I <sup>P</sup> = 0%            < 0.00001)	o] 5 05 0.12 43 0.1 35 0.10 33 0.20 08 0.13 08 0.13 0.10 07 0.13 01 0.07 0.13 0.13 0.12 0.13 0.13 0.12 0.13 0.12 0.13 0.12 0.13 0.12 0.12 0.12 0.13 0.12 0	SE         Weig           93         9.3           33         9.3           16         16.0           29         4.0           39         9.2           99         25.9           07         16.3           24         9.4           100.0           SE         Weig           93         17.0	Hazard Ratio IV, Fixed, 95% CI 0.67 [0.52, 0.86] 0.61 [0.47, 0.79] 0.61 [0.47, 0.79] 0.72 [0.59, 0.88] 0.65 [0.50, 0.85] 0.65 [0.50, 0.85] 0.66 [0.59, 0.81] 0.67 [0.55, 0.82] 0.70 [0.54, 0.91] 0.68 [0.62, 0.73] Hazard Ratio H IV, Fixed, 95% CI 0.067 [0.52, 0.86]	Hazard IV, Fixed + + + + + + + + + + + + + + + + + + +	Ratio 95% CI 10 Favours [control] Ratio 95% CI	100
E _	Study or Subgroup CANVAS Program Integrated Data CREDENCE DAPA HF DECLARE TIMI-58 EMPEROR-RED VERTIS CV Total (95% CI) Heterogeneity: Chi <sup>2</sup> = 1.29, df = 7 Test for overall effect: Z = 9.61 (P Study or Subgroup CANVAS Program Integrated Data CREDENCE	log[Hazard Rati           a         -0.400           -0.326         -0.446           -0.431         -0.326           -0.400         -0.356           (P = 0.99); I <sup>a</sup> = 0%         <0.00001)	o]	SE         Weig           93         9.3           33         9.3           34         9.3           29         4.0           39         9.2           99         25.9           07         16.3           24         9.4           100.0           SE         Weig           93         17.0           33         16.1	Hazard Ratio           ht         IV, Fixed, 95% CI           %         0.67 [0.52, 0.86]           %         0.61 [0.47, 0.79]           %         0.61 [0.47, 0.79]           %         0.64 [0.43, 0.95]           %         0.65 [0.50, 0.85]           %         0.65 [0.50, 0.85]           %         0.70 [0.54, 0.91]           %         0.68 [0.62, 0.73]           Hazard Ratio           ht         IV, Fixed, 95% CI           %         0.67 [0.52, 0.86]           %         0.67 [0.52, 0.73]	Hazard IV, Fixed 	Ratio 95% CI 10 Favours [control] Ratio 95% CI	100
E _	Study or Subgroup         CANVAS Program Integrated Data         CREDENCE         DAPA HF         DECLARE TIMI-58         EMPARGO OUTCOME         EMPEROR-Reduced         SCORED         VERTIS CV         Total (95% CI)         Heterogeneity: Chi² = 1.29, df = 7         Test for overall effect: Z = 9.61 (P         Study or Subgroup         CANVAS Program Integrated Data         CREDENCE         DECLARE TIMI-58	log[Hazard Rati           a         -0.400           -0.494         -0.325           -0.446         -0.436           -0.371         -0.400           -0.356         -0.356           (P = 0.99); I <sup>a</sup> = 0%         <0.00001)	o]	SE         Weig           93         9.3           33         9.3           16         16.0           29         4.0           39         9.2           99         25.9           07         16.3           24         9.4           100.0           SE         Weig           93         17.0           33         16.1           29         6.9	Hazard Ratio           IN, Fixed, 95% CI           %         0.67 [0.52, 0.86]           %         0.61 [0.47, 0.79]           %         0.64 [0.43, 0.95]           %         0.65 [0.50, 0.85]           %         0.67 [0.55, 0.82]           %         0.67 [0.55, 0.82]           %         0.67 [0.55, 0.82]           %         0.70 [0.54, 0.91]           %         0.68 [0.62, 0.73]           Hazard Ratio           ht         IV, Fixed, 95% CI           %         0.67 [0.52, 0.86]           %         0.61 [0.47, 0.79]           %         0.64 [0.43, 0.95]	Hazard IV, Fixed	Ratio 95% CI 10 Favours [control] Ratio 95% CI	100
E -	Study or Subgroup         CANVAS Program Integrated Data         CREDENCE         DAPA HF         DECLARE TIMI-58         EMPA-REG OUTCOME         EMPAROR Reduced         SCORED         VERTIS CV         Total (95% CI)         Heterogeneity: Chi <sup>2</sup> = 1.29, df = 7         Test for overall effect: Z = 9.61 (P · C)         Study or Subgroup         CANVAS Program Integrated Data         CREDENCE         DECLARE TIMI-58         EMPA-REG OUTCOME	log[Hazard Rati a -0.400 -0.494 -0.322 -0.446 -0.430 -0.430 -0.430 -0.430 -0.430 -0.430 (P = 0.99);  ≠ = 0% < 0.00001) log[Hazard Rati a -0.400 -0.494 -0.430 -0.430	0]	SE         Weig           93         9.3           33         9.3           16         16.0           29         4.0           39         9.2           99         25.9           07         16.3           24         9.4           100.0           SE         Weig           93         17.0           33         16.1           29         6.9           39         15.8	Hazard Ratio           ht         IV, Fixed, 95% CI           %         0.67 [0.52, 0.86]           %         0.61 [0.47, 0.79]           %         0.62 [0.59, 0.88]           %         0.65 [0.50, 0.85]           %         0.66 [0.50, 0.85]           %         0.67 [0.55, 0.82]           %         0.67 [0.55, 0.82]           %         0.68 [0.62, 0.73]           %         0.68 [0.62, 0.73]           %         0.66 [0.43, 0.95]           %         0.66 [0.43, 0.95]           %         0.66 [0.43, 0.95]	Hazard IV, Fixed + + + + + + + + + + + + + + + + + + +	Ratio .95% CI 10 Favours [control] Ratio .95% CI	100
E _	Study or Subgroup CANVAS Program Integrated Data CREDENCE DAPA HF DECLARE TIMI-58 EMPA-REG OUTCOME EMPEROR-Reduced SCORED VERTIS CV Total (95% CI) Heterogeneity: Chi <sup>2</sup> = 1.29, df = 7 Test for overall effect: Z = 9.61 (P Study or Subgroup CANVAS Program Integrated Data CREDENCE DECLARE TIMI-58 EMPA-REG OUTCOME SCORED VERTIS CV	log[Hazard Rati a -0.400 -0.494 -0.322 -0.446 -0.430 -0.371 -0.400 -0.356 (P = 0.99); I <sup>2</sup> = 0% < 0.00001) log[Hazard Rati a -0.400 -0.494 -0.444 -0.430 -0.430 -0.400	0]	SE         Weig           93         9.3           33         9.3           16         16.0           29         25.9           07         16.3           24         9.4           100.0           SE         Weig           93         17.0           33         16.1           29         2.9           93         17.0           33         16.1           29         9.3           39         15.8           07         28.0	Hazard Ratio IV, Fixed, 95% CI 0.67 [0.52, 0.86] 0.61 [0.47, 0.79] 0.72 [0.59, 0.88] 0.64 [0.43, 0.95] 0.65 [0.50, 0.85] 0.66 [0.50, 0.85] 0.66 [0.59, 0.81] 0.67 [0.55, 0.82] 0.70 [0.54, 0.91] 0.68 [0.62, 0.73] Hazard Ratio IV, Fixed, 95% CI 0.061 [0.47, 0.79] 0.64 [0.43, 0.95] 0.64 [0.43, 0.95] 0.64 [0.43, 0.95] 0.66 [0.50, 0.85] 0.66 [0.50, 0.85] 0.67 [0.55, 0.82]	Hazard IV, Fixed + + + + + + + + + + + + + + + + + + +	Ratio 95% CI 10 Favours [control] Ratio 95% CI	100
E _	Study or Subgroup CANVAS Program Integrated Data CREDENCE DAPA HF DECLARE TIMI-58 EMPA-REG OUTCOME EMPEROR-Reduced SCORED VERTIS CV Total (95% CI) Heterogeneity: Chi <sup>2</sup> = 1.29, df = 7 Test for overall effect: Z = 9.61 (P Study or Subgroup CANVAS Program Integrated Data CREDENCE DECLARE TIMI-58 EMPA-REG OUTCOME SCORED VERTIS CV	log[Hazard Rati a -0.400 -0.494 -0.322 -0.446 -0.431 -0.400 -0.356 (P = 0.99);  ₽ = 0% < 0.00001) log[Hazard Rati a -0.400 -0.494 -0.446 -0.433 -0.400 -0.496 -0.436	0]	SE         Weig           93         9.3           33         9.3           33         9.3           16         16.00           29         25.9           07         16.3           24         9.4           100.0           SE         Weig           93         17.0           33         16.1           29         6.9           30         15.8           29         16.9           30         15.8           07         28.0           24         16.2	Hazard Ratio           ht         IV, Fixed, 95% CI           %         0.67 [0.52, 0.86]           %         0.61 [0.47, 0.79]           %         0.72 [0.59, 0.88]           %         0.65 [0.50, 0.85]           %         0.65 [0.50, 0.85]           %         0.65 [0.50, 0.85]           %         0.65 [0.50, 0.81]           %         0.67 [0.55, 0.82]           %         0.70 [0.54, 0.91]           %         0.68 [0.62, 0.73]           %         0.68 [0.62, 0.73]           %         0.67 [0.52, 0.86]           %         0.67 [0.52, 0.86]           %         0.67 [0.52, 0.86]           %         0.67 [0.52, 0.86]           %         0.66 [0.43, 0.95]           %         0.66 [0.50, 0.85]           %         0.67 [0.55, 0.82]           %         0.67 [0.55, 0.82]           %         0.67 [0.55, 0.82]           %         0.67 [0.55, 0.82]           %         0.67 [0.55, 0.82]	Hazard IV, Fixed + + + + + + + + + + + + + + + + + + +	Ratio 95% CI 10 Favours [control] Ratio 95% CI	100
E _	Study or Subgroup CANVAS Program Integrated Data CREDENCE DAPA HF DECLARE TIMI-58 EMPEROR-Reduced SCORED VERTIS CV Total (95% CI) Heterogeneity: Chi <sup>2</sup> = 1.29, df = 7 Test for overall effect: Z = 9.61 (P · · Study or Subgroup CANVAS Program Integrated Data CREDENCE DECLARE TIMI-58 EMPA-REG OUTCOME SCORED VERTIS CV Total (95% CI)	log[Hazard Rati a -0.400 -0.494 -0.326 -0.446 -0.430 -0.371 -0.400 -0.356 (P = 0.99); I <sup>#</sup> = 0% < 0.00001) log[Hazard Rati a -0.400 -0.494 -0.446 -0.430 -0.436	0]	SE         Weig           93         9.9           33         9.3           16         16.0           29         4.0           39         9.2           99         25.9           07         16.3           24         9.4           100.0           SE         Weig           93         17.0           33         16.1           29         6.9           39         15.8           07         28.0           24         16.2           100.2         16.2	Hazard Ratio ht IV, Fixed, 95% CI 6.067 [0.52, 0.86] 6.061 [0.47, 0.79] 6.062 [0.59, 0.88] 6.064 [0.43, 0.95] 6.065 [0.50, 0.85] 6.069 [0.59, 0.81] 6.067 [0.55, 0.82] 6.070 [0.54, 0.91] 6.068 [0.62, 0.73] 6.068 [0.62, 0.73] 6.061 [0.47, 0.79] 6.064 [0.43, 0.95] 6.061 [0.47, 0.79] 6.064 [0.43, 0.95] 6.065 [0.50, 0.85] 6.070 [0.55, 0.82	Hazard IV, Fixed          -	Ratio 95% CI 10 Favours [control] Ratio 95% CI	100
E _	Study or Subgroup CANVAS Program Integrated Data CREDENCE DAPA HF DECLARE TIMI-58 EMPEROR-Reduced SCORED VERTIS CV Total (95% CI) Heterogeneity: Chi <sup>2</sup> = 1.29, df = 7 Test for overall effect: Z = 9.61 (P Study or Subgroup CANVAS Program Integrated Data CREDENCE DECLARE TIMI-58 EMPA-REG OUTCOME SCORED VERTIS CV Total (95% CI) Heterogeneity: Chi <sup>2</sup> = 0.62, df = 5	log[Hazard Rati           a         -0.400           -0.424         -0.324           -0.435         -0.446           -0.437         -0.430           -0.356         -0.356           (P = 0.99); IP = 0%         <0.00001)	0]	SE         Weig           93         9.3           33         9.3           34         9.3           29         4.0           39         9.2           99         25.9           07         16.3           24         9.4           100.0           SE         Weig           93         17.0           33         16.1           29         6.9           39         15.8           07         28.0           24         16.2           100.0	Hazard Ratio           ht         IV, Fixed, 95% CI           %         0.67 [0.52, 0.86]           %         0.61 [0.47, 0.79]           %         0.64 [0.43, 0.95]           %         0.65 [0.50, 0.85]           %         0.67 [0.55, 0.82]           %         0.70 [0.54, 0.91]           %         0.68 [0.62, 0.73]           %         0.67 [0.52, 0.86]           %         0.67 [0.52, 0.82]           %         0.67 [0.52, 0.82]           %         0.67 [0.52, 0.82]           %         0.67 [0.52, 0.82]           %         0.67 [0.52, 0.82]           %         0.67 [0.52, 0.82]           %         0.65 [0.50, 0.85]           %         0.65 [0.50, 0.85]           %         0.65 [0.50, 0.85]           %         0.65 [0.50, 0.85]           %         0.65 [0.50, 0.85]           %         0.66 [0.59, 0.73]	Hazard IV, Fixed	Ratio 95% CI 10 Favours [control] Ratio 95% CI	100
E _	Study or Subgroup         CANVAS Program Integrated Data CREDENCE         DAPA HF         DECLARE TIMI-58         EMPARGO OUTCOME         EMPEROR-Reduced         SCORED         VERTIS CV         Total (95% CI)         Heterogeneity: Chi² = 1.29, df = 7         Test for overall effect: Z = 9.61 (P -         Study or Subgroup         CANVAS Program Integrated Data CREDENCE         DECLARE TIMI-58         EMPA-REG OUTCOME         SCORED         VERTIS CV         Total (95% CI)         Heterogeneity: Chi² = 0.62, df = 5         Total (95% CI)         Heterogeneity: Chi² = 0.62, df = 5	log[Hazard Rati           a         -0.400           -0.494           -0.352           -0.446           -0.431           -0.356           (P = 0.99); I <sup>a</sup> = 0%           < 0.00001)	0]	SE         Weig           93         9.3           33         9.3           34         9.3           99         25.9           99         25.9           90         7           16.00.0           9         25.9           9         25.9           9         25.9           9         25.9           100.0         100.0           SE         Weig           93         17.0           33         16.1           29         6.9           39         15.8           07         28.0           24         16.2           100.0         100.0	Hazard Ratio ht IV, Fixed, 95% CI 0.67 [0.52, 0.86] 0.61 [0.47, 0.79] 0.72 [0.59, 0.88] 0.64 [0.43, 0.95] 0.65 [0.50, 0.85] 0.69 [0.59, 0.81] 0.67 [0.55, 0.82] 0.70 [0.54, 0.91] 0.68 [0.62, 0.73] Hazard Ratio ht IV, Fixed, 95% CI 1% 0.67 [0.52, 0.82] 0.64 [0.43, 0.95] 0.64 [0.43, 0.95] 0.66 [0.59, 0.73]	Hazard IV, Fixed	Ratio .95% CI 10 Favours [control] Ratio .95% CI	100
E _	Study or Subgroup         CANVAS Program Integrated Data         CREDENCE         DAPA HF         DECLARE TIMI-58         EMPA-REG OUTCOME         EMPARED OUTCOME         SCORED         VERTIS CV         Total (95% CI)         Heterogeneity: Chi <sup>2</sup> = 1.29, df = 7         Test for overall effect: Z = 9.61 (P ·         Study or Subgroup         CANVAS Program Integrated Data         CREDENCE         DECLARE TIMI-58         EMPA-REG OUTCOME         SCORED         VERTIS CV         Total (95% CI)         Heterogeneity: Chi <sup>2</sup> = 0.62, df = 5         Test for overall effect: Z = 7.81 (P ·	log[Hazard Rati           a         -0.400           -0.494         -0.322           -0.446         -0.433           -0.356         -0.356           (P = 0.99);  # = 0%         <0.00001)	0]	SE         Weig           93         9.3           33         9.3           16         16.0           29         25.9           99         25.9           07         16.3           24         9.4           100.0           SE         Weig           93         17.0           33         16.1           29         25.9           33         16.1           29         6.9           39         15.8           07         28.0           24         16.2           100.0         24	Hazard Ratio           ht         IV, Fixed, 95% CI           %         0.67 [0.52, 0.86]           %         0.61 [0.47, 0.79]           %         0.62 [0.59, 0.88]           %         0.65 [0.50, 0.85]           %         0.66 [0.59, 0.81]           %         0.67 [0.55, 0.82]           %         0.67 [0.55, 0.82]           %         0.68 [0.62, 0.73]           %         0.66 [0.59, 0.81]           %         0.67 [0.52, 0.82]           %         0.61 [0.47, 0.73]           %         0.61 [0.47, 0.79]           %         0.61 [0.47, 0.79]           %         0.65 [0.50, 0.85]           %         0.61 [0.43, 0.95]           %         0.65 [0.50, 0.85]           %         0.67 [0.55, 0.82]           %         0.67 [0.55, 0.82]           %         0.66 [0.59, 0.73]	Hazard IV, Fixed 	Ratio 95% CI 10 Favours [control] Ratio 95% CI 10 Favours [control]	100
E _	Study or Subgroup CANVAS Program Integrated Data CREDENCE DAPA HF DECLARE TIMI-58 EMPA-REG OUTCOME EMPEROR-Reduced SCORED VERTIS CV Total (95% CI) Heterogeneity: Chi <sup>2</sup> = 1.29, df = 7 Test for overall effect: Z = 9.61 (P Study or Subgroup CANVAS Program Integrated Data CREDENCE DECLARE TIMI-58 EMPA-REG OUTCOME SCORED VERTIS CV Total (95% CI) Heterogeneity: Chi <sup>2</sup> = 0.62, df = 5 Test for overall effect: Z = 7.81 (P	$\frac{\log[\text{Hazard Rati}}{-0.400}$ -0.494 -0.322 -0.446 -0.436 -0.436 -0.436 -0.436 -0.436 -0.436 -0.406 -0.356 (P = 0.99);  P = 0% -0.494 -0.444 -0.436 -0.490 -0.496 -0.356 (P = 0.99);  P = 0% < 0.00001)	0]	SE         Weig           93         9.3           33         9.3           34         9.4           29         25.9           07         16.3           24         9.4           100.0           SE         Weig           93         17.0           33         16.1           26.9         23.0           33         16.1           29         28.0           21         9.4           100.0         33           101.0         100.0	Hazard Ratio ht IV, Fixed, 95% CI 0.67 [0.52, 0.86] 0.61 [0.47, 0.79] 0.72 [0.59, 0.88] 0.65 [0.50, 0.85] 0.66 [0.50, 0.85] 0.66 [0.50, 0.81] 0.67 [0.55, 0.82] 0.70 [0.54, 0.91] 0.68 [0.62, 0.73] Hazard Ratio ht IV, Fixed, 95% CI 0.061 [0.47, 0.79] 0.64 [0.43, 0.95] 0.64 [0.43, 0.95] 0.64 [0.43, 0.95] 0.64 [0.43, 0.95] 0.64 [0.43, 0.95] 0.64 [0.43, 0.95] 0.64 [0.43, 0.95] 0.66 [0.55, 0.82] 0.70 [0.54, 0.91] 0.66 [0.59, 0.73]	Hazard IV, Fixed + + + + + + + + + + + + +	Ratio 95% CI 10 Favours [control] Ratio 95% CI 10 Favours [control] Patio	100
E _	Study or Subgroup CANVAS Program Integrated Data CREDENCE DAPA HF DECLARE TIMI-58 EMPEROR-Reduced SCORED VERTIS CV Total (95% CI) Heterogeneity: Chi <sup>2</sup> = 1.29, df = 7 Test for overall effect: Z = 9.61 (P · · Study or Subgroup CANVAS Program Integrated Data CREDENCE DECLARE TIMI-58 EMPA-REG OUTCOME SCORED VERTIS CV Total (95% CI) Heterogeneity: Chi <sup>2</sup> = 0.62, df = 5 Test for overall effect: Z = 7.81 (P ·	log[Hazard Rati           a         -0.400           -0.326         -0.446           -0.437         -0.371           -0.400         -0.356           (P = 0.99); I <sup>#</sup> = 0%         <0.00001)	o] 5 0.12 43 0.1 35 0.10 63 0.20 63 0.20 63 0.20 63 0.12 63 0.13 60 67 0.13 60 67 0.13 7	SE         Weig           93         9.3           33         9.3           36         16.0           29         25.9           90         25.9           91         7           100.0         100.0           SE         Weig           93         17.0           33         16.1           29         6.9           39         15.8           07         28.0           24         16.2           100.0         16.2	Hazard Ratio ht IV, Fixed, 95% CI 6.67 [0.52, 0.86] 6.63 [0.47, 0.79] 6.064 [0.47, 0.79] 6.065 [0.50, 0.85] 6.069 [0.59, 0.81] 6.067 [0.55, 0.82] 6.070 [0.54, 0.91] 7.0.68 [0.62, 0.73] 7.0.68 [0.62, 0.73] 7.0.68 [0.62, 0.73] 7.0.66 [0.59, 0.85] 7.0.66 [0.55, 0.82] 7.0.70 [0.54, 0.91] 7.0.66 [0.59, 0.73] 7.0.66 [0.59, 0.73] 7.0.66 [0.59, 0.73] 7.0.66 [0.59, 0.73] 7.0.66 [0.59, 0.73] 7.0.55 [0.52] 7.0.66 [0.59, 0.73] 7.0.65 [0.50, 0.55] 7.0.70 [0.54, 0.91] 7.0.66 [0.59, 0.73] 7.0.66 [0.59, 0.73] 7.0.65 [0.50, 0.55] 7.0.70 [0.54, 0.91] 7.0.70 [0.54, 0.91] 7.0.70 [0.54, 0.91] 7.0.70 [0.54, 0.91] 7.0.70 [0.54, 0.91] 7.0.70 [0.54, 0.91] 7.0.70 [0.55, 0.82] 7.0.70 [0.55, 0.82] 7.0.70 [0.54, 0.91] 7.0.70	Hazard IV, Fixed + + + + + + + + + + + + +	Ratio 95% CI 10 Favours [control] Ratio 95% CI 10 Favours [control] Ratio Favours [control] Ratio	100
E	Study or Subgroup         CANVAS Program Integrated Data         CREDENCE         DAPA HF         DECLARE TIMI-58         EMPEROR-Reduced         SCORED         VERTIS CV         Total (95% CI)         Heterogeneity: Chi² = 1.29, df = 7         Test for overall effect: Z = 9.61 (P ·         Study or Subgroup         CANVAS Program Integrated Data         CREDENCE         DECLARE TIMI-58         EMPA-REG OUTCOME         SCORED         VERTIS CV         Total (95% CI)         Heterogeneity: Chi² = 0.62, df = 5         Total (95% CI)         Heterogeneity: Chi² = 0.62, df = 5         Test for overall effect: Z = 7.81 (P ·	log[Hazard Rati           a         -0.490           -0.494         -0.326           -0.446         -0.430           -0.497         -0.356           (P = 0.99); I <sup>P</sup> = 0%         <0.00001)	o] 5 0.12 43 0.1 35 0.10 33 0.20 36 0.13 11 0.07 37 0.13 o] 5 0.10 37 0.13 o] 5 0.10 37 0.13 05 0.10 37 0.13 05 0.10 37 0.13 05 0.10 37 0.13 05 0.10 05 0.10 05 0.10 05 0.10 05 0.10 05 0.10 07 0.13 07 0.13 08 0.13 09 0.13 09 0.13 09 0.13 00 0	SE         Weig           93         9.3           33         9.3           34         9.2           99         25.9           97         16.3           24         9.4           100.0           SE         Weig           93         17.0           33         16.1           29         6.9           39         15.8           07         28.0           24         16.2           100.0         100.0	Hazard Ratio ht IV, Fixed, 95% CI 6 0.67 [0.52, 0.86] 6 0.61 [0.47, 0.79] 6 0.62 [0.59, 0.88] 6 0.64 [0.43, 0.95] 7 0.65 [0.50, 0.85] 7 0.65 [0.50, 0.85] 7 0.67 [0.55, 0.82] 7 0.70 [0.54, 0.91] 7 0.68 [0.62, 0.73] 8 0.67 [0.52, 0.86] 7 0.65 [0.50, 0.85] 7 0.66 [0.59, 0.81] 7 0.66 [0.59, 0.81] 7 0.66 [0.59, 0.73] 8 0.66 [0.59, 0.73] 8 0.66 [0.59, 0.73] 8 0.66 [0.59, 0.73] 8 0.66 [0.59, 0.73] 8 0.66 [0.59, 0.73] 8 0.66 [0.59, 0.73] 8 0.66 [0.59, 0.73] 8 0.66 [0.59, 0.73] 8 0.66 [0.59, 0.73] 8 0.66 [0.59, 0.73] 8 0.66 [0.59, 0.73] 8 0.66 [0.59, 0.73] 8 0.66 [0.59, 0.73] 8 0.66 [0.59, 0.73] 8 0.66 [0.59, 0.73] 8 0.66 [0.59, 0.73] 8 0.66 [0.59, 0.73] 8 0.65 [0.50, 0.55] 8 0.66 [0.59, 0.73] 8 0.66 [0.59, 0.73] 8 0.66 [0.59, 0.73] 8 0.65 [0.50, 0.55] 8 0.66 [0.59, 0.73] 8 0.65 [0.50, 0.55] 8 0.66 [0.59, 0.73] 8 0.66 [0.59, 0.73] 8 0.65 [0.50, 0.50] 8 0.66 [0.59, 0.73] 8 0.65 [0.50, 0.50] 8 0.66 [0.59, 0.73] 8 0.65 [0.50, 0.50] 9 0.66 [0.59, 0.73] 8 0.65 [0.50, 0.50] 9 0.65 [0.50, 0.50] 9 0.65 [0.50, 0.50] 9 0.65 [0.50, 0.50] 9 0.66 [0.59, 0.73] 9 0.66 [0.59, 0.73] 9 0.65 [0.50, 0.50] 9 0.50 [0.50 [0.50] 9 0.50 [0.50 [0.50] 9 0.50 [0.50 [0.50] 9 0.50 [0.50	Hazard IV, Fixed	Ratio 95% CI 10 Favours [control] Ratio 95% CI Favours [control] I0 Fatio 10 Favours [control] Ratio	100
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E F	Study or Subgroup         CANVAS Program Integrated Data CREDENCE         DAPA HF         DECLARE TIMI-58         EMPARGO OUTCOME         EMPEROR-Reduced         SCORED         VERTIS CV         Total (95% CI)         Heterogeneity: Chi <sup>2</sup> = 1.29, df = 7         Test for overall effect: Z = 9.61 (P -         Study or Subgroup         CANVAS Program Integrated Data CREDENCE         DECLARE TIMI-58         EMPA-REG OUTCOME         SCORED         VERTIS CV         Total (95% CI)         Heterogeneity: Chi <sup>2</sup> = 0.62, df = 5         Test for overall effect: Z = 7.81 (P -         Study or Subgroup       log[I         DAPA HF         EMPEROR-Reduced	log[Hazard Rati           a         -0.400           -0.494         -0.328           -0.446         -0.430           -0.356         -0.356           (P = 0.99); I <sup>a</sup> = 0%            < 0.00001)	0]	SE         Weig           93         9.3           33         9.3           34         9.3           99         25.9           99         25.9           90         7.16.3           24         9.4           100.0           SE         Weig           93         17.0           33         16.1           29         25.9           03         17.0           33         16.1           29         6.9           33         16.1           29         6.9           39         15.8           07         28.0           24         16.2           100.0         100.0           Veight         1           38.2%         1           51.8%         1	Hazard Ratio           IN, Fixed, 95% CI           %         0.67 [0.52, 0.86]           %         0.61 [0.47, 0.79]           %         0.62 [0.59, 0.88]           %         0.65 [0.50, 0.85]           %         0.65 [0.50, 0.85]           %         0.66 [0.59, 0.81]           %         0.70 [0.54, 0.91]           %         0.70 [0.54, 0.91]           %         0.66 [0.62, 0.73]           Hazard Ratio         N           ht         IV, Fixed, 95% CI           %         0.66 [0.50, 0.85]           %         0.66 [0.50, 0.85]           %         0.66 [0.50, 0.85]           %         0.66 [0.50, 0.85]           %         0.66 [0.50, 0.85]           %         0.66 [0.50, 0.85]           %         0.66 [0.59, 0.73]           %         0.66 [0.59, 0.73]           Hazard Ratio         V, Fixed, 95% CI           0.72 [0.59, 0.88]         0.69 [0.59, 0.81]	Hazard IV, Fixed 	Ratio .95% CI 10 Favours [control] Ratio .95% CI Favours [control] I Ratio .95% CI	100
E -	Study or Subgroup         CANVAS Program Integrated Data         CREDENCE         DAPA HF         DECLARE TIMI-58         EMPA-REG OUTCOME         EMPEROR-Reduced         SCORED         VERTIS CV         Total (95% CI)         Heterogeneity: Chi <sup>2</sup> = 1.29, df = 7         Test for overall effect: Z = 9.61 (P ·         Study or Subgroup         CANVAS Program Integrated Data         CREDENCE         DECLARE TIMI-58         EMPA-REG OUTCOME         SCORED         VERTIS CV         Total (95% CI)         Heterogeneity: Chi <sup>2</sup> = 0.62, df = 5         Test for overall effect: Z = 7.81 (P ·         Study or Subgroup       log[]         DAPA HF         EMPEROR-Reduced         Total (95% CI)	log[Hazard Rati           a         -0.400           -0.494         -0.328           -0.446         -0.430           -0.356         -0.400           (P = 0.99);  # = 0%         <0.00001)	o] 15 0.12 43 0.13 5 0.10 33 0.20 16 0.13 11 0.07 15 0.13 10 0.7 01 0.7 05 0.10 13 0.20 05 0.12 43 0.13 05 0.10 05 0.12 43 0.13 05 0.10 05 0.10 00	SE         Weig           93         9.3           33         9.3           34         9.3           99         25.9           99         25.9           90         7.16.3           24         9.4           100.0           SE         Weig           93         17.0           33         16.1           29         25.9           33         16.1           29         28.0           24         9.4           100.0         10.0           Veight         16.2           100.0         10.0           Veight         10.0	Hazard Ratio ht IV, Fixed, 95% CI 0.67 [0.52, 0.86] 0.61 [0.47, 0.79] 0.72 [0.59, 0.88] 0.64 [0.43, 0.95] 0.65 [0.50, 0.85] 0.66 [0.50, 0.81] 0.67 [0.55, 0.82] 0.70 [0.54, 0.91] 0.68 [0.62, 0.73] Hazard Ratio ht IV, Fixed, 95% CI 0.70 [0.54, 0.91] 0.66 [0.59, 0.83] 0.66 [0.59, 0.73] Hazard Ratio V, Fixed, 95% CI 0.72 [0.59, 0.88] 0.69 [0.59, 0.81]	Hazard IV, Fixed 	Ratio 95% CI 10 Favours [control] Ratio 95% CI Favours [control] I Ratio ,95% CI	100
E F	Study or Subgroup         CANVAS Program Integrated Data         CREDENCE         DAPA HF         DECLARE TIMI-58         EMPA-REG OUTCOME         EMPEROR-Reduced         SCORED         VERTIS CV         Total (95% CI)         Heterogeneity: Chi <sup>2</sup> = 1.29, df = 7         Test for overall effect: Z = 9.61 (Processing Concessing Concenter Concenter Concesing Concessing Concenter Concent	log[Hazard Rati           a         -0.400           -0.494         -0.322           -0.446         -0.430           -0.326         -0.400           -0.326         -0.400           -0.326         -0.400           -0.3285         0.1           -0.400         -0.400           -0.400         -0.400           -0.401         -0.400           -0.402         -0.400           -0.403         -0.400           -0.494         -0.444           -0.404         -0.400           -0.404         -0.400           -0.404         -0.400           -0.404         -0.400           -0.404         -0.400           -0.404         -0.400           -0.404         -0.400           -0.400         -0.400           -0.400         -0.400           -0.4000         -0.3600           (P = 0.99);  P = 0%            < 0.00001)	o] 5 0.12 43 0.13 5 0.10 63 0.20 63 0.20 63 0.20 63 0.20 63 0.20 63 0.20 63 0.13 63 0.20 63 0.20 6	SE         Weig           93         9.3           33         9.3           34         9.4           29         25.9           07         16.3           24         9.4           100.0         100.0           SE         Weig           93         17.0           33         16.1           26.9         25.9           93         17.0           33         16.1           26.2         100.0           24         9.4           12         6.9           39         15.8           07         28.0           24         16.2           100.0         100.0           Veight         1           38.2%         1           31.8%         1           00.0%         0	Hazard Ratio ht IV, Fixed, 95% CI 0.67 [0.52, 0.86] 0.61 [0.47, 0.79] 0.72 [0.59, 0.88] 0.64 [0.43, 0.95] 0.65 [0.50, 0.85] 0.66 [0.59, 0.81] 0.67 [0.55, 0.82] 0.70 [0.54, 0.91] 0.68 [0.62, 0.73] Hazard Ratio ht IV, Fixed, 95% CI 0.70 [0.54, 0.91] 0.66 [0.59, 0.73] Hazard Ratio V, Fixed, 95% CI 0.72 [0.59, 0.88] 0.72 [0.59, 0.88] 0.72 [0.59, 0.88] 0.72 [0.59, 0.88] 0.72 [0.59, 0.88] 0.72 [0.59, 0.88] 0.72 [0.59, 0.88] 0.73 [0.59, 0.88] 0.74 [0.59, 0.88] 0.75 [0.59, 0.88]	Hazard IV, Fixed 	Ratio 95% CI 10 Favours [control] Ratio 95% CI 10 Favours [control] Ratio , 95% CI	100
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**Figure 3.** Forest plot comparing the log hazard ratio of major outcome measures in patients receiving sodium-glucose co-transporter type 2 inhibitor versus placebo/other treatments, stratified based on DM status and HF severity. From above to below: 1. Cardiovascular death, in general (A), in DM patients regardless of baseline HF severity (B), and in HF patients regardless of DM status (C). 2. Hospitalization for heart failure, in general (D), in DM patients regardless of baseline HF severity (E), and in HF patients regardless of DM status (F).

А	SGLT2 Inh	ibitor	Placebo/C	ontrol		<b>Risk Difference</b>	Risk Difference
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl	M-H, Fixed, 95% CI
DAPA HE	106	1298	126	1307	97.0%	-0.01 [-0.04, 0.01]	
EMPA-TROPISM	0	40	1	40	3.0%	-0.03 [-0.09, 0.04]	
Total (95% CI)		1338		1347	100.0%	-0.02 [-0.04, 0.01]	•
Total events	106		127				
Heterogeneity: Chi <sup>2</sup> =	0.09, df = 1	(P = 0.7)	7); I² = 0%				
Test for overall effect:	Z=1.38 (P	= 0.17)					Placebo/Control SGLT2 Inhibitor
B							
D	SGLT2 Inh	ibitor	Placebo/C	ontrol		<b>Risk Difference</b>	Risk Difference
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl	M-H, Fixed, 95% Cl
DAPA HE	93	1298	146	1307	97.0%	-0.04 [-0.06, -0.02]	
EMPA-TROPISM	0	40	2	40	3.0%	-0.05 [-0.13, 0.03]	
Total (95% CI)		1338		1347	100.0%	-0.04 [-0.06, -0.02]	•
Total events	93		148				
Heterogeneity: Chi <sup>2</sup> =	0.06, df = 1	(P = 0.8)	1); <b>I</b> ≊ = 0%				
Test for overall effect:	Z = 3.66 (P	= 0.0002	2)				Placebo/Control_SGLT2 Inhibitor

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



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

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

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

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

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

# Conclusion

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

# Disclosure of conflict of interest

None.

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