Sodium-glucose co-transporter-2 inhibitors improve cardiovascular outcomes in heart failure with reduced ejection fraction regardless of ischemic etiology

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Background: Coronary artery disease remains the main underlying cause of heart failure (HF), despite the progress in prevention, diagnosis and treatment. Sodium-glucose co-transporter-2 inhibitors have been shown to improve surrogate cardiovascular outcomes in patients with HF with reduced ejection fraction (HFrEF), regardless of diabetes status.

Purpose: We sought to determine the effect of SGLT-2 inhibitors on the primary composite endpoint (cardiovascular death or hospitalization for HF) across the two hallmark trials in the HFrEF population (EMPEROR Reduced and DAPA-HF), according to ischemic or non-ischemic etiology of HF.

Methods: We pooled data from EMPEROR reduced and DAPA-HF trials in a total of 8,474 patients with HFrEF, performing a sub-analysis according to the presence of ischemic cardiomyopathy as the underlying cause of $\ensuremath{\mathsf{HFrEF}}$

Results: Treatment with SGLT-2 inhibitors resulted in a significant decrease in the risk for the primary composite outcome in patients with HFrEF of ischemic etiology, equal to 18% (RR=0.82, 95% Cl: 0.73–0.92, $|^2=0\%$). In patients with HFrEF of non-ischemic etiology, SGLT-2 inhibitors produced a significant decrease in the risk for the primary composite outcome equal to 18% (RR=0.72, 95% Cl: 0.63–0.82, $|^2=0\%$). Despite the greater effect in patients with non-ischemic HFrEF, no subgroup difference was detected (p=0.16). Generated results are summarized in Figure 1.

Conclusions: SGLT-2 inhibitors improve surrogate cardiovascular outcomes both in patients with ischemic and non-ischemic HFrEF.

	SGLT-2 inh	bitors	Place	bo		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI
1.1.1 Ischemic etiology	1						
DAPA-HF	223	1316	289	1358	29.5%	0.80 [0.68, 0.93]	
EMPEROR Reduced Subtotal (95% CI)	207	983 2299	236	946 2304	27.2% 56.7%	0.84 [0.72, 0.99] 0.82 [0.73, 0.92]	•
Total events	430		525				000000
Heterogeneity: Tau ² = 0	.00; Chi ² = 0	25, df = 1	(P = 0.6)	i1); I ² =	0%		
Test for overall effect: Z	= 3.45 (P = 0	0.0006)					
1.1.2 Non-ischemic eti	ology						
DAPA-HF	163	1057	213	1013	21.4%	0.73 [0.61, 0.88]	
EMPEROR Reduced Subtotal (95% CI)	154	880 1937	226	921 1934	21.9% 43.3%		•
Total events	317		439				12/14/42
Heterogeneity: Tau ² = 0	.00; Chi ² = 0	.04, df = 1	1 (P = 0.8)	(3); I ² =	0%		
Test for overall effect: Z	= 4.89 (P < 0	0.00001)					
Total (95% CI)		4236		4238	100.0%	0.78 [0.71, 0.85]	•
Total events	747		964				
Heterogeneity: Tau ² = 0	.00; Chi ² = 2	29, df = 3	3 (P = 0.5)	i1); I ² =	0%		0.5 0.7 1 1.5 2
Test for overall effect: Z	= 5.81 (P < 0	0.00001)					U.5 U.7 1 1.5 2 Favours SGLT-2 inhibitors Favours placebo
Test for subgroup differ	onene Chiz.	2 00 4	- 4 (D -	0.4.00	2 40.000		Favours ooc -2 minutors Favours placebo

Test for subgroup differences: Chi² = 2.00, df = 1 (P = 0.16), l² = 49.9%

Figure 1