## Safety and efficacy of SGLT2 inhibitors in diabetic and non-diabetic heart failure patients, a meta-analysis of randomized controlled trials

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**Background:** Heart failure (HF) is the most common cardiovascular causes of hospitalization in people over 60 years affecting about 64.3 million people worldwide. Few studies have investigated sodium glucose like transporter-2 inhibitors (SGLT-2I) role in diabetic and non-diabetic patients with HF.

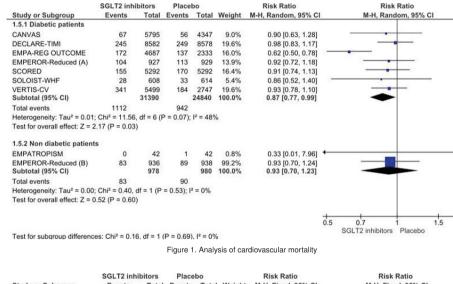
**Objective:** We conducted our meta-analysis to further investigate SGLT-2I role in diabetic and non-diabetic HF patients.

**Methods:** PubMed, Scopus, web of science, and Embase were searched. All clinical trials that compared the effect of SGLT2 inhibitors versus placebo on heart failure patients were included. Dichotomous data were extracted, pooled as risk ratio (RR) with 95% confidence interval, and analyzed via RevMan version 5.3 for windows using Mantel Haenszel (M-H) method.

**Results:** Twelve randomized clinical trials were included for analysis with

a total number of 69024 patients. SGLT2I significantly lowered the risk of hospitalization for heart failure (HHF) in diabetic (RR=0.68, 95% CI 0.63–0.74) and non-diabetic patients (RR=0.75, 95% CI 0.62–0.89). Also, it significantly lowered mortality risk in both diabetic (RR=0.87, 95% CI 0.77–0.99) and non-diabetic patients (RR=0.93, 95% CI 0.70–1.23). Further analyses for serious adverse events were conducted, and SGLT-2I showed a significant lower risk in diabetic (RR=0.94, 95% CI 0.90–0.98) and non-diabetic patients (RR=0.72, 95% CI 0.38–1.39), yet with no observed difference over placebo in the risk of stroke.

**Conclusion:** SGLT2 inhibitors showed a favorable effect in lowering cardiovascular mortality, HHF, and stroke in diabetic patients with heart failure. In non-diabetic patients, they significantly reduce HHF, yet with no difference on cardiovascular mortality and stroke. Therefore, more trials are needed to establish their effect in non-diabetic patients.



Study or Subgroup	SGLT2 inhibitors		Placebo		Risk Ratio		Risk Ratio	
	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed,	95% CI
1.1.1 Diabetic patients								
CANVAS	32	5795	38	4347	3.0%	0.63 [0.40, 1.01]	+ •	
DECLARE-TIMI	212	8582	286	8578	19.9%	0.74 [0.62, 0.88]		
EMPA-REG OUTCOME	126	4687	95	2333	8.8%	0.66 [0.51, 0.86]		
EMPEROR-Reduced (A)	221	927	337	929	23.4%	0.66 [0.57, 0.76]		
SCORED	152	5292	219	5292	15.2%	0.69 [0.57, 0.85]		
SOLOIST-WHF	194	608	297	614	20.5%	0.66 [0.57, 0.76]		
VERTIS-CV Subtotal (95% CI)	139	5499 31390	99	2747 24840	9.2% 100.0%	0.70 [0.54, 0.90] 0.68 [0.63, 0.74]	•	
Total events	1076		1371			• • •		
Heterogeneity: Chi <sup>2</sup> = 1.58, o	df = 6 (P = 0)	.95); 12 =	0%					
Test for overall effect: Z = 10								
1.1.2 Non diabetic patients								
EMPATROPISM	0	42	2	42	1.1%	0.20 [0.01, 4.04]	+	
EMPEROR-Reduced (B) Subtotal (95% CI)	167	963 1005	216	938 980	98.9% 100.0%	0.75 [0.63, 0.90] 0.75 [0.62, 0.89]		
Total events	167		218					
Heterogeneity: Chi <sup>2</sup> = 0.75, o	df = 1 (P = 0)	.39); 12 =	0%					
Test for overall effect: Z = 3.	17 (P = 0.00	)2)						
							0.5 0.7 1	1.5
								1.5 . acebo

st for subgroup differences:  $Chi^2 = 0.79$ , df = 1 (P = 0.37),  $I^2 = 0\%$ 

Figure 2. Analysis of hospitalization for HF