



EFFECTS OF SODIUM-GLUCOSE CO-TRANSPORTER 2 INHIBITORS ON HEART FAILURE IN CHRONIC KIDNEY DISEASE: A SYSTEMATIC REVIEW AND META-ANALYSIS

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RAS blockers and HHF risk in CKD

Review: Pharmacological interventions for heart failure in people with chronic kidney disease Comparison: 6 CHRONIC: ACEi OR ARB versus placebo Outcome: 3 Hospitalisation for heart failure

Study or subgroup	ACEi or ARB n/N	Placebo n/N	Risk Ratio M-H,Random,95% Cl	Weight	Risk Ratio M-H,Random,95% Cl	
1 ACEi versus placebo SOLVD (Treatment) 19	92 353/498	293/538	-	51.2 %	1.30 [1.18, 1.43]	
Subtotal (95% CI) Total events: 353 (ACEi o Heterogeneity: not applic Test for overall effect: Z :	498 r ARB), 293 (Placebo) able = 5.40 (P < 0.00001)	538	•	51.2 %	1.30 [1.18, 1.43]	
2 ARB versus placebo Cice 2010	56/165	92/167		48.8 %	0.62 [0.48, 0.79]	
Subtotal (95% CI) Total events: 56 (ACEi or Heterogeneity: not applic Test for overall effect: Z :	165 ARB), 92 (Placebo) able = 3.75 (P = 0.00018)	167	•	48.8 %	0.62 [0.48, 0.79]	_
Total (95% CI) Total events: 409 (ACEi o Heterogeneity: Tau ² = 0. Test for overall effect: Z : Test for subgroup differen	663 r ARB), 385 (Placebo) 28; Chi ² = 30.32, df = = 0.27 (P = 0.79) nces: Chi ² = 29.35, df	705 1 (P<0.00001); I ² =97% = 1 (P = 0.00), I ² =97%		100.0 %	0.90 [0.43, 1.90]	
		01 01		10		
	Le	ss with ACEi/ARB	Less with pl	acebo		





SGLT-2inh and HHF risk in T2DM

	Patients		Events	Events per patient-yea	1000 ars	Weight (%)	HR			HR (95% CI)
	Treatment (n)	Placebo (n)		Treatment	Placebo					
Patients with athero	sclerotic cardiov	ascular disease								
EMPA-REG OUTCOME	4687	2333	463	19.7	30.1	30.9	_ _			0.66 (0.55-0.79)
CANVAS Program	3756	2900	524	21.0	27.4	32.8	∎			0.77 (0.65-0.92)
DECLARE-TIMI 58	3474	3500	597	19.9	23.9	36.4	∎			0.83 (0.71–0.98
Fixed effects model f	for atherosclerot	ic cardiovascul	ar disease	(p<0·0001)			•			0·76 (0·69–0·84)
Patients with multip CANVAS Program	lle risk factors 2039	1447	128	8.9	9.8	30.2	_	_		0.83 (0.58–1.19)
DECLARE-TIMI 58	5108	5078	316	7 ∙0	8.4	69.8				0.84 (0.67–1.04)
Fixed effects model f	for multiple risk f	actors (p=0.06	534)							0·84 (0·69–1·01)
						0.35	0.50 1.00	Favours placebo	2.50	

Figure 2: Meta-analysis of SGLT2i trials on hospitalisation for heart failure and cardiovascular death stratified by the presence of established atherosclerotic cardiovascular disease

Atherosclerotic cardiovascular disease: Q statistic=3·49, p=0·17, I²=42·7%; multiple risk factors: Q statistic=0·00, p=0·96, I²=0%. The p value for subgroup differences was 0·41. Tests for subgroup differences were based on F tests in a random effect meta-regression estimated using restricted maximum likelihood and Hartung Knapp adjustment. HR=hazard ratio. SGLT2i=sodium-glucose cotransporter-2 inhibitors.





SGLT-2inh and HHF risk in heart failure



Months since Randomization

McMurray JJV, et al. N Engl J Med. 2019 Packer M, et al. N Engl J Med. 2020 Anker SD, et al. . N Engl J Med. 2021





SGLT-2inh and HHF risk in CKD

DAPA-CKD



CREDENCE

Table 2. Efficacy and Safety.*						
Variable	Canagliflozin	Placebo	Canagliflozin	Placebo	Hazard Ratio (95% CI)	P Value
	no./total no.		events/ 1000 patient-yr			
Secondary outcomes						
Cardiovascular death or hospitalization for heart failure	179/2202	253/2199	31.5	45.4	0.69 (0.57–0.83)	<0.001
Carolovascular ocatil, myocarolar marction, or stroke	211/2202	205/2155	50.7	40.7	0.00 (0.07 - 0.55)	0.01
Hospitalization for heart failure	89/2202	141/2199	15.7	25.3	0.61 (0.47–0.80)	<0.001
level, or renal death						
Death from any cause	168/2202	201/2199	29.0	35.0	0.83 (0.68-1.02)	NA
Cardiovascular death, myocardial infarction, stroke, or hospitalization for heart failure or unstable angina	273/2202	361/2199	49.4	66.9	0.74 (0.63–0.86)	NA
End-stage kidney disease, renal death, or cardiovascular death†	214/2202	287/2199	37.6	51.2	0.73 (0.61-0.87)	NA
Dialysis, kidney transplantation, or renal death†	78/2202	105/2199	13.6	18.6	0.72 (0.54-0.97)	NA

Heerspink, et al. N Engl J Med. 2020 Perkovic, et al. N Engl J Med. 2019

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We aimed to perform a meta-analysis exploring the effect of SGLT-2 inhibitors on HF events in patients with CKD and across subgroups defined by baseline kidney function.





Methods

- Systematic review and meta-analysis (PROSPERO ID: CRD42022382857).
- A literature search was conducted in major electronic databases (PubMed/MEDLINE, Scopus, Cochrane Library and Web of Science) up to 15 November 2022.
- Randomized controlled trials providing data on the effect of SGLT-2 inhibitors on the primary outcome, time to hospitalization or urgent visit for worsening HF in patients with prevalent CKD at baseline or across subgroups stratified by baseline eGFR were included.
- Primary outcome: time to hospitalization or urgent visit for worsening HF in patients with CKD





Study flow-chart

 12 studies with 89,191 participants



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Effects of SGLT-2inh on HF events in CKD

			Hazard Ratio	Hazard Ratio
Study or Subgroup	log[Hazard Ratio] S	E Weight	IV, Fixed, 95% CI	IV, Fixed, 95% Cl
CANVAS Program	-0.5621 0.206	3.6%	0.57 [0.38, 0.86]	
CREDENCE	-0.4891 0.135	8.3%	0.61 [0.47, 0.80]	_
DAPA-CKD	-0.6766 0.2052	2 3.6%	0.51 [0.34, 0.76]	
DAPA-HF	-0.4231 0.127	9.4%	0.66 [0.51, 0.84]	
DECLARE-TIMI 58	-0.3086 0.120	5 10.5%	0.73 [0.58, 0.93]	
DELIVER	-0.2862 0.0979	9 16.0%	0.75 [0.62, 0.91]	
EMPA-KIDNEY	-0.2263 0.1452	2 7.3%	0.80 [0.60, 1.06]	
EMPA-REG OUTCOME	-0.5347 0.207	3.6%	0.59 [0.39, 0.88]	
EMPEROR-Preserved	-0.4095 0.124	9.8%	0.66 [0.52, 0.85]	•
EMPEROR-Reduced	-0.312 0.127	§ 9.4%	0.73 [0.57, 0.94]	
SCORED	-0.4005 0.100	7 15.1%	0.67 [0.55, 0.82]	
VERTIS CV	-0.6931 0.212	2 3.4%	0.50 [0.33, 0.76]	32%
Total (95% CI)		100.0%	0.68 [0.63, 0.73]	\bullet
Heterogeneity: Chi ² = 9.03	, df = 11 (P = 0.62); l ² = 0%			
Test for overall effect: Z =	10.03 (P < 0.00001)			Favours SGLT-2 inhibitors Favours Placebo





Effects of SGLT-2inh on HF events in CKD Subgroup analysis according to SGLT-2inh type

			Hazard Ratio	Hazard Ratio				
Study or Subgroup	log[Hazard Ratio] S	E Weight	IV, Fixed, 95% CI	IV, Fixed, 95% CI				
4.1.1 Canagliflozin								
CANVAS Program	-0.5621 0.206	9 3.6%	0.57 [0.38, 0.86]					
CREDENCE	-0.4891 0.135	7 8.3%	0.61 [0.47, 0.80]					
Subtotal (95% CI)		11.9%	0.60 [0.48, 0.75]					
Heterogeneity: Chi ² = 0.09,	, df = 1 (P = 0.77); l² = 0%							
Test for overall effect: $Z = 4$	4.50 (P < 0.00001)							
4 1 2 Danagliflozin								
	-0.6766 0.205	2 3.6%	0 51 [0 34 0 76]					
DAPA-HE	-0.4231 0.127	7 94%	0.66 [0.51, 0.84]					
DECLARE-TIMI 58	-0.3086 0.120	5 10.5%	0.73 [0.58, 0.93]					
DELIVER	-0.2862 0.097	9 16.0%	0.75 [0.62, 0.91]	_				
Subtotal (95% CI)		39.5%	0.70 [0.62, 0.79]	\bullet				
Heterogeneity: Chi ² = 3.37,	, df = 3 (P = 0.34); l² = 11%							
Test for overall effect: Z = 5	5.79 (P < 0.00001)							
4.1.3 Empagliflozin								
EMPA-KIDNEY	-0.2263 0.145	2 7.3%	0.80 [0.60, 1.06]					
EMPA-REG OUTCOME	-0.5347 0.207	6 3.6%	0.59 [0.39, 0.88]					
EMPEROR-Preserved	-0.4095 0.124	7 9.8%	0.66 [0.52, 0.85]					
EMPEROR-Reduced	-0.312 0.127	6 9.4%	0.73 [0.57, 0.94]					
Subtotal (95% Cl)		30.1%	0.71 [0.61, 0.81]	•				
Heterogeneity: Chi ² = 1.83,	, df = 3 (P = 0.61); l ² = 0%							
Test for overall effect: $Z = 4$	4.90 (P < 0.00001)							
4.1.4 Sotagliflozin								
SCORED	-0.4005 0.100	7 15 1%	0 67 10 55 0 821					
Subtotal (95% CI)	0.4000 0.100	15.1%	0.67 [0.55, 0.82]					
Heterogeneity: Not applicat	ble							
Test for overall effect: $Z = 3$	3.98 (P < 0.0001)							
4.1.5 Ertugliflozin								
VERTIS CV	-0.6931 0.21	2 3.4%	0.50 [0.33, 0.76]					
Subtotal (95% CI)		3.4%	0.50 [0.33, 0.76]					
Heterogeneity: Not application	ble							
Test for overall effect: Z = 3.27 (P = 0.001)								
Total (95% CI)		100.0%	0.68 [0.63, 0.73]	▲				
Heterogeneity: $Chi^2 = 9.03$	$df = 11 (P = 0.62) \cdot I^2 = 0\%$							
Test for overall effect: $7 = 7$	10.03 (P < 0.00001)			0.5 0.7 1 1.5 2				
Test for subgroup difference	xes: Chi ² = 3.73, df = 4 (P =	1%	Favours SGL1-2 Inhibitors Favours placebo					
lest for subgroup difference	es: Chi ² = 3.73, at = 4 (P =	$(0.44), 1^2 = 0$	1%					





				Hazard Ratio	Hazard Ratio			
Study or Subgroup	log[Hazard Ratio]	SE	Weight	IV, Fixed, 95% CI	IV, Fixed, 95% CI			
2.1.1 No CKD/ CKD Stages 1-2								
CANVAS Program	-0.2698	0.1674	3.8%	0.76 [0.55, 1.06]				
CREDENCE	-0.3285	0.2513	1.7%	0.72 [0.44, 1.18]				
DAPA-HF	-0.2877	0.1224	7.1%	0.75 [0.59, 0.95]	ETT(
DECLARE-TIMI 58	-0.2877	0.0971	11.2%	0.75 [0.62, 0.91]	_			
DELIVER	-0.2055	0.1149	8.0%	0.81 [0.65, 1.02]				
EMPA-REG OUTCOME	-0.3567	0.182	3.2%	0.70 [0.49, 1.00]				
EMPEROR-Preserved	-0.1278	0.1468	4.9%	0.88 [0.66, 1.17]				
EMPEROR-Reduced	-0.5171	0.1436	5.1%	0.60 [0.45, 0.79]				
VERTIS CV	-0.1455	0.1694	3.7%	0.86 [0.62, 1.21]				
Subtotal (95% CI)			48.6%	0.76 [0.69, 0.83]	\bullet			
Heterogeneity: Chi ² = 5.07,	, df = 8 (P = 0.75); l ² =	= 0%						
Test for overall effect: Z = 5	5.92 (P < 0.00001)							
2.1.2 CKD Stages 3a-4								
CREDENCE	-0.5621	0.1558	4.4%	0.57 [0.42, 0.77]				
DAPA-HF	-0.4231	0.1277	6.5%	0.66 [0.51, 0.84]				
DECLARE-TIMI 58	-0.3538	0.2383	1.9%	0.70 [0.44, 1.12]				
DELIVER	-0.2862	0.0979	11.0%	0.75 [0.62, 0.91]	_			
EMPA-REG OUTCOME	-0.5347	0.2076	2.5%	0.59 [0.39, 0.88]				
EMPEROR-Preserved	-0.4095	0.1247	6.8%	0.66 [0.52, 0.85]				
EMPEROR-Reduced	-0.2099	0.1368	5.6%	0.81 [0.62, 1.06]				
SCORED	-0.4005	0.1007	10.4%	0.67 [0.55, 0.82]	_			
VERTIS CV	-0.6931	0.212	2.4%	0.50 [0.33, 0.76]				
Subtotal (95% CI)			51.4%	0.68 [0.62, 0.74]	\bullet			
Heterogeneity: Chi ² = 6.73,	, df = 8 (P = 0.57); l ² =	= 0%						
Test for overall effect: Z = 8	3.62 (P < 0.00001)							
Total (95% CI)			100.0%	0.72 [0.67, 0.76]	◆			
Heterogeneity: Chi ² = 14.9	3. df = 17 (P = 0.60):	$ ^{2} = 0\%$		- · -				
Test for overall effect: $7 = 7$	10.31 (P < 0.00001)	0.5 0.7 1 1.5 2						
Test for subgroup difference	$es: Chi^2 = 3.12 df = 1$	Favours SGL1-2 inhibitors Favours Placebo						

Effects of SGLT-2inh on HF events in CKD Subgroup analysis according to eGFR





Sensitivity analysis: patients with T2DM







Conclusions

- Treatment with SGLT-2 inhibitors led to a significant reduction in HF events in patients with CKD, with or without diabetes
- These beneficial effects are independent of GFR levels and CKD risk group
- These findings may change the landscape of HF treatment in patients with advanced CKD.





THANK YOU

