1ST DEPARTMENT OF
NEPHROLOGY
HIPPOKRATION HOSPITAL

ARISTOTLE
UNIVERSITY OF
THESSALONIKI

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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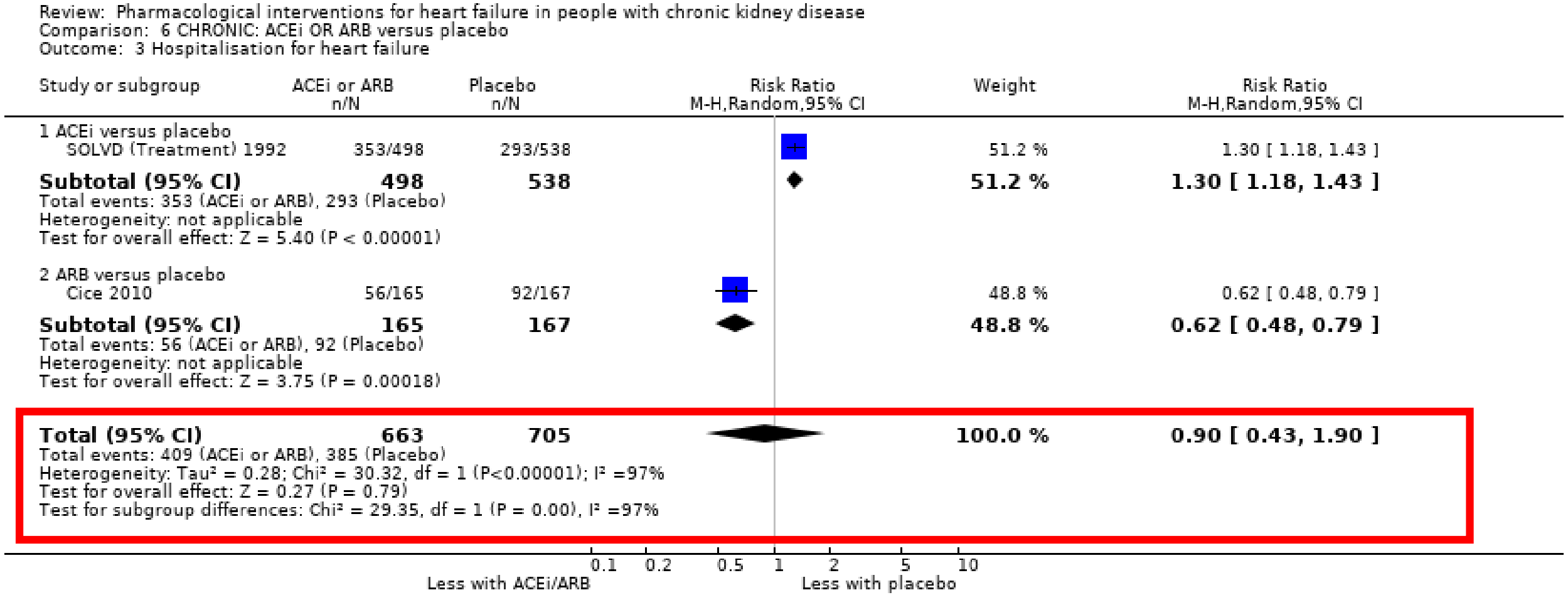
RAS blockers and HHF risk in CKD



SGLT-2inh and HHF risk in T2DM

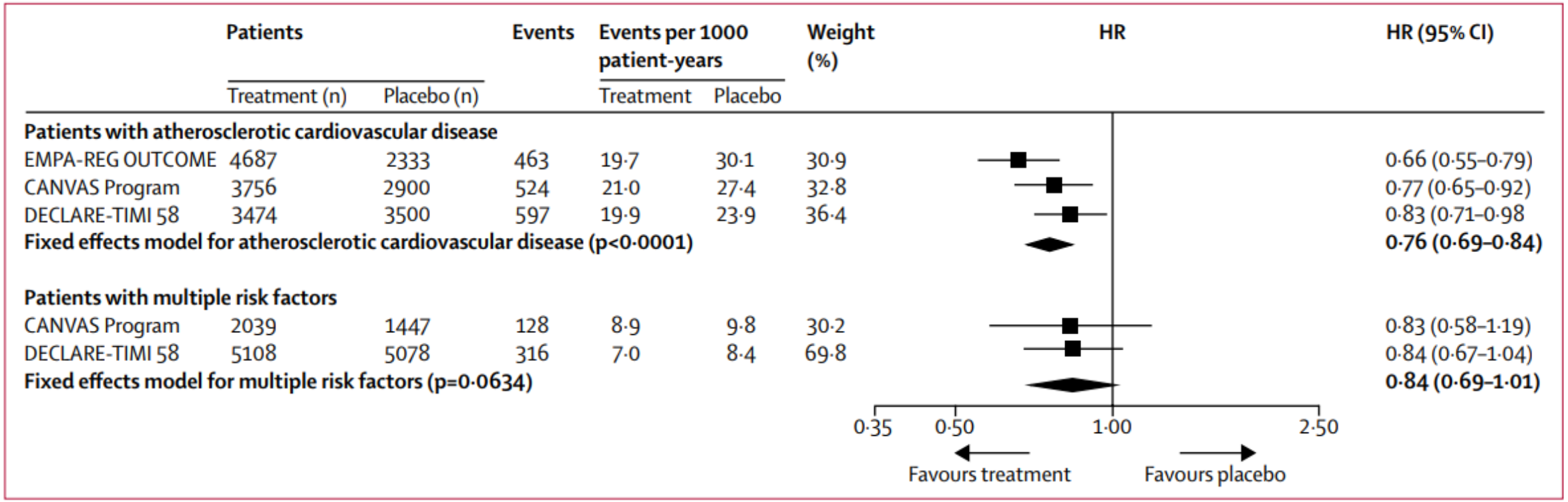


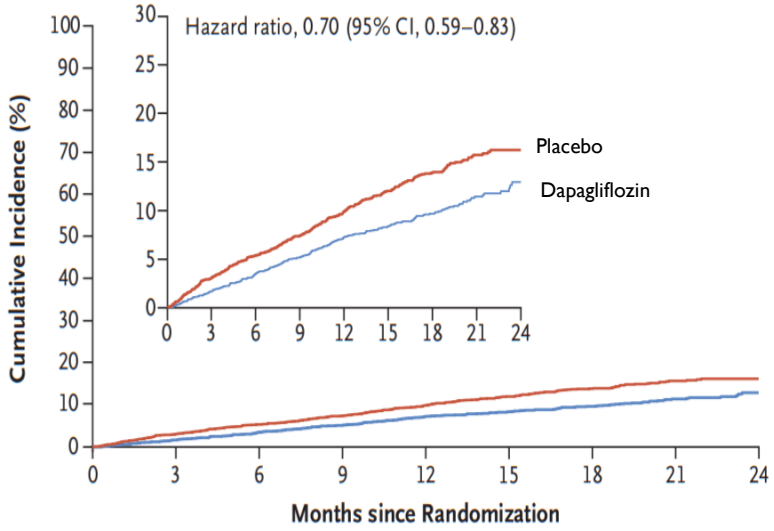
Figure 2: **Meta-analysis of SGLT2i trials on hospitalisation for heart failure and cardiovascular death stratified by the presence of established atherosclerotic cardiovascular disease**

Atherosclerotic cardiovascular disease: Q statistic=3·49, p=0·17, I^2=42·7%; multiple risk factors: Q statistic=0·00, p=0·96, I^2=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.

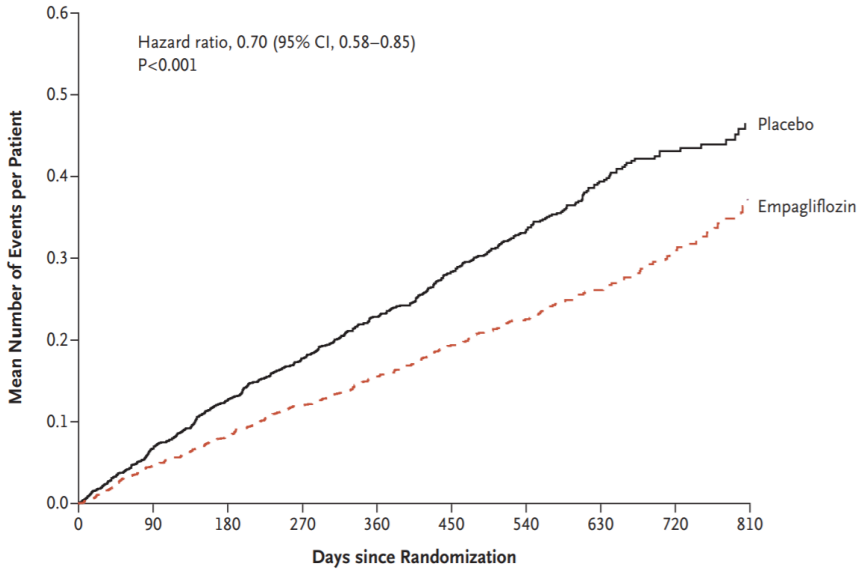
Zelniker et al, Lancet 2018

SGLT-2inh and HHF risk in heart failure

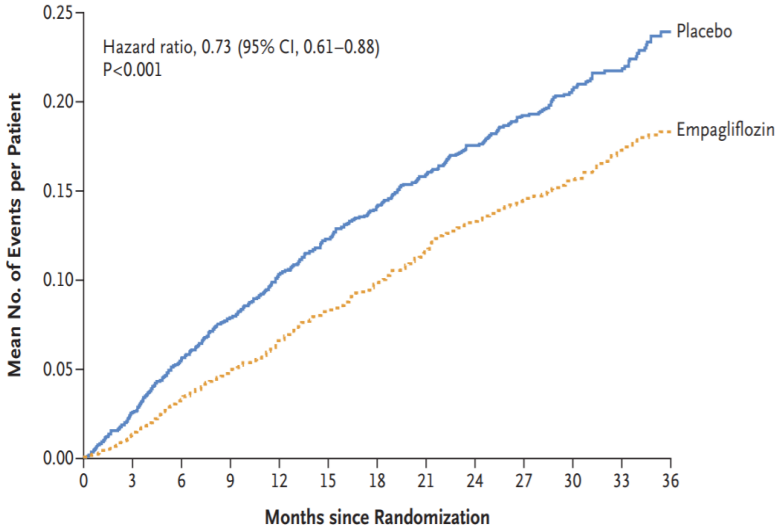
DAPA-HF



EMPEROR-Reduced



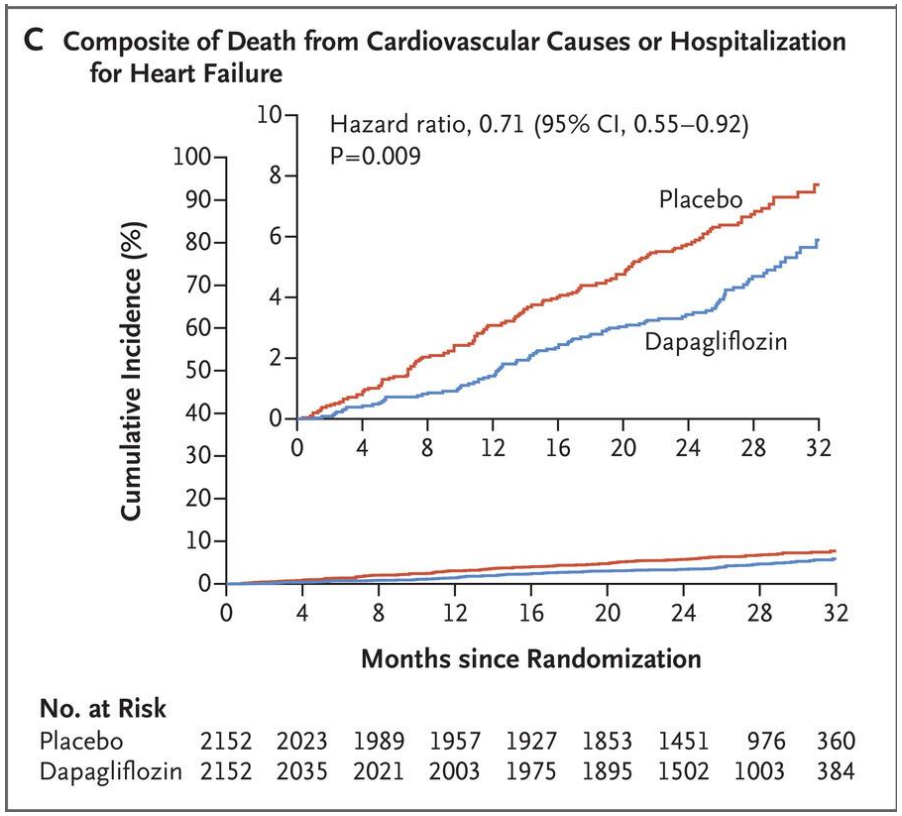
EMPEROR-Preserved



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
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

Aim

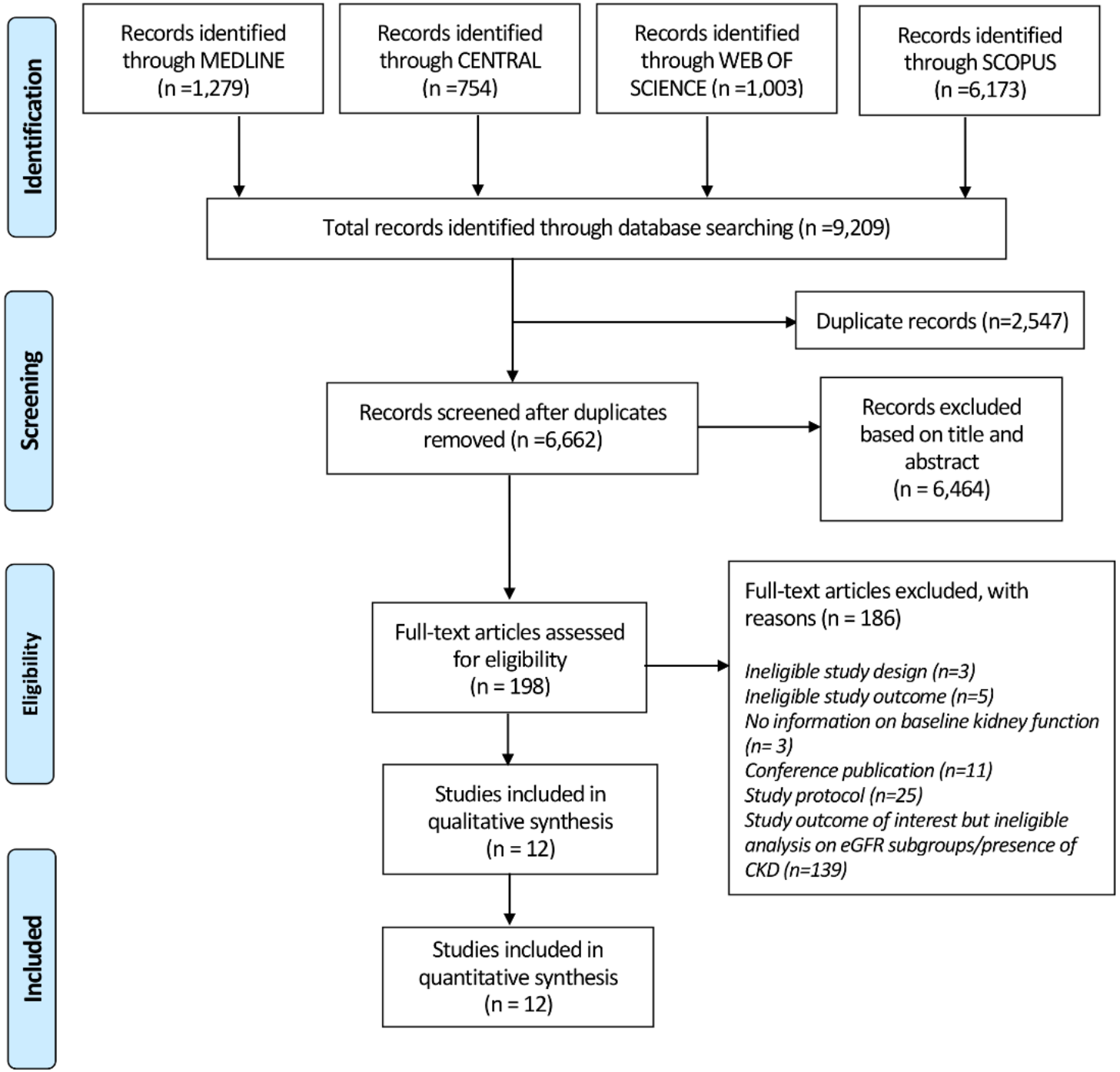
We aimed to perform a meta-analysis exploring the effect of SGLT-2 inhibitors on HF events in patients with CKD and across subgroups defined by baseline kidney function.

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

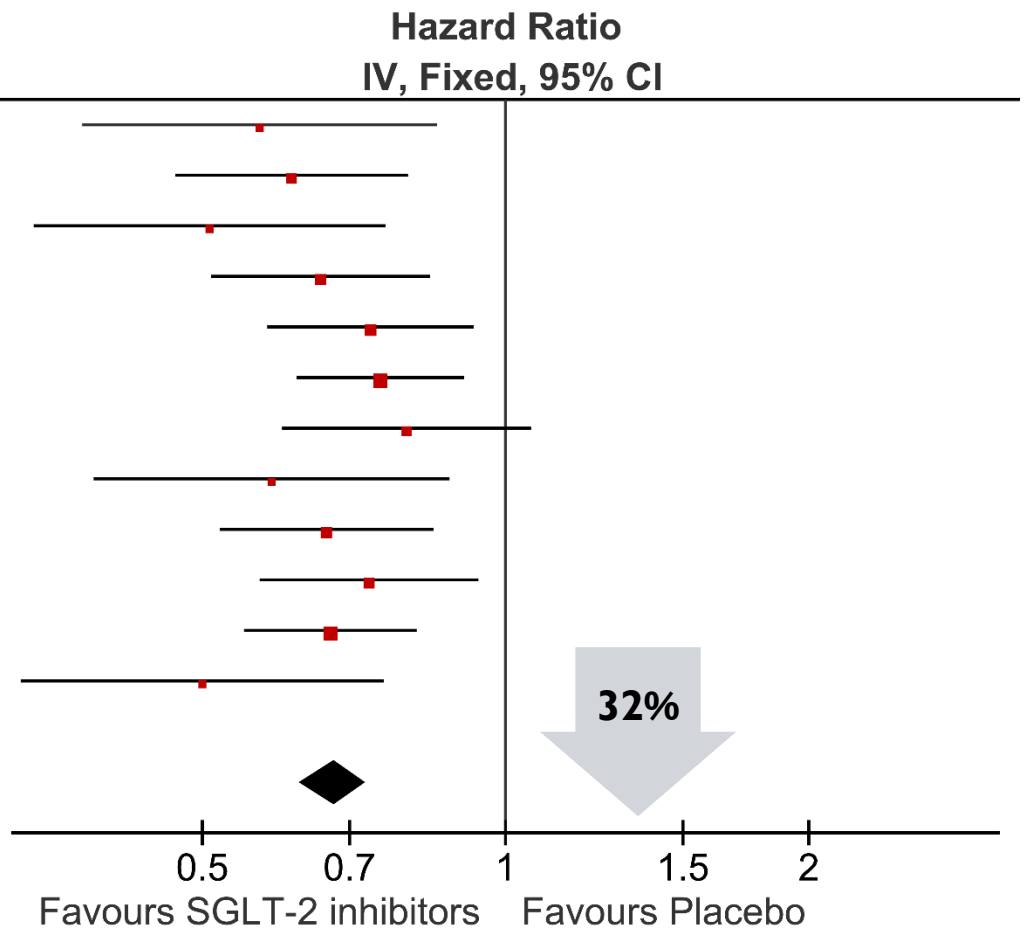


Effects of SGLT-2inh on HF events in CKD

Study or Subgroup	log[Hazard Ratio]	SE	Weight	Hazard Ratio IV, Fixed, 95% CI
CANVAS Program	-0.5621	0.2069	3.6%	0.57 [0.38, 0.86]
CREDENCE	-0.4891	0.1357	8.3%	0.61 [0.47, 0.80]
DAPA-CKD	-0.6766	0.2052	3.6%	0.51 [0.34, 0.76]
DAPA-HF	-0.4231	0.1277	9.4%	0.66 [0.51, 0.84]
DECLARE-TIMI 58	-0.3086	0.1205	10.5%	0.73 [0.58, 0.93]
DELIVER	-0.2862	0.0979	16.0%	0.75 [0.62, 0.91]
EMPA-KIDNEY	-0.2263	0.1452	7.3%	0.80 [0.60, 1.06]
EMPA-REG OUTCOME	-0.5347	0.2076	3.6%	0.59 [0.39, 0.88]
EMPEROR-Preserved	-0.4095	0.1247	9.8%	0.66 [0.52, 0.85]
EMPEROR-Reduced	-0.312	0.1276	9.4%	0.73 [0.57, 0.94]
SCORED	-0.4005	0.1007	15.1%	0.67 [0.55, 0.82]
VERTIS CV	-0.6931	0.212	3.4%	0.50 [0.33, 0.76]
Total (95% CI)			**100.0%**	**0.68 [0.63, 0.73]**

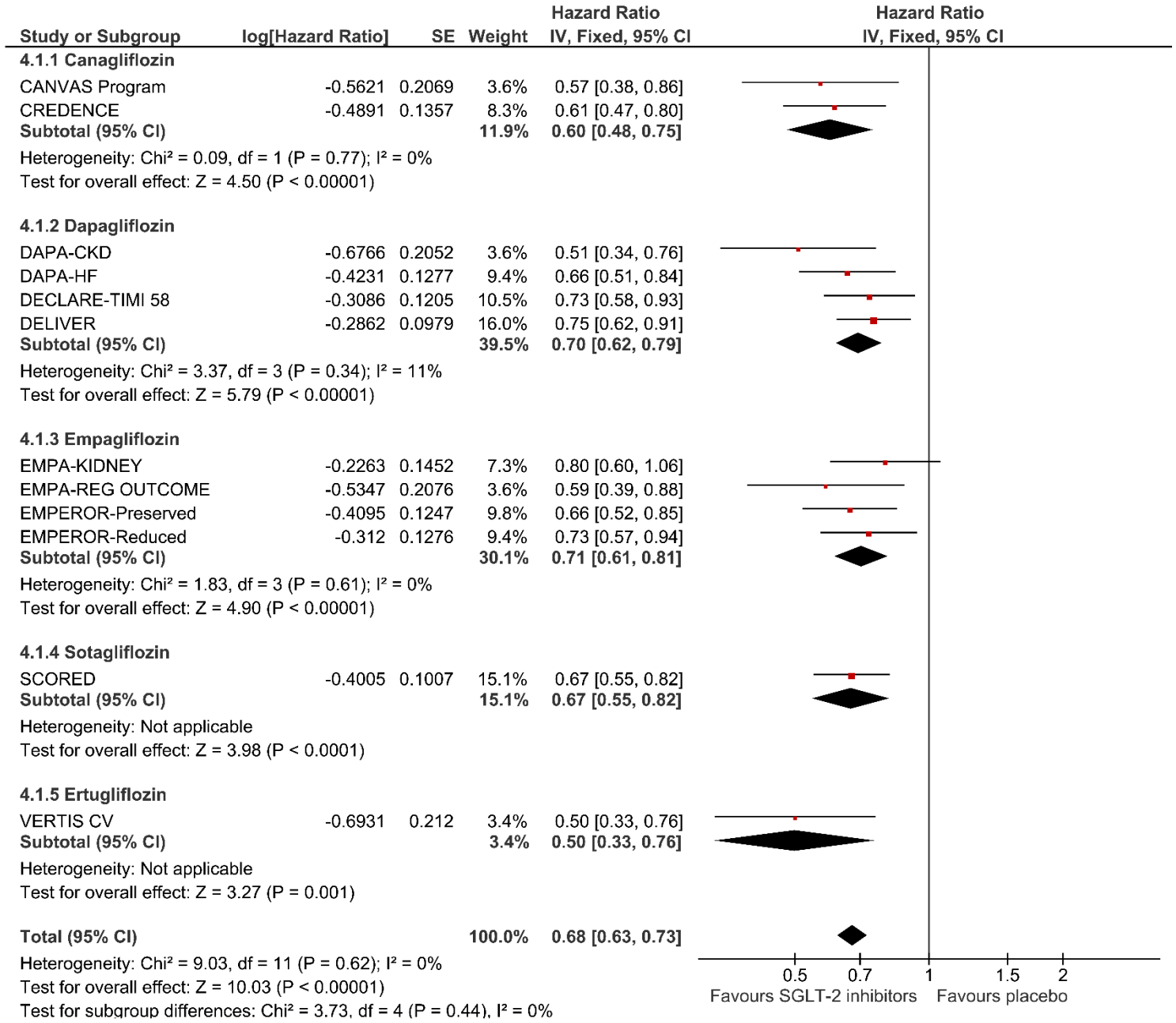
Heterogeneity: Chi² = 9.03, df = 11 (P = 0.62); I² = 0%

Test for overall effect: Z = 10.03 (P < 0.00001)

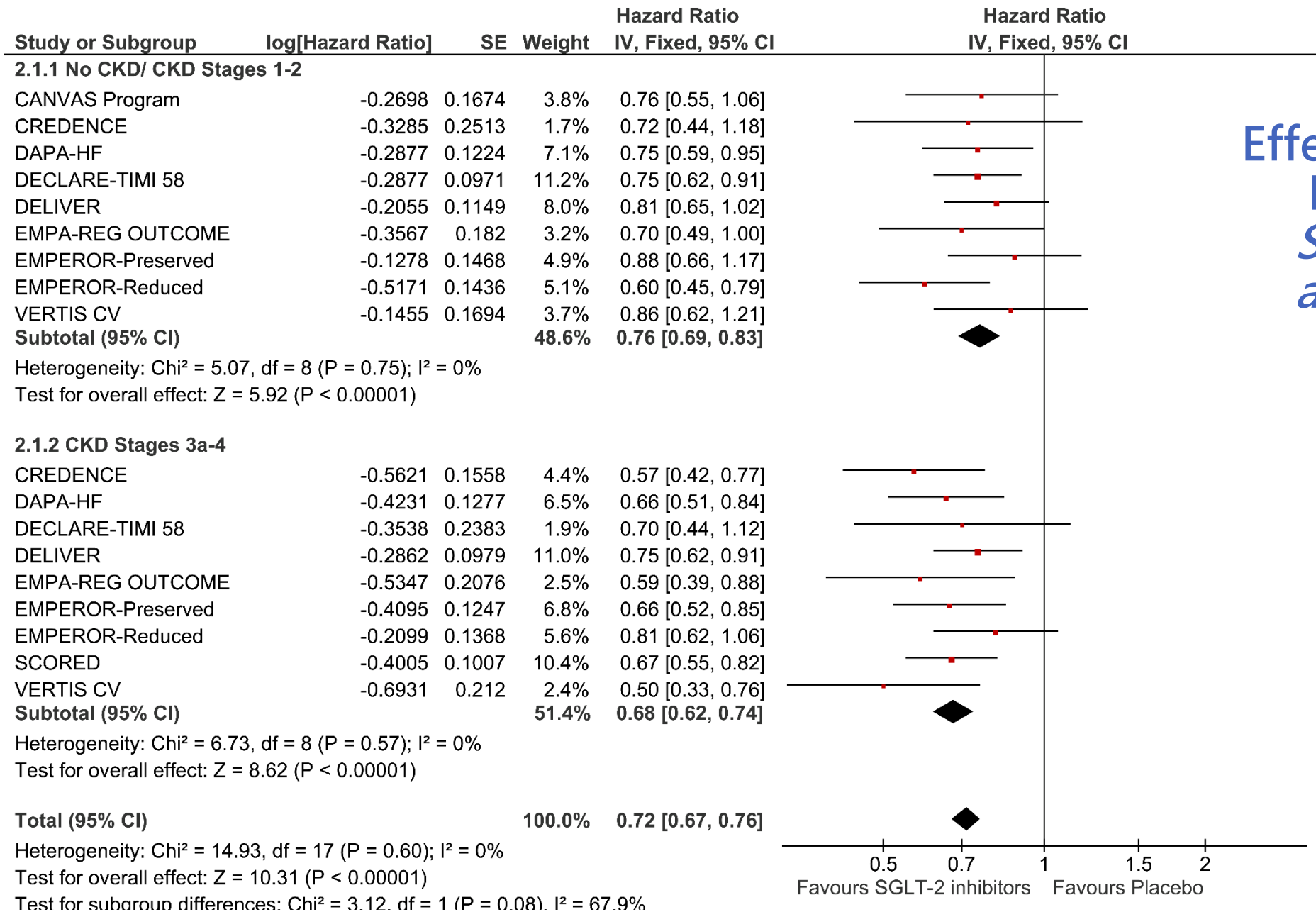


Effects of SGLT-2inh on HF events in CKD

Subgroup analysis according to SGLT-2inh type

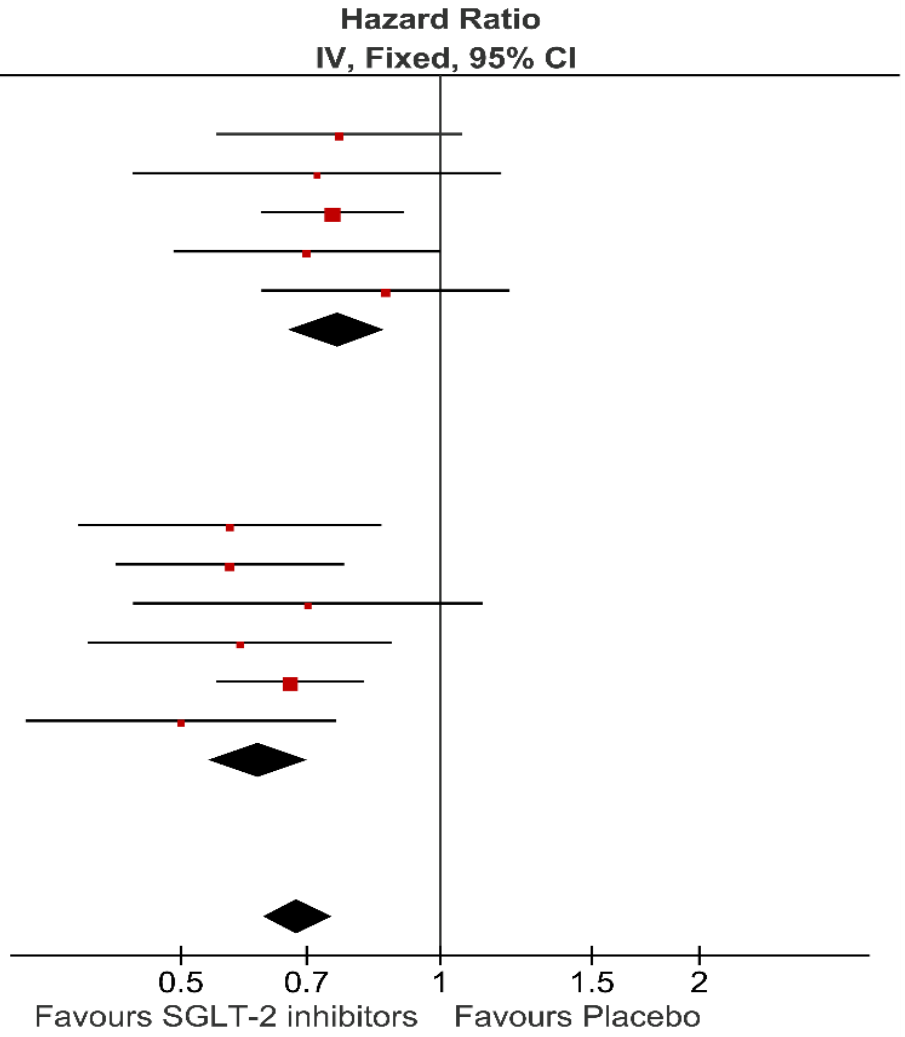


Effects of SGLT-2inh on HF events in CKD
Subgroup analysis according to eGFR



Sensitivity analysis: patients with T2DM

Study or Subgroup	log[Hazard Ratio]	SE	Weight	Hazard Ratio IV, Fixed, 95% CI
6.1.1 No CKD / CKD Stage 1/Stage 2				
CANVAS Program	-0.2698	0.1674	8.0%	0.76 [0.55, 1.06]
CREDENCE	-0.3285	0.2513	3.5%	0.72 [0.44, 1.18]
DECLARE-TIMI 58	-0.2877	0.0971	23.6%	0.75 [0.62, 0.91]
EMPA-REG OUTCOME	-0.3567	0.182	6.7%	0.70 [0.49, 1.00]
VERTIS CV	-0.1455	0.1694	7.8%	0.86 [0.62, 1.21]
Subtotal (95% CI)			**49.6%**	**0.76 [0.67, 0.87]**
Heterogeneity: Chi² = 0.85, df = 4 (P = 0.93); I² = 0%				
Test for overall effect: Z = 4.10 (P < 0.0001)				
6.1.2 CKD Stages 3a-4				
CANVAS Program	-0.5621	0.2069	5.2%	0.57 [0.38, 0.86]
CREDENCE	-0.5621	0.1558	9.2%	0.57 [0.42, 0.77]
DECLARE-TIMI 58	-0.3538	0.2383	3.9%	0.70 [0.44, 1.12]
EMPA-REG OUTCOME	-0.5347	0.2076	5.2%	0.59 [0.39, 0.88]
SCORED	-0.4005	0.1007	22.0%	0.67 [0.55, 0.82]
VERTIS CV	-0.6931	0.212	5.0%	0.50 [0.33, 0.76]
Subtotal (95% CI)			**50.4%**	**0.62 [0.54, 0.70]**
Heterogeneity: Chi² = 2.41, df = 5 (P = 0.79); I² = 0%				
Test for overall effect: Z = 7.30 (P < 0.00001)				
Total (95% CI)			**100.0%**	**0.68 [0.62, 0.75]**
Heterogeneity: Chi² = 8.24, df = 10 (P = 0.61); I² = 0%				
Test for overall effect: Z = 8.07 (P < 0.00001)				
Test for subgroup differences: Chi² = 4.98, df = 1 (P = 0.03), I² = 79.9%				



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