

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

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RAS blockers and mortality in CKD

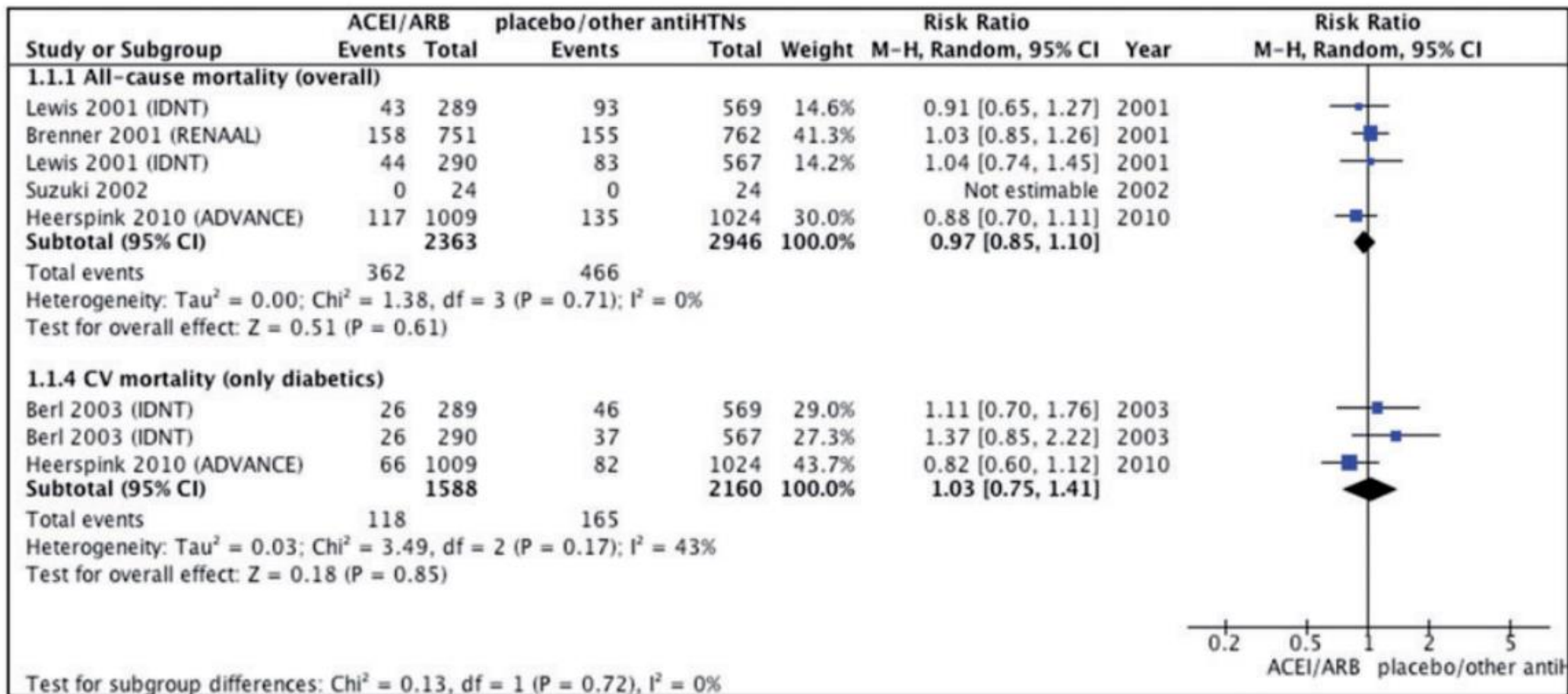
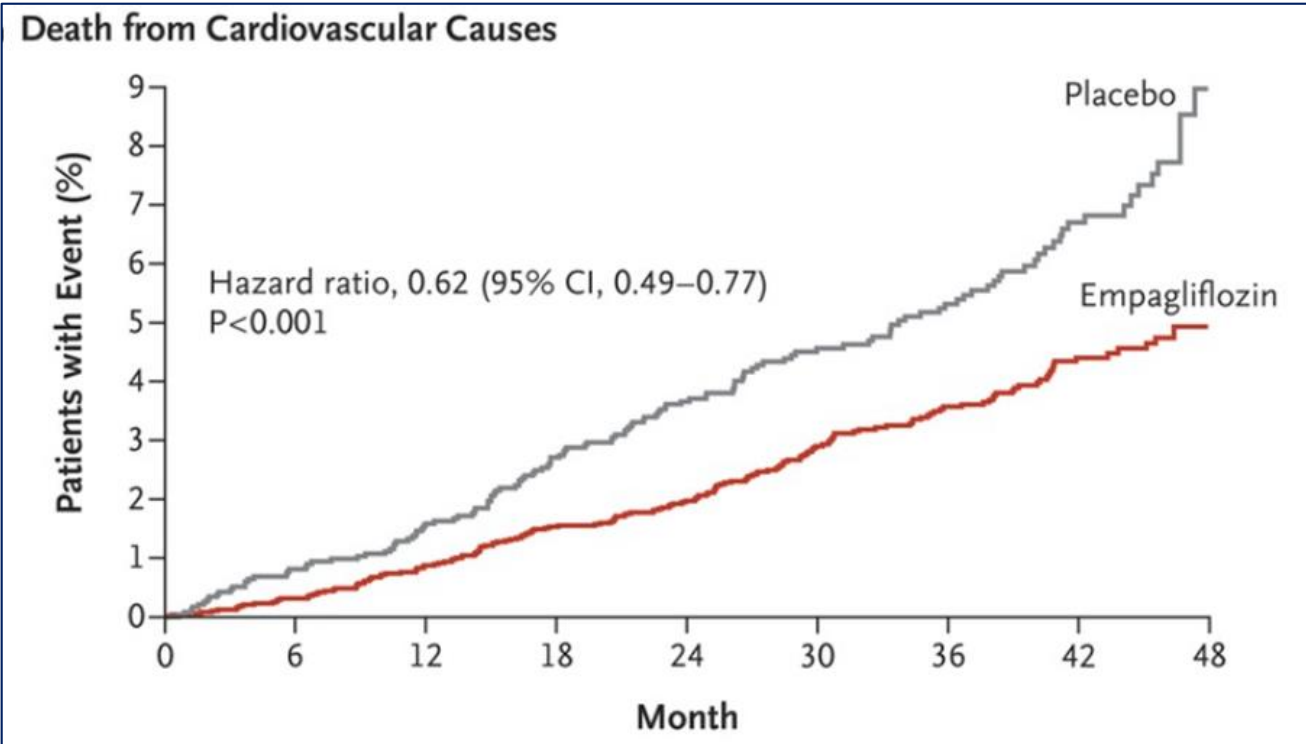


FIGURE 2: All-cause mortality and CV mortality: ACEIs/ARBs versus placebo/other antihypertensive treatment.

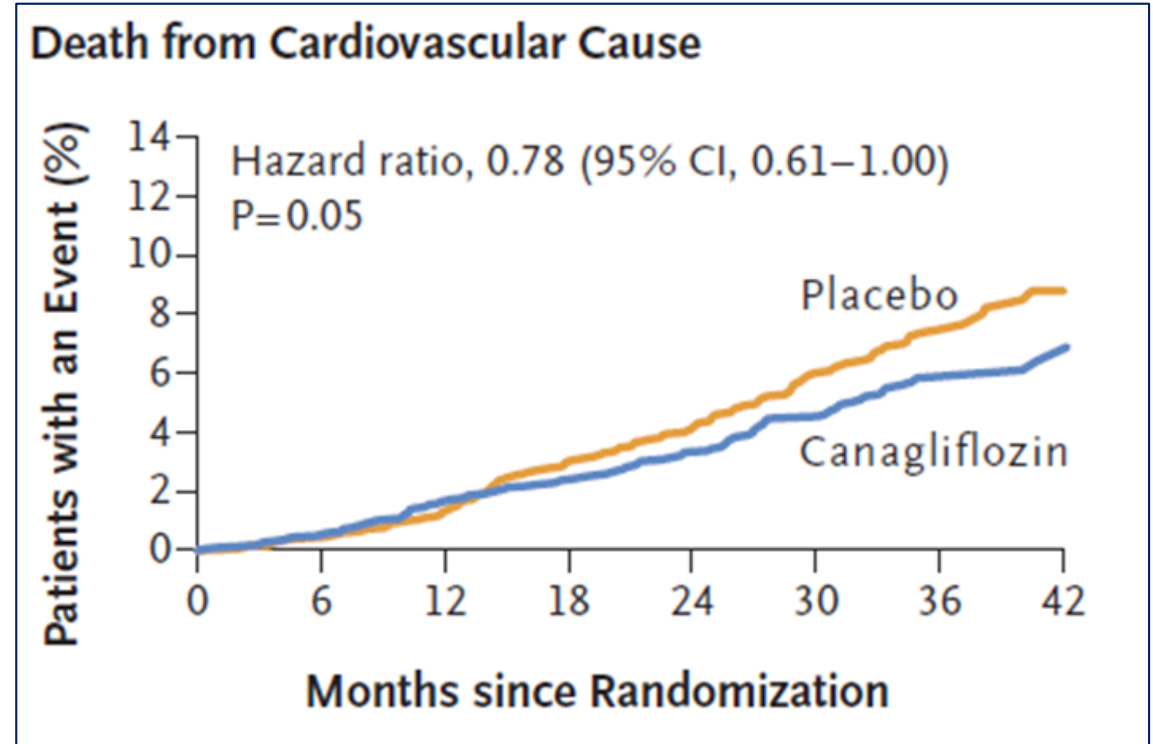
SGLT2i and CV mortality in T2DM

EMPA-REG OUTCOME

CREDESCENCE



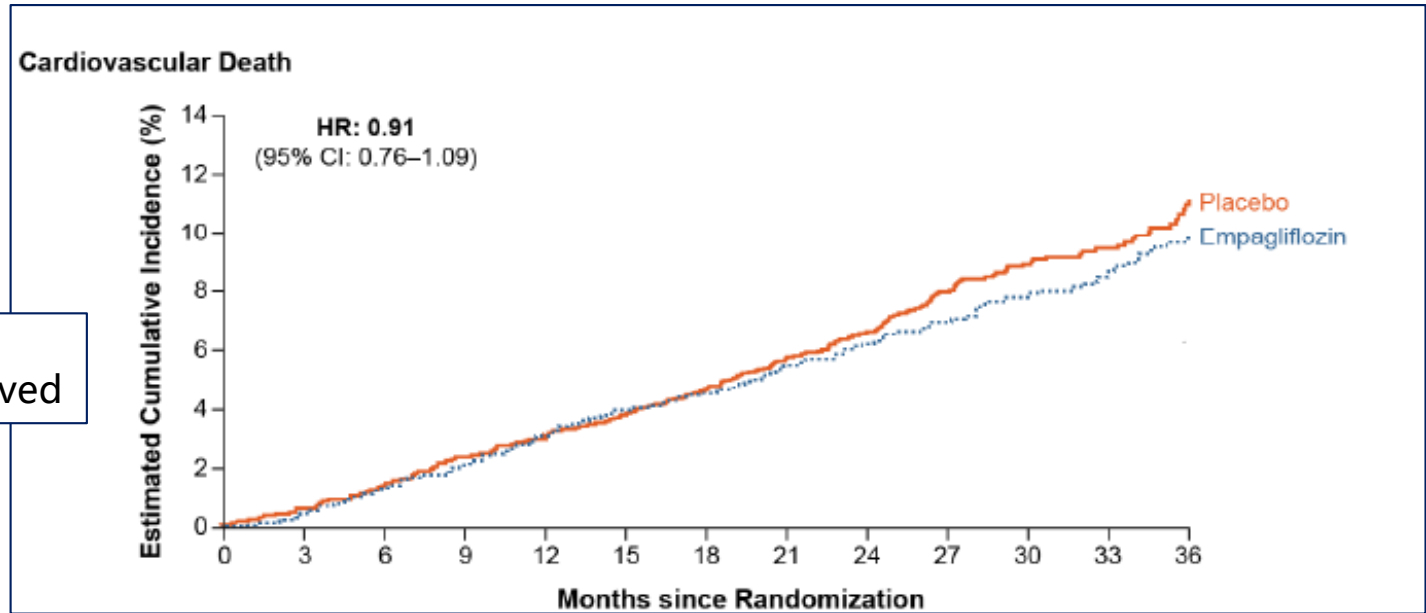
Zinman et al, NEJM 2015



Perkovic et al, NEJM 2019

SGLT2i and CV mortality in HF

HFpEF
- EMPEROR-Preserved



Anker et al, NEJM 2021

B Cardiovascular death

	Number with event/number of patients (%)		HR (95% CI)
	SGLT2 inhibitor	Placebo	
EMPEROR-Reduced	187/1863 (10.0%)	202/1867 (10.8%)	0.92 (0.75-1.12)
DAPA-HF	227/2373 (9.6%)	273/2371 (11.5%)	0.82 (0.69-0.98)
Total			0.86 (0.76-0.98)

Test for overall treatment effect p=0.027
Test for heterogeneity of effect p=0.40

HFrEF
- EMPEROR-Reduced
- DAPA-HF

Zelniker et al, Lancet 2018

Aim

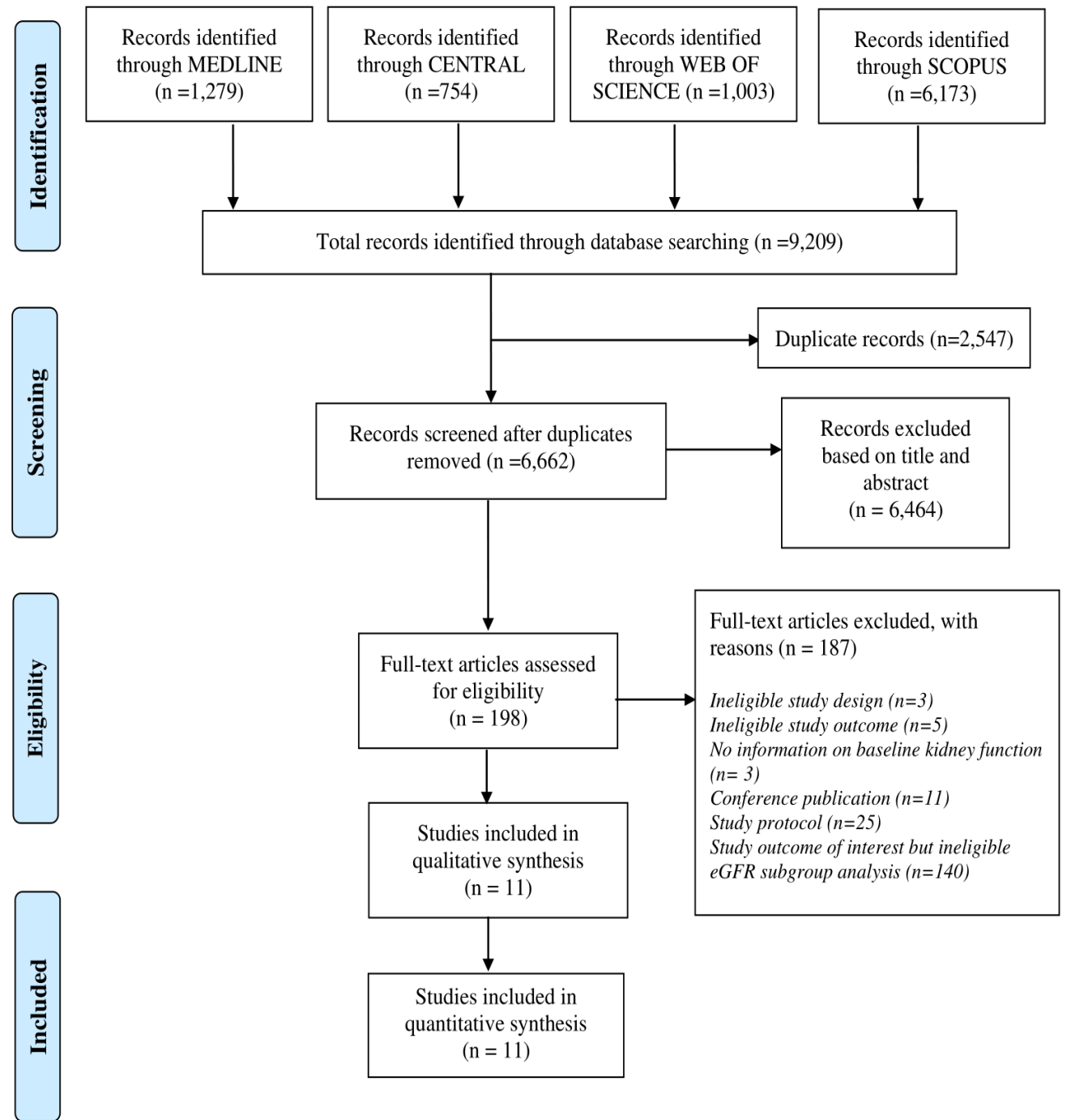
The aim of this meta-analysis was to evaluate the effect of SGLT2 inhibitors on CV mortality in patients with CKD and across subgroups defined by baseline kidney function

Methods

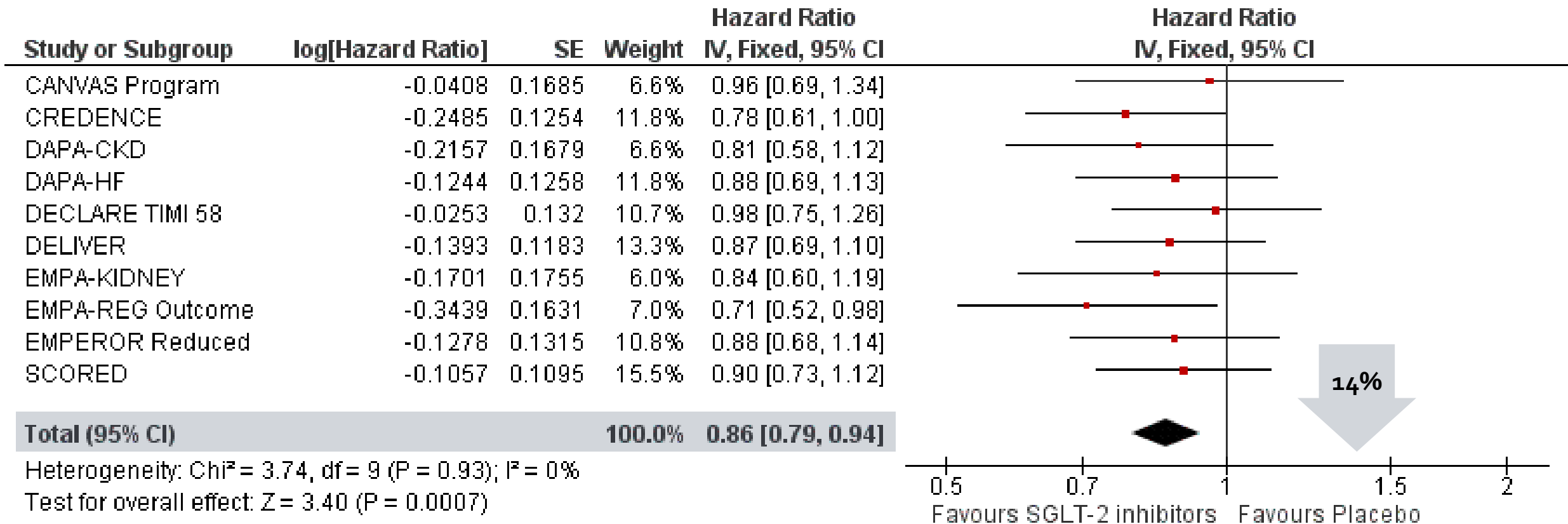
- Systematic review and meta-analysis (PROSPERO ID: CRD42022382863)
- A literature search was conducted in major electronic databases (PubMed/MEDLINE, Scopus, Cochrane Library and Web of Science) up to 15 November 2022.
- We included RCTs assessing the effect of SGLT-2 inhibitors (vs placebo or other active treatment) on the primary outcome in patients with prevalent CKD at baseline or across subgroups stratified by baseline eGFR.
- **Primary outcome:** CV mortality
- **Secondary outcomes:** all-cause mortality and major adverse CV events (MACE).

Study flow-chart

- 11 studies with 83,203 participants



Primary outcome: SGLT2i effects on CV mortality

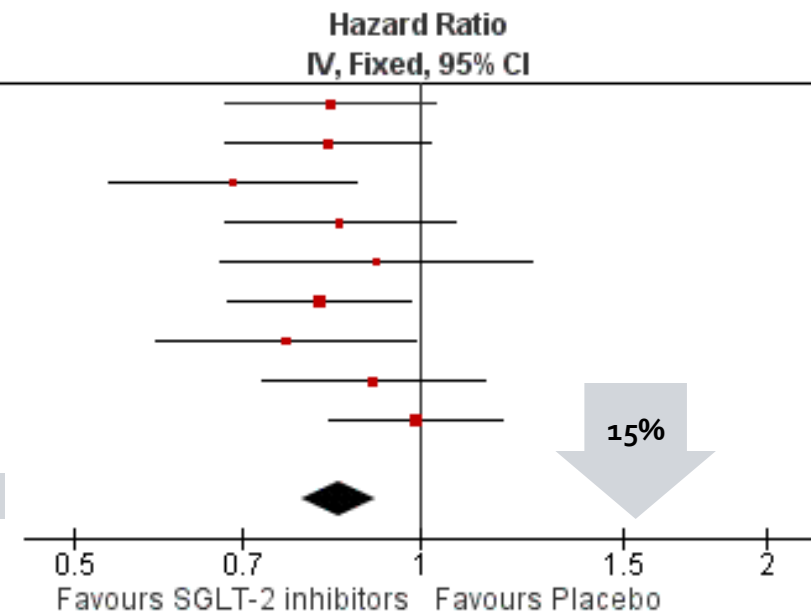


SGLT2i effects on all-cause mortality

Study or Subgroup	log[Hazard Ratio]	SE	Weight	Hazard Ratio IV, Fixed, 95% CI
CANVAS Program	-0.1803	0.1071	12.0%	0.84 [0.68, 1.03]
CREDESCENCE	-0.1863	0.1052	12.5%	0.83 [0.68, 1.02]
DAPA-CKD	-0.3769	0.1271	8.6%	0.69 [0.53, 0.88]
DAPA-HF	-0.1625	0.1174	10.0%	0.85 [0.68, 1.07]
DECLARE TIMI 58	-0.0899	0.1597	5.4%	0.91 [0.67, 1.25]
EMPA-KIDNEY	-0.2029	0.0932	15.9%	0.82 [0.68, 0.98]
EMPA-REG Outcome	-0.2692	0.1322	7.9%	0.76 [0.59, 0.99]
EMPEROR Reduced	-0.0943	0.115	10.4%	0.91 [0.73, 1.14]
SCORED	-0.0101	0.0896	17.2%	0.99 [0.83, 1.18]

Total (95% CI) 100.0% **0.85 [0.79, 0.91]**

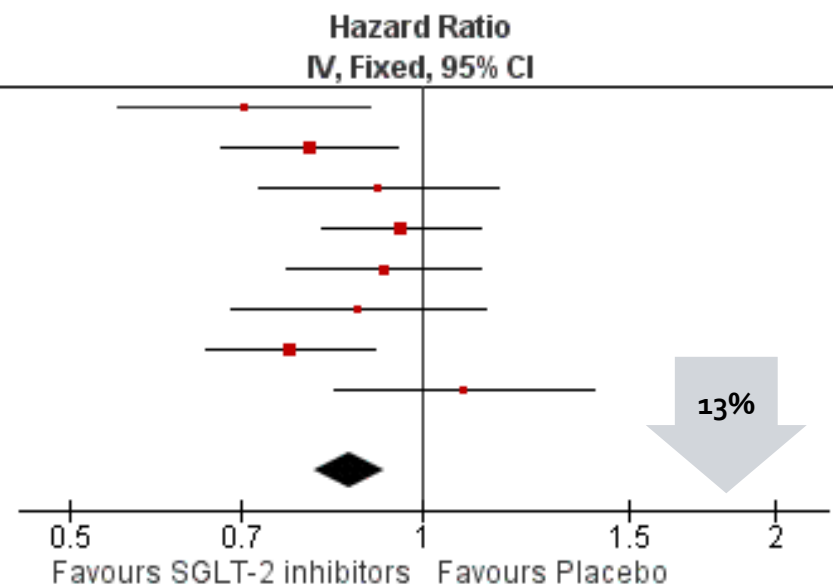
Heterogeneity: $\text{Chi}^2 = 7.21$, $\text{df} = 8$ ($P = 0.51$); $I^2 = 0\%$
 Test for overall effect: $Z = 4.40$ ($P < 0.0001$)



Study or Subgroup	log[Hazard Ratio]	SE	Weight	Hazard Ratio IV, Fixed, 95% CI
CANVAS Program	-0.3524	0.126	8.1%	0.70 [0.55, 0.90]
CREDESCENCE	-0.2231	0.0877	16.6%	0.80 [0.67, 0.95]
DAPA-CKD	-0.0877	0.1205	8.8%	0.92 [0.72, 1.16]
DECLARE TIMI 58	-0.0426	0.0795	20.3%	0.96 [0.82, 1.12]
EMPA-KIDNEY	-0.0769	0.0984	13.2%	0.93 [0.76, 1.12]
EMPA-REG Outcome	-0.1278	0.1276	7.9%	0.88 [0.69, 1.13]
SCORED	-0.2614	0.0852	17.6%	0.77 [0.65, 0.91]
VERTIS CV	0.0807	0.1305	7.5%	1.08 [0.84, 1.40]

Total (95% CI) 100.0% **0.87 [0.81, 0.93]**

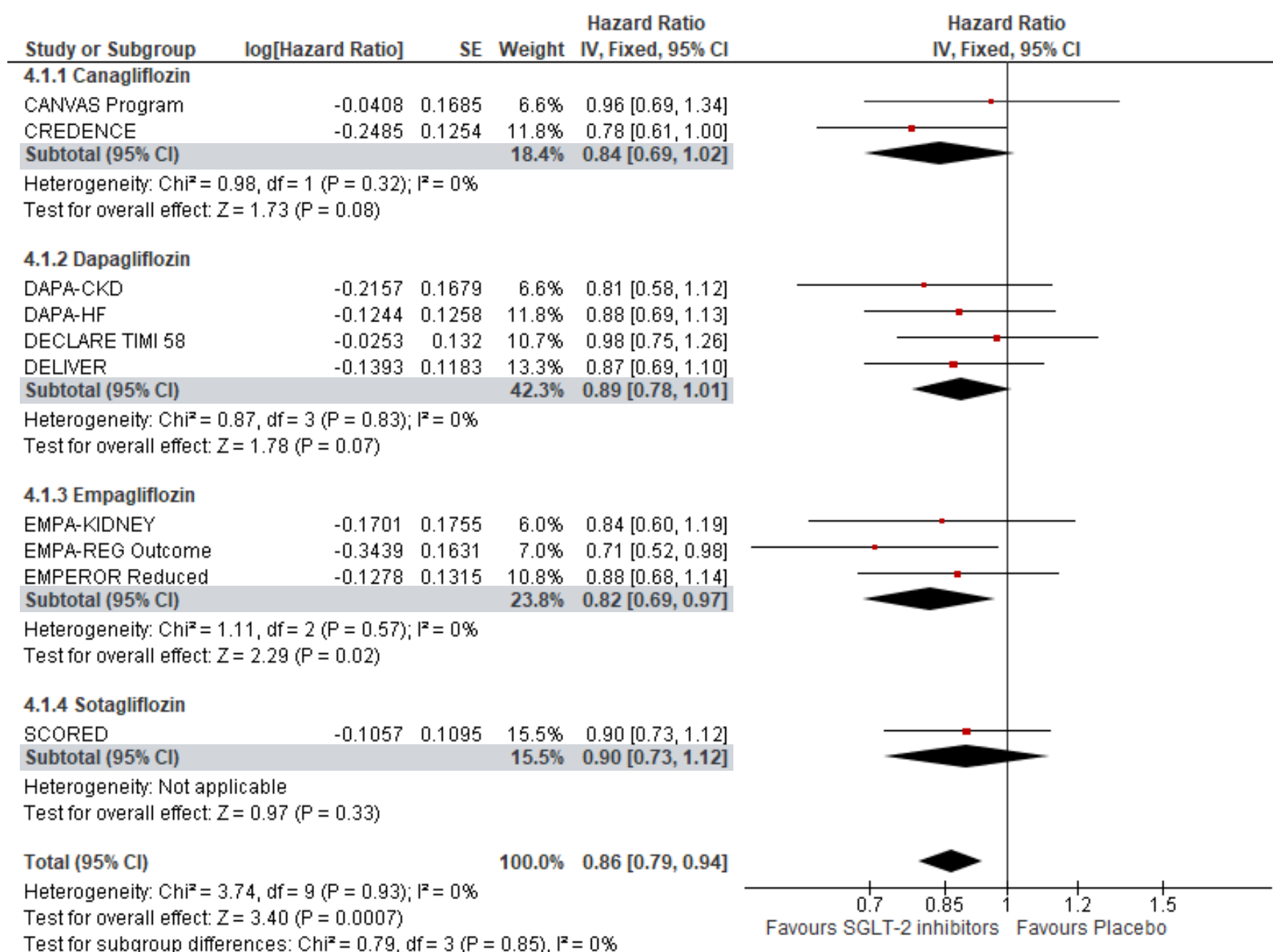
Heterogeneity: $\text{Chi}^2 = 10.74$, $\text{df} = 7$ ($P = 0.15$); $I^2 = 35\%$
 Test for overall effect: $Z = 3.97$ ($P < 0.0001$)



SGLT2i effects on MACE

SGLT2i effects on CV mortality

Subgroup analysis according to SGLT2i type



SGLT2i effects on CV mortality

Subgroup analysis according to eGFR

Study or Subgroup	log[Hazard Ratio]	SE	Weight	Hazard Ratio IV, Random, 95% CI
5.1.1 No CKD/CKD Stage 1/Stage 2				
CANVAS Program	-0.2357	0.2134	4.8%	0.79 [0.52, 1.20]
CREDENCE	-0.1278	0.2216	4.5%	0.88 [0.57, 1.36]
DAPA-HF	-0.2744	0.1292	9.5%	0.76 [0.59, 0.98]
DECLARE TIMI 58	0.131	0.1321	9.2%	1.14 [0.88, 1.48]
DELIVER	-0.0834	0.1398	8.6%	0.92 [0.70, 1.21]
EMPA-REG Outcome	-0.6349	0.1436	8.4%	0.53 [0.40, 0.70]
Subtotal (95% CI)			45.1%	0.82 [0.65, 1.02]

Heterogeneity: $\tau^2 = 0.06$; $\text{Chi}^2 = 16.61$, $\text{df} = 5$ ($P = 0.005$); $I^2 = 70\%$
 Test for overall effect: $Z = 1.75$ ($P = 0.08$)

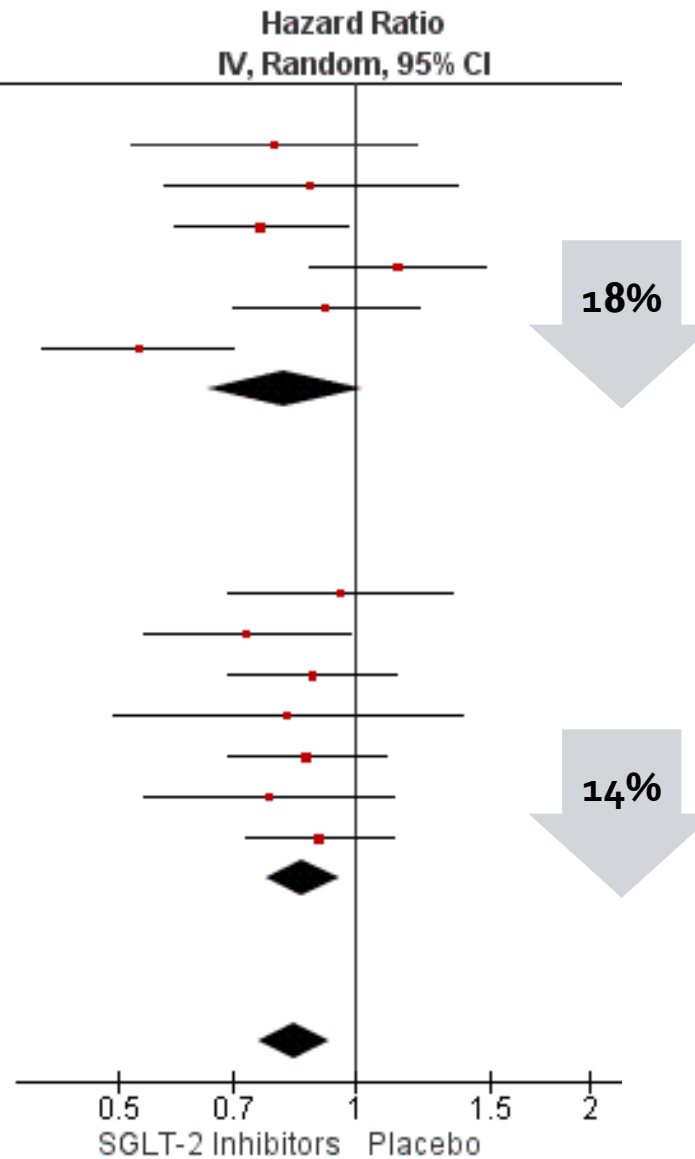
5.1.2 CKD Stages 3a-5

CANVAS Program	-0.0408	0.1685	6.8%	0.96 [0.69, 1.34]
CREDENCE	-0.3147	0.1538	7.7%	0.73 [0.54, 0.99]
DAPA-HF	-0.1233	0.1253	9.8%	0.88 [0.69, 1.13]
DECLARE TIMI 58	-0.1985	0.2627	3.4%	0.82 [0.49, 1.37]
DELIVER	-0.1393	0.1197	10.3%	0.87 [0.69, 1.10]
EMPA-REG Outcome	-0.2485	0.1876	5.8%	0.78 [0.54, 1.13]
SCORED	-0.102	0.1112	11.1%	0.90 [0.73, 1.12]
Subtotal (95% CI)			54.9%	0.86 [0.77, 0.96]

Heterogeneity: $\tau^2 = 0.00$; $\text{Chi}^2 = 2.12$, $\text{df} = 6$ ($P = 0.91$); $I^2 = 0\%$
 Test for overall effect: $Z = 2.76$ ($P = 0.006$)

Total (95% CI) **100.0%** **0.84 [0.75, 0.93]**

Heterogeneity: $\tau^2 = 0.01$; $\text{Chi}^2 = 19.08$, $\text{df} = 12$ ($P = 0.09$); $I^2 = 37\%$
 Test for overall effect: $Z = 3.34$ ($P = 0.0008$)
 Test for subgroup differences: $\text{Chi}^2 = 0.17$, $\text{df} = 1$ ($P = 0.68$), $I^2 = 0\%$

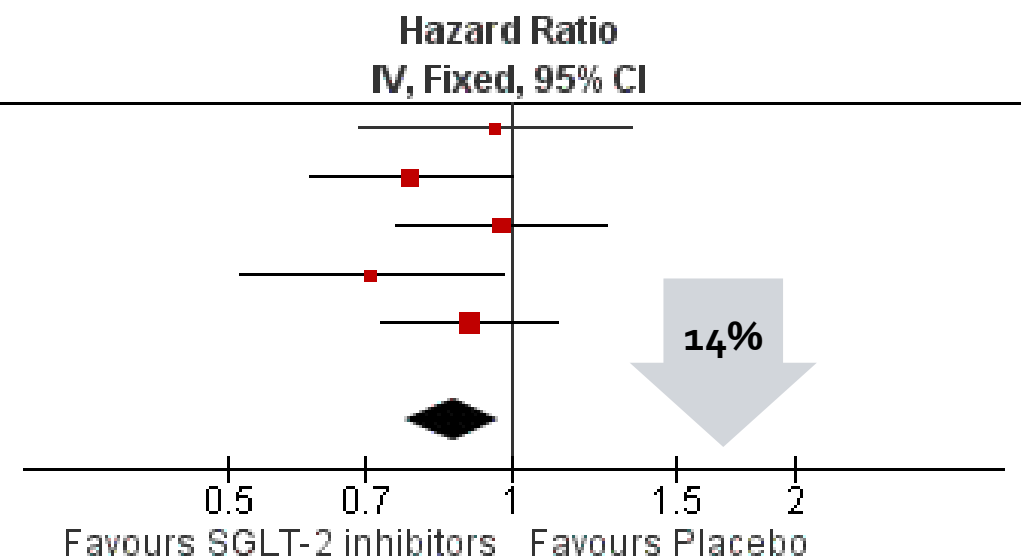


Sensitivity analysis: patients with T2DM

Study or Subgroup	log[Hazard Ratio]	SE	Weight	Hazard Ratio IV, Fixed, 95% CI
CANVAS Program	-0.0408	0.1685	12.7%	0.96 [0.69, 1.34]
CREDESCENCE	-0.2485	0.1254	22.9%	0.78 [0.61, 1.00]
DECLARE TIMI 58	-0.0253	0.132	20.7%	0.98 [0.75, 1.26]
EMPA-REG Outcome	-0.3439	0.1631	13.6%	0.71 [0.52, 0.98]
SCORED	-0.1057	0.1095	30.1%	0.90 [0.73, 1.12]
Total (95% CI)			100.0%	0.86 [0.77, 0.97]

Heterogeneity: $\text{Chi}^2 = 3.50$, $\text{df} = 4$ ($P = 0.48$); $I^2 = 0\%$

Test for overall effect: $Z = 2.43$ ($P = 0.02$)



Conclusions

- Treatment with SGLT-2 inhibitors led to a significant reduction in the risk for CV and all-cause mortality in CKD patients
- This beneficial effects remains unaltered also in high-risk groups, including patients with T2DM and lower eGFR.
- These findings support the use of these agents also for protection against cardiovascular events and death in CKD.

THANK YOU



Α΄ ΝΕΦΡΟΛΟΓΙΚΗ ΚΛΙΝΙΚΗ Α.Π.Θ
Γ.Ν.Θ. ΙΠΠΟΚΡΑΤΕΙΟ