HELLENIC SOCIETY OF NEPHROLOGY
ΕΛΛΗΝΙΚΗ ΝΕΦΡΟΛΟΓΙΚΗ ΕΤΑΙΡΕΙΑ
25th Hellenic Congress of NEFROLOGY
JUNE, 19-21 2024
MEGARON ATHENS CONCERT HALL
INTERNATIONAL CONFERENCE CENTRE - ATHENS, GREECE

SGLT-2 inhibitors and protection across different CKD aetiologies and stages

Richard Haynes

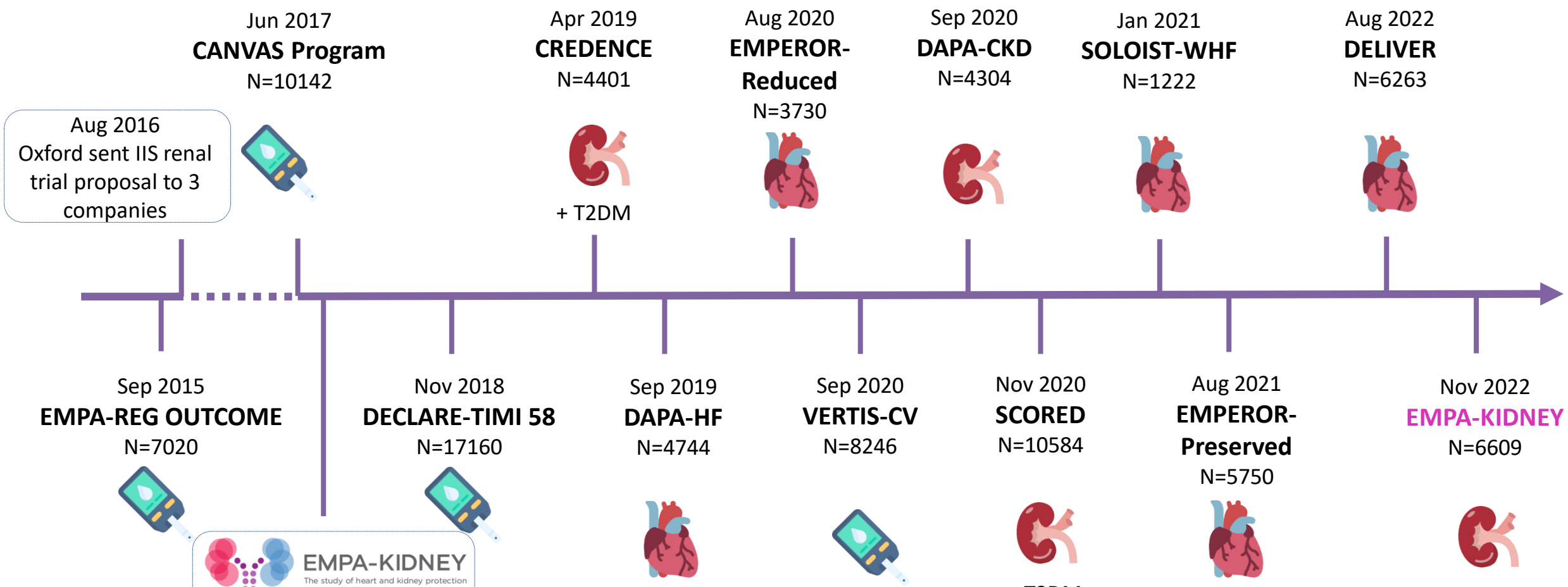
Professor of Renal Medicine & Clinical Trials, University of Oxford, UK

Disclosures

- Grant to run the EMPA-KIDNEY trial to the University of Oxford

- Other financial support from:
  - Eli Lilly & the UK Medical Research Council (MRC)
  - Follow a *long-standing departmental policy to decline honoraria*

SGLT2 inhibitor trials



IIS=investigator-initiated study
Dates = date of primary NEJM publication

EMPA-KIDNEY

EMPA-KIDNEY's double-blind placebo-controlled design

Population: Designed to assess the effects of SGLT2 inhibition in a broad range of ~6000 patients with CKD at risk of progression, incl. ≥1/3rd with diabetes & ≥ 1/3rd without

EMPA-KIDNEY

N Engl J Med 2023; 388:117-127

EMPA-KIDNEY's double-blind placebo-controlled design

Population: Designed to assess the effects of SGLT2 inhibition in a broad range of ~6000 patients with CKD at risk of progression, incl. ≥1/3rd with diabetes & ≥ 1/3rd without

Adults with CKD-EPI estimated GFR (eGFR):

20 to <45 mL/min/1.73 m^2; or

45 to <90 mL/min/1.73 m^2 with a urinary ACR of ≥200 mg/g (≥22.6 mg/mmol)

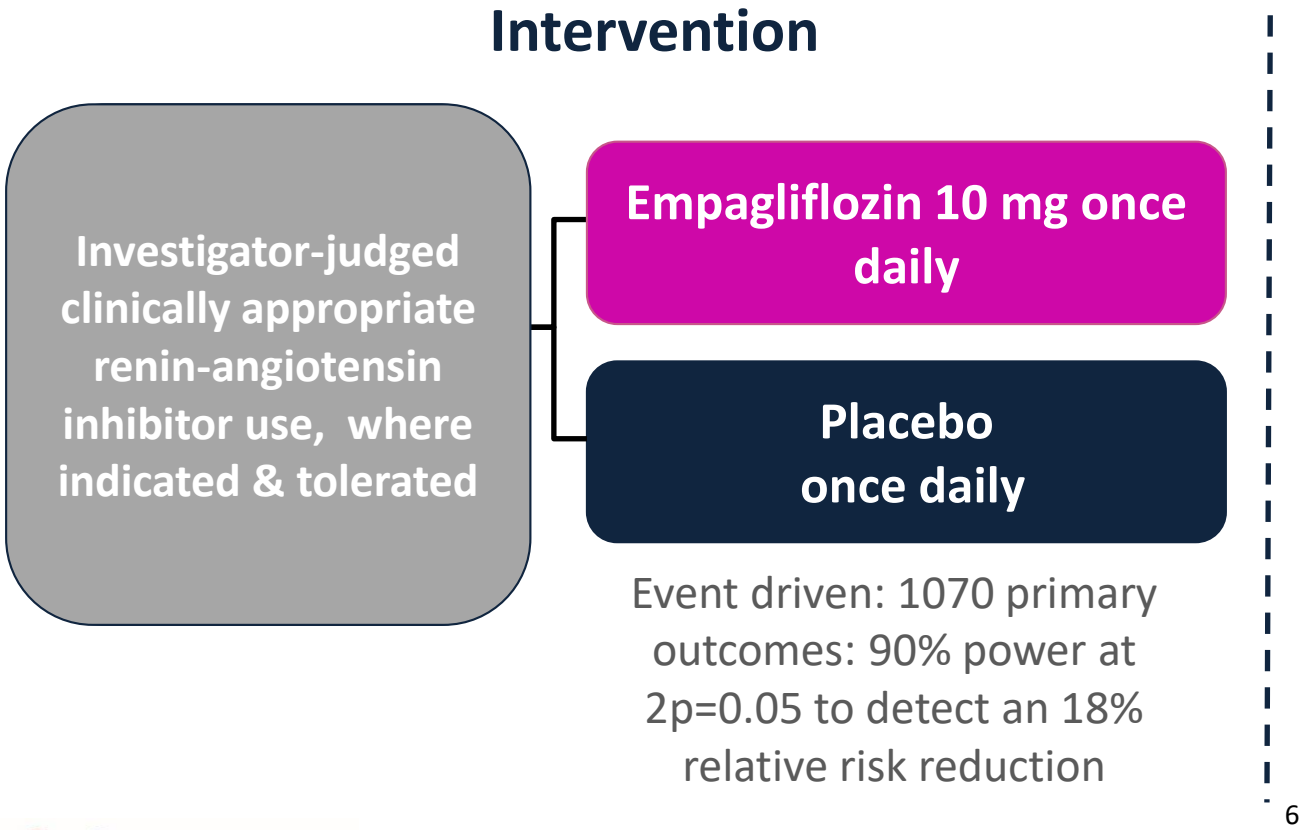
Excluded patients with polycystic kidney disease or transplant

EMPA-KIDNEY

N Engl J Med 2023; 388:117-127

EMPA-KIDNEY's double-blind placebo-controlled design

Population: Designed to assess the effects of SGLT2 inhibition in a broad range of ~6000 patients with CKD at risk of progression, incl. ≥1/3rd with diabetes & ≥ 1/3rd without



EMPA-KIDNEY

N Engl J Med 2023; 388:117-127

EMPA-KIDNEY's double-blind placebo-controlled design

Population: Designed to assess the effects of SGLT2 inhibition in a broad range of ~6000 patients with CKD at risk of progression, incl. ≥1/3rd with diabetes & ≥ 1/3rd without

Intervention

Investigator-judged clinically appropriate renin-angiotensin inhibitor use, where indicated & tolerated

- **Empagliflozin 10 mg once daily**
- **Placebo once daily**

Event driven: 1070 primary outcomes: 90% power at 2p=0.05 to detect an 18% relative risk reduction

Primary composite outcome

CV death OR **Kidney disease progression**

End-stage kidney disease (ESKD): Dialysis/kidney transplant
Renal death

eGFR change
≥40% eGFR decline, or to <10 mL/min/1.73m²

EMPA-KIDNEY

N Engl J Med 2023; 388:117-127

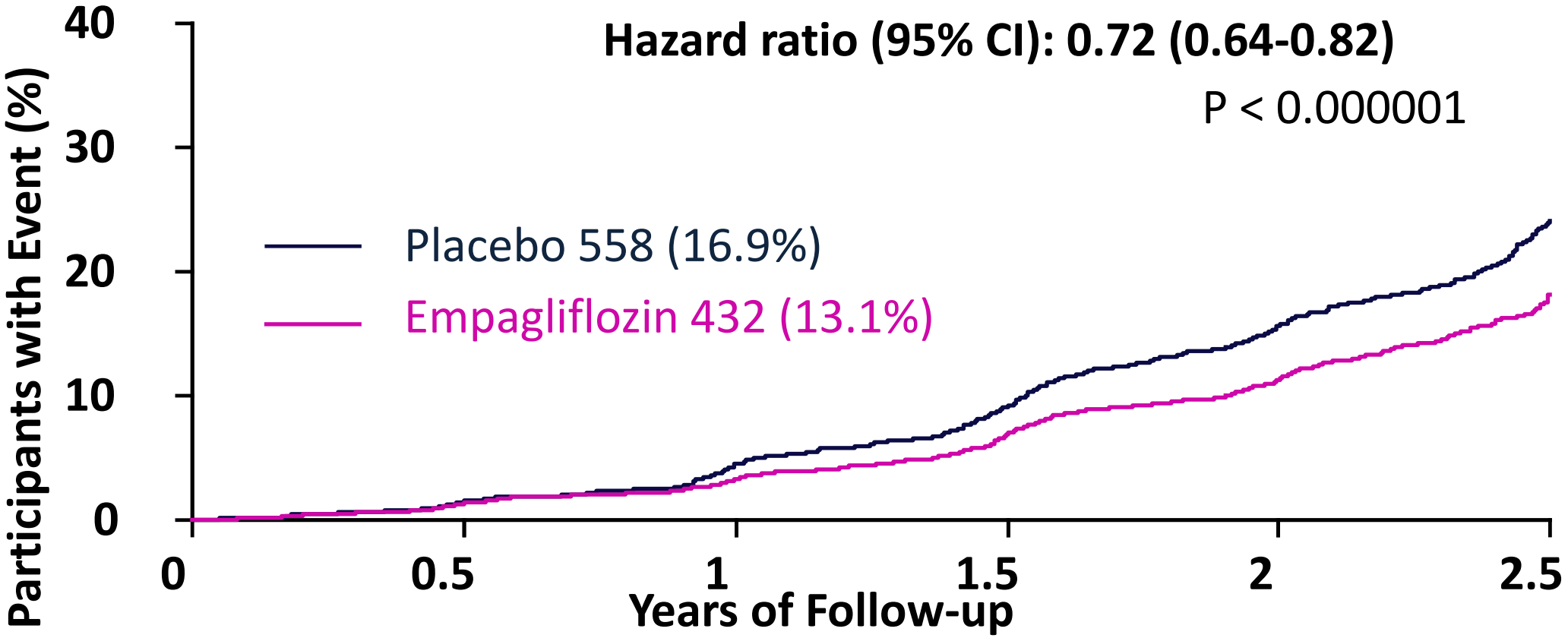
Baseline characteristics

	Empagliflozin (n=3304)	Placebo (n=3305)
Mean age at randomization (years)	63.9 ±13.9	63.8 ±13.9
Female	33%	33%
No prior diabetes	54%	54%
Mean estimated GFR (mL/min/1.73m^2)	37.4 ± 14.5	37.3 ± 14.4
<30	34%	35%
Median urinary ACR (mg/g)	331 (46-1061)	327 (54-1074)
<300 (A1-A2)	48%	48%
Non-diabetic cause of CKD	69%	69%

EMPA-KIDNEY

N Engl J Med 2023; 388:117-127

Primary composite outcome

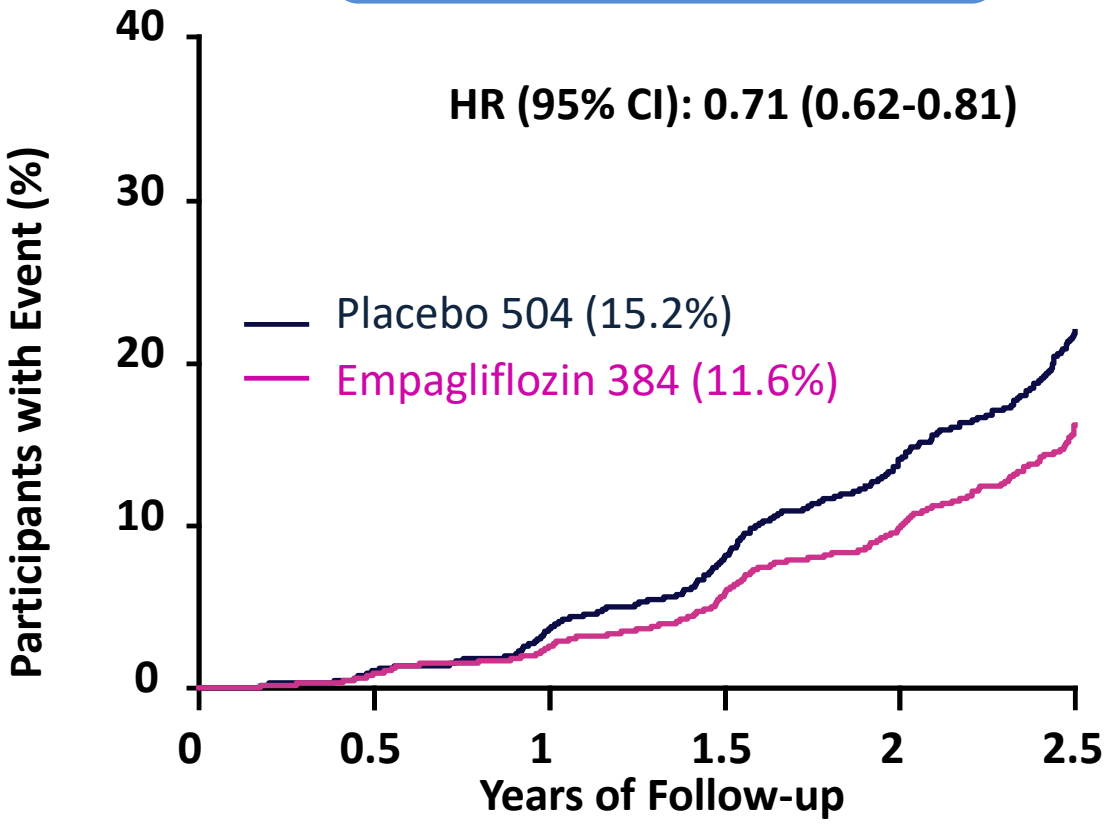


EMPA-KIDNEY

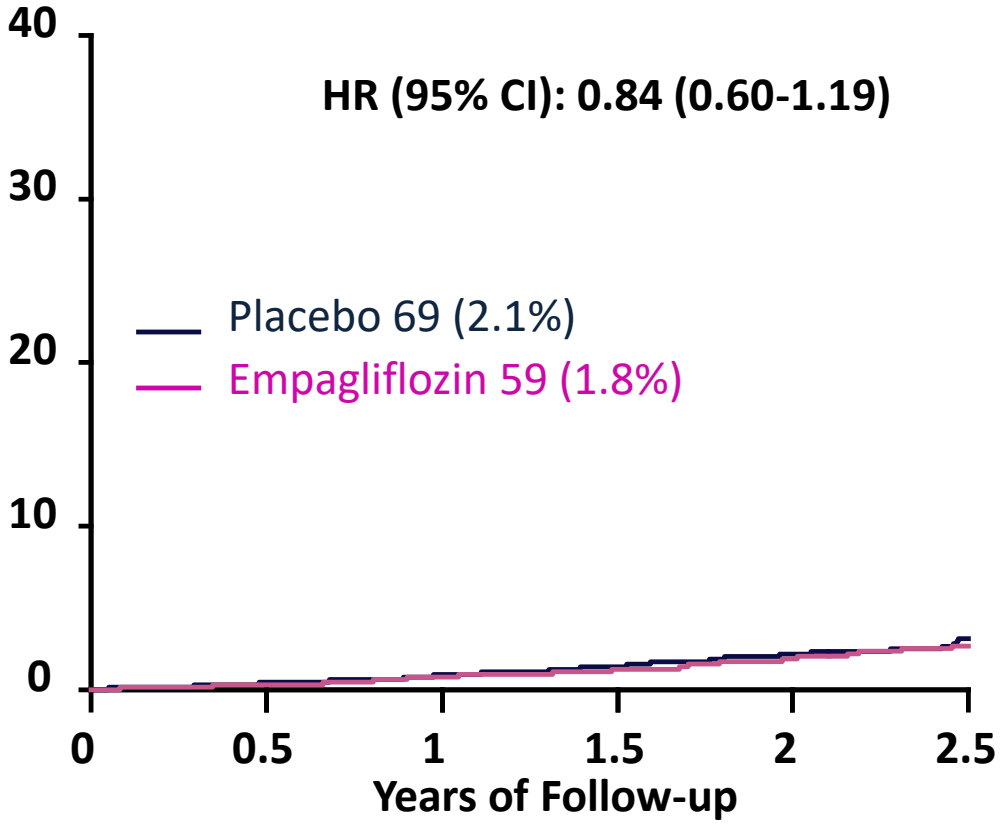
N Engl J Med 2023; 388:117-127

Components of the primary outcome

Kidney disease progression



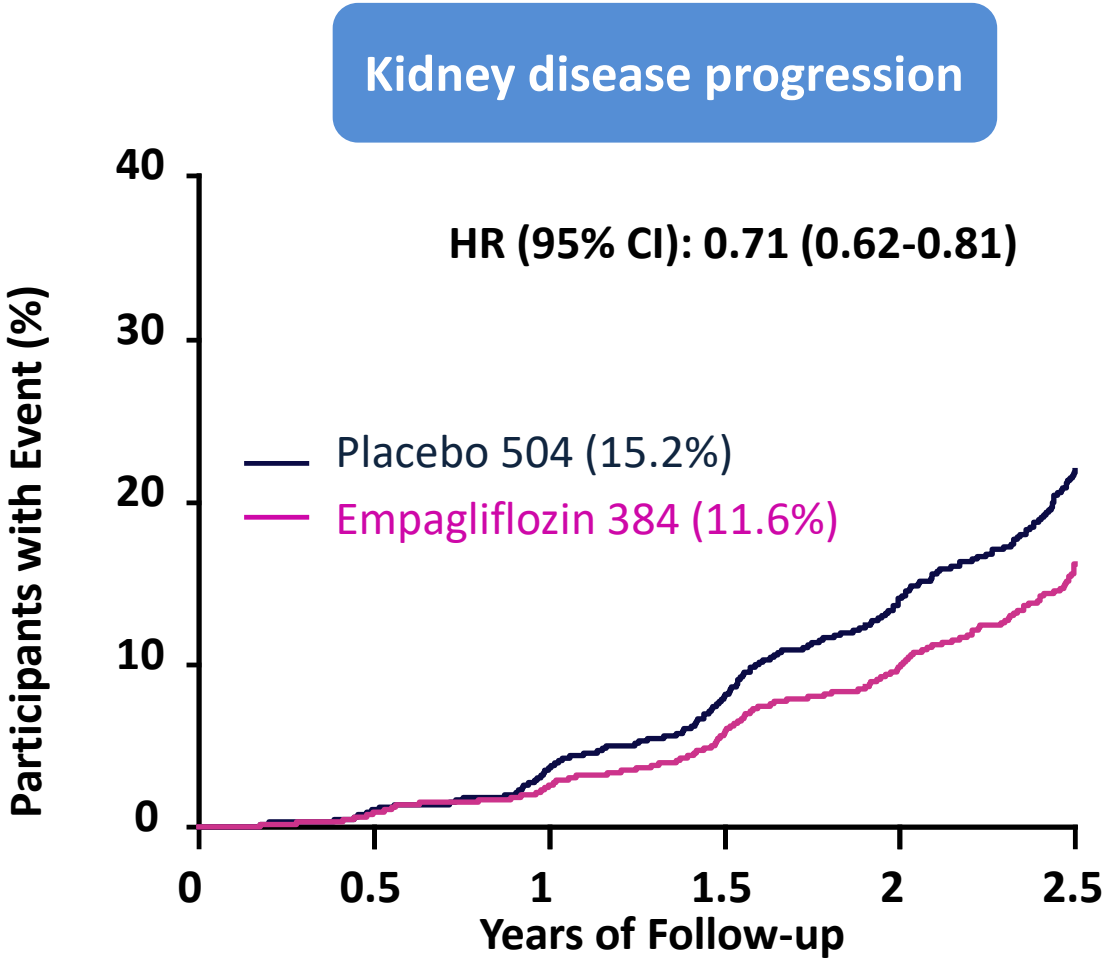
CV death

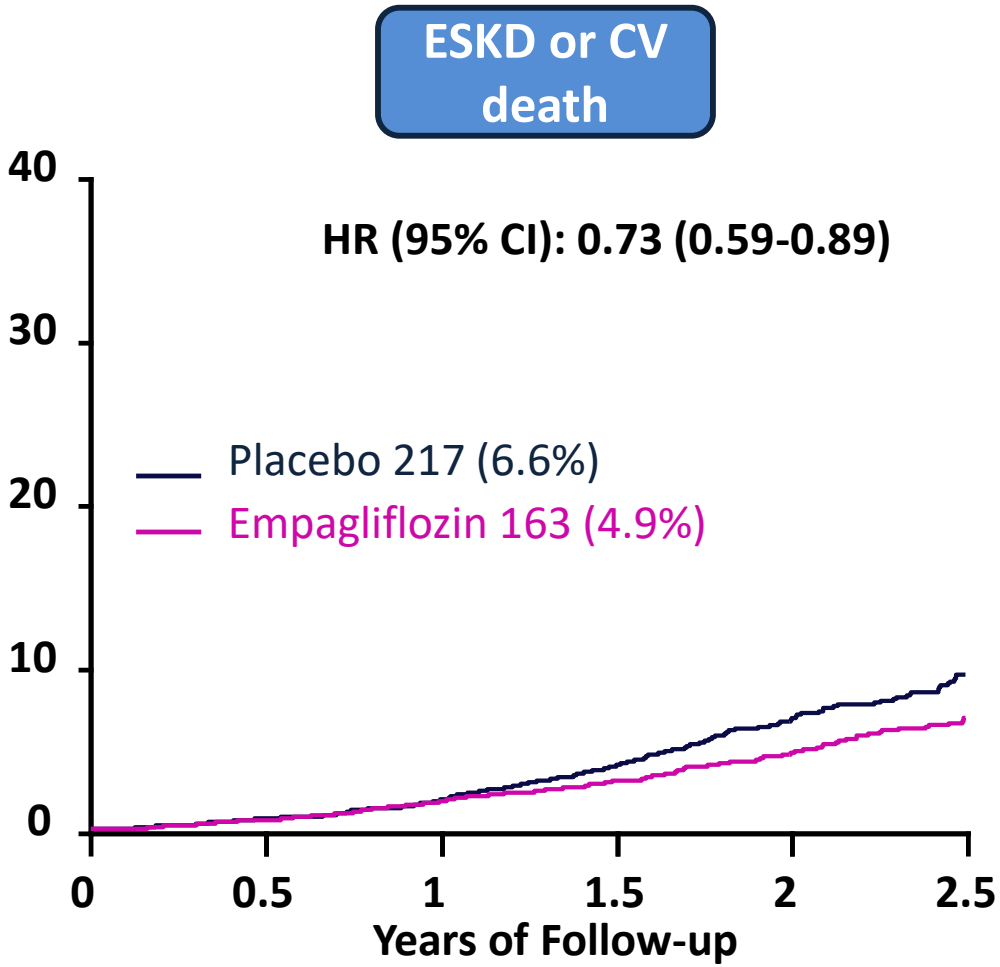


EMPA-KIDNEY

N Engl J Med 2023; 388:117-127

Components of the primary outcome



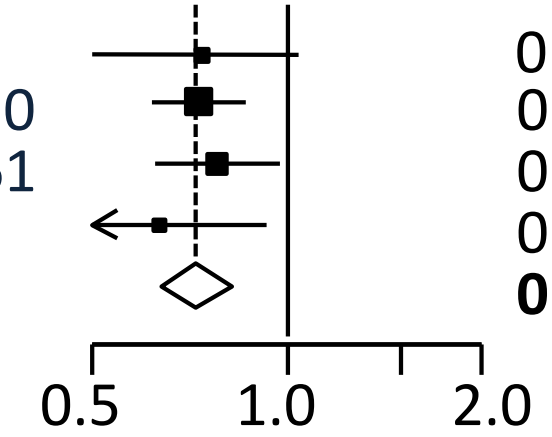


EMPA-KIDNEY

N Engl J Med 2023; 388:117-127

Primary outcome by kidney function (post-hoc)

eGFR mL/min/1.73m²	No. of events / participants: Empagliflozin	Placebo	Hazard ratio (95% CI)
< 20	47/123	64/131	0.73 (0.50–1.06)
≥ 20 < 30	200/1008	253/1020	0.74 (0.61–0.89)
≥ 30 <45	140/1467	175/1461	0.78 (0.62–0.97)
≥ 45	45/706	66/693	0.64 (0.44–0.93)
All participants			**0.72 (0.64–0.82)**

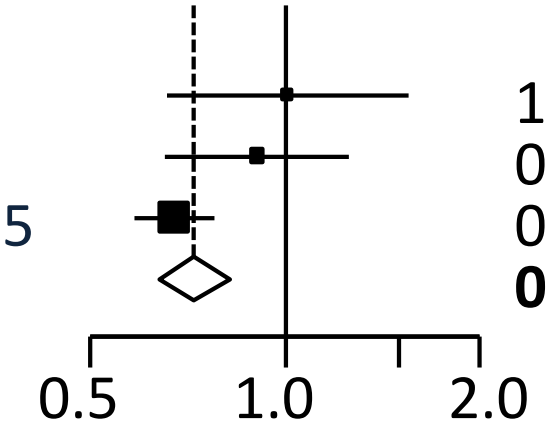


Trend P value= 0.81

EMPA-KIDNEY

Primary outcome by albuminuria

uACR mg/g		No. of events / participants: Empagliflozin	Placebo	Hazard Ratio (95% CI)
<30	(A1)	42/665	42/663	1.01 (0.66–1.55)
≥30 ≤300	(A2)	67/927	78/937	0.91 (0.65–1.26)
>300	(A3)	323/1712	438/1705	0.67 (0.58–0.78)
All participants				**0.72 (0.64–0.82)**



Trend P value= 0.02

EMPA-KIDNEY

N Engl J Med 2023; 388:117-127

eGFR slope analyses

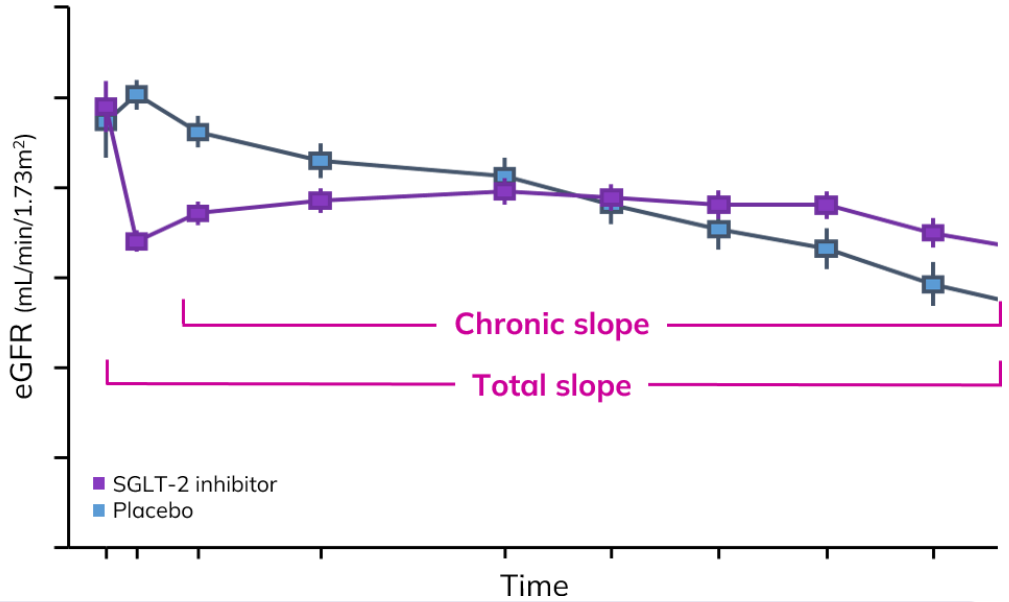
EMPA-KIDNEY tertiary efficacy outcomes:

Total slope

= baseline to last scheduled visit

Chronic slope

= 2 months to last scheduled visit



- Greater discrimination vs dichotomous outcomes
- Accepted surrogate outcome for CKD progression
- eGFR slope reduction by **0.5 to 1.0 mL/min/1.73 m²/year** considered clinically meaningful

EMPA-KIDNEY

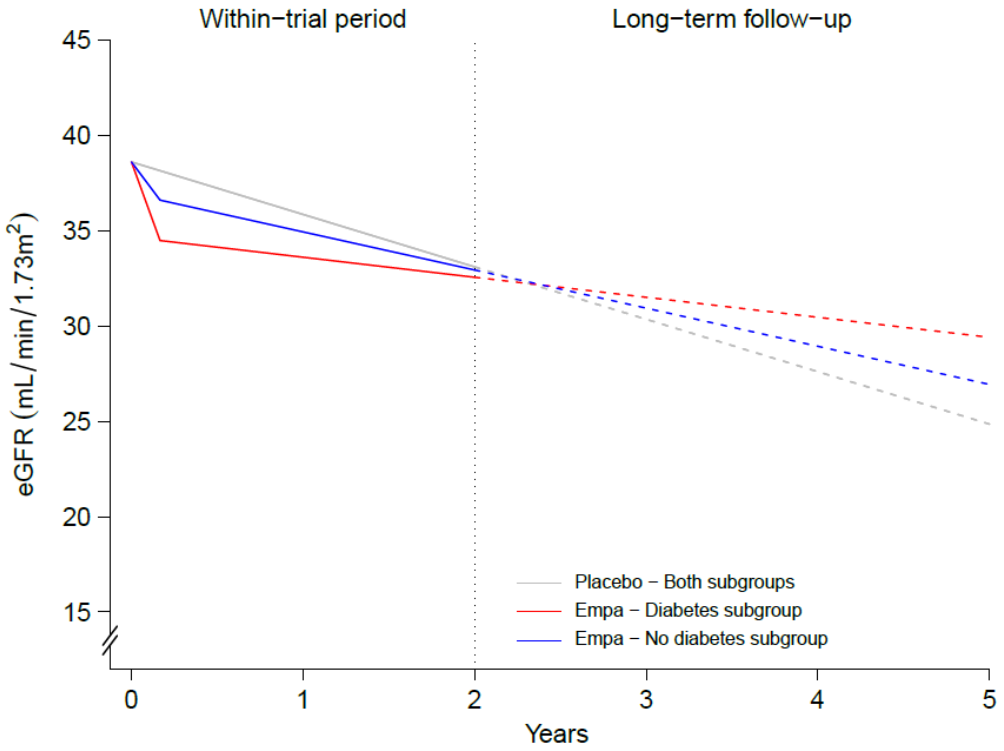
Inker LA et al. J Am Soc Nephrol. 2019 Sep;30(9):1735-1745;
Levey AS et al. Am J Kidney Dis. 2020 Jan;75(1):84-104.

Chronic slope *versus* total slope

- Meta-analysis of 66 trials suggested <u>total</u> slope correlates better with kidney failure outcome

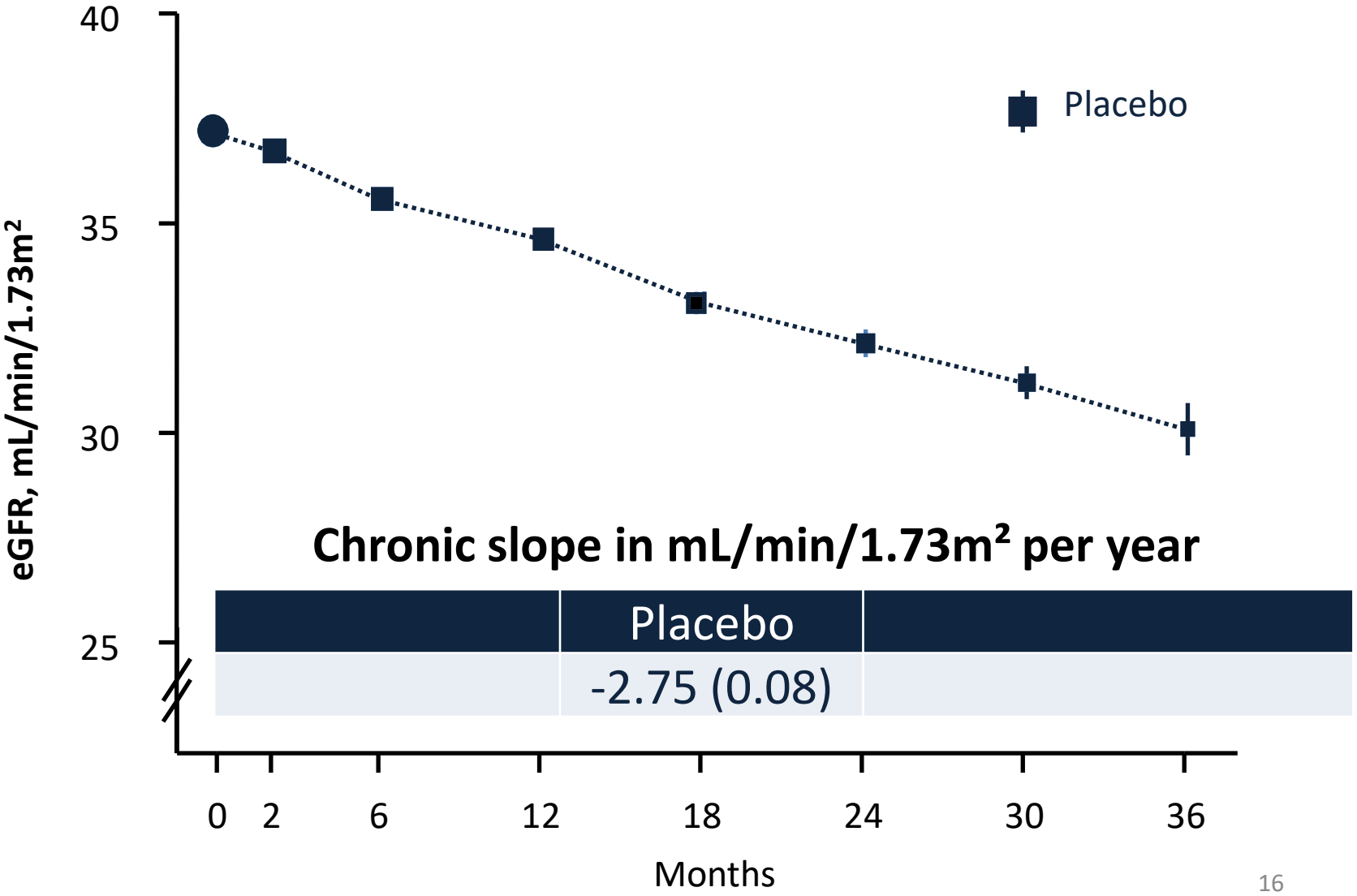
- However, that may be an artefact of restricting follow-up to 2-3 years

- <u>Chronic</u> slope likely to predict long-term benefit better



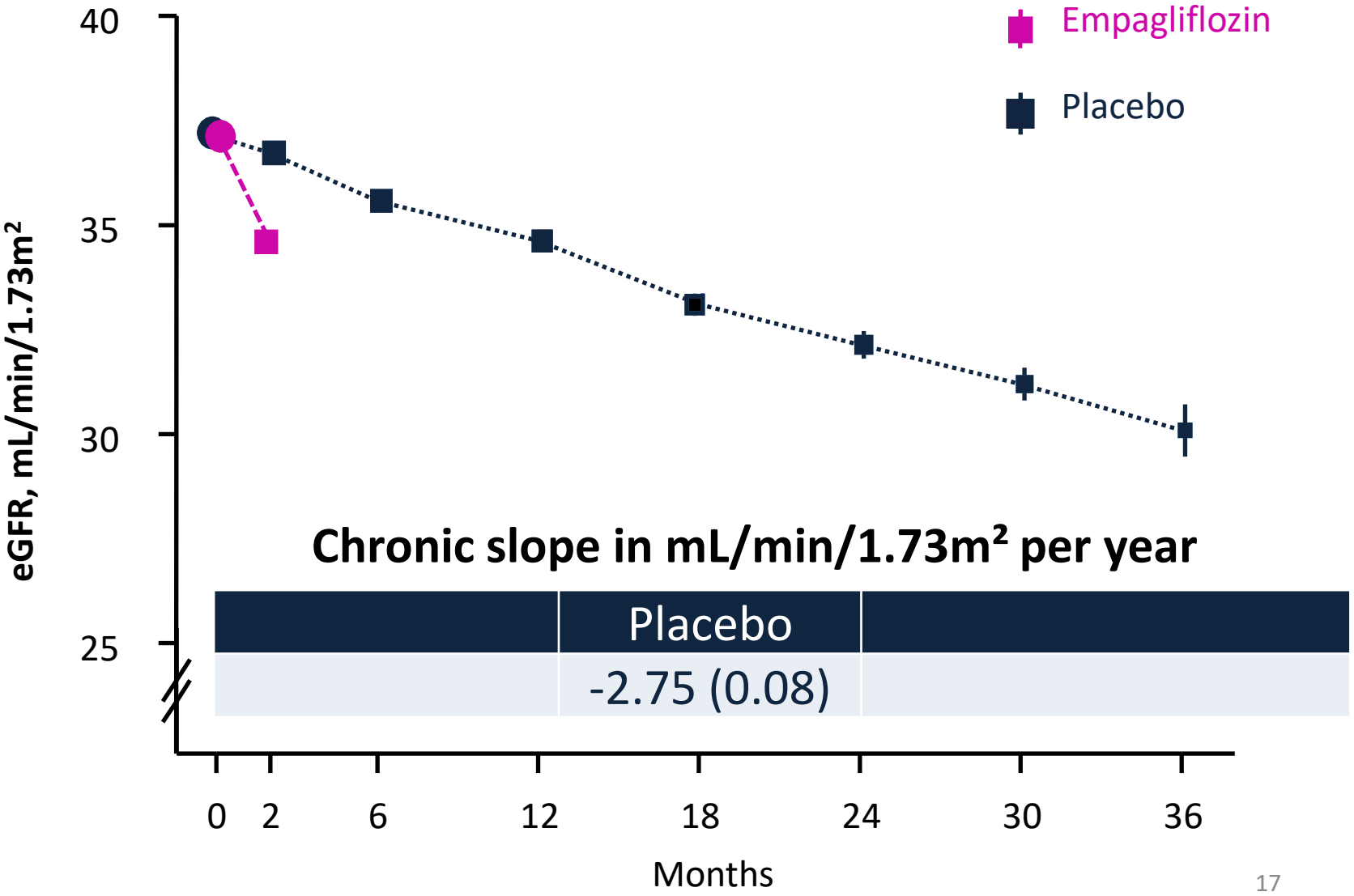
EMPA-KIDNEY

Annual rate of change of eGFR



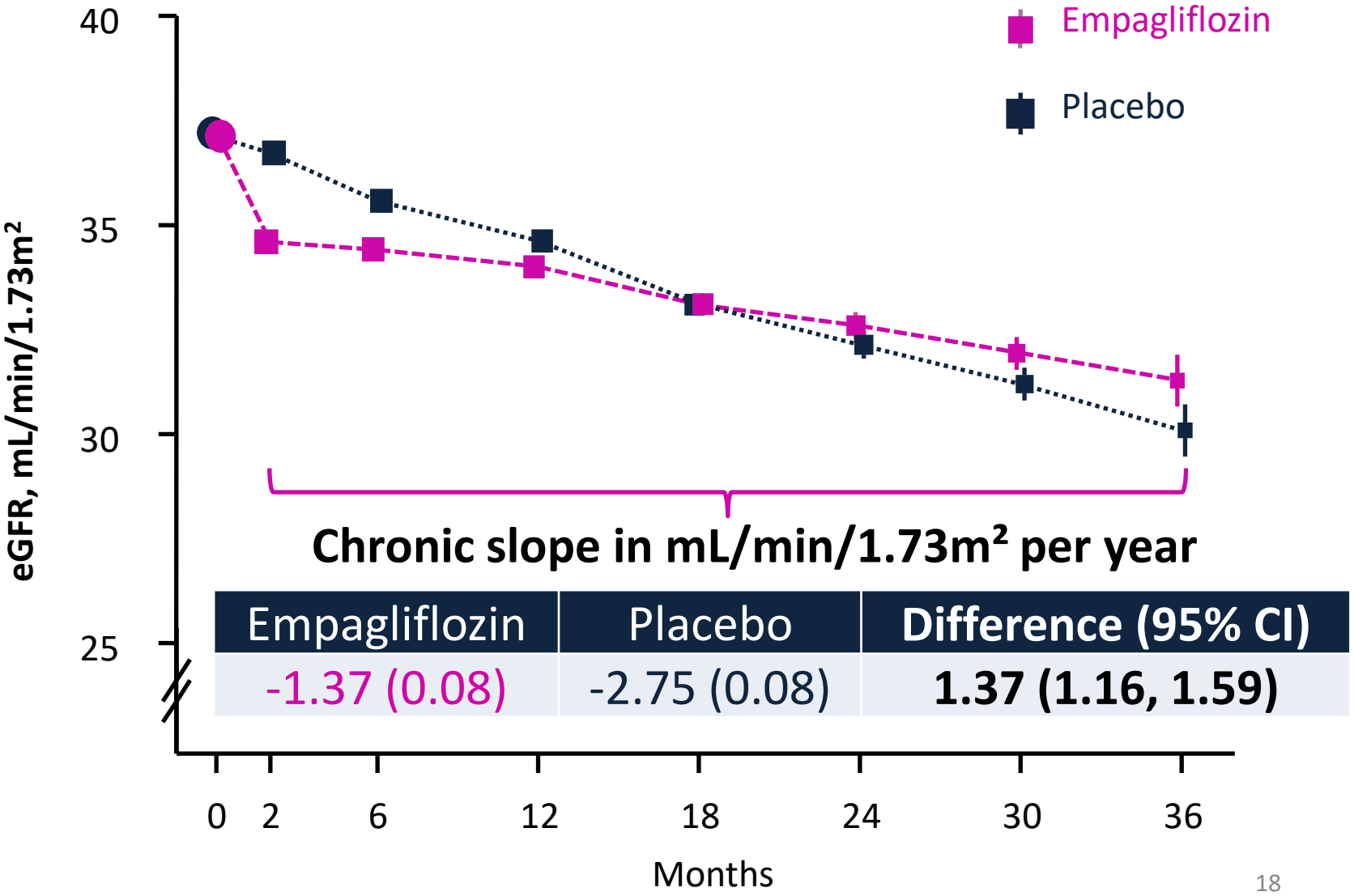
EMPA-KIDNEY

Annual rate of change of eGFR



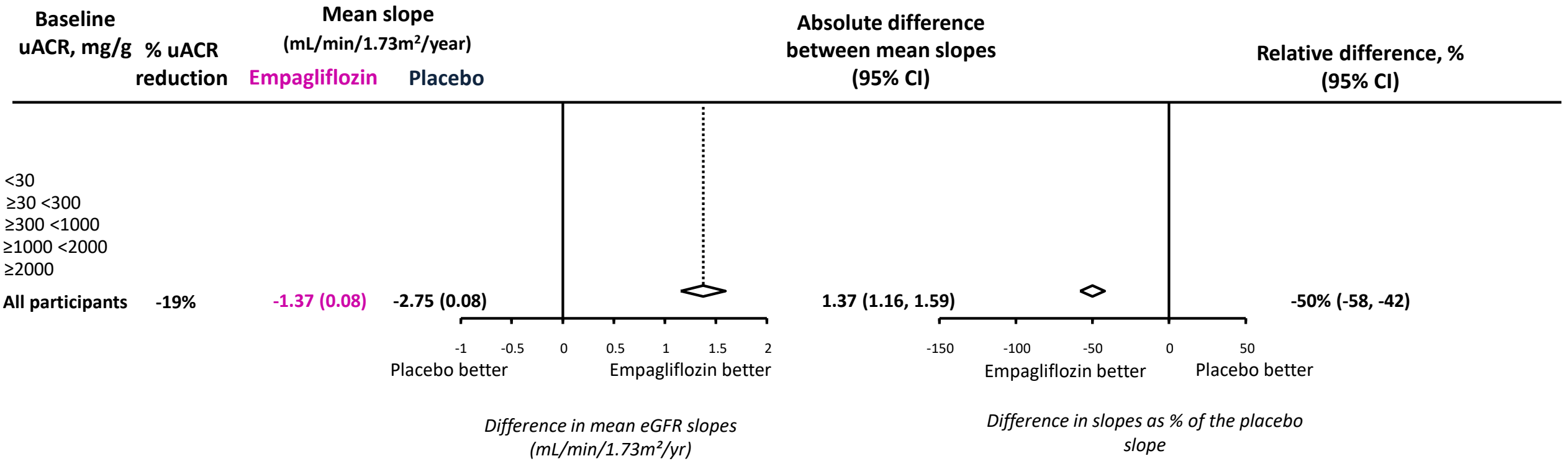
EMPA-KIDNEY

Annual rate of change of eGFR



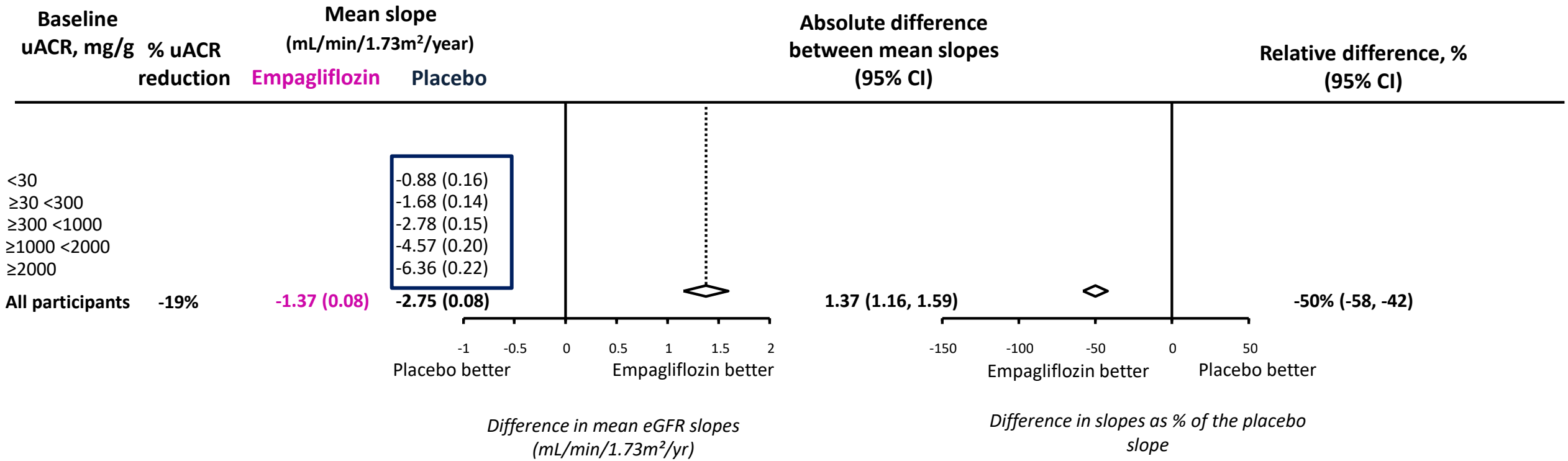
EMPA-KIDNEY

Chronic eGFR slopes by albuminuria



EMPA-KIDNEY

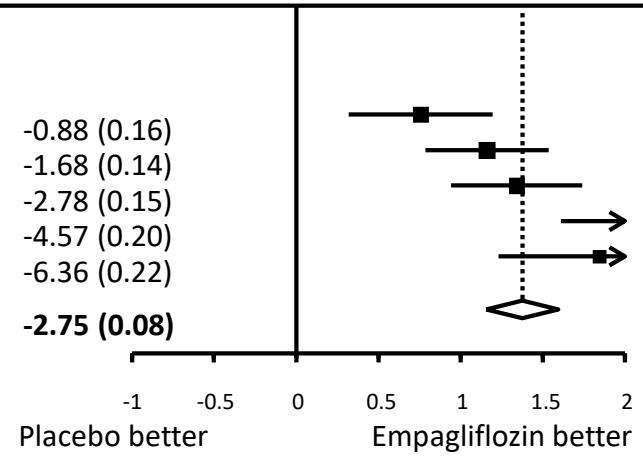
Chronic eGFR slopes by albuminuria



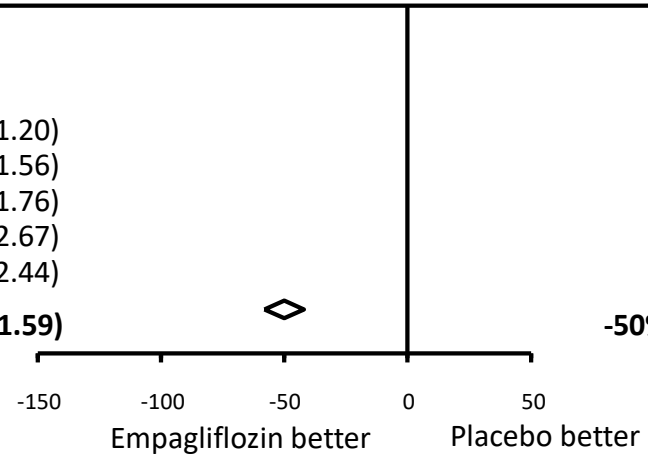
EMPA-KIDNEY

Chronic eGFR slopes by albuminuria

Baseline uACR, mg/g	% uACR reduction	Mean slope (mL/min/1.73m²/year) Empagliflozin	Mean slope (mL/min/1.73m²/year) Placebo	Absolute difference between mean slopes (95% CI)	Relative difference, % (95% CI)
<30		-0.11 (0.16)	-0.88 (0.16)	0.76 (0.32, 1.20)	
≥30 <300		-0.49 (0.14)	-1.68 (0.14)	1.19 (0.81, 1.56)	
≥300 <1000		-1.42 (0.14)	-2.78 (0.15)	1.35 (0.95, 1.76)	
≥1000 <2000		-2.43 (0.19)	-4.57 (0.20)	2.14 (1.61, 2.67)	
≥2000		-4.54 (0.23)	-6.36 (0.22)	1.82 (1.20, 2.44)	
All participants	**-19%**	**-1.37 (0.08)**	**-2.75 (0.08)**	**1.37 (1.16, 1.59)**	**-50% (-58, -42)**



Difference in mean eGFR slopes (mL/min/1.73m²/yr)

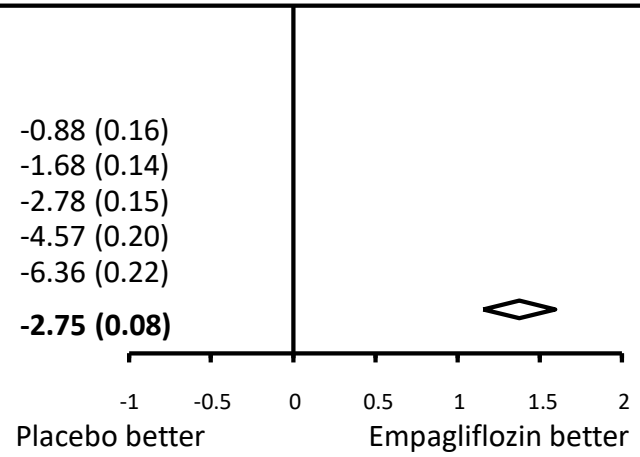


Difference in slopes as % of the placebo slope

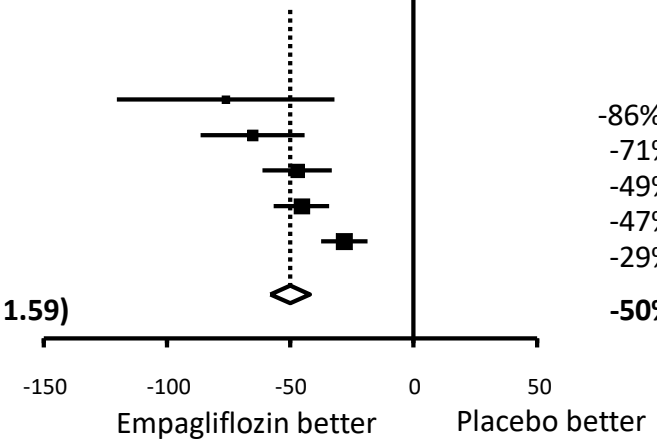
EMPA-KIDNEY

Chronic eGFR slopes by albuminuria

Baseline uACR, mg/g	% uACR reduction	Mean slope (mL/min/1.73m²/year) Empagliflozin	Mean slope (mL/min/1.73m²/year) Placebo	Absolute difference between mean slopes (95% CI)	Relative difference, % (95% CI)	Trend test for % difference
<30	-5%	-0.11 (0.16)	-0.88 (0.16)		-86% (-136, -36)	
≥30 <300	-17%	-0.49 (0.14)	-1.68 (0.14)		-71% (-93, -49)	
≥300 <1000	-32%	-1.42 (0.14)	-2.78 (0.15)		-49% (-63, -34)	P<0.0001
≥1000 <2000	-18%	-2.43 (0.19)	-4.57 (0.20)		-47% (-58, -36)	
≥2000	-19%	-4.54 (0.23)	-6.36 (0.22)		-29% (-38, -19)	
All participants	**-19%**	**-1.37 (0.08)**	**-2.75 (0.08)**	**1.37 (1.16, 1.59)**	**-50% (-58, -42)**	



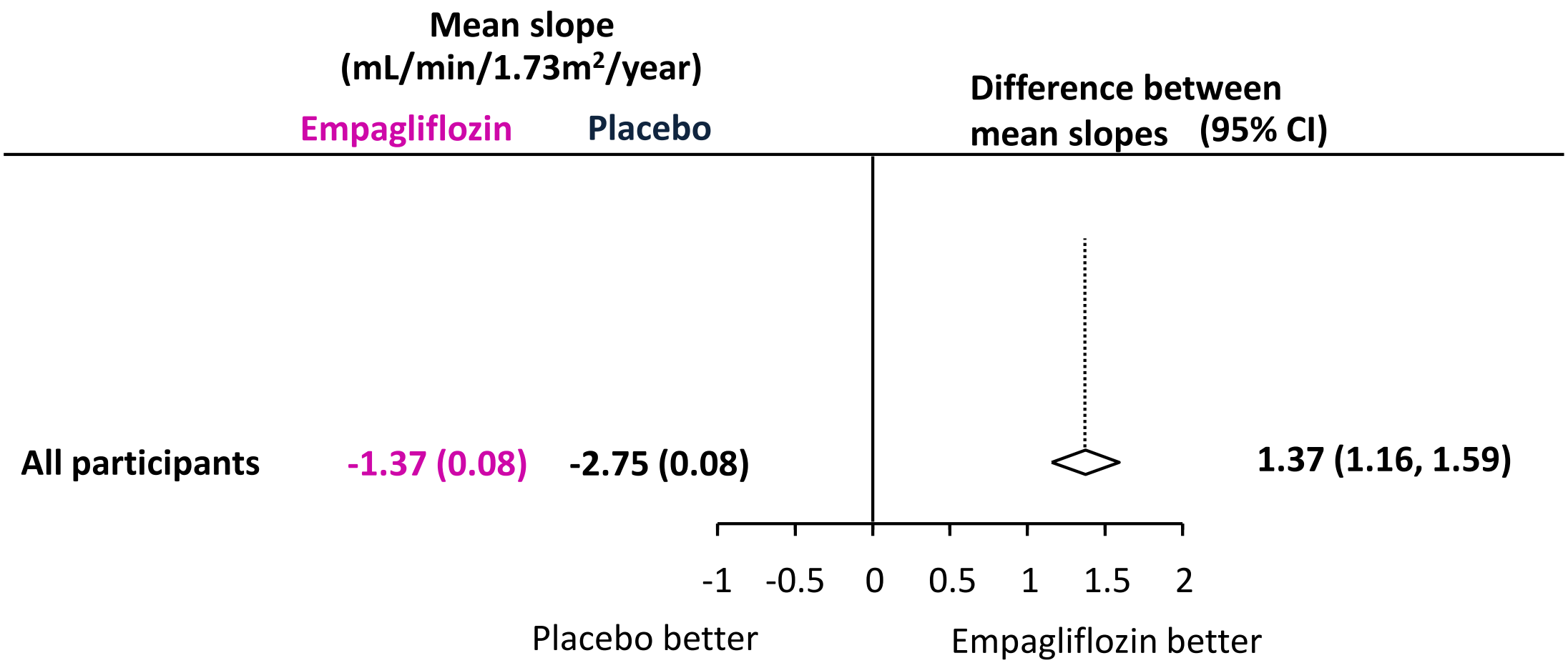
Difference in mean eGFR slopes (mL/min/1.73m²/yr)



Difference in slopes as % of the placebo slope

EMPA-KIDNEY

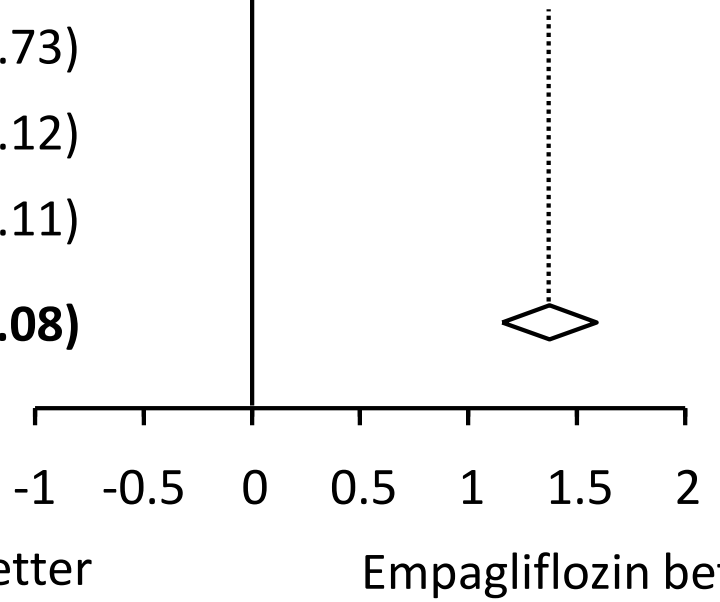
Effects on chronic eGFR slope by diabetes status



EMPA-KIDNEY

Effects on chronic eGFR slope by diabetes status

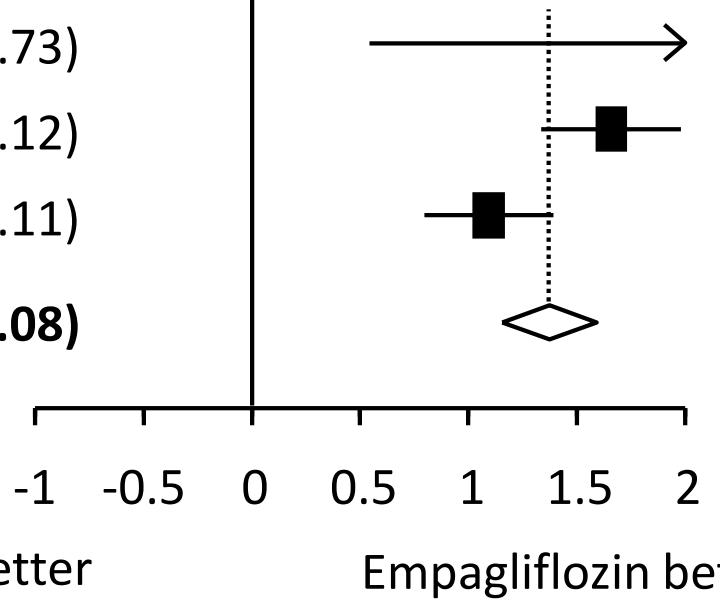
	Mean slope (mL/min/1.73m²/year)		Difference between mean slopes (95% CI)
	Empagliflozin	Placebo	
Type 1*		-2.78 (0.73)	
Type 2		-2.73 (0.12)	
No diabetes		-2.75 (0.11)	
All participants	**-1.37 (0.08)**	**-2.75 (0.08)**	**1.37 (1.16, 1.59)**



EMPA-KIDNEY * All patients with type 1 diabetes were provided with a ketone meter

Effects on chronic eGFR slope by diabetes status

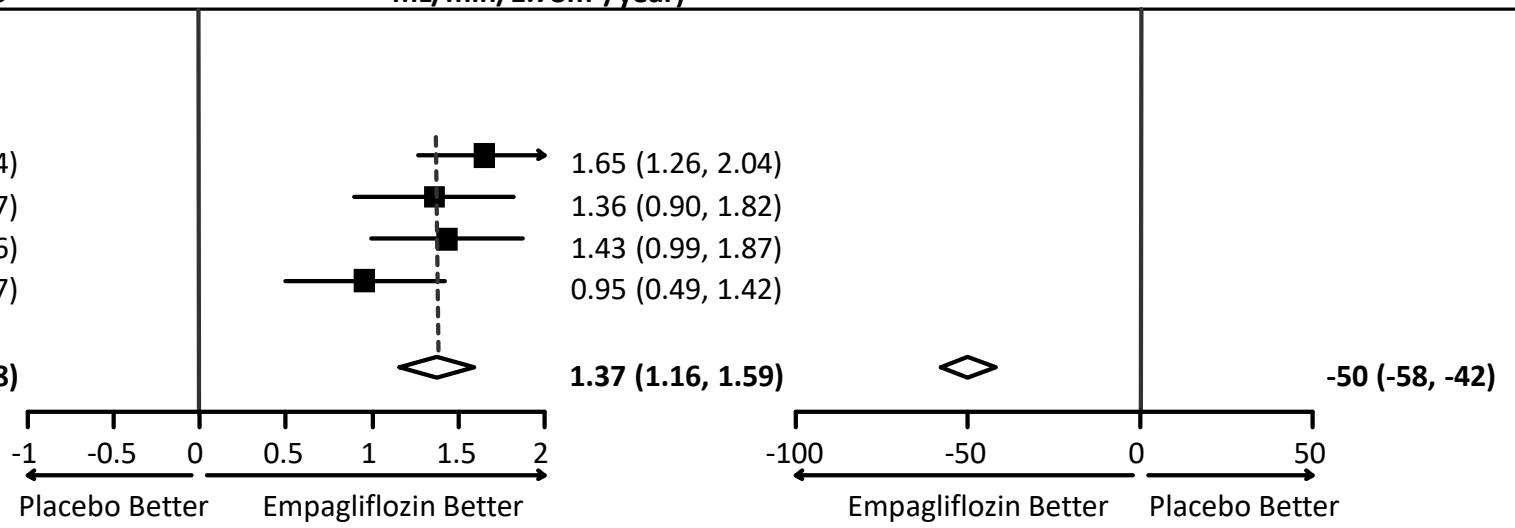
	Mean slope (mL/min/1.73m²/year)		Difference between mean slopes (95% CI)
	Empagliflozin	Placebo	
Type 1*	-0.23 (0.72)	-2.78 (0.73)	**2.55 (0.54, 4.55)**
Type 2	-1.07 (0.12)	-2.73 (0.12)	**1.66 (1.34, 1.98)**
No diabetes	-1.66 (0.11)	-2.75 (0.11)	**1.09 (0.79, 1.39)**
All participants	**-1.37 (0.08)**	**-2.75 (0.08)**	**1.37 (1.16, 1.59)**



EMPA-KIDNEY * All patients with type 1 diabetes were provided with a ketone meter

Chronic eGFR slopes by primary kidney diagnosis

	Mean (SE) slope, mL/min/1.73m²/year		Absolute difference (95% CI), mL/min/1.73m²/year)	Relative difference (95% CI), %	P_{het}
	Empagliflozin	Placebo			
CHRONIC SLOPE					
Causes of kidney disease					
Diabetic kidney disease	-1.16 (0.14)	-2.81 (0.14)	1.65 (1.26, 2.04)		
Hypertensive/renovascular	-0.84 (0.17)	-2.20 (0.17)	1.36 (0.90, 1.82)		
Glomerular disease	-2.17 (0.16)	-3.60 (0.16)	1.43 (0.99, 1.87)		
Other disease/unknown	-1.29 (0.17)	-2.25 (0.17)	0.95 (0.49, 1.42)		
All participants	**-1.37 (0.08)**	**-2.75 (0.08)**	**1.37 (1.16, 1.59)**	**-50 (-58, -42)**	



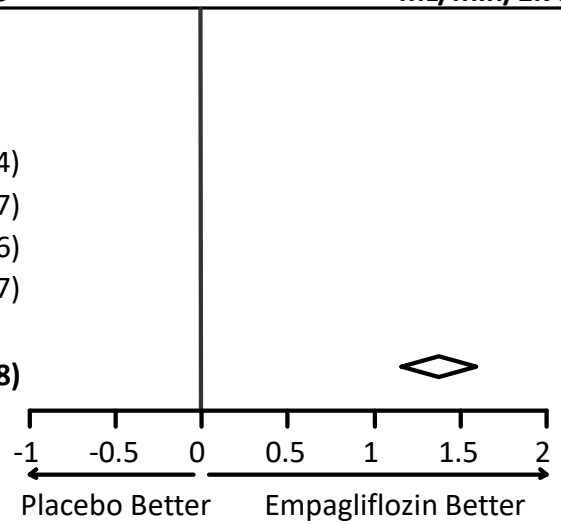
Difference in mean eGFR slopes (mL/min/1.73m²/yr)

Difference in slopes as % of the placebo slope

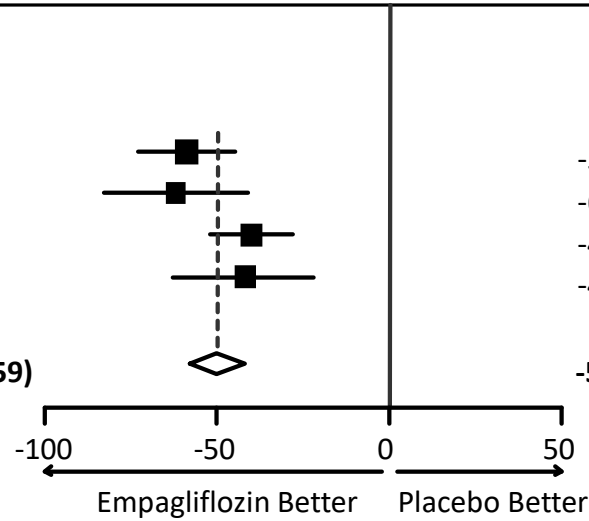
EMPA-KIDNEY
The study of heart and kidney protection with empagliflozin

Chronic eGFR slopes by primary kidney diagnosis

	Mean (SE) slope, mL/min/1.73m²/year		Absolute difference (95% CI), mL/min/1.73m²/year	Relative difference (95% CI), %	P_{het}
	Empagliflozin	Placebo			
CHRONIC SLOPE					
Causes of kidney disease					**p=0.11**
Diabetic kidney disease	-1.16 (0.14)	-2.81 (0.14)		-59 (-73, -45)	
Hypertensive/renovascular	-0.84 (0.17)	-2.20 (0.17)		-62 (-83, -41)	
Glomerular disease	-2.17 (0.16)	-3.60 (0.16)		-40 (-52, -28)	
Other disease/unknown	-1.29 (0.17)	-2.25 (0.17)		-42 (-63, -22)	
All participants	**-1.37 (0.08)**	**-2.75 (0.08)**	**1.37 (1.16, 1.59)**	**-50 (-58, -42)**	

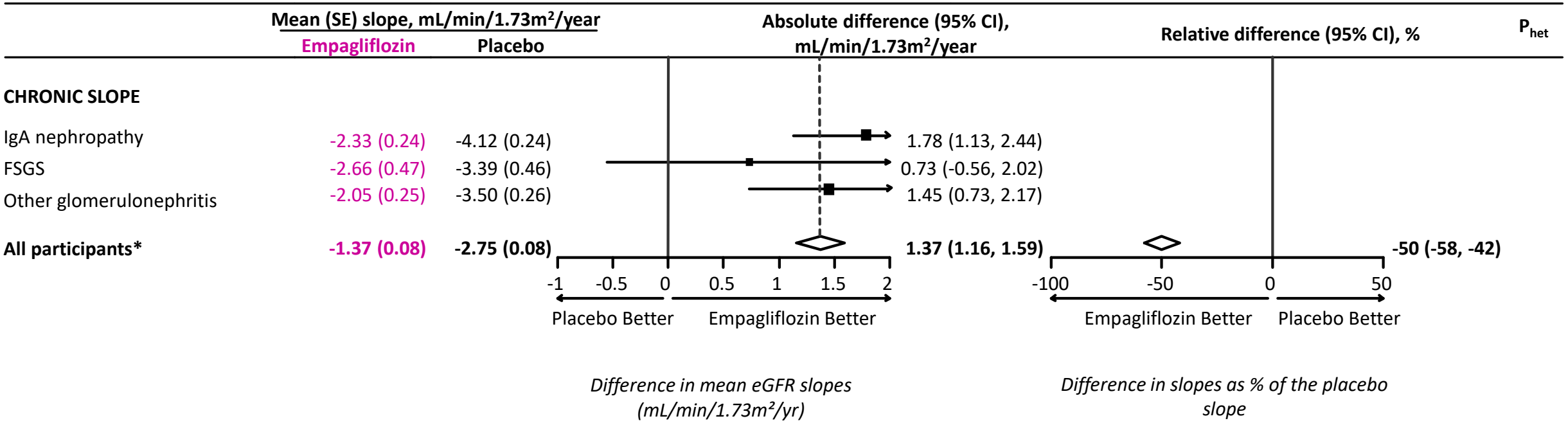


Difference in mean eGFR slopes (mL/min/1.73m²/yr)



Difference in slopes as % of the placebo slope

Chronic eGFR slopes by type of glomerular disease

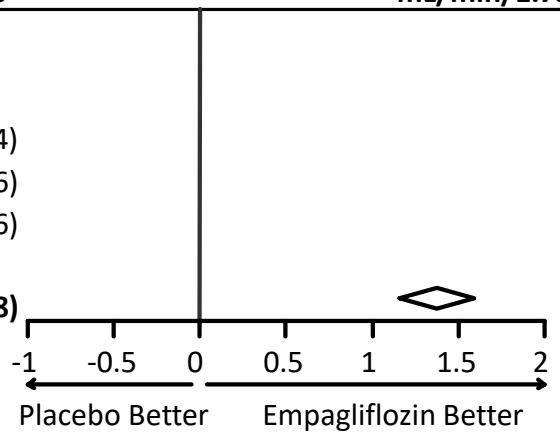


* Total row includes participants without glomerular disease

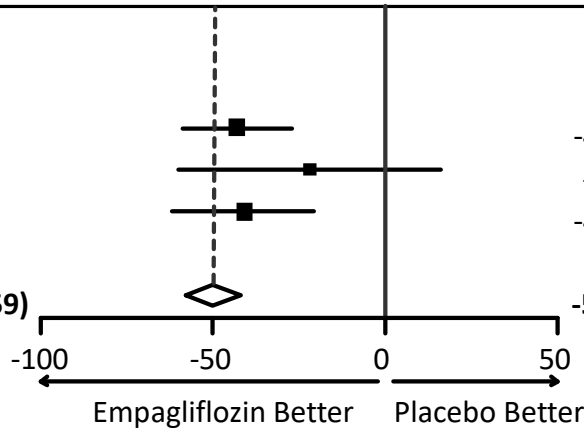
EMPA-KIDNEY

Chronic eGFR slopes by type of glomerular disease

	Mean (SE) slope, mL/min/1.73m²/year		Absolute difference (95% CI), mL/min/1.73m²/year	Relative difference (95% CI), %	P_{het}
	Empagliflozin	Placebo			
CHRONIC SLOPE					**p=0.58**
IgA nephropathy	-2.33 (0.24)	-4.12 (0.24)		-43 (-59, -27)	
FSGS	-2.66 (0.47)	-3.39 (0.46)		-22 (-60, 16)	
Other glomerulonephritis	-2.05 (0.25)	-3.50 (0.26)		-41 (-62, -21)	
All participants*	**-1.37 (0.08)**	**-2.75 (0.08)**	**1.37 (1.16, 1.59)**	**-50 (-58, -42)**	



Difference in mean eGFR slopes (mL/min/1.73m²/yr)



Difference in slopes as % of the placebo slope

* Total row includes participants without glomerular disease

EMPA-KIDNEY

EMPA-KIDNEY: 2022 Conclusions

- Randomized 6609 patients with CKD with a broad range of causes, and large numbers with low levels of kidney function & albuminuria

- Empagliflozin safely reduced the composite primary outcome of kidney disease progression or CV death by **28% (95% CI 18-36%)**

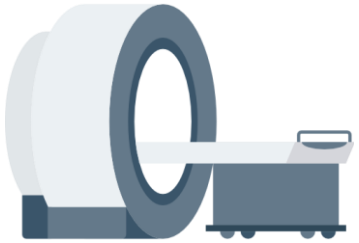
- Relative benefits were consistent in the patients with & without diabetes, and across the range of eGFR studied (to at least 20 mL/min/1.73m^2)

EMPA-KIDNEY

EMPA-KIDNEY: what's new & what's different?

- Slope analyses: Empagliflozin slowed chronic eGFR decline irrespective of:
  - Type of diabetes (including type 1 diabetes)
  - Level of albuminuria
  - Primary kidney diagnosis

What's next from EMPA-KIDNEY?



MRI substudy

Bioimpedance substudy

2 years of post-trial follow-up (health economics)

Urine tubular & other biomarkers

New trial designs… EASi-KIDNEY

Acknowledgements

We thank the 6609 participants, members of the committees, and coordinating and local site staff who make up the EMPA-KIDNEY Collaborative Group

https://www.empakidney.org/our-collaborators