60TH ERA CONGRESS
MILAN & VIRTUAL
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EMPA-KIDNEY
The study of heart and kidney protection with empagliflozin

Effects of Empagliflozin on Renal and Cardiac MRI Measures in Patients with Chronic Kidney Disease

Parminder Judge

on behalf of the

EMPA-KIDNEY Collaborative Group

Disclosures

- The EMPA-KIDNEY trial was initiated by the University of Oxford who led its design, analysis, and reporting with a Steering Committee of expert collaborators

- The trial was funded and sponsored by Boehringer Ingelheim

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

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 chronic kidney disease (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/1.73m^2

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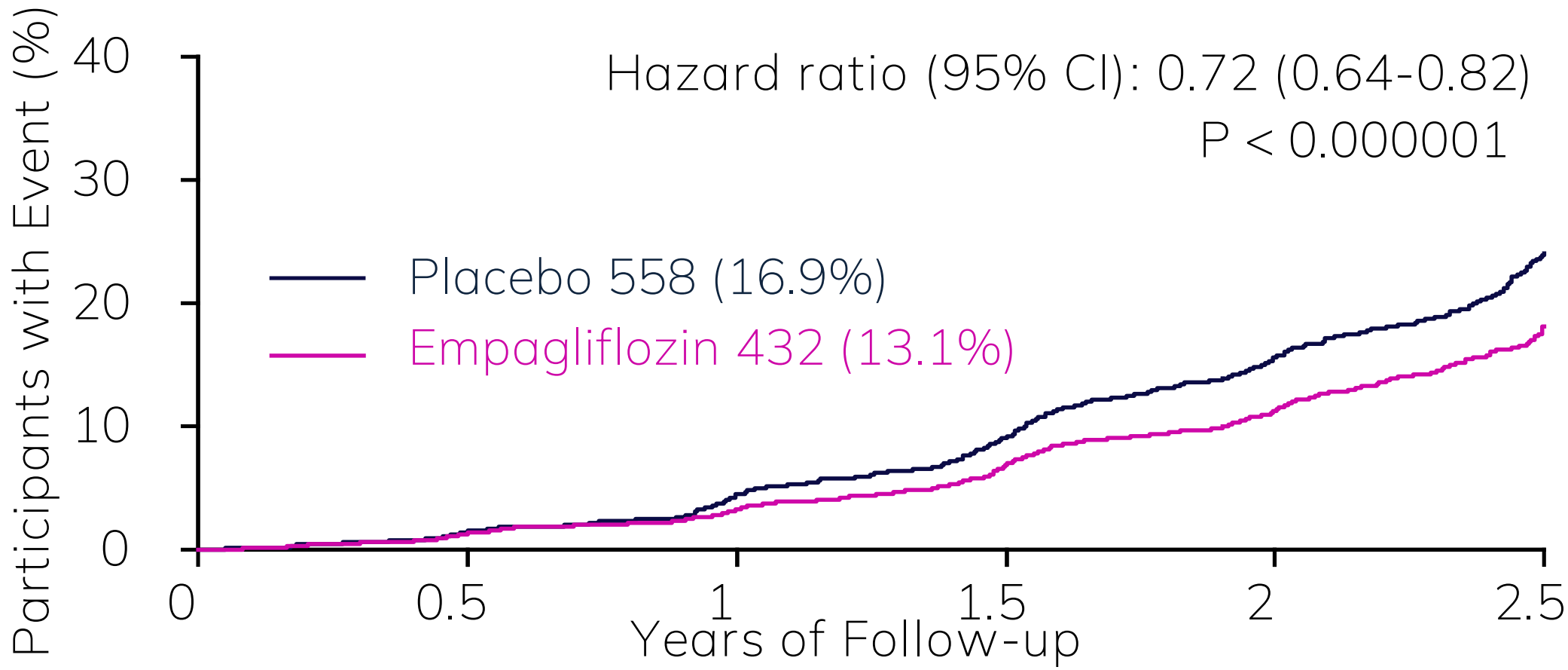
Primary Composite Outcome



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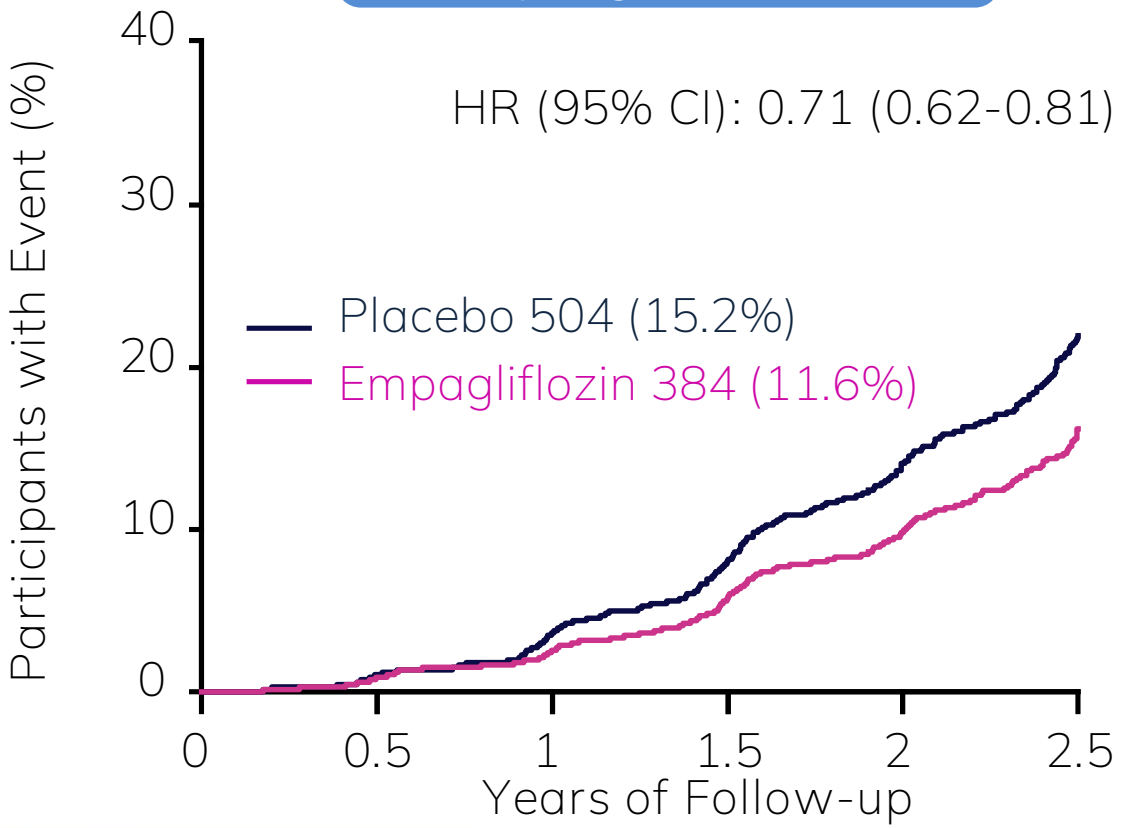
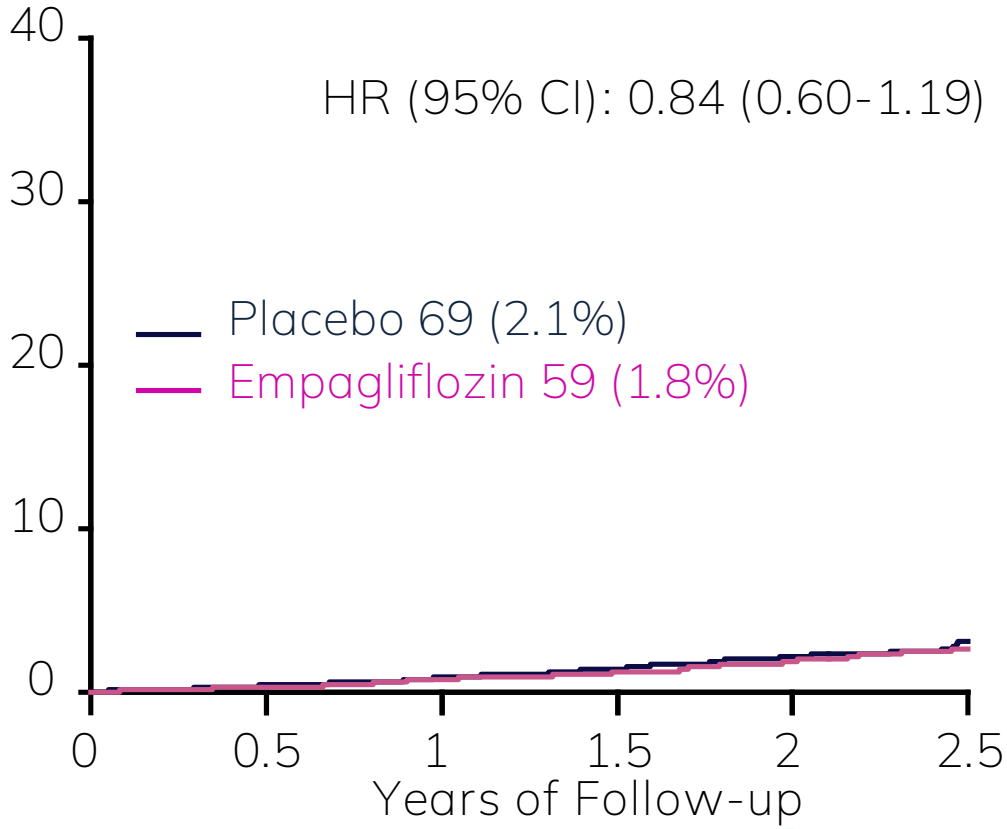
Components of the Primary Outcome

Kidney disease progression



CV death



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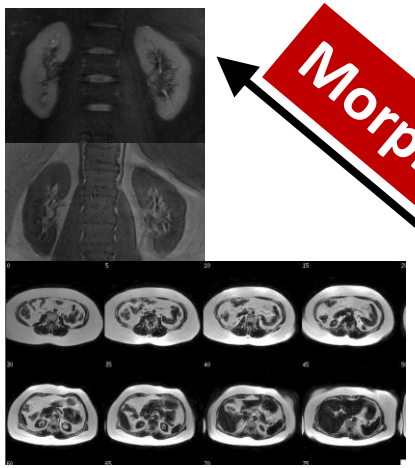
Multiparametric MRI protocol: Kidneys

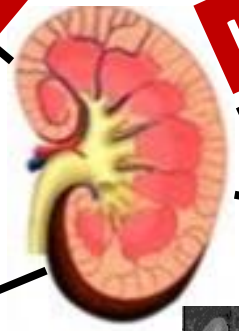
T2-weighted: TKV

T1-weighted: Cortex/Medulla Volume

mDIXON: Fat fraction

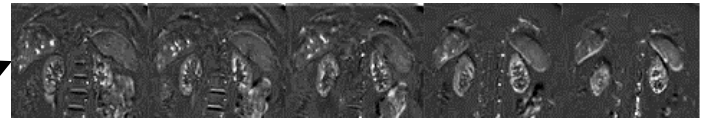


Morphology

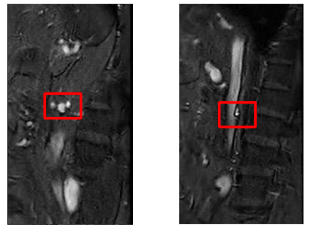


Haemodynamics

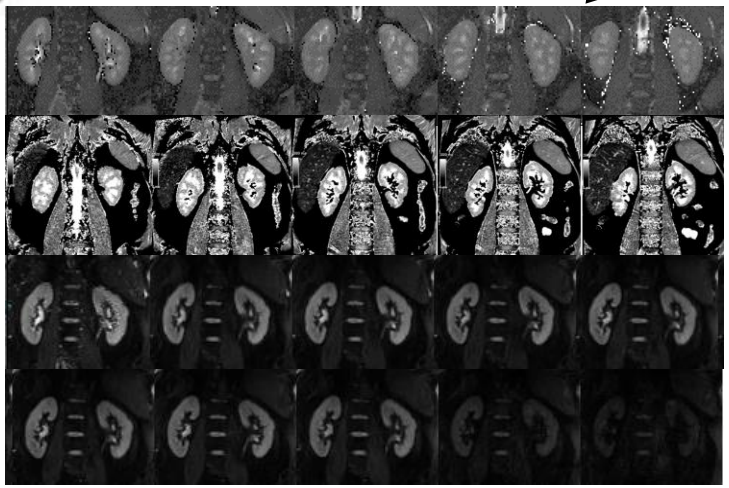
ASL perfusion



PC-MRI: Renal Artery Blood Flow



Microstructure



SE-EPI T1 mapping

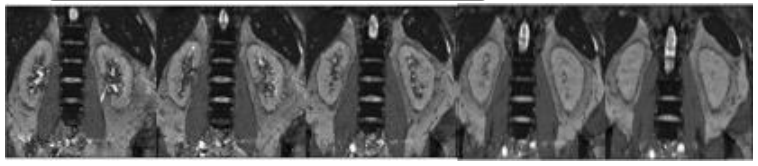
MOLLI T1 mapping

Diffusion Weighted Imaging: ADC, D, D*, f

Inflammation and fibrosis

Oxygenation

BOLD T2*-mapping



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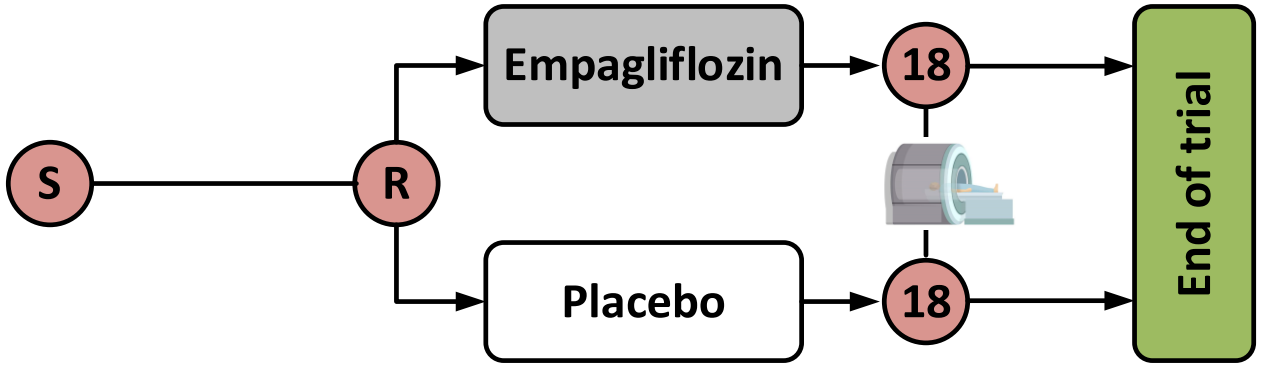
MRI sub-study design

- Mechanistic MRI sub-study to investigate effects of Empagliflozin on kidney and cardiac structure and function. Data collected across 4 sites.



- Primary outcome: Kidney cortex fibrosis/inflammation at ~18 months
- Secondary outcomes:
  - Kidney: medullary fibrosis, size, arterial flow, global perfusion, diffusion, oxygenation and fat content
  - Cardiac: LV mass, LV ejection fraction, LV fibrosis, diastolic function

Baseline characteristics of MRI substudy

	Empagliflozin (N=93)		Placebo (N=79)	
Age at randomization*, years	59.7	(15.5)	61.0	(15.2)
Female sex, n (%)	26	(28%)	19	(24%)
Diabetes, n (%)	22	(24%)	18	(23%)
Estimated GFR*, mL/min/1.73m^2	36.1	(14.2)	37.3	(10.9)
Urine ACR†, mg/g	285	(194-419)	200	(130-306)
NTpro-BNP†, ng/L	134	(59-247)	128	(71-314)

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* Mean (SD)
† Median (Q1-Q3)

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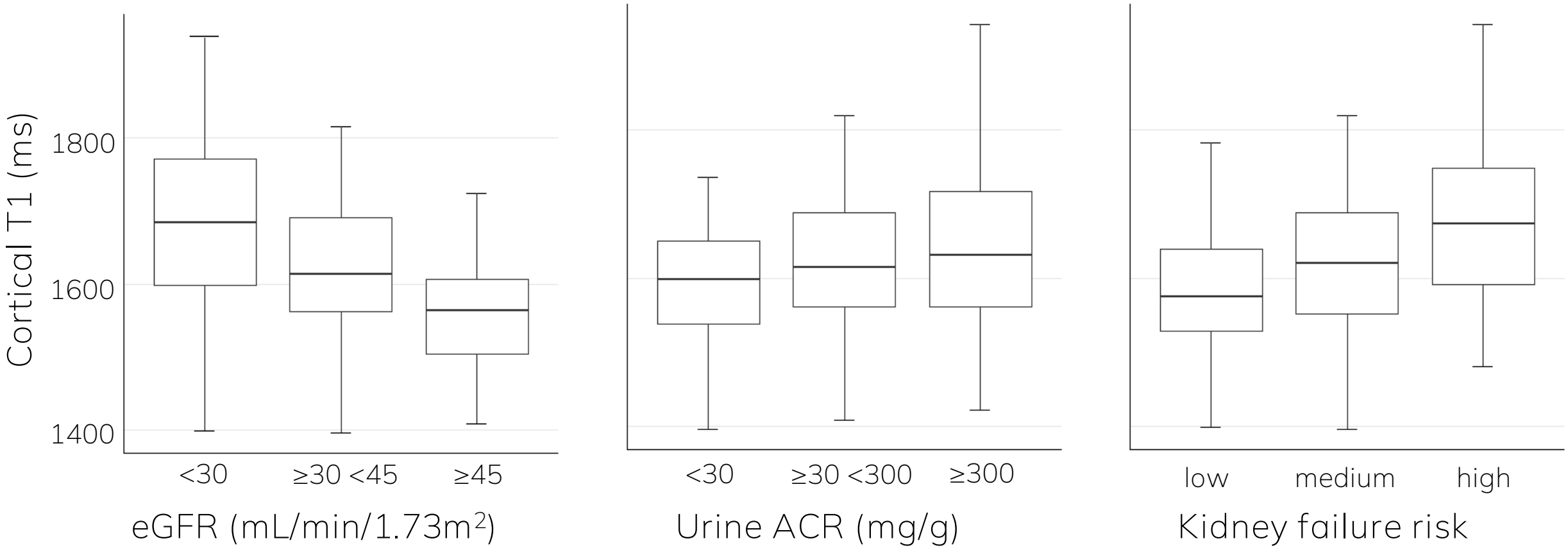
Associations with kidney cortex T1



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Results: Kidney MRI outcomes

Outcome	Empagliflozin (N=93)	Placebo (N=79)	Difference in means (95% CI)†	p value
Primary				
Cortical T1 MOLLI (ms)†		1634 (11)		
Secondary				
Medullary T1 MOLLI (ms)†		1923 (11)		

†Values are absolute differences in arithmetic means (95% confidence interval). The estimates and p values were derived from linear regression with adjustment for elements included in the minimization algorithm which determined treatment allocation (age, sex, prior diabetes, eGFR, and uACR).

Results: Kidney MRI outcomes

Outcome	Empagliflozin (N=93)	Placebo (N=79)	Difference in means (95% CI)†	p value
Primary				
Cortical T1 MOLLI (ms)†	1623 (10)	1634 (11)	-11 (-41, 18)	0.45
Secondary				
Medullary T1 MOLLI (ms)†	1930 (11)	1923 (11)	7 (-24, 37)	0.67

†Values are absolute differences in arithmetic means (95% confidence interval). The estimates and p values were derived from linear regression with adjustment for elements included in the minimization algorithm which determined treatment allocation (age, sex, prior diabetes, eGFR, and uACR).

Results: Cardiac MRI outcomes

Outcome	Empagliflozin (N=93)	Placebo (N=79)	Difference in means (95% CI)†	p value
Myocardial T1 MOLLI (ms)†	1275 (5)	1278 (5)	-3 (-16, 10)	0.67
Left ventricular ejection fraction (%)†	52 (1)	51 (1)	1 (-1, 4)	0.37
Left ventricular mass index (g/m^2)†	45 (1)	48 (1)	-3 (-5, 0)	0.07

†Values are absolute differences in arithmetic means (95% confidence interval). The estimates and p values were derived from linear regression with adjustment for elements included in the minimization algorithm which determined treatment allocation (age, sex, prior diabetes, eGFR, and uACR [but not region as the MRI substudy was only conducted in Europe]). Difference in systolic and diastolic BP: –2.6±0.3 mmHg & –0.5±0.2 mmHg respectively.

Preliminary Results of MRI Sub-study

- In this 172-participant EMPA-KIDNEY MRI substudy, compared to placebo, empagliflozin had no detectable effect on:
  - Kidney T1 MOLLI measure of inflammation/fibrosis
  - Cardiac measures of fibrosis (T1 MOLLI), ejection fraction and LV mass.

- Possible explanations for lack of effect include:
  - Limited power due to the single scan protocol with a distribution of aetiology
  - Attenuation of cardiac effects at low eGFR
  - Insufficient duration of exposure to Empagliflozin

- Future work will assess kidney haemodynamic, oxygenation and other microstructural related MRI measures, and cardiac strain & diastolic dysfunction.

Acknowledgements

- We thank the 172 participants, members of the committees, and coordinating and local site staff who make up this EMPA-KIDNEY substudy

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

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