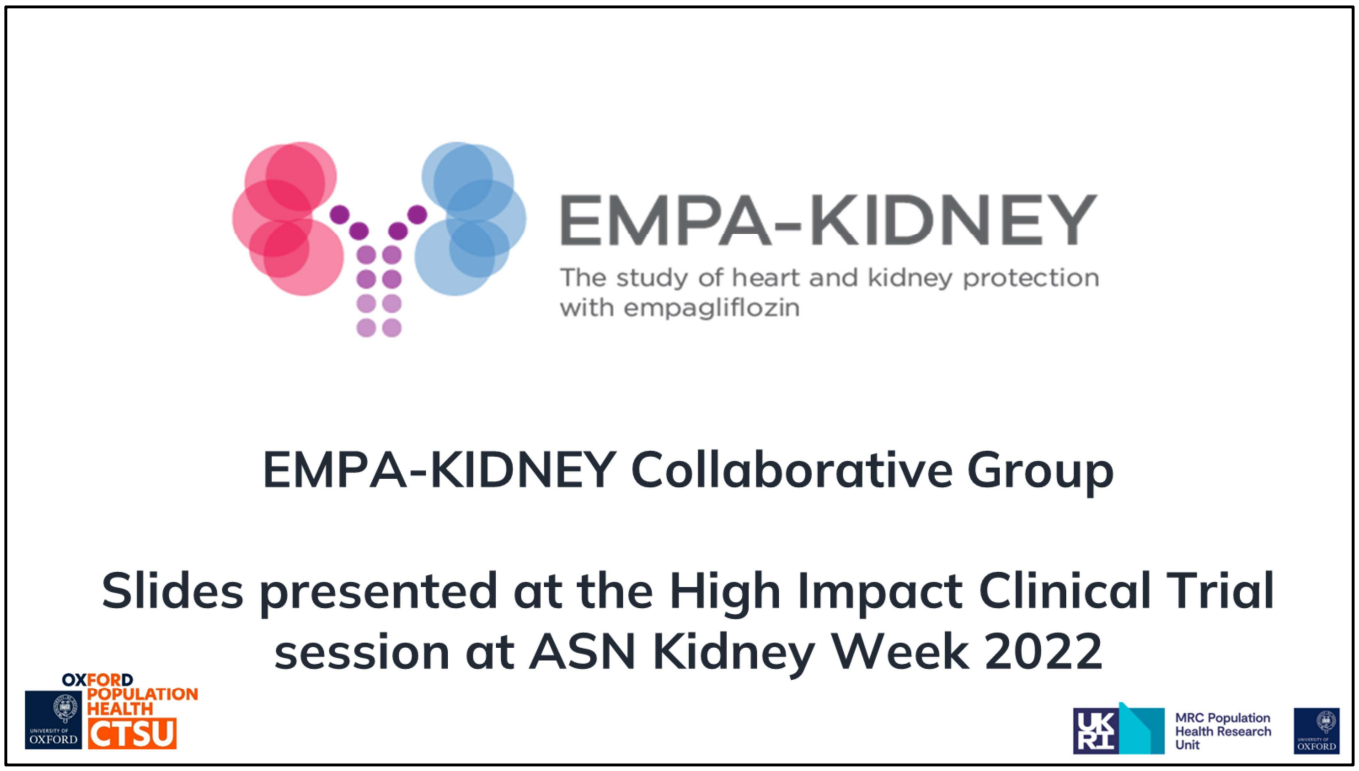

Speaker notes: This is an oral abstract presented at the High Impact Trials session at ASN Kidney Week 2022.

The EMPA-KIDNEY Collaborative group was co-led by Oxford-based trialists and nephrologists (William Herrington and Richard Haynes)

The group includes collaborators from 241 participating sites from 8 countries.

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)

EMPA-KIDNEY

MRC Population Health Research Unit

Speaker notes: The EMPAKIDNEY trial was initiated by the University of Oxford who led its design, analysis, and reporting with a Steering Committee of expert collaborators

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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

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Speaker notes: EMPA-KIDNEY is a large double-blind placebo-controlled trial

Our aim was to assess the effects of SGLT2 inhibition on a broad range of patients with chronic kidney disease at risk of progression, including at least 1/3rd with and 1/3rd without diabetes.

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

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

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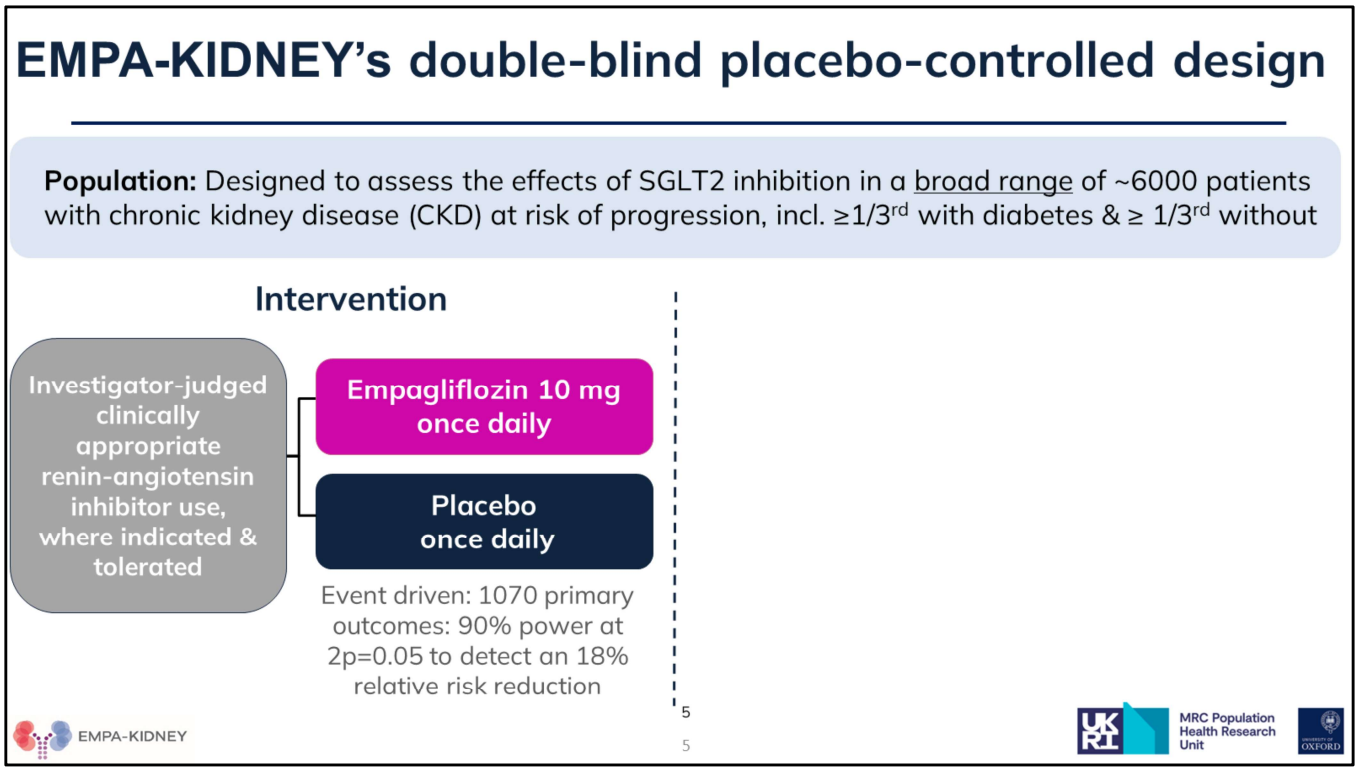
Speaker notes: Risk of progression was identified by simple inclusion criteria.

Participating adults were required to have evidence of an estimated GFR both historically and at Screening of 20 to 45

Or an eGFR of 45 to 90 with evidence of at least 200 milligrams per gram of albuminuria.

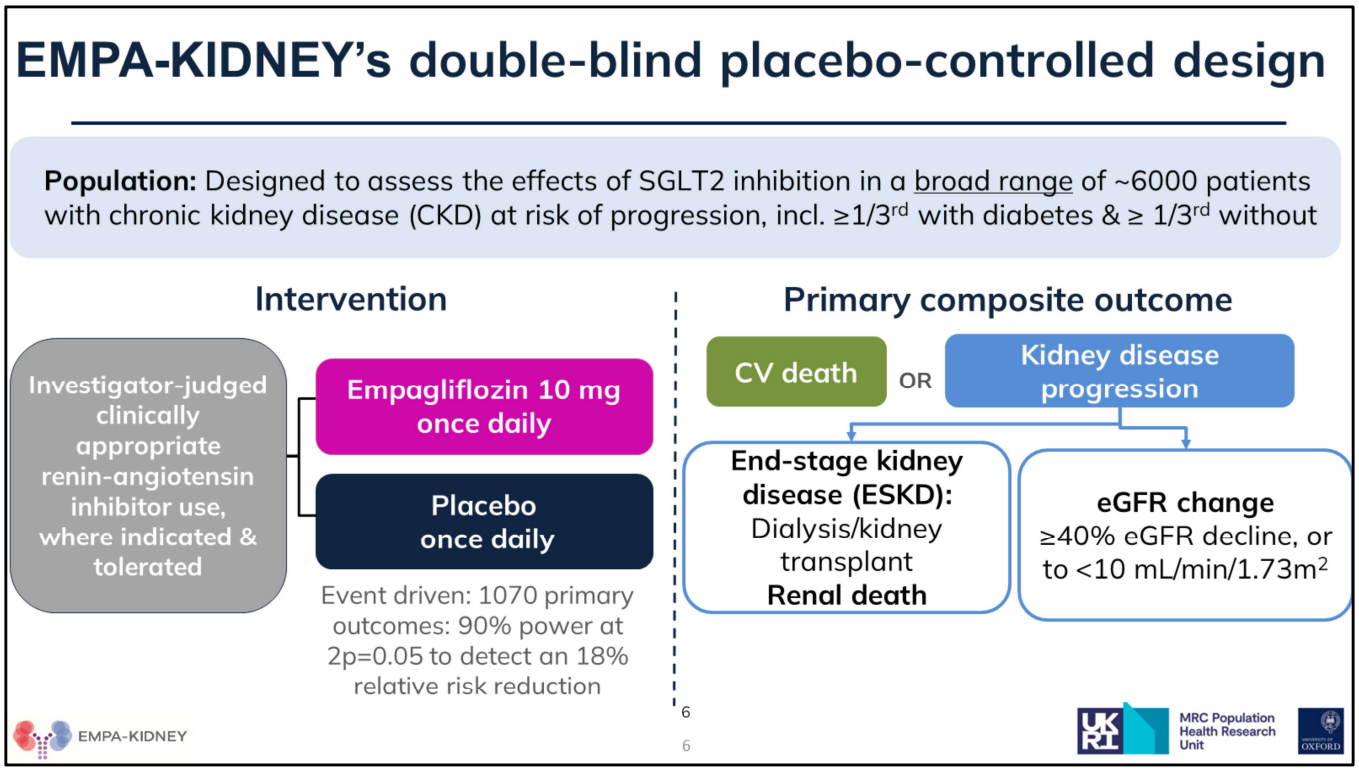
Exclusion were kept to a minimum to help ensure a widely generalizable result, but did exclude patients with polycystic kidney disease or a kidney transplant.



Speaker notes: Participants were required to be on background therapy with investigator-judged clinically appropriate renin-angiotensin inhibitor use, where indicated and tolerated.

They were randomized 1:1 to empagliflozin 10mg tablets once daily versus matching placebo

The trial was event driven aiming to accrue a minimum of 1070 primary outcomes.



Speaker notes: The primary outcome was a composite of CV death or kidney disease progression, which itself was defined as:

The need to commence maintenance dialysis or receive a kidney transplant, death from untreated end-stage kidney disease, or sustained declines in centrally measured estimated GFR of at least 40% from randomization or to below 10.

Sustained required measurement at two consecutive visits or the last scheduled visit.

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%

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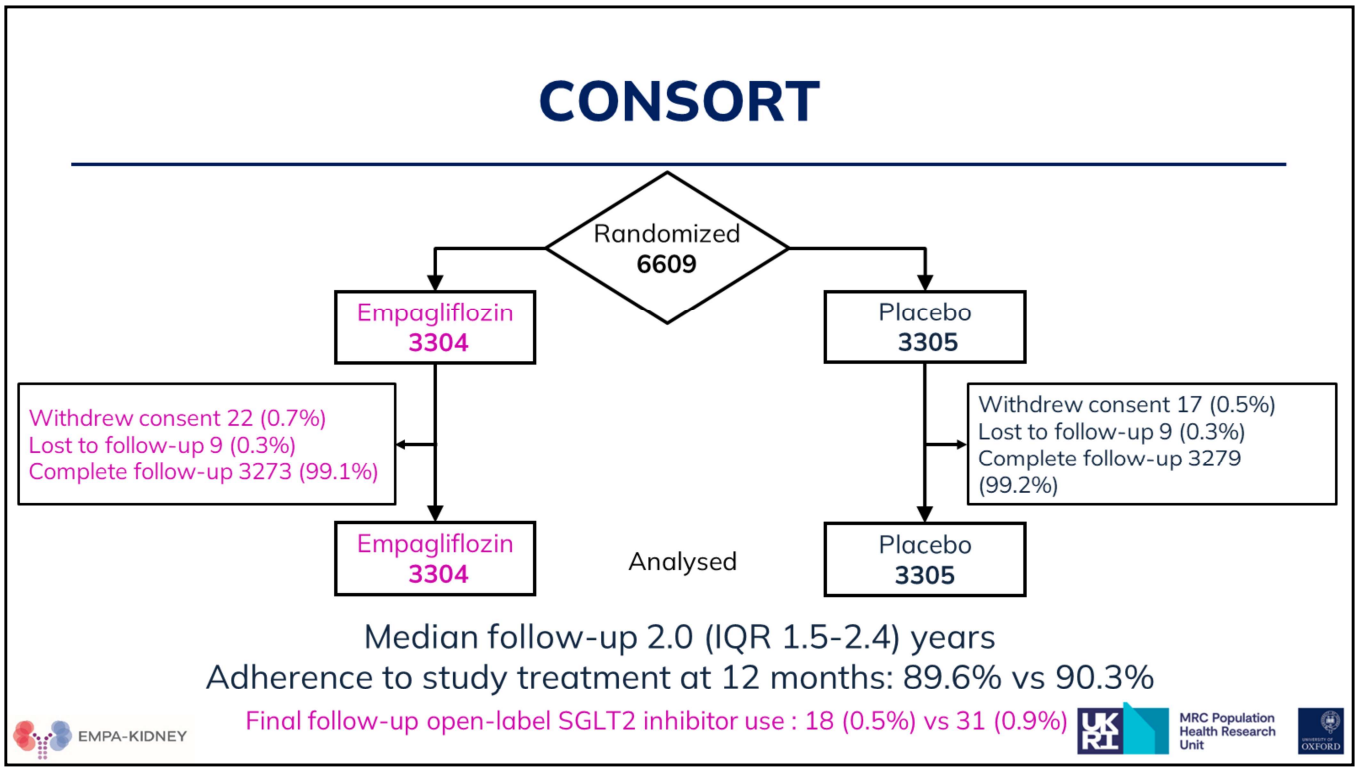
Speaker notes: Mean age at baseline was nearly 64 years, with one-third of participants of female sex, and just over one-half had no evidence diabetes at baseline.

Mean eGFR was 37, with about one third with an eGFR less than 30

Median urinary ACR was about 330 milligrams per gram, so about one-half of the trial had A1 or A2 disease.

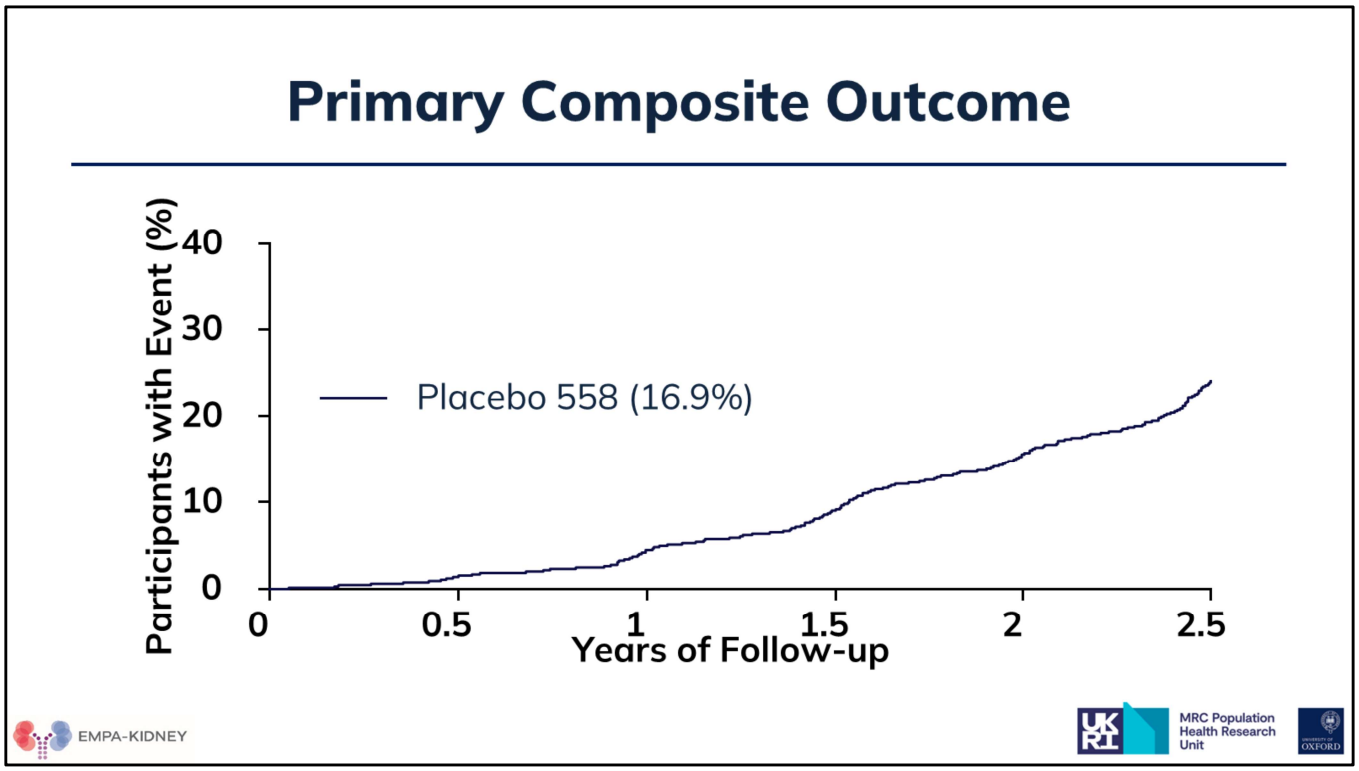
A broad range of primary kidney disease was represented, with 31% attributed to diabetic kidney disease.

25% were due to glomerular disease.



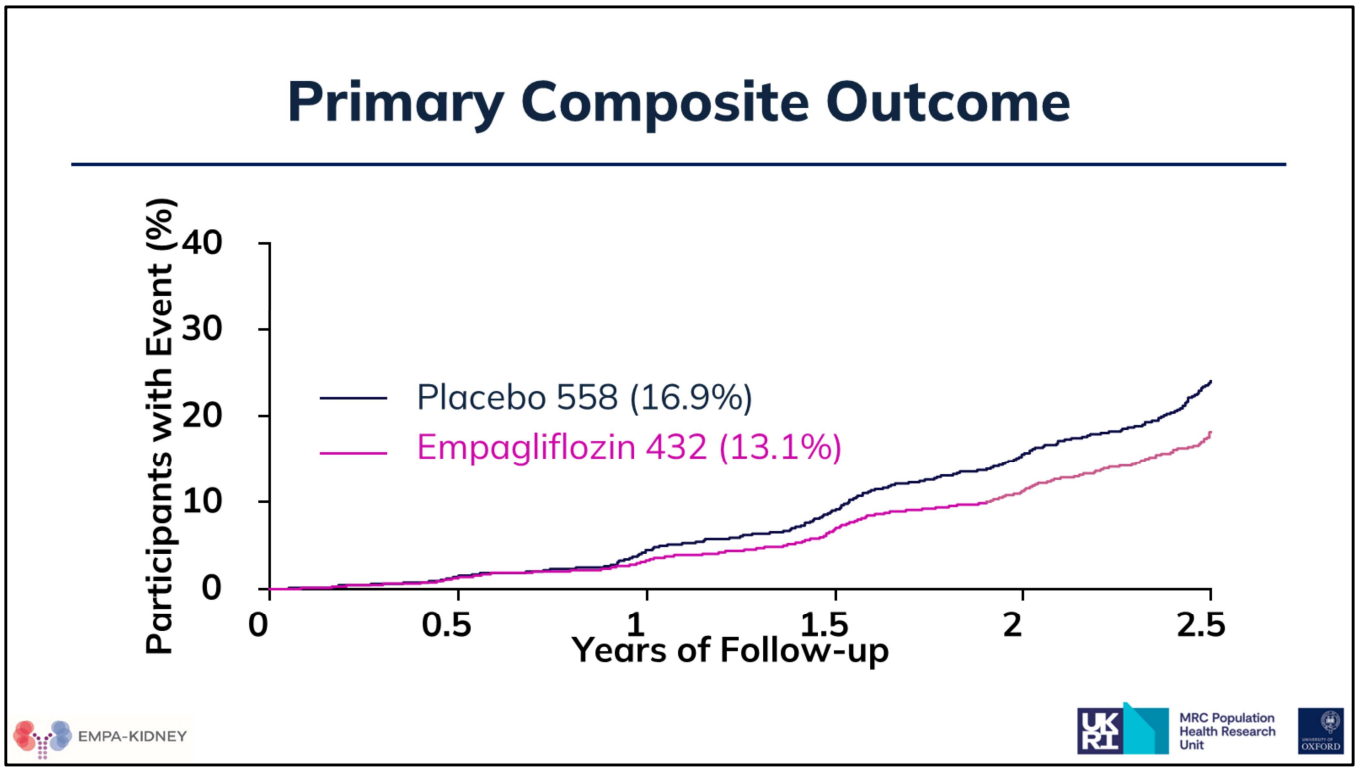
Speaker notes: On 7th March 2022, the independent data monitoring committee recommended the trial stop early after a single prespecified formal interim analysis, and on 5th July, all final follow-up visits were concluded, with over 99% completeness.

Median follow-up was 2 years with adherence at the midpoint of about 90% and less than 1% of participants starting open label SGLT2 inhibitors by final follow-up.

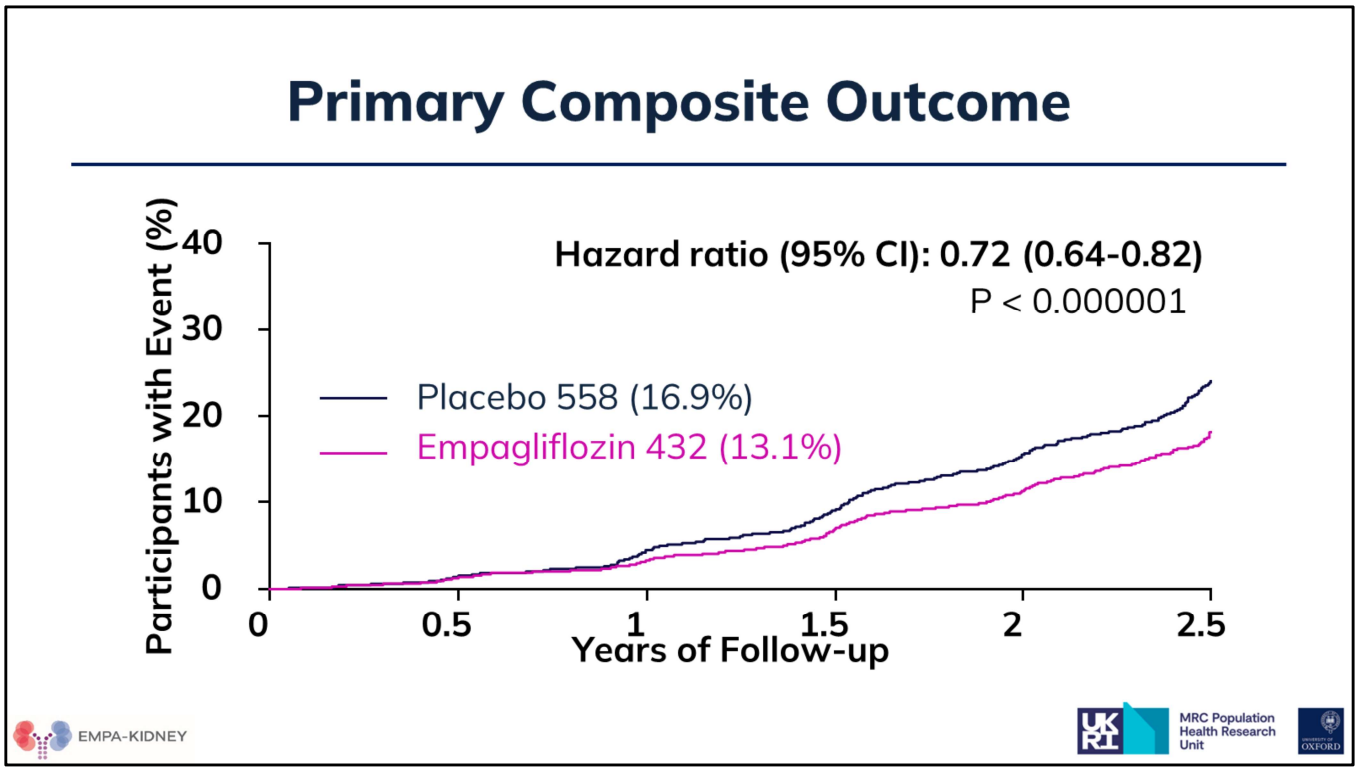


Speaker notes: This is the main result of EMPA-KIDNEY.

There were 558 primary outcomes in those allocated to placebo

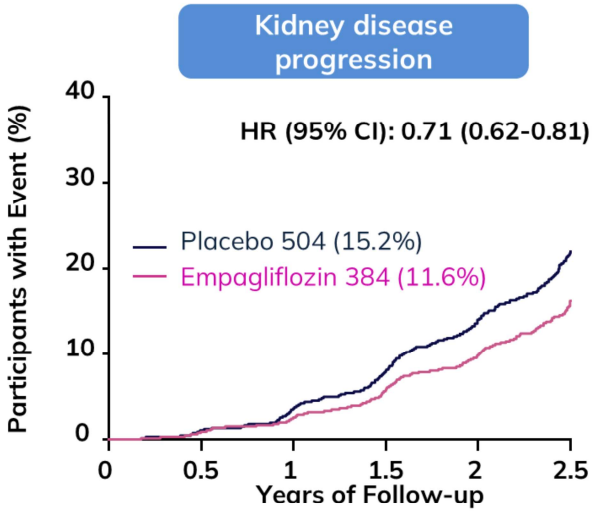


Speaker notes: And 432 among those allocated to empagliflozin.



Speaker notes: This equates to a highly statistically significant 28% relative risk reduction, with 95% confidence interval from 18% to 36%.

Components of the Primary Outcome



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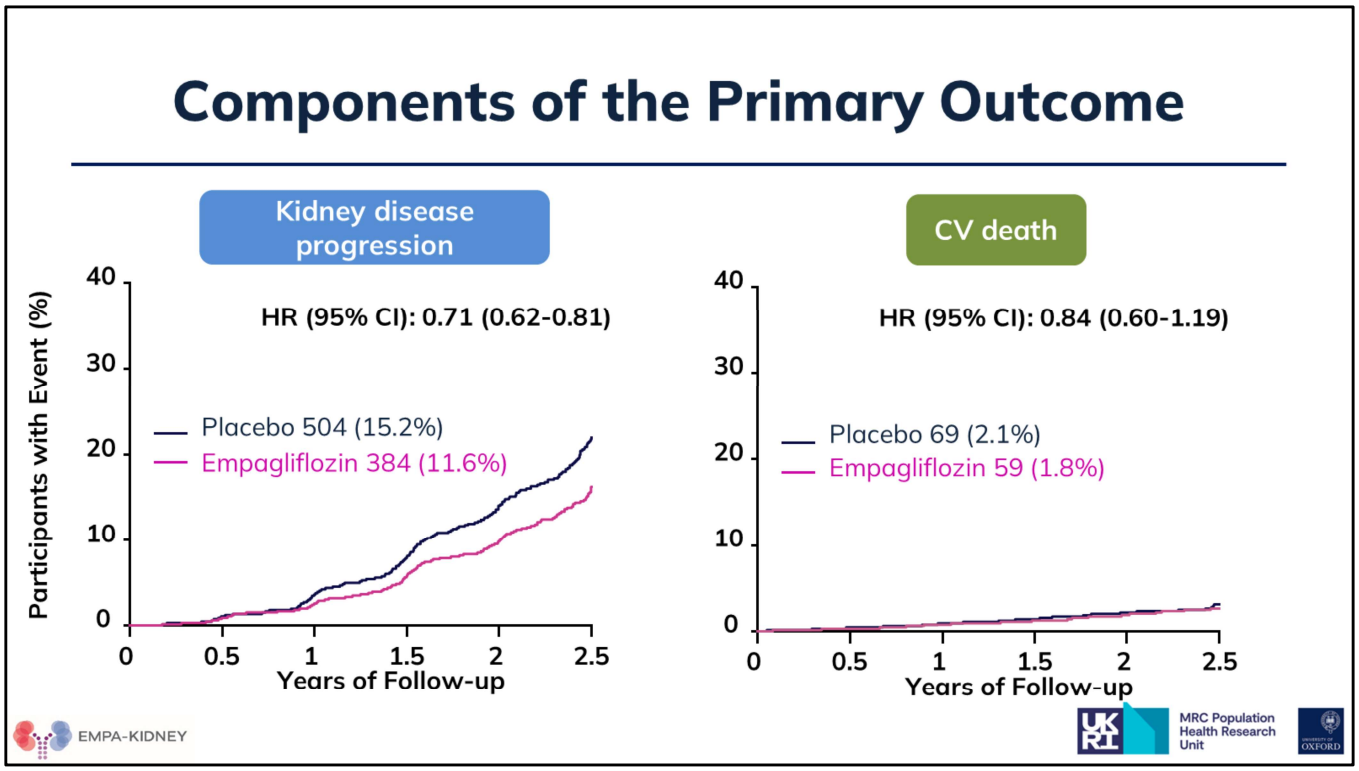
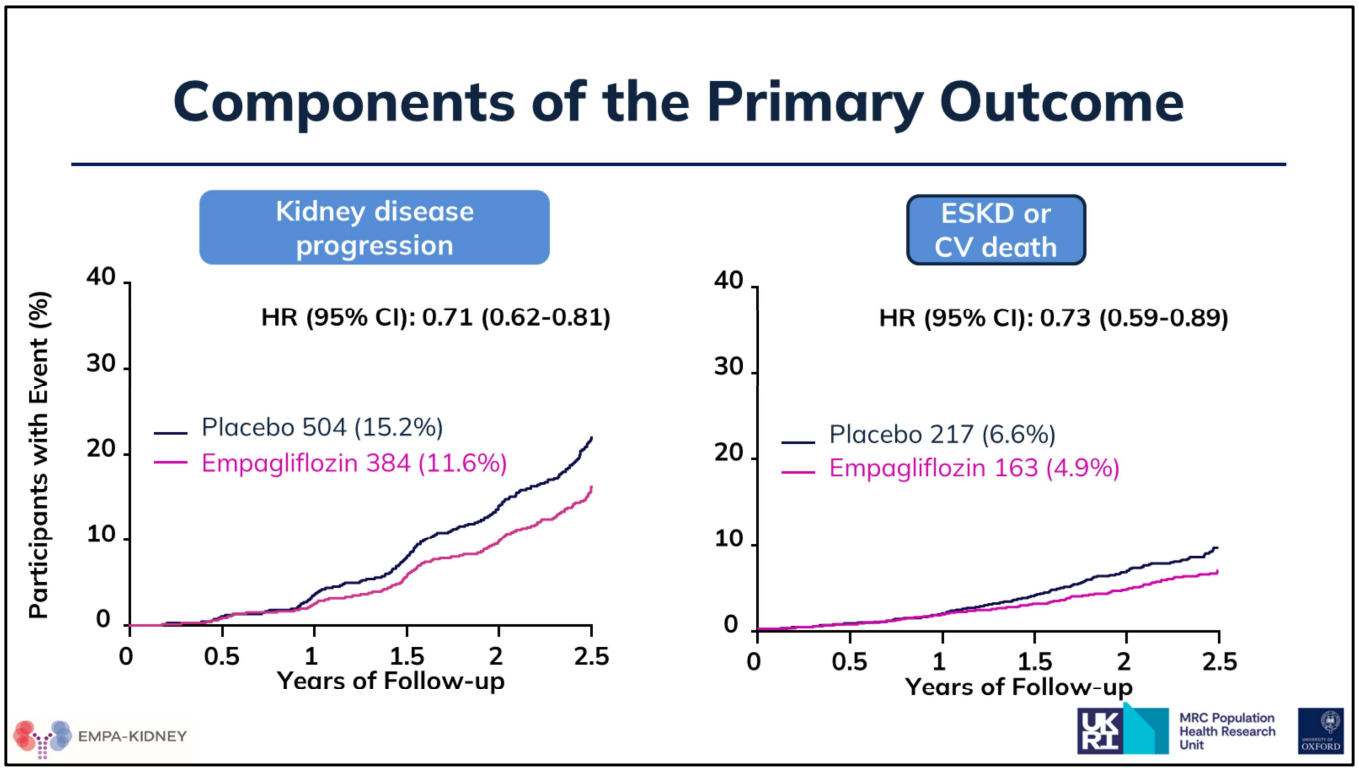
Speaker notes: As would be expected from a population of patients with low eGFR recruited from nephrology centres, kidney disease progression made up the majority of the 990 primary outcomes.

And there was a clear 29% reduction in the relative risk for this outcome.

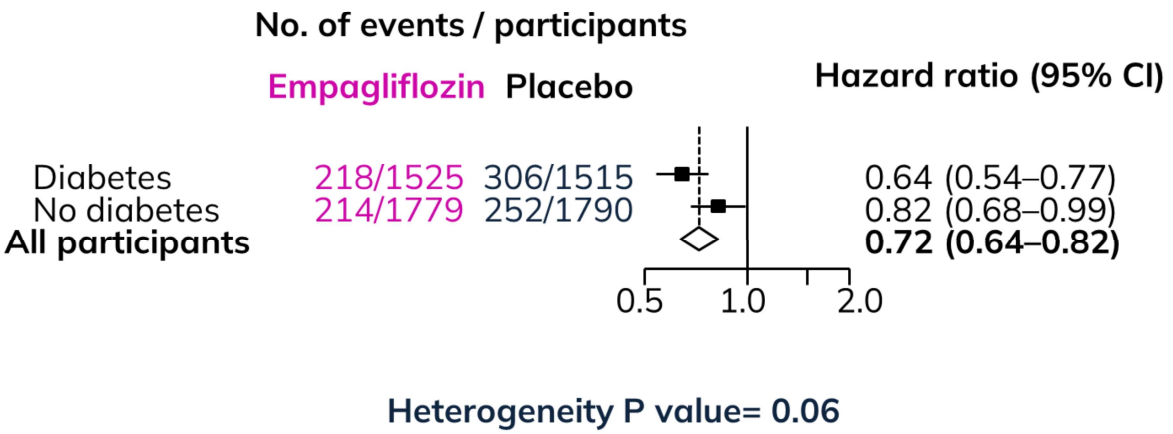


Speaker notes: In comparison, the rate of cardiovascular death in this population was low, and lower than expected meaning limited power to assess effects for this component of the primary composite outcome.



Speaker notes: In analyses of the other secondary composite outcome of time to first maintenance dialysis, kidney transplant or cardiovascular death, a clear 27% statistically significant reduction was evident.

Primary outcome by diabetes



Heterogeneity P value= 0.06

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Speaker notes: There were 3 key subgroups which were prespecified for emphasis, the first was by diabetes status at randomization

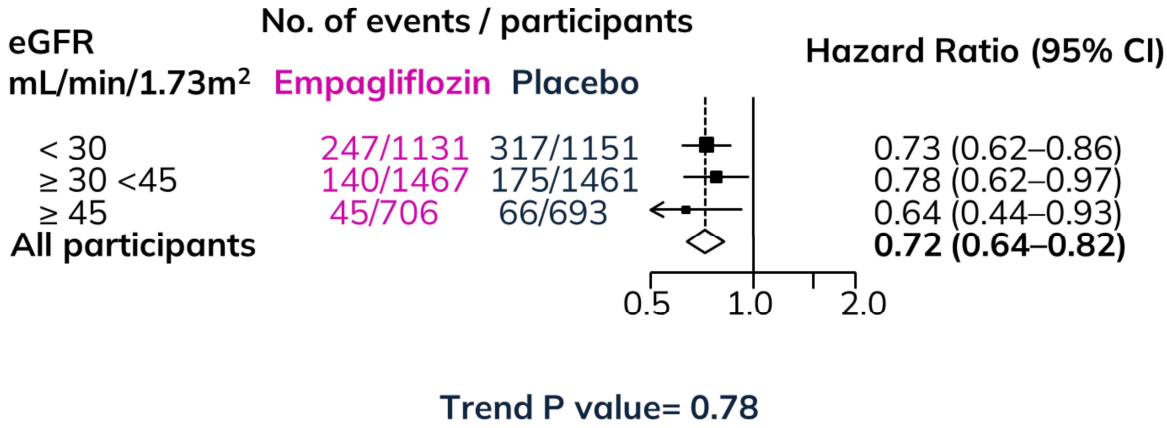
This forest plot shows the overall effect of Empagliflozin on the primary outcome in the diamond.

Above it is plotted the effects in patients with an without diabetes at recruitment.

There were 466 first primary outcomes in patients without diabetes, providing important information in this previously less studied group

The P value for the statistical test for effect modification, a heterogeneity test, was non-significant at 0.06, suggesting the best estimate of effect in people with or without diabetes is the overall result.

Primary outcome by kidney function



Trend P value= 0.78

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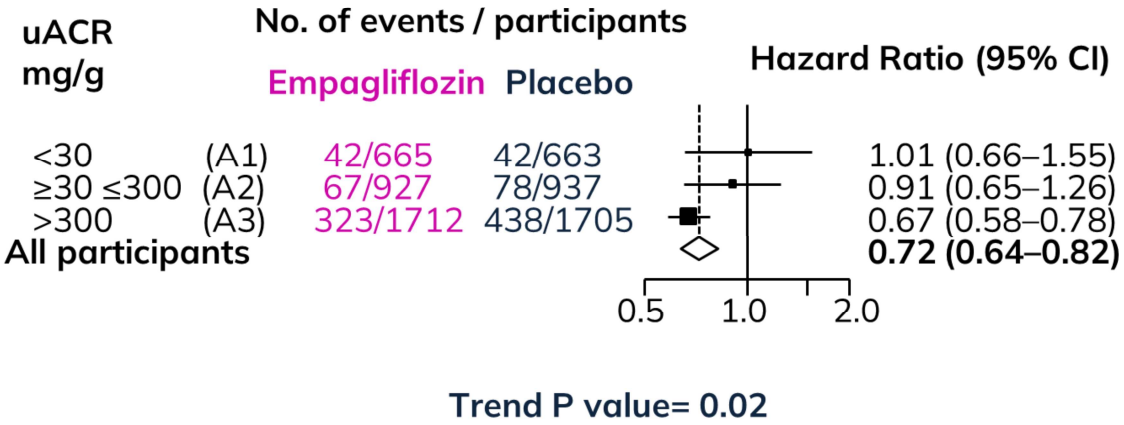
Speaker notes: This second forest plot shows the effects of Empagliflozin by different levels of kidney function.

There were 564 first primary outcomes in patients with an eGFR less than 30, again providing large amounts of new evidence in this less studied group.

Benefits appeared similar irrespective of baseline eGFR category.

Primary outcome by albuminuria



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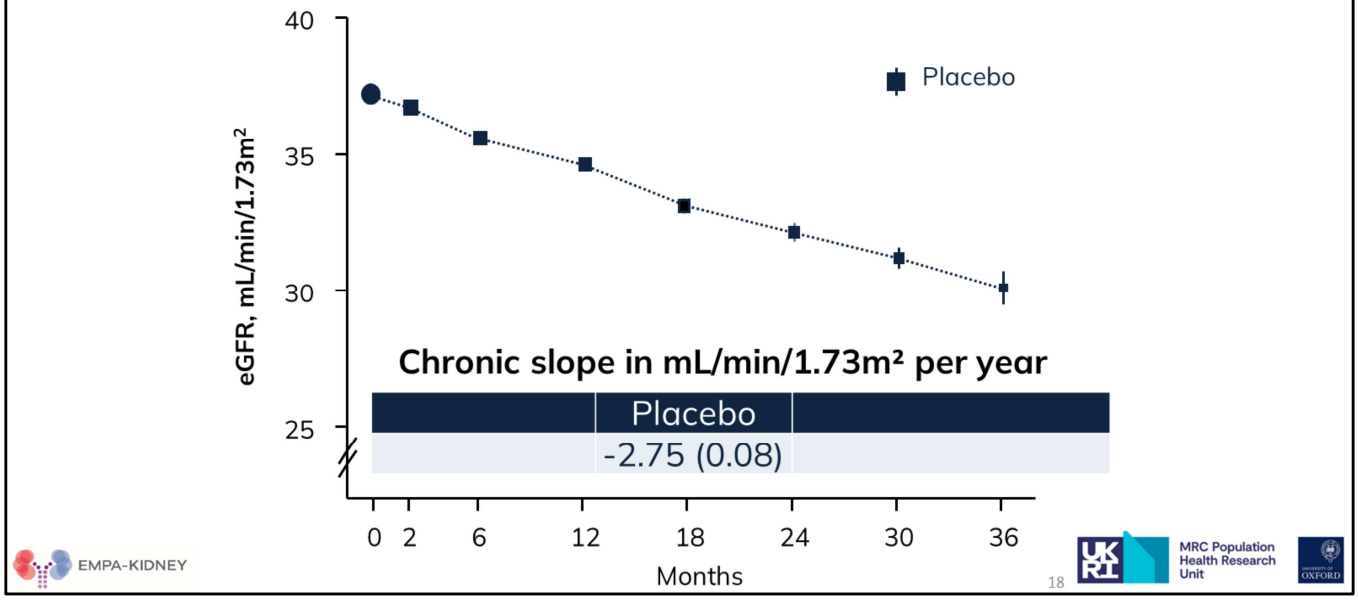
Speaker notes: This third forest plot shows the effects of Empagliflozin by different levels of albuminuria

On account of on average slower progression of CKD, there were only 229 outcomes in patients with a urine ACR less than 300 milligrams per gram, and only 84 outcomes in patients with normoalbuminuria.

The statistical trend test for effect modification was 0.02, suggesting effects of SGLT2 inhibition on kidney disease progression are larger in patients with higher levels of albuminuria.

The relative effects of empagliflozin on the primary outcome when similar in the other subgroup analyses, including analyses by different primary kidney diagnosis and by baseline comedication.

Annual rate of change of eGFR

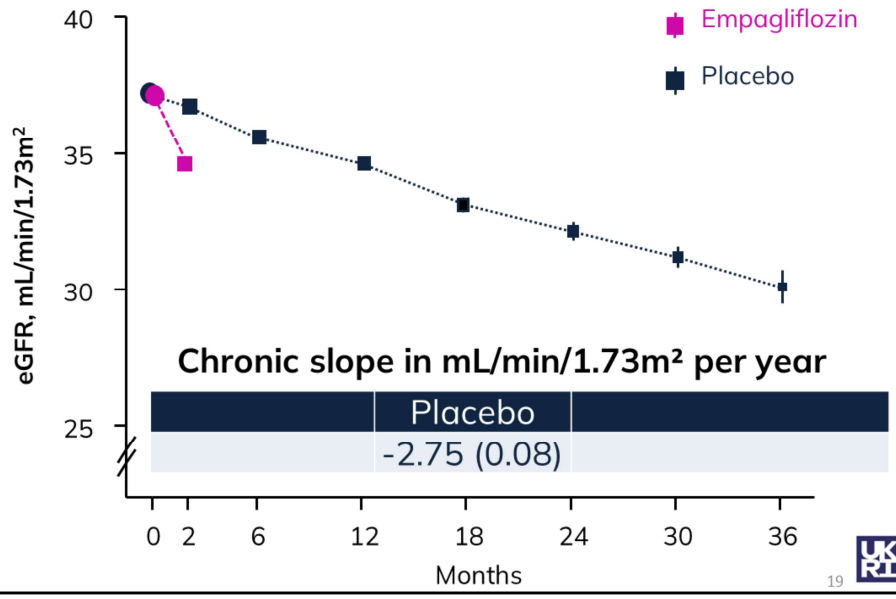


Speaker notes: Annual rate of change in eGFR as a tertiary outcome.

Plotted here is eGFR by time in the placebo group.

Fitting a slope analysis, on average patients in EMPA-KIDNEY progressed at a rate of 2.75 millilitres per minute per year.

Annual rate of change of eGFR



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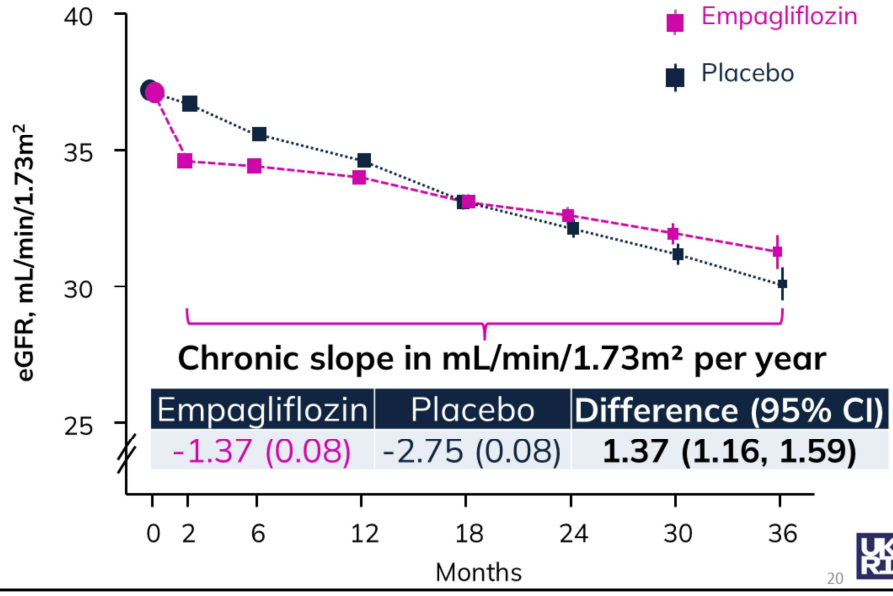
Speaker notes: On starting Empagliflozin there was the expected acute initial negative dip in eGFR.

Annual rate of change of eGFR



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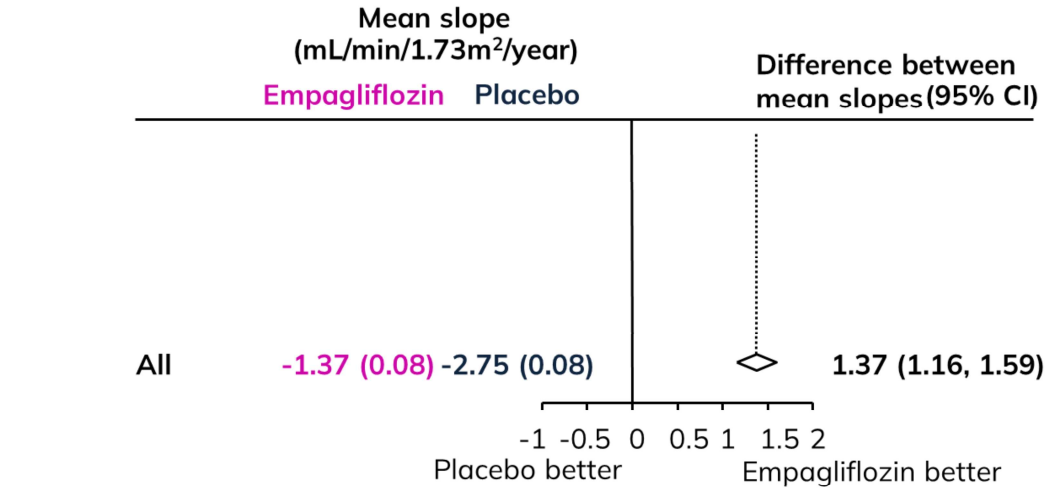
Speaker notes: hereafter, eGFR decline slowed to an average of 1.37 millilitres per minute per year. This equates to a difference between these two chronic eGFR slopes of 1.37.

This is equivalent to about a halving of the rate of decline in the chronic slope.

Empagliflozin slowed progression by 50%

Chronic eGFR slopes by albuminuria



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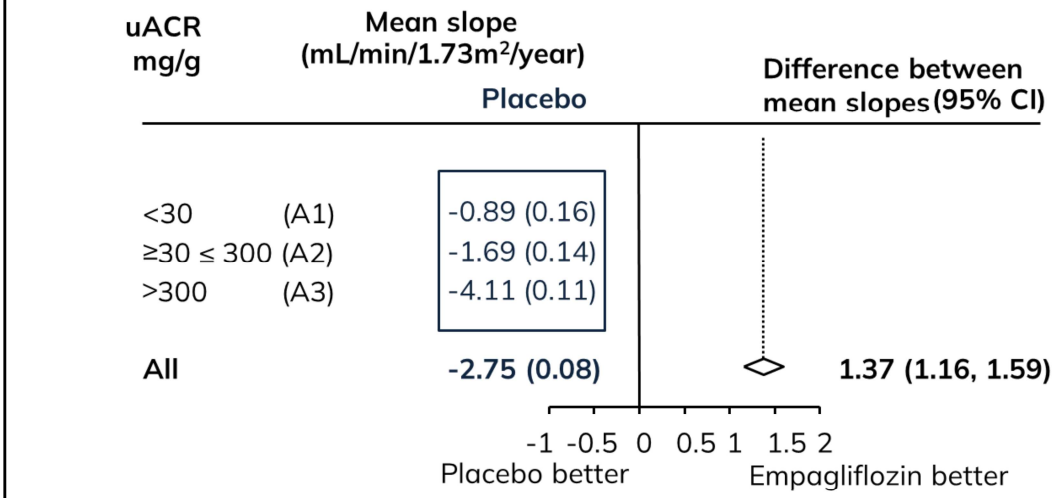
Speaker notes: This difference in between group mean chronic slope is now plotted in this forest plot as a diamond.

Given the observation of potential for albuminuria to modify the effect SGLT2 inhibition on the primary outcome, we elected to perform a prespecified exploratory subgroup analysis using this more sensitive outcome.

Chronic eGFR slopes by albuminuria



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Prespecified exploratory analyses

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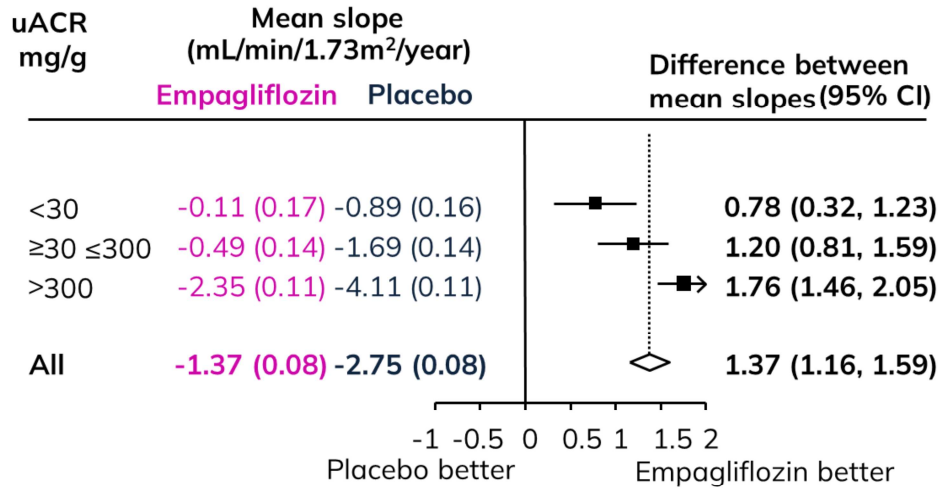
Speaker notes: In the placebo group, the chronic eGFR slope varied substantially by baseline level of albuminuria, from 0.89 millilitres per minute per year in patients with A1 levels of albuminuria to 4.11 in patients with A3 levels.

Chronic eGFR slopes by albuminuria



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Prespecified exploratory analyses

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Speaker notes: In the empagliflozin group, the rate of decline in eGFR decline slowed in ALL albuminuria subgroups.

The between group differences plotted in the boxes do show, however, that the absolute difference in the mean slopes did differ significantly across the albuminuria subgroups, with larger absolute benefits in those who were progressing faster.

Key secondary outcomes

	Empagliflozin (N=3304)	Placebo (N=3305)	Hazard ratio (95% CI)	P value
	n	n		
Hosp. for heart failure or CV death	131	152	0.84 (0.67-1.07)	0.15
Death from any cause†	148	167	0.87 (0.70-1.08)	0.21
	%/year	%/year		
All-cause hospitalization*	24.8	29.2	0.86 (0.78-0.95)	0.003

† 128/315 (41%) of deaths attributed to CV causes

* First & subsequent events (semi-parametric joint frailty model)

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Speaker notes: The three prespecified key secondary outcomes were based on non-kidney outcomes

There were 14% fewer hospitalizations from any cause in the empagliflozin group compared to the placebo group.

But no statistically significant effect on hospitalization for heart failure or cardiovascular death or death from any cause.

These analyses are limited by low power, but the point estimates are consistent with the totality of the evidence from other SGLT2 inhibitor trials.

Safety outcomes

Serious adverse events	Empagliflozin (N=3304)	Placebo (N=3305)	Hazard ratio (95% CI)
Urinary tract infection	52	54	0.94 (0.64-1.37)
Hyperkalemia	92	109	0.83 (0.63-1.09)
Acute kidney injury	107	135	0.78 (0.60-1.00)
Ketoacidosis	6	1	-
Lower limb amputation	28	19	1.43 (0.80-2.57)

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Speaker notes: For the key safety outcomes, ketoacidosis incidence was low, and occurred in 6 patients in the empagliflozin group versus 1 patient in the placebo group.

Lower limb amputations occurred in 28 patients in the empagliflozin group and 19 in the placebo group.

The incidence of serious urinary tract infections, hyperkalemia, and acute kidney injuries, and were broadly similar in each group.

EMPA-KIDNEY 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)
- Slope analyses: Empagliflozin slowed chronic eGFR decline in all albuminuria subgroups

Further details

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Empagliflozin in Patients with Chronic Kidney Disease

W.G. Herrington, N. Staplin, C. Wanner, J.B. Green, S.J. Hauske, J.R. Emberson, D. Preiss, P. Judge, K.J. Mayne, S.Y.A. Ng, E. Sammons, D. Zhu, M. Hill, W. Stevens, K. Wallendszus, S. Brenner, A.K. Cheung, Z.-H. Liu, J. Li, L.S. Hooi, W. Liu, T. Kadowaki, M. Nangaku, A. Levin, D. Cherney, A.P. Maggioni, R. Pontremoli, R. Deo, S. Goto, X. Rossello, K.R. Tuttle, D. Steubl, M. Petrini, D. Massey, J. Eilbracht, M. Brueckmann, M.J. Landray, C. Baigent, and R. Haynes, for the EMPA-KIDNEY Collaborative Group*

Patient information & slides at **www.empakidney.org**

@Oxford_NDPH

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Speaker notes: A full trial report of all prespecified analyses is available at New England Journal of Medicine.

These slides, a patient-orientated presentation, and other details are available on our website: www. empakidney.org

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