EMPA-KIDNEY

The study of heart and kidney protection with empagliflozin

Long-term Effects of Empagliflozin in Chronic Kidney Disease

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on behalf of the
EMPA-KIDNEY Collaborative Group

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We'd like to thank the ASN for the opportunity to present the results of EMPA-KIDNEY post-trial follow-up to you 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
  - Follow a long-standing departmental policy to decline personal honoraria

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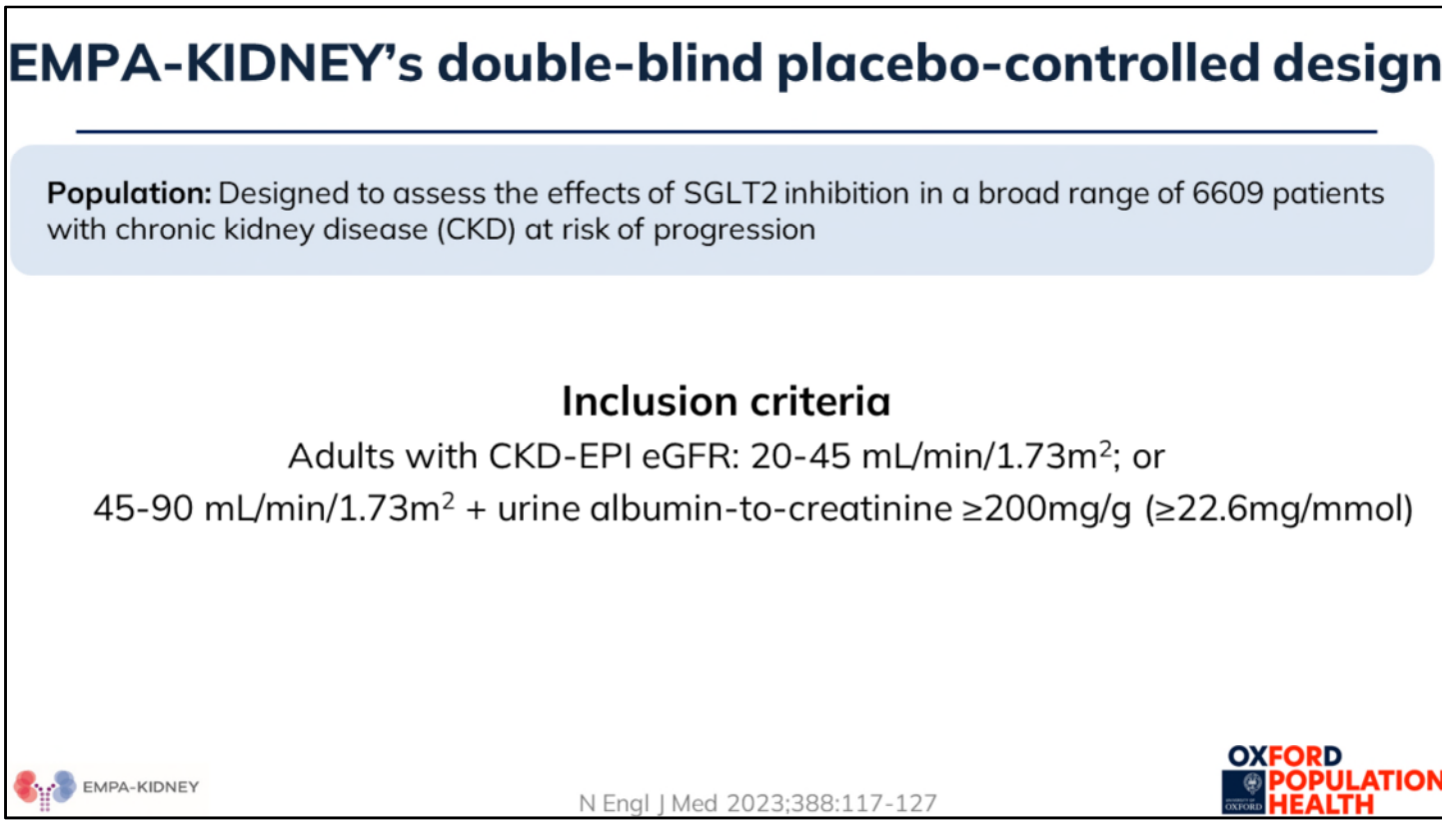
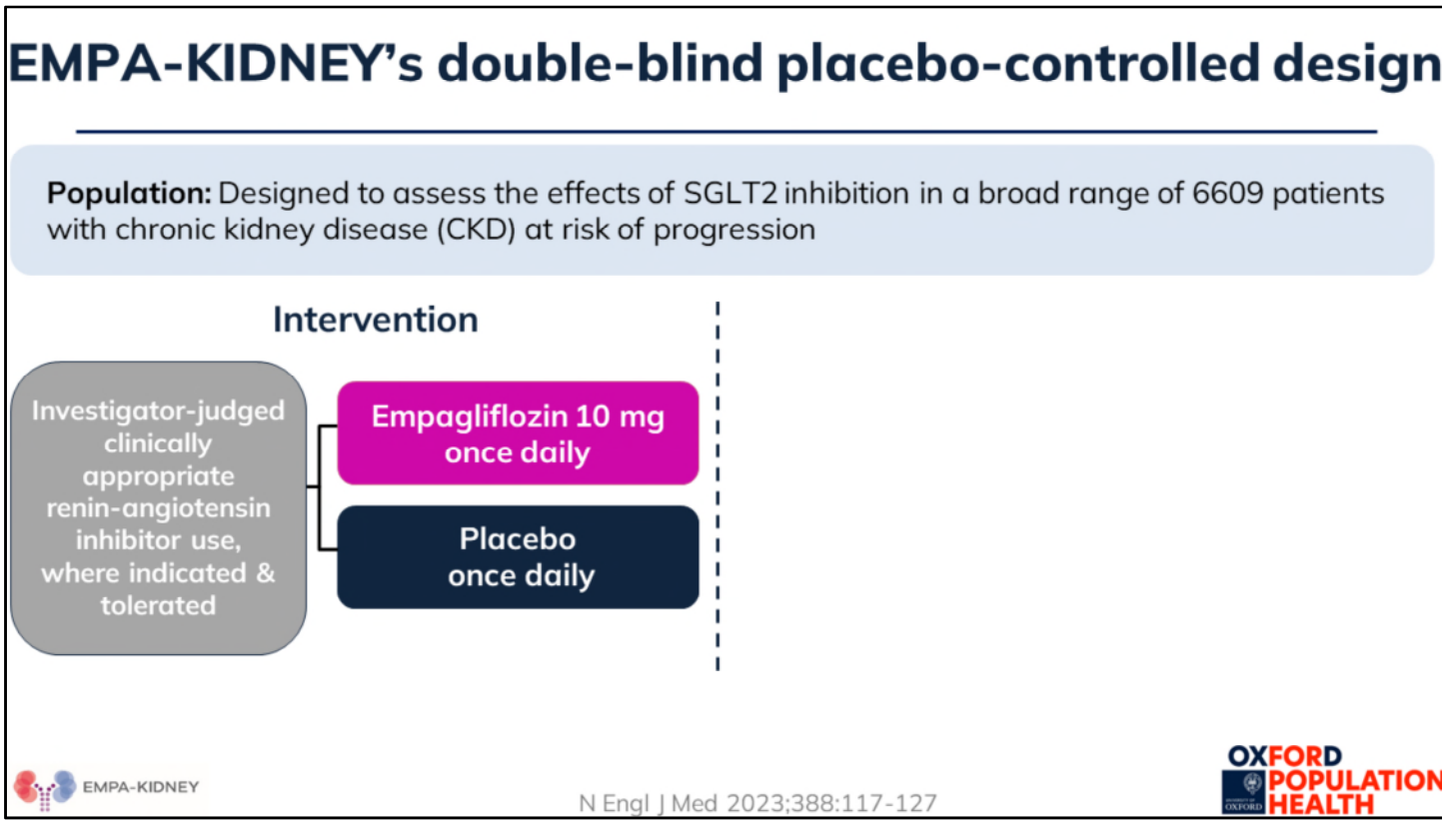


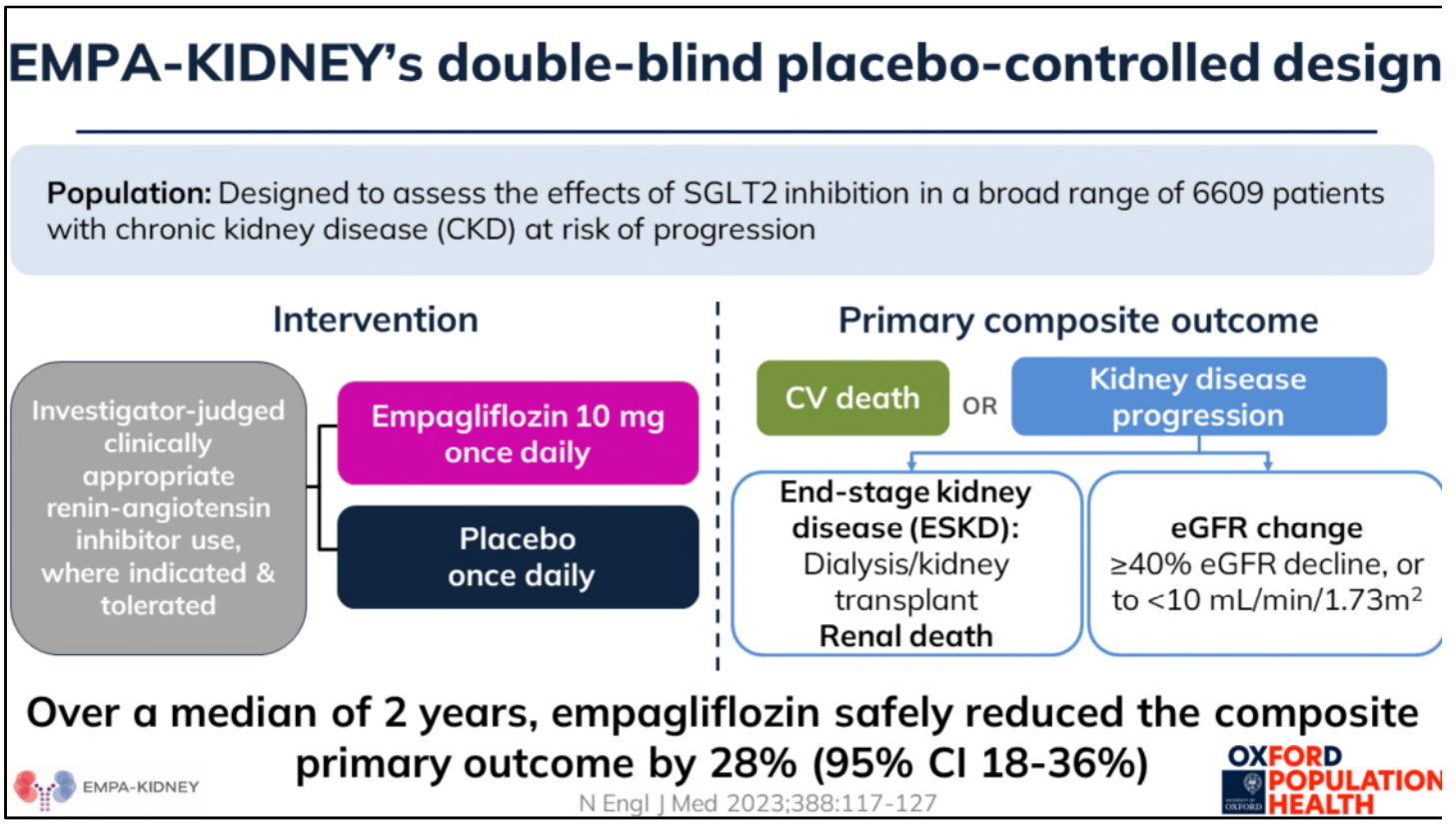
Two years ago in 2022 we reported the main results of the active trial at the ASN.

EMPA-KIDNEY was a double blind placebo controlled trial designed to assess the effects of SGLT2 inhibition in a broad range of 6609 patients with chronic kidney disease (CKD) at risk of progression

Simple inclusion criteria where adults with an eGFR between 20 and 45, or 45 to 90 with at least 200 mg/g of albuminuria.



Those on clinically appropriate RAS inhibition, where indicated and tolerated, were randomized 1:1 to empagliflozin versus matching placebo



And followed for the primary composite outcome of cardiovascular death or kidney disease progression, defined as receipt of maintenance dialysis or a kidney transplant, a sustained eGFR less than 10 or at least a 40% decline in eGFR from baseline.

The trial was reported early after only 2 years of median follow-up as empagliflozin had been found to safely reduce risk of the primary outcome by 28%.

Post-trial follow-up design

- Post-trial follow-up tests how effects evolve once a trial drug is stopped
  – i.e. no specific hypothesis testing
- After completion of the active trial, surviving EMPA-KIDNEY participants were observed post-trial for 2 additional years
- **No trial drug was issued in the post-trial period, but local doctors could prescribe SGLT2i**

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Post-trial follow-up tests how effects evolve once a trial drug is stopped.

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- **The original primary composite outcome was pre-specified to be assessed over the entirety of follow-up (i.e. from the start of the active trial to the end of the post-trial period)**

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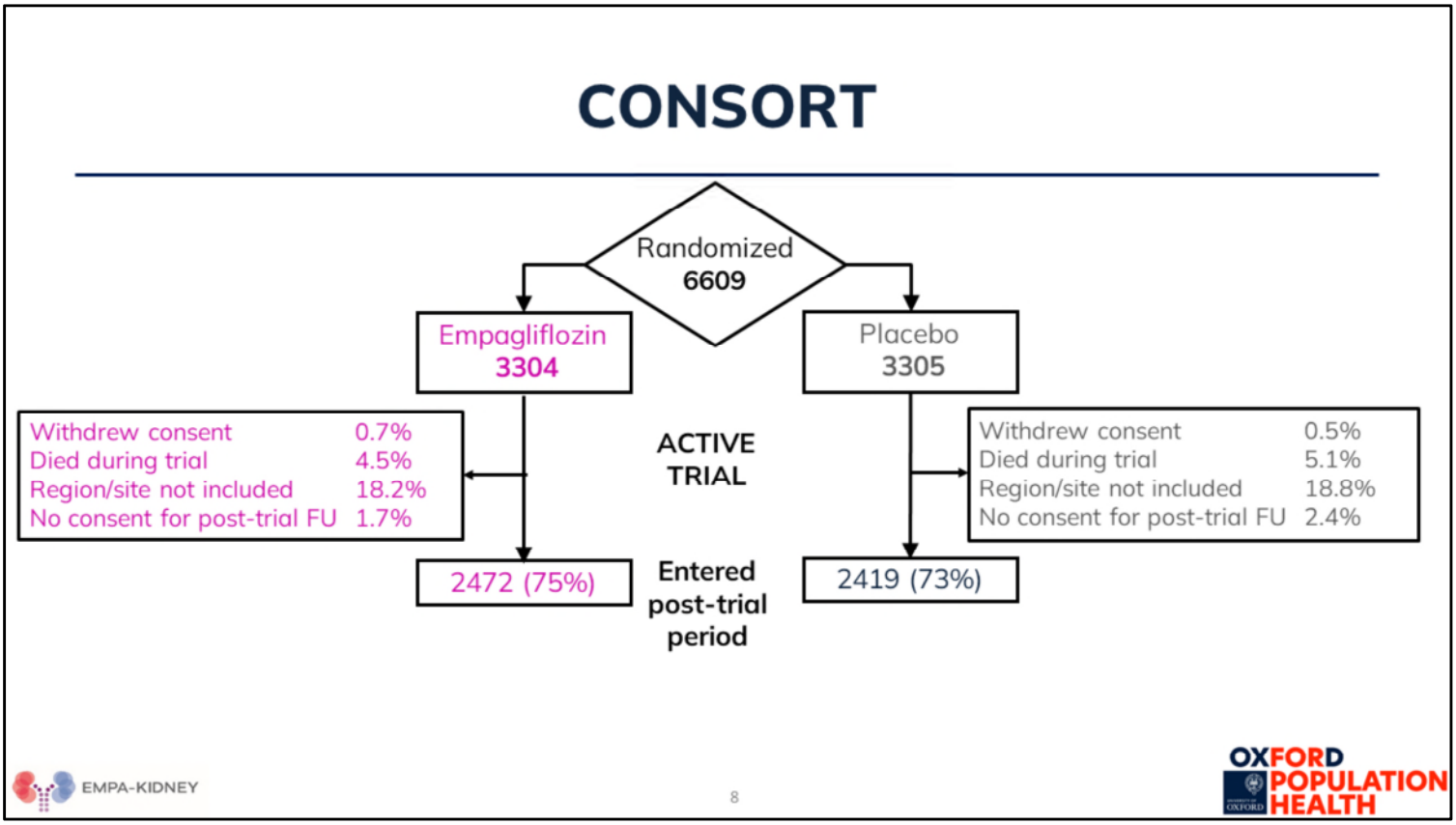
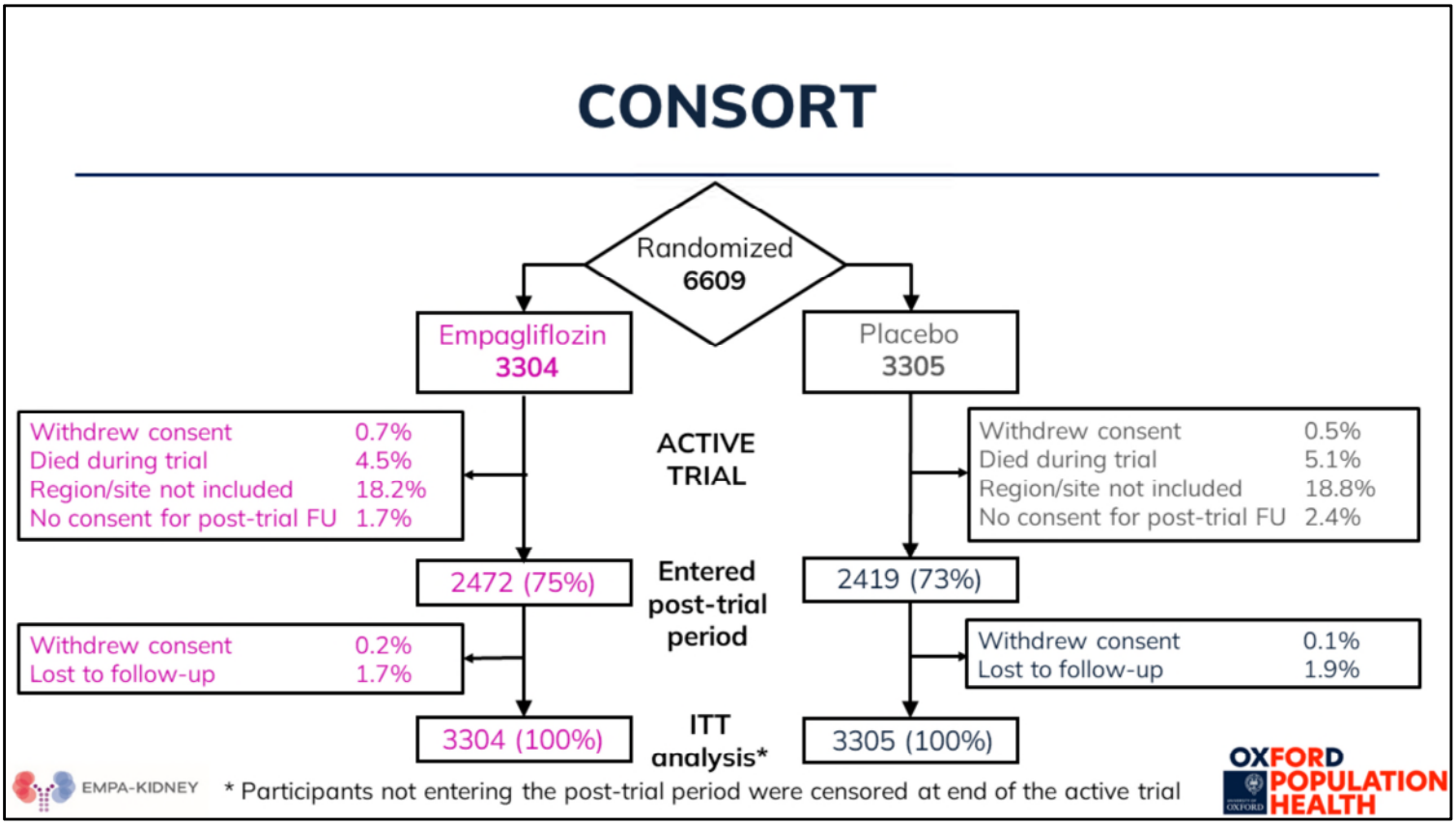
The post-trial primary outcome was the original primary outcome pre-specified to be assessed over the entirety of follow-up (i.e. from the start of the active trial to the end of the post-trial period)



4-5% of patients died during the active trial, and 18% were from non-participating sites, leaving about three quarters to enter the post-trial period



At the end of which less than 2% were lost to follow-up.

All 6609 participants were analysed.

Participants not entering the post-trial period were censored at end of the active trial

Post-trial cohort characteristics at randomization

	Empagliflozin (N=2472)	Placebo (N=2419)
Mean age at randomization (years)	63 ±14	63 ±14
Female	34%	34%
No prior diabetes	56%	58%
Mean estimated GFR (mL/min/1.73m^2)	37 ±14	37 ±14
<30	35%	35%
Median urinary ACR (mg/g)	324 (44-1045)	313 (45-1079)
≤300 (A1-A2)	49%	49%

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EMPA-KIDNEY represented a large number of the types of patents in nephrology clinics that had not been well studied in previous SGLT2i trials.

In the post-trial cohort, nearly 60% did not have diabetes, just over 1/3rd had an eGFR below 30

And about one-half had A1 or A2 levels of albuminuria.

Use of SGLT2 inhibitor over time

Blinding to original group allocation was maintained in >99% of participants throughout all follow-up

	SGLT2 inhibitor use*	
Follow-up	**Empagliflozin group**	**Placebo group**
Active trial - average use	90%	2%
	End of active trial: study drug stopped	
Post-trial – average use	43%	40%

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* Any SGLT2 inhibitor, not necessarily empagliflozin

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Blinding to original group allocation was maintained in >99% of participants throughout follow-up.

During the active trial average use of any SGLT2 inhibitor in the empagliflozin group was 90% compared to 2% in the placebo group

Post-trial these proportions became similar at 43% versus 40%.

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Loss of the between group difference in SGLT2i use post-trial enables assessment for any carry-over effect of allocation to empagliflozin

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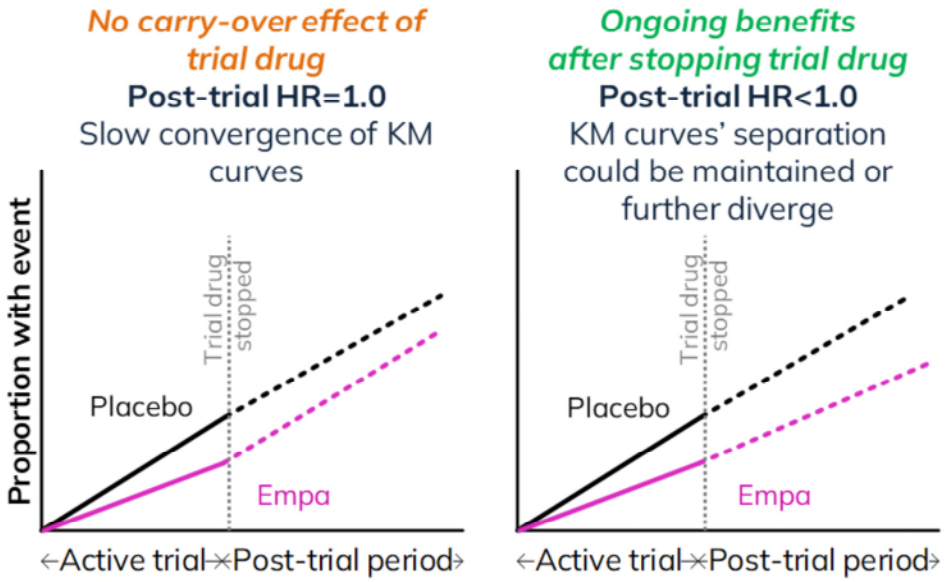
The loss of between group difference in the post-trial period enables assessments of any carry-over effect of allocation to empagliflozin.

Hypothetical post-trial scenarios



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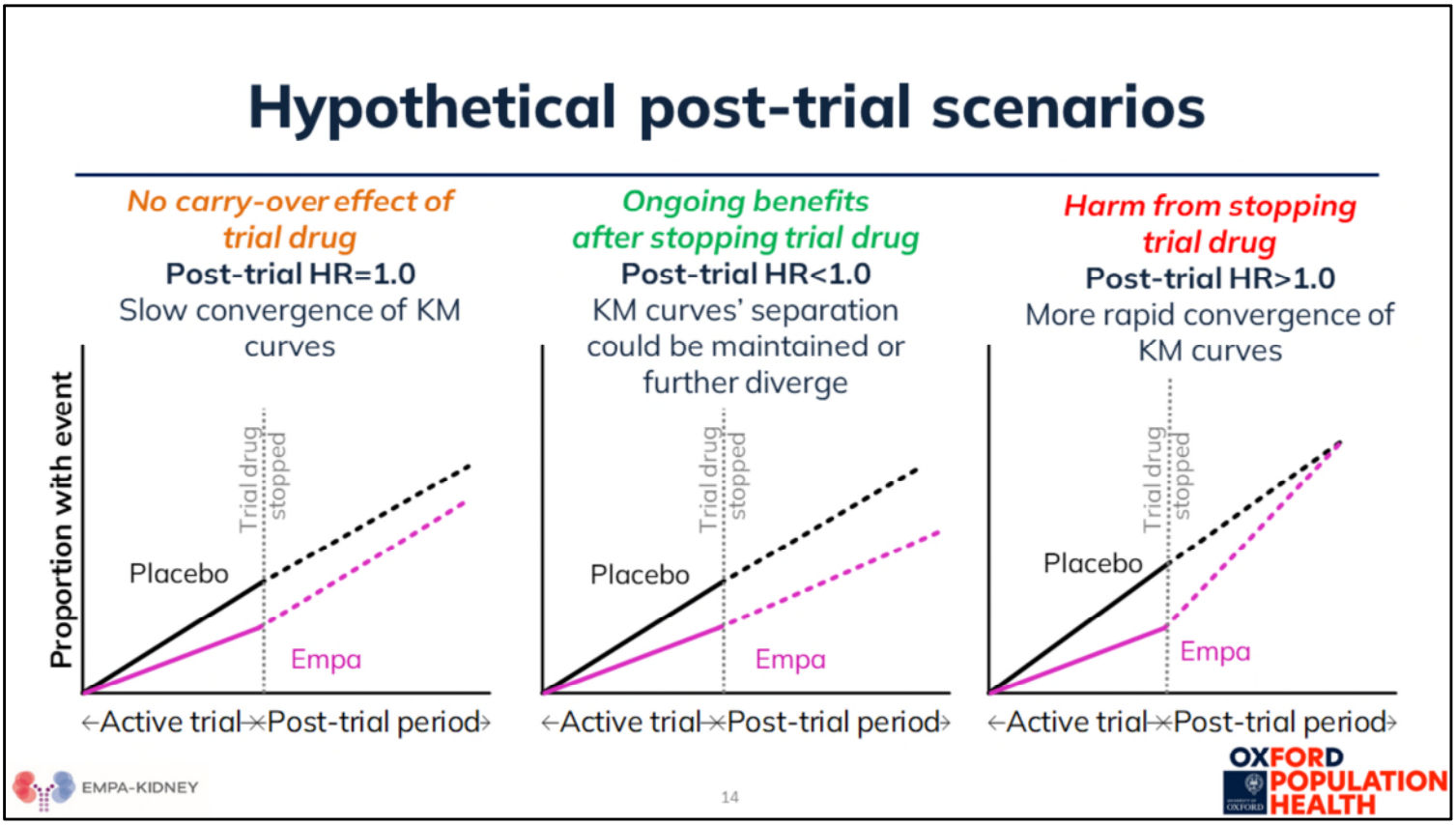
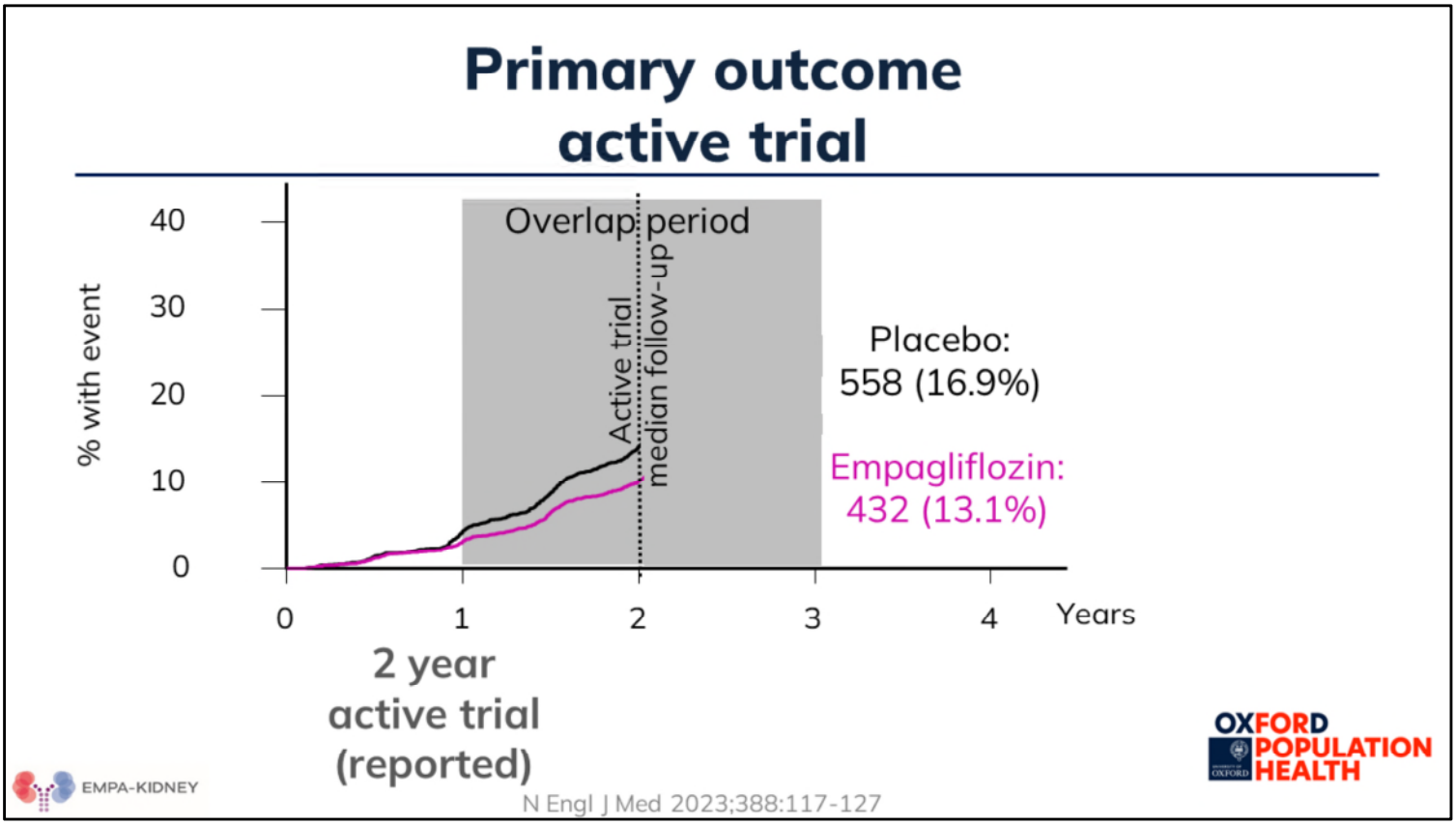
Hypothetically, in the absence of any carryover effect, Kaplan Meier curves would slowly converge.

An ongoing benefit post-trial would lead to maintenance of the curve, and it the effect was large, continued divergence.

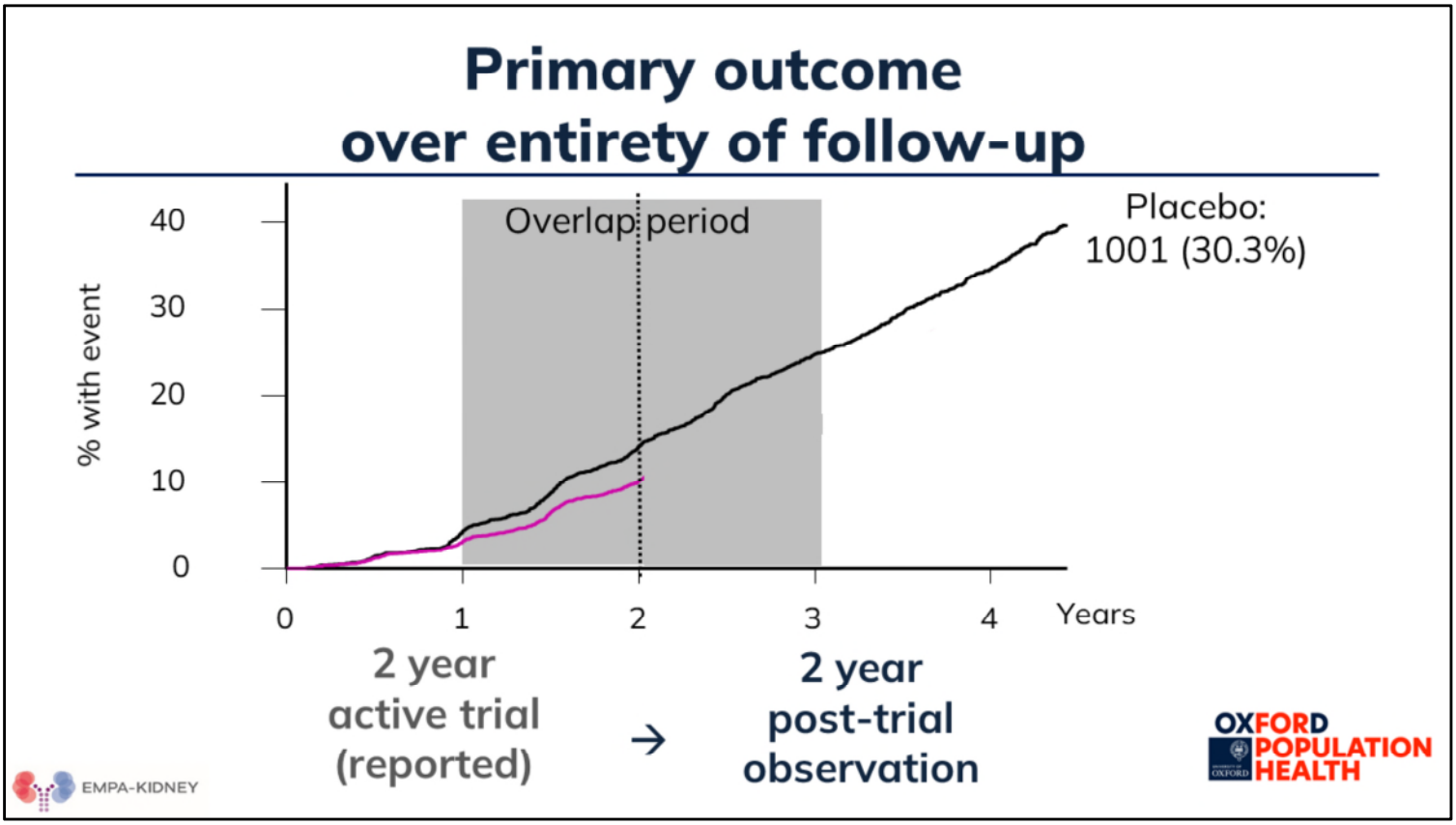


Conversely, if there was harm from stopping study treatment, curves would rapidly begin to converge.

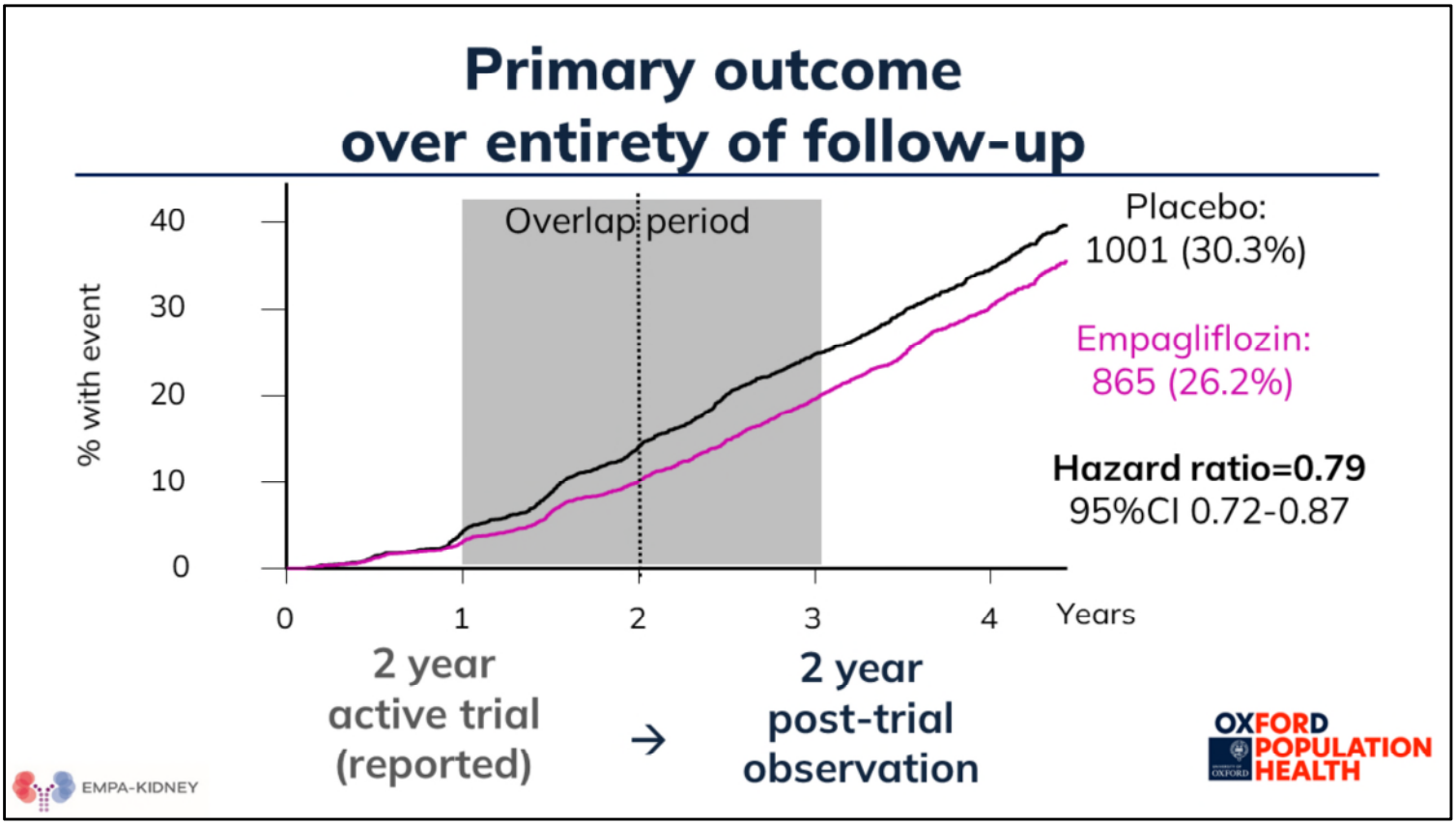


In the 2 years of the active trial, the previously reported benefits were clear.

558 vs 432 outcomes.

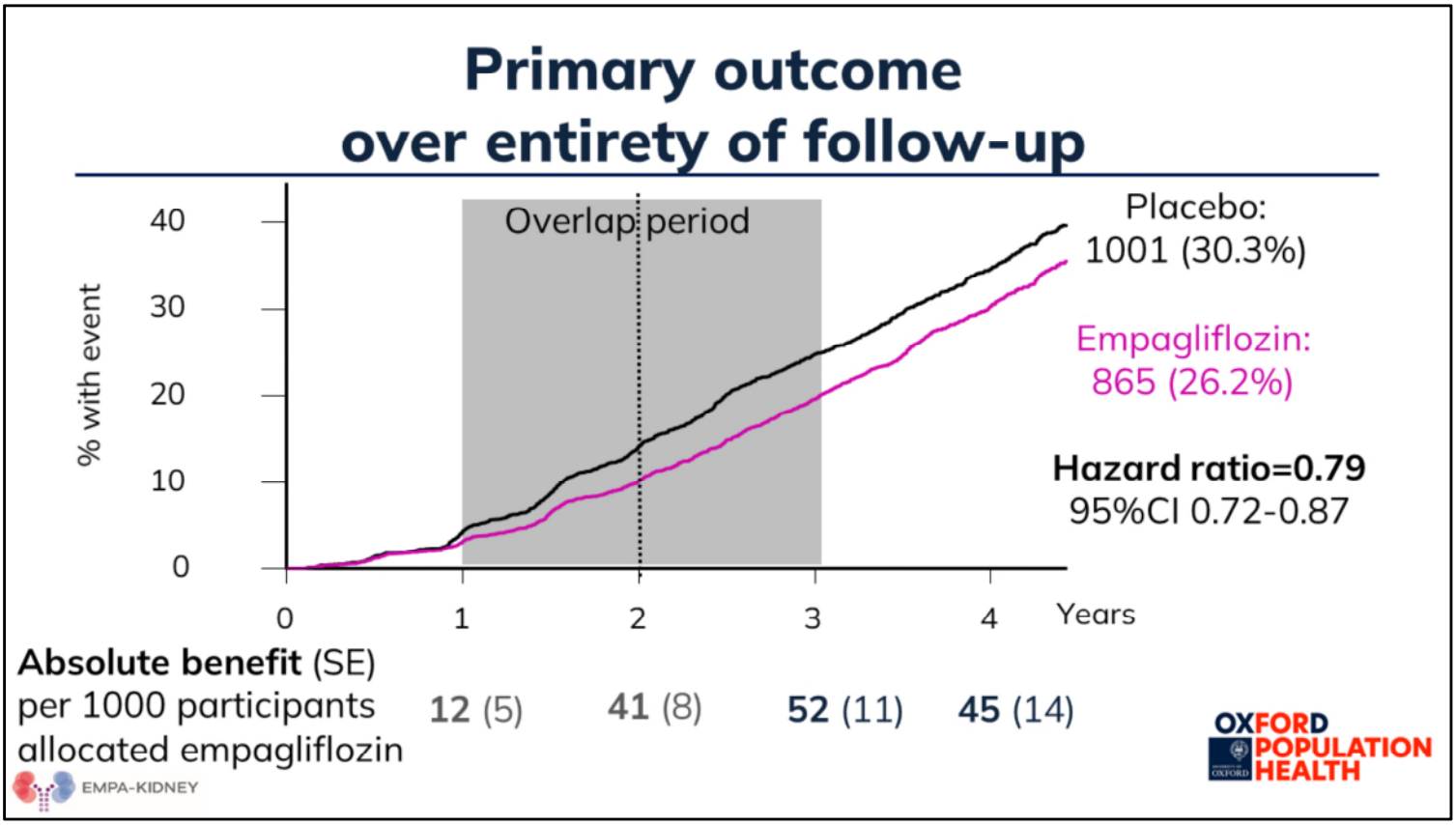


At the end of the 2 extra years of post-trial observation, there were 1001 participants with a primary outcome in the placebo group

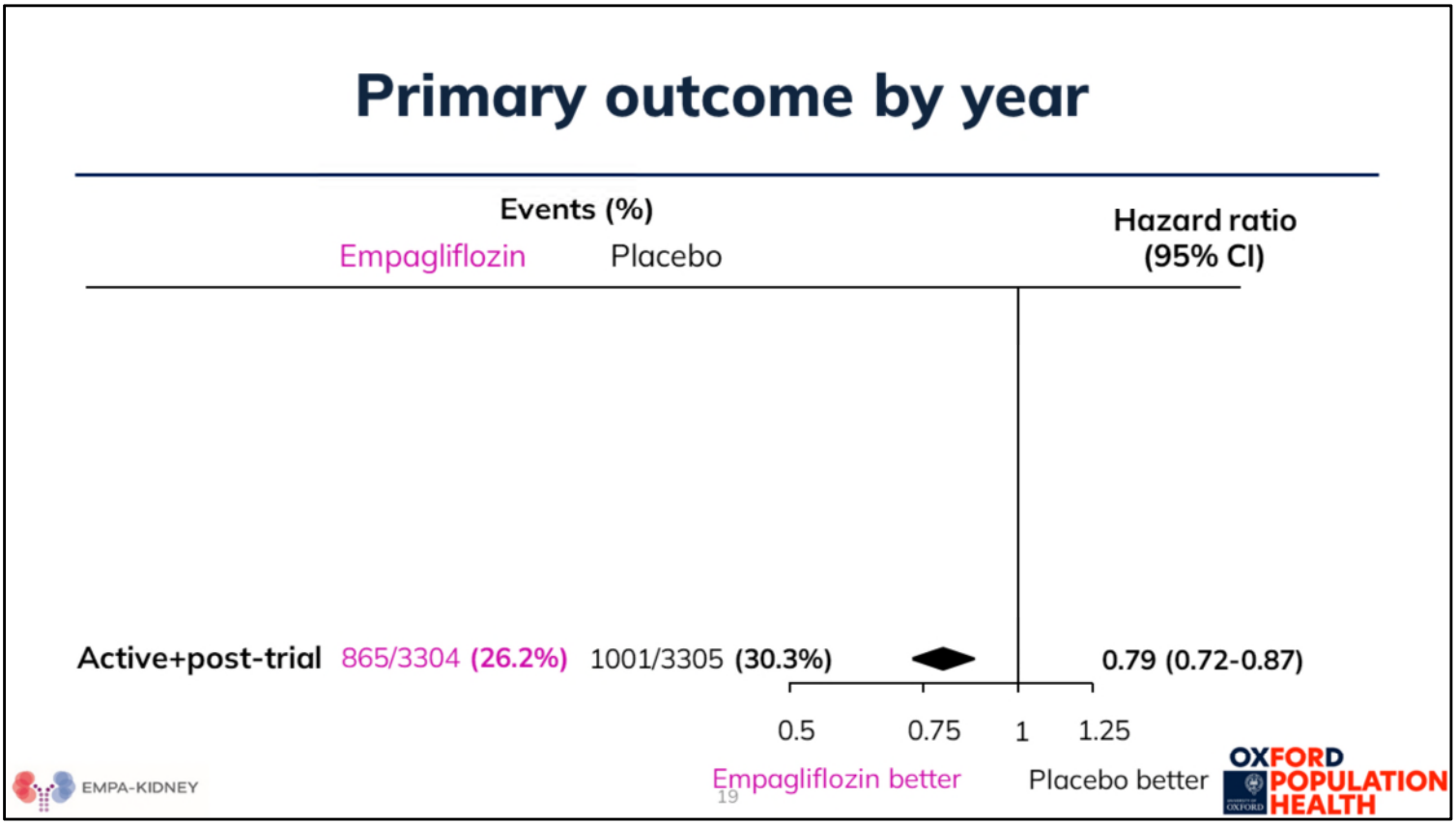


And 865 in the empagliflozin group.

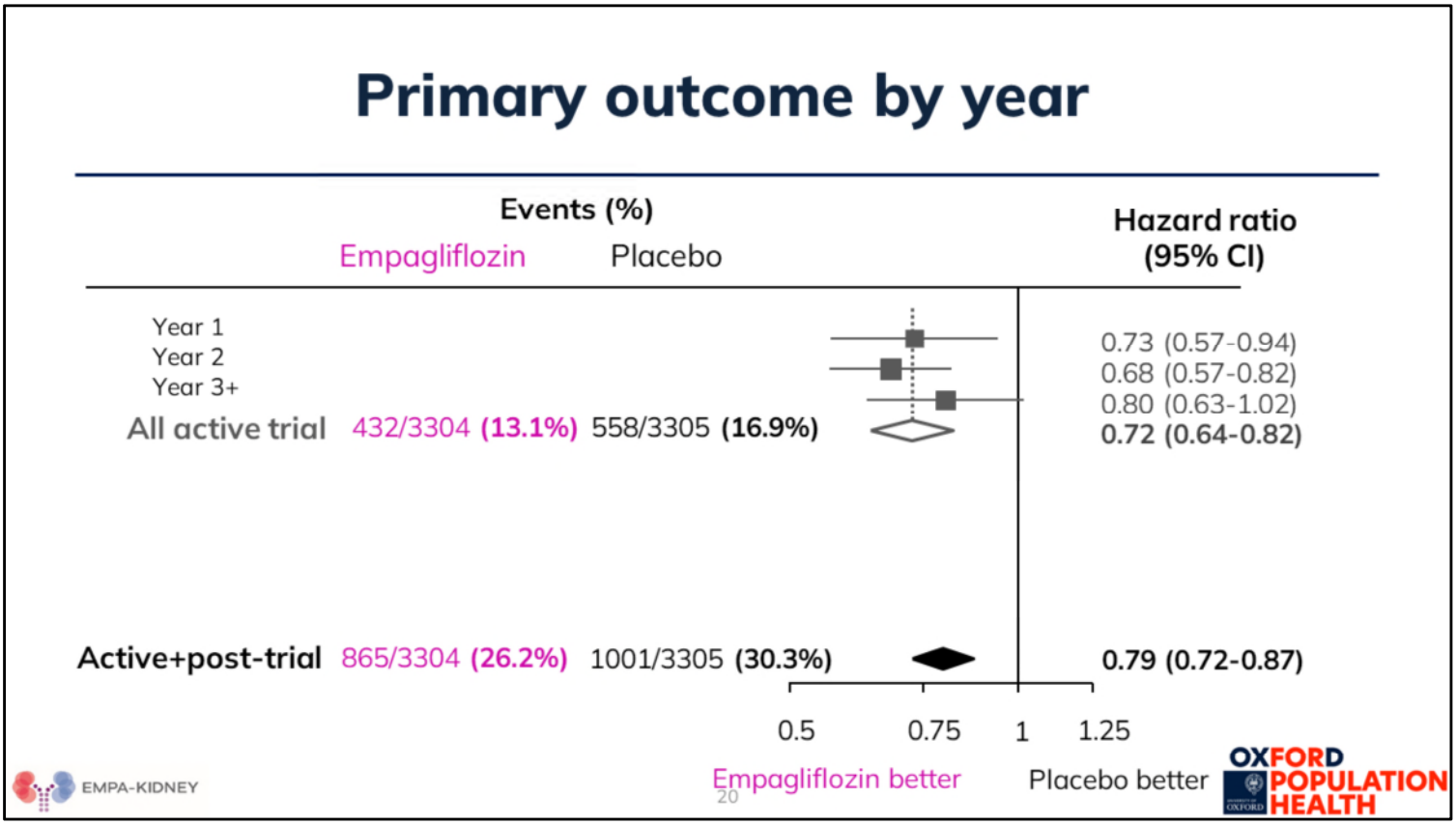
So 2 years of allocation and provision of empagliflozin led to a 21% relative reduction in risk of the primary outcome over the entire 4 year follow-up period.



Kaplan Meier curves initially continued to diverge, with the absolute difference maximal at about 3 years after randomization when there were 52 fewer participants with a primary outcome per 1000 allocated to empagliflozin.

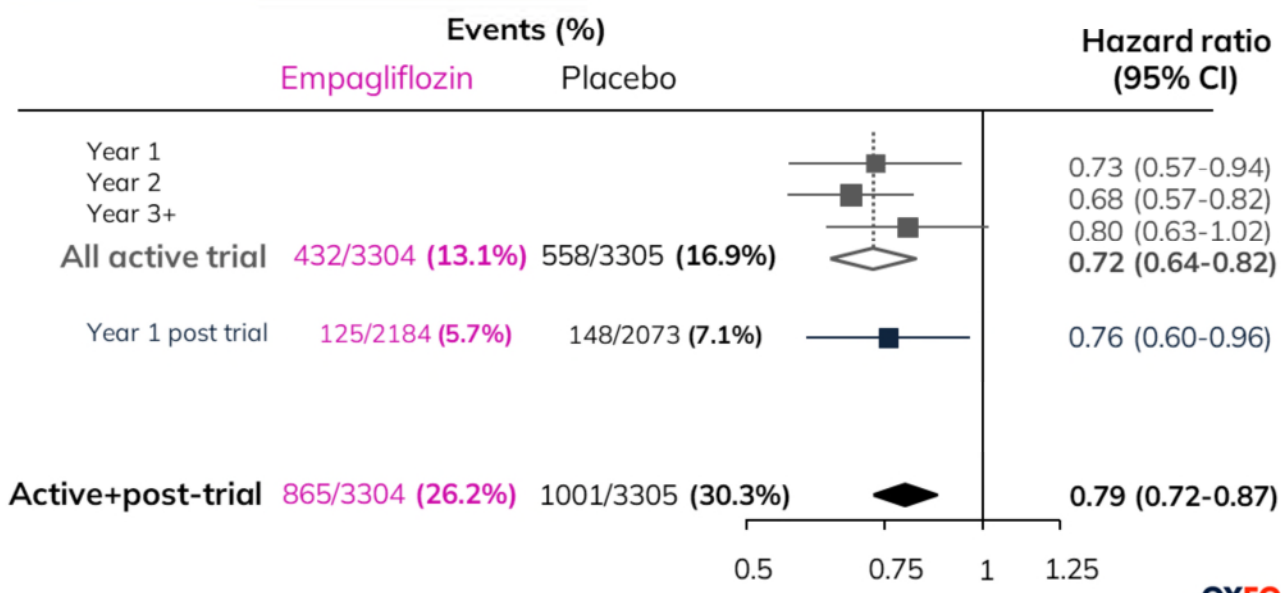


These results are now converted onto a forest plot, with the results of the combined trial periods in the diamond.

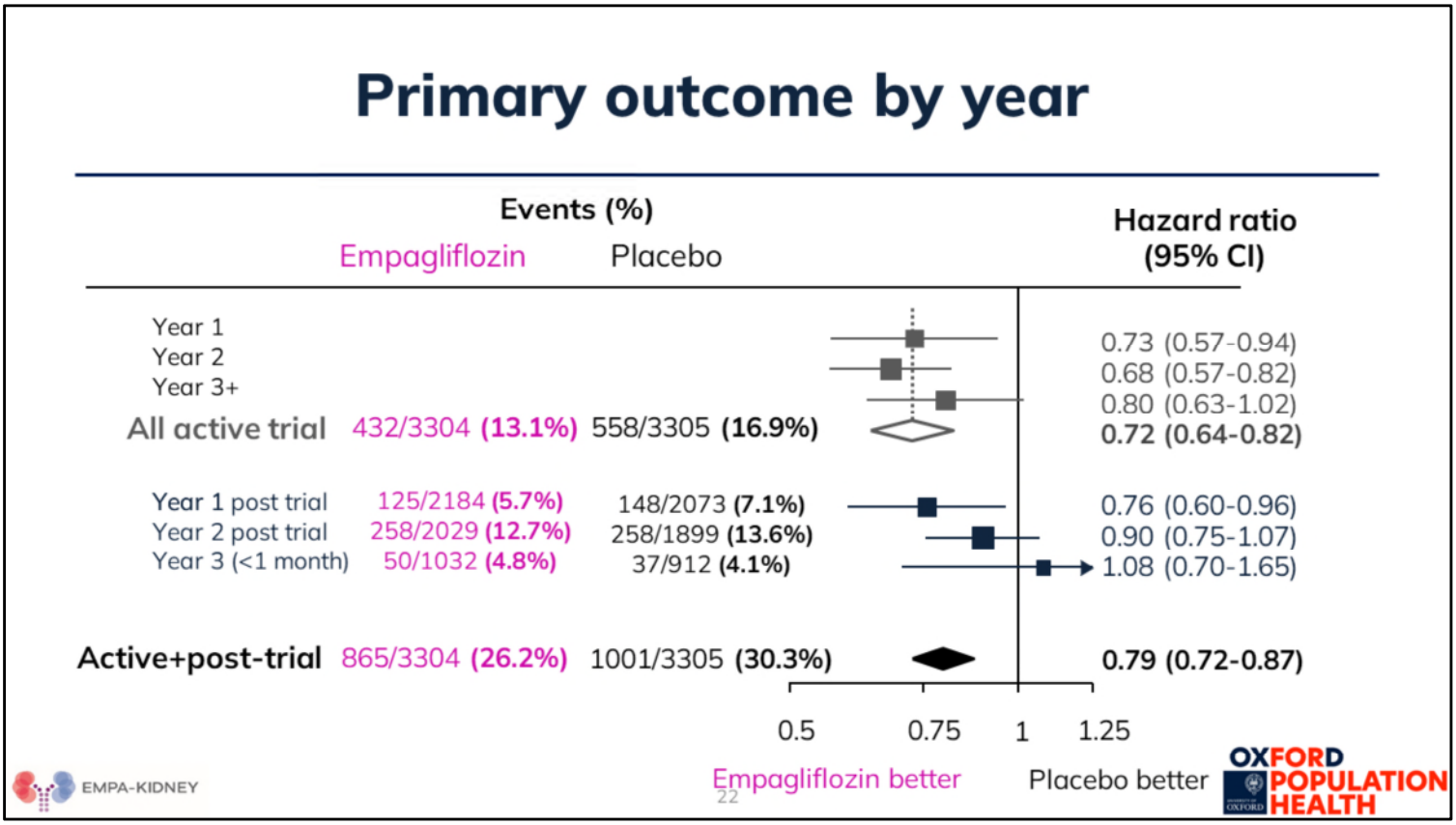


The effect was constituted from the 28% reduction in risk during the active trial,

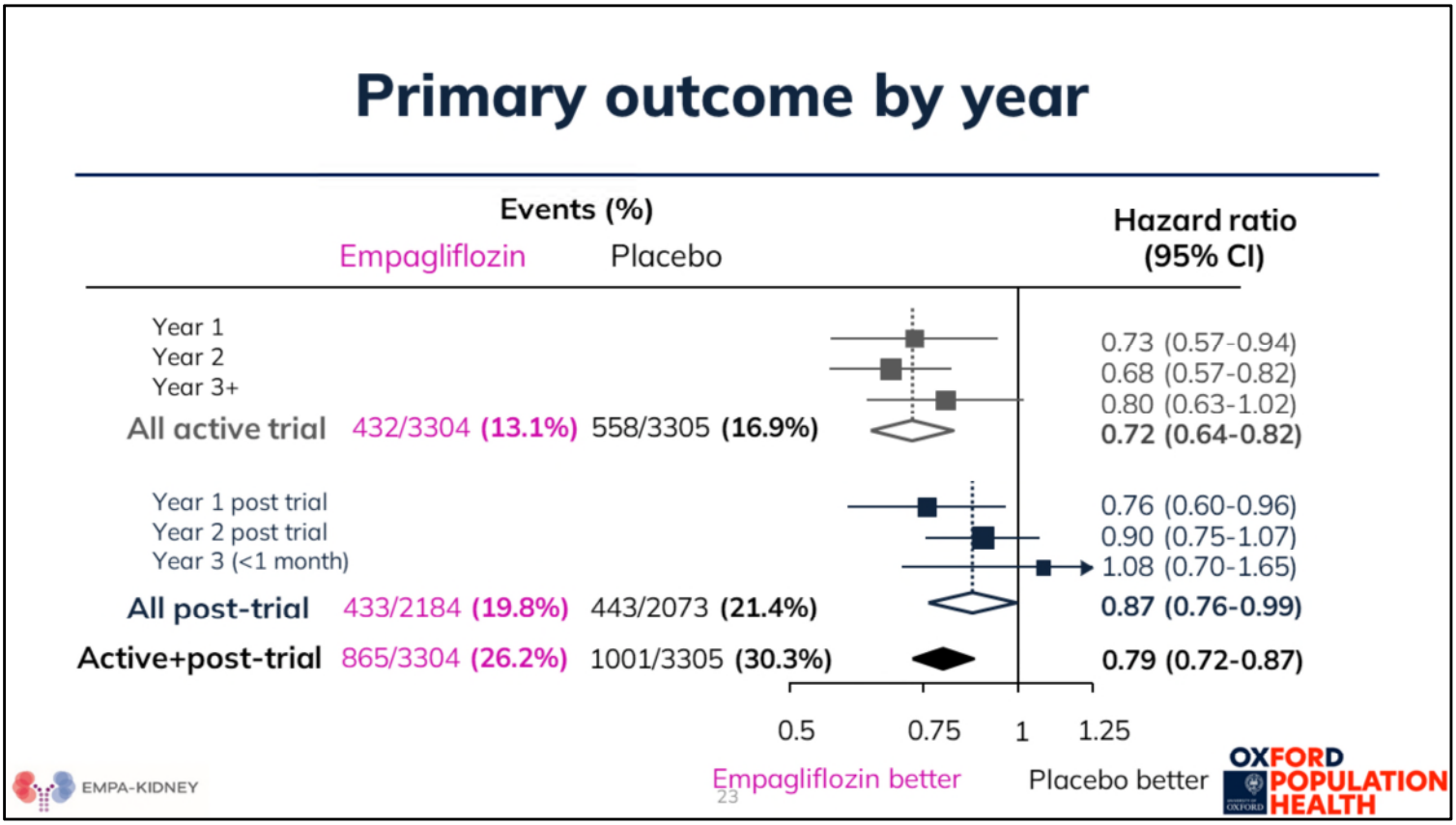
Primary outcome by year



Plus a 24% reduction in risk 1 year post-trial



And then no clear benefit in the second and short third years post-trial



Resulting in a net 13% reduction in risk during the post-trial period.

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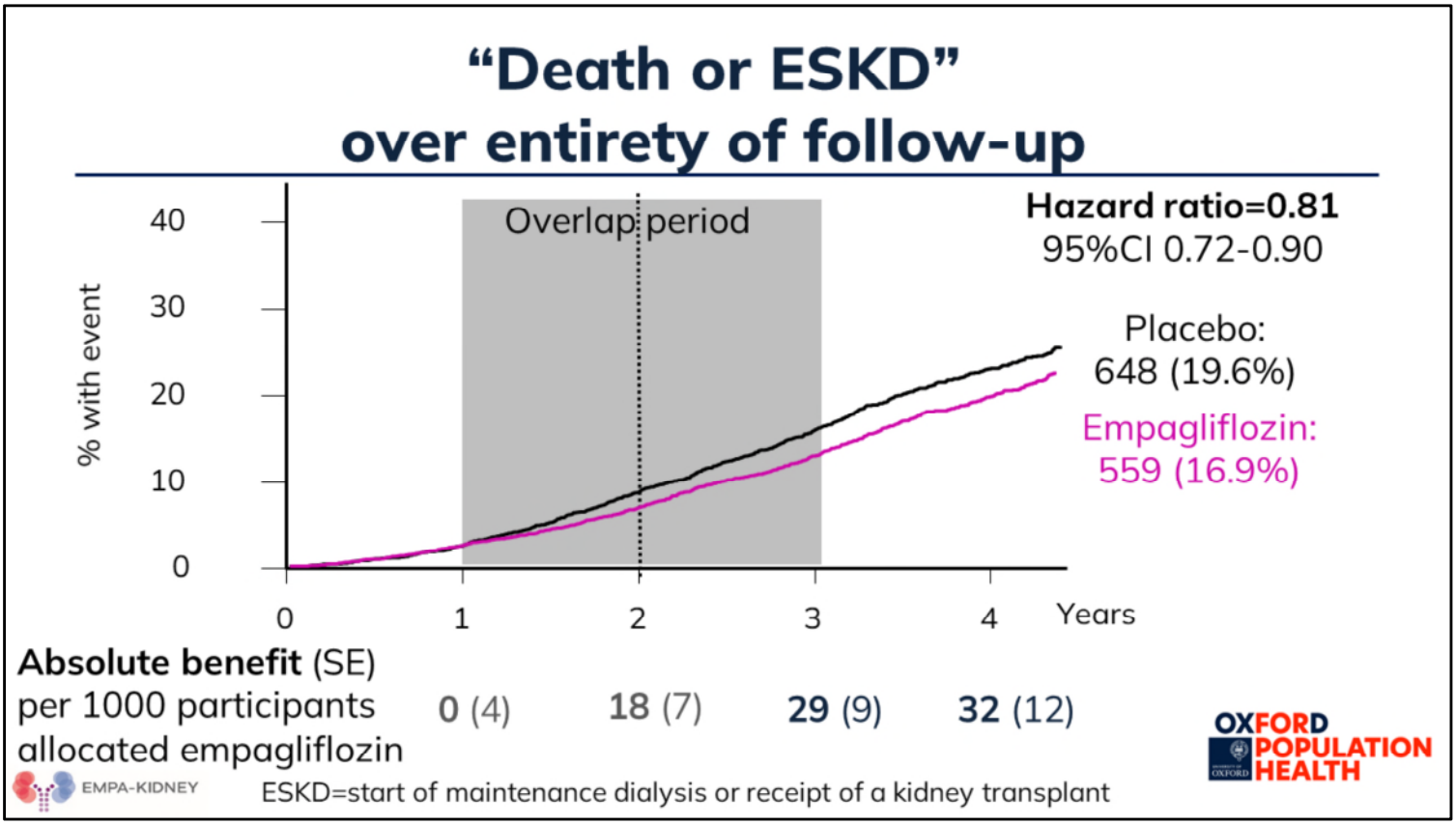

A key benefit of longer follow-up is the extra time to allow for accrual of more "hard" clinical outcomes that take time to develop

A key secondary outcome was the composite of death or end-stage kidney disease.

At the end of the post-trial period there were 648 versus 559 of such outcomes, a 19% reduction in risk for this outcome

With maximal absolute benefit of 32 fewer participants with this outcome per 1000 allocated to empagliflozin

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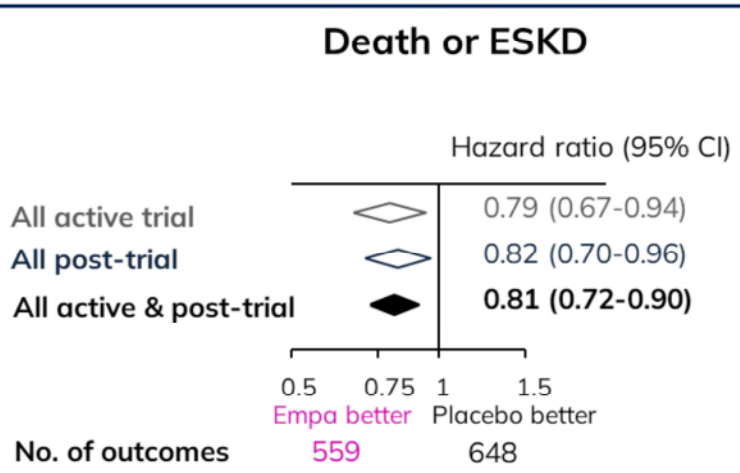
Key secondary composite outcomes



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ESKD=start of maintenance dialysis or receipt of a kidney transplant

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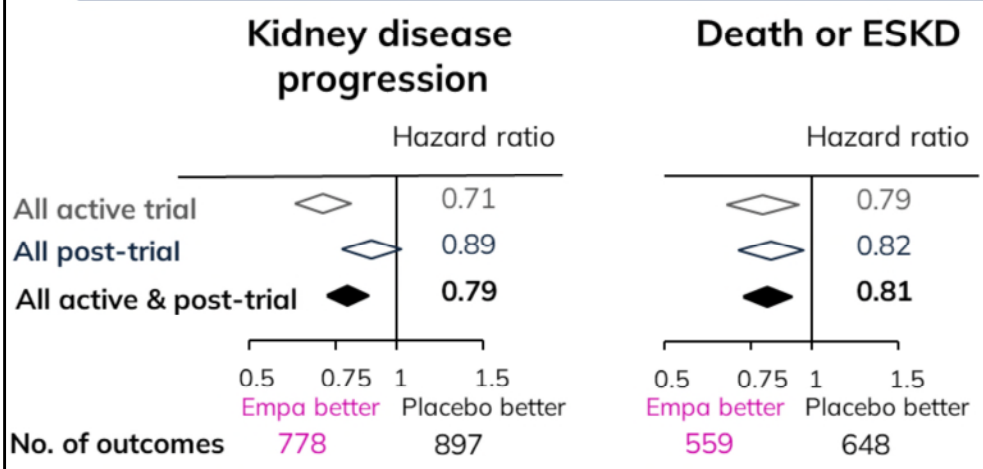
This same result is now provided in this Forest plot. The 19% reduction for the entire period was made up from a 21% reduction in risk in the active trial and an 18% reduction in risk post-trial.

Key secondary composite outcomes



Some of the observed post-trial benefit on eGFR components could result from the reversal of the small acute eGFR dip when trial drug was stopped.

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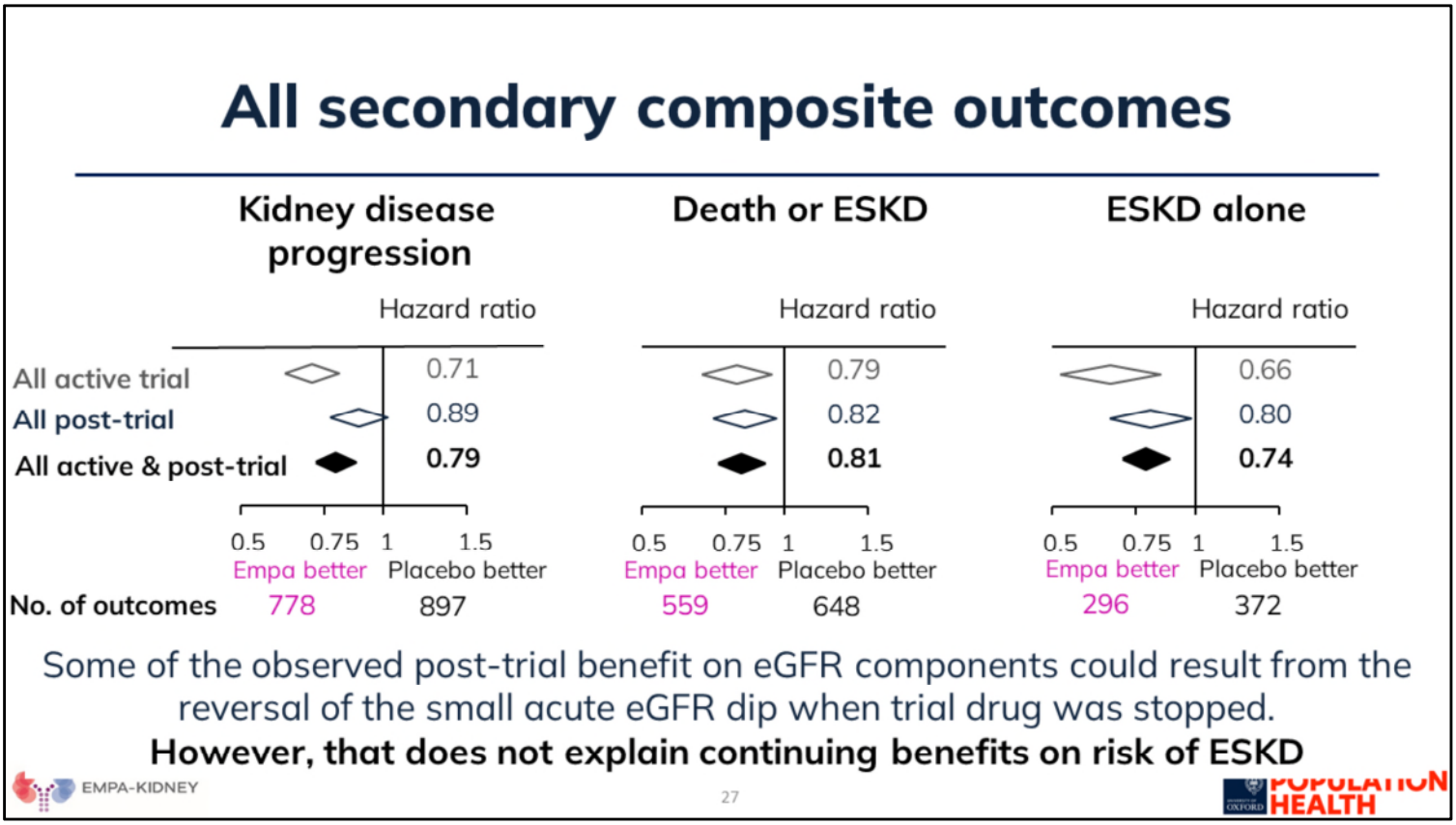
The left plot presents the same analyses for the outcome of any kidney disease progression.

897 versus 778 outcomes.

Some of the observed post-trial benefit on eGFR components could result from the reversal of the small acute eGFR dip when trial drug was stopped.



However, that does not explain continuing benefits on risk of ESKD.

Which was reduced by 34% during the active trial and 20% post-trial.

372 vs 296 outcomes.

A net quartering of the risk of ESKD over the entirety of follow-up.

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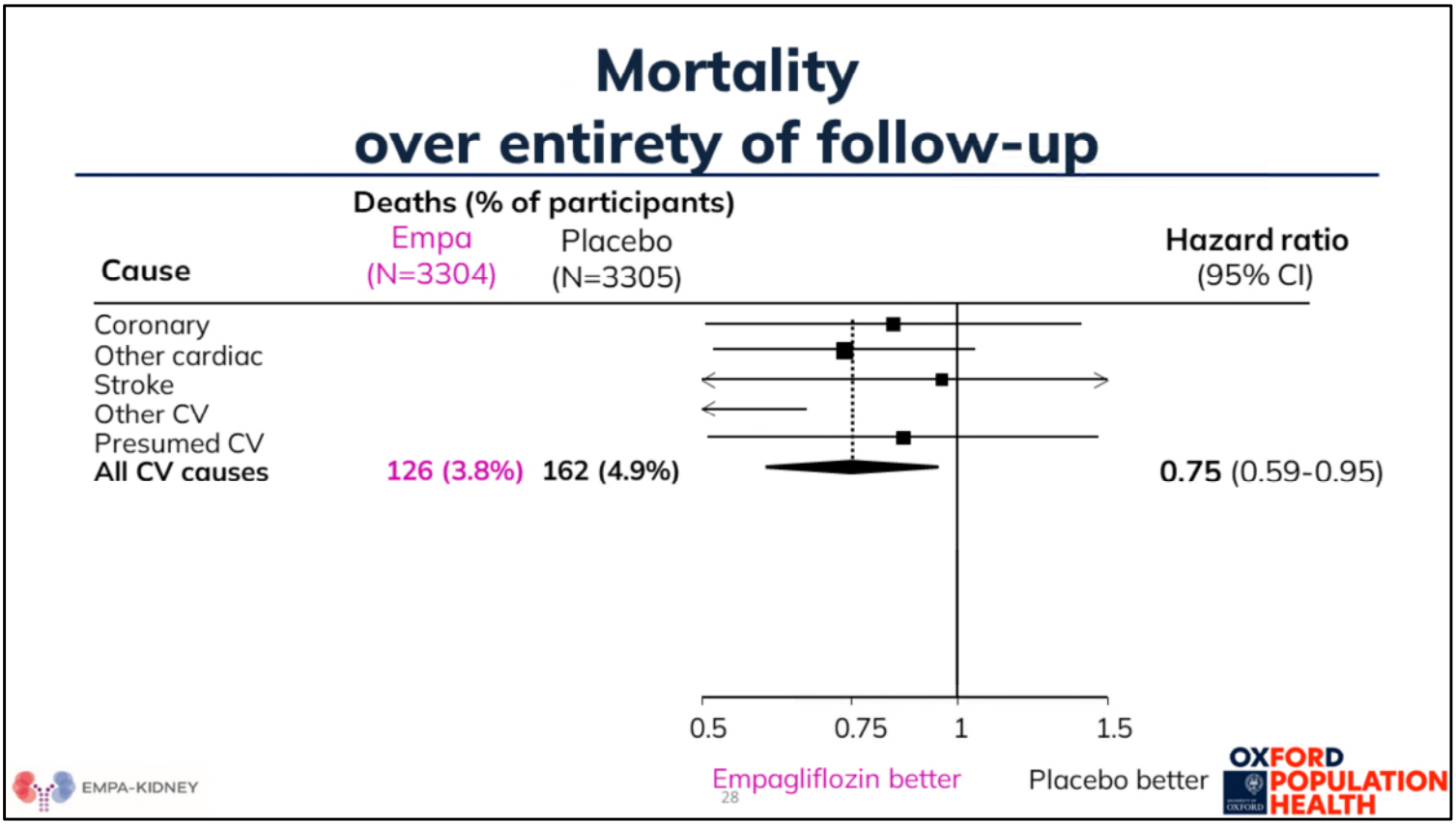
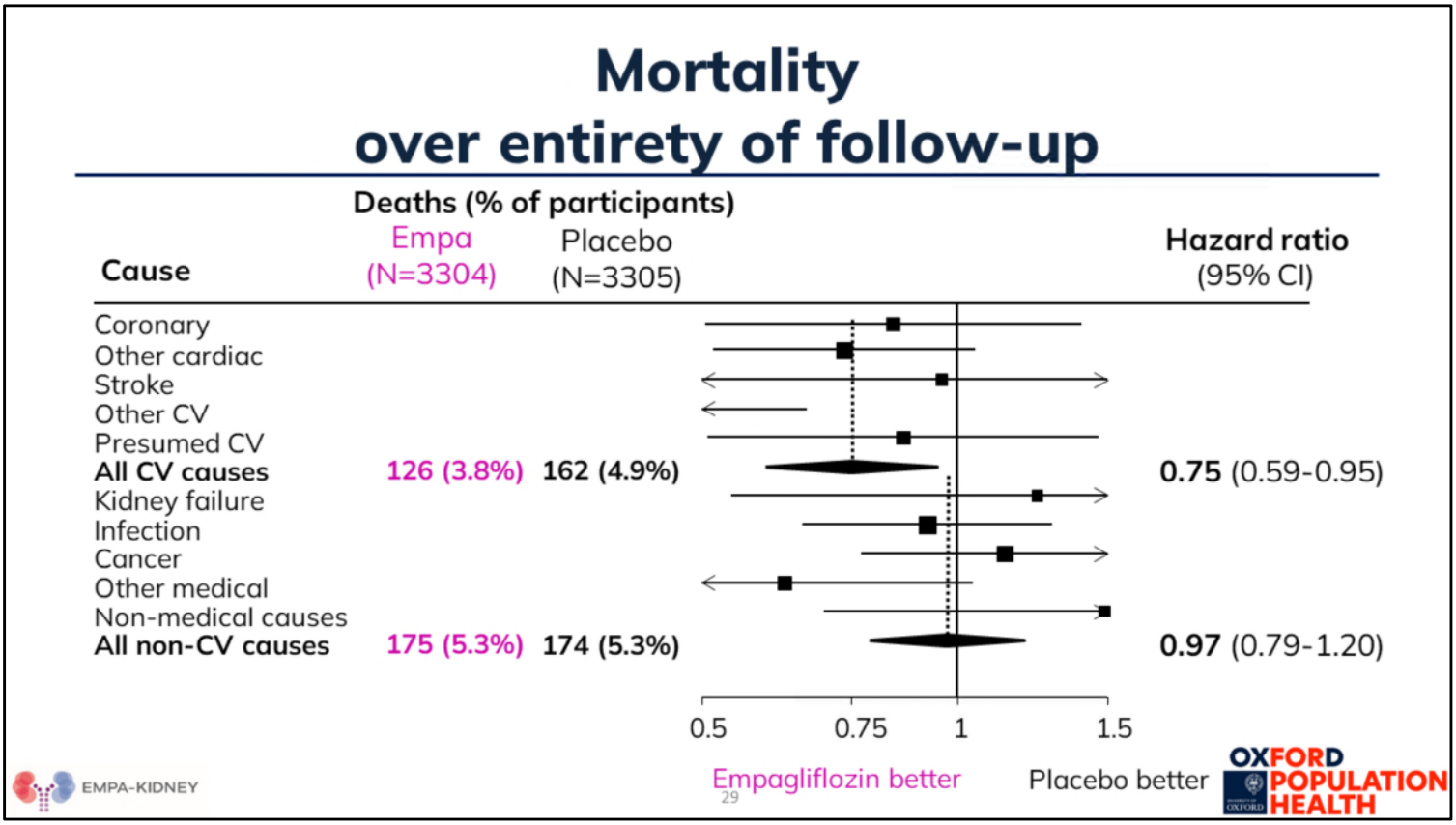
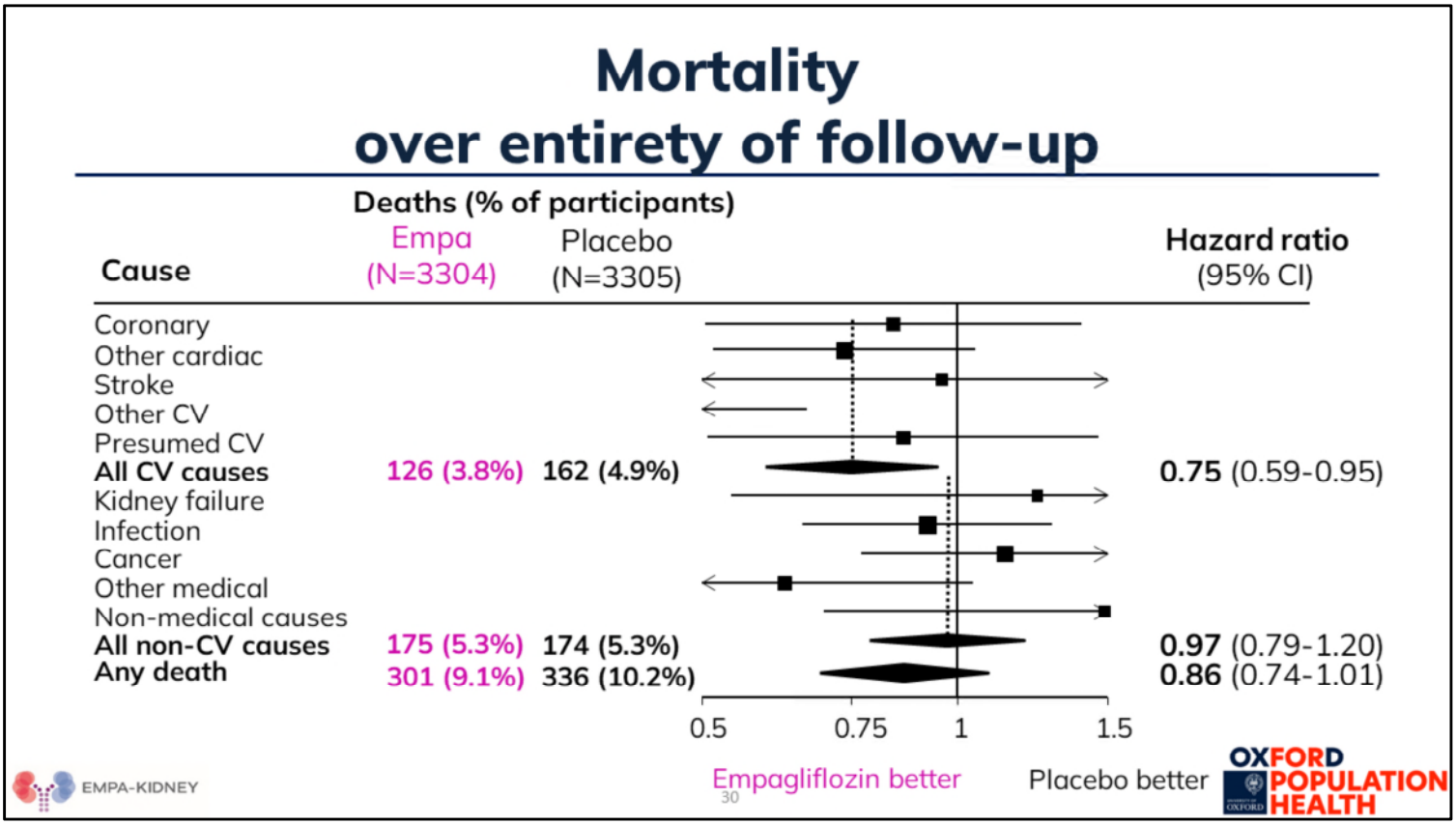


Breaking down the deaths, there were 162 versus 126 cardiovascular deaths, a 25% reduction in risk of this component of the primary outcome.



With no effect on risk of non-cardiovascular death, the key safety outcome for this post-trial observational period.

There we too few deaths in any subcategory to quantify effects precisely.

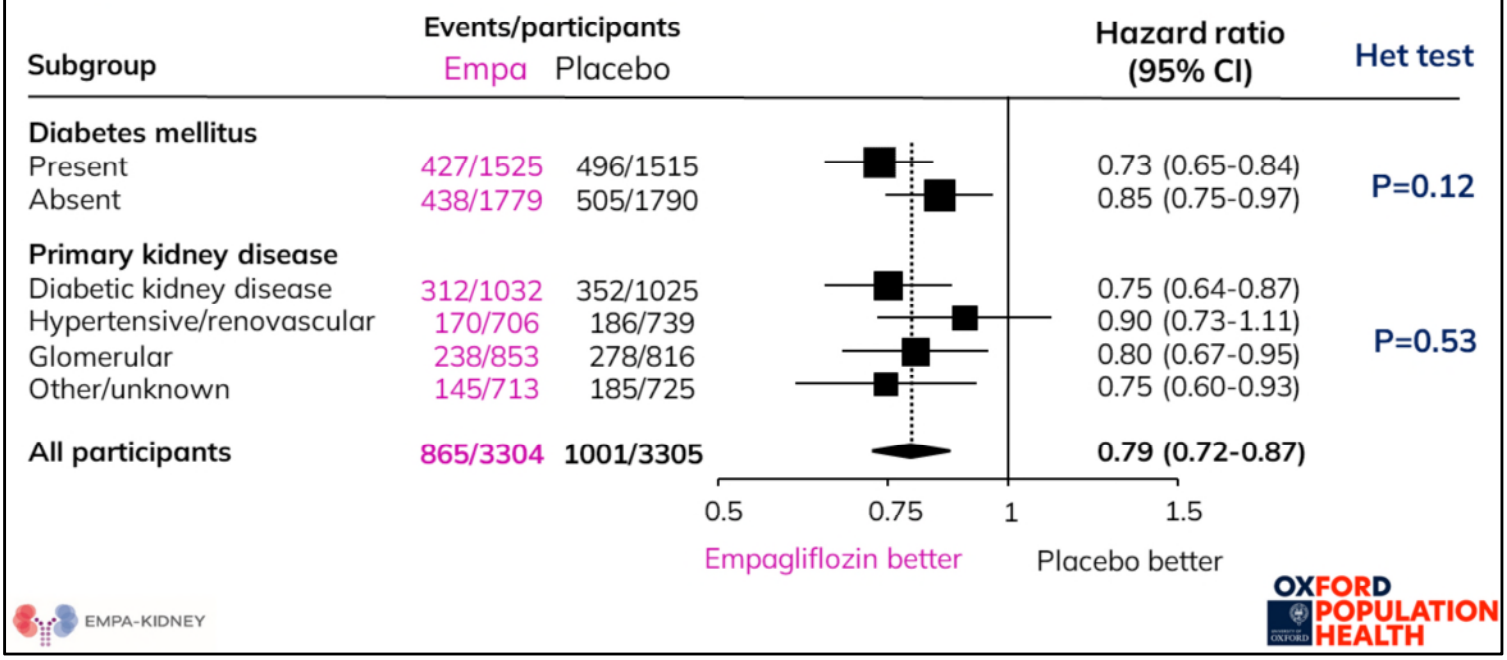


Once all combined, there were 336 versus 301 deaths from any cause.

Subgroup analyses of primary outcome

We pre-specified 4 key subgroup analyses for the primary outcome.

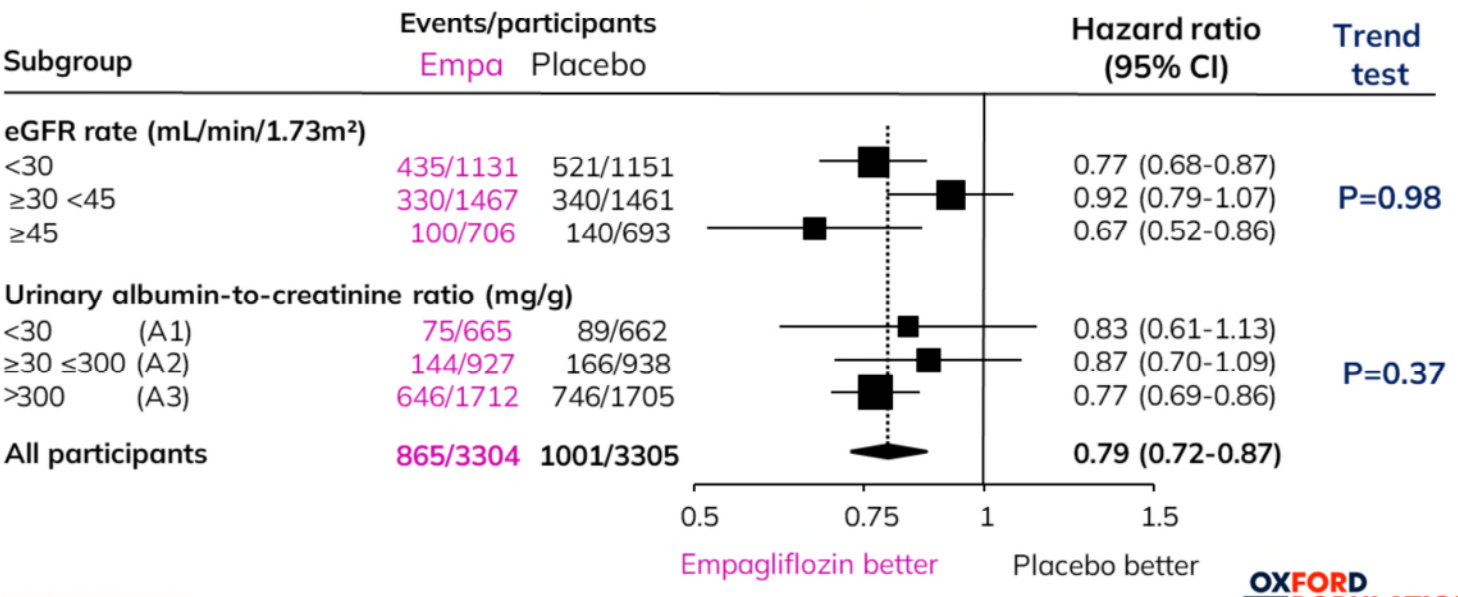
Primary outcome over entirety of follow-up by key subgroups



Over the entirety of follow-up, the 21% reduction in risk of the primary outcome appeared similar in patient with or without diabetes

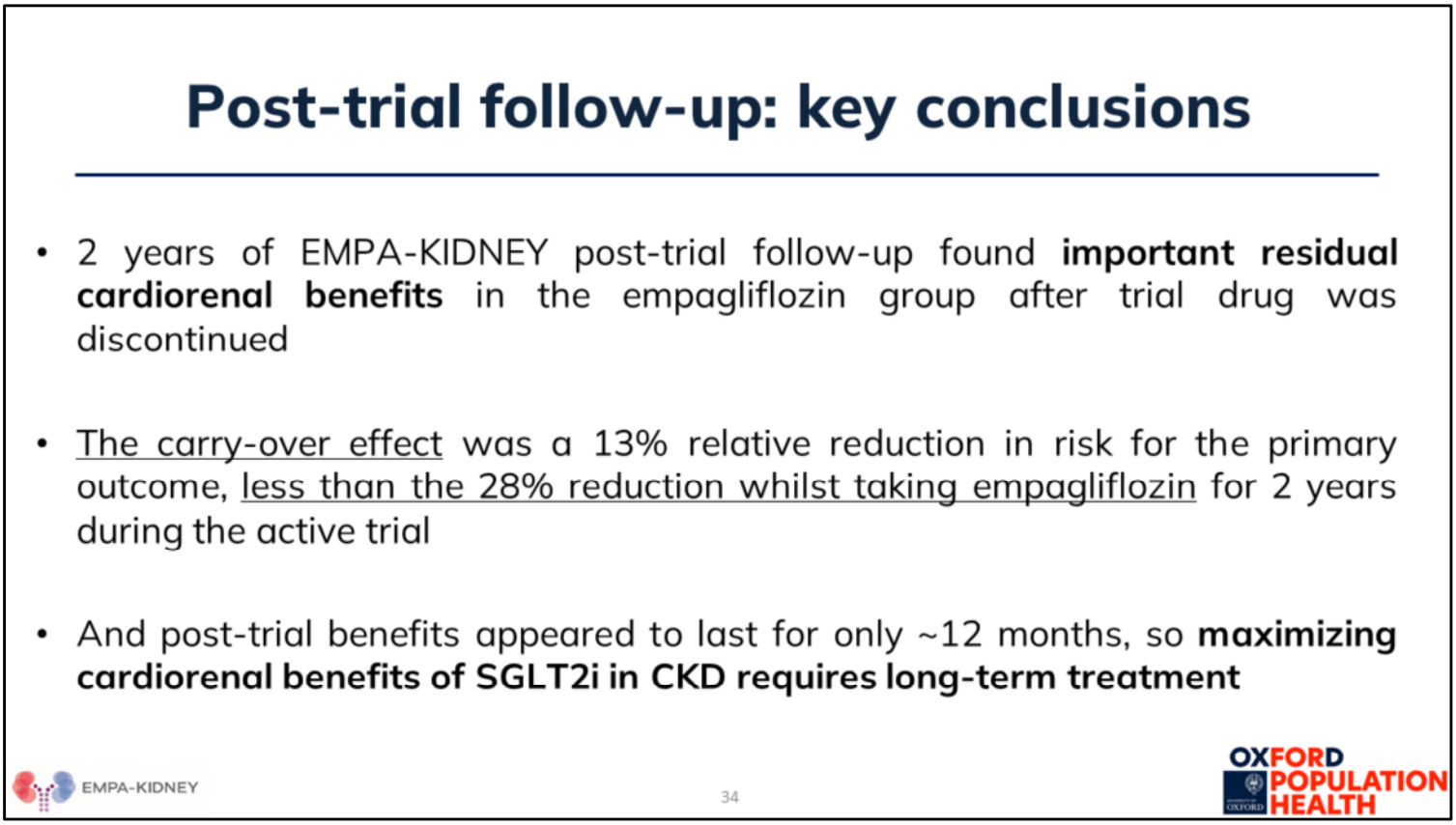
And by diabetic kidney disease versus hypertensive/renovascular vs glomerular vs other/unknown diseases.

Primary outcome over entirety of follow-up by key subgroups



Similarly, there was no evidence of effect modification by baseline GFR or level of albuminuria.

These findings are all consistent with analyses of the long-term eGFR slope from the active trial period which have shown that empagliflozin slowed progression in all these key subgroups.



In conclusion, 2 years of EMPA-KIDNEY post-trial follow-up found **important residual cardiorenal benefits** in the empagliflozin group after trial drug was discontinued

The carry-over effect was a 13% relative reduction in risk for the primary outcome, less than the 28% reduction whilst taking empagliflozin for 2 years during the active trial

And post-trial benefits appeared to last for only ~12 months, so **maximizing cardiorenal benefits of SGLT2i in CKD requires long-term treatment**

Post-trial follow-up: other conclusions

- Almost doubling of the number of first primary outcomes from 990 in the active trial to 1866 after post-trial follow-up helps address uncertainties resulting from the short active trial period
  - **Relative benefits** over the entirely of follow-up **were consistent in subgroups** split by different levels of albuminuria, diabetes status, levels of kidney function & primary kidney diagnosis
  - **There was reduced risk of CV death**, and no effect on non-CV deaths

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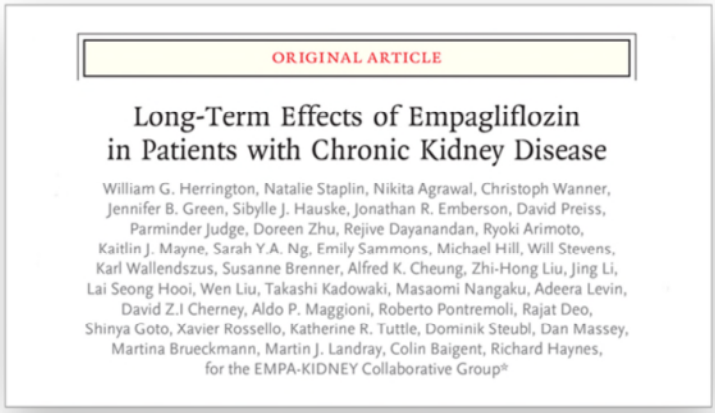
Further details

The NEW ENGLAND JOURNAL of MEDICINE



ORIGINAL ARTICLE

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William G. Herrington, Natalie Staplin, Nikita Agrawal, Christoph Wanner, Jennifer B. Green, Sibylle J. Hauske, Jonathan R. Emberson, David Preiss, Parminder Judge, Doreen Zhu, Rejive Dayanandan, Ryoki Arimoto, Kaitlin J. Mayne, Sarah Y.A. Ng, Emily Sammons, Michael Hill, Will Stevens, Karl Wallendszus, Susanne Brenner, Alfred K. Cheung, Zhi-Hong Liu, Jing Li, Lai Seong Hooi, Wen Liu, Takashi Kadowaki, Masaomi Nangaku, Adeera Levin, David Z.I Cherney, Aldo P. Maggioni, Roberto Pontremoli, Rajat Deo, Shinya Goto, Xavier Rossello, Katherine R. Tuttle, Dominik Steubl, Dan Massey, Martina Brueckmann, Martin J. Landray, Colin Baigent, Richard Haynes, for the EMPA-KIDNEY Collaborative Group*

Patient & other information at

www.empakidney.org

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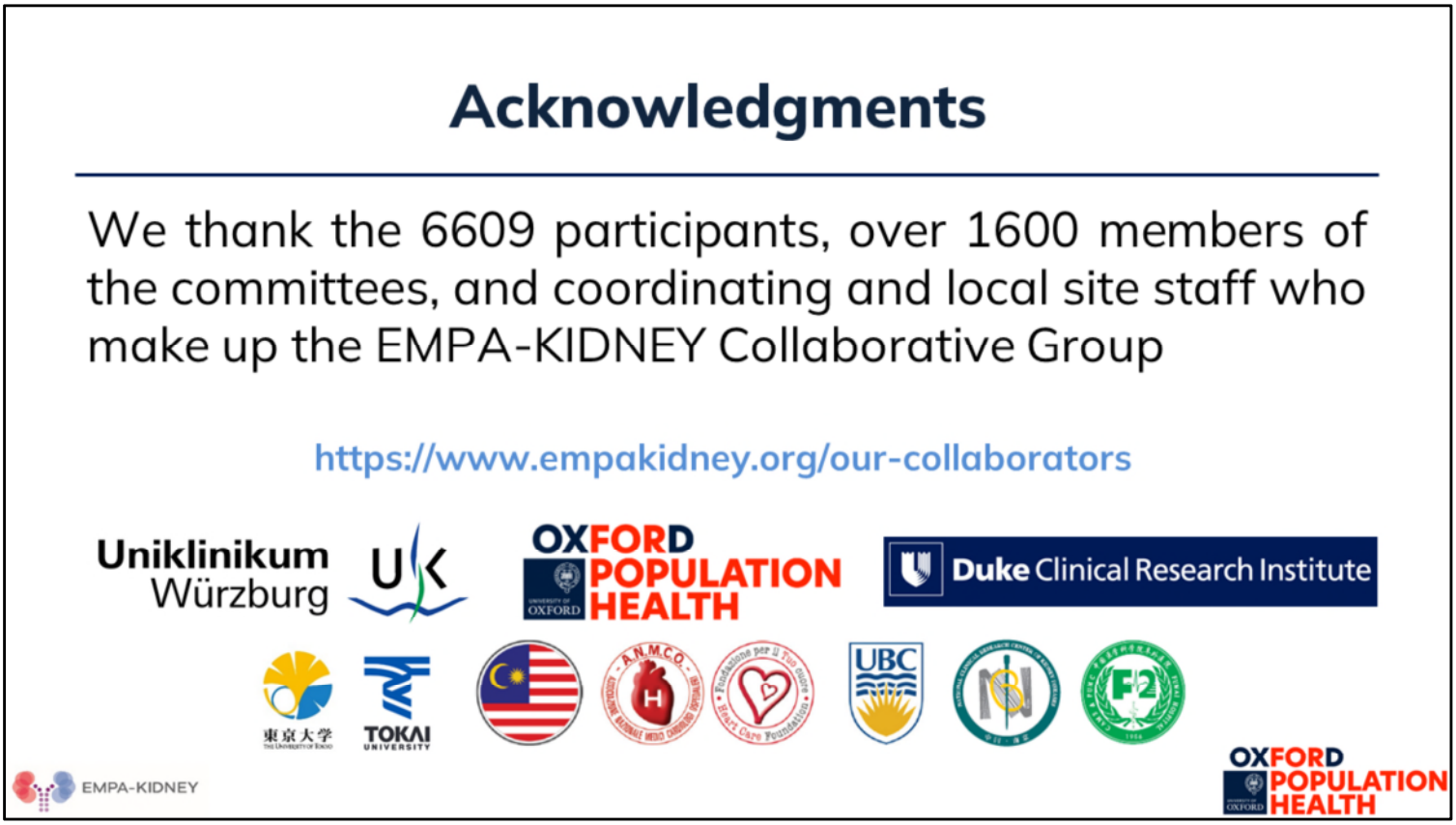
This is a complicated study to report.

For full details, please do see the full report in the New England Journal of Medicine.

These slides and other information are available on our website.



Our deep gratitude goes to the 6609 participants and over 1600 members of the committees, and coordinating and amazing local site staff who joined us on this mission to simplify trial conduct, recruit a widely generalizable population, and generate such important data for our community and patients.

We look forward to building continued collaboration and generating even larger-scale randomized data with you.

Thank you for listening.