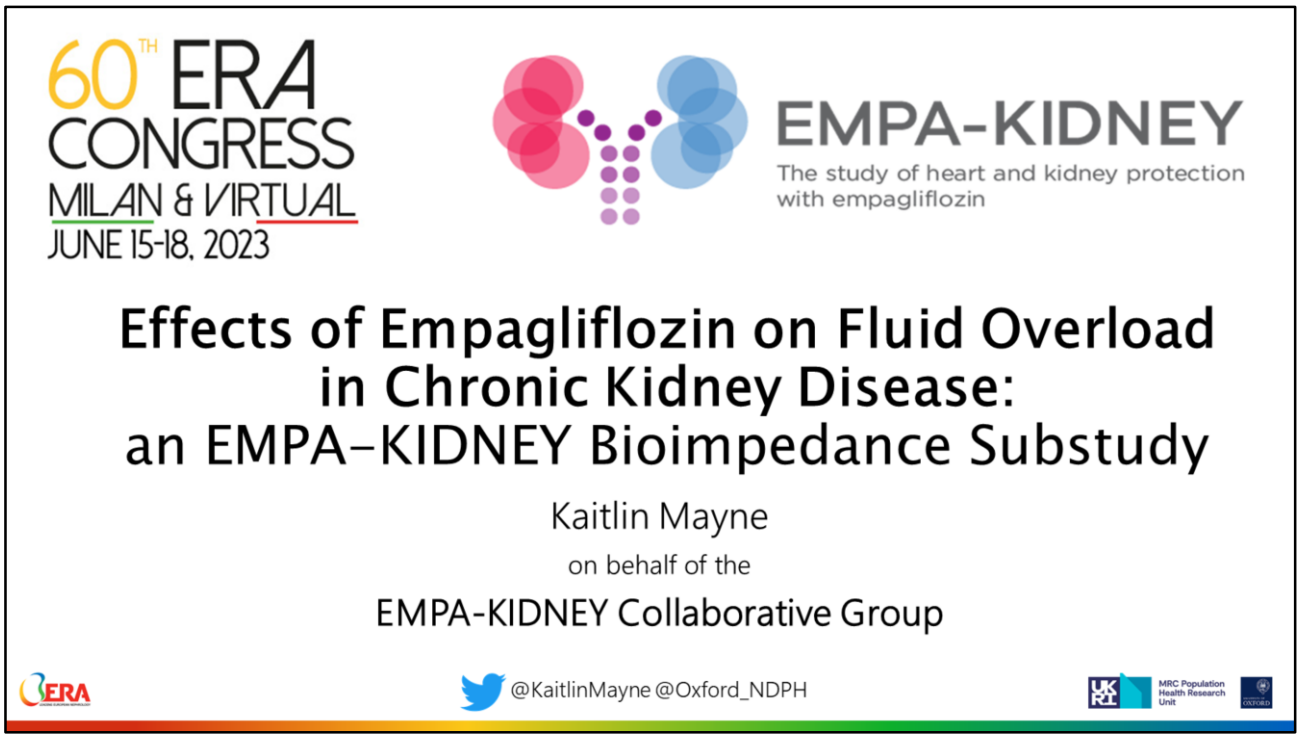
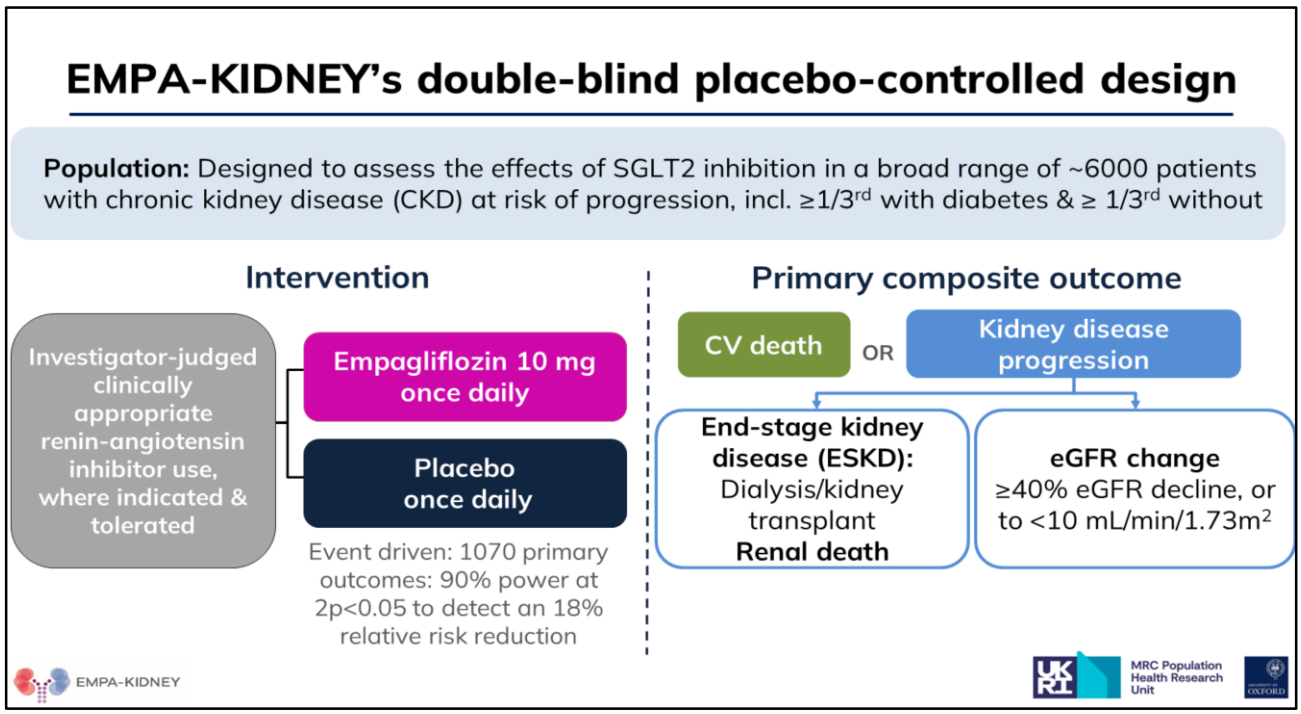



**THESE SLIDES WERE PRESENTED AT THE EUROPEAN RENAL ASSOCIATION CONGRESS ON 17TH JUNE 2023 AND ARE INCLUDED HERE WITH SCRIPTED COMMENTARY PROVIDED BENEATH EACH SLIDE**

# 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

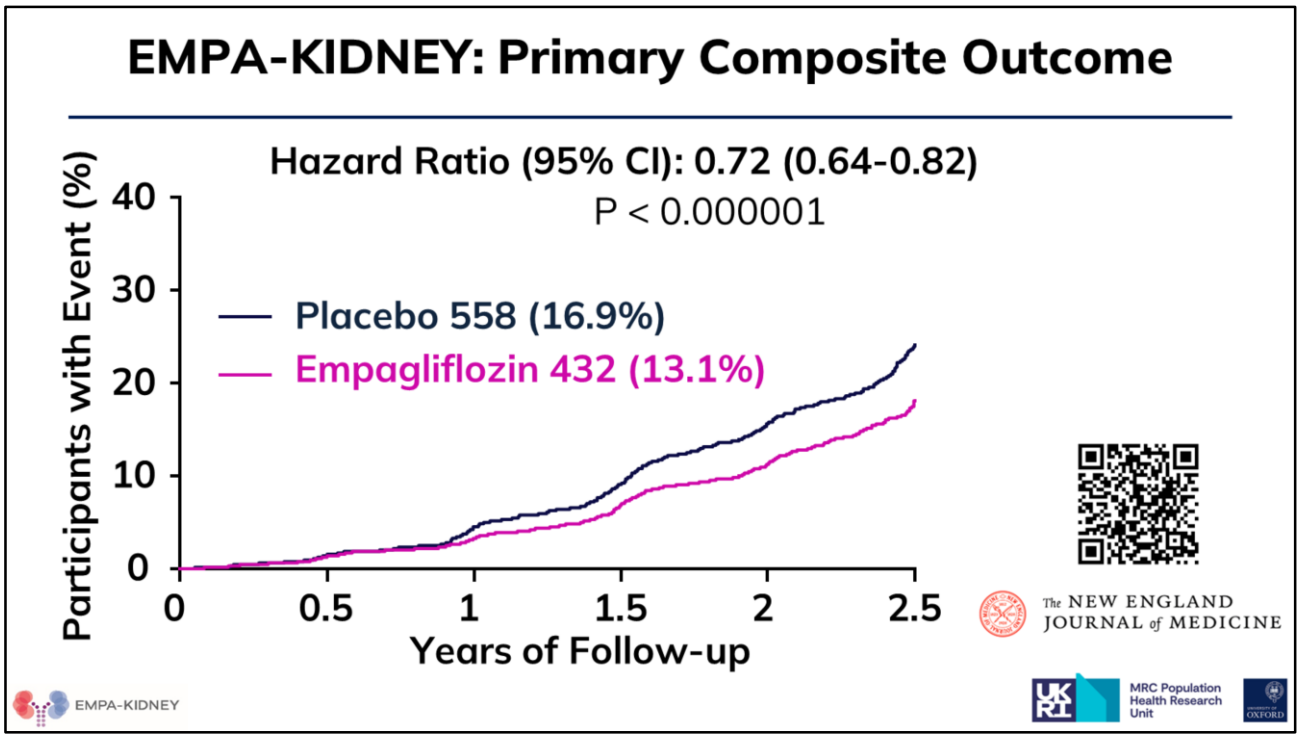



I'll begin by giving a brief overview of the design and primary results of the EMPA-KIDNEY trial which are reported in full in the NEJM paper which can be accessed via the QR code on the next slide

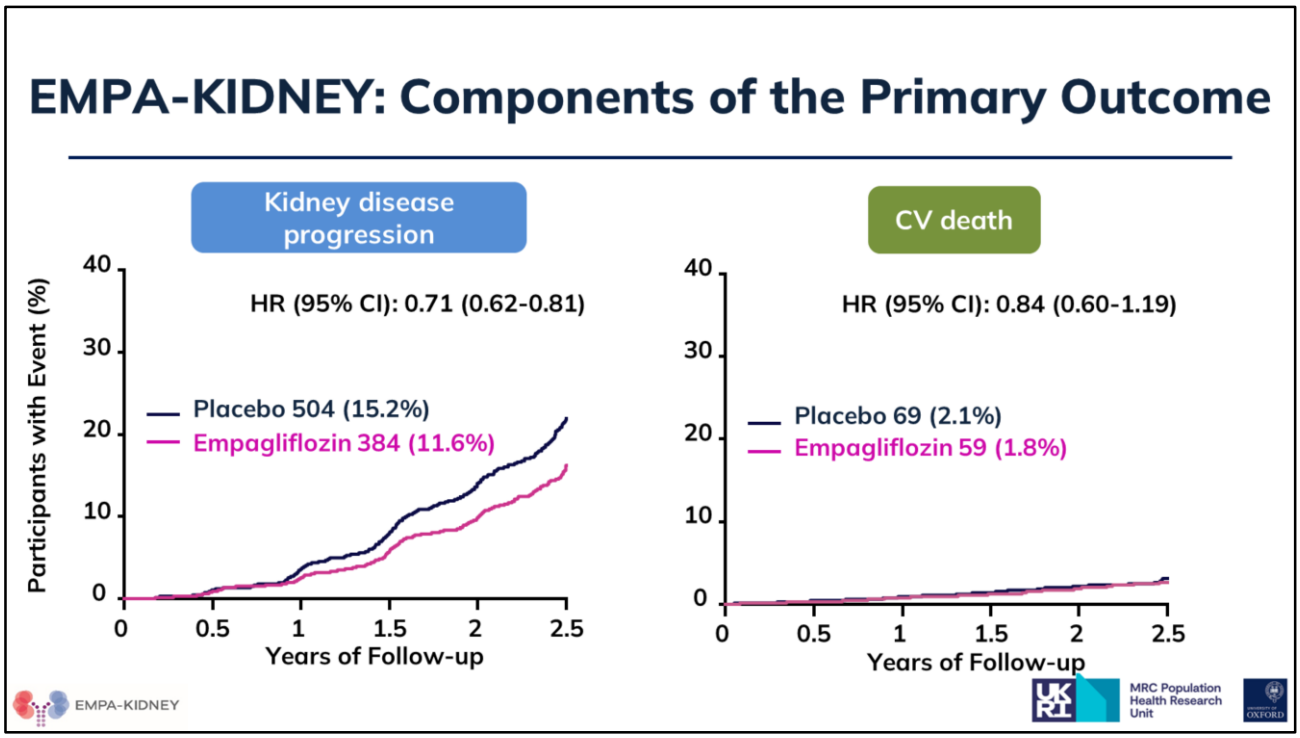
EMPA-KIDNEY was a double-blind placebo-controlled trial which randomised >6000 people with CKD with an eGFR between 20 and 90 to either empagliflozin or matching placebo

The primary outcome was a composite of kidney disease progression defined on the slide or cardiovascular death

The trial was stopped early due to efficacy in March 2022 at the pre-specified formal interim analysis




The result for the primary outcome is shown here: empagliflozin reduced the risk of kidney disease progression or cardiovascular death by 28%.




The majority of the primary outcome events were kidney disease progression
The rate of cardiovascular death in this population was low and lower than expected meaning limited power to assess effects for this component

# Other Assessments (full trial cohort)

| | Empagliflozin (n=3304) | Placebo (n=3305) | Difference (95% CI or SE) |
|---|---|---|---|
| Weight (kg) | 82.3 | 83.2 | -0.9 (0.1) |
| Systolic BP (mmHg) | 132.8 | 135.3 | -2.6 (0.3) |
| Diastolic BP (mmHg) | 76.3 | 76.8 | -0.5 (0.2) |
| HbA1c (mmol/mol) | | | |
| Prior diabetes | 53 (0.3) | 54 (0.3) | -0.9 (-1.6, 0.1) |
| No prior diabetes | 37 (0.1) | 37 (0.1) | -0.03 (-0.2, 0.2) |

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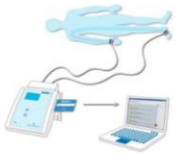
These results are already publicly available in the appendix of the NEJM paper
Highlighted here as these are of particular relevance to the bioimpedance substudy and may relate to effects on fluid and adiposity
Results shown on the slide are the study averages across all follow-up visits and we present the difference between the empagliflozin and placebo groups
Average weight and blood pressure across the study period were significantly lower in the empagliflozin group compared to placebo
with a difference in weight of just under 1kg
The effect on HbA1c was negligible with no appreciable effect in those without pre-existing diabetes
These effects on weight and BP have been demonstrated in previous SGLT2i trials but what we don't fully understand is the underlying mechanism or how much of the weight lost is fat vs fluid, particularly considering very minimal effects on HbA1c

# The EMPA-KIDNEY Bioimpedance Substudy

660 participants: UK & Germany



Fresenius Body Composition Monitor (BCM)
Measurements at 0 (Randomisation), 2 and 18 months

In CKD, do SGLT2 inhibitors cause weight loss by reduction in fluid (and/or fat)?

**Primary outcome: absolute "Fluid Overload" (Litres)**

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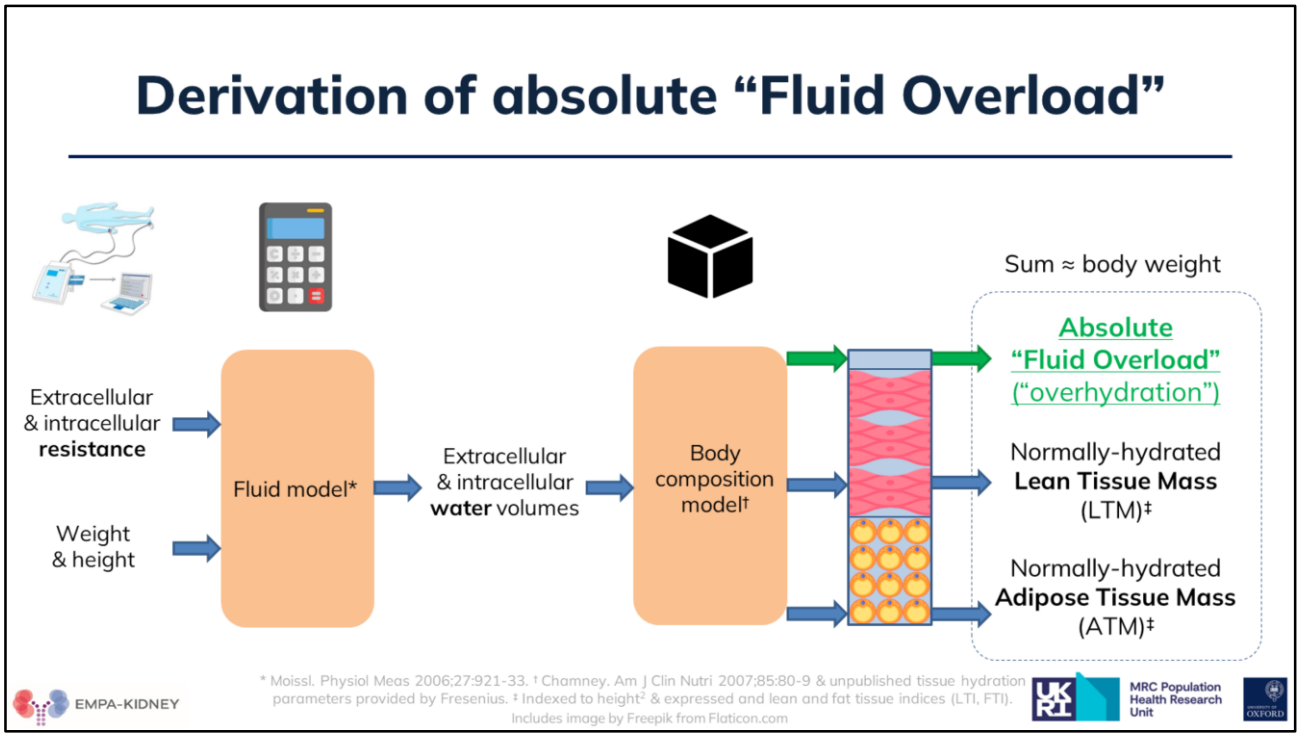
Which leads us on to the rationale for the bioimpedance substudy
The EMPA-KIDNEY bioimpedance substudy was conducted in around 10% of the main trial population, recruited from sites within the UK and Germany
We used the Fresenius Body Composition Monitor (BCM) to obtain measurements at baseline and twice during follow-up
The substudy was designed to assess changes in body composition, primarily fluid but also adiposity, in order to provide mechanistic insights into the effects of empagliflozin
The primary outcome was the between group difference in mean absolute Fluid Overload averaged over the follow-up period




This slide shows how the primary outcome variable is derived – important to appreciate these are derived parameters not measurements per se
The BCM device measures extracellular and intracellular resistance to a painless current applied via electrodes stuck to a patient's hands and feet
Published methodology is then applied using fluid and body composition models to produce the derived parameters used in analyses in the steps shown on the slide
Absolute Fluid Overload is the excess fluid volume in L also referred to in the literature as overhydration
Absolute Fluid Overload is the key parameter of interest, the substudy was not powered to assess effects on the adiposity parameters

# Bioimpedance Substudy Participant Characteristics (1)

| | Empagliflozin (N=332) | Placebo (N=328) |
|---|---|---|
| **Age**, years | 65.2 ± 14 | 64.1 ± 15 |
| **Female sex** | 31% | 31% |
| **Diabetes** | 41% | 37% |
| **Self-reported prior heart failure** | 19% | 23% |
| **Weight**, kg | 89.8 ± 20 | 87.9 ± 19 |
| **Systolic blood pressure**, mmHg | 137 ± 19 | 138 ± 19 |
| **Estimated GFR**, mL/min/1.73m$^2$ | 36 ± 13 | 36 ± 11 |
| **NTpro-BNP**, ng/L | 197 (90-596) | 225 (95-550) |

Data are mean ± SD; median (Q1-Q3); or %

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The substudy population were generally representative of the main trial population
Mean age was 64 years
Around one third of participants were female
The proportion with diabetes is slightly lower in the substudy vs the trial as a whole
whereas heart failure was more commonly reported in substudy participants vs the main trial (10% in main trial)
Weight appeared to be higher in those allocated empagliflozin but this difference was not statistically significant
And mean BMI though not shown on the slide was 30 in both groups
BP at baseline was relatively well-controlled
Mean eGFR was 36 and mean Ntpro-BNP was within the normal range

# Bioimpedance Substudy Participant Characteristics (2)

| | Empagliflozin (N=332) | Placebo (N=328) |
|---|---|---|
| **Absolute "Fluid Overload"**, Litres | 0.5 ± 1.7 | 0.3 ± 1.7 |
| **Relative "Fluid Overload"**, % | 1.9 ± 8.7 | 1.3 ± 8.3 |
| Moderate "Fluid Overload" | 21% | 17% |
| Severe "Fluid Overload" | 4% | 5% |
| **Extracellular water**, Litres | 19.0 ± 3.8 | 18.4 ± 3.7 |
| **Intracellular water**, Litres | 20.7 ± 4.5 | 20.1 ± 4.6 |
| **Lean tissue index**, kg/m$^2$ | 13.3 ± 3.1 | 12.9 ± 3.0 |
| **Fat tissue index**, kg/m$^2$ | 12.6 ± 5.4 | 12.5 ± 5.1 |

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Relative "Fluid Overload" >7% ≤15% = Moderate; >15% = Severe
Data are mean ± SD; or %

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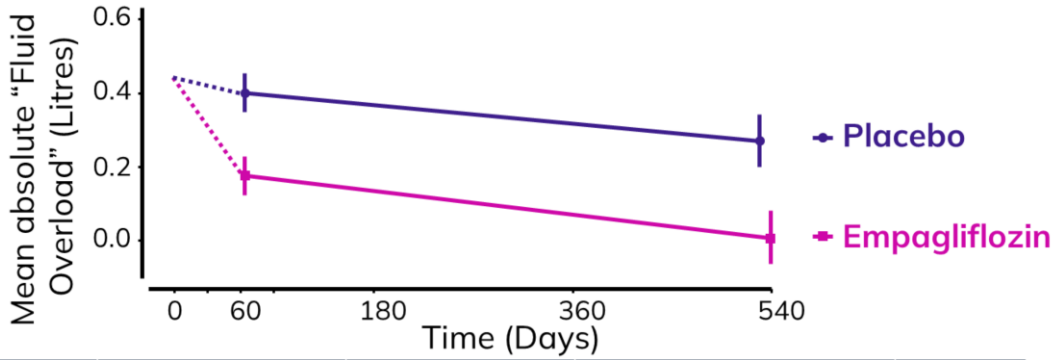
This slide shows the values for the bioimpedance parameters of interest at randomisation, no statistically significant difference in "Fluid Overload" between the groups
These values won't mean much unless familiar with the BCM – provide brief context:
Focusing on the Fluid Overload parameters at the top of the table, absolute FO in the first row which is the key parameter of interest analysed as the primary outcome; expressed in L and for this parameter the reference range is between -1.1 and +1.1 L (so our substudy population on average lies within the normal range)
Relative "Fluid Overload" is closely related to absolute "Fluid Overload" and calculated by indexing the absolute value in L to the ECW volume, commonly used in observational studies thought to allow comparison between individuals more appropriately
And from relative "Fluid Overload", you can see we've presented two categories for moderate and severe "Fluid Overload", the ranges for which are at the foot of the slide and the main thing to draw out here is that almost a quarter of the substudy participants have clinically significant levels of "Fluid Overload" at baseline
Both the fluid parameters and lean and fat tissue index values presented are approximately consistent with published observational studies using the BCM device in non-dialysis CKD populations

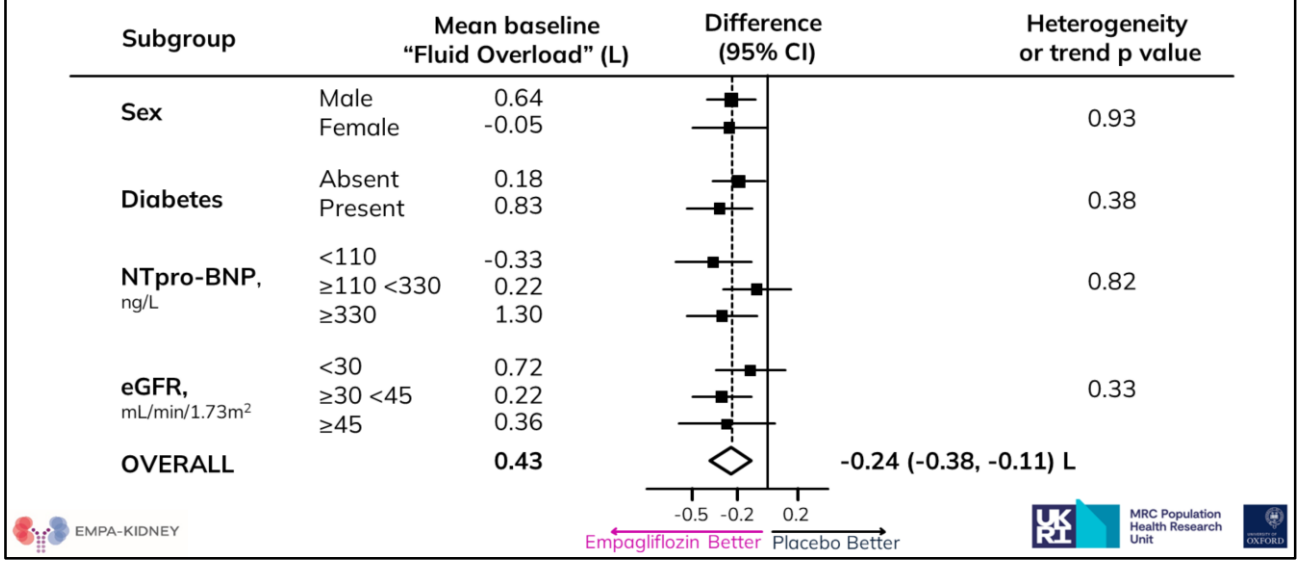
# Substudy Primary Outcome: "Fluid Overload" in Litres




| | Empagliflozin Mean (SE), L | Placebo Mean (SE), L | Absolute Difference (95% CI), L | P value |
|---|---|---|---|---|
| 2-months | 0.18±0.05 | 0.40±0.05 | -0.23 (-0.37, -0.08) | |
| 18-months | 0.01±0.07 | 0.27±0.07 | -0.26 (-0.46, -0.06) | |
| **Study average** | **0.10±0.05** | **0.34±0.05** | **-0.24 (-0.38, -0.11)** | **<0.001** |

This is the main result from the bioimpedance substudy
We calculated a weighted average of follow-up measurements adjusted for the baseline values and found that, overall, the absolute fluid overload value was 0.24 Litres lower in the empagliflozin group vs placebo, highly statistically significant difference
We had hypothesised that we might see a larger difference at the 2 month time period due to acute haemodynamic effects but that doesn't appear to be the case – effects were consistent at both time points and sustained to at least 18 months

# Change in "Fluid Overload" (Primary Outcome) by Pre-specified Subgroups



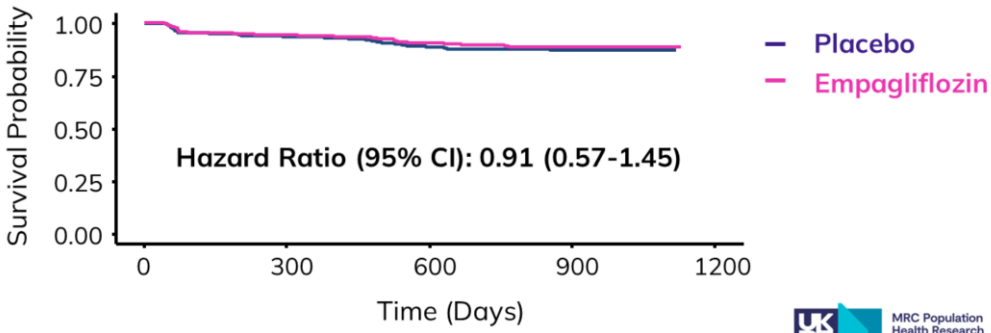

Subgroup analysis of the primary outcome found that effects of empagliflozin on absolute fluid overload were consistent irrespective of sex, diabetes, NTPro-BNP or eGFR at baseline

# Substudy Secondary Outcome
# Time-to-first composite outcome comprising:

- **Hospitalisation for (n=27) or death from Heart Failure (n=0)**
- **Development of new Clinically Significant "Fluid Overload"***

**Moderate**: Relative Fluid Overload >7% ≤15%; or

**Severe**: Relative Fluid Overload >15%

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*among those without this outcome at baseline

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Key secondary outcome was designed to make use of clinical outcome data on the basis that if a BCM measurement is missed due to hospitalisation for HF with fluid overload, incorporating this clinical outcome adds important information on fluid overload The term CSFO is one we have proposed in the absence of consensus from literature.
the thresholds used are commonly applied in observational studies although terminology differs
This was analysed on a time-to-event basis and all substudy analyses were pre-specified before the main results were known
We see no significant effect on this composite outcome and conclude that the substudy was underpowered to assess these effects due to unexpectedly lower cardiovascular event rates as presented earlier, in fact we didn't see any deaths from heart failure in the substudy population

*For additional information: going from moderate to severe* "Fluid Overload" *is approximately equivalent in litres to a change from 1.1 to 2.5 L and the primary outcome showed that the treatment effect of empagliflozin was a reduction of a quarter of a litre so although highly statistically significant, the effect is small in magnitude and further explains the lack of effect on this categorical outcome.*

# Bioimpedance Substudy
# Tertiary Outcomes

**Body weight**
-0.7 (-1.3, -0.1) kg

Images by Freepik from Flaticon.com

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Study average between-group difference (95% CI)

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Assessments of anthropometry were pre-specified tertiary assessments
In the substudy, body weight averaged across the study period was 0.7 kg lower in those allocated empagliflozin vs placebo

# Bioimpedance Substudy
# Tertiary Outcomes

**Extracellular water**
-0.5 (-0.7, -0.3) L

**Intracellular water**
-0.3 (-0.6, -0.0) L

**Body weight**
-0.7 (-1.3, -0.1) kg

Images by Freepik from Flaticon.com

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Study average between-group difference (95% CI)

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This difference in weight is largely explained by differences in fluid, in particular extracellular water
Which makes sense since the absolute FO parameter largely consists of ECW

# Bioimpedance Substudy
# Tertiary Outcomes

**Extracellular water**
-0.5 (-0.7, -0.3) L

**Intracellular water**
-0.3 (-0.6, -0.0) L

**Lean Tissue Index (LTI)**
-0.1 (-0.4, 0.1) kg/m$^2$

**Fat Tissue Index (FTI)**
-0.1 (-0.5, 0.3) kg/m$^2$

**Body weight**
-0.7 (-1.3, -0.1) kg

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Study average between-group difference (95% CI)

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And we found no statistically significant difference in fat mass between groups in the substudy
Bearing in mind the characteristics of the largely non-diabetic cohort with reduced kidney function in whom the glucosuric effects of these drugs are attenuated

# Bioimpedance Substudy Conclusions

- **660 EMPA-KIDNEY substudy participants** had serial bioimpedance measurements to derive "Fluid Overload" and adiposity parameters
- **Mean baseline derived "Fluid Overload" was 0.4 L**, with 24% of participants having a level consistent with clinically important fluid excess
- Empagliflozin caused fluid loss: **study-average "Fluid Overload" was 0.24 L lower in the empagliflozin group**
- Empagliflozin caused **weight loss (just under 1 kg)** through reductions in "Fluid Overload" with **no demonstrable effect on fat mass**
- These reductions persisted over 18 months and were **consistent across subgroups** by sex, diabetes, NTpro-BNP & eGFR

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# Acknowledgements

We thank the 660 participants, members of the committees, and coordinating and local site staff who make up this EMPA-KIDNEY substudy

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