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Kidney and Cardiovascular Effects of Canagliflozin According to Age and Sex: A Post Hoc Analysis of the CREDENCE Randomized Clinical Trial

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Abstract

Rationale & Objective: It is unclear whether the effect of canagliflozin on adverse kidney and cardiovascular events in those with diabetic kidney disease varies by age and sex. We assessed the effects of canagliflozin among age group categories and between sexes in the CREDENCE study.

Study Design: Secondary analysis of a randomized controlled trial.

Setting & Participants: Participants in the CREDENCE trial.

Intervention: Participants were randomly assigned to canagliflozin 100 mg daily or placebo.

Outcomes: Primary composite outcome of kidney failure, doubling of serum creatinine, or death due to kidney or cardiovascular disease. Pre-specified secondary and safety outcomes were also analyzed. Outcomes were evaluated by age at baseline (<60, 60-69, and ≥70 years) and sex in the intention-to-treat population using Cox regression models.

Results: The mean age of the cohort was 63.0±9.2 years and 34% were female. Older age and female sex were independently associated with a lower risk of the composite of adverse kidney outcomes. There was no evidence that the effect of canagliflozin on the primary outcome (a composite of kidney failure, a doubling of the serum creatinine, or death from kidney or cardiovascular causes) differed between age groups (HR 0.67, 95% CI 0.52 to 0.87; HR 0.63, 95% CI 0.48 to 0.82; and HR 0.89, 95% CI 0.61 to 1.29; for the <60, 60-69, and ≥70 year groups, respectively; $P_{interaction}$=0.3); or among females and males (HR 0.71, 95% CI 0.54 to 0.95; and HR 0.69, 95% CI 0.56 to 0.84, respectively; $P_{interaction}$=0.8). No differences in safety outcomes by age group or sex were observed.

Limitations: This was a post hoc analysis with multiple comparisons.

Conclusions: Canagliflozin consistently reduced the relative risk of kidney events in people with

diabetic kidney disease in both sexes and across age subgroups. Owing to higher background risk, the absolute reduction in adverse kidney outcomes was greater in younger participants.

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Trial Registration: The original CREDENCE trial was registered at ClinicalTrials.gov with study number NCT02065791.

Index words: Diabetic kidney disease; chronic kidney disease; diabetes; kidney outcomes; cardiovascular outcomes; sodium glucose co-transporter 2 inhibitors; canagliflozin; age; sex

Plain Language Summary:

The CREDENCE trial demonstrated significant kidney benefits with canagliflozin in participants with diabetic kidney disease. We analyzed the data to see if canagliflozin will be as effective and safe for those in the age groups of <60, 60-69, ≥70, and between sexes. Canagliflozin reduced the risk of the primary outcome (kidney failure, doubling of serum creatinine, death due to kidney or cardiovascular disease) similarly in the age groups and between sexes. The effect of canagliflozin on kidney outcomes was similar regardless of age or sex but was more pronounced in younger participants who were at higher risk of these events. Our study demonstrates that canagliflozin appears to be as effective and safe among different age categories and between sex.

Introduction

A personalized approach to treatment is important to ensure therapies are implemented where they will be beneficial, align with patient goals and avoid undue burden or harm. It is therefore important to know whether the efficacy or safety of a therapy varies between patients with different characteristics, co-morbidities, and baseline risk. Differences in both age and sex can modify the effect of treatments, reflecting differences in pharmacodynamics and drug-disease interaction for a variety of reasons.[1–3] For example, modelling of sex differences in the expression of electrolyte transporters in the diabetic kidney suggests the potential for differences in luminal chloride delivery to the macula densa with implications for the natriuretic and intra-renal hemodynamic effects of SGLT2 inhibition and with increasing age comes the accrual of medical comorbidities and changes in pharmacokinetics that may affect drug exposure.[4–6] Although not consistently demonstrated, the risk of progression to kidney failure and the slope of estimated glomerular filtration rate (eGFR) decline may be lower in females with chronic kidney disease (CKD) than in males.[7–9] Conversely, CKD and diabetes appear to attenuate the protective effect of female sex on cardiovascular risk.[10] Similarly, rates of geriatric conditions such as frailty, polypharmacy, cognitive decline, and falls are higher in the elderly with diabetes, which may increase the underlying risk and impact of adverse effects.[11,12] Finally, different underlying rates of disease progression or adverse event risk can translate into important differences in the absolute balance of risk and benefit, with the potential to influence treatment decisions even when relative risks and benefits remain similar.

SGLT2 inhibitors have now demonstrated benefits in kidney and cardiovascular (CV) outcomes in several large trials, including the Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation (CREDENCE) Trial, where canagliflozin reduced

the risk of the composite outcome of kidney failure, doubling of serum creatinine, and kidney or cardiovascular mortality by 30% in participants with diabetic kidney disease.[13] Whilst previous SGLT2 inhibitor trials have demonstrated consistent effects across age and sex, these trials have primarily focused on cardiovascular outcomes, often assessing age groups dichotomized at 65 years, with limited secondary and safety outcomes analyzed.[14–18] In this secondary analysis of the CREDENCE trial, we investigated whether the effects of canagliflozin on clinically important kidney, CV, and safety outcomes are consistent across age and sex.[13]

Methods

Study Design

The CREDENCE trial methods and statistical analysis have been published previously.[19] The CREDENCE trial was a multi-centre, double-blind, placebo-controlled, randomized trial evaluating the effects of canagliflozin 100mg on kidney, cardiovascular, and safety outcomes in people with T2DM and albuminuric CKD. Key inclusion criteria were age 30 years or older, with a diagnosis of T2DM, an eGFR of 30 to <90 mL/min/1.73m^2, and urinary albumin-to-creatinine ratio (UACR) >300 to 5000 mg/g. All participants were required to be receiving a stable maximum tolerated dose of angiotensin converting enzyme inhibitor/angiotensin receptor blocker for at least 4 weeks prior to randomization. Randomization was stratified according to the category of eGFR (30 to <45, 45 to <60, 60 to <90 mL/min/1.73m^2) at screening. Approval for the CREDENCE study was obtained from the relevant ethics committee for each site and informed consent was obtained from all participants.[19]

Study outcomes and participant subgroups

The primary outcome was a composite of kidney failure (defined as dialysis for at least 30 days, kidney transplantation, or an eGFR of <15 mL/min/1.73m^2 sustained for at least 30

days), doubling of serum creatinine, or death due to kidney or cardiovascular disease. For the present analysis, secondary outcomes were prespecified as the kidney disease composite outcome of kidney failure, doubling of serum creatinine, or death from kidney disease; cardiovascular death; the composite of non-fatal myocardial infarction (MI), stroke, and cardiovascular death; hospitalization for heart failure (HF); and all-cause death. Annual eGFR decline ('eGFR slope') was an additional secondary outcome. Pre-specified safety outcomes for the present analysis were any adverse event; serious adverse events (all, and those related to study drug); adverse events leading to discontinuation of study medication; fracture; amputation; volume depletion; hypoglycaemia; kidney related adverse events (including acute kidney injury); urinary tract infection; mycotic genital infections; and hospitalization (all-cause). Efficacy outcomes were determined in the intention-to-treat population; eGFR slope and safety outcomes were determined in the on-treatment population (i.e. events were considered while the participant was receiving study medication, or within 30 days of ceasing study medication).[5] As in the primary publication, fracture and amputation were determined in the on-study population (i.e. all events during follow up were considered in participants who had received at least one dose of study medication).[13] Outcomes with fewer than 10 events in each subgroup (canagliflozin and placebo combined) were not analysed. Outcomes were evaluated in subgroups by age (<60, 60-69, and ≥70 years) and sex (categorized as female or male per the original study database). A secondary analysis was performed restricted to participants aged 70 years or more, in which those aged 80 years or more were compared to those aged 70-79 years. Given the relatively small size of the cohort aged over 80 years, this analysis was restricted to the primary outcome and selected adverse events (volume depletion, kidney related adverse events, serious adverse events related to study drug, hospitalization, hypoglycemia, all adverse events, and serious adverse

events).

Overall Statistical Analysis

Outcomes were described using the Kaplan-Meier method, and analyzed using proportional subdistribution (Fine and Gray) and Cox proportional hazards models in the presence and absence of competing events, respectively. Models were stratified by screening eGFR. The main effect of age and sex on outcomes was assessed in unadjusted models and in adjusted models including both age (as a categorical variable) and sex, with the following potential confounders: race, history of cardiovascular disease, history of heart failure, smoking status, treatment allocation, use of statin, and baseline values of glycated hemoglobin, body mass index, systolic blood pressure, eGFR, urine albumin-to-creatinine ratio (log-transformed), low density lipoprotein-cholesterol, and triglycerides. The proportional hazards assumption was assessed by a formal test on Schoenfeld residuals. A further exploration of change in effect with time was made using a flexible parametric survival (Royston-Parmar) model which allows an estimation of a time-dependent hazard ratio.[20] The effect of canagliflozin on outcomes was evaluated within subgroups to determine hazard ratios and 95% confidence intervals.

The absolute risk difference (and 95% confidence intervals) between canagliflozin and placebo groups was estimated by multiplying the difference in incidence rates (per 1000 patient-years) by 2.5 years (approximating the median duration of the study).[21] A p-value of <0.05 was considered significant for main effects, but given the large number of comparisons being made, a p-value for interaction of <0.01 was chosen to reduce the risk of type 1 error.[22] Analysis was performed using SAS Enterprise Guide version 7.15 (SAS Institute Inc, Cary, USA) and Stata/IC 15.1 (StataCorp LLC, College Station, USA).

Effect modification

The hypothesis that the effects of canagliflozin differed between subgroups (i.e. heterogeneity) was tested by adding the subgroup and a treatment group by subgroup interaction term to the model. Heterogeneity by age was explored both as a three-value categorical variable and – to explore the possibility of non-linear differences in treatment effect – by modelling age as a continuous variable using a restricted cubic spline. Knot positions (10^{th}, 50^{th}, and 90^{th} centile) were chosen following the recommendation of Harrell and three knots was chosen as this resulted in the best fit (i.e. lowest Akaike Information Criterion) for the primary outcome in the overall population compared to models using 4, 5, 6 or 7 knots.[23] Owing to potential differential risk and cause of death across age groups, a sensitivity analysis was performed accounting for the competing risk of death for key age group analyses.[24]

Slope of eGFR decline

Change in eGFR over time was analyzed in the on-treatment population using a multi-slope mixed effects linear spline model with connected slopes from baseline to week 3, and week 3 to study end. The model included fixed effects for screening eGFR strata, baseline eGFR, category of interest (age or sex), trial visit, interaction between category of interest and visit, and interaction between baseline value and visit, along with random intercepts and slopes and assuming an unstructured covariance matrix.

Results

The CREDENCE trial randomized 4401 participants with T2DM and CKD, with a median follow-up duration of 2.62 years. The participants had a mean age of 63±9.2 years. At baseline, 1475 (33.5%), 1854 (42.1%), and 1072 (24.4%) participants were <60, 60-69, and ≥70 years, respectively (Table 1) The baseline characteristics by treatment group, age group, and sex are demonstrated in Table S1. The latter group was comprised predominantly (58.6%) of

participants aged 70-74 years (Figure S1). Of the total cohort, 2907 (66.1%) participants were male and 1494 (33.9%) were female (Table 1). The mean baseline eGFR was 56.2 mL/min/1.73m^2 and median UACR was 927 mg/g. Overall, 585 primary composite outcomes were recorded at a rate of 52.1 per 1000 patient-years.

Outcomes by age

The rate of the primary composite outcome of kidney failure, doubling of serum creatinine, or death due to kidney or cardiovascular disease was highest in the <60 years age group (65.9 per 1000 patient-years) and lower in the 60-69 and ≥70 age groups (48.4 and 40.4 per 1000 patient-years, respectively)(Figure 1A). After adjustment for confounding variables, those in the ≥70 age group retained a lower risk for the primary outcome (compared to the <60 age group; adjusted hazard ratio [aHR] 0.60, 95% CI 0.47 to 0.77; P<0.001)(Table S2). This was driven by lower adjusted estimates for risk of kidney-related components of the primary composite outcome in the ≥70 age group (aHR 0.32, 95% CI 0.22 to 0.48; P<0.001, and 0.30, 95% CI 0.20 to 0.45; P<0.001; for doubling serum creatinine and kidney failure, respectively)(Table S2). In contrast, adjusted risk of major adverse cardiovascular events, cardiovascular death, hospitalized heart failure, and all-cause death, increased with increasing age (Table S2). The rate of decline in eGFR after week 3 was lowest in the ≥70 age group (2.33ml/min/1.73m^2 per year), followed by the 60-69 age group (2.88ml/min/1.73m^2 per year) and both were significantly lower than in the <60 age group (4.24ml/min/1.73m^2 per year; difference from ≥70 age group 1.90ml/min/1.73m^2 per year, 95% CI 1.39 to 2.42; from 60-69 age group 1.35ml/min/1.73m^2 per year, 95% CI 0.92 to 1.79; P for both differences <0.001)(Figure 1C). There were no differences in the decline in eGFR to week 3. A sensitivity analysis was performed accounting for the competing risk for death (Table S3) which

demonstrated no significant differences from the primary outcome analysis.

Canagliflozin treatment effect by age

Canagliflozin reduced the risk of the primary composite outcome (HR 0.70 [95% CI: 0.59, 0.82]; P <0.001), with no evidence of heterogeneity of treatment effect by age in all participants (HR [95% CI]: 0.67 [0.52-0.87], 0.63 [0.48-0.82], and 0.89 [0.61-1.23] for the <60, 60-69, and ≥70 year groups, respectively)(Figure 2), regardless of whether age was treated as a categorical or continuous variable (P-interaction=0.3 [Figure 2] and 0.2 [Figure 3], respectively). The proportional hazards assumption was met, although visual inspection of the hazard ratio over time showed a tendency for increased benefit from canagliflozin as follow up time increased (Figure S2 and Table S4). In the overall CREDENCE study population, canagliflozin significantly reduced the risk of the secondary kidney composite outcome, doubling of serum creatinine, kidney failure, major adverse cardiovascular events, and hospitalization for heart failure.[13] Canagliflozin did not significantly reduce the risk of cardiovascular death or all-cause death. No significant differences were detected in the effect within age groups for these outcomes, including when age was analyzed as a continuous variable (Figure 2 and 3). These conclusions did not differ when death was treated as a competing risk, nor when time-dependent hazards were modelled (Figure S3). In the very elderly, there were 8 primary outcomes in participants aged 80 years or more at baseline (2 events in the canagliflozin group and 6 events in the placebo group) (Table S5). The absolute reduction in event rates were most prominent in the younger cohort, consistent with their higher baseline risk of kidney events compared to older participants. With the exception of heart failure, the absolute reduction in event rates was attenuated in those aged over 70 years (Figure 2).

Outcomes by Sex

The rates of the primary composite outcome were similar in males and females (52.7 and 51.0 per 1000 patient-years)(Figure 1B). Females had a lower risk of the primary composite outcome after adjustment for confounding variables (aHR 0.82, 95% CI 0.68 to 0.98, P=0.03)(Table S6). Similarly, the adjusted risks of the components of the primary composite outcome tended to be lower in females, although this did not reach statistical significance for all outcomes (Table S6). The slope of eGFR decline after week 3 did not differ between sexes (female 3.28 vs. male 3.14ml/min/1.73m^2 per year; difference 0.14ml/min/1.73m^2 per year, 95% CI 0.26 to 0.54; P=0.5) (Figure 1D). There was no difference in decline in eGFR to week 3.

Canagliflozin treatment effect by sex

There was no evidence that the effects of canagliflozin on the primary composite outcome and secondary outcomes differed by sex (HR [95% CI]: 0.71 [0.54-0.95] and 0.69 [0.56-0.84] for female and male, respectively; P-interaction 0.8) (Figure 4). The proportional hazards assumption was met. Visual inspection of the hazard ratio over time showed a tendency for increased benefit from canagliflozin as follow up time increased in females, with little apparent change in hazard ratio over time in males (Figure S2 and Table S4). There was no evidence that sex modified the effect of canagliflozin across age group categories for any of the tested outcomes (Table S7) and absolute difference in risk with canagliflozin was similar between sexes (Figure 4).

Safety Outcomes

The effect of canagliflozin on safety outcomes was consistent among age groups and by sex (Tables 2 and 3). Although the absolute number of events were low, there was no evidence that those aged 80 years or more were at greater risk of adverse events from canagliflozin than their counterparts aged 70-79, with similar rates of volume depletion, kidney related adverse

events, hospitalization, hypoglycemia, and all adverse events (Table S5). The rate of serious adverse events was numerically higher with canagliflozin (HR 2.09, 95% CI 1.16 to 3.78); compared with placebo (HR 0.94, 95% CI 0.77 to 1.15), but was driven by a small number of events and did not reach the prespecified threshold for a statistically significant interaction. Only two serious adverse events in this age group were judged as related to study drug (1 event in treatment group). While the absolute incidence of mycotic genital infections was higher in females than in males allocated to canagliflozin (12.9 vs. 8.5 per 1000 patient years), the relative increase in risk for genital infections tended to be higher in males (HR 9.30 vs. 2.10 in males and females) (Table 3) owing to low risk in the placebo group, although this difference did not reach significance against the pre-specified interaction threshold. No heterogeneity was observed with canagliflozin on fracture and urinary tract infection (P-interaction = 0.01, P-interaction = 0.04, respectively).

Discussion

In this secondary analysis of the CREDENCE trial, the effects of canagliflozin on kidney and cardiovascular events were consistent across age groups and sex. This builds on the previously reported consistency of canagliflozin on the primary composite and major adverse cardiovascular event endpoints between sex and age groups (<65 and ≥65 years).[13,25] We did not detect proportionally higher risk of a serious adverse event from canagliflozin treatment in any of our primary subgroups defined by age or sex. This is the first report confirming that the benefits of SGLT2 inhibitors on kidney outcomes are preserved across age in a high-risk population with albuminuric chronic kidney disease and T2DM, and follows analyses of previous cardiovascular and heart failure outcome trials, which have demonstrated consistent efficacy among older participants.[18,26–28]

While the relative benefits of canagliflozin were consistent across age groups, the lower risk of kidney events (even after adjustment for baseline differences) and lower eGFR slope in those aged over 70 years translated into a reduced absolute benefit. For example, the number needed to treat for those aged 70 and over to prevent one primary event was 90, compared to 17 for those aged under 60 years. In contrast, a subgroup analysis of the CANVAS trial, demonstrated greater impact on kidney outcomes with canagliflozin in those aged over 65 years, however, the baseline kidney risk in the CANVAS cohort was substantially lower than that of the CREDENCE population.[29] Yet both observations are tempered, not just by the post-hoc nature of the analyses, but also by the potential limitations in generalizing older patients enrolled in randomized studies to the general older population with diabetic kidney disease. The tendency for randomised trial cohorts to exclude older and frailer patients, is well known, and the generalizability (measured as proportion of patients eligible) of previous SGLT2 inhibitor trials to the general population with T2DM varies from 17-59%.[30–32] Observational studies have found variable associations between age and rate of decline in kidney function in the general population.[33–35] In populations referred to nephrology services, increasing age has been independently associated with a lower risk of doubling of serum creatinine and a slower decline in eGFR.[36–38] A higher prevalence of low- to moderately proteinuric vascular nephropathy in older CKD cohorts may contribute to this finding, as is suggested by the lower median albuminuria in patients aged >70 in the present study.[38] Fundamentally, a greater individual benefit (in terms of reduced decline in kidney function) from SGLT2 inhibitor therapy will, assuming consistent relative effects, accrue to those at greatest underlying risk of disease progression. While the present study provides no evidence to suggest that age affects the relative benefit of SGLT2 inhibitor therapy, it does suggest that the absolute benefit may be greatest in

younger patients with diabetic kidney disease.

The evidence for a difference in risk of kidney disease by sex in those with T2DM is inconsistent, with prior studies showing evidence for a higher risk in males, higher risk in females, or no difference between sexes.[7] Nevertheless, the present results show clear evidence that the beneficial effects of canagliflozin on both kidney and cardiovascular endpoints are similar in males and females. This is consistent with previously published secondary and pooled analyses examining cardiovascular efficacy of SGLT2 inhibitors.[22,39,40]

Canagliflozin demonstrated adverse effects consistent with the SGLT2 inhibitor class.[26] Although the absolute number of mycotic infections was higher in females than males, the present study and pooled analyses of previous trials have noted numerically greater relative risks in males. This reflects low baseline risk in males and in neither analysis did this interaction attain significance adjusted for multiple comparisons.[22] The consistency in rates of adverse effects across age groups is in keeping with other reports from major cardiovascular outcome SGLT2 inhibitor trials.[22,28] Observational studies in elderly patients have largely found SGLT2 inhibitors are well tolerated in older patients.[41,42] Although we also found no evidence that the efficacy of canagliflozin on the primary study endpoint, or the safety of this drug, was diminished in those aged 80 years or more, it is important to emphasize the limited number of participants in this age group. Dedicated studies that enroll the very elderly are required to properly determine the safety and efficacy of SGLT2 inhibitors in this vulnerable population.

The strengths of the present analysis include the ability to assess the effects of age and sex in a large trial of high-risk patients with albuminuria and reduced kidney function. The results were robust with similar results regardless of whether age was categorized or continuous. Nevertheless, the findings from this post-hoc analysis should be interpreted in light of some

limitations. First, the CREDENCE trial was not powered to detect differences in treatment effect by age or sex, a limitation compounded by the fact that the trial was stopped early due to efficacy for the primary endpoint. Secondly, we deliberately reduced the significance threshold to account for the risk of type 1 error with the multiple comparisons being made in this post-hoc analysis which may reduce the sensitivity to detect smaller differences between groups. There were relatively few females, black participants, and low numbers of patients at the extremes of age in the study which may limit the generalizability of these findings to these populations.

In conclusion, the CREDENCE data suggests that canagliflozin consistently improves kidney and cardiovascular outcomes with little variation in risk of adverse events in patients with type 2 diabetes and albuminuric chronic kidney disease across a broad range of ages and in both males and females. The absolute benefit of canagliflozin was greater in younger participants who were at higher risk of adverse kidney outcomes. These findings should help to clarify decision making for those with diabetes and chronic kidney disease.

Supplementary Material

Figure S1: Distribution of age within the study cohort
Figure S2: Effect of canagliflozin overall, by age group, and by sex, with time-dependent hazard ratios from flexible parametric survival models.
Figure S3: Sensitivity analysis of the effect of canagliflozin on primary and secondary outcomes by age with competing risk for death
Item S1. CREDENCE Trial Investigators
Table S1: Baseline characteristics by treatment group and age group and sex.
Table S2: Unadjusted and adjusted event rates and risk by age group
Table S3: Sensitivity analysis of event rates and risk by age group with competing risk for death
Table S4: Flexible parametric survival models
Table S5: Selected adverse events in participants aged 80 years or more, compared with those aged 70-79 years.
Table S6: Unadjusted and adjusted event rates and risk by sex
Table S7: Age group and sex interactions for efficacy endpoints

Article Information

CREDENCE Trial Investigators: A full list of the CREDENCE Trial Investigators is provided in Item S1.

Authors' Contributions: Research area and study design: TY, BS, AL, MJ. Data acquisition:

BS, GD. Data analysis and interpretation: TY, BS, GD, KC, AK, AL, MJ. Statistical analysis: BS, GD. Supervision or mentorship: CA, CP, RA, GB, DC, DZ, HH, BN, DW, CC, HZ, BZ, VP, AL, KW, MJ. Each author contributed important intellectual content during manuscript drafting or revision and agrees to be personally accountable for the individual's own contributions and to ensure that questions pertaining to the accuracy or integrity of any portion of the work, even one in which the author was not directly involved, are appropriately investigated and resolved, including with documentation in the literature if appropriate.

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Table 1: Baseline characteristics by age group and sex

	Age group			Sex		All
	<60	60-69	≥70	Female	Male	
N	1475	1854	1072	1494	2907	4401
Age (Years)	52.7±5.5	64.7±2.8	74.3±3.6	62.9±9.2	63.1±9.2	63.0±9.2
Female sex (%)	503 (34)	632 (42)	359 (24)	1494 (100)	0.0 (0.0)	1494 (34)
Race (%)						
White	861 (58)	1283 (69)	787 (73)	992 (66)	1939 (67)	2931 (67)
Black	105 (7)	70 (4)	49 (5)	102 (7)	122 (4)	224 (5)
Asian	374 (25)	346 (19)	157 (15)	245 (16)	632 (22)	877 (20)
Other	135 (9)	155 (8)	79 (7)	155 (10)	214 (7)	369 (8)
Current smoker (%)	265 (18)	262 (14)	112 (10)	133 (9)	506 (17)	639 (15)
Hypertension (%)	1402 (95)	1805 (97)	1053 (98)	1449 (97)	2811 (97)	4260 (97)
Heart failure (%)	161 (11)	309 (17)	182 (17)	257 (17)	395 (14)	652 (15)
Diabetes duration (years)	13.7±7.4	15.9 ±8.2	18.4 ±10.1	16.2±8.6	15.6±8.6	15.8±8.6
Cardiovascular disease (%)	589 (40)	986 (53)	645 (60)	695 (47)	1525 (53)	2220 (50)
Amputation (%)	98 (7)	97 (5)	39 (4)	51 (3)	183 (6)	234 (5)
BMI (kg/m2)	31.9±6.7	31.5 ±6.2	30.2 ±5.2	31.9±6.8	31.0±5.8	31.3±6.2
Blood pressure (mmHg)						
Systolic	137.9±15.4	140.4±15.5	142.1 ±15.7	140.2±15.8	139.9±15.5	140±15.6
Diastolic	80.7±8.7	78.0±9.3	75.5 ±9.5	77.5±9.1	78.7±9.5	78.3±9.4
Hemoglobin A1c (%)	8.5±1.4	8.2±1.3	8.0±1.2	8.5±1.4	8.1±1.2	8.3±1.3
eGFR (mL/min/1.73m2)	58.8±19.4	56.3±17.6	52.3 ±16.9	56.4±18.4	56.1±18.2	56.2±18.2
UACR (mg/g)	1108 (511-2337)	876.5 (473-1724)	742.5 (418-1493.5)	984 (460-1954)	888 (465-1776)	927 (463-1833)

Data are mean±standard deviation or number (%), unless otherwise specified.

Table 2: Adverse events by age group

	n/N Canagliflozin	n/N Placebo	Event rate Canagliflozin	Event rate Placebo	HR (95% CI)	P-value	P-interaction
Fracture							
<60	17/731	9/744	9.1	4.7	1.92 (0.86 to 4.31)	0.1	
60-69	28/950	35/904	11.3	15.2	0.75 (0.46 to 1.24)	0.3	0.2
70+	22/521	24/551	16.3	17.0	0.95 (0.53 to 1.69)	0.9	
Amputation							
<60	28/731	30/744	15.2	15.9	0.95 (0.57 to 1.59)	0.9	
60-69	33/950	25/904	13.4	10.8	1.23 (0.73 to 2.07)	0.4	0.8
70+	9/521	8/551	6.6	5.6	1.20 (0.46 to 3.11)	0.7	
Volume depletion							
<60	43/731	33/744	26.8	20.8	1.30 (0.83 to 2.05)	0.3	
60-69	56/950	38/903	26.2	19.0	1.42 (0.94 to 2.14)	0.1	0.7
70+	45/519	44/550	40.1	37.7	1.11 (0.73 to 1.69)	0.6	
Hypoglycaemia							
<60	77/731	73/744	50.4	48.3	1.06 (0.77 to 1.46)	0.7	
60-69	98/950	99/903	47.1	52.2	0.93 (0.70 to 1.23)	0.6	0.4
70+	50/519	68/550	45.3	61.3	0.75 (0.52 to 1.08)	0.1	
Kidney related events, including AKI							
<60	116/731	155/744	73.9	101.5	0.71 (0.56 to 0.90)	0.005	
60-69	113/950	145/903	53.2	74.4	0.71 (0.56 to 0.91)	0.006	0.9
70+	61/519	88/550	54.4	77.0	0.70 (0.50 to 0.96)	0.03	
Urinary tract infection							
<60	80/731	60/744	51.1	38.8	1.32 (0.94 to 1.84)	0.1	
60-69	92/950	94/903	43.6	48.8	0.91 (0.68 to 1.21)	0.5	0.2
70+	73/519	67/550	66.3	58.8	1.12 (0.80 to 1.56)	0.5	
Hospitalization							
<60	218/731	248/744	138.1	155.7	0.89 (0.74 to 1.07)	0.2	
60-69	314/950	349/904	153.3	186.4	0.83 (0.71 to 0.97)	0.02	0.4
70+	202/521	214/551	182.5	186.0	0.96 (0.79 to 1.17)	0.7	
Mycotic genital infections							
<60	14/731	6/744	8.5	3.4	2.38 (0.91 to 6.19)	0.08	
60-69	24/950	3/903	11.0	1.5	7.56 (2.28 to 25.11)	0.001	0.3
70+	12/519	4/550	10.3	3.3	3.11 (1.00 to 9.64)	0.05	
All adverse events							
<60	598/731	632/744	926.1	1103.7	0.88 (0.79 to 0.99)	0.03	
60-69	766/950	767/903	885.5	1095.3	0.87 (0.79 to 0.97)	0.009	0.9
70+	420/519	461/550	858.0	1050.7	0.85 (0.74 to 0.97)	0.02	
Serious adverse events							
<60	215/731	237/744	148.5	168.5	0.89 (0.74 to 1.07)	0.2	
60-69	312/950	352/903	165.8	207.9	0.81 (0.69 to 0.94)	0.005	0.2
70+	210/519	217/550	216.5	214.3	1.00 (0.82 to 1.20)	0.9	
Serious adverse events related to study drug							
<60	15/731	16/744	9.1	9.9	0.91 (0.45 to 1.85)	0.8	
60-69	26/950	13/903	11.8	6.4	1.87 (0.96 to 3.65)	0.06	0.3
70+	21/519	13/550	18.0	10.7	1.69 (0.84 to 3.38)	0.1	
Adverse events leading to drug withdrawal							
<60	88/731	90/744	53.4	55.5	0.95 (0.71 to 1.28)	0.8	
60-69	111/950	122/903	50.3	60.1	0.83 (0.64 to 1.07)	0.1	0.8
70+	68/519	74/550	57.7	61.4	0.94 (0.67 to 1.31)	0.7	

Hazard ratios and interactions from Cox proportional hazards regression. CI, confidence interval; HR, hazard ratio. Sensitivity analyses treating age as a continuous variable result in similar findings.

Table 3: Adverse events by sex

	n/N Canagliflozin	n/N Placebo	Event rate		HR (95% CI)	P-value	P-interaction
			Canagliflozin	Placebo			
Fracture							
Female	29/762	43/732	15.0	23.5	0.64 (0.40 to 1.02)	0.06	0.01
Male	38/1440	25/1467	10.1	6.6	1.55 (0.93 to 2.56)	0.09	
Amputation							
Female	15/762	13/732	7.7	6.9	1.11 (0.53 to 2.33)	0.8	0.9
Male	55/1440	50/1467	14.7	13.3	1.11 (0.76 to 1.63)	0.6	
Volume depletion							
Female	49/761	35/731	29.3	22.0	1.32 (0.86 to 2.04)	0.2	0.7
Male	95/1439	80/1466	29.8	25.3	1.20 (0.89 to 1.62)	0.2	
Hypoglycaemia							
Female	107/761	97/731	68.3	65.9	1.04 (0.79 to 1.37)	0.8	0.2
Male	118/1439	143/1466	37.5	47.0	0.83 (0.65 to 1.06)	0.1	
Kidney related events, including AKI							
Female	93/761	115/731	55.6	74.6	0.72 (0.55 to 0.95)	0.02	0.8
Male	197/1439	273/1466	62.7	88.7	0.70 (0.58 to 0.84)	0.0001	
Urinary tract infection							
Female	170/761	130/731	110.6	89.7	1.23 (0.98 to 1.54)	0.08	0.04
Male	75/1439	91/1466	23.2	28.7	0.82 (0.6 to 1.11)	0.2	
Hospitalization							
Female	236/762	244/732	144.8	155.0	0.92 (0.77 to 1.10)	0.4	0.6
Male	498/1440	567/1467	160.4	186.4	0.86 (0.77 to 0.97)	0.02	
Mycotic genital infections							
Female	22/761	10/731	12.6	6.1	2.10 (1.00 to 4.45)	0.05	0.04
Male	28/1439	3/1466	8.4	0.9	9.30 (2.83 to 30.60)	0.0002	
All adverse events							
Female	632/761	623/731	975.3	1143.2	0.89 (0.80 to 1.00)	0.04	0.7
Male	1152/1439	1237/1466	851.9	1060.2	0.86 (0.80 to 0.93)	0.0003	
Serious adverse events							
Female	246/761	243/731	163.9	173.2	0.94 (0.78 to 1.12)	0.5	0.3
Male	491/1439	563/1466	175.5	207.9	0.84 (0.75 to 0.95)	0.006	
Serious adverse events related to study drug							
Female	20/761	14/731	11.6	8.6	1.32 (0.67 to 2.61)	0.4	0.8
Male	42/1439	28/1466	12.8	8.6	1.51 (0.94 to 2.44)	0.09	
Adverse events leading to drug withdrawal							
Female	78/761	93/731	45.0	57.8	0.76 (0.57 to 1.03)	0.08	0.2
Male	189/1439	193/1466	57.3	59.5	0.97 (0.79 to 1.19)	0.8	

Hazard ratios and interactions from Cox proportional hazards regression. CI, confidence interval; HR, hazard ratio.

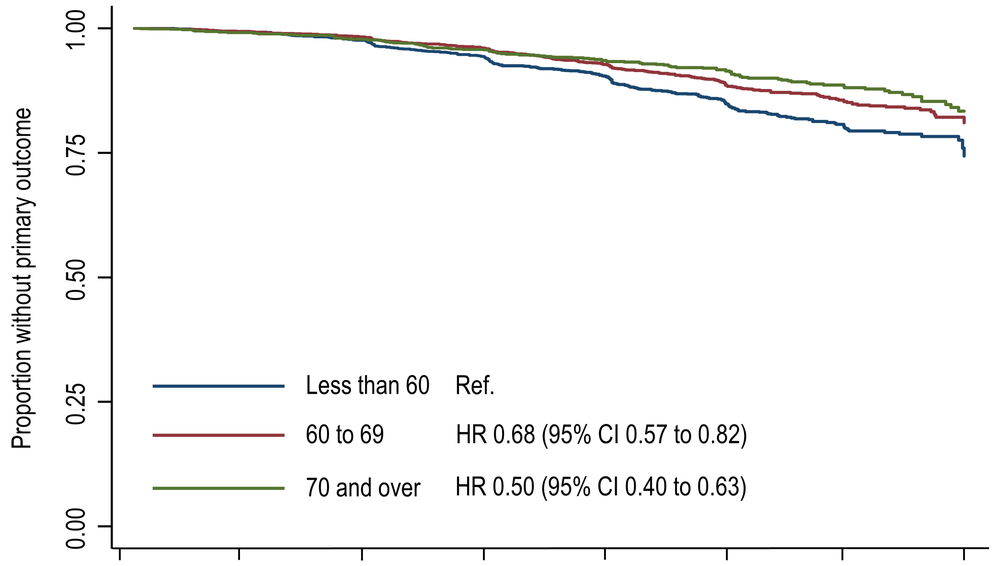
Figure 1: Time to occurrence of primary outcome and eGFR slope by age and sex.
A. Primary outcome Kaplan-Meier curves by age group. B. Primary outcome Kaplan-Meier curves by sex. C. eGFR slope by age group. D. eGFR slope by sex.
Analyses include participants in both canagliflozin and placebo groups. Hazard ratios are not adjusted for confounding variables (see text for adjusted HRs). Primary outcome comprises doubling of serum creatinine, kidney failure (dialysis, transplantation, or eGFR < 15ml/min/1.73m^2), cardiovascular or kidney death.

Figure 2: Effect of canagliflozin on primary and secondary outcomes by age.
Relative effect of canagliflozin and absolute difference in events per 1000 patients over 2.5 years.

Figure 3: Effect of canagliflozin on main outcomes by age, treating age as continuous variable.
Hazard ratio from Cox proportional hazards regression with age treated as restricted cubic spline variable.
Owing to wide confidence intervals at the extremes of the study population age range, figures have been truncated to the 5th to 95th centiles of age.

Figure 4: Effect of canagliflozin on primary and secondary outcomes by sex.
Relative effect of canagliflozin and absolute difference in events per 1000 patients over 2.5 years.

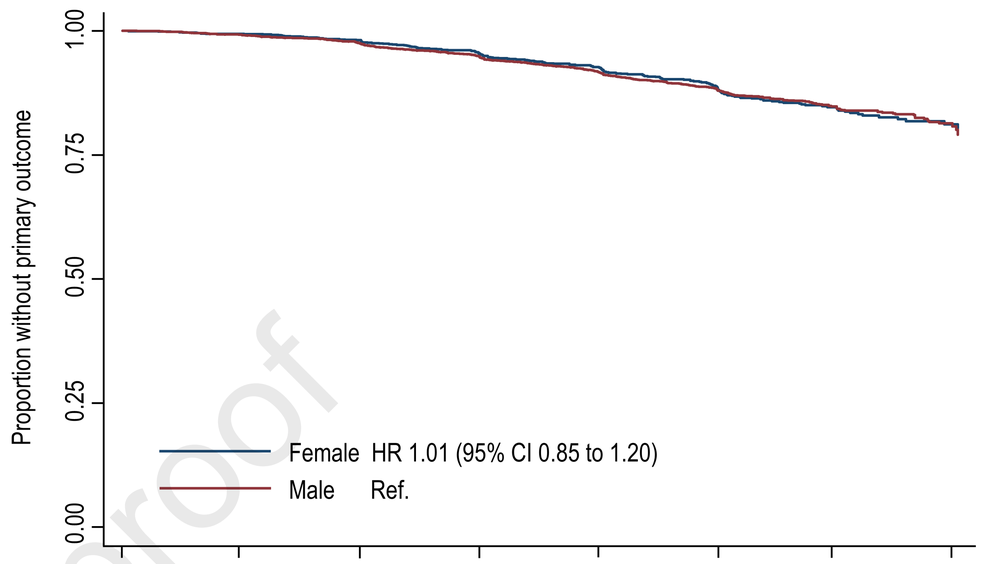
A



Number at risk

Less than 60	1475	1462	1425	1361	1125	709	370	96
60 to 69	1854	1836	1806	1754	1480	990	532	143
70 and over	1072	1061	1040	1003	867	603	342	106

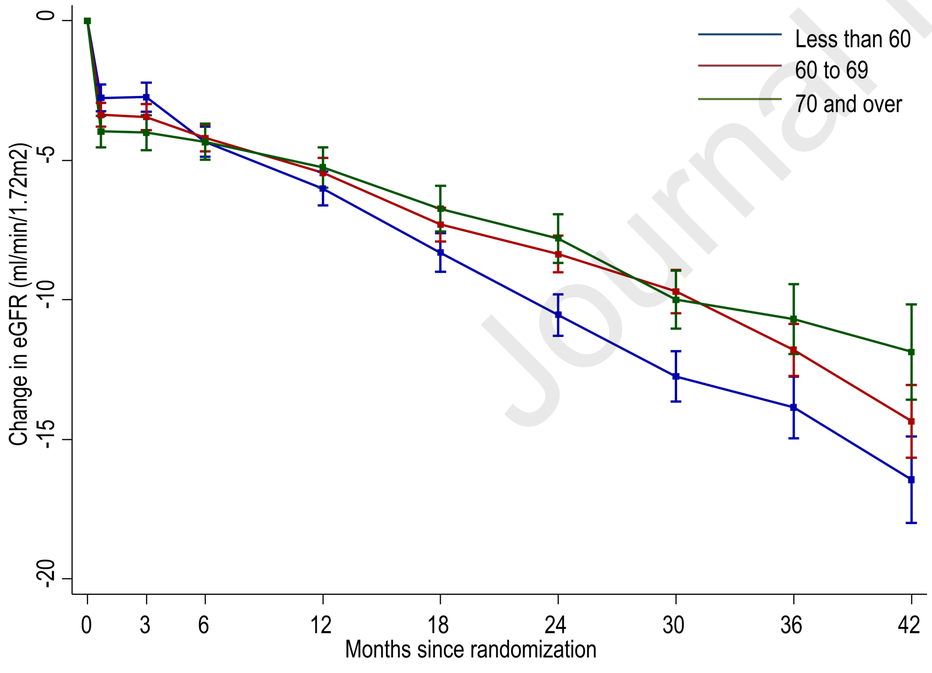
B



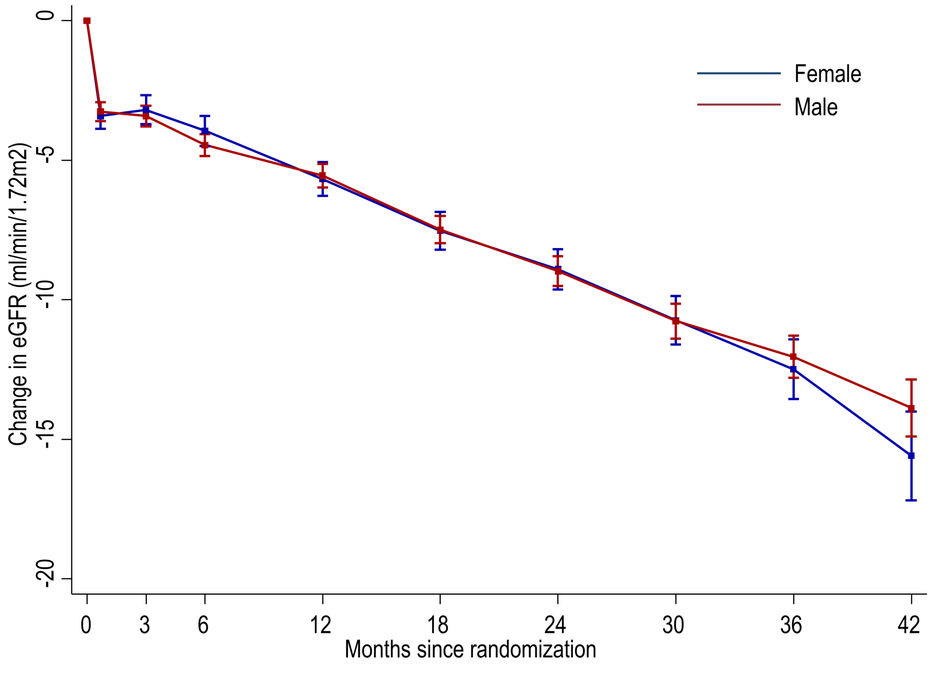
Number at risk

Female	1494	1482	1457	1402	1162	737	376	106
Male	2907	2877	2814	2716	2310	1565	868	239

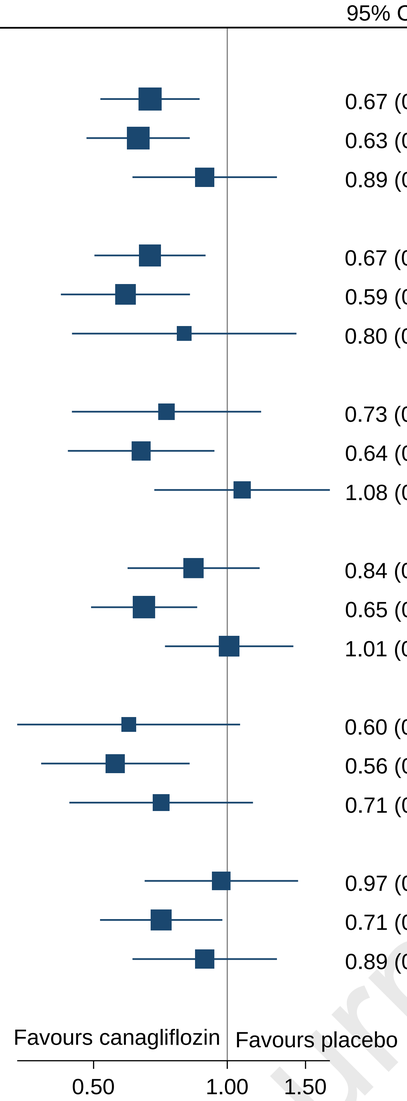
C

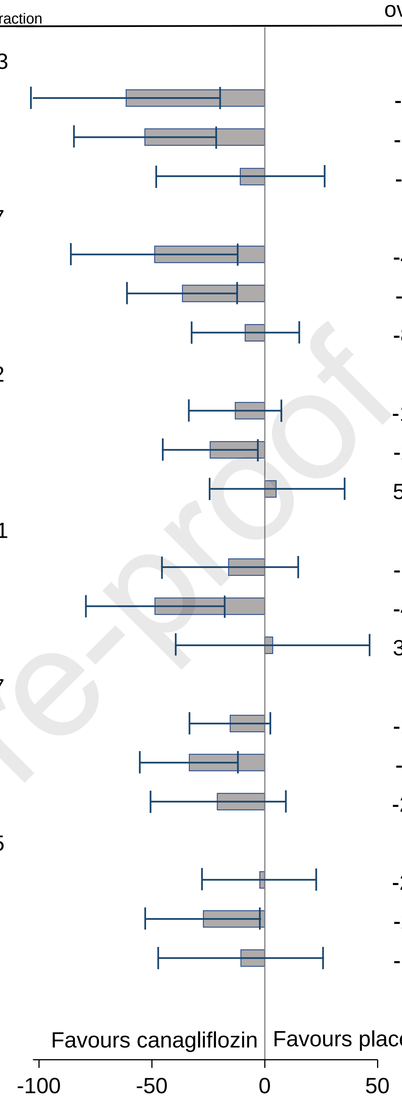


D

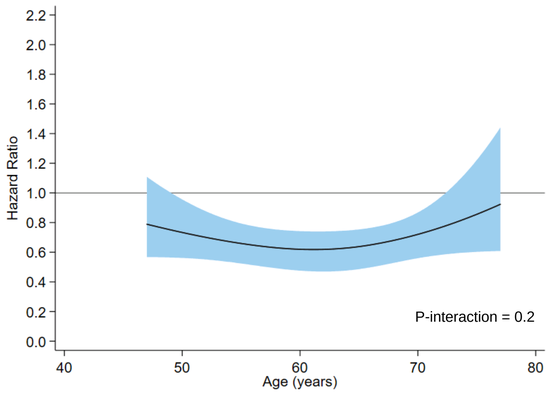


Outcome Age group	Event rate Cana/Placebo		Hazard Ratio 95% CI	P-value	$P_{interaction}$	Absolute reduction in events per 1000 patients over 2.5 years (95% CI)	Number needed to treat over 2.5 years
Primary composite outcome					0.3		
<60	53.7	78.1	0.67 (0.52, 0.87)	0.003		-61.1 (-102.7, -19.5)	17
60-69	38.3	59.4	0.63 (0.48, 0.82)	<0.001		-52.8 (-84.3, -21.3)	19
≥70	38.1	42.6	0.89 (0.61, 1.29)	0.5		-11.1 (-48.4, 26.1)	90
Kidney composite					0.7		
<60	42.2	61.7	0.67 (0.50, 0.89)	0.006		-48.9 (-85.8, -12.0)	21
60-69	22.6	37.2	0.59 (0.42, 0.82)	0.002		-36.5 (-61.1, -11.8)	28
≥70	14.7	18.2	0.80 (0.45, 1.44)	0.5		-8.7 (-32.4, 15.1)	115
Cardiovascular death					0.2		
<60	14.3	19.7	0.73 (0.45, 1.20)	0.2		-13.3 (-34.0, 7.3)	76
60-69	17.8	27.6	0.64 (0.44, 0.94)	0.02		-24.4 (-45.6, -3.2)	41
≥70	27.5	25.4	1.08 (0.68, 1.69)	0.8		5.3 (-24.7, 35.3)	189*
Major adverse cardiovascular event					0.1		
<60	32.1	38.4	0.84 (0.60, 1.19)	0.3		-15.7 (-45.9, 14.5)	64
60-69	36.0	55.4	0.65 (0.49, 0.85)	0.002		-48.7 (-79.4, -18.0)	21
≥70	52.9	51.5	1.01 (0.72, 1.40)	0.9		3.5 (-39.5, 46.4)	286*
Heart failure					0.7		
<60	9.6	15.8	0.60 (0.34, 1.08)	0.09		-15.5 (-33.5, 2.5)	65
60-69	17.0	30.4	0.56 (0.38, 0.82)	0.003		-33.6 (-55.7, -11.6)	30
≥70	21.5	29.9	0.71 (0.44, 1.14)	0.2		-20.9 (-50.8, 9.0)	48
All-cause mortality					0.5		
<60	24.9	25.9	0.97 (0.65, 1.44)	0.9		-2.3 (-27.6, 23.0)	435
60-69	27.4	38.2	0.71 (0.52, 0.98)	0.03		-27.1 (-52.6, -1.7)	37
≥70	37.7	41.9	0.89 (0.61, 1.29)	0.5		-10.5 (-47.2, 26.2)	96

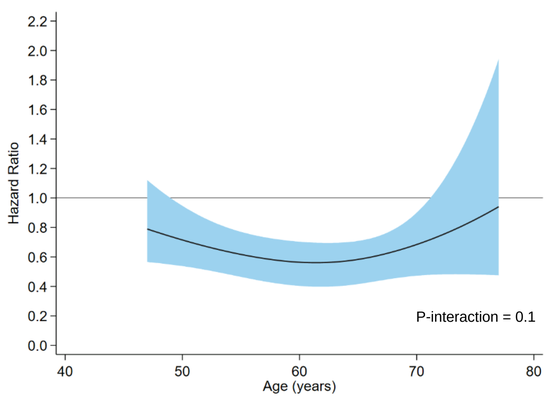




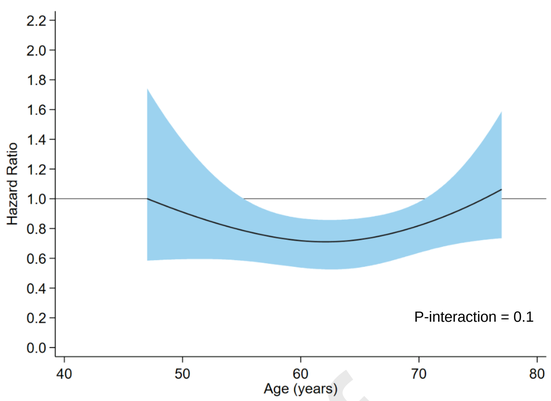
Primary composite outcome



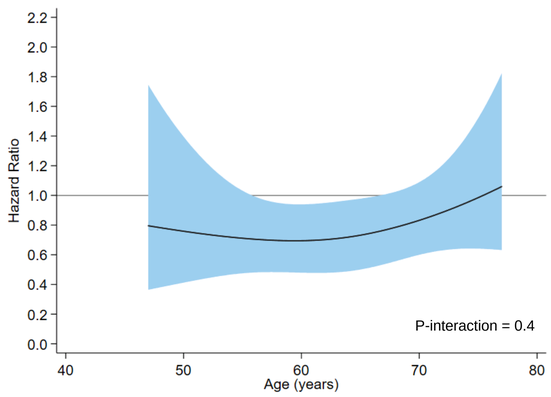
Kidney composite



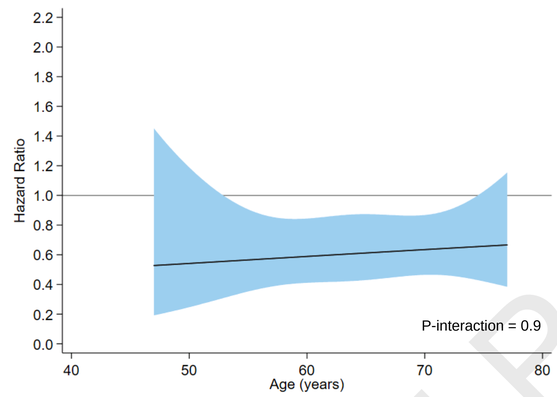
Major adverse cardiovascular event



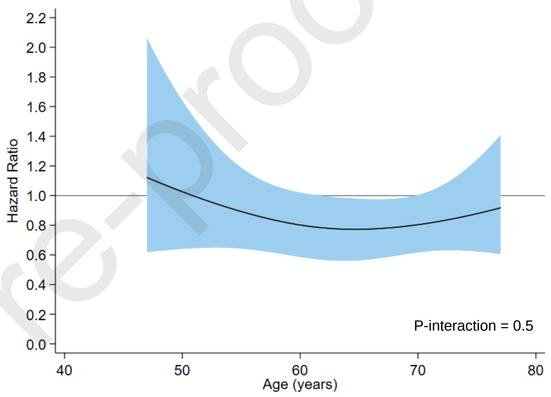
Cardiovascular death



Heart failure



All-cause mortality



Outcome Sex	Event rate Cana/Placebo		Hazard Ratio 95% CI	P-value	$P_{interaction}$	Absolute reduction in events per 1000 patients over 2.5 years (95% CI)	Number needed to treat over 2.5 years
Primary composite outcome					0.8		
Female	43.1	59.2	0.71 (0.54, 0.95)	0.02		-40.2 (-76.4, -4.0)	25
Male	43.3	62.3	0.69 (0.56, 0.84)	<0.001		-47.5 (-73.6, -21.4)	22
Kidney composite					0.7		
Female	25.5	40.2	0.61 (0.43, 0.88)	0.008		-36.9 (-65.9, -7.9)	28
Male	27.8	40.4	0.68 (0.53, 0.87)	0.002		-31.6 (-52.6, -10.7)	32
Cardiovascular death					0.7		
Female	19.3	23.2	0.83 (0.54, 1.28)	0.4		-9.6 (-32.6, 13.4)	105
Male	18.8	25.0	0.75 (0.56, 1.02)	0.07		-15.3 (-31.9, 1.2)	66
Major adverse cardiovascular event					0.5		
Female	37.7	42.9	0.87 (0.63, 1.20)	0.4		-13.2 (-45.3, 19.0)	76
Male	39.2	51.5	0.76 (0.61, 0.95)	0.01		-30.7 (-55.0, -6.4)	33
Heart failure					0.9		
Female	16.0	25.5	0.62 (0.40, 0.98)	0.04		-23.7 (-46.7, -0.7)	43
Male	15.5	25.3	0.61 (0.44, 0.85)	0.003		-24.5 (-40.7, -8.3)	41
All-cause mortality					0.7		
Female	28.5	32.1	0.88 (0.61, 1.27)	0.5		-9.1 (-36.5, 18.4)	110
Male	29.3	36.4	0.80 (0.63, 1.03)	0.08		-17.8 (-38.1, 2.5)	57