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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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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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 Canagliflozin and Renal Endpoints in Diabetes with Established Nephropathy Clinical Evaluation (CREDENCE) study.

Study Design: Secondary analysis of a randomized controlled trial.

Setting & Participants: Participants in the CREDENCE trial.

Intervention: Participants were randomly assigned to receive canagliflozin 100 mg/d or placebo.

Outcomes: Primary composite outcome of kidney failure, doubling of serum creatinine concentration, or death due to kidney or cardiovascular disease. Prespecified 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 serum creatinine concentration, or death from kidney or cardiovascular causes) differed between age groups (HRs, 0.67 [95% CI, 0.52-0.87], 0.63 [0.48-0.82], and 0.89 [0.61-1.29] for ages <60, 60-69, and ≥70 years, respectively; $P = 0.3$ for interaction) or sexes (HRs, 0.71 [95% CI, 0.54-0.95] and 0.69 [0.56-0.84] in women and men, respectively; $P = 0.8$ for interaction). 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. As a result of greater 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.

Visual Abstract online

Complete author and article information provided before references.

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A personalized approach to treatment is important to ensure that 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, comorbidities, and baseline risk. Differences in 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, modeling 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 intrarenal hemodynamic effects of sodium/glucose cotransporter 2 (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) decrease may be lower in female participants with chronic kidney disease (CKD) than in male participants.[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 elderly patients 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.

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 the safety and efficacy of canagliflozin differed among three age groups (<60, 60-69, and ≥70 years) and between sexes. Canagliflozin reduced the risk of the primary outcome (kidney failure, doubling of serum creatinine concentration, death due to kidney or cardiovascular disease) similarly among 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 similarly effective and safe among different age categories and between sexes.

SGLT2 inhibitors have now exhibited benefits in kidney and cardiovascular outcomes in several large trials, including the Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation (CREDENCE) trial, in which canagliflozin reduced the risk of the composite outcome of kidney failure, doubling of serum creatinine concentration, and kidney or cardiovascular mortality by 30% in participants with diabetic kidney disease.[13] Although 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, cardiovascular, 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 multicenter, double-blind, placebo-controlled, randomized trial evaluating the effects of canagliflozin 100mg/d on kidney, cardiovascular, and safety outcomes in people with type 2 diabetes mellitus (T2DM) and albuminuric CKD. Key inclusion criteria were age 30 years or older, a diagnosis of T2DM, an eGFR of 30 to <90 mL/min/1.73 m^2, and a urinary albumin-creatinine ratio of >300 to 5,000 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 before randomization. Randomization was stratified according to the category of eGFR (30 to <45, 45 to <60, or 60 to <90 mL/min/1.73 m^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 ≥30 days, kidney transplant, or an eGFR <15 mL/min/1.73 m^2 sustained for ≥30 days), doubling of serum creatinine concentration, 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 concentration, or death from kidney disease; cardiovascular death; the composite of nonfatal myocardial infarction, stroke, and cardiovascular death; hospitalization for heart failure; and all-cause death. Annual eGFR decrease ("eGFR slope") was an additional secondary outcome. Prespecified 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, hypoglycemia, 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 (ie, events were considered while the participant was receiving study medication or ≤30 days after ceasing study medication).[5] As in the primary publication, fracture and amputation were determined in the on-study population (ie, 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 analyzed. 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 in participants aged at least 70 years in which those aged 80 years or more were compared with those aged 70-79 years. Given the relatively small size of the cohort of patients older than 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 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 a statin, and baseline values of glycated hemoglobin, body mass index, systolic blood pressure, eGFR, urine albumin-creatinine ratio (log-transformed), low-density lipoprotein cholesterol level, and triglyceride level. 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 (HR).[20] The effect of canagliflozin on outcomes was evaluated within subgroups to determine HRs and 95% CIs.

The absolute risk difference (and 95% CIs) between canagliflozin and placebo groups was estimated by multiplying the difference in incidence rates (per 1,000 patient-years) by 2.5 years (approximating the median duration of the study).[21] A P value lower than 0.05 was considered significant for main effects, but, given the large number of comparisons being made, a P value for interaction lower than 0.01 was chosen to reduce the risk of type I error.[22] Analysis was performed using SAS Enterprise Guide version 7.15 (SAS Institute Inc) and Stata/IC 15.1 (StataCorp).

Effect Modification

The hypothesis that the effects of canagliflozin differed between subgroups (ie, heterogeneity) was tested by adding the subgroup and a treatment group–by–subgroup interaction term to the model. Heterogeneity by age was explored as a 3-value categorical variable and, to explore the possibility of nonlinear differences in treatment effect, by modeling age as a continuous variable using a restricted cubic spline. Knot positions (10th, 50th, and 90th centiles) were chosen following the recommendation of Harrell,[23] and a 3-knot model was chosen because this resulted in a better fit (ie, lowest Akaike information criterion) for the primary outcome in the overall population compared with models using 4, 5, 6, or 7 knots. Because of 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 Decrease

Change in eGFR over time was analyzed in the on-treatment population using a multislope mixed-effects linear spline model with connected slopes from baseline to week 3 and from week 3 to the end of the study. 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 4,401 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, 1,475 (33.5%), 1,854 (42.1%), and 1,072 (24.4%) participants were younger than 60, 60-69, and at least 70 years of age, respectively (Table 1). Baseline characteristics by treatment group, age group, and sex are shown in Table S1. The latter group was comprised predominantly (58.6%) of participants aged 70-74 years (Fig S1). Of the total cohort, 2,907 (66.1%) participants were male and 1,494 (33.9%) were female (Table 1). The mean baseline eGFR was 56.2 mL/min/1.73 m^2, and median urinary albumin-creatinine ratio was 927 mg/g. Overall, 585 primary composite outcomes were recorded at a rate of 52.1 per 1,000 patient-years.

Outcomes by Age

The rate of the primary composite outcome of kidney failure, doubling of serum creatinine concentration, or death due to kidney or cardiovascular disease was highest in the group of participants younger than 60 years of age (65.9 per 1,000 patient-years) and lower in the 2 older groups (48.4 and 40.4 per 1,000 patient-years for age 60-69 and ≥70 years, respectively; Fig 1A). After adjustment for confounding variables, participants at least 70 years of age retained a lower risk for the primary outcome (vs the group aged <60 years; adjusted HR, 0.60; 95% CI, 0.47-0.77; P < 0.001; Table S2). This was driven by lower adjusted estimates of risk of kidney-related components of the primary composite outcome in the group aged at least 70 years (adjusted HRs of 0.32 [95% CI, 0.22-0.48; P < 0.001] and 0.30 [95% CI, 0.20-0.45; P < 0.001] for doubling serum creatinine concentration and kidney failure, respectively; Table S2). In contrast, adjusted risks of major adverse cardiovascular events, cardiovascular death, hospitalization with heart failure, and all-cause death increased with increasing age (Table S2). The rate of decrease in eGFR after week 3 was lowest in the group of participants aged at least 70 years (2.33 mL/min/1.73 m^2 per year), followed by the age–60-69 group (2.88 mL/min/1.73 m^2 per year), and both were significantly lower than in the group of participants younger than 60 years (4.24 mL/min/1.73 m^2 per year; difference vs age ≥70 years, 1.90 mL/min/1.73 m^2 per year; 95% CI, 1.39-2.42; difference vs age 60-69 years, 1.35 mL/min/1.73 m^2 per year; 95% CI, 0.92-1.79; P < 0.001 for both differences; Fig 1C). There were no differences in the decrease in eGFR to week 3. A sensitivity analysis was performed accounting for the competing risk of 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

Table 1. Baseline Characteristics by Age Group and Sex

Characteristic	Age Group			Sex		All
	<60 y	60-69 y	≥70 y	Female	Male	
No. of patients	1,475	1,854	1,072	1,494	2,907	4,401
Age, y	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%)	1,494 (100%)	0.0	1,494 (34%)
Race						
White	861 (58%)	1,283 (69%)	787 (73%)	992 (66%)	1,939 (67%)	2,931 (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	1,402 (95%)	1,805 (97%)	1,053 (98%)	1,449 (97%)	2,811 (97%)	4,260 (97%)
Heart failure	161 (11%)	309 (17%)	182 (17%)	257 (17%)	395 (14%)	652 (15%)
Diabetes duration, y	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%)	1,525 (53%)	2,220 (50%)
Amputation	98 (7%)	97 (5%)	39 (4%)	51 (3%)	183 (6%)	234 (5%)
BMI, kg/m^2	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, mm Hg						
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 A_{1c}, %	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/1.73 m^2	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 (IQR)	1,108 (511-2,337)	876.5 (473-1,724)	742.5 (418-1,493.5)	984 (460-1,954)	888 (465-1,776)	927 (463-1,833)

Data presented as mean ± standard deviation where applicable. BMI, body mass index; eGFR, estimated glomerular filtration rate; UACR, urinary albumin-creatinine ratio.

no evidence of heterogeneity of treatment effect by age in all participants (HRs [95% CIs], 0.67 [0.52-0.87], 0.63 [0.48-0.82], and 0.89 [0.61-1.23] for the <60-year, 60-69–year, and ≥70-year age groups, respectively; Fig 2) regardless of whether age was treated as a categorical or continuous variable ($P = 0.3$ [Fig 2] and $P = 0.2$ [Fig 3] for interaction, respectively). The proportional hazards assumption was met, although visual inspection of the HR over time showed a tendency for increased benefit from canagliflozin as follow-up time increased (Fig S2; Table S4). In the overall CREDENCE study population, canagliflozin significantly reduced the risk of the secondary kidney composite outcome, doubling of serum creatinine concentration, 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 (Figs 2 and 3). These conclusions did not differ when death was treated as a competing risk or when time-dependent hazards were modeled (Fig S3). In the very elderly population, 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 reductions in event rates were most prominent in the younger cohort, consistent with their higher baseline risk of kidney events compared with older participants. With the exception of heart failure, the absolute reduction in event rates was attenuated in those older than 70 years (Fig 2).

Outcomes by Sex

Primary composite outcome rates were similar in male and female participants (52.7 and 51.0 per 1,000 patient-years; Fig 1B). Female participants had a lower risk of the primary composite outcome after adjustment for confounding variables (adjusted HR, 0.82; 95% CI, 0.68-0.98; $P = 0.03$; Table S6). Similarly, the adjusted risks of the components of the primary composite outcome tended to be lower in female participants, although this did not reach statistical significance for all outcomes (Table S6). The slope of eGFR decrease after week 3 did not differ between sexes (female, 3.28 mL/min/1.73 m^2 per year; male, 3.14 mL/min/1.73 m^2 per year; difference, 0.14 mL/min/1.73 m^2 per year; 95% CI, 0.26-0.54; $P = 0.5$; Fig 1D). There was no difference in decrease 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

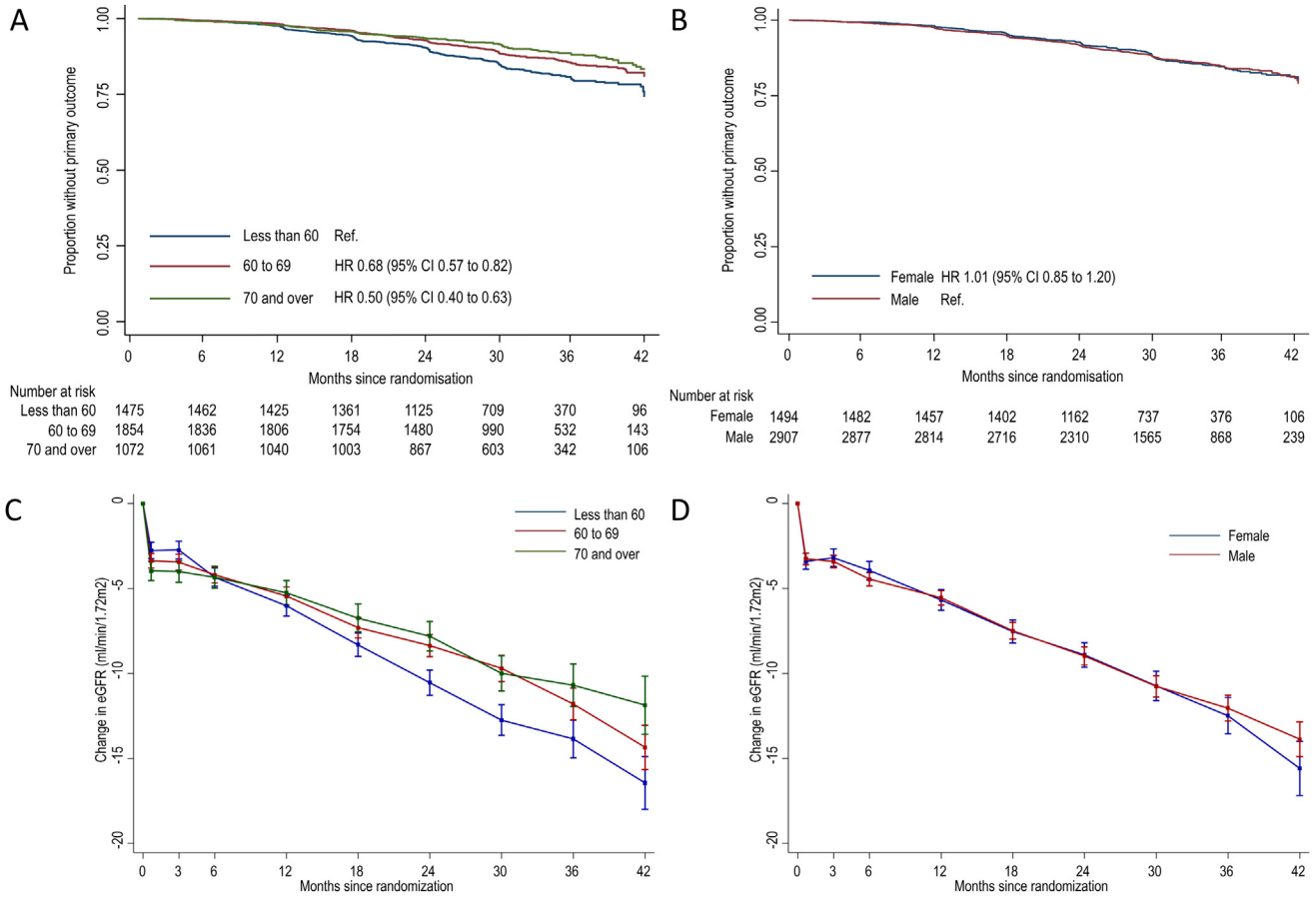

Figure 1. Time to occurrence of primary outcome and estimated glomerular filtration rate (eGFR) slope by age and sex. Primary outcome Kaplan-Meier curves by age group (A) and sex (B) and eGFR slopes by age group (C) and sex (D). Analyses include participants in the canagliflozin and placebo groups. Hazard ratios are not adjusted for confounding variables (see text for adjusted hazard ratios). Primary outcome comprises doubling of serum creatinine concentration, kidney failure (dialysis, transplant, or eGFR <15 mL/min/1.73 m^2), and cardiovascular or kidney death. HR, hazard ratio.

differed by sex (HRs [95% CIs], 0.71 [0.54-0.95] and 0.69 [0.56-0.84] for female and male participants, respectively; P = 0.8 for interaction; Fig 4). The proportional hazards assumption was met. Visual inspection of the HR over time showed a tendency for increased benefit from canagliflozin as follow-up time increased in female participants, with little apparent change in HR over time in male participants (Fig S2; 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 the absolute difference in risk with canagliflozin was similar between sexes (Fig 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 was 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 years, 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, 1.16-3.78) compared with placebo (HR, 0.94; 95% CI, 0.77-1.15), but was driven by a small number of events and did not reach the prespecified threshold for a statistically significant interaction. Only 2 serious adverse events in this age group were judged as related to study drug (one event in each treatment group). Whereas the absolute incidence of mycotic genital infections was higher in female participants than in male participants allocated to canagliflozin (12.9 vs 8.5 per 1,000 patient-years), the relative increase in risk for genital infections tended to be higher in male participants (HRs of 9.30 and 2.10 in male and female participants, respectively; Table 3) as a result of low risk in the placebo group, although this difference did not reach significance against the prespecified interaction threshold. No heterogeneity was observed with canagliflozin in terms of fracture and

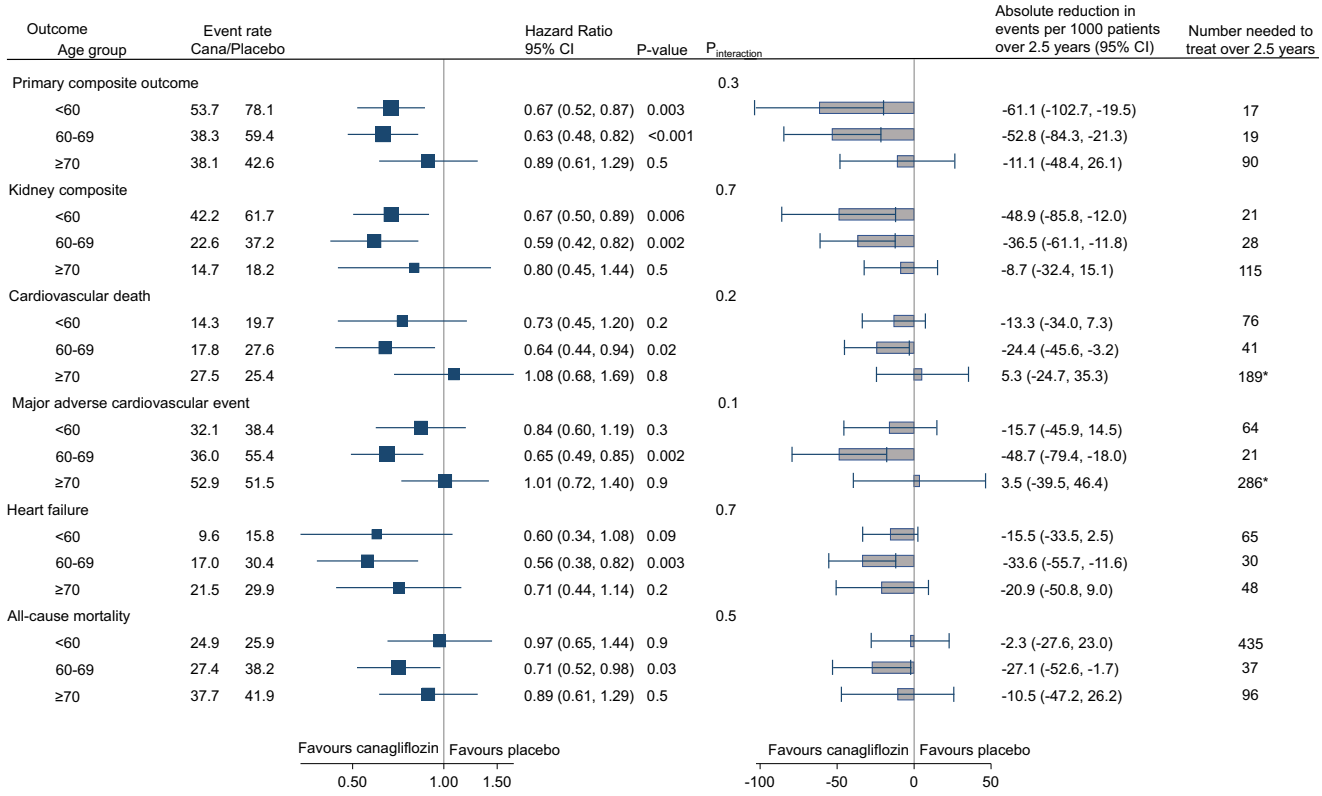

Figure 2. Effect of canagliflozin on primary and secondary outcomes by age: relative effect of canagliflozin and absolute difference in events per 1,000 patients over 2.5 years. Cana, canagliflozin.

urinary tract infection ($P = 0.01$ and $P = 0.04$ for interaction, 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 end points 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]

Although 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 older than 70 years translated into a reduced absolute benefit. For example, the number needed to treat for those aged 70 and older to prevent one primary event was 90, compared with 17 for those younger than 60 years. In contrast, a subgroup analysis of the Canagliflozin Cardiovascular Assessment Study trial demonstrated greater impact on kidney outcomes with canagliflozin in those older than 65 years; however, the baseline kidney risk in the Canagliflozin Cardiovascular Assessment Study cohort was substantially lower than that of the CREDENCE population.[29] However, 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 randomized trial cohorts to exclude older and frailer patients is well known, and the generalizability (measured as the proportion of patients eligible) of previous SGLT2 inhibitor trials to the general population with T2DM varies from 17% to 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 concentration and a slower decrease 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 older

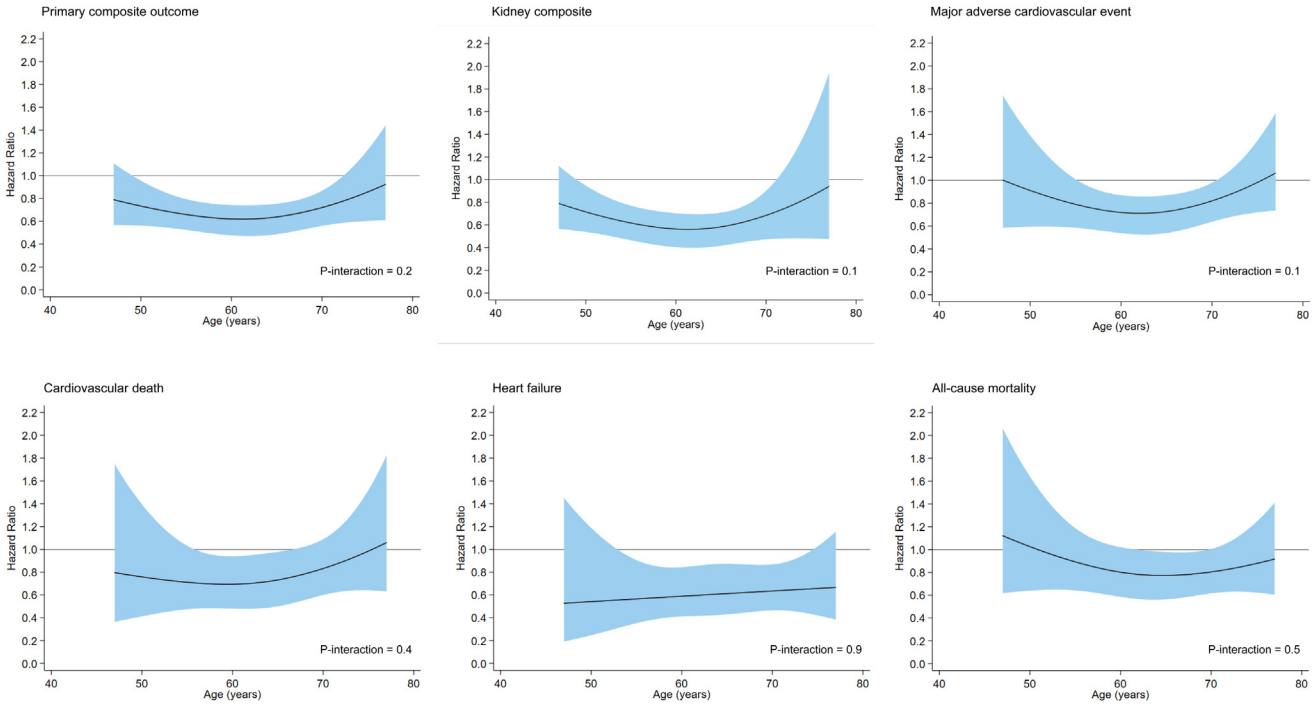

Figure 3. Effect of canagliflozin on main outcomes by age, treating age as a continuous variable. Hazard ratio from Cox proportional hazards regression with age treated as a restricted cubic spline variable. Because of wide CIs at the extremes of the study population age range, figures have been truncated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

than 70 years in the present study.[38] Fundamentally, a greater individual benefit (in terms of reduced decline in kidney function) of SGLT2 inhibitor therapy will, assuming consistent relative effects, accrue to those at greatest underlying risk of disease progression. Although the present study provides no evidence to suggest that age

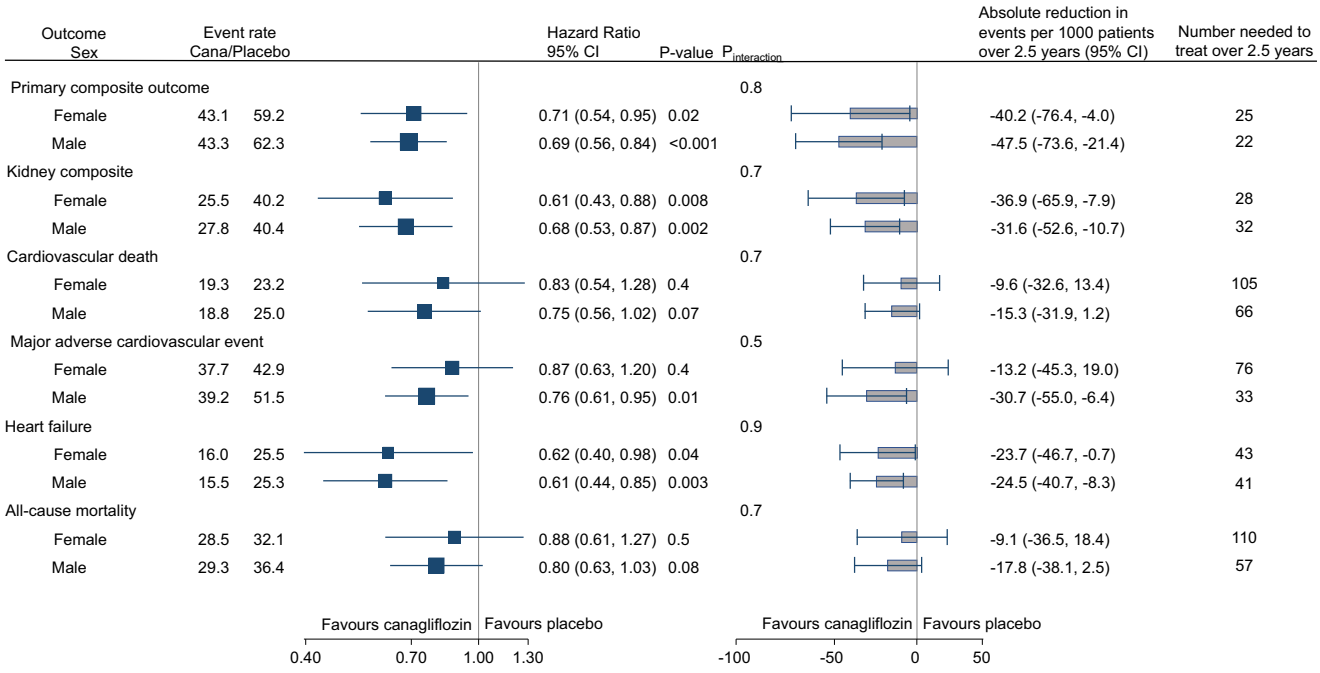

Figure 4. Effect of canagliflozin on primary and secondary outcomes by sex: relative effect of canagliflozin and absolute difference in events per 1,000 patients over 2.5 years. Cana, canagliflozin.

Table 2. Adverse Events by Age Group

Adverse Event	Incidence		Event Rate		HR (95% CI)	*P* Value	*P* for Interaction
	Canagliflozin	Placebo	Canagliflozin	Placebo			
Fracture							
Age <60 y	17/731	9/744	9.1	4.7	1.92 (0.86-4.31)	0.1	0.2
Age 60-69 y	28/950	35/904	11.3	15.2	0.75 (0.46-1.24)	0.3	
Age ≥70 y	22/521	24/551	16.3	17.0	0.95 (0.53-1.69)	0.9	
Amputation							
Age <60 y	28/731	30/744	15.2	15.9	0.95 (0.57-1.59)	0.9	0.8
Age 60-69 y	33/950	25/904	13.4	10.8	1.23 (0.73-2.07)	0.4	
Age ≥70 y	9/521	8/551	6.6	5.6	1.20 (0.46-3.11)	0.7	
Volume depletion							
Age <60 y	43/731	33/744	26.8	20.8	1.30 (0.83-2.05)	0.3	0.7
Age 60-69 y	56/950	38/903	26.2	19.0	1.42 (0.94-2.14)	0.1	
Age ≥70 y	45/519	44/550	40.1	37.7	1.11 (0.73-1.69)	0.6	
Hypoglycemia							
Age <60 y	77/731	73/744	50.4	48.3	1.06 (0.77-1.46)	0.7	0.4
Age 60-69 y	98/950	99/903	47.1	52.2	0.93 (0.70-1.23)	0.6	
Age ≥70 y	50/519	68/550	45.3	61.3	0.75 (0.52-1.08)	0.1	
Kidney-related events, including AKI							
Age <60 y	116/731	155/744	73.9	101.5	0.71 (0.56-0.90)	0.005	0.9
Age 60-69 y	113/950	145/903	53.2	74.4	0.71 (0.56-0.91)	0.006	
Age ≥70 y	61/519	88/550	54.4	77.0	0.70 (0.50-0.96)	0.03	
Urinary tract infection							
Age <60 y	80/731	60/744	51.1	38.8	1.32 (0.94-1.84)	0.1	0.2
Age 60-69 y	92/950	94/903	43.6	48.8	0.91 (0.68-1.21)	0.5	
Age ≥70 y	73/519	67/550	66.3	58.8	1.12 (0.80-1.56)	0.5	
Hospitalization							
Age <60 y	218/731	248/744	138.1	155.7	0.89 (0.74-1.07)	0.2	0.4
Age 60-69 y	314/950	349/904	153.3	186.4	0.83 (0.71-0.97)	0.02	
Age ≥70 y	202/521	214/551	182.5	186.0	0.96 (0.79-1.17)	0.7	
Mycotic genital infections							
Age <60 y	14/731	6/744	8.5	3.4	2.38 (0.91-6.19)	0.08	0.3
Age 60-69 y	24/950	3/903	11.0	1.5	7.56 (2.28-25.11)	0.001	
Age ≥70 y	12/519	4/550	10.3	3.3	3.11 (1.00-9.64)	0.05	
All adverse events							
Age <60 y	598/731	632/744	926.1	1,103.7	0.88 (0.79-0.99)	0.03	0.9
Age 60-69 y	766/950	767/903	885.5	1,095.3	0.87 (0.79-0.97)	0.009	
Age ≥70 y	420/519	461/550	858.0	1,050.7	0.85 (0.74-0.97)	0.02	
Serious adverse events							
Age <60 y	215/731	237/744	148.5	168.5	0.89 (0.74-1.07)	0.2	0.2
Age 60-69 y	312/950	352/903	165.8	207.9	0.81 (0.69-0.94)	0.005	
Age ≥70 y	210/519	217/550	216.5	214.3	1.00 (0.82-1.20)	0.9	
Serious adverse events related to study drug							
Age <60 y	15/731	16/744	9.1	9.9	0.91 (0.45-1.85)	0.8	0.3
Age 60-69 y	26/950	13/903	11.8	6.4	1.87 (0.96-3.65)	0.06	
Age ≥70 y	21/519	13/550	18.0	10.7	1.69 (0.84-3.38)	0.1	
Adverse events leading to drug withdrawal							
Age <60 y	88/731	90/744	53.4	55.5	0.95 (0.71-1.28)	0.8	0.8
Age 60-69 y	111/950	122/903	50.3	60.1	0.83 (0.64-1.07)	0.1	
Age ≥70 y	68/519	74/550	57.7	61.4	0.94 (0.67-1.31)	0.7	

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

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 of greater risk in male

Table 3. Adverse Events by Sex

Adverse Event	Incidence		Event Rate		HR (95% CI)	*P* Value	*P* for Interaction
	Canagliflozin	Placebo	Canagliflozin	Placebo			
Fracture							
Female	29/762	43/732	15.0	23.5	0.64 (0.40-1.02)	0.06	0.01
Male	38/1,440	25/1,467	10.1	6.6	1.55 (0.93-2.56)	0.09	
Amputation							
Female	15/762	13/732	7.7	6.9	1.11 (0.53-2.33)	0.8	0.9
Male	55/1,440	50/1,467	14.7	13.3	1.11 (0.76-1.63)	0.6	
Volume depletion							
Female	49/761	35/731	29.3	22.0	1.32 (0.86-2.04)	0.2	0.7
Male	95/1,439	80/1,466	29.8	25.3	1.20 (0.89-1.62)	0.2	
Hypoglycemia							
Female	107/761	97/731	68.3	65.9	1.04 (0.79-1.37)	0.8	0.2
Male	118/1,439	143/1,466	37.5	47.0	0.83 (0.65-1.06)	0.1	
Kidney-related events, including AKI							
Female	93/761	115/731	55.6	74.6	0.72 (0.55-0.95)	0.02	0.8
Male	197/1,439	273/1,466	62.7	88.7	0.70 (0.58-0.84)	0.0001	
Urinary tract infection							
Female	170/761	130/731	110.6	89.7	1.23 (0.98-1.54)	0.08	0.04
Male	75/1,439	91/1,466	23.2	28.7	0.82 (0.6-1.11)	0.2	
Hospitalization							
Female	236/762	244/732	144.8	155.0	0.92 (0.77-1.10)	0.4	0.6
Male	498/1,440	567/1,467	160.4	186.4	0.86 (0.77-0.97)	0.02	
Mycotic genital infections							
Female	22/761	10/731	12.6	6.1	2.10 (1.00-4.45)	0.05	0.04
Male	28/1,439	3/1,466	8.4	0.9	9.30 (2.83-30.60)	0.0002	
All adverse events							
Female	632/761	623/731	975.3	1143.2	0.89 (0.80-1.00)	0.04	0.7
Male	1152/1,439	1237/1,466	851.9	1060.2	0.86 (0.80-0.93)	0.0003	
Serious adverse events							
Female	246/761	243/731	163.9	173.2	0.94 (0.78-1.12)	0.5	0.3
Male	491/1,439	563/1,466	175.5	207.9	0.84 (0.75-0.95)	0.006	
Serious adverse events related to study drug							
Female	20/761	14/731	11.6	8.6	1.32 (0.67-2.61)	0.4	0.8
Male	42/1,439	28/1,466	12.8	8.6	1.51 (0.94-2.44)	0.09	
Adverse events leading to drug withdrawal							
Female	78/761	93/731	45.0	57.8	0.76 (0.57-1.03)	0.08	0.2
Male	189/1,439	193/1,466	57.3	59.5	0.97 (0.79-1.19)	0.8	

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

participants, greater risk in female participants, or no difference between sexes.[7] Nevertheless, the present results show clear evidence that the beneficial effects of canagliflozin on kidney and cardiovascular end points are similar in male and female participants. This is consistent with previously published secondary and pooled analyses examining cardiovascular efficacy of SGLT2 inhibitors.[22,39,40]

Canagliflozin was associated with adverse effects consistent with the SGLT2 inhibitor class.[26] Although the absolute number of mycotic infections was higher in female than male participants, the present study and pooled analyses of previous trials have noted numerically greater relative risks in male participants. This reflects low baseline risk in male participants, 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 of major cardiovascular outcomes with SGLT2 inhibitors.[22,28] Observational studies in elderly patients have largely found SGLT2 inhibitors to be well tolerated in older patients.[41,42] Although we also found no evidence that the efficacy of canagliflozin on the primary study end point 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 very elderly participants 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 patients at high risk 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 because of efficacy for the primary end point. Second, we deliberately reduced the significance threshold to account for the risk of type I error with the multiple comparisons made in this post hoc analysis, which may reduce the sensitivity to detect smaller differences between groups. There were relatively few female or Black participants, and there were 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 suggest that canagliflozin consistently improves kidney and cardiovascular outcomes with little variation in risk of adverse events in patients with T2DM and albuminuric chronic kidney disease across a broad range of ages and in male and female participants. 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

Supplementary File (PDF)

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 of death.

Item S1: CREDENCE Trial Investigators

Table S1: Baseline characteristics by treatment group, 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 of 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 end points

Article Information

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Kidney & Cardiovascular Effects of Canagliflozin According to Age & Sex

Participants

Post-hoc analysis of CREDENCE randomized clinical trial

N = 4,401 participants

- **Mean age: 63±9 years**
- **34% female**

Intervention

Participants randomly assigned to:

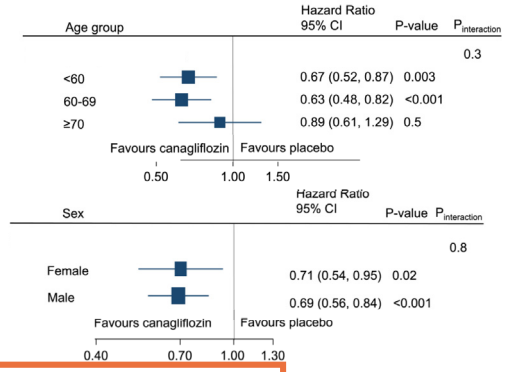
Canagliflozin (100 mg daily)

Placebo

Median follow up: 2.6 years

Outcome

Primary composite outcome: kidney failure, doubling of creatinine, death due to kidney or cardiovascular disease



CONCLUSION: Canagliflozin consistently reduced the relative risk of kidney events in people with diabetic kidney disease in both sexes and across age subgroups.

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