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Effect of Canagliflozin on Renal and Cardiovascular Outcomes across Different Levels of Albuminuria: Data from the CANVAS Program

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ABSTRACT

Background If SGLT2 inhibitors protect the kidneys by reducing albuminuria as hypothesized, people with type 2 diabetes mellitus (T2DM) with higher albuminuria should benefit more.

Methods We conducted a *post-hoc* analysis of data from the CANagliflozin cardioVascular Assessment Study (CANVAS) Program, which randomized 10,142 participants with T2DM and high cardiovascular risk to canagliflozin or placebo. We assessed effects of canagliflozin on renal, cardiovascular, and safety outcomes by baseline albuminuria. The trial included 2266 participants (22.3%) with moderately increased albuminuria (urinary albumin/creatinine ratio [UACR] 30–300 mg/g) and 760 (7.5%) with severely increased albuminuria (UACR >300 mg/g) at baseline.

Results Canagliflozin lowered albuminuria with greater proportional reductions in those with moderately and severely increased albuminuria (P heterogeneity<0.001). After week 13, canagliflozin slowed the annual loss of kidney function across albuminuria subgroups, with greater absolute reductions in participants with severely increased albuminuria (placebo-subtracted difference 3.01 ml/min per 1.73 m^2 per year; P heterogeneity<0.001). Heterogeneity for the renal composite outcome of 40% reduction in eGFR, ESKD, or renal-related death was driven by lesser effects in participants with moderately increased albuminuria (P heterogeneity=0.03), but no effect modification was observed when albuminuria was fitted as a continuous variable (P heterogeneity=0.94). Cardiovascular and safety outcomes were mostly consistent across albuminuria levels including increased risks for amputation across albuminuria subgroups (P heterogeneity=0.66). Greater absolute risk reductions in the renal composite outcome were observed in participants with severely increased albuminuria (P heterogeneity=0.004).

Conclusions The proportional effects of canagliflozin on renal and cardiovascular outcomes are mostly consistent across patients with different levels of albuminuria, but absolute benefits are greatest among those with severely increased albuminuria.

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CKD is one of the leading causes of morbidity and mortality in type 2 diabetes mellitus (T2DM), developing in approximately 40% of affected individuals.[1,2] Albuminuria is one of the earliest clinically detectable manifestations of kidney damage, and is an independent risk factor for cardiovascular events, kidney failure, and death.[3,4] Efforts to prevent these outcomes have targeted not only BP and glucose control, but also the lowering of albuminuria with renin-angiotensin system (RAS) blockade, which has been associated with subsequent renoprotection.[5,6]

Canagliflozin is a sodium glucose cotransporter 2 (SGLT2) inhibitor which promotes glycosuria and natriuresis, resulting in reductions in glycated hemoglobin (HbA1c), BP, and body weight.[7] Canagliflozin and other SGLT2 inhibitors also ameliorate albuminuria, resulting in an approximate one-third reduction in albuminuria in people with moderately or severely increased albuminuria.[8] These multiple metabolic benefits have translated into a reduction in cardiovascular events in large cardiovascular outcome trials.[9–13]

Most recently, the Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation (CREDENCE) trial demonstrated that canagliflozin reduces the risk of kidney failure by approximately 30% in people with established diabetic kidney disease.[14] Almost all participants in the CREDENCE trial had severely increased albuminuria at baseline with a median urinary albumin/creatinine ratio (UACR) of 927 mg/g.[14] There is therefore uncertainty as to whether the renal and cardiovascular benefits demonstrated in the CREDENCE trial are generalizable across a wider range of albuminuria, especially to people with T2DM and lesser degrees of albuminuria.

We hypothesized that by reducing albuminuria, SGLT2 inhibitors might be particularly beneficial for renal and perhaps also cardiovascular outcomes in people with T2DM and higher levels of albuminuria. We therefore undertook a range of *post-hoc* analyses of the CANagliflozin cardioVascular Assessment Study (CANVAS) Program to determine the effect of canagliflozin on renal, cardiovascular, and safety outcomes in people with T2DM according to baseline levels of albuminuria.

Significance Statement

Albuminuria commonly occurs in people with type 2 diabetes and is an independent risk factor for progression of kidney disease and cardiovascular events. SGLT2 inhibitors are thought to protect the kidneys by lowering albuminuria. If this is true, it suggests people with type 2 diabetes with higher levels of albuminuria would reap greater renoprotective benefits. The authors conducted a *post-hoc* analysis of data from the CANagliflozin cardioVascular Assessment Study (CANVAS) Program to assess renal, cardiovascular, and safety outcomes with canagliflozin by baseline albuminuria subgroups (urinary albumin/creatinine ratio <30, 30–300, and >300 mg/g). The data suggest that the relative effects of canagliflozin on renal and cardiovascular outcomes are mostly consistent across different levels of baseline albuminuria, but participants with severely increased albuminuria saw the largest absolute benefits.

METHODS

Study Design and Participants

The detailed methods and statistical analysis plan for the CANVAS Program have been published previously.[9] Briefly, the CANVAS Program comprised two multicenter, double-blind, placebo-controlled randomized trials (CANVAS [NCT01032639] and CANVAS-R [NCT01989754]) with identical key inclusion criteria that were designed to assess the cardiovascular safety and efficacy of the SGLT2 inhibitor, canagliflozin, along with effects on renal and safety outcomes in people with T2DM at high cardiovascular risk. The trials were conducted in 667 centers across 30 countries. Local institutional ethics committees approved the trial protocols at each site, and all participants provided written informed consent.

The trials included participants with T2DM and HbA1c levels ≥7.0% and ≤10.5% who were either 30 years or older with established atherosclerotic vascular disease, or 50 years or older with two or more cardiovascular risk factors. These risk factors included: duration of diabetes of at least 10 years, systolic BP higher than 140 mm Hg while receiving one or more antihypertensive agents, UACR of at least 30 mg/g, current smoking, or HDL cholesterol level of <1 mmol/L. Participants with a baseline eGFR <30 ml/min per 1.73 m^2 were excluded.

Randomization and Masking

All potentially eligible participants underwent a 2-week, single-blind, placebo run-in period before randomization. Randomization procedures differed between the trials. Participants in CANVAS were randomly assigned in a 1:1:1 ratio to receive canagliflozin 100 mg daily, canagliflozin 300 mg daily, or placebo; whereas participants in CANVAS-R were randomly assigned in a 1:1 ratio to receive canagliflozin 100 mg daily or matching placebo, with an optional increase to 300 mg or matching placebo daily starting from week 13. Randomization was performed centrally through a web-based response system with the use of a computer-generated randomization schedule with randomly permuted blocks that were prepared by the trial sponsor. All participants and trial staff were blinded to individual treatment allocations until the end of the trial.

Follow-Up Procedures

Face-to-face follow-up was scheduled at least three times in the first year and at intervals of 6 months thereafter. Serum creatinine was measured at least three times in the first year including at baseline, and then every 26 weeks. UACR was measured in first-morning void urine specimens at baseline and at week 12 and then annually in CANVAS, and every 26 weeks in CANVAS-R. Adverse event assessment was performed at each visit. Other glycemic and cardiovascular risk factor

management, including RAS blockade, was guided by best practice in accordance with local guidelines.

Outcomes

Definitions for all clinical outcomes in the CANVAS Program have been previously published.[9] The primary outcome was a composite of cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke. Other outcomes included cardiovascular death, fatal or nonfatal myocardial infarction, fatal or nonfatal stroke, hospitalized or fatal heart failure, and all-cause mortality. The renal outcomes of interest in this analysis were: (*1*) mean annualized difference in eGFR between canagliflozin and placebo; and (*2*) a sustained and independently adjudicated composite of 40% reduction in eGFR, ESKD, or renal death. The end point of 40% reduction in eGFR was sent for adjudication if sustained for two consecutive measures ≥30 days apart or occurring on the last available measure. eGFR was calculated using the Modification of Diet in Renal Disease equation using centrally measured serum creatinine collected at study visits. Central end point adjudication committees blinded to treatment allocation assessed cardiovascular, renal, and key safety outcomes.

Adverse events, both serious and nonserious, were collected in the CANVAS trial until early 2014, as mandated by the regulatory agencies as a requirement for initial approval for the use of canagliflozin. After this time, only serious adverse events, adverse events leading to study drug discontinuation, and selected adverse events of interest were collected in the CANVAS trial. This streamlined adverse event collection approach was used for the entirety of CANVAS-R. We therefore reported all adverse events for the CANVAS trial separately, along with all serious adverse events across the CANVAS Program.

Statistical Analyses

Baseline characteristics for participants with normal, moderately increased, and severely increased albuminuria at baseline (defined as UACR <30, 30–300, and >300 mg/g, respectively) were compared using chi-squared and ANOVA tests for categorical and continuous variables.

The effects of canagliflozin on intermediate outcomes and eGFR over time were calculated from baseline to week 312. The mean change in HbA1c, BP, and body weight over time and the difference between canagliflozin and placebo were analyzed using mixed effect models for repeated measurements that included all of the postbaseline data up to week 312 and the covariates for study, visit, treatment, baseline measures, and baseline-by-visit interactions. Because of the highly skewed distribution of UACR data, UACR data were log-transformed and the geometric mean of postbaseline UACR was estimated using a similar mixed effect model. Changes in albuminuria were calculated as the ratio of the geometric mean of postrandomization UACR measures with canagliflozin compared with placebo. We also included treatment by visit as a covariate when assessing the effect of canagliflozin on eGFR over time.

Because of the recognized nonlinear association between eGFR and time resulting from the acute hemodynamic effect of canagliflozin, the differences in eGFR slope between canagliflozin and placebo were assessed by a piecewise linear mixed effect model using an intention-to-treat approach over the total study duration and separately in two time periods: baseline to week 13 (acute slope), and week 13 to last available measures during the trial period (chronic slope). A time-spline variable measuring the follow-up time from week 13 was introduced in the model to accommodate the nonlinear trends of the eGFR time trajectory. eGFR data collected at the scheduled visits were regressed by the fixed effects with terms for treatment and study, and with linear covariates of time, time spline, and interactions of treatment by time and treatment by the spline variable. Intercept, time, and time spline were included as random effects to allow variation between participants. Time covariates included in the model were calculated in years to estimate annualized changes in eGFR.

The effects of canagliflozin on cardiovascular, renal, and safety outcomes were analyzed overall and in participants with normal, moderately increased, and severely increased albuminuria. Hazard ratios (HRs) and 95% CIs for the cardiovascular outcomes were estimated with Cox regression models for all canagliflozin groups combined versus placebo, with stratification according to trial and history of cardiovascular disease. The same method was used for the composite renal outcome, with adjustment for baseline eGFR (<60 or ≥60 ml/min per 1.73 m^2) and stratification by trial. Analyses for cardiovascular and renal outcomes were conducted on the full integrated data set using an intention-to-treat approach, which included all events that occurred at any time from randomization to the last follow-up date; participants were censored at the time of cardiovascular or noncardiovascular death or last trial contact date for those not experiencing an event or lost to follow-up. For the renal composite outcome, participants were censored when renal- or nonrenal-related deaths occurred, but not censored if any nonfatal types of events occurred. Annualized incidence rates were calculated per 1000 patient-years of follow-up. Sensitivity analyses adjusting for competing risk of death were performed for these outcomes using the Fine and Gray method.[15]

For safety outcomes, an on-treatment analysis was performed (using only events that occurred among participants who had a safety outcome while they were receiving canagliflozin or placebo, or within 30 days after discontinuation of drug or placebo). For amputation and fracture outcomes, analyses included participants who received at least one dose of canagliflozin or placebo and had an event at any time during follow-up.

The methods for determining heterogeneity of treatment effect involved adding UACR as a covariate and a term for UACR-by-treatment interaction to the relevant model to test for heterogeneity across albuminuria subgroups. Terms for UACR-by-time interaction were also included in the piecewise linear mixed model. The *P* heterogeneity values across subgroups were obtained using the likelihood ratio test. We explored heterogeneity further in a range of sensitivity analyses

by testing for trend across ordered UACR subgroups, performing interaction tests across deciles of baseline UACR, and assessing for effect modification using log-transformed UACR fitted as a continuous variable. Tests for trend in treatment effect across subgroups were performed using a similar approach as described above with UACR subgroups treated as ordered categories.

Absolute effects on select outcomes of interest per 1000 patients over 5 years and corresponding 95% CIs were estimated as the differences in the incidence rates between randomized treatment groups, using Poisson regression analysis with an assumption of constant annual event probabilities. We performed three pairwise comparisons across normal, moderately increased, and severely increased albuminuria subgroups and reported the lowest (*i.e.*, most conservative) *P* value to test for heterogeneity.

Analyses were performed with SAS software version 9.2, SAS Enterprise Guide version 7.11, and STATA software version 15.1.

Data from the CANVAS Program will be made available in the public domain *via* the Yale University Open Data Access Project (http://yoda.yale.edu/) once the product and relevant indications studied have been approved by regulators in Europe and the United States and the study has been completed for 18 months.

RESULTS

The CANVAS Program randomized 10,142 participants, 10,033 (98.9%) of whom had UACR measured at baseline. A total of 9734 participants (96%) completed the study, with a mean follow-up of 188.2 weeks, although mean length of follow-up was longer in CANVAS (296 weeks) than in CANVAS-R (108 weeks). At baseline, there were 7007 participants with normal albuminuria (69.1%), 2266 (22.3%) with moderately increased albuminuria, and another 760 (7.5%) with severely increased albuminuria. Baseline use of RAS blockade was high overall and higher across subgroups with increasing albuminuria, ranging from 79.2% to 82.6%.

Baseline characteristics of canagliflozin- and placebo-treated participants were mostly similar within each albuminuria subgroup (Table 1). Characteristics of participants by baseline albuminuria subgroups are also presented in Supplemental Table 1. Across progressively higher levels of albuminuria, participants were more likely to be male and have a longer duration of diabetes, higher systolic BP, and higher HbA1c (all $P<0.001$; Supplemental Table 1). The proportion of participants with established microvascular complications and a history of peripheral vascular disease and amputations increased with baseline albuminuria (all $P<0.001$; Supplemental Table 1). Mean eGFR was progressively lower across albuminuria subgroups, and participants were more likely to be treated with diuretics and insulin, and less likely to receive metformin and sulfonylureas (all $P<0.001$; Supplemental Table 1).

Intermediate Outcomes

The placebo-subtracted differences in HbA1c, systolic BP, body weight, and albuminuria varied in participants with normal, moderately increased, and severely increased albuminuria, likely due to differences in baseline eGFR across the subgroups (Figure 1). Proportional reductions in albuminuria increased with higher levels of albuminuria (*P* heterogeneity<0.001). Reductions in HbA1c were attenuated across progressively higher levels of albuminuria, with a similar pattern observed for body weight (*P* heterogeneity=0.002 and 0.08, respectively). In contrast, the effect on systolic BP was consistent across albuminuria subgroups (*P* heterogeneity=0.26). The effects on intermediate outcomes, displayed separately in canagliflozin- and placebo-treated participants, are summarized in Supplemental Figure 1.

Renal Outcomes

The effect of canagliflozin on eGFR slope varied during follow-up (Figure 2). Within 13 weeks, participants randomized to canagliflozin experienced a fall in eGFR, which was similar across subgroups with normal, moderately increased, and severely increased albuminuria (placebo-subtracted differences of -2.31, -2.50, and -2.73 ml/min per 1.73 m^2, respectively; *P* heterogeneity=0.66). From week 13 until the end of follow-up (*i.e.*, the chronic slope), canagliflozin attenuated the loss of kidney function across all levels of baseline albuminuria (Figure 2), with clear differences in the size of the treatment effect across subgroups (*P* heterogeneity<0.001). The annual rate of eGFR decline in placebo arms was progressively greater among higher categories of albuminuria (Figure 2). The corresponding annual mean difference in eGFR slope between canagliflozin and placebo was greatest in participants with severely increased albuminuria (placebo-subtracted difference of 3.01 ml/min per 1.73 m^2 per year) and lesser in those with normal and moderately increased albuminuria (placebo-subtracted differences of 1.06 and 0.99 ml/min per 1.73 m^2 per year, respectively; Figure 2). Total eGFR slope for the overall population and by albuminuria subgroups is summarized in Supplemental Table 2.

Heterogeneity was observed for the renal composite outcome across normal albuminuria (HR, 0.50; 95% CI, 0.33 to 0.77), moderately increased albuminuria (HR, 0.98; 95% CI, 0.60 to 1.60), and severely increased albuminuria subgroups (HR, 0.48; 95% CI, 0.31 to 0.74; *P* heterogeneity=0.03; Figure 3). The effect on the renal composite outcome adjusted for competing risk of death was similar, and is presented in Supplemental Table 3. However, there was no evidence of a trend in treatment effect across ordered albuminuria subgroups or when interaction tests were performed with log-transformed UACR fitted as a continuous variable (*P* trend=0.80 and *P* heterogeneity=0.94, respectively; Supplemental Table 4). The effect on the renal composite outcome was also consistent when participants were categorized into deciles based on UACR (*P* heterogeneity=0.33 and *P* trend=0.32; Supplemental Figure 2).

Table 1. Characteristics of canagliflozin- and placebo-treated participants by baseline albuminuria subgroups (UACR <30, 30–300, and >300 mg/g)

Characteristics	Normal Albuminuria (<30 mg/g)		Moderately Increased Albuminuria (30–300 mg/g)		Severely Increased Albuminuria (>300 mg/g)	
	Canagliflozin (*n*=4012)	Placebo (*n*=2995)	Canagliflozin (*n*=1322)	Placebo (*n*=944)	Canagliflozin (*n*=406)	Placebo (*n*=354)
Age, years, mean (SD)	63.0 (8.2)	63.2 (8.1)	63.8 (8.3)	64.2 (8.3)	63.4 (8.3)	64.0 (8.2)
Sex, no. (%)						
Male	2497 (62.2)	1835 (61.3)	936 (70.8)	638 (67.6)	284 (70.0)	248 (70.1)
Female	1515 (37.8)	1160 (38.7)	386 (29.2)	306 (32.4)	122 (30.0)	106 (29.9)
Race, no. (%)						
White	3129 (80.0)	2393 (79.9)	1030 (77.9)	722 (76.5)	301 (74.1)	272 (76.8)
Asian	527 (13.1)	323 (10.8)	187 (14.1)	137 (14.5)	62 (15.3)	47 (13.3)
Black	123 (3.1)	108 (3.6)	37 (2.8)	33 (3.5)	12 (3.0)	17 (4.8)
Other[a]	233 (5.8)	171 (5.7)	68 (5.1)	52 (5.5)	31 (7.6)	18 (5.1)
Current smoker, no. (%)	691 (17.2)	547 (18.3)	235 (17.8)	166 (17.6)	80 (19.7)	57 (16.1)
History of hypertension, no. (%)	3528 (87.9)	2682 (89.5)	1229 (93.0)	868 (91.9)	377 (92.9)	337 (95.2)
History of heart failure, no. (%)	526 (13.1)	439 (14.7)	200 (15.1)	149 (15.8)	63 (15.5)	59 (16.7)
Duration of diabetes, years, mean (SD)	12.9 (7.6)	13.2 (7.7)	14.4 (7.8)	14.3 (7.9)	15.4 (7.6)	16.0 (8.0)
Drug therapy, no. (%)						
Insulin	1862 (46.4)	1405 (46.9)	738 (55.8)	526 (55.7)	266 (65.5)	248 (70.1)
Sulfonylurea	1779 (44.3)	1310 (43.7)	586 (44.3)	388 (41.1)	145 (35.7)	118 (33.3)
Metformin	3120 (77.8)	2383 (79.6)	1022 (77.3)	705 (74.7)	260 (64.0)	243 (68.6)
GLP-1 receptor agonist	152 (3.8)	122 (4.1)	49 (3.7)	46 (4.9)	18 (4.4)	15 (4.2)
DPP-4 inhibitor	487 (12.1)	373 (12.5)	144 (10.9)	134 (14.2)	58 (14.3)	52 (14.7)
Statin	2978 (74.2)	2236 (74.7)	1007 (76.2)	727 (77.0)	305 (75.1)	272 (76.8)
Antithrombotic	2914 (72.6)	2224 (74.3)	977 (73.9)	705 (74.7)	306 (75.4)	274 (77.4)
RAAS inhibitor	3171 (79.0)	2378 (79.4)	1095 (82.8)	751 (79.6)	332 (81.8)	296 (83.6)
β-Blocker	2075 (51.7)	1654 (55.2)	726 (54.9)	513 (54.3)	214 (52.7)	188 (53.1)
Diuretic	1667 (41.6)	1271 (42.4)	644 (48.7)	452 (47.9)	200 (49.3)	202 (57.1)
Microvascular disease history, no. (%)						
Retinopathy	735 (18.3)	563 (18.8)	319 (24.1)	230 (24.4)	133 (32.8)	124 (35.1)
Nephropathy	434 (10.8)	359 (12.0)	370 (28.0)	244 (25.8)	178 (43.8)	169 (47.9)
Neuropathy	1136 (28.3)	892 (29.8)	477 (36.1)	282 (29.9)	154 (37.9)	127 (35.9)
Atherosclerotic vascular disease history, no. (%)[b]						
Coronary	2239 (55.8)	1754 (58.6)	751 (56.8)	517 (54.8)	214 (52.7)	190 (53.7)
Cerebrovascular	748 (18.6)	571 (19.1)	271 (20.5)	177 (18.8)	83 (20.4)	89 (25.1)
Peripheral	762 (19.0)	601 (20.1)	291 (22.0)	212 (22.5)	114 (28.1)	113 (31.9)
Any	2846 (70.9)	2218 (74.1)	955 (72.2)	673 (71.3)	287 (70.7)	271 (76.6)
Cardiovascular disease history, no. (%)[c]	2592 (64.6)	2008 (67.0)	863 (65.3)	610 (64.6)	266 (65.5)	253 (71.5)
History of amputation, no. (%)	62 (1.5)	40 (1.3)	45 (3.4)	28 (3.0)	28 (6.9)	32 (9.0)
Body mass index, kg/m^2, mean (SD)	31.9 (5.9)	31.8 (5.9)	32.1 (5.9)	32.5 (6.1)	32.1 (6.1)	31.8 (6.0)
Systolic BP, mm Hg, mean (SD)	134.6 (15.1)	135.2 (15.1)	139.4 (15.6)	139.2 (16.2)	145.1 (18.5)	144.8 (16.8)
Diastolic BP, mm Hg, mean (SD)	77.3 (9.4)	77.5 (9.5)	77.8 (10.0)	78.4 (10.1)	80.1 (10.0)	79.0 (9.8)
Glycated hemoglobin, %, mean (SD)	8.2 (0.9)	8.2 (0.9)	8.4 (1.0)	8.4 (0.9)	8.5 (1.0)	8.4 (0.9)
Total cholesterol, mmol/L, mean (SD)	4.3 (1.1)	4.4 (1.1)	4.4 (1.1)	4.3 (1.2)	4.7 (1.3)	4.5 (1.4)
Triglycerides, mmol/L, mean (SD)	1.9 (1.2)	1.9 (1.4)	2.2 (1.4)	2.2 (1.7)	2.4 (1.8)	2.3 (1.7)
HDL cholesterol, mmol/L, mean (SD)	1.2 (0.3)	1.2 (0.3)	1.1 (0.3)	1.1 (0.3)	1.2 (0.4)	1.1 (0.3)
LDL cholesterol, mmol/L, mean (SD)	2.3 (0.9)	2.3 (0.9)	2.3 (0.9)	2.2 (0.9)	2.5 (1.1)	2.4 (1.1)
LDL/HDL cholesterol ratio, mean (SD)	2.0 (0.9)	2.0 (0.9)	2.1 (0.9)	2.0 (0.9)	2.3 (1.1)	2.1 (1.0)
eGFR, ml/min per 1.73 m^2, mean (SD)	78.4 (19.5)	78.0 (19.9)	74.8 (20.9)	73.9 (21.9)	65.9 (22.2)	66.9 (22.5)
UACR, mg/g, median (interquartile range)	8.4 (5.7–13.4)	8.2 (5.7–13.2)	67.1 (42.6–127.2)	69.4 (44.6–120.5)	691.9 (433.2–1255.4)	763.2 (451.5–1394.1)

[a]Includes American Indian or Alaska Native, Native Hawaiian or other Pacific Islander, multiple, other, and unknown.
[b]Some participants had >1 type of atherosclerotic disease.
[c]As defined in the protocol.

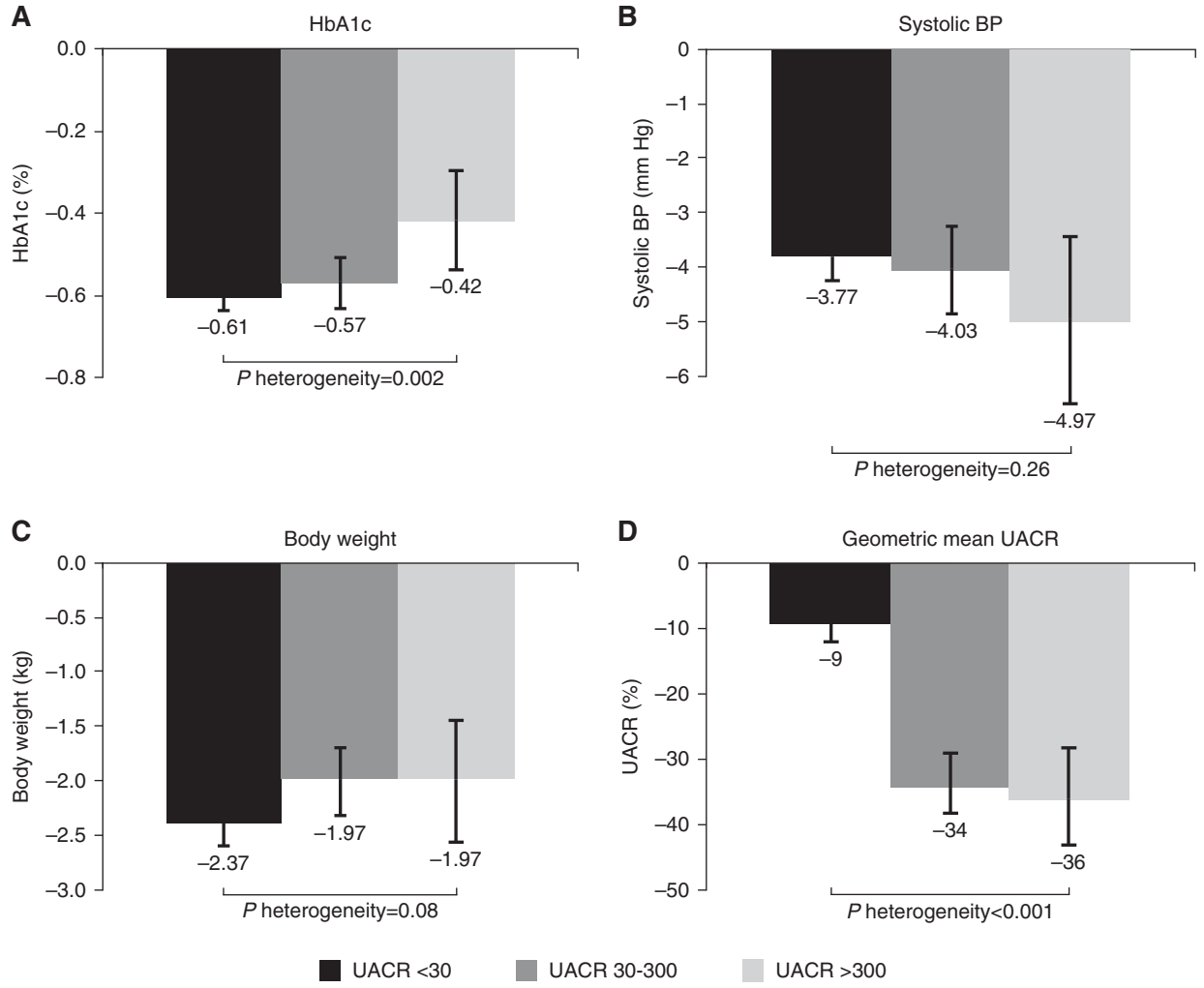


Figure 1. Placebo-subtracted differences in intermediate outcomes varied in participants with UACR <30, 30–300, and >300 mg/g at baseline.

Cardiovascular Outcomes

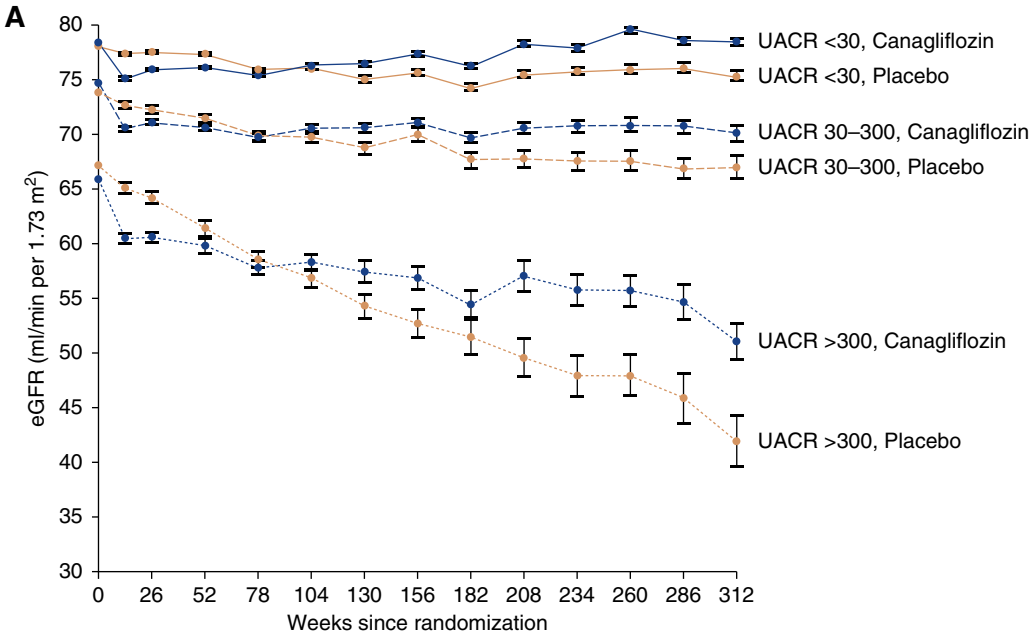
The relative effect of canagliflozin on the primary cardiovascular composite outcome in the overall trial population (HR, 0.86; 95% CI, 0.75 to 0.97) was consistent across albuminuria subgroups (*P* heterogeneity=0.46; Figure 3). The same was true for all other cardiovascular outcomes, as well as all-cause mortality (all *P* heterogeneity>0.20; Figure 3). Results were similar in sensitivity analyses adjusting for the competing risk of death (Supplemental Table 3). No heterogeneity was observed for any of these outcomes when interaction tests were undertaken testing for trends across ordinal subgroups, or using log-transformed UACR fitted as a continuous variable (Supplemental Table 4). Similarly, effects on the primary cardiovascular outcome, heart failure, and all-cause mortality were consistent across deciles of UACR (Supplemental Figure 2).

Absolute Effects

Absolute risk differences for canagliflozin versus placebo across different levels of albuminuria are summarized in Figure 4. The absolute risk reductions for most cardiovascular outcomes were consistent across albuminuria subgroups. Heterogeneity was observed for the renal composite outcome and for all-cause mortality; absolute risk reductions for these outcomes were larger in people with severely increased albuminuria (*P* heterogeneity=0.004 and 0.04, respectively). There was no statistically significant evidence of heterogeneity for the absolute effect on amputations (*P* heterogeneity=0.11), although the risk appeared numerically greater in the severely increased albuminuria subgroup, which had a higher proportion of participants with a prior history of amputations.

Safety Outcomes

The risks of most adverse outcomes with canagliflozin, including renal safety outcomes, were consistent across albuminuria subgroups (Figure 5, Supplemental Figure 3). The increased risk of amputation with canagliflozin observed in the overall trial population was consistent across albuminuria



Participants, n														
UACR <30	Canagliflozin	3960	3739	3613	3390	3206	2126	1622	1433	1498	1327	1408	1264	1231
	Placebo	2947	2788	2677	2473	2263	1239	742	636	646	564	587	523	504
UACR 30–300	Canagliflozin	1300	1232	1181	1098	1030	645	499	435	454	387	407	358	349
	Placebo	933	876	837	759	680	352	225	193	200	178	183	170	159
UACR >300	Canagliflozin	398	373	368	331	287	157	97	82	77	72	68	64	63
	Placebo	344	325	306	263	227	110	58	49	48	40	34	30	26

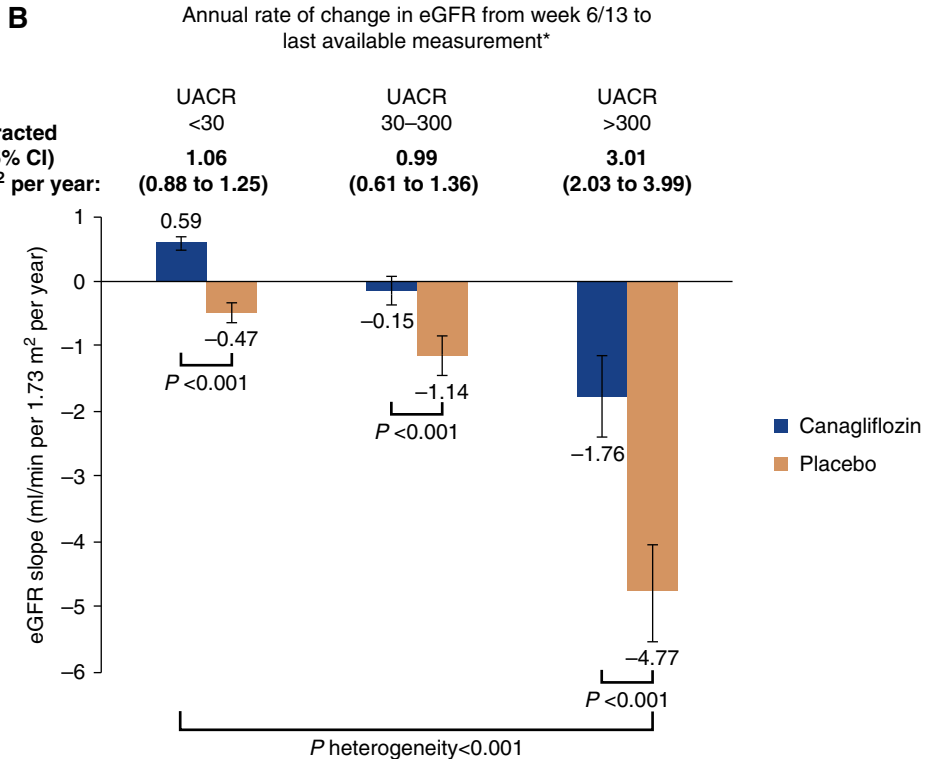


Figure 2. Canagliflozin slowed the loss of kidney function across all UACR subgroups. Effect of canagliflozin as indicated by (A) adjusted mean eGFR over time and (B) eGFR slope from week 6/13 until the end of follow-up, with the greatest effect in participants with UACR >300 mg/g at baseline. *Data are reported for week 6 in CANVAS and week 13 in CANVAS-R.

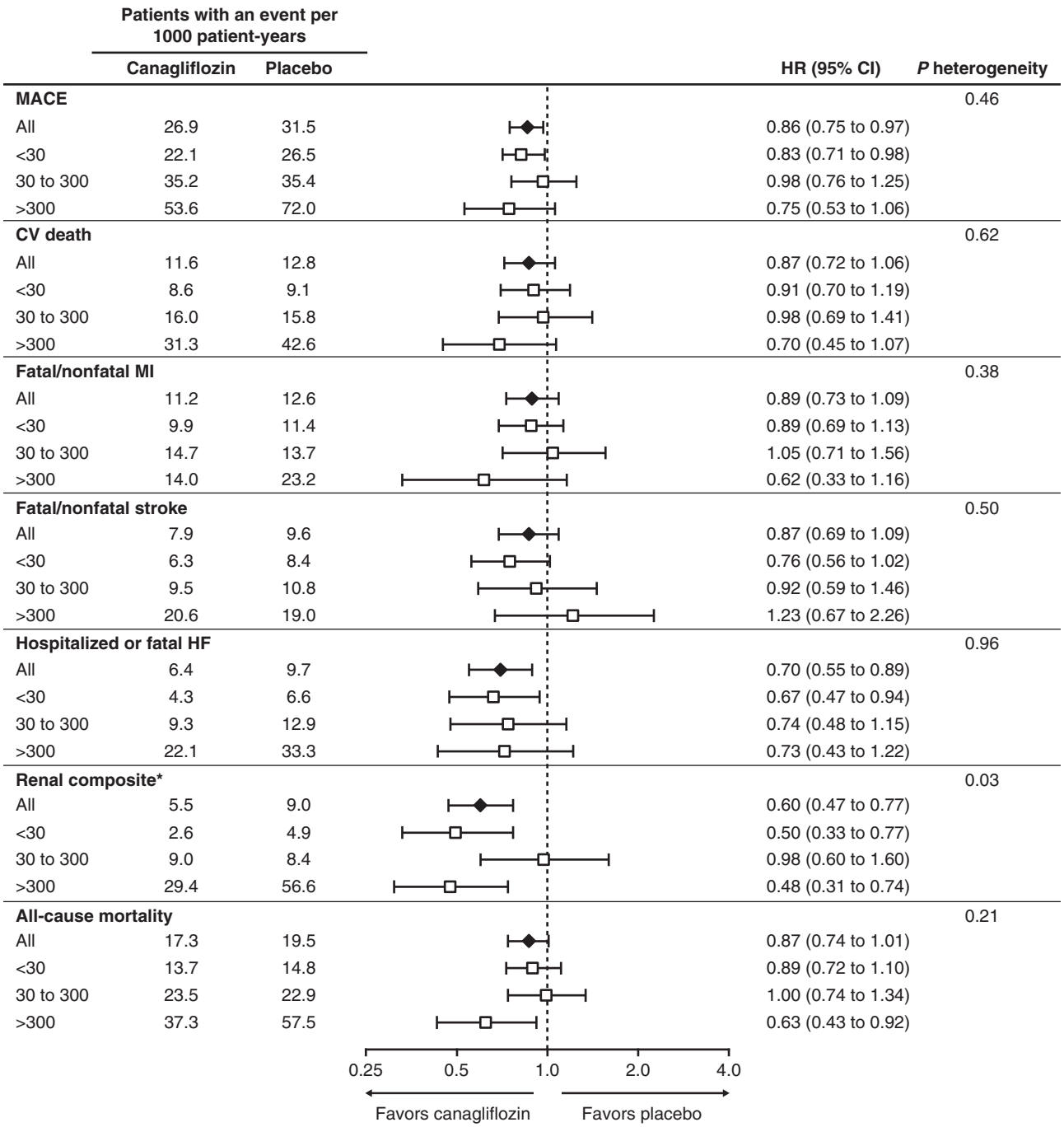


Figure 3. There was heterogeneity in the effect of canagliflozin on the renal composite outcome in participants with UACR <30, 30–300, and >300 mg/g at baseline, while effects on cardiovascular outcomes and all-cause mortality were consistent across UACR subgroups. *A 40% reduction in eGFR, ESKD, or renal death. CV, cardiovascular; HF, heart failure; HR, hazard ratio; MACE, major adverse cardiovascular events; MI, myocardial infarction.

subgroups (*P* heterogeneity=0.66). There was some evidence of heterogeneity for urinary tract infections and fractures (*P* heterogeneity=0.04 and 0.07, respectively). Heterogeneity for the fracture outcome remained when fitting UACR as a continuous variable (*P* heterogeneity=0.03). There was no evidence of heterogeneity in the risk of urinary tract infections when analyzing UACR as a continuous variable (*P* heterogeneity=0.22).

DISCUSSION

In this analysis of the CANVAS Program, canagliflozin slowed the loss of kidney function, as measured by eGFR slope, at all levels of albuminuria. The absolute effect on eGFR slope was approximately three times as large in people with severely increased albuminuria, and this was due, at least in part, to the

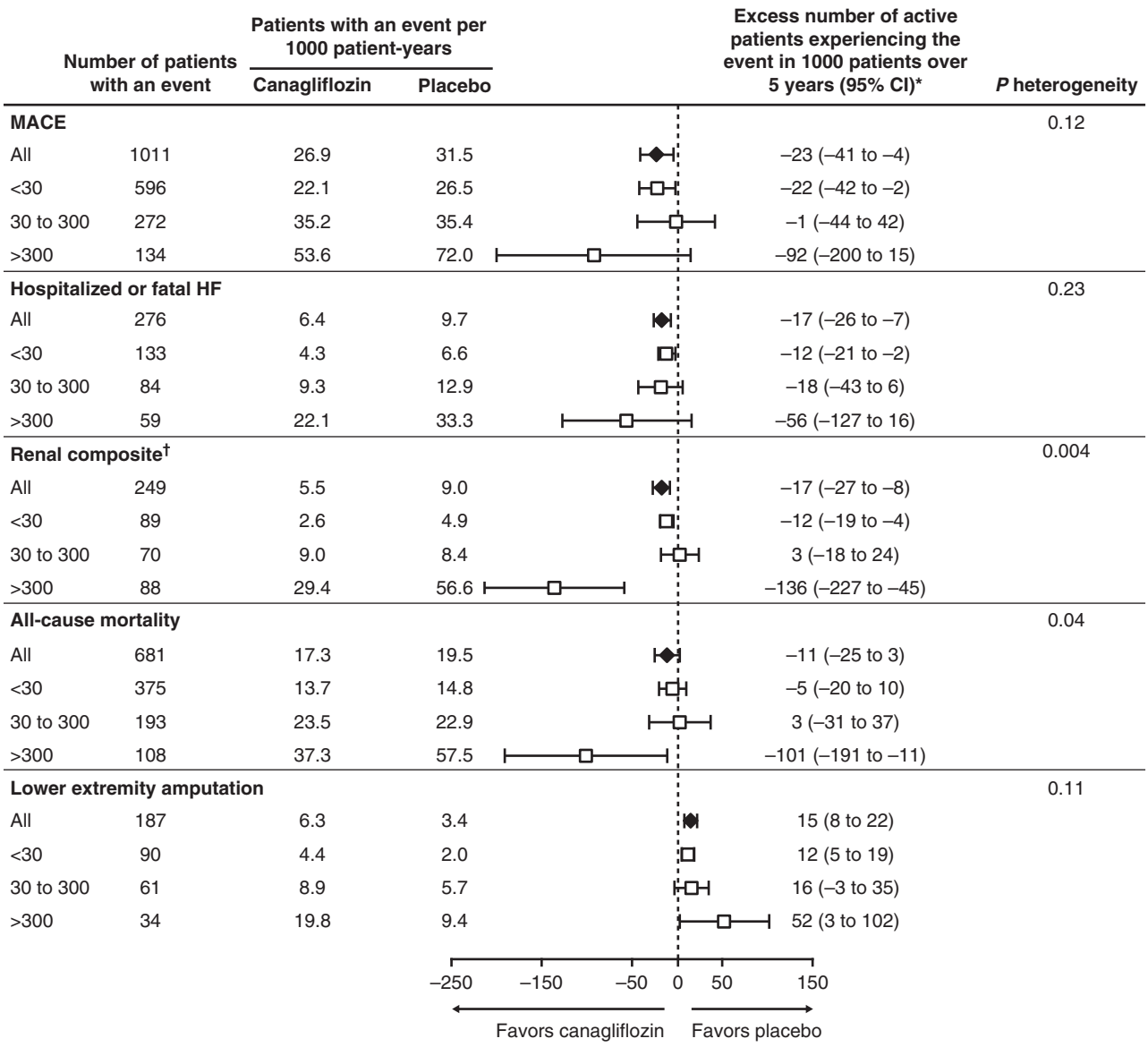


Figure 4. Absolute benefits per 1000 participants over 5 years with canagliflozin versus placebo were consistent across UACR subgroups for cardiovascular outcomes, but absolute risk reductions for the renal composite outcome and all-cause mortality were greatest in patients with UACR >300mg/g. *Excess number is relative to the placebo group. If the number is negative, then fewer participants in the canagliflozin group experienced the event compared with the placebo group. †A 40% reduction in eGFR, ESKD, or renal death. HF, heart failure; MACE, major adverse cardiovascular events.

much more rapid decline in kidney function in this group. Kidney function loss was essentially completely abrogated in canagliflozin-treated participants with normal or moderately increased albuminuria. Although there was some evidence of heterogeneity for the renal composite outcome across normal, moderately increased, and severely increased albuminuria subgroups, the unusual pattern of effect and the absence of heterogeneity in a range of sensitivity analyses, including when interaction tests were performed with albuminuria fitted continuously, suggest that this may have been a chance finding. While the largest absolute renal benefits were observed in participants with severely increased albuminuria, the evidence of renoprotection, even among participants with normal albuminuria, suggests that mechanisms other than those associated with albuminuria reduction might also be important.

The effects of SGLT2 inhibition have now been studied across a spectrum of urinary albumin excretion. Our findings are broadly consistent with those from the EMPA-REG OUTCOME trial, in which approximately 60% of participants had normal albuminuria at baseline. The EMPA-REG OUTCOME trial demonstrated that the effects of empagliflozin on cardiovascular and renal outcomes were consistent across different levels of albuminuria, with greater

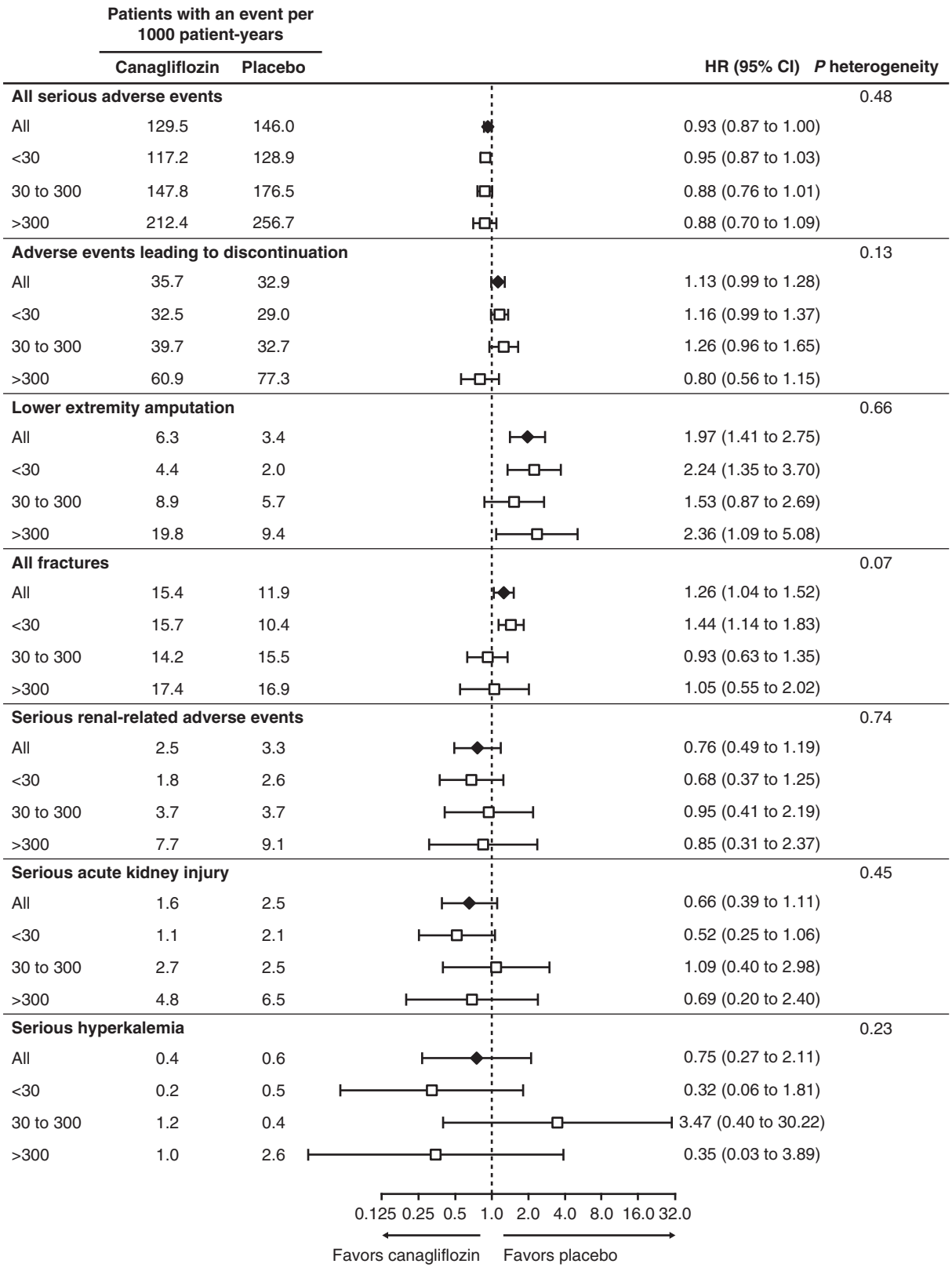


Figure 5. The risk of most safety outcomes collected across the CANVAS Program was consistent in participants with UACR <30, 30–300, and >300 mg/g at baseline. HR, hazard ratio.

effects on eGFR slope in participants with severely increased albuminuria.[16–18] The CREDENCE trial demonstrated clear reductions in the risk of kidney failure and cardiovascular events in a population with severely increased albuminuria. Taken together, the data suggest that SGLT2 inhibitors are likely to confer cardiovascular and kidney benefits across a range of albuminuria, with greater absolute benefits in those with higher levels of urinary albumin excretion.

A number of potential mechanisms of renoprotection with SGLT2 inhibitors have been postulated.[8] The acute decrease in eGFR with canagliflozin followed by long-term preservation of kidney function has been postulated to indicate decompression of the glomerulus and correction of glomerular hyperfiltration.[8,19] Hyperfiltration is critical in the pathogenesis of diabetic kidney disease, contributing to a number of structural changes that increase the susceptibility of the glomerular basement membrane to barotrauma, contributing to albuminuria, fibrosis, and loss of kidney function. Higher levels of albuminuria might therefore reflect the severity of renal injury from this mechanism. Conversely, others have postulated that changes in vascular (endothelial) function may play a key role.[20] In both cases the filtered albumin will increase; it has been proposed that this may lead to direct damage to the glomerulus and the tubule, and ultimately nephron loss.[21,22] Each of these could be consistent with our observations that the benefits of canagliflozin on renal outcomes, as measured by changes in eGFR slope and the absolute risk reduction for the composite renal outcome, are greatest in people with severely increased albuminuria, the individuals in whom raised glomerular pressure and/or albuminuria are driving the progression of kidney disease.

At the same time, it is recognized that our understanding of the clinical presentation of diabetic kidney disease is evolving.[23,24] Approximately 40% of people with T2DM have been reported to develop impaired kidney function without ever having albuminuria documented, with a variety of histologic changes on biopsy that appear distinct from individuals with classically progressive albuminuria.[25,26] These individuals may have other mechanisms of disease progression. The CANVAS Program data show that canagliflozin appears to stabilize kidney function and prevent the composite kidney outcome even in participants with normal urinary albumin excretion at baseline, despite substantially smaller effects on albuminuria. Mechanisms other than those associated with albuminuria reduction may be important; there is some experimental evidence that SGLT2 inhibitors improve renal oxygenation and promote anti-inflammatory and antifibrotic pathways.[27–30] Although individuals with T2DM and normal urinary albumin excretion are at low absolute risk for renal outcomes in the short term, the population prevalence is much higher than severely increased albuminuria,[31,32] and treatment of these individuals with an SGLT2 inhibitor may be an important strategy in reducing the long-term burden of kidney and cardiovascular disease due to T2DM.

Because the absolute risk of events was greater at higher levels of baseline albuminuria, the absolute benefits for renal outcomes and all-cause mortality were greatest in people with severely increased albuminuria. This translated into 5-year numbers needed to treat of seven and ten for these outcomes. Approximately 80% of participants in the CANVAS Program were already receiving RAS blockade at baseline as well as many other preventative therapies, indicating that the renoprotective effect of canagliflozin is achieved in addition to the effects of these agents.

The glycemic efficacy of SGLT2 inhibitors is dependent on kidney function,[33] and differing effects on HbA1c across albuminuria subgroups are likely due to differences in eGFR, which was progressively lower across subgroups with higher baseline albuminuria. The greater proportional reductions in albuminuria in participants with moderately and severely increased albuminuria did not appear to be driven by reductions in systolic BP, which were consistent across subgroups.

Albuminuria has been demonstrated to be among the strongest predictors of cardiovascular outcomes in T2DM.[34,35] The pathophysiologic link between albuminuria and cardiovascular risk is not entirely understood, but because albuminuria results primarily from injury to glomeruli, it is thought to be a marker of systemic endothelial damage.[36] These data suggest that the benefits of canagliflozin for the prevention of cardiovascular outcomes are at least as large in people with elevated levels of albuminuria, and are consistent with a similar analysis of the EMPA-REG OUTCOME trial.[16]

Although the risk of amputation and fractures was increased with canagliflozin in the CANVAS Program, no increased risk was observed in the CREDENCE trial.[14] It remains unclear whether this was due to differences in participant characteristics, trial protocols, or chance. Additionally, the risk of fracture was observed in CANVAS but not CANVAS-R, and the reason for heterogeneity in the fracture outcome across albuminuria subgroups also remains unclear.

This study benefits from a number of strengths. These data were derived from a large, multicenter, placebo-controlled, randomized trial program conducted to a high standard. Expert committees blinded to treatment allocations adjudicated all cardiovascular and renal outcomes. The use of continuous eGFR slope data also provided additional power to explore in more detail the renoprotective effect across albuminuria subgroups.

Our findings should be interpreted in light of some limitations. This study was a *post-hoc* analysis and was not explicitly powered to detect cardiovascular or renal benefits in each of the albuminuria subgroups. The reported *P* heterogeneity values were nominal in nature with no corrections applied for multiple comparisons. These *P* values should therefore be interpreted cautiously in light of the number of tests performed. The proportion of participants with severely increased albuminuria was relatively small in comparison to the overall trial population. The high proportion of participants in the

CANVAS Program with established cardiovascular disease may limit the generalizability of our findings to the broader population of patients with diabetic kidney disease. Nevertheless, this study represents one of the largest analyses to date of the influence of albuminuria on the effects of SGLT2 inhibition in people with T2DM.

Upcoming trials are expected to provide definitive information about cardiovascular and renal protection for this high-risk population. These include DAPA-CKD for dapagliflozin (NCT03036150),[37] EMPA-KIDNEY for empagliflozin (NCT03594110),[38] and SCORED with sotagliflozin (NCT03315143).[39] Some of these trials will also include participants with eGFR as low as 20 ml/min per 1.73 m^2, irrespective of levels of albuminuria.

In conclusion, the CANVAS Program data suggest that, among individuals with T2DM, canagliflozin improves renal outcomes. Protective effects on the kidney are observed even in participants with normal albuminuria, with greater absolute benefits among patients with severely increased albuminuria.

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Dr. Neuen, Dr. Ohkuma, Mr. Li, and Dr. Oh contributed to the analysis and interpretation of data. Drs. Neal and Matthews were cochairs of the CANVAS Program Steering Committee. Drs. de Zeeuw, Mahaffey, Fulcher, Jardine, and Perkovic contributed to the design and conduct of the study and the interpretation of the data. Drs. Neuen and Perkovic wrote the first draft of the manuscript; all authors contributed to subsequent drafts and approved the final version for submission.

DISCLOSURES

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SUPPLEMENTAL MATERIAL

This article contains the following supplemental material online at http://jasn.asnjournals.org/lookup/suppl/doi:10.1681/ASN.2019010064/-/DCSupplemental.

Supplemental Table 1. Characteristics of participants with UACR <30, 30–300, and >300 mg/g at baseline.

Supplemental Table 2. Effect on total eGFR slope* for the overall trial population and in participants with UACR <30, 30–300, and >300 mg/g at baseline.

Supplemental Table 3. Effect of canagliflozin on cardiovascular and renal outcomes by baseline albuminuria adjusted for competing risk of death.

Supplemental Table 4. Trend tests across UACR subgroups (<30, 30–300, and >300 mg/g) and interaction tests using log transformed UACR fitted as a continuous variable for cardiovascular and renal outcomes.

Supplemental Figure 1. Change in intermediate outcomes for canagliflozin and placebo treated participants by UACR (<30, 30–300, and >300 mg/g).

Supplemental Figure 2. Effect of canagliflozin on the (A) primary cardiovascular outcome, (B) hospitalized or fatal heart failure, (C) renal composite outcome, and (D) all-cause mortality in participants stratified into deciles of baseline UACR.

Supplemental Figure 3. Safety outcomes collected in CANVAS alone in participants with UACR <30, 30–300, and >300 mg/g at baseline.

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