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Cardiovascular Effects of Canagliflozin in Relation to Renal Function and Albuminuria

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ABSTRACT

BACKGROUND People with type 2 diabetes mellitus (T2DM) have elevated cardiovascular (CV) risk, including for hospitalization for heart failure (HHF). Canagliflozin reduced CV and kidney events in patients with T2DM and high CV risk or nephropathy in the CANVAS (CANagliflozin cardioVascular Assessment Study) Program and the CREDENCE (Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation) trial.

OBJECTIVES The aim of this study was to assess the effects of canagliflozin on CV outcomes according to baseline estimated glomerular filtration rate (eGFR) and urine albumin:creatinine ratio (UACR) in pooled patient-level data from the CANVAS Program and CREDENCE trial.

METHODS Canagliflozin effects on CV death or HHF were assessed by baseline eGFR (<45, 45-60, and >60 mL/min/1.73 m^2) and UACR (<30, 30-300, and >300 mg/g). HRs and 95% CIs were estimated by using Cox regression models overall and according to subgroups.

RESULTS A total of 14,543 participants from the CANVAS Program (N = 10,142) and the CREDENCE (N = 4,401) trial were included, with a mean age of 63 years, 35% female, 75% White, 13.2% with baseline eGFR <45 mL/min/1.73 m^2, and 31.9% with UACR >300 mg/g. Rates of CV death or HHF increased as eGFR declined and/or UACR increased. Canagliflozin significantly reduced CV death or HHF compared with placebo (19.4 vs 28.0 events per 1,000 patient-years; HR: 0.70; 95% CI: 0.62-0.79), with consistent results across eGFR and UACR categories (all *P* interaction >0.40).

CONCLUSIONS Risk of CV death or HHF was higher in those with lower baseline eGFR and/or higher UACR. Canagliflozin consistently reduced CV death or HHF in participants with T2DM and high CV risk or nephropathy regardless of baseline renal function or level of albuminuria. (Canagliflozin Cardiovascular Assessment Study [CANVAS], NCT01032629; A Study of the Effects of Canagliflozin [JNJ-24831754] on Renal Endpoints in Adult Participants With Type 2 Diabetes Mellitus [CANVAS-R], NCT01989754; and Evaluation of the Effects of Canagliflozin on Renal and Cardiovascular Outcomes in Participants With Diabetic Nephropathy [CREDENCE], NCT02065791)
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ABBREVIATIONS AND ACRONYMS

CV = cardiovascular

eGFR = estimated glomerular filtration rate

HHF = hospitalization for heart failure

SGLT2 = sodium-glucose cotransporter-2

T2DM = type 2 diabetes mellitus

UACR = urine albumin:creatinine ratio

People with type 2 diabetes mellitus (T2DM) have an elevated risk of cardiovascular (CV) events, including CV death or hospitalization for heart failure (HHF), particularly in the presence of chronic kidney disease.[1,2] Estimated glomerular filtration rate (eGFR) and albuminuria are complementary markers of chronic kidney disease that are each associated with an increased risk of adverse CV events, leading to recommendations for regular assessment of these parameters in patients with T2DM.[2-5]

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Canagliflozin is a sodium-glucose cotransporter-2 (SGLT2) inhibitor that decreased renal and CV events, including CV death or HHF, in patients with T2DM and elevated CV risk in the CANVAS (CANagliflozin cardioVascular Assessment Study) Program and in patients with T2DM and nephropathy in the CREDENCE (Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation) trial.[6,7] It has been postulated that the protective mechanisms of SGLT2 inhibition may be related in part to decreased glomerular hyperfiltration and albuminuria.[8] Secondary analyses investigating interactions between eGFR and canagliflozin outcomes have suggested largely consistent CV benefits of canagliflozin across eGFR subgroups in the CANVAS Program[9] and the CREDENCE trial[10]; the evidence, however, was borderline in CREDENCE that benefit for CV death or HHF may be greater in patients with a lower eGFR. In CREDENCE, although canagliflozin exhibited CV and renal benefit across albuminuria subgroups, absolute renal benefits were highest in those with severely increased albuminuria (urine albumin:creatinine ratio [UACR] >300 mg/g).[11] It remains uncertain whether the CV benefits of canagliflozin are generalizable regardless of baseline albuminuria and renal function across a wide range of people with T2DM and elevated CV risk or nephropathy, who are at elevated risk for adverse CV events (including CV death or HHF).

In these analyses of integrated data from the CANVAS Program and the CREDENCE trial, the risk of CV death or HHF, HHF, and CV death in subgroups defined according to baseline eGFR (<45, 45-60, and >60 mL/min/1.73 m^2) and UACR (<30, 30-300, and >300 mg/g) were investigated along with the CV benefits of canagliflozin across these subgroups.

METHODS

The study used an individual patient data meta-analysis from the CANVAS Program and CREDENCE trial. The trial protocols were reviewed by relevant regulatory authorities and ethics committees responsible at each trial site, and all participants provided written informed consent. The design and main results of the CANVAS Program[12-14] and the CREDENCE trial[6,7] have been previously published. The CANVAS Program comprises 2 randomized placebo controlled trials with 10,142 participants with increased CV risk that was designed to assess the CV safety and efficacy of canagliflozin compared with placebo. CREDENCE was a placebo-controlled trial of canagliflozin in 4,401 patients with T2DM and increased risk of progressive chronic kidney disease.

PARTICIPANTS. Participants in both studies had T2DM (glycated hemoglobin ≥7.0% and ≤10.5% and eGFR >30 mL/min/1.73 m^2). Participants in the CANVAS Program were either aged ≥30 years with a history of symptomatic atherosclerotic CV disease, or aged ≥50 years with ≥2 risk factors for CV disease. CREDENCE participants had T2DM with similar glycated hemoglobin values, eGFR 30 to <90 mL/min/1.73 m^2, and a UACR >300 to 5,000 mg/g.

RANDOMIZATION, TREATMENT, AND FOLLOW-UP. CANVAS Program and CREDENCE trial participants were randomly assigned to receive canagliflozin or placebo. Participants and all study and sponsor staff were blinded to individual treatment allocations. Glycemic, renal, and CV therapies were managed according to best practice. Face-to-face follow-up

Clinical data from the CANVAS Program (comprising the Canagliflozin Cardiovascular Assessment Study [CANVAS] and Canagliflozin Cardiovascular Assessment Study-Renal [CANVAS-R] trials) are available in the public domain via the Yale University Open Data Access Project. Data from the CREDENCE (Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation) trial will be made available in the public domain via the Yale University Open Data Access Project. Once the product and relevant indication studied have been approved by regulators in the United States and the European Union and the study has been completed for 18 months.

The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

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occurred at least once every 6 months after randomization, with alternating telephone follow-up between face-to-face assessments.

STATISTICAL ANALYSIS. Data were pooled from the CANVAS Program and the CREDENCE trial. All analyses used the intention-to-treat set unless otherwise specified. Demographic and baseline disease characteristics were summarized for each treatment group. Frequency counts and percentages were provided for the categorical variables. Summary statistics (number of subjects, mean ± SD, median [minimum and maximum]) were provided for the continuous variables.

The effects of canagliflozin compared with placebo on CV death or HHF, HHF, and CV death were assessed in subgroups defined according to baseline eGFR (<45, 45-60, and >60 mL/min/1.73 m^2) and UACR (<30, 30-300, and >300 mg/g). The Modification of Diet in Renal Disease equation was used to determine eGFR in the CANVAS Program analysis, and the CKD Epidemiology Collaboration Frequency equation was used in the CREDENCE trial.[6,7] Event rates per 1,000 patient-years of follow-up were calculated for all outcomes. HRs and 95% CIs were determined from Cox proportional regression models including treatment as the explanatory variable.

To assess heterogeneity of the treatment effects across subgroups of baseline eGFR and/or UACR for all outcomes, *P* values for the interaction of treatment by subgroup were obtained based on Cox proportional hazards regression, including terms of treatment, baseline eGFR and/or UACR subgroup, and their interaction. No adjustment was made for multiple comparisons.

RESULTS

PARTICIPANT CHARACTERISTICS. There were 10,142 participants in the CANVAS Program (4,330 in CANVAS and 5,812 in CANVAS-R), with an overall median follow-up of 2.4 years (IQR: 2.0-6.0 years). There were 4,401 participants in the CREDENCE trial, with a median follow-up of 2.6 years (IQR: 2.1-3.1 years). The CREDENCE trial was stopped in 2018 at the interim analysis for efficacy at the recommendation of the data monitoring committee. Among the total of 14,543 participants, the mean age was 63 years, 35% of participants were female, and 75% were White. Overall, 14,540 patients had available eGFR values at baseline and 14,434 patients had baseline UACR values available. Of the 14,540 participants with baseline eGFR measurements included in this analysis (**Table 1,** Supplemental Table 1), 1,919 (13.2%) participants had baseline eGFR <45 mL/min/1.73 m^2 (mean 36.7 mL/min/1.73 m^2), 2,972 (20.4%) participants had eGFR 45 to 60 mL/min/1.73 m^2 (mean 53.1 mL/min/1.73 m^2), and 9,649 (66.4%) participants had eGFR >60 mL/min/1.73 m^2 (mean 82.3 mL/min/1.73 m^2). Within these eGFR groups, 1,352 (70%), 1,380 (46%), and 1,901 (20%) participants, respectively, had baseline UACR >300 mg/g. In addition, within these groups, a total of 319 (16.6%), 471 (15.8%), and 1,321 (13.7%) had a history of heart failure at baseline. Baseline characteristics between participants assigned to receive canagliflozin vs placebo were balanced among eGFR groups (Supplemental Table 1).

EVENT RATES AND EFFECT OF CANAGLIFLOZIN ON CV OUTCOMES ACCORDING TO eGFR. Rates of CV death or HHF, HHF, and CV death increased as eGFR declined in this integrated analysis of the CANVAS Program and CREDENCE trial (**Central Illustration, Figure 1,** and Supplemental Figures 1 to 3). Overall, canagliflozin consistently decreased CV death or HHF, CV death, and HHF compared with placebo across all eGFR subgroups (all *P* heterogeneity >0.50).

EVENT RATES AND EFFECT OF CANAGLIFLOZIN ON CV OUTCOMES ACCORDING TO UACR. Rates of CV death, HHF, and CV death or HHF increased as UACR increased, with the highest rates in those with UACR >300 mg/g (**Central Illustration, Figure 2**). Canagliflozin consistently reduced CV events across UACR subgroups compared with placebo (all *P* heterogeneity >0.40).

EFFECT OF CANAGLIFLOZIN ON CARDIOVASCULAR OUTCOMES BY eGFR AND UACR. Within each eGFR group, rates of CV death or HHF, CV death, and HHF increased as UACR increased (**Central Illustration, Figure 3**). In participants assigned placebo, the risk of HHF was lowest in participants with UACR <30 mg/g and eGFR >60 mL/min/1.73 m^2 (corresponding to low renal risk according to Kidney Disease Improving Global Outcomes criteria) and greatest in those with UACR >300 mg/g and eGFR <45 mL/min/1.73 m^2 (corresponding to very high renal risk according to Kidney Disease Improving Global Outcomes criteria). Among placebo participants, HHF rates increased 6.5-fold between those with UACR 30 mg/g and UACR 300 mg/g and eGFR >60 mL/min/1.73 m^2 at baseline and almost 10-fold as eGFR declined from >60 to <45 mL/min/1.73 m^2 in those with UACR <30 mg/g at baseline.

Overall, compared with placebo, canagliflozin reduced the risk of CV events, including CV death or HHF, CV death, or HHF, across subgroups of UACR within each eGFR category. Among the 9 sets of subgroups examined in this analysis, there were 2 *P* values for homogeneity of effects across subgroups

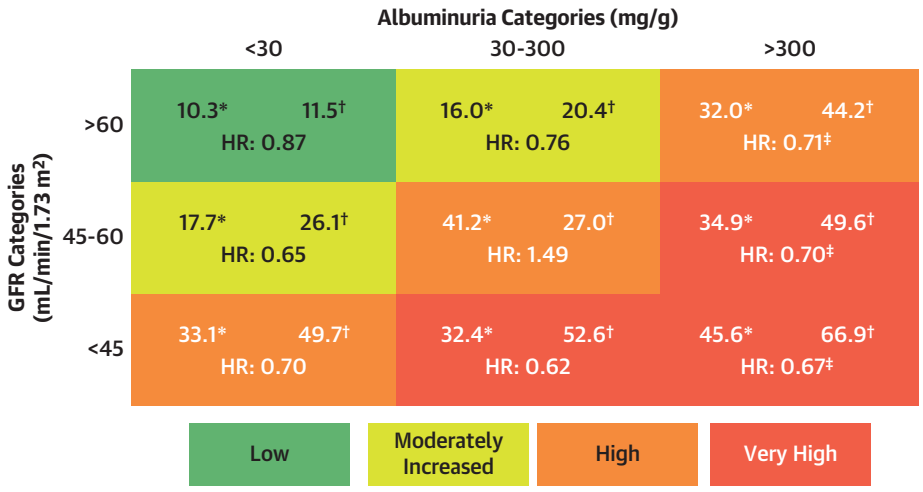
TABLE 1 Baseline Demographic Characteristics According to eGFR Categories in the Combined Data Set

	eGFR <45 mL/min/1.73 m² (n = 1,919)	eGFR 45 to 60 mL/min/1.73 m² (n = 2,972)	eGFR >60 mL/min/1.73 m² (n = 9,649)
Age, y	65.5 ± 9.2	65.3 ± 8.5	62.0 ± 8.2
Female	693 (36.1)	1,121 (37.7)	3,311 (34.3)
Race[a]			
White	1,330 (69.3)	2,204 (74.2)	7,338 (76.0)
Black	87 (4.5)	106 (3.6)	367 (3.8)
Asian	344 (17.9)	463 (15.6)	1,354 (14.0)
Other[b]	158 (8.2)	199 (6.7)	590 (6.1)
Region			
North America	576 (30.0)	783 (26.3)	2,252 (23.3)
Central/South America	311 (16.2)	447 (15.0)	1,204 (12.5)
Europe	510 (26.6)	853 (28.7)	3,110 (32.2)
Rest of the world	522 (27.2)	889 (29.9)	3,083 (32.0)
Current smoker	220 (11.5)	362 (12.2)	1,863 (19.3)
History of hypertension	1,862 (97.0)	2,835 (95.4)	8,685 (90.0)
History of heart failure	319 (16.6)	471 (15.8)	1,321 (13.7)
Duration of diabetes, y	16.9 ± 8.8	15.7 ± 8.4	13.2 ± 7.7
Drug therapy			
Insulin	1,348 (70.2)	1,861 (62.6)	4,770 (49.4)
Sulfonylurea	535 (27.9)	1,018 (34.3)	4,073 (42.2)
Biguanides	694 (36.2)	1,851 (62.3)	7,824 (81.1)
GLP-1 receptor agonist	71 (3.7)	123 (4.1)	396 (4.1)
DPP-4 inhibitor	329 (17.1)	463 (15.6)	1,220 (12.6)
Statin	1,450 (75.6)	2,200 (74.0)	6,985 (72.4)
Antithrombotic[c]	1,277 (66.5)	2,104 (70.8)	6,713 (69.6)
RAAS inhibitor	1,802 (93.9)	2,671 (89.9)	8,035 (83.3)
Beta-blocker	1,001 (52.2)	1,511 (50.8)	4,678 (48.5)
All diuretics	1,115 (58.1)	1,568 (52.8)	3,864 (40.0)
History of microvascular disease			
Retinopathy	774 (40.3)	1,030 (34.7)	2,206 (22.9)
Nephropathy	1,615 (84.2)	1,762 (59.3)	2,797 (29.0)
Neuropathy	848 (100.0)	1,217 (100.0)	3,191 (100.0)
History of atherosclerotic vascular disease[d]			
Coronary	794 (41.4)	1,407 (47.3)	4,832 (50.1)
Cerebrovascular	343 (17.9)	582 (19.6)	1,732 (18.0)
Peripheral	480 (25.0)	725 (24.4)	1,954 (20.3)
History of CV disease	1,117 (58.2)	1,843 (62.0)	5,914 (61.3)
History of amputation	106 (5.5)	139 (4.7)	227 (2.4)
Body mass index, kg/m²	31.7 ± 6.2	31.7 ± 6.1	31.8 ± 6.0
Systolic blood pressure, mm Hg	139.3 ± 17.1	138.6 ± 15.8	137.0 ± 15.5
Diastolic blood pressure, mm Hg	76.2 ± 10.1	77.1 ± 9.7	78.5 ± 9.4
HbA_{1c}, %	8.2 ± 1.2	8.2 ± 1.1	8.3 ± 1.0
Cholesterol, mmol/L			
Total	4.5 ± 1.3	4.5 ± 1.2	4.4 ± 1.2
HDL	1.1 ± 0.3	1.2 ± 0.3	1.2 ± 0.3
LDL	2.4 ± 1.0	2.4 ± 1.0	2.3 ± 1.0
Ratio of LDL to HDL	2.2 ± 1.1	2.2 ± 1.0	2.1 ± 1.0
Triglycerides, mmol/L	2.3 ± 1.5	2.2 ± 1.5	2.0 ± 1.5
eGFR, mL/min/1.73 m²	36.7 ± 5.4	53.1 ± 4.6	82.3 ± 15.9
UACR, mg/g	687.0 (229.0-1,745.0)	233.6 (13.8-964.0)	15.9 (7.2-133.8)
<30	249 (13.0)	992 (33.4)	5,795 (60.1)
30-300	312 (16.3)	582 (19.6)	1,868 (19.4)
>300	1,352 (70.5)	1,380 (46.4)	1,901 (19.7)

Values are mean ± SD, n (%), or median (IQR). [a]Percentages may not total 100% due to rounding. [b]Includes American Indian or Alaska Native, Native Hawaiian or other Pacific Islander, multiple, other, and unknown. [c]Includes anticoagulation and antiplatelet agents, including aspirin. [d]Some participants had ≥1 type of atherosclerotic disease.

DPP = dipeptidyl peptidase; eGFR = estimated glomerular filtration rate; GLP = glucagon-like peptide; HbA_{1c} = glycated hemoglobin; HDL = high-density lipoprotein; LDL = low-density lipoprotein; RAAS = renin-angiotensin-aldosterone system; UACR = urine albumin:creatinine ratio.

CENTRAL ILLUSTRATION **Cardiovascular Death or Hospitalization for Heart Failure According to Baseline Estimated Glomerular Filtration Rate and Urine Albumin:Creatinine Ratio Categories**



Sarraju A, et al. J Am Coll Cardiol. 2022;80(18):1721–1731.

Effects of canagliflozin compared with placebo on cardiovascular death or hospitalization for heart failure were assessed in subgroups defined according to baseline estimated glomerular filtration rate (<45, 45-60, and >60 mL/min/1.73 m^2) and urine albumin:creatinine ratio (<30, 30-300, and >300 mg/g) categorized by renal risk from low to very high. Annualized incidence rates per 1,000 patient-years of follow-up were calculated for all outcomes in addition to HRs and 95% CIs determined from Cox proportional regression models using treatment as the explanatory variable. Overall, rates of cardiovascular death or hospitalization for heart failure increased as estimated glomerular filtration rate declined and the urine albumin:creatinine ratio increased. 3-way interaction *P* value was 0.002. *Participants in the canagliflozin group with an event per 1,000 patient-years. †Participants in the placebo group with an event per 1,000 patient-years. ‡$P < 0.05$.

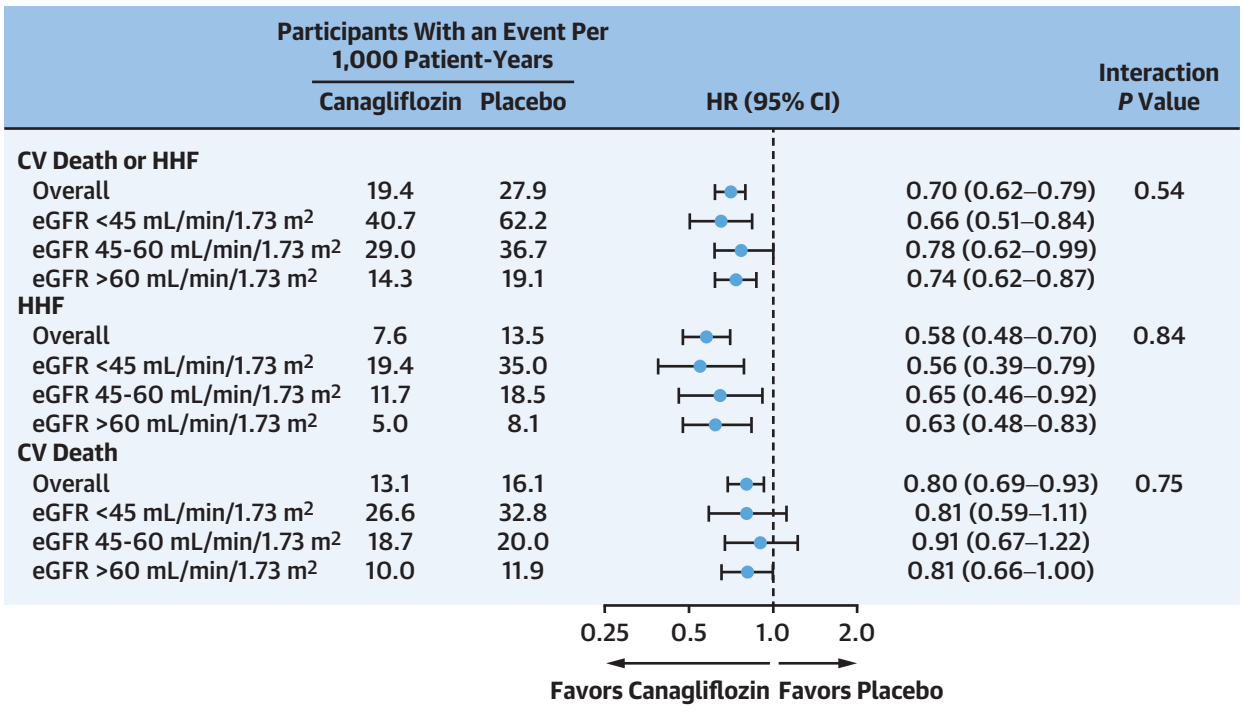
that reached standard levels of significance ($P = 0.02$ and $P = 0.04$), but there was no clear pattern of modification of the effects of canagliflozin identified.

DISCUSSION

In these integrated analyses of nearly 15,000 participants from the CANVAS Program and the CREDENCE trial, people with T2DM and reduced eGFR, increased UACR, and especially both, were at increased risk of CV events. CV death and HHF risk rose progressively with decreasing baseline eGFR and increasing UACR. Compared with placebo, canagliflozin consistently reduced the risk of CV death or HHF across subgroups defined according to eGFR or UACR, suggesting greatest absolute benefits in patients with the highest renal risk as indicated by low eGFR and high UACR. Significant heterogeneity values identified in the analyses by combined eGFR and UACR exhibited no clear pattern and likely occurred by chance. Together, these findings support the clinical use of eGFR and UACR as key complementary biomarkers to assess the risk of CV death or HHF in patients with T2DM, as well as the efficacy of canagliflozin for CV benefit in populations with T2DM and elevated CV risk or nephropathy regardless of baseline renal function or albuminuria.

This integrated CANVAS Program and CREDENCE trial analysis validates the CV prognostic importance of baseline renal function and albuminuria in T2DM. Among participants stratified according to eGFR only, participants with the lowest eGFR (<45 mL/min/1.73 m^2) exhibited the highest CV event rates. Among the albuminuria groups, the highest albuminuria (UACR >300 mg/g) group had the highest CV event rates. Among placebo-assigned participants within the highest eGFR group, those with high albuminuria (UACR >300 mg/g) experienced an ~6.5-fold higher event rate for HHF compared vs those with UACR <30 mg/g, suggesting that the combined assessment of both parameters allows more refined CV death or HHF risk assessment in patients with T2DM. The mechanisms of association between albuminuria and CV risk are not well defined and have been hypothesized to be related to vascular damage, endothelial dysfunction, and kidney injury leading to impaired systemic volume regulation.[15] Overall, our

FIGURE 1 **Effects of Canagliflozin on CV Outcomes According to Baseline eGFR**



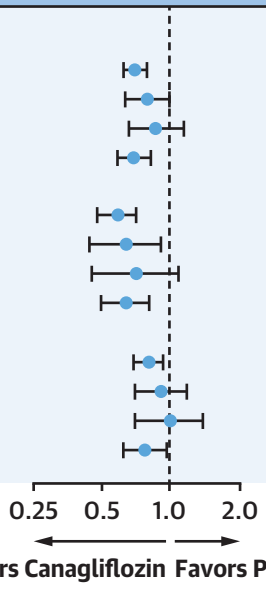
Effects of canagliflozin compared with placebo on cardiovascular (CV) death or hospitalization for heart failure (HHF) were assessed in subgroups defined according to baseline estimated glomerular filtration rate (eGFR) alone (<45, 45-60, and >60 mL/min/1.73 m^2). Annualized incidence rates per 1,000 patient-years of follow-up were calculated for all outcomes in addition to HRs and 95% CIs determined from Cox proportional regression models using treatment as the explanatory variable. To assess heterogeneity of the treatment effects across subgroups of baseline eGFR for all outcomes, *P* values for the interaction of treatment by subgroup were obtained based on Cox proportional hazards regression, including terms of treatment, baseline eGFR subgroup and their interaction.

findings provide a compelling rationale for the combined monitoring of eGFR and UACR in clinical practice across specialties to assess the risk of CV death or HHF in patients with T2DM.

Consistent proportional canagliflozin CV benefits across baseline eGFR subgroups among pooled CANVAS Program and CREDENCE participants in this study are consistent with other contemporary SGLT2 inhibitor studies. An analysis of the EMPA-REG OUTCOME (Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients) trial revealed that empagliflozin reduced the risk of CV death or HHF and HHF alone with consistent proportional effects according to baseline eGFR.[16] Consistent effects according to baseline eGFR were also reported for dapagliflozin for the outcomes of CV death or HHF and HHF alone in the DECLARE-TIMI 58 (Dapagliflozin Effect on Cardiovascular Events-Thrombolysis In Myocardial Infarction 58) study and for ertugliflozin for the outcome of CV death or HHF in the VERTIS-CV (Evaluation of Ertugliflozin Efficacy and Safety Cardiovascular Outcomes Trial) trial.[17,18] In data from CREDENCE, there was a potential interaction between eGFR and the effects of SGLT2 inhibitor vs placebo on preventing total stroke, with possible benefit in those with the lowest eGFR.[19] Another consistent finding in our study which is similar to other studies is that even though albuminuria is an independent CV risk factor in T2DM and may be related to SGLT2 inhibitor mechanisms, canagliflozin conferred CV death or HHF benefit regardless of albuminuria status at baseline, including across baseline eGFR groups.[20,21] In a recent exploratory analysis from the DECLARE-TIMI 58 trial, dapagliflozin reduced the incidence of a composite cardiorenal endpoint compared with placebo in all subgroups with UACR ≥30 mg/g.[22] In our study, although the absolute benefits of canagliflozin for CV death and HHF may be greatest among those with the highest renal risk (ie, those with low eGFR, high UACR, or both), the relative risk reductions were consistent and robust across eGFR and albuminuria categories. Particularly with the growing evidence of SGLT2 inhibitor benefit specifically in patients with

FIGURE 2 Effects of Canagliflozin on CV Outcomes According to Baseline UACR

	Participants With an Event Per 1,000 Patient-Years		HR (95% CI)	Interaction *P* Value
	Canagliflozin	Placebo		
CV Death or HHF				
Overall	19.4	28.0	0.69 (0.62–0.78)	0.41
<30 mg/g	11.9	14.7	0.78 (0.63–0.98)	
30-300 mg/g	21.7	25.0	0.86 (0.65–1.13)	
>300 mg/g	36.5	52.4	0.69 (0.58–0.82)	
HHF				
Overall	7.6	13.6	0.58 (0.48–0.70)	0.94
<30 mg/g	3.8	6.0	0.63 (0.44–0.90)	
30-300 mg/g	7.6	11.2	0.70 (0.45–1.07)	
>300 mg/g	17.5	27.8	0.63 (0.49–0.80)	
CV Death				
Overall	13.1	16.2	0.80 (0.69–0.92)	0.45
<30 mg/g	8.6	9.0	0.91 (0.70–1.18)	
30-300 mg/g	15.2	14.9	0.99 (0.70–1.38)	
>300 mg/g	22.8	29.1	0.77 (0.62–0.96)	



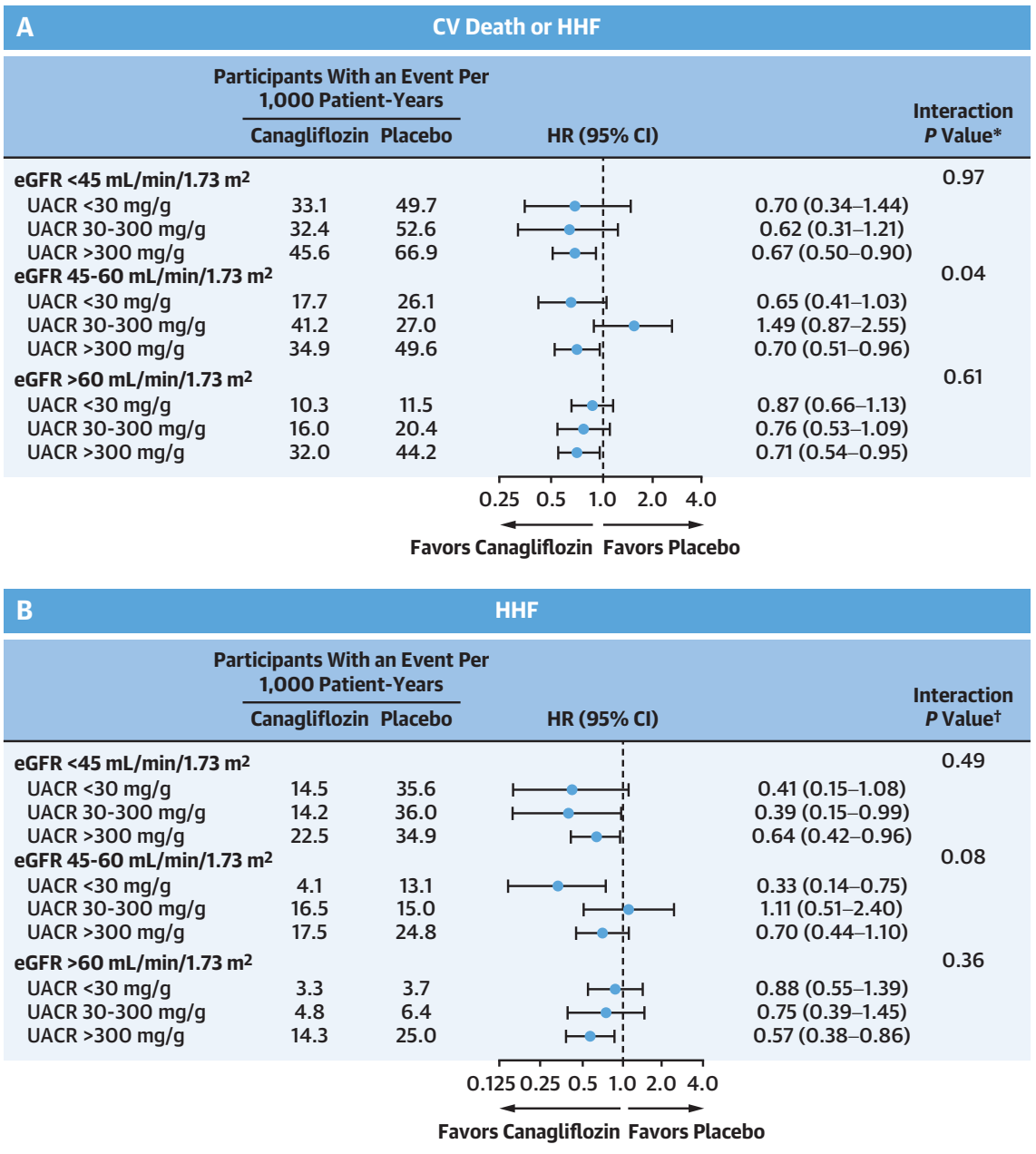
Effects of canagliflozin compared with placebo on CV death or HHF were assessed in subgroups defined by baseline urine albumin:creatinine ratio (UACR) alone (<30, 30-300, and >300 mg/g). Annualized incidence rates per 1,000 patient-years of follow-up were calculated for all outcomes in addition to HRs and 95% CIs determined from Cox proportional regression models using treatment as the explanatory variable. To assess heterogeneity of the treatment effects across subgroups of baseline UACR for all outcomes, *P* values for the interaction of treatment by subgroup were obtained based on Cox proportional hazards regression including terms of treatment, baseline UACR subgroup, and their interaction. Abbreviations as in Figure 1.

chronic kidney disease, our study provides important evidence to support the use of canagliflozin for CV death or HHF reduction efficacy in people with T2DM and elevated CV risk or nephropathy regardless of baseline renal function or albuminuria status.

Two of 9 subgroup analyses in patients with eGFR 45 to 60 mL/min/1.73 m^2 had *P* interaction values below the standard threshold for statistical significance; that is, for CV death or HHF (*P* interaction 0.04) and CV death alone (*P* interaction 0.02). Similar findings were not observed in the lower or higher eGFR groups, with discordant HR trends in the middle UACR group of 30 to 300 mg/g vs the higher and low groups of UACR <30 mg/g and >300 mg/g, respectively. These directionally inconsistent trends seem less biologically plausible and are most likely a result of chance in the setting of multiple hypothesis testing. A less likely explanation is an interaction between UACR and the CV effects of canagliflozin only in patients with baseline eGFR 45 to 60 mL/min/1.73 m^2 but not in the lower or higher eGFR groups.

STUDY STRENGTHS AND LIMITATIONS. As an integrated analysis of large, randomized trials, this study has certain strengths and limitations. The CANVAS Program and CREDENCE trials had rigorous clinical trial conduct, large sample sizes, careful outcome assessment by a blinded and independent adjudication committee in each study, and the inclusion of patients with renal dysfunction down to 30 mL/min/1.73 m^2. A total of 174 of 4,401 participants in CREDENCE had eGFR <30 mL/min/1.73 m^2 at randomization.[23] The CREDENCE trial was stopped early for efficacy at interim analysis in 2018 at the recommendation of the data monitoring committee; this reduced power to analyze secondary endpoints. However, the CV outcome findings in this study are broadly similar to those of other contemporary SGLT2 inhibitor studies. Measures of N-terminal pro-B-type natriuretic peptide are available in 4,300 patients from the CANVAS Program but not yet available for CREDENCE participants, and thus we were unable to incorporate N-terminal pro-B-type natriuretic

FIGURE 3 Effects of Canagliflozin on CV Outcomes According to Baseline eGFR/UACR



Effects of canagliflozin compared with placebo on CV death or HHF **(A)**, HHF **(B)**, and CV death **(C)** were assessed in subgroups defined according to eGFR (<45, 45-60, and >60 mL/min/1.73 m^2) and UACR (<30, 30-300, and >300 mg/g). Annualized incidence rates per 1,000 patient-years of follow-up were calculated for all outcomes in addition to HRs and 95% CIs determined from Cox proportional regression models using treatment as the explanatory variable. To assess heterogeneity of the treatment effects across subgroups of baseline eGFR and/or for all outcomes, *P* values for the interaction of treatment by subgroup were obtained based on Cox proportional hazards regression including terms of treatment, baseline eGFR and/or UACR subgroup, and their interaction. *Overall *P* value across eGFR and UACR subgroups is 0.002. *P* interaction values for the eGFR subgroups within each UACR subgroups are 0.47, 0.06, and 0.97 for the UACR <30, 30-300, and >300 mg/g subgroups, respectively. *P* interaction values for the UACR subgroups are shown within each eGFR subgroup. †Overall *P* value across eGFR and UACR subgroups is 0.022. *P* interaction values for the eGFR subgroups within each UACR subgroups are 0.05, 0.25, and 0.79 for the UACR <30, 30-300, and >300 mg/g subgroups, respectively. *P* interaction values for the UACR subgroups are shown within each eGFR subgroup. ‡Overall *P* value across eGFR and UACR subgroups is 0.011. *P* interaction values for the eGFR subgroups within each UACR subgroups are 0.90, 0.05, and 0.61 for the UACR <30, 30-300, and >300 mg/g subgroups, respectively. *P* interaction values for the UACR subgroups are shown within each eGFR subgroup. UACR = urine albumin:creatinine ratio; other abbreviations as in Figures 1 and 2.

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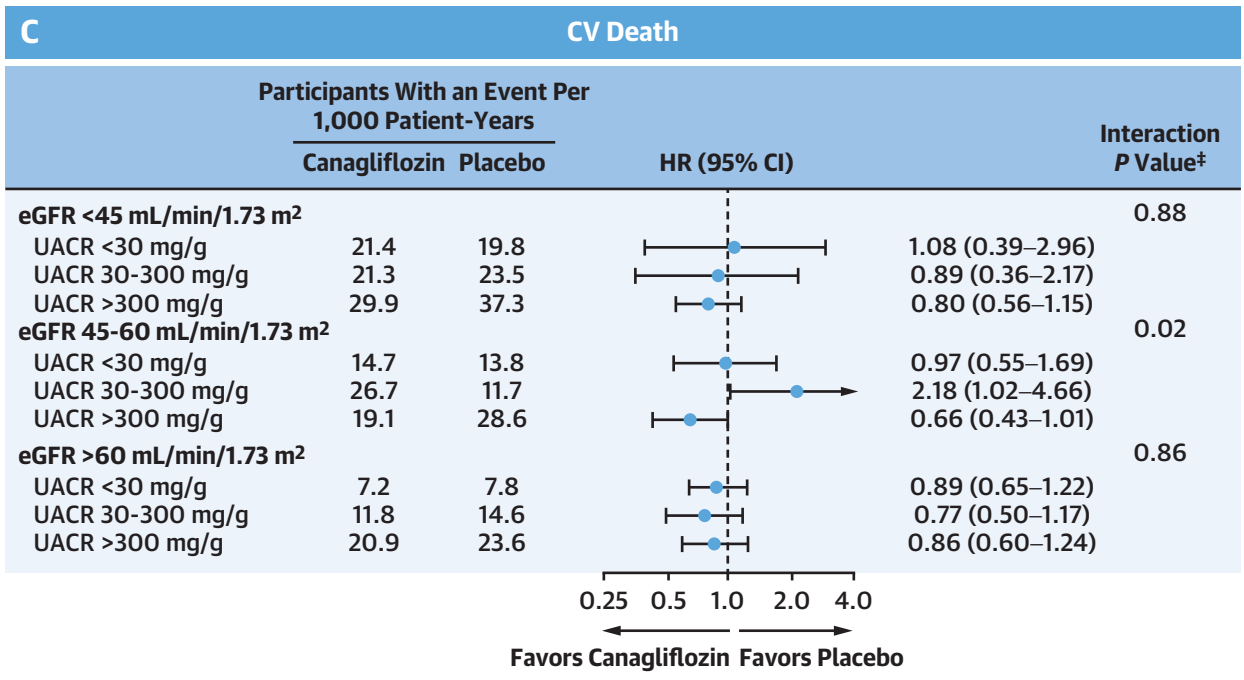
FIGURE 3 Continued



peptide into analyses of biomarkers and outcomes. This analysis of pooled CANVAS Program and CREDENCE patient level data was not prespecified. Study was not incorporated in statistical models, and uncontrolled effects by study may result in variation in outcomes by factors that differ between the studies. The use of different equations to estimate eGFR (Modification of Diet in Renal Disease in the CANVAS Program and CKD Epidemiology Collaboration Frequency in the CREDENCE trial) may represent a potential source of bias in the pooled analysis. Patients with type 1 diabetes or a history of dialysis or renal transplantation were excluded from the CANVAS Program and CREDENCE trial, which may limit generalizability among these populations.

CONCLUSIONS

In these integrated analyses from the CANVAS Program and the CREDENCE trial, rates of CV death or HHF, CV death, and HHF events increased with decreasing baseline eGFR and/or increasing UACR in patients with T2DM. Canagliflozin significantly reduced the risk of CV death or HHF, jointly and individually, in patients with T2DM and elevated CV risk or nephropathy; these results were consistent across eGFR or UACR subgroups. These results support the prognostic value of assessing eGFR and UACR in combination to assess future CV death or HHF risk when managing people with T2DM, as well as the efficacy of canagliflozin to reduce CV death or HHF risk in populations with T2DM and elevated CV risk or nephropathy regardless of baseline renal function or albuminuria status, with the likely greatest absolute benefits in the very high renal risk group.

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served as a consultant for Merck, Relypsa, Novo Nordisk, and AstraZeneca; has served on a steering committee for Vascular Dynamics; has served as Editor of the *American Journal of Nephrology* and *Nephrology*; has served as Editor-in-Chief of *UpToDate,* and Nephrology and Hypertension Section Editor of *UpToDate*; and has served as Associate Editor of *Diabetes Care*, *Hypertension Research*, and *Nephrology, Dialysis, and Transplantation*. Drs Blais, Damaraju, and Gogate are employees of Janssen Scientific Affairs, LLC. Dr Cannon has received research grants from Amgen, Better Therapeutics, Boehringer Ingelheim, Bristol Myers Squibb, Daiichi-Sankyo, Janssen, Merck, Novo Nordisk, and Pfizer; has received consulting fees from Aegerion, Alnylam, Amarin, Amgen, Applied Therapeutics, Ascendia, Boehringer Ingelheim, Bristol Myers Squibb, Eli Lilly, Janssen, Lexicon, Merck, Pfizer, Rhoshan, and Sanofi; and serves on Data and Safety Monitoring Boards for the Veterans Administration, Applied Therapeutics, and Novo Nordisk. Dr Cherney has received honoraria from Boehringer Ingelheim-Lilly, Merck, AstraZeneca, Sanofi, Mitsubishi-Tanabe, AbbVie, Janssen, Bayer, Prometic, Bristol Myers Squibb, and Novo Nordisk; and has received operational funding for clinical trials from Boehringer Ingelheim-Lilly, Merck, Janssen, Sanofi, AstraZeneca, and Novo Nordisk. 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Dr Levin serves as a scientific advisor to Boehringer Ingelheim, AstraZeneca, and the National Institute of Diabetes and Digestive and Kidney Diseases; is on the data safety and monitoring board for the National Institute of Diabetes and Digestive and Kidney Diseases, Kidney Precision Medicine, University of Washington Kidney Research Institute Scientific Advisory Committee; is funded by the Canadian Institute of Health Research and Kidney Foundation of Canada; and has received fees for time as CREDENCE National Coordinator from Janssen, directed to her academic team. Dr Lingvay has received institutional research payments from Novo Nordisk, Sanofi, Novartis, Pfizer, Merck, Mylan, and GI Dynamics; and has received personal fees for consultancy from AstraZeneca, Eli Lilly, TARGETPharma, Novo Nordisk, Boehringer Ingelheim, Janssen, MannKind, Valeritas, Intarcia, Intercept, Zealand Pharma, Bayer; and has received consultancy fees from Sanofi. Dr Mahaffey has received research grants or contracts from the American Heart Association, Apple, Inc, Bayer, California Institute Regenerative Medicine, Eidos, Ferring, Gilead, Google (Verily), Idorsia, Johnson & Johnson, Luitpold, PAC-12, Precordior, and Sanifit; has provided consulting or other services for Amgen, Applied Therapeutics, AstraZeneca, Bayer, CSL Behring, Elsevier, FibroGen, Inova, Johnson & Johnson, Lexicon, MyoKardia, Novartis, Novo Nordisk, Otsuka, PhaseBio, Portola, Quidel, Sanofi, and Theravance; and has equity in Precordior. Dr Neal has received institutional payments for research projects from Janssen; and has received fees for consultancy from Janssen, Merck Sharp & Dohme, and Mitsubishi Tanabe. Dr Perkovic has received fees for advisory boards, steering committee roles, or scientific presentations from AbbVie, Astellas, AstraZeneca, Bayer, Baxter, Bristol Myers Squibb, Boehringer Ingelheim, Dimerix, Durect, Eli Lilly, Gilead, GlaxoSmithKline, Janssen, Merck, Mitsubishi Tanabe, Mundipharma, Novartis, Novo Nordisk, Pfizer, PharmaLink, Relypsa, Retrophin, Sanofi, Servier, Vifor, and Tricida. Dr Weir serves as a scientific advisor to Akebia, AstraZeneca, Janssen, Boehringer Ingelheim, Vifor, Merck, Novo Nordisk, and Bayer; and receives grant support from the National Institute of Diabetes and Digestive and Kidney Diseases and the National Heart, Lung, and Blood Institute. Dr Sarraju has reported that he has no relationships relevant to the contents of this paper to disclose.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: In patients with T2DM and high CV risk or nephropathy, canagliflozin reduces the risk of CV death or HHF regardless of baseline kidney function or albuminuria.

TRANSLATIONAL OUTLOOK: Further studies are needed to define the role of SGLT-2 inhibitor treatment in conjunction with other therapeutic measures to mitigate CV risk, reduce HHF, and improve survival in patients with diabetes and impaired renal function or albuminuria.

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KEY WORDS canagliflozin, cardiovascular outcomes, diabetes, heart failure, SGLT2 inhibitor

APPENDIX For a supplemental table, please see the online version of this paper.