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Relative and Absolute Risk Reductions in Cardiovascular and Kidney Outcomes With Canagliflozin Across KDIGO Risk Categories: Findings From the CANVAS Program

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Rationale & Objective: Canagliflozin reduces the risk for cardiovascular and kidney outcomes in type 2 diabetes. This study aimed to assess the relative and absolute effects of canagliflozin on clinical outcomes across different KDIGO (Kidney Disease: Improving Global Outcomes) risk categories based on estimated glomerular filtration rate (eGFR) and urinary albumin-creatinine ratio.

Study Design: Post hoc analysis of the CANagliflozin cardioVascular Assessment Study (CANVAS) Program.

Settings & Participants: The CANVAS Program randomly assigned 10,142 participants with type 2 diabetes at high cardiovascular risk and with eGFR ≥ 30 mL/min/1.73 m^2 to treatment with canagliflozin or placebo.

Intervention(s): Canagliflozin or matching placebo.

Outcomes: The primary outcome was a composite of cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke, with a set of other cardiovascular and kidney prespecified outcomes.

Results: Of 10,142 participants, 10,031 (98.9%) had available baseline eGFR and urinary albumin-creatinine ratio data. The proportion of participants in low-, moderate-, high-, and very high–risk KDIGO categories was 58.6%, 25.8%, 10.6%, and 5.0%, respectively. The relative effect of canagliflozin on the primary outcome (HR, 0.86; 95% CI, 0.75-0.97) was consistent across KDIGO risk categories (P trend = 0.2), with similar results for other cardiovascular and kidney outcomes. Absolute reductions in the primary outcome were greater within higher KDIGO risk categories (P trend = 0.03) with a similar pattern of effect for the composite of cardiovascular death or hospitalization for heart failure (P trend = 0.06) and for chronic eGFR slope (P trend = 0.04).

Limitations: Predominantly a low kidney risk population, relatively few participants in higher KDIGO risk categories, and exclusion of individuals with eGFR < 30 mL/min/1.73 m^2.

Conclusions: Although the relative effects of canagliflozin are similar across KDIGO risk categories, absolute risk reductions are likely greater for individuals at higher KDIGO risk. The KDIGO classification system may be able to identify individuals who might derive greater benefits for end-organ protection from treatment with canagliflozin.

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Trial Registration: The original trials of the CANVAS Program were registered at ClinicalTrials.gov with study numbers NCT01032629 and NCT01989754.

Visual Abstract online

Complete author and article information provided before references.

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Sodium-glucose cotransporter 2 (SGLT2) inhibitors are a class of glucose-lowering agents that have been shown to reduce the risk for cardiovascular events in several large cardiovascular outcome trials.[1–3] Recently, the CREDENCE trial demonstrated that the SGLT2 inhibitor canagliflozin reduces the risk for kidney failure and cardiovascular events in people with type 2 diabetes mellitus (T2DM) and chronic kidney disease (CKD).[4]

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Lower estimated glomerular filtration rate (eGFR) and higher urinary albumin-creatinine ratio (UACR) independently predict kidney and cardiovascular events and all-cause mortality.[5–7] The 2012 KDIGO (Kidney Disease: Improving Global Outcomes) classification of CKD incorporates both eGFR and UACR into a 2-dimensional framework to stratify individuals according to their risk for a range of adverse outcomes, including cardiovascular events, acute kidney injury, kidney failure, and mortality.[8] The KDIGO classification system has played an important role in improving understanding of the epidemiology of CKD, as well as assessing severity and predicting adverse outcomes for individuals.

The CREDENCE trial recruited participants with severely increased albuminuria (UACR > 300 mg/g) and ∼60% had eGFR < 60 mL/min/1.73 m^2 at baseline; as a result, most participants were very high risk according to the KDIGO classification system. It is unclear whether the relative benefits for kidney and cardiovascular outcomes observed in the

PLAIN-LANGUAGE SUMMARY

Canagliflozin reduces the risk for cardiovascular and kidney outcomes in patients with type 2 diabetes. This post hoc analysis of the phase 3 randomized placebo-controlled CANagliflozin cardioVascular Assessment Study (CANVAS) Program (n = 10,142) assessed the effect of canagliflozin on these outcomes in participants with different levels of risk for chronic kidney disease outcomes, defined by the KDIGO (Kidney Disease: Improving Global Outcomes) classification based on estimated glomerular filtration rate and urinary albumin-creatinine ratio. The relative effects of canagliflozin on cardiovascular and kidney outcomes were similar across KDIGO risk categories, but absolute risk reductions were likely greater for individuals within higher-risk KDIGO categories. The KDIGO classification system may be able to be used to identify individuals who would derive greater benefits for end-organ protection from treatment with canagliflozin.

CREDENCE trial are generalizable to individuals in earlier stages of CKD, as defined by the KDIGO classification system, and whether the KDIGO classification of CKD can be used to estimate absolute risk reductions, identify those who might benefit most from treatment, and therefore support decision making in routine clinical practice.

We undertook a post hoc analysis of the CANVAS (CANagliflozin cardioVascular Assessment Study) Program to assess whether the relative effects of canagliflozin on cardiovascular, kidney, and safety outcomes varied by KDIGO risk categories and to determine any absolute differences in treatment effect across subgroups.

Methods

Trial Design and Participants

The CANVAS Program comprised 2 parallel, randomized, double-blind, placebo-controlled trials (CANVAS [ClinicalTrials.gov identifier NCT01032629] and CANVAS-R [ClinicalTrials.gov identifier NCT01989754]) in which individuals with T2DM and eGFR ≥ 30 mL/min/1.73 m^2 who had or were at high risk for cardiovascular disease were randomly assigned to treatment with canagliflozin or placebo. Detailed study methods and statistical analysis plan for the integrated analysis and reporting of the CANVAS Program have been previously published.[2,9] The protocols were approved by the ethics committees at each site. All participants provided written informed consent.

Randomization and Follow-up

Randomization was performed centrally through a web-based response system. All participants, care providers, investigators, and outcome assessors were blinded to treatment allocations until the end of the trials.

After randomization, face-to-face follow-up was scheduled 3 or more times in the first year and then alternated between face-to-face and telephone follow-up at 6-monthly intervals thereafter. Adverse event assessment was performed at each study visit. Other glycemic and cardiovascular risk factor management, including renin-angiotensin system blockade, was guided by best practice in accordance with local guidelines.

KDIGO Classification of CKD

We categorized participants with eGFR and UACR values at baseline into 4 risk categories according to the KDIGO classification system[8]: low (eGFR ≥ 60 mL/min/1.73 m^2 and UACR < 30 mg/g), moderate (eGFR 45-<60 mL/min/1.73 m^2 and UACR < 30 mg/g or eGFR ≥ 60 mL/min/1.73 m^2 and UACR of 30-300 mg/g), high (eGFR 30-<45 mL/min/1.73 m^2 and UACR < 30 mg/g, eGFR 45-<60 mL/min/1.73 m^2 and UACR 30-300 mg/g, or eGFR ≥ 60 mL/min/1.73 m^2 and UACR > 300 mg/g), and very high risk (eGFR < 30 mL/min/1.73 m^2 with any UACR, eGFR 30-<45 mL/min/1.73 m^2 and UACR ≥ 30 mg/g, or eGFR 45-<60 mL/min/1.73 m^2 and UACR > 300 mg/g).

Outcomes

Definitions for all outcomes in the CANVAS Program have been published.[2] The primary outcome was a composite of cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke. Other cardiovascular outcomes included cardiovascular death or hospitalization for heart failure, fatal or nonfatal myocardial infarction, fatal or nonfatal stroke, and fatal or nonfatal heart failure. We assessed 2 kidney outcomes: (1) sustained 40% decline in eGFR, kidney failure, or death due to kidney disease and (2) sustained 40% decline in eGFR, kidney failure, or death due to cardiovascular or kidney disease (ie, a composite cardiorenal outcome similar to the primary outcome in CREDENCE). To further assess the effect of canagliflozin on progression of kidney disease, we also assessed a continuous kidney outcome, eGFR slope, defined as the annual mean difference in eGFR between canagliflozin and placebo during acute and chronic treatment periods. Serum creatinine level collected at study visits was centrally measured, and eGFR was calculated using the Modification of Diet in Renal Disease (MDRD) Study equation.

Consistent with previous analyses, we separately reported all serious adverse events for the CANVAS Program along with serious or nonserious adverse events for the CANVAS trial alone due to differences in adverse event reporting between the trials.[10,11]

Statistical Analysis

Baseline characteristics for participants across KDIGO risk categories were compared using χ^2 and analysis of variance tests for categorical and continuous variables, respectively.

We assessed the relative effects of canagliflozin on cardiovascular, kidney, and safety outcomes overall and by baseline KDIGO risk categories using Cox regression and an intention-to-treat approach. Subgroup-by-treatment interaction terms were added to the relevant model to test for effect modification across subgroups. The P trend values across KDIGO risk categories were obtained using likelihood ratio tests. Annualized incidence rates were calculated per 1,000 patient-years of follow-up. Sensitivity analyses adjusting for competing risk for death were performed for these outcomes using the Fine and Gray method.[12]

We assessed the effect of canagliflozin on eGFR slope over the total study duration and separately during 2 periods: from baseline to week 13 (acute slope), and week 13 to last available measure during the trial (chronic slope). Effects on eGFR slope were estimated by a piecewise linear mixed-effect model using an intention-to-treat approach as previously described.[10,11,13] To assess trend in treatment effects on eGFR slope across subgroups, we performed the analysis separately for each subgroup, obtained estimated treatment effects and their standard errors (SEs), and compared the estimated effects between subgroups while accounting for the estimated SE within each subgroup using χ^2 test with *df* equal to 1 less than the number of subgroups being compared.

For safety outcomes, 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 30 or fewer days after discontinuation of randomized treatment. For amputation and fracture outcomes, analyses included participants who received 1 or more dose of canagliflozin or placebo and had an event at any time during follow-up.

Absolute effects on key outcomes of interest per 1,000 patients treated over 5 years and corresponding 95% CIs were estimated as the difference in incidence rates between canagliflozin- and placebo-treated participants using Poisson regression analysis with the assumption of constant annual event probabilities. Absolute risk reductions and 95% CIs between treatment groups were obtained using the delta method after postestimation from the Poisson regression model. To assess trend in absolute risk reductions across subgroups, we obtained estimated absolute treatment effects and their SEs for each subgroup. We then compared estimated effects across the ordered subgroups while accounting for the estimated SE within each subgroup using χ^2 test with 1 *df*.

Analyses were performed using SAS software, version 9.2; SAS Enterprise Guide, version 7.11 (SAS Institute); and STATA software, version 15.1 (StataCorp).

Results

The CANVAS Program included 10,142 participants, of whom 10,031 (98.9%) had both eGFR and UACR values at baseline. A total of 9,734 (96.0%) participants completed the trials with a mean follow-up of 188.2 weeks. At baseline, the number of overall participants in low-, moderate-, high-, and very high-risk KDIGO categories was 5,876 (58.6%), 2,587 (25.8%), 1,068 (10.6%), and 500 (5.0%), respectively (Fig 1).

Across progressively higher KDIGO risk categories, participants were more likely to be older, have a longer duration of diabetes, and have higher glycated hemoglobin levels (all $P < 0.0001$; Table 1). They were also more likely to have a history of cardiovascular disease, heart failure, or microvascular complications (all $P < 0.0001$). Baseline use of renin-angiotensin system (RAS) blockade was high overall (80.0%) and in each KDIGO risk group (Table 1). Characteristics of participants randomly assigned to the canagliflozin and placebo groups were generally similar within each of the KDIGO risk categories (Table S1).

Cardiovascular Outcomes

The relative effect of canagliflozin on cardiovascular outcomes across different KDIGO risk categories is displayed in Figure 2. In the overall population, canagliflozin reduced the risk for major adverse cardiovascular events (hazard ratio [HR], 0.86; 95% CI, 0.75-0.97), cardiovascular death or hospitalization for heart failure (HR, 0.78; 95% CI, 0.67-0.91), and heart failure alone (HR, 0.70; 95% CI, 0.55-0.89), with consistent relative effects across KDIGO risk categories (all P trend > 0.2). Likewise, there was no significant interaction between relative treatment effect and KDIGO risk category for all other cardiovascular outcomes (all P trend > 0.2; Fig 2). Results were essentially unchanged in sensitivity analyses adjusted for the competing risk for death (Table S2).

Kidney Outcomes

The effect of canagliflozin on 40% decline in eGFR, kidney failure, or death due to cardiovascular or kidney disease (HR, 0.77; 95% CI, 0.66-0.89) and the kidney-specific composite outcome excluding cardiovascular death (HR, 0.60; 95% CI, 0.47-0.77) did not vary significantly in a linear fashion across KDIGO categories (P trend = 0.6 and 0.8, respectively). Results were similar in sensitivity analyses adjusted for the competing risk for death (Table S2).

The absolute effect of canagliflozin on eGFR slope varied across different periods. Treatment with canagliflozin resulted in an acute decrease in eGFR within the first 13 weeks that was similar across KDIGO risk categories (P trend = 0.6; Fig 3A). From week 13 to the end of follow-up, the rate of decline in eGFR for placebo-treated participants increased across progressively higher KDIGO risk categories and as a result, the absolute effect of canagliflozin on eGFR slope was greater in higher KDIGO risk categories (P trend = 0.04; Fig 3B). The annual placebo-subtracted differences for total eGFR slope across subgroups are displayed in Table S3.

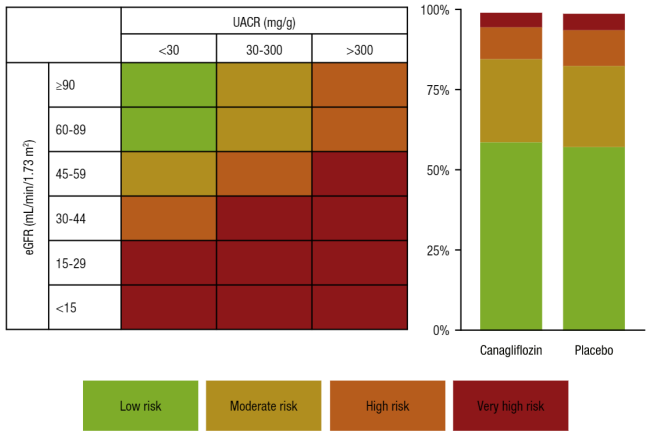

Figure 1. KDIGO (Kidney Disease: Improving Global Outcomes) classification of chronic kidney disease and proportion of canagliflozin- and placebo-treated participants in each KDIGO risk category. Differences in the proportion of participants randomly assigned to canagliflozin and placebo were due to differences in randomization ratios in the CANagliflozin cardioVascular Assessment Study (CANVAS) and CANVAS-R trials. Abbreviations: eGFR, estimated glomerular filtration rate; UACR, urinary albumin-creatinine ratio.

Safety Outcomes

The relative effects of canagliflozin on serious safety outcomes were similar across KDIGO risk categories (Fig 4). Risk for serious kidney-related adverse events, acute kidney injury, and hyperkalemia were not modified by KDIGO risk categories (all P trend > 0.2; Fig 4). The relative effect of canagliflozin on amputations was also not modified by KDIGO risk categories (P trend = 0.9; Fig 4). The relative effects of canagliflozin on serious and nonserious safety outcomes in the CANVAS trial alone are summarized in Figure S1. The risk for osmotic diuresis with canagliflozin attenuated across higher KDIGO risk categories (P trend = 0.01).

Absolute Effects

The absolute risk reduction with canagliflozin for the primary cardiovascular outcome increased across higher KDIGO risk categories (P trend = 0.03; Fig 5). A similar pattern of effect of borderline significance was observed for cardiovascular death or hospitalization for heart failure (P trend = 0.06). Point estimates for absolute effects on heart failure alone and kidney outcomes were also nominally greater across participants at higher KDIGO risk; however, these did not reach statistical significance (Fig 5). There was no evidence of an interaction for the absolute effect on amputations (P trend = 0.3; Fig 5).

Discussion

In this post hoc analysis of the CANVAS Program, we made 2 main observations. First, the relative effects of canagliflozin on cardiovascular and kidney outcomes were broadly similar across KDIGO risk categories. Second, because risk for these outcomes increased across progressively higher-risk categories, absolute risk reductions with canagliflozin for the primary outcome of major adverse cardiovascular events and the composite of cardiovascular death or hospitalization for heart failure increased in a graded and linear fashion across higher KDIGO risk categories. The absolute effect of canagliflozin on progression of kidney disease, as measured by chronic eGFR slope, also appeared to increase with higher KDIGO risk categories. These data suggest that the KDIGO classification of CKD can be used in clinical practice to identify people with T2DM in whom SGLT2 inhibition with canagliflozin is likely to result in the greatest treatment benefits.

It is not surprising that we found that the relative effects of canagliflozin on cardiovascular and kidney outcomes were consistent across KDIGO risk categories. Secondary analyses of large-scale SGLT2 inhibitor trials have found no evidence of interaction between treatment and eGFR or albuminuria (within the range of values studied),[10,11,14,15] a finding that has been reinforced in a recent meta-analysis of SGLT2 inhibitor cardiovascular and kidney outcome trials.[16] These findings contrast with data for RAS blockade

Table 1. Characteristics of Participants by Baseline KDIGO Risk Categories

	Low Risk (n = 5,876)	Moderate Risk (n = 2,587)	High Risk (n = 1,068)	Very High Risk (n = 500)
Age, y	62.1 ± 8.0	64.3 ± 8.2	65.9 ± 8.5	66.5 ± 8.2
Male sex	3,744 (63.7%)	1,686 (65.2%)	685 (64.1%)	322 (64.4%)
Race				
White	4,569 (77.8%)	2,045 (79.0%)	829 (77.6%)	402 (80.4%)
Asian	751 (12.8%)	329 (12.7%)	142 (13.3%)	61 (12.2%)
Black or African American	207 (3.5%)	77 (3.0%)	32 (3.0%)	14 (2.8%)
Other[a]	349 (5.9%)	136 (5.3%)	65 (6.1%)	23 (4.6%)
Current smoker[b]	1,122 (19.1%)	436 (16.9%)	154 (14.4%)	64 (12.8%)
History of hypertension	5,148 (87.6%)	2,386 (92.2%)	1,010 (94.6%)	475 (95.0%)
History of HF	760 (12.9%)	396 (15.3%)	186 (17.4%)	93 (18.6%)
Duration of diabetes, y	12.7 ± 7.4	14.1 ± 7.9	15.7 ± 8.2	16.9 ± 7.8
Drug therapy				
Insulin	2,633 (44.8%)	1,397 (54.0%)	656 (61.4%)	359 (71.8%)
Sulfonylurea	2,649 (45.1%)	1,109 (42.9%)	406 (38.0%)	160 (32.0%)
Metformin	4,810 (81.9%)	2,000 (77.3%)	706 (66.1%)	217 (43.4%)
GLP-1 receptor agonist	236 (4.0%)	93 (3.6%)	50 (4.7%)	23 (4.6%)
DPP-4 inhibitor	710 (12.1%)	312 (12.1%)	153 (14.3%)	73 (14.6%)
Statin	4,342 (73.9%)	1,950 (75.4%)	837 (78.4%)	396 (79.2%)
Antithrombotic	4,234 (72.1%)	1,944 (75.1%)	830 (77.7%)	392 (78.4%)
RAAS inhibitor	4,625 (78.7%)	2,114 (81.7%)	885 (82.9%)	397 (79.4%)
β-Blocker	3,015 (51.3%)	1,436 (55.5%)	615 (57.6%)	303 (60.6%)
Diuretic	2,265 (38.5%)	1,272 (49.2%)	582 (54.5%)	317 (63.4%)
Microvascular disease history[c]				
Retinopathy	1,042 (17.7%)	584 (22.6%)	300 (28.1%)	178 (35.7%)
Neuropathy	1,661 (28.3%)	842 (32.5%)	385 (36.0%)	180 (36.0%)
Atherosclerotic vascular disease history[d]				
Coronary	3,281 (55.8%)	1,458 (56.4%)	636 (59.6%)	290 (58.0%)
Cerebrovascular	1,064 (18.1%)	519 (20.1%)	242 (22.7%)	113 (22.6%)
Peripheral	1,102 (18.8%)	559 (21.6%)	286 (26.8%)	146 (29.2%)
CV disease history[e]	3,791 (64.5%)	1,695 (65.5%)	747 (69.9%)	358 (71.6%)
History of amputation	74 (1.3%)	66 (2.6%)	58 (5.4%)	37 (7.4%)
Body mass index, kg/m^2	31.7 ± 5.8	32.3 ± 6.1	32.2 ± 6.0	32.2 ± 6.2
Systolic BP, mm Hg	134.8 ± 15.0	138.4 ± 15.6	139.6 ± 17.5	142.5 ± 17.8
Diastolic BP, mm Hg	77.8 ± 9.3	77.8 ± 9.9	77.0 ± 10.2	76.8 ± 10.7
Glycated hemoglobin, %	8.2 ± 0.9	8.3 ± 1.0	8.4 ± 0.9	8.5 ± 1.0
Total cholesterol, mmol/L	4.3 ± 1.1	4.4 ± 1.1	4.5 ± 1.3	4.5 ± 1.2
Triglycerides, mmol/L	1.9 ± 1.3	2.1 ± 1.5	2.3 ± 1.6	2.3 ± 1.6
HDL-C, mmol/L	1.2 ± 0.3	1.2 ± 0.3	1.2 ± 0.3	1.1 ± 0.3
LDL-C, mmol/L	2.3 ± 0.9	2.3 ± 0.9	2.3 ± 1.0	2.3 ± 1.0
LDL-C:HDL-C ratio	2.0 ± 0.9	2.1 ± 0.9	2.1 ± 1.0	2.2 ± 1.0
eGFR, mL/min/1.73 m^2	83.6 ± 16.4	72.8 ± 19.9	61.8 ± 20.4	42.9 ± 8.9
eGFR < 60 mL/min/1.73 m^2	0 (0%)	888 (34.3%)	628 (58.8%)	500 (100%)
UACR, mg/g	8.2 [5.7-13.2]	41.3 [13.1-84.3]	152.5 [37.0-526.7]	445.9 [121.9-1,124.5]
UACR > 300 mg/g	0 (0%)	0 (0%)	440 (41.2%)	320 (64.0%)

Note: Values for categorical variables given as count (percent); for continuous variables, as mean ± standard deviation or median [interquartile range]. Abbreviations: BP, blood pressure; CV, cardiovascular; DPP-4, dipeptidyl peptidase 4; eGFR, estimated glomerular filtration rate; GLP-1, glucagon-like peptide 1; HDL-C, high-density lipoprotein-cholesterol; HF, heart failure; KDIGO, Kidney Disease: Improving Global Outcomes; LDL-C, low-density lipoprotein-cholesterol; RAAS, renin-angiotensin-aldosterone system; UACR, urinary albumin-creatinine ratio.

[a]Includes American Indian or Alaska Native, Native Hawaiian or Pacific Islander, multiple, other, and unknown.

[b]Three participants did not have smoking status recorded at baseline.

[c]Two participants did not have retinopathy recorded at baseline.

[d]Some participants had more than 1 type of atherosclerotic disease.

[e]As defined in the protocol.

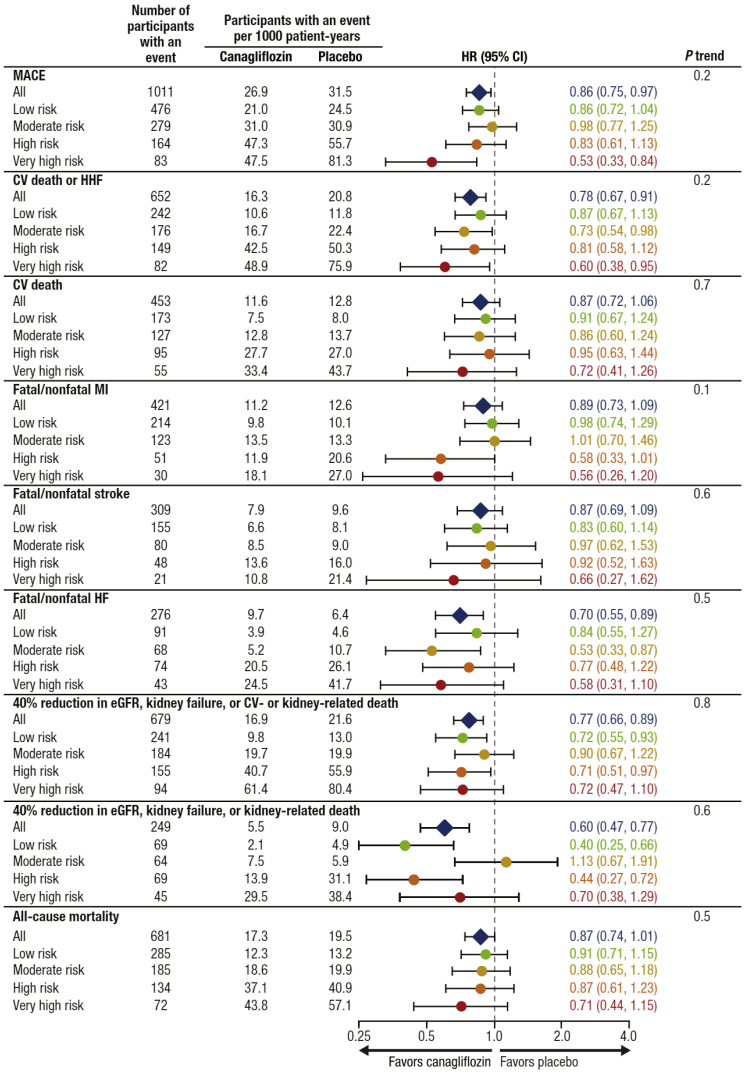

Figure 2. Relative effects of canagliflozin versus placebo on cardiovascular (CV) and kidney outcomes in participant subgroups defined by baseline KDIGO (Kidney Disease: Improving Global Outcomes) risk categories. Abbreviations: eGFR, estimated glomerular filtration rate; HF, heart failure; HHF, hospitalization for heart failure; HR, hazard ratio; MACE, major adverse cardiovascular event; MI, myocardial infarction.

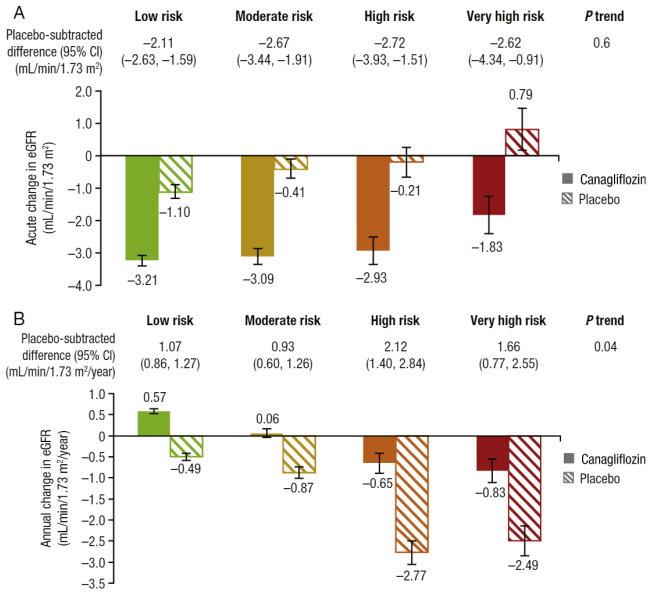

Figure 3. Absolute effect of canagliflozin versus placebo on (A) acute change in estimated glomerular filtration rate (eGFR) and (B) chronic eGFR slope (data are reported for week 6 in CANagliflozin cardioVascular Assessment Study (CANVAS) and week 13 in CANVAS-R) in participant subgroups defined by baseline KDIGO (Kidney Disease: Improving Global Outcomes) risk categories (eGFR values shown are mean ± standard error).

in nondiabetic kidney disease, for which the relative benefits of angiotensin-converting enzyme inhibitors increase with increasing albuminuria[17] and statin therapy, for which the relative effects on cardiovascular outcomes attenuate with declining eGFR.[18]

Although the KDIGO classification of CKD has been used to stratify the risk for adverse outcomes for individuals, it has very seldom been used to predict treatment response with SGLT2 inhibition or other commonly used cardioprotective therapies. We found that the KDIGO risk categories were useful in identifying participants in the CANVAS Program who were likely to derive greater absolute risk reductions for major adverse cardiovascular events and for cardiovascular death or hospitalization for heart failure. Point estimates for absolute risk reductions also appeared to increase across high KDIGO risk categories for hospitalization for heart failure alone and for the kidney-specific composite outcome. However, these did not reach statistical significance, possibly due to the smaller number of events for these outcomes. For the continuous kidney outcome of chronic eGFR slope, for which there was much greater power to assess differences in absolute treatment effect, the effect of canagliflozin appeared to increase across higher KDIGO risk subgroups.

There are likely to be multiple mechanisms, independent of glucose-lowering, that contribute to the beneficial cardiovascular and kidney effects of SGLT2 inhibitors. SGLT2 inhibitors are thought to reduce intraglomerular pressure by restoring tubuloglomerular feedback.[19] The hemodynamic nature of the acute decrease in eGFR with SGLT2 inhibitors is supported by off-treatment data demonstrating that the early "dip" in eGFR is reversible on drug cessation.[10,20] The mechanism by which SGLT2 inhibition reduces intraglomerular pressure is thought to be through increased distal sodium delivery to the macular densa and adenosine-mediated afferent arteriole vasoconstriction, which has been demonstrated at a single-nephron level in animal models and in people with type 1 diabetes with whole kidney hyperfiltration.[21,22] More recent data in T2DM have raised the possibility that efferent arteriolar tone may also be affected.[23] Regardless, reductions in intraglomerular pressure, along with enhanced natriuresis, are likely to play an important role not only in protection against kidney failure but also in

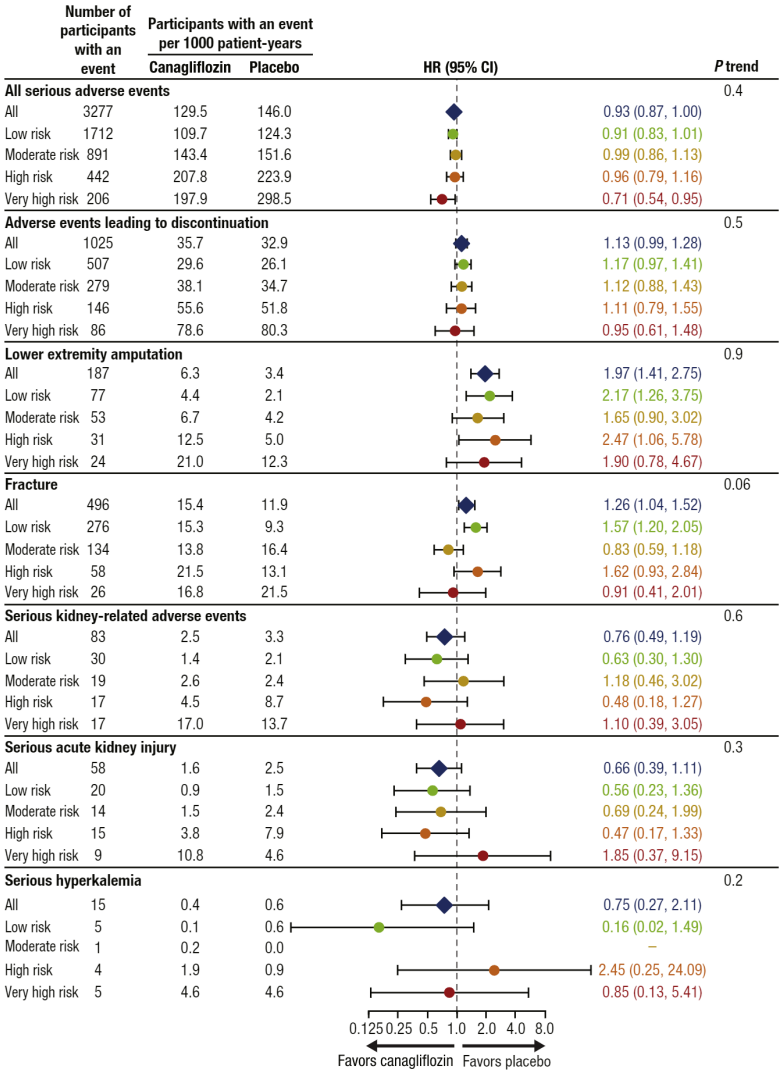

Figure 4. Relative effects of canagliflozin versus placebo on safety outcomes collected across the CANagliflozin cardioVascular Assessment Study (CANVAS) Program in participant subgroups defined by baseline KDIGO (Kidney Disease: Improving Global Outcomes) risk categories. Abbreviation: HR, hazard ratio.

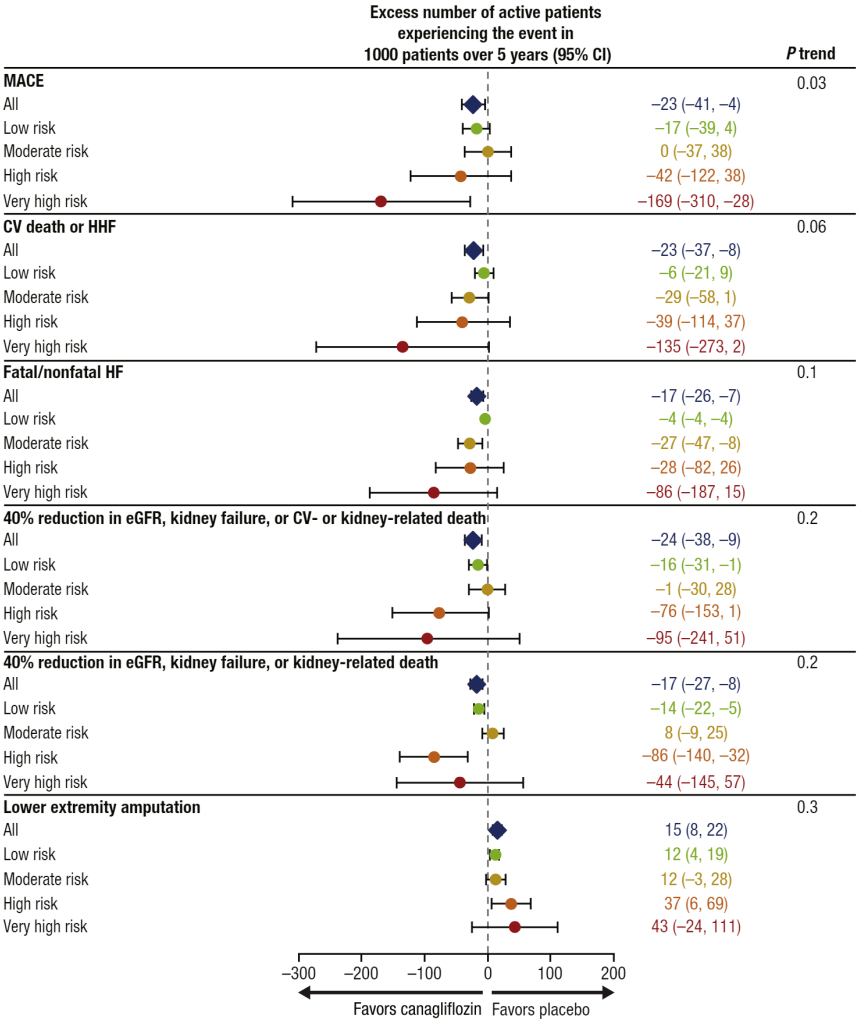

Figure 5. Absolute benefits and risks per 1,000 participants over 5 years with canagliflozin versus placebo in the overall population and in participant subgroups defined by baseline KDIGO (Kidney Disease: Improving Global Outcomes) risk categories. Abbreviations: CV, cardiovascular; eGFR, estimated glomerular filtration rate; HF, heart failure; HHF, hospitalization for heart failure; MACE, major adverse cardiovascular event.

reducing the risk for heart failure, especially in patients with CKD for whom subclinical volume overload is highly prevalent.[24] A number of other potential mechanisms have also been suggested, including protective effects on the vascular endothelium, anti-inflammatory actions, improvements in tubular oxygenation, and other direct cellular and metabolic effects.[25-27]

The validity of our findings is supported by the quality of data from the CANVAS Program clinical trials, which were conducted to a high standard with blinded outcome adjudication by expert committees. Approximately 80% of participants were treated with RAS blockade at baseline and use of other cardioprotective therapies was also high, demonstrating that the benefits of canagliflozin are achieved in addition to current standard of care. The use of continuous eGFR slope data provided additional explanatory power to investigate the kidney-protective effects of canagliflozin across KDIGO risk categories, an approach that has also been used for other major SGLT2 inhibitor trials, including CREDENCE.[11,28]

There are some important limitations to consider when interpreting our findings. This was a post hoc subgroup analysis and the trial was not designed to determine treatment effects in each of the KDIGO subgroups individually. The CANVAS Program included a relatively small proportion of participants in high or very high KDIGO risk categories and therefore our analysis may be underpowered to detect differences in treatment effects across subgroups. Individuals with eGFR < 30 mL/min/1.73 m^2 were excluded from the CANVAS Program (and other published SGLT2 inhibitor outcome trials) and thus it is uncertain whether these apply to individuals with more advanced kidney disease. Approximately two-thirds of participants had established atherosclerotic cardiovascular disease at baseline, which may limit the generalizability of these findings to the broader diabetic kidney disease population. However, the effect of canagliflozin was not modified by history of atherosclerotic cardiovascular disease in CREDENCE, in which approximately half the participants did not have established atherosclerotic cardiovascular disease at baseline.[29] The reported tests for trend were not adjusted for multiple comparisons and are therefore susceptible to the play of chance. Accepting these limitations, our findings are consistent with comparable analyses of the EMPA-REG OUTCOME trial[30,31] and represent one of the largest analyses to date of the effects of SGLT2 inhibition across the spectrum of kidney and/or cardiovascular risk.

The recently completed Dapagliflozin and Prevention of Adverse Outcomes in Chronic Kidney Disease (DAPA-CKD) study demonstrates benefits of dapagliflozin in patients with chronic kidney disease both with and without T2DM.[32] This trial included 4,304 patients with CKD with an eGFR between 25 and 75 mL/min/1.73 m^2 and UACR between 200 and 5,000 mg/g of whom 33% did not have T2DM at the time of recruitment. Ongoing trials involving CKD patients include EMPA-KIDNEY testing empagliflozin (ClinicalTrials.gov identifier NCT03594110), which will enroll participants with a baseline eGFR as low as 20 mL/min/1.73 m^2 irrespective of albuminuria.[33] Finally, the SCORED study testing sotagliflozin, a combined SGLT1/SGLT2 inhibitor (ClinicalTrials.gov identifier NCT03315143), will enroll patients with T2DM and an eGFR between 25 and ≤ 60 mL/min/1.73 m^2 irrespective of albuminuria.

In summary, although the relative effects of canagliflozin on cardiovascular and kidney outcomes are similar across KDIGO risk categories, absolute risk reductions are greater in individuals at higher KDIGO risk. These findings support the use of the KDIGO classification system to identify people with T2DM who may derive the greatest benefits for end-organ protection with canagliflozin.

Supplementary Material

Supplementary File (PDF)

Figure S1: Relative effects of canagliflozin on safety outcomes collected in CANVAS alone in participant subgroups defined by baseline KDIGO risk category.

Table S1: Characteristics of canagliflozin- and placebo-treated participants by baseline KDIGO risk category.

Table S2: Relative effects of canagliflozin on cardiovascular and kidney outcomes in participant subgroups defined by baseline KDIGO risk category adjusted for competing risk for death.

Table S3: Absolute effect of canagliflozin versus placebo on total eGFR slope by baseline KDIGO risk category.

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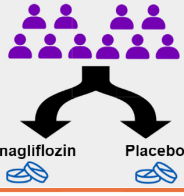
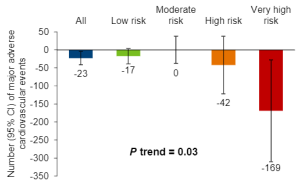
Risk Reductions in Cardiovascular and Kidney Outcomes With Canagliflozin Across KDIGO Risk Categories

Design	Population	Results
CANVAS Program Double-blind, placebo-controlled randomized trial	10,142 people with T2DM and eGFR ≥ 30 mL/min/1.73 m^2 at high cardiovascular risk	Major adverse cardiovascular events prevented per 1,000 patients treated over 5 years

667 centers
30 countries



KDIGO Risk Classification



CONCLUSION: Absolute risk reductions for cardiovascular disease with canagliflozin are likely greater for individuals at higher KDIGO risk.

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