Canagliflozin for Primary and Secondary Prevention of Cardiovascular Events

Results From the CANVAS Program (Canagliflozin Cardiovascular Assessment Study)

Editorial, see p 335

BACKGROUND: Canagliflozin is a sodium glucose cotransporter 2 inhibitor that significantly reduces the composite of cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke in patients with type 2 diabetes mellitus and elevated cardiovascular risk. The comparative effects among participants with and without a history of cardiovascular disease (secondary versus primary prevention) were prespecified for evaluation.

METHODS: The CANVAS Program (Canagliflozin Cardiovascular Assessment Study) randomly assigned 10 142 participants with type 2 diabetes mellitus to canagliflozin or placebo. The primary prevention cohort comprised individuals ≥50 years of age with ≥2 risk factors for cardiovascular events but with no prior cardiovascular event, and the secondary prevention cohort comprised individuals ≥30 years of age with a prior cardiovascular event. The primary end point was a composite of cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke. Secondary outcomes included heart failure hospitalization and a renal composite (40% reduction in estimated glomerular filtration rate, renal replacement therapy, or renal death).

RESULTS: Primary prevention participants (N=3486; 34%) were younger (63 versus 64 years of age), were more often female (45% versus 31%), and had a longer duration of diabetes mellitus (14 versus 13 years) compared with secondary prevention participants (N=6656; 66%). The primary end point event rate was higher in the secondary prevention group compared with the primary prevention group (36.9 versus 15.7/1000 patient-years, *P*<0.001). In the total cohort, the primary end point was reduced with canagliflozin compared with placebo (26.9 versus 31.5/1000 patient-years; hazard ratio [HR], 0.86; 95% confidence interval [CI], 0.75–0.97; *P*<0.001 for noninferiority, *P*=0.02 for superiority) with no statistical evidence of heterogeneity (interaction *P* value=0.18) between the primary (HR, 0.98; 95% CI, 0.74–1.30) and secondary prevention (HR, 0.82; 95% CI, 0.72–0.95) cohorts. Renal outcomes (HR, 0.59; 95% CI, 0.44–0.79 versus HR, 0.63; 95% CI, 0.39–1.02; interaction *P* value=0.73) and heart failure hospitalization (HR, 0.68; 95% CI, 0.51–0.90 versus HR, 0.64; 95% CI, 0.35–1.15; interaction *P* value=0.91) were similarly reduced in the secondary and primary prevention cohorts, respectively. Lower extremity amputations were similarly increased in the secondary and primary prevention cohorts (HR, 2.07; 95% CI, 1.43–3.00 versus HR, 1.52; 95% CI, 0.70–3.29; interaction *P* value=0.63).

CONCLUSIONS: Patients with type 2 diabetes mellitus and prior cardiovascular events had higher rates of cardiovascular outcomes compared with the primary prevention patients. Canagliflozin reduced cardiovascular and renal outcomes with no statistical evidence of heterogeneity of the treatment effect across the primary and secondary prevention groups. Additional studies will provide further insights into the effects of canagliflozin in these patient populations.

CLINICAL TRIAL REGISTRATION: URL: https://www.clinicaltrials.gov. Unique identifiers: NCT01032629 and NCT01989754.

Kenneth W. Mahaffey, MD
Bruce Neal, MB, ChB, PhD
Vlado Perkovic, MBBS, PhD
Dick de Zeeuw, MD, PhD
Greg Fulcher, MD
Ngozi Erondu, MD, PhD
Wayne Shaw, DSL
Elisa Fabbrini, MD, PhD
Tao Sun, PhD
Qiang Li, MBiostat, BPH, AStat
Mehul Desai, MD
David R. Matthews, DPhil, BM, BCh
On behalf of the CANVAS Program Collaborative Group

Correspondence to: Kenneth W. Mahaffey, MD, Department of Medicine, Stanford Center for Clinical Research, Stanford University School of Medicine, 300 Pasteur Dr, Grant S-102, Stanford, CA 94305. E-mail kenneth.mahaffey@stanford.edu

Sources of Funding, see page 333

Key Words: canagliflozin ■ clinical trial ■ diabetes mellitus ■ primary prevention ■ secondary prevention

Clinical Perspective

What Is New?

- Canagliflozin reduces cardiovascular and renal outcomes in patients with type 2 diabetes mellitus.
- No statistical evidence of heterogeneity was observed for the effects of canagliflozin on cardiovascular and renal outcomes in participants with prior cardiovascular events (secondary prevention) and without prior cardiovascular events but at elevated risk (primary prevention), although the power to detect differences was limited.
- Lower extremity amputations were uncommon but increased with canagliflozin without statistical evidence of heterogeneity between the secondary and primary prevention cohorts.

What Are the Clinical Implications?

- Patients with type 2 diabetes mellitus are at high risk for cardiovascular and renal outcomes.
- Canagliflozin should be considered to manage diabetes mellitus in patients at high risk for cardiovascular events to reduce cardiovascular and renal outcomes.
- Further study of canagliflozin in patients with type 2 diabetes mellitus without prior cardiac events is needed to better define the benefits on cardiovascular death, myocardial infarction, or stroke outcomes.
- Caution should be used in patients at risk for amputations.

Patients with type 2 diabetes mellitus suffer substantial morbidity and mortality from cardiovascular and renal disease.[1,2] Current drug therapies and lifestyle interventions are not adequate, with elevated relative and absolute risks of serious disease outcomes observed for both primary and secondary prevention cohorts. Although the largest absolute benefits of interventions for individual patients are achieved among those with established disease (secondary prevention), the large number of patients with diabetes mellitus without overt cardiovascular disease (primary prevention) makes knowledge about the effects of therapies on first events an additional priority.

The CANVAS Program (Canagliflozin Cardiovascular Assessment Study) was designed to assess the cardiovascular safety and efficacy of canagliflozin in a broad range of patients with type 2 diabetes mellitus.[3–6] The main results demonstrated that canagliflozin reduced the relative risk of cardiovascular death, nonfatal myocardial infarction (MI), or nonfatal stroke by 14% (P=0.02 for superiority) compared with placebo.[6] In addition, hospitalized heart failure and serious declines in renal function were reduced by 33% and 40%, respectively.[6] An unanticipated ≈2-fold increase in the risk of amputation was also observed.

By design, the CANVAS Program enrolled patients with and without prior cardiovascular disease to provide insight into the effects of canagliflozin in the primary and secondary prevention settings. In the analyses presented here, the efficacy and safety of canagliflozin are described separately for the primary and secondary prevention cohorts enrolled in the CANVAS Program.

METHODS

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 indication studied have been approved by regulators in the United States and European Union and the study has been completed for 18 months. The trial protocols and statistical analysis plans were published along with the primary CANVAS Program article.[6]

The design of the CANVAS Program has been published.[3–6] In brief, the CANVAS Program was a double-blind comparison of the effects of canagliflozin versus placebo made by combining data from 2 large-scale trials. The CANVAS Program was sponsored by Janssen Research & Development, LLC, and was conducted as a partnership between Janssen Research & Development, LLC, an academic Steering Committee (Appendix in the online-only Data Supplement), and an Academic Research Organization, George Clinical. The first draft of this article was written by the first author, with all coauthors contributing comments and approving the final draft for submission. The authors had access to all the data and ensured the accuracy of the analyses. All participants provided informed consent, and ethics approval was obtained for every center.

Participants

The criteria for inclusion and exclusion have been previously published.[3–6] Participants were men and women with type 2 diabetes mellitus (glycohemoglobin ≥7.0% and ≤10.5%) who were either ≥30 years of age with a history of symptomatic atherosclerotic cardiovascular events defined as stroke, MI, hospitalization for unstable angina, coronary artery bypass grafting, percutaneous coronary intervention, peripheral revascularization (surgical or percutaneous), and symptomatic with documented hemodynamically significant carotid or peripheral vascular disease or amputation secondary to vascular disease (secondary prevention cohort); or ≥50 years of age with no prior cardiovascular events but with ≥2 of the following cardiovascular risk factors: duration of diabetes mellitus ≥10 years, systolic blood pressure >140 mm Hg on ≥1 antihypertensive agents, current smoker, microalbuminuria or macroalbuminuria, or high-density lipoprotein cholesterol <1 mmol/L (primary prevention cohort). The primary and secondary prevention participants were categorized based on a review of their medical histories.

Randomized Treatment

Randomization was performed through a central web-based system and used a computer-generated randomization schedule. Participants were assigned to canagliflozin or placebo, and

Circulation. 2018;137:323–334. DOI: 10.1161/CIRCULATIONAHA.117.032038

use of other background therapy for glycemic management and other risk factor control was according to best practice instituted in line with local guidelines. By design, the secondary prevention cohort was to be ≈70% (minimum of 60%) of all patients.

Follow-Up

Follow-up after enrollment was scheduled quarterly for 1 year and then every 6 months until the end of the study. Every follow-up included inquiry about primary and secondary outcome events and serious adverse events. Serum creatinine measurement with estimated glomerular filtration rate was performed at least every 26 weeks.

Outcomes

The efficacy outcomes for these analyses were the composite of cardiovascular mortality, nonfatal MI, or nonfatal stroke; the individual components of the composite; hospitalization for heart failure; and all-cause mortality. Effects on the kidney were assessed using a composite renal outcome comprising a 40% reduction in estimated glomerular filtration rate, requirement for renal replacement therapy, or renal death. The safety events of interest were adverse events attributable to genital infection, urinary tract infection, volume depletion events, hypoglycemia, diabetic ketoacidosis, acute pancreatitis, renal adverse events, thromboembolism, cancer, fracture, and lower extremity amputation.

All major cardiovascular events, renal outcomes, and deaths as well as selected safety outcomes (diabetic ketoacidosis, acute pancreatitis, and fracture) were assessed by Endpoint Adjudication Committees (Appendix in the online-only Data Supplement) blinded to therapy. The definitions that were used for the clinical events have been published.[3–6]

Statistical Analysis

Evaluation of outcomes in the primary and secondary prevention participants was prespecified. Rates of cardiovascular disease, kidney disease, death outcomes, and selected adverse events were estimated for active and placebo groups combined. All analyses of the effects of canagliflozin compared with placebo on cardiovascular and renal outcomes were based on the intention-to-treat principle using all follow-up time (on or off study treatment) for all randomized participants. Safety outcomes were analyzed using an on-treatment approach (based on patient time and events accrued while on study drug or within 30 days of study drug discontinuation) except for diabetic ketoacidosis, fracture, cancer, and amputation outcomes, which were assessed using all follow-up time (on or off study treatment).

Hazard ratios (HRs) and 95% confidence intervals (CIs) were estimated for participants assigned to canagliflozin versus participants assigned to placebo separately for the primary and secondary prevention cohorts. Cardiovascular, death, and safety outcomes were analyzed using a stratified Cox proportional hazards regression model, with treatment as the exploratory variable and study as the stratification factor. Renal outcomes were analyzed using a stratified Cox proportional hazards model with treatment and the stage of baseline chronic kidney disease measured by estimated glomerular filtration rate (<60 or ≥60 mL/min/1.73 m^2) as the exploratory variables and study as the stratification factor. Homogeneity of treatment effects across the primary and secondary prevention groups was examined via a test for the treatment-by-prevention interaction by adding this term and the prevention cohort as covariates to the respective Cox proportional hazards model. The risk differences were calculated by subtracting the incidence rate (per 1000 patient-years) with placebo from the incidence rate with canagliflozin and multiplying by 5 years. Similarly, the CI was estimated by multiplying the lower and upper CI values by 5 years. Analyses were undertaken using SAS version 9.2 and SAS Enterprise Guide version 7.11. Analyses were performed by statisticians at Janssen with verification by a statistician at George Clinical.

RESULTS

Overall, 10 142 participants at 667 centers in 30 countries were enrolled in the CANVAS Program.[6] Mean follow-up was 188 weeks. Discontinuation of the study drug was similar with placebo and canagliflozin in the overall population (30% versus 29%) and in the secondary prevention (29% versus 30%) and primary prevention cohorts (31% versus 28%). Vital status was available for 99.6% of patients.[6]

Primary prevention participants (N = 3486; 34%) were younger (63 versus 64 years), were more often female (45% versus 31%), and had longer duration of diabetes mellitus (14 versus 13 years) compared with secondary prevention participants (N = 6656; 66%). Participants in the secondary prevention group had higher use of common cardiac medications, including statins, β-blockers, and antiplatelet agents, as well as insulin, but lower use of oral antihyperglycemic agents (Table 1). Within each of the primary and secondary prevention cohorts, participant characteristics were all well balanced across canagliflozin and placebo groups (Table 1).

Risks of Cardiovascular, Renal, Death, and Safety Outcomes in the Primary and Secondary Prevention Cohorts

Secondary prevention participants had higher rates of the primary cardiovascular composite outcome compared with the primary prevention participants (HR, 2.36; 95% CI, 2.03–2.74; P<0.001) (Table 2). There were also more hospitalizations for heart failure (HR, 2.64; 95% CI, 1.90–3.65), more deaths (HR, 1.86; 95% CI, 1.57–2.22), and more of the composite renal outcome (HR, 1.56; 95% CI, 1.18–2.06) in the secondary prevention compared with the primary prevention group. Rates of safety outcomes were not different except for lower extremity amputation (HR, 2.85; 95% CI, 1.95–4.16) and volume depletion events (HR, 1.42; 95% CI, 1.10–1.83), which were more frequent among the secondary prevention participants, and urinary tract infection, which was less common in the secondary prevention participants (HR, 0.81; 95% CI, 0.67–0.97).

Table 1. Baseline Characteristics of Primary and Secondary Prevention Cohorts in the CANVAS Program

Variable	Secondary Prevention			Primary Prevention			*P* Value (Secondary vs. Primary)
	Canagliflozin (n=3756)	Placebo (n=2900)	Total* (n=6656)	Canagliflozin (n=2039)	Placebo (n=1447)	Total (n=3486)	
Study, n (%)							<0.001†
CANVAS	1703 (45.3)	846 (29.2)	2549 (38.3)	1185 (58.1)	596 (41.2)	1781 (51.1)	
CANVAS-R	2053 (54.7)	2054 (70.8)	4107 (61.7)	854 (41.9)	851 (58.8)	1705 (48.9)	
Age, y, mean (SD)	63.5 (8.8)	63.8 (8.6)	63.6 (8.7)	62.7 (7.3)	62.8 (7.3)	62.7 (7.3)	<0.001‡
Female, n (%)	1121 (29.8)	935 (32.2)	2056 (30.9)	915 (44.9)	662 (45.7)	1577 (45.2)	<0.001†
Race, n (%)							<0.001†
White	2945 (78.4)	2307 (79.6)	5252 (78.9)	1563 (76.7)	1129 (78.0)	2692 (77.2)	
Asian	467 (12.4)	313 (10.8)	780 (11.7)	310 (15.2)	194 (13.4)	504 (14.5)	
Black or African American	114 (3.0)	104 (3.6)	218 (3.3)	62 (3.0)	56 (3.9)	118 (3.4)	
Other§	230 (6.1)	176 (6.1)	406 (6.1)	104 (5.1)	68 (4.7)	172 (4.9)	
Region, n (%)							<0.001†
North America	903 (24.0)	655 (22.6)	1558 (23.4)	522 (25.6)	350 (24.2)	872 (25.0)	
Central/South America	360 (9.6)	368 (12.7)	728 (10.9)	177 (8.7)	116 (8.0)	293 (8.4)	
Europe	1309 (34.9)	1026 (35.4)	2335 (35.1)	734 (36.0)	540 (37.3)	1274 (36.5)	
Rest of world	1184 (31.5)	851 (29.3)	2035 (30.6)	606 (29.7)	441 (30.5)	1047 (30.0)	
Current smoker, n (%)	524 (14.0)	417 (14.4)	941 (14.1)	496 (24.3)	369 (25.5)	865 (24.8)	<0.001†
History of hypertension, n (%)	3332 (88.7)	2612 (90.1)	5944 (89.3)	1856 (91.0)	1325 (91.6)	3181 (91.3)	0.002†
History of heart failure, n (%)	658 (17.5)	516 (17.8)	1174 (17.6)	145 (7.1)	142 (9.8)	287 (8.2)	<0.001†
Duration of diabetes mellitus, y, mean (SD)	13.0 (8.3)	13.4 (8.4)	13.2 (8.3)	14.3 (6.5)	14.2 (6.5)	14.3 (6.5)	<0.001‡
Drug therapy, n (%)							
Insulin	1927 (51.3)	1488 (51.3)	3415 (51.3)	963 (47.2)	717 (49.6)	1680 (48.2)	0.003†
Sulfonylurea	1542 (41.1)	1185 (40.9)	2727 (41.0)	986 (48.4)	648 (44.8)	1634 (46.9)	<0.001†
Metformin	2767 (73.7)	2185 (75.3)	4952 (74.4)	1680 (82.4)	1193 (82.4)	2873 (82.4)	<0.001†
GLP-1 receptor agonist	136 (3.6)	110 (3.8)	246 (3.7)	86 (4.2)	75 (5.2)	161 (4.6)	0.02†
DPP-4 inhibitor	413 (11.0)	350 (12.1)	763 (11.5)	284 (13.9)	214 (14.8)	498 (14.3)	<0.001†
Statin	3046 (81.1)	2352 (81.1)	5398 (81.1)	1284 (63.0)	918 (63.4)	2202 (63.2)	<0.001†
Antithrombotic‖	3264 (86.9)	2498 (86.1)	5762 (86.6)	972 (47.7)	737 (50.9)	1709 (49.0)	<0.001†
RAAS inhibitor	2997 (79.8)	2312 (79.7)	5309 (79.8)	1648 (80.8)	1159 (80.1)	2807 (80.5)	0.36†
β-blocker	2387 (63.6)	1887 (65.1)	4274 (64.2)	652 (32.0)	495 (34.2)	1147 (32.9)	<0.001†
Diuretics	1647 (43.8)	1296 (44.7)	2943 (44.2)	889 (43.6)	658 (45.5)	1547 (44.4)	0.88†
Calcium channel blocker	1241 (33.0)	1018 (35.1)	2259 (33.9)	689 (33.8)	495 (34.2)	1184 (34.0)	0.98†
Microvascular disease history, n (%)							
Retinopathy	808 (21.5)	642 (22.1)	1450 (21.8)	395 (19.4)	284 (19.6)	679 (19.5)	0.007†
Nephropathy	632 (16.8)	495 (17.1)	1127 (16.9)	362 (17.8)	285 (19.7)	647 (18.6)	0.04†
Neuropathy	1234 (32.9)	898 (31.0)	2132 (32.0)	553 (27.1)	425 (29.4)	978 (28.1)	<0.001†
Symptomatic atherosclerotic cardiovascular events, n (%)¶							<0.001†
Myocardial infarction	1644 (43.8)	1294 (44.6)	2938 (44.1)	16 (0.8)	2 (0.1)	18 (0.5)	
Hospitalization for unstable angina	402 (10.7)	325 (11.2)	727 (10.9)	0	0	0	
Coronary revascularization	1997 (53.2)	1564 (53.9)	3561 (53.5)	2 (0.1)	1 (0.1)	3 (0.1)	
PCI	1443 (38.4)	1113 (38.4)	2556 (38.4)	2 (0.1)	0	2 (0.1)	
CABG	774 (20.6)	652 (22.5)	1426 (21.4)	0	1 (0.1)	1 (<0.1)	
Unspecified	24 (0.6)	14 (0.5)	38 (0.6)	0	0	0	

(*Continued*)

Table 1. Continued

Variable	Secondary Prevention			Primary Prevention			*P* Value (Secondary vs. Primary)
	Canagliflozin (n=3756)	Placebo (n=2900)	Total* (n=6656)	Canagliflozin (n=2039)	Placebo (n=1447)	Total (n=3486)	
Stroke	733 (19.5)	543 (18.7)	1276 (19.2)	6 (0.3)	9 (0.6)	15 (0.4)	
Carotid revascularization	47 (1.3)	32 (1.1)	79 (1.2)	0	0	0	
Surgical	42 (1.1)	21 (0.7)	63 (0.9)	0	0	0	
Percutaneous	7 (0.2)	12 (0.4)	19 (0.3)	0	0	0	
Unspecified	1 (<0.1)	0	1 (<0.1)	0	0	0	
Peripheral revascularization (surgical or percutaneous)	271 (7.2)	251 (8.7)	522 (7.8)	3 (0.1)	0	3 (0.1)	
Amputation	119 (3.2)	99 (3.4)	218 (3.3)	17 (0.8)	3 (0.2)	20 (0.6)	
Body mass index, kg/m^2, mean (SD)	31.8 (5.8)	31.7 (5.8)	31.8 (5.8)	32.2 (6.2)	32.5 (6.3)	32.3 (6.2)	<0.001‡
Systolic BP, mm Hg, mean (SD)	134.6 (16.0)	135.5 (16.3)	135.0 (16.1)	139.9 (14.8)	139.8 (14.2)	139.8 (14.5)	<0.001‡
Diastolic BP, mm Hg, mean (SD)	76.7 (9.6)	76.9 (9.7)	76.8 (9.6)	79.4 (9.5)	79.6 (9.5)	79.5 (9.5)	<0.001‡
Glycohemoglobin, %, mean (SD)	8.2 (0.9)	8.2 (0.9)	8.2 (0.9)	8.3 (1.0)	8.3 (0.9)	8.3 (0.9)	0.30‡
Total cholesterol, mmol/L, mean (SD)	4.3 (1.2)	4.3 (1.2)	4.3 (1.2)	4.5 (1.1)	4.5 (1.1)	4.5 (1.1)	<0.001‡
Triglycerides, mmol/L, mean (SD)	2.0 (1.4)	2.0 (1.6)	2.0 (1.5)	2.0 (1.2)	2.0 (1.5)	2.0 (1.3)	0.29‡
HDL cholesterol, mmol/L, mean (SD)	1.2 (0.3)	1.2 (0.3)	1.2 (0.3)	1.2 (0.3)	1.2 (0.3)	1.2 (0.3)	<0.001‡
LDL cholesterol, mmol/L, mean (SD)	2.2 (0.9)	2.3 (0.9)	2.2 (0.9)	2.4 (0.9)	2.4 (0.9)	2.4 (0.9)	<0.001‡
LDL/HDL cholesterol ratio, mean (SD)	2.0 (1.0)	2.0 (0.9)	2.0 (0.9)	2.1 (0.9)	2.1 (0.9)	2.1 (0.9)	0.001‡
eGFR, mL/min/1.73 m^2, mean (SD)	75.6 (20.5)	75.3 (21.0)	75.5 (20.7)	78.6 (19.7)	78.0 (20.5)	78.3 (20.0)	<0.001‡
Albumin-creatinine ratio, mg/g, median (IQR)#	12.4 (6.6–42.3)	12.1 (6.6–43.4)	12.2 (6.6–42.4)	12.3 (6.8–40.0)	12.4 (6.6–45.2)	12.3 (6.7–40.7)	0.81**
Normoalbuminuria, n (%)	2592 (69.7)	2008 (69.9)	4600 (69.8)	1420 (70.3)	987 (69.4)	2407 (70.0)	0.67††
Microalbuminuria, n (%)	863 (23.2)	610 (21.2)	1473 (22.3)	459 (22.7)	334 (23.5)	793 (23.0)	
Macroalbuminuria, n (%)	266 (7.1)	253 (8.7)	519 (7.9)	140 (6.9)	101 (7.1)	241 (7.0)	

ANOVA indicates analysis of variance; BP, blood pressure; CABG, coronary artery bypass grafting; CANVAS, Canagliflozin Cardiovascular Assessment Study; CANVAS-R, Canagliflozin Cardiovascular Assessment Study–Renal; DPP-4, dipeptidyl peptidase-4; eGFR, estimated glomerular filtration rate; GLP-1, glucagon-like peptide-1; HDL, high-density lipoprotein; IQR, interquartile range; ITT, intention-to-treat; LDL, low-density lipoprotein; PCI, percutaneous coronary intervention; RAAS, renin-angiotensin-aldosterone system; and SD, standard deviation.

*One participant was randomized at 2 different sites, and only the first randomization is included in the ITT analysis set.

†*P* value corresponds to Generalized Cochran-Mantel-Haenszel test for no general association.

‡*P* value corresponds to the test for no difference between primary and secondary cohorts from ANOVA model with prevention cohort as a factor.

§Includes American Indian or Alaska Native, Native Hawaiian or other Pacific Islander, multiple, other, and unknown.

‖Includes antiplatelets and anticoagulants.

¶Some participants had ≥1 type of atherosclerotic disease.

#Values for albuminuria categories calculated based on patients with available baseline albuminuria data: N of 3721 for canagliflozin, 2871 for placebo, and 6592 for the total population in the secondary prevention cohort and N of 2019 for canagliflozin, 1422 for placebo, and 3441 for the total population in the primary prevention cohort.

******P* value corresponds to Wilcoxon rank sum test of equal medians.

††*P* value corresponds to Van Elteren test for no association.

Effects of Canagliflozin on Cardiovascular and Renal Outcomes in Primary and Secondary Prevention Cohorts

The primary end point was reduced with canagliflozin compared with placebo (26.9 versus 31.5/1000 patient-years; HR, 0.86; 95% CI, 0.75–0.97; *P*<0.001 for non-inferiority, *P*=0.02 for superiority) in the total cohort, with no statistical evidence of heterogeneity (*P*=0.18) between the primary (HR, 0.98; 95% CI, 0.74–1.30) and secondary (HR, 0.82; 95% CI, 0.72–0.95) prevention groups (Figure 1). Likewise, no statistical evidence of heterogeneity was found between the primary and secondary prevention cohorts for hospitalization for heart failure, all-cause mortality, and the composite renal outcome (all *P* values for homogeneity ≥0.10) (Figure 1). Kaplan-Meier curves for the composite cardiovascular outcome, cardiovascular death, hospitalization for heart failure, all-cause mortality, and the composite renal outcome are shown in Figure 2.

Effects of Canagliflozin on Safety Outcomes in Primary and Secondary Prevention Cohorts

The rates of adverse events, including genital infections, urinary tract infections, fractures, diabetic ketoacidosis, and acute pancreatitis, were not statistically different be-

Table 2. Rates of Events for Cardiovascular Disease, Kidney Disease, Fatal Outcomes, and Safety Events for the Primary and Secondary Prevention Cohorts in the CANVAS Program in the Active and Control Groups Combined

Variable	Number of Participants	Event Rate (95% CI) per 1000 Patient-Years		Hazard Ratio (95% CI)	*P* Value
		Secondary Prevention (n=6656)	Primary Prevention (n=3486)		
CV death, nonfatal MI, or nonfatal stroke	1011	36.9 (34.4–39.6)	15.7 (13.7–18.0)	2.36 (2.03–2.74)	<0.001
CV death	453	15.6 (14.0–17.3)	6.4 (5.1–7.8)	2.51 (1.99–3.16)	<0.001
Nonfatal MI	374	13.8 (12.3–15.5)	5.1 (4.0–6.4)	2.72 (2.09–3.53)	<0.001
Nonfatal stroke	274	9.4 (8.2–10.8)	4.7 (3.6–6.0)	1.93 (1.46–2.56)	<0.001
Hospitalization for any cause	3486	149.9 (144.1–155.9)	85.1 (79.9–90.6)	1.68 (1.56–1.81)	<0.001
Hospitalization for heart failure	243	8.9 (7.7–10.2)	3.2 (2.4–4.3)	2.64 (1.90–3.65)	<0.001
CV death or hospitalization for heart failure	652	23.5 (21.5–25.5)	9.2 (7.7–11.0)	2.55 (2.10–3.10)	<0.001
All-cause mortality	681	21.9 (20.0–23.9)	12.0 (10.3–14.0)	1.86 (1.57–2.22)	<0.001
Progression of albuminuria	2455	111.9 (106.5–117.5)	91.1 (85.0–97.5)	1.19 (1.09–1.29)	<0.001
40% reduction in eGFR, renal replacement therapy, or renal death	249	8.0 (6.9–9.3)	5.1 (3.9–6.4)	1.56 (1.18–2.06)	0.002
Safety outcomes					
Male genital infections*	497	26.5 (23.7–29.6)	29.0 (24.9–33.7)	0.87 (0.72–1.05)	0.14
Female genital infections†	196	59.6 (48.0–73.2)	57.1 (46.7–69.2)	1.02 (0.77–1.35)	0.89
Urinary tract infections†	443	38.0 (33.3–43.1)	47.1 (40.9–54.0)	0.80 (0.67–0.97)	0.02
Lower extremity amputation	187	6.9 (5.9–8.1)	2.4 (1.6–3.3)	2.85 (1.95–4.16)	<0.001
All fracture	496	14.1 (12.6–15.8)	14.0 (12.1–16.1)	1.03 (0.86–1.24)	0.76
Low-trauma fracture	379	10.8 (9.5–12.3)	10.4 (8.7–12.3)	1.06 (0.86–1.31)	0.56
Diabetic ketoacidosis	18	0.4 (0.2–0.7)	0.7 (0.3–1.3)	0.48 (0.19–1.22)	0.12
Acute pancreatitis	13	0.5 (0.2–0.9)	0.4 (0.1–0.9)	1.44 (0.44–4.72)	0.54
Volume depletion events†	266	28.1 (24.1–32.5)	19.6 (15.8–24.2)	1.42 (1.10–1.83)	0.007
Hypoglycemia†	551	57.4 (51.4–63.9)	50.7 (44.2–58.0)	1.12 (0.94–1.33)	0.20
Renal adverse events†	214	21.5 (18.0–25.4)	16.8 (13.2–20.9)	1.28 (0.97–1.69)	0.08
Thromboembolism	52	1.5 (1.0–2.2)	2.1 (1.4–3.1)	0.74 (0.43–1.28)	0.28
Renal cell cancer	17	0.5 (0.3–0.9)	0.4 (0.1–0.8)	1.70 (0.60–4.83)	0.32
Bladder cancer	38	1.0 (0.6–1.5)	1.1 (0.6–1.8)	0.94 (0.49–1.81)	0.85
Breast cancer	37	2.6 (1.5–4.2)	3.2 (2.0–5.0)	0.82 (0.43–1.58)	0.55

CANVAS indicates Canagliflozin Cardiovascular Assessment Study; CANVAS-R, Canagliflozin Cardiovascular Assessment Study–Renal; CI, confidence interval; CV, cardiovascular; eGFR, estimated glomerular filtration rate; and MI, myocardial infarction.

*Includes balanitis and phimosis.

†For these adverse events, the annualized event rates are reported with data from CANVAS alone through January 7, 2014, because after this time, only serious adverse events or adverse events leading to discontinuation were collected. In CANVAS-R, only serious adverse events or adverse events leading to discontinuation were collected. Owing to the differences between the 2 trials in methods of collection of the data, an integrated analysis of these adverse events is not possible.

tween treatment groups in the primary and secondary prevention participants (Figure 3). The adverse event profile for canagliflozin compared with placebo was consistent in the primary and secondary prevention participants (all interaction *P* values ≥0.07).

Risk Differences for Cardiovascular, Renal, and Amputation Outcomes in Primary and Secondary Prevention Participants

Figure 4 shows the event rates and risk differences for the primary composite (cardiovascular death, nonfatal MI, or nonfatal stroke), hospitalization for heart failure, renal composite outcome, and amputation for canagliflozin compared with placebo in the overall study, the secondary prevention participants, and the primary prevention participants.

DISCUSSION

The CANVAS Program included patients with established cardiovascular disease and those at risk for cardiovascular disease. Overall, 34% of participants were included in the primary prevention group. Secondary

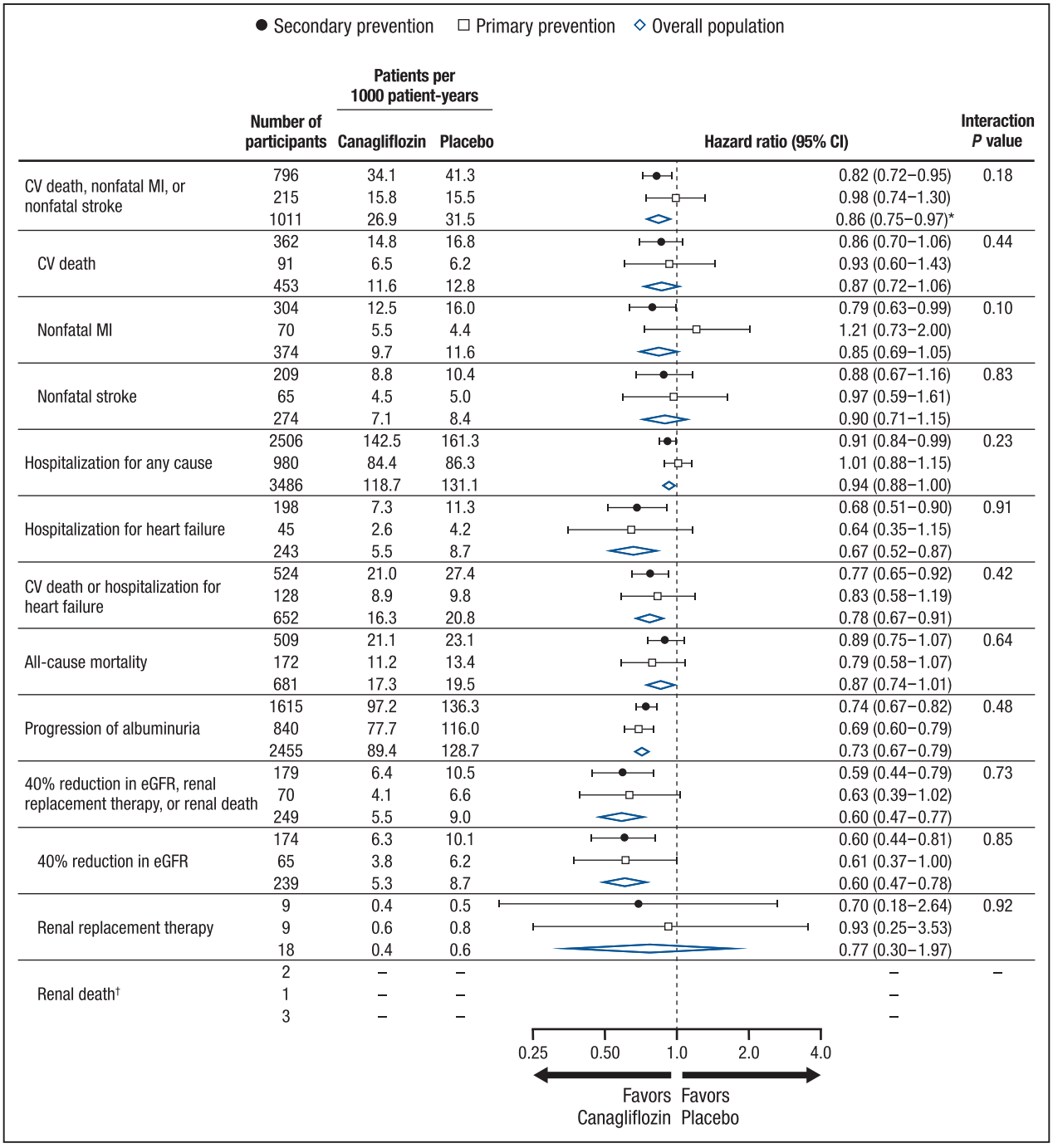

Figure 1. Comparative effects of canagliflozin and placebo on cardiovascular, kidney, and mortality outcomes in the total population and the primary and secondary prevention cohorts in the CANVAS Program.
Hazard ratios and 95% CIs were estimated using Cox regression models, with stratification by trial for all canagliflozin groups combined vs. placebo. CANVAS indicates Canagliflozin Cardiovascular Assessment Study; CI, confidence interval; CV, cardiovascular; eGFR, estimated glomerular filtration rate; HR, hazard ratio; and MI, myocardial infarction. *P<0.001 for noninferiority and P=0.02 for superiority for the primary outcome of CV death, nonfatal MI, or nonfatal stroke in the overall population. †Incidence rates and HRs not calculated because of the small number of events.

prevention participants had higher rates of cardiovascular and renal outcomes compared with the primary prevention participants. Canagliflozin reduced the composite risk of cardiovascular death, nonfatal MI, or nonfatal stroke compared with placebo, and there was no statistical evidence of heterogeneity in the proportional treatment effect in the primary prevention and secondary prevention participants. Canagliflozin was also associated with better hospitalization for heart failure and renal outcomes, with a similar proportional

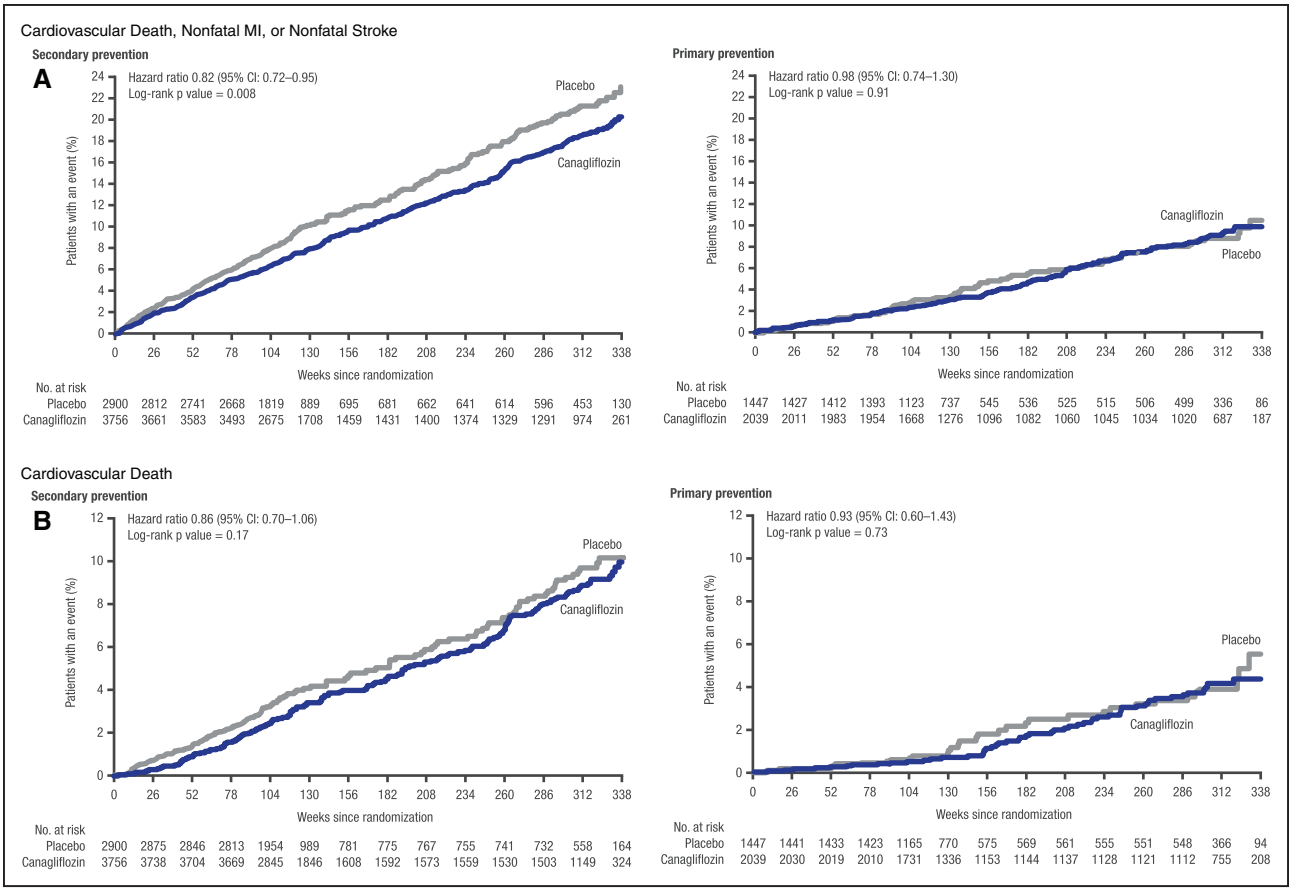

Figure 2. Effects of canagliflozin and placebo on cardiovascular and renal outcomes by primary and secondary prevention cohorts in the CANVAS Program.

CANVAS indicates Canagliflozin Cardiovascular Assessment Study; CI, confidence interval; MI, myocardial infarction; and eGFR, estimated glomerular filtration rate. (*continued*)

reduction achieved for the primary and secondary prevention participants.

Some large cardiovascular outcome clinical trials in patients with type 2 diabetes mellitus have included primary and secondary prevention cohorts by design using various inclusion and exclusion criteria.[7–11] However, others did not include a primary prevention cohort.[12,13] For the CANVAS Program, the primary prevention cohort included participants ≥50 years of age, whereas other programs typically used 40 or 50 years of age to define the entry criteria. Compared with trials with primary prevention participants,[7–11] the CANVAS Program included a higher proportion in the primary prevention group (≈35% versus ≈15% to 25%). Similar to other programs, cardiovascular event rates were lower in the primary prevention participants, but there was no evidence of heterogeneity in relative treatment effects in the primary and secondary prevention groups by statistical testing. The design and results from the CANVAS Program suggest that a broader group of patients has been studied with canagliflozin compared with other drugs, including an SGLT2 inhibitor.[12]

The absolute reductions in cardiovascular events with canagliflozin were numerically greater in patients in the secondary prevention cohort compared with the primary prevention cohort. The relative reductions in cardiovascular events, however, showed no statistical evidence of heterogeneity between the 2 prevention groups. There appeared to be consistent reductions in hospitalization for heart failure and renal outcomes in the primary and secondary prevention participants, as well as increases in amputations in both groups that were numerically less frequent than the reductions in cardiovascular and renal outcomes. The composite outcome (cardiovascular death, nonfatal MI, nonfatal stroke) was also clearly reduced in the secondary prevention population. Although formal statistical testing did not find evidence of heterogeneity in the results for this outcome in the primary prevention population, more data are required because the interaction testing has limited power based on the size of the subpopulation. The ongoing CREDENCE study (Canagliflozin and Renal Endpoints in Diabetes With Established Nephropathy Clinical Evaluation; ClinicalTrials.org; NCT02065791) will provide more evidence on the effects of canagliflozin on clinical renal

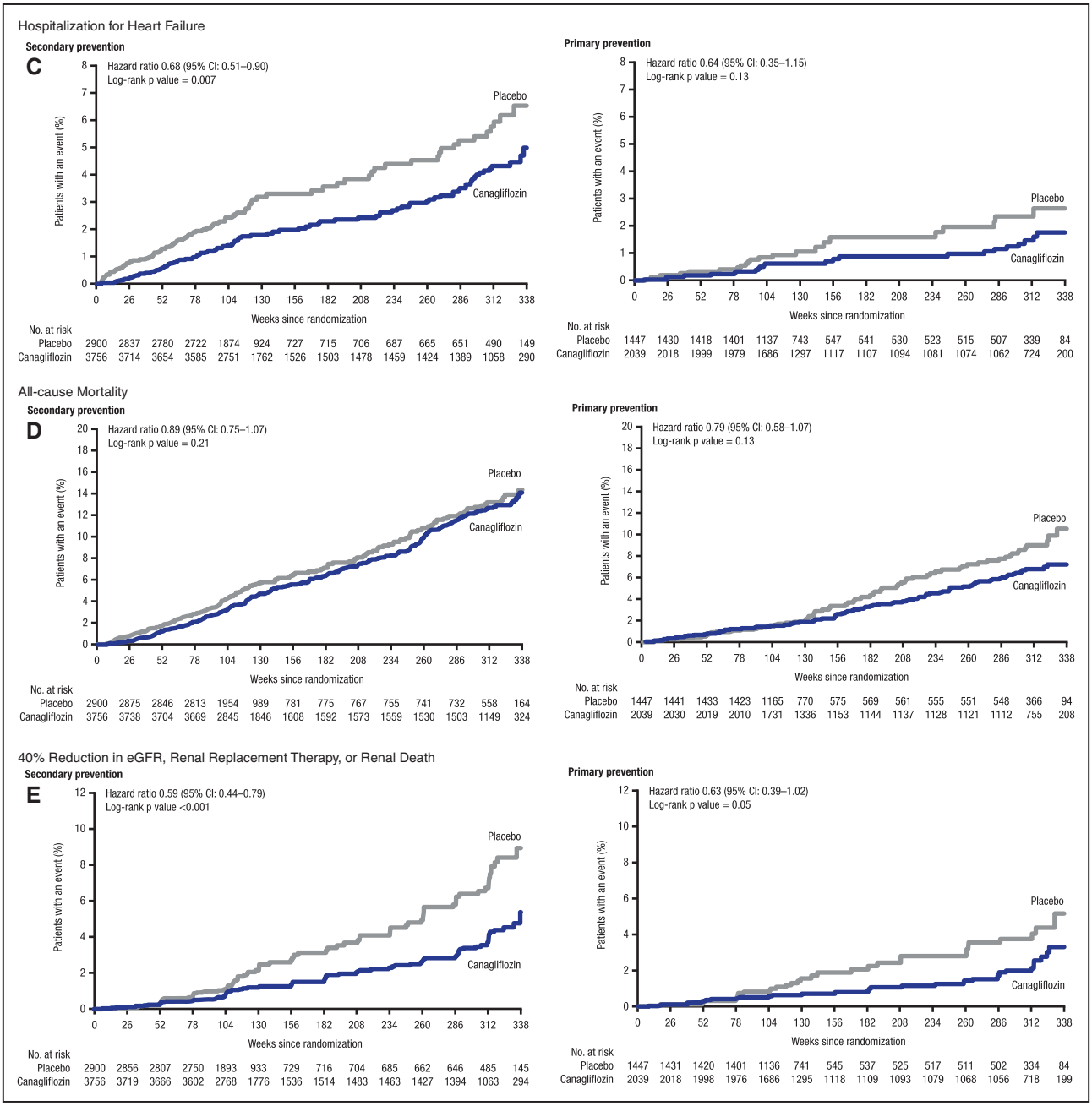

Figure 2 Continued.

outcomes, including end-stage kidney disease and renal and cardiovascular death, whereas the DECLARE (Multicenter Trial to Evaluate the Effect of Dapagliflozin on the Incidence of Cardiovascular Events; ClinicalTrials.org; NCT01730534) will provide additional data regarding the effects of SGLT2 inhibition in primary prevention.

The general safety profile of SGLT2 inhibitors has been well described.[6,14] The rates of common adverse events in the CANVAS Program were generally similar in participants in the primary and secondary prevention groups. Bone fractures have been reported previously with canagliflozin,[6,15] and consistent findings were observed in the primary and secondary prevention participants in the CANVAS Program. The rate of lower extremity amputation was ≈3-fold higher in the secondary prevention group compared with the primary prevention group. A statistically significant 2-fold increase in lower extremity amputation with canagliflozin versus placebo was observed in the secondary prevention group, with a statistically similar result between canagliflozin and placebo in the primary prevention group, although only 33 events were reported in that group. Additional analyses of these findings are ongoing to understand the potential mechanism for amputations with canagliflozin. Until

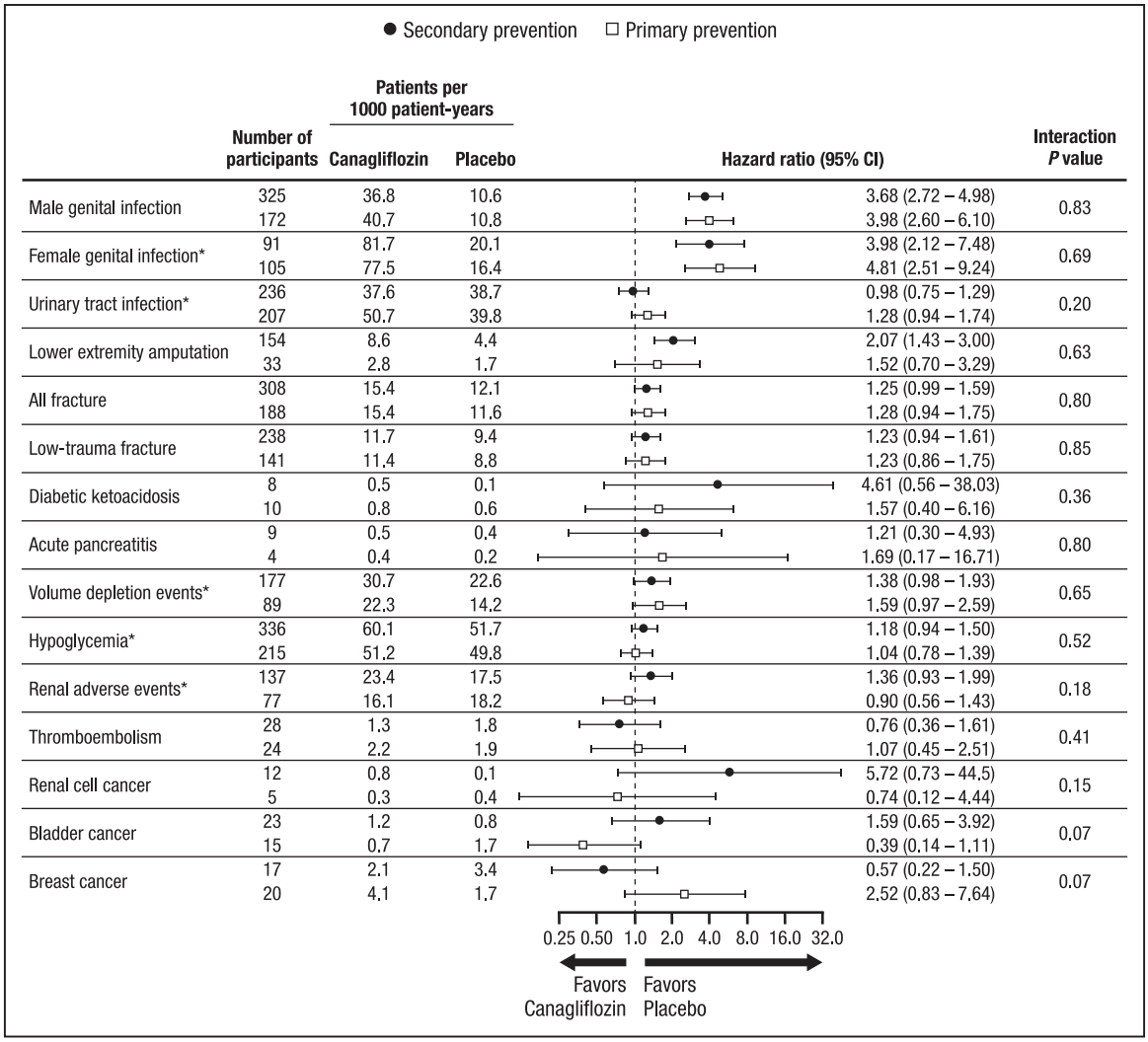

Figure 3. Summary of adverse events in the primary and secondary prevention cohorts in the CANVAS Program. CANVAS indicates Canagliflozin Cardiovascular Assessment Study; CANVAS-R, Canagliflozin Cardiovascular Assessment Study–Renal; and CI, confidence interval. *For these adverse events, the annualized event rates are reported with data from CANVAS alone through January 7, 2014, because after this time, only serious adverse events or adverse events leading to discontinuation were collected. In CANVAS-R, only serious adverse events or adverse events leading to discontinuation were collected. Owing to the differences between the 2 trials in methods of collection of the data, an integrated analysis of these adverse events is not possible.

further information is available, caution should be used in patients at risk for amputations.

The balance of cardiovascular and renal benefits compared with the major safety event of amputations was evaluated by calculating the number of patients with events prevented or caused over 5 years for 1000 treated patients. A favorable profile was observed for the overall study population, with 23 fewer cardiovascular death, nonfatal MI, or nonfatal stroke events; 16 fewer hospitalizations for heart failure; and 18 fewer renal outcomes (40% reduction in estimated glomerular filtration rate, requirement for renal replacement therapy, or renal death) occurring in canagliflozin-treated patients compared with placebo, with an excess of 15 lower extremity amputations (10 toe or metatarsal, 5 above the ankle). As expected, numerically more events were prevented in the higher risk secondary prevention group compared with the primary prevention participants, and in both cohorts the number of excess amputation events was numerically lower than the number of cardiorenal outcomes that were prevented. These data may be helpful to clinicians and patients for shared clinical decisions in the management of diabetes mellitus to reduce cardiovascular and renal outcomes.

Limitations

These analyses have several limitations. The trial was not designed with appropriate statistical power to show definitive treatment differences in the outcomes

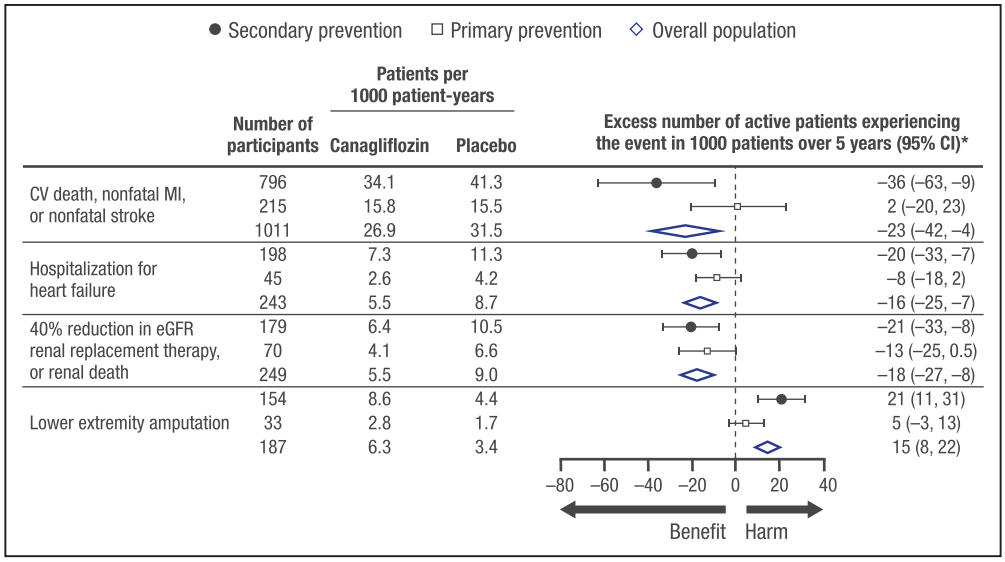

Figure 4. Benefits and risks per 1000 patients over 5 years with canagliflozin vs. placebo in the overall population, secondary prevention cohort, and primary prevention cohort.
CI indicates confidence interval; CV, cardiovascular; eGFR, estimated glomerular filtration rate; and MI, myocardial infarction. *Excess number is relative to the placebo group. If the number is negative, then fewer subjects in the canagliflozin group experienced the event compared with the placebo group.

in primary and secondary prevention participants. The primary prevention cohort was smaller, was lower-risk, and accrued fewer events than the secondary prevention cohort, and therefore the ability to exclude heterogeneity between the primary and secondary prevention cohorts is limited. The primary and secondary prevention participants were categorized based on investigator-reported inclusion and exclusion criteria and were not confirmed. We did not screen patients for subclinical atherosclerotic vascular disease in this large international trial, so patients with asymptomatic cardiovascular disease or clinically silent prior cardiovascular events could have been included in the primary prevention cohort. We followed participants for ≈3.5 years; however, glucose-lowering agents are often used for a much longer duration, well beyond the horizon of this study. Further study with longer follow-up in a primary prevention population could potentially identify more long-term benefits because of greater life expectancy.

Conclusions

In the CANVAS Program, which evaluated patients with type 2 diabetes mellitus and elevated cardiovascular risk, participants with prior cardiovascular events (secondary prevention) compared with those without prior cardiovascular events (primary prevention) had greater absolute rates of cardiovascular, renal, and death outcomes. Canagliflozin reduced cardiovascular and renal outcomes overall, with no statistical evidence of heterogeneity of canagliflozin effects between the primary and secondary prevention participants.

ACKNOWLEDGMENTS

The authors thank all investigators, study teams, and patients for participating in these studies. Medical writing support was provided by Kimberly Dittmar, PhD, of MedErgy.

SOURCES OF FUNDING

The CANVAS Program was supported by Janssen Research & Development, LLC. Medical writing support was funded by Janssen Global Services, LLC. Canagliflozin has been developed by Janssen Research & Development, LLC, in collaboration with Mitsubishi Tanabe Pharma Corp.

DISCLOSURES

Dr Mahaffey's financial disclosures can be viewed at http://med.stanford.edu/profiles/kenneth-mahaffey. Dr Neal reports receiving research support from the Australian National Health and Medical Research Council Principal Research Fellowship and from Janssen, Roche, Servier, and Merck Schering Plough; and serving on advisory boards or involvement in continuing medical education programs for Abbott, Janssen, Novartis, Pfizer, Roche, and Servier, with any consultancy, honoraria, or travel support paid to his institution. Dr Perkovic reports receiving research support from the Australian National Health and Medical Research Council (Senior Research Fellowship and Program Grant); serving on Steering Committees for AbbVie, Boehringer Ingelheim, GlaxoSmithKline, Janssen, Novartis, and Pfizer; and serving on advisory boards or speaking at scientific meetings for AbbVie, Astellas, AstraZeneca, Bayer, Baxter, Bristol-Myers Squibb, Boehringer Ingelheim, Durect, Eli Lilly, Gilead, GlaxoSmithKline, Janssen, Merck, Novartis, Novo Nordisk, Pfizer, Pharmalink, Relypsa, Retrophin, Roche, Sanofi,

Servier, and Vitae. Dr de Zeeuw reports serving on advisory boards or as a speaker for AbbVie, Astellas, Eli Lilly, Fresenius, Janssen, Boehringer Ingelheim, Bayer, and Mitsubishi-Tanabe, with all consultancy honoraria paid to his institution. Dr Fulcher reports receiving research support from Novo Nordisk and serving on advisory boards and as a consultant for Janssen, Novo Nordisk, Boehringer Ingelheim, and Merck Sharp and Dohme. Dr Li reports being a full-time employee of the George Institute for Global Health. Drs Erondu, Shaw, Fabbrini, Sun, and Desai report being full-time employees of Janssen Research & Development, LLC. Dr Matthews reports receiving research support from Janssen; serving on advisory boards and as a consultant for Novo Nordisk, Novartis, Eli Lilly, Sanofi-Aventis, Janssen, and Servier; and giving lectures for Novo Nordisk, Servier, Sanofi-Aventis, Eli Lilly, Novartis, Janssen, Mitsubishi Tanabe, and Aché Laboratories.

AFFILIATIONS

Department of Medicine, Stanford Center for Clinical Research, Stanford University School of Medicine, CA (K.W.M.). George Institute for Global Health, Faculty of Medicine, University of New South Wales, Sydney, Australia (B.N., V.P., Q.L.). Charles Perkins Centre, University of Sydney, Australia (B.N.). Faculty of Medicine, University of New South Wales, Sydney, Australia (B.N.). Imperial College London, UK (B.N.). Royal North Shore Hospital and University of Sydney, Australia (V.P., G.F.). University of Groningen, University Medical Center Groningen, The Netherlands (D.d.Z.). Janssen Research & Development, LLC, Raritan, NJ (N.E., W.S., E.F., T.S., M.D.). Oxford Centre for Diabetes, Endocrinology and Metabolism and Harris Manchester College, University of Oxford, UK (D.R.M.).

FOOTNOTES

Received October 2, 2017; accepted October 27, 2017.

The online-only Data Supplement is available with this article at http://circ.ahajournals.org/lookup/suppl/doi:10.1161/CIRCULATIONAHA.117.032038/-/DC1.

Circulation is available at http://circ.ahajournals.org.

REFERENCES

1. Guariguata L, Whiting DR, Hambleton I, Beagley J, Linnenkamp U, Shaw JE. Global estimates of diabetes prevalence for 2013 and projections for 2035. *Diabetes Res Clin Pract*. 2014;103:137–149. doi: 10.1016/j.diabres.2013.11.002.
2. Liyanage T, Ninomiya T, Jha V, Neal B, Patrice HM, Okpechi I, Zhao MH, Lv J, Garg AX, Knight J, Rodgers A, Gallagher M, Kotwal S, Cass A, Perkovic V. Worldwide access to treatment for end-stage kidney disease: a systematic review. *Lancet*. 2015;385:1975–1982. doi: 10.1016/S0140-6736(14)61601-9.
3. Neal B, Perkovic V, de Zeeuw D, Mahaffey KW, Fulcher G, Stein P, Desai M, Shaw W, Jiang J, Vercruysse F, Meininger G, Matthews D. Rationale, design, and baseline characteristics of the CANagliflozin cardioVascular Assessment Study (CANVAS): a randomized placebo-controlled trial. *Am Heart J*. 2013;166:217.e11–223.e11. doi: 10.1016/j.ahj.2013.05.007.
4. Neal B, Perkovic V, Matthews DR, Mahaffey KW, Fulcher G, Meininger G, Erondu N, Desai M, Shaw W, Vercruysse F, Yee J, Deng H, de Zeeuw D; CANVAS-R Trial Collaborative Group. Rationale, design and baseline characteristics of the CANagliflozin cardioVascular Assessment Study-Renal (CANVAS-R): a randomized, placebo-controlled trial. *Diabetes Obes Metab*. 2017;19:387–393. doi: 10.1111/dom.12829.
5. Neal B, Perkovic V, Mahaffey KW, Fulcher G, Erondu N, Desai M, Shaw W, Law G, Walton MK, Rosenthal N, de Zeeuw D, Matthews DR; CANVAS Program Collaborative Group. Optimizing the analysis strategy for the CANVAS Program: a prespecified plan for the integrated analyses of the CANVAS and CANVAS-R trials. *Diabetes Obes Metab*. 2017;19:926–935. doi: 10.1111/dom.12924.
6. Neal B, Perkovic V, Mahaffey KW, de Zeeuw D, Fulcher G, Erondu N, Shaw W, Law G, Desai M, Matthews DR; CANVAS Program Collaborative Group. Canagliflozin and cardiovascular and renal events in type 2 diabetes. *N Engl J Med*. 2017;377:644–657. doi: 10.1056/NEJMoa1611925.
7. Marso SP, Bain SC, Consoli A, Eliaschewitz FG, Jódar E, Leiter LA, Lingvay I, Rosenstock J, Seufert J, Warren ML, Woo V, Hansen O, Holst AG, Pettersson J, Vilsbøll T; SUSTAIN-6 Investigators. Semaglutide and cardiovascular outcomes in patients with type 2 diabetes. *N Engl J Med*. 2016;375:1834–1844. doi: 10.1056/NEJMoa1607141.
8. Marso SP, Daniels GH, Brown-Frandsen K, Kristensen P, Mann JF, Nauck MA, Nissen SE, Pocock S, Poulter NR, Ravn LS, Steinberg WM, Stockner M, Zinman B, Bergenstal RM, Buse JB; LEADER Steering Committee; LEADER Trial Investigators. Liraglutide and cardiovascular outcomes in type 2 diabetes. *N Engl J Med*. 2016;375:311–322. doi: 10.1056/NEJMoa1603827.
9. Scirica BM, Bhatt DL, Braunwald E, Steg PG, Davidson J, Hirshberg B, Ohman P, Frederich R, Wiviott SD, Hoffman EB, Cavender MA, Udell JA, Desai NR, Mosenzon O, McGuire DK, Ray KK, Leiter LA, Raz I; SAVOR-TIMI 53 Steering Committee and Investigators. Saxagliptin and cardiovascular outcomes in patients with type 2 diabetes mellitus. *N Engl J Med*. 2013;369:1317–1326. doi: 10.1056/NEJMoa1307684.
10. Marso SP, McGuire DK, Zinman B, Poulter NR, Emerson SS, Pieber TR, Pratley RE, Haahr PM, Lange M, Frandsen KB, Rabøl R, Buse JB. Design of DEVOTE (Trial Comparing Cardiovascular Safety of Insulin Degludec vs Insulin Glargine in Patients With Type 2 Diabetes at High Risk of Cardiovascular Events) - DEVOTE 1. *Am Heart J*. 2016;179:175–183. doi: 10.1016/j.ahj.2016.06.004.
11. Holman RR, Bethel MA, Mentz RJ, Thompson VP, Lokhnygina Y, Buse JB, Chan JC, Choi J, Gustavson SM, Iqbal N, Maggioni AP, Marso SP, Öhman P, Pagidipati NJ, Poulter N, Ramachandran A, Zinman B, Hernandez AF; EXSCEL Study Group. Effects of once-weekly exenatide on cardiovascular outcomes in type 2 diabetes. *N Engl J Med*. 2017;377:1228–1239. doi: 10.1056/NEJMoa1612917.
12. Zinman B, Wanner C, Lachin JM, Fitchett D, Bluhmki E, Hantel S, Mattheus M, Devins T, Johansen OE, Woerle HJ, Broedl UC, Inzucchi SE; EMPA-REG OUTCOME Investigators. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. *N Engl J Med*. 2015;373:2117–2128. doi: 10.1056/NEJMoa1504720.
13. Green JB, Bethel MA, Paul SK, Ring A, Kaufman KD, Shapiro DR, Califf RM, Holman RR. Rationale, design, and organization of a randomized, controlled Trial Evaluating Cardiovascular Outcomes with Sitagliptin (TECOS) in patients with type 2 diabetes and established cardiovascular disease. *Am Heart J*. 2013;166:983.e7–989.e7. doi: 10.1016/j.ahj.2013.09.003.
14. Wu JH, Foote C, Blomster J, Toyama T, Perkovic V, Sundström J, Neal B. Effects of sodium-glucose cotransporter-2 inhibitors on cardiovascular events, death, and major safety outcomes in adults with type 2 diabetes: a systematic review and meta-analysis. *Lancet Diabetes Endocrinol*. 2016;4:411–419. doi: 10.1016/S2213-8587(16)00052-8.
15. Watts NB, Bilezikian JP, Usiskin K, Edwards R, Desai M, Law G, Meininger G. Effects of canagliflozin on fracture risk in patients with type 2 diabetes mellitus. *J Clin Endocrinol Metab*. 2016;101:157–166. doi: 10.1210/jc.2015-3167.

Canagliflozin for Primary and Secondary Prevention of Cardiovascular Events: Results From the CANVAS Program (Canagliflozin Cardiovascular Assessment Study)

Kenneth W. Mahaffey, Bruce Neal, Vlado Perkovic, Dick de Zeeuw, Greg Fulcher, Ngozi Erondu, Wayne Shaw, Elisa Fabbrini, Tao Sun, Qiang Li, Mehul Desai and David R. Matthews
On behalf of the CANVAS Program Collaborative Group

Circulation. 2018;137:323-334; originally published online November 13, 2017;
doi: 10.1161/CIRCULATIONAHA.117.032038
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231

Print ISSN: 0009-7322. Online ISSN: 1524-4539

SUPPPLEMENTAL MATERIAL

Supplementary Appendix 1. CANVAS Program committees

Steering Committee

David R. Matthews (Co-chair), Bruce Neal (Co-chair), Greg Fulcher, Kenneth W. Mahaffey,

Vlado Perkovic, Mehul Desai (Sponsor), Dick de Zeeuw

Independent Data Monitoring Committee

Philip Home (Chair), Jeffrey L. Anderson, Ian W. Campbell, John Lachin (withdrew in September 2015),

Daniel Scharfstein, Scott D. Solomon, Robert G. Uzzo

Cardiovascular Adjudication Committee

Greg Fulcher (Chair), John Amerena, Clara Chow, Gemma Figtree, John French, Graham Hillis, Mark A.

Hlatky, Bronwyn Jenkins, Nicholas J. Leeper, Richard Lindley, Barry McGrath, Alison Street, John Watson

Renal Adjudication Committee

Greg Fulcher (Chair), Shahnaz Shahinfar, Tara Chang, Arjun D. Sinha, Phyllis August

Safety Adjudication

Fracture Adjudication: Bioclinica

Diabetic Ketoacidosis Adjudication: Baim Institute for Clinical Research

Pancreatitis Adjudication Committee: Adam Cheifetz (Chair), Sunil Sheth, Joseph Feuerstein

Dr. Carolyn Lam: Hello from the American Heart Association meeting in Anaheim. I'm Dr. Carolyn Lam, associate editor from Circulation at National Heart Centre in Duke National University of Singapore and I'm so pleased to be here with the Circulation team led by editor in chief Dr. Joe Hill, as well as with Dr. Laura Mauri, senior editor from Brigham and Women's Hospital, and Dr. Dharam Kumbhani, associate editor from UT Southwestern. Boy, we've got lots to discuss. I mean, I want to just first start with congratulating you, Joe. We have got quite a number of simultaneous publications here at the AHA.

Dr. Joseph Hill: I appreciate that, Carolyn. Don't congratulate me. We have a team that is a privilege to work with. One of the initiatives that we launched right from the start was a desire to foster and shine a bright light on emerging science at the major meetings around the world. Often, that involves simultaneous publication.

I'm proud to say that we have 11 simultaneous publications, a record for us here at AHA. Most of them are clinical trials. A few are clinical science, and two of them are young investigators who are competing in the various different competitions. We reached out to them a few weeks ago and offered them the opportunity to submit to us, of course with no guarantees, and our standard remains the same, but we promised that we would provide them with an external peer review. Two of them made it through the process and they will be simultaneously published with their presentations here in Anaheim.

Dr. Carolyn Lam: Wow, well you heard it. A record 11 simultaneous publications. We've got a lot to talk about. Let me just maybe group the topics a little bit. Let's start with talking about peripheral artery disease. I think there are at least three papers around that area, and then we'll talk about coronary artery disease, and almost focusing more on implementation science, papers, there are two there, and then of course we have to talk about heart failure. Dharam, could you start? Tell us about the FOURIER PAD trial.

Dr. Dharam Kumbhani: Yeah. It's very exciting to have clinical trials in the PAD realm. FOURIER PAD is certainly really well done sub-study of the FOURIER trial. As you remember, this was a landmark trial, which compared a PCSK9 inhibitor Evolocumab in two doses, two placebo. The overall trial was done in about 27,000 patients who were followed for a median of 2.2 years. In this trial, Marc Bonaca and investigators, they looked at the PAD subset, which were about 13% of the total cohort. Now, they specifically set out to look at how patients with PAD, during this trial and very gratifyingly, they also specifically assessed how patients with PAD did as far as limb events, not just cardiovascular events.

At the outset, not surprisingly, patients with PAD had a higher risk of cardiovascular events by, I think it was about 60% higher for the primary end point compared with patients who did not have PAD. There was really no, in fact, modification by PAD in that the benefit of Evolocumab that we saw in the overall trial was preserved among the patients with PAD as well as those

without PAD. However, because patients with PAD had higher event rates, the absolute risk reductions were higher in patients with PAD.

Then, these investigators looked specifically at the incidents of major adverse limb events, which is a composite of acute limb ischemia, urgent revasc, and major amputations. What they show is that in the overall cohort, there is a 42% reduction in the risk of these major adverse limb events with Evolocumab compared with placebo. Obviously, the effect is significantly higher in patients with PAD. Although the benefit wasn't noted in the PAD subset specifically, the overall p-value for interaction was negative.

One of the really exciting things about this paper is that just like investigators have shown a monotonic reduction in cardiovascular event rates with LDL reduction, similarly, the investigators show a reduction in limb events, which is dose related and the same way in a monotonic fashion with Evolocumab. I think this is really exciting and I think this will be a very important paper for the field.

Dr. Carolyn Lam: Yeah. Dharam, that was beautifully summarized but once you start talking about the peripheral artery disease and this lack of interaction on effects and so on, I think of the CANVAS trial results that were reported at this meeting too. If I could maybe briefly summarize what the authors did in this circumstance, they looked at the more than 10,000 patients in the CANVAS trial who were randomized into Canagliflozin versus placebo in diabetic patients but this time they looked at whether or not there was a difference in effect with the primary prevention cohort versus the secondary prevention.

Primary prevention meaning those adults who had diabetes and risk factors but no established cardiovascular disease and the secondary prevention were those with peripheral artery disease, for example, and other established cardiovascular disease. The same thing, a lack of interaction, which I think is really important because it was the same sort of idea that the overall risk of cardiovascular events was lower in the primary prevention group. Looking at them as a subgroup alone, you didn't get the p-value that crossed the limit because the power was less in a lower risk group, but the lack of statistical interaction really gives us additional information, I think, that Canagliflozin and maybe the SGLT2s in general may be effective for primary prevention in diabetic patients. What do you think?

Dr. Dharam Kumbhani: Yeah. I mean, I think certainly, very interesting findings along those lines. As you pointed out, the event rates are much lower in the primary prevention cohort. All the confidence intervals overlap one, but because all the p-values for interaction for the three-point maze, the four-point maze, et cetera, one would say that there really isn't a difference between the primary and the secondary prevention subgroups. You would potentially have the same benefit in that subgroup as well.

Dr. Carolyn Lam: Fortunately or unfortunately, in that same study, they looked at the risk of amputations and there was a lack of interaction too for that meaning there was

a higher risk of amputations with Canagliflozin versus placebo. That of course is a really hot topic now, isn't it? I just wanted to point out though, when you look at it in the primary prevention group, there are only 33 events. What do you think? It spells caution but further look needs to be done? Yeah. Contrast that with the EMPA-REG outcome PAD analysis. You want to tell us about it?

Dr. Dharam Kumbhani: Yeah. Once the Canagliflozin CANVAS findings came out showing a high rate of amputations with Canagliflozin, the Empagliflozin, the EMPA-REG outcome's investigators went back and looked at the PAD subset in EMPA-REG outcomes. This was about 20% of the total cohort. I will say that unlike FOURIER, which we just discussed, the ascertainment of amputations was not prospectively defined for this trial and it was really obtained from the CRF forms.

However, having said that, it did not appear that amputation rates were higher with Empagliflozin. They did not break it down by the different doses but one assumes that the benefit is consistent between the two doses that they study. One would imagine the PAD patients would have a higher rate overall, which it was, but even in that group, it was about 6% over three years and there was really no difference between the patients who received Empagliflozin versus those who got placebo.

Dr. Carolyn Lam: That EMPA-REG outcome paper, I mean, interestingly, it was a research letter. Joe, you've been watching this whole field unfold right now and our journal has published so many good papers, including CVD REAL, all in this space. Could you comment on that a little bit and the research letter concept and the fact that we're publishing so many of these interesting papers in this topic?

Dr. Joseph Hill: Well, Carolyn, as you inferred, this field is evolving very rapidly. Now, the interface between metabolic disease and diabetes and heart disease is blurring. Some of these diabetic drugs are really emerging as heart failure drugs, it looks like and so there's a great deal of interest in exploring that and trying to find underlying mechanisms. It's an incredibly exciting time. In parallel with that, we are publishing research letters now for papers where, again, our bar starts with validity. Our bar doesn't change but if it's a story that can be communicated with really one multi-paneled figure and an 800word text, then that is a nice bite-size piece of information that we can get out to our readership. We're publishing one or two a week now. Overall, it appears to be well received and I think it's an effective vehicle for conveying certain types of our content.

Dr. Carolyn Lam: Frankly, it's such a delight to read, isn't it? It's hard to write. I think the shorter, the harder to write but this just goes to show how equally important they are.

Dr. Joseph Hill: Absolutely.

Dr. Carolyn Lam: That we're discussing it here. Well, let's go on to the next topic then, coronary artery disease. Regionalization of the care. I'll say that again, regionalization of the care. Would you like to comment on the two papers that are simultaneously

being published? One would be the ACCELERATOR-2 trial. That's in the U.S. Then, a second from New Zealand, the ICare-ACS trial. Slightly different but-

Dr. Joseph Hill: Well, that's exactly right. Often, we know what to do but we don't do what we know we need to do in medicine. The implementation of what we already know is an area of hot research and is an area that's evolving rapidly. These two studies, ACCELERATOR-2 here in the United States, focused on regionalization of the interface between EMS systems and EDs, how to get patients identified in the hospital to their device, whether it's a stent or a balloon pump or whatever it is. The first medical contact to device was the metric and by implementing what we already know, the AHA mission lifeline principles, these investigators were able to optimize this regionalization, so there wasn't so much variability across these 12 metropolitan regions. As a consequence, the time to first medical contact to device was shortened, and there was in fact a striking, maybe even surprising, mortality benefit.

Dr. Carolyn Lam: Exactly. That was striking to me too.

Dr. Joseph Hill: From the street to the lab, another paper from New Zealand that you referred to called ICare-ACS focused on doing a better job in the emergency department with serial ECGs and serial high sensitivity troponins, risk stratification algorithms and they found that, again, by developing these clinical pathways within the ED, they were able to shorten the length of stay in the ED and the length of stay in the hospital.

Dr. Carolyn Lam: Yeah. I thought those were amazing and then also from different parts of the world, really strong public health messages as well. Laura, you take care of these ACS patients right on there. What did you think of these papers?

Dr. Laura Mauri: No, I agree. I think that we've, in the past, focused on science and focused on clinical trials but ultimately, none of that matters if we don't deliver the healthcare to the patient. I think this is just a growing field and I'm glad that we're emphasizing it in circulation.

Dr. Carolyn Lam: Absolutely. If we would now go to another area that is really increasing in prevalence throughout the world. Heart failure, and of course, heart failure with preserved ejection fraction.

Dr. Joseph Hill: Your favorite topic.

Dr. Carolyn Lam: Congratulations, Laura on the paper that you're presenting, that is being presented at this meeting, the REDUCE LAP trial. Could you tell us a little bit more about that?

Dr. Laura Mauri: Sure. Yes, as you know, it's a really challenging field, heart failure with preserved ejection fraction. There aren't a lot of therapies that we have. We really don't have great medical therapy. This study actually looks at a medical device to treat

patients. It really is a feasibility study, so it's a relatively small trial, just over 90 patients but it's randomized. We know in the device arena, as in all trials, how important randomization is but also blinding. This was actually a sham-controlled blinded trial really designed to look at this interatrial shunt device in patients who have an elevated wedge pressure.

The REDUCE LAP stands for reduce left atrial pressure. That was the primary endpoint, was pulmonary capillary wedge pressure. This was not only looked at the safety, which showed that the device placement was very safe, but at the same time also looked at the proof of concept that by placing the shunt device, there was actually a reduction in wedge pressure over a period of exercise. It needs to be followed on. It's certainly just the first phase of trials but a pretty good standard with the sham control.

Dr. Carolyn Lam: Yeah, well, congratulations again. I mean, this follows … There was a previous publication of the single arm trial and now, this is the first randomized sham-controlled, and the results are consistent. It's a very difficult trial to carry out. HFpEF patients are notoriously difficult to recruit. Could you tell us a little bit about what it was like successfully completing this trial?

Dr. Laura Mauri: Yeah. Well, we had very enthusiastic centers and principal investigators, Ted Feldman and Sanjiv Shah. I think what it really required in this early phase was sites that were committed to characterizing the exercise physiology. The next stage of rolling this out to a broader number of sites and a larger number of patients to see if there's a clinical effect will really be more focused on the clinical endpoints and quality of life because ultimately that's the goal, is to improve symptoms in these patients.

Dr. Carolyn Lam: What I love about the design and the whole concept, it's so simple and elegant. We almost sometimes forget that HFpEF is heart failure, which means that by definition, there's raised filling pressures. It's hemodynamic at the end and this is just a simple concept of offloading the left atrium. That's so beautiful but it does come with some questions. Every time you mention this to someone, they go, “What about, I don't know, Eisenmenger's syndrome developing later?” The right side, volume overload, pulmonary hypertension, what about atrial fibrillation down the line? How about the safety parts of it?

Dr. Laura Mauri: Right, so the procedural safety was excellent but then I think you raise really important questions and these patients are still in follow-up but looking at the report here at this meeting, there was no pulmonary hypertension in excess in the shunt treated arm. The patient selection was towards patients who had higher wedge compared with right atrial pressure and among those patients, there was no evidence of RV overload. At least at this stage things look good to go on to the next step.

Dr. Carolyn Lam: That's wonderful and exciting. We definitely need a therapy for HFpEF. Joe, would you like to highlight any other trial? We have 11. We've discussed six.

Dr. Joseph Hill: Tonight at the editorial board meeting, we will be saluting these two young investigators who are presenting their work in this competition and simultaneously publishing their work. We've invited these young investigators and their mentor and they will present a short talk to the editorial board dinner. It's an effort to salute and recognize these early career investigators, to congratulate them on outstanding work. We're pleased and privileged to publish it, so I'm particularly excited about that.

Dr. Carolyn Lam: Wow, Joe. That is great. Thank you. I didn't know that was happening either. That's fabulous. Dharam or Laura, any other highlights that you may want to mention in this meeting?

Dr. Laura Mauri: I think that it's just been a wonderful kickoff to the meeting. We've covered, I think, many of the really important trials so it's really exciting to be able to see the work in print.

Dr. Carolyn Lam: That’s great, and to discuss it as well.

Dr. Dharam Kumbhani: Yeah, I agree. This is really exciting and hopefully, we can keep growing from strength to strength every year.

Dr. Carolyn Lam: Yep. You heard it right here everyone. We are going to grow from strength to strength under your leadership and with this great team, so thank you very much for joining us today.