Circulation

ORIGINAL RESEARCH ARTICLE

Canagliflozin and Heart Failure in Type 2 Diabetes Mellitus

Results From the CANVAS Program (Canagliflozin Cardiovascular Assessment Study)

BACKGROUND: Canagliflozin is a sodium glucose cotransporter 2 inhibitor that reduces the risk of cardiovascular events. We report the effects on heart failure and cardiovascular death overall, in those with and without a baseline history of heart failure, and in other participant subgroups.

METHODS: The CANVAS Program (Canagliflozin Cardiovascular Assessment Study) enrolled 10 142 participants with type 2 diabetes mellitus and high cardiovascular risk. Participants were randomly assigned to canagliflozin or placebo and followed for a mean of 188 weeks. The primary end point for these analyses was adjudicated cardiovascular death or hospitalized heart failure.

RESULTS: Participants with a history of heart failure at baseline (14.4%) were more frequently women, white, and hypertensive and had a history of prior cardiovascular disease (all $P<0.001$). Greater proportions of these patients were using therapies such as blockers of the renin angiotensin aldosterone system, diuretics, and β-blockers at baseline (all $P<0.001$). Overall, cardiovascular death or hospitalized heart failure was reduced in those treated with canagliflozin compared with placebo (16.3 versus 20.8 per 1000 patient-years; hazard ratio [HR], 0.78; 95% confidence interval [CI], 0.67–0.91), as was fatal or hospitalized heart failure (HR, 0.70; 95% CI, 0.55–0.89) and hospitalized heart failure alone (HR, 0.67; 95% CI, 0.52–0.87). The benefit on cardiovascular death or hospitalized heart failure may be greater in patients with a prior history of heart failure (HR, 0.61; 95% CI, 0.46–0.80) compared with those without heart failure at baseline (HR, 0.87; 95% CI, 0.72–1.06; P interaction =0.021). The effects of canagliflozin compared with placebo on other cardiovascular outcomes and key safety outcomes were similar in participants with and without heart failure at baseline (all interaction P values >0.130), except for a possibly reduced absolute rate of events attributable to osmotic diuresis among those with a prior history of heart failure (P=0.03).

CONCLUSIONS: In patients with type 2 diabetes mellitus and an elevated risk of cardiovascular disease, canagliflozin reduced the risk of cardiovascular death or hospitalized heart failure across a broad range of different patient subgroups. Benefits may be greater in those with a history of heart failure at baseline.

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Clinical Perspective

What Is New?

- The sodium glucose cotransporter 2 inhibitor canagliflozin reduced the risk of a range of composite and cause-specific heart failure outcomes.
- Benefits from canagliflozin may be greater in those with a history of heart failure.
- There was no evidence that patients with a history of heart failure were likely to suffer higher rates of adverse events from canagliflozin.

What Are the Clinical Implications?

- Patients with type 2 diabetes mellitus at risk of heart failure are particularly likely to benefit from treatment with canagliflozin.
- Beneficial effects of canagliflozin on heart failure outcomes are likely to be accrued on top of other therapies for heart failure management.

Type 2 diabetes mellitus is associated with a substantial risk of cardiovascular and renal disease, including heart failure.[1–3] Heart failure in diabetes mellitus is attributed to macrovascular and microvascular dysfunction, volume overload, impaired renal function, and direct effects of diabetes mellitus and insulin resistance on cardiac myocytes.[4–7] Mortality outcomes for patients with type 2 diabetes mellitus and heart failure are worse than for patients with either of the diseases alone, with a median survival of just 4 years.[8] Before the introduction of sodium glucose cotransporter 2 (SGLT2) inhibitors, treatment with glucose-lowering agents has not been shown to reduce heart failure hospitalization,[9] and there is evidence of increased risks of heart failure in some trials of dipeptidyl peptidase-4 inhibitors[10,11] and the thiazolidinedione class.[9] Two landmark clinical trials using inhibitors of SGLT2—EMPA-REG OUTCOME[12] and the CANVAS Program (Canagliflozin Cardiovascular Assessment Study)[13]—have demonstrated reductions in the risk of hospitalization for heart failure, with benefits of empagliflozin reported across a broad range of patient groups.[14] The present analyses explored in further detail the effects of canagliflozin on heart failure and determined the effects of canagliflozin on a range of efficacy and safety outcomes among CANVAS Program participants with and without a history of heart failure at baseline.

METHODS

Program Design

The study design, characteristics of participants, and main results of the CANVAS Program have previously been published.[13,15] In brief, the CANVAS Program, comprising the 2 similarly designed and conducted trials, CANVAS and CANVAS-R (CANVAS-Renal), was designed to assess the cardiovascular and renal safety and efficacy of canagliflozin compared with placebo, and also assess how any potential benefits might balance against risks. In total, 667 centers in 30 countries were involved in the 2 trials that were scheduled for joint closeout and analysis when ≥688 cardiovascular events and ≥78 weeks of follow-up had been accrued for the last randomized participant, which occurred in February 2017. A complete list of investigators and committees in the CANVAS Program is provided in the Appendix in the online-only Data Supplement. 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.[13]

Participants

Participants included in the CANVAS Program were men and women with type 2 diabetes mellitus (glycohemoglobin ≥7.0% and ≤10.5% and estimated glomerular filtration rate >30 mL/min/1.73 m^2). Participants were also required to be either ≥30 years of age with a history of symptomatic atherosclerotic cardiovascular disease or ≥50 years of age with ≥2 risk factors for cardiovascular disease (duration of diabetes mellitus ≥10 years, systolic blood pressure >140 mm Hg while on ≥1 antihypertensive agents, current smoker, documented microalbuminuria or macroalbuminuria, or documented high-density lipoprotein cholesterol <1 mmol/L). Patients with New York Association Class IV heart failure were excluded. The definition of heart failure at baseline was based on physician review of the patient's medical history at the first visit, with no requirement for collection of diagnostic biomarkers or the conduct of echocardiography. All participants provided informed consent, and ethics approval was obtained for every center.

Randomization, Treatment, and Follow-up

After a 2-week, single-blind, placebo run-in period, participants were randomized centrally through an interactive web response system using a computer-generated randomization schedule prepared by the study sponsor using randomly permuted blocks. Participants in CANVAS were assigned in a 1:1:1 ratio to canagliflozin 300 mg, canagliflozin 100 mg, or matching placebo, and participants in CANVAS-R were randomly assigned in a 1:1 ratio to canagliflozin or matching placebo, administered at an initial dose of 100 mg daily with optional uptitration to 300 mg from week 13. Participants and all study and sponsor staff were masked to individual treatment allocations until the completion of the study. Use of other background therapy for glycemic management, treatment of heart failure, and other risk factor control was according to best practices instituted in line with local guidelines.

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Participants were followed after randomization in a face-to-face follow-up that was scheduled for 3 visits in the first year and at 6-month intervals thereafter, with alternating telephone follow-up between face-to-face assessments. 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 in both trials. Participants who prematurely discontinued study treatment continued scheduled follow-up wherever possible, with extensive efforts made to obtain full outcome data for all participants during the final follow-up window that spanned from November 2016 to February 2017.

Outcomes

The primary outcome for these analyses was the composite of cardiovascular death or hospitalized heart failure. The detailed criteria used to define outcomes are included in the Appendix in the online-only Data Supplement. Cardiovascular death included death resulting from an acute myocardial infarction, sudden cardiac death, death because of heart failure, death because of stroke, and death because of other cardiovascular causes. Hospitalized heart failure was an event that required an admission to an inpatient unit or a visit to an emergency department, resulting in a ≥24-hour stay and ≥1 clinical symptoms of worsening heart failure, ≥2 physical signs of heart failure and a need for additional or increased therapy, and the absence of other non-cardiac etiology or other cardiac etiology that might explain the presentation.

Secondary outcomes were fatal or hospitalized heart failure, fatal heart failure, hospitalized heart failure, the composite of major adverse cardiovascular events (cardiovascular death, nonfatal myocardial infarction, and nonfatal stroke), fatal or nonfatal myocardial infarction, fatal or nonfatal stroke, all-cause mortality, and serious decline in kidney function (defined as a composite of 40% reduction in estimated glomerular filtration rate sustained for ≥2 consecutive measures, the need for renal replacement therapy, or death from renal causes). The safety outcomes assessed were all serious adverse events and all adverse events leading to discontinuation, as well as amputation, fracture, osmotic diuresis–related adverse events (according to the Medical Dictionary for Regulatory Activities preferred terms: increase in urine output such as polyuria, pollakiuria, micturition urgency and nocturia, as well as those related to thirst; polydipsia, dry mouth, throat dry, or tongue dry), and volume depletion–related adverse events. End point adjudication committees adjudicated all cardiovascular outcomes, renal outcomes, deaths, and fractures. Fatal heart failure events were those with heart failure adjudicated as the proximate cause of death.

Statistical Analysis

Categorical variables were summarized as the number of patients with corresponding percentages, and continuous variables were summarized as the mean and standard deviation. Differences in baseline characteristics between participants with a history of heart failure compared with participants with no history of heart failure were evaluated using a χ^2 test for categorical variables, a *t* test for continuous normally distributed variables, and a Wilcoxon 2-sample test for continuous variables with a skewed distribution (distributions were evaluated using an Anderson–Darling test).

Efficacy analyses were based on the full integrated dataset and the intent-to-treat approach, with the comparison being between all participants assigned to canagliflozin (regardless of dose) and all participants assigned to placebo. Annualized incidence rates per 1000 patient-years of follow-up were calculated for all outcomes in addition to hazard ratios (HRs) and 95% confidence intervals (CIs) determined from Cox regression models that included a trial stratification factor. Absolute risk differences for 1000 patients over 5 years and corresponding 95% CIs were estimated as the differences in the incidence rates between randomized treatment groups using a Poisson regression analysis with an assumption of constant annual event probabilities.[16] On-treatment analysis (based on patients who experienced a safety outcome while on study drug or in ≤30 days of study drug discontinuation) was used for the safety outcomes, except for amputation and fracture, which were assessed using intent-to-treat analyses. For all outcome analyses, we tested the homogeneity of treatment effects across the 2 contributing trials using *P* values for interactions based on the joint test in the Cox regression models, and the same approach was used for testing comparability of effects across subgroups defined by baseline participant characteristics. There was no formal statistical adjustment for multiple comparisons, and *P* values were interpreted in light of the many assessments made. Analysis of recurrent hospitalization for heart failure was assessed with an Andersen–Gill model. Analyses were performed using SAS version 9.2, SAS Enterprise Guide version 7.1, and STATA version 13.1.

RESULTS

There were 10 142 patients with type 2 diabetes mellitus in the CANVAS Program, and the mean follow-up time was 188.2 weeks. Mean age was 63.3 years, 35.8% of participants were women, the mean duration of diabetes mellitus was 13.5 years, and 65.6% had a history of cardiovascular disease. In addition, 1461 (14.4%) participants reported a history of heart failure at baseline. These participants were significantly different from the remaining participants in most aspects of demographics and disease history, in addition to exhibiting greater use of concomitant therapies used for the management of heart failure, including diuretics, renin angiotensin aldosterone system blockers, and β-blockers, but lower usage of statins and metformin (all $P<0.001$; Table). There were 203 cardiovascular deaths or hospitalized heart failure events recorded among those participants who reported a history of heart failure at baseline and 449 among those who did not.

Table. Baseline Characteristics of Participants With and Without Heart Failure at Baseline

Variable	Participants With Heart Failure			Participants Without Heart Failure			*P* Value Heart Failure vs No Heart Failure
	Canagliflozin (n=803)	Placebo (n=658)	Total (n=1461)	Canagliflozin (n=4992)	Placebo (n=3689)	Total (n=8681)	
Age, y, mean (SD)	64.1 (8.3)	63.4 (8.3)	63.8 (8.3)	63.1 (8.3)	63.5 (8.2)	63.2 (8.2)	0.025
Female, n (%)	346 (43.1)	302 (45.9)	648 (44.4)	1690 (33.9)	1295 (35.1)	2985 (34.4)	<0.001
Race, n (%)							<0.001
White	741 (92.3)	601 (91.3)	1342 (91.9)	3767 (75.5)	2835 (76.9)	6602 (76.1)	
Asian	19 (2.4)	24 (3.6)	43 (2.9)	758 (15.2)	483 (13.1)	1241 (14.3)	
Black or African American	15 (1.9)	13 (2.0)	28 (1.9)	161 (3.2)	147 (4.0)	308 (3.6)	
Other*	28 (3.5)	20 (3.0)	48 (3.3)	306 (6.1)	224 (6.1)	530 (6.1)	
Current smoker, n (%)	118 (14.7)	112 (17.0)	230 (15.7)	902 (18.1)	674 (18.3)	1576 (18.2)	0.025
History of hypertension, n (%)	766 (95.4)	626 (95.1)	1392 (95.3)	4422 (88.6)	3311 (89.8)	7733 (89.1)	<0.001
Duration of diabetes mellitus, y, mean (SD)§	11.9 (7.9)	12.2 (7.7)	12.0 (7.8)	13.7 (7.7)	13.9 (7.8)	13.8 (7.7)	<0.001‖
Microvascular disease history, n (%)							
Retinopathy	271 (33.7)	242 (36.8)	513 (35.1)	932 (18.7)	684 (18.5)	1616 (18.6)	<0.001
Nephropathy	210 (26.2)	185 (28.1)	395 (27.0)	784 (15.7)	595 (16.1)	1379 (15.9)	<0.001
Neuropathy	412 (51.3)	353 (53.6)	765 (52.4)	1375 (27.5)	970 (26.3)	2345 (27.0)	<0.001
Atherosclerotic vascular disease history, n (%)†							
Coronary	681 (84.8)	529 (80.4)	1210 (82.8)	2553 (51.1)	1958 (53.1)	4511 (52.0)	<0.001
Cerebrovascular	280 (34.9)	216 (32.8)	496 (34.0)	833 (16.7)	629 (17.1)	1462 (16.8)	<0.001
Peripheral	266 (33.1)	223 (33.9)	489 (33.5)	910 (18.2)	714 (19.4)	1624 (18.7)	<0.001
Any	757 (94.3)	608 (92.4)	1365 (93.4)	3370 (67.5)	2589 (70.2)	5959 (68.6)	<0.001
Cardiovascular disease history, n (%)‡	658 (81.9)	516 (78.4)	1174 (80.4)	3098 (62.1)	2384 (64.6)	5482 (63.2)	<0.001
History of atrial fibrillation, n (%)	110 (13.7)	101 (15.4)	211 (14.4)	241 (4.8)	161 (4.4)	402 (4.6)	<0.001
History of amputation, n (%)	16 (2.0)	20 (3.0)	36 (2.5)	120 (2.4)	82 (2.2)	202 (2.3)	0.749
Body mass index, kg/m^2, mean (SD)§	33.1 (5.9)	33.2 (5.9)	33.2 (5.9)	31.8 (5.9)	31.7 (5.9)	31.8 (5.9)	<0.001‖
Systolic blood pressure, mm Hg, mean (SD)	136.9 (14.9)	136.5 (14.3)	136.7 (14.6)	136.4 (15.9)	137.0 (16.0)	136.6 (15.9)	0.800
Diastolic blood pressure, mm Hg, mean (SD)	79.9 (9.5)	79.3 (9.4)	79.6 (9.4)	77.3 (9.6)	77.5 (9.7)	77.4 (9.7)	<0.001
Glycated hemoglobin, %, mean (SD)	8.4 (1.0)	8.4 (1.0)	8.4 (1.0)	8.2 (0.9)	8.2 (0.9)	8.2 (0.9)	<0.001‖
LDL cholesterol, mmol/L, mean (SD)§	2.6 (1.1)	2.6 (1.1)	2.6 (1.1)	2.2 (0.9)	2.2 (0.9)	2.2 (0.9)	<0.001‖
LDL/HDL cholesterol ratio, mean (SD)§	2.3 (1.0)	2.3 (1.1)	2.3 (1.0)	2.0 (0.9)	2.0 (0.9)	2.0 (0.9)	<0.001‖
Estimated glomerular filtration rate, mL/min/1.73 m^2, mean (SD)§	72.7 (19.5)	73.3 (19.8)	73.0 (19.6)	77.3 (20.3)	76.7 (21.0)	77.1 (20.6)	<0.001‖
Micro- or macroalbuminuria, n (%)§	263 (33.3)	208 (32.2)	471 (32.8)	1465 (29.6)	1090 (29.9)	2555 (29.7)	0.019
Concomitant drug therapies, n (%)							
Diuretic	488 (60.8)	390 (59.3)	878 (60.1)	2048 (41.0)	1564 (42.4)	3612 (41.6)	<0.001
Loop diuretic	201 (25.0)	178 (27.1)	379 (25.9)	515 (10.3)	414 (11.2)	929 (10.7)	<0.001
Renin-angiotensin-aldosterone system blocker	680 (84.7)	572 (86.9)	1252 (85.7)	3965 (79.4)	2899 (78.6)	6864 (79.1)	<0.001
β-Blocker	566 (70.5)	463 (70.4)	1029 (70.4)	2473 (49.5)	1919 (52.0)	4392 (50.6)	<0.001
Statin	558 (69.5)	448 (68.1)	1006 (68.9)	3772 (75.6)	2822 (76.5)	6594 (76.0)	<0.001
Antithrombotic	680 (84.7)	553 (84.0)	1233 (84.4)	3556 (71.2)	2682 (72.7)	6238 (71.9)	<0.001
Insulin	383 (47.7)	320 (48.6)	703 (48.1)	2507 (50.2)	1885 (51.1)	4392 (50.6)	0.080
Metformin	542 (67.5)	451 (68.5)	993 (68.0)	3905 (78.2)	2927 (79.3)	6832 (78.7)	<0.001
Sulfonylurea	376 (46.8)	287 (43.6)	663 (45.4)	2152 (43.1)	1546 (41.9)	3698 (42.6)	0.047
Thiazolidinedione	14 (1.7)	6 (0.9)	20 (1.4)	293 (5.9)	179 (4.9)	472 (5.4)	<0.001

(*Continued*)

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Table. Continued

Variable	Participants With Heart Failure			Participants Without Heart Failure			*P* Value Heart Failure vs No Heart Failure
	Canagliflozin (n=803)	Placebo (n=658)	Total (n=1461)	Canagliflozin (n=4992)	Placebo (n=3689)	Total (n=8681)	
Dipeptidyl peptidase-4 inhibitor	56 (7.0)	54 (8.2)	110 (7.5)	641 (12.8)	510 (13.8)	1151 (13.3)	<0.001
Glucagon-like peptide-1 receptor agonist	14 (1.7)	12 (1.8)	26 (1.8)	208 (4.2)	173 (4.7)	381 (4.4)	<0.001

HDL indicates high-density lipoprotein; LDL, low-density lipoprotein; and SD, standard deviation.

*Includes American Indian or Alaska Native, Native Hawaiian or other Pacific Islander, multiple races, other races, and unknown race.

†Some participants had ≥1 type of atherosclerotic disease.

‡As defined in the protocol.

§Values for duration of diabetes mellitus categories were calculated based on 5790 patients for canagliflozin, 4341 for placebo, and 10 131 for the total population. Values for body mass index categories were calculated based on 5787 patients for canagliflozin, 4341 for placebo, and 10 128 for the total population. Values for LDL cholesterol categories were calculated based on 5731 patients for canagliflozin, 4287 for placebo, and 10 018 for the total population. Values for estimated glomerular filtration rate categories were calculated based on 5794 patients for canagliflozin, 4346 for placebo, and 10 140 for the total population. Values for albuminuria categories were calculated based on 5740 patients for canagliflozin, 4293 for placebo, and 10 033 for the total population.

‖Comparison of heart failure versus non–heart failure was analyzed with a Wilcoxon 2-sample test.

Effects of Canagliflozin on Heart Failure Outcomes (Overall and in Patient Subgroups)

Compared with placebo, canagliflozin was associated with significantly lower risks of cardiovascular death or hospitalized heart failure (HR, 0.78; 95% CI, 0.67–0.91), fatal or hospitalized heart failure (HR, 0.70; 95% CI, 0.55–0.89), as well as hospitalized heart failure alone (HR, 0.67; 95% CI, 0.52–0.87). There was no clear separate effect on fatal heart failure (HR, 0.89; 95% CI, 0.49–1.60) for which there were few events and wide CIs (Figure 1). A subsidiary analysis of the primary outcome that accounted for competing mortality resulted in an HR estimate of 0.66 (95% CI, 0.51–0.84). The benefit on cardiovascular death or hospitalized heart failure was borderline significantly (*P* interaction =0.021) greater in patients with a prior history of heart failure (HR, 0.61; 95% CI, 0.46–0.80) compared with those without heart failure at baseline (HR, 0.87; 95% CI, 0.72–1.06; Figure 2). The absolute risk differences were –106.97 (95% CI, –171.59 to –42.34) per 1000 patient-years for participants with a history of heart failure at baseline and –8.36 (95% CI, –22.08 to 5.36) per 1000 patient-years for participants without a history of heart failure at baseline (*P* interaction =0.003).

Rates of heart failure varied according to baseline characteristics such as age, renal function, and other disease history characteristics, but effects of canagliflozin on cardiovascular death or hospitalized heart failure were mostly comparable across participant subgroups (Figure 3). Nominally significant interaction was observed with respect to the cardiovascular death or hospitalized heart failure outcome for several subgroups, including patients with higher versus lower body mass index, lower versus higher baseline glycohemoglobin, with versus without background use of diuretic therapy, and with versus without background metformin use (all *P* interaction >0.02; Figure 3). Participants randomized to canagliflozin treatment had less recurrent hospitalizations for heart failure during follow-up compared with participants assigned to placebo (HR, 0.68; 95% CI, 0.47–0.96). In the CANVAS trial, in which participants were assigned at random to placebo, canagliflozin 100 mg, or canagliflozin 300 mg, there was no evidence that the effects on cardiovascular death or hospitalized heart failure varied by dose (100 mg versus placebo: HR, 0.82; 95% CI, 0.65–1.03; and 300 mg versus placebo: HR, 0.82; 95% CI, 0.65–1.03). Among the subset of participants who reported a history of heart failure and loop diuretic use at baseline (n=379), the HR for the primary outcome was 0.54 (95% CI, 0.37–0.78).

Effects of Canagliflozin on Cardiovascular, Kidney, and Death Outcomes in Patients With and Without Heart Failure at Baseline

Proportional effects of canagliflozin compared with placebo were comparable in patients with and without heart failure at baseline for major adverse cardiovascular events, cardiovascular death, myocardial infarction, stroke, all-cause mortality, and serious decline in kidney function (all *P* interaction >0.160; Figure 2). Patients with a history of heart failure were at higher absolute risk of most outcomes. Although the numeric values for risk differences were typically greater among participants with a history of heart failure compared with those without, none reached statistical significance (all *P* interaction >0.130).

Safety Outcomes

Compared with placebo, canagliflozin has established associations with increased risks of amputation, fracture, and volume depletion, but there was no evidence of proportional differences in these risks between patients with and without heart failure at baseline (all *P*

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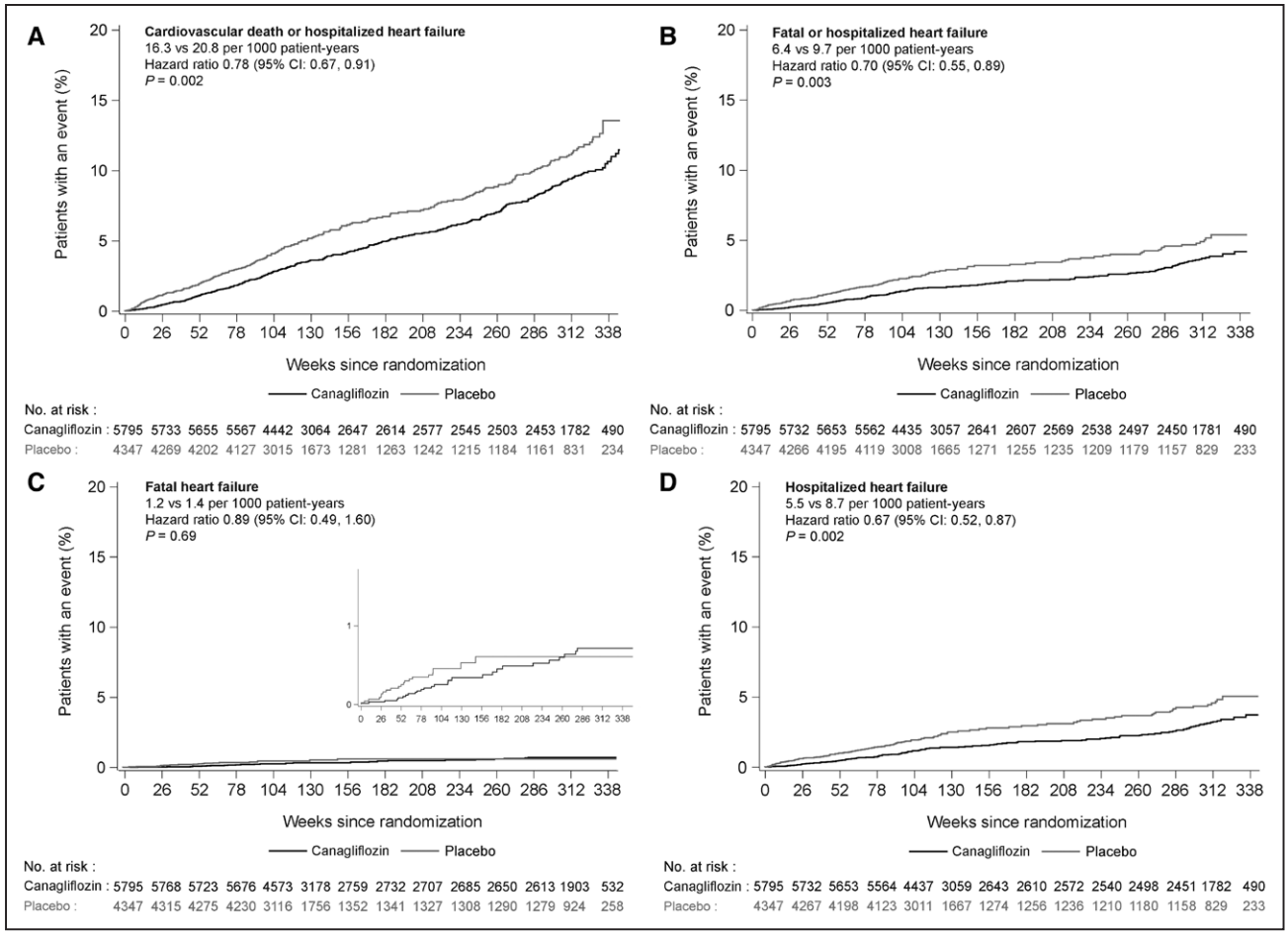

Figure 1. Effects of canagliflozin on heart failure outcomes.
A through **D**, Effects of canagliflozin on cardiovascular death or hospitalized heart failure (**A**), fatal or hospitalized heart failure (**B**), fatal heart failure (**C**), and hospitalized heart failure (**D**). CI indicates confidence interval.

interaction >0.160; Figure 4). The absolute risk of osmotic diuresis-related events, another established risk of therapy, was significantly lower in patients with a history of heart failure compared with those without (*P* interaction =0.029; Figure 4).

DISCUSSION

Patients with type 2 diabetes mellitus and established cardiovascular disease or at high risk of cardiovascular events who were treated with canagliflozin experienced significantly reduced rates of cardiovascular death or hospitalized heart failure. Benefits may be greater in those with a history of heart failure compared with those without. Effects were apparent across a broad range of participant subgroups, including those using established treatments for the prevention of heart failure, such as blockade of the renin angiotensin aldosterone system, diuretics, and β-blockers.

Other cardiovascular outcomes and death generally occurred more frequently in patients with a history of heart failure compared with those without, but both sets of participants experienced comparable reductions in the risks of these outcomes with the use of canagliflozin. Labeled adverse effects of canagliflozin on amputation and fracture were comparable among patients with and without heart failure at baseline, but there were possibly lower absolute risks of adverse events related to osmotic diuresis among patients with heart failure. There was no statistical evidence that adverse events attributable to volume depletion or acute kidney injury were differentially increased by treatment with canagliflozin in those with heart failure compared with those without heart failure, although CIs about estimates were wide.

The benefits for heart failure outcomes appeared early during follow-up, suggesting a mode of action driven primarily by volume and hemodynamic effects. Reductions in preload and afterload stemming from natriuresis,[14] systemic blood pressure lowering,[17] modification of the intrarenal renin angiotensin axis,[18] and reduction in arterial stiffness[19] may all contribute to the protection afforded. Preservation of renal function and

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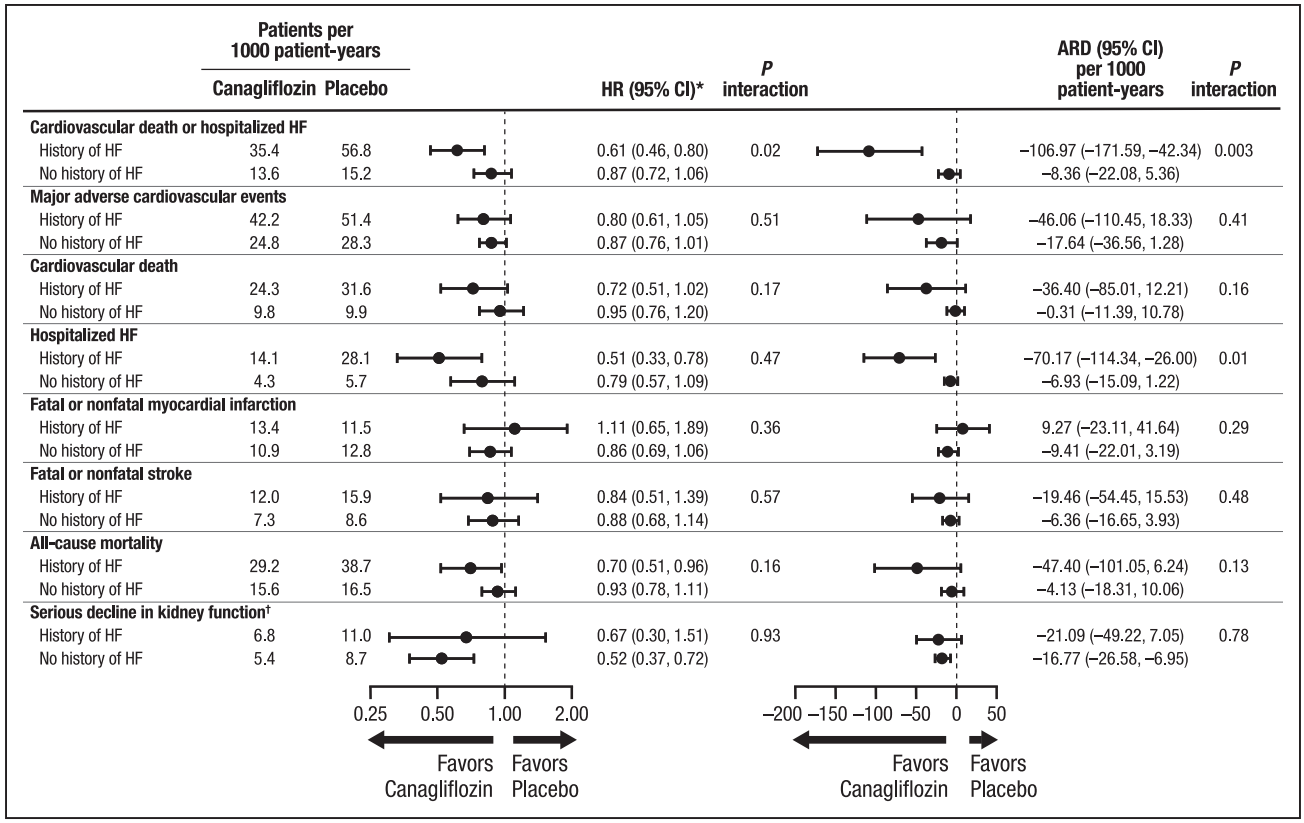

Figure 2. Proportional and absolute effects of canagliflozin compared with placebo on cardiovascular and renal outcomes in patients with and without a history of heart failure at baseline.
ARD indicates absolute risk difference over 5 years; CI, confidence interval; HF, heart failure; and HR, hazard ratio. *HR (canagliflozin compared to placebo) and its 95% CI are estimated using a Cox proportional hazard model including treatment as the explanatory variable. The model for CV death is stratified by prior CV disease subgroup and study. The models of renal endpoints are stratified for stage of baseline chronic kidney disease, measured by estimated glomerular filtration rate (<60, ≥60 mL/min/1.73 m^2) and by study. †Serious decline in kidney function was defined as a 40% reduction in the estimated glomerular filtration rate, the need for renal replacement therapy, or death from renal causes.

the mitigation of volume overload achieved with SGLT2 inhibition also probably contributed to the observed reduction in heart failure risk. By contrast, antiatherosclerotic effects of SGLT2 inhibition mediated through effects on glucose, blood pressure, and obesity are unlikely to have played a major role in the large and early benefit observed for this outcome.

There may also be direct positive effects of SGLT2 inhibition on cardiac metabolism that are attributable to a shift from fatty acids to ketone bodies as the substrate for myocardial energy generation. Metabolic studies have shown that the hypertrophied and failing heart uses ketone bodies as an alternate fuel source,[20,21] and increased hepatic neogenesis of ketone bodies is an established effect of SGLT2 inhibitors.[22,23] Enhanced cardiac efficiency may also be facilitated by increased oxygen delivery resulting from SGLT2 inhibitor–associated hemoconcentration.[18] Although the SGLT2 receptor is expressed primarily on the luminal surface of the proximal tubule in the kidney, there has been 1 report of SGLT2 expression in heart tissue.[24]

The findings reported here are strengthened by the rigorous design and conduct of the trial, the prespecification of heart failure as an outcome of interest, and the careful masked adjudication of all relevant events by an expert committee. Capturing the different modes of heart failure death as a separate cause-specific outcome is challenging and may underestimate the fatal disease burden attributable to heart failure. Accordingly, we selected the composite of cardiovascular death and hospitalized heart failure as the primary outcome because of its clinical relevance while also reporting on other more narrowly defined outcomes incorporating events explicitly defined as heart failure death. The relatively few primary outcome events recorded limits the capacity to detect effects and makes difficult interpretation of borderline significant findings (eg, the interactions of canagliflozin treatment and heart failure prevention with baseline characteristics, such as obesity and use of some drug therapies). Interpretation is further complicated by the overlap in these baseline characteristics

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	Number of events	Patients per 1000 patient-years: Canagliflozin	Patients per 1000 patient-years: Placebo	HR (95% CI)	*P* interaction
Study					
CANVAS	427	16.4	19.9	0.82 (0.67, 0.99)	0.46
CANVAS-R	225	15.9	21.9	0.72 (0.55, 0.94)	
Age					
<65 years	259	10.4	15.5	0.65 (0.51, 0.83)	0.09
≥65 years	393	24.4	27.9	0.87 (0.71, 1.07)	
Region					
North America	161	16.8	18.2	0.87 (0.63, 1.20)	0.69
Central America and South America	56	20.5	25.4	0.84 (0.50, 1.43)	
Europe	247	17.5	23.9	0.74 (0.57, 0.95)	
Rest of world	188	13.8	18.3	0.75 (0.56, 1.01)	
BMI					
<30 kg/m^2	211	14.2	14.5	1.01 (0.76, 1.34)	0.03
≥30 kg/m^2	439	17.5	25.1	0.68 (0.56, 0.82)	
Blood pressure					
Systolic ≥140 mmHg or diastolic ≥90 mmHg	312	17.1	23.8	0.72 (0.58, 0.91)	0.30
Systolic <140 mmHg and diastolic <90 mmHg	340	15.7	18.3	0.84 (0.68, 1.05)	
Diabetes duration					
≥10 years	495	17.7	22.6	0.79 (0.66, 0.94)	0.74
<10 years	155	12.6	16.6	0.75 (0.54, 1.03)	
Baseline glycated hemoglobin					
<8%	254	15.2	16.1	0.97 (0.75, 1.24)	0.04
≥8%	652	17.1	24.6	0.68 (0.55, 0.83)	
Baseline eGFR					
30-60 mL/min/1.73 m^2	226	31.6	41.4	0.75 (0.57, 0.98)	0.41
60-90 mL/min/1.73 m^2	325	14.7	16.8	0.86 (0.69, 1.08)	
≥90 mL/min/1.73 m^2	101	9.7	14.3	0.65 (0.43, 0.96)	
History of CV disease					
Yes	524	21.0	27.4	0.77 (0.65, 0.92)	0.42
No	128	8.9	9.8	0.83 (0.58, 1.19)	
History of atrial fibrillation					
Yes	113	50.9	72.6	0.72 (0.49, 1.05)	0.47
No	539	14.3	17.9	0.79 (0.66, 0.94)	
Baseline insulin use					
Yes	392	19.7	25.0	0.77 (0.63, 0.94)	0.96
No	260	12.9	16.5	0.80 (0.63, 1.03)	
Baseline metformin use					
Yes	394	13.5	15.4	0.88 (0.72, 1.08)	0.03
No	258	24.8	39.1	0.64 (0.50, 0.82)	
Baseline DPP-4 inhibitor use					
Yes	49	9.8	17.9	0.58 (0.33, 1.04)	0.20
No	603	17.0	21.1	0.80 (0.68, 0.94)	
Baseline thiazolidinedione use					
Yes	25	10.9	9.8	0.99 (0.43, 2.33)	0.55
No	627	16.7	21.5	0.77 (0.66, 0.91)	
Baseline RAAS use					
Yes	548	17.1	21.8	0.78 (0.66, 0.93)	0.93
No	104	13.0	16.8	0.78 (0.53, 1.16)	
Baseline β-blocker use					
Yes	428	19.7	27.8	0.70 (0.58, 0.85)	0.06
No	224	12.6	13.1	0.96 (0.73, 1.26)	
Baseline diuretic use					
Yes	408	22.0	31.7	0.71 (0.58, 0.86)	0.03
No	244	11.9	12.1	0.93 (0.72, 1.21)	
Baseline loop diuretic use					
Yes	231	47.9	69.1	0.72 (0.55, 0.93)	0.18
No	421	12.4	14.3	0.83 (0.68, 1.01)	
Baseline non-loop diuretic use					
Yes	177	13.2	18.1	0.71 (0.53, 0.96)	0.53
No	475	17.7	22.1	0.81 (0.67, 0.97)	

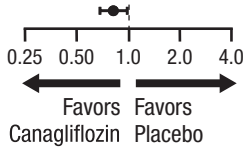

Figure 3. Effects on cardiovascular death or hospitalized heart failure in subgroups defined by demographic and disease characteristics.

History of CV disease–yes indicates patients were included on the basis of atherosclerotic cardiovascular disease history, whereas history of CV disease–no indicates patients were included on the basis of risk factors alone. BMI indicates body mass index; CANVAS, Canagliflozin Cardiovascular Assessment Study; CANVAS-R, Canagliflozin Cardiovascular Assessment Study–Renal; CI, confidence interval; CV, cardiovascular; DPP-4, dipeptidyl peptidase-4; eGFR, estimated glomerular filtration rate; HR, hazard ratio; and RAAS, renin angiotensin aldosterone system.

across participant subgroups. The limited documentation of heart failure at baseline, and specifically the absence of systematically collected baseline biomarkers or echocardiography data, meant that the estimated prevalence of established heart failure was imperfect and there was likely some misclassification of patients according to the presence or absence of heart failure at baseline. It was also not possible to classify baseline heart failure according to preservation or reduction in ejection fraction. The low rates of loop diuretic use among patients with heart failure at baseline suggests that most had nonsevere disease and raises additional uncertainty about the heart failure diagnoses at baseline in some patients.

The effects on heart failure observed within the CANVAS Program appear mostly comparable to those

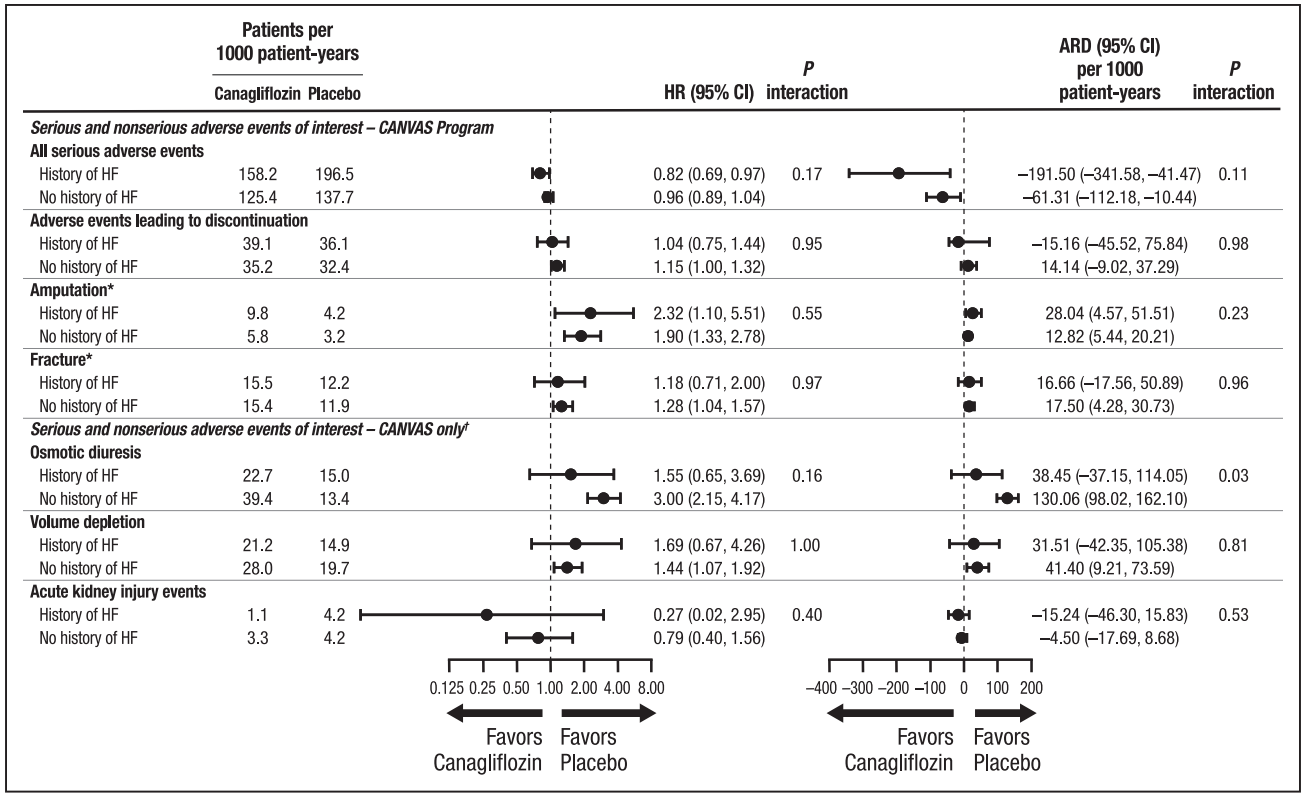

Figure 4. Proportional and absolute effects of canagliflozin compared with placebo on key safety outcome in patients with and without a history of heart failure at baseline.
ARD indicates absolute risk difference over 5 years; CANVAS, Canagliflozin Cardiovascular Assessment Study; ITT, intent-to-treat; CANVAS-R, Canagliflozin Cardiovascular Assessment Study–Renal; CI, confidence interval; HF, heart failure; and HR, hazard ratio. *Based on ITT dataset, whereas all other analyses based on on-treatment dataset. †For these adverse events, the annualized incidence rates are reported based on the CANVAS study alone through January 7, 2014, because, after this time, only serious adverse events or adverse events leading to discontinuation were collected. In the CANVAS-R study, only serious adverse events or adverse events leading to discontinuation were collected for these events.

reported for the EMPA-REG OUTCOME trial. An exception was the observation of a borderline significant greater proportional risk reduction for individuals with a history of heart failure at baseline in the CANVAS Program, which was not matched by a corresponding finding in the analyses of the EMPA-REG OUTCOME trial. This might reflect the different characteristics of the included populations or the slightly different criteria used to define heart failure outcomes between the 2 studies. However, the multiple and post hoc analyses of heart failure done for the CANVAS Program and EMPA-REG OUTCOME had limited statistical power to test for interactions, and the risk of missing real differences or observing spurious chance differences is high.

The CANVAS Program data provide clear evidence of the protective effects of canagliflozin on heart failure and, in conjunction with EMPA-REG OUTCOME, suggest an important role for SGLT2 inhibitors in the prevention of heart failure among patients with type 2 diabetes mellitus. Additional data from ongoing trials in diabetes mellitus will further clarify the impact of SGLT2 inhibitors on this major cause of mortality and morbidity[25,26] and confirm or refute hypotheses raised by the CANVAS and EMPA-REG OUTCOME trial findings. A series of new trials specifically exploring mechanisms and testing effects on heart failure outcomes among patients without diabetes mellitus[27–30] will also provide further insight into the mode of action by which benefits are achieved. In conclusion, among patients with type 2 diabetes mellitus and an elevated risk of cardiovascular disease, canagliflozin reduced the risk of cardiovascular death or hospitalized heart failure across a broad range of different patient groups and in addition to concomitant therapies for heart failure. Benefits may be greater in patients with a baseline history of heart failure compared with those without a history of heart failure.

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Canagliflozin and Heart Failure in Type 2 Diabetes Mellitus: Results From the CANVAS Program (Canagliflozin Cardiovascular Assessment Study)

Karin Rådholm, Gemma Figtree, Vlado Perkovic, Scott D. Solomon, Kenneth W. Mahaffey, Dick de Zeeuw, Greg Fulcher, Terrance D. Barrett, Wayne Shaw, Mehul Desai, David R. Matthews and Bruce Neal

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SUPPLEMENTAL MATERIAL

Supplemental Appendix 1. CANVAS Program sites and investigators

CANVAS

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Fracture Adjudication: Bioclinica

Diabetic Ketoacidosis Adjudication: Baim Institute for Clinical Research

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

Supplemental Appendix 3. CANVAS Program cardiovascular death and heart failure criteria

Definition of Cardiovascular Death

Cardiovascular death includes death resulting from an acute MI, sudden cardiac death, death due to heart failure, death due to stroke, and death due to other cardiovascular causes, as follows:

1. **Death Due to Acute MI** refers to a death by any mechanism (arrhythmia, heart failure [HF], low output) within 30 days after a MI related to the immediate consequences of the myocardial infarction, such as progressive congestive heart failure (CHF), inadequate cardiac output, or recalcitrant arrhythmia. If these events occur after a "break" (e.g., a CHF- and arrhythmia-free period of at least a week), they should be designated by the immediate cause, even though the MI may have increased the risk of that event (e.g., late arrhythmic death becomes more likely after an acute MI). The acute MI should be verified to the extent possible by the diagnostic criteria outlined for acute MI or by autopsy findings showing recent MI or recent coronary thrombus. Sudden cardiac death, if accompanied by symptoms suggestive of myocardial ischemia, new ST elevation, new left bundle branch block (LBBB), or evidence of fresh thrombus by coronary angiography and/or at autopsy should be considered death resulting from an acute MI, even if death occurs before blood samples or 12-lead electrocardiogram (ECG) could be obtained, or at a time before the appearance of cardiac biomarkers in the blood. Death resulting from a procedure to treat a MI (percutaneous coronary intervention [PCI], coronary artery bypass graft surgery [CABG]), or to treat a complication resulting from MI, should also be considered death due to acute MI.

   Death resulting from a procedure to treat myocardial ischemia (angina) or death due to a MI that occurs as a direct consequence of a cardiovascular investigation/procedure/operation should be considered as a death due to other cardiovascular causes.

2. **Sudden Cardiac Death** refers to a death that occurs unexpectedly, not following an acute MI, and includes the following deaths:
   a. Death witnessed and instantaneous without new or worsening symptoms
   b. Death witnessed within 60 minutes of the onset of new or worsening cardiac symptoms, unless the symptoms suggest acute MI
   c. Death witnessed and attributed to an identified arrhythmia (e.g., captured on an ECG recording, witnessed on a monitor, or unwitnessed but found on implantable cardioverter-defibrillator review)
   d. Death after unsuccessful resuscitation from cardiac arrest
   e. Death after successful resuscitation from cardiac arrest and without identification of a noncardiac etiology (postcardiac arrest syndrome)
   f. Unwitnessed death without other cause of death (information regarding the patient's clinical status preceding death should be provided, if available)

General Considerations

- A subject seen alive and clinically stable 12-24 hours prior to being found dead without any evidence or information of a specific cause of death should be classified as "sudden cardiac death." Typical scenarios include:
  - Subject well the previous day but found dead in bed the next day
  - Subject found dead at home on the couch with the television on
- Deaths for which there is no information beyond "Patient found dead at home" may be classified as "death due to other cardiovascular causes" or in some trials, "undetermined cause of death." Please see *Definition of Undetermined Cause of Death*, for full details.

3. **Death Due to HF or Cardiogenic Shock** refers to a death occurring in the context of clinically worsening symptoms and/or signs of heart failure without evidence of another cause of death and not following an acute MI. Note that deaths due to HF can have various etiologies, including one or more acute MIs (late effect), ischemic or nonischemic cardiomyopathy, or valve disease.

   Death due to HF or Cardiogenic Shock should include sudden death occurring during an admission for worsening heart failure as well as death from progressive HF or cardiogenic shock following implantation of a mechanical-assist device.

   New or worsening signs and/or symptoms of CHF include any of the following:

   a. New or increasing symptoms and/or signs of HF requiring the initiation of, or an increase in, treatment directed at HF or occurring in a patient already receiving maximal therapy for HF
   b. HF symptoms or signs requiring continuous intravenous therapy or chronic oxygen administration for hypoxia due to pulmonary edema
   c. Confinement to bed predominantly due to HF symptoms
   d. Pulmonary edema sufficient to cause tachypnea and distress **not** occurring in the context of an acute MI, worsening renal function, or as the consequence of an arrhythmia occurring in the absence of worsening heart failure
   e. Cardiogenic shock **not** occurring in the context of an acute MI or as the consequence of an arrhythmia occurring in the absence of worsening HF

      Cardiogenic shock is defined as systolic blood pressure (SBP) <90 mmHg for greater than 1 hour, not responsive to fluid resuscitation and/or heart rate correction, and felt to be secondary to cardiac dysfunction and associated with at least one of the following signs of hypoperfusion:
      - Cool, clammy skin ***or***
      - Oliguria (urine output <30 ml/hour) ***or***
      - Altered sensorium ***or***
      - Cardiac index <2.2 l/min/m^2

      Cardiogenic shock can also be defined if SBP <90 mmHg and increases to ≥90 mmHg in less than 1 hour with positive inotropic or vasopressor agents alone and/or with mechanical support.

General Considerations

HF may have a number of underlying causes, including acute or chronic ischemia, structural heart disease (e.g., hypertrophic cardiomyopathy), and valvular heart disease. Where treatments are likely to have specific effects, and it is likely to be possible to distinguish between the various causes, then it may be reasonable to separate out the relevant treatment effects. For example, obesity drugs such as fenfluramine (pondimin) and dexfenfluramine (redux) were found to be associated with the development of valvular heart disease and pulmonary hypertension. In other cases, the aggregation implied by the definition above may be more appropriate.

4. **Death Due to Stroke** refers to death occurring up to 30 days after a stroke that is either due to the stroke or caused by a complication of the stroke.

5. **Death Due to Other Cardiovascular Causes** refers to a cardiovascular death not included in the above categories (e.g., dysrhythmia unrelated to sudden cardiac death, pulmonary embolism, cardiovascular intervention [other than one related to an acute MI], aortic aneurysm rupture, or peripheral arterial disease). Mortal complications of cardiac surgery or nonsurgical revascularization should be classified as cardiovascular deaths.

Hospitalized Congestive Heart Failure

HF requiring hospitalization is defined as an event that meets the following criteria:

1. Requires hospitalization defined as an admission to an inpatient unit or a visit to an emergency department that results in at least a 24-hour stay (or a date change if the time of admission/discharge is not available).

   AND

2. Clinical symptoms of HF, including ≥1 of the following new or worsening conditions:
   - Dyspnea
   - Orthopnea
   - Paroxysmal nocturnal dyspnea
   - Increasing fatigue/worsening exercise tolerance

   AND

3. Physical signs of HF, including ≥2 of the following:
   - Edema (greater than 2+ lower extremity)
   - Pulmonary crackles greater than basilar (pulmonary edema must be sufficient to cause tachypnea and distress not occurring in the context of an acute MI or as the consequence of an arrhythmia occurring in the absence of worsening HF)
   - Jugular venous distension
   - Tachypnea (respiratory rate >20 breaths/minute)
   - Rapid weight gain
   - S3 gallop
   - Increasing abdominal distension or ascites
   - Hepatojugular reflux
   - Radiological evidence of worsening HF
   - A right heart catheterization within 24 hours of admission showing a pulmonary

capillary wedge pressure (pulmonary artery occlusion pressure) ≥18 mmHg or a cardiac output <2.2 l/min/m^2

Note: biomarker results (e.g., brain natriuretic peptide [BNP]) consistent with CHF will be supportive of this diagnosis, but the elevation in BNP cannot be due to other conditions such as cor pulmonale, pulmonary embolus, primary pulmonary hypertension, or congenital heart disease. Increasing levels of BNP, although not exceeding the ULN, may also be supportive of the diagnosis of CHF in selected cases (e.g., morbid obesity).

AND

4. Need for additional/increased therapy
   - Initiation of, or an increase in, treatment directed at HF or occurring in a patient already receiving maximal therapy for HF and including ≥1 of the following:
     - Initiation of or a significant augmentation in oral therapy for the treatment of CHF
     - Initiation of intravenous diuretic, inotrope, or vasodilator therapy
     - Up-titration of intravenous therapy, if already on therapy
     - Initiation of mechanical or surgical intervention (mechanical circulatory support, heart transplantation or ventricular pacing to improve cardiac function), or the use of ultrafiltration, hemofiltration, or dialysis that is specifically directed at treatment of HF.

AND

5. No other noncardiac etiology (such as chronic obstructive pulmonary disease, hepatic cirrhosis, acute renal failure, or venous insufficiency) and no other cardiac etiology (such as pulmonary embolus, cor pulmonale, primary pulmonary hypertension, or congenital heart disease) for signs or symptoms is identified.

   Note: it is recognized that some patients may have multiple simultaneous disease processes. Nevertheless, for the endpoint event of HF requiring hospitalization, the diagnosis of CHF would need to be the primary disease process accounting for the above signs and symptoms.