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RESEARCH LETTER

Effects of Canagliflozin on Heart Failure Outcomes Associated With Preserved and Reduced Ejection Fraction in Type 2 Diabetes Mellitus

Results From the CANVAS Program

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Patients with type 2 diabetes mellitus are at high risk of developing heart failure (HF).[1] Sodium glucose cotransporter 2 (SGLT2) inhibitors have been demonstrated, in large-scale trials, to reduce the risk of HF events in patients with type 2 diabetes mellitus deemed to be at high risk based on established cardiovascular disease or multiple risk factors.[2–4] However, it is unclear whether benefits are experienced across the broad spectrum of HF patients that includes those with preserved ejection fraction (HFpEF) and those with reduced ejection fraction (HFrEF).

The goal of the present analyses was to define the potentially distinct effects on HF events with preserved versus reduced ejection fraction (EF) in the CANVAS (Canagliflozin Cardiovascular Assessment Study) Program. Participants with type 2 diabetes mellitus aged ≥30 years with a history of symptomatic atherosclerotic cardiovascular disease or aged ≥50 years with 2 or more risk factors for cardiovascular disease were randomized to receive canagliflozin or placebo and followed up as described previously.[3] Patients with New York Heart Association functional class IV HF were excluded. Use of other background therapy for glycemic management, treatment of HF, and other risk factor control was according to best practice. The trials comprising the CANVAS Program (CANVAS and CANVAS-R [–Renal]) were approved by the ethics committees at each site, and all participants provided written informed consent. The primary outcome for the CANVAS Program was the composite of nonfatal stroke, nonfatal myocardial infarction, or cardiovascular death. HF events were initially assessed by an end point adjudication committee using a prespecified set of criteria. The assignment of each event as being in the context of preserved or reduced EF was done by a retrospective secondary review of the medical record data by one of the members of the original adjudication committee who was blinded to individual participant treatment assignment (G.A.F.). Echocardiography or left ventriculography performed as part of routine clinical care was used to make the determination of EF. HFpEF was defined as an HF event for which EF of ≥50% was documented during the HF admission. HFrEF was defined as an HF event for which EF was documented as <50% during the HF admission, or there was a prior report of reduced EF with no documented evidence of recovery. All other events were defined as HF with unknown EF (HFuEF).

There were 10 142 patients in the CANVAS Program, with a mean follow-up of 188.2 weeks. Mean age was 63.3 years; 35.8% of participants were women; and 65.6% had a history of cardiovascular disease, including 1461 (14.4%) with a history of HF at baseline (with no requirement for preserved or reduced EF classification). A total of 276 of the 10 142 participants had a fatal or hospitalized HF event during follow-up, and 61 of these participants had >1 HF event. In total, there were 101 participants who had a first HF event of preserved EF, 122 who had a first HF event with reduced EF, and 61 who had a first HF event with unknown EF. The number of first HF events adds to

Key Words: canagliflozin ■ heart failure ■ randomized trial ■ SGLT2 inhibitor ■ type 2 diabetes mellitus

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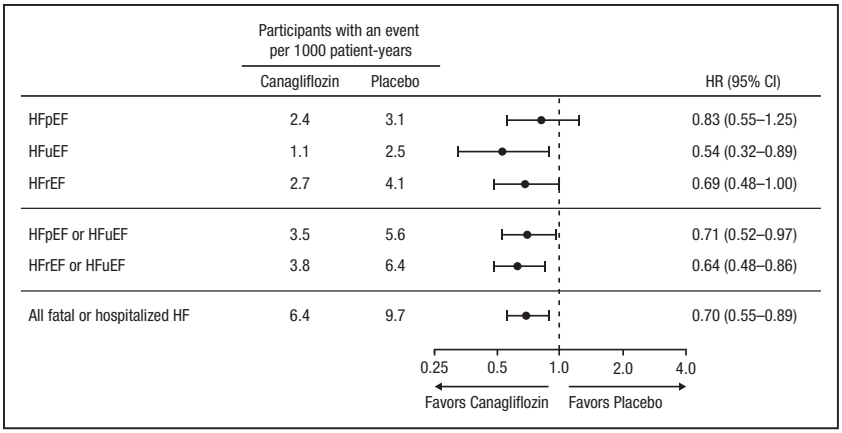

Figure. Effects of canagliflozin vs placebo on all fatal or hospitalized HF and on HF with preserved ejection fraction, reduced ejection fraction, and unknown ejection fraction. HF indicates heart failure; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; HFuEF, heart failure with unknown ejection fraction; and HR, hazard ratio.

>276 participants because 8 patients experienced a first HF event of >1 type (eg, unknown EF event in year 1 followed by reduced EF event in year 2).

Participants who had an HFpEF event were more likely to be female (37.6% versus 16.4%; $P<0.001$) than those with HFrEF events and were more likely to have a history of hypertension (96.0% versus 86.9%; $P=0.014$). Those who had HFpEF events also had a higher mean systolic blood pressure at baseline than those who had an HFrEF event (142.8 mm Hg versus 134.4 mm Hg; $P<0.001$), a higher prevalence of microvascular disease (65.4% versus 51.6%; $P=0.041$), a lower prevalence of macrovascular disease (65.4% versus 77.9%; $P=0.038$), and a higher body mass index (37.2 kg/m^2 versus 33.7 kg/m^2; $P<0.001$).

Overall, as previously reported, canagliflozin reduced fatal or hospitalized HF events compared with placebo (hazard ratio, 0.70; 95% CI, 0.55–0.89).[2] As shown in the Figure, the hazard ratios were 0.69 (95% CI, 0.48–1.00) for HFrEF events, 0.83 (95% CI, 0.55–1.25) for HFpEF events, and 0.54 (95% CI, 0.32–0.89) for HFuEF events. In the sensitivity analysis in which HFuEF events were assumed to be HFpEF, the updated hazard ratio for HFpEF events was 0.71 (95% CI, 0.52–0.97), and when HFuEF events were assumed to be HFrEF events, the updated hazard ratio for HFrEF events was 0.64 (95% CI, 0.48–0.86). Analyses adjusted for competing risk of death were performed with the Fine and Gray analysis approach and produced similar findings.

In summary, canagliflozin reduced the overall risk of HF events in patients with type 2 diabetes mellitus and high cardiovascular risk, with no clear difference in effects on HFrEF versus HFpEF events. This may provide some hope for patients with diabetes mellitus and HFpEF, in which no prior intervention has been shown to have clear clinical benefits. However, this study was limited by its reliance on EF measurements at the time of the event and not at baseline, and additional data from dedicated HFpEF trials are required.

ARTICLE INFORMATION

Data sharing: Data from this study 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.

Clinical Trial Registration: URL: https://www.clinicaltrials.gov. Unique identifiers: NCT01032629 and NCT01989754.

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