Effects of canagliflozin on heart failure outcomes associated with preserved and reduced ejection fraction in type 2 diabetes: results from the CANVAS Program

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Clinical Trial Registration

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Keywords

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Patients with type 2 diabetes mellitus are at high risk of developing heart failure (HF).[1] Sodium glucose co-transporter 2 (SGLT2) inhibitors have been demonstrated, in large scale trials, to reduce the risk of HF events in patients with type 2 diabetes 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 (HFpEF) as well as reduced ejection fraction (HFrEF).

The goal of the current analyses was to define the potentially distinct effects on HF events with preserved versus reduced EF in the CANagliflozin cardioVascular Assessment Study (CANVAS) Program. Participants with type 2 diabetes aged ≥30 years with a history of symptomatic atherosclerotic cardiovascular disease, or ≥50 years with two or more risk factors for cardiovascular disease were randomized to receive canagliflozin or placebo and followed as previously described. Patients with New York Association 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 primary outcome for the main study was the composite of non-fatal stroke, non-fatal myocardial infarction or cardiovascular death. HF events were initially assessed by an Endpoint Adjudication Committee using a pre-specified set of criteria. The assignments of each event as being in the context of preserved (pEF) or reduced (rEF) EF were 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 (GF). Echocardiography or left ventriculography done as part of routine clinical care was used to make the determination of EF. HFpEF was defined as a HF event for which EF of ≥50% was documented during the event period. HFrEF was defined as a HF event for which EF was documented as <50% during the event admission, or there was a prior report of rEF with no documented evidence of recovery. All other events were defined as HF with unknown EF.

There were 10,142 patients in the CANVAS Program with a mean follow-up time 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 pEF or rEF classification). 276 of the 10,142 participants had a fatal or hospitalized HF event during follow-up and 61 of these participants had more than one HF event. In total there were 101 participants that had a first HF event pEF; 122 that had a first HF event with rEF; and 61 that had a first HF event with unknown EF. The number of first HF events adds to >276 participants due to 8 patients experiencing a first HF event of more than one type (e.g. unknown EF event in year 1 followed by reduced EF event in year 2).

Participants who had a HFpEF event were more likely to be female (37.6 vs 16.4%; p <0.001) than those with HFrEF events, and were more likely to have a history of hypertension (96.0 vs 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 vs 134.4 mmHg; p <0.001), a higher prevalence of microvascular disease (65.4 vs 51.6%; p = 0.041), a lower prevalence of macrovascular disease (65.4 vs 77.9%; p = 0.038) and a higher body mass index (37.2 vs 33.7 kg/m^2; p <0.001).

Overall, as previously reported, canagliflozin reduced fatal or hospitalized HF events compared to placebo (HR 0.70; 95% CI 0.55 - 0.89).[2] As shown in Figure 1, the HR for HFrEF events was 0.69 (95% CI 0.48 - 1.00), for HFpEF events was 0.83 (95% CI 0.55 - 1.25) and for HFuEF events was 0.54 (95% CI 0.32 - 0.89). In the sensitivity analysis where HFuEF events were assumed to be HFpEF, the updated HR for HFpEF events was 0.71 (95% CI 0.52-0.97) and if HFuEF events were assumed to be HFrEF events, the updated HR for HFrEF events was 0.64 (95% CI 0.48-0.86).

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

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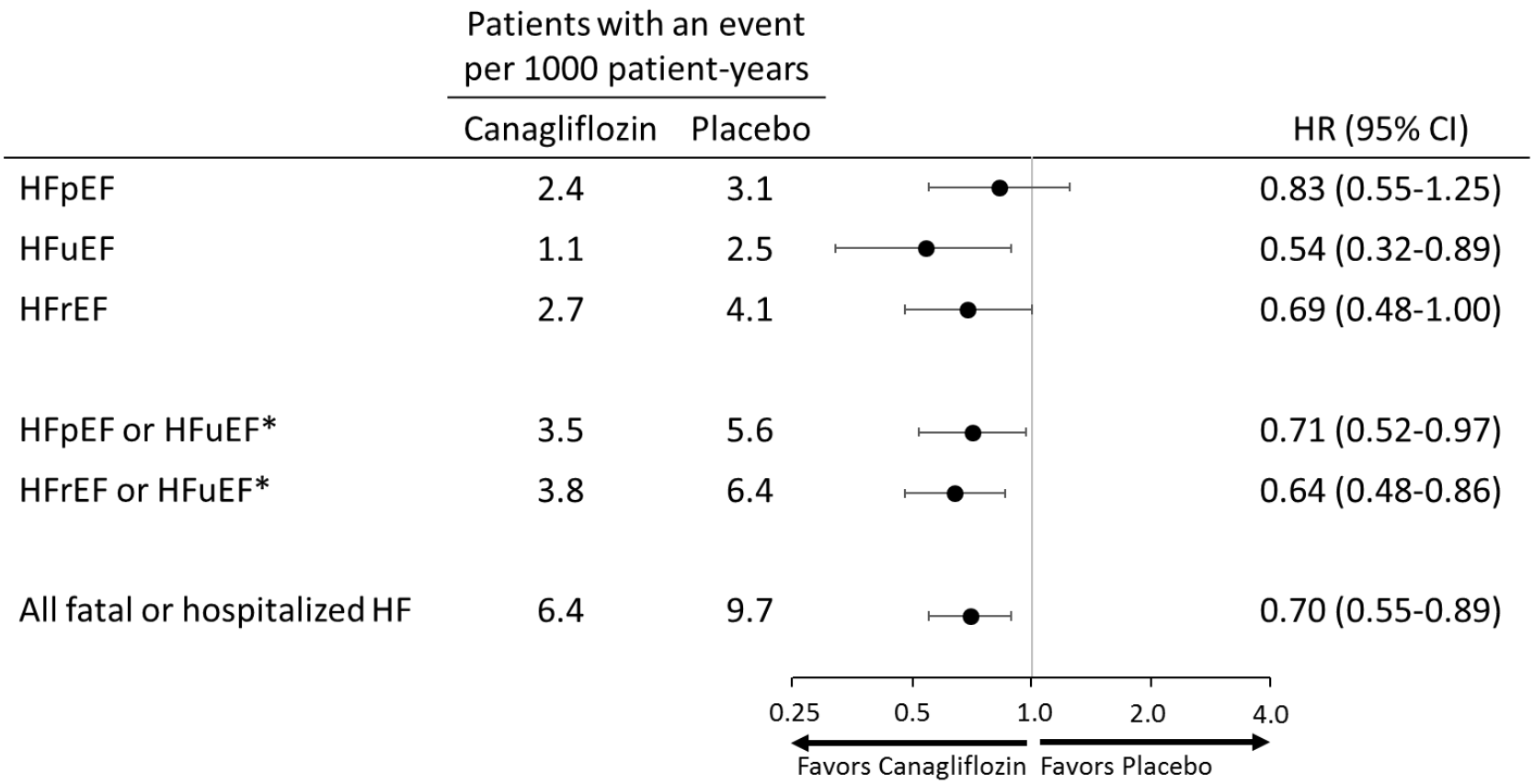
REFERENCES

1. Cavender MA, Steg PG, Smith SC, Jr., Eagle K, Ohman EM, Goto S, Kuder J, Im K, Wilson PW, Bhatt DL and Investigators RR. Impact of diabetes mellitus on hospitalization for heart failure, cardiovascular events, and death: outcomes at 4 years from the reduction of atherothrombosis for continued health (REACH) registry. *Circulation*. 2015;132:923-31.
2. Radholm K, Figtree G, Perkovic V, Solomon SD, Mahaffey KW, de Zeeuw D, Fulcher G, Barrett TD, Shaw W, Desai M, Matthews DR and Neal B. Canagliflozin and heart failure in type 2 diabetes mellitus: results from the CANVAS Program (Canagliflozin Cardiovascular Assessment Study). *Circulation*. 2018:CIRCULATIONAHA.118.034222.
3. Neal B, Perkovic V, Mahaffey KW, de Zeeuw D, Fulcher G, Erondu N, Shaw W, Law G, Desai M, Matthews D and on behalf of the CANVAS Program Collaborative Group. Canagliflozin and cardiovascular and renal events in type 2 diabetes. *N Engl J Med*. 2017;377:644-657.
4. Zinman B, Wanner C, Lachin JM, Fitchett D, Bluhmki E, Hantel S, Mattheus M, Devins T, Johansen OE, Woerle HJ, Broedl UC and Inzucchi SE. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. *N Engl J Med*. 2015;373:2117-28.

Figure 1 Effects of canagliflozin versus placebo on all fatal or hospitalized heart failure, heart failure with preserved ejection fraction, reduced ejection fraction and unknown ejection fraction.



HR, hazard ratio; CI, confidence interval; HF, heart failure; rEF, reduced ejection fraction; pEF, preserved ejection fraction; uEF, unknown ejection fraction.

*Sensitivity analyses were calculated using the first HF event for participants during follow up (n = 276).