



Efficacy of Ertugliflozin on Heart Failure–Related Events in Patients With Type 2 Diabetes Mellitus and Established Atherosclerotic Cardiovascular Disease

Results of the VERTIS CV Trial

Editorial, see p 2216

BACKGROUND: In patients with type 2 diabetes mellitus, sodium-glucose cotransporter 2 inhibitors reduce the risk of hospitalization for heart failure (HHF). We assessed the effect of ertugliflozin on HHF and related outcomes.

METHODS: VERTIS CV (Evaluation of Ertugliflozin Efficacy and Safety Cardiovascular Outcomes Trial), a double-blind, placebo-controlled trial, randomly assigned patients with type 2 diabetes mellitus and atherosclerotic cardiovascular (CV) disease to once-daily ertugliflozin 5 mg, 15 mg, or placebo. Prespecified secondary analyses compared ertugliflozin (pooled doses) versus placebo on time to first event of HHF and composite of HHF/CV death, overall and stratified by prespecified characteristics. Cox proportional hazards modeling was used with the Fine and Gray method to account for competing mortality risk, and Andersen-Gill modeling to analyze total (first+recurrent) HHF and total HHF/CV death events.

RESULTS: A total of 8246 patients were randomly assigned to ertugliflozin (n=5499) or placebo (n=2747); n=1958 (23.7%) had a history of heart failure (HF) and n=5006 (60.7%) had pretrial ejection fraction (EF) available, including n=959 with EF ≤45%. Ertugliflozin did not significantly reduce first HHF/CV death (hazard ratio [HR], 0.88 [95% CI, 0.75–1.03]). Overall, ertugliflozin reduced risk for first HHF (HR, 0.70 [95% CI, 0.54–0.90]; *P*=0.006). Previous HF did not modify this effect (HF: HR, 0.63 [95% CI, 0.44–0.90]; no HF: HR, 0.79 [95% CI, 0.54–1.15]; *P* interaction=0.40). In patients with HF, the risk reduction for first HHF was similar for those with reduced EF ≤45% versus preserved EF >45% or unknown. However, in the overall population, the risk reduction tended to be greater for those with EF ≤45% (HR, 0.48 [95% CI, 0.30–0.76]) versus EF >45% (HR, 0.86 [95% CI, 0.58–1.29]). Effect on risk for first HHF was consistent across most subgroups, but greater benefit of ertugliflozin was observed in 3 populations: baseline estimated glomerular filtration rate <60 mL·min⁻¹·1.73 m⁻², albuminuria, and diuretic use (each *P* interaction <0.05). Ertugliflozin reduced total events of HHF (rate ratio, 0.70 [95% CI, 0.56–0.87]) and total HHF/CV death (rate ratio, 0.83 [95% CI, 0.72–0.96]).

CONCLUSIONS: In patients with type 2 diabetes mellitus, ertugliflozin reduced the risk for first and total HHF and total HHF/CV death, adding further support for the use of sodium-glucose cotransporter 2 inhibitors in primary and secondary prevention of HHF.

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Clinical Perspective

What Is New?

- VERTIS CV (Evaluation of Ertugliflozin Efficacy and Safety Cardiovascular Outcomes Trial), a study in patients with type 2 diabetes mellitus and cardiovascular disease, enrolled a large proportion of participants with history of heart failure (HF) and known pretrial ejection fraction.
- Ertugliflozin treatment reduced first and total hospitalization for HF events with relative risk for first hospitalization for HF events being similarly beneficial (1) in those with and without a history of HF, and (2) in those with a history of HF, with reduced ejection fraction $\leq 45\%$ or preserved ejection fraction $>45\%$.
- The effect of ertugliflozin on risk for first hospitalization for HF was consistent across most baseline subgroups, but a greater benefit of ertugliflozin was observed in 3 populations: estimated glomerular filtration rate $<60 \text{ mL}\cdot\text{min}^{-1}\cdot 1.73 \text{ m}^{-2}$, albuminuria, and diuretic use.

What Are the Clinical Implications?

- The present results support current guidance recommending the use of sodium-glucose cotransporter 2 inhibitors to reduce risk of HF events.
- The results also complement emerging evidence suggesting greater benefit on HF events in those with impaired kidney function, and those taking diuretics.

Patients with type 2 diabetes mellitus (T2DM) are at high risk for heart failure (HF).¹⁻⁴ The lifetime adjusted cumulative hazard for incident HF in patients with T2DM, hypertension, and obesity with an index age of 55 years reaches 60%.⁵ Moreover, patients with T2DM represent a substantial proportion of patients hospitalized for HF. In a large global registry, patients with history of atherothrombosis and T2DM had a 30% greater risk of hospitalization for HF (HHF) than patients with atherothrombosis but without T2DM.⁶ In a large European registry, T2DM was prevalent in approximately one-half of all patients admitted for HF in 1 year at 211 cardiology centers.⁷ In comparison with those patients without diabetes, patients with diabetes had higher cumulative rates of in-hospital and 1-year mortality, and 1-year HF rehospitalization, even when adjusting for multiple clinical risk factors.⁷

Results from clinical outcome trials with glucose-lowering therapies have yielded mixed results with regard to effects on HF risk, with some increasing, many neutral, and some decreasing risk.⁸ Six clinical outcome trials with 4 different sodium-glucose cotransporter 2 (SGLT2) inhibitors in patients with T2DM, including

VERTIS CV (Evaluation of Ertugliflozin Efficacy and Safety Cardiovascular Outcomes Trial) with ertugliflozin, have demonstrated consistent reduction in risk for first HHF (with hazard ratios [HRs] ranging from 0.61 to 0.73 in the overall population) across a range of patients with and without atherosclerotic cardiovascular disease (ASCVD), and in populations with reduced estimated glomerular filtration rate (eGFR), as well,⁹⁻¹³ and in populations with or without T2DM with HF and reduced ejection fraction (EF) at baseline.¹⁴ Accordingly, the American Diabetes Association consensus report,¹⁵ the European Society of Cardiology with the European Association for the Study of Diabetes practice guidelines,¹⁶ and a statement from the American Heart Association and the Heart Failure Society of America¹⁷ have recommended the use of SGLT2 inhibitors in patients with T2DM to reduce the risk of HHF events.

The primary results of the VERTIS CV trial have been published recently.⁹ This cardiovascular (CV) safety trial, performed to satisfy the 2008 guidance from regulatory agencies for new antihyperglycemic agents,^{18,19} found that patients with T2DM with ASCVD randomly assigned to ertugliflozin 5 mg or 15 mg achieved the primary objective of noninferiority to placebo in time to first major adverse CV event, a composite end point of CV death, nonfatal myocardial infarction, or nonfatal stroke (hazard ratio [HR], 0.97 [95.6% CI, 0.85–1.11]; $P<0.001$ for noninferiority). The first secondary outcome in the hierarchical testing sequence was superiority for the time to composite of CV death or HHF, which was not met (HR, 0.88 [95.8% CI, 0.75–1.03]; $P=0.11$ for superiority); therefore, formal hypothesis testing ended with this end point.⁹ In this report, we present results from prespecified analyses of the effect of ertugliflozin versus placebo on a series of HF-related outcomes from the VERTIS CV randomized clinical trial.

METHODS

On request, and subject to review, Pfizer will provide the data that support the findings of this study. Subject to certain criteria, conditions, and exceptions, Pfizer may also provide access to the related individual anonymized participant data. See <https://www.pfizer.com/science/clinical-trials/trial-data-and-results> for more information.

Trial Design, Patient Population, and Treatment

The trial design, baseline characteristics, and main results of VERTIS CV have been published previously.^{9,20} In brief, VERTIS CV was a randomized, double-blind, multicenter trial in patients with T2DM (glycohemoglobin 7.0%–10.5%) and established ASCVD, including coronary, cerebrovascular, and peripheral vascular disease, comparing the effects of ertugliflozin with placebo on CV, renal, and metabolic outcomes. Patients were randomly assigned in a 1:1:1 ratio to ertugliflozin 5 mg, ertugliflozin 15 mg, or matching placebo

once daily added to background standard-of-care diabetes therapy. VERTIS CV was initiated in 2013. Based on evolving knowledge of the potential role of SGLT2 inhibitors in reducing the risk of CV events, the study was amended in 2016 to increase patient sample size so that these potential benefits could be assessed with adequate statistical power. Therefore, patients were recruited in 2 cohorts of ≈ 4000 patients each. General inclusion/exclusion criteria were the same for the 2 cohorts with the exception of excluding patients with HF and New York Heart Association class III and IV for cohort 1 and class IV only for cohort 2. To better characterize the VERTIS CV population, medical history of HF was collected at study entry. In addition, pretrial EF was captured from medical records when available in the overall population, retrospectively for cohort 1 and prospectively for cohort 2. The trial was conducted in accordance with the Declaration of Helsinki and the International Conference on Harmonisation Good Clinical Practice Guidelines and was approved by local authorities. An independent ethics committee or institutional review board approved the clinical protocol at each study center. All patients provided written informed consent.

Outcomes

The primary trial outcome was the time to first major adverse cardiovascular event. The key secondary outcomes included in the hierarchical statistical testing sequence were the time to first occurrence of the composite of CV death or HHF; time to CV death; and time to the first occurrence of a renal composite of renal death, renal replacement therapy, or doubling of serum creatinine. In addition, several prespecified secondary objectives included time to first HHF and total HHF/CV death (not censored at the time of the first event), which are the focus of this report.⁹

Prespecified analysis of total (first+recurrent) HHF and subgroup analyses were also performed. Subgroup analyses included the following baseline characteristics: sex, race, ethnicity, region, body mass index, diabetes duration, glycohemoglobin, albuminuria, eGFR, EF, previous HF, baseline CV conditions, and baseline medications including diuretics, mineralocorticoid receptor antagonists, β -blockers, angiotensin-converting enzyme inhibitors/angiotensin receptor blockers, insulin, and metformin.

The narrow HF standardized MedDRA query was used to determine if a patient had a history of HF at baseline. Prespecified analyses of outcomes were conducted based on pretrial EF $\leq 45\%$, $>45\%$, and unknown, both in the subset with previous HF and in the overall study population.

All CV outcomes were centrally adjudicated in a blinded manner by the independent Cardiovascular Endpoint Adjudication Committee based on previously published standardized definitions.⁹ In brief, HHF was defined as an event meeting the following criteria: (1) admission to the hospital with a primary diagnosis of HF; (2) a length-of-stay of at least 24 hours; (3) documented evidence of new or worsening symptoms of HF; (4) physical, laboratory, or diagnostic criteria for new or worsening HF; and (5) initiation or intensification of treatment specifically for HF.

Statistical Methods

Analyses were prespecified in a separate statistical analysis plan that was finalized before unblinding of the trial. Analyses were performed on an intention-to-treat basis using all randomly assigned patients and all time on-study for each patient comparing the effects of pooled ertugliflozin versus placebo.

Baseline characteristics are summarized with frequencies and percentages for categorical variables and with means and standard deviations for continuous variables. Baseline characteristics are summarized in subgroups based on history of HF at baseline (present, absent) and EF (reduced, preserved, or unknown). Reduced EF was defined as an available pretrial EF $\leq 45\%$.

The main outcomes analyzed were HHF and the composite of HHF with CV death. Time to first event was analyzed using stratified Cox proportional hazards models including cohort as the stratification factor and treatment as an explanatory factor to estimate HRs and 95% CIs. The method of Fine and Gray was used to account for competing risk of non-CV mortality in analyses of first HHF/CV death (composite) and of all-cause mortality in analyses of first HHF.²¹ Recurrent events were analyzed using the Andersen-Gill model to estimate rate ratios and 95% CIs. Recurrent events were also summarized by the number of patients with 1, 2, and ≥ 3 events. The method of mean cumulative count was used to graphically summarize total HHF events as a cumulative number of events per 100 patients over time.²² Multivariable analyses included region as the stratification factor and indicators of baseline CV disease status as additional explanatory factors. Baseline CV disease status comprised separate model terms for the presence or absence of coronary artery disease, cerebrovascular disease, peripheral vascular disease, previous myocardial infarction, and previous stroke.

Subgroup analyses based on history of HF, pretrial EF, and other factors were also conducted including assessment of treatment by subgroup interactions. Forest plots were used to summarize the results of subgroup analyses.

Analyses were performed with SAS software version 9.3 (SAS Institute Inc). Results were considered statistically significant with a 2-sided $P < 0.05$ or 95% CI excluding 1.0, with no adjustment for multiple comparisons.

RESULTS

A total of 8246 patients were randomly assigned to ertugliflozin ($n=5499$) or placebo ($n=2747$); $n=1958$ (23.7%) had previous HF and $n=5006$ (60.7%) had pretrial EF available, including $n=959$ with EF $\leq 45\%$. Among the 1958 patients with history of HF at baseline, EF data were available in 1485 (76%) patients, among whom 1007 (68%) had EF $>45\%$ and 478 (32%) had EF $\leq 45\%$. Patients were followed for a mean of 3.5 years (median 3.0 years). The Table summarizes the baseline characteristics of the study population categorized according to the presence or absence of history of HF. The baseline characteristics, in general, were well balanced between placebo and ertugliflozin. Patients with a history of HF tended

Table. Baseline Demographics and Clinical Characteristics in Patients With or Without History of Heart Failure and by Pretrial Ejection Fraction

Demographics and characteristics	HF, EF ≤45% (n=478)		HF, EF >45% (n=1007)		HF, EF unknown (n=473)		Total HF (n=1958)		Total no HF (n=6288)	
	Placebo (n=159)	Ertugliflozin (n=319)	Placebo (n=327)	Ertugliflozin (n=680)	Placebo (n=186)	Ertugliflozin (n=287)	Placebo (n=672)	Ertugliflozin (n=1286)	Placebo (n=2075)	Ertugliflozin (n=4213)
Age, y	64.2 (7.3)	64.4 (7.9)	64.7 (8.2)	63.8 (8.3)	64.9 (7.3)	64.8 (7.0)	64.7 (7.8)	64.2 (7.9)	64.3 (8.1)	64.4 (8.2)
Male, %	83.0	83.1	63.3	65.6	55.9	62.7	65.9	69.3	70.4	70.6
Region, %										
North America	18.2	18.2	9.8	9.4	9.7	8.7	11.8	11.4	25.3	25.2
South America	6.3	3.8	1.8	0.9	2.7	2.1	3.1	1.9	10.5	10.9
Europe	66.0	67.4	84.7	86.8	83.3	83.3	79.9	81.2	48.6	48.6
Asia	4.4	6.3	2.8	1.5	2.2	2.4	3.0	2.9	7.4	7.4
South Africa	1.3	2.5	0.3	0.6	0.5	2.4	0.6	1.5	5.9	5.5
Australia/New Zealand	3.8	1.9	0.6	0.9	1.6	1.0	1.6	1.2	2.3	2.4
Body mass index, kg/m ²	32.1 (4.7)	32.3 (5.5)	32.9 (5.3)	32.6 (5.3)	33.0 (5.5)	32.7 (5.9)	32.7 (5.2)	32.5 (5.5)	31.8 (5.5)	31.7 (5.3)
Glycohemoglobin, %	8.2 (1.0)	8.3 (0.9)	8.3 (0.8)	8.3 (1.0)	8.3 (1.0)	8.3 (0.9)	8.3 (0.9)	8.3 (0.9)	8.2 (1.0)	8.2 (1.0)
Duration of type 2 diabetes, y	13.4 (8.9)	13.0 (8.2)	11.6 (7.5)	11.4 (8.0)	12.4 (7.3)	11.8 (7.5)	12.3 (7.8)	11.9 (8.0)	13.4 (8.6)	13.2 (8.3)
History of dyslipidemia, %	66.7	68.7	56.0	51.8	54.8	48.8	58.2	55.3	81.2	80.5
Current tobacco use, %	16.4	13.2	7.0	8.4	10.2	9.8	10.1	9.9	15.1	14.6
History of hypertension, %	90.6	92.5	96.3	94.0	92.5	92.0	93.9	93.2	90.6	90.5
Antihyperglycemic agents, n=2, %	59.1	47.3	53.8	50.3	51.6	50.5	54.5	49.6	50.7	49.9
Antihyperglycemic agents, ≥3, %	10.1	14.7	9.5	10.7	14.5	9.1	11.0	11.4	18.3	17.3
Estimated glomerular filtration rate, mL·min ⁻¹ ·1.73 m ⁻² , %										
<30	1.3	1.6	0.6	0.4	0.0	0.7	0.6	0.8	0.3	0.3
30 to <60	32.1	26.6	24.8	20.3	23.1	23.0	26.0	22.5	20.4	21.1
60 to <90	47.8	50.8	50.2	55.4	57.5	54.4	51.6	54.0	53.7	53.0
≥90	18.9	21.0	24.5	23.8	19.4	22.0	21.7	22.7	25.6	25.6
Albuminuria, %										
Normal	49.1	52.4	59.0	58.7	50.5	56.8	54.3	56.7	59.4	58.3
Micro	38.4	34.8	27.8	28.2	31.2	31.7	31.3	30.6	30.6	29.7
Macro	10.7	11.3	9.8	10.1	16.7	9.8	11.9	10.3	7.8	9.0
Type of atherosclerotic cardiovascular disease, %										
Coronary artery disease	96.9	94.4	90.2	87.2	62.4	63.4	84.1	83.7	74.6	72.8
Peripheral artery disease	15.1	16.6	10.4	12.1	20.4	20.9	14.3	15.2	20.0	19.8
Cerebrovascular disease	11.3	16.0	22.6	23.4	43.0	41.5	25.6	25.6	21.3	22.5
New York Heart Association functional classification, %										
Class I	20.8	17.6	25.7	22.5	27.4	30.0	25.0	22.9	-	-
Class II	67.3	64.3	67.6	67.1	66.1	62.0	67.1	65.2	-	-
Class III	8.8	13.5	4.6	7.1	4.3	3.8	5.5	7.9	-	-
Class IV	0	0	0	0.1	0	0	0	0.1	-	-
Baseline medications, %										
Antiplatelets	85.5	85.6	90.5	84.7	77.4	82.9	85.7	84.5	84.6	84.5
Antihypertensives										
Angiotensin-converting enzyme inhibitors or angiotensin receptor blockers	90.6	84.3	86.5	84.3	78.5	82.2	85.3	83.8	80.3	80.0
β-Blocking agents	90.6	88.7	79.8	77.6	71.0	70.0	79.9	78.7	65.8	65.9

(Continued)

Table. Continued

Demographics and characteristics	HF, EF ≤45% (n=478)		HF, EF >45% (n=1007)		HF, EF unknown (n=473)		Total HF (n=1958)		Total no HF (n=6288)	
	Placebo (n=159)	Ertugliflozin (n=319)	Placebo (n=327)	Ertugliflozin (n=680)	Placebo (n=186)	Ertugliflozin (n=287)	Placebo (n=672)	Ertugliflozin (n=1286)	Placebo (n=2075)	Ertugliflozin (n=4213)
Calcium channel blockers	21.4	24.5	34.6	36.3	39.2	33.8	32.7	32.8	35.2	33.8
Nonloop diuretic	18.2	18.8	32.1	29.3	31.7	28.6	28.7	26.5	27.9	27.7
Loop diuretic	56.6	49.8	22.9	23.4	22.6	18.8	30.8	28.9	10.6	10.8
Mineralocorticoid receptor antagonists	40.9	41.7	9.5	12.6	9.1	11.8	16.8	19.7	5.3	4.7
Lipid-lowering drugs										
Statins	84.9	89.0	83.8	83.1	69.9	72.8	80.2	82.3	82.1	81.8
Ezetimibe	6.3	3.1	1.2	1.2	2.2	1.4	2.7	1.7	4.7	3.7

Data are mean (standard deviation) unless otherwise stated. EF indicates ejection fraction; and HF, heart failure.

to have higher prevalence of macroalbuminuria and coronary artery disease. Of the patients with HF with EF ≤45%, a greater proportion was male and more were classified with New York Heart Association class III functional status. Patients with no history of HF tended to have a higher prevalence of dyslipidemia and were taking ≥3 antihyperglycemic agents.

First Event Analyses

The outcome of risk for first HHF was lower in patients on ertugliflozin (pooled doses) versus placebo (139/5499 [2.5%] versus 99/2747 [3.6%]; HR, 0.70 [95% CI, 0.54–0.90]; $P=0.006$). For ertugliflozin 5 mg versus placebo (71/2752 [2.6%] versus 99/2747 [3.6%]), the HR was 0.71 (95% CI, 0.52–0.97) and for ertugliflozin 15 mg versus placebo (68/2747 [2.5%] versus 99/2747 [3.6%]), the HR was 0.68 (95% CI, 0.50–0.93). Figure 1 depicts the HRs for time to first HHF for the pooled dose comparison of ertugliflozin versus placebo and by individual dose (Figure 1A). The event rates per 100 patient-years were similar in the 2 ertugliflozin treatment groups (0.75 per 100 patient-years in ertugliflozin 5 mg and 0.72 per 100 patient-years in ertugliflozin 15 mg) contrasted with the placebo group (1.05 per 100 patient-years).

Figure 1 also depicts the HRs for time to first composite of HHF/CV death for the pooled dose comparison of ertugliflozin versus placebo and by individual dose (Figure 1B). Pooled ertugliflozin did not significantly reduce first HHF/CV death (HR, 0.88 [95% CI, 0.75–1.03]). The event rates per 100 patient-years in the ertugliflozin arms were similar (2.36 and 2.33 for 5 mg and 15 mg, respectively), with similar HRs in comparison with placebo (5 mg: 224/2752 [8.1%] versus placebo 250/2747 [9.1%]; HR, 0.89 [95% CI, 0.74–1.06]; and 15 mg: 220/2747 [8.0%] versus placebo 250/2747 [9.1%]; HR, 0.88 [95% CI, 0.73–1.05]).

Total Events Analyses

The total number of events for HHF and the composite of total CV death or HHF normalized for number of patients are presented in Figure 2. In these analyses of total events by the Andersen-Gill model, adjusting for history of HF and CV disease at baseline (presence of coronary artery disease, cerebrovascular disease, peripheral vascular disease, previous myocardial infarction, and previous stroke), ertugliflozin reduced total HHF (rate ratio, 0.70 [95% CI, 0.56–0.87]; $P=0.001$). Consistent with the reduction in risk for first HHF and lower rate of recurrent HHF events, the analysis of total CV death or HHF using the Andersen-Gill model showed a reduction in total events (rate ratio, 0.83 [95% CI, 0.72–0.96]; $P=0.011$). The effect on the composite of total HHF or CV death events appears to be largely attributable to the reduction in HHF-related events. Recurrent hospital admission for HHF and subsequent mortality in patients with first HHF event were lower in patients treated with ertugliflozin in comparison with placebo (Table I in the Data Supplement).

Time to Onset of Effect (First Event and Cumulative Incidence of Total HHF Events) and Subgroup Analyses for Time to First Event

The cumulative incidences of first and total (first+recurrent) HHF events are presented in Figure 3. Ertugliflozin treatment demonstrated an early separation from placebo for both the first event and total HHF events, indicating an early effect on reduction of HHF.

Figure 4 provides results of subgroup analyses of risk for first HHF by history of HF or by pretreatment EF in those randomly assigned to ertugliflozin (pooled doses) versus placebo. In these prespecified analyses, previous HF status did not modify the effect of ertugliflozin on risk for first HHF: previous HF (ertugliflozin 69/1286 [5.4%]; placebo 55/672 [8.2%]) HR, 0.63 (95% CI, 0.44–0.90) versus no previous HF (ertugliflozin 70/4213 [1.7%]; placebo

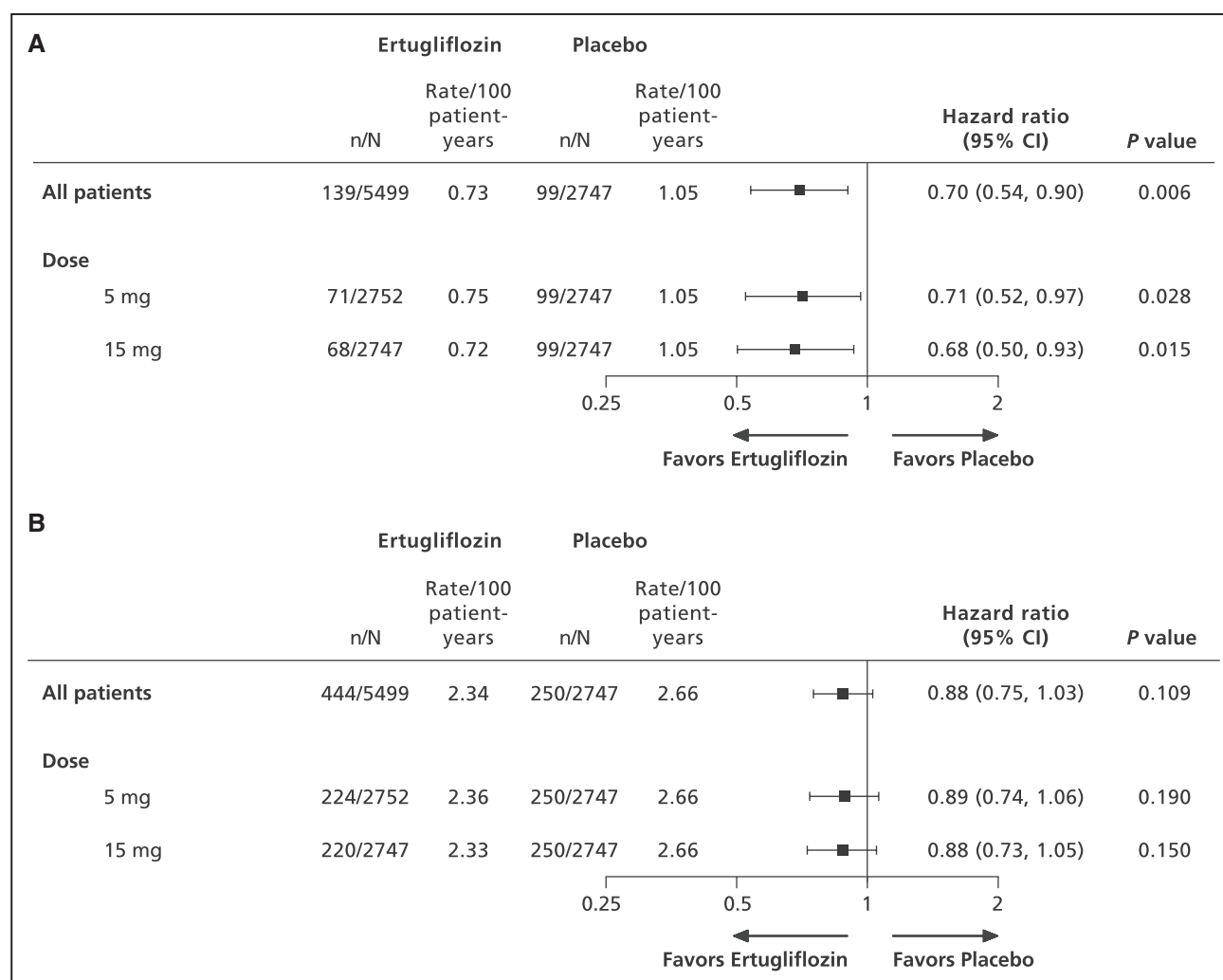


Figure 1. Time to first event analyses.

Time to first hospitalization for heart failure (A) and composite of hospitalization for heart failure/cardiovascular death (B), overall and by the dose of ertugliflozin using the Fine and Gray method. CI indicates confidence interval.

44/2075 [2.1%]) HR, 0.79 (95% CI, 0.54–1.15; *P* interaction=0.40). Because a substantial proportion of patients had pretrial EF without the presence of HF at baseline, ertugliflozin effects on risk for first HHF by pretrial EF, independent of previous HF status, was also examined and showed HR for first HHF of 0.48 (95% CI, 0.30–0.76) for EF ≤45% (ertugliflozin 37/638 [5.8%] versus placebo 37/321 [11.5%]); HR, 0.86 (95% CI, 0.58–1.29) for EF >45% (ertugliflozin 66/2724 [2.4%] versus placebo 37/1323 [2.8%]); and HR, 0.75 (95% CI, 0.45–1.25) for EF unknown (ertugliflozin 36/2137 [1.7%] versus placebo 25/1103 [2.3%]; *P* interaction=0.15; Figure 4). In a similar analysis comparing patients with EF ≤45% versus EF >45% combined with EF unknown, the *P* interaction was 0.06 (Figure I in the Data Supplement).

Figure 5 shows results of risk for first HHF by baseline HF status and pretrial EF, listing results by HF or no HF and with EF ≤45%, >45%, or unknown. The *P* value for interaction was not significant, suggesting that effects on risk for first HHF were similar in patients with HF

and EF ≤45%, >45%, or unknown. Figure II in the Data Supplement shows the results of analyses on risk for first composite of HHF/CV death, CV death, or all-cause death based on the presence or absence of HF at baseline and pretrial EF, and similarly shows no significant interactions.

Ertugliflozin effects on total events of HHF or CV death by pretrial EF, independent of previous HF status, were HR, 0.60 (95% CI, 0.45–0.81) for EF ≤45% (ertugliflozin 117/638 [18.3%] versus placebo 88/321 [27.4%]); HR, 0.86 (95% CI, 0.70–1.07) for EF >45% (ertugliflozin 236/2724 [8.7%] versus placebo 131/1323 [9.9%]); and HR, 0.94 (95% CI, 0.74–1.20) for EF unknown (ertugliflozin 186/2137 [8.7%] versus placebo 108/1103 [9.8%]; *P* interaction=0.11; Table II in the Data Supplement).

Subgroup analyses of risk for first HHF based on baseline demographics and clinical characteristics and baseline use of background medications showed consistent results across different subgroups (Figures III–V in the Data Supplement). As presented in Figure 6, the risk reduction of ertugliflozin on first HHF was greater in those with

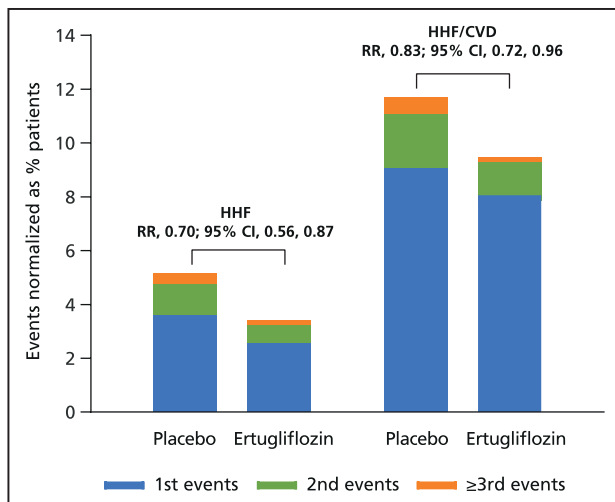


Figure 2. Percentage of patients with first and subsequent events by treatment.

Analyses were conducted using the Andersen-Gill model. The prespecified analysis of total HHF was not adjusted for the competing risk of all-cause death because there was no difference between treatment groups in the competing risk event (death) and analyses of first HHF using the Fine and Gray method to adjust for competing risk of death produced similar results to the unadjusted analyses of first HHF. CVD indicates cardiovascular death; HHF, hospitalization for heart failure; and RR, rate ratio.

baseline eGFR $<60 \text{ mL} \cdot \text{min}^{-1} \cdot 1.73 \text{ m}^{-2}$, albuminuria, and those taking diuretics and the subgroup on loop diuretics (P interaction=0.04; 0.04; 0.02; 0.01, respectively).

DISCUSSION

The overall results of VERTIS CV together with the recently published meta-analysis indicate that the effect of

ertugliflozin on HHF in patients with T2DM with ASCVD is consistent with that found across the class of SGLT2 inhibitors.^{9,23} In the current prespecified analyses, we report more detailed data with ertugliflozin on HF-related outcomes. In comparison with other recent SGLT2 inhibitor CV outcome trials in patients with T2DM, the VERTIS CV population included the largest proportion of patients with a history of HF, 23.7% of the overall trial population, similar to the proportion found in a typical diabetes clinical practice (20%–30%).²⁴ VERTIS CV also had the largest set of data on pretrial EF available, for 60.7% of patients in the trial, facilitating additional analyses of CV outcomes based on the presence or absence of HF history, and EF values, as well.

Overall, patients included in VERTIS CV were well treated with guideline-directed medical therapy for use in patients with T2DM and established ASCVD, including β -blockers, angiotensin-converting enzyme inhibitors/angiotensin receptor blockers, antiplatelets, and statins. Use of diuretics, specifically loop diuretics, and mineralocorticoid receptor antagonists were higher in patients with HF history as expected for this population. Although CV disease treatments were balanced in general, the proportion of patients reported as taking statins and mineralocorticoid receptor antagonists at baseline was slightly higher in VERTIS CV than the proportion in the other SGLT2 inhibitor CV outcome trials. In those with a history of HF in comparison with those without a history of HF, and those with HF and EF $\leq 45\%$ in comparison with those with HF and EF $>45\%$ or EF unknown, the baseline use of diuretics, especially loop diuretics, was

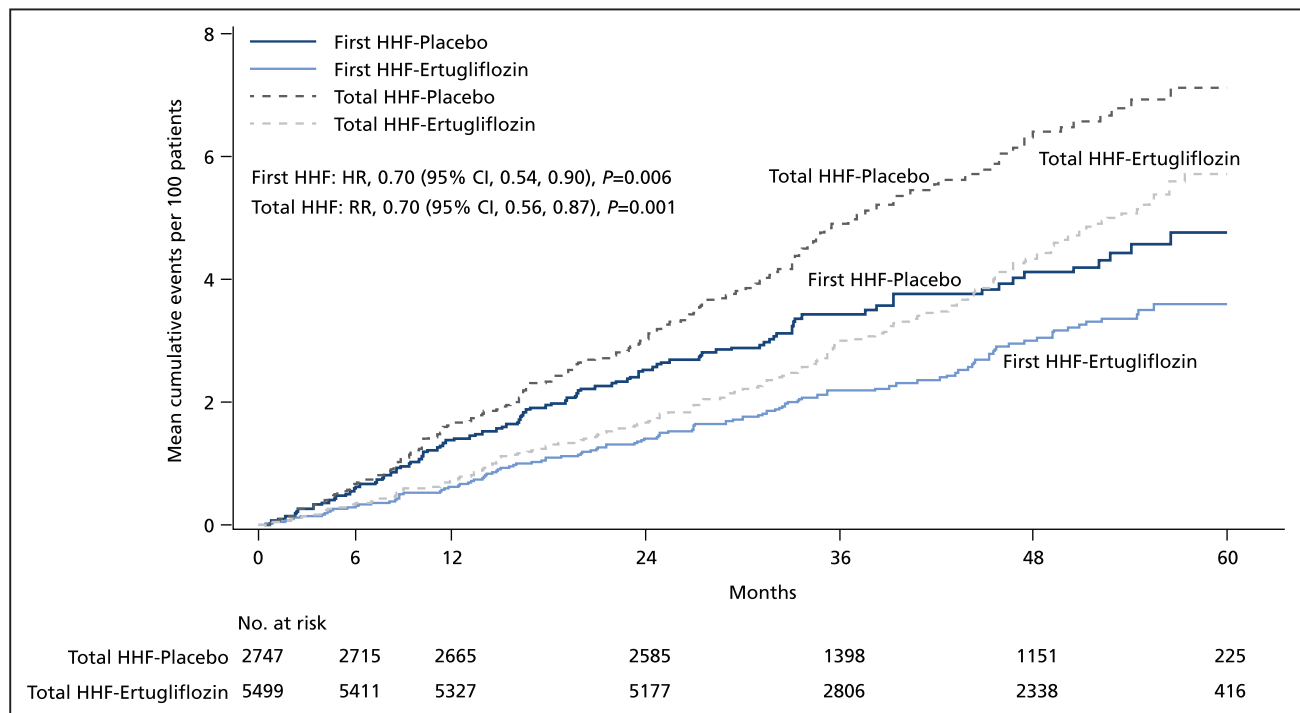


Figure 3. Cumulative incidence of first and total (first+recurrent) HHF events.

Ertugliflozin includes 5 mg and 15 mg doses. CI indicates confidence interval; HHF, hospitalization for heart failure; and HR, hazard ratio.

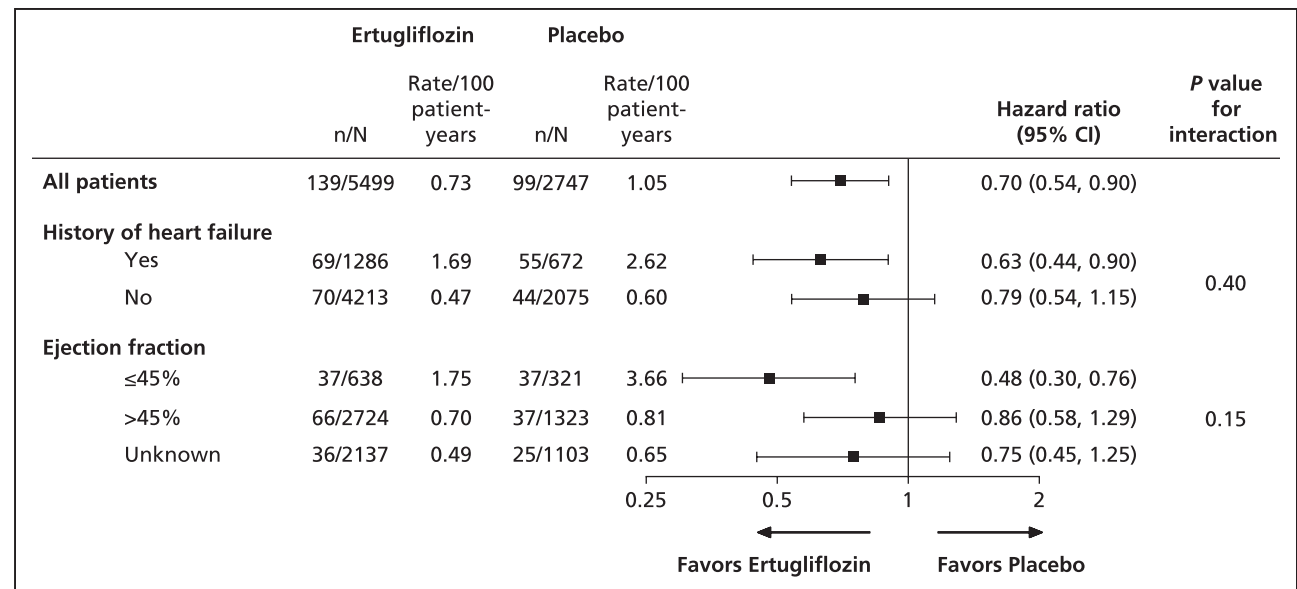


Figure 4. Time to first hospitalization for heart failure overall and by history of heart failure at baseline or by pretrial ejection fraction. CI indicates confidence interval.

notably higher. The group of patients with HF and reduced EF (EF ≤45%) had, as expected, a higher proportion of males and a higher proportion of patients with New York Heart Association class III functional status.

To date, although CV outcome trials with SGLT2 inhibitors in patients with T2DM have shown heterogeneous results with regard to the effects on CV death (HRs ranging from 0.62 to 0.98), there has been remarkable consistency in the observed reduction in risk for first event of HHF across these trials, with HRs ranging from 0.61 to 0.73.²³ In VERTIS CV, the magnitude and timing of the reduction in risk of HHF, with consistent demonstration of an early benefit after study drug initiation, and the consistency of effect between doses correspond to what has been reported for other members of the

SGLT2 inhibitor class in patients with T2DM and different levels of CV risk (with and without ASCVD).^{10,12,13} Similar findings have been reported in trial populations with albuminuric diabetic kidney disease,¹¹ and with HF and reduced EF with or without T2DM.¹⁴

This report further characterizes the effects of ertugliflozin on HHF events by baseline subgroups. Most clinical, demographic, and background treatment characteristics in VERTIS CV had no apparent modifying effect on risk for first HHF with ertugliflozin treatment. Specifically, a history of HF, although representing a subgroup of higher absolute risk for HHF, had no apparent influence on the relative risk reduction of ertugliflozin treatment. With regard to background treatment, findings with diuretics overall and specifically loop diuretics

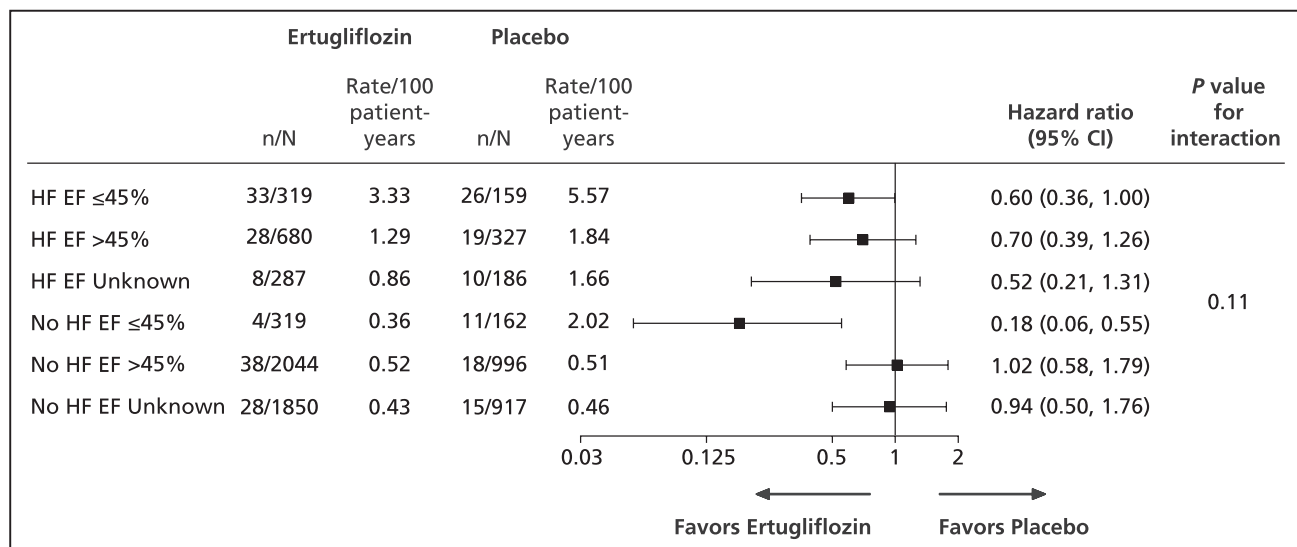


Figure 5. Time to first hospitalization for HF by history of HF at baseline and pretrial ejection fraction. CI indicates confidence interval; EF, ejection fraction; and HF, heart failure.

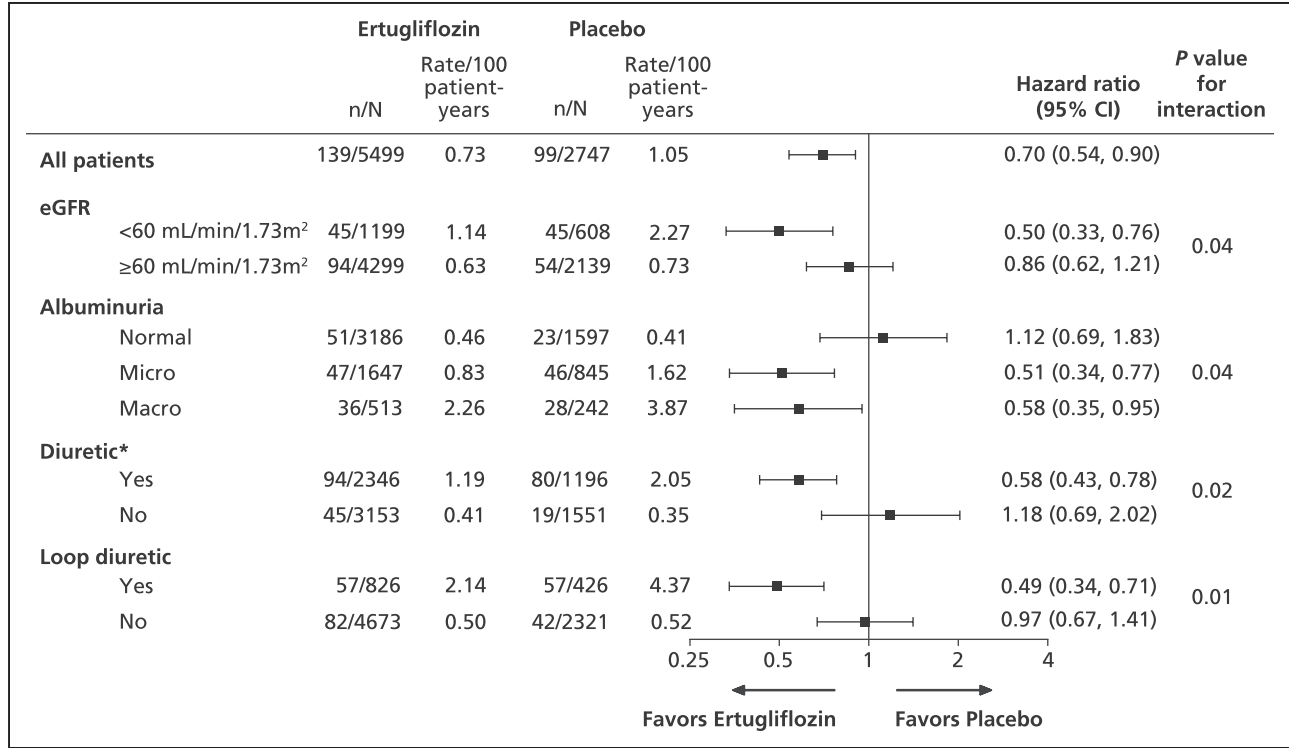


Figure 6. Time to first hospitalization for heart failure overall and by eGFR, albuminuria, and use of diuretic and loop diuretic at baseline. *Includes loop and nonloop diuretics and mineralocorticoid antagonists. CI indicates confidence interval; eGFR, estimated glomerular filtration rate.

suggest that the treatment effect of ertugliflozin on the time to first HHF outcome appears favorable. Effect modification by diuretic use was also previously suggested for the composite of HHF/CV death.⁹ Favorable interactions with diuretics on HHF and other CV outcomes have also been noted for other members of the SGLT2 inhibitor class.¹⁰ In the DAPA-HF trial (Dapagliflozin and Prevention of Adverse Outcomes in Heart Failure), which had a very high proportion (>93%) of patients taking diuretics at baseline, a favorable impact of dapagliflozin on time to HHF was demonstrated.¹⁴ SGLT2 inhibitors are functional in the proximal tubule, proximal to the site of frequently used diuretic agents, and impacting sodium, chloride, and water handling in the renal tubule; hence, functional interaction with diuretics has mechanistic plausibility.^{25,26}

The mechanistic plausibility of potential effect modification by ertugliflozin on risk for first HHF in patients with reduced eGFR and those with albuminuria also has supporting evidence from other members of the SGLT2 inhibitor class.^{11,27} Consistent with the results from VERTIS CV, in a meta-analysis of CV outcome studies of SGLT2 inhibitors that included canagliflozin, dapagliflozin, and empagliflozin, the reduction in HHF was suggested to be greater in patients with an eGFR <60 mL·min⁻¹·1.73 m⁻²,²⁸ and in the CREDENCE trial (Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation) that specifically studied patients with

reduced eGFR and albuminuria, there was clear benefit with regard to HHF.¹¹

Because the time to first event outcome does not account for recurrent events of HHF or subsequent mortality, the VERTIS CV protocol prespecified analyses of total HHF and the composite total HHF/CV death to better assess effects on net morbidity burden. Although the effect on risk for first event of the composite of HHF/CV death did not achieve statistical significance in the primary VERTIS CV analysis,⁹ the present prespecified secondary analysis indicates that ertugliflozin reduced total events of HHF/CV death by 17% and total HHF events by 30%.

Subgroup analyses of the overall study population based on EF regardless of the presence or absence of HF suggested that the HR estimated for EF ≤45% was lower with ertugliflozin treatment than that for EF >45% or unknown EF, although the interaction test was not statistically significant. When the EF categories were split into those with and without a history of HF, the results were consistent with the overall results. Data from DAPA-HF in patients with reduced EF, together with ongoing trials in populations with HF with preserved or reduced EF, will provide additional insights into patient populations that may benefit the most from SGLT2 inhibition with regard to CV-related outcomes.

Limitations

Results of EF analyses, although suggestive of potentially greater benefit in patients with reduced EF, has potential limitations because EF was obtained from medical records abstraction instead of by measurement at trial entry, which might not reflect EF at the time of randomization, and data were not available on $\approx 40\%$ of the trial cohort. The grouping of patients with EF $>45\%$ with those with unknown EF also has potential limitations. In addition, because of the limited number of patients in each subgroup, the analyses are not powered to detect statistically significant differences. Finally, these analyses are not corrected for multiplicity.

Conclusions

Ertugliflozin reduced risk for first HHF, for total HHF, and for total HHF/CV death events in patients with T2DM in the VERTIS CV trial, findings consistent with those reported for other members of the SGLT2 inhibitor class,^{10–13,23} and provide additional supportive evidence for the use of SGLT2 inhibition in patients with T2DM to prevent HF-related outcomes.

ARTICLE INFORMATION

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Supplemental Materials

Data Supplement Tables I–II

Data Supplement Figures I–V

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