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Cardiovascular and Renal Outcomes with Ertugliflozin by Baseline Use of Renin-Angiotensin-Aldosterone System Inhibitors or Diuretics, Including Mineralocorticoid Receptor Antagonist: Analyses from the VERTIS CV Trial

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Cardiovascular disease · Ertugliflozin · SGLT2 inhibitor · Type 2 diabetes

Abstract

Introduction: VERTIS CV was a placebo-controlled cardiovascular (CV) outcome trial evaluating the sodium-glucose cotransporter 2 inhibitor ertugliflozin in patients with type 2 diabetes and established atherosclerotic CV disease. The aim of the current analyses was to evaluate VERTIS CV cardiorenal outcomes according to baseline use of renin-angiotensin-aldosterone system (RAAS) inhibitors or diuretics, including mineralocorticoid receptor antagonists (MRAs). ***Methods:*** Participants received ertugliflozin 5 mg, ertugliflozin 15 mg, or placebo once daily and were followed for a mean of 3.5 years. Prespecified CV and kidney outcomes were analyzed by Cox proportional hazard modeling in participant subgroups defined by baseline use of RAAS inhibitors (angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers) or diuretics (loop diuretics, non-loop diuretics, MRAs), with interaction testing to assess for treatment effect modification. ***Results:*** A total of 8,246 patients were randomized in VERTIS CV. At baseline, 6,686 (81%) participants were being treated with RAAS inhibitors, 3,542 (43%) with diuretics, 1,252 (15%) with loop diuretics, and 674 (8%) with MRAs. No significant interactions were observed for cardiorenal outcomes by baseline use of RAAS inhibitors or MRAs ($p_{interaction} > 0.05$ for all). Statistically

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significant interactions for a first event of hospitalization for heart failure (HHF) or CV death, and of HHF (alone), were observed with baseline use of diuretics, including loop diuretics, with an increased benefit of ertugliflozin treatment versus placebo. ***Conclusion:*** In VERTIS CV, baseline use of diuretics, particularly loop diuretics, identified a subgroup that demonstrated greater benefit with ertugliflozin on first HHF/CV death and HHF outcomes, with no modification of treatment effect observed with baseline use of RAAS inhibitors or MRAs. There was no evidence of treatment effect on the kidney composite outcomes by baseline use of RAAS inhibitors, diuretics, loop diuretics, or MRAs.

Introduction

Overactivity of the renin-angiotensin-aldosterone system (RAAS), which plays a critical role in maintaining blood pressure, fluid homeostasis, electrolyte balance, and cardiorenal function, is associated with the development of hypertension, chronic kidney disease (CKD), and risk of cardiovascular (CV) events [1]. These cardiorenal conditions are frequent comorbidities in patients with type 2 diabetes (T2D) [2], contributing to the increased risk of morbidity and mortality in these patients. Medications that modulate the activity of the RAAS have been shown to be renoprotective and reduce the risk of hospitalization for heart failure (HHF) in patients with T2D [3].

Sodium-glucose cotransporter 2 (SGLT2) inhibitors are antihyperglycemic medications that act at the level of the kidney by inducing glucosuria, with concomitant effects of natriuresis and diuresis [4]. CV outcomes trials (CVOTs) in participants with T2D have demonstrated that treatment with SGLT2 inhibitors can reduce the risk of HHF and preserve kidney function, with some also reducing the risk of major adverse CV events (MACE; a composite of CV death, nonfatal myocardial infarction [MI], or nonfatal stroke) and CV death (alone) [5–13]. A large proportion of participants with T2D enrolled in CVOTs of SGLT2 inhibitors were taking RAAS inhibitors or diuretics at baseline, with ~80% of patients on RAAS inhibitors and ~40–45% of patients on diuretics [5, 6, 8, 9]. Although some studies have suggested an incremental cardiorenal benefit when these medications are used in combination with SGLT2 inhibition [14, 15], further analyses are required to examine whether background RAAS inhibitor/diuretic use modifies the treatment effect of SGLT2 inhibitors.

In the VERTIS CV trial – the CVOT for the SGLT2 inhibitor ertugliflozin conducted in patients with T2D and atherosclerotic CV disease – ertugliflozin met the noninferiority criterion for the primary endpoint of MACE [9]. Although superiority for the key secondary endpoints of HHF or CV death, CV death, and a kidney composite outcome of a doubling of serum creatine from baseline, dialysis/transplantation, or renal death was not achieved [9], prespecified secondary analyses demonstrated a 30% reduction in the relative risk of HHF (first and total) [10], and a 34% reduction in the relative risk of an exploratory kidney composite outcome of a sustained ≥40% reduction from baseline in estimated glomerular filtration rate (eGFR), dialysis/transplantation, or renal death [13]. Here, we report the results of prespecified secondary analyses of the VERTIS CV trial data that assessed the effects of ertugliflozin on CV and kidney outcomes according to baseline use of RAAS inhibitors or diuretics, which included loop diuretics, non-loop diuretics, and mineralocorticoid receptor antagonists (MRAs).

Methods

Trial Design and Participants

The detailed protocol, statistical analysis plan, and primary findings of the VERTIS CV trial (NCT01986881) have been published [9, 16]. VERTIS CV was a multicenter, randomized, double-blind, placebo-controlled, parallel-group, event-driven trial conducted to assess the CV safety and efficacy of ertugliflozin compared with placebo. Participants were randomly assigned (1:1:1) to oral, once daily ertugliflozin 5 mg, ertugliflozin 15 mg, or placebo, in addition to background standard-of-care treatment.

Eligible participants were ≥40 years of age with T2D (glycated hemoglobin [HbA1c] 7.0–10.5%, inclusive) and stable, established atherosclerotic CV disease involving the coronary, cerebrovascular, and/or peripheral arterial systems. Key exclusion criteria included a history of type 1 diabetes or ketoacidosis, or an eGFR <30 mL/min/1.73 m^2.

Study Outcomes

The primary outcome of VERTIS CV was time to first MACE, which was a composite of CV death, nonfatal MI, or nonfatal stroke. Key secondary outcomes were HHF or CV death; CV death (alone); and a kidney composite outcome of a doubling of the serum creatinine level from baseline, dialysis/transplantation, or renal death. Additional secondary outcomes included HHF (alone), and an exploratory kidney composite outcome of a sustained ≥40% reduction from baseline in eGFR (defined as the occurrence of a value that met the cutoff criterion that was followed, more

than 30 days later, by a subsequent value that also met the cutoff criterion), dialysis/transplantation, or renal death [13]. The outcome of time to initiation of a loop diuretic in participants not being treated with loop diuretics at baseline was also assessed. Safety outcomes included adverse events (AE), including prespecified AEs, AEs of special interest (hypoglycemia and AEs associated with urinary tract infection [UTI], genital mycotic infection, and hypovolemia) and selected laboratory measures (eGFR, potassium and hemoglobin). Details of the statistical analyses are described in the online supplementary material (for all online suppl. material, see https://doi.org/10.1159/000543162).

Results

Baseline Characteristics

A total of 8,246 patients were randomized in VERTIS CV; 8,238 participants received at least one dose of ertugliflozin or placebo [9, 16]. Of the 8,246 patients randomized, at baseline, 6,686 (81%) participants were being treated with RAAS inhibitors and 3,542 (43%) participants were being treated with diuretics, including 1,252 (15%) with loop diuretics, 2,278 (28%) with non-loop diuretics, and 674 (8%) with MRAs, either as monotherapy or as combination therapy.

Baseline demographic and clinical characteristics of participants using RAAS inhibitor, diuretic, loop diuretic, and MRA use at baseline are shown in Table 1. Although characteristics were generally well-balanced across medications, and between users and non-users of each medication, some differences were noted. Mean baseline eGFR was lower in participants who used diuretics, including loop diuretics and MRAs, compared with non-users (Table 1). Consistent with this, a greater proportion of participants using these medications at baseline had impaired kidney function (the proportion of participants with a mean eGFR <60 mL/min/1.73 m^2 at baseline) than non-users. The use of RAAS inhibitors at baseline did not appear to be associated with decreased kidney function according to baseline eGFR (Table 1). Consistent with their indicated uses, a greater proportion of participants with baseline use of RAAS inhibitors or diuretics, including loop diuretics and MRAs, had a greater burden of CV disease and its associated risk factors at study entry compared with non-users, including hypertension, coronary artery disease, and heart failure. Coadministration of other CV medications, such as β-blockers, anticoagulants, and statins, was more common in participants using RAAS inhibitors, loop diuretics, or MRAs at baseline compared with non-users (Table 1). It is especially notable that 57.4% of participants using MRAs at baseline were also using loop diuretics at baseline versus 11.4% of non-users; conversely, 30.9% of participants using loop diuretics at baseline were also using MRAs at baseline versus 4.1% of non-users, demonstrating that loop diuretic and MRA use disproportionately track together.

Cardiorenal Outcomes

By RAAS Inhibitor, Diuretic, Loop Diuretic, or MRA Use

The effects of ertugliflozin versus placebo on CV and kidney outcomes in participant subgroups defined by baseline RAAS inhibitor, diuretic, loop diuretic, or MRA use are shown in Figure 1. There was no significant difference in the effect of ertugliflozin on the primary MACE outcome between patients with versus without baseline use of RAAS inhibitors, diuretics, loop diuretics, or MRAs (all $p_{interaction} > 0.05$) (Fig. 1).

Of the secondary outcomes assessed, ertugliflozin treatment was associated with greater reductions in risk of first events of HHF/CV death (HR [95% CI], 0.74 [0.61, 0.91]; $p_{interaction} = 0.01$) and of HHF (HR [95% CI], 0.58 [0.43, 0.78]; $p_{interaction} = 0.02$) in participants using diuretics compared with those not using diuretics at baseline (Fig. 1). A similar pattern in terms of greater reductions in risk of HHF/CV death (HR [95% CI], 0.65 [0.50, 0.85]; $p_{interaction} = 0.006$) and HHF (HR [95% CI], 0.49 [0.34, 0.71]; $p_{interaction} = 0.01$) with ertugliflozin was also observed in participants using loop diuretics at baseline compared with non-users (Fig. 1). However, no significant interactions were observed for the remaining CV outcome of CV death or for the kidney composite outcomes (based on either a doubling of serum creatinine or a sustained ≥40% reduction in eGFR) in participants with versus without baseline diuretic or loop diuretic use (all $p_{interaction} > 0.05$; Fig. 1). No significant interactions were observed for any of the secondary CV and kidney outcomes in participants with versus without baseline use of RAAS inhibitors or MRAs (all $p_{interaction} > 0.05$; Fig. 1).

By Diuretic Class Use

To further investigate the potential modifying effect of baseline diuretic use, the effects of ertugliflozin versus placebo on the secondary CV and kidney outcomes in participant subgroups defined by baseline use of different diuretic classes were assessed and are shown in Figure 2. When participants were subdivided into those with baseline use of loop diuretics and/or MRAs (both indicated for heart failure and disproportionately track together and are used by those with a history of heart failure in VERTIS CV; see Table 1), all other diuretics, or no diuretics, significant interactions were noted for first events of HHF/CV death ($p_{interaction} = 0.01$) and of HHF ($p_{interaction} = 0.03$), with users

Table 1. Baseline demographic and clinical characteristics by baseline use of RAAS inhibitor, diuretic, loop diuretic, and MRA medications

Characteristics	Baseline medication use							
	RAAS inhibitors		diuretics		loop diuretics		MRAs	
	yes (n = 6,686)	no (n = 1,560)	yes (n = 3,542)	no (n = 4,704)	yes (n = 1,252)	no (n = 6,994)	yes (n = 674)	no (n = 7,572)
Age, years	64.4 (8.0)	64.1 (8.5)	65.1 (7.8)	63.8 (8.3)	66.1 (7.9)	64.1 (8.1)	65.2 (7.9)	64.3 (8.1)
Male sex, n (%)	4,663 (69.7)	1,106 (70.9)	2,378 (67.1)	3,391 (72.1)	876 (70.0)	4,893 (70.0)	499 (74.0)	5,270 (69.6)
BMI, kg/m^2	32.1 (5.4)	31.2 (5.4)	33.2 (5.4)	31.0 (5.2)	34.4 (5.7)	31.5 (5.2)	33.3 (5.7)	31.8 (5.4)
White race, n (%)	5,903 (88.3)	1,337 (85.7)	3,176 (89.7)	4,064 (86.4)	1,099 (87.8)	6,141 (87.8)	602 (89.3)	6,638 (87.7)
eGFR, mL/min/1.73 m^2	75.4 (20.6)	78.3 (21.6)	71.7 (20.8)	79.2 (20.4)	66.3 (20.4)	77.7 (20.5)	69.3 (20.5)	76.6 (20.8)
<60 mL/min/1.73 m^2, n (%)	1,503 (22.5)	304 (19.5)	1,020 (28.8)	787 (16.7)	487 (38.9)	1,320 (18.9)	228 (33.8)	1,579 (20.9)
≥60–<90 mL/min/1.73 m^2, n (%)	3,585 (53.6)	805 (51.6)	1,876 (53.0)	2,514 (53.4)	598 (47.8)	3,792 (54.2)	340 (50.4)	4,050 (53.5)
≥90 mL/min/1.73 m^2, n (%)	1,597 (23.9)	451 (28.9)	646 (18.2)	1,402 (29.8)	167 (13.3)	1,881 (26.9)	106 (15.7)	1,942 (25.6)
Duration of T2D, years	13.1 (8.4)	12.2 (7.9)	13.5 (8.5)	12.5 (8.2)	15.0 (9.0)	12.6 (8.2)	13.0 (8.1)	13.0 (8.3)
HbA_{1c}, %	8.2 (0.9)	8.3 (1.0)	8.2 (0.9)	8.2 (1.0)	8.2 (0.9)	8.2 (1.0)	8.2 (1.0)	8.2 (1.0)
Disease history, n (%)								
Hypertension	6,368 (95.2)	1,155 (74.0)	3,418 (96.5)	4,105 (87.3)	1,186 (94.7)	6,337 (90.6)	633 (93.9)	6,890 (91.0)
Dyslipidemia	5,085 (76.1)	1,092 (70.0)	2,724 (76.9)	3,453 (73.4)	1,026 (81.9)	5,151 (73.6)	520 (77.2)	5,657 (74.7)
CAD	5,131 (76.7)	1,125 (72.1)	2,732 (77.1)	3,524 (74.9)	1,100 (87.9)	5,156 (73.7)	612 (90.8)	5,644 (74.5)
HF	1,651 (24.7)	307 (19.7)	1,125 (31.8)	833 (17.7)	579 (46.2)	1,379 (19.7)	366 (54.3)	1,592 (21.0)
DMD	2,608 (39.0)	553 (35.4)	1,506 (42.5)	1,655 (35.2)	621 (49.6)	2,540 (36.3)	270 (40.1)	2,891 (38.2)
Medication use, n (%)								
RAAS inhibitors	6,686 (100)	0 (0.0)	3,154 (89.0)	3,532 (75.1)	1,056 (84.3)	5,630 (80.5)	577 (85.6)	6,109 (80.7)
Diuretics	3,154 (47.2)	388 (24.9)	3,542 (100)	0 (0.0)	1,252 (100)	2,290 (32.7)	674 (100)	2,868 (37.9)
Loop diuretics	1,056 (15.8)	196 (12.6)	1,252 (35.3)	0 (0.0)	1,252 (100)	0 (0.0)	387 (57.4)	865 (11.4)
MRAs	577 (8.6)	97 (6.2)	674 (19.0)	0 (0.0)	387 (30.9)	287 (4.1)	674 (100)	0 (0.0)
β-blockers	4,705 (70.4)	987 (63.3)	2,665 (75.2)	3,027 (64.3)	1,050 (83.9)	4,642 (66.4)	584 (86.6)	5,108 (67.5)
Calcium channel blockers	2,421 (36.2)	376 (24.1)	1,405 (39.7)	1,392 (29.6)	461 (36.8)	2,336 (33.4)	205 (30.4)	2,592 (34.2)
Anticoagulants	6,031 (90.2)	1,295 (83.0)	3,175 (89.6)	4,151 (88.2)	1,153 (92.1)	6,173 (88.3)	636 (94.4)	6,690 (88.4)
Statins	5,601 (83.8)	1,146 (73.5)	2,964 (83.7)	3,783 (80.4)	1,094 (87.4)	5,653 (80.8)	590 (87.5)	6,157 (81.3)

In VERTIS CV, diuretic use included use of loop diuretics, non-loop diuretics, and/or MRAs. Data are mean (SD) or n (%) where indicated. BMI, body mass index; CAD, coronary artery disease; DMD, diabetic microvascular disease; eGFR, estimated glomerular filtration rate; HbA_{1c}, glycated hemoglobin; HF, heart failure; MRA(s), mineralocorticoid receptor antagonist(s); RAAS, renin-angiotensin-aldosterone system; SD, standard deviation; T2D, type 2 diabetes.

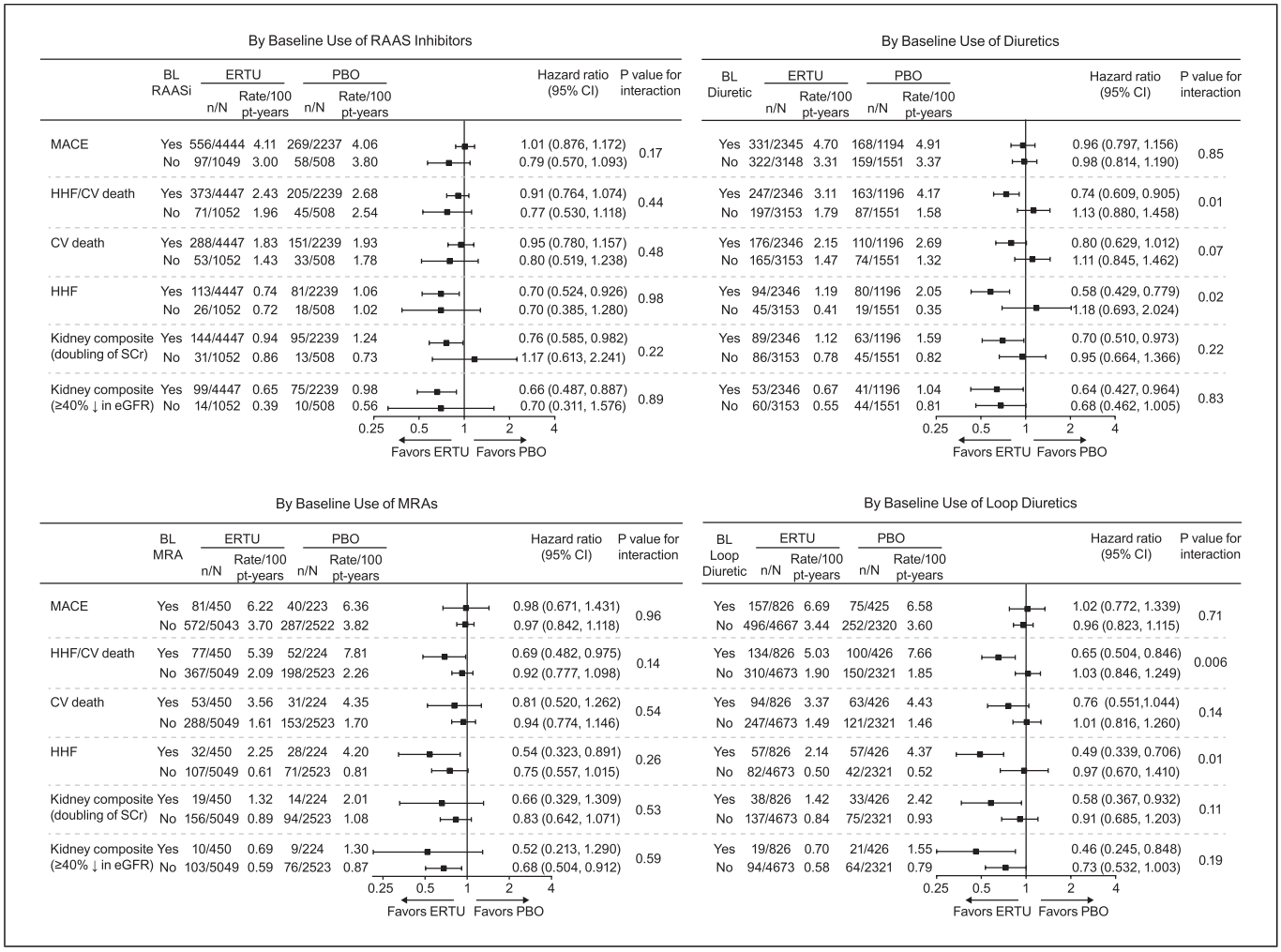


Fig. 1. Effects of ertugliflozin on cardiorenal outcomes by baseline use of RAAS inhibitor, diuretic, loop diuretic, and MRA medications.

of loop diuretics/MRAs showing the greatest benefit and users of all other diuretics showing an intermediate benefit. The same pattern did not reach statistical significance for the outcome of CV death, or the kidney composite outcome based on a doubling of serum creatinine (Fig. 2).

Total Events by Diuretic or Loop Diuretic Use

An analysis of the effects of ertugliflozin versus placebo on the total number of HHF/CV deaths and HHF events over the course of the VERTIS CV trial was also conducted. The assessment of total events was quantitatively consistent with the analysis of first events, in that ertugliflozin treatment was associated with greater reductions in the risk of these outcomes in participant subgroups with baseline use of diuretics or loop diuretics compared with non-users (all $p_{\text{interaction}} < 0.05$; Fig. 3).

First and Total HHF Events by Diuretic or Loop Diuretic Use Adjusted for Baseline eGFR

Sensitivity analyses showed that the effect of ertugliflozin was maintained with adjustment for baseline eGFR with ertugliflozin treatment with greater reductions in risk of both first and total events of HHF in participants using diuretics or loop diuretics compared with non-users (all $p_{\text{interaction}} < 0.05$; online suppl. Fig. S1).

Initiation of Loop Diuretics

For those participants not taking loop diuretics at baseline, there was a significantly reduced likelihood of initiation of loop diuretics during the study in those randomized to ertugliflozin compared with placebo (HR [95% CI], 0.85 [0.73, 0.99]; $p = 0.033$), with the curves diverging early and consistently over the study duration (online suppl. Fig. S2).

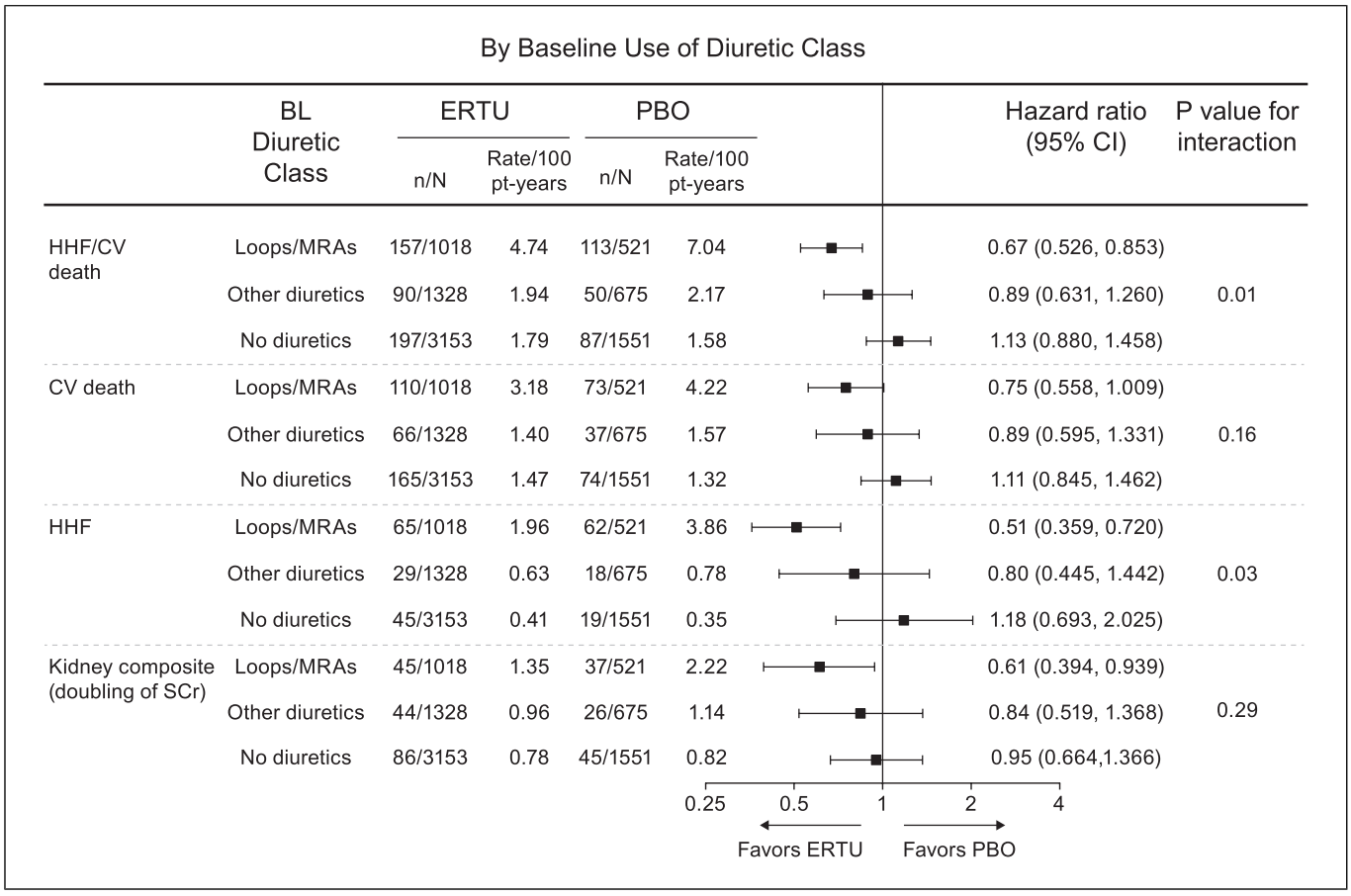


Fig. 2. Effects of ertugliflozin on cardiorenal outcomes by baseline use of different classes of diuretic medications. The analyses of outcomes were performed on an intention-to-treat basis using all participants and all time on-study for each patient. For all analyses, pooled ertugliflozin doses (5 mg and 15 mg) were compared with placebo using stratified Cox proportional hazards models that included treatment, subgroup, and treatment-by-subgroup interaction as explanatory factors and cohort category as a stratification factor. The kidney composite endpoint was defined as the composite of kidney death, kidney dialysis/transplant, or doubling of serum Cr from baseline. BL, baseline; CI, confidence interval; Cr, creatinine; CV, cardiovascular; ERTU, ertugliflozin; HHF, hospitalization for heart failure; Loops, loop diuretics; MRA(s), mineralocorticoid receptor antagonist(s); PBO, placebo; pt, participant.

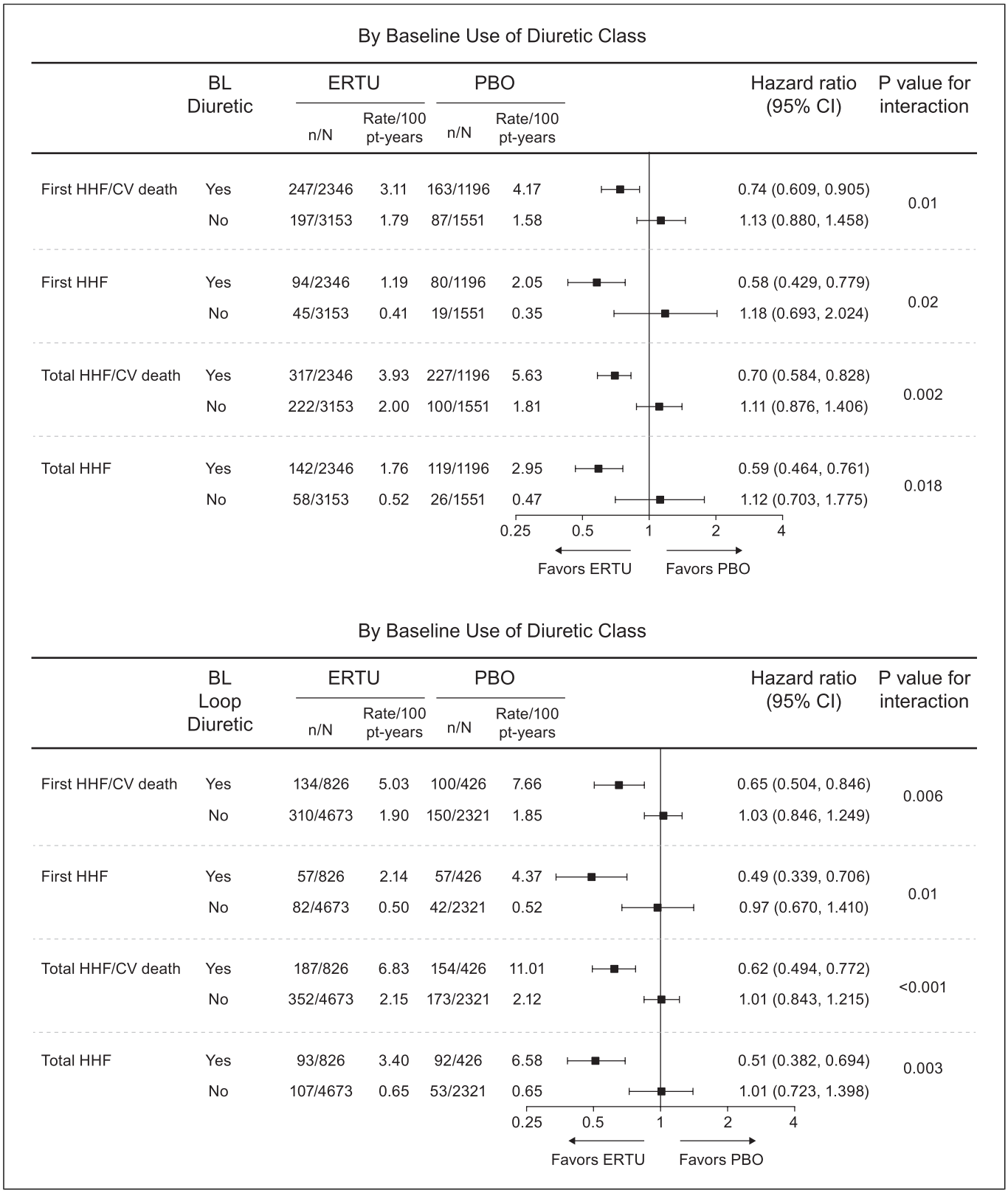
Safety Outcomes

General AEs

The incidence of AEs, deaths, and discontinuations due to AEs generally did not notably differ across treatment groups or across participant subgroups defined by baseline use of RAAS inhibitors (online suppl. Table 1) or by baseline use of diuretics (online suppl. Table 2). The incidence of serious AEs (SAEs) did not differ across treatment groups (online suppl. Table 1 and 2) or by baseline RAAS inhibitor use (online suppl. Table 1). However, the incidence of SAEs was greater in both the ertugliflozin and placebo groups among participants using diuretics at baseline compared with non-users (online suppl. Table 2).

AEs of Special Interest

The incidence of UTIs was slightly higher in participants who used diuretics at baseline versus non-users, irrespective of treatment group (online suppl. Table 2), with the caveat that there was a greater proportion of women in the subgroup of participants with baseline diuretic use (Table 1). Although there was no difference in the incidence of UTIs across treatment groups in participants using diuretics at baseline, UTI incidence was higher with ertugliflozin versus placebo in non-users of diuretics. The incidence of genital mycotic infections was higher in both men and women with ertugliflozin versus placebo irrespective of diuretic use at baseline (online suppl. Table 2).



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The risk of hypovolemia with ertugliflozin versus placebo generally did not differ across treatment groups, either overall or across participant subgroups defined by baseline use of diuretics (online suppl. Table 2; S3). An observed increase in the incidence of hypovolemia with ertugliflozin 5 mg in non-users of diuretics reached statistical significance ($p = 0.04$); however, this was not observed in the ertugliflozin 15-mg treatment group in this group of non-users of diuretics.

Other AEs of Interest

Changes in selected laboratory measures defined by baseline use of RAAS inhibitors or by baseline use of diuretics are shown in online supplementary Tables 1 and 2, respectively. The proportion of participants with a decrease in eGFR of >50% from baseline was low across all treatment groups for both users and non-users of RAAS inhibitors (online suppl. Table 1) and of diuretics (online suppl. Table 2). The incidence of a >50% decrease in eGFR was numerically smaller in users of RAAS inhibitors with ertugliflozin compared with placebo, while the incidence was similar between ertugliflozin and placebo groups among RAAS inhibitor non-users (online suppl. Table 1). Treatment with ertugliflozin did not affect the incidence of hyperkalemia (according to predetermined criteria of increased potassium levels) compared with placebo in both users and non-users of RAAS inhibitors (online suppl. Table 1) and of diuretics (online suppl. Table 2), with the exception of ertugliflozin 5 mg in non-users of diuretics at baseline for one of the criteria (an increase of ≥1.0 mEq/L and value greater than the upper limit of normal [ULN]) (online suppl. Table 2). No effect of ertugliflozin on the incidence of hypokalemia (according to a predetermined criterion of a decrease in potassium levels by ≥ 1.0 mEq/L and value less than the lower limit of normal) was observed across the participant subgroups. Ertugliflozin was associated with an increase in the incidence of raised hemoglobin level (an increase of >2.0 g/dL, with or without the value greater than the ULN) versus placebo in both users and non-users of RAAS inhibitors (online suppl. Table 1) and of diuretics (online suppl. Table 2).

Discussion

Overall, the VERTIS CV trial showed no significant effect of ertugliflozin on the endpoints of MACE, CV death, or the kidney composite outcome based on a doubling of serum creatine. This subgroup analysis of VERTIS CV trial data by baseline use of RAAS inhibitors, diuretics, loop diuretics, or MRAs showed no evidence for heterogeneity for these endpoints, or the alternative kidney composite outcome based on a sustained ≥40% reduction in eGFR. The trial did, however, identify ertugliflozin treatment as reducing the risk of the prespecified endpoints of first and total HHF and total but not first HHF/CV death. For these HHF endpoints (first and total HHF/CV death and HHF [alone]), a subgroup analysis by baseline use of (all) diuretics, or of (only) loop diuretics, showed heterogeneity of treatment effect, with those on baseline diuretics showing greater efficacy with ertugliflozin treatment. Though similar in pattern, no statistical evidence of heterogeneity in the renal composite based on a sustained ≥40% reduction in eGFR was seen.

Further subgroup analyses by baseline use of diuretics indicated for heart failure treatment (loop diuretics and/or MRAs), diuretics not specifically indicated for heart failure treatment (all other diuretics), or no baseline use of diuretics showed the treatment effect of ertugliflozin on first events of HHF/CV death and HHF was heterogeneous. The greatest reductions in risk were observed in the subgroup of participants using loop diuretics/MRAs, with the subgroup on other diuretics showing an intermediate treatment effect, and the non-users of diuretics showing the least evidence of a treatment effect. While the mean baseline eGFR was lower in participants using diuretics, including loop diuretics, the significant effect of ertugliflozin on HHF endpoints was maintained in sensitivity analyses adjusting for baseline eGFR (all $p_{interaction} < 0.05$), suggesting that the effect is not explained simply by differences in eGFR between the subgroups. For the endpoints of CV death and the kidney composite outcome based on a doubling of serum creatinine, a similar analysis did not demonstrate statistical heterogeneity.

Fig. 3. Effects of ertugliflozin on first and total events of HHF/CV death and HHF by baseline use of diuretic and loop diuretic medications. The analyses of outcomes were performed on an intention-to-treat basis using all participants and all time on-study for each patient. For analyses of first events, pooled ertugliflozin doses (5 mg and 15 mg) were compared with placebo using stratified Cox proportional hazards models that included treatment, subgroup, and treatment-by-subgroup interaction as explanatory factors and cohort category as a stratification factor. For analyses of total events, pooled ertugliflozin doses (5 mg and 15 mg) were compared with placebo using a stratified Andersen-Gill model with similar terms including the interaction of treatment-by-subgroup. BL, baseline; CI, confidence interval; CV, cardiovascular; ERTU, ertugliflozin; HHF, hospitalization for heart failure; PBO, placebo; pt, participant.

In light of these results suggesting that those on loop diuretics have higher event rates for heart failure, and greater relative benefit of ertugliflozin treatment, another notable finding of this analysis was that participants randomized to ertugliflozin not being treated with loop diuretics at baseline had a significantly reduced likelihood of initiating a loop diuretic during the trial compared with patients who received placebo, with a 15% reduction in the relative risk of a new loop diuretic initiation with ertugliflozin.

Several hypotheses may be raised to account for the apparently greater benefit of ertugliflozin on HHF-related endpoints in participants treated with loop diuretics at baseline. One is that SGLT2 inhibitor treatment causes slight increases in serum chloride, and promotes increased sodium chloride delivery to the Na-K-2Cl cotransporter through proximal natriuretic effects [17]. Since the mechanism of action of loop diuretics is mediated by chloride binding to a Na-K-2Cl cotransporter, it has been suggested that proximal natriuretics such as SGLT2 inhibitors augment loop diuretic effectiveness, leading to greater clinical benefits [18]. A second, but potentially related, concept is that SGLT2 inhibitors reduce the neurohormonal activation elicited by diuretic treatment [19, 20]. Other hypotheses might point to the obvious association that loop diuretics have with those with heart failure and CKD. Specific studies in these patient populations support the reduction in HHF in these cohorts [9, 10, 21, 22].

Other SGLT2 inhibitor CVOTs have reported results that are relevant to the data reported here for diuretics (online suppl. Table 3). First events of the prespecified exploratory endpoint of HHF/CV death were reduced with canagliflozin treatment in the CANVAS program [6]. Subgroup analyses revealed heterogeneity in baseline diuretic use ($p_{\text{interaction}} = 0.03$) favoring those on diuretics at baseline [23]. These results are in line with those reported here for the VERTIS CV trial. Results consistent with the overall diuretic use group were observed when the CANVAS data were restricted to those on loop diuretics at baseline, but this effect was not significantly different compared with non-users of loop diuretics ($p_{\text{interaction}} = 0.18$) [23]. An analysis of the endpoint of HHF alone in CANVAS also did not demonstrate heterogeneity in baseline diuretic use ($p_{\text{interaction}} = 0.58$) [14]. The CANVAS primary endpoint of MACE was statistically reduced by canagliflozin treatment. This endpoint also showed notable heterogeneity ($p_{\text{interaction}} < 0.0001$) favoring those on baseline diuretics and was the only prespecified participant subgroup to demonstrate heterogeneity [6, 14].

No heterogeneity of treatment effect was observed with empagliflozin in the EMPA-REG OUTCOME trial for the primary MACE outcome, the individual component of CV death, or the renal composite endpoint based on a doubling of serum creatinine in subgroups defined by either baseline RAAS inhibitor or diuretic use ($p_{\text{interaction}} > 0.1$ for all) [5, 24]. The lack of heterogeneity reported for these endpoints in these subgroups is also what we report here. Analyses of endpoints related to heart failure by baseline diuretic use were conducted differently to the analyses of the MACE, CV death, and renal endpoints in the EMPA-REG OUTCOME trial, the CANVAS analyses discussed above, and the analyses reported here for the VERTIS CV trial because the analyses by baseline diuretic use were conducted in subgroups further stratified by presence or absence of heart failure at baseline – hence, a 4-subgroup analysis that may have reduced the power to detect heterogeneity [25]. Analyzed this way, baseline use of loop diuretics (in participants with or without heart failure at baseline), or of thiazide diuretics (in participants without heart failure at baseline), demonstrated no heterogeneity in the effect of empagliflozin treatment between user groups across a range of CV outcomes, including the heart failure outcomes of HHF/CV death and HHF ($p_{\text{interaction}} > 0.1$ for all) [25].

The effects of dapagliflozin on CV outcomes by baseline use of RAAS inhibitors or diuretics were not reported for the DECLARE TIMI-58 trial [8]. However, the composite renal endpoint (which included a sustained ≥40% reduction in eGFR) demonstrated consistency by baseline ACE inhibitor/ARB use ($p_{\text{interaction}} = 0.16$). In contrast, the benefit on the kidney composite was attenuated for those on baseline diuretics [26].

In the VERTIS CV trial, baseline use of these background CV medications ranged from 8% of participants for MRAs up to ~80% for RAAS inhibitors; nearly half of the participants were using diuretics, with 15% using loop diuretics, at baseline. However, coadministration of these medications was not independent among VERTIS CV trial participants. For example, participants on baseline MRAs were five-fold more likely also to be taking loop diuretics than non-users of MRAs; similarly, those on baseline loop diuretics were eight-fold more likely to also be taking MRAs than non-users of loop diuretics. No evidence of an independent modification of the effect of ertugliflozin on CV or kidney outcomes was observed in the analysis of VERTIS CV trial data by baseline use of MRAs. As the overall proportion of participants on baseline MRAs was low, and with over half of these patients also taking loop diuretics, it is likely there was

insufficient power to detect a specific effect according to MRA use. However, the results of the analysis of the effects of ertugliflozin on these outcomes in the subgroup of participants using loop diuretics and/or MRAs at baseline were consistent with the significant interaction of treatment effects observed in the specific analysis of loop diuretic use. Despite demonstrated safety and efficacy profiles of MRAs in reducing mortality and HHF in patients with heart failure [27], the broader use of steroidal MRAs in patients with T2D, where concomitant kidney impairment is prevalent, has been limited due to associated adverse effects including hyperkalemia, acute kidney injury, and worsening kidney function. However, the recent approval by the US Food and Drug Administration of the nonsteroidal MRA finerenone to reduce eGFR decline, CV death, nonfatal MI, and HHF in adult patients with T2D-associated CKD [28, 29] creates a wider potential for investigating treatment interactions between MRAs and SGLT2 inhibitors in patients with T2D [30].

In VERTIS CV, the safety profile of ertugliflozin in participants using RAAS inhibitors or diuretics at baseline was similar to that seen in the overall trial population [9] and in those participants not taking these background medications at baseline (this study), with no safety signals of concern observed with concomitant use of these agents. Previously, an increased risk of hypovolemia AEs has been observed with the use of SGLT2 inhibitors in patients with T2D, especially in older patients or those being treated with diuretics [31, 32]. In the current analyses, however, the incidence of hypovolemia in participants using or not using diuretics at baseline was low and not notably different between treatment groups.

Limitations of these analyses include the definition of the participant subgroups according to baseline use of the CV medications assessed rather than their use throughout the trial. Additionally, the use of these background therapies was not randomized but rather prescribed based on a patient's individual treatment requirements. Hence, differences in baseline characteristics between these subgroups could have affected risk profiles and influenced outcomes. Additionally, many participants were taking multiple CV medications across various classes and these combinations could have affected the findings. Small patient numbers in some subgroups, specifically those using MRAs at baseline, limit the conclusions that can be drawn from those particular analyses. Finally, as the analyses were a mix of prespecified and post hoc analyses and were not subject to multiplicity adjustment, the results should be considered hypothesis generating.

In VERTIS CV, baseline use of diuretics, especially loop diuretics, may identify a population with a greater treatment effect of ertugliflozin on first and total HHF/CV death and HHF outcomes. Ertugliflozin was also associated with a delay in initiation of loop diuretic use in participants who were not taking loop diuretics at baseline. These findings emphasize the safety and efficacy of ertugliflozin in patients using common CV medications.

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Statement of Ethics

The VERTIS CV trial (ClinicalTrials.gov identifier: NCT01986881) was conducted in compliance with the ethical principles of the Declaration of Helsinki and in compliance with all International Conference on Harmonization Good Clinical Practice Guidelines. The final protocol and informed consent documentation were reviewed and approved by the Institutional Review Board or independent Ethics Committee for each investigational center. This full list of participating site and Ethics Committees can be found at DOI: 10.1056/NEJMoa2004967. Written informed consent was obtained from all trial participants.

Conflict of Interest Statement

D.Z.I.C. has received consulting fees and/or speaking honorarium from AstraZeneca, Bayer, Boehringer Ingelheim, Eli Lilly, Janssen, Merck & Co. Inc., Rahway, NJ, USA, Mitsubishi-Tanabe, Novo Nordisk, Prometic, and Sanofi and has received operating funds from AstraZeneca, Boehringer Ingelheim, Eli Lilly, Janssen, Merck & Co. Inc., Rahway, NJ, USA, Novo Nordisk, and Sanofi.Novo Nordisk, and Sanofi. R.E.P. has received grants (directed to his institution) from Hanmi Pharmaceutical Co., Ltd, Janssen, Metavention, Novo Nordisk, Poxel SA, and Sanofi; has received consulting fees (directed to his institution) from AstraZeneca, Corcept Therapeutics Incorporated, Glytec LLC, Hanmi Pharmaceutical Co., Ltd, Janssen, Merck & Co., Inc., Rahway, NJ, USA, Mundipharma, Novo Nordisk, Pfizer, Sanofi, Scohia Pharma Inc., and Sun Pharmaceutical Industries; and has received support for attending meetings/travel (directed to his institution or to the travel provider) from AstraZeneca, Glytec LLC, Merck & Co., Inc., Rahway, NJ, USA, Mundipharma, Novo Nordisk, and Pfizer. F.C. has received research grants from the Swedish Research Council, Swedish Heart & Lung Foundation, and King Gustav V and Queen Victoria Foundation and has received consulting fees

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Author Contributions

D.Z.I.C., R.F., R.E.P., F.C., S.D.-J., A.P., I.G., N.B.C., J.P.M., U.M., and C.P.C. are responsible for the work described in this article. All authors were involved in at least one of the following: study conception; design of work; or acquisition, analysis and interpretation of data; critically reviewing and revising the article for important intellectual content; providing final approval of the published version; accepting responsibility for the work and/or the conduct of the study; and access to the data.

Data Availability Statement

The data that support the findings of this study are not publicly available due to their containing information that could compromise the privacy of the research participants. Upon 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 de-identified participant data. See https://www.pfizer.com/science/clinical-trials/trial-data-and-results for more information.

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