KI REPORTS
KIReports.org
CLINICAL RESEARCH

Heart and Kidney Outcomes With Ertugliflozin in People with Non-albuminuric Diabetic Kidney Disease: A *post hoc* Analysis from the Randomized VERTIS CV Trial

David Z.I. Cherney[1], Samuel Dagogo-Jack[2], Francesco Cosentino[3], Richard E. Pratley[4], Robert Frederich[5], Mario Maldonado[6], Chih-Chin Liu[7], Christopher P. Cannon[8], and for the VERTIS CV Investigators

[1]Division of Nephrology, University of Toronto, Toronto, Ontario, Canada; [2]Division of Endocrinology, Diabetes & Metabolism & Director, Clinical Research Center, University of Tennessee Health Science Center, Memphis, Tennessee, USA; [3]Unit of Cardiology, Karolinska Institute & Karolinska University Hospital, Stockholm, Sweden; [4]AdventHealth Translational Research Institute, Orlando, Florida, USA; [5]Pfizer, Inc., Groton, Connecticut, USA; [6]MSD Limited, London, UK; [7]Merck & Co., Inc., Kenilworth, New Jersey, USA; and [8]Cardiovascular Division, Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts, USA

Introduction: Using data from the VERTIS CV trial (NCT01986881), the impact of ertugliflozin in patients with nonalbuminuric diabetic kidney disease (DKD-non-Alb) was assessed.

Methods: Patients with type 2 diabetes mellitus (T2DM) and atherosclerotic cardiovascular disease (ASCVD) were randomized to ertugliflozin or placebo. Subgroups were defined by estimated glomerular filtration rate (eGFR) (ml/min per 1.73 m^2) and urinary albumin-to-creatinine ratios (UACRs) (mg/g): DKD-Non-Alb (eGFR $< 60 +$ UACR < 30, $n = 867$); Alb DKD stage 3 (DKD stage 3 Alb, eGFR $< 60 +$ UACR ≥ 30, $n = 891$); Alb DKD stages 1 + 2 (DKD stages 1–2 Alb, eGFR $\geq 60 +$ UACR ≥ 30, $n = 2356$); and no DKD (non-DKD, eGFR $\geq 60 +$ UACR < 30, $n = 3916$). eGFR slopes, eGFR and UACR over time, time to first event of a prespecified exploratory kidney composite outcome, albuminuria progression, and hospitalization for heart failure (HHF) were assessed.

Results: Total eGFR slopes (ml/min per 1.73 m^2 per year; weeks 0–260) with placebo were −0.23, −1.27, −2.29, and −1.19 for the DKD-Non-Alb, DKD stage 3 Alb, DKD stages 1 to 2 Alb, and non-DKD subgroups, respectively ($P < 0.0001$). Similar trends were found with ertugliflozin but with reduced rates of decline. Ertugliflozin treatment resulted in a significant reduction in the risk for albuminuria progression across subgroups, with Alb subgroups having the largest relative risk reduction ($P_{interaction} = 0.04$). The hazard ratios (HRs) for ertugliflozin revealing reduction in the risk of the exploratory kidney composite outcome versus placebo was consistent across subgroups ($P_{interaction} = 0.34$). Alb and the DKD-non-Alb subgroups had a larger relative risk reduction in the HHF outcome compared with other subgroups ($P_{interaction} = 0.046$).

Conclusion: Among the subgroups, participants with DKD-non-Alb had the slowest rate of eGFR decline. Ertugliflozin treatment resulted in reductions in albuminuria and slower decline in eGFR across subgroups. The effect of ertugliflozin on the HHF outcome was larger in those with more advanced kidney disease.

Kidney Int Rep (2022) **7,** 1782–1792; https://doi.org/10.1016/j.ekir.2022.05.007
KEYWORDS: albuminuria; diabetic kidney disease; ertugliflozin; sodium-glucose cotransporter 2 inhibitor; type 2 diabetes mellitus
© 2022 [Author/Employing Institution]. Published by Elsevier Inc. on behalf of the International Society of Nephrology. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

DKDis a leading cause of end-stage kidney disease globally.[1] The classical paradigm for the clinical course of DKD is a progressive natural history characterized by gradually increasing albuminuria and a decline in GFR leading to end-stage kidney disease.[2] Risk markers for DKD, including albuminuria and eGFR impairment, are also associated with the development of ASCVD, HHF, and mortality.[3,4] There has been growing recognition that some patients with DKD do not follow the classical pathway to end-stage kidney disease characterized by progressive albuminuria and instead exhibit progressive eGFR decline in the presence

Correspondence: David Z.I. Cherney, Division of Nephrology, University of Toronto, Toronto General Hospital, 585 University Avenue, 8N-845, Toronto, Ontario M5G 2N2, Canada. E-mail: david.cherney@uhn.ca

Received 7 April 2022; accepted 2 May 2022; published online 13 May 2022

of normal levels of UACR.[2] Although the mechanisms responsible for this DKD-non-Alb phenotype remain incompletely understood,[2] several factors may be responsible, including the use of medications that block the renin–angiotensin–aldosterone system and thereby attenuate albuminuria.[1] In addition, the DKD-non-Alb clinical phenotype is associated with the development of kidney disease in elderly patients with diabetes,[2] in whom ischemia may contribute to DKD progression. Ischemia may impair kidney function while reducing intraglomerular pressure and associated albuminuria.[1,2,5]

Regardless of the pathophysiological basis for the DKD-non-Alb clinical presentation, it is important to understand the risk factors linked with DKD-non-Alb to identify those at risk for this condition, and thereby potentially institute earlier therapies. Insights into the natural history of DKD-non-Alb are needed to understand the role for emerging therapies, including SGLT2 inhibitors, which may prevent eGFR loss even in the absence of albuminuria.

To better understand the role of SGLT2 inhibition in patients with DKD-non-Alb, we evaluated the VERTIS CV trial cohort, which included a large proportion of patients with incidental DKD. VERTIS CV was a cardiovascular outcomes trial (NCT01986881) that assessed the effects of ertugliflozin compared with placebo in patients with T2DM and established ASCVD.[6–8] A prespecified exploratory kidney composite outcome (sustained ≥40% decrease in eGFR from baseline, dialysis/transplantation, or kidney death) revealed a 34% relative risk reduction with ertugliflozin versus placebo.[7] The prespecified secondary outcome of time to first HHF event revealed a 30% relative risk reduction with ertugliflozin versus placebo and a 30% reduction in total HHF events.[6,9] In the VERTIS CV trial, 21.9% of the subjects at baseline had an eGFR <60 ml/min per 1.73 m^2.[7] The goal of this *post hoc* analysis was to evaluate participants with DKD-non-Alb compared with the other subgroups from the VERTIS CV trial to better understand the impact of DKD-non-Alb on subsequent kidney disease progression and HHF and to compare the effects of ertugliflozin across the 4 groups.

METHODS

The VERTIS CV trial (protocol MK-8835-004-01; NCT01986881) was a multicenter, randomized, double-blind, placebo-controlled, event-driven trial in patients with T2DM and established ASCVD comparing placebo with 2 doses of ertugliflozin (5 mg and 15 mg). The VERTIS CV trial design, eligibility, primary results, kidney end points, and full study protocol have been previously published.[6–8,10]

Study Population

The trial recruited patients with T2DM and established ASCVD who had a baseline screening eGFR ≥30 ml/min per 1.73 m^2. The trial was approved by the appropriate institutional review boards and regulatory agencies, with all participants providing written informed consent.[6–8,10]

Classification by Baseline eGFR and Alb Status

In this *post hoc* analysis, patients required both a baseline serum creatinine measure (needed to estimate GFR using the Modification of Diet in Renal Disease formula)[11] and a baseline UACR measure for subgroup stratification. On the basis of these 2 criteria, patients were assigned to 1 of the following 4 subgroups based on baseline clinical presentation of DKD:

1. DKD-non-Alb: baseline eGFR <60 ml/min per 1.73 m^2 and UACR <30 mg/g;
2. Alb DKD stage 3 (DKD stage 3 Alb): baseline eGFR <60 ml/min per 1.73 m^2 and UACR ≥30 mg/g;
3. Alb DKD stages 1 and 2 (DKD stages 1–2 Alb): baseline eGFR ≥60 ml/min per 1.73 m^2 and UACR ≥30 mg/g; and
4. no DKD (non-DKD): baseline eGFR ≥60 ml/min per 1.73 m^2 and UACR <30 mg/g.

Outcomes

We evaluated the following in all subgroups by treatment: baseline characteristics, eGFR over time (at baseline and weeks 6, 18, 52, 104, 156, 208, and 260), eGFR slopes, and UACR.

The slopes for changes in eGFR per week or per year were analyzed by random coefficient models. Least square mean differences between ertugliflozin (observations from both doses were pooled for all analyses) and placebo for the weekly or yearly eGFR slopes were assessed for the following 5 periods:

1. acute eGFR "dip" period: weekly slope from week 0 (baseline) to week 6;
2. post-eGFR "dip" readjustment period: yearly slope from week 6 to week 52;
3. postadjustment chronic period: yearly slope from week 52 to week 260;
4. chronic slope: yearly slope from week 6 to week 260; and
5. total yearly slope from week 0 (baseline) to week 260.

The time to first event of progression of albuminuria (progression from normoalbuminuria [UACR <30 mg/g] to microalbuminuria or macroalbuminuria [UACR 30–300 mg/g or >300 mg/g, respectively], or progression from microalbuminuria to macroalbuminuria) was analyzed for ertugliflozin versus placebo by subgroup.

Patients with baseline macroalbuminuria were excluded from the analysis. The time to first event of a kidney composite end point (comprising sustained ≥40% decline in eGFR, chronic kidney replacement therapy [dialysis or transplantation], or kidney death) and the time to first HHF were also analyzed for ertugliflozin versus placebo by subgroup.

Statistical Analysis

The analyses of eGFR and UACR were performed on the full analysis set (randomized participants who received 1 or more doses of blinded study medication and had 1 or more measurements of the analysis end point). The analyses of eGFR and UACR were performed on the pooled ertugliflozin population and placebo. Data after the initiation of glycemic rescue therapy were included; however, data obtained >2 days after the last dose of study medication were excluded from the eGFR and UACR outcomes analyses.

Least squares mean changes from baseline over time by subgroup were estimated using the repeated measures analysis of covariance method.[12] The repeated measures analysis of covariance models adjusted for the baseline value of the outcome variable, baseline glycated hemoglobin (HbA1c), treatment, visit, subgroup, treatment-by-subgroup interaction, and treatment-by-subgroup-by-visit interaction. Visit was treated as a categorical variable. An unstructured covariance matrix was used to model the correlation among repeated measurements.

The eGFR slope models included the eGFR value as a response variable, with treatment, visit, baseline HbA1c, baseline eGFR, and treatment-by-visit interaction as linear covariates. Visit was treated as a continuous variable. The model enabled individual participant slopes to vary by random effects of intercept and time. An unstructured covariance matrix was used to model the correlation of random effects. Missing data were not imputed. The random effects model used a likelihood-based estimation, which produced unbiased estimates for data missing at random. Treatment-by-subgroup interaction was tested by generalized random coefficient models with treatment, time, subgroup, and treatment-by-subgroup interaction as linear covariates. The *P* values of eGFR slopes by subgroups in the ertugliflozin or placebo groups were estimated by models including eGFR values as response variables, with subgroup, visit, baseline HbA1c, baseline eGFR, and subgroup-by-visit interaction as linear covariates, whereas visit was treated as a continuous variable. The interactions ($P_{\text{interaction}}$) of treatment-by-subgroup were tested to determine whether the effect of ertugliflozin versus placebo was modified by the subgroups.

Owing to the non-normal distribution of UACR, UACR data were log transformed before the analysis. The adjusted mean percentage change (derived from exponentiation of adjusted estimates from the repeated measures analysis of covariance model) in UACR with 95% CIs are presented by treatment and time point. The difference between ertugliflozin treatment and placebo in mean percentage change in UACR from baseline was estimated and presented.

The time-to-event outcomes were analyzed using a stratified Cox proportional hazards model, which included treatment, subgroup, and treatment-by-subgroup interaction, with cohort as a stratification factor (cohort 1 [participants randomized before protocol amendment, between December 2013 and July 2015] and cohort 2 [participants randomized after protocol amendment, in 2016 and beyond]). Time-to-event outcome analyses were performed with data from all randomized patients (the intention-to-treat population) for the prespecified exploratory kidney composite end point and time to first HHF. Data from all patients as treated were used for the analysis of time to progression of albuminuria. Patients with baseline UACR >300 mg/g were excluded from the time to progression of albuminuria analysis. No multiplicity adjustment was made for this *post hoc* analysis. Baseline characteristics were summarized using descriptive statistics. The analyses were performed using SAS software, version 9.4 (SAS Institute, Cary, NC).

RESULTS

Baseline Characteristics

In the VERTIS CV trial, 8030 participants had both baseline eGFR and UACR measurements. At baseline, 867 (10.8%), 891 (11.1%), 2356 (29.3%), and 3916 (48.8%) patients had DKD-non-Alb, DKD stage 3 Alb, DKD stages 1 to 2 Alb, and non-DKD, respectively. Table 1 displays the baseline demographic and clinical characteristics of the 4 evaluated subgroups. The 2 subgroups with baseline eGFR <60 ml/min per 1.73 m^2 (DKD-non-Alb and DKD stage 3 Alb) tended to be older, with a longer duration of T2DM, a higher baseline use of insulin and diuretics (including loop diuretics and mineralocorticoid receptor antagonists), and a lower baseline use of biguanides compared with the DKD stages 1 to 2 Alb and non-DKD subgroups. Renin–angiotensin–aldosterone system inhibitor use was similar across the 4 subgroups. The 2 subgroups with elevated albuminuria at baseline (DKD stage 3 Alb and DKD stages 1–2 Alb) tended to have a higher mean HbA1c and systolic blood pressure (SBP) than the non-Alb subgroups (DKD-non-Alb and non-DKD). Alb subgroups had a greater baseline use of insulin than the

Table 1. Baseline demographic and clinical characteristics (intention-to-treat population)

Characteristic	DKD-non-Alb (n = 867) (10.8%)	DKD stage 3 Alb (n = 891) (11.1%)	DKD stages 1–2 Alb (n = 2356) (29.3%)	Non-DKD (n = 3916) (48.8%)
Age, yr	68.7 (7.3)	67.6 (7.8)	63.2 (7.7)	63.4 (7.9)
Age, yr	69.0 (64.0–74.0)	68.0 (63.0–73.0)	63.0 (58.0–68.0)	64.0 (58.0–69.0)
Female, n (%)	363 (41.9)	270 (30.3)	559 (23.7)	1211 (30.9)
BMI, kg/m^2	32.6 (5.4)	32.2 (5.6)	32.0 (5.3)	31.6 (5.3)
BMI, kg/m^2	31.9 (28.9–35.4)	31.7 (28.4–35.3)	31.5 (28.6–35.2)	31.0 (27.9–34.5)
Duration of T2DM, yr	15.4 (9.4)	16.1 (8.6)	13.0 (8.1)	11.8 (7.8)
Duration of T2DM, yr	14.3 (8.7–20.2)	15.4 (9.7–21.3)	11.6 (7.0–17.2)	10.3 (6.0–15.9)
Current smoker	60 (6.9)	88 (9.9)	383 (16.3)	562 (14.4)
Past smoker	345 (39.8)	393 (44.1)	936 (39.7)	1560 (39.8)
Never smoked	462 (53.3)	410 (46.0)	1036 (44.0)	1794 (45.8)
HbA1c, %	8.1 (0.9)	8.3 (0.9)	8.4 (1.0)	8.1 (0.9)
HbA1c, %	8.0 (7.5–8.7)	8.2 (7.7–8.9)	8.3 (7.6–9.1)	8.0 (7.4–8.8)
UACR, mg/g	8.0 (4.0–16.0)	125.0 (59.0–419.0)	84.0 (47.0–226.5)	8.0 (4.0–14.0)
eGFR, ml/min per 1.73 m^2 (MDRD)	49.8 (7.7)	47.9 (8.2)	83.3 (16.9)	83.6 (16.4)
eGFR, ml/min per 1.73 m^2 (MDRD)	51.0 (45.0–56.0)	49.0 (42.0–55.0)	81.0 (70.0–94.0)	81.0 (71.0–93.0)
SBP, mm Hg	130.2 (14.5)	136.8 (14.5)	136.3 (13.5)	131.6 (13.1)
SBP, mm Hg	130.8 (121.0–140.3)	136.7 (127.7–147.0)	136.2 (127.3–145.3)	131.7 (123.0–140.7)
Hb, g/dl	13.5 (1.4)	13.5 (1.5)	14.2 (1.4)	14.1 (1.3)
Hb, g/dl	13.5 (12.6–14.5)	13.4 (12.5–14.5)	14.2 (13.3–15.1)	14.1 (13.3–14.9)
Serum triglyceride, mg/dl	178.0 (123.2)	196.3 (114.5)	191.0 (124.3)	171.8 (106.4)
Serum triglyceride, mg/dl	154.0 (114.0–209.0)	168.0 (123.0–241.0)	159.5 (115.0–226.0)	146.0 (106.0–207.0)
Serum LDL-C, mg/dl	85.7 (33.8)	88.9 (41.0)	90.3 (39.3)	89.2 (37.8)
Serum LDL-C, mg/dl	79.0 (61.0–104.0)	81.0 (60.0–109.0)	82.9 (62.0–112.0)	82.0 (61.0–110.0)
Serum HDL-C, mg/dl	43.8 (12.0)	42.9 (12.2)	43.1 (12.3)	44.4 (12.0)
Serum HDL-C, mg/dl	42.5 (36.0–50.0)	40.5 (35.0–50.0)	41.0 (35.0–50.0)	43.0 (36.0–51.0)
Glucose-lowering agents				
Metformin	560 (64.6)	535 (60.0)	1895 (80.4)	3148 (80.4)
Insulin	475 (54.8)	558 (62.6)	1157 (49.1)	1603 (40.9)
Antihypertensive agents	846 (97.6)	873 (98.0)	2231 (94.7)	3701 (94.5)
RAAS inhibitors	709 (81.8)	749 (84.1)	1929 (81.9)	3129 (79.9)
Diuretics	489 (56.4)	507 (56.9)	947 (40.2)	1517 (38.7)
Loop diuretics	219 (25.3)	258 (29.0)	317 (13.5)	431 (11.0)
MRA	123 (14.2)	97 (10.9)	155 (6.6)	283 (7.2)
Lipid-modifying agents	756 (87.2)	774 (86.9)	1933 (82.0)	3323 (84.9)
History of CAD	712 (82.1)	673 (75.5)	1723 (73.1)	2978 (76.0)
History of HF	221 (25.5)	244 (27.4)	573 (24.3)	873 (22.3)

BMI, body mass index; CAD, coronary artery disease; DKD-non-Alb, nonalbuminuric diabetic kidney disease; DKD stages 1–2 Alb, albuminuric stages 1 and 2 diabetic kidney disease; DKD stage 3 Alb, albuminuric stage 3 diabetic kidney disease; eGFR, estimated glomerular filtration rate; Hb, hemoglobin; HbA1c, glycated hemoglobin; HDL-C, high-density lipoprotein cholesterol; HF, heart failure; LDL-C, low-density lipoprotein cholesterol; MDRD, Modification of Diet in Renal Disease; MRA, mineralocorticoid receptor antagonist; Non-DKD, nondiabetic kidney disease; RAAS, renin–angiotensin–aldosterone system; SBP, systolic blood pressure; T2DM, type 2 diabetes mellitus; UACR, urinary albumin-to-creatinine ratio. Participants required both baseline eGFR and UACR values. Values are mean (SD), n (%), or median (interquartile range).

corresponding non-Alb groups. The DKD-non-Alb subgroup had a higher proportion of female patients, participants who had no history of tobacco use, and patients with coronary artery disease compared with the other 3 subgroups. Compared with the DKD stage 3 Alb subgroup, the DKD-non-Alb subgroup had a lower use of loop diuretics, but a higher use of mineralocorticoid receptor antagonists. Within each subgroup, baseline demographic and clinical characteristics were generally balanced between those randomized to ertugliflozin and placebo (Supplementary Table S1).

Acute eGFR Dip Period—Weekly Changes in eGFR From Weeks 0 to 6

During the acute eGFR "dip" period (week 0 [baseline] to week 6), placebo-treated subgroups with eGFR <60 ml/min per 1.73 m^2 (DKD-non-Alb and DKD stage 3 Alb) had an increase in mean eGFR, whereas placebo-treated subgroups with eGFR ≥60 ml/min per 1.73 m^2 (DKD stages 1–2 Alb and non-DKD) had a decrease in mean eGFR. Acute eGFR slopes (ml/min per 1.73 m^2 per week [95% CI]) in those randomized to placebo were 0.53 (0.35–0.71), 0.24 (0.07–0.41), −0.14 (−0.32 to 0.03), and −0.23 (−0.37 to −0.08) in the DKD-non-Alb, DKD stage 3 Alb, DKD stages 1 to 2 Alb, and non-DKD subgroups, respectively ($P < 0.0001$; Figure 1 and Figure 2a and Supplementary Tables S2 and S3).

In patients treated with ertugliflozin, those with eGFR <60 ml/min per 1.73 m^2 had slower rates of eGFR decline during the acute eGFR "dip" period, which was slowest in the DKD-non-Alb subgroup, compared with the DKD stages 1 to 2 Alb and non-DKD subgroups ($P < 0.0001$;

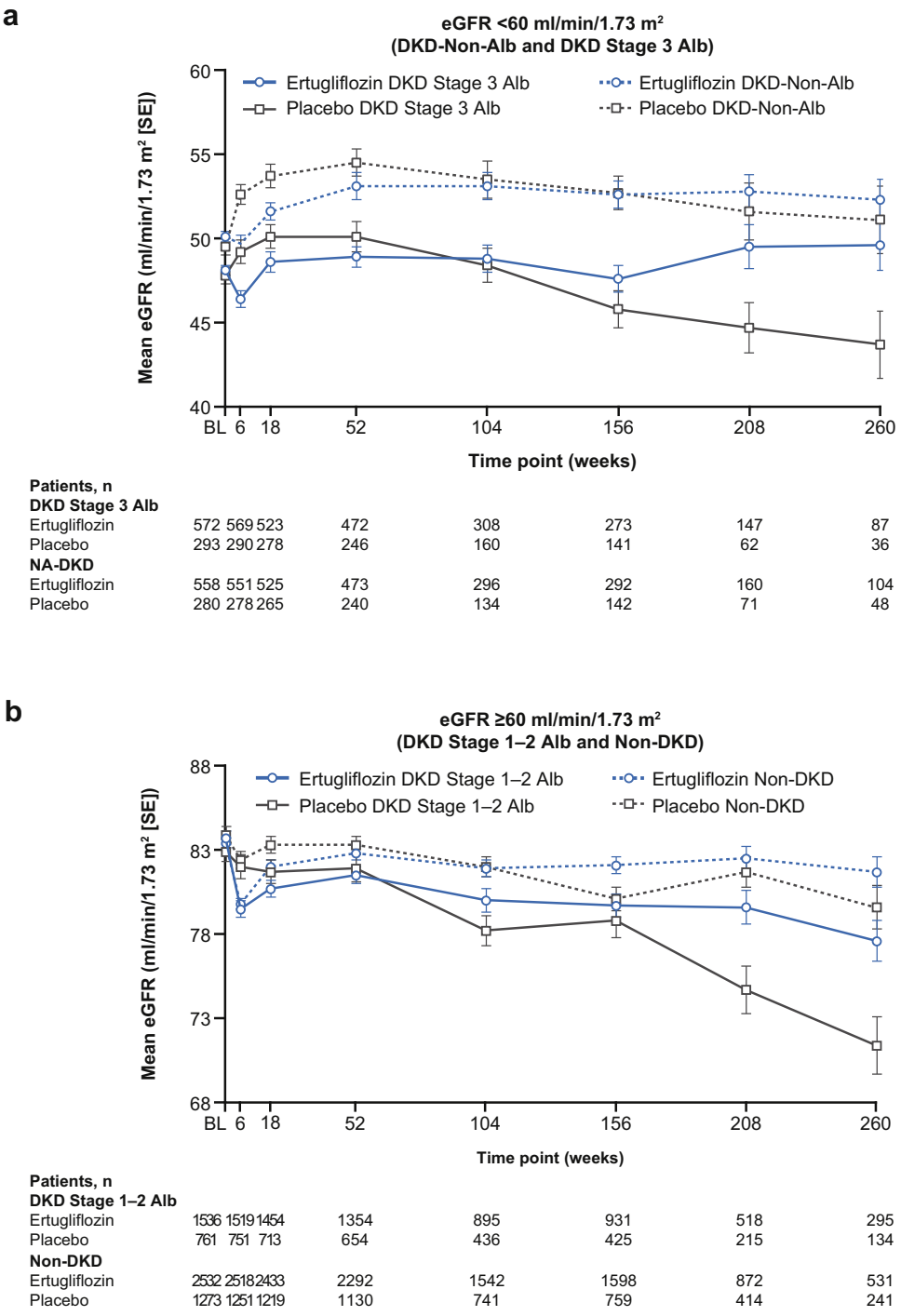

Figure 1. Mean eGFR over time in (a) the subgroups with baseline eGFR <60 ml/min per 1.73 m^2 (b) and in the groups with baseline eGFR ≥60 ml/min per 1.73 m^2 (FAS population). Participants required both baseline eGFR and UACR values for inclusion in the analysis. BL, baseline; DKD-non-Alb, nonalbuminuric diabetic kidney disease; DKD stages 1–2 Alb, albuminuric stages 1 and 2 diabetic kidney disease; DKD stage 3 Alb, albuminuric stage 3 diabetic kidney disease; eGFR, estimated glomerular filtration rate; FAS, full analysis set; non-DKD, nondiabetic kidney disease; UACR, urinary albumin-to-creatinine ratio.

Figure 1 and Figure 2b and Supplementary Tables S2 and S3). Treatment with ertugliflozin was associated with a consistent reduction in eGFR compared with placebo in all subgroups (with a similar effect across subgroups), in line with what is known about SGLT2 inhibitor-induced acute hemodynamic effects ($P_{interaction}$ = 0.68, Figure 1 and Figure 2c and Supplementary Tables S2 and S3).

Post-eGFR Dip Readjustment Period—Yearly Changes in eGFR From Weeks 6 to 52

During the post-eGFR "dip" readjustment period (weeks 6 to 52), eGFR trajectories were generally unchanged in all placebo-treated subgroups, with yearly eGFR slopes close to 0 (P = 0.82; Supplementary Figure S1A). Mean eGFR increased during weeks 6 to

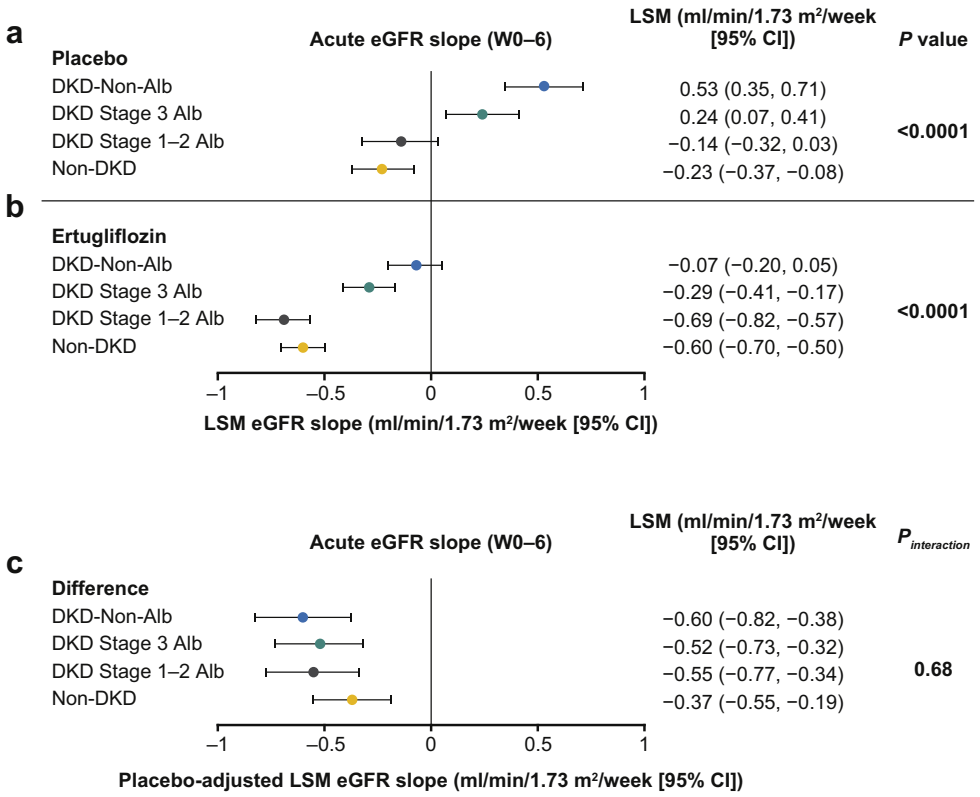

Figure 2. Weekly eGFR slope in the acute "dip" period (week 0 to week 6) in (a) patients randomized to placebo, (b) patients randomized to ertugliflozin, with the (c) placebo-adjusted values illustrated (FAS population). Participants required both baseline eGFR and UACR values for inclusion in the analysis. CI, confidence interval; DKD-non-Alb, nonalbuminuric diabetic kidney disease; DKD stages 1–2 Alb, albuminuric stages 1 and 2 diabetic kidney disease; DKD stage 3 Alb, albuminuric stage 3 diabetic kidney disease; eGFR, estimated glomerular filtration rate; FAS, full analysis set; LSM, least squares mean; non-DKD, nondiabetic kidney disease; UACR, urinary albumin-to-creatinine ratio; W, week.

52 in all ertugliflozin-treated subgroups, with a higher increase observed in subgroups with a baseline UACR <30 mg/g (DKD-non-Alb and non-DKD) compared with other subgroups. eGFR slopes (ml/min per 1.73 m^2 per year [95% CI]) in those randomized to ertugliflozin were 2.47 (1.44–3.50), 0.64 (−0.42 to 1.70), 0.83 (−0.01 to 1.67), and 2.12 (1.53 to 2.71) in the DKD-non-Alb, DKD stage 3 Alb, DKD stages 1 to 2 Alb, and non-DKD subgroups, respectively ($P = 0.01$; Supplementary Figure S1B and Supplementary Table S3). Placebo-adjusted eGFR slopes during weeks 6 to 52 reflected the increase in eGFR during weeks 6 to 52 with ertugliflozin, with a similar effect across subgroups ($P_{interaction} = 0.88$; Supplementary Figure S1C).

Postadjustment Chronic Period—Yearly Changes in eGFR From Weeks 52 to 260

During the postadjustment chronic period (weeks 52 to 260), a slower rate of yearly eGFR decline was observed in subgroups with a baseline UACR <30 mg/g (DKD-non-Alb and non-DKD, with the slowest yearly eGFR decline in the DKD-non-Alb subgroup) compared with other subgroups, regardless of treatment allocation ($P \leq 0.0001$; Figure 1, Supplementary Figure S2A and B and Supplementary Table S3). Treatment with ertugliflozin was associated with a slower rate of eGFR decline compared with placebo in all subgroups, without interaction by subgroup ($P_{interaction} = 0.90$; Supplementary Figure S2C and Supplementary Table S3).

Total and Chronic eGFR Slopes—Yearly Changes in eGFR From Weeks 0 or 6 to 260

During weeks 0 to 260, compared with the other subgroups, the DKD-non-Alb subgroup had the slowest rate of yearly eGFR decline, whereas the DKD stages 1 to 2 Alb subgroup had the fastest rate of yearly eGFR decline, regardless of treatment allocation ($P < 0.0001$; Figure 3a and b). In patients treated with placebo, total eGFR slopes (ml/min per 1.73 m^2 per year [95% CI]) were −0.23 (−0.51 to 0.04), −1.27 (−1.57 to −0.96), −2.29 (−2.56 to −2.02), and −1.19 (−1.37 to −1.01) in the DKD-non-Alb, DKD stage 3 Alb, DKD stages 1 to 2 Alb, and non-DKD subgroups, respectively (Figure 3a and Supplementary Table S3). Treatment with ertugliflozin resulted in a significantly slower rate of yearly eGFR decline in all subgroups compared with placebo without interaction by subgroup; the placebo-adjusted eGFR slopes (ml/min per 1.73 m^2 per year [95% CI]) during weeks 0 to 260 were 0.55 (0.22–0.88),

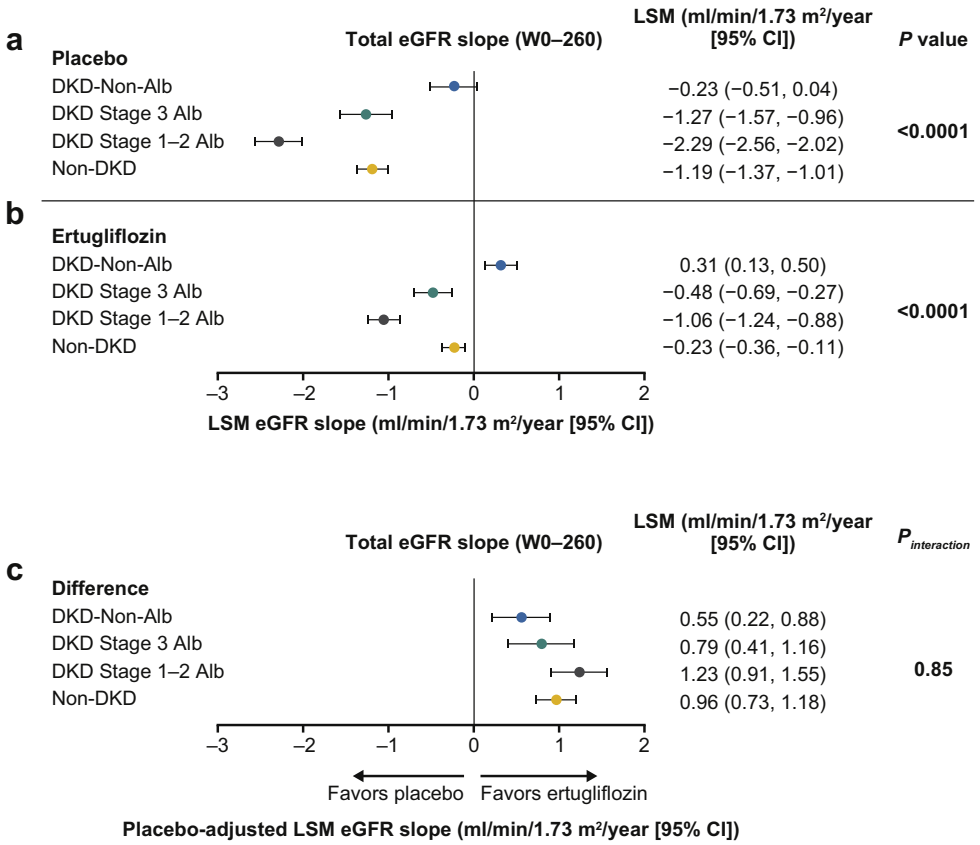

Figure 3. Yearly eGFR slope in the total period (week 0 to week 260) in (a) patients randomized to placebo, (b) patients randomized to ertugliflozin, (c) with the placebo-adjusted values illustrated (FAS population). Participants required both baseline eGFR and UACR values for inclusion in the analysis. CI, confidence interval; DKD-non-Alb, nonalbuminuric diabetic kidney disease; DKD stages 1–2 Alb, albuminuric stages 1 and 2 diabetic kidney disease; DKD stage 3 Alb, albuminuric stage 3 diabetic kidney disease; eGFR, estimated glomerular filtration rate; FAS, full analysis set; LSM, least squares mean; non-DKD, nondiabetic kidney disease; UACR, urinary albumin-to-creatinine ratio; W, week.

0.79 (0.41–1.16), 1.23 (0.91–1.55), and 0.96 (0.73–1.18) in the DKD-non-Alb, DKD stage 3 Alb, DKD stages 1 to 2 Alb, and non-DKD subgroups, respectively ($P_{\text{interaction}} = 0.85$; Figure 3c and Supplementary Table S3). Overall, similar results were found with yearly chronic eGFR slopes (weeks 6 to 260; Supplementary Figure S3A–C and Supplementary Table S3).

Changes in UACR and Progression of Albuminuria

At year 5, percent change from baseline in UACR (95% CI) with ertugliflozin compared with placebo was −17.0% (−39.5 to 13.8), −14.5% (−39.2 to 20.1), −28.5% (−40.2 to −14.6), and −8.0% (−19.5 to 5.0) in the DKD-non-Alb, DKD stage 3 Alb, DKD stages 1 to 2 Alb, and non-DKD subgroups, respectively (Supplementary Figure S4A–D). Ertugliflozin was associated with a reduced risk of progression of albuminuria in all subgroups compared with placebo, with the greatest relative risk reduction in the Alb subgroups (Supplementary Table S4). The HRs (95% CIs) were 0.79 (0.63–0.99), 0.68 (0.47–0.98), 0.61 (0.49–0.76), and 0.86 (0.77–0.96) in the DKD-non-Alb, DKD stage 3 Alb, DKD stages 1 to 2 Alb, and non-DKD subgroups, respectively ($P_{\text{interaction}} = 0.04$).

Prespecified Exploratory Kidney Composite Outcome

In the overall population, treatment with ertugliflozin compared with placebo was associated with a 34% relative reduction in the risk for the prespecified exploratory kidney composite outcome of sustained ≥40% reduction from baseline in eGFR, chronic kidney dialysis (CKD)/transplant, or kidney death, with a HR (95% CI) of 0.66 (0.50–0.88).[7] The impact of ertugliflozin on the prespecified exploratory kidney composite outcome did not differ across subgroups compared with placebo. The HRs (95% CIs) were 0.82 (0.20–3.44), 0.90 (0.49–1.68), 0.66 (0.43–1.02), and 0.44 (0.26–0.74) in the DKD-non-Alb, DKD stage 3 Alb, DKD stages 1 to 2 Alb, and non-DKD subgroups, respectively ($P_{\text{interaction}} = 0.34$; Supplementary Table S5). In this analysis, the DKD-non-Alb subgroup had the lowest event rate for the prespecified exploratory kidney composite outcome compared with the other subgroups.

HHF Outcome

In the overall population, the prespecified secondary outcome of time to first HHF had a 30% relative risk reduction with ertugliflozin versus placebo, with a HR (95% CI) of 0.70 (0.54–0.90).[9] Ertugliflozin was associated with a reduced relative risk of time to first HHF in higher risk subgroups (DKD-non-Alb, DKD stage 3 Alb, and DKD stages 1–2 Alb) compared with placebo. The HRs (95% CIs) were 0.72 (0.31–1.69), 0.45 (0.28–0.73), 0.64 (0.42–0.97), and 1.38 (0.75–2.54) in the DKD-non-Alb, DKD stage 3 Alb, DKD stages 1 to 2 Alb, and non-DKD subgroups, respectively ($P_{\text{interaction}} = 0.046$; Supplementary Table S6). In this analysis, the non-DKD subgroup had the lowest event rate for time to first HHF.

DISCUSSION

There are 4 major observations in this report. Our first major observation was the composition of the cohort with respect to the clinical DKD profile. Consistent with previous observations in people with T2DM, the proportion of participants with DKD-non-Alb was 10.8% in the overall VERTIS CV cohort. Among patients with baseline eGFR <60 ml/min per 1.73 m^2 in VERTIS CV, 49.3% had DKD-non-Alb, similar to what has been described in other populations.[13] Patients with eGFR <60 ml/min per 1.73 m^2 at baseline in these analyses tended to be older, with a longer duration of T2DM, and requiring more insulin, lipid-modifying medications, and antihypertensive medications including diuretics, but with a lower use of metformin. Those with elevated albuminuria at baseline had anticipated clinical risk factors, such as higher SBP and HbA1c. Finally, for patients with DKD-non-Alb, previous studies have identified that females and individuals who had no history of tobacco use with improved glycemic control have increased preservation of normoalbuminuria, even with declining kidney function.[13] In these analyses, a larger proportion of females and individuals with no history of tobacco use was observed in the DKD-non-Alb subgroup compared with the other subgroups.

The second observation was the acute increase in eGFR observed in placebo groups with baseline eGFR <60 ml/min per 1.73 m^2. We have described this finding in previous analyses from VERTIS CV.[7,8] The increase in eGFR in the placebo group in patients with CKD stage 3 has also been observed in the analyses of eGFR over time in other SGLT2 inhibitor cardiovascular outcomes trials.[14–16] In addition, in a cohort of patients from an observational study using a Taiwanese database, an initial increase in eGFR was observed in patients taking glucose-lowering agents other than SGLT2 inhibitors.[17] In the SGLT2 inhibitor cardiovascular outcomes trials, these subgroups of patients with CKD stage 3 had relatively low baseline UACR compared with patients from 2 SGLT2 inhibitor kidney outcomes studies who had elevated albuminuria levels at baseline, in which an increase in eGFR in the placebo groups was not observed.[18,19] The basis for these eGFR changes in patients treated with placebo with CKD stage 3 and relatively low levels of albuminuria is not known, but it may be secondary to an improved diet (with lower sodium intake), which most often occurs when patients enter clinical studies, or regression to the mean.

In the current analysis, our third observation was that, in both placebo- and ertugliflozin-treated groups, chronic and total eGFR declines were slower in the DKD-non-Alb subgroup, followed by the non-DKD subgroup, with more rapid rates of eGFR decline in the DKD stages 1 to 2 Alb and DKD stage 3 Alb subgroups. We also observed a differential effect of eGFR decline in patients with similar baseline albuminuria levels whereby patients in the DKD stages 1 to 2 Alb subgroup had faster rates of eGFR decline compared with the DKD stage 3 Alb subgroup. Treatment with ertugliflozin compared with placebo resulted in significantly lower chronic (weeks 6 to 260) and total (weeks 0 to 260) eGFR slopes in all 4 subgroups. In a report from the EMPA-REG OUTCOME trial,[20] the overall population was divided into the following 3 groups: patients with overt DKD (UACR >300 mg/g, regardless of eGFR), non-overt DKD (eGFR <60 ml/min per 1.73 m^2 with UACR ≤300 mg/g), and all others (eGFR ≥60 ml/min per 1.73 m^2 and UACR ≤300 mg/g). In the analysis from the EMPA-REG OUTCOME trial, chronic eGFR slope (week 4 to end of study) in patients randomized to placebo with overt DKD had a faster rate of eGFR decline than the non-overt DKD group (−6.00 and −0.74 ml/min per 1.73 m^2 per year, respectively).[20] In the VERTIS CV cohort, the comparable chronic eGFR slope (weeks 6 to 260) in patients randomized to placebo with macroalbuminuria at baseline (UACR >300 mg/g, regardless of baseline eGFR) was −3.3 ml/min per 1.73 m^2 per year.[8] For reasons that are not understood, the VERTIS CV, the placebo-treated population had a slower rate of eGFR decline compared with the EMPA-REG OUTCOME placebo-treated population.[21]

Our fourth major observation was that, among patients randomized to placebo, the DKD-non-Alb subgroup had the lowest risk for the prespecified exploratory kidney composite outcome compared with the other groups, with an event rate of 0.3 per 100 person-years. The reduced risk for the prespecified exploratory kidney composite outcome in the DKD-non-Alb cohort is consistent with the finding that this group had the slowest rate of eGFR decline, as the prespecified exploratory kidney composite outcome is driven mainly by the sustained ≥40% decline from baseline in eGFR.[7] In addition, these findings are also in agreement with results from the Chronic Renal Insufficiency study in patients with T2DM and reduced eGFR.[5]

In the Chronic Renal Insufficiency study, the absence of albuminuria was associated with a reduced risk for end-stage kidney disease, progression of CKD, and decline in eGFR slope.[5] The reported effect of ertugliflozin on the kidney composite outcome was consistent across the studied groups ($P_{\text{Interaction}} = 0.34$). For HHF end points, treatment with ertugliflozin was associated with a larger relative risk reduction in time to first HHF in patients with either elevated albuminuria and/or low eGFR at baseline compared with other kidney function subgroups,[22] highlighting the larger heart failure benefits of ertugliflozin on patients with compromised kidney function who also have a high event rate for this outcome. Patients treated with placebo in the non-DKD subgroup had the lowest event rate for time to first HHF. The non-DKD subgroup had the lowest use of diuretics, including loop diuretics, at baseline compared with the other subgroups, irrespective of treatment randomization. These differences may have a role in the observed ertugliflozin treatment effect variation in the HHF outcome, in keeping with previous analyses from VERTIS CV.[9]

This analysis does have limitations. First, it was a *post hoc* analysis and *P* values were not adjusted for multiplicity. Owing to the lack of multiplicity adjustment, these results are hypothesis generating. Finally, although there may be important differences between patients with microalbuminuria (UACR ≥30 and ≤300 mg/g) and macroalbuminuria (UACR >300 m/g) at baseline, especially within the DKD stage 3 Alb subgroup, further stratification analysis is unlikely to have sufficient power to detect differences.

In VERTIS CV, participants with DKD-non-Alb at baseline had the slowest rate of long-term eGFR decline and a lower risk for the prespecified exploratory kidney composite outcome. However, ertugliflozin was associated with reducing the risk of eGFR decline and the prespecified exploratory kidney composite outcome in all subgroups. The effect of ertugliflozin on the reduction in the risk for time to first HHF was larger in subgroups with more advanced kidney disease (patients with UACR ≥30 mg/g at baseline and/or eGFR <60 ml/min per 1.73 m^2) and are resultantly at higher risk for this outcome.

DISCLOSURE

DZIC has received consulting fees or speaking honorarium, or both, from AbbVie, Astellas, AstraZeneca, Bayer, Boehringer Ingelheim-Eli Lilly, Bristol-Myers Squibb, Janssen, JNJ, MAZE, Merck & Co., Inc., Mitsubishi-Tanabe, Novo Nordisk, Otsuka, Prometic, and Sanofi; has received operating funds from AstraZeneca, Boehringer Ingelheim-Lilly, Janssen, Merck & Co., Inc., Novo Nordisk, and Sanofi; and has served as a scientific advisor or member of AstraZeneca, Boehringer Ingelheim, Janssen, Merck & Co., Inc., Novo Nordisk, and Sanofi. SD-J has led clinical trials for AstraZeneca, Bayer, Boehringer Ingelheim, and Novo Nordisk, Inc.; has received fees from AstraZeneca, Bayer, Boehringer Ingelheim, Janssen, Merck & Co., Inc., and Sanofi; and holds equity interests in Jana Care, Inc., and Aerami Therapeutics. FC has received fees from Abbott, AstraZeneca, Bayer, Boehringer Ingelheim, Bristol Myers Squibb, Lilly, Merck Sharp & Dohme, Novo Nordisk, and Pfizer; and research grants from the King Gustav V and Queen Victoria Foundation, the Swedish Heart & Lung Foundation, and the Swedish Research Council. REP is an employee of AdventHealth Translational Research Institute; has received (directed to his institution) speaker fees from Novo Nordisk; has received speaker fees and consulting fees from Merck & Co., Inc.; has received grants from Hanmi Pharmaceuticals Co., Janssen, Lexicon Pharmaceuticals, Metavention, Novo Nordisk, Poxel SA, and Sanofi; and has received consulting fees from AstraZeneca, Corcept Therapeutics Incorporated, Glytec LLC, Janssen, Mundipharma, Novo Nordisk, Pfizer, Sanofi, Scohia Pharma Inc., and Sun Pharmaceutical Industries. RF is an employee of Pfizer Inc., may own shares/stock options in Pfizer Inc., and may own stock in Bristol Myers Squibb. MM is an employee of Merck Sharp & Dohme UK and may own stock and/or stock options in Merck & Co., Inc. (Kenilworth, NJ). C-CL is an employee of Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., and may own stock and/or stock options in Merck & Co., Inc. CPC reports research grants and consulting fees from Pfizer Inc. and Merck & Co., Inc.; and research grants and consulting fees from Amgen, Boehringer Ingelheim, Bristol-Myers Squibb, and Janssen, research grants from Better Therapeutics, Daiichi Sankyo, and Novo Nordisk, and consulting fees from Aegerion/Amryt, Alnylam, Amarin, Applied Therapeutics, Ascendia, Lexicon, Sanofi, Eli Lilly, and Rhoshan, and reports serving on the Data and Safety Monitoring Boards for the Veteran's Administration, Applied Therapeutics and NovoNordisk, outside the submitted work.

ACKNOWLEDGMENTS

Funding for this research was provided by Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA, in collaboration with Pfizer Inc. (New York, NY). The authors thank the patients, their families, and all investigators involved in the VERTIS CV study. Some of the results from these analyses were presented at the annual meeting of the American Society of Nephrology 2021 (Kidney Week). Medical writing and/or editorial assistance was provided by Moamen Hammad, PhD, and Ian Norton, PhD, both of Scion, London, UK. This assistance was funded by Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA, and Pfizer Inc. The Sponsor was involved in the study design, collection, analysis, and interpretation of data,

including data checking of information provided in the manuscript. However, ultimate responsibility for opinions, conclusions, and data interpretation lies with the authors.

The list of investigators can be found with the primary publication: Cannon CP, Pratley R, Dagogo-Jack S, et al., for the VERTIS CV Investigators. Cardiovascular outcomes with ertugliflozin in type 2 diabetes. *N Engl J Med*. 2020;383:1425–1435. https://doi.org/10.1056/NEJMoa2004967.

DATA SHARING

Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA, data sharing policy, including restrictions, is available at http://engagezone.msd.com/ds_documentation.php. Requests for access to the clinical study data can be submitted through the EngageZone site or via e-mail to dataaccess@merck.com.

AUTHOR CONTRIBUTIONS

DZIC, SD-J, MM, and CPC substantially contributed to the conception, design, or planning of the study. RF substantially contributed to the acquisition of the data. DZIC, SD-J, FC, REP, RF, MM, C-CL, and CPC substantially contributed to the analysis of the data and/or interpretation of the results. DZIC and MM substantially contributed to the drafting of the manuscript. All authors substantially contributed to critically reviewing or revising the manuscript for important intellectual content.

SUPPLEMENTARY MATERIAL

Supplementary File (PDF)

Figure S1. Yearly eGFR slope in the post-dip readjustment period (week 6 to week 52) in (A) patients randomized to placebo, (B) patients randomized to ertugliflozin, (C) with the placebo-adjusted values illustrated (FAS population).

Figure S2. Yearly eGFR slope in the post-readjustment period (week 52 to week 260) in (A) patients randomized to placebo, (B) patients randomized to ertugliflozin, (C) with the placebo-adjusted values illustrated (FAS population).

Figure S3. Yearly eGFR slope in the chronic period (week 6 to week 260) in (A) patients randomized to placebo, (B) patients randomized to ertugliflozin, (C) with the placebo-adjusted values illustrated (FAS population).

Figure S4. Percent change from baseline in UACR in the (A) DKD-non-Alb, (B) non-DKD, (C) DKD stage 3 Alb, and (D) DKD stages 1 to 2 Alb groups by treatment.

Table S1. Baseline demographic and clinical characteristics by treatment group (intention-to-treat population).

Table S2. Mean change from baseline in eGFR.

Table S3. eGFR slopes across all investigated periods.

Table S4. Cox proportional hazards model for time to first progression of albuminuria.

Table S5. Cox proportional hazards model for time to first prespecified exploratory kidney composite (comprising sustained ≥40% decline in eGFR, chronic kidney replacement therapy [dialysis or transplantation], or kidney death).

Table S6. Cox proportional hazards model for time to first hospitalization for heart failure.

CONSORT checklist.

REFERENCES

1. Koye DN, Magliano DJ, Nelson RG, Pavkov ME. The global epidemiology of diabetes and kidney disease. *Adv Chronic Kidney Dis*. 2018;25:121–132. https://doi.org/10.1053/j.ackd.2017.10.011
2. Marshall SM. Natural history and clinical characteristics of CKD in type 1 and type 2 diabetes mellitus. *Adv Chronic Kidney Dis*. 2014;21:267–272. https://doi.org/10.1053/j.ackd.2014.03.007
3. Maqbool M, Cooper ME, Jandeleit-Dahm KAM. Cardiovascular disease and diabetic kidney disease. *Semin Nephrol*. 2018;38:217–232. https://doi.org/10.1016/j.semnephrol.2018.02.003
4. Wetmore JB, Li S, Ton TGN, et al. Association of diabetes-related kidney disease with cardiovascular and non-cardiovascular outcomes: a retrospective cohort study. *BMC Endocr Disord*. 2019;19:89. https://doi.org/10.1186/s12902-019-0417-9
5. Koye DN, Magliano DJ, Reid CM, et al. Risk of progression of nonalbuminuric CKD to end-stage kidney disease in people with diabetes: the CRIC (Chronic Renal Insufficiency Cohort) Study. *Am J Kidney Dis*. 2018;72:653–661. https://doi.org/10.1053/j.ajkd.2018.02.364
6. Cannon CP, Pratley R, Dagogo-Jack S, et al. Cardiovascular outcomes with ertugliflozin in type 2 diabetes. *N Engl J Med*. 2020;383:1425–1435. https://doi.org/10.1056/NEJMoa2004967
7. Cherney DZI, Charbonnel B, Cosentino F, et al. Effects of ertugliflozin on kidney composite outcomes, renal function and albuminuria in patients with type 2 diabetes mellitus: an analysis from the randomised VERTIS CV trial. *Diabetologia*. 2021;64:1256–1267. https://doi.org/10.1007/s00125-021-05407-5
8. Cherney DZI, Cosentino F, Dagogo-Jack S, et al. Ertugliflozin and slope of chronic eGFR: prespecified analyses from the randomized VERTIS CV trial. *Clin J Am Soc Nephrol*. 2021;16:1345–1354. https://doi.org/10.2215/CJN.01130121
9. Cosentino F, Cannon CP, Cherney DZI, et al. 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. *Circulation*. 2020;142:2205–2215. https://doi.org/10.1161/CIRCULATIONAHA.120.050255
10. Cannon CP, McGuire DK, Pratley R, et al. Design and baseline characteristics of the eValuation of ERTugliflozin efflcacy and Safety CardioVascular outcomes trial (VERTIS-CV). *Am Heart J*. 2018;206:11–23. https://doi.org/10.1016/j.ahj.2018.08.016
11. Levey AS, Coresh J, Greene T, et al. Using standardized serum creatinine values in the modification of diet in renal disease study equation for estimating glomerular filtration rate. *Ann Intern Med*. 2006;145:247–254. https://doi.org/10.7326/0003-4819-145-4-200608150-00004
12. Mallinckrod CH, Lane PW, Schnell D, et al. Recommendations for the primary analysis of continuous endpoints in longitudinal clinical trials. *Drug Inf J*. 2008;42:303–319. https://doi.org/10.1177/009286150804200402

13. Klimontov VV, Korbut AI. Albuminuric and non-albuminuric patterns of chronic kidney disease in type 2 diabetes. *Diabetes Metab Syndr*. 2019;13:474–479. https://doi.org/10.1016/j.dsx.2018.11.014

14. Wanner C, Inzucchi SE, Lachin JM, et al. Empagliflozin and progression of kidney disease in type 2 diabetes. *N Engl J Med*. 2016;375:323–334. https://doi.org/10.1056/NEJMoa1515920

15. Neuen BL, Ohkuma T, Neal B, et al. Cardiovascular and renal outcomes with canagliflozin according to baseline kidney function. *Circulation*. 2018;138:1537–1550. https://doi.org/10.1161/CIRCULATIONAHA.118.035901

16. Mosenzon O, Wiviott SD, Cahn A, et al. Effects of dapagliflozin on development and progression of kidney disease in patients with type 2 diabetes: an analysis from the DECLARE-TIMI 58 randomised trial. *Lancet Diabetes Endocrinol*. 2019;7:606–617. https://doi.org/10.1016/S2213-8587(19)30180-9

17. Lin F-J, Wang C-C, Hsu C-N, et al. Renoprotective effect of SGLT-2 inhibitors among type 2 diabetes patients with different baseline kidney function: a multi-center study. *Cardiovasc Diabetol*. 2021;20:203. https://doi.org/10.1186/s12933-021-01396-2

18. Perkovic V, Jardine MJ, Neal B, et al. Canagliflozin and renal outcomes in type 2 diabetes and nephropathy. *N Engl J Med*. 2019;380:2295–2306. https://doi.org/10.1056/NEJMoa1811744

19. Heerspink HJL, Stefansson BV, Correa-Rotter R, et al. Dapagliflozin in patients with chronic kidney disease. *N Engl J Med*. 2020;383:1436–1446. https://doi.org/10.1056/NEJMoa2024816

20. Wanner C, Inzucchi SE, Zinman B, et al. Consistent effects of empagliflozin on cardiovascular and kidney outcomes irrespective of diabetic kidney disease categories: insights from the EMPA-REG OUTCOME trial. *Diabetes Obes Metab*. 2020;22:2335–2347. https://doi.org/10.1111/dom.14158

21. van Raalte DH, Bjornstad P, Heerspink HJL, et al. Importance of standardizing renal outcomes in clinical trials: illustration by recent sodium glucose cotransporter 2 inhibitor studies. *Kidney Int*. 2021;99:768–770. https://doi.org/10.1016/j.kint.2020.12.006

22. Cherney DZI, McGuire DK, Charbonnel B, et al. Gradient of risk and associations with cardiovascular efficacy of ertugliflozin by measures of kidney function: observations from VERTIS CV. *Circulation*. 2021;143:602–605. https://doi.org/10.1161/CIRCULATIONAHA.120.051901