Ertugliflozin and Slope of Chronic eGFR
Prespecified Analyses from the Randomized VERTIS CV Trial

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Abstract

Background and objectives A reduction in the rate of eGFR decline, with preservation of ≥0.75 ml/min per 1.73 m^2 per year, has been proposed as a surrogate for kidney disease progression. We report results from prespecified analyses assessing effects of ertugliflozin versus placebo on eGFR slope from the eValuation of ERTugliflozin effIcacy and Safety CardioVascular outcomes (VERTIS CV) trial (NCT01986881).

Design, setting, participants, & measurements Patients with type 2 diabetes mellitus and established atherosclerotic cardiovascular disease were randomized to placebo, ertugliflozin 5 mg, and ertugliflozin 15 mg (1:1:1). The analyses compared the effect of ertugliflozin (pooled doses, n=5499) versus placebo (n=2747) on eGFR slope per week and per year by random coefficient models. Study periods (weeks 0–6 and weeks 6–52) and total and chronic slopes (week 0 or week 6 to weeks 104, 156, 208, and 260) were modeled separately and by baseline kidney status.

Results In the overall population, for weeks 0–6, the least squares mean eGFR slopes (ml/min per 1.73 m^2 per week [95% confidence interval (95% CI)]) were −0.07 (−0.16 to 0.03) and −0.54 (−0.61 to −0.48) for the placebo and ertugliflozin groups, respectively; the difference was −0.47 (−0.59 to −0.36). During weeks 6–52, least squares mean eGFR slopes (ml/min per 1.73 m^2 per year [95% CI]) were −0.12 (−0.70 to 0.46) and 1.62 (1.21 to 2.02) for the placebo and ertugliflozin groups, respectively; the difference was 1.74 (1.03 to 2.45). For weeks 6–156, least squares mean eGFR slopes (ml/min per 1.73 m^2 per year [95% CI]) were −1.51 (−1.70 to −1.32) and −0.32 (−0.45 to −0.19) for the placebo and ertugliflozin groups, respectively; the difference was 1.19 (0.95 to 1.42). During weeks 0–156, the placebo-adjusted difference in least squares mean slope was 1.06 (0.85 to 1.27). These findings were consistent by baseline kidney status.

Conclusions Ertugliflozin has a favorable placebo-adjusted eGFR slope >0.75 ml/min per 1.73 m^2 per year, documenting the kidney function preservation underlying the clinical benefits of ertugliflozin on kidney disease progression in patients with type 2 diabetes mellitus and atherosclerotic cardiovascular disease.

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Introduction

Beyond reducing blood pressure and albuminuria, and metabolic risk parameters including glycated hemoglobin (HbA_{1c}) and weight, some sodium-glucose cotransporter 2 (SGLT2) inhibitors have demonstrated reductions in the risk of clinical CKD progression in people with and without type 2 diabetes mellitus (1,2). Clinical protection against CKD progression with SGLT2 inhibitors has been attributed to several glucose-lowering independent factors (3–6). CKD is closely associated with cardiovascular morbidity and mortality (7). Kidney function loss, reflected by the rate of decline in estimated glomerular filtration (eGFR slope), is a predictor of CKD risk and a surrogate for kidney failure (8,9). Attenuation of changes in eGFR slope has been used as a surrogate in clinical studies assessing the potential for kidney protection by pharmacologic agents (1,2,10,11). The use of eGFR slopes, rather than dichotomous categoric outcomes (8), is potentially advantageous owing to it being a continuous variable with greater potential for discrimination and the ability of novel therapies to demonstrate an effect on eGFR slope over relatively brief periods of time. Results from previous modeling analyses demonstrate that preservation of eGFR slope by ≥0.75 ml/min per 1.73 m^2 per year over 3 years predicts clinically relevant delay of CKD progression with at least 96% probability (9).

In previous work involving the eValuation of ERTugliflozin effIcacy and Safety CardioVascular outcomes (VERTIS CV) study population, we reported that

although ertugliflozin had a nonsignificant 21% relative risk reduction in the risk of events of doubling of serum creatinine (*i.e.*, corresponding to a decline in eGFR by 57%), the risk of events of a sustained 40% decline from baseline in eGFR was significantly reduced by 35% (12). Ertugliflozin also preserved eGFR by approximately 3 ml/min per 1.73 m^2 compared with placebo after 5 years, and lowered albuminuria, especially in patients with microalbuminuria or macroalbuminuria at baseline (while still on study drug). The aim of the current prespecified exploratory analysis was to elucidate the effect of ertugliflozin treatment on eGFR slope compared with placebo in the VERTIS CV study.

Materials and Methods

The VERTIS CV study was an event-driven study comparing two doses of ertugliflozin (5 mg and 15 mg) with placebo. The design, primary results, and full study protocol of the VERTIS CV study have been previously published (13,14).

Study Population

The full details of study eligibility criteria have been previously described (13,14). The study recruited patients with type 2 diabetes mellitus and established atherosclerotic cardiovascular disease who had a baseline eGFR≥30 ml/min per 1.73 m^2. The study was conducted in accordance with the principles of Good Clinical Practice and was approved by the appropriate institutional review boards and regulatory agencies, with all participants providing written, informed consent. The trial was conducted in accordance with the Declaration of Helsinki and was consistent with Good Clinical Practice and applicable regulatory requirements.

eGFR Slope Analyses

In this prespecified exploratory analysis, the slopes for changes in eGFR per week or per year were analyzed by random coefficient models (eGFR was calculated using the Modification of Diet in Renal Disease formula). A central laboratory measurement for serum creatinine (to estimate the GFR) was performed at baseline; weeks 0, 6, 12, 18, 26, 39, and 52; and every 4 months up to 5 years. Least squares 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 four 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 52;
3) chronic slope: yearly slopes from week 6 to weeks 104, 156, 208, and 260; and
4) total yearly slope from week 0 (baseline) to weeks 52, 104, 156, 208, and 260.

Chronic slope was investigated to omit the period when the known hemodynamic effects of SGLT2 inhibitors may confound the effect of ertugliflozin on longer-term kidney function decline. By contrast, total slope was used as a measure of long-term eGFR decline that also included the initial, reversible hemodynamic eGFR "dip" (and may therefore underestimate the magnitude of kidney function preservation).

Weekly and yearly eGFR slopes were assessed for the overall population and by three baseline kidney status classification schemes: eGFR, urinary albumin-to-creatinine ratio (UACR), and the Kidney Disease Improving Global Outcomes in Chronic Kidney Disease (KDIGO CKD) risk categories, which combine eGFR and UACR. A full description of the subgroups can be viewed in the Supplemental Material.

Statistical Analyses

The slope analyses were performed on the basis of the full analysis set (randomized participants who received one or more doses of blinded study medication and had one or more measurements of the analysis end point). Data collected after initiation of glycemic rescue therapy were included; however, data obtained >2 days after the last dose of study medication were excluded from the analyses of the eGFR. Weekly and yearly eGFR slopes were analyzed by generalized random coefficient models. The models included the eGFR value as a response variable, with treatment, time, baseline HbA_{1c}, baseline eGFR, and treatment-by-time interaction as linear covariates. Time 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. All analyses were exploratory and prespecified; they were defined in a separate kidney statistical analysis plan that was completed before database lock. The analyses were performed using SAS version 9.4.

Results

Baseline Characteristics

A total of 8246 patients were randomized and followed for a median of 3.0 years. Of these, 2747 received placebo and 5499 received ertugliflozin (5 mg or 15 mg; pooled for this analysis). Patient demographic and baseline clinical characteristics for the overall population and by baseline kidney status have been previously reported and are summarized in Table 1 by treatment group for the overall population (12). Baseline eGFR values were available for 2747 and 5498 patients for the placebo and ertugliflozin groups, respectively. Of the study participants, 2048 (24.8%), 4390 (53.2%), and 1807 (21.9%) had eGFR G1, G2, and G3 at baseline, respectively. In subgroups defined by baseline albuminuria status, 4783 (59.6%), 2492 (31.0%), and 755 (9.4%) study participants had normoalbuminuria, microalbuminuria, and macroalbuminuria, respectively. At baseline, 3916 (48.8%), 2568 (32.0%), and 1548 (19.3%) patients were assigned to the KDIGO CKD low-risk, moderate-risk, and high-/very high-risk categories, respectively.

Overall eGFR Over Time

Mean eGFR over time has been previously reported and is displayed in Figure 1 (12). After the initial decrease from baseline in eGFR in the ertugliflozin group at week 6, there was an increase in eGFR toward baseline that continued up

Table 1. Baseline demographic and disease characteristics of the overall population from the eValuation of ERTugliflozin effIcacy and Safety CardioVascular outcomes clinical trial (intention to treat)

Characteristic	Placebo (*n*=2747)	Ertugliflozin, Pooled (*n*=5499)	Total (*n*=8246)
Female sex, *n* (%)	844 (31)	1633 (30)	2477 (30)
Age, yr	64±8	64±8	64±8
HbA_{1c}, %	8.2±0.9	8.2±1.0	8.2±1.0
Duration of type 2 diabetes mellitus, yr	13±8	13±8	13±8
Hemoglobin, g/dl	14.0±1.4	14.0±1.4	14.0±1.4
BMI, kg/m^2	32.0±5.5	31.9±5.3	32.0±5.4
eGFR, ml/min per 1.73 m^2 (MDRD)	76±21	76±21	76±21
UACR, mg/g	19 (6–67)	18 (6–69)	19 (6–68)
Systolic BP, mmHg	133±14	133±14	133±14
Glucose-lowering agents, *n* (%)			
Insulin	1344 (49)	2556 (46)	3900 (47)
Biguanides	2124 (77)	4168 (76)	6292 (76)
Antihypertensive agents, *n* (%)			
Any antihypertensive	2632 (96)	5221 (95)	7853 (95)
RAAS inhibitor	2239 (82)	4447 (81)	6686 (81)
Diuretic	1196 (44)	2346 (43)	3542 (43)
Loop diuretic	426 (16)	826 (15)	1252 (15)
Mineralocorticoids receptor antagonists	224 (8)	450 (8)	674 (8)
Antiplatelet or antithrombotic drugs, *n* (%)	2446 (89)	4880 (89)	7326 (89)
Lipid-lowering agents, *n* (%)	2313 (84)	4655 (85)	6968 (85)
eGFR category, *n* (%)[a]			
eGFR G1 (eGFR≥90 ml/min per 1.73 m^2)	678 (25)	1370 (25)	2048 (25)
eGFR G2 (eGFR≥60 and <90 ml/min per 1.73 m^2)	1461 (53)	2929 (53)	4390 (53)
eGFR G3 (eGFR<60 ml/min per 1.73 m^2)	608 (22)	1199 (22)	1807 (22)
UACR category, *n* (%)[b]			
Normoalbuminuria	1597 (60)	3186 (60)	4783 (60)
Microalbuminuria	845 (31)	1647 (31)	2492 (31)
Macroalbuminuria	242 (9)	513 (10)	755 (9)
KDIGO CKD risk category, *n* (%)[c]			
Low risk of CKD	1307 (49)	2609 (49)	3916 (49)
Moderate risk of CKD	859 (32)	1709 (32)	2568 (32)
High/very high risk of CKD	517 (19)	1031 (19)	1548 (19)

Values are mean±SD or median (interquartile range) unless otherwise stated. Table adapted from ref. 12. HbA_{1c}, glvcated hemoglobin; BMI, body mass index; MDRD, Modification of Diet in Renal Disease; UACR, urinary albumin-to-creatinine ratio; RAAS, renin-angiotensin-aldosterone system; KDIGO CKD, Kidney Disease Improving Global Outcomes in Chronic Kidney Disease.
[a]Participants required a baseline eGFR value for classification: *n*=2747 for placebo; *n*=5498 for ertuglifozin, pooled; *n*=8245 total.
[b]Participants required a baseline UACR value for classification: *n*=2684 for placebo; *n*=5346 for ertugliflozin, pooled; *n*=8030 total.
[c]Participants required baseline eGFR and UACR values for classification: *n*=2683 for placebo; *n*=5349 for ertuglifozin, pooled; *n*=8032 total.

to week 52, followed by an attenuation in the decline of eGFR over time compared with placebo. The placebo-adjusted least squares mean differences from baseline in eGFR (ml/min per 1.73 m^2 [95% confidence interval (95% CI)]) with ertugliflozin were −2.79 (−3.30 to −2.29) at week 6, −0.49 (−1.09 to 0.11) at week 52, 1.21 (0.47 to 1.95) at week 156, and 3.02 (1.80 to 4.23) at week 260.

Acute eGFR Dip Period—Weekly Changes in eGFR for Weeks 0–6

During the acute period (from week 0 to 6), least squares mean eGFR slopes (ml/min per 1.73 m^2 per week [95% CI]) were −0.07 (−0.16 to 0.03) and −0.54 (−0.61 to −0.48) for the placebo and ertugliflozin groups, respectively (Figure 2A); placebo-adjusted least squares mean difference in eGFR slope (ml/min per 1.73 m^2 per week [95% CI]) was −0.47 (−0.59 to −0.36) (P<0.001). Similar findings were observed for the placebo-adjusted differences in slopes in subgroups defined by baseline kidney status (Table 2). There were differences when separately assessing the ertugliflozin and placebo groups by baseline eGFR and the KDIGO CKD risk categories. In patients taking placebo, a negative eGFR slope was observed in the eGFR G1 and KDIGO CKD low-risk subgroups, whereas eGFR slope was neutral in the eGFR G2 and KDIGO CKD moderate-risk subgroups and a positive eGFR slope was observed in the eGFR G3 and KDIGO high-/very high-risk subgroups. In patients taking ertugliflozin, all acute eGFR slopes were negative; however, the weekly eGFR slope was larger in the eGFR G1 subgroup and lowest in the eGFR G3 subgroup, with no overlap of the 95% CIs observed, suggestive of a significant difference (Table 2).

Post–Acute eGFR Dip Readjustment Period—Yearly Changes in eGFR for Weeks 6–52

During weeks 6–52, least squares mean eGFR slopes (ml/min per 1.73 m^2 per year [95% CI]) were −0.12 (−0.70 to 0.46) and 1.62 (1.21 to 2.02) for the placebo and ertugliflozin groups, respectively (Figure 2B); placebo-adjusted least squares mean difference in eGFR slope (ml/min per 1.73 m^2 per year [95% CI]) was 1.74 (1.03 to 2.45) (P<0.001). Similar findings were observed in subgroups defined by baseline kidney function category (Table 2).

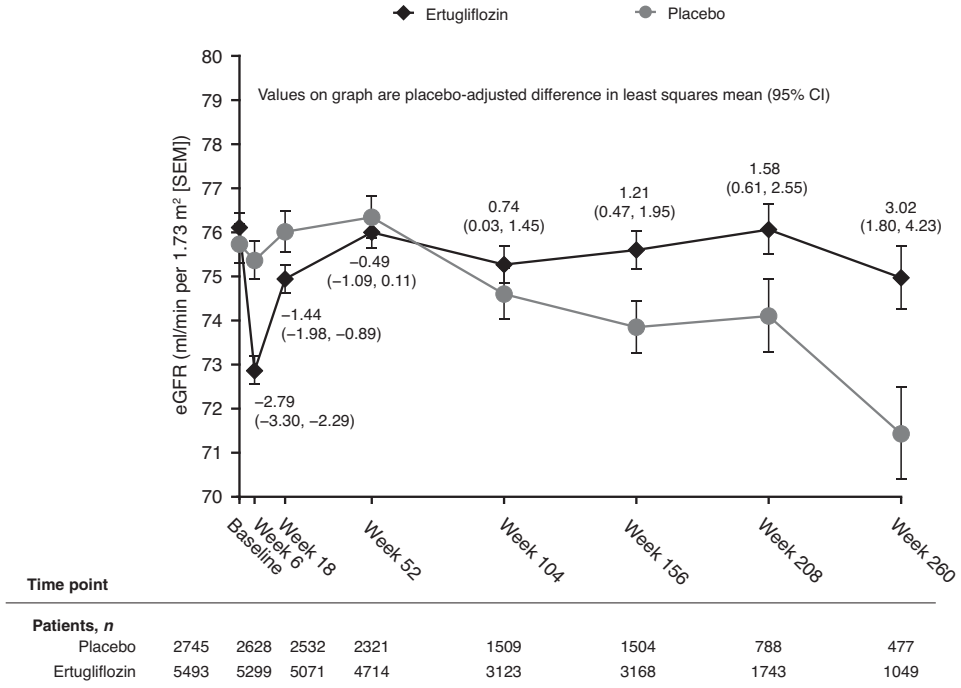

Figure 1. | **Mean eGFR over time in the overall population using the MDRD equation.** Analysis was performed on the full analysis set. Figure from ref. 12 under the terms of the Creative Commons Attribution 4.0 International license (http://creativecommons.org/licenses/by/4.0/). 95% CI, 95% confidence interval; MDRD, Modification of Diet in Renal Disease.

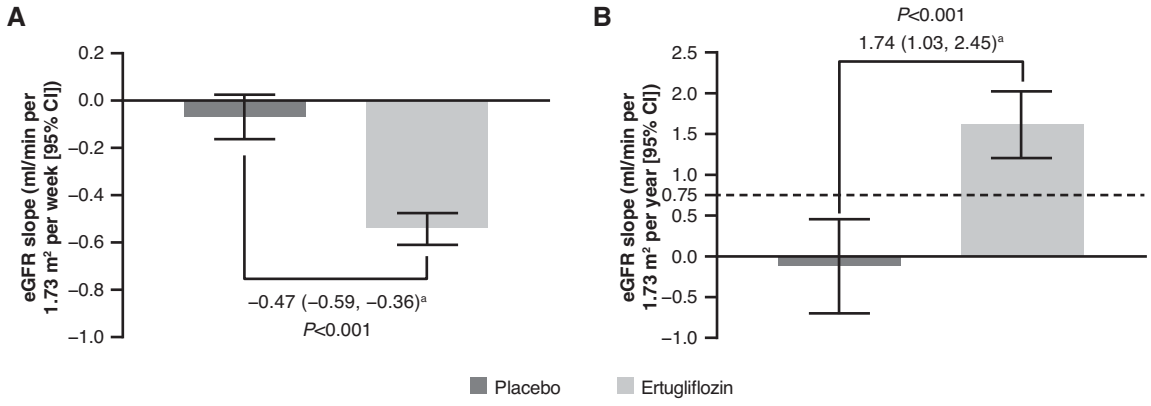

Figure 2. | **Weekly eGFR slope during the acute eGFR dip period (weeks 0–6) by treatment group and yearly eGFR slope during the post–acute eGFR dip readjustment period (weeks 6–52) by treatment group.** (A) Weekly eGFR slope (weeks 0–6) and (B) yearly eGFR slope (weeks 6–52). Preservation of ≥0.75 ml/min per 1.73 m^2 per year on eGFR slope predicts protection against CKD (9). 95% CI, 95% confidence interval; LSM, least squares mean. Analysis was performed on the full analysis set. [a]Placebo-adjusted difference in LSM (95% CI).

Chronic eGFR Slopes

Chronic yearly eGFR slopes (from week 6 to weeks 104, 156, 208, and 260) by treatment group are summarized in Figure 3 and Supplemental Table 1. For all reported periods, the rate of eGFR decline (defined by eGFR slope; ml/min per 1.73 m^2 per year) with ertugliflozin was slower than with placebo. The placebo-adjusted least squares mean chronic eGFR slopes (ml/min per 1.73 m^2 per year [95% CI]) were 1.43 (1.07 to 1.78), 1.19 (0.95 to 1.42), 1.03 (0.84 to 1.22), and 1.02 (0.84 to 1.20), for the week 6 to weeks 104, 156, 208, and 260 periods, respectively, with all P values <0.001. Similar findings were observed in subgroups defined by baseline kidney status (Figure 3, Supplemental Table 2), in which all placebo-adjusted least squares mean differences in chronic eGFR slopes were statistically significant and >0.75 ml/min per 1.73 m^2 per year.

Total eGFR Slopes

Total eGFR slopes (from week 0 to weeks 52, 104, 156, 208, and 260) by treatment group are summarized in Supplemental Table 1. For all reported periods, the rate of eGFR decline (defined by eGFR slope; ml/min per 1.73 m^2 per year) with ertugliflozin was slower than with placebo. The placebo-adjusted least squares mean chronic eGFR

Table 2. eGFR slope during the acute "dip" period (per week) and the readjustment period (per year), by baseline kidney status

Time Period	eGFR G1 (eGFR≥90 ml/min per 1.73 m^2)			eGFR G2 (eGFR≥60 and <90 ml/min per 1.73 m^2)			eGFR G3 (eGFR<60 ml/min per 1.73 m^2)		
	Placebo	Ertugliflozin	Difference[a]	Placebo	Ertugliflozin	Difference[a]	Placebo	Ertugliflozin	Difference[a]
Weeks 0–6[b]	−0.61 (−0.86 to −0.36)	−1.13 (−1.30 to −0.96)	−0.52 (−0.82 to −0.22)	−0.01 (−0.10 to 0.08)	−0.42 (−0.48 to −0.35)	−0.41 (−0.52 to −0.30)	0.38 (0.26 to 0.50)	−0.18 (−0.27 to −0.10)	−0.57 (−0.72 to −0.42)
Weeks 6–52[c]	−0.14 (−1.58 to 1.31)	1.97 (0.95 to 3.00)	2.11 (0.33 to 3.89)	−0.27 (−1.00 to 0.47)	1.49 (0.98 to 2.00)	1.76 (0.87 to 2.66)	0.25 (−0.77 to 1.26)	1.49 (0.76 to 2.22)	1.25 (−0.01 to 2.50)
	Normoalbuminuria			**Microalbuminuria**			**Macroalbuminuria**		
Weeks 0–6[b]	−0.09 (−0.22 to 0.04)	−0.51 (−0.60 to −0.41)	−0.42 (−0.58 to −0.26)	−0.03 (−0.20 to 0.13)	−0.55 (−0.67 to −0.43)	−0.52 (−0.72 to −0.32)	−0.05 (−0.3 to 0.21)	−0.68 (−0.85 to −0.50)	−0.63 (−0.94 to −0.32)
Weeks 6–52[c]	0.03 (−0.71 to 0.77)	2.18 (1.66 to 2.71)	2.16 (1.25 to 3.06)	−0.05 (−1.13 to 1.04)	1.13 (0.36 to 1.90)	1.18 (−0.15 to 2.51)	−1.53 (−3.59 to 0.54)	−0.36 (−1.78 to 1.05)	1.16 (−1.34 to 3.66)
	KDIGO CKD Low Risk			**KDIGO CKD Moderate Risk**			**KDIGO CKD High/Very High Risk**		
Weeks 0–6[b]	−0.23 (−0.37 to −0.08)	−0.60 (−0.70 to −0.50)	−0.37 (−0.55 to −0.19)	−0.00 (−0.18 to 0.17)	−0.51 (−0.63 to −0.39)	−0.51 (−0.72 to −0.30)	0.22 (0.03 to 0.41)	−0.42 (−0.56 to −0.29)	−0.64 (−0.88 to −0.41)
Weeks 6–52[c]	−0.08 (−0.92 to 0.76)	2.12 (1.53 to 2.71)	2.20 (1.17 to 3.23)	−0.08 (−1.16 to 0.99)	1.53 (0.78 to 2.29)	1.62 (0.30 to 2.93)	−0.35 (−1.59 to 0.89)	0.38 (−0.49 to 1.25)	0.73 (−0.78 to 2.25)

Analysis was performed on the full analysis set population. KDIGO CKD, Kidney Disease Improving Global Outcomes in Chronic Kidney Disease.
[a]Difference versus placebo (least squares mean [95% confidence interval]).
[b]eGFR slope (least squares mean), ml/min per 1.73 m^2 per week (95% confidence interval).
[c]eGFR slope (least squares mean), ml/min per 1.73 m^2 per year (95% confidence interval).

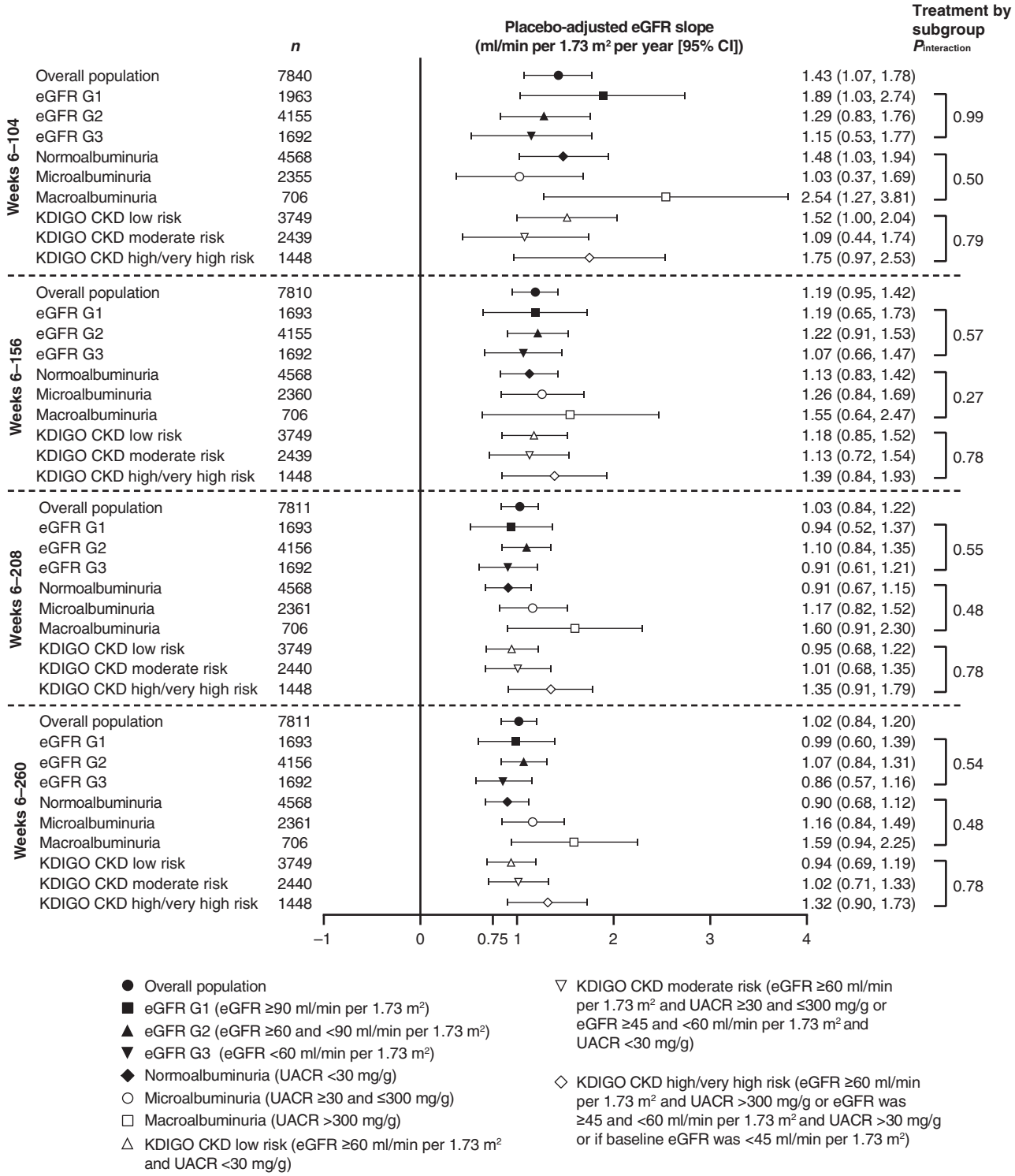

Figure 3. | **Placebo-adjusted chronic yearly slopes from week 6 in the overall population and by baseline kidney function.** Preservation of ≥0.75 ml/min per 1.73 m^2 per year on eGFR slope predicts protection against CKD (9). Analysis was performed on the full analysis set. 95% CI, 95% confidence interval; KDIGO CKD, Kidney Disease Improving Global Outcomes in Chronic Kidney Disease; UACR, urinary albumin-to-creatinine ratio.

slopes (ml/min per 1.73 m^2 per year [95% CI]) were 0.89 (0.33 to 1.46), 1.13 (0.83 to 1.43), 1.06 (0.85 to 1.27), 0.96 (0.79 to 1.13), and 0.96 (0.80 to 1.11), for the week 0 to weeks 52, 104, 156, 208, and 260 periods, respectively, with all P values <0.003. Similar findings were generally observed in subgroups defined by baseline kidney status category (Figure 4, Supplemental Table 2), in which placebo-adjusted chronic eGFR slopes were statistically significant and >0.75 ml/

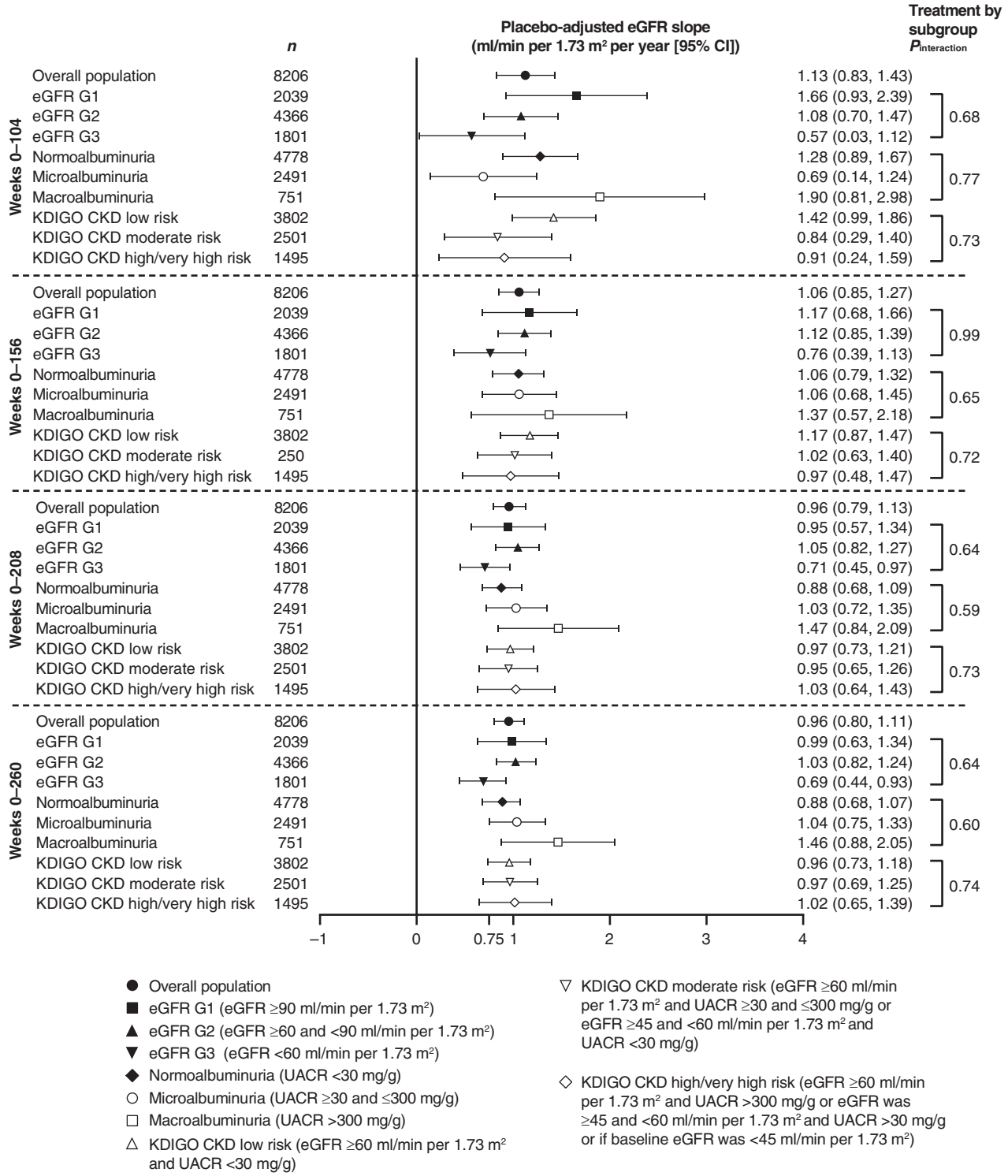

Figure 4. | **Placebo-adjusted total yearly slopes from week 0 in the overall population and by baseline kidney function.** Preservation of ≥0.75 ml/min per 1.73 m² per year on eGFR slope predicts protection against CKD (9). Analysis was performed on the full analysis set. 95% CI, 95% confidence interval; KDIGO CKD, Kidney Disease Improving Global Outcomes in Chronic Kidney Disease; UACR, urinary albumin-to-creatinine ratio.

min per 1.73 m² per year for many of the subgroups, with the exception of the microalbuminuria subgroup during week 0 to weeks 52 and 104, the macroalbuminuria subgroup during week 0 to week 52, and for most time periods from week 0 for the eGFR G3 subgroup.

Discussion

The identification of reasonable clinical surrogates for kidney protection is a major nephrology research priority. Recent trials have used the risk of reaching a sustained significant percentage decline in eGFR over time as a

surrogate for clinical end points in kidney outcome studies. There is an emerging consensus that a ≥40% decline in eGFR is the most appropriate measure under most circumstances (8). However, these surrogates may not be applicable to all populations, to all interventions, or in early stages of kidney disease (9). Another method to assess significant kidney function loss over time involves the use of eGFR slope as a surrogate for kidney failure. Using eGFR slope as a surrogate for CKD progression in clinical studies has been supported by National Kidney Foundation working groups (8) and has the added benefit of allowing for a smaller sample size (15). In analyses by Levey, Inker, and others, a treatment effect of ≥0.75 ml/min per 1.73 m^2 per year on slope over 3 years in sufficiently powered studies predicts a clinical benefit on CKD progress with at least 96% probability (8,9). Therefore, beyond assessing the effect of ertugliflozin on more traditional definitions of kidney function loss, which have been reported elsewhere (12), we examined the effect of ertugliflozin on acute and chronic slopes. In this analysis from the VERTIS CV study, ertugliflozin had a favorable effect on eGFR change over time compared with placebo, reflected by a greater preservation of kidney function during the chronic treatment period after 6 weeks.

SGLT2 inhibitors induce a characteristic and reversible acute "dip" in eGFR after initiation of treatment. In a mechanistic study, this effect occurred within 24 hours, in conjunction with an increase in natriuresis, after a single dose of the SGLT2 inhibitor empagliflozin (16). The initial rapid rate of change has been most closely linked with an acute hemodynamic effect on renal tubuloglomerular feedback, secondary to acute blockade of tubular sodium reabsorption in the S1 segment of the proximal tubule, leading to afferent vasoconstriction under the influence of adenosine (6,17,18). Our earliest observation was consistent with these mechanisms and previous observations; treatment with ertugliflozin induced an expected greater degree of weekly eGFR decline from week 0 to 6. The initial mean eGFR "dip" associated with SGLT2 inhibitor treatment is commonly observed in clinical studies and in practice (19). After the initial eGFR change, from week 6 to 52, eGFR values returned toward baseline with ertugliflozin. Although the mechanisms responsible for this subsequent increase in eGFR over time are not fully understood, it might represent an adaptation in downstream sodium reabsorption pathways. These may include tubular sodium-glucose cotransporter 1 or sodium-hydrogen exchanger bioactivity, leading to a new state of tubuloglomerular feedback equilibrium and afferent redilatation (20–22).

On the basis of these well-established acute hemodynamic effects of SGLT2 inhibitors, the most informative period related to long-term benefits of these therapies is the chronic slope, after the initial change (week 6 in VERTIS CV), and for 3 or more years (8,9). Data from VERTIS CV meet criteria outlined for the use of eGFR slope as a reasonable surrogate measure of kidney protection (*i.e.*, study duration and sample size). Importantly, the treatment effect of ertugliflozin on eGFR slope slowed the rate of decline in both chronic and total eGFR slope, compared with placebo, by a meaningful amount, as defined by a threshold of ≥0.75 ml/min per 1.73 m^2 per year (9). Even when examined according to subgroups by eGFR, UACR, and KDIGO CKD risk category, chronic eGFR slope decline was significantly reduced with ertugliflozin in all investigated subgroups, compared with placebo.

The effect of ertugliflozin on attenuating eGFR decline was consistently beneficial in analyses from 2 to up to 5 years of follow-up and was consistent with previous studies with ertugliflozin. In a pooled analysis of two phase 3 studies from the ertugliflozin clinical development program, 2-year comparator-adjusted chronic eGFR slopes (from week 6) were between 1.56 and 2.60 ml/min per 1.73 m^2 per year (3). Similar data around eGFR slope have been reported with other SGLT2 inhibitors, supporting the concept that kidney protection is broadly seen with these therapies, including in dedicated diabetic kidney disease cohort trials, such as the Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation (CREDENCE) trial (1), and in previous cardiovascular outcome trials. In the Canagliflozin Cardiovascular Assessment Study (CANVAS) Program (median follow-up period of 20.9 months), the placebo-adjusted chronic eGFR slope was +1.2 ml/min per 1.73 m^2 per year from week 13 onwards with canagliflozin (23). In the Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients-Removing Excess Glucose (EMPA-REG OUTCOME) study, from week 4 to the last value on treatment (median follow-up period of 3.1 years), chronic eGFR slopes were −1.46 and 0.23 ml/min per 1.73 m^2 per year in the placebo and empagliflozin groups, respectively (10). Similar benefits were recently reported in the Empagliflozin Outcome Trial in Patients With Chronic Heart Failure With Reduced Ejection Fraction (EMPEROR-Reduced), in which total slope was better preserved with empagliflozin compared with placebo, with a placebo-adjusted eGFR slope of 1.73 ml/min per 1.73 m^2 per year over a median follow-up of 16 months (11). These protective effects were emphasized by the observation that after an off-drug washout period at the end of the trial, eGFR rebounded almost back to baseline, augmenting the placebo-adjusted preservation of eGFR in patients treated with empagliflozin (24). Most recently, in the Dapagliflozin and Prevention of Adverse Outcomes in CKD study, from week 2 to month 30, reductions in eGFR were reduced with dapagliflozin compared with placebo, with a between-group difference of 1.92 ml/min per 1.73 m^2 per year (2). The current analyses from VERTIS CV further illustrate the potential for kidney function benefits achieved with SGLT2 inhibition, even in a cohort that had a relatively low overall risk for CKD progression. Protection against CKD progression may be especially important in light of the close relationship between kidney function loss and the development of heart failure. As SGLT2 inhibitors preserve eGFR and reduce heart failure progression, the effects in the kidney may lead to better salt and water homeostasis, thereby keeping patients out of the hospital (25,26).

Our analysis does have limitations. First, we report prespecified exploratory end points that were not controlled for type 1 error. Although eGFR slope is an important surrogate marker of long-term kidney risk, it does have limitations due to variability of the measurement in response to factors such as hydration and changes to medication. We minimized the effect of measurement variability with the use of a large sample size and further recognize that eGFR variability would have biased our analysis toward null. An assessment of

eGFR after discontinuation of study drug was not performed in this study, because in other studies of SGLT2 inhibitors (including a study with ertugliflozin), eGFR increases upon cessation of the medication (10,23,27). Finally, we had insufficient power to adequately assess slope in some of the subgroups, especially those with advanced kidney disease at baseline, who made up <20% of the overall patient population.

In conclusion, ertugliflozin was associated with clinically relevant preservation of eGFR compared with placebo in the VERTIS CV study cohort involving patients with type 2 diabetes mellitus and established atherosclerotic cardiovascular disease, a benefit that may contribute to end-organ protection with SGLT2 inhibitors.

Disclosures

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The sponsor was involved in the study design; collection, analysis, and interpretation of data; and data checking of information provided in the manuscript. However, ultimate responsibility for opinions, conclusions, and data interpretation lies with the authors.

Data Sharing Statement

The data sharing policy of Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, 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* email to dataaccess@merck.com.

Supplemental Material

This article contains the following supplemental material online at http://cjasn.asnjournals.org/lookup/suppl/doi:10.2215/CJN.01130121/-/DCSupplemental.

Supplemental Summary 1. VERTIS CV Investigators.

Supplemental Table 1. Chronic and total yearly eGFR slope in the overall population.

Supplemental Table 2. Chronic and total yearly eGFR slope analyses by baseline kidney status.

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