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Effects of Once-Weekly Semaglutide on Kidney Disease Outcomes by KDIGO Risk Category in the SUSTAIN 6 Trial

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Introduction: Glucagon-like peptide-1 receptor agonists (GLP-1RAs) are recommended by Kidney Disease: Improving Global Outcomes (KDIGO) as risk-based treatment for hyperglycemia, weight management, and cardiovascular (CV) risk reduction in people with type 2 diabetes (T2D) and chronic kidney disease (CKD). The aim of this *post hoc* analysis was to assess treatment effects of once weekly semaglutide on kidney disease outcomes by KDIGO risk category and on changes in KDIGO risk category, compared with placebo.

Methods: Participants with T2D and established CV disease or at high CV risk treated with once weekly semaglutide or placebo in SUSTAIN 6 (NCT01720446) were stratified by baseline KDIGO risk category (low [$n = 1596$], moderate [$n = 831$], high [$n = 445$], very high [$n = 366$]). Treatment effect was analyzed for a kidney disease composite end point (macroalbuminuria, serum creatinine doubling and estimated glomerular filtration rate [eGFR] < 45 ml/min per 1.73 m^2, kidney replacement therapy, or death due to kidney disease) from baseline to 2 years.

Results: The treatment effect of semaglutide versus placebo was consistent across KDIGO categories for the kidney disease composite end point (hazard ratio [95% confidence interval (CI)]: 0.35 [0.07–1.72], 0.42 [0.25–0.72], 0.87 [0.45–1.71], and 0.72 [0.42–1.23] for low, moderate, high, and very high risk categories, respectively; *P* interaction = 0.28). Participants receiving semaglutide were more likely to move to a lower KDIGO risk category (odds ratio: 1.69; 95% CI: [1.32–2.16]) and less likely to move to a higher KDIGO risk category versus placebo (odds ratio: 0.71; 95% CI: [0.59–0.86]).

Conclusion: Once weekly semaglutide versus placebo reduced risks of kidney disease end points and improved risk categories irrespective of baseline KDIGO risk.

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Diabetes is one of the most common causes of CKD and the leading cause of kidney failure worldwide; moreover, approximately 40% of people with T2D develop CKD.[1-5] People with T2D and CKD are at high risk of CV disease, including heart failure and atherosclerotic CV disease.[6,7] GLP-1RAs are used for the treatment of T2D because of the beneficial effects on hyperglycemia and body weight.[8,9] Findings from CV outcomes trials (CVOTs) and clinical trials assessing glycemic control with GLP-1RAs have demonstrated the CV safety; and for some agents, improvements in CV outcomes in people with T2D and at risk of CV events.[10-15] In addition, beneficial effects on kidney disease outcomes were observed with GLP-1RAs in these trials, including reductions in albuminuria or slowing of kidney function loss.[10,12,13,15-19] At present, GLP-1RAs are considered risk-based treatment for hyperglycemia, weight management, and atherosclerotic CV risk for patients with T2D and CKD.[20,21]

In the SUSTAIN 6 CVOT, once weekly subcutaneous semaglutide, a GLP-1RA, significantly reduced the risk of a composite end point of CV mortality, nonfatal myocardial infarction, or nonfatal stroke compared with placebo, in people with T2D with established CV

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disease or at high CV risk.[10] In addition, the risk of the secondary kidney disease outcome (macroalbuminuria, serum creatinine doubling and eGFR < 45 ml/min per 1.73 m^2, kidney replacement therapy, or death due to kidney disease) was significantly lower with once weekly semaglutide versus placebo.[10] Moreover, a *post hoc* analysis of data from SUSTAIN 6 pooled with data from the PIONEER 6 trial of once daily oral semaglutide showed that semaglutide slowed decline in eGFR.[19] The KDIGO risk classification uses a combined assessment of both albuminuria and eGFR to categorize risk of progression to kidney failure, CV events, and death.[22] The aim of this *post hoc* analysis of SUSTAIN 6 was to investigate the effects of once weekly semaglutide on kidney disease outcomes across KDIGO risk categories and determine its impact to cause changes in participant's KDIGO risk category at the end of the trial compared with placebo.

METHODS

Study Design

The SUSTAIN 6 (NCT01720446) study design has been reported previously.[10] Adults with T2D and established CV disease or a high CV risk were randomized 1:1:1:1 to receive once weekly semaglutide (0.5 mg or 1.0 mg) or volume matched placebo in addition to standard of care for 2 years. Eligible participants were aged ≥50 years and had established CV disease or CKD, or aged ≥60 years with CV risk factors. Participants with kidney failure treated by dialysis or transplant were excluded. Accordingly, the SUSTAIN 6 study protocol was approved by the institutional review boards and ethics committees at each study center and the study was conducted in compliance with the International Conference on Harmonization Good Clinical Practice guidelines and the Declaration of Helsinki.[23,24]

In this *post hoc* analysis, participants from SUSTAIN 6 with baseline eGFR and urine albumin-to-creatinine ratio (UACR) values were pooled by treatment and stratified into 4 subgroups by KDIGO risk category at baseline, which were defined by baseline eGFR and UACR levels as low risk, moderate risk, high risk, and very high risk, as outlined in Figure 1.[25] Data from the PIONEER 6 trial of once daily oral semaglutide was not included, because UACR was not systematically collected in that trial.

Outcomes

The rate of occurrence of a kidney disease composite outcome among participants categorized in higher KDIGO risk categories compared with those in the low KDIGO risk category was evaluated. The kidney disease composite outcome was defined as persistent macroalbuminuria (UACR >300 mg/d; confirmed by a second measurement after 12 weeks), persistent doubling of the serum creatinine level and eGFR (per the modification of diet in renal disease equation) < 45 ml/min per 1.73 m^2, the need for kidney replacement therapy, or death due to kidney disease.

The treatment effect of once weekly semaglutide compared with placebo on the kidney disease composite outcome, eGFR slope, and change in UACR was also assessed from baseline to the end of treatment at 2

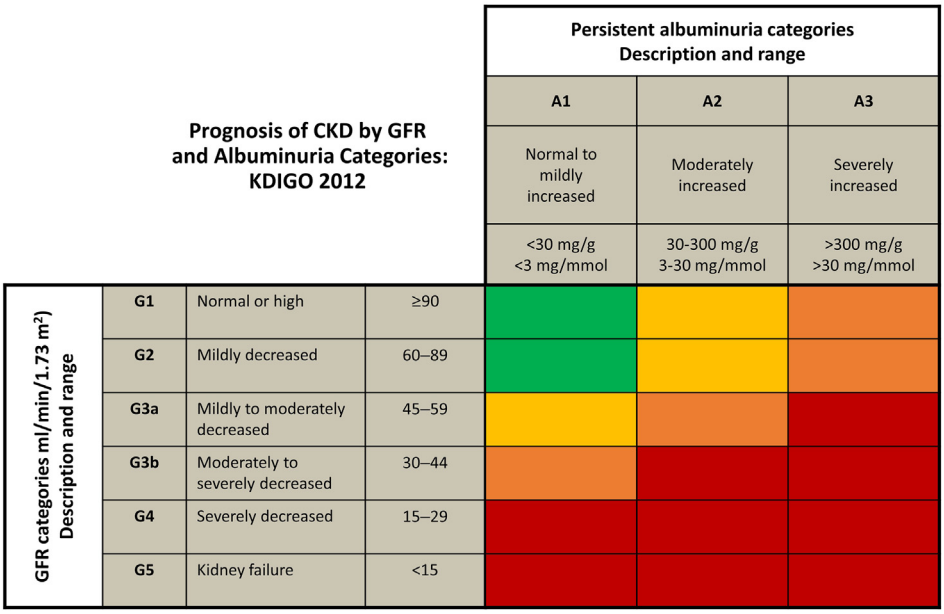

Figure 1. KDIGO heatmap for prognosis of CKD. Green: low risk (if no other markers of kidney disease, no CKD); Yellow: moderately increased risk; Orange: high risk; Red: very high risk. Figure reprinted from Kidney International Supplements, volume 3, KDIGO 2012 clinical practice guideline for the evaluation and management of chronic kidney disease, pp 1-163. Copyright (2023), with permission from Elsevier. CKD, chronic kidney disease; GFR, glomerular filtration rate; KDIGO, Kidney Disease: Improving Global Outcomes.

years. Lastly, the proportion of participants who moved to a higher or to a lower KDIGO risk category and the contributors for this change in KDIGO risk category, with regard to changes in UACR and eGFR, were also evaluated at the end of treatment.

Statistical Analyses

All randomized participants in the study were included in the full analysis set, which was used to assess baseline characteristics, while in-trial data were used for the efficacy results. The treatment effect of semaglutide versus placebo on time to the first kidney disease composite outcome was analyzed using a Cox proportional hazards model, with treatment (semaglutide or placebo) by KDIGO category as fixed factors and stratified by all possible combinations of the 3 stratification factors used in randomization (evidence of CV disease, insulin treatment, eGFR $<$ 30 ml/min per 1.73 m^2). Change in eGFR at the end of treatment was assessed using random slope modeling, with change from baseline as dependent variable and time interacting with treatment by KDIGO category adjusted for baseline eGFR. Change in UACR at end of treatment was assessed using a mixed model for repeated measurements with treatment by KDIGO category and baseline UACR, all nested within trial visit included as factors. Owing to skewness in the UACR distribution, these values were log-transformed in the mixed model.

Logistic regression was used to assess the odds of changing to a higher or lower KDIGO risk category in each treatment group, with treatment as an explanatory variable. To account for potential differences in baseline characteristics, a sensitivity analysis was performed, adjusted for age, sex, diabetes duration, glucose lowering medication, smoking status, previous myocardial infarction, stroke, or transient ischemic attack, geographic region, glycated hemoglobin, and eGFR at baseline. A further analysis of change in KDIGO risk category up to 1 year was conducted. No adjustment for multiplicity resting was performed. P values $<$ 0.05 were considered statistically significant.

RESULTS

Baseline Characteristics

In this *post hoc* analysis, 3238 participants of the 3297 randomized in SUSTAIN 6 were included and stratified according to their KDIGO risk categories, as detailed on Table 1. Baseline characteristics were comparable across KDIGO risk categories between those on semaglutide and placebo (Table 1). The median follow-up time in SUSTAIN 6 was 2.1 years.

Kidney Disease Outcomes

Regardless of treatment allocation, the kidney disease composite end point was reached by more participants in the very high (15.3%), high (7.9%), and moderate (7.3%) KDIGO risk categories than in the low KDIGO risk category (0.5%; Supplementary Table S1).

The benefit of semaglutide versus placebo was comparable across KDIGO risk categories at end of treatment, with fewer participants receiving semaglutide experiencing the composite kidney disease end point than those who received placebo (Figure 2). In addition, there was a smaller decline in eGFR slope (Figure 3) and smaller increase in UACR (Figure 4) in participants receiving semaglutide compared with those receiving placebo. Although there was no significant interaction by KDIGO categories, the effects of semaglutide on eGFR slope in participants in the highest risk categories were numerically greater than with placebo.

Changes in KDIGO Risk Category

Participants receiving semaglutide were less likely to move to a higher KDIGO risk category by the end of the 2-year treatment period (Figure 5a; odds ratio: 0.71 [95% CI: 0.59–0.86], $P = 0.0003$) and more likely to move to a lower KDIGO risk category compared with those receiving placebo at end of treatment (Figure 5b; odds ratio: 1.69 [95% CI: 1.32–2.16], $P < 0.0001$). Comparable results were observed after 1 year of treatment (Supplementary Figure S1).

Change in UACR was the main driver for regression of KDIGO risk category observed with both semaglutide and placebo, particularly for those in the lower KDIGO categories (Figure 6). In contrast, change in eGFR was the main driver for progression of KDIGO category for those at high KDIGO risk in both the semaglutide and placebo categories (Figure 6). Similar results were observed after 1 year of treatment (Supplementary Table S2).

DISCUSSION

This *post hoc* analysis of SUSTAIN 6 data found that participants in higher KDIGO risk categories (moderate, high, and very high) were at substantially greater risk of the kidney disease composite end point compared with participants in the low KDIGO risk category. Progression to a higher CKD risk category is common, and the risk of CVD and all-cause mortality increases with higher CKD risk category.[26,27] The benefits of once weekly semaglutide on the kidney disease composite end point, eGFR slope, and albuminuria in participants from the SUSTAIN 6 study were observed across KDIGO risk categories without evidence of heterogeneity, thereby indicating benefit to participants

Table 1. Baseline characteristics according to KDIGO risk category

Characteristics	Low risk (n = 1596)	Moderate risk (n = 831)	High risk (n = 445)	Very high risk (n = 366)
Age, yr	63.6 (7.1)	65.1 (7.0)	66.1 (7.7)	66.5 (8.0)
Male, n (%)	962 (60.3)	514 (61.9)	276 (62.0)	214 (58.5)
Body weight, kg	92.3 (19.4)	92.4 (21.3)	92.9 (22.5)	89.4 (21.7)
BMI, kg/m^2	32.7 (6.0)	32.9 (6.2)	33.2 (6.7)	32.6 (6.5)
T2D duration, yr	12.5 (7.8)	13.8 (7.7)	15.9 (8.3)	17.5 (8.2)
HbA_{1c}, %	8.6 (1.4)	8.8 (1.5)	8.8 (1.6)	8.8 (1.5)
eGFR (CKD-EPI), ml/min per 1.73 m^2	87.6 (13.3)	77.5 (19.1)	62.3 (20.8)	36.4 (11.2)
UACR, mg/g	6.1 (111.3)	41.2 (224.9)	129.3 (763.7)	399.7 (398.9)
Systolic blood pressure, mm Hg	133.6 (15.7)	135.8 (16.7)	137.6 (18.4)	142.1 (20.3)
Diastolic blood pressure, mm Hg	77.3 (9.6)	76.5 (10.0)	77.0 (10.2)	77.4 (11.5)
LDL cholesterol, mmol/l	2.3 (0.9)	2.3 (0.9)	2.4 (1.0)	2.5 (1.1)
Current smoker, n (%)	186 (11.7)	112 (13.5)	61 (13.7)	38 (10.4)
Prior CV event, n (%)	759 (47.6)	360 (43.3)	166 (37.3)	138 (37.3)
Prior myocardial infarction	572 (35.8)	259 (31.2)	125 (28.1)	92 (25.1)
Prior stroke or transient ischemic attack	255 (16.0)	128 (15.4)	61 (13.7)	58 (15.8)
Baseline medication, n (%)				
Glucose-lowering medication	1547 (96.9)	806 (97.0)	419 (94.2)	328 (89.6)
Insulin	641 (40.2)	398 (47.9)	244 (54.8)	236 (64.5)
Metformin	1337 (83.8)	649 (78.1)	269 (60.4)	118 (32.2)
Sulfonylureas	734 (46.0)	362 (43.6)	171 (38.4)	121 (33.1)
Thiazolidinediones	25 (1.6)	16 (1.9)	15 (3.4)	15 (4.1)
SGLT-2 inhibitors	4 (0.3)	0	1 (0.2)	0
Other	8 (0.5)	4 (0.5)	4 (0.9)	7 (1.9)
Blood pressure-lowering medication	1474 (92.4)	777 (93.5)	423 (95.1)	353 (96.4)
RAAS inhibitors	1276 (79.9)	686 (82.6)	374 (84.0)	295 (80.6)
Diuretics	529 (33.1)	299 (36.0)	202 (45.4)	204 (55.7)
Lipid-lowering medication	1216 (76.2)	616 (74.1)	347 (78.0)	295 (80.6)
Statins	1173 (73.5)	583 (70.2)	328 (73.7)	271 (74.0)
Fibrates	130 (8.1)	89 (10.7)	59 (13.3)	66 (18.0)
Ezetimibe	55 (3.4)	33 (4.0)	23 (5.2)	15 (4.1)
PCSK-9 inhibitors	0	0	0	0
Other	5 (0.3)	0	0	0

BMI, body mass index; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; CV, cardiovascular; eGFR, estimated glomerular filtration rate; HbA_{1c}, glycated hemoglobin; LDL, low-density lipoprotein; PCSK-9, proprotein convertase subtilisin/kexin type 9; RAAS, renin-angiotensin-aldosterone system; SGLT-2, sodium-glucose cotransporter 2; T2D, type 2 diabetes; UACR, urine albumin-to-creatinine ratio.
Data are presented as mean (standard deviation) unless otherwise stated.

irrespective of CKD severity. Although there was homogeneity in these results, the effects of once weekly semaglutide versus placebo on eGFR slope appeared to be numerically greater in those at the highest KDIGO risk categories. This finding is consistent with a meta-analysis of 14 studies, which showed that the participants with highest kidney failure risk might benefit most from interventions that reduce eGFR slope.[28] Of note, the same meta-analysis showed that slower eGFR decline was associated with lower kidney failure risk

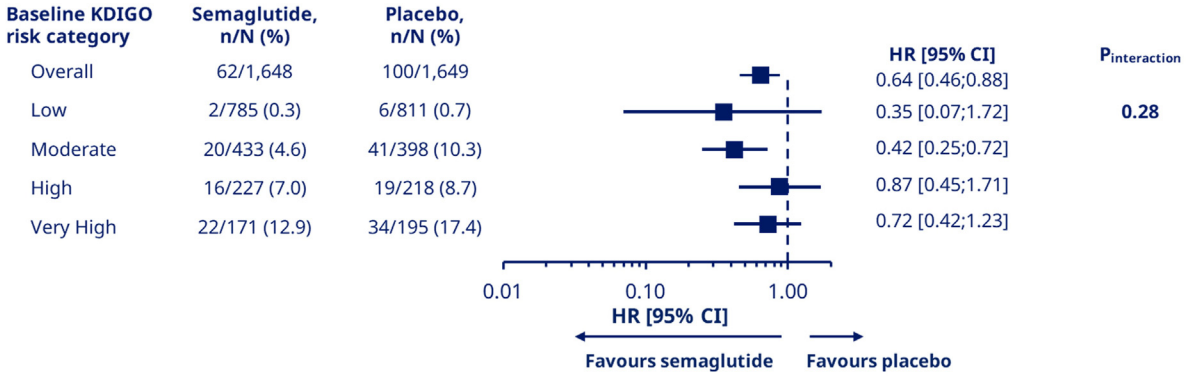

Figure 2. Kidney disease composite outcome by KDIGO risk category at baseline. Kidney disease composite end point was defined as persistent macroalbuminuria, persistent doubling of the serum creatinine level and estimated glomerular filtration rate per modification of diet in renal disease <45 ml/min per 1.73 m^2, the need for kidney replacement therapy, or death due to kidney disease. CI, confidence interval; HR, hazard ratio; KDIGO, Kidney Disease: Improving Global Outcomes.

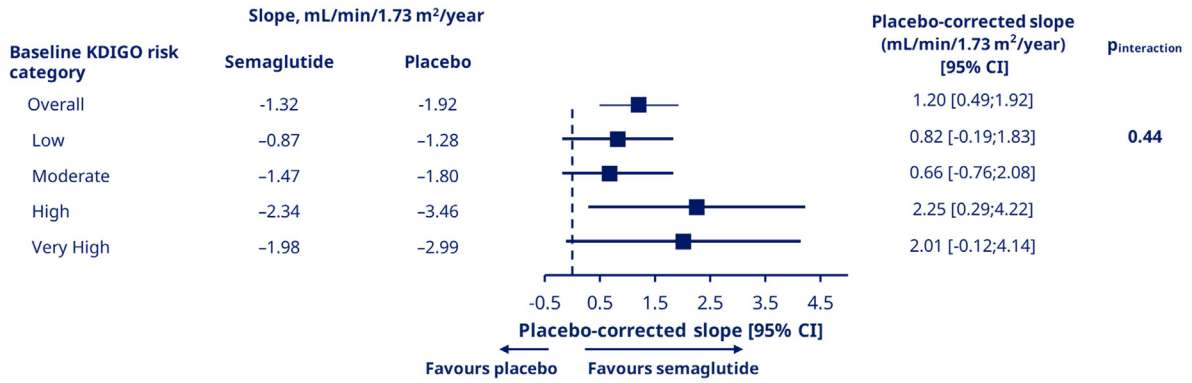

Figure 3. eGFR slope from baseline to end of treatment by KDIGO risk category. CI, confidence interval; eGFR, estimated glomerular filtration rate; KDIGO, Kidney Disease: Improving Global Outcomes.

regardless of baseline eGFR, reinforcing eGFR slope as a clinically relevant end point because it strongly predicts kidney failure.[28,29]

Analyses of GLP-1RA studies have also demonstrated kidney benefits in those with CKD, CV disease, or at high risk of CV disease.[17] In a *post hoc* analysis of the SUSTAIN 6 and PIONEER 6 CVOTs, a reduction in the annual decline of eGFR with semaglutide versus placebo was shown and a reduction in UACR was shown for once weekly subcutaneous semaglutide versus placebo (UACR data were not collected in PIONEER 6).[19] The LEADER trial, a CVOT of the GLP-1RA, liraglutide, demonstrated a reduction in a kidney composite outcome with liraglutide versus placebo, with a *post hoc* analysis demonstrating smaller increases in UACR, and a smaller decline in eGFR over the trial.[30] Findings from an exploratory analysis using results from the LEADER trial suggest that UACR was a potential mediator of the effect of liraglutide on major adverse CV events, along with glycated hemoglobin.[31] The AWARD-7 trial, which studied patients with T2D and CKD, demonstrated significantly smaller declines in eGFR with dulaglutide versus insulin glargine over the duration of the trial.[18] A *post hoc* analysis of the CVOT with dulaglutide, the REWIND trial, also demonstrated a reduction in a composite kidney outcome (macroalbuminuria, ≥30% decline in eGFR, or kidney replacement therapy) with dulaglutide versus placebo.[32] Similar treatment effects were observed with exenatide in a prespecified analysis of the EXSCEL CVOT, in which an adjusted composite kidney outcome (macroalbuminuria, ≥40% decline in eGFR, kidney replacement therapy, or death due to kidney disease) was significantly lower in participants with T2D receiving exenatide compared with placebo.[33] Although it is not yet clear exactly how GLP-1RAs benefit patients with respect to kidney disease end points, it is thought that they may have direct actions on the kidney, in addition to the known benefits for weight reduction and glycemic control.[34,35]

It has been proposed that GLP-1RAs may prevent renal oxidative stress by inhibiting nicotinamide adenine dinucleotide phosphate oxidase.[16] Inhibition of nuclear factor kappa B activation, which plays a pivotal role in the inflammatory pathways that are involved in the development of diabetic kidney disease, has been reported in studies with GLP-1RAs.[16] GLP-1RAs may also be conferring kidney protective benefits through

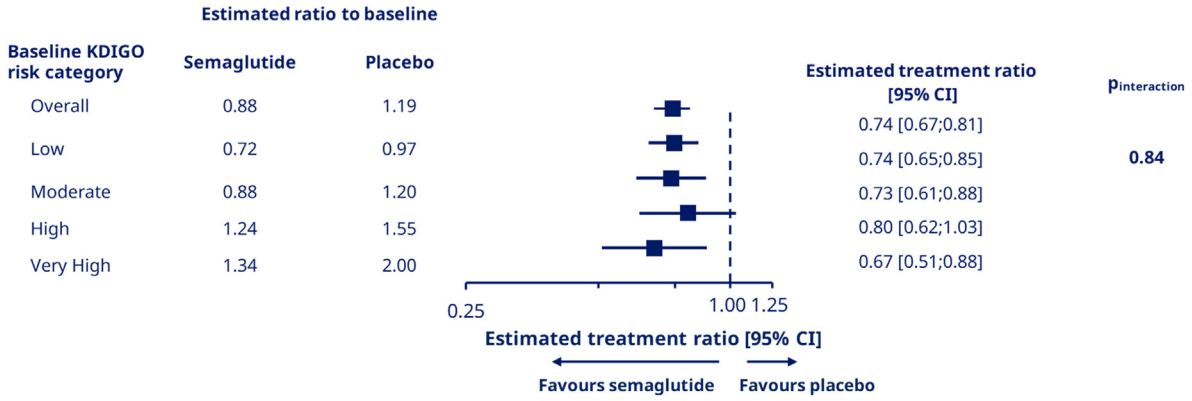

Figure 4. Change from baseline to end of treatment in UACR by KDIGO risk category. CI, confidence interval; KDIGO, Kidney Disease: Improving Global Outcomes; UACR, urine albumin-to-creatinine ratio.

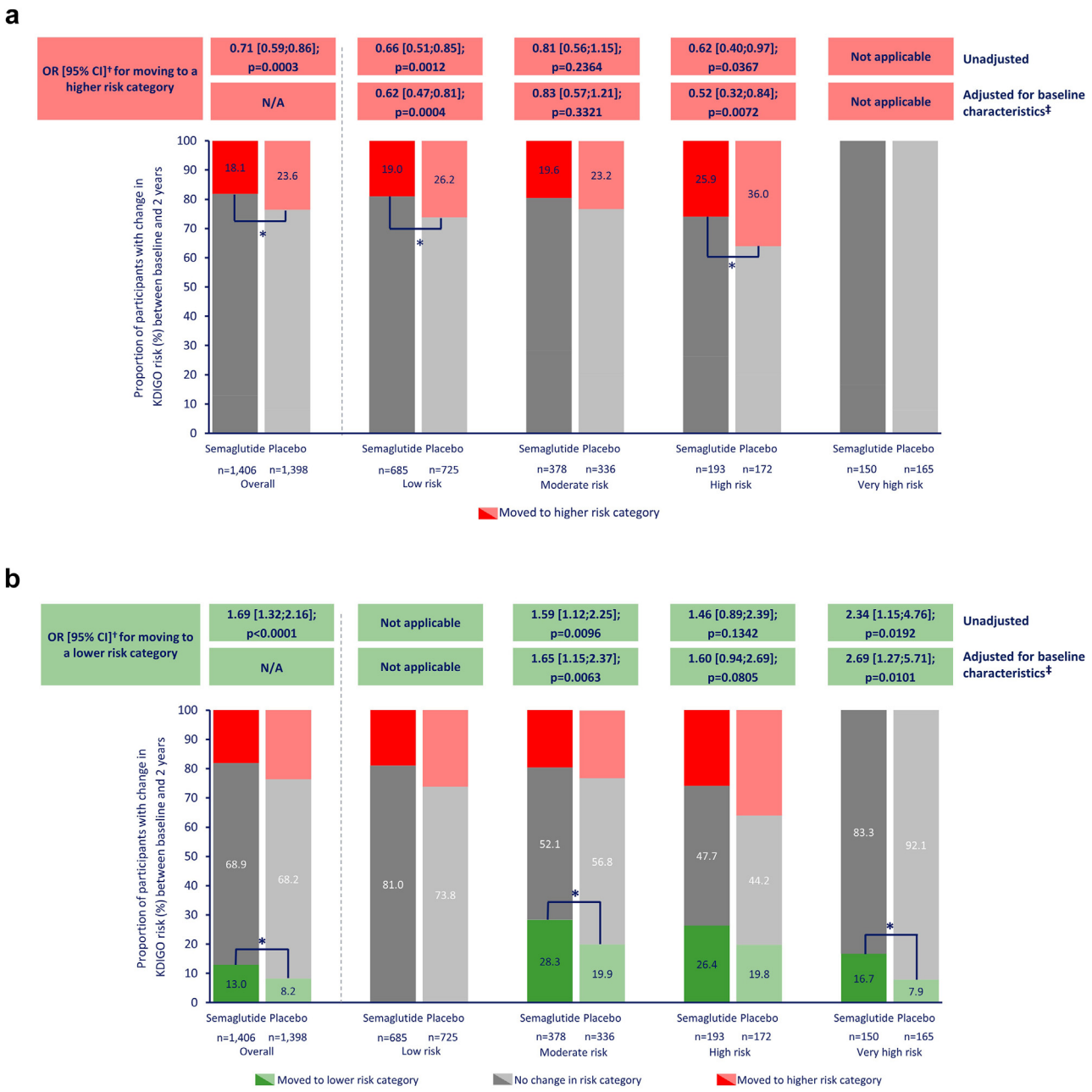

Figure 5. Participants progressing to (a) a higher KDIGO risk category or (b) a lower KDIGO risk category at end of treatment (2 years). *Statistically significant ($P < 0.05$). † OR is obtained for OW semaglutide versus placebo by logistic regression. ‡ Adjusted baseline characteristics include: age, gender, diabetes duration, antidiabetic medication, smoking status, previous myocardial infarction/stroke/transient ischemic attack, geographic region and estimated glomerular filtration rate at baseline. Data from 2804 of the 3297 subjects randomized in SUSTAIN 6 were available for this *post hoc* analysis. CI, confidence interval; KDIGO, Kidney Disease: Improving Global Outcomes; OR, odds ratio; OW, once weekly.

attenuation of kidney fibrosis and stimulation of natriuresis.[16] However, understanding of these mechanisms is still emerging and further research is required to fully elucidate how kidney benefits may be mediated.

The KDIGO risk classification utilizes a combined assessment of both eGFR and UACR for prognosis in CKD. Consequently, change in either component, or both, can lead to change in risk category. Participants receiving once weekly semaglutide were significantly more likely to move to a lower KDIGO risk category and less likely to move to a higher risk category by the end of the trial, compared with participants receiving placebo. Changes in both UACR and eGFR contributed to shifts in KDIGO risk categories. However, for most participants, this outcome was due to changes in UACR, as expected for a study population selected for high CV risk, most of whom did not have low eGFR at baseline. Similarly, for those who progressed in KDIGO risk category, in both treatment groups, this was

Risk category at baseline	Due to change in UACR (%)[a]		Due to change in eGFR (%)[a]		Due to change in eGFR and UACR (%)[a]	
	Semaglutide	Placebo	Semaglutide	Placebo	Semaglutide	Placebo
Change to a higher KDIGO risk category						
Low	11.5	17.5	6.4	7.3	1.0	1.4
Moderate	8.2	11.3	8.5	9.2	2.9	2.7
High	5.2	6.4	17.1	23.8	3.6	5.8
Change to a lower KDIGO risk category						
Moderate	23.3	14.0	5.0	6.0	0	0
High	14.5	14.0	10.9	5.2	1.0	0.6
Very high	6.0	4.2	4.0	2.4	6.7	1.2

Figure 6. Contributors to change in KDIGO risk category at end of treatment. Baseline and week 104 measurements of eGFR-CKD-EPI and UACR were used to calculate KDIGO category for each participant. The proportion of participants who experienced a change in KDIGO risk category due to changes in UACR, eGFR or both are displayed. (a) Percentages are based on the total number of participants in each treatment group for each KDIGO risk category. Cells with darker shading are indicative of a larger proportion of participants experiencing a change in KDIGO risk due to change in UACR, eGFR, or both at end of treatment. CKD-KPI, Chronic Kidney Disease Epidemiology Collaboration; eGFR, estimated glomerular filtration rate; KDIGO, Kidney Disease: Improving Global Outcomes; UACR, urine albumin-to-creatinine ratio.

primarily due to changes in UACR among those at low risk. For those in the high KDIGO risk category at baseline who moved to the very high KDIGO risk category by end of treatment, this shift was predominantly due to further decline in eGFR. Interpretations on the contribution of eGFR and UACR to cause change in KDIGO risk category should be made with caution given the relatively short, 2 year duration of the SUSTAIN 6 trial. In addition, most participants were categorized in the low or moderate KDIGO risk categories, and therefore these results may not be representative of those in higher KDIGO risk categories. These results underscore the utility of the pragmatic KDIGO classification system in the context of individualized risk assessment and evaluation of the effect of interventions with regard to CKD progression. In a retrospective cohort study, patients with CKD and T2D who were classified in the moderate or high KDIGO risk categories and progressed to a more severe risk category within 5 years from baseline had significantly higher annual medical costs than nonprogressors.[36] A similar cohort study showed that health care resource utilization and medical costs in patients with CKD were substantially high early in the disease continuum and increased in line with CKD progression.[37] Thus, improvements in KDIGO risk category may potentially reduce the associated health care costs in this patient population.

In addition, the consistency of semaglutide's effect in different stages of CKD progression suggests it may be a candidate for the management of people with T2D and concomitant CKD, potentially in combination with other agents with proven kidney protective benefits. Lastly, our findings underscore the importance of screening for kidney disease in patients with T2D, which may not be performed systematically in the current clinical setting.[38–40]

As a *post hoc* analysis, this study has noteworthy limitations. In particular, there was a relatively small number of kidney disease events, notably in the low risk KDIGO category, limiting the statistical power of the current analysis and the interpretation of the results, particularly with regard to the consistency of treatment effect across KDIGO categories and for each kidney disease outcome assessed.

The ongoing FLOW kidney outcomes trial (NCT03819153) will provide further insights on the potential kidney protective effects of once weekly semaglutide in people with T2D and CKD over a longer time frame (up to 5 years), specifically for those who are at the highest risk for kidney disease progression. Moreover, another ongoing trial, REMODEL (NCT04865770), which is investigating the mechanism of action of semaglutide in the kidneys by tissue interrogation from biopsies and magnetic resonance imaging in people with T2D and CKD, will provide further insights on effects of semaglutide on the kidney.

In conclusion, once weekly semaglutide versus placebo reduced risks of kidney disease end points

comparably across KDIGO risk categories. Participants receiving once weekly semaglutide were more likely to move to a lower KDIGO risk category and less likely to move to a higher KDIGO risk category compared with those receiving placebo.

DISCLOSURE

KRT has received consulting fees or honoraria for AstraZeneca, Bayer, Boehringer Ingelheim, Eli Lilly and Company, Goldfinch Bio, Novo Nordisk, and Travere. KRT is Chair of the NIDDK/NIH, George Clinical Institute Drug Safety Monitoring Board, and Chair of the American Society of Nephrology Diabetic Kidney Disease Collaborative. KRT has received grants for investigator-initiated studies from Bayer, Goldfinch Bio, and Travere outside the submitted work. KRT is supported by NIH research grants R01MD014712, U2CDK114886, UL1TR002319, U54DK083912, U01DK100846, OT2HL161847, UM1AI109568, and CDC project number 75D301-21-P-12254. SCB has received honoraria or support for attending meetings from AstraZeneca, Boehringer Ingelheim, Eli Lilly and Company, Menarini, Novo Nordisk, and Roche. SCB is a member of the Inversago data safety monitoring board. HB-T is an employee and stockholder of Novo Nordisk A/S. KK has received consultant fees from Abbot, Amgen, Applied Therapeutics, AstraZeneca, Bayer, Boehringer Ingelheim, Lilly, Merck Sharp & Dohme, Napp, Novartis, Novo Nordisk, Sanofi-Aventis, Servier, Oramed Pharmaceuticals, and Roche. KK is a Member of KDIGO Diabetes and CKD Guideline Group. KK is supported by the National Institute for Health Research (NIHR) Applied Research Collaboration East Midlands (ARC EM) and the NIHR Leicester Biomedical Research Center (BRC). SR is an employee and stockholder of Novo Nordisk A/S. ES is an employee of Novo Nordisk A/S. DZC has received grants or contracts from AstraZeneca, Boehringer Ingelheim-Lilly, CSL-Behring, Janssen, Merck, Novo Nordisk, and Sanofi. DZC has received consulting fees or honoraria from Abbvie, AstraZeneca, Bayer, Bristol-Myers Squibb, Boehringer Ingelheim-Lilly, CSL-Behring, Gilead, GSK, Inversago, Janssen, Lexicon, Maze, Merck, Mitsubishi-Tanabe, Novartis, Novo-Nordisk, Otsuka, Prometic, Sanofi, and Youngene. DZC has received support for attending meetings from AstraZeneca, Bayer, Boehringer Ingelheim-Lilly, Janssen, Merck, Novo-Nordisk, and Sanofi and has received operational funding for clinical trials from AstraZeneca.

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DATA AVAILABILITY STATEMENT

The datasets used and/or analyzed in the *post hoc* analysis are available from the corresponding author on reasonable request.

AUTHOR CONTRIBUTIONS

SR analyzed the data for this *post hoc* analysis. All authors were involved in the data interpretation, manuscript development and reviewing the manuscript. All authors read and approved the final manuscript for publication.

SUPPLEMENTARY MATERIAL

Supplementary File (PDF)

Figure S1. Participants progressing to (A) a higher KDIGO risk category or (B) a lower KDIGO risk category at 1 year.
Table S1. Participants experiencing kidney disease composite events per KDIGO category at end of treatment.
Table S2. Contributors to change in KDIGO risk category at 1 year.
CONSORT Checklist.

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