ORIGINAL ARTICLE

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Effect of semaglutide on kidney function across different levels of baseline HbA_{1c}, blood pressure, body weight and albuminuria in SUSTAIN 6 and PIONEER 6

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ABSTRACT

Background. This *post hoc* analysis explored the effects of semaglutide on estimated glomerular filtration (eGFR) slope by baseline glycemic control, blood pressure (BP), body mass index (BMI) and albuminuria status in people with type 2 diabetes and high cardiovascular risk.

Methods. Pooled SUSTAIN 6 (Trial to Evaluate Cardiovascular and Other Long-Term Outcomes With Semaglutide in Subjects With Type 2 Diabetes) and PIONEER 6 (A Trial Investigating the Cardiovascular Safety of Oral Semaglutide in Subjects With Type 2 Diabetes) data were analyzed for change in eGFR slope by baseline hemoglobin A1c (HbA_{1c}) (<8%/≥8%; <64/≥64 mmol/mol), systolic BP (<140/90/≥140/90 mmHg) and BMI (<30/≥30 kg/m^2). SUSTAIN 6 data were analyzed by baseline urinary albumin:creatinine ratio (UACR; <30/30–300/>300 mg/g).

Results. The estimated absolute treatment differences overall in eGFR slope (95% confidence intervals) favored semaglutide versus placebo in the pooled analysis [0.59 (0.29; 0.89) mL/min/1.73 m^2/year] and in SUSTAIN 6 [0.60 (0.24; 0.96) mL/min/1.73 m^2/year]; the absolute benefit was consistent across all HbA_{1c}, BP, BMI and UACR subgroups (all *P*-interaction >.5).

Conclusion. A clinically meaningful reduction in risk of chronic kidney disease progression was observed with semaglutide versus placebo regardless of HbA_{1c}, BP, BMI, and UACR levels.

Keywords: cardiovascular risk, diabetes, eGFR decline, semaglutide

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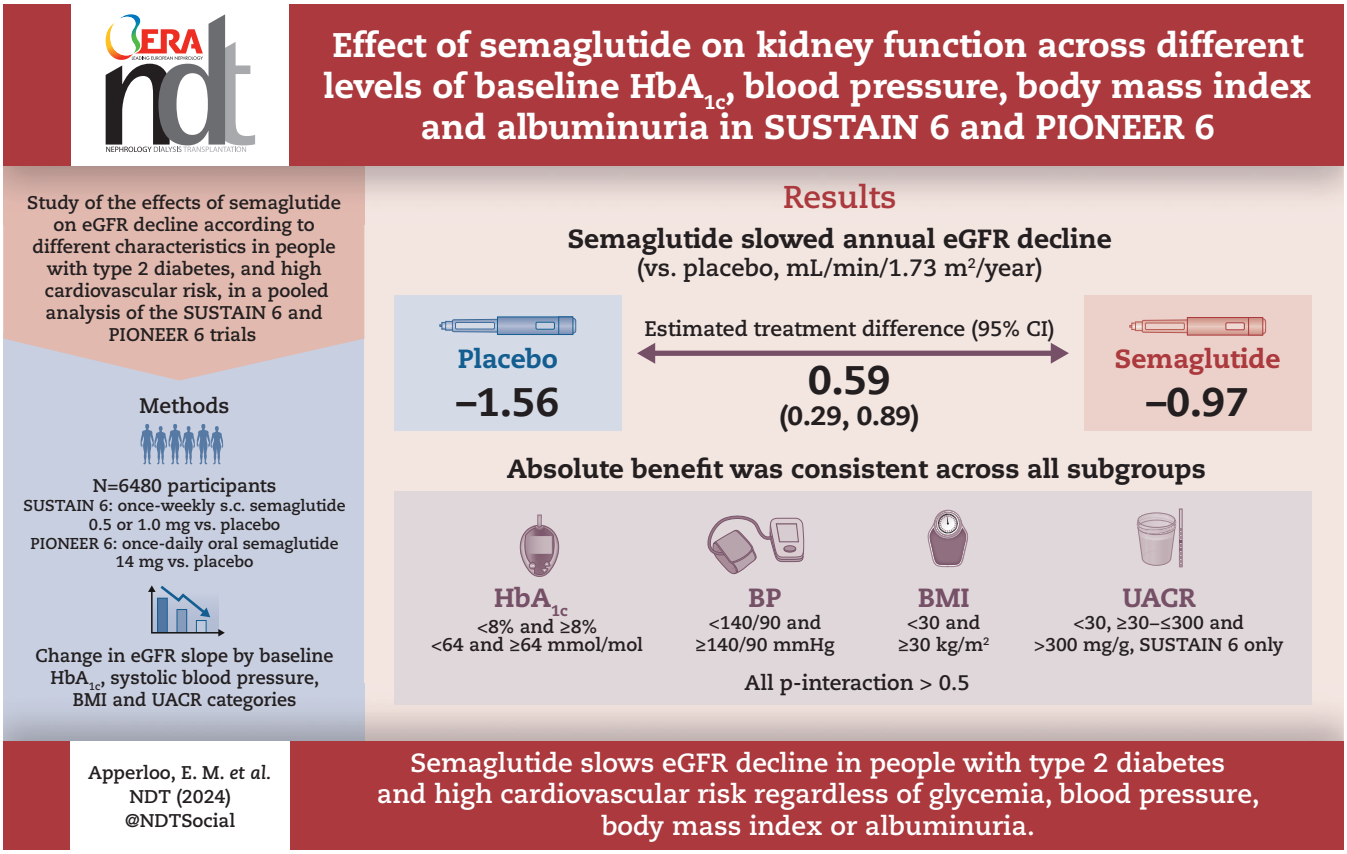
GRAPHICAL ABSTRACT



KEY LEARNING POINTS

What was known:

- Glucagon-like peptide 1 receptor agonists (GLP-1 RAs) reduce hyperglycemia, body weight and atherosclerotic disease in patients with type 2 diabetes.
- *Post hoc* analyses suggest that GLP-1 RAs also slow kidney function decline.
- Whether these benefits on estimated glomerular filtration rate (eGFR) decline are consistent regardless of baseline chronic kidney disease (CKD) risk factors is unknown.

This study adds:

- Semaglutide slows absolute eGFR decline in people with type 2 diabetes at high cardiovascular risk, regardless of glycemic, blood pressure, body mass index or albuminuria status.
- This suggests a potential role for semaglutide to confer kidney protection in a broad population of people with type 2 diabetes at high cardiovascular risk.

Potential impact:

- This study suggests a potential impact of semaglutide on kidney outcomes in a broad population with type 2 diabetes.
- These results in conjunction with other evidence about kidney and cardiovascular protective effects of GLP-1 RAs, including the FLOW trial, support a role for GLP-1 RA in the management of CKD in type 2 diabetes.

INTRODUCTION

The risk of progressive kidney function loss and incidence of cardiovascular disease events remains high in people with type 2 diabetes and chronic kidney disease (CKD), despite optimal guidelines recommending treatments including renin–angiotensin system inhibitors and sodium–glucose co-transporter 2 (SGLT-2) inhibitors [1]. Additional treatment strategies to lower albuminuria and kidney function decline are therefore needed.

Glucagon-like peptide 1 receptor agonists (GLP-1 RAs) are currently recommended as treatment for hyperglycemia, weight management and atherosclerotic cardiovascular disease in people with type 2 diabetes [1, 2]. In addition, analyses from cardiovascular outcomes trials have suggested that these agents also

Table 1: Baseline characteristics across HbA_{1c}, BP and UACR subgroups.

	HbA_{1c} subgroups				BP subgroups				BMI subgroup				UACR subgroups					
	<8% (<64 mmol/mol)		≥8% (≥64 mmol/mol)		<140/90 mmHg		≥140/90 mmHg		<30 kg/m²		≥30 kg/m²		<30 mg/g		≥30–≤300 mg/g		>300 mg/g	
	GLP-1 RA	Placebo	GLP-1 RA	Placebo	GLP-1 RA	Placebo	GLP-1 RA	Placebo	GLP-1 RA	Placebo	GLP-1 RA	Placebo	GLP-1 RA	Placebo	GLP-1 RA	Placebo	GLP-1 RA	Placebo
n	1393	1433	1836	1790	1870	1876	1368	1365	1246	1213	1989	2024	948	986	472	412	196	224
Age, years	66.3 (7.2)	66.6 (7.3)	64.5 (7.1)	64.6 (7.3)	64.6 (7.2)	65.2 (7.4)	66.1 (7.1)	65.9 (7.3)	66.0 (7.5)	65.9 (7.5)	64.8 (7.0)	65.2 (7.3)	64.6 (7.2)	64.5 (7.7)	65.2 (7.3)	65.7 (7.3)	63.7 (7.1)	63.3 (7.0)
Male, *N* (%)	923 (66.3)	977 (68.2)	1166 (63.5)	1093 (61.1)	1213 (64.9)	1237 (65.9)	883 (64.5)	844 (61.8)	887 (71.2)	874 (72.1)	1206 (60.6)	1203 (59.4)	553 (58.3)	572 (58.0)	324 (68.6)	261 (63.3)	115 (58.7)	141 (62.9)
BMI, kg/m²	32.4 (6.3)	32.6 (6.3)	32.7 (6.5)	32.5 (6.3)	32.3 (6.5)	32.0 (6.2)	32.9 (6.3)	33.2 (6.4)	26.7 (2.4)	26.7 (2.4)	36.2 (5.3)	36.1 (5.2)	32.9 (6.2)	32.8 (5.9)	32.7 (6.1)	62.5 (6.3)	32.5 (6.5)	33.0 (6.7)
HbA_{1c}, %	7.2 (0.6)	7.1 (0.6)	9.4 (1.3)	9.4 (1.4)	8.4 (1.6)	8.4 (1.6)	8.4 (1.5)	8.4 (1.6)	8.4 (1.6)	8.4 (1.6)	8.4 (1.5)	8.4 (1.5)	8.6 (1.4)	8.5 (1.3)	8.8 (1.5)	8.9 (1.6)	9.2 (1.6)	9.2 (1.7)
SBP, mmHg	135.6 (17.9)	135.3 (17.5)	135.9 (17.2)	135.6 (17.1)	124.5 (10.4)	124.3 (10.4)	151.2 (13.0)	150.8 (12.3)	134.5 (17.1)	133.9 (17.0)	136.5 (17.7)	136.4 (17.3)	133.0 (15.8)	133.2 (16.0)	137.4 (17.2)	135.3 (15.6)	147.1 (20.1)	144.5 (19.2)
T2D duration, years	13.8 (8.6)	13.6 (8.5)	14.9 (8.2)	14.9 (8.1)	13.9 (8.2)	14.3 (8.3)	15.1 (8.5)	14.4 (8.3)	15.2 (8.5)	15.0 (8.5)	13.9 (8.2)	14.0 (8.2)	13.2 (8.1)	12.6 (7.9)	14.6 (7.7)	14.3 (7.9)	17.2 (8.5)	16.8 (8.2)
eGFR, mL/min/1.73 m²[a]	73.7 (21.1)	73.0 (21.7)	76.0 (22.3)	76.8 (22.3)	76.0 (21.8)	75.6 (21.8)	73.5 (21.8)	74.4 (22.6)	75.8 (21.3)	75.4 (22.1)	74.5 (22.1)	74.9 (22.1)	80.4 (19.7)	80.5 (20.4)	73.3 (22.6)	74.0 (23.4)	58.6 (25.9)	58.5 (26.0)
Prior CV event, *N* (%)	617 (44.3)	676 (47.2)	797 (43.4)	782 (43.7)	859 (45.9)	851 (45.4)	560 (40.9)	614 (45.0)	571 (45.8)	557 (45.9)	845 (42.5)	907 (44.8)	439 (46.3)	467 (47.4)	194 (41.1)	159 (38.6)	77 (39.3)	87 (38.8)
RAAS medication, *N* (%)	1161 (83.3)	1165 (81.3)	1479 (80.6)	1426 (79.7)	1487 (79.5)	1475 (78.6)	1158 (84.6)	1129 (82.7)	985 (79.1)	897 (73.9)	1657 (83.3)	1704 (84.2)	767 (80.9)	782 (79.3)	395 (83.7)	341 (82.8)	157 (80.1)	189 (84.4)
UACR, mg/g[b]	18.0 (576.2)	16.5 (627.3)	29.5 (763.8)	29.7 (834.5)	17.1 (523.2)	16.9 (512.6)	40.3 (855.2)	38.0 (1143)	27.1 (738.4)	26.1 (837.4)	23.4 (690.6)	22.5 (747.5)	6.2 (115.7)	6.0 (111.2)	83.6 (73.2)	83.7 (70.9)	1025 (104.5)	961 (99.9)

Data are mean (standard deviation) unless otherwise indicated.
[a] Chronic Kidney Disease-Epidemiology Collaboration.
[b] Presented as geometric mean (% coefficient of variation).
CV, cardiovascular; RAAS, renin–aldosterone–angiotensin system; SBP, systolic blood pressure; T2D, type 2 diabetes.

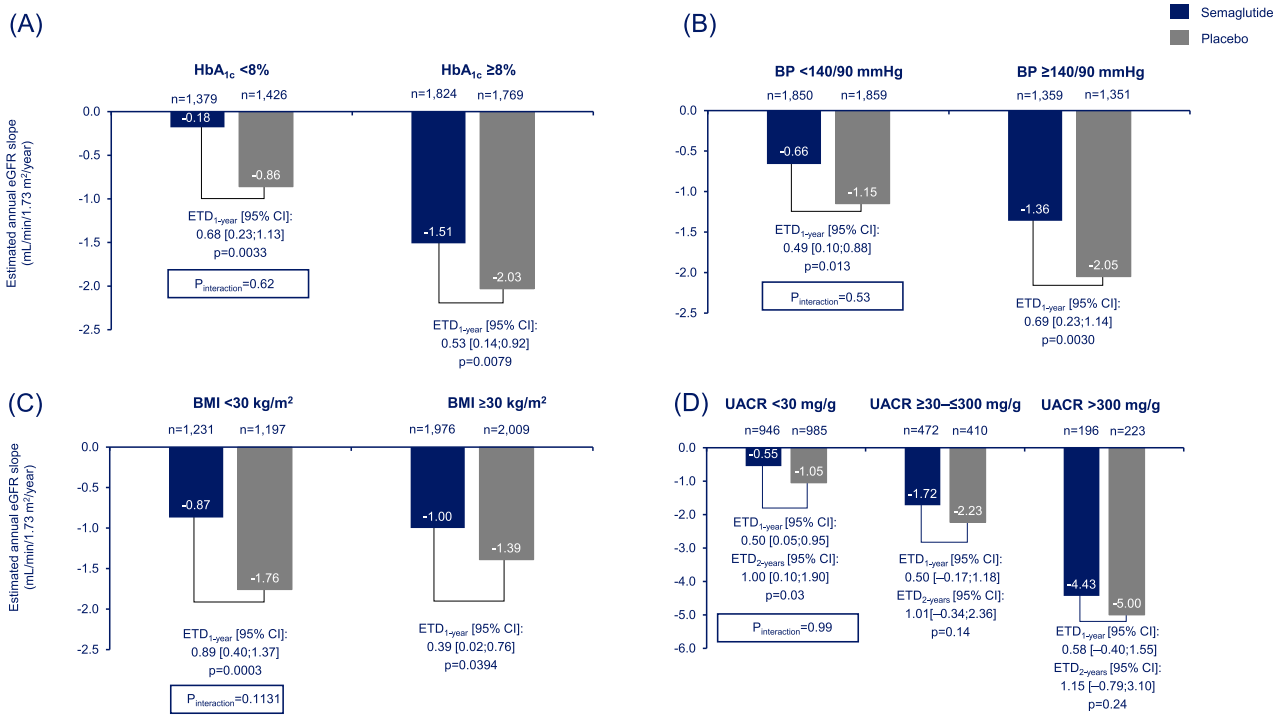


Figure 1: Analysis of eGFR slope by baseline HbA_{1c} (**A**), BP (**B**), BMI (**C**) and UACR (**D**) subgroups (unadjusted*). Estimated treatment differences are shown at 1 year for HbA_{1c} and BP subgroups, and at 1 and 2 years for the UACR subgroups. *Random slope model of repeated eGFR measures analyzed with eGFR value as dependent variable adjusted by baseline value, and time interacting with treatment and subgroup. Intercept and slopes of effect of time are assumed to vary randomly among individuals based on a two-dimensional normal distribution. CI, confidence interval; ETD, estimated treatment difference; geom., geometric; $p_{interaction}$, interaction *P*-value.

slow the decline in kidney function [3–5]. In *post hoc* analyses from the SUSTAIN (Trial to Evaluate Cardiovascular and Other Long-Term Outcomes With Semaglutide in Subjects With Type 2 Diabetes) and PIONEER (A Trial Investigating the Cardiovascular Safety of Oral Semaglutide in Subjects With Type 2 Diabetes) clinical trial programs, semaglutide available in once-weekly subcutaneous and once-daily oral formulations, lowered hemoglobin A1c (HbA_{1c}) across estimated glomerular filtration rate (eGFR) levels and slowed the rate of eGFR decline [3, 6]. Whether these benefits on eGFR decline are consistent in people with type 2 diabetes regardless of baseline CKD risk factors, including HbA_{1c}, blood pressure (BP), body mass index (BMI) and urinary albumin:creatinine ratio (UACR), is of clinical interest and the aim of the present study.

MATERIALS AND METHODS

We conducted a *post hoc* analysis of pooled data from the SUSTAIN 6 and PIONEER 6 trials. The design and primary results were published previously [5, 7, 8]. In short, both trials recruited people with type 2 diabetes and high cardiovascular risk, defined as age ≥50 years with established cardiovascular disease or CKD, or age ≥60 years with cardiovascular risk factors. Participants were randomized to semaglutide or placebo in addition to standard-of-care treatment. Exclusion criteria for both trials included kidney failure treated by chronic hemodialysis or peritoneal dialysis; PIONEER 6 additionally excluded those with an eGFR <30 mL/min/1.73 m^2. In SUSTAIN 6, participants received once-weekly subcutaneous semaglutide 0.5 or 1.0 mg for 2 years (median follow-up, 104 weeks), whereas participants in PIONEER 6 received once-daily oral semaglutide 14 mg (median observation period, 15.9 months).

In SUSTAIN 6 and PIONEER 6, vital signs and clinical chemistry including serum creatinine and HbA_{1c} were recorded throughout follow-up. The Chronic Kidney Disease-Epidemiology Collaboration (CKD-EPI) equation was used to estimate GFR [9]. UACR was only measured in SUSTAIN 6; therefore, the effects of semaglutide versus placebo by baseline UACR were only performed in the SUSTAIN 6 trial population. Data from SUSTAIN 6 and PIONEER 6 were analyzed for change in eGFR slope by baseline HbA_{1c} (<8% and ≥8%; <64 and ≥64 mmol/mol), by baseline BP (<140/90 and ≥140/90 mmHg), baseline BMI (<30 and ≥30 kg/m^2) and by baseline UACR (<30, ≥30–≤300 and >300 mg/g; SUSTAIN 6 only). BP and HbA_{1c} cut-offs were chosen based on the American Diabetes Association 2022 guidelines for HbA_{1c} and BP control [2, 10]. The UACR thresholds were chosen based on the KDIGO CKD guideline [11].

The main analysis focuses on the absolute change in eGFR slope with semaglutide versus placebo after 1 year for baseline HbA_{1c}, BP and BMI subgroups, and after 1 and 2 years for baseline UACR subgroups. A random slope model of repeated eGFR measures was used with eGFR value as a dependent variable adjusted by baseline value, and time interacting with treatment and subgroup. Intercept and slopes of effect of time were assumed to vary randomly among individuals based on a two-dimensional normal distribution. The analyses were first performed in the overall population and subsequently among those with baseline eGFR ≥30–<60 mL/min/1.73 m^2 and ≥60 mL/min/1.73 m^2. To account for potential differences in baseline characteristics, a sensitivity analysis for the eGFR slope analysis was performed adjusting for age, sex, diabetes duration, anti-diabetes medication, smoking status, previous cardiovascular events, geographic region and eGFR at baseline. The interaction *P*-value evaluated the po-

Parameter	Estimated annual eGFR slope (mL/min/1.73 m²/year)		ETD [95% CI]	p-value	Interaction p-value
	Semaglutide	Placebo			
eGFR ≥30–<60 mL/min/1.73 m²					
HbA_{1c}, % (n)					
<8%	0.50 (349)	−0.65 (383)	1.15 [0.23;2.07]	0.014	0.93
≥8%	−0.74 (428)	−1.84 (390)	1.09 [0.25;1.93]	0.011	
BP, % (n)					
<140/90 mmHg	0.05 (437)	−0.85 (450)	0.91 [0.09;1.72]	0.030	0.53
≥140/90 mmHg	−0.56 (342)	−1.87 (327)	1.31 [0.36;2.25]	0.0067	
UACR, % (n)					
<30 mg/g	1.00 (155)	−0.05 (161)	1.05 [−0.04;2.14]	0.06	0.83
≥30–≤300 mg/g	−0.80 (133)	−1.83 (114)	1.03 [−0.22;2.27]	0.11	
>300 mg/g	−4.18 (66)	−4.69 (91)	0.51 [−1.01; 2.03]	0.51	
eGFR >60 mL/min/1.73m²					
HbA_{1c}, % (n)					
<8%	−0.38 (1,005)	−0.94 (1,012)	0.56 [0.03;1.08]	0.037	0.50
≥8%	−1.76 (1,350)	−2.08 (1,342)	0.32 [−0.12;0.77]	0.15	
BP, % (n)					
<140/90 mmHg	−0.93 (1,380)	−1.30 (1,379)	0.37 [−0.07;0.82]	0.10	0.77
≥140/90 mmHg	−1.56 (979)	−2.04 (986)	0.48 [−0.05;1.00]	0.075	
UACR, % (n)					
<30 mg/g	−0.90 (783)	−1.28 (810)	0.38 [−0.11;0.88]	0.13	0.84
≥30–≤300 mg/g	−2.22 (327)	−2.43 (288)	0.21 [−0.60;1.02]	0.61	
>300 mg/g	−5.00 (95)	−5.68 (99)	0.69 [−0.76;2.14]	0.35	

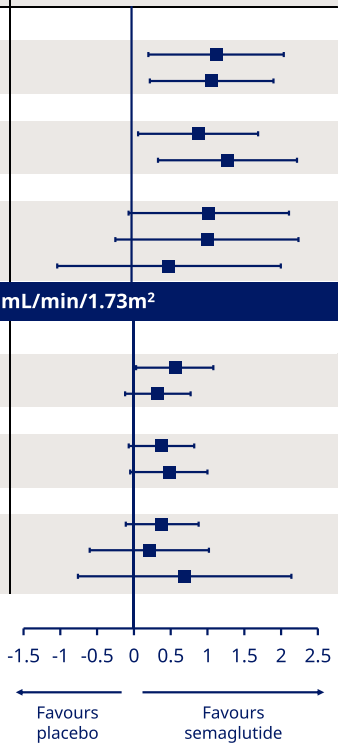


Figure 2: Analysis of eGFR slope by baseline HbA_{1c}, BP and UACR, stratified by eGFR ≥30–<60 mL/min/1.73 m² and ≥60 mL/min/1.73 m² (unadjusted*). Estimated treatment differences are shown at 1 year for all subgroups. *Random slope model of repeated eGFR measures analyzed with eGFR value as dependent variable adjusted by baseline value, and time interacting with treatment and subgroup. Intercept and slopes of effect of time are assumed to vary randomly among individuals based on a two-dimensional normal distribution. CI, confidence interval; ETD, estimated treatment difference; $p_{interaction}$, interaction *P*-value.

tential treatment heterogeneity of absolute eGFR change across subgroups.

RESULTS

Overall, 6480 participants with available eGFR measurements were included in this analysis. Baseline characteristics are presented for each HbA_{1c}, BP, BMI and UACR subgroup in Table 1. Baseline characteristics were generally similar across the subgroups, except for higher BP and lower eGFR in people with UACR >300 mg/g versus other UACR subgroups.

In the pooled population, annual eGFR slope was –0.97 mL/min/1.73 m² in the semaglutide group and –1.56 mL/min/1.73 m² in the placebo group [difference (95% confidence interval) 0.59 (0.29; 0.89) mL/min/1.73 m²/year] [3]. The effect of semaglutide versus placebo on eGFR decline at year 1 was consistent across baseline HbA_{1c}, BP and BMI subgroups (Fig. 1A, B and C, respectively). In the SUSTAIN 6 trial, eGFR slope was –1.32 mL/min/1.73 m² in the semaglutide group compared with –1.92 mL/min/1.73 m² in the placebo group [difference 0.60 (0.24; 0.96) mL/min/1.73 m²/year] [3]. eGFR decline was more pronounced among participants with more severe albuminuria at baseline (Fig. 1D). However, the absolute effect of semaglutide in reducing eGFR decline did not vary across baseline UACR subgroups (interaction *P*-value .99; Fig. 1). Effects were similar in the subgroups of participants with baseline eGFR ≥30–<60 mL/min/1.73 m² and ≥60 mL/min/1.73 m² (Fig. 2). Adjusting these analyses for covariates did not materially alter these findings (Fig. 3).

DISCUSSION

This *post hoc* pooled analysis of two cardiovascular outcome trials suggests that semaglutide reduced the rate of eGFR slope decline versus placebo in people with type 2 diabetes at high cardiovascular risk, regardless of baseline glycemia, BP and albuminuria status. These results add to existing evidence about the potential kidney protective effects of GLP-1 RAs in people with type 2 diabetes and support the initiation of GLP-1 RA–based treatments to slow eGFR decline across a broad spectrum of people at varying degrees of risk of CKD progression.

The effects of semaglutide on eGFR slope were observed in people treated according to standard of care, including >80% renin–angiotensin system inhibitor use. As expected, the rate of eGFR decline was more pronounced in the subgroups with higher HbA_{1c}, BP or albuminuria. However, the absolute benefits of semaglutide in slowing eGFR decline did not vary across these subgroups. From a clinical practice perspective, eGFR decline was most pronounced among participants with severely increased albuminuria, supporting the early identification of CKD in order to provide timely initiation of kidney-protective therapies, and thereby reduce the risk of albuminuria progression and eGFR decline. Participants

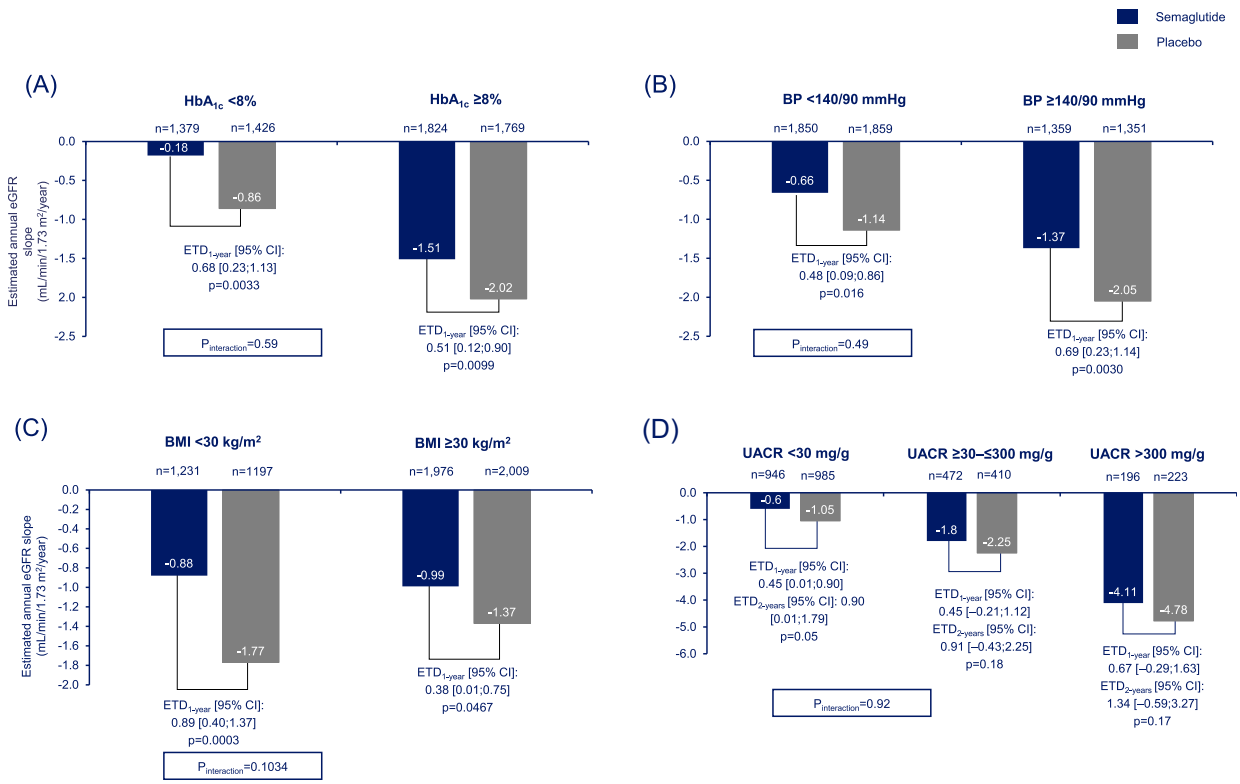


Figure 3: Analysis of eGFR slope by baseline HbA_{1c} (**A**), BP (**B**), BMI (**C**) and UACR (**D**) subgroups (adjusted*). Estimated treatment differences are shown at 1 year for HbA_{1c} and BP subgroups, and at 1 and 2 years for the UACR subgroups. *Adjusted for age, sex, diabetes duration, antidiabetes medication, smoking status, previous myocardial infarction/stroke/transient ischemic attack and geographic region. CI, confidence interval; ETD, estimated treatment difference; $p_{interaction}$, interaction *P*-value.

with pre-existing CKD stage 3 (eGFR ≥30–<60 mL/min/1.73 m^2) are also at high risk of kidney failure [1]. In this subgroup, a previous analysis showed that semaglutide reduced the eGFR slope by 1.06 (95% confidence interval 0.45; 1.67) mL/min/1.73 m^2/year from placebo [3].

The reduction in eGFR slope observed with semaglutide relative to placebo may translate into a clinically relevant risk reduction in kidney outcomes based on a meta-analysis of 66 clinical trials, demonstrating that interventions that reduce eGFR decline between 0.5 and 1.0 mL/min/1.73 m^2/year provide confidence that these therapies will also reduce the risk of kidney failure [12]. The follow-up of our trials was too short to study the effects of semaglutide on kidney endpoints. The FLOW (A Research Study to See How Semaglutide Works Compared to Placebo in People With Type 2 Diabetes and Chronic Kidney Disease) trial is a dedicated kidney outcome trial designed to assess the efficacy and safety of semaglutide in 3534 participants with type 2 diabetes and CKD. At baseline, 16% of the participants used SGLT-2 inhibitors which enables assessment of the effects of semaglutide in combination with SGLT-2 inhibitors [13]. Following a planned interim the trial met certain pre-specified criteria for stopping the trial early for efficacy. Results of the trial are expected in 2024.

A mediation analysis of the SUSTAIN 6 and LEADER (Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results) trials has suggested that the kidney-related benefits of once-weekly semaglutide and once-daily liraglutide may be moderately mediated by reductions in HbA_{1c} and systolic BP; however, other direct or indirect mechanisms may also provide kidney-protective effects [14]. Other possible pathophysiological mechanisms underlying the benefits of semaglutide are not completely understood but may involve direct effects on kidney function, such as beneficial effects on endothelial function, increased natriuresis through inhibition of the sodium-hydrogen exchanger or anti-inflammatory or anti-fibrotic effects [15]. Dedicated mechanistic studies, REMODEL (A Research Study to Find Out How Semaglutide Works in the Kidneys Compared to Placebo, in People With Type 2 Diabetes and Chronic Kidney Disease) and SMART (SeMaglutide and Albuminuria Reduction Trial in Obese Individuals Without Diabetes) [16, 17], are ongoing to provide more insight into the pharmacological effects of semaglutide on kidney function in people with CKD attributed to type 2 diabetes or people without type 2 diabetes and with obesity.

This study has limitations, the most obvious being that this was a *post hoc* analysis and therefore subject to chance findings. Secondly, we estimated GFR using the CKD-EPI creatinine-based estimation equation. It is important to assess whether the observed benefits of semaglutide on eGFR-creatinine reflect true benefits in underlying kidney function or are biased because of changes in body weight. We note that in the SUSTAIN 6 and PIONEER 6 studies the 2–4 kg reduction in body weight observed with semaglutide 0.5 mg and 1.0 mg was less compared with the higher doses of semaglutide 2.4 mg indicated for the treatment of obesity [18]. We therefore believe it is unlikely that the observed effects in the current study are a measurement artefact due to the body weight reduction. Nevertheless, the ongoing SMART study [17], which determines the effects of semaglutide 2.4 mg once weekly compared with placebo on iohexol-measured GFR aims to provide more insights into the optimal measurement of kidney function

in the setting of significant weight loss in people with overweight or obesity and CKD. Additionally, in the PIONEER 6 trial, UACR was not measured and the follow-up duration was relatively short [median time in the trial including follow-up was 15.9 months (range 0.4–20.0 months)] [8], limiting our ability to characterize the longer-term effect of oral semaglutide on eGFR. Thirdly, only people with type 2 diabetes and high cardiovascular risk were included, limiting generalizability to a broader type 2 diabetes population or those without diabetes.

In conclusion, this *post hoc* analysis of the SUSTAIN 6 and PIONEER 6 trials suggests that semaglutide slows absolute eGFR decline in people with type 2 diabetes at high cardiovascular risk, regardless of glycemic, BP or albuminuria status. This suggests a potential role for semaglutide to confer kidney protection in a broad population of people with type 2 diabetes.

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FUNDING

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AUTHORS' CONTRIBUTIONS

E.M.A. and H.J.L.H. drafted the manuscript. S.R. conducted the analyses. All authors interpreted the data, critically reviewed and edited the draft, and provided final approval for submission.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author, H.J.L.H.

CONFLICT OF INTEREST STATEMENT

E.M.A. reports no conflicts of interest. D.Z.I.C. has received honoraria from Boehringer Ingelheim-Lilly, Merck, AstraZeneca, Sanofi, Mitsubishi-Tanabe, Abbvie, Janssen, Bayer, Prometic, BMS, Maze, Gilead, CSL-Behring, Otsuka, Novartis, Youngene, Lexicon, Inversago, GSK and Novo Nordisk; and has received operational funding for clinical trials from Boehringer Ingelheim-Lilly, Merck, Janssen, Sanofi, AstraZeneca, CSL-Behring and Novo Nordisk. J.F.E.M. reports grants from Novo Nordisk, the European Union and McMaster University Hamilton, Canada; consulting fees from Novo Nordisk, AstraZeneca, Bayer and Boehringer Ingelheim; honoraria from Novo Nordisk, AstraZeneca, Bayer, Fresenius and Novartis; and has participated on a data safety monitoring board or advisory board for AstraZeneca, Bayer, Sanofi and Boehringer Ingelheim as well as a leadership role in the KDIGO group. K.R.T. is supported by NIH research grants R01MD014712, U2CDK114886, UL1TR002319, U54DK083912, U01DK100846, OT2HL161847, UM1AI109568 and CDC project number 75D301-21-P-12254. She has also received investigator-initiated grant support from Travere and Bayer Pharmaceuticals outside of the submitted work. She reports consultancy fees from AstraZeneca, Boehringer Ingelheim, Eli Lilly and Company, Novo Nordisk and Travere. H.J.L.H. is consultant for AstraZeneca, Bayer, Boehringer Ingelheim, CSL-Behring, Eli-Lilly and Company, Gilead, Janssen, Novartis, Novo Nordisk, and Travere Pharmaceuticals. He received research support from Abbvie, AstraZeneca, Boehringer Ingelheim, Janssen and Novo Nordisk. A.B.K., S.R. and B.V. are Novo Nordisk employees. Data included in this manuscript were presented as abstracts to the American Society of Nephrology Annual Meeting in 2022.

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