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Impact of Oral Semaglutide on Kidney Outcomes in People With Type 2 Diabetes: Results From the SOUL Randomized Trial

Johannes F.E. Mann, Nikolaus Marx, John E. Deanfield, Scott S. Emerson, Silvio E. Inzucchi, Darren K. McGuire, Sharon L. Mulvagh, Rodica Pop-Busui, Neil R. Poulter, Mads D.M. Engelmann, G. Kees Hovingh, Nicolas Belmar, Thomas Idorn, Ole Kleist Jeppesen, Andreas L. Birkenfeld, Aslam Amod, Boris Mankovsky, Cyrus Desouza, Juan J. Gorgojo-Martinez, Rosario Arechavaleta, Shih-Te Tu, and John B. Buse, on behalf of the SOUL Study Group

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In the Semaglutide Cardiovascular Outcomes Trial (SOUL), Oral Semaglutide Did Not Significantly Reduce Major Kidney Outcomes but Moderately Slowed eGFR Decline Compared With Placebo

Design

Randomized, double-blind, parallel-group trial comparing oral semaglutide with placebo

Participants

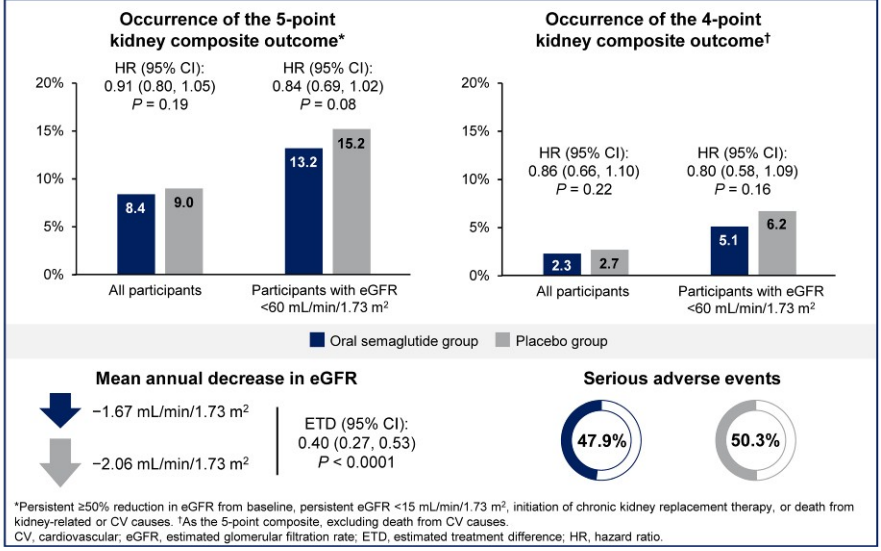
People aged ≥50 years with type 2 diabetes and evidence of atherosclerotic cardiovascular disease and/or chronic kidney disease

Randomized participants: 9,650

Mean follow-up: 47.5 months

eGFR at baseline: Mean: 73.8 mL/min/1.73 m² <60 mL/min/1.73 m² subgroup: 2,816 (29.2%) participants

Results



*Persistent ≥50% reduction in eGFR from baseline, persistent eGFR <15 mL/min/1.73 m², initiation of chronic kidney replacement therapy, or death from kidney-related or CV causes. †As the 5-point composite, excluding death from CV causes.
CV, cardiovascular; eGFR, estimated glomerular filtration rate; ETD, estimated treatment difference; HR, hazard ratio.

ARTICLE HIGHLIGHTS

- **Why did we undertake this study?**
  Once-weekly subcutaneous semaglutide improves kidney outcomes versus placebo in people with type 2 diabetes (T2D) and chronic kidney disease (CKD); however, the effect of oral semaglutide is unknown.
- **What is the specific question we wanted to answer?**
  Does oral semaglutide reduce risk of major adverse kidney outcomes in people with T2D, cardiovascular disease (CVD), and/or CKD?
- **What did we find?**
  In this prespecified analysis of the SOUL trial, oral semaglutide numerically reduced major kidney outcomes in participants with T2D, CVD, and/or CKD. Mean annual estimated glomerular filtration rate decrease was less with oral semaglutide than placebo.
- **What are the implications of our findings?**
  The effect of oral semaglutide on kidney risk remains unclear, and trials dedicated to kidney outcomes are required.

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Impact of Oral Semaglutide on Kidney Outcomes in People With Type 2 Diabetes: Results From the SOUL Randomized Trial

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OBJECTIVE

To examine the effects of oral semaglutide on kidney outcomes in people with type 2 diabetes (T2D) and atherosclerotic cardiovascular disease (ASCVD) and/or chronic kidney disease (CKD).

RESEARCH DESIGN AND METHODS

SOUL (NCT03914326), a double-blind randomized controlled trial, compared oral semaglutide with placebo in people with T2D, ASCVD, and/or CKD, showing a 14% reduction in risk of major adverse cardiovascular (CV) events. Prespecified kidney outcomes included a five-point composite (≥50% decrease in estimated glomerular filtration rate [eGFR], persistent eGFR <15 mL/min/1.73 m^2, initiation of chronic kidney replacement therapy, or death from kidney or CV causes); a four-point composite (excluding CV death); and eGFR decline. Prespecified subgroups were also assessed, including those with eGFR <60 mL/min/1.73 m^2 at baseline.

RESULTS

Among 9,650 participants, mean eGFR was 73.8 mL/min/1.73 m^2, and follow-up was 47.5 months. The five-point outcome occurred in 403 (8.4%) and 435 (9.0%) participants taking oral semaglutide versus placebo, respectively (hazard ratio [HR] 0.91; 95% CI 0.80, 1.05; $P = 0.19$). The four-point outcome occurred in 112 (2.3%) and 129 (2.7%) participants, respectively (HR 0.86; 95% CI 0.66, 1.10; $P = 0.22$). Mean annual eGFR decline was less with oral semaglutide than placebo (−1.67 vs. −2.06 mL/min/1.73 m^2; estimated treatment difference 0.40 [95% CI 0.27, 0.53; $P < 0.0001$). These effects were similar across most subgroups, including those with eGFR <60 mL/min/1.73 m^2. Serious adverse events occurred at similar rates in both groups.

CONCLUSIONS

In people with T2D and ASCVD and/or CKD but with overall mostly preserved eGFR, orally administered semaglutide, compared with placebo, did not significantly reduce adverse kidney outcomes but did slow the decline in eGFR.

People with type 2 diabetes (T2D), particularly those with cardiovascular disease (CVD), are at high risk for chronic kidney disease (CKD) and kidney failure. As such, prevention of incident kidney disease and delaying progression of established disease are paramount. Contemporary guidelines (1,2) recommend the use of inhibitors of the renin-angiotensin-aldosterone system (RAAS), sodium–glucose cotransporter 2

ORIGINAL ARTICLE

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inhibitors (SGLT2is), nonsteroidal mineralocorticoid receptor antagonists, and glucagon-like peptide 1 receptor agonists (GLP-1RAs) in people living with T2D and CKD.

In the Evaluate Renal Function With Semaglutide Once Weekly (FLOW) trial, once-weekly treatment with subcutaneously administered semaglutide, a GLP-1RA, resulted in improved kidney and cardiovascular (CV) outcomes and greater overall survival compared with placebo (3) in a high-kidney-risk population with CKD and diabetes. Meta-analyses in people with diabetes and at high CV risk but low kidney risk also suggested kidney benefit with subcutaneously administered GLP-1RAs (4,5).

It is unknown whether oral semaglutide may also improve kidney outcomes in people with T2D at high CV risk but who do not necessarily have underlying CKD. Therefore, the effects of oral semaglutide on kidney outcomes were examined in the Semaglutide Cardiovascular Outcomes Trial (SOUL) (ClinicalTrials.gov identifier: NCT03914326) in a prespecified secondary analysis. The benefit of oral semaglutide on major adverse CV events, together with two composite kidney outcomes, has already been published (6). We now report in detail the effects of oral semaglutide on kidney outcomes, including effects on the components of the composite outcomes; on changes in estimated glomerular filtration rate (eGFR); and on multiple subgroups, including those with elevated kidney risk. Oral semaglutide compared with placebo demonstrated a relative risk reduction of 14% in a composite outcome that included first event of nonfatal myocardial infarction, nonfatal stroke, or CV death but no significant benefit on the composite kidney outcomes.

RESEARCH DESIGN AND METHODS

Study Design and Oversight

SOUL was a randomized, double-blind, parallel-group, placebo-controlled CV outcomes trial comparing once-daily oral semaglutide 14 mg with placebo in people with T2D with atherosclerotic CVD and/or CKD and receiving standard of care. Details of the trial design, methods, and baseline clinical characteristics of participants have been previously published (7). The protocol and statistical analysis plan are also available with the publication of the primary outcome (6). The trial was approved by institutional review boards and was conducted in compliance with the International Conference for Harmonization Good Clinical Practice guidelines, applicable regulatory requirements, and in accordance with the Declaration of Helsinki. Review and approval by independent ethics committees and institutional review boards were mandated prior to the commencement of the trial at each site. All participants provided written informed consent. Participants with T2D and atherosclerotic CVD and/or CKD (defined as eGFR <60 mL/min/1.73 m^2 with no lower limit for the present analysis) were randomly assigned (1:1) to oral semaglutide at a daily dose up to 14 mg or matching placebo, both in addition to standard of care. At screening, participants with CKD receiving kidney replacement therapy (KRT) (either dialysis or kidney transplant) were excluded. Participants who initiated KRT during the trial continued receiving their randomized treatment. Clinical characteristics of participants are detailed in Supplementary Table 1.

Kidney Outcomes

The main kidney outcome was a five-point composite of a persistent (defined as two consecutive laboratory assessments meeting the eGFR criteria with at least 4 weeks apart) ≥50% reduction in eGFR from baseline, persistent eGFR <15 mL/min/1.73 m^2, initiation of long-term KRT (dialysis or kidney transplant), or death from kidney-related or CV causes. A four-point kidney-specific composite outcome, excluding death from CV causes from the five-point composite, was also examined, as well as the annual rate of change in eGFR from baseline to the end of treatment (total eGFR slope), using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation. Data were analyzed using an intention-to-treat approach. Kidney outcomes were ascertained at trial visits and at the end of treatment. Serum creatinine was measured at baseline, at week 13, at week 52 and annually thereafter, and at end of treatment. All above-mentioned kidney outcomes, except eGFR-related outcomes, were adjudicated by an independent committee of experts blinded to treatment assignment; eGFR-related outcomes had to be confirmed by a second measurement within at least 4 weeks.

Subgroups

Participants were divided into the following prespecified subgroups: baseline eGFR <60 and ≥60 mL/min/1.73 m^2 and according to SGLT2i use (yes/no) at baseline. Outcomes are reported for each subgroup.

Laboratory Assessments

Laboratory tests were done centrally (ICON, Warrington, PA). Serum creatinine was measured enzymatically and calibrated to isotope dilution mass spectrometry values (Roche, Basel, Switzerland; Hitachi, Tokyo, Japan), and eGFR was estimated using the 2009 CKD-EPI equation (8). Urinary parameters, including albumin and creatinine, were not measured in this trial.

Statistical Analysis

The required sample size was based on the primary CV outcome. Although not powered for kidney outcomes and calculated post hoc, the trial had an 89% power to detect a 20% relative risk reduction between oral semaglutide and placebo for the five-point composite kidney outcome and a 43% power for the four-point composite kidney outcome (excluding CV death) based on the placebo incidence rates of 2.3 and 0.7 events per 100 patient-years, respectively.

Prespecified time-to-event analyses applied a Cox proportional hazards model with treatment as a factor, and for subgroup analyses, an interaction term

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**A complete list of the SOUL trial committees and investigators can be found in the supplementary material online.*

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between treatment and subgroup was added as a factor. The SOUL trial implemented hierarchical testing in which a significant effect of oral semaglutide had to be shown at each step before the next outcome could be tested for significance. Superiority for the primary outcome was established (4); however, there was no statistical significance for the secondary confirmatory outcome, the five-point composite kidney outcome. Therefore, analyses of further secondary outcomes, as in the current study, remained exploratory. For kidney events, competing risks were non–CV-related deaths and non–kidney-related deaths, and observations were censored at the time of competing risk. All randomized participants were included and followed up from the time of randomization until death, end of follow-up, or loss to follow-up, whichever came first. The annual rate of change in eGFR (total eGFR slope) was compared between treatment groups based on a linear random regression model on eGFR values with treatment, time (as a continuous variable), and treatment-time interaction as fixed effects and including participant effect as a random intercept and time as a random slope. The random intercept and slope were assumed to be bivariate, with a mean of 0 and an unstructured covariance matrix. The independent error term was assumed to be identical and normally distributed with a mean of 0. Subgroups at increased kidney risk were defined before unblinding. No adjustment for multiplicity or α-protection was performed. All *P* values, unless otherwise noted, are two-sided, and values <0.05 were considered significant. All statistical analyses were performed using SAS 9.4 software (SAS Institute, Cary, NC). Novo Nordisk maintained the clinical database and performed the statistical analyses.

Data and Resource Availability

The data collected for this study will not be made available to others.

RESULTS

Patient disposition has been summarized in McGuire et al. (6). In total, 9,650 patients were randomized (4,825 each to oral semaglutide or placebo). Mean ± SD follow-up time was 47.5 ± 10.9 months, and the mean compliance in the on-treatment period was 87.4%. Baseline characteristics were balanced between treatment groups (6) and are shown in Supplementary Table 1. Mean age was 66.1 years, blood pressure 134.6/76.7 mmHg, BMI 31.1 kg/m^2, and eGFR 73.83 mL/min/1.73 m^2, with 29.2% of patients having an eGFR of <60 mL/min/1.73 m^2 and 2.5% an eGFR of <30 mL/min/1.73 m^2. Overall, 78.9% of participants reported baseline use of RAAS blockers (3,982 [41.3%] ACE inhibitors, 3,697 [38.3%] angiotensin receptor blockers), and 6,201 (64.3%) received β-blockers, 3,572 (37.0%) calcium channel blockers, 892 (9.2%) aldosterone antagonists, 8,572 (88.8%) lipid-lowering drugs, 4,889 (50.7%) insulin, 7,262 (75.3%) metformin, and 2,596 (26.9%) SGLT2is at randomization.

Composite Kidney Outcomes

The five-point composite kidney outcome occurred in 403 of 4,825 participants (8.4%) in the oral semaglutide group and 435 of 4,825 participants (9.0%) in the placebo group (hazard ratio [HR] 0.91; 95% CI 0.80, 1.05; *P* = 0.19) (Fig. 1*A*). The four-point kidney-specific composite outcome (excluding CV death from the five-point outcome) occurred in 112 of 4,825 participants (2.3%) in the oral semaglutide group and 129 of 4,825 participants (2.7%) in the placebo group (HR 0.86; 95% CI 0.66, 1.10; *P* = 0.22) (Fig. 1*B*).

In the subgroup with baseline eGFR <60 mL/min/1.73 m^2, the five-point composite kidney outcome occurred in 185 of 1,405 participants (13.2%) in the oral semaglutide group and 214 of 1,411 participants (14.2%) in the placebo group (HR 0.84; 95% CI 0.69, 1.02; *P* = 0.08) (Fig. 1*C*), and the four-point kidney-specific composite outcome occurred in 72 of 1,405 participants (5.1%) in the oral semaglutide group and 87 of 1,411 participants (6.2%) in the placebo group (HR 0.80; 95% CI 0.58, 1.09; *P* = 0.16) (Fig. 1*D*). Supplementary Fig. 1*A* and *B* depict the respective data of the subgroup with a baseline eGFR ≥60 mL/min/1.73 m^2 for the five- and four-point composite kidney outcomes. Table 1 subdivides the composite kidney outcome data into their individual components and demonstrates that the five-point composite kidney outcome was dominated by CV death. Although fewer events occurred with oral semaglutide versus placebo for all outcomes, none of the treatment differences reached statistical significance.

Annual Rate of Change in eGFR (Total Slope) Over Time

The mean annual rate of change in eGFR (Fig. 2*A*) was less in the oral semaglutide group than in the placebo group (−1.67 vs. −2.06 mL/min/1.73 m^2; estimated treatment difference [ETD] 0.40; 95% CI 0.27, 0.53; *P* < 0.0001). The effects of oral semaglutide in reducing the eGFR decline was numerically larger in the subgroup with eGFR <60 mL/min/1.73 m^2 at baseline (oral semaglutide −1.04 vs. placebo −1.59 mL/min/1.73 m^2; ETD 0.55; 95% CI 0.31, 0.80; *P* < 0.0001) (Fig. 2*B*) versus eGFR ≥60 mL/min/1.73 m^2 (oral semaglutide −1.93 vs. placebo −2.27 mL/min/1.73 m^2; ETD 0.34; 95% CI 0.19, 0.49; *P* < 0.0001) (Fig. 2*C*), although the *P* value for subgroup interaction was not significant (*P* = 0.15). The differences at each time point are shown in Supplementary Table 2.

Composite Kidney Outcomes in Further Subgroups, Including SGLT2i Use at Baseline

The effects of oral semaglutide on the five- and four-point composite kidney outcomes were similar across many subgroups (Fig. 3 and Supplementary Fig. 2 for the five- and four-point composite outcomes, respectively). However, for the five-point kidney outcomes, oral semaglutide appeared to be more beneficial in participants with a baseline HbA_{1c} value >8% ($P_{interaction}$ = 0.068) and users of metformin ($P_{interaction}$ = 0.031). For the four-point kidney outcomes, oral semaglutide seemed to be more beneficial in participants with a baseline HbA_{1c} value >8% ($P_{interaction}$ = 0.047) and of non-Hispanic ethnicity ($P_{interaction}$ = 0.034).

In participants receiving an SGLT2i at baseline, the five-point kidney composite outcome occurred in 79 of 1,296 (6.1%) receiving oral semaglutide vs. 71 of 1,300 (5.5%) receiving placebo (HR 1.10; 95% CI 0.80, 1.52). In the subgroup without SGLT2i use at baseline, the five-point kidney end point occurred in 324 of 3,529 participants (9.2%) vs. 364 of 3,525 participants (10.3%) in the oral semaglutide and placebo groups, respectively (HR 0.88; 95% CI 0.75, 1.02; $P_{interaction}$ = 0.204) (Supplementary Fig. 3). The four-point kidney-specific outcome occurred in 14 of 1,296 participants

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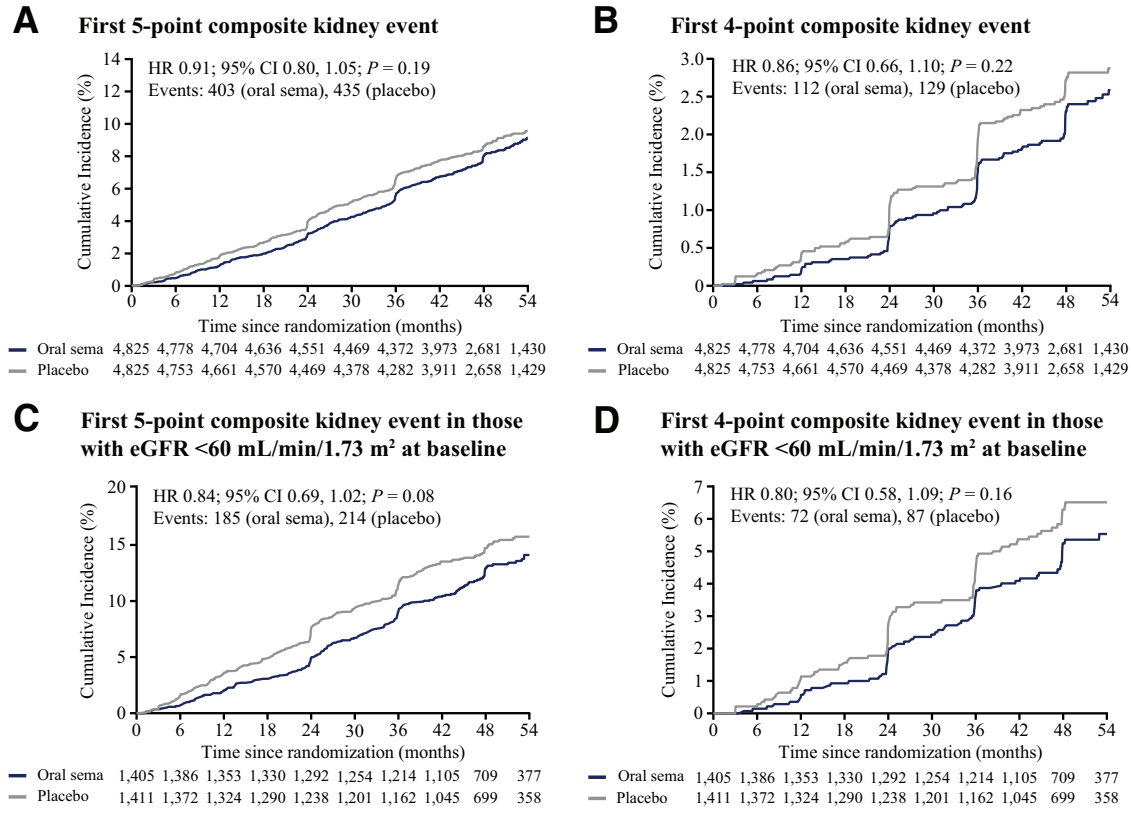


Figure 1—Composite kidney outcomes in the overall population and participants with eGFR <60 mL/min/1.73 m^2 at baseline. *A–D*: Data are from the in-trial period from the full analysis set. Cumulative incidence estimates were based on time from randomization to first composite kidney event with non–CV-related and non–kidney-related death modeled as competing risks using the Aalen-Johansen estimator. Participants without events of interest were censored at the end of their in-trial observation period. Events not related to eGFR were confirmed by the events adjudication committee. eGFR was calculated using the CKD-EPI equation. Time from randomization to first composite kidney event was analyzed using a Cox proportional hazards model with treatment as a categorical fixed factor and based on the available number of events for analysis. Numbers under each graph represent the number of participants at risk. sema, semaglutide.

(1.1%) in the oral semaglutide group vs. 12 of 1,300 participants (0.9%) in the placebo group who reported SGLT2i use at baseline (HR 1.15; 95% CI 0.53, 2.53), while in the subgroup without SGLT2i use at baseline, this occurred in 98 of 3,529 participants (2.8%) vs. 117 of 3,525 participants (3.3%) in the oral semaglutide and placebo groups, respectively (HR 0.82; 95% CI 0.63, 1.08; $P_{interaction}$ = 0.420).

Table 1—Individual kidney outcomes

	Semaglutide		Placebo		
Outcome	Events, *n*	Incidence rate, per 100 participant -years	Events, *n*	Incidence rate, per 100 participant -years	HR (95% CI)
Five-point composite	403	2.1	435	2.3	0.91 (0.80, 1.05)
Four-point composite	112	0.6	129	0.7	0.86 (0.66, 1.10)
≥50% eGFR loss	71	0.4	86	0.5	0.81 (0.59, 1.11)
eGFR <15 mL/min/1.73 m^2	23	0.1	33	0.2	0.69 (0.40, 1.16)
Chronic KRT	40	0.2	48	0.3	0.82 (0.54, 1.25)
CV death	301	1.6	320	1.7	0.93 (0.80, 1.09)
Kidney death	1	<0.1	7	<0.1	0.14 (0.01, 0.79)
All death	528	2.8	577	3.0	0.91 (0.80, 1.02)

Data are from the in-trial period.

In participants using SGLT2i at baseline, annual decline of eGFR with oral semaglutide versus placebo was −1.36 vs. −1.53 mL/min/1.73 m^2 (ETD 0.17; 95% CI −0.08, 0.41; P = 0.17) and in those without SGLT2i use, −1.78 vs. −2.26 mL/min/1.73 m^2 per year, respectively, for the full analysis set (ETD 0.48; 95% CI 0.33, 0.63; $P < 0.0001$). There was a significant interaction of the SGLT2i subgroup with the treatment effect (P = 0.03), with oral semaglutide versus placebo having a greater benefit on eGFR decline in participants who were not using SGLT2is compared with those who were using SGLT2is at baseline.

Other Outcomes and Adverse Events

Nonprespecified outcomes included the composite of doubling of serum creatinine or KRT with no significant differences between randomized groups. Serious adverse events were reported in the 2,312 participants (47.9%) receiving oral

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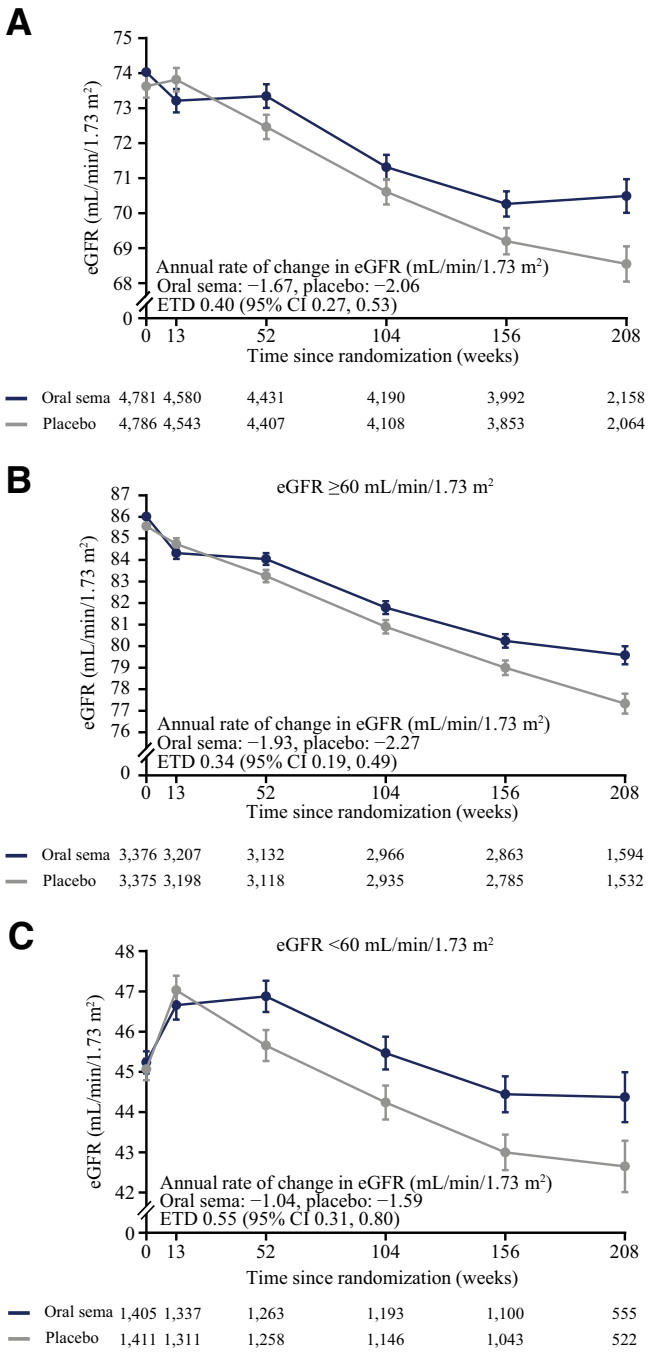


Figure 2—Mean eGFR (mL/min/1.73 m^2) over time. *A*: Overall population. *B*: Participants with eGFR ≥60 mL/min/1.73 m^2 at baseline. *C*: Participants with eGFR <60 mL/min/1.73 m^2 at baseline. Observed data from the in-trial period were from the full analysis set. Error bars are ± standard error of the mean. Numbers under each panel represent the number of participants contributing to the means. sema, semaglutide.

semaglutide and 2,427 (50.3%) receiving placebo. Treatment with oral semaglutide versus placebo was not associated with an increased rate of serious kidney adverse events (1.19 vs. 1.45 per 100 patient-years), including acute kidney injury (0.76 vs. 0.93 per 100 patient-years) based on adverse event reporting.

CONCLUSIONS

In this prespecified analysis of the SOUL trial, oral semaglutide added to standard of care numerically reduced the number of major kidney outcomes in participants with T2D and CVD and/or CKD, as defined for the current analysis; however, these benefits were not statistically significant. This trial was not powered for major kidney outcomes, and its primary kidney outcome was dominated by CV death. Despite this, we did find that oral semaglutide moderately reduced eGFR loss over the mean follow-up of 48 months, both in the overall trial population and in participants with eGFR <60 mL/min/1.73 m^2 at baseline, the latter being at higher risk of kidney disease progression.

Kidney function was not compromised at baseline in the majority of participants, as reflected by the large proportions of participants with an eGFR of 60–90 mL/min/1.73 m^2 (38.8%) and >90 mL/min/1.73 m^2 (31.1%) at baseline (7). The annual loss of kidney function (defined by the slope of decline in eGFR) was small, and any benefit of oral semaglutide on eGFR loss may not have had enough time to translate into a reduction of hard kidney outcomes.

Our findings add to the evidence base of the impact of semaglutide and GLP-1RAs on kidney function in people with T2D and represent the only long-term data available on the effect of oral semaglutide, or any oral GLP-1RA, on the kidney. The only other large T2D trial with oral semaglutide focusing on cardio-kidney outcomes was Peptide Innovation for Early Diabetes Treatment (PIONEER 6), with ∼3,200 participants followed up for a mean of 15 months (9). In that trial, loss of eGFR did not differ between the placebo or oral semaglutide arms (10). Although urine albumin was not measured in SOUL, this study nevertheless expands the evidence base of kidney safety of GLP-1RAs while suggesting long-term kidney benefits on CKD progression through their effects on decline in eGFR, similar to the FLOW trial (3) but in a population with T2D and mostly preserved eGFR and lower kidney risk.

A subcutaneous formulation of semaglutide was previously examined for its effects on kidney outcomes in people with T2D and established CKD in the dedicated FLOW trial (3). In FLOW, patients with CKD (defined as eGFR 50–75 mL/min/1.73 m^2 and a urinary albumin-to-creatinine ratio of >300 to <5,000 or an eGFR of 25 to <50 mL/min/1.73 m^2 and a urinary albumin-to-creatinine ratio of >100 to <5,000) were randomized to once-weekly subcutaneous semaglutide 1.0 mg or placebo while receiving standard of care (3). Semaglutide treatment

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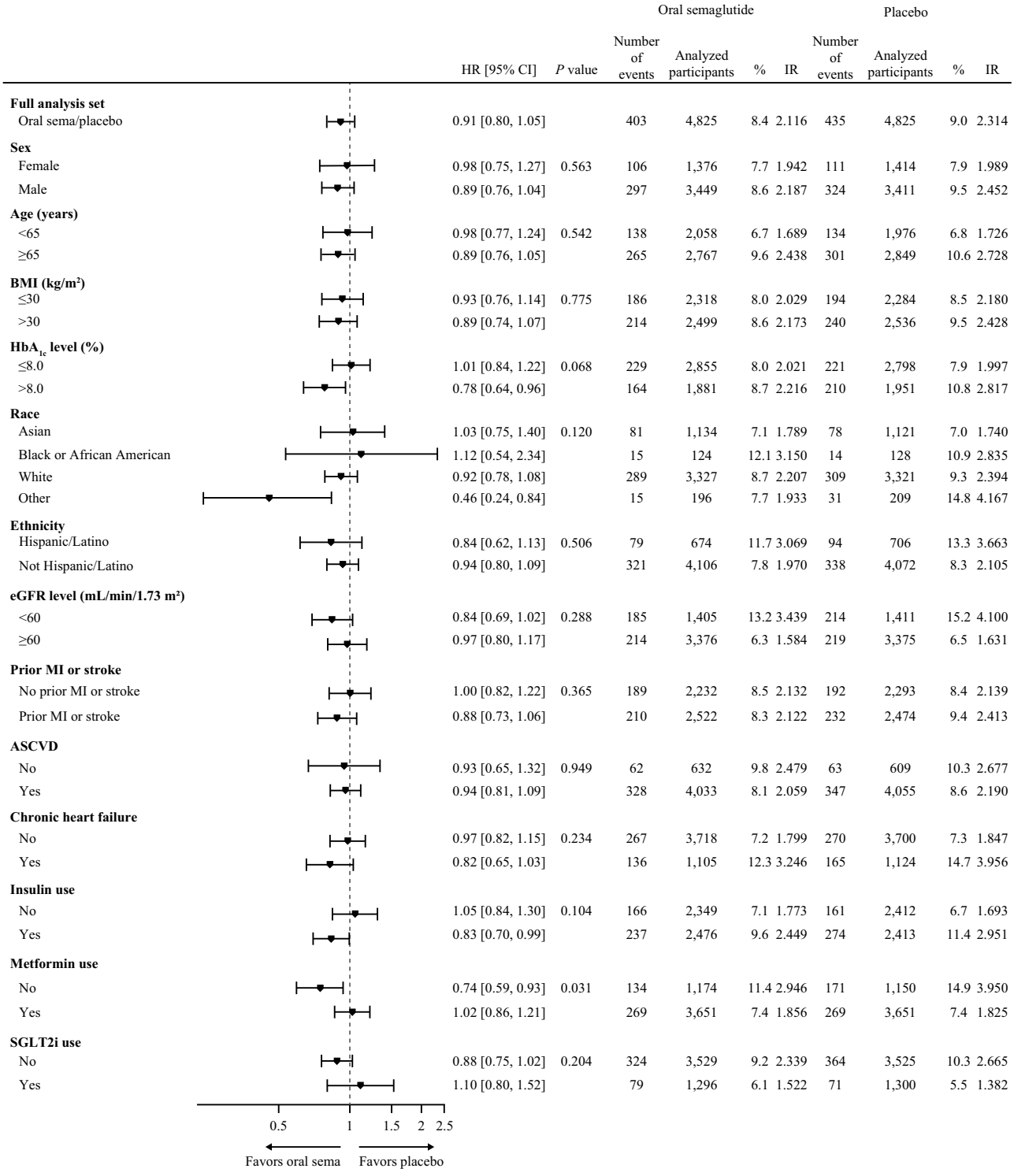


Figure 3—Subgroup analysis of the five-point composite kidney outcome. Data are from the in-trial period. For the subgroup analyses, estimated HRs and corresponding 95% CIs were calculated using a Cox proportional hazards model with interaction between treatment group and the relevant subgroup as fixed factors. HbA_{1c} level of 8% corresponds to 64 mmol/mol. *P* value for test of no interaction effect. MI, myocardial infarction; sema, semaglutide.

resulted in a 24% (relative) or 4.5% (absolute) reduction of the five-point kidney composite outcome. This reduction was driven by both kidney and CV components of the composite outcome, which were defined the same way as in SOUL (3). FLOW and SOUL were conducted over 3.4 and 4 years, respectively, but the five-point kidney outcome incidence rate in the placebo arms was much higher in the former (7.5 vs. 2.3 per 100 patient-years) (3,6). Apart from these large differences in total outcomes, we also observed differences in the relative contribution of the components between the trials. CV death contributed 35% of the five-point composite outcomes in FLOW (3), while a much larger proportion (71%) was

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observed in SOUL. Conversely, kidney-specific outcomes contributed 65% to the five-point composite in FLOW but only 29% in SOUL. Data on albuminuria were not collected in the SOUL trial, precluding us from drawing firm conclusions on the overall kidney status of the participants. The mean eGFR was 73.8 mL/min/1.73 m^2, indicating that people at low risk of CKD progression were included in SOUL. Despite the HRs for oral semaglutide versus placebo for all kidney and CV components of the five-point composite being <1 (HRs of 0.69–0.91), there was limited power to detect a statistically significant difference.

Kidney function has been evaluated in 11 completed GLP-1RA trials, which have recently been reviewed in two meta-analyses from 2021 (4) and 2024 (5). The majority of data stemmed from CV outcome trials that randomized people with T2D at high CV risk, of whom ~20% had CKD but <10% had grade A3 albuminuria (macroalbuminuria), the hallmark of progressive kidney disease. Both meta-analyses demonstrated that GLP-1RAs significantly reduced kidney events, whether they included new-onset grade A3 albuminuria in the kidney composite outcome (4) or not (5).

The mean baseline eGFR of participants of SOUL was 74 mL/min/1.73 m^2, and subsequent loss of eGFR in SOUL was small (oral semaglutide, 1.67 mL/min/1.73 m^2 per year; placebo, 2.06 mL/min/1.73 m^2 per year). Participants received standard of care that included inhibition of the RAAS in most, lipid-lowering therapy in >80%, and reasonable control of blood pressure and a wide array of glucose-lowering therapies, including SGLT2is, in >25% of participants, albeit SGLT2is were not considered standard of care at the time of trial initiation. The kidney-related data, more specifically the eGFR loss data of SOUL, are consistent with other trials enrolling participants with relatively low kidney risk, namely Researching Cardiovascular Events With a Weekly Incretin in Diabetes (REWIND) (11); Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results (LEADER) (12); and Semaglutide Effects on Cardiovascular Outcomes in People With Overweight or Obesity (SELECT) (13).

The impact of semaglutide on patients receiving SGLT2is is of great interest, as these have major beneficial effects on the kidney (14). In the 2,596 participants reporting SGLT2i use at baseline in SOUL, there were only 26 first events of the four-point kidney composite outcome, including 9 first events of kidney failure and 17 first events of persistent ≥50% reduction in eGFR. The interaction of SGLT2i use at baseline with the kidney effects of oral semaglutide was not significant, but statistical power was lacking. However, the benefit of oral semaglutide on preserving eGFR appeared to be greater in participants not using an SGLT2i than in those using an SGLT2i. In the FLOW trial, benefits of semaglutide on kidney failure were not statistically attenuated by concomitant SGLT2i use (15). Other reports on the interaction of SGLT2i with effects of GLP-1RAs have yielded somewhat discordant results. For example, in the Effect of Efpeglenatide on Cardiovascular Outcomes (AMPLITUDE-O) trial, baseline SGLT2i use did not impact kidney benefits of efpeglenatide, another GLP-1RA (16). Large meta-analyses have consistently detected no heterogeneity in either the CV or kidney benefits of GLP-1RAs based on prevalent use of SGLT2is (4,5,17). Furthermore, a recent observational study of a large registry from the U.K. investigated long-term users of GLP-1RAs who started an SGLT2i, as well as long-term users of SGLT2is initiating a GLP-1RA (18). The authors concluded that the combination of both drug classes was associated with a lower risk of major adverse CV events and serious kidney disease events compared with either drug class alone. Apart from the kidney outcomes, the primary CV outcome of SOUL appeared to be independent of baseline SGLT2i use (17), as was the CV outcome in the FLOW trial (15). Ultimately, the benefit of the combined use of a GLP-1RA with an SGLT2i will only be clarified by an appropriate outcome trial comparing the combination with their monotherapies.

Mechanisms for the kidney-protective effects of semaglutide and other GLP-1RAs are currently not fully elucidated. Potential factors include the indirect modification of kidney risk through lowering glucose levels, body weight, and blood pressure (19). In addition, direct mechanisms may contribute, such as increased natriuresis, reduction in oxidative stress, less inflammation, and fibrosis, as well as certain hemodynamic effects (20–22). Notably, at least two mediation analyses indicated that the indirect effects are likely to only play a minor role. For example, the impact of the treatment-associated improvements in blood pressure on kidney outcomes was modest (18,23). A previous post hoc analysis of the LEADER trial demonstrated that statistical adjustment for HbA_{1c} at baseline and HbA_{1c} changes during the trial did not materially alter liraglutide's effect on kidney outcomes (12). Similarly, a post hoc analysis of the FLOW trial with semaglutide demonstrated that neither baseline BMI nor change in body weight had an effect on kidney outcomes (24). Additionally, dulaglutide and insulin lowered HbA_{1c} to the same extent in the Assessment of Weekly Administration of Reagent Dulaglutide-7 (AWARD-7) trial. Yet, patients receiving dulaglutide had a significantly slower eGFR decrease compared with insulin in the trial (25), again suggesting that hyperglycemia improvement is not the critical determinant of the observed beneficial effect on kidney function with GLP-1RAs. The Rethinking Model of Outpatient Diabetes Care Using eHealth (REMODEL) trial (26) is currently examining the potential direct kidney mechanism(s) of action of once-weekly semaglutide using, among other assessments, functional MRI and kidney biopsies (morphometrics, single nucleus, and spatial transcriptomics) and is expected to provide further insights into underlying mechanisms (27).

There are limitations to the current analysis. As mentioned, the mean baseline eGFR of participants in SOUL was 74 mL/min/1.73 m^2. The trial protocol and statistical analysis plan prespecified the composite kidney outcome as a secondary end point, for which there was limited power. The analyses of the composite kidney outcome in the subgroups were not corrected for multiple testing. Urine albumin or protein were not part of the inclusion/exclusion criteria and were not measured during the trial, which impeded our ability to optimally define the kidney risk categories of the SOUL population. Participants were followed up for 4 years, but relatively few developed kidney failure during this interval because we enrolled a population with relatively preserved eGFR. Indeed, CV death was the dominant component of the main five-point composite kidney outcome. Furthermore, participants were

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followed up for 3–5 years, and we can therefore not extrapolate to longer-term effects.

In conclusion, in patients with T2D with CV disease and/or CKD, oral semaglutide on a background of standard of care did not elicit a statistically significant difference in major kidney outcomes compared with placebo. However, slowing of eGFR decline was observed in semaglutide-treated patients, and no kidney-related safety concerns were observed. Further studies are required, including in cohorts with more advanced CKD, to better understand the kidney benefit of oral semaglutide.

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