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Effects of Semaglutide on Chronic Kidney Disease in Patients with Type 2 Diabetes

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ABSTRACT

BACKGROUND

Patients with type 2 diabetes and chronic kidney disease are at high risk for kidney failure, cardiovascular events, and death. Whether treatment with semaglutide would mitigate these risks is unknown.

METHODS

We randomly assigned patients with type 2 diabetes and chronic kidney disease (defined by an estimated glomerular filtration rate [eGFR] of 50 to 75 ml per minute per 1.73 m^2 of body-surface area and a urinary albumin-to-creatinine ratio [with albumin measured in milligrams and creatinine measured in grams] of >300 and <5000 or an eGFR of 25 to <50 ml per minute per 1.73 m^2 and a urinary albumin-to-creatinine ratio of >100 and <5000) to receive subcutaneous semaglutide at a dose of 1.0 mg weekly or placebo. The primary outcome was major kidney disease events, a composite of the onset of kidney failure (dialysis, transplantation, or an eGFR of <15 ml per minute per 1.73 m^2), at least a 50% reduction in the eGFR from baseline, or death from kidney-related or cardiovascular causes. Prespecified confirmatory secondary outcomes were tested hierarchically.

RESULTS

Among the 3533 participants who underwent randomization (1767 in the semaglutide group and 1766 in the placebo group), median follow-up was 3.4 years, after early trial cessation was recommended at a prespecified interim analysis. The risk of a primary-outcome event was 24% lower in the semaglutide group than in the placebo group (331 vs. 410 first events; hazard ratio, 0.76; 95% confidence interval [CI], 0.66 to 0.88; P=0.0003). Results were similar for a composite of the kidney-specific components of the primary outcome (hazard ratio, 0.79; 95% CI, 0.66 to 0.94) and for death from cardiovascular causes (hazard ratio, 0.71; 95% CI, 0.56 to 0.89). The results for all confirmatory secondary outcomes favored semaglutide: the mean annual eGFR slope was less steep (indicating a slower decrease) by 1.16 ml per minute per 1.73 m^2 in the semaglutide group (P<0.001), the risk of major cardiovascular events 18% lower (hazard ratio, 0.82; 95% CI, 0.68 to 0.98; P=0.029), and the risk of death from any cause 20% lower (hazard ratio, 0.80; 95% CI, 0.67 to 0.95, P=0.01). Serious adverse events were reported in a lower percentage of participants in the semaglutide group than in the placebo group (49.6% vs. 53.8%).

CONCLUSIONS

Semaglutide reduced the risk of clinically important kidney outcomes and death from cardiovascular causes in patients with type 2 diabetes and chronic kidney disease. (Funded by Novo Nordisk; FLOW ClinicalTrials.gov number, NCT03819153.)

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*The FLOW Trial Committees and Investigators are listed in the Supplementary Appendix, available at NEJM.org.

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CME

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More than half a billion people globally are affected by chronic kidney disease and are at high risk for kidney failure, cardiovascular events, and death.[1] Type 2 diabetes is the most frequent cause of chronic kidney disease in many countries. Renin–angiotensin system (RAS) inhibitors,[2,3] sodium–glucose cotransporter 2 (SGLT2) inhibitors, and finerenone have been shown to protect the kidneys and reduce the risk of adverse cardiovascular outcomes[4-8] and therefore are guideline-directed medical therapies for chronic kidney disease in patients with type 2 diabetes.[9,10] Nevertheless, many patients continue to lose kidney function and go on to have kidney failure or to die, most commonly from cardiovascular events. Thus, the effects of therapies such as glucagon-like peptide 1 (GLP-1) receptor agonists are of great interest.[11]

The FLOW (Evaluate Renal Function with Semaglutide Once Weekly) trial assessed the efficacy and safety of subcutaneous semaglutide at a dose of 1.0 mg once weekly for the prevention of kidney failure, substantial loss of kidney function, and death from kidney-related or cardiovascular causes in patients with type 2 diabetes and chronic kidney disease.

Methods

Trial Design and Oversight

We published the design of this international, double-blind, randomized, placebo-controlled trial previously.[12] The trial was overseen by an academic-led steering committee (see the Supplementary Appendix, available with the full text of this article at NEJM.org) in partnership with the trial sponsor, Novo Nordisk, which also managed trial operations. The trial steering committee provided overall leadership; oversaw trial design, conduct, and analysis; and was responsible for reporting the results. Analyses were conducted by the sponsor and were independently verified with the use of the original data by Statogen Consulting. The first author wrote the first draft of the manuscript, and all the authors contributed to subsequent revisions. Technical editorial assistance was provided by OpenHealth and funded by the sponsor. The authors had access to the full data set, made the decision to submit the manuscript for publication, and vouch for the accuracy and completeness of the data and for the fidelity of the trial to the protocol (available at NEJM.org).

Relevant approval from regulatory authorities and institutional review boards was obtained. Each participant provided written informed consent before undergoing any trial-related procedures.

Participants

Adults with type 2 diabetes (glycated hemoglobin level, ≤10%) were eligible for inclusion in the trial if they had high-risk chronic kidney disease and were receiving a stable maximal labeled dose (or the maximal dose without unacceptable side effects) of RAS inhibitors (angiotensin-converting–enzyme inhibitor or angiotensin-receptor blocker). Kidney disease was defined by an estimated glomerular filtration rate (eGFR) of 25 to 75 ml per minute per 1.73 m^2 of body-surface area (calculated with the serum creatinine level and the Chronic Kidney Disease Epidemiology Collaboration [CKD-EPI] 2009 formula,[13] which were used to calculate all reported eGFR values unless otherwise indicated), with a urinary albumin-to-creatinine ratio (with albumin measured in milligrams and creatinine measured in grams) of greater than 300 and less than 5000 if the eGFR was 50 ml per minute per 1.73 m^2 or higher or a urinary albumin-to-creatinine ratio of greater than 100 and less than 5000 if the eGFR was 25 to less than 50 ml per minute per 1.73 m^2. Patients who were unable to receive RAS inhibition because of side effects were eligible for inclusion. A full list of inclusion and exclusion criteria, including a range of specific kidney disease diagnoses, is provided in the Supplementary Appendix.

Trial Procedures

Eligible participants were randomly assigned in a 1:1 ratio to receive semaglutide or matching placebo with the use of a central interactive Web-based response system. The use of SGLT2 inhibitors and mineralocorticoid-receptor antagonists (MRAs) was permitted, and randomization was stratified according to SGLT2 inhibitor use at baseline. An 8-week dose-escalation regimen was used, with dose escalation (as long as unacceptable side effects did not occur) from 0.25 mg per week for 4 weeks and 0.5 mg per week for another 4 weeks, followed by a maintenance dose of 1.0 mg per week throughout the remainder of the treatment period. If unacceptable adverse effects occurred, dose-escalation intervals could be extended, treatment could be paused,

or lower maintenance doses could be used. Laboratory-based inclusion criteria were based on local laboratory values recorded within 90 days before the screening visit or central laboratory values recorded at screening or at optional prescreening visits.

TRIAL OUTCOMES

The primary outcome was major kidney disease events, a composite of onset of kidney failure (initiation of long-term dialysis, kidney transplantation, or a reduction in the eGFR to <15 ml per minute per 1.73 m^2 sustained for ≥28 days), a sustained (for ≥28 days) 50% or greater reduction in eGFR from baseline, or death from kidney-related or cardiovascular causes. Three key confirmatory secondary outcomes were defined and assessed with the use of a formal hierarchical testing strategy: total eGFR slope (i.e., the annual rate of change in eGFR from randomization to the end of the trial); major cardiovascular events (a composite of nonfatal myocardial infarction, nonfatal stroke, or death from cardiovascular causes), assessed in a time-to-first-event analysis; and death from any cause. A range of additional supportive secondary, exploratory, and other outcomes were also prespecified and are listed in the Supplementary Appendix.

Safety was assessed by collecting data on all serious adverse events, adverse events leading to discontinuation of semaglutide or placebo, and adverse events of special interest. Primary and secondary outcomes other than eGFR assessments derived from the central laboratory were adjudicated in a blinded fashion by an event adjudication committee (see the Supplementary Appendix).

STATISTICAL ANALYSIS

This trial was event driven. We calculated that a minimum of 854 primary-outcome events would provide 90% power to detect a 20% lower relative risk in the semaglutide group than in the placebo group at an overall one-sided significance level of 2.5%. An interim analysis of efficacy was planned for after two thirds of the total planned number of primary-outcome events had occurred.

Efficacy analyses were based on the intention-to-treat principle and included all unique participants who underwent randomization, irrespective of adherence to semaglutide or placebo or changes to background medications. Time-to-first-event outcomes were analyzed with a stratified Cox proportional-hazards model with randomization assignment (semaglutide or placebo) as a fixed factor and stratified according to SGLT2 inhibitor use at baseline. P values were obtained from a score test. For the primary outcome, the hazard ratio, 95% confidence interval, and P value were adjusted for the group sequential design with the use of likelihood-ratio ordering. The eGFR slope was analyzed with a linear mixed-effects model with randomization assignment, SGLT2 inhibitor use at baseline, time, and the interaction between randomization assignment and time as fixed effects, participant as a random intercept, and time as a random slope. Missing data were not imputed.

If superiority was confirmed for the primary outcome, testing of the confirmatory secondary outcomes was performed in a prespecified hierarchical order to ensure type I error control. To account for the prespecified interim analysis, the nominal significance level for the primary and confirmatory secondary outcomes was calculated with the Lan–DeMets alpha-spending function and the actual observed number of primary-outcome events available for the primary analysis. On the basis of the available number of events, the one-sided nominal significance level for the primary and confirmatory secondary outcomes was updated to 0.0161 (equivalent to a two-sided level of 0.0322, which is used in this report). Details are provided in the Supplementary Appendix.

Continuous supportive secondary outcomes were assessed by analysis of covariance with the use of multiple imputation for missing values under a missing-at-random assumption. Analyses of supportive and exploratory outcomes were not adjusted for multiplicity, and confidence intervals for these outcomes should not be used in place of hypothesis testing. All statistical analyses were performed with SAS software, version 9.4 TS1M5 (SAS Institute).

RESULTS

TRIAL PARTICIPANTS

The trial was conducted at 387 sites in 28 countries (see the Supplementary Appendix), with recruitment occurring from June 2019 through May 2021. Among the 5581 screened candidates (Fig. S1 in the Supplementary Appendix), 3533 met the entry criteria and were randomly assigned to the semaglutide group (1767 participants) or the pla-

Table 1. Characteristics of the Participants at Baseline.*

Characteristic	Semaglutide (N=1767)	Placebo (N=1766)	Total (N=3533)
Age — yr	66.6±9.0	66.7±9.0	66.6±9.0
Female sex — no. (%)	519 (29.4)	550 (31.1)	1069 (30.3)
Geographic region — no. (%)			
Asia	478 (27.1)	434 (24.6)	912 (25.8)
Europe	472 (26.7)	491 (27.8)	963 (27.3)
North America	423 (23.9)	442 (25.0)	865 (24.5)
Other	394 (22.3)	399 (22.6)	793 (22.4)
Race or ethnic group — no. (%)†			
White	1155 (65.4)	1168 (66.1)	2323 (65.8)
Asian	439 (24.8)	407 (23.0)	846 (23.9)
Black	78 (4.4)	82 (4.6)	160 (4.5)
Other	95 (5.4)	109 (6.2)	204 (5.8)
Hispanic or Latinx ethnic group — no. (%)†			
Yes	273 (15.4)	283 (16.0)	556 (15.7)
No	1421 (80.4)	1411 (79.9)	2832 (80.2)
Not reported	73 (4.1)	72 (4.1)	145 (4.1)
Glycated hemoglobin level — %	7.8±1.3	7.8±1.3	7.8±1.3
Body-mass index‡	31.9±6.1	32.0±6.5	32.0±6.3
Body weight — kg	89.5±19.8	89.8±21.2	89.6±20.5
Systolic blood pressure — mm Hg	138.9±16.1	138.4±15.4	138.6±15.8
Diastolic blood pressure — mm Hg	76.8±10.0	76.1±10.0	76.4±10.0
Diabetes duration — no. (%)			
<15 yr	774 (43.8)	753 (42.6)	1527 (43.2)
≥15 yr	992 (56.1)	1013 (57.4)	2005 (56.8)
Previous myocardial infarction or stroke — no. (%)	405 (22.9)	403 (22.8)	808 (22.9)
Chronic heart failure — no. (%)	342 (19.4)	336 (19.0)	678 (19.2)
Smoking status — no. (%)§			
Current smoker	223 (12.6)	206 (11.7)	429 (12.1)
Previous smoker	661 (37.4)	696 (39.4)	1357 (38.4)
Never smoked	883 (50.0)	864 (48.9)	1747 (49.4)
eGFR — ml/min/1.73 m^2¶	46.9±15.6	47.1±14.7	47.0±15.2
eGFR distribution — no. (%)¶			
≥60 ml/min/1.73 m^2	366 (20.7)	353 (20.0)	719 (20.4)
≥45 to <60 ml/min/1.73 m^2	515 (29.1)	540 (30.6)	1055 (29.9)
≥30 to <45 ml/min/1.73 m^2	667 (37.7)	691 (39.1)	1358 (38.4)
<30 ml/min/1.73 m^2	218 (12.3)	182 (10.3)	400 (11.3)
Median urinary albumin-to-creatinine ratio‖	582.3	557.8	567.6
Category of albuminuria — no. (%)**			
A1, normoalbuminuria	52 (2.9)	57 (3.2)	109 (3.1)
A2, microalbuminuria	509 (28.8)	495 (28.0)	1004 (28.4)
A3, macroalbuminuria	1205 (68.2)	1214 (68.7)	2419 (68.5)

Table 1. (Continued.)

Characteristic	Semaglutide (N=1767)	Placebo (N=1766)	Total (N=3533)
Medication use — no. (%)			
SGLT2 inhibitor	277 (15.7)	273 (15.5)	550 (15.6)
ACE inhibitor	625 (35.4)	615 (34.8)	1240 (35.1)
ARB	1066 (60.3)	1061 (60.1)	2127 (60.2)
Lipid-lowering drug	1418 (80.2)	1416 (80.2)	2834 (80.2)
Diuretic agent	870 (49.2)	910 (51.5)	1780 (50.4)
Insulin	1083 (61.3)	1085 (61.4)	2168 (61.4)

* Plus–minus values are means ±SD. For all characteristics except the urinary albumin-to-creatinine ratio and estimated glomerular filtration rate (eGFR), baseline was defined as the eligible assessment associated with the randomization visit if it was performed before or at the date of first dose. If the assessment was missing or performed after the date of first dose, the assessment from the screening visit was used. Percentages may not total 100 because of rounding. ACE denotes angiotensin-converting enzyme, ARB angiotensin-receptor blocker, and SGLT2 sodium–glucose cotransporter 2.

† Race and ethnic group were reported by the participants. "Other" includes American Indian or Alaska Native, Native Hawaiian or other Pacific Islander, and "not reported."

‡ The body-mass index is the weight in kilograms divided by the square of the height in meters.

§ Smoking was defined as smoking at least one cigarette or the equivalent daily.

¶ For eGFR, the baseline assessment is defined as the mean of the two assessments from the randomization visit and the screening visit. If only one of the assessments was available, it was used as the baseline assessment. The mean eGFR and the eGFR categories are based on the serum creatinine level and the Chronic Kidney Disease Epidemiology Collaboration 2009 equation.

‖ The urinary albumin-to-creatinine ratio was calculated with albumin measured in milligrams and creatinine measured in grams.

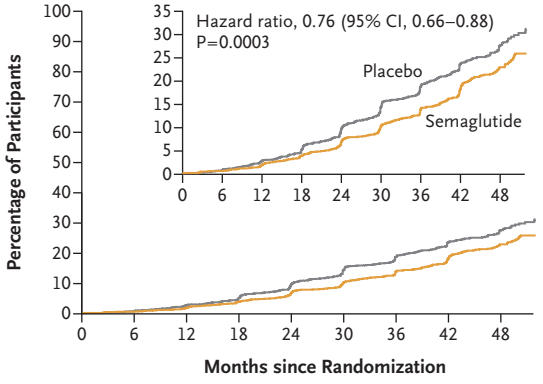
** Albuminuria categories are based on the urinary albumin-to-creatinine ratio, and the baseline assessment is defined as the mean of the two assessments from the randomization visit. If only one of the assessments was available, it was used as the baseline assessment. Normoalbuminuria is defined by a urinary albumin-to-creatinine ratio of less than 30, microalbuminuria by a ratio of at least 30 and less than 300, and macroalbuminuria by a ratio of 300 or greater.

cebo group (1766 participants) and included in the analyses. Four participants underwent randomization more than once, and only the first randomization was included in analyses; one participant was excluded from the analysis because of a lack of adherence to Good Clinical Practice guidelines at the relevant site.

The baseline characteristics of the participants were well balanced between the groups (Table 1 and Table S1). The mean age was 66.6 years, and 1069 participants (30.3%) were women. The mean eGFR was 47.0 ml per minute per 1.73 m^2, and the median urinary albumin-to-creatinine ratio (with albumin measured in milligrams and creatinine measured in grams) was 567.6. According to the Kidney Disease: Improving Global Outcomes risk calculators,[14] 68% of the participants were at very high risk for kidney disease progression, kidney failure, cardiovascular events, or death. The participants in the trial were broadly representative of the relevant population and consistent with those in previous trials,[4,5,8] as described in Table S2.

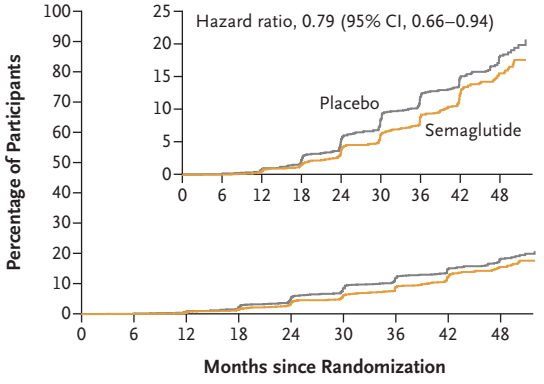
A prespecified single interim analysis was triggered in October 2023 after approximately 570 primary-outcome events had accrued. An independent data and safety monitoring committee reviewed the data and recommended early completion of the trial for efficacy. This recommendation was accepted, participants were recalled for final visits, and the trial was completed with the final participant visit occurring on January 9, 2024. At the time of completion of the trial, the median participant follow-up was 3.4 years (range, 0 to 4.5). The trial was closed early at two sites in Russia that had been sanctioned by the sponsor, and 14 participants at the affected sites ended participation early. In total, 34 participants withdrew consent, and vital status was able to be confirmed at the end of trial for 3482 participants (98.6%). Semaglutide or placebo was permanently discontinued by 26% of participants

A First Major Kidney Disease Event



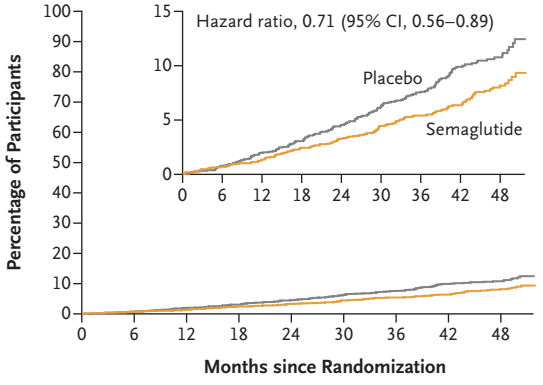
No. at Risk									
Placebo	1766	1736	1682	1605	1516	1408	1048	660	354
Semaglutide	1767	1738	1693	1640	1572	1489	1131	742	392

B First Kidney-Specific Component Event



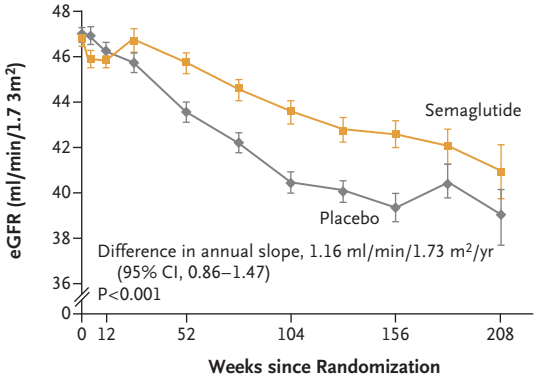
No. at Risk									
Placebo	1766	1736	1682	1605	1516	1408	1048	660	354
Semaglutide	1767	1738	1693	1640	1572	1489	1131	742	392

C Death from Cardiovascular Causes



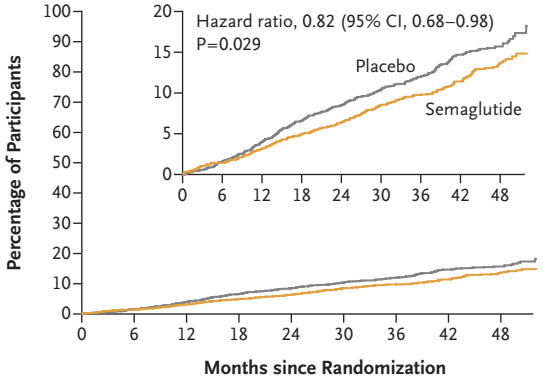
No. at Risk									
Placebo	1766	1737	1697	1641	1601	1544	1185	772	437
Semaglutide	1767	1739	1703	1665	1627	1583	1234	838	460

D Total eGFR Slope



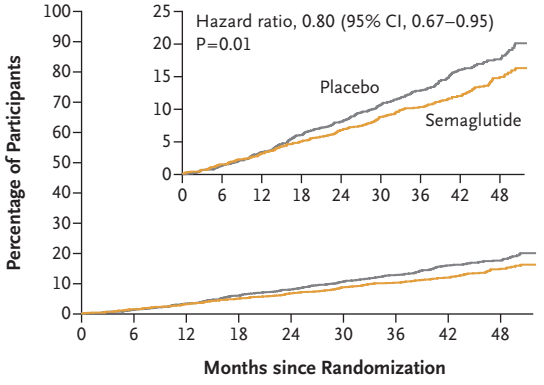
No. at Risk									
Placebo	1766	1663	1573	1609	1490	1441	1284	876	609	199
Semaglutide	1766	1665	1590	1606	1521	1468	1345	952	651	218

E First Major Cardiovascular Event



No. at Risk									
Placebo	1766	1721	1663	1583	1535	1478	1133	731	418
Semaglutide	1767	1725	1672	1622	1575	1515	1176	793	430

F Death from Any Cause



No. at Risk									
Placebo	1766	1737	1697	1641	1601	1544	1185	772	437
Semaglutide	1767	1739	1703	1665	1627	1583	1234	838	460

Figure 1 (facing page). Primary and Confirmatory Secondary Outcomes.

Shown are cumulative incidence plots of the primary outcome, major kidney disease events (a composite of the onset of kidney failure [dialysis, transplantation, or an estimated glomerular filtration rate {eGFR} of <15 ml per minute per 1.73 m^2 of body-surface area], ≥50% reduction in eGFR from baseline, or death from kidney-related or cardiovascular causes) and several confirmatory secondary outcomes: kidney-specific components of the primary outcome (persistent ≥50% reduction in eGFR, persistent eGFR of <15 ml per minute per 1.73 m^2, initiation of long-term renal-replacement therapy, or death from kidney-related causes), death from cardiovascular causes, total eGFR slope, major cardiovascular events (a composite of nonfatal myocardial infarction, nonfatal stroke, or death from cardiovascular causes), and death from any cause. Cumulative incidence estimates are based on the time from randomization to the first event, with death not included in the outcome modeled as a competing risk with the use of the Aalen–Johansen estimator. Data from participants without events of interest were censored at the end of each participant's in-trial observation period. Estimates are based on a Cox proportional-hazards model with treatment as a categorical fixed factor and stratified according to sodium–glucose cotransporter 2 (SGLT2) inhibitor use at baseline. The eGFR data are least-squares means from a mixed model for repeated measures with treatment as a fixed factor; I bars indicate the standard error. The annual rate of change in eGFR was analyzed with a linear random-effects model with randomization assignment, SGLT2 inhibitor use at baseline, time (as a continuous variable), and the interaction of randomization with time as fixed effects and including the participant effect as a random intercept and time as a random slope. On the basis of the available number of primary-outcome events, the nominal significance level was updated to 0.0322 with the use of the Lan–DeMets alpha-spending function. Events that are not related to eGFR were confirmed by the event adjudication committee. The eGFR was calculated with the serum creatinine level and the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) 2009 formula.[13] The P value cutoff for significance was 0.032 in Panels A, D, E, and F. Insets show the same data on an expanded y axis.

during the trial, with adherence to the trial regimen averaging 89% of the planned time during the trial period.

PRIMARY OUTCOME

Primary-outcome events occurred less frequently in the semaglutide group than in the placebo group (331 first events [5.8 per 100 patient-years of follow-up] vs. 410 first events [7.5 per 100 patient-years]), which resulted in a 24% lower relative risk of the primary outcome in the semaglutide group (hazard ratio, 0.76; 95% confidence interval [CI], 0.66 to 0.88; P=0.0003) (Fig. 1 and Table 2). The number of persons who would need to be treated over 3 years to prevent one primary-outcome event was 20 (95% CI, 14 to 40). Lower risk with semaglutide was also observed for a composite of the kidney-specific components of the primary outcome (hazard ratio, 0.79; 95% CI, 0.66 to 0.94), as well as for death from cardiovascular causes (hazard ratio, 0.71; 95% CI, 0.56 to 0.89) (Table 2). Results were consistent across the range of prespecified sensitivity analyses (Table S3) and were broadly consistent across prespecified participant subgroups (Fig. 2).

CONFIRMATORY SECONDARY OUTCOMES

Benefits were observed for the three confirmatory secondary outcomes tested in a hierarchical fashion, all of which had two-sided P values below the prespecified interim analysis threshold of 0.0322 (Table 2). The mean annual slope of the eGFR was significantly less steep (indicating a slower decrease) in the semaglutide group than in the placebo group (–2.19 vs. –3.36 ml per minute per 1.73 m^2 per year; between-group difference, 1.16; 95% CI, 0.86 to 1.47; P<0.001) (Fig. 1D).

The risk of major cardiovascular events was 18% lower in the semaglutide group than in the placebo group (212 vs. 254 events; hazard ratio, 0.82; 95% CI, 0.68 to 0.98; P=0.029) (Fig. 1E). Effects on the individual components of this composite outcome are shown in Table 2; findings for myocardial infarction and death from cardiovascular causes were consistent with those in the primary analysis, but the findings for stroke showed a numerical imbalance in favor of placebo.

The risk of death from any cause was 20% lower in the semaglutide group than in the placebo group (227 vs. 279 events; hazard ratio, 0.80; 95% CI, 0.67 to 0.95, P=0.01) (Fig. 1F). Over 3 years, 45 persons (95% CI, 23 to 623) would need to be treated to prevent one major cardiovascular event, and 39 (95% CI, 21 to 238) would need to be treated to prevent one death from any cause.

Table 2. Efficacy and Safety Outcomes.*

Outcome	Semaglutide (N=1767)	Placebo (N=1766)	Hazard Ratio (95% CI)	Estimated Difference (95% CI)	P Value
Primary outcome: major kidney disease events — no. (%)†	331 (18.7)	410 (23.2)	0.76 (0.66 to 0.88)	—	0.0003
Components of primary outcome — no. (%)					
Persistent ≥50% reduction from baseline in eGFR	165 (9.3)	213 (12.1)	0.73 (0.59 to 0.89)	—	—
Persistent eGFR <15 ml/min/1.73 m^2	92 (5.2)	110 (6.2)	0.80 (0.61 to 1.06)	—	—
Initiation of kidney-replacement therapy	87 (4.9)	100 (5.7)	0.84 (0.63 to 1.12)	—	—
Death from kidney-related causes	5 (0.3)	5 (0.3)	0.97 (0.27 to 3.49)	—	—
Death from cardiovascular causes	123 (7.0)	169 (9.6)	0.71 (0.56 to 0.89)	—	—
Composite of kidney-specific components of the primary outcome	218 (12.3)	260 (14.7)	0.79 (0.66 to 0.94)	—	—
Confirmatory secondary outcomes					
Mean annual rate of change in eGFR — ml/min/1.73 m^2	−2.19	−3.36	—	1.16 (0.86 to 1.47)	<0.001
Major cardiovascular events — no. (%)	212 (12.0)	254 (14.4)	0.82 (0.68 to 0.98)	—	0.029
Death from cardiovascular causes	123 (7.0)	169 (9.6)	0.71 (0.56 to 0.89)	—	—
Nonfatal myocardial infarction	52 (2.9)	64 (3.6)	0.80 (0.55 to 1.15)	—	—
Nonfatal stroke	63 (3.6)	51 (2.9)	1.22 (0.84 to 1.77)	—	—
Death from any cause — no. (%)	227 (12.8)	279 (15.8)	0.80 (0.67 to 0.95)	—	0.01
Supportive secondary outcomes					
Ratio of urinary albumin-to-creatinine ratio at week 104 to urinary albumin-to-creatinine ratio at baseline	0.60	0.88	0.68 (0.62 to 0.75)‡	—	—
Mean change in body weight from baseline to week 104 — kg	−5.55	−1.45	—	−4.10 (−4.56 to −3.65)	—
Mean change in glycated hemoglobin level from baseline to week 104 — percentage points	−0.87	−0.06	—	−0.81 (−0.90 to −0.72)	—
Mean change in systolic blood pressure from baseline to week 104 — mm Hg	−3.79	−1.55	—	−2.23 (−3.33 to −1.13)	—
Mean change in diastolic blood pressure from baseline to week 104 — mm Hg	−0.23	−1.01	—	0.78 (0.16 to 1.41)	—
Mean change in eGFR from baseline to week 12 — ml/min/1.73 m^2	−1.07	−1.05	—	−0.03 (−0.56 to 0.51)	—
Mean annual rate of change in eGFR from week 12 to end of trial — ml/min/1.73 m^2	−2.36	−3.30	—	0.94 (0.62 to 1.26)	—
Mean change in eGFR by the cystatin C equation from baseline to week 104 — ml/min/1.73 m^2	−2.01	−5.41	—	3.39 (2.63 to 4.15)	—

Major adverse limb event in a time-to-first-event analysis — no. of events	16	28	0.56 (0.30 to 1.02)	—	—	
No. of severe hypoglycemic episodes	47	46	1.02 (0.62 to 1.67)‡	—	—	
Supplementary analysis: death from noncardiovascular and non–kidney-related causes in a time-to-first-event analysis — no. of events	99	105	0.93 (0.70 to 1.22)	—	—	

* Data are for the full analysis population from the in-trial period (from randomization to the end of trial participation). Composite kidney disease events and composite major cardiovascular events were analyzed in a time-to-first-event analysis with the use of a Cox proportional-hazards model with treatment as a categorical fixed factor and stratified according to SGLT2 inhibitor use at baseline. Data from participants without events of interest were censored at the end of their in-trial period. The nominal significance level was updated to 0.0322 with the use of the Lan–DeMets alpha-spending function. The eGFR was calculated with serum creatinine level and the Chronic Kidney Disease Epidemiology Collaboration formula. Events not related to the eGFR were confirmed by the event adjudication committee. "Persistent" was defined as two consecutive measurements at least 4 weeks apart fulfilling the criteria. Death from cardiovascular causes, as confirmed by the event adjudication committee, includes both death from cardiovascular causes and death from undetermined causes adjudicated by that committee.

† The primary outcome was major kidney disease events, a composite of the onset of kidney failure (dialysis, transplantation, or an eGFR of <15 ml per minute per 1.73 m^2), at least a 50% reduction in eGFR from baseline, or death from kidney-related or cardiovascular causes. Adjustment for the group sequential design was performed with the use of likelihood-ratio ordering.

‡ Value is the ratio of the value in the semaglutide group to the value in the placebo group.

OTHER EFFICACY OUTCOMES

The results for additional efficacy outcomes are shown in Figure S2. At 104 weeks, the urinary albumin-to-creatinine ratio was reduced by 12% in the placebo group, as compared with 40% in the semaglutide group; the ratio of the value at week 104 to the value at baseline was 32% lower (95% CI, 25 to 38) in the semaglutide group than in the placebo group. Loss of kidney function, as indicated by the cystatin C–based eGFR, was lower by 3.39 ml per minute per 1.73 m^2 (95% CI, 2.63 to 4.15) in the semaglutide group than in the placebo group at week 104. A post hoc analysis of the change in creatinine-based eGFR from baseline to week 104 showed an almost identical difference of 3.30 ml per minute per 1.73 m^2 (95% CI, 2.43 to 4.17).

At week 104, the mean reduction in body weight was 4.10 kg greater (95% CI, 3.65 to 4.56) in the semaglutide group than in the placebo group, the mean reduction in the glycated hemoglobin level was 0.81 percentage points greater (95% CI, 0.72 to 0.90), and the mean reduction in systolic blood pressure was 2.23 mm Hg greater (95% CI, 1.13 to 3.33). However, the mean reduction in diastolic blood pressure was 0.78 mm Hg greater (95% CI, 0.16 to 1.41) with placebo than with semaglutide.

SAFETY OUTCOMES

Serious adverse events (Table 3 and Tables S4 and S5) were reported in fewer participants in the semaglutide group than in the placebo group (877 [49.6%] vs. 950 [53.8%]), primarily because fewer participants in the semaglutide group were reported to have serious infections or infestations (317 [17.9%] vs. 376 [21.3%]) or serious cardiovascular disorders (273 [15.4%] vs. 319 [18.1%]). Eye disorders reported as serious adverse events were more common among participants who received semaglutide than among those who received placebo (53 [3.0%] vs. 30 [1.7%]), whereas the numbers of systematically recorded diabetic retinopathy events were similar in the two groups (504 events among 402 participants [22.8%] in the semaglutide group and 483 events among 398 participants [22.5%] in the placebo group). Adverse events leading to permanent discontinuation of semaglutide or placebo were more common in the semaglutide group than in the placebo group (233 [13.2%] vs. 211 [11.9%]); this finding was driven mainly by discontinuation

Subgroup	Semaglutide	Placebo	Hazard Ratio (95% CI)
	no. of participants with event/no. of participants in analysis		
Primary analysis, all patients	331/1767	410/1766	0.76 (0.66–0.88)
Sex			
Female	88/519	127/550	0.70 (0.53–0.92)
Male	243/1248	283/1216	0.79 (0.66–0.94)
Age			
<65 yr	131/633	175/652	0.71 (0.57–0.90)
≥65 to <75 yr	160/816	170/773	0.85 (0.69–1.06)
≥75 yr	40/318	65/341	0.63 (0.42–0.93)
Body-mass index			
≤30	142/734	164/733	0.82 (0.65–1.03)
>30	189/1031	244/1029	0.73 (0.61–0.89)
Duration of diabetes			
<15 yr	148/774	153/753	0.90 (0.72–1.13)
≥15 yr	183/992	257/1013	0.68 (0.56–0.82)
Glycated hemoglobin			
≤8.0%	200/1106	251/1093	0.75 (0.62–0.90)
>8.0%	131/659	159/672	0.79 (0.63–1.00)
≤7.0%	104/536	147/571	0.69 (0.54–0.89)
>7.0%	227/1229	263/1194	0.80 (0.67–0.96)
Geographic region			
North America	98/423	102/442	0.98 (0.74–1.30)
Europe	65/472	104/491	0.61 (0.45–0.83)
Asia	98/478	98/434	0.85 (0.65–1.13)
Other	70/394	106/399	0.62 (0.46–0.84)
Race or ethnic group			
Asian	95/439	95/407	0.86 (0.64–1.14)
Black	20/78	24/82	0.81 (0.44–1.46)
White	197/1155	260/1168	0.73 (0.61–0.88)
Other	11/56	21/69	0.63 (0.29–1.28)
Hispanic or Latinx ethnic group			
Yes	57/273	89/283	0.61 (0.43–0.85)
No	261/1421	298/1411	0.83 (0.70–0.98)
Estimated GFR			
≥60 ml/min/1.73 m^2	41/366	59/353	0.64 (0.43–0.96)
≥45 to <60 ml/min/1.73 m^2	80/515	103/540	0.78 (0.58–1.04)
≥30 to <45 ml/min/1.73 m^2	137/667	181/691	0.74 (0.59–0.92)
<30 ml/min/1.73 m^2	73/218	67/182	0.81 (0.58–1.13)
Urinary albumin-to-creatinine ratio			
<300	55/561	62/552	0.86 (0.60–1.23)
≥300	276/1205	348/1214	0.74 (0.63–0.87)
Cardiovascular disease			
No previous myocardial infarction or stroke	240/1345	308/1343	0.73 (0.62–0.87)
Previous myocardial infarction of stroke	87/405	93/403	0.91 (0.68–1.22)
Chronic heart failure			
No	264/1424	322/1430	0.79 (0.67–0.93)
Yes	67/342	88/336	0.67 (0.49–0.93)
Insulin use			
No	114/684	129/681	0.85 (0.66–1.09)
Yes	217/1083	281/1085	0.72 (0.61–0.86)
Metformin use			
No	193/859	219/842	0.80 (0.66–0.97)
Yes	138/908	191/924	0.71 (0.57–0.88)
SGLT2 inhibitor use			
No	290/1490	372/1493	0.73 (0.63–0.85)
Yes	41/277	38/273	1.07 (0.69–1.67)

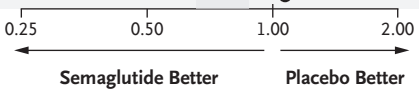


Figure 2 (facing page). Subgroup Analysis of the Primary Outcome.

For the primary analysis, the hazard ratio and confidence interval were adjusted for the group sequential design with the use of likelihood-ratio ordering. For the subgroup analyses, estimated hazard ratios and corresponding confidence intervals were calculated in a stratified Cox proportional-hazards model with the interaction between randomly assigned group and the relevant subgroup as a fixed factor. The model is stratified according to SGLT2 inhibitor use at baseline. Gray shading highlights the 95% confidence interval for the result in the overall population. The body-mass index is the weight in kilograms divided by the square of the height in meters. Race and ethnic group were reported by the participants; "other" includes American Indian or Alaska Native, Native Hawaiian or other Pacific Islander, and "not reported." For the urinary albumin-to-creatinine ratio, albumin was measured in milligrams and creatinine in grams.

because of gastrointestinal disorders (79 [4.5%] vs. 20 [1.1%]).

DISCUSSION

In our trial involving patients with type 2 diabetes and chronic kidney disease, semaglutide at a dose of 1.0 mg once weekly significantly reduced the risk of major kidney disease events (the primary outcome), by 24%. Semaglutide also reduced the risk of major cardiovascular events and death from any cause while slowing the annual loss of kidney function by a mean of 1.16 ml per minute per 1.73 m^2. These benefits reflect important clinical effects on kidney, cardiovascular, and survival outcomes among high-risk patients, particularly given the reassuring safety findings, and support a therapeutic role for semaglutide in this population.

The use of GLP-1 receptor agonists in broader populations with type 2 diabetes has previously been shown to improve glycemic control, decrease body weight, and reduce cardiovascular events.[11,15,16] However, previous dedicated trials addressing clinically important kidney outcomes, such as kidney failure or a substantial decline in the eGFR, have been lacking. The effects on secondary and post hoc kidney outcomes in clinical trials of GLP-1 receptor agonists for cardiovascular outcomes and glycemic control have suggested benefits.[15] The magnitude of the benefits observed in our trial provides confidence that the use of semaglutide in patients with type 2 diabetes and chronic kidney disease will reduce the risk of kidney failure and slow the decline in the eGFR, as well as reduce the risk of cardiovascular events and death.

Few previous trials of GLP-1 receptor agonists have recruited substantial numbers of participants with considerably reduced kidney function. The cardiovascular and survival benefits of semaglutide in such patients are particularly important, since they are among the populations at highest risk for cardiovascular disease and death.

Because three other guideline-directed medical therapies have been shown to have benefits in patients with type 2 diabetes and chronic kidney disease (RAS inhibition, SGLT2 inhibition, and mineralocorticoid-receptor antagonism with finerenone),[17] clinicians and patients will need to consider the order and priority of use for semaglutide (and, once studied, other GLP-1 receptor agonists). Although studies of SGLT2 inhibitors in patients with chronic kidney disease have clearly identified important benefits with respect to kidney outcomes,[4-6] the findings regarding effects on major cardiovascular events and death from any cause in this population have been mixed. In the context of the favorable safety profile, the benefits for these outcomes shown in the present trial provide a rationale for consideration of the use of semaglutide along with these other proven therapies as part of the initial therapeutic options in this patient population. Combination therapy is likely to be important in the future, and we found no clear heterogeneity of effect among patients receiving SGLT2 inhibitors at baseline as compared with those who were not, although the statistical power of this analysis was limited. Further analyses of these data are planned, and studies assessing approaches to combination therapy should be a priority.

The mechanisms of kidney protection with semaglutide are likely to be multifactorial. Although a reduction in kidney and cardiovascular risk factors may contribute, a previous mediation analysis showed that these factors only modestly mediated effects on kidney outcomes.[11] In addition, the effect of semaglutide was unrelated to changes in body weight regardless of whether the eGFR was computed with serum creatinine, cystatin C, or both,[18,19] and consistent effects on creatinine-based and cystatin C–based eGFR were identified in this trial. On the basis of experimental models and biomarker data, the direct

Table 3. Safety Outcomes.

Adverse Event	Semaglutide (N=1767)	Placebo (N=1766)
	no. of participants (%)	
Serious adverse event	877 (49.6)	950 (53.8)
Adverse event leading to permanent discontinuation of semaglutide or placebo	233 (13.2)	211 (11.9)
Prespecified adverse events of special interest		
Diabetic retinopathy*	402 (22.8)	398 (22.5)
Covid-19–related disorder	358 (20.3)	404 (22.9)
Serious adverse event: cardiovascular disorder	273 (15.4)	319 (18.1)
Heart failure*	133 (7.5)	175 (9.9)
Acute kidney failure*	172 (9.7)	182 (10.3)
Malignant tumor*	120 (6.8)	104 (5.9)
Serious adverse event: gastrointestinal disorder	95 (5.4)	94 (5.3)
Serious adverse event: rare event	48 (2.7)	57 (3.2)
Acute gallbladder disease*	32 (1.8)	39 (2.2)
Severe hypoglycemia*	37 (2.1)	37 (2.1)
Medication error*	15 (0.8)	13 (0.7)
Serious adverse event: hepatic disorder	18 (1.0)	20 (1.1)
Acute pancreatitis*	10 (0.6)	7 (0.4)
Serious adverse event: allergic reaction	6 (0.3)	9 (0.5)
Serious adverse event: abuse and misuse	1 (0.1)	4 (0.2)
Serious adverse event: suspected transmission of infectious agent through semaglutide or placebo	0	1 (0.1)

* Data were from an additional data-collection form; data for all other prespecified events of special interest were collected by means of a *Medical Dictionary for Regulatory Activities* search.

effects of GLP-1 receptor agonists on the kidney may include decreases in inflammation, oxidative stress, and fibrosis. Intrinsic kidney and immune cells contain the GLP-1 receptor, and GLP-1 receptor agonists reduce cellular expression of proinflammatory and profibrotic mediators.[20-23]

Our trial has important strengths. This trial of a GLP-1 receptor agonist in a population of patients with chronic kidney disease and type 2 diabetes assessed clinically important outcomes, and significant benefits were shown for kidney and cardiovascular outcomes and death from any cause. The trial was large and rigorous and provides clear conclusions about benefits and risks. It also has some important limitations. Because SGLT2 inhibitors and nonsteroidal MRAs had not been approved for kidney protection at the time the trial was initiated, the number of participants who were receiving these agents at baseline was modest, which limited our ability to assess the effects of combination therapy. The trial was also not powered to detect differences within and between important subgroups, and most participants identified their race as White, whereas kidney disease disproportionately affects marginalized populations, especially Black and Indigenous persons. The effects on kidney function may not be generalizable to other populations, such as those at lower risk, and the trial was not powered to separately detect effects on kidney failure. Finally, it is possible that modest weight loss could slightly lower serum creatinine levels, but the almost identical effects on the cystatin C–based and creatinine-based eGFR indicate that this is unlikely to meaningfully influence the trial results.

In this trial, semaglutide reduced the risk of clinically important kidney outcomes, major cardiovascular events, and death from any cause in participants with type 2 diabetes and chronic kidney disease.

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A data sharing statement provided by the authors is available with the full text of this article at NEJM.org.

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