ORIGINAL ARTICLE

Cardiovascular and Renal Outcomes with Efpeglenatide in Type 2 Diabetes

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ABSTRACT

BACKGROUND

Four glucagon-like peptide-1 (GLP-1) receptor agonists that are structurally similar to human GLP-1 have been shown to reduce the risk of adverse cardiovascular events among persons with type 2 diabetes. The effect of an exendin-based GLP-1 receptor agonist, efpeglenatide, on cardiovascular and renal outcomes in patients with type 2 diabetes who are also at high risk for adverse cardiovascular events is uncertain.

METHODS

In this randomized, placebo-controlled trial conducted at 344 sites across 28 countries, we evaluated efpeglenatide in participants with type 2 diabetes and either a history of cardiovascular disease or current kidney disease (defined as an estimated glomerular filtration rate of 25.0 to 59.9 ml per minute per 1.73 m^2 of body-surface area) plus at least one other cardiovascular risk factor. Participants were randomly assigned in a 1:1:1 ratio to receive weekly subcutaneous injections of efpeglenatide at a dose of 4 or 6 mg or placebo. Randomization was stratified according to use of sodium–glucose cotransporter 2 inhibitors. The primary outcome was the first major adverse cardiovascular event (MACE; a composite of nonfatal myocardial infarction, nonfatal stroke, or death from cardiovascular or undetermined causes).

RESULTS

A total of 4076 participants were enrolled; 2717 were assigned to receive efpeglenatide and 1359 to receive placebo. During a median follow-up of 1.81 years, an incident MACE occurred in 189 participants (7.0%) assigned to receive efpeglenatide (3.9 events per 100 person-years) and 125 participants (9.2%) assigned to receive placebo (5.3 events per 100 person-years) (hazard ratio, 0.73; 95% confidence interval [CI], 0.58 to 0.92; P<0.001 for noninferiority; P=0.007 for superiority). A composite renal outcome event (a decrease in kidney function or macroalbuminuria) occurred in 353 participants (13.0%) assigned to receive efpeglenatide and in 250 participants (18.4%) assigned to receive placebo (hazard ratio, 0.68; 95% CI, 0.57 to 0.79; P<0.001). Diarrhea, constipation, nausea, vomiting, or bloating occurred more frequently with efpeglenatide than with placebo.

CONCLUSIONS

In this trial involving participants with type 2 diabetes who had either a history of cardiovascular disease or current kidney disease plus at least one other cardiovascular risk factor, the risk of cardiovascular events was lower among those who received weekly subcutaneous injections of efpeglenatide at a dose of 4 or 6 mg than among those who received placebo. (Funded by Sanofi; AMPLITUDE-O ClinicalTrials.gov number, NCT03496298.)

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This article was published on June 28, 2021, at NEJM.org.

N Engl J Med 2021;385:896-907.
DOI: 10.1056/NEJMoa2108269

The incidence of adverse cardiovascular events among persons with diabetes is triple that among persons without diabetes[1]; the incidence of adverse renal events is also high among persons with diabetes.[2] The incidence of adverse cardiovascular events rises with increasing duration of diabetes,[3] increasing glycated hemoglobin level,[4] increasing urinary albumin-to-creatinine ratio,[5] the presence of kidney dysfunction,[6] a history of cardiovascular disease,[7] and the presence of other cardiovascular risk factors. Similar factors increase the incidence of adverse renal events.[8,9] Although the effects of glucagon-like peptide-1 (GLP-1) receptor agonists on cardiovascular and renal outcomes in persons with cardiovascular disease have been reported,[10] their effects on these outcomes when those agents are taken alone or in combination with a sodium–glucose cotransporter 2 (SGLT2) inhibitor[11] are unknown, because these trials included very few persons who were receiving an SGLT2 inhibitor.

Efpeglenatide, a GLP-1 receptor agonist administered weekly by means of subcutaneous injection, has been shown to lower glucose levels without causing hypoglycemia.[12,13] The drug consists of a modified exendin-4 molecule conjugated with an IgG4 Fc fragment.[14] Its mechanism of action is akin to that of GLP-1 receptor agonists that are structurally similar to human GLP-1, which have been shown to reduce the risk of adverse cardiovascular events.[10] This similarity and an acceptable safety profile suggest that efpeglenatide may also have cardiovascular and renal benefits in patients with diabetes and concomitant cardiovascular disease, kidney disease, or both.

METHODS

TRIAL DESIGN AND PARTICIPANTS

We conducted an international, randomized, controlled trial (the AMPLITUDE-O trial) at 344 sites in 28 countries.[15] The trial was designed by the sponsor (Sanofi) in conjunction with an independent international steering committee. Sanofi also managed the trial sites and collected the data. The final verified data were transferred to the Population Health Research Institute in Hamilton, Canada, where all the analyses to be included in the manuscript were performed. The initial draft of the manuscript was written by the first author, who had full access to the data. All the authors contributed to the manuscript, agreed to submit the manuscript for publication, and vouch for the integrity, accuracy, and completeness of the data and for the fidelity of the trial to the protocol and analysis plans. The trial was approved by research ethics boards at each participating site, and written informed consent was obtained from all the participants.

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Persons with type 2 diabetes mellitus and a glycated hemoglobin level greater than 7% were enrolled if they were at least 18 years of age and had a history of cardiovascular disease (defined as coronary artery disease, stroke, or peripheral artery disease) or if they were at least 50 (if male) or 55 (if female) years of age and had kidney disease (defined as an estimated glomerular filtration rate [eGFR] of 25.0 to 59.9 ml per minute per 1.73 m^2 of body-surface area) and at least one additional cardiovascular risk factor.[15] Key exclusion criteria were gastroparesis, uncontrolled reflux, prolonged nausea or vomiting, severe retinal disease, pancreatitis, or use of a GLP-1 receptor agonist or a dipeptidyl peptidase 4 (DPP-4) inhibitor within the previous 3 months. A complete list of inclusion and exclusion criteria are provided in the protocol and in the Supplementary Appendix, available with the full text of this article at NEJM.org.

RANDOMIZATION AND MASKING

The participants were randomly assigned in a 1:1:1 ratio to receive efpeglenatide at a weekly dose of 2 mg for 4 weeks and then 4 mg per week until the end of the trial; efpeglenatide at a dose of 2 mg per week for 4 weeks, then 4 mg per week for 4 weeks, and then 6 mg per week until the end of the trial; or placebo. The treatment period was from the time of randomization until the end of the trial, death, or discontinuation of the assigned regimen. The trial medications and placebo were provided in identically appearing prefilled syringes in a blinded manner. Randomization was performed through an interactive Web-response system and was stratified according to current or potential future use of SGLT2 inhibitors (i.e., current use at the time of randomization, SGLT2 inhibitor likely to be added to therapy, or SGLT2 inhibitor unlikely to be added to therapy) to minimize between-group differences in therapy with various cardioprotective medications. Only the data monitoring committee had access to unmasked data until the database lock.

TRIAL PROCEDURES

Efpeglenatide or placebo was added to each participant's current therapy in a blinded manner. If the baseline glycated hemoglobin level was lower than 7.5%, investigators could reduce any dose of insulin, sulfonylurea, or meglitinide to minimize hypoglycemia. Subsequently, the use of glucose-lowering drugs remained unchanged for the first 12 weeks, after which any such drug except for a GLP-1 receptor agonist or a DPP-4 inhibitor could be added. Trial visits occurred at 12 weeks after randomization, 24 weeks after randomization, and then every 24 weeks thereafter until the final visit; participants were also contacted by telephone during the 24-week intervals. Participants who missed up to two doses of efpeglenatide or placebo were encouraged to restart their usual dose unless there was a contraindication. If three or more consecutive doses were missed, the dose-adjustment period was restarted in a blinded manner. Unless consent was revoked, participants were followed until the end of the trial, regardless of adherence. The participants who had continued to receive efpeglenatide or placebo through the end of the trial discontinued the assigned regimen and had a final off-drug assessment 6 weeks later. Because of a funding decision made by the sponsor that was unrelated to any trial data, final visits began before the prespecified number of 330 participants with a primary outcome event had accrued.

OUTCOMES

The primary outcome was the first occurrence of a major adverse cardiovascular event (MACE; a composite of nonfatal myocardial infarction, nonfatal stroke, or death from cardiovascular or undetermined causes). Key secondary outcomes included an expanded MACE composite outcome (MACE, coronary revascularization, or hospitalization for unstable angina) and a composite renal outcome (incident macroalbuminuria [defined as a urinary albumin-to-creatinine ratio of >300, as measured in milligrams of albumin to grams of creatinine, or >33.9, as measured in milligrams of albumin to millimoles of creatinine], plus an increase in the urinary albumin-to-creatinine ratio of ≥30% from baseline, a sustained decrease in the eGFR of ≥40% for ≥30 days, renal-replacement therapy for ≥90 days, or a sustained eGFR of <15 ml per minute per 1.73 m^2 for ≥30 days).

Additional outcomes included the components of the expanded MACE outcome and composite renal outcome, death from any cause, hospitalization for heart failure, glycated hemoglobin level, vital signs, weight, presence of antibodies against efpeglenatide, pancreatic enzyme levels, and other laboratory test results.[15] Three additional composite secondary outcomes were defined before unblinding: MACE or death from noncardiovascular causes; a kidney-function outcome (a decrease in the eGFR of ≥40% for ≥30 days, end-stage kidney disease [defined as dialysis for ≥90 days, kidney transplantation, or an eGFR of <15 ml per minute per 1.73 m^2 for ≥30 days], or death from any cause); and MACE, death from noncardiovascular causes, hospitalization for heart failure, or a kidney-function outcome event. An independent clinical end-point committee, the members of which were unaware of the trial-group assignments, adjudicated all deaths, myocardial infarctions, strokes, hospitalizations for unstable angina or heart failure, and pancreatic events. Spontaneously reported and prespecified adverse events were documented at each visit.

STATISTICAL ANALYSIS

We estimated that a sample size of 4000 participants followed for up to 3 years (with a primary outcome event occurring in 330 participants) would provide the trial with more than 99% power and 90% power to show noninferiority of efpeglenatide to placebo at noninferiority margins of 1.8 and 1.3, respectively (as suggested in a 2008 regulatory guidance[16]). This estimation was calculated on the basis of the following assumptions: an incidence of MACE of 3.7% for the estimated 27% of participants who would be receiving an SGLT2 inhibitor during the trial and an incidence of 4.4% for the remaining participants, a recruitment period of 12 months, an annual rate of discontinuation of efpeglenatide or placebo of 2%, and a two-sided type 1 error rate of 5%. It was also assumed that the data from both efpeglenatide dose groups would be pooled for the comparison with placebo. The noninferiority margin represents the upper bound of the 95% confidence interval of the hazard ratio for a primary outcome event.

All analyses were performed in accordance with two prespecified plans and were finalized before any unblinding occurred (see the Supple-

mentary Appendix). In accordance with the intention-to-treat principle, all outcomes that occurred between the time of randomization and the last assessment were counted. Data from participants were censored at two different time points: for the analyses of cardiovascular outcomes or death, data were censored at the last date of follow-up, and for the analyses of renal outcomes, data were censored at the last day that data on renal outcome status were available. Continuous variables were summarized as mean values with standard deviations or median values with interquartile ranges, and categorical variables were summarized as counts and percentages. Changes in continuous variables over time were analyzed with the use of a mixed-effects model for repeated measures fitted through restricted maximum likelihood estimation. The baseline value was treated as the covariate and the participant as a random effect. Geographic region (United States and Canada, Mexico and Central and South America, Europe, or other), the randomization stratification factor regarding SGLT2 inhibitor use, assigned trial group, trial visit, and trial-group–by–visit interaction were treated as fixed effects.

Incidence rates of a particular composite outcome event and the frequency of the total burden of single or composite outcome events were summarized as the number of events per 100 person-years of follow-up for that outcome. Kaplan–Meier curves were used to display cumulative risks, and Cox proportional-hazards models adjusted for geographic region and the randomization stratification factor were used to estimate the hazard ratios and 95% confidence intervals for the effect of efpeglenatide (with data from both dose groups combined) on the primary and secondary outcomes. Unless death from noncardiovascular causes was included in a composite outcome, it was not adjusted for as a competing risk in the Cox models. Assumptions of the Cox models were verified by plotting the log of the negative log of the survival function against the log of survival time. The proportional-means model[17] was used to estimate the hazard ratio and 95% confidence interval for the total burden of events, including recurrent events. Missing data were assumed to be missing at random. P values were one-sided for noninferiority and two-sided for superiority. The effect of efpeglenatide within subgroups was assessed by including the subgroups and interaction terms in the Cox proportional-hazards models.

If noninferiority was shown with respect to the primary outcome at both the 1.8 and 1.3 margin, the outcomes were assessed hierarchically for superiority in the following order: incident MACE; the expanded MACE outcome; the composite renal outcome; MACE or death from noncardiovascular causes; the kidney-function outcome; and MACE, death from noncardiovascular causes, hospitalization for heart failure, or a kidney-function outcome event. The testing was continued until a result of an outcome analysis did not reach significance. Sample size was calculated with the use of PASS 13 software (NCSS), and all other statistical analyses were performed with the use of SAS software, version 9.4 (SAS Institute).

RESULTS

PARTICIPANTS

A total of 5732 patients underwent screening between May 11, 2018, and April 25, 2019. Eligibility criteria were met by 4076 participants, who then underwent randomization — 1359 participants were assigned to receive the 4-mg dose of efpeglenatide, 1358 to receive the 6-mg dose of efpeglenatide, and 1359 to receive placebo. Follow-up ended on December 10, 2020, after a median follow-up period of 1.81 years (interquartile range, 1.69 to 1.98), for a total follow-up of 7395.4 person-years. At that time, status with respect to the primary outcome was known for 3941 of the 4076 participants (96.7%), and the vital status was known for 4073 (99.9%) (Fig. S1 and Table S1 in the Supplementary Appendix). The participants assigned to receive efpeglenatide were exposed to the drug for 88.9% of their maximum follow-up time, and those assigned to receive placebo were exposed to placebo 91.1% of their maximum follow-up time.

BASELINE CHARACTERISTICS

The mean (±SD) age of the participants was 64.5±8.2 years; 1954 (47.9%) were younger than 65 years of age, and 1344 (33.0%) were female (Table 1). A total of 3650 participants (89.6%) had a history of cardiovascular disease, 1287 (31.6%) had an eGFR of less than 60 ml per minute per 1.73 m^2, 888 (21.8%) had both cardiovascular disease and a low eGFR, and 618

Table 1. Demographic and Clinical Characteristics of the Trial Participants at Baseline.*

Characteristic	All Participants (N=4076)	Efpeglenatide, 4 or 6 mg (N=2717)	Placebo (N=1359)
Age — yr	64.5±8.2	64.6±8.2	64.4±8.3
Female sex — no. (%)	1344 (33.0)	925 (34.0)	419 (30.8)
Geographic region — no. (%)			
Canada and United States	1079 (26.5)	728 (26.8)	351 (25.8)
Mexico and Central and South America	924 (22.7)	605 (22.3)	319 (23.5)
Europe	1285 (31.5)	862 (31.7)	423 (31.1)
Other	788 (19.3)	522 (19.2)	266 (19.6)
White race — no. (%)†	3534 (86.7)	2372 (87.3)	1162 (85.5)
Duration of diabetes — yr	15.4±8.8	15.6±8.8	15.1±8.7
Current use of tobacco — no. (%)	633 (15.5)	427 (15.7)	206 (15.2)
History of cardiovascular disease — no. (%)‡	3650 (89.6)	2420 (89.1)	1230 (90.5)
Current kidney disease — no. (%)§	1287 (31.6)	863 (31.8)	424 (31.2)
History of cardiovascular disease and current kidney disease — no. (%)	888 (21.8)	585 (21.5)	303 (22.3)
History of heart failure — no. (%)	737 (18.1)	487 (17.9)	250 (18.4)
History of hypertension — no. (%)	3722 (91.3)	2484 (91.4)	1238 (91.1)
History of diabetic retinopathy — no. (%)¶	1342 (32.9)	912 (33.6)	430 (31.6)
Albuminuria — no. (%)‖	1977 (48.5)	1319 (48.5)	658 (48.4)
Body-mass index**	32.7±6.2	32.9±6.2	32.4±6.0
Heart rate — beats/min	72.8±10.6	72.8±10.6	72.8±10.7
Systolic blood pressure — mm Hg	134.9±15.5	135.1±15.5	134.4±15.6
Diastolic blood pressure — mm Hg	76.7±9.7	76.8±9.7	76.6±9.8
Glycated hemoglobin level — %	8.91±1.48	8.90±1.46	8.94±1.52
eGFR — ml/min/1.73 m^2	72.4 (22.4)	72.2 (21.9)	72.9 (23.3)
Median albumin-to-creatinine ratio (IQR)††	28.3 (9.7–114.2)	28.3 (8.9–119.5)	28.3 (9.7–106.7)
Cholesterol level — mmol/liter			
Total cholesterol	4.21±1.23	4.21±1.24	4.21±1.22
LDL cholesterol	2.07±0.98	2.07±0.98	2.08±0.97
HDL cholesterol	1.11±0.31	1.12±0.31	1.10±0.31
Median triglycerides (IQR) — mmol/liter	1.91 (1.37–2.75)	1.90 (1.36–2.74)	1.93 (1.40–2.75)
Medication use — no. (%)			
Any insulin	2560 (62.8)	1720 (63.3)	840 (61.8)
Metformin	2985 (73.2)	1993 (73.4)	992 (73.0)
Sulfonylurea	1036 (25.4)	695 (25.6)	341 (25.1)
SGLT2 inhibitor	618 (15.2)	412 (15.2)	206 (15.2)
No glucose-lowering drug	85 (2.1)	57 (2.1)	28 (2.1)
ACE inhibitor, ARB, or ARN inhibitor	3262 (80.0)	2177 (80.1)	1085 (79.8)
Beta-blocker	2670 (65.5)	1795 (66.1)	875 (64.4)
Statin	3294 (80.8)	2202 (81.0)	1092 (80.4)
Fibrate	350 (8.6)	233 (8.6)	117 (8.6)
Acetylsalicylic acid	2768 (67.9)	1855 (68.3)	913 (67.2)

Table 1. (Continued.)

Characteristic	All Participants (N=4076)	Efpeglenatide, 4 or 6 mg (N=2717)	Placebo (N=1359)
Other antiplatelet drug	1049 (25.7)	705 (25.9)	344 (25.3)

* Plus–minus values are means ±SD. To convert the values for cholesterol and triglycerides to milligrams per deciliter, divide by 0.02586 and by 0.01129, respectively. ACE denotes angiotensin-converting enzyme, ARB angiotensin receptor blocker, ARN angiotensin receptor–neprilysin, HDL high-density lipoprotein, IQR interquartile range, LDL low-density lipoprotein, and SGLT2 sodium–glucose cotransporter 2.

† Race was reported by the participants.

‡ A history of cardiovascular disease included coronary artery disease (i.e., previous myocardial infarction, ≥50% stenosis in the left main coronary artery or in at least two other coronary arteries, revascularization of either two or more coronary arteries or one coronary artery with ≥50% stenosis in another, or ≥50% stenosis in one coronary artery with either a noninvasive test showing ischemia or hospitalization for unstable angina in the previous 12 months), stroke, or peripheral artery disease (i.e., limb angioplasty, peripheral-artery stent revascularization or bypass surgery, limb or foot amputation due to circulatory insufficiency, ankle–brachial index of <0.9 [the ankle–brachial index is the ratio of the systolic blood pressure in the ankle to the blood pressure in the upper arm, with lower values indicating possible narrowing of the arteries in the legs], or angiographic evidence).

§ Kidney disease was defined as an estimated glomerular filtration rate (eGFR) of 25.0 to 59.9 ml per minute per 1.73 m^2 of body-surface area. The eGFR was calculated with the use of the four-variable Modification of Diet in Renal Disease formula: $175 \times (\text{serum creatinine level [}\mu\text{mol per liter]}/88.4)^{-1.154} \times \text{age (year)}^{-0.203} \times 1.212$ (if Black) $\times 0.742$ (if female).

¶ A history of diabetic retinopathy was reported by the participant or was determined according to documented vitrectomy, laser therapy, or ocular injections.

‖ Albuminuria was defined as an albumin-to-creatinine ratio of at least 30, as measured in milligrams of albumin to grams of creatinine, or at least 3.39, as measured in milligrams of albumin to millimoles of creatinine.

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

†† The albumin-to-creatinine ratio was measured as milligrams of albumin to grams of creatinine.

(15.2%) were using an SGLT2 inhibitor at baseline. Similar percentages of participants in the efpeglenatide groups and the placebo group were receiving various glucose-lowering or cardioprotective drugs at baseline (Table 1). However, at the last trial visit (Table S2), a greater percentage of participants in the placebo group than in the efpeglenatide groups (pooled data) were taking a DPP-4 inhibitor (1.9% vs. 0.9%, P=0.005) or an SGLT2 inhibitor (21.2% vs. 17.5%, P=0.004).

TRIAL OUTCOMES

During follow-up (Table 2), 189 of 2717 participants (7.0%) assigned to receive efpeglenatide and 125 of 1359 participants (9.2%) assigned to receive placebo had at least one MACE (3.9 vs. 5.3 events per 100 person-years; hazard ratio, 0.73; 95% confidence interval [CI], 0.58 to 0.92; P<0.001 for noninferiority at both the 1.8 and 1.3 margins and P=0.007 for superiority). Thus, an estimated 46 similar patients would need to be treated with efpeglenatide for 1.8 years to prevent one MACE (Table S3). The results of exploratory analyses suggested a possible dose–response effect, with estimated hazard ratios of 0.82 (95% CI, 0.63 to 1.06) for the comparison between the 4-mg efpeglenatide group and the placebo group and 0.65 (95% CI, 0.50 to 0.86) for the comparison between the 6-mg efpeglenatide group and the placebo group (Fig. S2).

Participants assigned to receive efpeglenatide also reported a significantly lower incidence of at least one expanded MACE composite event (hazard ratio, 0.79; 95% CI, 0.65 to 0.96; P=0.02), a renal composite outcome event (hazard ratio, 0.68; 95% CI, 0.57 to 0.79; P<0.001), and a MACE or death from noncardiovascular causes (hazard ratio, 0.73; 95% CI, 0.59 to 0.91; P=0.004) (Fig. 1). The median time to death from noncardiovascular causes among all trial participants was 1.81 years (interquartile range, 1.69 to 1.98). Other outcomes, including analyses of recurrent events, are reported in Table 2, Table S4, and Figure S3.

Analyses of the evident effect of efpeglenatide on the primary outcome within predefined, clinically relevant subgroups of participants (Fig. 2) showed no variation with sex, age, race, duration of diabetes, glycated hemoglobin level, body-mass index, eGFR, history of cardiovascular disease, use of SGLT2 inhibitors, or use of metformin. Point estimates of effect across the four geographic regions showed wide variation and

Table 2. Adjudicated First Events.*

Event	Efpeglenatide, 4 or 6 mg (N=2717)		Placebo (N=1359)		Hazard Ratio (95% CI)	P Value for Noninferiority	P Value for Superiority
	no. of participants (%)	*no. of events/100 person-years*	*no. of participants (%)*	*no. of events/100 person-years*			
Primary outcome: incident MACE†	189 (7.0)	3.9	125 (9.2)	5.3	0.73 (0.58–0.92)	<0.001‡	0.007
Expanded MACE composite outcome event§	257 (9.5)	5.4	158 (11.6)	6.8	0.79 (0.65–0.96)		0.02
Composite renal outcome event¶	353 (13.0)	7.7	250 (18.4)	11.6	0.68 (0.57–0.79)		<0.001
MACE or death from noncardiovascular causes	216 (7.9)	4.5	143 (10.5)	6.0	0.73 (0.59–0.91)		0.004
Kidney-function outcome event‖	121 (4.5)	2.5	76 (5.6)	3.1	0.77 (0.57–1.02)		0.07
MACE, death from noncardiovascular causes, hospitalization for heart failure, or kidney-function outcome event	243 (8.9)	5.1	164 (12.1)	7.0	0.71 (0.59–0.87)		
Myocardial infarction	91 (3.3)	1.9	58 (4.3)	2.4	0.75 (0.54–1.05)		
Nonfatal myocardial infarction	85 (3.1)	1.7	53 (3.9)	2.2	0.78 (0.55–1.10)		
Stroke	47 (1.7)	1.0	31 (2.3)	1.3	0.74 (0.47–1.17)		
Nonfatal stroke	41 (1.5)	0.8	25 (1.8)	1.0	0.80 (0.48–1.31)		
Cardiovascular mortality	75 (2.8)	1.5	50 (3.7)	2.1	0.72 (0.50–1.03)		
Total mortality	111 (4.1)	2.2	69 (5.1)	2.8	0.78 (0.58–1.06)		
Coronary revascularization	126 (4.6)	2.6	66 (4.9)	2.8	0.93 (0.69–1.26)		
Unstable angina	6 (0.2)	0.1	4 (0.3)	0.2	0.55 (0.13–2.35)		
Incident macroalbuminuria	348 (12.8)	7.6	244 (18.0)	11.3	0.68 (0.58–0.80)		
Heart failure	40 (1.5)	0.8	31 (2.3)	1.3	0.61 (0.38–0.98)		

* CI denotes confidence interval.
† A major adverse cardiovascular event (MACE) was a composite of nonfatal myocardial infarction, nonfatal stroke, or death from cardiovascular or undetermined causes.
‡ The P value for noninferiority is for an upper bound of the 95% confidence interval of the hazard ratio for an incident MACE of both 1.8 or less and 1.3 or less.
§ Expanded MACE was a composite of MACE, coronary revascularization, or hospitalization for unstable angina.
¶ The composite renal outcome was incident macroalbuminuria (defined as a urinary albumin-to-creatinine ratio of >300, as measured in milligrams of albumin to grams of creatinine, or >33.9, as measured in milligrams of albumin to millimoles of creatinine), plus an increase in the urinary albumin-to-creatinine ratio of at least 30% from baseline, a sustained decrease in the eGFR of at least 40% for 30 days or more, renal-replacement therapy for 90 days or more, and a sustained eGFR of less than 15 ml per minute per 1.73 m^2 for 30 days or more.
‖ The kidney-function outcome was a composite of a decrease in the eGFR of at least 40% for 30 days or more, end-stage kidney disease (defined as dialysis for ≥90 days, kidney transplantation, or an eGFR of <15 ml per minute per 1.73 m^2 for ≥30 days), or death from any cause.

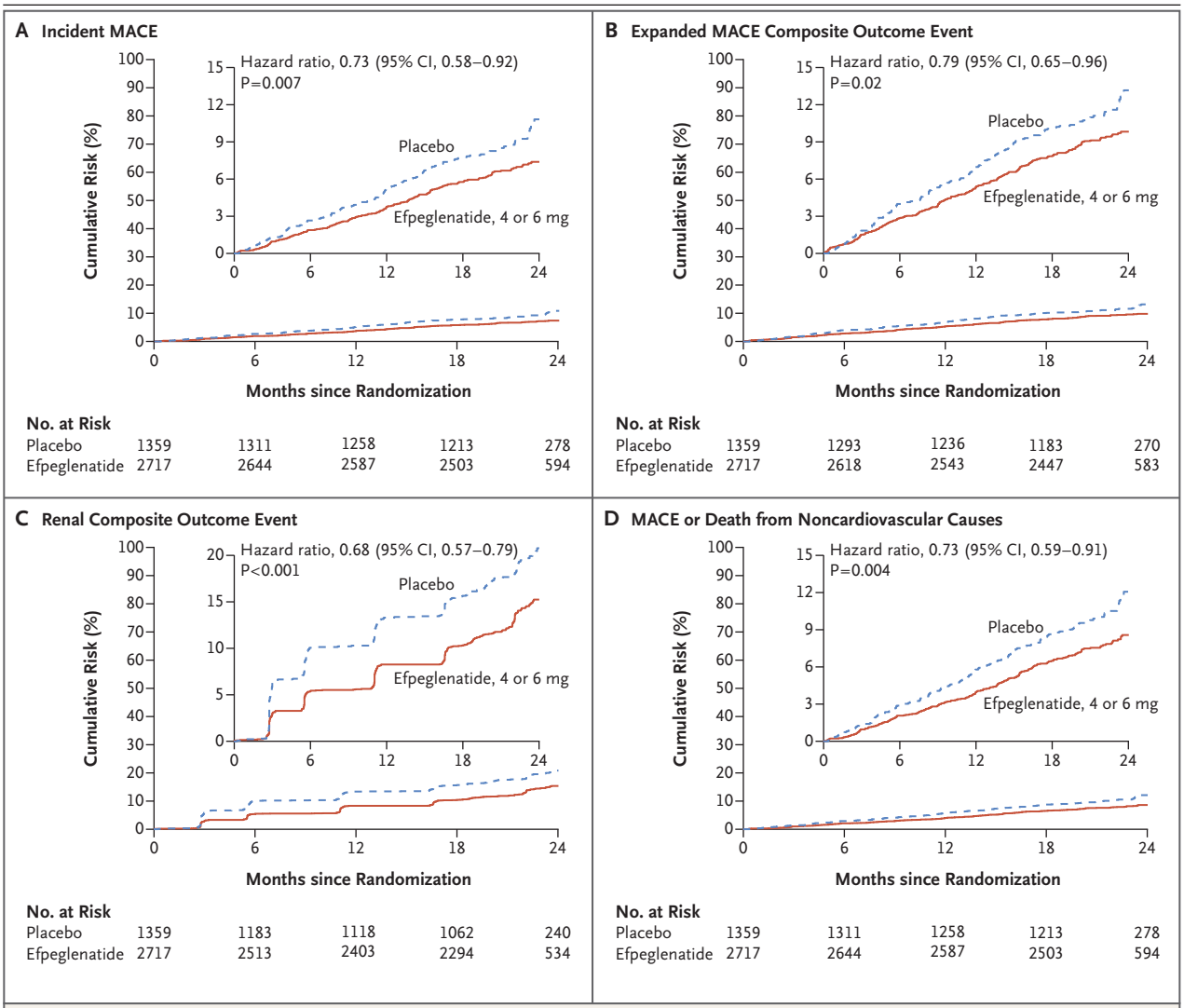

Figure 1. Major Cardiovascular and Renal Outcomes.

Shown are the cumulative risks of an incident major adverse cardiovascular event (MACE; the primary composite outcome of nonfatal myocardial infarction, nonfatal stroke, or death from cardiovascular or undetermined causes) (Panel A); an expanded MACE composite outcome event (a key secondary outcome comprising MACE, coronary revascularization, or hospitalization for unstable angina) (Panel B); a composite renal outcome event (a key secondary outcome comprising incident macroalbuminuria [defined as a urinary albumin-to-creatinine ratio of >300, as measured in milligrams of albumin to grams of creatinine, or >33.9, as measured in milligrams of albumin to millimoles of creatinine], plus an increase in the urinary albumin-to-creatinine ratio of ≥30% from baseline, a sustained decrease in the estimated glomerular filtration rate [eGFR] of ≥40% for ≥30 days, renal-replacement therapy for ≥90 days, or a sustained eGFR of <15 ml per minute per 1.73 m^2 for ≥30 days) (Panel C); and MACE or death from noncardiovascular causes (a secondary composite outcome) (Panel D). The risks of these outcome events were shown to be lower with efpeglenatide than with placebo. The inset in each panel shows the same data on an expanded y axis.

overlapping confidence intervals that may indicate heterogeneity of effect.

The effect of efpeglenatide on least-squares mean differences in continuous variables (efpeglenatide vs. placebo) during the follow-up period included a glycated hemoglobin level that was lower by 1.24% (95% CI, 1.17 to 1.32); a body-mass index (the weight in kilograms divided by the square of the height in meters) that was lower by 0.9 (95% CI, 0.8 to 1.0); a body weight that was lower by 2.6 kg (95% CI, 2.3 to 2.9); systolic and diastolic blood pressures that were

Subgroup	Efpeglenatide, 4 or 6 mg	Placebo	Efpeglenatide, 4 or 6 mg	Placebo	Hazard Ratio for an Incident MACE (95% CI)
	no. of events/total no. (%)		*no. of events per 100 person-yr*		
Overall	189/2717 (7.0)	125/1359 (9.2)	3.9	5.3	0.73 (0.58–0.92)
Sex					
Male	142/1792 (7.9)	88/940 (9.4)	4.5	5.4	0.81 (0.62–1.06)
Female	47/925 (5.1)	37/419 (8.8)	2.8	5.0	0.56 (0.36–0.86)
Age					
<65 yr	86/1281 (6.7)	57/673 (8.5)	3.8	4.9	0.78 (0.56–1.09)
≥65 yr	103/1436 (7.2)	68/686 (9.9)	4.0	5.7	0.69 (0.51–0.94)
Race					
White	168/2372 (7.1)	114/1162 (9.8)	4.0	5.6	0.70 (0.55–0.89)
Black	8/93 (8.6)	3/50 (6.0)	4.8	3.4	1.31 (0.34–5.02)
Asian	8/169 (4.7)	6/98 (6.1)	2.7	3.4	0.69 (0.22–2.15)
Other	5/83 (6.0)	2/49 (4.1)	3.4	2.3	—
Geographic region					
United States and Canada	72/728 (9.9)	28/351 (8.0)	5.4	4.4	1.20 (0.78–1.89)
Mexico and Central and South America	26/605 (4.3)	30/319 (9.4)	2.4	5.5	0.44 (0.26–0.74)
Europe	56/862 (6.5)	45/423 (10.6)	3.7	6.3	0.59 (0.40–0.87)
Other	35/522 (6.7)	22/266 (8.3)	3.8	4.7	0.79 (0.46–1.36)
Duration of diabetes					
<10 yr	47/763 (6.2)	32/424 (7.5)	3.4	4.3	0.79 (0.50–1.24)
≥10 yr	142/1953 (7.3)	93/935 (9.9)	4.1	5.7	0.70 (0.54–0.91)
Glycated hemoglobin					
<8%	57/863 (6.6)	35/420 (8.3)	3.7	4.7	0.73 (0.47–1.13)
≥8%	132/1854 (7.1)	90/939 (9.6)	4.0	5.5	0.71 (0.54–0.93)
BMI					
<31.9	87/1324 (6.6)	73/702 (10.4)	3.7	6.0	0.61 (0.45–0.83)
≥31.9	102/1390 (7.3)	52/657 (7.9)	4.1	4.5	0.90 (0.64–1.26)
eGFR					
<71.5 mg/ml/1.73 m^2	107/1371 (7.8)	74/666 (11.1)	4.4	6.4	0.67 (0.50–0.91)
≥71.5 mg/ml/1.73 m^2	82/1346 (6.1)	51/691 (7.4)	3.4	4.2	0.81 (0.57–1.15)
History of cardiovascular disease					
Yes	177/2420 (7.3)	122/1230 (9.9)	4.1	5.7	0.71 (0.57–0.90)
No	12/297 (4.0)	3/129 (2.3)	2.2	1.3	1.71 (0.48–6.07)
SGLT2 inhibitor use at baseline					
Yes	25/412 (6.1)	17/206 (8.3)	3.4	4.7	0.70 (0.37–1.30)
No	164/2305 (7.1)	108/1153 (9.4)	4.0	5.4	0.74 (0.58–0.94)
Metformin use at baseline					
Yes	127/1993 (6.4)	87/992 (8.8)	3.6	5.0	0.70 (0.53–0.92)
No	62/724 (8.6)	38/367 (10.4)	4.9	6.0	0.80 (0.54–1.20)

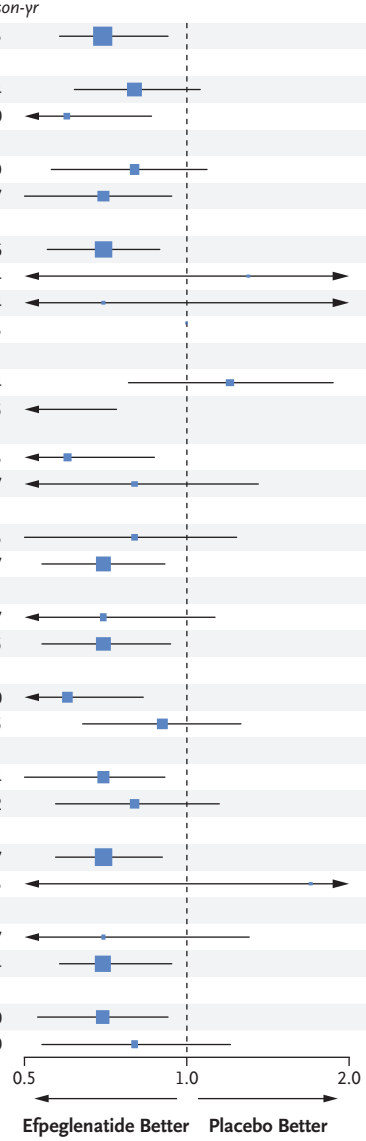

Figure 2. Prespecified Subgroup Analyses of Incident MACE (the Primary Efficacy Outcome).

Race was reported by the participants. The hazard ratio was not calculated for "other" race because there were too few participants with events. The body-mass index (BMI) is the weight in kilograms divided by the square of the height in meters. SGLT2 denotes sodium–glucose cotransporter 2.

lower by 1.5 mm Hg (95% CI, 0.8 to 2.2) and 0.6 mm Hg (95% CI, 0.2 to 1.0), respectively; a pulse pressure that was lower by 2.1 mm Hg (95% CI, 1.4 to 2.7); a heart rate that was higher by 3.9 beats per minute (95% CI, 3.4 to 4.4); a low-density lipoprotein cholesterol level that was lower by 2.7 mg per deciliter (95% CI, 1.2 to 4.6) (0.07 mmol per liter [95% CI, 0.03 to 0.12]); a urinary albumin-to-creatinine ratio that was lower by 21% (95% CI, 14 to 28), and a least-squares mean eGFR that was higher by 0.9 ml per minute per 1.73 m^2 (95% CI, 0.3 to 1.5) (Table S5

Table 3. Adverse Events of Special Interest.*

Event	Efpeglenatide, 4 or 6 mg (N=2717)	Placebo (N=1359)	P Value†
	number (percent)		
Discontinuation of assigned regimen because of adverse events	147 (5.4)	49 (3.6)	0.02
Severe gastrointestinal event	90 (3.3)	25 (1.8)	0.009
Constipation, diarrhea, nausea, vomiting, or bloating	32 (1.2)	6 (0.4)	0.03
Other severe gastrointestinal event	59 (2.2)	19 (1.4)	0.10
Confirmed pancreatic event	32 (1.2)	15 (1.1)	0.87
Confirmed pancreatic cancer	2 (<0.1)	3 (0.2)	NA
Confirmed pancreatitis	11 (0.4)	7 (0.5)	0.59
Any cancer	72 (2.6)	37 (2.7)	0.81
Rise in calcitonin level of >20 pg/ml	41 (1.5)	20 (1.5)	0.99
Thyroid C-cell neoplasm	0	0	NA
Severe hypoglycemia	24 (0.9)	13 (1.0)	0.67
Diabetic retinopathy and related complications	47 (1.7)	27 (2.0)	0.50
Acute kidney failure	88 (3.2)	39 (2.9)	0.62
Severe injection-site reaction	0	1 (<0.1)	NA
Severe allergic reactions	5 (0.2)	1 (<0.1)	NA
Severe immune complex disease	13 (0.5)	1 (<0.1)	0.10

* Participants could be counted more than once for an event. NA denotes not applicable.
† P values are from Cox models for the relationship between random assignment to efpeglenatide and each adverse event, adjusted for geographic region and use of sodium–glucose cotransporter 2 inhibitors (randomization stratification factor).

and Fig. S4). The apparent change in the eGFR with time suggested consistent effects during follow-up (Fig. S5). The numbers of participants with missing data for these variables are provided in Table S6.

ADVERSE EFFECTS

The percentage of participants who reported severe gastrointestinal adverse effects was higher among those assigned to receive efpeglenatide than among those assigned to receive placebo (P=0.009) (Table 3), and the percentage of those who reported constipation, diarrhea, nausea, vomiting, or bloating was also higher among those assigned to receive efpeglenatide (P=0.03). Other prespecified safety outcomes (Table 3) and other adverse effects (Tables S7 and S8) were similar among the participants assigned to receive efpeglenatide and those assigned to receive placebo.

DISCUSSION

In this cardiovascular outcomes trial, weekly subcutaneous injections of efpeglenatide (4 or 6 mg) for a median of 1.8 years led to a 27% lower risk of incident MACE and a 32% lower risk of a composite renal outcome event than placebo among persons with type 2 diabetes and either a history of cardiovascular disease or current kidney disease. The results suggest that these cardiovascular and renal benefits occurred independently of the baseline use of SGLT2 inhibitors, the baseline use of metformin, and the baseline eGFR. The participants in the two efpeglenatide groups had gastrointestinal adverse events (as have also been observed in prior trials of other GLP-1 receptor agonists), but there was no evidence of retinal, pancreatic, or thyroid-related events.

The previously reported salutary effects of

GLP-1 receptor agonists on cardiovascular and renal outcomes[10] were observed in our trial population, which included more high-risk patients and had a higher prevalence of kidney disease than seven previously completed cardiovascular outcomes trials of GLP-1 receptor agonists. We observed a high incidence of MACE in the placebo group (5.3 per 100 person-years), but the hazard ratio was 27% lower among the participants assigned to receive efpeglenatide. Moreover, the fact that these findings accrued with a long-acting exendin-4–based GLP-1 receptor agonist suggests that the cardiovascular benefits of this class of agents are not restricted to GLP-1 receptor agonists that are structurally similar to human GLP-1. Finally, the concomitant use of an SGLT2 inhibitor by more than 15% of the participants during the trial and the overlapping confidence intervals for the cardiovascular effects with or without SGLT2 inhibitors suggest that the beneficial cardiovascular effects of efpeglenatide may be independent of those of an SGLT2 inhibitor.

A variety of possibilities may account for the protective effects of efpeglenatide on the heart and the kidneys. The drug significantly reduced several risk factors for both cardiovascular and kidney disease, including glycated hemoglobin level,[18] blood pressure,[19] body-mass index,[20] low-density lipoprotein cholesterol level,[21] eGFR, and the albumin-to-creatinine ratio.[22] Indeed, published mediation analyses from cardiovascular outcomes trials of other GLP-1 receptor agonists have suggested that their cardiovascular or renal benefits (or both) may be partially mediated by their effects on glycated hemoglobin level, blood pressure, or the albumin-to-creatinine ratio,[23-25] and a meta-regression analysis suggested a linear relation between the degree of lowering of glycated hemoglobin level and the hazard of MACE with GLP-1 receptor agonists.[26] The observed reductions in the eGFR, pulse pressure, and risk of a composite renal outcome event in this trial suggest that efpeglenatide may also have salutary endothelial and microvascular effects, as has been suggested for other GLP-1 receptor agonists.[27,28] Other possible mechanisms include antiinflammatory, antifibrotic, antiatherosclerotic, vasodilatory, and other hemodynamic effects, as noted in studies of other GLP-1 receptor agonists.[29,30]

Limitations of our trial include the short follow-up period, the occurrence of a primary outcome event in a lower number of participants than originally planned (314 vs. 330), and selection for previous cardiovascular or kidney disease, which limit the power of our trial and its generalizability to lower-risk persons with type 2 diabetes. Strengths of our trial include the high adherence and retention, the recruitment of a high-risk population for the assessment of cardiovascular and renal outcomes, and the inclusion of an appreciable number of participants who were receiving an SGLT2 inhibitor. These features, plus the fact that a high proportion of all participants were receiving guideline-recommended cardioprotective and renal protective therapies, suggest that the results of the current trial are generalizable to similar high-risk patients with type 2 diabetes.

The results of our trial show that efpeglenatide reduces the risk of serious adverse cardiovascular and renal events among persons with type 2 diabetes and either a history of cardiovascular disease or current kidney disease.

Supported by Sanofi.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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

We thank all the participants and all the AMPLITUDE-O committee members, investigators, and site personnel for their contributions to the trial.

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