Exploring the Relationship Between Efpeglenatide Dose and Cardiovascular Outcomes in Type 2 Diabetes: Insights From the AMPLITUDE-O Trial

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Background:

In the AMPLITUDE-O (Effect of Efpeglenatide on Cardiovascular Outcomes) cardiovascular outcomes trial, adding either 4 mg or 6 mg weekly of the glucagon-like peptide-1 receptor agonist efpeglenatide to usual care reduced major adverse cardiovascular events (MACE) in people with type 2 diabetes at high cardiovascular risk. Whether these benefits are dose related remains uncertain.

Methods:

Participants were randomly assigned in a 1:1:1 ratio to placebo, 4 mg or 6 mg of efpeglenatide. The effect of 6 mg versus placebo and of 4 mg versus placebo on MACE (a nonfatal myocardial infarction, nonfatal stroke, or death from cardiovascular or unknown causes) and on all the secondary composite cardiovascular and kidney outcomes was assessed. A dose-response relationship was assessed using the log-rank test and χ^2 statistic for trend.

Results:

During a median follow-up of 1.8 years, MACE occurred in 125 (9.2%) participants assigned to placebo, 84 (6.2%) participants assigned to 6 mg of efpeglenatide (hazard ratio [HR], 0.65 [95% CI, 0.5–0.86]; *P*=0.0027), and 105 (7.7%) assigned to 4 mg of efpeglenatide (HR, 0.82 [95% CI, 0.63–1.06]; *P*=0.14). Participants receiving high-dose efpeglenatide also experienced fewer secondary outcomes, including the composite of MACE, coronary revascularization, or hospitalization for unstable angina (HR, 0.73 for 6 mg, *P*=0.011; HR, 0.85 for 4 mg, *P*=0.17), a kidney composite outcome comprising sustained new macroalbuminuria, a ≥40% decline in estimated glomerular filtration rate or renal failure (HR, 0.63 for 6 mg, *P*<0.0001; HR, 0.73 for 4 mg, *P*=0.0009), MACE or any death (HR, 0.67 for 6 mg, *P*=0.0021; HR, 0.81 for 4 mg, *P*=0.08), a kidney function outcome comprising a sustained ≥40% decline in estimated glomerular filtration rate, renal failure, or death (HR, 0.61 for 6 mg, *P*=0.0072; HR, 0.97 for 4 mg, *P*=0.83), and the composite of MACE, any death, heart failure hospitalization, or the kidney function outcome (HR, 0.63 for 6 mg, *P*=0.0002; HR, 0.81 for 4 mg, *P*=0.067). A clear dose-response was noted for all primary and secondary outcomes (all *P* for trend ≤0.018).

Conclusions:

The graded salutary relationship between efpeglenatide dose and cardiovascular outcomes suggests that titrating efpeglenatide and potentially other glucagon-like peptide-1 receptor agonists to high doses may maximize their cardiovascular and renal benefits.

Registration:

URL: https://www.clinicaltrials.gov; Unique identifier: NCT03496298.

Clinical Perspective

What Is New?

- These analyses detected an incremental dose-response effect of the glucagon-like peptide-1 receptor agonist efpeglenatide (ie, placebo, to 4 mg to 6 mg) on the hazard of major adverse cardiovascular events (MACE).
- A dose-response effect was also detected on all prespecified secondary outcomes, including expanded MACE (including coronary revascularization or unstable angina), MACE or any death, the kidney composite outcome (macroalbuminuria, a decrease in estimated glomerular filtration rate by ≥40%, renal replacement therapy, or a sustained estimated glomerular filtration rate <15 $mL \cdot min^{-1} \cdot 1.73\ m^{-2}$), an additional prespecified kidney composite that excluded macroalbuminuria and included death, and a composite outcome that included MACE, this additional kidney composite, or heart failure hospitalization.

What Are the Clinical Implications?

- Middle-aged and older patients with type 2 diabetes and high risk for cardiovascular outcomes are likely to derive the most cardiovascular and renal benefits from high-dose efpeglenatide.
- Higher doses or higher potency of other glucagon-like peptide-1 receptor agonist drugs may confer even greater cardiovascular and renal benefits than those seen to date.
- Titration of these drugs to the highest tolerated dose may confer maximal preventive benefits.

Nonstandard Abbreviations and Acronyms

eGFR	estimated glomerular filtration rate
GLP-1 RA	glucagon-like peptide-1 receptor agonist
HbA1c	hemoglobin A1c
MACE	major adverse cardiovascular events

The incidence of cardiovascular events has slowly decreased in people with and without diabetes during the past 20 years.[1,2] Despite these secular trends and the growing use of cardioprotective therapies that have been proven effective for people with type 2 diabetes, these individuals continue to have a 1.5- to 3-fold higher incidence of these events than people without diabetes.[3] Although the precise reasons for this higher risk remain unclear, these observations support ongoing efforts to identify cardioprotective therapies with high efficacy. Glucagon-like peptide-1 receptor agonists (GLP-1 RAs) are a class of drugs that meet these criteria. Large cardiovascular outcomes trials clearly show that several GLP-1 RAs reduce cardiovascular outcomes[4,5] while also reducing hemoglobin A1c (HbA1c), systolic pressure, pulse pressure, weight, and low-density lipoprotein cholesterol.[6,7] Whether their cardioprotective effects are related to drug dose or potency remains uncertain, but important to ascertain because of the recent introduction of high-dose and high-potency agents for diabetes and weight loss indications.[8,9]

Efpeglenatide is an exendin-based GLP-1 RA with an elimination half-life of ≈155 hours.[10] The AMPLITUDE-O trial (Effect of Efpeglenatide on Cardiovascular Outcomes) randomly assigned 4076 people with type 2 diabetes at high cardiovascular risk to the addition of weekly subcutaneous injections of placebo, 4 mg of efpeglenatide , or 6 mg of efpeglenatide in a 1:1:1 ratio.[11] As previously reported, participants who were randomly assigned to the pooled 4-mg and 6-mg groups experienced a 27% reduced hazard of the first major adverse cardiovascular events (MACE) during a median follow-up period of 1.81 years.[12] The random assignment to 2 different doses of efpeglenatide provides a unique opportunity to estimate the cardiovascular effects of the 6-mg dose versus placebo and to determine the relationship of dose to cardiovascular outcomes in this population.

Methods

As previously reported, the AMPLITUDE-O trial was conducted at 344 sites in 28 countries. It was led by an international steering committee with sponsorship by Sanofi, and all data were analyzed at the Population Health Research Institute in Hamilton, Canada. Research ethics committees at each site approved the trial, and each participant provided written informed consent.

Participants

Trial participants included people with type 2 diabetes who were either ≥18 years of age with previous coronary artery disease, stroke, or peripheral artery disease, or who were ≥50 years of age (if male) and 55 years of age (if female) with chronic kidney disease (defined as an estimated glomerular filtration rate [eGFR] of 25–59.9 $mL \cdot min^{-1} \cdot 1.73\ m^{-2}$), and at least one additional cardiovascular risk factor. Participants with a history of gastroparesis, prolonged nausea or vomiting, uncontrolled reflux, severe retinal disease, or pancreatitis were excluded, as were those who were using a GLP-1 RA or a dipeptidyl peptidase 4 inhibitor in the preceding 3 months. The full list of inclusion and exclusion criteria has previously been published,[11,12] and the key criteria are summarized in Table S1.

Trial Intervention

Participants were randomly assigned to 1 of 3 different groups according to a permuted-block randomization schedule with a fixed block size at a 1:1:1 ratio, after stratification by current, likely, or unlikely use of concomitant sodium-glucose cotransporter-2 inhibitors. Participants in these groups added weekly subcutaneous injections of 6 mg or 4 mg of efpeglenatide or placebo to their usual diabetes regimen. Participants assigned to an active drug began therapy with 2 mg weekly for 4 weeks and increased the dose every 4 weeks until the final dose was reached. Investigators had the option of reducing the dose of insulin, sulfonylureas, or meglitinides for participants whose baseline hemoglobin A1c (HbA1c) was <7.5% at the time of randomization, after which the dose of glucose-lowering drugs remained unchanged until the 12-week visit. Subsequent visits were at 24 weeks and then every 24

weeks. Participants, site personnel, the project office, and study leadership personnel were all masked to the assigned intervention. An unmasked independent data-monitoring committee reviewed accruing data on a regular basis.

Outcomes

The primary outcome was the first occurrence of a MACE comprising a nonfatal myocardial infarction, nonfatal stroke, or death from cardiovascular or unknown causes. The prespecified secondary outcomes included an expanded MACE composite (MACE, coronary revascularization, or hospitalization for unstable angina), a kidney composite outcome (incident macroalbuminuria defined as a urinary albumin:creatinine ratio >33.9 mg/mmol with a ≥30% rise from baseline, a decrease in eGFR by ≥40% for ≥30 days, renal replacement therapy for ≥90 days, or an eGFR <15 $mL \cdot min^{-1} \cdot 1.73\ m^{-2}$ for ≥30 days), MACE or any death, a composite kidney function outcome (the kidney composite outcome without the macroalbuminuria component or any death), and the composite of MACE, any death, heart failure hospitalization, or the kidney function outcome. These outcomes, and additional outcomes as well, are listed in Table S2. All deaths, myocardial infarctions, strokes, hospitalizations for unstable angina or heart failure, and pancreatic events were adjudicated by a masked, independent clinical end point committee. Continuous variables were collected at baseline and ≥5 times afterward (at 3, 6, 12, 18, and 24 months). Finally, 2 additional outcomes were assessed for these analyses; these were the previously reported kidney disease index, calculated as a geometric mean of 1/eGFR and Ln(100×albumin:creatinine ratio),[13] and a new categorical outcome of optimal diabetes control, defined as the first occurrence of an HbA1c of <7% in the absence of any weight gain or episode of severe hypoglycemia.

Statistical Analysis

The planned sample size of 4000 participants in the main study was estimated to have 90% power to show noninferiority (at the 1.3 noninferiority margin) of the combined 4-mg and 6-mg dose groups versus the placebo group during a follow-up period of up to 3 years. No separate sample size estimates were done for the current post hoc exploratory analyses.

The intention-to-treat principle was used for all analyses, with censorship for cardiovascular outcomes or death at the last follow-up date, and, for kidney outcomes, the last day that kidney outcome status was available. All statistical analyses were adjusted for geographic region and the sodium-glucose cotransporter-2 inhibitor–related randomization stratification factor described earlier. Least squares mean differences in continuous variables over time were analyzed using mixed-effects models with repeated measures that were fitted using restricted maximum likelihood estimation, with the baseline value as a covariate and the participant as a random effect. Fixed effects were region, stratification factor, trial visit, assigned treatment by visit interaction, and assigned treatment. The effect of the intervention on categorical variables was illustrated using Kaplan-Meier curves and analyzed using Cox proportional hazards models, according to the previously defined, prespecified hierarchal testing strategy for the primary and secondary outcomes that was used for the main article[12] (Table S2). Proportionality was assessed by plotting the log of the negative log of the survival function against the log of the survival time. Finally, the hypothesis of a graded increase in effect with an increasing dose of efpeglenatide was tested using a log-rank test for trend across the 3 Kaplan-Meier curves for each outcome. All analyses were conducted using SAS software version 9.4 (SAS Institute).

Results

Baseline characteristics for participants assigned to 6 mg or 4 mg of efpeglenatide and placebo were balanced across all 3 treatment groups and are summarized in Table 1. As previously reported, the mean age±SD for the entire cohort was 64.5±8.2 years, 33% were women, and 87% reported White ancestry.

The mean diabetes duration was 15.4±8.8 years, the mean HbA1c at baseline was 8.9±1.5%, and 62.8% of participants were taking insulin. Previous cardiovascular disease was reported for 89.5% of participants, 31.6% had an eGFR <60 mL·min^{-1}·1.73 m^{-2}, and 48.5% had a urine albumin:creatinine ratio ≥30 mg/g. Statins were used by 81% of participants, sodium-glucose cotransporter-2 inhibitors by 15%, renin angiotensin system drugs by 80%, beta-blockers by 65.5%, and aspirin by 68%.

Table 1. Baseline Characteristics

Characteristics	Overall	4 mg of efpeglenatide	6 mg of efpeglenatide	Placebo
Randomized	4076	1359	1358	1359
Age, y, mean±SD	64.5±8.2	64.6±8.2	64.7±8.2	64.4±8.3
Females	1344 (33.0)	442 (32.5)	483 (35.6)	419 (30.8)
White ancestry	3534 (86.7)	1192 (87.7)	1180 (86.9)	1162 (85.5)
Diabetes duration, mean±SD	15.4±8.8	15.7±8.9	15.5±8.8	15.1±8.7
Current tobacco use	633 (15.5)	229 (16.9)	198 (14.6)	206 (15.2)
Previous cardiovascular disease*	3650 (89.5)	1205 (88.7)	1215 (89.5)	1230 (90.5)
eGFR <60 mL·min^{-1}·1.73 m^{-2}†	1287 (31.6)	428 (31.5)	435 (32.0)	424 (31.2)
Previous cardiovascular disease and eGFR <60 mL·min^{-1}·1.73 m^{-2}	888 (21.8)	283 (20.8)	302 (22.2)	303 (22.3)
Previous heart failure	737 (18.1)	236 (17.4)	251 (18.5)	250 (18.4)
Previous hypertension	3722 (91.3)	1236 (90.9)	1248 (91.9)	1238 (91.1)
Previous diabetic retinopathy‡	1342 (32.9)	442 (32.5)	470 (34.6)	430 (31.6)
Albuminuria, %§	1977 (48.5)	657 (48.3)	662 (48.7)	658 (48.4)
Body mass index, kg/m^2, mean±SD	32.7±6.2	32.8±6.2	32.9±6.2	32.4±6.0
Heart rate, beats/min, mean±SD	72.8±10.6	72.9±10.5	72.7±10.7	72.8±10.7
Systolic blood pressure, mean±SD	134.9±15.5	135.4±15.3	134.9±15.7	134.4±15.6
Diastolic blood pressure, mean±SD	76.7±9.74	76.8±9.6	76.7±9.8	76.6±9.8
Hemoglobin A1c (%), mean±SD	8.9±1.5	8.8±1.4	9.0±1.5	8.9±1.5
eGFR, mL·min^{-1}·1.73 m^{-2}†	72.4±22.4	72.22±21.9	72.1±22.0	72.9±23.3

Characteristics	Overall	4 mg of efpeglenatide	6 mg of efpeglenatide	Placebo
Median urine albumin:creatinine ratio, mg/mmol	3.16 (1.13–12.88)	3.16 (1.13–13.56)	3.05 (1.02–13.11)	3.16 (1.13–11.98)
Kidney Disease Index, mean±SD	0.300±0.077	0.300±0.077	0.300±0.077	0.300 0.078
Cholesterol, mmol/L, mean±SD	4.21±1.23	4.21±1.26	4.21±1.21	4.21±1.22
Low-density lipoprotein cholesterol, mmol/L, mean±SD	2.07±0.98	2.07±0.98	2.07±0.98	2.08±0.97
High-density lipoprotein cholesterol, mmol/L, mean±SD	1.11±0.31	1.12±0.31	1.12±0.30	1.10±0.31
Median triglycerides, mmol/L	1.91 (1.37–2.75)	1.90 (1.35–2.73)	1.91 (1.37–2.75)	1.93 (1.40–2.75)
Any insulin	2560 (62.8)	853 (62.8)	867 (63.8)	840 (61.8)
Metformin	2985 (73.2)	988 (72.7)	1005 (74.0)	992 (73.0)
Sulfonylurea	1036 (25.4)	337 (24.8)	358 (26.4)	341 (25.1)
Sodium-glucose cotransporter 2 inhibitor	618 (15.2)	211 (15.5)	201 (14.8)	206 (15.2)
No glucose-lowering drug	85 (2.10)	27 (2.0)	30 (2.2)	28 (2.1)
Angiotensin-converting enzyme inhibitor or angiotensin receptor blocker or angiotensin receptor-neprilysin inhibitor	3262 (80.0)	1081 (79.5)	1096 (80.7)	1085 (79.8)
Beta-blocker	2670 (65.5)	898 (66.1)	897 (66.1)	875 (64.4)
Statin	3294 (80.8)	1099 (80.9)	1103 (81.2)	1092 (80.4)
Fibrate	350 (8.6)	115 (8.5)	118 (8.7)	117 (8.6)
Acetylsalicylic acid	2768 (67.9)	945 (69.5)	910 (67.0)	913 (67.2)
Other antiplatelet drugs	1049 (25.7)	363 (26.7)	342 (25.2)	344 (25.3)

Mean±SD, median (interquartile range), or n (%) are shown. eGFR indicates estimated glomerular filtration rate.

* Coronary artery disease (ie, previous myocardial infarction, ≥50% stenosis in the left main or ≥2 other coronary arteries, revascularization of either ≥2 coronary arteries or 1 coronary with ≥50% stenosis in another, or ≥50% stenosis in 1 coronary with either a noninvasive test demonstrating ischemia or an unstable angina hospitalization in the preceding 12 months); stroke, or peripheral artery disease (ie, limb angioplasty, peripheral artery stenting or bypass, limb or foot amputation resulting from circulatory insufficiency, ankle-brachial index <0.9, or angiographic evidence).

† eGFR by the 4-variable Modification of Diet in Renal Disease formula: 175×[serum creatinine (µmol/L)/88.4]–1.154×age (year)–0.203×1.212 (if Black)×0.742 (if female).

‡ Self-reported or vitrectomy, laser therapy, or ocular injections.

§ Urine albumin:creatinine ratio ≥30 mg/g or 3.39 mg/mmol; the Kidney Disease Index is geometric mean of 1/eGFR and Ln(100×urine albumin:creatinine ratio)

The median follow-up time of participants assigned to 6 mg or 4 mg of efpeglenatide or placebo weekly was 1.8, 1.8, and 1.8 years, respectively. At the end of follow-up, vital status was known in 1357 (99.9%), 1358 (99.9%), and 1358 (99.9%) of participants, and primary outcome status was known for 96.7%, 97.3%, and 96.2% of participants assigned to these 3 groups (Figure S1). Participants assigned to 6 mg or 4 mg of efpeglenatide and placebo took the study drug for 89%, 89%, and 91% of their maximum follow-up time, respectively. The study drug was discontinued because of adverse events in 3.6% of placebo participants, 5.8% of efpeglenatide (6 mg) participants (*P*=0.0081 versus placebo), and 5% of efpeglenatide (4 mg) participants (*P*=0.087 versus placebo). Severe gastrointestinal events were reported in 1.8% of placebo participants, 3.4% of efpeglenatide (6 mg) participants (*P*=0.012 versus placebo), and 3.2% of efpeglenatide (4 mg) participants (*P*=0.026 versus placebo with no other significant differences between the treatment groups (Table S3).

During follow-up (Table 2), 125 (9.2%) participants assigned to placebo experienced a MACE, compared with 84 (6.2%) assigned to 6 mg of efpeglenatide (hazard ratio [HR], 0.65 [95% CI, 0.50–0.86]; *P*=0.0027) and 105 (7.7%) assigned to 4 mg of efpeglenatide (HR, 0.82 [95% CI, 0.63–1.06]; *P*=0.14), with event curves beginning to separate within the first 6 months (Figure 1A). On the basis of the prespecified hierarchical testing strategy for the main article,[12] a statistically significant reduced HR for 6 mg of efpeglenatide versus placebo was also noted for the expanded MACE composite (Figure 1B; HR, 0.73 [95% CI, 0.58–0.93]; *P*=0.011), the kidney composite outcome (Figure 1C; HR, 0.63 [95% CI, 0.52–0.77]; *P*<0.0001), MACE or any death (Figure 1D; HR, 0.67 [95% CI, 0.52–0.86]; *P*=0.0021), the composite kidney function outcome (Figure 1E; HR, 0.61 [95% CI, 0.42–0.87]; *P*=0.0072), and the composite of MACE, any death, heart failure hospitalization, or the kidney function outcome (Figure 1F; HR, 0.63 [95% CI, 0.49–0.81]; *P*=0.0002). Several other differences were noted in exploratory analyses of 6 mg of efpeglenatide versus placebo. These included a reduced hazard of fatal or nonfatal myocardial infarction (HR, 0.64 [95% CI, 0.43–0.96]), both cardiovascular and total mortality (HR, 0.55 [95% CI, 0.35–0.88] and HR, 0.66 [95% CI, 0.45–0.95], respectively), incident macroalbuminuria (HR, 0.65 [95% CI, 0.53–0.79]), and incident heart failure hospitalization (HR, 0.50 [95% CI, 0.27–0.92]). Finally, compared with participants assigned to weekly placebo, those assigned to 6 mg of efpeglenatide weekly were 8 times more likely to achieve optimal diabetes control as defined earlier (HR, 8.05 [95% CI, 6.46–10.03])

Table 2. Outcomes and Event Rates by Assigned Efpeglenatide Dose or Placebo

Outcomes	6 mg of efpeglenatide (n=1358)		4 mg efpeglenatide (n=1358)		Placebo (n=1359)	
	n (%)	n/100py	n (%)	n/100py	n (%)	n/100py
MACE	84 (6.2)	3.5	105 (7.7)	4.4	125 (9.2)	5.3
Expanded MACE*	119 (8.8)	5.0	138 (10.2)	5.8	158 (11.6)	6.8
Kidney composite outcome†	166 (12.2)	7.2	187 (13.8)	8.3	250 (18.4)	11.6
MACE or any death	98 (7.2)	4.0	118 (8.7)	4.9	143 (10.5)	6.0
Kidney function outcome‡	47 (3.5)	1.9	74 (5.4)	3.0	76 (5.6)	3.1
MACE, any death, heart failure, kidney function outcome	107 (7.9)	4.4	136 (10.0)	5.7	164 (12.1)	7.0
Myocardial infarction	38 (2.8)	1.6	53 (3.9)	2.2	58 (4.3)	2.4
Nonfatal myocardial infarction	38 (2.8)	1.6	47 (3.5)	1.9	53 (3.9)	2.2
Stroke	25 (1.8)	1.0	22 (1.6)	0.9	31 (2.3)	1.3
Nonfatal Stroke	23 (1.7)	0.9	18 (1.3)	0.7	25 (1.8)	1.0
Cardiovascular mortality	28 (2.1)	1.1	47 (3.5)	1.9	50 (3.7)	2.0
Total mortality	46 (3.4)	1.9	65 (4.8)	2.6	69 (5.1)	2.8
Coronary revascularization	61 (4.5)	2.5	65 (4.8)	2.7	66 (4.9)	2.8
Unstable angina	5 (0.4)	0.2	1 (<0.1)	<0.1	4 (0.3)	0.2
New macroalbuminuria	166 (12.2)	7.2	182 (13.4)	8.0	244 (18.0)	11.3

Outcomes	6 mg of efpeglenatide (n=1358)		4 mg efpeglenatide (n=1358)		Placebo (n=1359)	
	n (%)	n/100py	n (%)	n/100py	n (%)	n/100py
Heart failure hospitalization	16 (1.2)	0.6	24 (1.8)	1.0	31 (2.3)	1.3
Optimal diabetes control§	585 (43.1)	37.6	556 (40.9)	35.1	92 (6.8)	4.0

MACE indicates major adverse cardiovascular events; and n/100py, n/100 person-years of follow-up.

* MACE or coronary revascularization or hospitalization for unstable angina;

† Incident macroalbuminuria (urine albumin:creatinine >33.9 mg/mmol with ≥30% rise from baseline), decrease in eGFR by ≥40% for ≥30 days, renal replacement therapy for ≥90 days, or eGFR <15 $mL \cdot min^{-1} \cdot 1.73\ m^{-2}$ for ≥30 days.

‡ The composite of either the kidney composite outcome (with the exclusion of the albuminuria criteria) or all-cause death.

§ First occurrence of hemoglobin A1c <7% in someone whose weight at that time is ≤ baseline weight with no severe hypoglycemia event by that time.

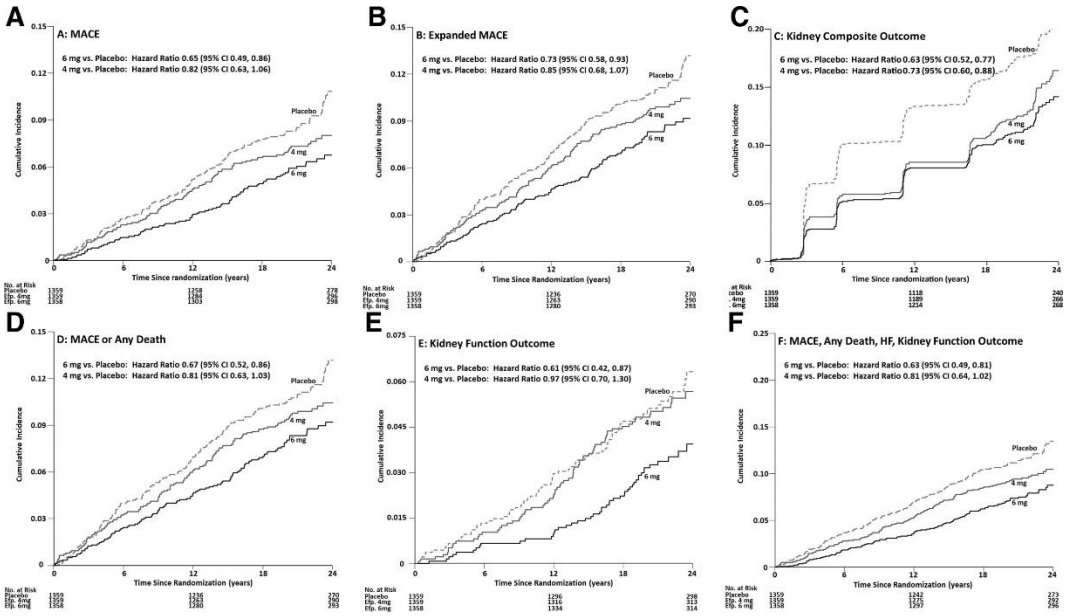

Figure 1. ***The cumulative incidence of various categorical outcomes for participants assigned to weekly injections of placebo (red dashed lines), 4 mg of efpeglenatide (blue lines), and 6 mg of efpeglenatide (black lines) is shown. A****, Major adverse cardiovascular events (MACE).* ***B****, MACE or coronary revascularization or hospitalization for unstable angina (expanded MACE).* ***C****, The kidney composite outcome (urine albumin:creatinine >33.9 mg/mmol with ≥30% rise from baseline, decrease in estimated glomerular filtration rate (eGFR) by ≥40% for ≥30 days, renal replacement therapy for ≥90 days, or eGFR <15 mL·min^{-1}·1.73 m^{-2} for ≥30 days.* ***D****, MACE or any death.* ***E****, The kidney function outcome (decrease in eGFR by ≥40% for ≥30 days, renal replacement therapy for ≥90 days, or an eGFR <15 mL·min^{-1}·1.73 m^{-2} for ≥30 days or any death).* ***F****, MACE, heart failure hospitalization or the kidney function outcome. Efp indicates efpeglenatide; and HF, heart failure.*

In contrast to the salutary effects of the 6-mg dose, the only primary or secondary outcome significantly reduced by the lower dose of 4 mg of efpeglenatide was the kidney composite outcome (HR, 0.73 [95% CI, 0.60–0.88]; *P*=0.0009). Exploratory analyses were also consistent with differences in new macroalbuminuria (HR, 0.72 [95% CI, 0.60–0.88]) and optimal glycemic control versus placebo (HR, 7.53 [95% CI, 6.04–9.39]). There was a clear dose-response relationship for MACE, expanded MACE, the kidney composite outcome, MACE or any death, the kidney function outcome, the composite of MACE, any death, heart failure, or the kidney function outcome, and myocardial infarction (*P*<0.05 for all; Table 3). Significant differences between participants receiving 6 mg versus 4 mg of efpeglenatide weekly (Table 3) were only noted for the kidney function outcome (*P*=0.012) and cardiovascular mortality (*P*=0.027).

Table 3. Effect of 6 mg vs 4 mg of Efpeglenatide per Week vs Placebo on Clinical Outcomes

Outcomes	6 mg of efpeglenatide vs placebo		4 mg of efpeglenatide vs placebo		*P* (trend)*	*P* (6 vs 4 mg)†
	Hazard ratio (95% CI)	*P*†	Hazard ratio (95% CI)	*P*†		
MACE	0.65 (0.50–0.86)	0.0027	0.82 (0.63–1.06)	0.14	0.0030	0.13
Expanded MACE‡	0.73 (0.58–0.93)	0.011	0.85 (0.68–1.07)	0.17	0.012	0.23
Kidney composite outcome§	0.63 (0.52–0.77)	<0.0001	0.73 (0.60–0.88)	0.0009	<0.001	0.18
MACE or any death	0.67 (0.52–0.86)	0.0021	0.81 (0.63–1.03)	0.08	0.0019	0.17
Kidney function outcome‖	0.61 (0.42–0.87)	0.0072	0.97 (0.70–1.33)	0.83	0.018	0.012
MACE, any death, heart failure, kidney function outcome	0.63 (0.49–0.81)	0.0002	0.81 (0.64–1.02)	0.067	<0.001	0.059
Myocardial infarction	0.64 (0.43–0.96)	0.033	0.89 (0.61–1.30)	0.55	0.048	0.12
Nonfatal myocardial infarction	0.70 (0.46–1.06)	0.094	0.87 (0.59–1.28)	0.47	0.11	0.35
Stroke	0.79 (0.47–1.34)	0.38	0.70 (0.40–1.20)	0.19	0.29	0.65
Nonfatal stroke	0.90 (0.51–1.59)	0.71	0.71 (0.39–1.30)	0.26	0.58	0.42
Cardiovascular mortality	0.55 (0.35–0.88)	0.012	0.93 (0.62–1.38)	0.72	0.024	0.027
Total mortality	0.66 (0.45–0.95)	0.027	0.93 (0.66–1.30)	0.67	0.044	0.064
Coronary revascularization	0.90 (0.64–1.28)	0.57	0.96 (0.68–1.36)	0.83	0.61	0.72
Unstable angina	N/A	N/A	N/A	N/A	0.95	N/A
New macroalbuminuria	0.65 (0.53–0.79)	<0.0001	0.72 (0.60–0.88)	0.0009	<0.001	0.30

Outcomes	6 mg of efpeglenatide vs placebo		4 mg of efpeglenatide vs placebo		*P* (trend)*	*P* (6 vs 4 mg)†
	Hazard ratio (95% CI)	*P*†	Hazard ratio (95% CI)	*P*†		
Heart failure hospitalization	0.50 (0.27–0.92)	0.025	0.75 (0.44–1.27)	0.28	0.027	0.23
Optimal diabetes control¶	8.05 (6.46–10.03)	<0.0001	7.53 (6.04–9.39)	<0.0001	<0.001	0.34

MACE indicates major adverse cardiovascular events; and N/A, not available.

* *P* values are based on a log–rank test for trend across the 3 Kaplan-Meier curves for each outcome.

† *P* values are from the Cox model.

‡ MACE or coronary revascularization or hospitalization for unstable angina;

§ New macroalbuminuria (urine albumin:creatinine >33.9 mg/mmol with ≥30% rise from baseline), decrease in eGFR by ≥40% for ≥30 days, renal replacement therapy for ≥90 days, or eGFR <15 $mL \cdot min^{-1} \cdot 1.73\ m^{-2}$ for ≥30 days;

‖ The composite of either the kidney composite outcome (with the exclusion of the albuminuria criteria) or all–cause death.

¶ First occurrence of hemoglobin A1c <7% in someone whose weight at that time is ≤ baseline weight with no severe hypoglycemia event by that time.

The effect of the 2 doses of efpeglenatide (6 mg and 4 mg) versus placebo on the least squares mean difference of various continuous measures is noted in Figure 2, Table 4, and Table S4. Clinical measures that were lower than placebo during follow-up included HbA1c (1.31% [95% CI, 1.21–1.41]), pulse pressure (2.05 mm [95% CI, 1.44–2.65]), weight (2.73 kg [95% CI, 2.31–3.16]), low-density lipoprotein cholesterol (0.09 mmol/L [95% CI, 0.02–0.15]), the urine albumin:creatinine ratio (21% lower [95% CI, 10–30]), and the kidney disease index (0.0128 units [95% CI, 0.0092–0.0164]). Measures that were higher were heart rate (4.28 beats/min [95% CI, 3.64–4.92]) and the eGFR (1.27 $mL \cdot min^{-1} \cdot 1.75\ m^{-2}$ [95% CI, 0.41–2.12]). Smaller differences were noted for 4 mg of efpeglenatide versus placebo with respect to these measures.

Table 4. Effect of 6 mg of Epfeglenatide per Week on Clinical and Biochemical Variables

Efpeglenatide dose		Placebo	Adjusted LSM difference		
6 mg/wk LSM (SE)	4 mg/wk LSM (SE)	LSM (SE)	6 mg vs placebo difference (95% CI)	4 mg vs placebo difference (95%CI)	
Hemoglobin A1c, %	–1.48 (0.03)	–1.35 (0.03)	–0.17 (0.03)	–1.31 (–1.41, –1.21)	–1.18 (–1.28 to –1.08)
Systolic blood pressure, mm Hg	–2.63 (0.31)	–2.49 (0.31)	–1.08 (0.32)	–1.55 (–2.53 to –0.56)	–1.41 (–2.39 to –0.43)
Diastolic blood pressure, mm Hg	0.40 (0.19)	0.54 (0.19)	–0.11 (0.19)	0.51 (–0.08 to 1.10)	0.65 (0.06 to 1.24)
Pulse pressure, mm Hg	–3.00 (0.27)	–3.01 (0.26)	–0.96 (0.27)	–2.04 (–2.87 to –1.21)	–2.05 (–2.88 to –1.22)
Heart rate, beats/min	5.00 (0.20)	4.22 (0.20)	0.72 (0.21)	4.28 (3.64 to 4.92)	3.50 (2.87 to 4.14)
Body mass index, kg/m^2	–1.20 (0.05)	–1.10 (0.05)	–0.23 (0.05)	–0.97 (–1.12 to –0.82)	–0.87 (–1.02 to –0.72)
Body weight, kg	–3.35 (0.13)	–3.07 (0.13)	–0.62 (0.13)	–2.73 (–3.16 to –2.31)	–2.46 (–2.88 to –2.03)
Low-density lipoprotein cholesterol, mmol/L	–0.06 (0.02)	–0.04 (0.02)	0.02 (0.02)	–0.09 (–0.15 to –0.02)	–0.06 (–0.13 to 0.01)
Ln (triglyceride)	0.2 (1.1)	0.2 (1.1)	0.26 (1.1)	0.77 (0.55 to 1.07)	0.78 (0.57 to 1.08)
eGFR	–1.99 (0.27)	–2.76 (0.27)	–3.26 (0.27)	1.27 (0.41 to 2.12)	0.51 (–0.35 to 1.36)
Ln (UACR)	0.64 (1.04)	0.63 (1.04)	0.81 (1.04)	0.79 (0.70 to 0.90)	0.78 (0.69 to 0.89)
Kidney Disease Index	0.00015 (0.0011)	0.0033 (0.0011)	0.0129 (0.0011)	–0.0128 (–0.0164 to –0.0092)	–0.0096 (–0.0132 to –0.0060)

The table summarizes the least squares mean (LSM) changes from baseline and the between-group difference in changes for continuous variables throughout the duration of the trial. Analyses were done using a mixed-effects model for repeated measures using restricted maximum likelihood, with the baseline value as the covariate, the participant as a random effect, and fixed effects for assigned treatment, region, randomization strata, visit, and treatment-by-visit interaction. Kidney Disease Index = geometric mean of 1/eGFR and Ln(100×UACR). eGFR indicates estimated glomerular filtration rate; and Ln (UACR), natural logarithm of urine albumin/creatinine ratio.

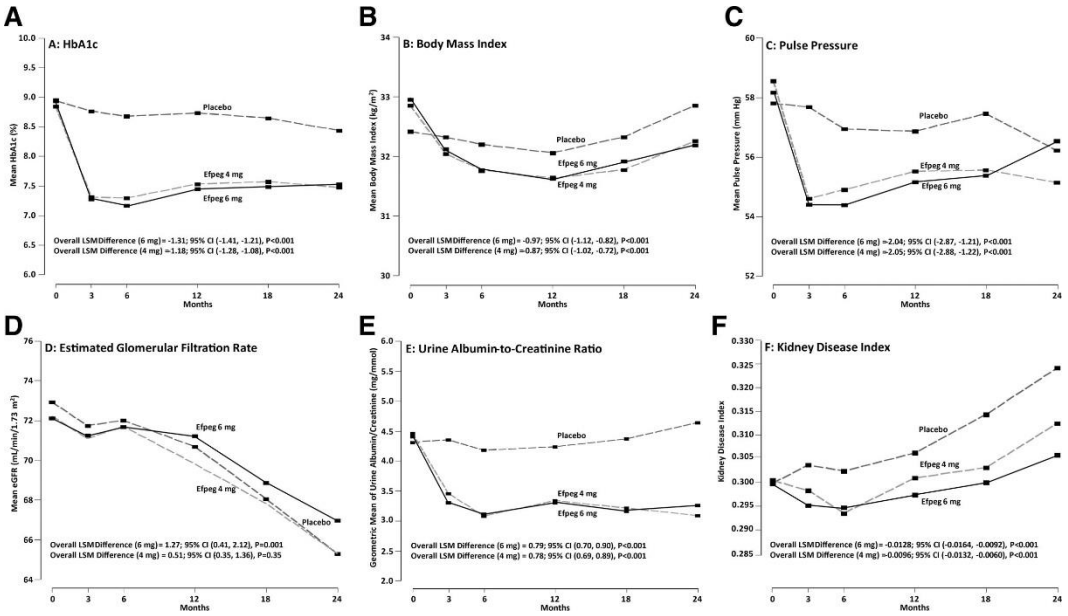

Figure 2. ***Effect of 6 mg of efpeglenatide (black lines), 4 mg of efpeglenatide (green dashed lines), and placebo (red dashed lines) on various continuous outcomes.*** *The values and standard errors for each data point are listed in Table S4.* ***A****, Hemoglobin A1c (HbA1c).* ***B****, Body mass index.* ***C****, Pulse pressure (systolic blood pressure – diastolic blood pressure).* ***D****, Estimated glomerular filtration rate (eGFR).* ***E****, Urine albumin to creatinine ratio (UACR).* ***F****, Kidney disease index (the geometric mean of 1/eGFR and ln(100×UACR). Efpeg indicates efpeglenatide; and LSM, least squares mean.*

Discussion

In the AMPLITUDE-O trial, people who were randomly assigned to either 4 mg or 6 mg of efpeglenatide weekly had a 27% reduced hazard of the primary outcome (MACE) compared with placebo.[12] They also had a significantly reduced hazard of the first 4 secondary outcomes. The current analyses show that the benefit of efpeglenatide was related to the assigned dose, with the higher 6-mg efpeglenatide dose achieving the lowest hazard of MACE and all the secondary outcomes. Thus, the 6-mg dose reduced the hazard of MACE by 35% and the hazard of all the secondary outcomes by 27% to 39%, whereas the 4-mg dose only reduced the hazard of one secondary outcome (the kidney composite outcome). Moreover, the 6-mg dose was associated with a 36% reduced hazard of myocardial infarction, a 45% reduced hazard of cardiovascular death, a 34% reduced hazard of all-cause death, and a 50% reduced hazard of heart failure hospitalization. The observed absolute risk reduction of 3.0% for the primary outcome suggests that ≈34 people comparable to those enrolled in the AMPLITUDE-O trial cardiovascular would need to be treated with 6 mg of efpeglenatide weekly for 1.8 years to prevent one MACE. Finally, these analyses were also somewhat consistent with a dose-response effect of efpeglenatide-related benefits regarding HbA1c, weight, blood pressure, eGFR, albuminuria, and a composite measure of these 2 kidney risk factors (the kidney disease index), with only a modest 1.6% absolute difference in severe gastrointestinal adverse events.

This dose-response effect on clinical outcomes is consistent with the previously reported clear dose-response effect on the concentration of efpeglenatide in pharmacokinetic studies.[10] This has several implications. First, it may account for the neutral result observed in the ELIXA Trial (Evaluation of Lixisenatide in Acute Coronary Syndrome),[14] EXSCEL (Exenatide Study of Cardiovascular Event Lowering trial),[15] and PIONEER 6 trial (Peptide Innovation for Early Diabetes Treatment),[16] in which either the potency of the GLP-1 RA or the dose that was used may not have been sufficiently high to yield a detectable cardiovascular benefit. It also strongly suggests that ongoing cardiovascular outcome trials

with a higher dose or more potent GLP-1 RAs, including 2.4 mg of semaglutide [8] and the dual GLP-1 and glucose-dependent insulinotropic polypeptide receptor agonist tirzepatide (NCT04255433)[17] may report clear cardiovascular benefits. An exploratory analysis of the link between different doses of tirzepatide and incident cardiovascular outcomes is consistent with a sizeable dose-response benefit.[18]

Reasons for the salutary benefit of efpeglenatide on the primary and secondary outcomes remain unclear. Explanations include direct effects of the drug on the vasculature (with higher doses having larger effects) or indirect effects through improved modifiable cardiovascular risk factors, including HbA1c, blood pressure, low-density lipoprotein, and kidney-related outcomes, or both. For example, a possible role of HbA1c is supported by a meta-regression analysis of GLP-1 RA outcomes trials showing a relationship between the degree of glucose-lowering and cardiovascular benefit,[19] mediation analyses from specific GLP-1 RA trials reporting that the glucose-lowering effect may account for up to 83% and 33% of its cardiovascular and renal effect, respectively,[20,21] and Mendelian randomization analyses demonstrating a causal relationship between HbA1c and cardiovascular outcomes.[22–24] Alternatively, changes in HbA1c and other cardiovascular risk factors in response to efpeglenatide may simply be markers for its effect on other mediating pathways.

Strengths of these analyses include the fact that they come from a randomized placebo-controlled cardiovascular outcomes trial, masked adjudication of the cardiovascular outcomes, high levels of adherence, retention, and outcome ascertainment, and high use of other cardioprotective therapies. They are limited by the relatively short duration of follow-up, the predominantly White participants, and the fact that the comparison of 6 mg of efpeglenatide versus placebo was not a prespecified analysis and was therefore exploratory.

These findings, and the related evidence reviewed here, collectively and strongly support the use of high-dose efpeglenatide to reduce cardiovascular outcomes in high-risk people. They also strongly suggest that higher GLP-1 RA doses and more potent molecules are likely to confer even greater cardiovascular and renal benefits than those seen to date.

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