ORIGINAL ARTICLE

Cardiovascular Outcomes with Ertugliflozin in Type 2 Diabetes

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ABSTRACT

BACKGROUND

The cardiovascular effects of ertugliflozin, an inhibitor of sodium–glucose cotransporter 2, have not been established.

METHODS

In a multicenter, double-blind trial, we randomly assigned patients with type 2 diabetes and atherosclerotic cardiovascular disease to receive 5 mg or 15 mg of ertugliflozin or placebo once daily. With the data from the two ertugliflozin dose groups pooled for analysis, the primary objective was to show the noninferiority of ertugliflozin to placebo with respect to the primary outcome, major adverse cardiovascular events (a composite of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke). The noninferiority margin was 1.3 (upper boundary of a 95.6% confidence interval for the hazard ratio [ertugliflozin vs. placebo] for major adverse cardiovascular events). The first key secondary outcome was a composite of death from cardiovascular causes or hospitalization for heart failure.

RESULTS

A total of 8246 patients underwent randomization and were followed for a mean of 3.5 years. Among 8238 patients who received at least one dose of ertugliflozin or placebo, a major adverse cardiovascular event occurred in 653 of 5493 patients (11.9%) in the ertugliflozin group and in 327 of 2745 patients (11.9%) in the placebo group (hazard ratio, 0.97; 95.6% confidence interval [CI], 0.85 to 1.11; P<0.001 for noninferiority). Death from cardiovascular causes or hospitalization for heart failure occurred in 444 of 5499 patients (8.1%) in the ertugliflozin group and in 250 of 2747 patients (9.1%) in the placebo group (hazard ratio, 0.88; 95.8% CI, 0.75 to 1.03; P=0.11 for superiority). The hazard ratio for death from cardiovascular causes was 0.92 (95.8% CI, 0.77 to 1.11), and the hazard ratio for death from renal causes, renal replacement therapy, or doubling of the serum creatinine level was 0.81 (95.8% CI, 0.63 to 1.04). Amputations were performed in 54 patients (2.0%) who received the 5-mg dose of ertugliflozin and in 57 patients (2.1%) who received the 15-mg dose, as compared with 45 patients (1.6%) who received placebo.

CONCLUSIONS

Among patients with type 2 diabetes and atherosclerotic cardiovascular disease, ertugliflozin was noninferior to placebo with respect to major adverse cardiovascular events. (Funded by Merck Sharp & Dohme and Pfizer; VERTIS CV ClinicalTrials.gov number, NCT01986881.)

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*A complete list of the VERTIS CV investigators is provided in the Supplementary Appendix, available at NEJM.org.

This article was published on September 23, 2020, at NEJM.org.

N Engl J Med 2020;383:1425-35.
DOI: 10.1056/NEJMoa2004967

Cardiovascular disease is the leading cause of illness and death in patients with type 2 diabetes.[1-3] Type 2 diabetes is also a major risk factor for the development of heart failure and progression of renal disease.[4,5] Previous trials that evaluated the effects of sodium–glucose cotransporter 2 (SGLT2) inhibitors on cardiovascular and kidney outcomes have shown consistent benefits with respect to certain outcomes such as hospitalization for heart failure and progression of renal disease.[6-8]

Ertugliflozin is an oral, selective SGLT2 inhibitor that was approved by the Food and Drug Administration (FDA) in the United States and by regulatory authorities in other countries for the improvement of glycemic control in adults with type 2 diabetes.[9,10] The FDA has mandated that cardiovascular safety be evaluated in trials of new glucose-lowering drugs, including SGLT2 inhibitors.[11] The long-term effects of ertugliflozin on cardiovascular and renal outcomes were assessed in the Evaluation of Ertugliflozin Efficacy and Safety Cardiovascular Outcomes Trial (VERTIS CV).

Methods

Trial Design and Oversight

This multicenter, double-blind, randomized, placebo-controlled, event-driven, noninferiority trial involved patients with type 2 diabetes and established atherosclerotic cardiovascular disease.[12] The protocol (available with the full text of this article at NEJM.org) was approved by the relevant regulatory authorities and ethics committees responsible for each trial site.

In collaboration with a group of academic investigators who comprised the scientific advisory committee, representatives of the sponsors (Merck Sharp & Dohme [a subsidiary of Merck] and Pfizer) designed and oversaw the conduct of the trial. A clinical research organization, Parexel International, selected and monitored the trial sites and managed and stored the data, with oversight from the sponsors. An independent, external data and safety monitoring committee monitored the interim unblinded data. Lists of the trial committee members, investigators, and sites are provided in Section S1 in the Supplementary Appendix, available at NEJM.org; information regarding data handling and quality assurance is provided in Section S2.

Analyses were performed by employees of Parexel International, and the results were independently confirmed by the sponsors with the use of original data. The academic authors ensured the accuracy and completeness of the data and were able to request additional analyses at their discretion. The first and last authors drafted the first version of the manuscript, and all the authors contributed to revisions. The decision to submit the manuscript for publication was made jointly by the authors, who vouch for the completeness and accuracy of the data and for the fidelity of the trial to the protocol.

Protocol Revision

As reported previously,[12] the original protocol was finalized in August 2013 and included a planned sample size of approximately 4000 patients. After the results of the Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients (EMPA-REG OUTCOME) became available,[6] the protocol was amended in March 2016 without knowledge of any interim results. The key changes were to double the sample size to approximately 8000 patients and to include efficacy objectives for superiority with respect to cardiovascular and renal outcomes. Patients who had been enrolled in the trial before the March 2016 amendment were designated as cohort 1, and those who were enrolled after the March 2016 amendment were designated as cohort 2.

Trial Population

A full list of the trial eligibility criteria is provided in Section S2. Patients were eligible if they were at least 40 years of age and had type 2 diabetes (with a glycated hemoglobin level of 7.0 to 10.5%) and established atherosclerotic cardiovascular disease involving the coronary, cerebrovascular, or peripheral arterial systems. Key exclusion criteria were a history of type 1 diabetes or ketoacidosis and an estimated glomerular filtration rate below 30 ml per minute per 1.73 m^2 of body-surface area. All the patients provided written informed consent.

Trial Procedures

Eligible patients were randomly assigned in a 1:1:1 ratio to receive 5 mg or 15 mg of ertugliflozin or matching placebo once daily, added to background standard-of-care treatment. Randomization was performed at a central location with the use of an interactive voice-response system and was based on a computer-generated schedule with randomly permuted blocks, stratified according to geographic region. The rationale for the selec-

tion of the ertugliflozin dose and a detailed description of the randomization criteria are provided in Section S2.

Doses of background antihyperglycemic medication were held constant for the initial 18 weeks of the trial except in the patients who met the criteria for glycemic rescue (Section S3) and those with clinically significant hypoglycemia. Patients who discontinued ertugliflozin or placebo prematurely were followed for outcomes, except if they withdrew consent or were lost to further follow-up. Extensive efforts were made to collect full outcome data from all the patients.

TRIAL OUTCOMES

The primary outcome, assessed in a time-to-event analysis, was a composite of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke (i.e., a major adverse cardiovascular event). The key secondary outcomes, assessed in time-to-event analyses and in a hierarchical statistical testing sequence, were a composite of death from cardiovascular causes or hospitalization for heart failure; death from cardiovascular causes; and a composite of death from renal causes, renal replacement therapy, or doubling of the serum creatinine level. Additional outcomes and definitions are provided in Section S4. All the primary and secondary outcome events were centrally adjudicated by a cardiovascular adjudication committee in a blinded manner. The trial included three glycemic substudies (results not reported here) (Section S5).

Changes from baseline in glycemic measures, body weight, and blood pressure were also assessed. Safety was assessed on the basis of adverse-event monitoring and, for certain adverse events (e.g., genital mycotic infection, hypovolemia, and amputations), on the basis of a priori definitions (Section S6).

STATISTICAL ANALYSIS

Sample size and power for the analyses of the primary and key secondary outcomes have been described previously[12]; the original sample-size calculation before the March 2016 protocol revision is outlined in Section S7. For the final sample-size calculation, we estimated that, with a total of 8000 patients, 939 primary major adverse cardiovascular events would be accrued in approximately 6.1 years. With the data from the two ertugliflozin dose groups pooled for analysis, the trial had approximately 96% power to show noninferiority of ertugliflozin to placebo (the primary objective) by ruling out a hazard ratio for major adverse cardiovascular events of 1.3, in accordance with guidelines from the FDA; the power was determined under the assumption of no difference between the trial groups (i.e., hazard ratio for major adverse cardiovascular events of 1.0). If noninferiority was shown for the primary outcome, then tests of superiority for the key secondary outcomes (a composite of death from cardiovascular causes or hospitalization for heart failure; death from cardiovascular causes; and a composite of death from renal causes, renal replacement therapy, or doubling of the serum creatinine level) were to be performed with the use of a sequentially rejective graphical testing procedure.[13]

The noninferiority analysis of the primary outcome was performed with data from all the patients who had undergone randomization and received at least one dose of ertugliflozin or placebo. For the patients who discontinued the assigned trial regimen prematurely, only major adverse cardiovascular events that occurred up to 365 days after the confirmed last dose were included in the primary analysis, in accordance with guidance from the FDA. Tests of superiority with respect to the secondary outcomes were performed on an intention-to-treat basis in all patients who had undergone randomization, with no limit on the time window for the ascertainment of outcomes. These analyses were also performed according to cohort (cohort 1 vs. cohort 2). Sensitivity analyses were performed with the use of an intention-to-treat approach and an on-treatment approach, in which confirmed events that occurred between the day of the first dose of ertugliflozin or placebo and 14 days after the last dose were included in the analysis (Section S7).

One preplanned interim analysis had been scheduled to evaluate efficacy and futility with the use of a Lan–DeMets alpha-spending function with an O'Brien–Fleming boundary to control the type I error rate[14]; this analysis took place after 715 major adverse cardiovascular events (73%) had accrued among the patients during treatment and up to 365 days after the last dose and after 351 deaths from cardiovascular causes had accrued among the patients in the intention-to-treat population. The trial was continued on the basis of the results of this interim analysis. The testing boundaries and confidence intervals for the final analyses were adjusted according to the actual alpha spent at the interim analysis (Section S7).

A stratified Cox proportional-hazards model that included the trial group as a covariate and cohort of enrollment as the stratification factor was used to evaluate the primary outcome. After adjustment for the interim analysis, the upper boundary of a two-sided 95.6% confidence interval for the hazard ratio was used for the noninferiority test. The Kaplan–Meier method was used to estimate the cumulative incidence (first occurrence) of an outcome event over time in each trial group. Additional details are provided in Section S7.

The data from the two ertugliflozin dose groups were prespecified to be pooled for the assessment of cardiovascular and renal outcomes. Individual trial-group responses are presented for safety outcomes. Safety analyses included all patients who had undergone randomization and received at least one dose of ertugliflozin or placebo.

RESULTS

PATIENTS

From December 2013 through July 2015 and from June 2016 through April 2017, a total of 8246 patients were enrolled in two cohorts (4023 patients in cohort 1 and 4223 patients in cohort 2). Patients were randomly assigned to receive ertugliflozin (5499 patients) or placebo (2747 patients) and were followed at 567 centers in 34 countries (Fig. 1). The reasons that some patients did not proceed to randomization after screening are listed in Table S1 in the Supplementary Appendix. A total of 8238 patients received at least one dose of ertugliflozin or placebo and were included in the noninferiority analysis of the primary outcome and in the analysis of safety.

The baseline characteristics of the patients were well balanced between the ertugliflozin group and the placebo group (Table 1). The mean age of the patients was 64.4 years, the mean duration of diabetes was 13.0 years, and the mean glycated hemoglobin level was 8.2%. Coronary artery disease was present in 75.9% of the patients, cerebrovascular disease in 22.9%, and peripheral arterial disease in 18.7%; a total of 23.7% had a history of heart failure. Use of cardiovascular and antihyperglycemic medications was largely balanced between the trial groups at baseline and also at the end of the trial, with the exception of diuretics, which were used more often in the placebo group than in the ertugliflozin group at the end of the trial (Table S2).

FOLLOW-UP

The final follow-up window was from September 2019 through December 2019; the last patient visit took place on December 27, 2019. The mean duration of follow-up was 3.5 years (4.3 years in cohort 1 and 2.7 years in cohort 2), and the corresponding median duration was 3.0 years (4.6 years in cohort 1 and 2.7 years in cohort 2). Ertugliflozin was administered over a mean period of 2.9 years, and placebo over a mean period of 2.8 years (Table S3). The trial regimen was permanently discontinued before trial completion — for reasons other than death — by 23.5% of the patients in the ertugliflozin group and by 27.9% of the patients in the placebo group (Table S4). Final vital status was known for 99.3% of the patients.

CARDIOVASCULAR AND RENAL OUTCOMES

A major adverse cardiovascular event (the primary outcome) occurred in 653 of 5493 patients (11.9%) in the ertugliflozin group and in 327 of 2745 patients (11.9%) in the placebo group (hazard ratio, 0.97; 95.6% confidence interval [CI], 0.85 to 1.11; $P<0.001$ for noninferiority) (Fig. 2A and Table 2). Death from cardiovascular causes or hospitalization for heart failure (the first key secondary outcome) occurred in 444 of 5499 patients (8.1%) in the ertugliflozin group and in 250 of 2747 patients (9.1%) in the placebo group (hazard ratio, 0.88; 95.8% CI, 0.75 to 1.03; $P=0.11$ for superiority) (Fig. 2B and Table 2). With respect to the other key secondary outcomes, the hazard ratio (ertugliflozin vs. placebo) for death from cardiovascular causes was 0.92 (95.8% CI, 0.77 to 1.11) (Fig. 2C and Table 2), and the hazard ratio for death from renal causes, renal replacement therapy, or doubling of the serum creatinine level was 0.81 (95.8% CI, 0.63 to 1.04) (Fig. 2D and Table 2).

The results for the other secondary outcomes that were not included in the testing hierarchy are provided in Table 2. The hazard ratio (ertugliflozin vs. placebo) for hospitalization for heart failure was 0.70 (95% CI, 0.54 to 0.90) (Table 2 and Fig. S1), and the hazard ratio for death from any cause was 0.93 (95% CI, 0.80 to 1.08). The results of sensitivity analyses (Tables S5 through S7) were generally consistent with those shown in Table 2. The results were also generally con-

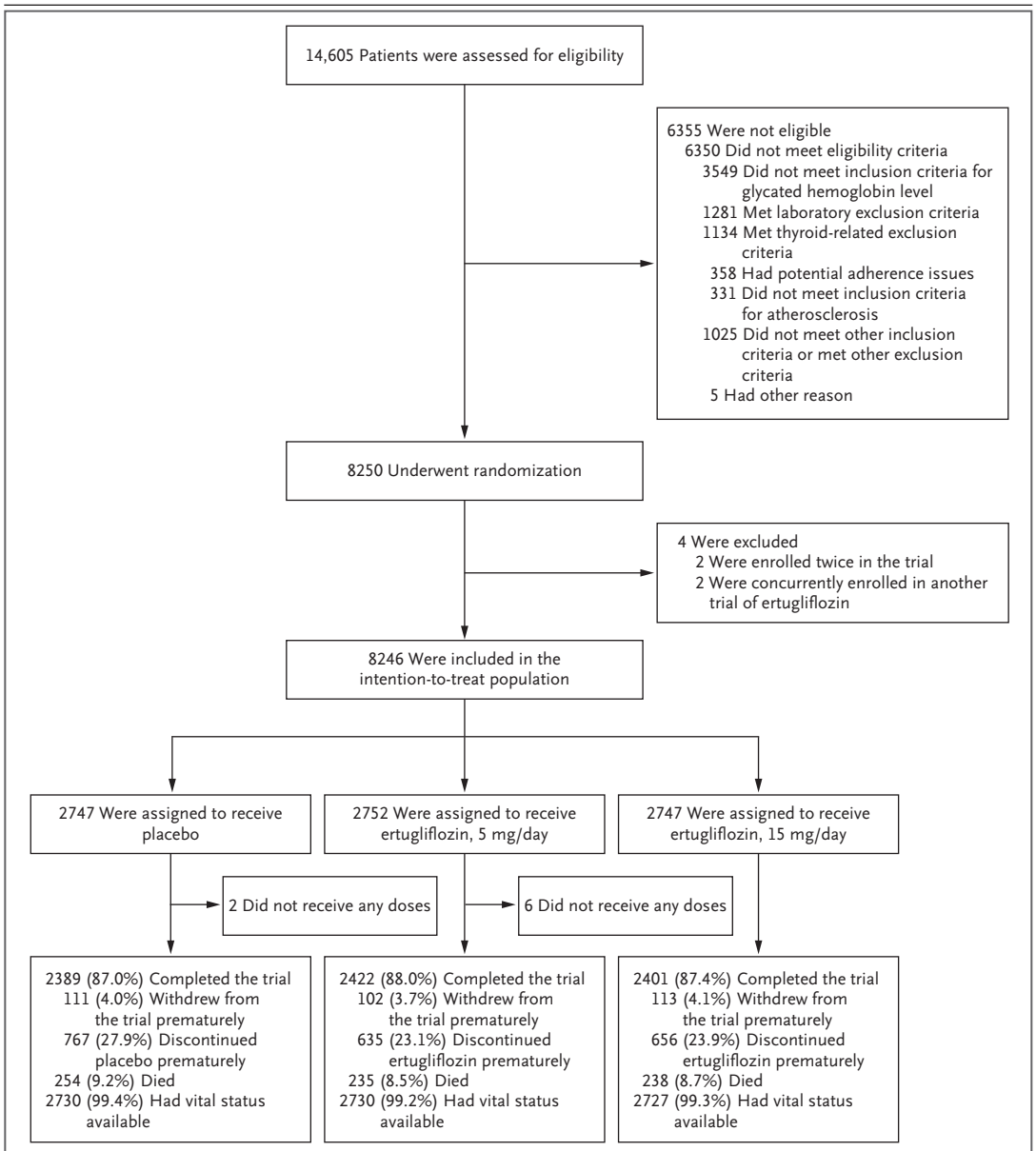

Figure 1. Screening, Randomization, and Follow-up.

Patients were counted only once in the calculation of the total number of patients who did not meet eligibility criteria, although a patient may be listed for more than one reason.

sistent across subgroups with regard to the primary outcome (Fig. S2) and the composite outcome of death from cardiovascular causes or hospitalization for heart failure (Fig. S3). The results for the two ertugliflozin dose groups, as compared with the placebo group, are provided in Figure S4 and Table S8.

METABOLIC RESULTS

At week 18, the least-squares mean difference from baseline in the glycated hemoglobin level was −0.70% (95% CI, −0.73 to −0.67) among the patients who received the 5-mg dose of ertugliflozin, −0.72% (95% CI, −0.75 to −0.69) among those who received the 15-mg dose of ertugliflozin, and −0.22% (95% CI, −0.25 to −0.19) among those who received placebo. The least-squares mean changes from baseline in glycated hemoglobin level, body weight, and systolic blood pressure over the trial period are shown in Figures S5 through S7. At 1 year, body weight had decreased by a mean (±SD) of 2.4±3.9 kg with the 5-mg

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

Characteristic	Ertugliflozin (N=5499)†	Placebo (N=2747)
Age — yr	64.4±8.1	64.4±8.0
Male sex — no. (%)	3866 (70.3)	1903 (69.3)
Race — no. (%)‡		
White	4826 (87.8)	2414 (87.9)
Black	166 (3.0)	69 (2.5)
Asian	336 (6.1)	162 (5.9)
Other	171 (3.1)	102 (3.7)
Region — no. (%)		
North America	1208 (22.0)	605 (22.0)
South America	484 (8.8)	239 (8.7)
Europe	3091 (56.2)	1546 (56.3)
Asia	350 (6.4)	173 (6.3)
South Africa	251 (4.6)	126 (4.6)
Australia and New Zealand	115 (2.1)	58 (2.1)
Body-mass index§	31.9±5.4	32.0±5.5
Duration of type 2 diabetes — yr¶	12.9±8.3	13.1±8.4
Glycated hemoglobin — %‖	8.2±1.0	8.2±0.9
Total cholesterol — mg/dl**	168.9±46.9	168.3±45.5
Low-density lipoprotein cholesterol — mg/dl††	89.3±38.5	88.8±37.7
High-density lipoprotein cholesterol — mg/dl‡‡	43.7±12.0	43.9±12.3
Triglycerides — mg/dl§§	181.4±119.2	178.9±104.7
Blood pressure — mm Hg¶¶		
Systolic	133.5±13.7	133.1±13.9
Diastolic	76.8±8.3	76.4±8.7
Estimated GFR — ml/min/1.73 m^2‖‖		
Mean value	76.1±20.9	75.7±20.8
Value of <60 ml/min/1.73 m^2 — no. (%)	1199 (21.8)	608 (22.1)
Coronary artery disease — no. (%)	4144 (75.4)	2112 (76.9)
Cerebrovascular disease — no. (%)	1276 (23.2)	613 (22.3)
Peripheral arterial disease — no. (%)	1029 (18.7)	512 (18.6)
Heart failure — no. (%)	1286 (23.4)	672 (24.5)
Myocardial infarction — no. (%)	2625 (47.7)	1329 (48.4)
Coronary revascularization — no. (%)	3179 (57.8)	1612 (58.7)
Coronary-artery bypass graft	1223 (22.2)	599 (21.8)
Percutaneous coronary intervention	2301 (41.8)	1184 (43.1)
Stroke — no. (%)	1181 (21.5)	558 (20.3)

* Plus–minus values are means ±SD. To convert the values for cholesterol to millimoles per liter, multiply by 0.02586. To convert the values for triglycerides to millimoles per liter, multiply by 0.01129. Percentage may not total 100 because of rounding.
† The data from the patients who received the 5-mg dose of ertugliflozin and from those who received the 15-mg dose were pooled.
‡ Race was reported by the patients.
§ Body-mass index is the weight in kilograms divided by the square of the height in meters. Data were available for 5496 patients in the ertugliflozin group and 2747 patients in the placebo group.
¶ Data were available for 5493 patients in the ertugliflozin group and 2745 patients in the placebo group.
‖ Data were available for 5474 patients in the ertugliflozin group and 2732 patients in the placebo group.
** Data were available for 5412 patients in the ertugliflozin group and 2703 patients in the placebo group.
†† Data were available for 5407 patients in the ertugliflozin group and 2698 patients in the placebo group.
‡‡ Data were available for 5411 patients in the ertugliflozin group and 2704 patients in the placebo group.
§§ Data were available for 5474 patients in the ertugliflozin group and 2734 patients in the placebo group.
¶¶ Data were available for 5481 patients in the ertugliflozin group and 2740 patients in the placebo group.
‖‖ The estimated glomerular filtration rate (GFR) was calculated with the Modification of Diet in Renal Disease equation. Data were available for 5498 patients in the ertugliflozin group and 2747 patients in the placebo group.

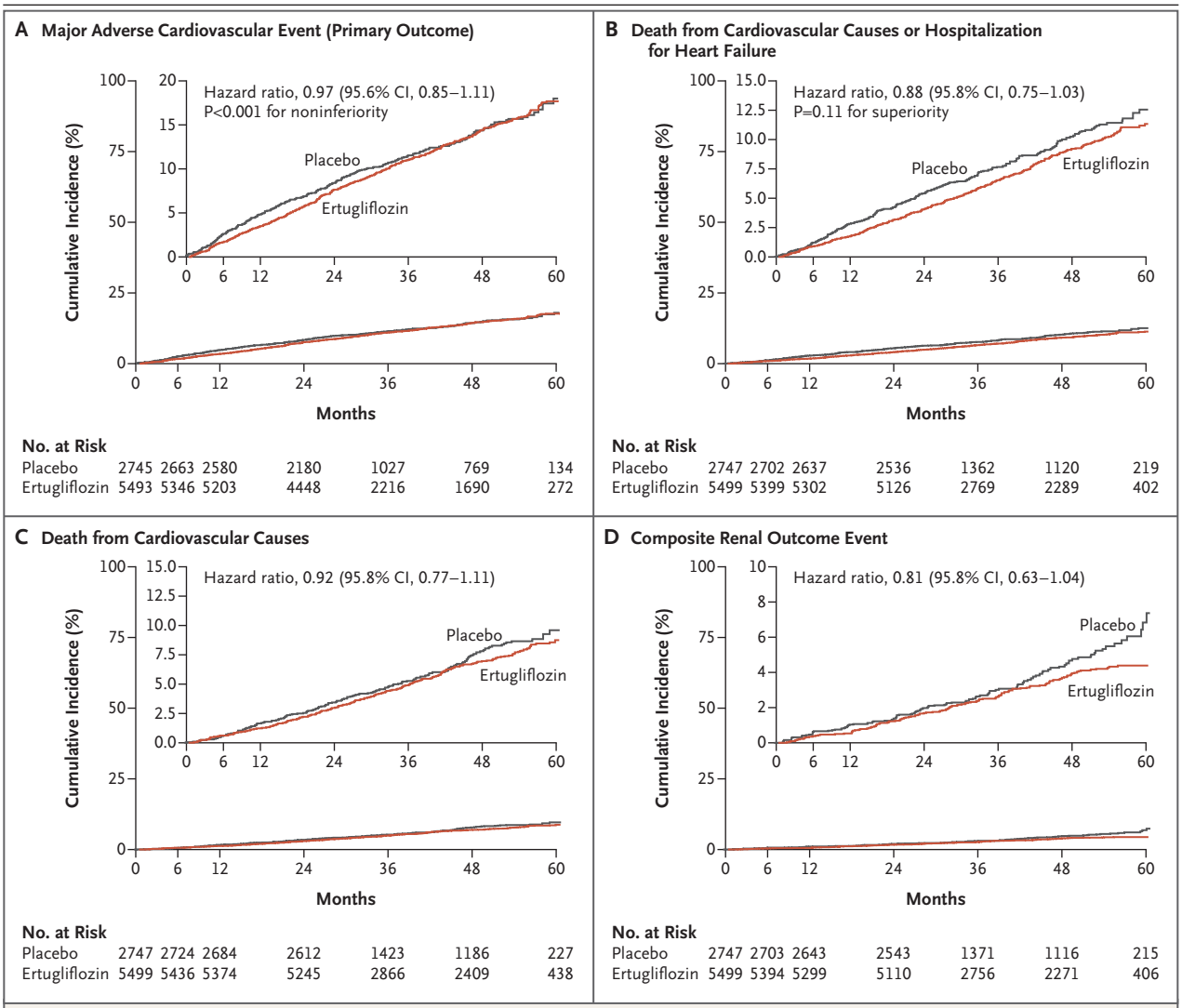

Figure 2. Primary and Key Secondary Outcomes.

Shown are Kaplan–Meier curves of the cumulative incidence (first occurrence) of a major adverse cardiovascular event, defined as a composite of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke (the primary outcome) (Panel A), and of key secondary outcome events that included a composite of death from cardiovascular causes or hospitalization for heart failure (Panel B), death from cardiovascular causes (Panel C), and a composite renal outcome event (death from renal causes, renal replacement therapy, or doubling of the serum creatinine level) (Panel D). The insets in each panel show the same data on an enlarged y axis. The noninferiority analysis of the primary outcome was performed with data from all the patients who had undergone randomization and received at least one dose of ertugliflozin (5493 patients) or placebo (2745 patients). For patients who discontinued the trial regimen prematurely, only major adverse cardiovascular events that occurred up to 365 days after the confirmed last dose were included in the primary analysis. The superiority analyses of the key secondary outcomes were performed on an intention-to-treat basis with data from all the patients who had undergone randomization to receive ertugliflozin (5499 patients) or placebo (2747 patients), with no limit on the time window for the ascertainment of outcomes.

dose of ertugliflozin and by 2.8±4.0 kg with the 15-mg dose of ertugliflozin, as compared with 0.4±3.6 kg with placebo.

SAFETY OUTCOMES

The incidence of serious adverse events and adverse events leading to permanent discontinuation of the trial regimen did not differ significantly between either ertugliflozin dose group and the placebo group (Table 3 and Table S9). More urinary tract infections and genital mycotic infections were reported in each of the ertugliflozin dose groups than in the placebo group. No cases of Fournier's gangrene were reported in any group. The incidence of serious acute kidney injury, serious urinary tract infection, hypovolemia,

Table 2. Primary and Secondary Outcomes.*

Outcome	Ertugliflozin†		Placebo		Hazard Ratio (CI)‡	P Value§
	no. of patients/ total no. (%)	*no. of events/ 100 patient-yr*	*no. of patients/ total no. (%)*	*no. of events/ 100 patient-yr*		
Primary outcome						
Death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke	653/5493 (11.9)	3.9	327/2745 (11.9)	4.0	0.97 (0.85–1.11)	<0.001
Key secondary outcomes						
Death from cardiovascular causes or hospitalization for heart failure	444/5499 (8.1)	2.3	250/2747 (9.1)	2.7	0.88 (0.75–1.03)	0.11
Death from cardiovascular causes	341/5499 (6.2)	1.8	184/2747 (6.7)	1.9	0.92 (0.77–1.11)	
Death from renal causes, renal replacement therapy, or doubling of the serum creatinine level	175/5499 (3.2)	0.9	108/2747 (3.9)	1.2	0.81 (0.63–1.04)	
Death from renal causes	0/5499	NA	0/2747	NA	NA	
Renal replacement therapy	7/5499 (0.1)	NA	3/2747 (0.1)	NA	NA	
Doubling of serum creatinine level	168/5499 (3.1)	NA	105/2747 (3.8)	NA	NA	
Other secondary outcomes						
Death from cardiovascular causes, nonfatal myocardial infarction, nonfatal stroke, or hospitalization for unstable angina	823/5499 (15.0)	4.5	439/2747 (16.0)	4.9	0.92 (0.82–1.04)	
Fatal or nonfatal myocardial infarction	330/5499 (6.0)	1.8	158/2747 (5.8)	1.7	1.04 (0.86–1.26)	
Fatal or nonfatal stroke	185/5499 (3.4)	1.0	87/2747 (3.2)	0.9	1.06 (0.82–1.37)	
Hospitalization for heart failure	139/5499 (2.5)	0.7	99/2747 (3.6)	1.1	0.70 (0.54–0.90)	
Nonfatal myocardial infarction	310/5499 (5.6)	1.7	148/2747 (5.4)	1.6	1.04 (0.86–1. 27)	
Nonfatal stroke	157/5499 (2.9)	0.8	78/2747 (2.8)	0.8	1.00 (0.76–1.32)	
Death from any cause	473/5499 (8.6)	2.4	254/2747 (9.2)	2.6	0.93 (0.80–1.08)	

* The noninferiority analysis of the primary outcome was performed with data from all the patients who had undergone randomization and received at least one dose of ertugliflozin (5493 patients) or placebo (2745 patients). For patients who permanently discontinued the trial regimen prematurely, only major adverse cardiovascular events (death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke) that occurred up to 365 days after the confirmed last dose were included in the primary analysis. The superiority analyses of the key secondary outcomes and the analyses of the other secondary outcomes were performed on an intention-to-treat basis with data from all the patients who had undergone randomization to receive ertugliflozin (5499 patients) or placebo (2747 patients), with no limit on the time window for the ascertainment of outcomes. NA denotes not available.

† The data from the patients who received the 5-mg dose of ertugliflozin and from those who received the 15-mg dose were pooled in the analyses of the primary and secondary outcomes.

‡ The hazard ratio for a primary outcome event is reported with a 95.6% confidence interval (adjusted to account for the interim analysis). The hazard ratio for a key secondary outcome event is reported with a 95.8% confidence interval (adjusted to account for the interim analysis). The hazard ratios for other secondary outcome events are reported with a 95% confidence interval.

§ A one-sided P value is shown for the test of noninferiority for the primary outcome, and a two-sided P value is shown for the test of superiority for the first key secondary composite outcome of death from cardiovascular causes or hospitalization for heart failure. The incidence of death from cardiovascular causes or hospitalization for heart failure (the first key secondary composite outcome) did not differ significantly between the trial groups; therefore, in accordance with the prespecified hierarchical testing procedure, further statistical testing of other outcomes was not performed.

fractures, or symptomatic or severe hypoglycemia did not differ significantly between either ertugliflozin dose group and the placebo group.

Amputations were performed in 54 patients (2.0%) who received the 5-mg dose of ertugliflozin and in 57 patients (2.1%) who received the 15-mg dose, as compared with 45 patients (1.6%) who received placebo (Table S10). Diabetic ketoacidosis occurred in 7 patients (0.3%) who received the 5-mg dose of ertugliflozin and in 12 patients (0.4%) who received the 15-mg dose, as compared with 2 patients (0.1%) who received placebo.

DISCUSSION

In this trial involving patients with type 2 diabetes and established atherosclerotic cardiovascular disease, ertugliflozin, when added to guideline-directed secondary prevention therapies, was shown to be noninferior to placebo with respect to major adverse cardiovascular events. The incidence of death from cardiovascular causes or hospitalization for heart failure (the first key secondary composite outcome) did not differ significantly between the trial groups; therefore, in accordance with the prespecified hierarchical testing procedure, further statistical testing of other outcomes was not performed.

We do not have a clear explanation about why our results did not reach significance, whereas significance was reached for many (but not all) end points in previous cardiovascular outcomes trials of SGLT2 inhibitors.[6-8] Our trial population of patients with atherosclerotic cardiovascular disease was broadly similar to those in previous trials, with rates of major adverse cardiovascular events of approximately 4% per year. In VERTIS CV, as compared with previous trials, the doses used were pharmacologically similar with regard to SGLT2 inhibition and the pharmacodynamic effects observed were similar with regard to the effects on glycated hemoglobin level, body weight, and blood pressure. However, differences exist among the trials, which might explain some differences in outcomes. Secular trends of more intensive secondary preventive therapies over recent years could have had a greater effect in our trial than in earlier trials. The selectivity of ertugliflozin for SGLT2 over SGLT1 is high and is similar to that of empagliflozin,[15] but we cannot exclude the possibility that differences among the agents in this class may result in real differences in outcomes. It is also possible that the effects of the individual agents are actually similar; the confidence intervals in VERTIS CV overlap those in previous trials.

Although the secondary outcome of hospitalization for heart failure was not tested statistically, the hazard ratio and confidence interval, as well as the time course of these adjudicated events, are consistent with the effects observed in previous trials of SGLT2 inhibitors.[6-8] In contrast, no significant benefit of ertugliflozin was observed for the renal composite outcome (death from renal causes, renal replacement therapy, or doubling of the serum creatinine level) in VERTIS CV, whereas previous trials of other SGLT2 inhibitors have shown consistent reductions in the risk of both albuminuria and clinical renal composite outcomes.[7,8,16] Moreover, in the CREDENCE (Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation) trial involving patients with type 2 diabetes, macroalbuminuria (defined as a urinary albumin-to-creatinine ratio of >300 to 5000, with albumin measured in milligrams and creatinine in grams), and an estimated glomerular filtration rate of 30 to less than 90 ml per minute per 1.73 m^2, the relative risk of the primary outcome (a composite of end-stage kidney disease, a doubling of the serum creatinine level, or death from renal or cardiovascular causes) was 30% lower with canagliflozin than with placebo.[17] Definitions of renal end points differ across trials, so further analyses of our trial with the use of these different end points are warranted.

The adverse events seen with ertugliflozin were consistent with the known risks of the medicines in the SGLT2 inhibitor class. As expected, genital mycotic infections occurred more frequently among women and among men in either ertugliflozin dose group than among those in the placebo group. The percentage of patients who underwent amputation was numerically — but not significantly — higher in either ertugliflozin dose group than in the placebo group, and the percentage of patients who had diabetic ketoacidosis was higher in either ertugliflozin dose group than in the placebo group (statistical testing was not performed).

In this multicenter, double-blind, randomized, controlled trial involving patients with type 2 diabetes and atherosclerotic cardiovascular disease, ertugliflozin was shown to be noninferior to placebo with respect to the composite out-

Table 3. Adverse Events.*

Adverse Event	Ertugliflozin, 5 mg (N = 2746)	Ertugliflozin, 15 mg (N = 2747)	Placebo (N = 2745)	Risk Difference, Ertugliflozin, 5 mg, vs. Placebo (95% CI)	P Value	Risk Difference, Ertugliflozin, 15 mg, vs. Placebo (95% CI)	P Value
	number of patients (percent)						
Any adverse event	2357 (85.8)	2325 (84.6)	2349 (85.6)	0.3 (–1.6 to 2.1)	—	–0.9 (–2.8 to 0.9)	—
Serious adverse event	958 (34.9)	937 (34.1)	990 (36.1)	1.2 (–3.7 to 1.4)	—	–2.0 (–4.5 to 0.6)	—
Adverse event leading to permanent discontinuation of the trial regimen	207 (7.5)	201 (7.3)	188 (6.8)	0.7 (–0.7 to 2.1)	—	0.5 (–0.9 to 1.8)	—
Adverse event leading to death	131 (4.8)	134 (4.9)	117 (4.3)	0.5 (–0.6 to 1.6)	—	0.6 (–0.5 to 1.7)	—
Selected adverse events							
Urinary tract infection	336 (12.2)	330 (12.0)	279 (10.2)	2.1 (0.4 to 3.7)	0.02	1.8 (0.2 to 3.5)	0.03
Serious urinary tract infection	25 (0.9)	12 (0.4)	22 (0.8)	—		—	
Genital mycotic infection in women†	48 (6.0)	65 (7.8)	20 (2.4)	3.6 (1.8 to 5.7)	<0.001	5.4 (3.4 to 7.7)	<0.001
Genital mycotic infection in men‡	86 (4.4)	98 (5.1)	22 (1.2)	3.3 (2.3 to 4.3)	<0.001	4.0 (2.9 to 5.1)	<0.001
Symptomatic hypoglycemia§	768 (28.0)	728 (26.5)	790 (28.8)	–0.8 (–3.2 to 1.6)	0.51	–2.3 (–4.6 to 0.1)	0.06
Severe hypoglycemia¶	136 (5.0)	148 (5.4)	162 (5.9)	–0.9 (–2.2 to 0.3)		–0.5 (–1.7 to 0.7)	
Hypovolemia	118 (4.3)	118 (4.3)	106 (3.9)	0.4 (–0.6 to 1.5)	0.42	0.4 (–0.6 to 1.5)	0.42
Acute kidney injury	48 (1.7)	53 (1.9)	60 (2.2)	–0.4 (–1.2 to 0.3)		–0.3 (–1.0 to 0.5)	
Serious acute kidney injury	24 (0.9)	18 (0.7)	22 (0.8)	—	—	—	—
Diabetic ketoacidosis‖**	7 (0.3)	12 (0.4)	2 (0.1)	—	—	—	—
Pancreatitis‖							
Acute	12 (0.4)	5 (0.2)	10 (0.4)	—	—	—	—
Chronic	1 (<0.1)	2 (0.1)	5 (0.2)	—	—	—	—
Fracture‖	99 (3.6)	102 (3.7)	98 (3.6)	—	—	—	—
Amputation	54 (2.0)	57 (2.1)	45 (1.6)	—	—	—	—
Hepatic events‖††	6 (0.2)	6 (0.2)	8 (0.3)	—	—	—	—

* Data are reported for patients who had one or more event and who had received at least one dose of ertugliflozin or placebo. All events occurred within 14 days after the final dose of ertugliflozin or placebo, including events that occurred after the initiation of glycemic rescue medication, with the exception of events of diabetic ketoacidosis, pancreatitis, fracture, and amputation. Events of diabetic ketoacidosis, pancreatitis, fracture, and amputation are reported for the patients who were included in the postrandomization follow-up period, which included all the patients who had available data after randomization, with no limit on the time window for the ascertainment of outcomes. The risk difference, 95% confidence interval, and P value are provided for certain prespecified events in accordance with the statistical analysis plan.

† A total of 798 women received the 5-mg dose of ertugliflozin, 832 received the 15-mg dose of ertugliflozin, and 844 received placebo.

‡ A total of 1948 men received the 5-mg dose of ertugliflozin, 1915 received the 15-mg dose of ertugliflozin, and 1901 received placebo.

§ Symptomatic hypoglycemia was defined as an event with clinical symptoms that were reported by the investigator as hypoglycemia (biochemical documentation not required).

¶ Severe hypoglycemia was defined as any episode of hypoglycemia for which assistance was needed.

‖ This event was adjudicated in a blinded manner by the independent adjudication committee for the specific adverse event (pancreatitis, fracture, or hepatic events) or by the internal review committee of sponsor representatives (diabetic ketoacidosis) (Section S6).

** Data are reported for the patients who were assessed as having a certain, probable, or possible likelihood of meeting the case definition of ketoacidosis.

†† Data are reported for the patients who were assessed as having a very likely, probable, or possible likelihood of causal association.

come of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke.

Supported by Merck Sharp & Dohme (a subsidiary of Merck) and Pfizer.

Dr. Cannon reports receiving grant support and consulting fees from Amgen, Boehringer Ingelheim, Bristol-Myers Squibb, and Janssen, grant support from Daiichi Sankyo, and consulting fees from Aegerion, Alnylam, Amarin, Applied Clinical Therapeutics, Ascendia, Corvidia, HLS Therapeutics, Innovent, Kowa, Sanofi, Eli Lilly, and Rhoshan; Dr. Pratley, receiving consulting fees, paid to AdventHealth, from AstraZeneca, Glytec, Merck, Mundipharma, Pfizer, Scohia Pharma, and Sun Pharmaceuticals, grant support, paid to AdventHealth, from Hanmi Pharmaceutical, Lexicon Pharmaceuticals, and Poxel, grant support and consulting fees, paid to AdventHealth, from Janssen and Sanofi, grant support, consulting fees, and lecture fees, all paid to AdventHealth, from Novo Nordisk, and consulting fees from Sanofi U.S.; Dr. Dagogo-Jack, receiving consulting fees from and leading clinical trials for AstraZeneca and Boehringer Ingelheim, receiving consulting fees from Janssen, Merck, and Sanofi, leading clinical trials for Novo Nordisk, and holding equity interest in Jana Care and Aerami Therapeutics; Dr. Charbonnel, receiving consulting fees, lecture fees, and travel support from AstraZeneca, Boehringer Ingelheim, Lilly, Merck Sharp & Dohme, Novo Nordisk, Sanofi, Takeda, and Mundipharma; Dr. Cosentino, receiving consulting fees from Abbott, AstraZeneca, Bayer, Bristol-Myers Squibb, Merck Sharp & Dohme, Novo Nordisk, Pfizer, and Mundipharma; Dr. Cherney, receiving advisory board fees and operating funds from AstraZeneca, Boehringer Ingelheim, Janssen, Merck, Sanofi, and Novo Nordisk, advisory board fees and consulting fees from Bayer, advisory board fees, consulting fees, and operating fees from Eli Lilly, and consulting fees from Prometic and Mitsubishi-Tanabe; and Dr. McGuire, receiving consulting fees and fees for serving on executive committees from Boehringer Ingelheim, Sanofi U.S., and AstraZeneca, fees for serving on a data monitoring committee from Janssen Research and Development, consulting fees, advisory board fees, and fees for serving on executive committees from Lilly USA and Novo Nordisk, fees for serving on a data monitoring committee from GlaxoSmithKline, fees for serving on executive committees from Lexicon and Eisai, fees for serving on a steering committee from Esperion, consulting fees from Metavant, Applied Therapeutics, and Afimmune, fees for serving on an executive committee from Pfizer, and fees for serving on an executive committee and advisory board fees from Merck Sharp & Dohme. No other potential conflict of interest relevant to this article was reported.

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 Gregory Golm, Ph.D., and Douglas S. Lee, Ph.D., for their contributions to the development of the trial protocol and for critical review of an earlier version of the manuscript and Marion James, Ph.D., of Engage Scientific Solutions for assistance with the formatting and submission of the manuscript for publication (funded by Merck and Pfizer).

APPENDIX

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