ORIGINAL ARTICLE

Bempedoic Acid and Cardiovascular Outcomes in Statin-Intolerant Patients

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ABSTRACT

BACKGROUND

Bempedoic acid, an ATP citrate lyase inhibitor, reduces low-density lipoprotein (LDL) cholesterol levels and is associated with a low incidence of muscle-related adverse events; its effects on cardiovascular outcomes remain uncertain.

METHODS

We conducted a double-blind, randomized, placebo-controlled trial involving patients who were unable or unwilling to take statins owing to unacceptable adverse effects ("statin-intolerant" patients) and had, or were at high risk for, cardiovascular disease. The patients were assigned to receive oral bempedoic acid, 180 mg daily, or placebo. The primary end point was a four-component composite of major adverse cardiovascular events, defined as death from cardiovascular causes, nonfatal myocardial infarction, nonfatal stroke, or coronary revascularization.

RESULTS

A total of 13,970 patients underwent randomization; 6992 were assigned to the bempedoic acid group and 6978 to the placebo group. The median duration of follow-up was 40.6 months. The mean LDL cholesterol level at baseline was 139.0 mg per deciliter in both groups, and after 6 months, the reduction in the level was greater with bempedoic acid than with placebo by 29.2 mg per deciliter; the observed difference in the percent reductions was 21.1 percentage points in favor of bempedoic acid. The incidence of a primary end-point event was significantly lower with bempedoic acid than with placebo (819 patients [11.7%] vs. 927 [13.3%]; hazard ratio, 0.87; 95% confidence interval [CI], 0.79 to 0.96; P=0.004), as were the incidences of a composite of death from cardiovascular causes, nonfatal stroke, or nonfatal myocardial infarction (575 [8.2%] vs. 663 [9.5%]; hazard ratio, 0.85; 95% CI, 0.76 to 0.96; P=0.006); fatal or nonfatal myocardial infarction (261 [3.7%] vs. 334 [4.8%]; hazard ratio, 0.77; 95% CI, 0.66 to 0.91; P=0.002); and coronary revascularization (435 [6.2%] vs. 529 [7.6%]; hazard ratio, 0.81; 95% CI, 0.72 to 0.92; P=0.001). Bempedoic acid had no significant effects on fatal or nonfatal stroke, death from cardiovascular causes, and death from any cause. The incidences of gout and cholelithiasis were higher with bempedoic acid than with placebo (3.1% vs. 2.1% and 2.2% vs. 1.2%, respectively), as were the incidences of small increases in serum creatinine, uric acid, and hepatic-enzyme levels.

CONCLUSIONS

Among statin-intolerant patients, treatment with bempedoic acid was associated with a lower risk of major adverse cardiovascular events (death from cardiovascular causes, nonfatal myocardial infarction, nonfatal stroke, or coronary revascularization). (Funded by Esperion Therapeutics; CLEAR Outcomes ClinicalTrials.gov number, NCT02993406.)

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*A list of the investigators in the CLEAR Outcomes trial is provided in the Supplementary Appendix, available at NEJM.org.

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Administration of statins to lower elevated levels of low-density lipoprotein (LDL) cholesterol is the cornerstone of contemporary therapy to reduce the risk of major adverse cardiovascular events in patients for whom primary or secondary prevention is clinically indicated.[1] However, 7 to 29% of patients report adverse musculoskeletal effects that prevent them from using statins or limit their ability to receive guideline-recommended doses.[2-4] Withdrawal from statin therapy is associated with an increased risk of adverse cardiovascular events.[5] Bempedoic acid is an ATP citrate lyase inhibitor that targets cholesterol synthesis upstream of 3-hydroxy-3-methylglutaryl coenzyme A reductase, the enzyme inhibited by statins.[6] Bempedoic acid is similar to statins in that it reduces hepatic cholesterol synthesis and raises LDL receptor expression, thereby increasing clearance of LDL cholesterol from the circulation.[6] However, bempedoic acid is a prodrug that is activated in the liver and not in most peripheral tissues, including skeletal muscle, a factor that may reduce the potential for adverse effects on muscles.[6-10]

In several studies, bempedoic acid reduced the level of LDL cholesterol by 17 to 28%, a finding that, in 2020, prompted its approval by the Food and Drug Administration and the European Medicines Agency for this indication.[9-12] However, data from randomized, controlled trials on the effects of bempedoic acid on cardiovascular events are lacking. We conducted the CLEAR (Cholesterol Lowering via Bempedoic Acid [ECT1002], an ACL-Inhibiting Regimen) Outcomes trial to determine the effects of bempedoic acid on adverse cardiovascular events in a mixed population of patients for whom primary or secondary prevention is clinically indicated but who were unable or unwilling to take guideline-recommended doses of statins.[13]

Methods

Trial Organization and Oversight

This double-blind, randomized, placebo-controlled trial involved patients at 1250 sites in 32 countries (see the Supplementary Appendix, available with the full text of this article at NEJM.org). The trial was designed by the sponsor, Esperion Therapeutics, in collaboration with the Cleveland Clinic Coordinating Center for Clinical Research (C5Research) and an academic executive committee. The protocol, available at NEJM.org, was approved by the ethics committees at the participating sites. A contract research organization collected the data. At completion of the trial, the database was transferred to C5Research, where statisticians conducted the data analyses. An independent data monitoring committee reviewed safety and efficacy data during the trial. The first author wrote the first draft of the manuscript, which was reviewed and approved by all the authors. The sponsor reviewed the manuscript and provided suggested revisions, but the final decision on content was reserved for the academic authors with no restrictions on the right to publish. The first author vouches for the accuracy and completeness of the data and for the fidelity of the trial to the protocol and statistical analysis plan, available with the protocol.

Trial Population

Patients 18 to 85 years of age were eligible if they met either of two criteria for increased cardiovascular risk — a previous cardiovascular event (secondary-prevention patients) or clinical features that placed them at high risk for a cardiovascular event (primary-prevention patients).[13] All the patients provided written informed consent. Eligible patients had to report being unable or unwilling to receive statins owing to an adverse effect that had started or increased during statin therapy and resolved or improved after statin therapy was discontinued ("statin-intolerant" patients). The patients were required to provide written confirmation that they were statin intolerant and aware of the benefits of statins in reducing the risk of cardiovascular events, including death, as well as acknowledge that many patients who are unable to receive an administered statin can receive a different statin or dose; the site investigators were also required to confirm and acknowledge these statements with respect to the patients. The form that was signed by the patients and site investigators is included in the Supplementary Appendix. Patients who were receiving a very low average daily statin dose (as defined in the Supplementary Appendix) without unacceptable adverse effects could be enrolled. Other lipid-lowering therapies were permitted, such as ezetimibe, niacin, bile acid resins, fibrates, or proprotein convertase subtilisin–kexin type 9 (PCSK9) inhibitors, administered as monotherapy or in combinations. Full

inclusion and exclusion criteria have been previously published[13] and are provided in the Supplementary Appendix.

RANDOMIZATION AND TRIAL REGIMENS

Eligible patients entered a 4-week run-in period during which they received single-blind placebo. If patients could not receive placebo because of unacceptable adverse effects or if adherence was less than 80% according to the tablet count, they were deemed to be ineligible for randomization. Patients who successfully completed the run-in period were randomly assigned in a 1:1 ratio to receive bempedoic acid at a daily oral dose of 180 mg or matching placebo. At 6 months after randomization, the central laboratory began to notify the investigator, who remained unaware of the trial-group assignments and laboratory values, if the LDL cholesterol level in a patient was 25% or higher than the baseline level. Such patients were counseled on healthy dietary guidelines and reminded to take all lipid-regulating medications. If repeat testing confirmed that the LDL cholesterol level exceeded the threshold, the investigator could adjust the lipid-lowering regimen according to the standard of care and local guidelines.

TRIAL END POINTS

The primary end point was a four-component composite of major adverse cardiovascular events, defined as death from cardiovascular causes, nonfatal myocardial infarction, nonfatal stroke, or coronary revascularization, as assessed in a time-to-first-event analysis. Key secondary end points, also assessed in a time-to-first-event analysis and tested in a hierarchical order, included a three-component composite of death from cardiovascular causes, nonfatal stroke, or nonfatal myocardial infarction; fatal or nonfatal myocardial infarction; coronary revascularization; fatal or nonfatal stroke; death from cardiovascular causes; and death from any cause. End points were adjudicated by the C5Research clinical end-points committee, the members of which were unaware of the trial-group assignments. Trial end-point definitions are provided in the Supplementary Appendix.

STATISTICAL ANALYSIS

This event-driven trial was designed to provide at least 90% power to detect a 15% reduction in the relative risk of a primary end-point event at an overall two-sided significance level of 0.05. For the trial to have 90% power, a minimum of 1620 primary end-point events were required to have occurred. At least 24 months of follow-up of all the patients and at least 810 key secondary end-point events were also required for study completion. We estimated that bempedoic acid or placebo would be administered for a median of 42 months and that the rate of loss to follow-up would be 1% per year. Assuming a 3.59% annual event rate in the placebo group, we calculated that for the event threshold to be reached, 12,600 patients would need to be enrolled, which was subsequently amended to 14,000 patients after hospitalization for unstable angina was omitted from the primary composite end point. No interim efficacy analyses were conducted. A hierarchical approach was prespecified to evaluate sequentially the primary end point and each of the six key secondary efficacy end points; statistical significance at each step was required to test the next hypothesis, thereby preserving the study-wise type I error rate at 5%. All efficacy analyses were based on the intention-to-treat principle. All efficacy end points were analyzed with the use of a Cox proportional-hazards model that included the trial-group assignment as a factor to generate the hazard ratio and 95% confidence interval. P values were obtained with the use of a two-sided log-rank test.

RESULTS

RANDOMIZATION, PATIENT CHARACTERISTICS, AND FOLLOW-UP

Between December 2016 and August 2019, a total of 13,970 patients underwent randomization; 6992 were assigned to the bempedoic acid group and 6978 to the placebo group. The flow of patients through the trial is shown in Figure S1 in the Supplementary Appendix. The baseline characteristics of the patients in the trial groups were similar (Table 1 and Table S1). The mean (±SD) age was 65.5±9.0 years, 6740 patients (48.2%) were female, 6373 (45.6%) had diabetes, 9764 (69.9%) had had a previous cardiovascular event, 3174 (22.7%) were taking a statin, and 1612 (11.5%) were receiving ezetimibe. The mean LDL-cholesterol level was 139.0 mg per deciliter (3.59 mmol per liter), the mean high-density lipoprotein cholesterol level 49.5 mg per deciliter

Table 1. Demographic and Baseline Patient Characteristics in the Intention-to-Treat Population.*

Characteristic	Bempedoic Acid (N=6992)	Placebo (N=6978)
Age		
Mean — yr	65.5±9.0	65.5±8.9
Distribution — no. (%)		
<65 yr	2859 (40.9)	2907 (41.7)
≥65 to <75 yr	3070 (43.9)	3027 (43.4)
≥75 yr	1063 (15.2)	1044 (15.0)
Female sex — no. (%)	3361 (48.1)	3379 (48.4)
White race — no. (%)†	6397 (91.5)	6335 (90.8)
Hispanic or Latinx — no. (%)†	1190 (17.0)	1143 (16.4)
Body-mass index‡	29.9±5.2	30.0±5.2
LDL cholesterol		
Mean value — mg/dl	139.0±34.9	139.0±35.2
Distribution — no. (%)		
<130 mg/dl	3074 (44.0)	3089 (44.3)
≥130 to <160 mg/dl	2213 (31.7)	2250 (32.2)
≥160 mg/dl	1705 (24.4)	1639 (23.5)
HDL cholesterol — mg/dl	49.6±13.3	49.4±13.3
Non-HDL cholesterol — mg/dl	173.8±39.5	173.9±40.2
Total cholesterol — mg/dl	223.5±40.6	223.3±41.1
Median triglycerides (IQR) — mg/dl	159.5 (118.0–216.5)	158.5 (118.0–215.0)
Median high-sensitivity CRP (IQR) — mg/liter	2.3 (1.2–4.5)	2.3 (1.2–4.5)
Estimated GFR — no. (%)		
≥90 ml/min/1.73 m^2	1216 (17.4)	1233 (17.7)
≥60 to <90 ml/min/1.73 m^2	4322 (61.8)	4282 (61.4)
≥30 to <60 ml/min/1.73 m^2	1437 (20.6)	1444 (20.7)
Cardiovascular risk category — no. (%)		
Primary prevention	2100 (30.0)	2106 (30.2)
Secondary prevention	4892 (70.0)	4872 (69.8)
Coronary artery disease	3574 (51.1)	3536 (50.7)
Peripheral arterial disease	794 (11.4)	830 (11.9)
Cerebrovascular atherosclerotic disease	1027 (14.7)	1040 (14.9)
Glycemic status — no. (%)		
Diabetes§	3144 (45.0)	3229 (46.3)
Inadequately controlled diabetes¶	1356 (19.4)	1369 (19.6)
Statin use — no. (%)	1601 (22.9)	1573 (22.5)
Ezetimibe use — no. (%)	803 (11.5)	809 (11.6)

* Plus–minus values are means ±SD. The intention-to-treat population included all the patients who underwent randomization. Percentages may not total 100 because of rounding. 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. CRP denotes C-reactive protein, GFR glomerular filtration rate, HDL high-density lipoprotein, IQR interquartile range, and LDL low-density lipoprotein.
† Race and Hispanic or Latinx ethnic group were reported by the patient.
‡ The body-mass index is the weight in kilograms divided by the square of the height in meters.
§ At baseline, diabetes was defined as a medical history of type 2 diabetes, previous use of glucose-lowering medication, a glycated hemoglobin measurement of 6.5% or greater, or two or more fasting glucose measurements of 126 mg per deciliter (7.0 mmol per liter) or greater at baseline.
¶ Inadequately controlled diabetes was defined as diabetes and a glycated hemoglobin level of 7.0% or greater at baseline.

(1.28 mmol per liter), the median triglyceride level 159.0 mg per deciliter (1.80 mmol per liter), and the median high-sensitivity C-reactive protein (CRP) level 2.3 mg per liter.

Patients were followed for a median of 40.6 months. Premature discontinuation of the trial regimen occurred in 2035 patients (29.1%) in the bempedoic acid group and in 2212 patients (31.7%) in the placebo group. The duration of exposure to bempedoic acid and to placebo was similar, with patients receiving the assigned regimen for 82.7% and 81.0%, respectively, of potential follow-up time. A complete assessment of the primary end point was available for 13,313 patients (95.3%), and vital status was available for 13,886 (99.4%). Data on the key efficacy end points at the trial sites in Ukraine were censored after the start of the conflict on February 24, 2022.

EFFECT ON LDL CHOLESTEROL AND HIGH-SENSITIVITY CRP

Observed data are reported without imputation unless otherwise noted. The effects of the trial regimens over time on LDL cholesterol and high-sensitivity CRP are shown in Figure 1. The mean LDL cholesterol level after 6 months of treatment with bempedoic acid was 107.0 mg per deciliter (2.77 mmol per liter), as compared with 136.0 mg per deciliter (3.52 mmol per liter) with placebo, for a difference of 29.2 mg per deciliter (0.76 mmol per liter); the observed difference in the percent reductions was 21.1 percentage points (95% confidence interval [CI], 20.3 to 21.9) in favor of bempedoic acid. At 6 months, the decrease in LDL cholesterol level, adjusted with the use of a pattern-mixture model for missing data, was 20.3 percentage points (Table 2). The time-averaged difference in the reduction in LDL cholesterol level between the bempedoic acid group and the placebo group over the duration of the trial was 22.0 mg per deciliter (0.57 mmol per liter); the difference in the percent reductions was 15.9 percentage points in favor of bempedoic acid. Among the patients in the placebo group, 15.6% received additional lipid-lowering therapy, as compared with 9.4% of the patients in the bempedoic acid group. At 6 months, the difference in the percent change in the median high-sensitivity CRP level was –21.6 percentage points (95% CI, –23.7 to –19.6) in favor of bempedoic acid. Data on the effects of the trial regimens on tertiary lipid biomarkers are provided in Table S2.

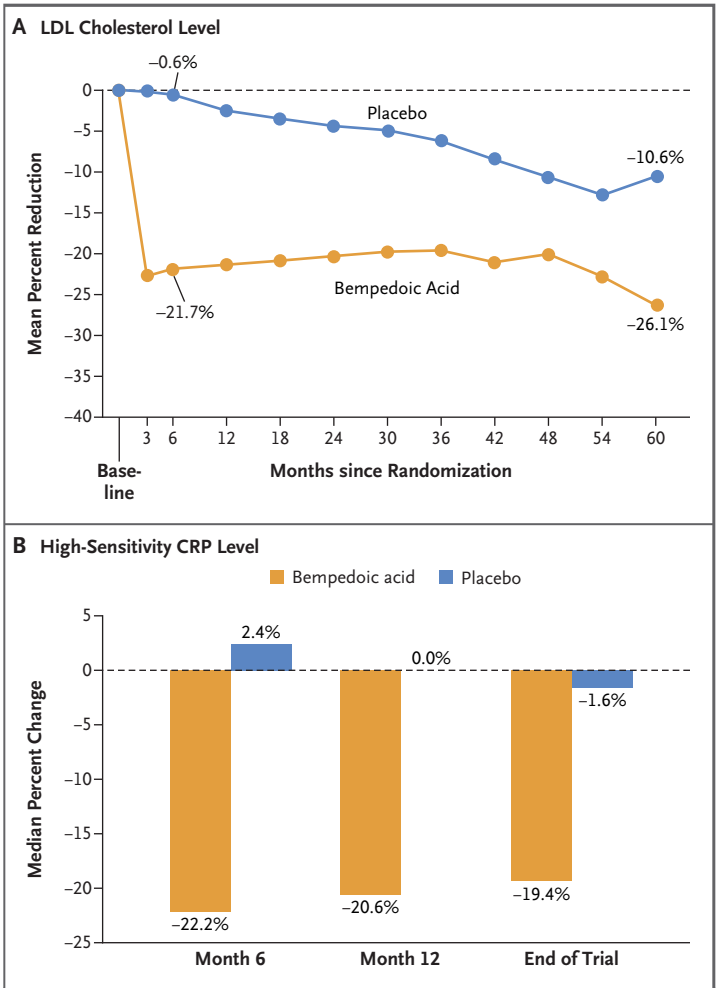


Figure 1. Changes in LDL Cholesterol and High-Sensitivity CRP Levels over Time.

Panel A shows the percent changes from baseline in the low-density lipoprotein (LDL) cholesterol level in the bempedoic acid group and placebo group throughout the trial. The mean baseline LDL cholesterol level in both groups was 139.0 mg per deciliter. The time-averaged difference in the reduction in LDL cholesterol level between the bempedoic acid group and the placebo group over the duration of the trial was –22.0 mg per deciliter (–0.57 mmol per liter); the difference in percent reduction was 15.9 percentage points in favor of bempedoic acid. To convert the values for cholesterol to millimoles per liter, multiply by 0.02586. Panel B shows the changes from baseline in the high-sensitivity C-reactive protein (CRP) level in the bempedoic acid group and placebo group at several time points during the trial. The median baseline high-sensitivity CRP was 2.3 mg per liter.

Table 2. Efficacy End Points in the Intention-to-Treat Population.*

Outcome	Bempedoic Acid (N=6992)	Placebo (N=6978)	Difference (95% CI)*	P Value†
Primary efficacy end point				
Four-component MACE — no. (%)‡	819 (11.7)	927 (13.3)	0.87 (0.79 to 0.96)	0.004
Key secondary efficacy end points				
Three-component MACE — no. (%)§	575 (8.2)	663 (9.5)	0.85 (0.76 to 0.96)	0.006
Fatal or nonfatal myocardial infarction — no. (%)	261 (3.7)	334 (4.8)	0.77 (0.66 to 0.91)	0.002
Coronary revascularization — no. (%)	435 (6.2)	529 (7.6)	0.81 (0.72 to 0.92)	0.001
Fatal or nonfatal stroke — no. (%)	135 (1.9)	158 (2.3)	0.85 (0.67 to 1.07)	0.16
Death from cardiovascular causes — no. (%)	269 (3.8)	257 (3.7)	1.04 (0.88 to 1.24)	
Death from any cause — no. (%)	434 (6.2)	420 (6.0)	1.03 (0.90 to 1.18)	
Additional secondary end points				
Death from any cause, nonfatal myocardial infarction, nonfatal stroke, or coronary revascularization — no. (%)	962 (13.8)	1062 (15.2)	0.89 (0.82 to 0.97)	
Five-component MACE — no. (%)¶	831 (11.9)	952 (13.6)	0.86 (0.78 to 0.94)	
Hospitalization for unstable angina — no. (%)	91 (1.3)	137 (2.0)	0.66 (0.50 to 0.86)	
New-onset type 2 diabetes mellitus — no./total no. (%)‖	429/3848 (11.1)	433/3749 (11.5)	0.95 (0.83 to 1.09)	
Change from baseline in secondary lipid and biomarker efficacy end points				
Mean percent change in mean LDL cholesterol level at 6 mo (95% CI)**	−21.1 (−21.6 to −20.5)	−0.8 (−1.4 to −0.2)	−20.3 (−21.1 to −19.5)	
Median percent change in high-sensitivity CRP level at 6 mo (95% CI)	−22.2 (−23.5 to −20.8)	2.4 (0.0 to 4.2)	−21.6 (−23.7 to −19.6)	
Mean percentage-point change in glycated hemoglobin level at 12 mo in patients with inadequately controlled type 2 diabetes mellitus (95% CI)**††	−0.04 (−0.12 to 0.03)	−0.01 (−0.09 to 0.06)	−0.03 (−0.14 to 0.08)	

* The patients were followed for a median of 40.6 months. Differences are given as the hazard ratio for the primary efficacy end point, the key secondary efficacy end points, and the additional secondary end points and as the percentage-point difference for the changes from baseline in secondary lipid and biomarker efficacy end points.
† As prespecified in the hierarchical testing procedure, all P values after the first nonsignificant P value are not presented.
‡ The primary efficacy end point was a four-component composite of adjudicated major adverse cardiovascular events (MACE), defined as death from cardiovascular causes, nonfatal myocardial infarction, nonfatal stroke, or coronary revascularization, as assessed in a time-to-first-event analysis.
§ The first key secondary end point was a three-component MACE, defined as death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke.
¶ The five-component MACE was defined as death from cardiovascular causes, nonfatal myocardial infarction, nonfatal stroke, coronary revascularization, or hospitalization for unstable angina.
‖ New-onset type 2 diabetes mellitus was defined as a glycated hemoglobin level of 6.5% or greater or two or more fasting glucose measurements of 126 mg per deciliter (7.0 mmol per liter) or greater in patients with a baseline glycemic status of no diabetes.
** Results were adjusted for baseline LDL cholesterol or glycated hemoglobin levels with the use of a pattern-mixture model for missing data.
†† Inadequately controlled type 2 diabetes was defined as type 2 diabetes and a glycated hemoglobin level of 7% or greater at baseline.

EFFICACY END POINTS

A primary end-point event (death from cardiovascular causes, nonfatal myocardial infarction, nonfatal stroke, or coronary revascularization) occurred in 819 patients (11.7%) in the bempedoic acid group and in 927 patients (13.3%) in the placebo group (hazard ratio, 0.87; 95% CI, 0.79 to 0.96; P=0.004) (Table 2 and Fig. 2A). The risk of events with respect to the first three key secondary end points was significantly lower with bempedoic acid than with placebo. Death from cardiovascular causes, nonfatal stroke, or nonfatal myocardial infarction (the first key secondary end point) occurred in 575 patients

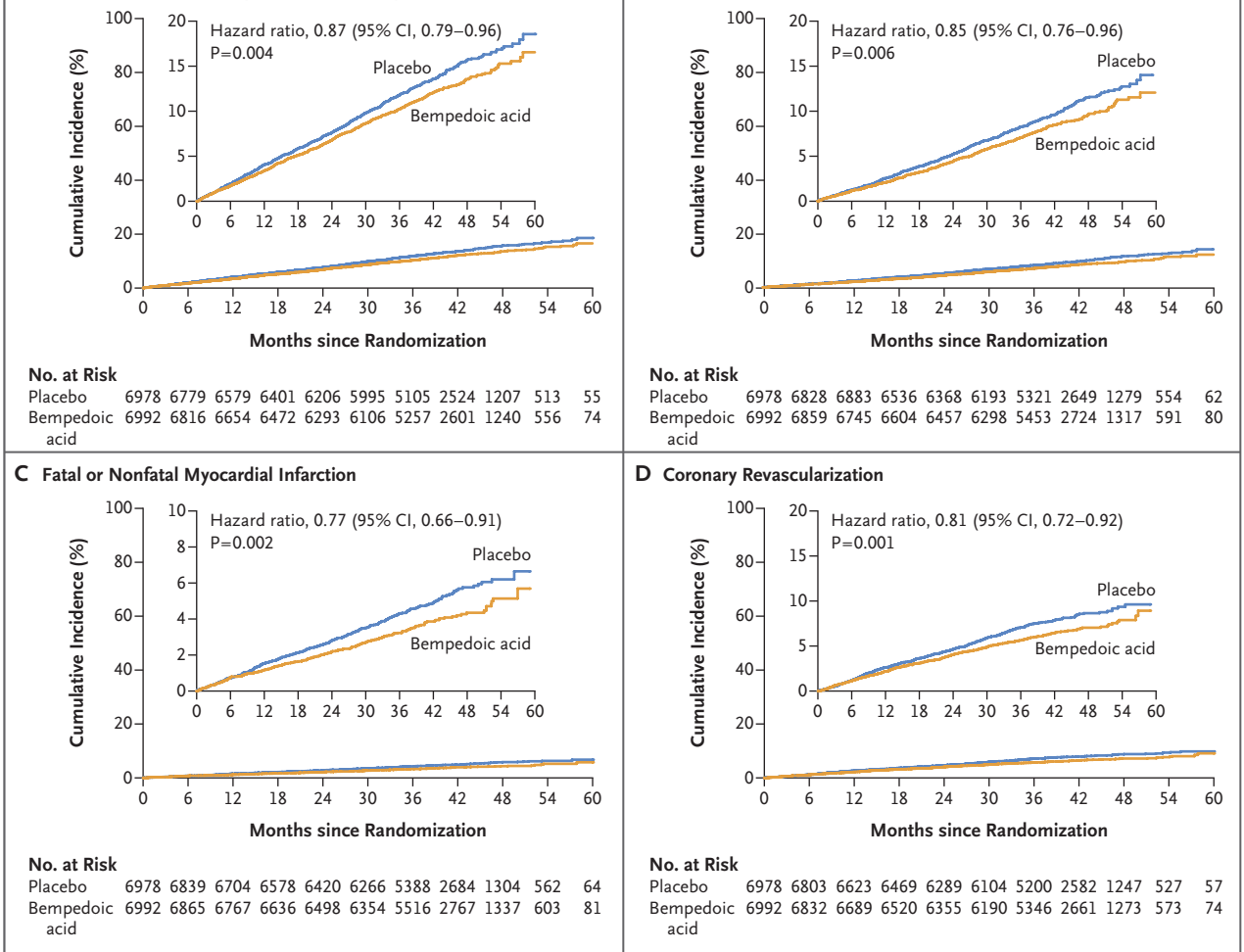


Figure 2. Cumulative Incidence of Cardiovascular Events.

Panel A shows the cumulative incidence of a primary end-point event, a four-component composite of major adverse cardiovascular events (MACE), defined as death from cardiovascular causes, nonfatal myocardial infarction, nonfatal stroke, or coronary revascularization. Panel B shows the cumulative incidence of a three-component MACE, defined as death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke (the first key secondary end point). Panel C shows the cumulative incidence of fatal or nonfatal myocardial infarction (the second key secondary end point). Panel D shows the cumulative incidence of coronary revascularization (the third key secondary end point). The definitions of all end points are provided in the Supplementary Appendix. In each panel, the inset shows the same data on an enlarged y axis. The P values were calculated with the use of the log-rank test.

(8.2%) in the bempedoic acid group and in 663 patients (9.5%) in the placebo group (hazard ratio, 0.85; 95% CI, 0.76 to 0.96; P=0.006) (Table 2 and Fig. 2B). Fatal or nonfatal myocardial infarction (the second key secondary end point) occurred in 261 patients (3.7%) in the bempedoic acid group and in 334 patients (4.8%) in the placebo group (hazard ratio, 0.77; 95% CI, 0.66 to 0.91; P=0.002) (Table 2 and Fig. 2C). Coronary revascularization (the third key secondary end point) occurred in 435 patients (6.2%) in the bempedoic acid group and in 529 patients (7.6%) in the placebo group (hazard ratio, 0.81; 95% CI, 0.72 to 0.92; P=0.001) (Table 2 and Fig. 2D). The results for the other key secondary end points (fatal or nonfatal stroke, death from cardiovascular causes, and death from any cause) did not differ significantly between the bempedoic acid

group and the placebo group (Table 2 and Fig. S2). Results of a prespecified subgroup analysis of the primary end point are provided in Figure S3.

ADVERSE EVENTS

Adverse events are reported in Table 3 and Table S3. The overall incidences of adverse events, serious adverse events, and adverse events leading to discontinuation of the trial regimen did not differ meaningfully between the bempedoic acid group and the placebo group. The incidences of investigator-reported prespecified adverse events of special interest were similar in the two trial groups except for elevations in the hepatic-enzyme level (4.5% in the bempedoic acid group vs. 3.0% in the placebo group) and renal events (11.5% in the bempedoic acid group vs. 8.6% in the placebo group). Myalgias were reported in 5.6% of the patients in the bempedoic acid group and in 6.8% of those in the placebo group. Investigators reported rhabdomyolysis in eight patients (0.06%), two of whom (one in each trial group) met the diagnostic criteria for rhabdomyolysis (Tables S4).[2] Elevations in liver aminotransferase levels of more than three times the upper limit of the normal range occurred more frequently in the bempedoic acid group than in the placebo group, and the mean changes from baseline in the creatinine and uric acid levels were greater in the bempedoic acid group. The incidence of hyperuricemia was higher in the bempedoic acid group than in the placebo group (10.9% vs. 5.6%), as were the incidences of gout (3.1% vs. 2.1%) and cholelithiasis (2.2% vs. 1.2%).

DISCUSSION

Among patients for whom primary or secondary prevention of cardiovascular disease is clinically indicated but who were unable or unwilling to take guideline-recommended doses of statins, the risk of a primary end-point event (death from cardiovascular causes, nonfatal myocardial infarction, nonfatal stroke, or coronary revascularization) was significantly lower by 13% with bempedoic acid than with placebo after a median of 40.6 months of follow-up, with an absolute between-group difference in incidence of 1.6 percentage points. Hierarchical testing of the first three key secondary end points also showed significant benefits with bempedoic acid over placebo. The risk of death from cardiovascular causes, nonfatal stroke, or nonfatal myocardial infarction (the first key secondary end point) was 15% lower with bempedoic acid than with placebo, and the risks of fatal or nonfatal myocardial infarction and coronary revascularization were 23% lower and 19% lower, respectively. At 6 months, the observed reduction in mean LDL cholesterol level in the bempedoic acid group was greater than that in the placebo group, and bempedoic acid reduced the high-sensitivity CRP level as compared with placebo.

Treatment with bempedoic acid appeared to lead to few adverse events, and the incidences of discontinuation for any reason, including adverse musculoskeletal effects, were similar to those with placebo. The occurrence of other prespecified adverse events of special interest, including new-onset or worsening of diabetes mellitus, hypoglycemia and metabolic acidosis, neurocognitive disorders, atrial fibrillation, tendinopathies including tendon rupture, and malignant conditions, did not differ meaningfully between the two trial groups. As previously reported, a reduction in the renal tubular excretion of uric acid and creatinine was observed in the bempedoic acid group, and the incidences of elevated hepatic-enzyme levels and gout were higher with bempedoic acid than with placebo.[9,10,14] The incidence of cholelithiasis was higher with bempedoic acid than with placebo, a finding that had not been observed in previous trials.

The observed lower incidence of cardiovascular events suggests that bempedoic acid is among the medications that lower the LDL cholesterol level and have clinically meaningful cardiovascular benefits. However, there are important differences between bempedoic acid and other LDL cholesterol–lowering drugs. Because bempedoic acid is a prodrug that requires activation by an enzyme (very-long-chain acyl-CoA synthetase 1) that is present primarily in the liver, the use of this drug may avoid the muscle-related adverse effects that are reported by some patients taking statins.[5-9] Because the incidence of reports of muscle-related adverse effects in the bempedoic acid group and placebo group was similar, the findings support the use of bempedoic acid as an alternative LDL cholesterol–lowering therapy in patients who are unable or unwilling to take statins.

The effects of bempedoic acid are consistent with the event reduction predicted in the meta-

analysis by the Cholesterol Treatment Trialists Collaboration.[15] The time-averaged reduction in LDL cholesterol level of 22.0 mg per deciliter over the duration of the trial would be expected to lead to the approximate relative reduction in the risk of cardiovascular events that was observed. The effects of bempedoic acid on cardiovascular outcomes were similar to those observed in other trials of LDL cholesterol–lowering nonstatin therapies. Two different PCSK9 inhibitors showed larger decreases in the LDL cholesterol level but only a 15% reduction in the risk of a primary end-point event (slightly different from that specified in our trial), which is potentially the result of the short median duration of treatment in both trials and the mandated reduction or discontinuation of therapy for LDL cholesterol levels deemed to be too low in the trial of alirocumab.[16,17] The effect size in the current trial was greater than the 6% reduction in the risk of cardiovascular events observed for a time-averaged difference of 16 mg per deciliter (0.41 mmol per liter) in the LDL cholesterol level with ezetimibe as compared with placebo during a follow-up of 6 years.[18] None of these LDL cholesterol–lowering nonstatin therapies, including bempedoic acid, reduced the risk of death from cardiovascular causes, which may reflect the effectiveness of contemporary adjunctive therapies, the need for a longer treatment duration to reduce this risk, or a lack of effect of the drugs on mortality.

Differences in effects were also observed between bempedoic acid and statins or other lipid-lowering nonstatin therapies. Unlike statins, bempedoic acid, as compared with placebo, did not increase glycated hemoglobin levels or the incidence of new-onset diabetes.[19] Six months of treatment with bempedoic acid resulted in a 21.6% reduction in the high-sensitivity CRP level relative to placebo. Although statins reduce the high-sensitivity CRP level, neither PCSK9 inhibitors nor ezetimibe monotherapy have shown reductions in biomarkers associated with inflammation. Further study is needed to determine whether the reduction in the high-sensitivity CRP level with bempedoic acid contributed to the observed benefits.

The trial enrolled a mixture of patients for whom primary or secondary prevention of cardiovascular disease is clinically indicated. Although the incidence of a primary end-point event was higher among the patients with preexisting cardiovascular disease, the hazard ratio in the primary-prevention subgroup was lower than that in the secondary prevention population. The results of the other prespecified subgroup analyses showed similar effects with respect to the primary efficacy end point. In our trial, women composed 48% of the patient population, a larger fraction of female patients than that in other recent cardiovascular outcome trials. The hazard ratio for a primary end-point event among women was similar to that among men. Subgroups analyses were not adjusted for multiplicity and therefore do not provide definitive conclusions.

In designing the current trial, we recognized that statins have shown major cardiovascular benefits in multiple clinical trials and are recommended by all global guidelines as the first-line treatment in patients at increased risk for adverse cardiovascular events. Thus, the patients who were considering participation in the trial were informed about the established benefits of statins and appropriately accepted the possibility of receiving placebo instead of the active drug. The concept of statin intolerance remains controversial, with some recent studies suggesting that reported adverse effects represent an anticipation of harm, often described as the nocebo effect.[20,21] Whether real or perceived, statin intolerance remains a vexing clinical problem that can prevent patients who are guideline-eligible for statin treatment from reaching LDL cholesterol levels associated with clinical benefits.[5] Accordingly, alternative nonstatin therapies are needed to manage the LDL cholesterol level in these patients.

A major limitation of our trial was the inclusion of only patients who had reported that they were unable or unwilling to take statins, a factor that resulted in a high mean LDL cholesterol level at baseline. The effects of bempedoic acid on cardiovascular events in populations with lower LDL cholesterol levels and in patients taking conventional therapeutic doses of statins were not studied.

In this randomized, placebo-controlled trial involving patients for whom primary or secondary prevention of cardiovascular disease is clinically indicated but who were unable or unwilling to take recommended doses of statins, treatment with bempedoic acid during a median follow-up

Table 3. Investigator-Reported Adverse Events and Laboratory Safety-Related Findings in the Safety Population.*

Event	Bempedoic Acid (N=7001)	Placebo (N=6964)
Any adverse event that started or worsened after the first dose of a trial agent — no. (%)	6040 (86.3)	5919 (85.0)
Serious adverse event that started or worsened after the first dose of a trial agent — no. (%)	1767 (25.2)	1733 (24.9)
Adverse event leading to discontinuation of the trial regimen — no. (%)	759 (10.8)	722 (10.4)
Prespecified adverse events of special interest		
Myalgia — no. (%)	393 (5.6)	471 (6.8)
Discontinuation of the trial regimen because of myalgia — no. (%)	124 (1.8)	129 (1.9)
New-onset diabetes in patients without diabetes at baseline — no./total no. (%)	621/3856 (16.1)	640/3740 (17.1)
New-onset diabetes in patients with prediabetes at baseline — no./total no. (%)†	569/2918 (19.5)	586/2877 (20.4)
New-onset diabetes in patients with normoglycemia at baseline — no./total no. (%)†	52/938 (5.5)	54/863 (6.3)
Worsening hyperglycemia — no./total no. (%)‡	713/3145 (22.7)	746/3224 (23.1)
Hypoglycemia — no. (%)	304 (4.3)	267 (3.8)
Metabolic acidosis — no. (%)	13 (0.2)	11 (0.2)
Elevated hepatic-enzyme level — no. (%)	317 (4.5)	209 (3.0)
Renal impairment — no. (%)	802 (11.5)	599 (8.6)
Neurocognitive disorders — no. (%)	58 (0.8)	69 (1.0)
Atrial fibrillation — no. (%)	229 (3.3)	246 (3.5)
Adjudicated tendon rupture — no. (%)	86 (1.2)	66 (0.9)
Tendinopathies — no. (%)	118 (1.7)	128 (1.8)
Malignant conditions — no. (%)	321 (4.6)	341 (4.9)
Other adverse events — no. (%)		
Hyperuricemia	763 (10.9)	393 (5.6)
Gout	215 (3.1)	143 (2.1)
Cholelithiasis	152 (2.2)	81 (1.2)
Laboratory results after 6 mo — mg/dl		
Change from baseline in uric acid level	0.76±1.2	−0.03±1.0
Change from baseline in creatinine level	0.05±0.2	0.01±0.2
Laboratory results after 12 mo		
Change from baseline in glycated hemoglobin level — %§	0.04±0.74	0.06±0.70
Abnormal enzyme level at any visit — no. (%)		
Creatine kinase level >5× ULN, single occurrence	45 (0.6)	40 (0.6)
Creatine kinase level >5× ULN, repeated and confirmed	8 (0.1)	8 (0.1)
Creatine kinase level >10× ULN, single occurrence	18 (0.3)	15 (0.2)
Creatine kinase level >10× ULN, repeated and confirmed	2 (<0.1)	4 (0.1)
Alanine aminotransferase level >3× ULN¶	83 (1.2)	53 (0.8)
Aspartate aminotransferase level >3× ULN¶	80 (1.1)	43 (0.6)

Table 3. (Continued.)

* Plus–minus values are means ±SD. The safety population included all patients who underwent randomization and received at least one dose of bempedoic acid or placebo; patients who received any dose of double-blind bempedoic acid were placed in the bempedoic acid group in the safety analyses. To convert the values for creatinine to micromoles per liter, multiply by 88.4. To convert the values for uric acid to micromoles per liter, multiply by 59.48. ULN denotes upper limit of the normal range.
† Prediabetes at baseline was defined as no medical history of diabetes plus a glycated hemoglobin level of 5.7 to less than 6.5% or one or more fasting glucose measurements of 100 mg per deciliter (5.6 mmol per liter) or greater but not more than one fasting glucose measurement of 126 mg per deciliter (7.0 mmol per liter) or greater. Patients with normoglycemia at baseline did not meet the criteria for prediabetes.
‡ Worsening hyperglycemia was assessed in patients with diabetes at baseline.
§ Change from baseline in the glycated hemoglobin level was not a prespecified safety measure.
¶ Measurements were repeated and elevations confirmed.

of 40.6 months significantly lowered the risk of major adverse cardiovascular events (death from cardiovascular causes, nonfatal myocardial infarction, nonfatal stroke, or coronary revascularization).

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APPENDIX

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REFERENCES

1. Grundy SM, Stone NJ, Bailey AL, et al. 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA guideline on the management of blood cholesterol: a report of the American College of Cardiology/American Heart Association Task Force on clinical practice guidelines. Circulation 2019;139(25):e1082-e1143.
2. Stroes ES, Thompson PD, Corsini A, et al. Statin-associated muscle symptoms: impact on statin therapy — European Atherosclerosis Society Consensus Panel statement on assessment, aetiology and management. Eur Heart J 2015;36:1012-22.
3. Bytyçi I, Penson PE, Mikhailidis DP, et al. Prevalence of statin intolerance: a meta-analysis. Eur Heart J 2022;43:3213-23.
4. Hovingh GK, Gandra SR, McKendrick J, et al. Identification and management of patients with statin-associated symptoms in clinical practice: a clinician survey. Atherosclerosis 2016;245:111-7.
5. Zhang H, Plutzky J, Shubina M, Turchin A. Continued statin prescriptions after adverse reactions and patient outcomes: a cohort study. Ann Intern Med 2017;167:221-7.
6. Pinkosky SL, Newton RS, Day EA, et al. Liver-specific ATP-citrate lyase inhibition by bempedoic acid decreases LDL-C and attenuates atherosclerosis. Nat Commun 2016;7:13457.
7. Thompson PD, Rubino J, Janik MJ, et al. Use of ETC-1002 to treat hypercholesterolemia in patients with statin intolerance. J Clin Lipidol 2015;9:295-304.
8. Ballantyne CM, Davidson MH, Macdougall DE, et al. Efficacy and safety of a novel dual modulator of adenosine triphosphate-citrate lyase and adenosine monophosphate-activated protein kinase in patients with hypercholesterolemia: results of a multicenter, randomized, double-blind, placebo-controlled, parallel-group trial. J Am Coll Cardiol 2013;62:1154-62.
9. Ray KK, Bays HE, Catapano AL, et al. Safety and efficacy of bempedoic acid to reduce LDL cholesterol. N Engl J Med 2019;380:1022-32.
10. Goldberg AC, Leiter LA, Stroes ESG, et al. Effect of bempedoic acid vs placebo added to maximally tolerated statins on low-density lipoprotein cholesterol in patients at high risk for cardiovascular disease: the CLEAR Wisdom randomized clinical trial. JAMA 2019;322:1780-8.
11. Ballantyne CM, Banach M, Mancini GBJ, et al. Efficacy and safety of bempedoic acid added to ezetimibe in statin-intolerant patients with hypercholesterolemia: a randomized, placebo-controlled study. Atherosclerosis 2018;277:195-203.
12. Laufs U, Banach M, Mancini GBJ, et al. Efficacy and safety of bempedoic acid in patients with hypercholesterolemia and statin intolerance. J Am Heart Assoc 2019;8(7):e011662-112.
13. Nicholls SJ, Lincoff AM, Bays HE, et al. Rationale and design of the CLEAR-out-

comes trial: evaluating the effect of bempedoic acid on cardiovascular events in patients with statin intolerance. Am Heart J 2021;235:104-12.
14. Bays HE, Banach M, Catapano AL, et al. Bempedoic acid safety analysis: pooled data from 4 phase 3 trials. J Clin Lipid. 2020;14:649-659.e6.
15. Cholesterol Treatment Trialists' (CTT) Collaborators. Efficacy and safety of more intensive lowering of LDL cholesterol: a meta-analysis of data from 170,000 participants in 26 randomised trials. Lancet 2010;376:1670-81.
16. Sabatine MS, Giugliano RP, Keech AC, et al. Evolocumab and clinical outcomes in patients with cardiovascular disease. N Engl J Med 2017;376:1713-22.
17. Schwartz GG, Steg PG, Szarek M, et al. Alirocumab and cardiovascular outcomes after acute coronary syndrome. N Engl J Med 2018;379:2097-107.
18. Cannon CP, Blazing MA, Giugliano RP, et al. Ezetimibe added to statin therapy after acute coronary syndromes. N Engl J Med 2015;372:2387-97.
19. Sattar N, Preiss D, Murray HM, et al. Statins and risk of incident diabetes: a collaborative meta-analysis of randomised statin trials. Lancet 2010;375:735-42.
20. Cholesterol Treatment Trialists' Collaboration. Effect of statin therapy on muscle symptoms: an individual participant data meta-analysis of large-scale, randomised, double-blind trials. Lancet 2022;400:832-45.
21. Wood FA, Howard JP, Finegold JA, et al. N-of-1 trial of a statin, placebo, or no treatment to assess side effects. N Engl J Med 2020;383:2182-4.
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