Evacetrapib and Cardiovascular Outcomes in High-Risk Vascular Disease

ORIGINAL ARTICLE

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ABSTRACT

BACKGROUND

The cholesteryl ester transfer protein inhibitor evacetrapib substantially raises the high-density lipoprotein (HDL) cholesterol level, reduces the low-density lipoprotein (LDL) cholesterol level, and enhances cellular cholesterol efflux capacity. We sought to determine the effect of evacetrapib on major adverse cardiovascular outcomes in patients with high-risk vascular disease.

METHODS

In a multicenter, randomized, double-blind, placebo-controlled phase 3 trial, we enrolled 12,092 patients who had at least one of the following conditions: an acute coronary syndrome within the previous 30 to 365 days, cerebrovascular atherosclerotic disease, peripheral vascular arterial disease, or diabetes mellitus with coronary artery disease. Patients were randomly assigned to receive either evacetrapib at a dose of 130 mg or matching placebo, administered daily, in addition to standard medical therapy. The primary efficacy end point was the first occurrence of any component of the composite of death from cardiovascular causes, myocardial infarction, stroke, coronary revascularization, or hospitalization for unstable angina.

RESULTS

At 3 months, a 31.1% decrease in the mean LDL cholesterol level was observed with evacetrapib versus a 6.0% increase with placebo, and a 133.2% increase in the mean HDL cholesterol level was seen with evacetrapib versus a 1.6% increase with placebo. After 1363 of the planned 1670 primary end-point events had occurred, the data and safety monitoring board recommended that the trial be terminated early because of a lack of efficacy. After a median of 26 months of evacetrapib or placebo, a primary end-point event occurred in 12.9% of the patients in the evacetrapib group and in 12.8% of those in the placebo group (hazard ratio, 1.01; 95% confidence interval, 0.91 to 1.11; P=0.91).

CONCLUSIONS

Although the cholesteryl ester transfer protein inhibitor evacetrapib had favorable effects on established lipid biomarkers, treatment with evacetrapib did not result in a lower rate of cardiovascular events than placebo among patients with high-risk vascular disease. (Funded by Eli Lilly; ACCELERATE ClinicalTrials.gov number, NCT01687998.)

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*A complete list of investigators in the Assessment of Clinical Effects of Cholesteryl Ester Transfer Protein Inhibition with Evacetrapib in Patients at a High Risk for Vascular Outcomes (ACCELERATE) trial is provided in the Supplementary Appendix, available at NEJM.org.

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Pharmacologic reduction of the low-density lipoprotein (LDL) cholesterol level with statins substantially decreases the risks of death and complications from cardiovascular causes.[1,2] Considerable interest has focused on the identification of approaches that might further reduce cardiovascular-event rates among high-risk patients.[3] Epidemiologic studies have shown inverse associations between high-density lipoprotein (HDL) cholesterol levels and cardiovascular outcomes,[4-6] a correlation that persists despite treatment with statins.[7] Nevertheless, therapeutic interventions that raise the HDL cholesterol level have not been shown to reduce cardiovascular risk.

Cholesteryl ester transfer protein (CETP) modulates the transfer of esterified cholesterol from HDL to apolipoprotein B–containing lipoproteins.[8] Two drugs that inhibit CETP were evaluated previously in trials that assessed cardiovascular outcomes. Treatment with one of these drugs, torcetrapib, in combination with atorvastatin, increased HDL cholesterol levels by approximately 70% from baseline and reduced LDL cholesterol levels by 25% but was associated with higher rates of death and cardiovascular events than the rates with atorvastatin alone, a finding that was thought to be a result of off-target toxic effects (increased blood pressure and increased plasma levels of aldosterone).[9] Treatment with the second drug, dalcetrapib, did not result in a lower rate of cardiovascular events than placebo among patients with a recent acute coronary syndrome, but it increased HDL cholesterol levels by only 30% from baseline and had no effect on LDL cholesterol levels.[10] Thus, the hypothesis that a potent CETP inhibitor might reduce the risk of cardiovascular events has not been tested definitively.

Evacetrapib is a CETP inhibitor with no evidence of torcetrapib-like off-target effects. In a phase 2 trial, evacetrapib increased HDL cholesterol levels by as much as 130% from baseline and reduced LDL cholesterol levels by nearly 35%.[11] In the Assessment of Clinical Effects of Cholesteryl Ester Transfer Protein Inhibition with Evacetrapib in Patients at a High Risk for Vascular Outcomes (ACCELERATE) trial, we tested the hypothesis that the addition of evacetrapib to standard medical therapy would result in a lower risk of death or complications from cardiovascular causes than placebo among patients with high-risk vascular disease.

Methods

Trial Design and Organization

We conducted this multicenter, randomized, double-blind, placebo-controlled, phase 3 event-driven trial at 543 sites in 36 countries. The trial design has been described previously.[12] The trial was sponsored by Eli Lilly and was coordinated by the Cleveland Clinic Coordinating Center for Clinical Research (C5Research) and Covance (Princeton, NJ). The trial protocol, which is available with the full text of this article at NEJM.org, was designed by the sponsor and the executive committee. The appropriate national and institutional regulatory and ethics boards approved the protocol. All the patients provided written informed consent.

The executive committee, together with physician national coordinators from each involved country, were responsible for the scientific conduct of the trial. An independent data and safety monitoring board had access to unblinded data. The sponsor shared responsibility for site selection, trial oversight, data collection, and regulatory oversight with C5Research and Covance. The clinical database was maintained by Covance and was subsequently transferred to C5Research for independent statistical analysis.

The first author wrote the first version of the manuscript and made revisions on the basis of input from the coauthors, including authors who were employees of the sponsor. The sponsor had no role in the decision to submit the manuscript for publication. All the authors vouch for the completeness and accuracy of the data and all analyses and for the fidelity of the trial to the protocol.

Trial Population

Patients were eligible for enrollment in the trial if they were 18 years of age or older and had high-risk vascular disease, which was defined as the presence of at least one of the following conditions: an acute coronary syndrome within the previous 30 to 365 days, cerebrovascular atherosclerotic disease, peripheral vascular arterial disease, or diabetes mellitus with coronary artery disease. Patients had to have been treated with a statin for at least 30 days before screening, unless they had documented unacceptable side effects from statins or had a contraindication to statins. Patients were required to have an HDL cholesterol level of less than 80 mg per deciliter (2.10 mmol per liter) and a triglyceride level of less than 400 mg

per deciliter (4.52 mmol per liter). The LDL cholesterol levels at enrollment were to be no more than 10 mg per deciliter (0.25 mmol per liter) above target levels that were specified at the investigator's discretion (a target LDL cholesterol level of <100 mg per deciliter [2.60 mmol per liter] or <70 mg per deciliter [1.80 mmol per liter]), unless the patient had already been receiving a maximum tolerated dose of statin for at least 30 days, had documented unacceptable side effects from statins, or had a contraindication to statin therapy. Key exclusion criteria were an acute coronary syndrome, stroke, or transient ischemic attack that had occurred within the previous 30 days or planned coronary angiography or revascularization. Full details of the inclusion and exclusion criteria are provided in the Supplementary Appendix, available at NEJM.org.

TRIAL REGIMEN

Patients were randomly assigned, in a 1:1 ratio, with the use of an interactive voice-response system to receive evacetrapib at an oral dose of 130 mg or matching placebo, administered daily, in addition to standard, guideline-based care for high-risk vascular disease and its risk factors. To avoid unblinding due to the anticipated effects of evacetrapib on lipid levels, the trial team remained unaware of the patients' lipid profiles, which were measured at a central laboratory. Although the investigators were generally not informed of the results of lipid testing at the central laboratory and lipid levels were not to be measured at local laboratories, investigators were informed if the LDL cholesterol levels exceeded specified targets to allow adjustment of lipid-lowering therapies.

END POINTS

The primary efficacy end point was the first occurrence of any component of the composite of death from cardiovascular causes, myocardial infarction, stroke, coronary revascularization, or hospitalization for unstable angina. Secondary efficacy end points, which were to be tested hierarchically, included the mean percent change from baseline in the HDL cholesterol level and the LDL cholesterol level at 3 months; the composite of death from cardiovascular causes, myocardial infarction, or stroke; all-cause mortality; and individual components of the primary efficacy end point. Specific safety measures included pulse; blood pressure; and adverse events, including laboratory markers of muscle injury or renal injury. An independent clinical-events committee, whose members were unaware of the trial-group assignments, adjudicated the end points of death, myocardial infarction, stroke, coronary revascularization, and hospitalization for unstable angina. Definitions of the components of the primary end point are provided in the Supplementary Appendix.

STATISTICAL ANALYSIS

We estimated an annual event rate of 5% for the primary end point in the placebo group on the basis of data from trials involving similar populations.[9,13-16] Under this assumption, we estimated that a sample of 12,000 patients, with an average of 3 years of follow-up, would provide the trial with 84% power to detect a risk of a composite end-point event that was 13.5% lower with evacetrapib than with placebo, using a log-rank test at a two-sided alpha level of 0.05 (additional details regarding the calculation of the sample size are provided in the Supplementary Appendix). The trial was to continue until all three of the following criteria were met: at least 1670 adjudicated primary composite end-point events had occurred; at least 700 adjudicated secondary composite end-point events of death from cardiovascular causes, myocardial infarction, or stroke had occurred; and at least 1.5 years had elapsed since the last patient underwent randomization.

No interim analysis for superiority was planned. A futility assessment was to be performed by the data and safety monitoring board after the adjudication of approximately 75% of the targeted composite end-point events, at which time the board could recommend that the trial be stopped early if the conditional power for a significant between-group difference in the risk of a composite end-point event at a two-sided alpha level of 0.05 by the end of the trial was less than 5%.

Analyses were based on the intention-to-treat population, which included all the patients who underwent randomization. Data from patients who withdrew consent or were lost to follow-up were censored at the time of withdrawal or at the time that the patient was last known to be free from having a composite end-point event. Kaplan–Meier time-to-event plots were constructed for clinical events, and clinical-event rates were summarized according to trial regimen. The trial regimens were compared with the use of a log-rank test. If the analysis of the primary end point showed that treatment with evacetrapib was associated with

a risk of a composite end-point event that was lower than the risk with placebo, secondary efficacy end points were subsequently to be evaluated hierarchically, guided by a gatekeeping testing strategy, with each hypothesis evaluated at a two-sided significance level of 0.05.

RESULTS

RANDOMIZATION, CHARACTERISTICS OF THE PATIENTS, AND FOLLOW-UP

From October 2012 through December 2013, a total of 12,092 patients underwent randomization; 6038 patients were assigned to receive evacetrapib and 6054 to receive placebo (Fig. S1 in the Supplementary Appendix). The demographic and clinical characteristics of the patients at baseline are summarized in Table 1. Approximately one third of the patients had had a recent acute coronary syndrome at a median of 5.6 months before randomization. More than 96% of the patients were receiving statin therapy at the time of randomization, and 46% were receiving a high-intensity statin, as defined according to current guidelines.[17] The mean baseline level of HDL cholesterol was 45.3 mg per deciliter (1.17 mmol per liter), and the mean baseline level of LDL cholesterol was 81.3 mg per deciliter (2.10 mmol per liter).

The data and safety monitoring board conducted an interim analysis for futility on October 7, 2015, after 1363 primary composite end-point events had been observed (82% of the expected number of events for the final analysis). A total of 691 events had occurred in the evacetrapib group and 672 in the placebo group (hazard ratio for a composite end-point event with evacetrapib vs. placebo, 1.03; 95% confidence interval [CI], 0.93 to 1.15; P=0.58). On the basis of these findings, the data and safety monitoring board recommended that the trial be stopped for futility. Both the executive committee and the sponsor accepted this recommendation, and the trial was terminated on October 12, 2015. At the completion of follow-up and the finalization of the trial database on April 6, 2016, a total of 1555 adjudicated primary end-point events had occurred (93% of the expected number of events for the final analysis).

The median overall duration of follow-up was 28 months (interquartile range, 26 to 30). Patients received their trial regimen for a median of 26 months (interquartile range, 23 to 29). Fewer patients discontinued the trial regimen prematurely in the evacetrapib group than in the placebo group (1025 patients [17.0%] vs. 1139 [18.8%], P=0.02) (Fig. S2 in the Supplementary Appendix). Complete end-point information was available for 11,860 patients (98.1%). Final vital status was unknown for 40 patients (0.3%), of whom 16 (0.1%) were lost to follow-up and 24 (0.2%) withdrew consent.

TRIAL OUTCOMES AND LIPID LEVELS

Changes in lipoprotein levels over the course of the trial are shown in Figure 1 and Table 2. At 3 months, patients who received evacetrapib had a mean percent increase from baseline in the HDL cholesterol level of 133.2%, as compared with a mean percent increase of 1.6% that was observed in patients who received placebo (between-group difference, 131.6 percentage points; 95% CI, 130.0 to 133.1; P<0.001). The mean LDL cholesterol level decreased by 31.1% in the evacetrapib group and increased by 6.0% in the placebo group (between-group difference, −37.1 percentage points; 95% CI, −38.1 to −36.1; P<0.001).

A primary efficacy end-point event of the composite of death from cardiovascular causes, myocardial infarction, stroke, coronary revascularization, or hospitalization for unstable angina occurred in 779 patients (12.9%) in the evacetrapib group and in 776 (12.8%) in the placebo group (hazard ratio, 1.01; 95% CI, 0.91 to 1.11; P=0.91) (Fig. 2 and Table 2). Because no significant difference was observed for the primary end point, the analyses of the secondary outcomes were considered to be exploratory (Table 2, and Figs. S3, S4, and S5 in the Supplementary Appendix). A secondary end-point event of the composite of death from cardiovascular causes, myocardial infarction, or stroke occurred in 437 patients (7.2%) in the evacetrapib group and in 453 (7.5%) in the placebo group (hazard ratio, 0.97; 95% CI, 0.85 to 1.10; P=0.59). The incidence of death from any cause (unadjusted for multiple comparisons) was significantly lower with evacetrapib than with placebo (P=0.04). No significant differences in the rates of other efficacy end points were observed between the two groups. No clinically relevant differences were observed between the two trial groups among prespecified subgroups in the intention-to-treat population that were defined according to baseline clinical characteristics, baseline lipid levels, or concomitant lipid-lowering therapies (Fig. S6 in the Supplementary Appendix).

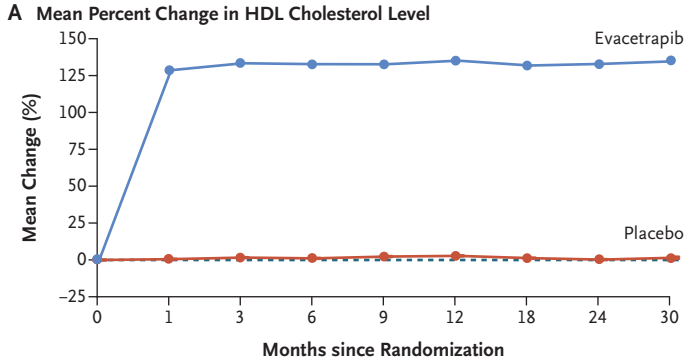
ADVERSE EVENTS AND OTHER SAFETY FINDINGS

Selected adverse events and laboratory values are presented in Table 3. Hypertension was reported

Table 1. Characteristics of the Patients at Baseline.*

Characteristic	Evacetrapib (N=6038)	Placebo (N=6054)
Age — yr	64.8±9.4	65.0±9.5
Male sex — no. (%)	4648 (77.0)	4660 (77.0)
Race — no./total no. (%)†		
White	4933/6008 (82.1)	4971/6021 (82.6)
Black	141/6008 (2.3)	153/6021 (2.5)
Asian	650/6008 (10.8)	640/6021 (10.6)
Other	284/6008 (4.7)	257/6021 (4.3)
Geographic region of enrollment — no. (%)		
United States or Canada	2861 (47.4)	2859 (47.2)
Europe	1683 (27.9)	1695 (28.0)
Asia	592 (9.8)	598 (9.9)
Rest of world‡	902 (14.9)	902 (14.9)
Index diagnosis§		
Acute coronary syndrome — no. (%)¶	1794 (29.7)	1851 (30.6)
Mean no. of months from acute coronary syndrome to randomization	5.5	5.7
Cerebrovascular atherosclerotic disease — no. (%)	730 (12.1)	710 (11.7)
Peripheral vascular arterial disease — no. (%)	855 (14.2)	819 (13.5)
Diabetes mellitus, type 1 or type 2 with coronary artery disease — no. (%)	3902 (64.6)	3889 (64.2)
Cardiovascular risk factor — no. (%)		
Hypertension	5272 (87.3)	5301 (87.6)
Diabetes mellitus, type 1 or type 2	4127 (68.4)	4109 (67.9)
Current smoking	1004 (16.6)	953 (15.7)
Previous myocardial infarction — no. (%)	3620 (60.0)	3637 (60.1)
Previous percutaneous coronary intervention — no. (%)	3849 (63.7)	3914 (64.7)
Previous coronary-artery bypass graft — no. (%)	1614 (26.7)	1572 (26.0)
Lipids		
HDL cholesterol — mg/dl	45.3±11.7	45.3±11.7
LDL cholesterol — mg/dl	81.6±28.4	81.1±27.8
Median triglycerides (IQR) — mg/dl	128 (95–179)	128 (94–178)
Apolipoprotein A1 — mg/dl	139.0±25.5	138.8±25.3
Apolipoprotein B — mg/dl	78.6±22.3	78.0±21.6
Median lipoprotein(a) (IQR) — nmol/liter	29.1 (11.1–106.8)	29.1 (10.8–108.1)
Median high-sensitivity C-reactive protein (IQR) — mg/liter	1.52 (0.75–3.3)	1.48 (0.74–3.3)
Systolic blood pressure — mm Hg	130.9±16.5	130.9±16.3
Medication — no. (%)		
Any statin	5819 (96.4)	5846 (96.6)
High-intensity statin‖	2749 (45.5)	2798 (46.2)
Medication to treat high blood pressure	5254 (87.0)	5306 (87.6)
Aspirin	5019 (83.1)	4988 (82.4)

* Plus–minus values are means ±SD. There were no significant differences between the trial groups in any of the characteristics evaluated at baseline (P<0.05). To convert the values for high-density lipoprotein (HDL) cholesterol and low-density lipoprotein (LDL) cholesterol to millimoles per liter, multiply by 0.02586. To convert the values for triglycerides to millimoles per liter, multiply by 0.01129. IQR denotes interquartile range.
† Race was determined by patient report.
‡ This category included Argentina, Australia, Brazil, Israel, Mexico, New Zealand, Russia, South Africa, Turkey, and Ukraine.
§ Patients could have had more than one index diagnosis.
¶ Patients had had an acute coronary syndrome within 30 to 365 days before randomization.
‖ A high-intensity statin was defined as the two highest dosages of atorvastatin (40 or 80 mg) or rosuvastatin (20 or 40 mg).



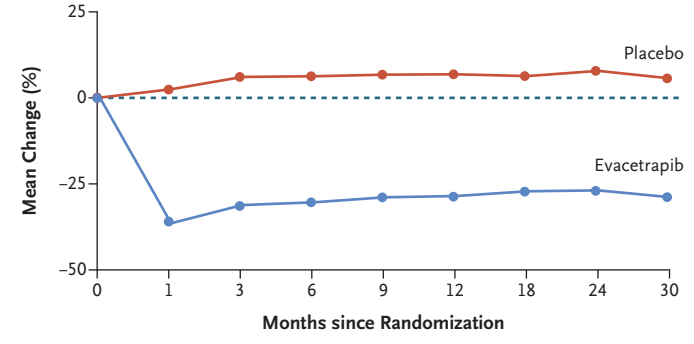
Mean Percent Change at 3 Mo

Evacetrapib, 133.2±57.2%

Placebo, 1.6±17.5%

Difference, 131.6 percentage points (95% CI, 130.0 to 133.1); P<0.001

	Baseline	At 3 Mo
Evacetrapib	45.3±11.7 mg/dl	104.1±31.4 mg/dl
Placebo	45.3±11.7 mg/dl	45.6±12.3 mg/dl



Mean Change at 3 Mo

Evacetrapib, −31.1±27.6%

Placebo, 6.0±29.0%

Difference, −37.1 percentage points (95% CI, −38.1 to −36.1); P<0.001

	Baseline	At 3 Mo
Evacetrapib	81.6±28.4 mg/dl	54.7±26.4 mg/dl
Placebo	81.1±27.8 mg/dl	83.7±30.8 mg/dl

Figure 1. Mean Percent Changes from Baseline in High-Density Lipoprotein (HDL) Cholesterol Levels and Low-Density Lipoprotein (LDL) Cholesterol Levels over Time.

Plus–minus values are means ±SD. To convert the values for cholesterol to millimoles per liter, multiply by 0.02586.

as an adverse event in a significantly higher percentage of patients in the evacetrapib group than in the placebo group (11.4% vs. 10.1%, P=0.02). The mean (±SD) absolute change from baseline in the systolic blood pressure was slightly greater in the evacetrapib group than in the placebo group (1.2±14.4 mm Hg vs. 0±14.3 mm Hg, P<0.001). The median percent increase from baseline in the level of high-sensitivity C-reactive protein was greater in the evacetrapib group than in the placebo group (8.6% [interquartile range, −27.0 to 63.3] vs. 0% [interquartile range, −32.1 to 52.4], P<0.001). A lower percentage of patients in the evacetrapib group than in the placebo group had an increase in the creatine kinase level of 3 or more times the upper limit of the normal range (2.4% vs. 3.1%). There were no other clinically relevant differences between the two trial groups with respect to safety variables.

DISCUSSION

The ACCELERATE trial evaluated whether the potent inhibition of CETP by evacetrapib, when added to standard-of-care therapy in patients with high-risk vascular disease, would improve long-term cardiovascular outcomes. Evacetrapib was associated with a mean decrease in the LDL cholesterol level that was 37.1 percentage points greater than the change with placebo and with a mean increase in the HDL cholesterol level that was 131.6 percentage points greater than the increase with placebo. Despite these favorable changes in the lipoprotein levels, treatment with evacetrapib did not result in a lower risk of death from cardiovascular causes, myocardial infarction, stroke, coronary revascularization, or hospitalization for unstable angina.

Several lines of evidence have provided a rationale for the idea that pharmacologic inhibition of CETP might reduce the risk of cardiovascular outcomes. Epidemiologic studies consistently correlate higher HDL cholesterol levels with fewer cardiovascular events.[4-7] Genetic polymorphisms that reduce CETP activity increase HDL cholesterol levels and have been associated with lower risks of cardiovascular outcomes in some, but not all, studies.[18-21] Pharmacologic inhibition of CETP in animal models that express this protein has been shown to reduce atherosclerosis.[22] Previous clinical investigations have not adequately tested this treatment strategy. Treatment with torcetrapib was limited by off-target toxic effects that led to higher blood pressure and worse cardiovascular outcomes than were observed in the placebo group.[9] Treatment with dalcetrapib resulted in only small increases in the HDL cholesterol level and had no effect on the LDL cholesterol level.[10]

We had anticipated that the marked effects of evacetrapib on lipid levels would position the ACCELERATE trial to assess decisively the effect of CETP inhibition on clinical outcomes. In a

Table 2. Primary and Secondary Efficacy End-Point Events and Lipid Effects.

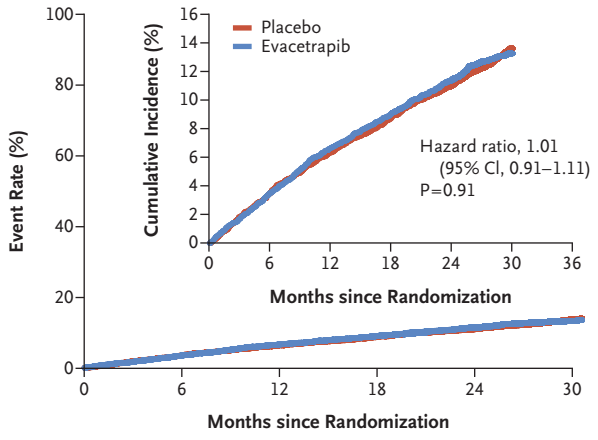
Event or Laboratory Variable	Evacetrapib (N=6038)	Placebo (N=6054)	Hazard Ratio (95% CI)	P Value*
Primary composite end point — no. (%)†	779 (12.9)	776 (12.8)	1.01 (0.91 to 1.11)	0.91
Death from cardiovascular causes	143 (2.4)	166 (2.7)	0.86 (0.69 to 1.08)	0.19
Myocardial infarction	258 (4.3)	259 (4.3)	1.00 (0.84 to 1.18)	0.97
Stroke	94 (1.6)	98 (1.6)	0.96 (0.72 to 1.27)	0.77
Hospitalization for unstable angina	155 (2.6)	146 (2.4)	1.06 (0.85 to 1.33)	0.60
Coronary revascularization	487 (8.1)	485 (8.0)	1.01 (0.89 to 1.14)	0.94
Secondary composite end point — no. (%)‡	437 (7.2)	453 (7.5)	0.97 (0.85 to 1.10)	0.59
All-cause mortality — no. (%)	231 (3.8)	276 (4.6)	0.84 (0.70 to 1.00)	0.04
Lipids — % change§				
HDL cholesterol	133.2±57.2	1.6±17.5	—	<0.001
LDL cholesterol	−31.1±27.6	6.0±29.0	—	<0.001
Median triglycerides (IQR)	−6.0 (−24 to 16.7)	0 (−17.7 to 22.8)	—	<0.001
Apolipoprotein A1	50.5±30.8	1.1±21.5	—	<0.001
Apolipoprotein B	−15.5±22.3	3.8±22.0	—	<0.001
Median lipoprotein(a) (IQR)	−22.3 (−50.6 to 0)	0 (−15.4 to 14.9)	—	<0.001

* P values were calculated with the use of a log-rank test.
† The primary composite end point was the first occurrence of any component of the composite of death from cardiovascular causes, myocardial infarction, stroke, coronary revascularization, or hospitalization for unstable angina in the time-to-event analysis. Data for all end-point events, irrespective of whether the event was the patient's first occurrence of the event, are shown.
‡ The secondary composite end point was the first occurrence of any component of the composite of death from cardiovascular causes, myocardial infarction, or stroke in the time-to-event analysis.
§ The percent change is the difference between the values at baseline and month 3, divided by the baseline value, and multiplied by 100.

Table 3. Adverse Events, Laboratory Findings, and Blood Pressure.*

Variable	Evacetrapib (N=6038)	Placebo (N=6054)	P Value†
Hypertension — no. (%)‡	686 (11.4)	609 (10.1)	0.02
Torsades de pointes or QT prolongation — no. (%)	45 (0.7)	59 (1.0)	0.17
Basal-cell carcinoma — no. (%)	109 (1.8)	84 (1.4)	0.07
Squamous-cell carcinoma — no. (%)	38 (0.6)	35 (0.6)	0.72
Prostate cancer — no./total no. (%)	30/4648 (0.6)	40/4658 (0.9)§	0.23
Creatine kinase ≥3× ULN — no./total no. (%)	141/5993 (2.4)	188/6007 (3.1)	0.01
Alanine aminotransferase ≥3× ULN — no./total no. (%)	34/5993 (0.6)	43/6007 (0.7)	0.31
Total bilirubin ≥2× ULN — no./total no. (%)	7/5995 (0.1)	16/6007 (0.3)	0.06
Absolute change in blood pressure — mm Hg			
Systolic	1.2±14.4	0±14.3	<0.001
Diastolic	0.4±8.4	−0.1±8.4	0.01
Median high-sensitivity C-reactive protein (IQR) — % change at 3 months	8.6 (−27.0 to 63.3)	0 (−32.1 to 52.4)	<0.001

* ULN denotes upper limit of the normal range.
† P values were calculated with the use of the chi-square test.
‡ The broad classification of hypertension was reported as an adverse event.
§ Data were missing for two men.



No. at Risk						
Placebo	6054	5825	5629	5455	4977	1629
Evacetrapib	6038	5816	5603	5438	4959	1626

Figure 2. Cumulative Kaplan–Meier Estimates of Time to First Occurrence of a Primary Composite End-Point Event.

The primary efficacy end point was the first occurrence of any component of the composite of death from cardiovascular causes, myocardial infarction, stroke, coronary revascularization, or hospitalization for unstable angina in the time-to-event analysis. The cumulative incidence (inset) is the percentage of patients in each trial group who had at least one primary composite end-point event over the course of the trial.

phase 2 trial, evacetrapib was associated with an increase from baseline in the HDL cholesterol level of as much as 130% and with a decrease in the LDL cholesterol level of nearly 35%,[11] changes that were similar to those seen in our trial. The changes in the HDL cholesterol levels included an increase in lipid-depleted pre-beta HDL particles.[23] Treatment with evacetrapib in a phase 2 trial also resulted in an increase in cellular cholesterol efflux capacity by means of ATP-binding cassette transporter A1 (ABCA1) and non-ABCA1 mechanisms.[23] The negative results of the current trial therefore reinforce the principle that biologic plausibility and beneficial effects on surrogate end points do not obviate the need for adequately powered outcome trials of new therapeutic agents.

Several explanations are possible as to why evacetrapib did not result in a lower risk of cardiovascular events than placebo in this trial. Epidemiologic associations between the HDL cholesterol level and the risk of cardiovascular events have been observed primarily in patients who were healthy initially. Beneficial vascular effects of HDL particles, such as cholesterol efflux capacity, may be attenuated in patients who have coronary artery disease or acute coronary syndromes, as compared with healthy trial participants, and a number of mechanisms have been proposed regarding the possible causes of such HDL dysfunction.[24,25] Alternatively, some clinicians have expressed concern that the inhibition of CETP pathways may produce HDL particles that are dysfunctional,[26] although the protective effects of genetic loss-of-function polymorphisms of CETP do not support this hypothesis. The profile of change in HDL lipid particles and the enhancement of cellular cholesterol efflux with evacetrapib suggest that the HDL cholesterol produced by this agent should be functional, but this concept of functionality[27,28] has yet to be validated as a predictor of therapeutic benefit. Moreover, HDL particles possess other properties that are thought to be vasoprotective,[24] and the effect of CETP inhibition on these properties is unknown.

Even if HDL cholesterol is dismissed as a modifiable risk factor in patients with vascular disease, it is surprising that the decrease of 37 percentage points in the LDL cholesterol level that was observed with evacetrapib, as compared with placebo, in this trial did not result in a beneficial effect on cardiovascular events. This magnitude of reduction in the LDL cholesterol level is commensurate with the magnitude that has been observed with moderate-intensity statin therapy and that would be expected to produce an approximately 15% lower risk of major coronary events.[2] It is conceivable that mechanisms of reduction in the LDL cholesterol level that are specific to CETP inhibition, in contrast to the LDL cholesterol–receptor up-regulation that is induced by statins and ezetimibe, affect LDL cholesterol in ways that do not influence cardiovascular risk. Although treatment with evacetrapib has resulted in reductions of 60 to 70% in the levels of small dense LDL particles,[29] effects on the total number of LDL particles and on apolipoprotein B levels (reductions of 22% and 20%, respectively) are considerably less pronounced. The effect on the atherogenicity of the polydisperse LDL cholesterol pattern in association with CETP deficiency or inhibition remains unknown.[30]

We cannot exclude the possibility that CETP inhibition or evacetrapib itself produced an unmeasured toxic effect that offset the beneficial lipid effects. The observed mean increase in systolic blood pressure that was associated with evacetrapib in this trial (1.2 mm Hg) was small as compared with the increase of 5.4 mm Hg that was induced by torcetrapib in an earlier trial[9] and

was unlikely to be of sufficient magnitude to worsen cardiovascular outcomes directly. Nevertheless, this finding may be a marker of more profound adverse neuroendocrine or vasomotor effects. Similarly, patients who received evacetrapib had a slight increase in the level of C-reactive protein, which, although small, contrasts with the effects of statins[31] and may signal heightened inflammatory responses to CETP inhibition.

The 2-year duration of treatment with evacetrapib in this trial may have been insufficient to show a benefit of lipid modification by means of CETP inhibition. However, previous trials of statins in high-risk patients have shown a divergence of time-to-event curves as early as 3 to 6 months after the initiation of therapy,[14,32-34] and the 24% reduction in the LDL cholesterol level that was associated with ezetimibe was reflected in a divergence of survival curves by 1 year.[35] In contrast, time-to-event curves showed no hint of separation over the course of the entire 26-month follow-up of the current trial. Thus, it seems unlikely that a beneficial effect of evacetrapib would have been revealed if treatment had been continued for a longer period.

In conclusion, we compared evacetrapib with placebo in patients who had high-risk vascular disease. Treatment with evacetrapib was associated with an increase in the HDL cholesterol level and a reduction in the LDL cholesterol level that were both significant and substantial, but evacetrapib treatment did not have a beneficial effect on cardiovascular outcomes.

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APPENDIX

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