ORIGINAL ARTICLE

Effects of Anacetrapib in Patients with Atherosclerotic Vascular Disease

The HPS3/TIMI55–REVEAL Collaborative Group*

ABSTRACT

BACKGROUND

Patients with atherosclerotic vascular disease remain at high risk for cardiovascular events despite effective statin-based treatment of low-density lipoprotein (LDL) cholesterol levels. The inhibition of cholesteryl ester transfer protein (CETP) by anacetrapib reduces LDL cholesterol levels and increases high-density lipoprotein (HDL) cholesterol levels. However, trials of other CETP inhibitors have shown neutral or adverse effects on cardiovascular outcomes.

METHODS

We conducted a randomized, double-blind, placebo-controlled trial involving 30,449 adults with atherosclerotic vascular disease who were receiving intensive atorvastatin therapy and who had a mean LDL cholesterol level of 61 mg per deciliter (1.58 mmol per liter), a mean non-HDL cholesterol level of 92 mg per deciliter (2.38 mmol per liter), and a mean HDL cholesterol level of 40 mg per deciliter (1.03 mmol per liter). The patients were assigned to receive either 100 mg of anacetrapib once daily (15,225 patients) or matching placebo (15,224 patients). The primary outcome was the first major coronary event, a composite of coronary death, myocardial infarction, or coronary revascularization.

RESULTS

During the median follow-up period of 4.1 years, the primary outcome occurred in significantly fewer patients in the anacetrapib group than in the placebo group (1640 of 15,225 patients [10.8%] vs. 1803 of 15,224 patients [11.8%]; rate ratio, 0.91; 95% confidence interval, 0.85 to 0.97; P=0.004). The relative difference in risk was similar across multiple prespecified subgroups. At the trial midpoint, the mean level of HDL cholesterol was higher by 43 mg per deciliter (1.12 mmol per liter) in the anacetrapib group than in the placebo group (a relative difference of 104%), and the mean level of non-HDL cholesterol was lower by 17 mg per deciliter (0.44 mmol per liter), a relative difference of –18%. There were no significant between-group differences in the risk of death, cancer, or other serious adverse events.

CONCLUSIONS

Among patients with atherosclerotic vascular disease who were receiving intensive statin therapy, the use of anacetrapib resulted in a lower incidence of major coronary events than the use of placebo. (Funded by Merck and others; Current Controlled Trials number, ISRCTN48678192; ClinicalTrials.gov number, NCT01252953; and EudraCT number, 2010-023467-18.)

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Evidence from large-scale, randomized trials has shown that each reduction of 40 mg per deciliter (1 mmol per liter) in the level of low-density lipoprotein (LDL) cholesterol reduces the risk of coronary events (including coronary death, myocardial infarction, and revascularization procedures) and ischemic stroke by approximately one quarter during each year after the first year of administration (when the effect is smaller).[1] Moreover, further reductions in LDL cholesterol levels have been shown to produce additional reductions in cardiovascular risk.[2-4] Nevertheless, these risks remain high among persons with atherosclerotic vascular disease.[3-5] Although higher levels of high-density lipoprotein (HDL) cholesterol are associated with a lower risk of vascular events, previous trials have not shown that raising HDL cholesterol levels reduces risk.[5,6]

Cholesteryl ester transfer protein (CETP) facilitates the exchange of cholesteryl esters and triglycerides between HDL particles and atherogenic particles containing apolipoprotein B in the blood.[7] Pharmacologic inhibition of CETP can produce substantial increases in HDL cholesterol levels, along with reductions in levels of non-HDL cholesterol (particularly LDL cholesterol). However, previous randomized clinical outcomes trials of CETP inhibitor therapy were stopped after approximately 2 years of follow-up because of either hazards associated with the therapy or an apparent lack of efficacy.[8-10]

Anacetrapib is a potent CETP inhibitor that has been found to have an acceptable side-effect profile in previous, smaller studies.[11,12] Here, we report the findings of the phase 3 Randomized Evaluation of the Effects of Anacetrapib through Lipid Modification (REVEAL) trial, which assessed the clinical efficacy and safety of anacetrapib (at a dose of 100 mg once daily) for approximately 4 years among more than 30,000 patients with preexisting atherosclerotic vascular disease who were receiving effective statin therapy.[13]

Methods

Trial Organization and Oversight

The trial was designed and conducted by independent investigators (supported by the British Heart Foundation and Medical Research Council) in the Clinical Trial Service Unit at the University of Oxford (the regulatory trial sponsor), Oxford, United Kingdom, in collaboration with the Thrombolysis in Myocardial Infarction (TIMI) Study Group at Brigham and Women's Hospital and Harvard Medical School in Boston, along with other members of the steering committee and Merck. Merck also funded the trial and provided the trial drugs. The trial protocol, available with the full text of this article at NEJM.org, was approved by all the relevant institutional review boards and regulatory authorities. The trial design, methods, and recruitment activities, which build on those of previous Heart Protection Study (HPS) trials conducted by the Clinical Trial Service Unit at the University of Oxford, have been reported previously.[13]

The manuscript was prepared by the writing committee and was then reviewed and approved by all voting members of the steering committee. Merck provided comments on the draft manuscript but otherwise had no role in the preparation of the manuscript or in the decision to submit it for publication. The first and last members of the writing committee vouch for the completeness and accuracy of the data and for the fidelity of the trial to the protocol.

Patients

Men and women who were older than 50 years of age were considered to be eligible if they had a history of myocardial infarction, cerebrovascular atherosclerotic disease, peripheral-artery disease, or diabetes with symptomatic coronary heart disease. Key exclusion criteria were an acute coronary event or stroke less than 3 months before randomization; a planned coronary revascularization procedure; clinically significant liver, kidney, inflammatory muscle, or other disease; current treatment with a fibrate, niacin, or any drug contraindicated with anacetrapib or atorvastatin; a previous adverse reaction to a statin; and known poor adherence to clinic visits or medication.[13] All the patients provided written informed consent.

Trial Procedures

All eligible patients entered a prerandomization run-in phase in which atorvastatin was administered with the intention of reducing the LDL cholesterol level to below 77 mg per deciliter (2.0 mmol per liter).[13] After 8 to 12 weeks, patients were excluded if they no longer met the eligibility criteria, had not adhered to the atorvastatin regimen, or had a total cholesterol level of more than 155 mg per deciliter (4.0 mmol per

liter), as measured by means of a desktop chemical assay (Reflotron Plus, Roche Diagnostics). Eligible patients were then assigned with the use of minimized randomization[14] to receive 100 mg of anacetrapib once daily or matching placebo in addition to the atorvastatin regimen.

Routine follow-up visits were scheduled at 2 and 6 months after randomization, and then every 6 months until the end of the trial. All serious adverse events (including potential trial outcomes), nonserious adverse events attributed to a trial drug or resulting in its discontinuation, and any symptoms of muscle pain or weakness or suggestive of hepatitis were recorded. All other nonserious adverse events were recorded for the patients in North America only. Blood pressure was measured at every visit with the use of an Omron BP760 or an equivalent local model (see the Methods section in Supplementary Appendix 1, available at NEJM.org). Blood samples were checked for evidence of liver or muscle injury at every visit. At selected visits, samples were sent for central analysis (including of blood lipids) and archiving.[13]

PRIMARY AND SECONDARY OUTCOMES

The prespecified primary outcome was the first major coronary event (a composite of coronary death, myocardial infarction, or coronary revascularization). Secondary outcomes were major atherosclerotic events (a composite of coronary death, myocardial infarction, or presumed ischemic stroke), presumed ischemic stroke (i.e., not known to be hemorrhagic), and major vascular events (a composite of major coronary events or presumed ischemic stroke). Details regarding tertiary and other efficacy and safety assessments are provided in the data analysis plan in Supplementary Appendix 1. All reports of possible primary and secondary outcomes, strokes, cancers, deaths, and serious liver or muscle events were centrally adjudicated by clinicians in a blinded fashion on the basis of prespecified definitions.[13] Adjudication was completed for more than 99.9% of relevant reports (see the Methods section in Supplementary Appendix 1).

STATISTICAL ANALYSIS

The data analysis plan was published on the trial website (www.revealtrial.org) when all the members of the steering committee were still unaware of the trial results according to group assignment (see the description of the data analysis plan in Supplementary Appendix 1).[13] We assumed an annual rate of major coronary events of 1.8% in the placebo group and determined that a sample size of 30,000 patients with a median follow-up of 4 years would provide the trial with a power of 88% at a two-tailed P value of less than 0.01 (and 96% power at $P<0.05$) to detect a 15% lower risk of major coronary events in the anacetrapib group than in the placebo group.[13] In prespecified analyses, we used the log-rank method to conduct an intention-to-treat comparison of the time until the first event of interest between the patients in the anacetrapib group and those in the placebo group.[15] With a stepwise approach, if the between-group difference in the primary outcome was significant at a two-tailed P value of less than 0.05, we would test for the secondary outcome of major atherosclerotic events; if that between-group difference was significant, we would test for presumed ischemic stroke. The components of the primary outcome and the remaining secondary outcome of major vascular events were to be assessed without adjustment. The full database is held and analyses performed by the Clinical Trial Service Unit at the University of Oxford.

RESULTS

PATIENTS

From August 2011 through October 2013, a total of 30,449 patients underwent randomization at 431 sites in Europe, North America, and China (Fig. S1 in Supplementary Appendix 1). All the data from one other site in the United States were excluded because of major protocol violations. (Details are provided in the data analysis plan in Supplementary Appendix 1.[13]) The mean age of the patients was 67 years; a history of coronary heart disease was reported by 88% of the patients, cerebrovascular disease by 22%, peripheral-artery disease by 8%, and diabetes mellitus by 37% (Table 1). The cholesterol levels were well controlled by the atorvastatin regimen; at baseline, the mean LDL cholesterol level was 61 mg per deciliter (1.58 mmol per liter), the mean non-HDL cholesterol level was 92 mg per deciliter (2.38 mmol per liter), and the mean HDL cholesterol level was 40 mg per deciliter (1.03 mmol per liter).

Of the 30,449 patients, 2277 (7.5%) died during the follow-up period; 28,096 (92.3%) survived

Table 1. Characteristics of the Patients at Baseline.*

Characteristic	Anacetrapib (N = 15,225)	Placebo (N = 15,224)	All Patients (N = 30,449)
Age			
Mean — yr	67±8	67±8	67±8
Age group — no. (%)			
<65	6,634 (43.6)	6,643 (43.6)	13,277 (43.6)
65 to <70	3,380 (22.2)	3,377 (22.2)	6,757 (22.2)
≥70	5,211 (34.2)	5,204 (34.2)	10,415 (34.2)
Sex — no. (%)			
Male	12,769 (83.9)	12,765 (83.8)	25,534 (83.9)
Female	2,456 (16.1)	2,459 (16.2)	4,915 (16.1)
Previous disease — no. (%)†			
Coronary heart disease	13,325 (87.5)	13,354 (87.7)	26,679 (87.6)
Cerebrovascular disease	3,385 (22.2)	3,396 (22.3)	6,781 (22.3)
Peripheral-artery disease	1,229 (8.1)	1,206 (7.9)	2,435 (8.0)
Diabetes	5,654 (37.1)	5,666 (37.2)	11,320 (37.2)
Heart failure	902 (5.9)	869 (5.7)	1,771 (5.8)
Region — no. (%)			
Europe	7,863 (51.6)	7,875 (51.7)	15,738 (51.7)
North America	3,048 (20.0)	3,034 (19.9)	6,082 (20.0)
China	4,314 (28.3)	4,315 (28.3)	8,629 (28.3)
Systolic blood pressure			
Mean — mm Hg	131.3±18.5	131.1±18.5	131.2±18.5
Level — no. (%)			
<125 mm Hg	5,678 (37.3)	5,760 (37.8)	11,438 (37.6)
125 to <140 mm Hg	4,819 (31.7)	4,740 (31.1)	9,559 (31.4)
≥140 mm Hg	4,728 (31.1)	4,724 (31.0)	9,452 (31.0)
Diastolic blood pressure			
Mean — mm Hg	78.1±10.9	78.0±11.0	78.1±11.0
Level — no. (%)			
<75 mm Hg	5,656 (37.1)	5,790 (38.0)	11,446 (37.6)
75 to <85 mm Hg	5,408 (35.5)	5,277 (34.7)	10,685 (35.1)
≥85 mm Hg	4,161 (27.3)	4,157 (27.3)	8,318 (27.3)
Body-mass index‡			
Mean	28.6±5.0	28.6±5.1	28.6±5.1
Level — no. (%)			
<25	3,447 (22.6)	3,361 (22.1)	6,808 (22.4)
25 to <30	6,949 (45.6)	6,995 (45.9)	13,944 (45.8)
≥30	4,829 (31.7)	4,868 (32.0)	9,697 (31.8)
LDL cholesterol			
Mean — mg/dl	61±15	61±15	61±15
Level — no. (%)			
<54 mg/dl	5,023 (33.0)	5,077 (33.3)	10,100 (33.2)
54 to <66 mg/dl	4,643 (30.5)	4,705 (30.9)	9,348 (30.7)
≥66 mg/dl	5,559 (36.5)	5,442 (35.7)	11,001 (36.1)

Table 1. (Continued.)

Characteristic	Anacetrapib (N=15,225)	Placebo (N=15,224)	All Patients (N=30,449)
Non-HDL cholesterol			
Mean — mg/dl	92±19	92±19	92±19
Level — no. (%)			
<85 mg/dl	5,642 (37.1)	5,701 (37.4)	11,343 (37.3)
85 to <101 mg/dl	4,896 (32.2)	4,853 (31.9)	9,749 (32.0)
≥101 mg/dl	4,687 (30.8)	4,670 (30.7)	9,357 (30.7)
HDL cholesterol			
Mean — mg/dl	40±10	40±10	40±10
Level — no. (%)			
<35 mg/dl	4,583 (30.1)	4,590 (30.1)	9,173 (30.1)
35 to <43 mg/dl	5,438 (35.7)	5,269 (34.6)	10,707 (35.2)
≥43 mg/dl	5,204 (34.2)	5,365 (35.2)	10,569 (34.7)
Glomerular filtration rate§			
Mean — ml/min/1.73 m^2	83±17	83±17	83±17
Level — no. (%)			
<60 ml/min/1.73 m^2	1,655 (10.9)	1,698 (11.2)	3,353 (11.0)
≥60 ml/min/1.73 m^2	13,570 (89.1)	13,526 (88.8)	27,096 (89.0)

* Plus–minus values are means ±SD. There were no significant differences in any of the baseline characteristics between the trial groups. Percentages may not total 100 because of rounding. To convert cholesterol values to millimoles per liter, multiply by 0.02586. HDL denotes high-density lipoprotein, and LDL low-density lipoprotein.
† The patients could have more than one of these conditions.
‡ The body-mass index is the weight in kilograms divided by the square of the height in meters.
§ The estimated glomerular filtration rate was calculated with the use of the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation.

until the final follow-up (including 235 [0.8%] followed up through a review of medical records), 33 (0.1%) withdrew consent, and 43 (0.1%) were lost to follow-up. The median duration of follow-up was 4.1 years (mean, 3.8).

ADHERENCE AND LIPID LEVELS

Rates of adherence to the assigned trial drug and lipid levels were assessed approximately 2 years after half the patients had undergone randomization (defined as the midpoint of the trial). Rates of adherence in the two groups were similar at the trial midpoint (89.9% for anacetrapib and 89.7% for placebo) (Table S1 in Supplementary Appendix 1). There were no significant differences in the number of patients who stopped taking anacetrapib as compared with placebo before the end of the trial, either overall (13.5% in each group) or for any specific reason (Table S2 in Supplementary Appendix 1). Rates of adherence to either the atorvastatin regimen or an alternative statin regimen were also high (94.6% and 94.7%).

At the trial midpoint, the mean level of HDL cholesterol was higher by 43 mg per deciliter (1.12 mmol per liter) in the anacetrapib group than in the placebo group, a relative difference of 104%, and the mean level of non-HDL cholesterol was lower by 17 mg per deciliter (0.44 mmol per liter), a relative difference of –18% (Table 2). The mean LDL cholesterol level was lower by 26 mg per deciliter (0.68 mmol per liter) in the anacetrapib group than in the placebo group as measured on a direct assay (which underestimates the LDL cholesterol level among patients treated with anacetrapib[16]), a relative difference of –41%, and lower by 11 mg per deciliter (0.28 mmol per liter) as measured on beta quantification in a randomly selected subgroup of 2000 patients, a relative difference of –17% (Table 2). The mean level of apolipoprotein A1 was higher by 42 mg per deciliter (0.42 g per liter) in the

Table 2. Effects of Anacetrapib on Blood Lipids and Lipoproteins at Trial Midpoint.*

Lipid or Lipoprotein	Anacetrapib (N=15,225)	Placebo (N=15,224)	Absolute Difference†	Relative Difference
				percent
Mean LDL cholesterol (mg/dl)				
Direct method	38	64	–26	–41
Beta quantification‡	53	63	–11	–17
Mean non-HDL cholesterol (mg/dl)	79	96	–17	–18
Mean HDL cholesterol (mg/dl)	85	42	43	104
Mean apolipoprotein A1 (mg/dl)	160	118	42	36
Mean apolipoprotein B (mg/dl)	54	66	–12	–18
Mean triglycerides (mg/dl)	136	146	–10	–7
Mean lipoprotein(a) (nmol/liter)	43	58	–15	–25

* Nonfasting blood samples for central laboratory assays and storage were scheduled to be taken from all surviving patients at a follow-up visit approximately 2 years after half the patients had undergone randomization (defined as the trial midpoint). Samples were collected a median of 716 days (interquartile range, 565 to 750) after randomization, and measured results were available for analysis for 93% of all the patients. In addition, lipid values — with the exclusion of LDL cholesterol levels as calculated by beta quantification and lipoprotein(a) levels, for which insufficient data were available — were imputed, as detailed in the Methods section of Supplementary Appendix 1. Imputation had no substantive effect on the absolute or proportional differences as calculated on the basis of measured values. Triglyceride and lipoprotein(a) levels are skewed. The median triglyceride level was 113 mg per deciliter (interquartile range, 83 to 162) in the anacetrapib group and 123 mg per deciliter (interquartile range, 87 to 176) in the placebo group. The median level of lipoprotein(a) was 10 nmol per liter (interquartile range, 4 to 55) in the anacetrapib group and 22 nmol per liter (interquartile range, 9 to 87) in the placebo group. To convert cholesterol values to millimoles per liter, multiply by 0.02586. To convert triglyceride values to millimoles per liter, multiply by 0.01129. To convert apolipoprotein values to grams per liter, multiply by 0.01.

† The absolute difference is the value in the anacetrapib group minus the value in the placebo group. P<0.001 for all comparisons.

‡ A random subgroup of 2000 patients was selected for a comparison of two different LDL cholesterol assays. LDL cholesterol was measured by beta quantification in samples obtained 2 years after randomization, and the results were available for 92% of the selected patients. For comparison, the mean LDL cholesterol level, as measured by the direct method in the same samples, was 39 mg per deciliter in the anacetrapib group versus 64 mg per deciliter in the placebo group, for an absolute difference of –26 mg per deciliter and a relative difference of –40%.

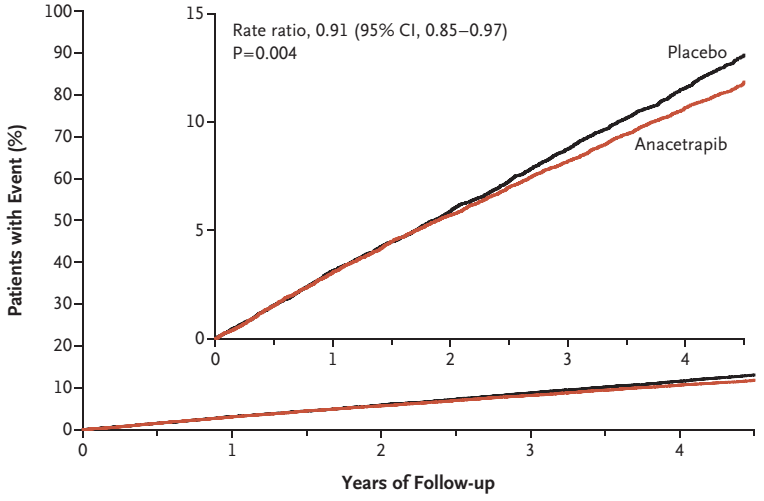
anacetrapib group than in the placebo group (a relative difference of 36%), the mean level of apolipoprotein B was lower by 12 mg per deciliter (0.12 g per liter, a relative difference of –18%), and the mean level of lipoprotein(a) was lower by 15 nmol per liter (a relative difference of –25%).

EFFECTS ON VASCULAR EVENTS

During the follow-up period, the primary outcome occurred in significantly fewer patients in the anacetrapib group than in the placebo group (1640 of 15,225 patients [10.8%] vs. 1803 of 15,224 patients [11.8%]; rate ratio, 0.91; 95% confidence interval [CI], 0.85 to 0.97; P=0.004) (Fig. 1A). In a prespecified analysis, there was a significantly lower rate of major coronary events that occurred more than 1 year after randomization in the anacetrapib group (rate ratio, 0.88; 95% CI, 0.81 to 0.95; P=0.001) (Fig. 1B). There was no significant between-group difference in the incidence of major coronary events during the first year of follow-up (rate ratio, 0.98; 95% CI, 0.86 to 1.11), although there was a suggestion of greater risk reductions during later years of treatment (P=0.03 in an exploratory test for trend) (Fig. 1B).

In analyses of the separate components of the primary outcome, the risk of myocardial infarction was significantly lower in the anacetrapib group than in the placebo group (rate ratio, 0.87; 95% CI, 0.78 to 0.96; P=0.007), but there was no significant between-group difference in the risk of coronary death (rate ratio, 0.92; 95% CI, 0.80 to 1.06; P=0.25), although the rate ratios were similar (Fig. 2). The incidence of the prespecified outcome of myocardial infarction or coronary death was significantly lower in the anacetrapib group (rate ratio, 0.89; 95% CI, 0.81 to 0.97;

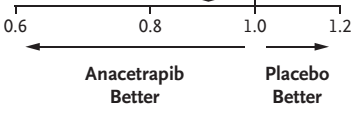
A First Major Coronary Event



No. at Risk					
Placebo	15,224	14,649	14,088	13,293	8993
Anacetrapib	15,225	14,656	14,104	13,359	9193
Benefit per 1000 patients in anacetrapib group		1±2	2±3	6±3	9±4

B First Major Coronary Event, According to Year of Follow-up

Year of First Event	Anacetrapib (N=15,225)	Placebo (N=15,224)	Rate Ratio (95% CI)	P Value
	no. of patients with event (%)			
1	465 (3.1)	476 (3.1)	0.98 (0.86–1.11)	
2	398 (2.7)	414 (2.8)	0.96 (0.84–1.10)	
3	370 (2.6)	427 (3.0)	0.86 (0.75–0.99)	
≥4	407 (3.0)	486 (3.7)	0.83 (0.73–0.94)	
>1	**1175 (8.0)**	**1327 (9.1)**	**0.88 (0.81–0.95)**	**0.001**
All	**1640 (10.8)**	**1803 (11.8)**	**0.91 (0.85–0.97)**	**0.004**



Test for trend across years, χ^2=4.87 (P=0.03)
Test for heterogeneity between ≤1 yr and >1 yr, χ^2=1.82 (P=0.18)

Figure 1. First Major Coronary Event during Follow-up.

Panel A shows a Kaplan–Meier plot of the first major coronary event (a composite of coronary death, myocardial infarction, or coronary revascularization) during follow-up. The numbers of patients at risk at the start of each year of follow-up are shown, along with the mean (±SE) absolute differences in incidence rates between the patients in the anacetrapib group and those in the placebo group. The inset graph shows the same data on an expanded y axis. Panel B shows rate ratios for the first major coronary event among the patients in the anacetrapib group versus those in the placebo group, according to the period of follow-up. The numbers at risk decline with each year of follow-up because of censoring, so the percentages are the number of events as a proportion of the number at risk. For each year of follow-up, rate ratios are plotted as squares, with the size of each square proportional to the amount of statistical information that was available; the horizontal lines represent 95% confidence intervals (CIs), and the dashed vertical line indicates the overall rate ratio for the effect of anacetrapib on the first major coronary event. For prespecified composite periods of follow-up (indicated in bold text), rate ratios and their corresponding 95% confidence intervals are represented by diamonds, and P values are shown. Squares or diamonds to the left of the solid vertical line indicate benefit with anacetrapib, but the comparison is significant (P<0.05) only if the horizontal line or diamond does not overlap with the solid vertical line.

P=0.008). The rate of coronary revascularization procedures (including surgical and percutaneous interventions) was significantly lower in the anacetrapib group than in the placebo group (rate ratio, 0.90; 95% CI, 0.83 to 0.97; P=0.01), with the effect appearing to be largely restricted to urgent procedures (rate ratio, 0.80; 95% CI, 0.70 to 0.90; P<0.001) rather than routine proce-

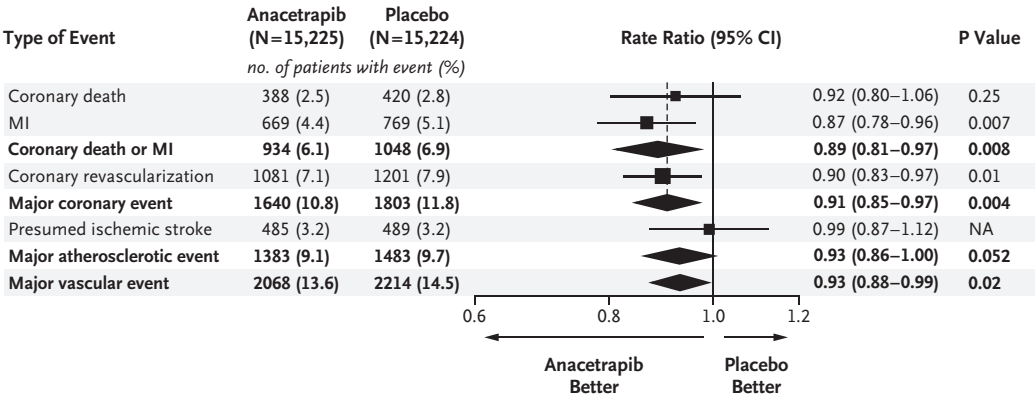


Figure 2. Primary and Secondary Outcomes.

The primary outcome was a major coronary event (a composite of coronary death, myocardial infarction [MI], or coronary revascularization). Secondary outcomes were a major atherosclerotic event (coronary death, MI, or presumed ischemic stroke), presumed ischemic stroke (i.e., not known to be hemorrhagic), and a major vascular event (major coronary event or presumed ischemic stroke). The composite of coronary death or MI was a prespecified tertiary outcome. A single patient may have had multiple events and therefore may contribute information to more than one row. The size of each square for rate ratio is proportional to the amount of statistical information that was available, the horizontal lines represent 95% confidence intervals, and the dashed vertical line indicates the overall rate ratio for the effect of anacetrapib on the first major coronary event. For composite outcomes, rate ratios and their corresponding 95% confidence intervals are represented by bold text and diamonds. In accordance with the data analysis plan, since the outcome of a major atherosclerotic event did not reach significance, there was no hypothesis testing for presumed ischemic stroke, so no P value is shown (as indicated by NA for not applicable).

dures (rate ratio, 0.97; 95% CI, 0.87 to 1.07; P=0.50) (Table S3 in Supplementary Appendix 1).

The between-group difference in the rate of the secondary composite outcome of major atherosclerotic events (i.e., myocardial infarction, coronary death, or presumed ischemic stroke) was not significant (rate ratio, 0.93; 95% CI, 0.86 to 1.00; P=0.052) (Fig. 2). Consequently, the effect of anacetrapib on presumed ischemic stroke (rate ratio, 0.99; 95% CI, 0.87 to 1.12) was not formally tested. However, there was a significant reduction in the secondary outcome of major vascular events (i.e., major coronary event or presumed ischemic stroke) (rate ratio, 0.93; 95% CI, 0.88 to 0.99; P=0.02), and the results were consistent for the components of this end point. There were no apparent effects on hemorrhagic stroke, on noncoronary revascularization procedures, or on hospitalization for heart failure (Table S3 in Supplementary Appendix 1).

The proportional effects of anacetrapib on major coronary events were compared across 23 prespecified subgroup categories (Fig. S2 in Supplementary Appendix 1). There was no significant evidence of differential proportional effects within any of these categories, with only one category (the use of an angiotensin-converting–enzyme inhibitor or angiotensin-receptor blocker at baseline vs. no such use) that resulted in a nominal P value for heterogeneity of less than 0.05, a difference that was not significant after adjustment for multiple comparisons.

EFFECTS ON DEATH, CANCER, AND OTHER ADVERSE EVENTS

There were no significant effects of anacetrapib on rates of death from cardiovascular causes (3.4% with anacetrapib vs. 3.7% with placebo, P=0.17), death from all noncardiovascular causes (4.0% vs. 3.9%, P=0.77), or death from all causes combined (7.4% vs. 7.6%, P=0.46) (Fig. S3 in Supplementary Appendix 1). There were also no significant effects on the incidence of fatal or nonfatal cancer, either overall (6.4% vs. 6.3%, P=0.71) or at any prespecified site (Fig. S4 in Supplementary Appendix 1). There were no significant excesses in any major category of serious or nonserious adverse events (Table S4 in Supplementary Appendix 1). Detailed tabulations of adverse events are provided in Supplementary Appendix 2, available at NEJM.org.

Among the patients without diabetes mellitus

at baseline, the incidence of new-onset diabetes mellitus was lower in the anacetrapib group than in the placebo group (5.3% vs. 6.0%; rate ratio, 0.89; 95% CI, 0.79 to 1.00; P=0.0496), and the mean glycated hemoglobin level was 0.03 percentage point lower (Table S5 in Supplementary Appendix 1). However, there was no apparent effect on glycated hemoglobin level among the patients with diabetes at baseline.

Patients in the anacetrapib group had slightly higher blood-pressure levels than did those in the placebo group, with higher levels of systolic blood pressure (by 0.7 mm Hg) and diastolic blood pressure (by 0.3 mm Hg) at the final visit. However, there was no significant difference in the rates of serious adverse events attributed to hypertension (1.0% in the anacetrapib group vs. 0.9% in the placebo group) (Table S6 in Supplementary Appendix 1). By the end of the trial, an estimated glomerular filtration rate (GFR) of less than 60 ml per minute per 1.73 m^2 of body-surface area had developed in more patients in the anacetrapib group than in the placebo group (11.5% vs. 10.6%, P=0.04), but there were no significant between-group differences in the development of albuminuria. In exploratory analyses, there were no significant between-group differences in the proportions of patients with a 40% decline in the estimated GFR between the baseline visit and the final visit or with serious adverse events attributed to renal failure.

Regarding any effects on muscles, there were slightly higher rates of moderate elevations in creatine kinase (10 to 40 times the upper limit of the normal range) in the anacetrapib group than in the placebo group but slightly lower rates of more severe elevations (>40 times the upper limit of the normal range) (Table S7 in Supplementary Appendix 1). There was no evidence of adverse effects associated with anacetrapib on macular degeneration (in contrast to previous genetic studies[17]), liver disorders, or mood or cognitive function (Tables S6 and S7 in Supplementary Appendix 1).[18,19]

DISCUSSION

In this randomized trial, we found that the addition of the CETP inhibitor anacetrapib at a dose of 100 mg daily to intensive statin therapy for approximately 4 years resulted in a lower incidence of major coronary events than the addition of placebo among patients with preexisting atherosclerotic vascular disease, despite very well-controlled baseline LDL cholesterol levels (mean, 61 mg per deciliter [1.58 mmol per liter]). The proportional risk reductions appeared to be larger with more prolonged follow-up.

Our trial has a number of strengths that facilitated assessments of both efficacy and safety, including recruitment of a large number of patients, high treatment adherence, follow-up for a median of more than 4 years, and a large number of clinical outcomes. Our results contrast with those reported from clinical outcome trials of other CETP inhibitors. The Investigation of Lipid Level Management to Understand its Impact in Atherosclerotic Events (ILLUMINATE) trial was terminated early because of excess risks of cardiac events and death with torcetrapib, findings that have been attributed to off-target drug effects.[8,20,21] Subsequently, the Effects of Dalcetrapib in Patients with a Recent Acute Coronary Syndrome (Dal-OUTCOMES) trial and the Assessment of Clinical Effects of Cholesteryl Ester Transfer Protein Inhibition with Evacetrapib in Patients at a High Risk for Vascular Outcomes (ACCELERATE) were both stopped early after approximately 2 years of treatment because of an apparent lack of efficacy.[9,10] Dalcetrapib is a relatively weak CETP inhibitor that does not lower LDL cholesterol at the dose tested in Dal-OUTCOMES,[9] whereas evacetrapib has effects on blood lipid levels similar to those of anacetrapib.[10] However, ACCELERATE differed from our trial in several ways. In particular, it involved fewer patients (12,092 vs. 30,449), a shorter treatment period (median, 26 months vs. 50 months), and fewer primary cardiovascular outcomes (1555 vs. 3443). Our trial results suggest that the full effects of anacetrapib may take at least a year of treatment to emerge. A similar pattern has been observed in randomized trials of other lipid-lowering drugs.[2-4] Consequently, the follow-up duration of just over 2 years in ACCELERATE may have been too short to allow an effect on vascular events to emerge.

It is not possible to determine the mechanism by which anacetrapib reduced the risk of major coronary events in this trial. On the basis of evidence from trials of statin therapy,[2] the lower level of non-HDL cholesterol (by 17 mg per deciliter) in the anacetrapib group than in the placebo group as seen in our trial would be anticipated to result in a 10% relative reduction in the risk of coronary death or myocardial infarction

(Fig. S5 in Supplementary Appendix 1), a finding that is entirely consistent with the 11% reduction that we observed. This result reduces the likelihood that other actions of anacetrapib played a major role in modifying the risk of coronary events. In particular, the higher mean level of HDL cholesterol in the anacetrapib group (by 43 mg per deciliter) does not appear to have had as large an effect on coronary events as would be anticipated on the basis of observational studies.[22] Analyses of genetic variants in CETP also indicate that differences in coronary risk are related largely to differences in LDL cholesterol levels.[23] LDL cholesterol levels were particularly well controlled among the patients throughout our trial. The beneficial effects of anacetrapib may be greater among patients with higher baseline LDL cholesterol levels, in whom the absolute reductions in LDL cholesterol levels may be greater.

During a median of 4 years of follow-up, anacetrapib treatment was not associated with any of the previously hypothesized adverse effects of very low levels of cholesterol (e.g., reduced cognitive function, increased cancer incidence, or nonvascular death).[24] Unlike previous and much smaller studies of anacetrapib,[11,25] our trial showed a slightly higher level of systolic blood pressure (0.7 mm Hg) in the anacetrapib group than in the placebo group, a difference that was similar in magnitude to effects reported for dalcetrapib and evacetrapib but much smaller than the increase of 5 mm Hg seen with torcetrapib.[8-10] In addition, the risk of the development of an estimated GFR of less than 60 ml per minute per 1.73 m^2 was slightly higher. As has been observed with torcetrapib[26] and evacetrapib[27] (but not with dalcetrapib[9]), anacetrapib was associated with a lower incidence of new-onset diabetes, which contrasts with the small increase seen with statins[28] or, to a greater extent, niacin.[5]

Our trial has certain limitations. LDL cholesterol levels were very well controlled, and the median follow-up was only 4 years, so our findings may not be generalizable to patients with longer-term use of anacetrapib and those with higher LDL cholesterol levels. Anacetrapib continues to accumulate in adipose tissue with prolonged administration,[29] and although plasma levels fall substantially after cessation of treatment, levels in adipose tissue decline only minimally after 1 year.[29,30] No substantial safety issues were identified during the trial, but follow-up for clinical outcomes in trial patients is being continued for at least an additional 2 years after the end of the treatment period to assess longer-term safety, as well as efficacy.

In conclusion, we found that the addition of the CETP inhibitor anacetrapib to intensive statin treatment in patients with atherosclerotic vascular disease resulted in a significantly lower incidence of major coronary events than the addition of placebo during 4 years of treatment.

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