ORIGINAL ARTICLE

Safety of Anacetrapib in Patients with or at High Risk for Coronary Heart Disease

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ABSTRACT

BACKGROUND

Anacetrapib is a cholesteryl ester transfer protein inhibitor that raises high-density lipoprotein (HDL) cholesterol and reduces low-density lipoprotein (LDL) cholesterol.

METHODS

We conducted a randomized, double-blind, placebo-controlled trial to assess the efficacy and safety profile of anacetrapib in patients with coronary heart disease or at high risk for coronary heart disease. Eligible patients who were taking a statin and who had an LDL cholesterol level that was consistent with that recommended in guidelines were assigned to receive 100 mg of anacetrapib or placebo daily for 18 months. The primary end points were the percent change from baseline in LDL cholesterol at 24 weeks (HDL cholesterol level was a secondary end point) and the safety and side-effect profile of anacetrapib through 76 weeks. Cardiovascular events and deaths were prospectively adjudicated.

RESULTS

A total of 1623 patients underwent randomization. By 24 weeks, the LDL cholesterol level had been reduced from 81 mg per deciliter (2.1 mmol per liter) to 45 mg per deciliter (1.2 mmol per liter) in the anacetrapib group, as compared with a reduction from 82 mg per deciliter (2.1 mmol per liter) to 77 mg per deciliter (2.0 mmol per liter) in the placebo group ($P<0.001$) — a 39.8% reduction with anacetrapib beyond that seen with placebo. In addition, the HDL cholesterol level increased from 41 mg per deciliter (1.0 mmol per liter) to 101 mg per deciliter (2.6 mmol per liter) in the anacetrapib group, as compared with an increase from 40 mg per deciliter (1.0 mmol per liter) to 46 mg per deciliter (1.2 mmol per liter) in the placebo group ($P<0.001$) — a 138.1% increase with anacetrapib beyond that seen with placebo. Through 76 weeks, no changes were noted in blood pressure or electrolyte or aldosterone levels with anacetrapib as compared with placebo. Prespecified adjudicated cardiovascular events occurred in 16 patients treated with anacetrapib (2.0%) and 21 patients receiving placebo (2.6%) ($P=0.40$). The prespecified Bayesian analysis indicated that this event distribution provided a predictive probability (confidence) of 94% that anacetrapib would not be associated with a 25% increase in cardiovascular events, as seen with torcetrapib.

CONCLUSIONS

Treatment with anacetrapib had robust effects on LDL and HDL cholesterol, had an acceptable side-effect profile, and, within the limits of the power of this study, did not result in the adverse cardiovascular effects observed with torcetrapib. (Funded by Merck Research Laboratories; ClinicalTrials.gov number, NCT00685776.)

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*The Determining the Efficacy and Tolerability of CETP Inhibition with Anacetrapib (DEFINE) study investigators and committee members are listed in the Supplementary Appendix, available at NEJM.org.

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Elevated low-density lipoprotein (LDL) cholesterol and reduced high-density lipoprotein (HDL) cholesterol are major risk factors for the development of cardiovascular disease. Lowering LDL cholesterol with 3-hydroxy-3-methylglutaryl-coenzyme A reductase inhibitors (statins) reduces the risk of cardiovascular events in patients with coronary heart disease, as well as in those without coronary heart disease.[1] In many patients, however, a high residual risk of cardiovascular events persists despite aggressive statin therapy to lower LDL cholesterol, especially when other lipid abnormalities, such as low HDL cholesterol, persist after statin therapy.[2-4] Accordingly, targeting additional lipid risk factors is an approach that is currently recommended to further reduce the risk of cardiovascular disease.

One approach to raising HDL cholesterol is to inhibit the cholesteryl ester transfer protein (CETP), a plasma protein that promotes the transfer of cholesteryl esters from HDL and other lipoprotein fractions.[5] Drugs that inhibit CETP increase HDL cholesterol, and some lower LDL cholesterol. However, the development of torcetrapib, the first CETP inhibitor that was tested in a clinical outcomes trial, was terminated after the drug was shown to cause an excess of deaths and cardiovascular events.[6] Treatment with torcetrapib increased blood pressure and circulating aldosterone levels and altered serum electrolyte levels.[6] Subsequent studies indicated that these adverse effects of torcetrapib were unrelated to the inhibition of CETP[7-9] and are not necessarily shared by other members of the class of CETP inhibitors. Anacetrapib is an orally active, potent, selective CETP inhibitor that has had an acceptable side-effect profile in initial studies involving healthy volunteers and patients with hyperlipidemia.[9,10] The current study was designed to evaluate the side-effect and overall safety profile and the effects on lipid levels of anacetrapib in patients with coronary heart disease or risk factors for coronary heart disease.

Methods

Study Protocol and Oversight

Details of the Determining the Efficacy and Tolerability of CETP Inhibition with Anacetrapib (DEFINE) trial have been published previously (www.ahjonline.com/article/S0002-8703(09)00566-3/abstract).[11] The study protocol was reviewed and approved by the institutional review board at each participating center.

The study was sponsored by Merck Research Laboratories. The first draft and all revisions of the manuscript were prepared by the first author, with edits and revisions provided by all the coauthors. The study cochairs (the first and last authors) made the decision to submit the manuscript for publication, and all the authors assume responsibility for the accuracy and completeness of the reported data as well as the fidelity of the study to the published protocol.

Study Population

All patients provided written informed consent to participate in the study. Eligible patients were between 18 and 80 years of age, had prior known coronary heart disease or were at high risk for coronary heart disease (Framingham Risk score of >20% per 10 years, as defined by the National Cholesterol Education Program Adult Treatment Panel III),[12] and had an LDL cholesterol level between 50 and 100 mg per deciliter (1.3 and 2.6 mmol per liter) while taking a statin with or without other lipid-modifying medications, an HDL cholesterol level of less than 60 mg per deciliter (1.6 mmol per liter), and a triglyceride level of 400 mg per deciliter (4.5 mmol per liter) or less. Patients were excluded if they had severe chronic heart failure, uncontrolled hypertension, or cardiac arrhythmias; if they had had, within the previous 3 months, a myocardial infarction, percutaneous coronary intervention, coronary-artery bypass grafting, unstable angina, or stroke; if they had active or chronic hepatobiliary or hepatic disease or severe renal impairment; or if they were being treated with warfarin or potent CYP3A4 inhibitors or inducers.

Study Design

Patients were entered into a 2-week, single-blind, placebo run-in phase. Those who had more than 75% adherence to the regimen were eligible for inclusion in the study. Eligible patients were then randomly assigned in a double-blind fashion, in a 1:1 ratio, to receive 100 mg of anacetrapib or matching placebo daily. The selection of the 100-mg dose was based on stochastic modeling and simulation that linked anacetrapib plasma concentrations with data on HDL and LDL cholesterol from phase 1 and phase 2 studies.[9,10] The modeling data indicated that a dose of 100 mg would be on the plateau portion of the dose–

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response curve and would achieve near maximal efficacy with respect to LDL and HDL cholesterol levels. Patients were instructed to take one tablet daily with a meal. Patients returned for study visits at regular intervals (every 6 to 8 weeks) for an assessment of adverse events, precise measurements of blood pressure with the use of a BpTRU automated blood-pressure monitor (BpTRU Medical Devices), and collection of blood samples for measurements of plasma lipids and for use in laboratory tests to assess the safety of the drug.

LDL cholesterol levels were calculated with the use of the Friedewald equation: LDL cholesterol = total cholesterol − (HDL cholesterol + [triglycerides ÷ 5]). If the triglyceride level was more than 400 mg per deciliter, LDL cholesterol was measured by means of preparative ultracentrifugation separation. Plasma cholesterol and triglyceride levels were determined with the use of enzymatic methods. HDL cholesterol was measured after dextran sulfate precipitation of the apolipoprotein beta-containing lipoproteins (LDL and very-low-density-lipoprotein) in whole plasma. Apolipoprotein B and apolipoprotein A-I were measured with the use of an immunonephelometric assay, and lipoprotein(a) was measured with the use of an immunoturbidimetric assay. If the measurements of lipoprotein(a) were below the detectable limit (8.9 nmol per liter), values were imputed as one half of the detection limit. All laboratory measurements were performed by the core laboratory for the study (PPD).

The investigators and the sponsor were unaware of the results of the lipid measurements from the time of the randomization visit forward. If a patient's LDL cholesterol level was less than 25 mg per deciliter (0.6 mmol per liter) at two consecutive measurements, the study drug was discontinued.

CONCOMITANT TREATMENT

Patients were instructed to follow the Therapeutic Lifestyle Changes diet recommended by the National Cholesterol Education Program Adult Treatment Panel III[12] or a similar cholesterol-lowering diet and to continue taking lipid-modifying therapies for the duration of the study. If a patient's LDL cholesterol level was more than 15% above 100 mg per deciliter, the test was repeated; if the results were confirmed and adherence to taking the medication was verified, the investigators were prompted to adjust the LDL-cholesterol–lowering medications. All patients, including those who discontinued the study drug, were followed for an assessment of safety for a 12-week period after the 76-week study-treatment phase, with a visit (or a telephone call at the time of the intended follow-up visit) at week 88.

END POINTS

The primary efficacy end points were the percentage change from baseline in LDL cholesterol after 24 weeks of treatment and the safety and side-effect assessments (i.e., assessment of adverse events; laboratory testing related to safety, including measurement of electrolyte and aldosterone levels; and assessment of vital signs, including blood-pressure measurement, electrocardiography, and physical examination) throughout the 76-week treatment period. The change in LDL cholesterol level was selected as the primary efficacy end point because LDL cholesterol is a recognized target for the reduction of cardiovascular risk, and anacetrapib has been shown to affect this lipid factor.[9,10] Secondary efficacy end points included the change in LDL cholesterol from baseline to week 76 and the levels of HDL cholesterol, non-HDL cholesterol, apolipoprotein B, and apolipoprotein A-I after 24 and 76 weeks of treatment.

Key safety variables or adverse events of special interest that were identified a priori included blood pressure; hepatic, muscle-related, and aldosterone-related electrolyte levels; and specific adverse events (myalgia, rhabdomyolysis, prespecified adjudicated serious cardiovascular events, and death from any cause). The prespecified cardiovascular composite end point that was used for the evaluation of safety comprised death from cardiovascular causes, nonfatal myocardial infarction, nonfatal stroke, and hospitalization for unstable angina. The definitions of these variables have been published previously.[11] All serious cardiovascular events and deaths from any cause were adjudicated by an external, independent adjudication committee whose members were unaware of the patients' group assignments. Reports of revascularization and heart failure were collected and adjudicated but were not part of the prespecified cardiovascular composite end point. The primary time of analysis for clinical safety end points was the period from randomization to the end of the 76-week treatment phase of the study for patients who completed the study and to the intended date of the week 76 visit for patients who discontinued the study before week 76. Assessments were per-

formed separately for prespecified adjudicated cardiovascular events and deaths that occurred after the end of the treatment phase (i.e., between weeks 76 and 88).

DATA MONITORING AND INTERIM ANALYSES

The DEFINE trial was designed as a safety study.[11] An external, independent safety monitoring committee whose members were aware of the patients' group assignments was responsible for reviewing safety data on a regular basis throughout the study to ensure patient safety. An independent statistical group supported the safety monitoring committee by performing analyses, including those proposed by the safety monitoring committee, independently of the sponsor. Prespecified interim safety analyses were performed at 6 months and at 12 months to examine the effects of the study treatment on key safety end points, including blood pressure, electrolyte and aldosterone levels, and the limited number of cardiovascular events reported. As specified in the protocol, the 6-month report (with group assignments unconcealed) on the interim analyses of safety and of efficacy with respect to lipid variables was shared with the cochairs of the study steering committee, who in turn shared it with the sponsor. In addition, the safety analysis performed at 12 months was shared with the sponsor's data monitoring committee whose members were not part of the trial's operational team. These prespecified interim analyses were used by the sponsor specifically to inform the planning of a larger, definitive outcomes trial that was being considered pending the results of these safety analyses. Throughout the trial, the steering committee and the study sponsor remained unaware of the individual treatment-level data.

STATISTICAL ANALYSIS

All statistical analyses were performed by the independent data analysis center (see the Supplementary Appendix, available with the full text of this article at NEJM.org). All patients who had undergone randomization and had received at least one dose of the study drug were included in the safety analysis. The study had ample power to assess end points of efficacy with respect to lipid variables; it was intended to provide a safety profile for anacetrapib. For the evaluation of clinical safety with respect to cardiovascular events, which was based on assumptions published previously,[11] we computed Bayesian predictive probabilities (i.e., confidence levels) to rule out a 25% increase in cardiovascular events,[13] the level that was observed with torcetrapib in the Investigation of Lipid Level Management to Understand Its Impact in Atherosclerotic Events trial (ILLUMINATE; ClinicalTrials.gov number, NCT00134264).[6]

RESULTS

STUDY POPULATION

Between April 1, 2008, and January 15, 2009, a total of 2757 patients were screened at 153 centers in 20 countries. Of the 2757 patients who were screened, 1697 entered the placebo run-in phase, and 1623 were randomly assigned to a study group (Fig. 1 in the Supplementary Appendix). As specified by the protocol, the study drug was discontinued in any patient who had an LDL cholesterol level of less than 25 mg per deciliter at two consecutive measurements; this occurred in 142 patients in the anacetrapib group (17.6%) and 1 patient in the placebo group (0.1%). The proportion of patients who discontinued the study drug for other reasons was balanced between the groups, with 14.6% and 17.4% of patients discontinuing anacetrapib and placebo, respectively (Fig. 1 in the Supplementary Appendix). Patients took the assigned study drug for a mean of 424 days in the anacetrapib group and a mean of 483 days in the placebo group. As of October 26, 2010, follow-up assessments, with ascertainment of clinical safety end points, were complete in 99.1% and 99.4% of the patients in the anacetrapib and placebo groups, respectively. The baseline characteristics of the patients who were enrolled in the study are shown in Table 1. The mean age was 63 years; 54.7% of the patients had prior coronary heart disease, and 45.3% had risk factors for coronary heart disease. At baseline, the mean HDL cholesterol level was 41 mg per deciliter (1.1 mmol per liter), and the mean LDL cholesterol level was 81 mg per deciliter (2.1 mmol per liter); 99.3% of the patients were taking statins.

CHANGES IN LIPID LEVELS

By 24 weeks, LDL cholesterol levels had decreased from 81 mg per deciliter to 45 mg per deciliter (1.2 mmol per liter) in the anacetrapib group, as compared with a change from 82 mg per deciliter (2.1 mmol per liter) to 77 mg per deciliter (2.0 mmol per liter) in the placebo group — a 39.8% reduction with anacetrapib beyond that seen with placebo ($P<0.001$) (Table 2). HDL cho-

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Table 1. Baseline Characteristics of the Study Patients.*

Characteristic	Anacetrapib (N=811)	Placebo (N=812)
Age — yr	62.5±8.7	62.9±9.0
Male sex — no. (%)	629 (77.6)	618 (76.1)
Body-mass index†	30.4±5.5	30.1±5.2
Race or ethnic group — no. (%)‡		
White	686 (84.6)	669 (82.4)
Asian	54 (6.7)	69 (8.5)
Black	22 (2.7)	19 (2.3)
Multiracial	42 (5.2)	47 (5.8)
Other	7 (0.9)	8 (1.0)
Prior coronary heart disease — no. (%)	447 (55.1)	441 (54.3)
High risk for coronary heart disease — no. (%)§	364 (44.9)	371 (45.7)
Prior myocardial infarction — no. (%)	182 (22.4)	185 (22.8)
Hypertension — no. (%)	560 (69.1)	541 (66.6)
Diabetes — no. (%)	430 (53.0)	432 (53.2)
Statin therapy — no. (%)	807 (99.5)	805 (99.1)
Simvastatin	367 (45.3)	372 (45.8)
Atorvastatin	276 (34.0)	275 (33.9)
Rosuvastatin	104 (12.8)	86 (10.6)
Other	60 (7.4)	72 (8.9)
Cholesterol — mg/dl¶		
LDL	81.4±21.3	82.2±20.7
HDL	40.5±9.3	40.4±9.1

* Plus–minus values are means ±SD. There were no significant differences between the two treatment groups. HDL denotes high-density lipoprotein, and LDL low-density lipoprotein.
† The body-mass index is the weight in kilograms divided by the square of the height in meters.
‡ Race or ethnic group was determined by the investigators.
§ A patient was considered to be at high risk if he or she had a calculated Framingham Risk score of more than 20% per 10 years, as defined by the National Cholesterol Education Program Adult Treatment Panel III.
¶ The lipid measurements were obtained at the time of the randomization visit at the end of the placebo run-in period.

lesterol levels had increased from 41 mg per deciliter to 101 mg per deciliter (2.6 mmol per liter) in the anacetrapib group, as compared with a change from 40 mg per deciliter (1.0 mmol per liter) to 46 mg per deciliter (1.2 mmol per liter) in the placebo group — a 138.1% increase with anacetrapib beyond that seen with placebo (P<0.001) (Table 2). In the anacetrapib group, apolipoprotein B levels decreased by 21.0% and apolipoprotein A-I levels increased by 44.7% beyond the changes seen in the placebo group (P<0.001) (Table 2). Treatment with anacetrapib was associated with a 31.7% reduction in non-HDL cholesterol, a 36.4% reduction in lipoprotein(a) levels, and a 6.8% reduction in triglyceride levels, beyond the changes seen in the placebo group. All the changes in lipid levels were sustained throughout the 76-week treatment period (Fig. 1A). There were no significant differences in C-reactive protein levels between the two treatment groups (Table 2).

SAFETY VARIABLES

There were no appreciable differences between the anacetrapib group and the placebo group in the percentage of patients with adverse events that were thought to be related to the study drug or that led to its discontinuation (Table 3). There were also no significant differences between the two groups in the mean change in systolic or diastolic blood pressure or in the percentage of patients with a reported increase in blood pressure (Table 3 and Fig. 1B, and Table 1 in the Supplementary Appendix). There were no significant between-group differences in serum levels of potassium, chloride, bicarbonate, or aldosterone (Table 3, and Tables 1 and 2 in the Supplementary Appendix). In the case of serum levels of

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Table 2. Changes in Lipid and C-Reactive Protein Levels during the Study Period.*

Variable	Baseline		Week 24				Week 76			
	No. of Patients with Data	Level	No. of Patients with Data	Level	Change from Baseline	Change from Baseline beyond That with Placebo (95% CI)	No. of Patients with Data	Level	Change from Baseline	Change from Baseline beyond That with Placebo (95% CI)
						percent				*percent*
LDL cholesterol — mg/dl										
Placebo	794	82.2	742	76.8	−4.8±0.9		663	76.7	−4.3±1.0	
Anacetrapib	794	81.2	683	44.7	−44.5±0.9	−39.8 (−42.1 to −37.5)†	536	48.9	−40.5±1.0	−36.2 (−38.7 to −33.6)†
HDL cholesterol — mg/dl										
Placebo	797	40.4	744	45.5	14.7±1.6		664	44.9	12.3±1.6	
Anacetrapib	797	40.5	686	101.2	152.8±1.6	138.1 (133.9 to 142.4)†	541	102.3	151.1±1.6	138.8 (134.5 to 143.0)†
Non-HDL cholesterol — mg/dl										
Placebo	797	111.1	744	104.8	−4.3±0.7		664	104.8	−3.8±0.8	
Anacetrapib	797	109.7	686	69.7	−36.1±0.8	−31.7 (−33.6 to −29.8)†	541	73.0	−33.2±0.9	−29.4 (−31.6 to −27.3)†
Apolipoprotein B — mg/dl										
Placebo	779	88.9	777	89.2	2.0±0.7		675	85.5	−2.2±0.7	
Anacetrapib	780	88.4	775	70.1	−19.1±0.7	−21.0 (−22.7 to −19.3)†	572	69.6	−20.5±0.8	−18.3 (−20.2 to −16.4)†
Apolipoprotein A-I — mg/dl										
Placebo	780	142.8	777	144.9	2.8±0.8		675	141.1	−0.6±0.7	
Anacetrapib	778	142.5	774	208.0	47.4±0.8	44.7 (42.8 to 46.5)†	571	203.0	41.7±0.8	42.3 (40.5 to 44.1)†
Total cholesterol — mg/dl										
Placebo	797	151.5	744	150.3	0.2±0.6		665	149.7	−0.1±0.7	
Anacetrapib	799	150.3	689	170.8	13.9±0.7	13.7 (12.0 to 15.3)	543	175.2	15.5±0.7	15.6 (13.8 to 17.3)
Triglycerides — mg/dl										
Placebo	797	128.0	744	128.0	−2.9±37.2		667	124.0	−2.5±38.4	
Anacetrapib	799	127.0	689	112.0	−8.8±34.4	−6.8 (−9.9 to −3.9)	544	107.0	−6.9±38.7	−5.3 (−8.9 to −1.7)
Lipoprotein(a) — nmol/liter										
Placebo	768	25.9	765	29.6	0.5±32.9		668	31.3	9.4±35.1	
Anacetrapib	762	26.8	758	14.8	−23.8±50.5	−36.4 (−40.7 to −32.3)	560	16.4	−17.1±52.1	−38.8 (−44.5 to −33.9)
C-reactive protein — mg/liter										
Placebo	783	1.6	776	1.6	0.0±80.7		681	1.4	−5.9±75.6	
Anacetrapib	779	1.4	776	1.7	16.7±79.2	10.0 (3.2 to 16.7)	573	1.5	11.9±93.5	18.3 (10.7 to 25.5)

* Levels, percentage change (±SE) from baseline, and percentage change from baseline beyond that with placebo are means for all variables except for triglycerides, lipoprotein(a), and C-reactive protein, for which medians (±SD) are shown; changes from baseline were calculated with the least-squares method. 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. CI denotes confidence interval.
† P<0.001.

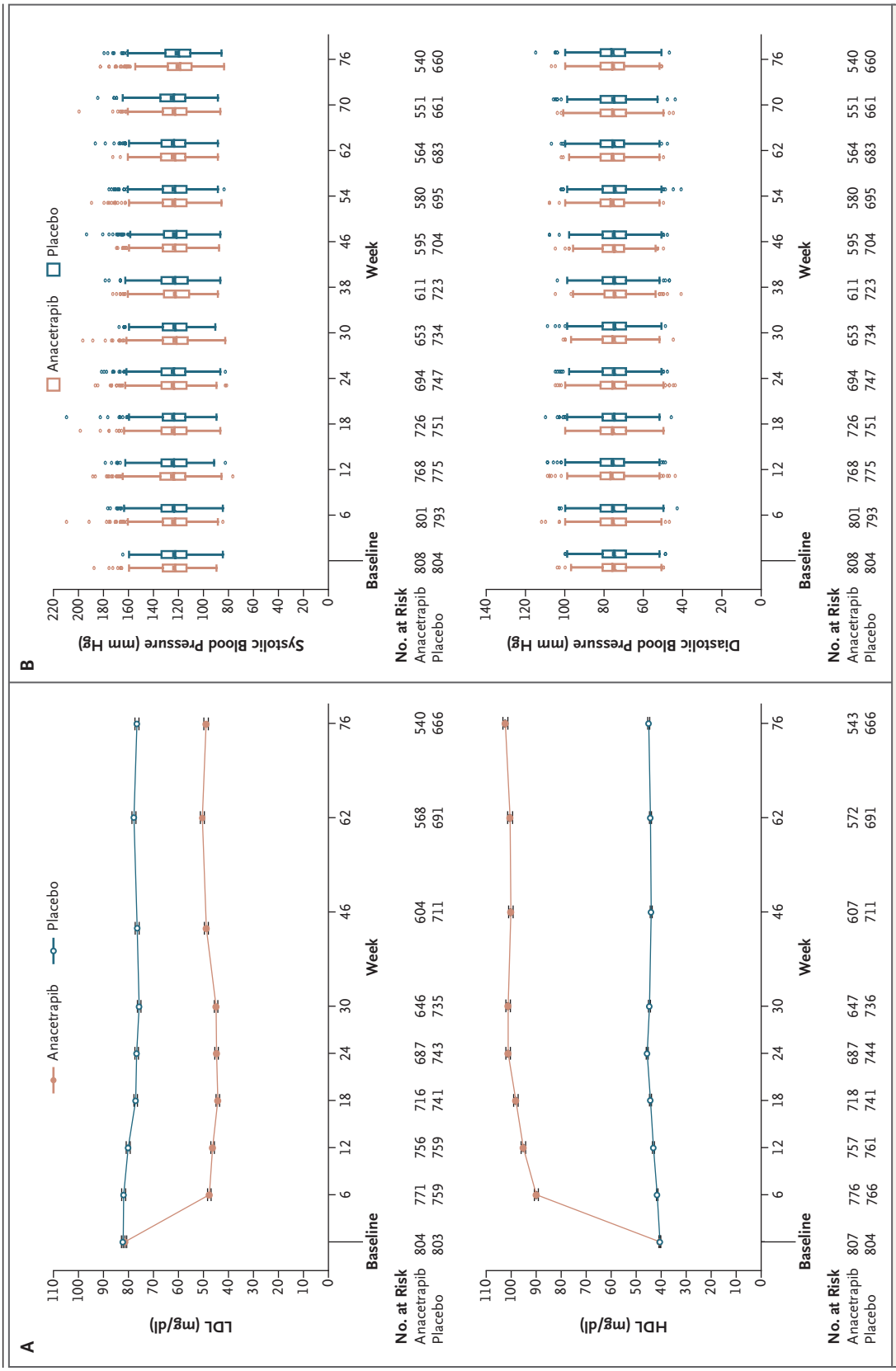

Figure 1. Changes in Cholesterol Levels and Blood Pressure during the Study Period.

Panel A shows low-density lipoprotein (LDL) and high-density lipoprotein (HDL) cholesterol levels in the anacetrapib and placebo groups from baseline to week 76. Horizontal bars indicate standard errors. To convert the values for LDL and HDL cholesterol to millimoles per liter, multiply by 0.02586. Panel B shows systolic and diastolic blood pressure from baseline to week 76. Boxes indicate the interquartile ranges; the lines within the boxes are medians. The vertical lines represent 1.5 times the interquartile range (above the upper end of the range and below the lower end of the range); the short horizontal lines indicate the last data points that fall within 1.5 times the interquartile range. The dots beyond those lines indicate outliers.

Table 3. Rates of Adverse Events and Safety Variables of Interest through Week 76.*

Adverse Event or Safety Variable	Anacetrapib	Placebo	Absolute Difference	P Value
	no./total no. (%)		*percentage points (95% CI)*	
Adverse events				
Drug-related adverse event	92/808 (11.4)	86/804 (10.7)	0.7 (–2.4 to 3.8)	
Clinical adverse event leading to discontinuation of study drug	44/808 (5.4)	46/804 (5.7)	–0.2 (–2.5 to 2.2)	
Drug-related adverse event leading to discontinuation of study drug	22/808 (2.7)	18/804 (2.2)	0.5 (–1.1 to 2.1)	
Serious adverse event	123/808 (15.2)	119/804 (14.8)	0.2 (–3.3 to 3.7)	
Drug-related serious adverse event	2/808 (0.2)	4/804 (0.5)	–0.2 (–1.1 to 0.5)	
Safety variables of interest				
Elevation in systolic BP ≥10 mm Hg	502/802 (62.6)	514/797 (64.5)	–1.9 (–6.6 to 2.8)	0.43
Elevation in systolic BP ≥15 mm Hg	354/802 (44.1)	377/797 (47.3)	–3.2 (–8.0 to 1.7)	0.20
Elevation in diastolic BP ≥10 mm Hg	326/802 (40.6)	319/797 (40.0)	0.6 (–4.2 to 5.4)	0.80
Serum sodium >ULN	86/800 (10.8)	84/797 (10.5)	0.2 (–2.8 to 3.2)	0.89
Serum chloride >ULN	23/800 (2.9)	27/797 (3.4)	–0.5 (–2.3 to 1.2)	0.56
Serum bicarbonate >ULN	11/800 (1.4)	17/797 (2.1)	–0.8 (–2.2 to 0.6)	0.25
Serum potassium <lower limit of the normal range	38/800 (4.8)	38/797 (4.8)	–0.0 (–2.2 to 2.1)	0.99
Confirmed elevations of ALT or AST ≥3× ULN	1/800 (0.1)	8/797 (1.0)	–0.9 (–1.9 to –0.2)	0.02
Creatine kinase ≥10× ULN	0/800	2/797 (0.3)	–0.3 (–0.9 to 0.2)	0.16
Any muscle symptom	32/808 (4.0)	28/804 (3.5)	0.5 (–1.4 to 2.4)	0.61

* ALT denotes alanine aminotransferase, AST aspartate aminotransferase, BP blood pressure, CI confidence interval, and ULN upper limit of the normal range.

sodium, there was no significant between-group difference in the percentage of patients with values greater than the upper limit of the normal range at 76 weeks (Table 3). The mean changes in sodium levels from baseline to 76 weeks were –0.96 mmol per liter and –1.2 mmol per liter in the anacetrapib and placebo groups, respectively (P=0.02). There were no cases of rhabdomyolysis in either study group and no significant differences in the percentages of patients with myalgias or other muscle symptoms or with elevations in creatine kinase (Table 3). Significantly fewer patients in the anacetrapib group than in the placebo group had levels of liver enzymes that were greater than 3 times the upper limit of the normal range in consecutive measurements (1 vs. 8, P=0.02) (Table 3). Among patients with diabetes, there was no significant difference between the groups in glycemic control; there was a trend toward a lower glycated hemoglobin level with anacetrapib at 24 weeks and at 76 weeks (Table 1 in the Supplementary Appendix).

CLINICAL END POINTS

During the 76-week study-treatment phase, the prespecified, adjudicated composite cardiovascular end point (death from cardiovascular causes, myocardial infarction, hospitalization for unstable angina, or stroke) occurred in 16 patients in the anacetrapib group (2.0%) as compared with 21 in the placebo group (2.6%) (P=0.40; hazard ratio, 0.76; 95% confidence interval, 0.39 to 1.45) (Table 4). The prespecified Bayesian analysis indicated that this event distribution provided 94% predictive probability (confidence) that anacetrapib would not be associated with the 25% increase in cardiovascular adverse events that was seen with torcetrapib. Death from any cause occurred in 11 patients in the anacetrapib group and 8 in the placebo group (P=0.50). Significantly fewer patients in the anacetrapib group than in the placebo group underwent revascularization (8 vs. 28, P=0.001) (Table 4). Heart failure developed in very few patients. In a post hoc analysis of a composite end point assessed in other trials[2-4] — death from any cause, myocardial infarction, stroke, unstable angina, or revascularization — an event occurred in 27 patients in the anacetrapib group (3.3%) as compared with 43 in the placebo group (5.3%) (P=0.048). In the 3 months after the 76-week treatment period, during which none of the patients were receiving the assigned

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study drug, there was 1 death in the anacetrapib group and there were 4 deaths in the placebo group (Table 3 in the Supplementary Appendix); thus, there were 12 deaths in each group through week 88.

DISCUSSION

This moderate-size safety study shows that anacetrapib, when used concomitantly with statin therapy, had substantial effects on plasma lipid levels. Treatment with anacetrapib, as compared with placebo, increased HDL cholesterol levels by 138.1%, decreased LDL cholesterol levels by 39.8%, and decreased non-HDL cholesterol levels by 31.7% — effects that are two to four times as large as those with other CETP inhibitors that have been tested to date.[5,8] The effects of anacetrapib therapy on apolipoprotein A-I and apolipoprotein B levels paralleled the effects on HDL cholesterol levels and LDL cholesterol levels, respectively, and, as compared with placebo, resulted in a substantial (36.4%) reduction in levels of lipoprotein(a), another atherogenic lipid particle that is relatively unaffected by statin therapy. The ratio of LDL cholesterol to HDL cholesterol was reduced from 2.1 at baseline to just 0.5 at both 24 and 76 weeks among patients treated with the combination of a statin and anacetrapib — a level that, to our knowledge, has not been achieved previously.

Treatment with anacetrapib had an acceptable side-effect profile and was not associated with an increase in liver enzyme levels or with myalgia, both of which are well-known side effects of statins.[1] Concern about the safety of inhibiting CETP was expressed when the results of the ILLUMINATE trial showed that treatment with the CETP inhibitor torcetrapib was associated with an excess of both cardiovascular events and deaths from any cause.[6] In addition, torcetrapib increased blood pressure, altered serum electrolyte levels, and increased serum aldosterone levels, which may have accounted for the adverse clinical outcomes.[6] It was subsequently shown that torcetrapib induces synthesis of both aldosterone and cortisol in adrenal cortical cells.[7,14] In contrast, in the current study, anacetrapib treatment did not alter blood pressure, electrolyte levels, or serum aldosterone levels, and the distribution of cardiovascular events between the two treatment groups provided a 94% predictive probability (confidence) that treatment with anacetrapib is not associated with the rate of adverse cardiovascular effects reported with torcetrapib.[6] These findings have opened the door to retesting the hypothesis that inhibition of CETP is cardioprotective.

Table 4. Cardiovascular Events during the Treatment Phase of the Study.*

Event	Anacetrapib (N=808)	Placebo (N=804)
	number (percent)	
Prespecified, adjudicated cardiovascular safety end point	16 (2.0)	21 (2.6)
Death from cardiovascular causes	4 (0.5)	1 (0.1)
Nonfatal myocardial infarction	6 (0.7)	9 (1.1)
Hospitalization for unstable angina	1 (0.1)	6 (0.7)
Nonfatal stroke	5 (0.6)	5 (0.6)
Death from any cause	11 (1.4)	8 (1.0)
Heart failure	3 (0.4)	4 (0.5)
Revascularization	8 (1.0)	28 (3.5)
PCI	6 (0.7)	25 (3.1)
CABG	2 (0.2)	3 (0.4)

* The duration of the treatment phase of the study was 76 weeks. CABG denotes coronary-artery bypass grafting, and PCI percutaneous coronary intervention.

One question that has been raised, however, is whether the HDL particles generated by the inhibition of CETP retain their atheroprotective function. Given the complex biologic characteristics of HDL and the role it plays in reverse cholesterol transport, the exact role of CETP inhibition has been debated. Inhibition of CETP increases the concentration of apolipoprotein A-I, the major HDL protein, and increases the size of HDL particles. However, concerns about the functionality of HDL particles isolated from patients who are taking CETP inhibitors has been largely defused by recent investigations. In vitro studies have shown that HDL particles isolated from patients treated with torcetrapib[15] and from patients treated with anacetrapib[16] have a normal or even an enhanced ability to promote the efflux of cholesterol from macrophages in vitro.[16] Furthermore, the enhanced functionality of HDL particles in patients treated with anacetrapib is greater at higher HDL cholesterol concentrations.[16]

Questions have also been raised about therapies that increase HDL cholesterol levels because of the conflicting results of epidemiologic studies examining the relationship between CETP activity and cardiovascular outcomes.[17,18] However, a recent meta-analysis of 92 studies involving 113,833 participants concluded that the CETP

genotypes that have been shown to have lower CETP activity were associated with a decreased coronary risk.[17] The magnitude of this reduction was similar to risk reductions that would have been predicted from published population studies[18] for a corresponding difference in HDL cholesterol concentrations.

Several limitations of the current study should be considered. First, the study is too small to provide definitive results regarding the overall safety or efficacy of anacetrapib. Second, since most of the study participants were white, additional safety data are required from patients of other races or ethnic groups, notably Asians, in whom drug metabolism of the lipid agents, such as statins, may be different. Third, given previous uncertainty regarding the safety of extremely low levels of LDL cholesterol, the protocol mandated the discontinuation of the study drug if the LDL cholesterol level was less than 25 mg per deciliter at two consecutive measurements; thus, the study provides no information about the long-term safety of reducing LDL cholesterol to such extremely low levels.

Nonetheless, this study showed that treatment with anacetrapib led to very large increases in HDL cholesterol and significant reductions in LDL cholesterol and other atherogenic particles and had an acceptable side-effect profile. The questions of whether further reductions in LDL cholesterol levels, below the levels currently achieved with statins, will be of benefit and whether raising HDL cholesterol levels is of clinical benefit will need to be addressed in larger trials. Within the limits of the power of this study, our data provide reassurance that inhibition of CETP, when not accompanied by the off-target effects of torcetrapib, may not have adverse cardiovascular effects. These initial results provide a rationale for conducting a large clinical outcomes trial involving patients with cardiovascular disease who are at high risk for recurrent events.

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