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Effects of the CETP Inhibitor Evacetrapib Administered as Monotherapy or in Combination With Statins on HDL and LDL Cholesterol

A Randomized Controlled Trial

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THE DEVELOPMENT OF STATINS for reducing low-density lipoprotein cholesterol (LDL-C) has revolutionized cardiovascular disease prevention.¹⁻⁶ Nonetheless, cardiovascular disease remains the number one cause of death.⁷ Accordingly, considerable efforts have focused on development of novel therapeutic agents designed to address residual cardiovascular risk. Because individuals from the general population with elevations of high-density lipoprotein cholesterol (HDL-C) have a reduced incidence of coronary heart disease,⁸ it has been assumed that finding an appropriate therapy to increase HDL-C levels would yield substantial clinical benefit.

However, development of drugs that increase HDL-C levels has been challenging and fraught with failures, including the premature termination of

For editorial comment see p 2153.

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Context Interest remains high in cholesteryl ester transfer protein (CETP) inhibitors as cardioprotective agents. Few studies have documented the efficacy and safety of CETP inhibitors in combination with commonly used statins.

Objective To examine the biochemical effects, safety, and tolerability of evacetrapib, as monotherapy and in combination with statins, in patients with dyslipidemia.

Design, Setting, and Participants Randomized controlled trial conducted among 398 patients with elevated low-density lipoprotein cholesterol (LDL-C) or low high-density lipoprotein cholesterol (HDL-C) levels from April 2010 to January 2011 at community and academic centers in the United States and Europe.

Interventions Following dietary lead-in, patients were randomly assigned to receive placebo (n=38); evacetrapib monotherapy, 30 mg/d (n=40), 100 mg/d (n=39), or 500 mg/d (n=42); or statin therapy (n=239) (simvastatin, 40 mg/d; atorvastatin, 20 mg/d; or rosuvastatin, 10 mg/d) with or without evacetrapib, 100 mg/d, for 12 weeks.

Main Outcome Measures The co-primary end points were percentage changes from baseline in HDL-C and LDL-C after 12 weeks of treatment.

Results The mean baseline HDL-C level was 55.1 (SD, 15.3) mg/dL and the mean baseline LDL-C level was 144.3 (SD, 26.6) mg/dL. As monotherapy, evacetrapib produced dose-dependent increases in HDL-C of 30.0 to 66.0 mg/dL (53.6% to 128.8%) compared with a decrease with placebo of -0.7 mg/dL (-3.0%; $P < .001$ for all compared with placebo) and decreases in LDL-C of -20.5 to -51.4 mg/dL (-13.6% to -35.9%) compared with an increase with placebo of 7.2 mg/dL (3.9%; $P < .001$ for all compared with placebo). In combination with statin therapy, evacetrapib, 100 mg/d, produced increases in HDL-C of 42.1 to 50.5 mg/dL (78.5% to 88.5%; $P < .001$ for all compared with statin monotherapy) and decreases in LDL-C of -67.1 to -75.8 mg/dL (-11.2% to -13.9%; $P < .001$ for all compared with statin monotherapy). Compared with evacetrapib monotherapy, the combination of statins and evacetrapib resulted in greater reductions in LDL-C ($P < .001$) but no greater increase in HDL-C ($P = .39$). Although the study was underpowered, no adverse effects were observed.

Conclusions Compared with placebo or statin monotherapy, evacetrapib as monotherapy or in combination with statins increased HDL-C levels and decreased LDL-C levels. The effects on cardiovascular outcomes require further investigation.

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a large outcomes trial studying the effects of the cholesteryl ester transfer protein (CETP) inhibitor torcetrapib.⁹ Despite failure of the first drug in the class, considerable interest remains in CETP inhibition as a therapeutic strategy, by virtue of the ability of these agents to substantially increase HDL-C levels and, in some cases, reduce LDL-C levels.¹⁰ The observation that CETP inhibition has a favorable effect on atherosclerotic lesion formation in animal species that express CETP¹¹ provides hope for potential benefit for humans.

While several CETP inhibitors are currently undergoing clinical evaluation, their effects in combination with the most commonly used statins have not been fully characterized. Evacetrapib is a novel, potent CETP inhibitor that has shown no demonstrable effects on blood pressure or adrenal synthesis of aldosterone or cortisol in pre-clinical studies.¹² The current study evaluated the biochemical efficacy, safety, and tolerability of evacetrapib as monotherapy and in combination with statin agents commonly used in clinical practice.

METHODS

Study Design

The study was a multicenter, randomized, double-blind, parallel, placebo-controlled clinical trial. The trial was designed by the Cleveland Clinic Coordinating Center for Clinical Research in collaboration with the sponsor. The institutional review boards of all participating centers approved the protocol and all patients provided written informed consent. Patients were at least 18 years old and were eligible on the basis of meeting low HDL-C or high LDL-C criteria, in the presence of triglyceride levels less than 400 mg/dL, after the dietary lead-in period. (To convert HDL-C and LDL-C to millimoles per liter, multiply by 0.0259. To convert triglycerides to millimoles per liter, multiply by 0.0113.)

Patients meeting the low HDL-C criteria had an HDL-C level of less than 45 mg/dL for men or 50 mg/dL for women,

with an LDL-C level that currently met the National Cholesterol Education Program (NCEP) Adult Treatment Panel III goal. Patients meeting the high LDL-C criteria had an LDL-C level between 100 and 190 mg/dL in the presence of 0 or 1 risk factors; between 100 and 160 mg/dL with at least 2 risk factors and a 10-year coronary risk of less than 10%; or between 100 and 130 mg/dL with at least 2 risk factors and a 10-year risk of 10% to 20%, in the presence of any level of HDL-C.

Patients were excluded if they had any clinical manifestation of atherosclerotic disease, hypertension (systolic blood pressure >140 mm Hg or diastolic blood pressure >90 mm Hg), documented hyperaldosteronism, uncontrolled diabetes (hemoglobin A_{1c} ≥8%), or significant liver, kidney, cardiac, or neuromuscular disease.

All patients entered a 2- to 8-week dietary lead-in period to evaluate the effect of the NCEP Therapeutic Lifestyle Changes diet and permit wash-out of any lipid-modifying therapies. The study evaluated the effects of 12 weeks of treatment with evacetrapib as monotherapy and in combination with statins. For the monotherapy evaluation, patients were randomly assigned to receive either placebo or evacetrapib at a dosage of 30 mg/d, 100 mg/d, or 500 mg/d. Monotherapy dosages were selected based on modeling of the results from phase 1 studies, in combination with literature data from other CETP inhibitors in development. For the combination treatment groups, patients were randomly assigned to receive either placebo or evacetrapib, 100 mg/d, in combination with the 3 most commonly prescribed statins, at typical dosages prescribed in clinical practice (simvastatin, 40 mg/d; atorvastatin, 20 mg/d; or rosuvastatin, 10 mg/d). Assignment to statin groups was performed during randomization to 1 of the 10 treatment groups. Randomization was performed by an interactive voice response system and was stratified according to geographic region and baseline levels of HDL-C and triglycerides.

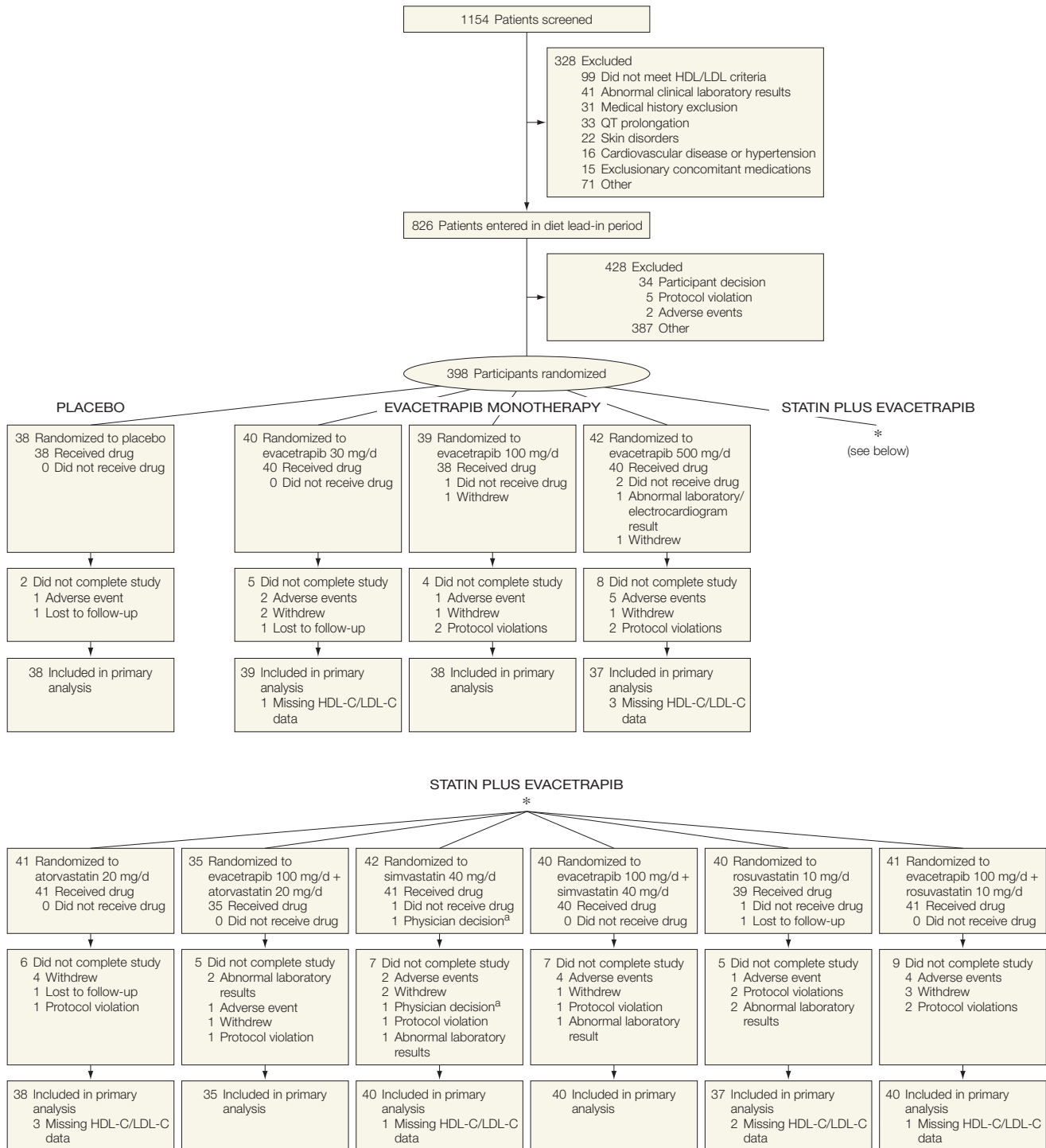
Clinic Visits and Laboratory Tests

Patients were examined during scheduled visits at weeks 2, 4, 8, and 12 during the treatment phase and a follow-up visit 4 to 6 weeks after cessation of the study drug. Lipoprotein levels and safety laboratory measurements were obtained at all visits. Blood pressure was measured at each visit by 3 replicate measurements using a standard automated blood pressure device. A central laboratory (Covance) performed all biochemical determinations. Standard lipid profiles (LDL-C, HDL-C, and triglycerides) were determined by enzymatic assay. High-sensitivity C-reactive protein (CRP) was determined by immunonephelometry. Measurement of CETP mass in serum samples was performed by enzyme-linked immunosorbent assay. Serum CETP activity was measured by fluorometric assay and expressed after correction for the maximum inhibitable CETP activity with evacetrapib. All reported cardiovascular events and rashes were evaluated and adjudicated by a blinded clinical end-point committee.

Statistical Analysis

A sample size of 35 patients per group was calculated to provide 87% power to simultaneously detect a 40% (SD, 30%) increase in HDL-C and 10% (SD, 15%) decrease in LDL-C compared with a statin alone for each of the combined therapy groups (.10 type I error rate for a 2-sided test). These changes reflect an increase in HDL-C greater than observed with niacin therapy¹³ and an incremental reduction in LDL-C of at least 10% in addition to statin therapy, both thought to be of potential clinical benefit. Demographic and baseline information are summarized using frequencies for categorical variables and means with standard deviations or medians with interquartile ranges for continuous variables.

The efficacy analyses were performed in the modified intention-to-treat population, consisting of those with a baseline and at least 1

Figure 1. Study Flow

The final disposition of patients in each group includes all patients assigned to study drug. Patients who withdrew from the study include those who discontinued due to participant or physician decision. Adverse events include discontinuations due to adverse events or abnormal laboratory or electrocardiographic results. HDL-C indicates high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol.

^aIncludes 1 participant who was withdrawn by the physician because of incarceration and 1 participant because of QT prolongation.

postbaseline efficacy measurement. For the monotherapy evaluation of evacetrapib, comparisons were made between each individual dosage and placebo. The statin combination evaluation reflects comparisons of each individual statin with that statin in combination with evacetrapib, 100 mg/d. In addition, evacetrapib, 100 mg/d, monotherapy was compared with evacetrapib, 100 mg/d, in combination with any statin.

A mixed model for repeated measurements was used to evaluate the percentage change from baseline in primary and secondary laboratory

measurements. The model included terms for baseline measurement, treatment group, visit, and treatment \times visit interaction. Least-squares means with 90% confidence intervals are reported. The safety analyses were conducted to evaluate change from baseline in the safety profile in the intention-to-treat population using the same modeling strategy. Safety data are reported as least-squares means with 90% confidence intervals or as frequencies. All analyses were conducted using SAS, version 9.2 (SAS Institute Inc) and were performed by academic statisticians (M.S., B.H.).

RESULTS

Participants

Between April 15, 2010, and January 14, 2011, 1154 patients were screened in the study at 70 sites. A total of 398 patients proceeded to the randomization phase of the study. The dispositions of these patients are shown in FIGURE 1. Baseline characteristics of the patients are shown in TABLE 1, TABLE 2, and eTable 1 (available at <http://www.jama.com>). Characteristics were similar for all treatment groups and are presented as summary data. The mean age was 58.3 years and approximately 56% of patients were women. Baseline lipid profiles were as follows: for LDL-C, mean, 144.3 (SD, 26.6) mg/dL; for HDL-C, mean, 55.1 (SD, 15.3) mg/dL; and for triglycerides, median, 121.3 (interquartile range, 88.6-176.3) mg/dL.

Lipoprotein Effects

Percentage changes in lipoprotein and apolipoprotein measurements and C-reactive protein are summarized in TABLE 3, TABLE 4, eTable 2, and eTable 3. Evacetrapib monotherapy produced dose-dependent increases in HDL-C ranging from 30.0 to 66.0 mg/dL (53.6% to 128.8%; $P < .001$ compared with placebo) and decreases in LDL-C of -20.5 to -51.4 mg/dL (-13.6% to -35.9% ; $P < .001$ compared with placebo). A significant 26.7-mg/dL (10.8%) reduction in triglyceride levels also was observed with the 500-mg/d dosage ($P = .006$ compared with placebo). These effects resulted in dose-dependent reductions in non-HDL-C by -23.2 to -45.8 mg/dL (-12.9% to -26.4% ; $P < .001$ compared with placebo) and apolipoprotein B by -13.8 to -29.7 mg/dL (-12.4% to -26.6% ; $P < .001$ compared with placebo).

When administered in combination with statin therapy, evacetrapib, 100 mg/d, increased HDL-C levels by 42.1 to 50.5 mg/dL (78.5% to 88.5%; $P < .001$ compared with statin alone) and resulted in greater reductions in LDL-C ($P < .001$) and non-HDL-C ($P < .05$ for atorvastatin and rosuvastatin) compared with effects observed with statin monotherapy. Compared with evacetra-

Table 1. Baseline Characteristics (Monotherapy Evaluation)^a

Characteristics	Placebo (n = 38)	Evacetrapib		
		30 mg/d (n = 40)	100 mg/d (n = 38)	500 mg/d (n = 40)
Age, y	55.2 (10.5)	58.5 (11.1)	58.5 (9.2)	58.8 (12.2)
Female, No. (%)	20 (52.6)	23 (57.5)	22 (57.9)	21 (52.5)
Body mass index ^b	29.8 (6.1)	29.8 (7.8)	27.6 (5.7)	29.0 (5.6)
Metabolic syndrome, No. (%) ^c	11 (28.9)	7 (17.5)	8 (21.1)	12 (30.0)
Hypertension, No. (%)	13 (34.2)	15 (37.5)	10 (26.3)	18 (45.0)
Diabetes, No. (%)	1 (2.6)	3 (7.5)	0	4 (10.0)
Smoker, No. (%)	6 (15.8)	5 (12.5)	4 (10.5)	5 (12.5)
Blood pressure, mm Hg				
Systolic	122.3 (9.7)	124.4 (11.0)	120.2 (11.3)	124.7 (8.3)
Diastolic	77.4 (6.3)	78.7 (7.3)	74.6 (8.7)	78.1 (8.0)
LDL-C, mg/dL	147.3 (21.6)	143.5 (26.0)	148.0 (25.0)	135.7 (26.0)
HDL-C, mg/dL	53.0 (11.8)	54.7 (12.0)	57.0 (14.1)	54.7 (16.3)
Triglycerides, median (IQR), mg/dL	113.4 (84.1-204.6)	120.0 (99.6-161.6)	121.8 (88.6-164.7)	116.9 (76.6-178.0)
Non-HDL-C, mg/dL	175.4 (29.2)	168.8 (27.3)	171.6 (27.3)	160.5 (26.7)
Apo B, mg/dL	110.2 (17.4)	108.0 (18.7)	107.8 (16.3)	100.2 (19.3)
Apo A-I, mg/dL	152.8 (26.2)	156.9 (24.6)	156.9 (24.0)	153.9 (29.7)
Apo A-II, mg/dL	38.3 (5.0)	39.8 (5.8)	40.1 (5.7)	39.1 (6.5)
Apo E, mg/dL	5.1 (1.1)	4.9 (1.0)	4.7 (1.0)	5.0 (1.3)
hsCRP, median (IQR), mg/L	1.7 (0.7-5.7)	1.4 (0.7-4.4)	1.3 (0.8-2.2)	1.8 (0.9-4.6)
CETP mass, μ g	2.2 (0.4)	2.3 (0.4)	2.2 (0.4)	2.3 (0.5)
CETP activity, pmol/mL/min	23.1 (5.0)	22.9 (4.5)	23.0 (5.9)	23.4 (5.5)

Abbreviations: Apo, apolipoprotein; CETP, cholesteryl ester transfer protein; HDL-C, high-density lipoprotein cholesterol; hsCRP, high-sensitivity C-reactive protein; IQR, interquartile range; LDL-C, low-density lipoprotein cholesterol.

SI conversions: To convert HDL-C and LDL-C to mmol/L, multiply by 0.0259; to convert triglycerides to mmol/L, multiply by 0.0113.

^aData are presented as mean (SD) unless otherwise indicated.

^bBody mass index was calculated as weight in kilograms divided by height in meters squared.

^cMetabolic syndrome incidence was determined using the criteria of the National Cholesterol Education Program, defined as at least 3 of the following: waist circumference ≥ 102 cm (men) or ≥ 88 cm (women); fasting triglycerides ≥ 150 mg/dL; HDL-C < 40 mg/dL (men) or < 50 mg/dL (women); blood pressure $\geq 130/85$ mm Hg; and fasting plasma glucose ≥ 110 mg/dL.

pib monotherapy, the combination of a statin and evacetrapib resulted in greater reductions in LDL-C by 71.0 vs 34.2 mg/dL (48.6% vs 23.7%; $P < .001$) but no greater increase in HDL-C by 45.9 vs 48.4 mg/dL (86.8% vs 91.3%; $P = .39$), consistent with known lipid effects of statins. Increases in HDL-C and decreases in atherogenic lipid levels with evacetrapib administration occurred rapidly, with most of these effects observed at 2 weeks.

Increases in HDL-C with evacetrapib produced dose-dependent increases in apolipoprotein A-I ranging from 35.7 to 72.6 mg/dL (22.7% to 49.6%; $P < .001$ compared with placebo), in apolipoprotein A-II by 4.8 to 7.4 mg/dL (12.7% to 19.7%; $P < .001$ compared with placebo), and in apolipoprotein E by 5.7 to 9.2 mg/dL (15.8% to 83.7%; $P < .001$ for the 2

highest dosages compared with placebo). A dose-dependent decrease in CETP activity ranging from -11.5 to -20.8 pmol/mL per minute (-49.5% to -89.1%; $P < .001$ compared with placebo) and an increase in CETP mass ranging from 1.5 to 3.2 μg (63.9% to 136.7%; $P < .001$ compared with placebo) were observed with evacetrapib monotherapy. C-reactive protein levels remained unchanged during 12 weeks of administration of evacetrapib, either as monotherapy or in combination with statins.

Within prespecified subgroups, there were significant interactions for evacetrapib monotherapy and placebo, with greater percentage increases in HDL-C (eFigure 1) among patients who were younger ($P = .002$), had lower baseline HDL-C ($P < .001$), and had higher baseline triglycerides ($P = .005$). Similarly,

significant interactions were observed with greater percentage decreases in LDL-C among patients who were younger ($P = .03$) and had lower baseline LDL-C levels ($P = .03$).

Safety Assessment

Adverse event rates and laboratory safety measurements are summarized in TABLE 5, and achieved blood pressure levels are shown in eFigure 2. Administration of evacetrapib as monotherapy was not associated with an increase in blood pressure compared with placebo. A greater increase in diastolic blood pressure was observed when evacetrapib, 100 mg/d, was administered in combination with simvastatin, 40 mg/d, compared with simvastatin monotherapy ($P = .02$). No other differences were observed in diastolic or systolic blood pressure changes

Table 2. Baseline Characteristics (Statin Combination Evaluation)^a

Characteristics	Atorvastatin, 20 mg/d		Simvastatin, 40 mg/d		Rosuvastatin, 10 mg/d	
	With Placebo (n = 41)	With Evacetrapib, 100 mg/d (n = 35)	With Placebo (n = 41)	With Evacetrapib, 100 mg/d (n = 40)	With Placebo (n = 39)	With Evacetrapib, 100 mg/d (n = 41)
Age, y	57.8 (11.3)	57.4 (11.8)	61.3 (10.0)	58.4 (9.0)	57.4 (12.6)	59.7 (10.1)
Female, No. (%)	26 (63.4)	18 (51.4)	29 (70.7)	25 (62.5)	13 (33.3)	23 (56.1)
Body mass index ^b	28.8 (5.1)	30.0 (7.5)	28.3 (5.0)	29.9 (5.3)	28.3 (4.2)	28.4 (5.3)
Metabolic syndrome, No. (%) ^c	13 (31.7)	9 (25.7)	11 (26.8)	14 (35.0)	7 (17.9)	9 (22.0)
Hypertension, No. (%)	16 (39.0)	13 (37.1)	10 (24.4)	18 (45.0)	11 (28.2)	14 (34.1)
Diabetes, No. (%)	2 (4.9)	1 (2.9)	2 (4.9)	0	0	3 (7.3)
Smoker, No. (%)	11 (26.8)	4 (11.4)	6 (14.6)	3 (7.5)	8 (20.5)	6 (14.6)
Blood pressure, mm Hg						
Systolic	125.1 (11.9)	122.9 (12.7)	121.1 (13.0)	122.0 (14.2)	123.2 (10.8)	122.0 (12.4)
Diastolic	79.4 (7.5)	78.9 (7.6)	76.0 (9.1)	77.3 (8.3)	76.3 (7.2)	77.8 (8.0)
LDL-C, mg/dL	139.0 (26.7)	143.6 (26.0)	154.8 (35.1)	143.7 (29.1)	141.6 (23.8)	145.7 (21.8)
HDL-C, mg/dL	53.9 (17.0)	55.7 (18.2)	57.3 (16.2)	53.7 (13.6)	53.5 (15.2)	57.8 (18.1)
Triglycerides, median (IQR), mg/dL	128.4 (88.6-186.9)	123.1 (79.7-165.6)	128.4 (86.8-168.3)	120.0 (94.8-181.1)	129.3 (94.8-179.8)	118.7 (85.0-163.9)
Non-HDL-C, mg/dL	169.3 (28.8)	168.9 (29.1)	183.2 (42.5)	170.3 (33.2)	167.2 (26.5)	171.2 (23.0)
Apo B, mg/dL	106.1 (17.6)	105.6 (18.9)	110.1 (17.7)	108.6 (21.6)	108.4 (22.0)	106.0 (17.1)
Apo A-I, mg/dL	157.4 (35.0)	154.2 (31.8)	162.4 (33.5)	154.0 (28.1)	157.2 (35.7)	161.6 (36.5)
Apo A-II, mg/dL	38.5 (7.3)	39.3 (6.1)	39.0 (5.4)	38.6 (6.1)	39.9 (5.9)	40.3 (6.4)
Apo E, mg/dL	5.5 (2.1)	4.8 (1.3)	5.5 (2.8)	5.0 (1.1)	4.6 (1.3)	5.1 (1.3)
hsCRP, median (IQR), mg/L	1.8 (0.7-3.2)	1.8 (0.8-3.5)	1.3 (0.7-3.7)	1.5 (1.0-2.8)	1.3 (0.7-2.6)	1.4 (0.7-3.4)
CETP mass, μg	2.4 (0.4)	2.2 (0.4)	2.4 (0.7)	2.3 (0.4)	2.2 (0.4)	2.2 (0.4)
CETP activity, pmol/mL/min	24.7 (5.7)	23.3 (5.7)	23.8 (5.3)	22.5 (5.3)	22.6 (5.5)	23.4 (5.7)

Abbreviations: Apo, apolipoprotein; CETP, cholesteryl ester transfer protein; HDL-C, high-density lipoprotein cholesterol; hsCRP, high-sensitivity C-reactive protein; IQR, interquartile range; LDL-C, low-density lipoprotein cholesterol.

SI conversions: To convert HDL-C and LDL-C to mmol/L, multiply by 0.0259; to convert triglycerides to mmol/L, multiply by 0.0113.

^aData are presented as mean (SD) unless otherwise indicated.

^bBody mass index was calculated as weight in kilograms divided by height in meters squared.

^cMetabolic syndrome incidence was determined using the criteria of the National Cholesterol Education Program, defined as at least 3 of the following: waist circumference ≥ 102 cm (men) or ≥ 88 cm (women); fasting triglycerides ≥ 150 mg/dL; HDL-C < 40 mg/dL (men) or < 50 mg/dL (women); blood pressure $\geq 130/85$ mm Hg; and fasting plasma glucose ≥ 110 mg/dL.

when evacetrapib was administered in combination with statin therapy. No differences were observed between patients treated with or without evacetrapib with regard to the rate of systolic blood pressure elevations in excess of 15 mm Hg. No significant changes in aldosterone, cortisol, or electrolytes were observed with administration of evacetrapib.

There was no difference between evacetrapib and control groups in either the monotherapy or statin combination studies with regard to the rate of treatment-related adverse events and discontinuation rates. Two significant rashes were observed during the course of the study. One participant treated with simvastatin monotherapy developed angioedema, which resolved with steroids and study drug discontinuation. A second participant treated with evacetrapib, 100 mg/d, in combination with rosuvastatin developed a morbilliform reaction 40 days after cessation of

study drug that resolved with conservative measures. Evacetrapib administered as monotherapy or in combination with statin therapy was not associated with significant laboratory abnormalities related to liver, kidney, or muscle toxicity. No adjudicated cardiovascular events were observed during the study.

COMMENT

Current guidelines for lipid-modulating therapy in both primary and secondary prevention populations emphasize reduction in apolipoprotein B-containing atherogenic lipoproteins.^{14,15} Although this approach has yielded major clinical benefits, residual risk remains substantial¹⁶ and has eluded effective treatment for decades. Essentially, no new classes of antiatherosclerotic therapies with clinically proven benefits have emerged since the introduction of statins in 1987. Considerable current interest has focused on drugs that increase HDL-C

levels, although these efforts have not yet yielded drugs with benefits on clinical outcomes. Drugs that inhibit CETP produce the largest increases in HDL-C levels and represent a potentially important strategy for addressing residual risk in statin-treated patients.

In the current study, we characterized the lipid efficacy, safety, and tolerability of a novel CETP inhibitor, evacetrapib, in patients with either hypercholesterolemia or low HDL-C levels. The study demonstrated that CETP inhibition with evacetrapib produced marked alterations in important lipoproteins, including large increases in HDL-C levels and decreases in LDL-C levels. The magnitude of these changes was substantial, demonstrating increases in HDL-C levels exceeding 125% and decreases in LDL-C levels exceeding 35% for the highest tested dosage. These HDL-C changes were significantly greater among patients with lower levels of HDL-C or higher triglyceride levels at baseline. Although

Table 3. Change in Laboratory Measures (Monotherapy Evaluation)^a

Measures	Placebo (n = 38)	Evacetrapib		
		30 mg/d (n = 40)	100 mg/d (n = 38)	500 mg/d (n = 40)
LDL-C, mg/dL				
Follow-up	153.3 (32.8)	124.4 (26.8)	114.8 (34.0)	87.4 (24.8)
Absolute change	7.2 (0 to 14.4)	-20.5 (-27.8 to -13.3)	-31.7 (-39.0 to -24.4)	-51.4 (-58.9 to -43.9)
Percentage change	3.9 (-1.0 to 8.9)	-13.6 (-18.6 to -8.7)	-22.3 (-27.3 to -17.3)	-35.9 (-41.1 to -30.7)
Relative change		-17.6 (-24.6 to -10.5) ^b	-26.2 (-33.2 to -19.2) ^b	-39.8 (-47.0 to -32.7) ^b
HDL-C, mg/dL				
Follow-up	51.6 (13.7)	87.1 (24.0)	108.6 (28.9)	126.1 (25.7)
Absolute change	-0.7 (-5.6 to 4.3)	30.0 (25.1 to 35.0)	50.9 (45.9 to 55.9)	66.0 (60.8 to 71.1)
Percentage change	-3.0 (-12.3 to 6.2)	53.6 (44.4 to 62.9)	94.6 (85.2 to 104.0)	128.8 (119.2 to 138.4)
Relative change		56.7 (43.6 to 69.8) ^b	97.6 (84.5 to 110.8) ^b	131.9 (118.5 to 145.2) ^b
Triglycerides, mg/dL				
Follow-up, median (IQR)	121.3 (86.4 to 178.9)	106.3 (85.0 to 147.9)	113.4 (83.3 to 148.8)	94.8 (80.6 to 121.3)
Absolute change	-0.5 (-12.4 to 11.4)	-13.2 (-25.2 to -1.2)	-9.8 (-21.8 to 2.3)	-26.7 (-39.1 to -14.4)
Percentage change	9.3 (1.0 to 17.5)	-3.1 (-11.4 to 5.2)	-3.1 (-11.5 to 5.2)	-10.8 (-19.4 to -2.2)
Relative change		-12.4 (-24.1 to -0.6)	-12.4 (-24.2 to -0.6)	-20.1 (-32.0 to -8.2) ^c
CRP, mg/L ^d				
Follow-up, median (IQR)	1.8 (1.0 to 4.0)	1.7 (0.6 to 6.4)	1.2 (0.8 to 3.2)	1.7 (0.7 to 5.6)
Absolute change	-1.7 (-4.4 to 1.0)	0.9 (-1.7 to 3.6)	1.2 (-1.4 to 3.9)	0.9 (-1.6 to 3.5)
Percentage change	75.5 (5.9 to 145.1)	127.8 (58.7 to 196.9)	76.6 (7.2 to 146.0)	120.0 (53.5 to 186.4)
Relative change		52.3 (-45.5 to 150.1)	1.1 (-97.5 to 99.8)	44.5 (-51.5 to 140.5)

Abbreviations: CRP, C-reactive protein; HDL-C, high-density lipoprotein cholesterol; IQR, interquartile range; LDL-C, low-density lipoprotein cholesterol.

SI conversions: To convert HDL-C and LDL-C to mmol/L, multiply by 0.0259; to convert triglycerides to mmol/L, multiply by 0.0113.

^aFollow-up values are mean (SD) unless otherwise noted. Absolute changes are least-squares mean changes from baseline until follow-up visit 7 from analysis of covariance model (90% CI) unless otherwise noted. Percentage changes are least-squares mean percentage changes from baseline until follow-up visit 7 from analysis of covariance model (90% CI) unless otherwise noted. Relative changes are differences in percentage changes between placebo and evacetrapib counterpart.

^b $P < .001$.

^c $P < .01$.

^dLast-observation-carried-forward data are applied in the analysis.

evacetrapib was well tolerated, the study was underpowered to rule out uncommon adverse effects.

Because of the robust clinical benefits of statins, any new lipid-modulating agent will likely be administered on a background of statin therapy. Accordingly, we tested evacetrapib both as monotherapy and in combination with the most commonly used dosages of the most frequently prescribed statins. In combination with a broad range of statins, evacetrapib produced a similar degree of HDL-C increase compared with evacetrapib monotherapy, reaching 94% for the 100-mg/d dosage. Similarly, while the incremental decreases in LDL-C were predictably smaller in combination with statins than observed with monotherapy, these changes still repre-

sented potentially useful effects, resulting in 11% to 14% additional LDL-C lowering. These preliminary findings suggest that evacetrapib could be administered with statins and may yield potentially clinically important incremental effects on lipoproteins. The finding of less LDL-C lowering with evacetrapib monotherapy in patients with higher baseline LDL-C levels needs further investigation.

The initial enthusiasm for CETP inhibitors waned following reports that torcetrapib did not slow disease progression¹⁷⁻¹⁹ and increased mortality.⁹ Some observers postulated that these adverse findings reflected a potential detrimental effect of CETP inhibition on HDL functionality.²⁰ However, subsequent investigations determined that

torcetrapib had off-target effects that likely contributed to the observed adverse effect on cardiovascular outcomes.²¹ Accordingly, there is renewed interest in the pursuit of other CETP inhibitors that lack such off-target effects but retain the favorable lipid effects. Subsequent development of all novel CETP inhibitors has required comprehensive characterization of safety and tolerability. Equipoise for the study of evacetrapib in dyslipidemic patients was provided by the lack of apparent off-target adverse effects in phase 1 studies and the potential of this agent to provide clinically important effects on lipoproteins.

In the current 12-week study, administration of evacetrapib was well

Table 4. Change in Laboratory Measures (Statin Combination Evaluation)^a

Measures	Atorvastatin, 20 mg/d		Simvastatin, 40 mg/d		Rosuvastatin, 10 mg/d	
	With Placebo (n = 41)	With Evacetrapib (n = 35)	With Placebo (n = 41)	With Evacetrapib (n = 40)	With Placebo (n = 39)	With Evacetrapib (n = 41)
LDL-C, mg/dL						
Follow-up	90.8 (26.7)	71.2 (37.5)	95.7 (25.8)	73.1 (34.2)	84.7 (25.4)	65.7 (23.8)
Absolute change	-49.5 (-56.8 to -42.3)	-70.5 (-78.1 to -62.8)	-51.3 (-58.5 to -44.2)	-67.1 (-74.5 to -59.8)	-57.7 (-65.0 to -50.4)	-75.8 (-83.1 to -68.4)
Percentage change	-33.6 (-38.6 to -28.7)	-47.6 (-52.8 to -42.3)	-34.9 (-39.8 to -29.8)	-46.1 (-51.1 to -41.0)	-38.8 (-43.8 to -33.8)	-52.3 (-57.3 to -47.3)
Relative change		-13.9 (-21.2 to -6.7) ^b		-11.2 (-18.3 to -4.2) ^b		-13.5 (-20.6 to -6.4) ^b
HDL-C, mg/dL						
Follow-up	54.8 (18.9)	98.8 (31.8)	61.0 (17.4)	97.5 (29.9)	54.6 (12.5)	114.5 (33.9)
Absolute change	1.3 (-3.7 to 6.4)	42.1 (36.9 to 47.4)	2.9 (-2.0 to 7.7)	45.1 (40.1 to 50.1)	2.7 (-2.3 to 7.7)	50.5 (45.5 to 55.5)
Percentage change	1.4 (-8.0 to 10.8)	79.9 (70.1 to 89.8)	7.3 (-1.8 to 16.4)	86.6 (77.3 to 96.0)	5.5 (-3.9 to 15.0)	94.0 (84.7 to 103.4)
Relative change		78.5 (64.9 to 92.1) ^c		79.3 (66.2 to 92.4) ^c		88.5 (75.2 to 101.8) ^c
Triglycerides, mg/dL						
Follow-up, median (IQR)	101.0 (72.6 to 145.3)	88.6 (70.0 to 119.6)	93.0 (72.6 to 124.4)	100.1 (78.8 to 116.9)	101.0 (72.6 to 133.7)	82.4 (66.4 to 122.2)
Absolute change	-21.3 (-33.2 to -9.3)	-30.8 (-43.6 to -18.1)	-31.2 (-42.9 to -19.4)	-28.2 (-40.5 to -16.0)	-28.8 (-40.8 to -16.8)	-38.2 (-50.4 to -26.0)
Percentage change	-7.7 (-16.1 to 0.6)	-13.4 (-22.2 to -4.6)	-16.1 (-24.3 to -7.9)	-15.0 (-23.5 to -6.6)	-14.6 (-22.9 to -6.2)	-22.4 (-30.9 to -13.9)
Relative change		-5.7 (-17.8 to 6.5)		1.0 (-10.7 to 12.8)		-7.9 (-19.8 to 4.1)
CRP, mg/L ^d						
Follow-up, median (IQR)	1.0 (0.6 to 2.5)	1.0 (0.6 to 3.4)	1.0 (0.6 to 2.4)	1.8 (0.9 to 3.7)	1.0 (0.5 to 1.6)	1.3 (0.5 to 2.6)
Absolute change	4.4 (1.8 to 7.0)	-0.5 (-3.2 to 2.3)	0.3 (-2.3 to 2.9)	0.7 (-1.8 to 3.3)	0 (-2.5 to 2.6)	-0.2 (-2.7 to 2.3)
Percentage change	27.9 (-40.3 to 96.0)	10.2 (-60.8 to 81.2)	-9.4 (-77.6 to 58.8)	50.5 (-16.8 to 117.9)	-0.3 (-67.7 to 67.2)	6.1 (-59.5 to 71.7)
Relative change		-17.7 (-116.0 to 80.7)		60.0 (-35.8 to 155.7)		6.4 (-87.6 to 100.4)

Abbreviations: CRP, C-reactive protein; HDL-C, high-density lipoprotein cholesterol; IQR, interquartile range; LDL-C, low-density lipoprotein cholesterol.

SI conversions: To convert HDL-C and LDL-C to mmol/L, multiply by 0.0259; to convert triglycerides to mmol/L, multiply by 0.0113.

^aFollow-up data are mean (SD) unless otherwise indicated. Absolute changes are least-squares mean changes from baseline until follow-up visit 7 from analysis of covariance model (90% CI) unless otherwise indicated. Percentage changes are least-squares mean percentage changes from baseline until follow-up visit 7 from analysis of covariance model (90% CI) unless otherwise indicated. Relative changes are differences in percentage changes between placebo and evacetrapib counterpart.

^b $P < .01$.

^c $P < .001$.

^dLast-observation-carried-forward data are applied in the analysis.

Table 5. Safety Data^a

Measures	Placebo (n = 38)	Evacetrapib			Statin Monotherapy (n = 121)	Statin + Evacetrapib, 100 mg/d (n = 116)
		30 mg/d (n = 40)	100 mg/d (n = 38)	500 mg/d (n = 40)		
Drug-related adverse events, No. (%)	7 (18.4)	8 (20.0)	5 (13.2)	10 (25.0)	22 (18.2)	31 (26.7)
Adverse events leading to discontinuation, No. (%)	1 (2.6)	2 (5.0)	1 (2.6)	5 (12.5)	3 (2.5)	9 (7.8)
Serious adverse events, No. (%)	0	0	0	1 (2.5)	1 (0.8)	2 (1.7)
Drug-related serious adverse events, No. (%)	0	0	0	0	0	0
Elevation in systolic blood pressure \geq 15 mm Hg, No. (%) ^b	4 (10.5)	9 (23.1)	5 (13.2)	8 (20.0)	23 (19.3)	25 (21.6)
Elevation in diastolic blood pressure \geq 10 mm Hg, No. (%) ^b	10 (26.3)	7 (17.9)	9 (23.7)	11 (27.5)	30 (25.2)	23 (19.8)
Creatinine >ULN, No. (%) ^b	1 (2.6)	1 (2.6)	2 (5.2)	4 (10.0)	9 (7.6)	6 (5.2)
Creatine kinase >5 \times ULN, No. (%) ^b	1 (2.6)	0	0	0	2 (1.7)	2 (1.7)
Alanine aminotransferase >3 \times ULN, No. (%) ^b	0	0	0	0	0	1 (0.9)
Aldosterone, ng/dL ^c						
Baseline	8.30 (8.108)	7.71 (8.17)	5.97 (4.27)	6.73 (5.94)	7.67 (5.29)	6.99 (4.38)
Follow-up	6.54 (4.67)	6.87 (4.80)	7.77 (6.74)	6.76 (5.49)	6.34 (5.63)	6.82 (5.26)
Absolute change	-1.00 (-2.69 to 0.68)	-0.45 (-2.17 to 1.27)	0.96 (-0.75 to 2.67)	-0.30 (-2.06 to 1.45)	-1.12 (-2.11 to -0.13)	-0.45 (-1.48 to 0.58)
Percentage change	112.84 (14.94 to 210.74)	90.37 (-9.17 to 189.91)	69.84 (-29.07 to 168.74)	271.04 (169.64 to 372.44)	34.88 (-22.15 to 91.91)	30.93 (-27.60 to 89.46)
Relative change		-22.47 (-162.03 to 117.09)	-43.00 (-182.18 to 96.17)	158.20 (17.23 to 299.17) ^d		-3.95 (-85.65 to 77.75)
Salivary cortisol, μ g/dL ^{c,e}						
Baseline	0.11 (0.12)	0.10 (0.17)	0.07 (0.07)	0.07 (0.06)	0.07 (0.06)	0.07 (0.08)
Follow-up	0.08 (0.12)	0.06 (0.05)	0.07 (0.05)	0.09 (0.09)	0.10 (0.16)	0.08 (0.09)
Absolute change	-0.003 (-0.05 to 0.04)	-0.03 (-0.08 to 0.02)	0.002 (-0.05 to 0.05)	0.004 (-0.05 to 0.06)	0.03 (0.001 to 0.05)	0.01 (-0.02 to 0.03)
Percentage change	6.53 (-68.79 to 81.86)	9.96 (-65.44 to 85.36)	109.05 (33.59 to 184.52)	63.11 (-20.79 to 147.01)	64.78 (22.04 to 107.51)	32.10 (-12.90 to 77.11)
Relative change		3.42 (-102.55 to 109.41)	102.52 (-4.13 to 209.18)	56.58 (-56.47 to 169.62)		-32.67 (-94.77 to 29.42)
Sodium, mEq/L ^c						
Baseline	142.32 (3.36)	141.65 (2.95)	141.92 (3.16)	141.28 (2.47)	141.45 (2.55)	141.28 (2.52)
Follow-up	142.03 (2.89)	141.89 (2.59)	142.09 (3.01)	142.00 (2.76)	142.48 (2.94)	142.18 (2.55)
Absolute change	0.11 (-0.70 to 0.92)	0.26 (-0.56 to 1.08)	0.27 (-0.55 to 1.10)	0.47 (-0.38 to 1.31)	0.83 (0.36 to 1.30)	0.62 (0.13 to 1.11)
Percentage change	0.11 (-0.46 to 0.68)	0.21 (-0.36 to 0.79)	0.23 (-0.35 to 0.80)	0.36 (-0.23 to 0.95)		0.45 (0.11 to 0.80)
Relative change		0.10 (-0.71 to 0.91)	0.11 (-0.70 to 0.92)	0.25 (-0.58 to 1.07)		-0.15 (-0.62 to 0.33)
Potassium, mEq/L ^c						
Baseline	2.87 (0.33)	3.90 (0.36)	3.86 (0.30)	3.80 (0.34)	3.91 (0.29)	3.92 (0.35)
Follow-up	3.84 (0.29)	3.91 (0.33)	3.96 (0.39)	3.86 (0.28)	3.92 (0.25)	3.88 (0.28)
Absolute change	-0.01 (-0.10 to 0.08)	0.03 (-0.06 to 0.12)	0.06 (-0.03 to 0.16)	0.02 (-0.07 to 0.12)	0.02 (-0.04 to 0.07)	-0.01 (-0.06 to 0.05)
Percentage change		1.39 (-1.04 to 3.81)	1.78 (-0.65 to 4.21)	0.94 (-1.57 to 3.44)	0.85 (-0.54 to 2.25)	0.35 (-1.11 to 1.81)
Relative change	0.21 (-2.19 to 2.61)	1.18 (-2.24 to 4.59)	1.57 (-1.85 to 4.99)	0.73 (-2.74 to 4.20)		-0.50 (-2.52 to 1.51)
Bicarbonate, mEq/L ^c						
Baseline	22.62 (3.59)	22.79 (3.00)	23.28 (2.93)	22.92 (3.09)	22.74 (3.34)	22.98 (3.02)
Follow-up	22.75 (3.25)	23.31 (2.46)	23.29 (2.76)	23.22 (3.26)	23.34 (3.09)	23.47 (2.48)
Absolute change	0.27 (-0.44 to 0.98)	0.41 (-0.31 to 1.12)	0.60 (-0.11 to 1.31)	0.51 (-0.23 to 1.25)	0.66 (0.25 to 1.06)	0.80 (0.38 to 1.23)
Percentage change	2.01 (-1.25 to 5.28)	2.50 (-0.80 to 5.79)	3.34 (0.06 to 6.62)	2.56 (-0.85 to 5.98)	4.03 (2.15 to 5.91)	4.59 (2.64 to 6.54)
Relative change		0.48 (-4.16 to 5.12)	1.33 (-3.29 to 5.95)	0.55 (-4.17 to 5.28)		0.56 (-2.15 to 3.27)

Abbreviation: ULN, upper limit of normal.

^aThe denominators shown are the intention-to-treat population for the individual treatment groups.^bPatients without a postbaseline measurement are excluded from the analysis.^cBaseline and follow-up data are mean (SD) unless otherwise indicated. Baseline is defined as the last nonmissing observation prior to the first dose of study medication. If the first dose date were unavailable, the treatment dispense date from the interactive voice response system was used. Follow-up is defined as the observation at visit 7 unless otherwise indicated. Absolute changes are least-squares mean changes from baseline until follow-up visit 7 from analysis of covariance model (95% CI) unless otherwise indicated. Percentage changes are least-squares mean percentage changes from baseline until follow-up visit 7 from analysis of covariance model (95% CI) unless otherwise indicated. Relative changes are differences in percentage changes between placebo and evacetrapib counterpart.^d $P < .05$.^eFollow-up is defined as the observation at visit 6. Absolute changes are least-squares means changes from baseline until follow-up visit 6 from analysis of covariance model (95% CI). Percentage changes are least-squares mean percentage changes from baseline until follow-up visit 6 from analysis of covariance model (95% CI).

tolerated, with a low rate of treatment-related adverse events or discontinuation of therapy. No increase in blood pressure was observed in evacetrapib-treated patients, and no effects on mineralocorticoid and glucocorticoid activity were observed. These data suggest that evacetrapib favorably affects lipoproteins without apparent major toxic effects. Because a few rashes occurred during early-phase studies, we also carefully collected information on skin changes during the current study. No evidence emerged suggesting serious drug eruptions with evacetrapib. However, a full safety assessment of evac-

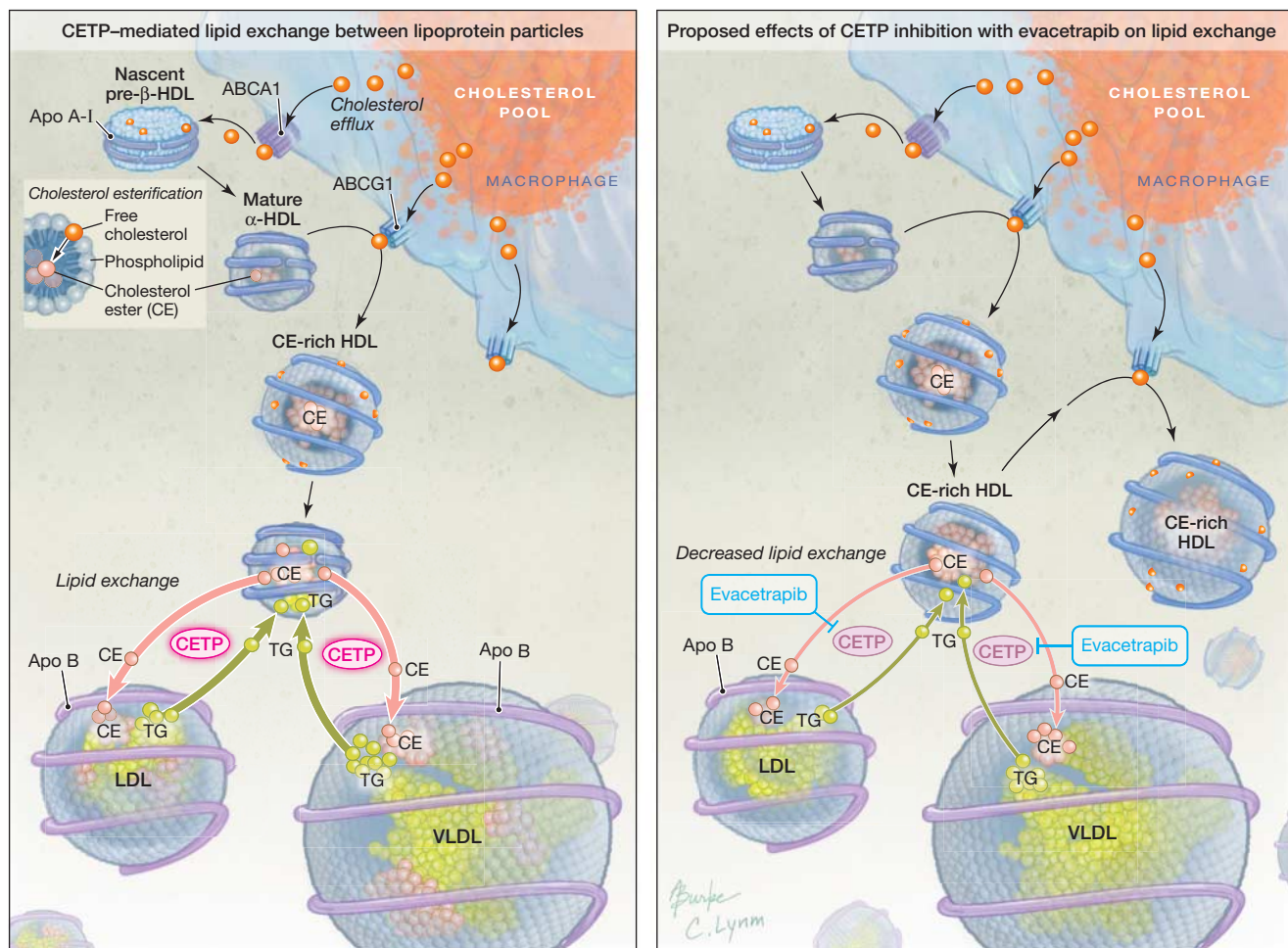
etrapib will require exposure of a much larger number of patients.

In addition to standard lipid measurements, we performed a comprehensive analysis of the effects of evacetrapib on the major apolipoproteins carried on HDL particles. Both apolipoproteins A-I and A-II increased substantially with administration of evacetrapib, a finding that likely reflects a predominant increase in concentrations of larger HDL particles as a result of accumulation of cholesteryl ester. A marked increase in circulating apolipoprotein E levels was also observed, which may be relevant be-

cause previous reports with torcetrapib demonstrated that apolipoprotein E enrichment of HDL particles was associated with an increase in cholesterol efflux capacity.²²

Free cholesterol efflux to HDL particles and subsequent transfer to other lipid particles have been demonstrated to involve highly complex pathways (FIGURE 2).²³ The effects of evacetrapib on HDL subclasses and composition continue to be elucidated, and the impact of this agent on lipid transport would require additional investigations. Although CETP inhibitors have been developed primar-

Figure 2. Proposed Mechanism of Evacetrapib on Lipid Exchange Between Lipoprotein Particles



The left panel illustrates exchange of cholesteryl ester and triglycerides (TG) between high-density lipoprotein (HDL), low-density lipoprotein (LDL), and very low-density lipoprotein (VLDL) particles. The right panel illustrates the proposed effects of evacetrapib, which inhibits lipid exchange via the CETP (cholesteryl ester transfer protein) pathway. This mechanism theoretically results in HDL particles that contain greater amounts of cholesterol, and LDL particles that contain lesser amounts of cholesterol, resulting in an increase in circulating levels of HDL cholesterol and a decrease in LDL cholesterol.

ily to increase HDL-C levels, more potent members of this class also lower LDL-C.²⁴ The current study demonstrates that evacetrapib has favorable effects on LDL-C and apolipoprotein B in both monotherapy- and statin-treated patients. Although these effects may ultimately translate into cardiovascular benefits, the role of CETP inhibition as a therapeutic strategy to reduce cardiovascular events remains to be established.

Epidemiological studies of the relationship between CETP and cardiovascular risk have shown variable results, with some¹⁰ but not all^{25,26} investigators reporting an association between low CETP activity and protection against cardiovascular disease. Studies in animal models generally show that reduced CETP activity is atheroprotective,^{11,27,28} but not all animals have lipid metabolic pathways comparable with that of humans. The inability of torcetrapib to slow disease progression in humans raised concerns about HDL functionality. However, there is currently no evidence that CETP inhibitors impair the ability of HDL to promote efflux of cholesterol. Post hoc analysis of torcetrapib trials showed that patients with the largest increases in HDL-C exhibited regression of coronary atherosclerosis²⁹ and fewer cardiovascular events.³⁰

However, a number of other issues remain unresolved. The current study included numerous parallel treatment groups with multiple unadjusted statistical comparisons. While the analysis prespecified a type I error rate of .10 for efficacy measures, additional testing with an error rate of .05 did not alter the findings (eTable 3). Predictably, CETP mass increased, although it is unknown if this has any effect beyond lipid transfer. The optimal degree of CETP inhibition has not been elucidated. Recent speculation suggests that dalcetrapib, a less potent CETP inhibitor, may selectively modulate CETP pathways in a manner that preserves levels of lipid-deplete pre- β HDL.³¹ However, the cardiovascular effects of this finding remain uncertain.

No studies have yet demonstrated that any CETP inhibitor reduces disease progression or promotes plaque regression.

Two additional CETP inhibitors are currently undergoing clinical evaluation. The lipid changes observed with evacetrapib appeared to be more similar to those of anacetrapib, producing substantial elevation of HDL-C and lowering of LDL-C. Evacetrapib, like both anacetrapib and dalcetrapib, appeared to be well tolerated with no discernible adverse effects on blood pressure and mineralocorticoid levels. Ultimately, the benefits of each of these novel CETP inhibitors must be determined through prospective, randomized, clinical outcome trials. The results of the current study provide the foundation for a large phase 3 clinical trial designed to assess the efficacy and safety of evacetrapib.

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Acquisition of data: Wang, McErean.

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Study supervision: Krueger.

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Role of the Sponsor: Eli Lilly participated actively in designing the study, developing the protocol, and provided logistical support during the trial. Monitoring of the study was performed by a contract research organization, Quintiles, under contract with the sponsor. The sponsor maintained the trial database. Statistical analysis was performed by statisticians employed by Eli Lilly, although the analyses reported in the article represent those performed by the academic statisticians (Mr Shao and Dr Hu). After completion of the trial, as specified in the study contract, a complete copy of the database was transferred to the Cleveland Clinic Coordinating Center for Clinical Research, where analyses were verified by the independent statisticians, Mr Shao and Dr Hu. The manuscript was prepared by Dr Nicholls and modified after consultation with the co-authors. The sponsor was permitted to review the manuscript and suggest changes, but the final decision on content was exclusively retained by the academic authors.

Independent Statistical Analysis: For the purpose of the academic interpretation of the study, Mr Shao and Dr Hu performed all primary statistical analyses. All results presented in the article were performed by Dr Hu. Mr Shao is an employee of the Cleveland Clinic Coordinating Center for Clinical Research. Dr Hu is a faculty member within the Department of Quantitative Health Sciences at the Cleveland Clinic Lerner College of Medicine of Case Western Reserve University.

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Online-Only Material: eTables 1, 2, and 3, eFigures 1 and 2, and the Author Video Interview are available at <http://www.jama.com>.

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