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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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 rosvastatin, 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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EFFECTS OF EVACETRAPIB ON LIPIDS

a large outcomes trial studying the effects of the cholesteryl ester transfer protein (CETP) inhibitor torcetrapib. 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. The observation that CETP inhibition has a favorable effect on atherosclerotic lesion formation in animal species that express inhibitable CETP activity with evacetrapib 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 preclinical studies. 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, uncontrollable diabetes (hemoglobin A1c ≥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 washout 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.

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 therapy 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.

*Includes 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 × 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 evacetrapib monotherapy, the addition of evacetrapib, 100 mg/d, to each individual statin was shown to result in significant reductions in LDL-C ranging from 5.4 to 12.4 mg/dL (−4.9% to −12.4%; P < .005 for each combination).
EFFECTS OF EVACETRAPIB ON LIPIDS

Table 2. Baseline Characteristics (Statin Combination Evaluation)a

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Atorvastatin, 20 mg/d</th>
<th>Simvastatin, 40 mg/d</th>
<th>Rosuvastatin, 10 mg/d</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>With Placebo (n = 41)</td>
<td>With Placebo (n = 39)</td>
<td>With Placebo (n = 40)</td>
</tr>
<tr>
<td>Age, y</td>
<td>57.8 (11.3)</td>
<td>57.4 (11.8)</td>
<td>61.3 (10.0)</td>
</tr>
<tr>
<td>Female, No. (%)</td>
<td>26 (63.4)</td>
<td>18 (51.4)</td>
<td>29 (70.7)</td>
</tr>
<tr>
<td>Body mass indexb</td>
<td>28.8 (5.1)</td>
<td>30.0 (7.5)</td>
<td>28.3 (5.0)</td>
</tr>
<tr>
<td>Metabolic syndrome, No. (%)c</td>
<td>13 (31.7)</td>
<td>9 (25.7)</td>
<td>11 (26.8)</td>
</tr>
<tr>
<td>Hypertension, No. (%)</td>
<td>16 (39.0)</td>
<td>13 (37.1)</td>
<td>10 (24.4)</td>
</tr>
<tr>
<td>Diabetes, No. (%)</td>
<td>2 (4.9)</td>
<td>1 (2.9)</td>
<td>2 (4.9)</td>
</tr>
<tr>
<td>Smoker, No. (%)</td>
<td>11 (26.8)</td>
<td>4 (11.4)</td>
<td>3 (7.3)</td>
</tr>
<tr>
<td>Blood pressure, mm Hg</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic</td>
<td>125.1 (11.9)</td>
<td>122.9 (12.7)</td>
<td>121.1 (13.0)</td>
</tr>
<tr>
<td>Diastolic</td>
<td>79.4 (7.5)</td>
<td>78.9 (7.6)</td>
<td>76.0 (9.1)</td>
</tr>
<tr>
<td>LDL-C, mg/dL</td>
<td>139.0 (26.7)</td>
<td>143.6 (26.0)</td>
<td>154.8 (35.1)</td>
</tr>
<tr>
<td>HDL-C, mg/dL</td>
<td>53.9 (17.0)</td>
<td>55.7 (18.2)</td>
<td>57.3 (16.2)</td>
</tr>
<tr>
<td>Triglycerides, median (IQR), mg/dL</td>
<td>128.4 (88.6-186.9)</td>
<td>123.1 (79.7-165.6)</td>
<td>128.4 (86.8-168.3)</td>
</tr>
<tr>
<td>Non–HDL-C, mg/dL</td>
<td>169.3 (28.8)</td>
<td>168.9 (29.1)</td>
<td>183.2 (42.5)</td>
</tr>
<tr>
<td>Apo A-I, mg/dL</td>
<td>38.5 (7.3)</td>
<td>39.3 (6.1)</td>
<td>39.0 (5.4)</td>
</tr>
<tr>
<td>Apo A-II, mg/dL</td>
<td>5.5 (2.1)</td>
<td>4.8 (1.3)</td>
<td>5.5 (2.8)</td>
</tr>
<tr>
<td>hsCRP, median (IQR), mg/L</td>
<td>1.8 (0.7-3.2)</td>
<td>1.8 (0.8-3.5)</td>
<td>1.3 (0.7-3.7)</td>
</tr>
<tr>
<td>CETP mass, µg</td>
<td>2.4 (0.4)</td>
<td>2.2 (0.4)</td>
<td>2.4 (0.7)</td>
</tr>
<tr>
<td>CETP activity, pmol/mL/min</td>
<td>24.7 (5.7)</td>
<td>23.5 (6.7)</td>
<td>23.8 (5.3)</td>
</tr>
</tbody>
</table>

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.

Data are presented as mean (SD) unless otherwise indicated.

Body 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 ≥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.\textsuperscript{14,15} Although this approach has yielded major clinical benefits, residual risk remains substantial\textsuperscript{16} 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)\textsuperscript{a}

<table>
<thead>
<tr>
<th>Measures</th>
<th>Placebo (n = 38)</th>
<th>30 mg/d (n = 40)</th>
<th>100 mg/d (n = 38)</th>
<th>500 mg/d (n = 40)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>LDL-C, mg/dL</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Follow-up</td>
<td>153.3 (32.8)</td>
<td>124.4 (26.8)</td>
<td>114.8 (34.0)</td>
<td>87.4 (24.8)</td>
</tr>
<tr>
<td>Absolute change</td>
<td>7.2 (0 to 14.4)</td>
<td>−20.5 (−27.8 to −13.3)</td>
<td>−31.7 (−39.0 to −24.4)</td>
<td>−51.4 (−58.9 to −43.9)</td>
</tr>
<tr>
<td>Percentage change</td>
<td>3.9 (−1.0 to 8.9)</td>
<td>−13.6 (−18.6 to −8.7)</td>
<td>−22.3 (−27.2 to −17.3)</td>
<td>−35.9 (−41.1 to −30.7)</td>
</tr>
<tr>
<td>Relative change</td>
<td>−17.6 (−24.6 to −10.5)</td>
<td>−26.2 (−33.2 to −19.2)</td>
<td>−39.8 (−47.0 to −32.7)</td>
<td></td>
</tr>
<tr>
<td><strong>HDL-C, mg/dL</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Follow-up</td>
<td>51.6 (13.7)</td>
<td>87.1 (24.0)</td>
<td>108.6 (28.9)</td>
<td>126.1 (25.7)</td>
</tr>
<tr>
<td>Absolute change</td>
<td>−0.7 (−5.6 to 4.3)</td>
<td>30.0 (25.1 to 35.0)</td>
<td>50.9 (45.9 to 55.9)</td>
<td>66.0 (80.8 to 71.1)</td>
</tr>
<tr>
<td>Percentage change</td>
<td>−3.0 (−12.3 to 6.2)</td>
<td>53.6 (44.4 to 62.9)</td>
<td>94.6 (85.2 to 104.0)</td>
<td>128.8 (119.2 to 138.4)</td>
</tr>
<tr>
<td>Relative change</td>
<td>56.7 (43.6 to 69.8)</td>
<td>97.6 (84.5 to 110.8)</td>
<td>131.9 (118.5 to 145.2)</td>
<td></td>
</tr>
<tr>
<td><strong>Triglycerides, mg/dL</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Follow-up, median (IQR)</td>
<td>121.3 (86.4 to 179.9)</td>
<td>106.3 (85.0 to 147.9)</td>
<td>113.4 (83.3 to 148.8)</td>
<td>94.8 (80.6 to 121.3)</td>
</tr>
<tr>
<td>Absolute change</td>
<td>−0.5 (−12.4 to 11.4)</td>
<td>−13.2 (−25.2 to −1.2)</td>
<td>−9.8 (−21.8 to 2.3)</td>
<td>−26.7 (−39.1 to −14.4)</td>
</tr>
<tr>
<td>Percentage change</td>
<td>9.3 (1.0 to 17.5)</td>
<td>−3.1 (−11.4 to 5.2)</td>
<td>−3.1 (−11.5 to 5.2)</td>
<td>−10.8 (−19.4 to −2.2)</td>
</tr>
<tr>
<td>Relative change</td>
<td>−12.4 (−24.1 to −0.6)</td>
<td>−12.4 (−24.2 to −0.6)</td>
<td>−20.1 (−32.0 to −8.2)</td>
<td></td>
</tr>
<tr>
<td><strong>CRP, mg/L</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Follow-up, median (IQR)</td>
<td>1.8 (1.0 to 4.0)</td>
<td>1.7 (0.6 to 6.4)</td>
<td>1.2 (0.8 to 3.2)</td>
<td>1.7 (0.7 to 5.6)</td>
</tr>
<tr>
<td>Absolute change</td>
<td>−1.7 (−4.4 to 1.0)</td>
<td>0.9 (−1.7 to 3.4)</td>
<td>1.2 (1.4 to 3.9)</td>
<td>0.9 (−1.6 to 3.5)</td>
</tr>
<tr>
<td>Percentage change</td>
<td>75.5 (5.9 to 145.1)</td>
<td>127.8 (58.7 to 186.9)</td>
<td>76.6 (7.2 to 146.0)</td>
<td>120.0 (63.5 to 186.4)</td>
</tr>
<tr>
<td>Relative change</td>
<td>52.3 (−45.5 to 150.1)</td>
<td>1.1 (−97.5 to 99.8)</td>
<td>44.5 (−51.5 to 140.5)</td>
<td></td>
</tr>
</tbody>
</table>

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

SI conversions: To convert LDL-C and triglycerides to mmol/L, multiply by 0.0259; to convert CRP to mg/L, multiply by 0.0115.

*Follow-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.

\textsuperscript{a}Last-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 represented 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 tolerated, the study was underpowered to rule out uncommon adverse effects.

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

<table>
<thead>
<tr>
<th>Measures</th>
<th>With Placebo (n = 41)</th>
<th>With Evacetrapib (n = 35)</th>
<th>With Placebo (n = 40)</th>
<th>With Evacetrapib (n = 41)</th>
</tr>
</thead>
<tbody>
<tr>
<td>LDL-C, mg/dL Follow-up</td>
<td>90.8 (26.7)</td>
<td>71.2 (37.5)</td>
<td>95.7 (25.8)</td>
<td>73.1 (34.2)</td>
</tr>
<tr>
<td>Absolute change</td>
<td>−49.5 (−56.8 to −42.3)</td>
<td>−70.5 (−81.8 to −62.8)</td>
<td>−51.3 (−65.5 to −44.2)</td>
<td>−47.1 (−74.5 to −59.8)</td>
</tr>
<tr>
<td>Percentage change</td>
<td>−33.6 (−38.6 to −29.7)</td>
<td>−47.6 (−52.8 to −42.3)</td>
<td>−34.9 (−39.8 to −29.8)</td>
<td>−44.1 (−51.1 to −41.0)</td>
</tr>
<tr>
<td>Relative change</td>
<td>−13.9 (−21.2 to −6.7)</td>
<td>−11.2 (−18.3 to −4.2)</td>
<td>−13.5 (−20.6 to −6.4)</td>
<td></td>
</tr>
<tr>
<td>HDL-C, mg/dL Follow-up</td>
<td>54.8 (18.9)</td>
<td>98.8 (31.8)</td>
<td>61.0 (17.4)</td>
<td>97.5 (29.9)</td>
</tr>
<tr>
<td>Absolute change</td>
<td>1.3 (3.7 to 6.4)</td>
<td>42.1 (36.9 to 47.4)</td>
<td>2.9 (2.0 to 7.7)</td>
<td>45.1 (40.1 to 50.1)</td>
</tr>
<tr>
<td>Percentage change</td>
<td>1.4 (−8.0 to 10.8)</td>
<td>79.9 (70.1 to 89.8)</td>
<td>7.3 (−1.8 to 16.4)</td>
<td>86.6 (77.3 to 96.0)</td>
</tr>
<tr>
<td>Relative change</td>
<td>78.5 (64.9 to 92.1)</td>
<td>79.3 (66.2 to 92.4)</td>
<td>5.5 (−3.9 to 15.0)</td>
<td>94.0 (84.7 to 103.4)</td>
</tr>
<tr>
<td>Triglycerides, mg/dL Follow-up, median (IQR)</td>
<td>101.0 (72.6 to 145.3)</td>
<td>88.6 (70.0 to 119.6)</td>
<td>93.0 (72.6 to 124.4)</td>
<td>100.1 (78.8 to 116.9)</td>
</tr>
<tr>
<td>Absolute change</td>
<td>−21.3 (−33.2 to −9.3)</td>
<td>−30.8 (−43.6 to −18.1)</td>
<td>−31.2 (−42.9 to −19.4)</td>
<td>−28.2 (−40.5 to −16.0)</td>
</tr>
<tr>
<td>Percentage change</td>
<td>−16.7 (−24.3 to −7.9)</td>
<td>−31.6 (−42.9 to −18.1)</td>
<td>−16.1 (−24.3 to −7.9)</td>
<td>−16.1 (−23.5 to −6.6)</td>
</tr>
<tr>
<td>Relative change</td>
<td>−5.7 (−17.8 to 6.5)</td>
<td>−32.2 (−44.6 to −14.6)</td>
<td>−14.6 (−22.9 to −6.2)</td>
<td>−22.4 (−30.9 to −13.9)</td>
</tr>
<tr>
<td>CRP, mg/L Follow-up, median (IQR)</td>
<td>1.0 (0.6 to 2.5)</td>
<td>1.0 (0.6 to 3.4)</td>
<td>1.0 (0.6 to 2.4)</td>
<td>1.0 (0.9 to 3.7)</td>
</tr>
<tr>
<td>Absolute change</td>
<td>4.4 (1.8 to 7.0)</td>
<td>−0.5 (−3.2 to 2.3)</td>
<td>0.3 (−2.3 to 2.9)</td>
<td>0.7 (−1.8 to 3.3)</td>
</tr>
<tr>
<td>Percentage change</td>
<td>27.9 (−40.3 to 96.0)</td>
<td>10.2 (−60.8 to 81.2)</td>
<td>−9.4 (−77.6 to 58.8)</td>
<td>50.5 (−16.8 to 117.9)</td>
</tr>
<tr>
<td>Relative change</td>
<td>−17.7 (−116.0 to 80.7)</td>
<td>60.0 (−35.8 to 155.7)</td>
<td>6.4 (−87.6 to 100.4)</td>
<td></td>
</tr>
</tbody>
</table>

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.

4Follow-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.

5P < .01.
6P < .001.
7Last-observation-carried-forward data are applied in the analysis.

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Table 5. Safety Data

<table>
<thead>
<tr>
<th>Measures</th>
<th>Placebo (n = 38)</th>
<th>30 mg/d (n = 40)</th>
<th>100 mg/d (n = 38)</th>
<th>500 mg/d (n = 40)</th>
<th>Statin Monotherapy (n = 121)</th>
<th>Statin + Evacetrapib, 100 mg/d (n = 116)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drug-related adverse events, No. (%)</td>
<td>7 (18.4)</td>
<td>8 (20.5)</td>
<td>5 (13.2)</td>
<td>10 (25.0)</td>
<td>22 (18.2)</td>
<td>31 (26.1)</td>
</tr>
<tr>
<td>Adverse events leading to discontinuation, No. (%)</td>
<td>1 (2.6)</td>
<td>2 (5.0)</td>
<td>1 (2.6)</td>
<td>5 (12.5)</td>
<td>3 (2.5)</td>
<td>9 (7.8)</td>
</tr>
<tr>
<td>Serious adverse events, No. (%)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1 (2.5)</td>
<td>1 (0.8)</td>
<td>2 (1.7)</td>
</tr>
<tr>
<td>Drug-related serious adverse events, No. (%)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Elevation in systolic blood pressure ≥15 mm Hg, No. (%)</td>
<td>10 (26.3)</td>
<td>7 (17.9)</td>
<td>9 (23.1)</td>
<td>8 (20.0)</td>
<td>23 (19.3)</td>
<td>25 (21.6)</td>
</tr>
<tr>
<td>Elevation in diastolic blood pressure ≥10 mm Hg, No. (%)</td>
<td>1 (2.6)</td>
<td>1 (2.6)</td>
<td>2 (5.2)</td>
<td>4 (10.0)</td>
<td>9 (7.6)</td>
<td>6 (5.2)</td>
</tr>
<tr>
<td>Creatinine &gt;ULN, No. (%)</td>
<td>1 (2.6)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>2 (1.7)</td>
<td>2 (1.7)</td>
</tr>
<tr>
<td>Alanine aminotransferase &gt;5 × ULN, No. (%)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1 (0.9)</td>
<td>0</td>
</tr>
<tr>
<td>Aldosterone, ng/dL</td>
<td>8.30 (8.108)</td>
<td>7.71 (8.17)</td>
<td>5.97 (4.27)</td>
<td>6.73 (5.94)</td>
<td>7.67 (6.29)</td>
<td>6.99 (4.38)</td>
</tr>
<tr>
<td>Baseline</td>
<td>6.84 (4.67)</td>
<td>6.87 (4.80)</td>
<td>7.77 (6.74)</td>
<td>6.76 (5.49)</td>
<td>6.34 (6.63)</td>
<td>6.82 (5.26)</td>
</tr>
<tr>
<td>Follow-up</td>
<td>−1.00</td>
<td>−0.45</td>
<td>0.96</td>
<td>−0.30</td>
<td>−1.12</td>
<td>−0.45</td>
</tr>
<tr>
<td>Absolute change</td>
<td>(−2.69 to 0.68)</td>
<td>(−2.18 to 1.27)</td>
<td>(−0.75 to 2.67)</td>
<td>(−2.06 to 1.45)</td>
<td>(−2.11 to −1.03)</td>
<td>(−1.48 to 0.58)</td>
</tr>
<tr>
<td>Percentage change</td>
<td>3.09</td>
<td>4.51</td>
<td>7.11</td>
<td>7.78</td>
<td>10.87</td>
<td>11.29</td>
</tr>
<tr>
<td>Relative change</td>
<td>−22.47</td>
<td>−43.00</td>
<td>158.20</td>
<td>(−162.03 to 117.99)</td>
<td>(−182.18 to 96.17)</td>
<td>(17.23 to 299.17)</td>
</tr>
<tr>
<td>Potassium, mEq/L</td>
<td>3.42</td>
<td>3.05</td>
<td>3.51</td>
<td>3.96</td>
<td>4.25</td>
<td>4.17</td>
</tr>
<tr>
<td>Baseline</td>
<td>3.42</td>
<td>3.05</td>
<td>3.51</td>
<td>3.96</td>
<td>4.25</td>
<td>4.17</td>
</tr>
<tr>
<td>Follow-up</td>
<td>3.42</td>
<td>3.05</td>
<td>3.51</td>
<td>3.96</td>
<td>4.25</td>
<td>4.17</td>
</tr>
<tr>
<td>Absolute change</td>
<td>0 (−0.05 to 0.04)</td>
<td>0 (−0.05 to 0.04)</td>
<td>0 (−0.05 to 0.05)</td>
<td>0 (−0.05 to 0.06)</td>
<td>0 (−0.05 to 0.06)</td>
<td>0 (−0.05 to 0.06)</td>
</tr>
<tr>
<td>Percentage change</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Relative change</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Abbreviation: ULN, upper limit of normal.

The denominators shown are the intention-to-treat population for the individual treatment groups.

aPatients without a postbaseline measurement are excluded from the analysis.

bBaseline 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.

p < 0.05.

Follow-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 evacetrapib 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 because 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.

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EFFECTS OF EVACETRAPIB ON LIPIDS

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

Epidemiological studies of the rela-
tionship between CETP and cardio-
vascular risk have shown variable results,
with some 10 but not all 25,26 investiga-
tors reporting an association between
low CETP activity and protection against cardiovascular disease. Stud-
ies in animal models generally show
that reduced CETP activity is athero-
protective, 11,27,28 but not all animals have
lipid metabolic pathways comparable with that of humans. The inability of
torcetrapib to slow disease progres-
sion in humans raised concerns about
HDL functionality. However, there is
currently no evidence that CETP in-
hibitors 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 coro-
nary atherosclerosis 29 and fewer car-
diovascular events. 30

However, a number of other issues
remain unresolved. The current study
included numerous parallel treatment
groups with multiple unadjusted sta-
tistical comparisons. While the analy-
sis prespecified a type I error rate of .10
for efficacy measures, additional test-
ing with an error rate of .05 did not alter
the findings (eTable 3). Predict-
ably, CETP mass increased, although
it is unknown if this has any effect be-
yond lipid transfer. The optimal de-
gree of CETP inhibition has not been elucidated. Recent speculation sug-
gests that dalcetrapib, a less potent
CETP inhibitor, may selectively modu-
late CETP pathways in a manner that
preserves levels of lipid-deplete pre-β
HDL. 30 However, the cardiovascular ef-
fects of this finding remain uncertain.

No studies have yet demonstrated that
any CETP inhibitor reduces disease pro-
gression or promotes plaque regres-
sion.

Two additional CETP inhibitors are
currently undergoing clinical evalua-
tion. The lipid changes observed with
 evacetrapib appeared to be more simi-
lar to those of anacetrapib, producing
substantial elevation of HDL-C and low-
ering of LDL-C. Evacetrapib, like both
anacetrapib and dalcetrapib, appeared
to be well tolerated with no discern-
ible adverse effects on blood pressure
and mineralocorticoid levels. Ulti-
mately, the benefits of each of these
novel CETP inhibitors must be deter-
mmed through prospective, random-
ized, clinical outcome trials. The
results of the current study provide the
foundation for a large phase 3 clinical
design to assess the efficacy and safety
of evacetrapib.

Author Contributions: Drs Nicholls and Nissen and the
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search had full and independent access to all of the data in
the study, and Dr Nicholls takes responsibility for the intel-
ligence of the data and the accuracy of the data analysis.

Study concept and design: Nicholls, Krueger, Wang,
McEerlean, Nissen.

Acquisition of data: Wang, McEerlean.

Analysis and interpretation of data: Nicholls, Brewer,

Drafting of the manuscript: Nicholls, Wang, Nissen.

Critical revision of the manuscript for important in-
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Study supervision: Krueger.

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or. The sponsor maintained the trial database. Sta-
tistical analysis was performed by statisticians employed
by Eli Lilly, although the analyses reported in the ar-
ticle represent those performed by the academic stat-
isticians (Mr Shao and Dr Hu). Approval for the
reporting of the current study by the sponsor, the
inclusion of any additional analyses, or the publication
of the study was provided by Eli Lilly.

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epidermic interaction between Shao and Hu performed all primary statistical
analyses. All results presented in the article were performed by Dr Hu. Mr Shao is an employee of the
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EFFECTS OF EVACETRAPIB ON LIPIDS

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