Effects of Dalcetrapib in Patients with a Recent Acute Coronary Syndrome

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ABSTRACT

BACKGROUND
In observational analyses, higher levels of high-density lipoprotein (HDL) cholesterol have been associated with a lower risk of coronary heart disease events. However, whether raising HDL cholesterol levels therapeutically reduces cardiovascular risk remains uncertain. Inhibition of cholesteryl ester transfer protein (CETP) raises HDL cholesterol levels and might therefore improve cardiovascular outcomes.

METHODS
We randomly assigned 15,871 patients who had had a recent acute coronary syndrome to receive the CETP inhibitor dalcetrapib, at a dose of 600 mg daily, or placebo, in addition to the best available evidence-based care. The primary efficacy end point was a composite of death from coronary heart disease, nonfatal myocardial infarction, ischemic stroke, unstable angina, or cardiac arrest with resuscitation.

RESULTS
At the time of randomization, the mean HDL cholesterol level was 42 mg per deciliter (1.1 mmol per liter), and the mean low-density lipoprotein (LDL) cholesterol level was 76 mg per deciliter (2.0 mmol per liter). Over the course of the trial, HDL cholesterol levels increased from baseline by 4 to 11% in the placebo group and by 31 to 40% in the dalcetrapib group. Dalcetrapib had a minimal effect on LDL cholesterol levels. Patients were followed for a median of 31 months. At a prespecified interim analysis that included 1135 primary end-point events (71% of the projected total number), the independent data and safety monitoring board recommended termination of the trial for futility. As compared with placebo, dalcetrapib did not alter the risk of the primary end point (cumulative event rate, 8.0% and 8.3%, respectively; hazard ratio with dalcetrapib, 1.04; 95% confidence interval, 0.93 to 1.16; P=0.52) and did not have a significant effect on any component of the primary end point or total mortality. The median C-reactive protein level was 0.2 mg per liter higher and the mean systolic blood pressure was 0.6 mm Hg higher with dalcetrapib as compared with placebo (P<0.001 for both comparisons).

CONCLUSIONS
In patients who had had a recent acute coronary syndrome, dalcetrapib increased HDL cholesterol levels but did not reduce the risk of recurrent cardiovascular events. (Funded by F. Hoffmann–La Roche; dal-OUTCOMES ClinicalTrials.gov number, NCT00658515.)
HIGH-DENSITY LIPOPROTEINS (HDLs) participate in the process of cellular cholesterol efflux and may have additional protective effects against atherothrombosis.1 An inverse association between levels of HDL cholesterol and incident events of coronary heart disease has been shown in observational studies2-3 and persists in most post hoc analyses and meta-analyses of trials of statin therapy for patients with cardiovascular risk factors, chronic cardiovascular disease, or recent acute coronary syndrome.4-10 However, it remains uncertain whether pharmacologic intervention that raises HDL cholesterol levels results in decreased cardiovascular risk.11-16 Moreover, changes in HDL cholesterol levels may not reflect changes in the physiologic functions of HDLs.17

Cholesteryl ester transfer protein (CETP) mediates the transfer of cholesteryl ester from HDLs to atherogenic lipoprotein particles containing apolipoprotein B, such as low-density lipoprotein (LDL). In most,18-20 but not all,21 analyses, genetic polymorphisms resulting in a lower mass or activity of CETP are associated with higher HDL cholesterol levels, lower LDL cholesterol levels, and a lower risk of coronary heart disease. These observations have led to the development of CETP inhibitors as drugs that might reduce cardiovascular risk.

Torcetrapib, the first CETP inhibitor to be evaluated in a phase 3 clinical trial,22 increased HDL cholesterol levels by more than 70% and decreased LDL cholesterol levels by 25% but caused excess morbidity and mortality associated with elevation of aldosterone levels and blood pressure. Dalcetrapib is a CETP inhibitor that raised HDL cholesterol levels by approximately 30% in phase 2 studies, without significant effects on LDL cholesterol levels, blood pressure, or circulating neurohormones.23,24 We designed a phase 3 trial, the dal-OUTCOMES study, to evaluate the effects of dalcetrapib on cardiovascular risk among patients with a recent acute coronary syndrome.

METHODS

STUDY OVERSIGHT

The protocol, which is available with the full text of this article at NEJM.org, was conceived by members of the independent academic executive steering committee, developed by that committee in conjunction with the sponsor (F. Hoffmann–La Roche), and approved by the responsible regulatory agencies and ethics committees. Quintiles (a clinical research organization), Montreal Heart Institute Coordinating Center, and Cleveland Clinic Coordinating Center for Clinical Research managed the study and collected the data. An independent data and safety monitoring board monitored the trial and performed analyses of unblinded data. The analyses reported in this article were performed by two of the authors with input from all the authors. The members of the executive steering committee made the decision to submit the manuscript for publication and assume responsibility for the completeness and accuracy of the data and for the fidelity of the study to the protocol.

STUDY POPULATION

Details of the study design have been published previously.25 Patients 45 years of age or older who provided written informed consent were eligible to participate if they had been hospitalized for an acute coronary syndrome characterized by elevated cardiac biomarkers, with symptoms of acute myocardial ischemia, ischemic electrocardiographic abnormalities that were new or presumed to be new, or loss of viable myocardium on imaging. Patients without elevated cardiac biomarkers were eligible to participate if symptoms of acute myocardial ischemia were accompanied by electrocardiographic changes that were new or presumed to be new and by additional evidence of obstructive coronary disease.25 Patients who had a myocardial infarction associated with percutaneous coronary intervention were also eligible.25 All patients had to be following individualized, evidence-based programs for lowering their LDL cholesterol levels by means of statin therapy (if they did not have unacceptable side effects) and diet, with a target LDL cholesterol level of 100 mg per deciliter (2.6 mmol per liter) or lower and preferably 70 mg per deciliter (1.8 mmol per liter) or lower. However, no specific statin agent or dose was specified, and patients were not excluded if the LDL cholesterol...
level remained above 100 mg per deciliter. There were no exclusions on the basis of the HDL cholesterol level; however, patients with serum triglyceride levels of 400 mg per deciliter (4.5 mmol per liter) or higher were excluded. Other exclusion criteria are listed in the Supplementary Appendix, available at NEJM.org.

STUDY PROCEDURES
We entered patients who met the inclusion criteria into a single-blind, placebo run-in period to assess adherence, ensure that no exclusion criteria were met, and allow time for metabolic steady state to be achieved after the index acute coronary event. After 4 to 12 weeks of run-in, and no later than 12 weeks after the index event, qualifying patients were randomly assigned, in a 1:1 ratio, to receive dalcetrapib at a dose of 600 mg daily or matching placebo, with randomization stratified according to country and status with respect to cardiac biomarker levels (elevated or not elevated) at the time of the index event.

STUDY END POINTS
The primary efficacy end point was a composite of death from coronary heart disease, a major nonfatal coronary event (myocardial infarction, hospitalization for unstable angina with objective evidence of acute myocardial ischemia, or cardiac arrest with resuscitation), or ischemic stroke. Secondary efficacy end points included each component of the primary composite end point, unanticipated coronary revascularization (not including revascularization for restenosis at the previous intervention site), death from any cause, and changes in levels of circulating lipoproteins and inflammatory markers.

STATISTICAL ANALYSIS
The primary efficacy analysis, which was performed according to the intention-to-treat principle, was based on the time to the first occurrence of any component of the primary composite end point in any patient from the time of randomization to the termination of the trial. We projected that with 1600 primary end-point events, the study would have 90% power to detect a 15% reduction in the relative risk of an event with dalcetrapib as compared with placebo, assuming an average baseline HDL cholesterol level of 40 mg per deciliter (1.0 mmol per liter) and an increase of approximately 11 mg per deciliter (0.3 mmol per liter) with dalcetrapib. Two interim analyses, including an analysis for futility, were to be performed after approximately 800 and 1120 primary end-point events had occurred. Estimates of hazard ratios and 95% confidence intervals for comparisons of dalcetrapib with placebo were calculated with the use of Cox proportional-hazards models stratified according to region and type of index event. Event rates are presented as 3-year Kaplan–Meier estimates. Continuous data are presented as means and standard deviations, unless otherwise indicated. Additional analytic methods are described in the Supplementary Appendix.

RESULTS

PATIENTS
From April 2008 through July 2010, a total of 15,871 patients were enrolled at 935 sites in 27 countries and were included in the intention-to-treat population; 87% of the patients had elevated cardiac biomarkers at the time of the qualifying acute coronary event (with the elevation related to percutaneous coronary intervention in 2% of the patients), and 13% of the patients did not. The median time from the qualifying event to random assignment was 61 days. The baseline characteristics of the two study groups (assessed at the time of randomization) were well matched (Table 1). Most patients in the two groups were treated with aspirin, statins, thienopyridines, beta-blockers, and angiotensin-converting–enzyme (ACE) inhibitors or angiotensin-receptor blockers (ARBs) and underwent a coronary revascularization procedure between the time of the qualifying event and random assignment. The mean baseline LDL cholesterol level was 76 mg per deciliter (2.0 mmol per liter) (with a level of 100 mg per deciliter or lower in 86% of the patients), the mean HDL cholesterol level was 42 mg per deciliter (1.1 mmol per liter), the mean apolipoprotein A1 level was 137 mg per deciliter, and the mean apolipoprotein B level was 81 mg per deciliter.

At the second prespecified interim analysis, which included 1135 primary end-point events (71% of those projected), the independent data and safety monitoring board recommended termination of the trial for futility, in accordance...
with prespecified criteria (see the Supplementary Appendix). The sponsor and executive steering committee accepted this recommendation and terminated the trial; the median follow-up period was 31 months. Before termination of the study, the study drug had been discontinued in 21% of the patients in the dalcetrapib group and in 19% of the patients in the placebo group for reasons other than death. During the time they were receiving the study drug, 89% of the patients in both groups had at least 80% adherence to the prescribed regimen. A total of 2.3% of the

### Table 1. Baseline Characteristics of the Patients.*

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Placebo (N = 7933)</th>
<th>Dalcetrapib (N = 7938)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age — yr</strong></td>
<td>60.1±9.1</td>
<td>60.3±9.1</td>
</tr>
<tr>
<td><strong>Female sex — no. (%)</strong></td>
<td>1497 (19)</td>
<td>1573 (20)</td>
</tr>
<tr>
<td><strong>Race — no. (%)†</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>7015 (88)</td>
<td>7008 (88)</td>
</tr>
<tr>
<td>Asian</td>
<td>602 (8)</td>
<td>630 (8)</td>
</tr>
<tr>
<td>Black</td>
<td>193 (2)</td>
<td>175 (2)</td>
</tr>
<tr>
<td>Other</td>
<td>123 (2)</td>
<td>125 (2)</td>
</tr>
<tr>
<td><strong>Body-mass index‡</strong></td>
<td>28.6±5.1</td>
<td>28.6±5.0</td>
</tr>
<tr>
<td><strong>Region of enrollment — no. (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Europe or Israel</td>
<td>3954 (50)</td>
<td>3959 (50)</td>
</tr>
<tr>
<td>North America</td>
<td>2521 (32)</td>
<td>2522 (32)</td>
</tr>
<tr>
<td>South America</td>
<td>639 (8)</td>
<td>639 (8)</td>
</tr>
<tr>
<td>Asia</td>
<td>526 (7)</td>
<td>524 (7)</td>
</tr>
<tr>
<td>Australia, New Zealand, or South Africa</td>
<td>293 (4)</td>
<td>294 (4)</td>
</tr>
<tr>
<td><strong>Cardiovascular risk factors — no./total no. (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>5419/7933 (68)</td>
<td>5336/7938 (67)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>1952/7933 (25)</td>
<td>1930/7938 (24)</td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>5753/7933 (73)</td>
<td>5736/7938 (72)</td>
</tr>
<tr>
<td>Current smoker</td>
<td>1651/7933 (21)</td>
<td>1672/7938 (21)</td>
</tr>
<tr>
<td>Metabolic syndrome§</td>
<td>4973/7914 (63)</td>
<td>4963/7920 (63)</td>
</tr>
<tr>
<td><strong>Cardiovascular disease history — no. (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>1196 (15)</td>
<td>1276 (16)</td>
</tr>
<tr>
<td>PCI</td>
<td>1150 (14)</td>
<td>1159 (15)</td>
</tr>
<tr>
<td>CABG</td>
<td>462 (6)</td>
<td>432 (5)</td>
</tr>
<tr>
<td>Stroke</td>
<td>272 (3)</td>
<td>265 (3)</td>
</tr>
<tr>
<td>Peripheral arterial disease</td>
<td>583 (7)</td>
<td>568 (7)</td>
</tr>
<tr>
<td>NYHA class I or II congestive heart failure</td>
<td>1220 (15)</td>
<td>1233 (16)</td>
</tr>
<tr>
<td><strong>Index diagnosis — no. (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Spontaneous myocardial infarction</td>
<td>6717 (85)</td>
<td>6745 (85)</td>
</tr>
<tr>
<td>STEMI</td>
<td>3611 (46)</td>
<td>3639 (46)</td>
</tr>
<tr>
<td>NSTEMI</td>
<td>3106 (39)</td>
<td>3105 (39)</td>
</tr>
<tr>
<td>Myocardial infarction related to PCI</td>
<td>149 (2)</td>
<td>174 (2)</td>
</tr>
<tr>
<td>Unstable angina without elevated biomarkers</td>
<td>1064 (13)</td>
<td>1019 (13)</td>
</tr>
<tr>
<td>PCI or CABG for index event</td>
<td>7222 (91)</td>
<td>7244 (91)</td>
</tr>
</tbody>
</table>
patients in the dalcetrapib group and 2.0% of those in the placebo group withdrew consent, and an additional 1.6% and 1.3%, respectively, were lost to follow-up, with unknown final vital status.

**Lipoproteins and Glycemic Control**

Over the course of the trial, HDL cholesterol levels increased from baseline by 4 to 11% in the placebo group and by 31 to 40% in the dalcetrapib group. Dalcetrapib had a minimal effect on LDL cholesterol levels (Fig. 1). Triglyceride levels increased from baseline by 6 to 17% in the placebo group and by 4 to 10% in the dalcetrapib group (see the Supplementary Appendix). Apolipoprotein A1 levels were increased by 10% after 3 months of treatment with dalcetrapib and by 9% at the end of the trial ($P<0.001$), with a minimal effect on levels of apolipoprotein B. Treatment with dalcetrapib had no effect on fasting plasma glucose or glycated hemoglobin levels (see the Supplementary Appendix).
End Points

Dalcetrapib had no significant effect on the primary end point, which occurred in 8.3% of the patients in the dalcetrapib group and in 8.0% of the patients in the placebo group (hazard ratio with dalcetrapib, 1.04; 95% confidence interval, 0.93 to 1.16; P=0.52) (Fig. 2). Dalcetrapib also had no significant effect on the rate of any component of the primary end point, on the rate of unanticipated coronary revascularization, or on the rate of death from any cause (Table 2). Pre-specified subgroup analyses showed no significant effect of dalcetrapib on the primary end point (see the Supplementary Appendix).
ASSOCIATION BETWEEN LIPOPROTEIN LEVELS
AND END POINTS

There was no significant association in either group between the baseline HDL cholesterol level (i.e., the level measured at randomization) and the risk of the primary end point, either in univariate analysis or in multivariate analysis adjusted for the factors listed in Figure 3A. There was no significant interaction between the baseline HDL cholesterol level and the group assignment with respect to the risk of the primary end point. In contrast, significant positive univariate relationships were identified in both treatment groups between the baseline values for LDL cholesterol, very-low-density lipoprotein cholesterol, apolipoprotein B, glycated hemoglobin, high-sensitivity C-reactive protein, and systolic blood pressure and the risk of the primary end point (see the Supplementary Appendix).

Although the distribution of HDL cholesterol levels was shifted as a result of dalcetrapib treatment, there was no significant association in either group between the change in HDL cholesterol levels from baseline to month 1 of the assigned regimen and the risk of the primary end point after month 1 (Fig. 3B). Associations were absent in a multivariate analysis that was adjusted for the characteristics listed in Figure 3A and for the changes from baseline to month 1 in systolic blood pressure and LDL cholesterol levels. There was no significant interaction between the change in HDL cholesterol levels from baseline to month 1 and the risk of the primary end point after month 1 showed similar findings (see the Supplementary Appendix).

There was no significant association in either group between the apolipoprotein A1 level measured at baseline and the risk of the primary end point or between the apolipoprotein A1 level measured at month 3 of the assigned regimen and the risk of the primary end point after month 3 (see the Supplementary Appendix).

C-REACTIVE PROTEIN

At baseline, the median high-sensitivity C-reactive protein level was similar in the two groups (1.5 mg per liter). Three months after randomization, the median C-reactive protein level was 1.4 mg per liter in the placebo group and 1.6 mg per liter in the dalcetrapib group (a difference of 18%, as calculated with the use of analysis of variance after log transformation; P<0.001).

SAFETY

Dalcetrapib had a generally acceptable side-effect profile. However, the mean systolic blood pressure remained approximately 0.6 mm Hg higher in the dalcetrapib group than in the placebo group (P<0.001). There were no significant between-group differences in diastolic blood pressure; pulse rate; levels of plasma aldosterone, potassium, or bicarbonate; or the number of prescribed antihypertensive medications. Hypertension was reported more frequently as an adverse or serious adverse event in the dalcetrapib group than in the placebo group (see the Supplementary Appendix). Diarrhea occurred more frequently in the dalcetrapib group than in the placebo group (in 563 patients vs. 358 patients), leading to discontinuation of the study drug in 1.4% and 0.3% of the patients in the two groups, respectively. More patients in the dalcetrapib group than in the placebo group had insomnia (169 patients vs. 133 patients). There were no significant differences between the groups in new
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discussion

The dal-OUTCOMES trial evaluated whether treatment with the CETP inhibitor dalcetrapib modified cardiovascular risk in patients who had had a recent acute coronary syndrome. Despite the finding that dalcetrapib, as compared with placebo, produced a substantial increase in HDL cholesterol levels, it had no significant effect on major cardiovascular outcomes, including the rate of death from coronary heart disease and the rates of myocardial infarction, ischemic stroke, unstable angina, cardiac arrest with resuscitation, and unanticipated coronary revascularization. No net benefit or harm was evident in any major subgroup of the study cohort. Because dalcetrapib had minimal effects on levels of LDL cholesterol and apolipoprotein B and a small effect on triglyceride levels, the dal-OUTCOMES trial may provide the purest test to date of the value of therapeutic intervention to raise HDL cholesterol levels in patients with coronary heart disease.

There are several possible explanations for the lack of benefit of dalcetrapib treatment. First, and in contrast to findings in epidemiologic analyses and post hoc analyses of data from some placebo-controlled trials of statins, no association was shown between HDL cholesterol levels and cardiovascular risk among the patients evaluated in this trial, even those in the placebo group. The absence of such an association may indicate that HDL cholesterol levels are no longer a determinant of risk when patients are treated with the type of evidence-based therapies that were used in the trial, including statins, dual antiplatelet therapy, beta-blockers, ACE inhibitors or ARBs, and coronary revascularization procedures. Another possibility is that HDLs are protective in healthy persons who do not have established cardiovascular disease but that their composition is altered in the presence of cardiovascular disease, rendering them non-protective even at high levels or after therapeutic intervention. Specifically, the composition and function of HDLs might have been altered in an adverse fashion after the qualifying acute coro-

Table 2. Primary and Secondary End-Point Events.*

<table>
<thead>
<tr>
<th>End Point</th>
<th>Placebo (N = 7933)</th>
<th>Dalcetrapib (N = 7938)</th>
<th>Hazard Ratio with Dalcetrapib (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with Event no. (%) Event Rate % (95% CI) Event Rate % (95% CI)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primary end point</td>
<td>633 (8.0) 9.1 (8.4–9.9)</td>
<td>656 (8.3) 9.2 (8.5–9.9)</td>
<td>1.04 (0.93–1.16)</td>
<td>0.52</td>
</tr>
<tr>
<td>Death from coronary heart disease</td>
<td>125 (1.6) 1.8 (1.5–2.2)</td>
<td>118 (1.5) 1.6 (1.3–1.9)</td>
<td>0.94 (0.73–1.21)</td>
<td>0.66</td>
</tr>
<tr>
<td>Nonfatal acute myocardial infarction</td>
<td>407 (5.1) 6.0 (5.4–6.7)</td>
<td>414 (5.2) 5.9 (5.3–6.5)</td>
<td>1.02 (0.89–1.17)</td>
<td>0.80</td>
</tr>
<tr>
<td>Hospitalization for unstable angina with objective evidence of acute myocardial ischemia</td>
<td>92 (1.2) 1.3 (1.0–1.5)</td>
<td>84 (1.1) 1.3 (1.0–1.6)</td>
<td>0.91 (0.68–1.22)</td>
<td>0.54</td>
</tr>
<tr>
<td>Cardiac arrest with resuscitation</td>
<td>10 (0.1) 0.1 (0.0–0.2)</td>
<td>14 (0.2) 0.2 (0.1–0.3)</td>
<td>1.41 (0.63–3.18)</td>
<td>0.40</td>
</tr>
<tr>
<td>Stroke of presumed atherothrombotic cause</td>
<td>73 (0.9) 1.0 (0.8–1.2)</td>
<td>91 (1.1) 1.4 (1.1–1.7)</td>
<td>1.25 (0.92–1.70)</td>
<td>0.16</td>
</tr>
<tr>
<td>Death from any cause</td>
<td>229 (2.9) 3.4 (2.9–3.9)</td>
<td>226 (2.8) 3.1 (2.7–3.6)</td>
<td>0.99 (0.82–1.19)</td>
<td>0.90</td>
</tr>
<tr>
<td>Unanticipated coronary revascularization procedure†</td>
<td>672 (8.5) 9.6 (8.9–10.3)</td>
<td>674 (8.5) 9.5 (8.8–10.3)</td>
<td>1.00 (0.90–1.11)</td>
<td>0.97</td>
</tr>
</tbody>
</table>

* The primary efficacy end point was a composite of death from coronary heart disease, major nonfatal coronary events (acute myocardial infarction, hospitalization for unstable angina with objective evidence of acute myocardial ischemia, or cardiac arrest with resuscitation), or stroke of presumed atherothrombotic cause. Secondary efficacy end-point events included each component of the primary composite end point, unanticipated coronary revascularization (not including revascularization for restenosis at the previous intervention site), and death from any cause. Event rates are Kaplan–Meier estimates through 36 months.
† Data are for procedures other than those for restenosis at the previous intervention site.
The mean increase of 0.6 mm Hg in systolic blood pressure with dalcetrapib is unlikely to be offset by other, unfavorable effects of treatment. However, other manifestations of acute-phase response after myocardial infarction wane before 61 days, which was the median time from the index event to the time of random assignment in this trial. Moreover, we observed neither an early harm nor a later benefit of treatment but rather a neutral effect of treatment throughout an observation period of up to 3 years, well into the chronic phase of coronary heart disease. Therefore, it is unlikely that dalcetrapib would have shown a benefit after an even longer period of follow-up. Finally, measurements of HDL cholesterol levels may not reflect the physiologic functions of HDLs, including reverse cholesterol transport. It remains unknown whether dalcetrapib affected the function of HDLs in this study.

It is also possible that favorable effects of dalcetrapib with respect to HDL cholesterol were offset by other, unfavorable effects of treatment. The mean increase of 0.6 mm Hg in systolic blood pressure with dalcetrapib is unlikely to have had major direct clinical consequences but might indicate other underlying adverse vas-
cular effects. Similarly, the 18% increase in the median C-reactive protein level with dalce-trapib might indicate a proinflammatory effect of treatment associated with a greater risk of cardiovascular events.8 Modest but significant increases in blood pressure or C-reactive protein levels have also been observed in patients with or at high risk for coronary heart disease who were treated with torcetrapib or anacetrapib.22,23 Since the structure of dalce-trapib is dissimilar to that of the other two agents,32 the composite findings may indicate adverse effects of CETP inhibition, rather than specific off-target effects of individual agents.

It is unlikely that a clinically meaningful benefit of dalce-trapib went undetected owing to a type 2 statistical error. On the basis of the results observed for the primary efficacy measure, there is only a 1.1% likelihood of a true re-duction of 10% or more. Moreover, dalce-trapib had concordantly neutral effects on all compo-nents of the primary end point and on the rate of coronary revascularization.

In summary, the addition of dalce-trapib to standard therapy after an acute coronary syn-drome raised the levels of HDL cholesterol and apolipoprotein A1 and had minimal effects on levels of LDL cholesterol and apolipoprotein B. In addition, triglyceride levels increased less in the dalce-trapib group than in the placebo group. The risk of major cardiovascular outcomes was not significantly altered. It remains possible that agents that inhibit CETP and raise HDL cholesterol levels to a greater degree than did dalce-trapib and that also lower LDL cholesterol levels33,33 will prove to have clinical effects different from those of dalce-trapib.

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We thank the patients who participated in this trial, the study coordinators, and the investigators (see the Supplementary Appendix) at all 935 study sites.

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