

## ORIGINAL ARTICLE

# Effects of Dalcetrapib in Patients with a Recent Acute Coronary Syndrome

Gregory G. Schwartz, M.D., Ph.D., Anders G. Olsson, M.D., Ph.D., Markus Abt, Ph.D., Christie M. Ballantyne, M.D., Philip J. Barter, M.D., Ph.D., Jochen Brumm, Ph.D., Bernard R. Chaitman, M.D., Ingar M. Holme, Ph.D., David Kallend, M.B., B.S., Lawrence A. Leiter, M.D., Eran Leitersdorf, M.D., John J.V. McMurray, M.D., Hardi Mundl, M.D., Stephen J. Nicholls, M.B., B.S., Ph.D., Prediman K. Shah, M.D., Jean-Claude Tardif, M.D., and R. Scott Wright, M.D.,  
for the dal-OUTCOMES Investigators\*

## 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.)

From the Veterans Affairs Medical Center and University of Colorado School of Medicine, Denver (G.G.S.); Stockholm Heart Center, Stockholm and Linköping University, Linköping, Sweden (A.G.O.); F. Hoffmann–La Roche, Basel, Switzerland (M.A., J.B., D.K., H.M.); Baylor College of Medicine and Methodist DeBakey Heart and Vascular Center, Houston (C.M.B.); Heart Research Institute, Sydney (P.J.B.); Saint Louis University, St. Louis (B.R.C.); Oslo University Hospital, Ullevål, Oslo (I.M.H.); Keenan Research Centre, Li Ka Shing Knowledge Institute of St. Michael's Hospital, University of Toronto, Toronto (L.A.L.); Hadassah Hebrew University Medical Center, Jerusalem, Israel (E.L.); British Heart Foundation Cardiovascular Research Centre, University of Glasgow, Glasgow, United Kingdom (J.J.V.M.); South Australian Health and Medical Research Institute, University of Adelaide, Adelaide, SA, Australia (S.J.N.); Cedars–Sinai Heart Institute, Los Angeles (P.K.S.); Montreal Heart Institute, Université de Montréal, Montreal (J.-C.T.); and Mayo Clinic, Rochester, MN (R.S.W.). Address reprint requests to Dr. Schwartz at the Cardiology Section (111B), VA Medical Center, 1055 Clermont St., Denver, CO 80220, or at [gregory.schwartz@va.gov](mailto:gregory.schwartz@va.gov).

\*The investigators in the dal-OUTCOMES trial are listed in the Supplementary Appendix, available at [NEJM.org](http://NEJM.org).

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**H**IGH-DENSITY LIPOPROTEINS (HDLs) participate in the process of cellular cholesterol efflux and may have additional protective effects against atherothrombosis.<sup>1</sup> An inverse association between levels of HDL cholesterol and incident events of coronary heart disease has been shown in observational studies<sup>2,3</sup> 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.<sup>4-10</sup> However, it remains uncertain whether pharmacologic intervention that raises HDL cholesterol levels results in decreased cardiovascular risk.<sup>11-16</sup> Moreover, changes in HDL cholesterol levels may not reflect changes in the physiologic functions of HDLs.<sup>17</sup>

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,<sup>18-20</sup> but not all,<sup>21</sup> 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,<sup>22</sup> 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.<sup>23,24</sup> 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 who are employees of the sponsor and were independently confirmed by the academic statistician on the executive steering committee. All drafts of the manuscript were written by the first author 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.<sup>25</sup> 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.<sup>25</sup> Patients who had a myocardial infarction associated with percutaneous coronary intervention were also eligible.<sup>25</sup> 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

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

Table 1. (Continued.)		
Characteristic	Placebo (N=7933)	Dalcetrapib (N=7938)
Time from index event to randomization — days		
Mean	61	61
Range	16–184	18–181
Medications — no. (%)		
Statin	7736 (98)	7722 (97)
Aspirin	7694 (97)	7705 (97)
Clopidogrel, ticlopidine, or prasugrel	7060 (89)	7071 (89)
Beta-blocker	6946 (88)	6931 (87)
ACE inhibitor or ARB	6271 (79)	6300 (79)
Lipids, lipoproteins, and apolipoproteins — mg/dl¶		
LDL cholesterol	75.8±25.9	76.4±26.4
HDL cholesterol	42.2±11.5	42.5±11.7
Triglycerides	133.0±73.6	134.2±73.6
Apolipoprotein B	81.1±22.2	81.5±22.4
Apolipoprotein A1	137.2±24.2	137.5±24.4
Glycated hemoglobin — %	6.0±0.86	6.0±0.86
Creatinine clearance <60 ml/min/1.73 m <sup>2</sup> — no./total no. (%)**	854/7916 (11)	838/7915 (11)
C-reactive protein — mg/liter††		
Median	1.5	1.5
Interquartile range	0.8–3.6	0.7–3.6

\* Plus-minus values are means ±SD. There was no significant difference between the groups in any baseline characteristic. Additional information on baseline characteristics is contained in the Supplementary Appendix. To convert the values for cholesterol to millimoles per liter, multiply by 0.02586. To convert the values for triglycerides to millimoles per liter, multiply by 0.01129. ACE denotes angiotensin-converting enzyme, ARB angiotensin-receptor blocker, CABG coronary-artery bypass grafting, NSTEMI non-ST-segment elevation myocardial infarction, NYHA New York Heart Association, PCI percutaneous coronary intervention, and STEMI ST-segment elevation myocardial infarction.

† Race was self-reported.

‡ The body-mass index is the weight in kilograms divided by the square of the height in meters.

§ The metabolic syndrome was defined according to the criteria of the International Diabetes Federation.

¶ Data on lipoprotein levels were available for 7907 patients in the placebo group and 7910 in the dalcetrapib group; data on apolipoprotein levels were available for 7734 patients in the placebo group and 7736 in the dalcetrapib group.

|| Data on glycated hemoglobin levels were available for 7908 patients in the placebo group and 7911 in the dalcetrapib group.

\*\* Creatinine clearance was estimated with the use of the Cockcroft–Gault equation.

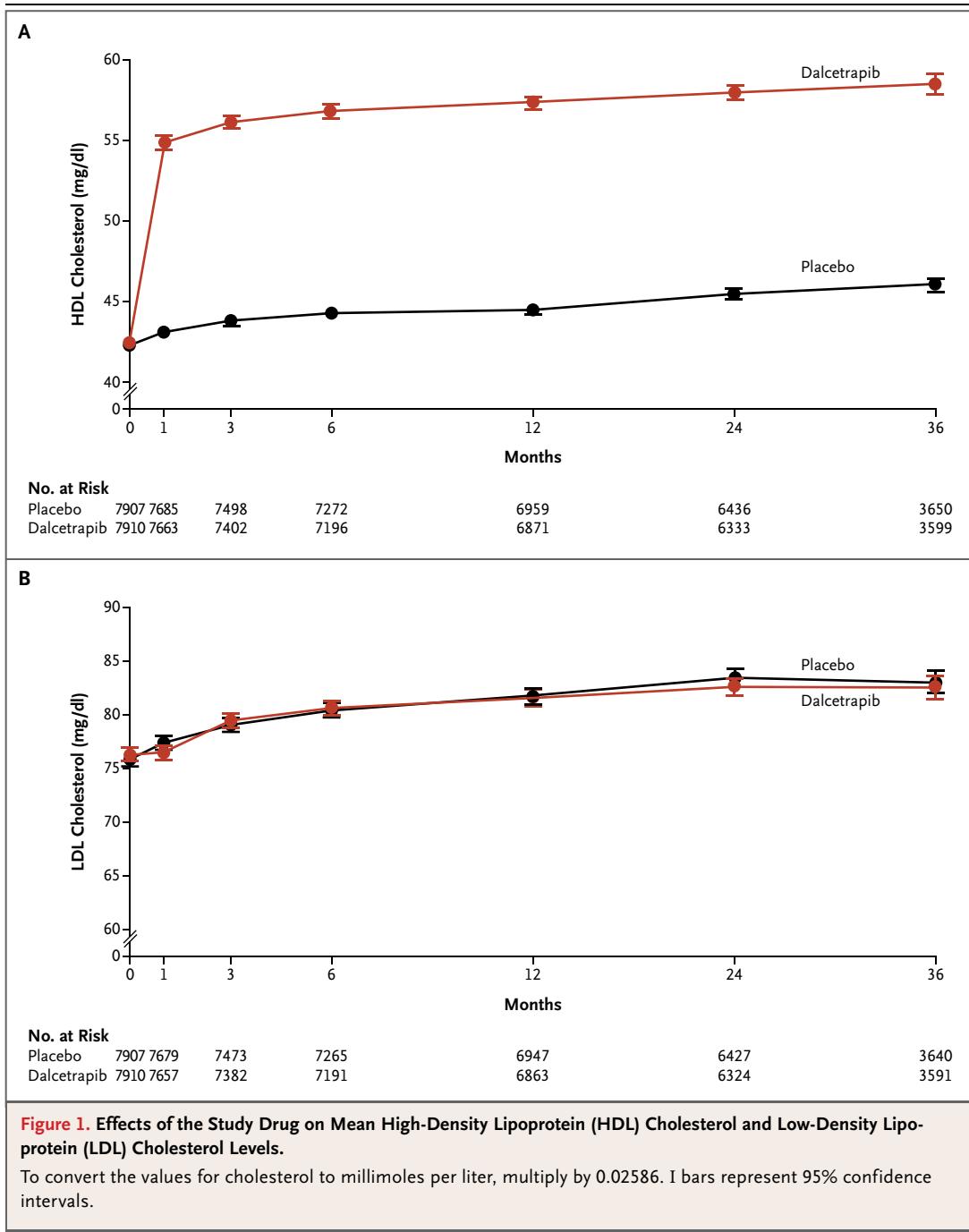
†† Data on C-reactive protein levels were available for 7469 patients in the placebo group and 7469 in the dalcetrapib group.

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 ef-

fect 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). Prespecified subgroup analyses showed no significant effect of dalcetrapib on the primary end point (see the Supplementary Appendix).

### ASSOCIATION BETWEEN LIPOPROTEIN LEVELS AND END POINTS

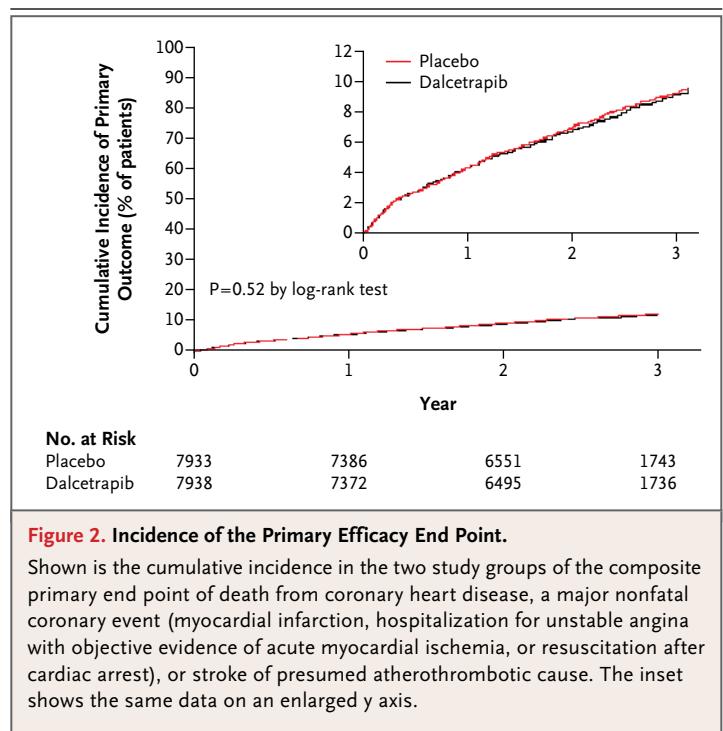
There was no significant association in either group between the baseline HDL cholesterol level (i.e., the level measured at randomization) and the risk of the primary end point, either in univariate analysis or in multivariate analysis adjusted for the factors listed in Figure 3A. There was no significant 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 group assignment with respect to the risk of the primary end point after month 1. Analysis of the association between the absolute level of HDL cholesterol at 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



**Figure 2. Incidence of the Primary Efficacy End Point.**

Shown is the cumulative incidence in the two study groups of the composite primary end point 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 resuscitation after cardiac arrest), or stroke of presumed atherothrombotic cause. The inset shows the same data on an enlarged y axis.

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

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

End Point	Placebo (N=7933)		Dalcetrapib (N=7938)		Hazard Ratio with Dalcetrapib (95% CI)	P Value
	Patients with Event	Event Rate at 3 Yr	Patients with Event	Event Rate at 3 Yr		
	no. (%)	% (95% CI)	no. (%)	% (95% CI)		
Primary end point	633 (8.0)	9.1 (8.4–9.9)	656 (8.3)	9.2 (8.5–9.9)	1.04 (0.93–1.16)	0.52
Death from coronary heart disease	125 (1.6)	1.8 (1.5–2.2)	118 (1.5)	1.6 (1.3–1.9)	0.94 (0.73–1.21)	0.66
Nonfatal acute myocardial infarction	407 (5.1)	6.0 (5.4–6.7)	414 (5.2)	5.9 (5.3–6.5)	1.02 (0.89–1.17)	0.80
Hospitalization for unstable angina with objective evidence of acute myocardial ischemia	92 (1.2)	1.3 (1.0–1.5)	84 (1.1)	1.3 (1.0–1.6)	0.91 (0.68–1.22)	0.54
Cardiac arrest with resuscitation	10 (0.1)	0.1 (0.0–0.2)	14 (0.2)	0.2 (0.1–0.3)	1.41 (0.63–3.18)	0.40
Stroke of presumed atherothrom- botic cause	73 (0.9)	1.0 (0.8–1.2)	91 (1.1)	1.4 (1.1–1.7)	1.25 (0.92–1.70)	0.16
Death from any cause	229 (2.9)	3.4 (2.9–3.9)	226 (2.8)	3.1 (2.7–3.6)	0.99 (0.82–1.19)	0.90
Unanticipated coronary revasculariza- tion procedure†	672 (8.5)	9.6 (8.9–10.3)	674 (8.5)	9.5 (8.8–10.3)	1.00 (0.90–1.11)	0.97

\* 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.

diagnoses of or deaths from cancers or infections (see the Supplementary Appendix). Dalcetrapib had no significant effect on measures of hepatic or renal function or on creatine kinase levels.

## DISCUSSION

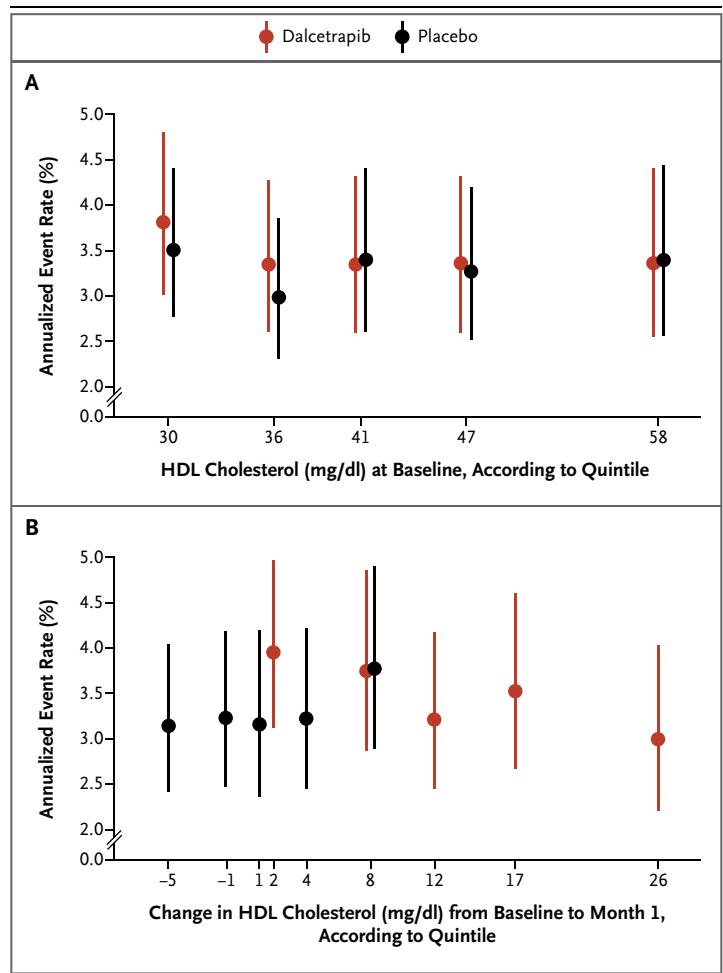
The dal-OUTCOMES trial evaluated whether treatment with the CETP inhibitor dalcetrapib modified cardiovascular risk in patients who had had a recent acute coronary syndrome. Despite the finding that dalcetrapib, as compared with placebo, produced a substantial increase in HDL cholesterol levels, it had 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,<sup>2-7</sup> 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-

**Figure 3. Association between HDL Cholesterol Level and Risk of the Primary End Point.**

Panel A shows the annualized risk of the primary end point according to quintile of HDL cholesterol level at baseline (quintile 1,  $\leq 33$  mg per deciliter; quintile 2,  $>33$  to 38 mg per deciliter; quintile 3,  $>38$  to 43 mg per deciliter; quintile 4,  $>43$  to 51 mg per deciliter; and quintile 5,  $>51$  mg per deciliter). Panel B shows the annualized risk of the primary end point beginning 1 month after randomization according to quintiles of change in HDL cholesterol levels from baseline to 1 month after randomization (quintiles of change for dalcetrapib,  $\leq 5$  mg per deciliter,  $>5$  to 9 mg per deciliter,  $>9$  to 14 mg per deciliter,  $>14$  to 20 mg per deciliter, and  $>20$  mg per deciliter; quintiles of change for placebo,  $\leq -3$  mg per deciliter or less, greater than  $-3$  to 0 mg per deciliter,  $>0$  to 2 mg per deciliter,  $>2$  to 5 mg per deciliter, and  $>5$  mg per deciliter). The position of each quintile of HDL cholesterol on the x axis corresponds to the median value of HDL cholesterol within that quintile. (In Panel A, the data positions on the x axis for the two treatment groups are offset from the common median by 0.30 mg per deciliter to avoid overlap.) Data for rates are plotted as point estimates with 95% confidence intervals. Associations in Panels A and B have been adjusted for age; sex; geographic region; body-mass index; waist-to-hip ratio; status with respect to a history of diabetes, hypercholesterolemia, hypertension, metabolic syndrome, previous myocardial infarction, unstable angina, or percutaneous coronary intervention; smoking status at the time of randomization; presence or absence of impaired glomerular filtration rate ( $<60$  ml per minute per  $1.73$  m<sup>2</sup>); and baseline LDL cholesterol level. Associations in Panel B have been additionally adjusted for the change from baseline to month 1 in systolic blood pressure, LDL cholesterol level, and C-reactive protein level. In Panel A, there was no significant main effect of HDL cholesterol on the risk of the primary end point in either the dalcetrapib group or the placebo group ( $P=0.77$  for both comparisons). There was no significant interaction between group assignment and baseline HDL cholesterol level with respect to the risk of the primary end point ( $P=0.94$ ). In Panel B, there was no significant main effect of the change in HDL cholesterol level from baseline to month 1 with respect to the risk of the primary end point after month 1 in either the dalcetrapib group ( $P=0.23$ ) or the placebo group ( $P=0.62$ ). There was no significant interaction between group assignment and change in HDL cholesterol level from baseline to month 1 with respect to the risk of the primary end point after month 1 ( $P=0.15$ ).



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.<sup>29</sup> 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<sup>30</sup> but might indicate other underlying adverse vas-

nary event, owing to the acute-phase response that occurs in the wake of myocardial infarction.<sup>26,27</sup> However, other manifestations of acute-phase response after myocardial infarction wane before 61 days,<sup>28</sup> which was the median time from the index event to the time of random

cular effects. Similarly, the 18% increase in the median C-reactive protein level with dalcetrapib might indicate a proinflammatory effect of treatment associated with a greater risk of cardiovascular events.<sup>8</sup> 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.<sup>22,31</sup> Since the structure of dalcetrapib is dissimilar to that of the other two agents,<sup>32</sup> 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 dalcetrapib 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 risk reduction of 10% or more. Moreover, dalcetrapib had concordantly neutral effects on all components of the primary end point and on the rate of coronary revascularization.

In summary, the addition of dalcetrapib to standard therapy after an acute coronary syndrome 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 dalcetrapib 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 dalcetrapib and that also lower LDL cholesterol levels<sup>31,33</sup> will prove to have clinical effects different from those of dalcetrapib.

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