

## ORIGINAL ARTICLE

# Effect of Torcetrapib on the Progression of Coronary Atherosclerosis

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## ABSTRACT

**BACKGROUND**

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Levels of high-density lipoprotein (HDL) cholesterol are inversely related to cardiovascular risk. Torcetrapib, a cholesteryl ester transfer protein (CETP) inhibitor, increases HDL cholesterol levels, but the functional effects associated with this mechanism remain uncertain.

**METHODS**

A total of 1188 patients with coronary disease underwent intravascular ultrasonography. After treatment with atorvastatin to reduce levels of low-density lipoprotein (LDL) cholesterol to less than 100 mg per deciliter (2.59 mmol per liter), patients were randomly assigned to receive either atorvastatin monotherapy or atorvastatin plus 60 mg of torcetrapib daily. After 24 months, disease progression was measured by repeated intravascular ultrasonography in 910 patients (77%).

**RESULTS**

After 24 months, as compared with atorvastatin monotherapy, the effect of torcetrapib–atorvastatin therapy was an approximate 61% relative increase in HDL cholesterol and a 20% relative decrease in LDL cholesterol, reaching a ratio of LDL cholesterol to HDL cholesterol of less than 1.0. Torcetrapib was also associated with an increase in systolic blood pressure of 4.6 mm Hg. The percent atheroma volume (the primary efficacy measure) increased by 0.19% in the atorvastatin-only group and by 0.12% in the torcetrapib–atorvastatin group ( $P=0.72$ ). A secondary measure, the change in normalized atheroma volume, showed a small favorable effect for torcetrapib ( $P=0.02$ ), but there was no significant difference in the change in atheroma volume for the most diseased vessel segment.

**CONCLUSIONS**

The CETP inhibitor torcetrapib was associated with a substantial increase in HDL cholesterol and decrease in LDL cholesterol. It was also associated with an increase in blood pressure, and there was no significant decrease in the progression of coronary atherosclerosis. The lack of efficacy may be related to the mechanism of action of this drug class or to molecule-specific adverse effects. (ClinicalTrials.gov number, NCT00134173.)

\*Investigators and committees of the Investigation of Lipid Level Management Using Coronary Ultrasound to Assess Reduction of Atherosclerosis by CETP Inhibition and HDL Elevation (ILLUSTRATE) trial are listed in the Supplementary Appendix, available with the full text of this article at [www.nejm.org](http://www.nejm.org).

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**E**PIDEMIOLOGIC STUDIES DEMONSTRATE an inverse relationship between levels of high-density lipoprotein (HDL) cholesterol and the incidence of cardiovascular disease.<sup>1</sup> Limited clinical trials have suggested that an increase in HDL cholesterol levels may reduce the progression of coronary atherosclerosis and decrease cardiovascular morbidity.<sup>2,3</sup> Cholesteryl ester transfer protein (CETP) facilitates the transfer of cholesteryl ester from HDL cholesterol to low-density lipoprotein (LDL) cholesterol and very-low-density lipoprotein (VLDL) cholesterol. Recently, the administration of the CETP inhibitor torcetrapib has been shown to increase HDL cholesterol levels by more than 50%.<sup>4</sup> However, the effectiveness of CETP inhibition as a strategy for antiatherosclerotic therapy has been controversial.<sup>5-7</sup> Specific concern about the benefits and risks of torcetrapib emerged when initial clinical trials demonstrated a dose-dependent increase in blood pressure.<sup>8</sup>

The development program for torcetrapib included three clinical trials of similar design, using coronary intravascular ultrasonography or carotid ultrasonography to determine whether partial inhibition of CETP with torcetrapib, administered with atorvastatin, would provide an additional antiatherosclerotic benefit, as compared with atorvastatin alone. After completion of these imaging trials but before the unblinding of the results, the data safety and monitoring board for a large torcetrapib clinical trial, called the Investigation of Lipid Level Management to Understand Its Impact in Atherosclerotic Events (ILLUMINATE) trial (NCT00134264), recommended that the study be terminated after an increase was observed in adverse cardiovascular events, including death from all causes.<sup>9</sup> The sponsor promptly suspended the entire torcetrapib development program.<sup>9</sup> We now report the results of the trial using intravascular ultrasonography as originally planned, with the additional use of these data to understand the mechanisms for adverse cardiovascular outcomes observed in the suspended torcetrapib trial.

## METHODS

### STUDY DESIGN

The Investigation of Lipid Level Management Using Coronary Ultrasound to Assess Reduction of Atherosclerosis by CETP Inhibition and HDL Elevation (ILLUSTRATE) trial was a prospective, randomized, multicenter, double-blind clinical trial.

The randomization was stratified according to geographic region (North America or Europe) and the dose of atorvastatin with the use of a permuted-block size of 4. The trial was designed by the Cleveland Clinic Cardiovascular Coordinating Center in collaboration with the sponsor. Institutional review boards at each study center approved the protocol, and patients provided written informed consent.

Patients between the ages of 18 and 75 years were eligible if they had undergone clinically indicated cardiac catheterization showing at least one stenosis on angiography with at least 20% narrowing and if the target vessel had less than 50% obstruction throughout a segment of 40 mm or longer. Patients were excluded from the study if the left main coronary artery had more than 50% obstruction, if the blood pressure was more than 140/90 mm Hg despite treatment, if the triglyceride level was more than 500 mg per deciliter (5.65 mmol per liter), or if the creatinine level was more than 1.7 times the upper limit of normal.

During a run-in phase of 4 to 10 weeks, patients were counseled on therapeutic lifestyle changes<sup>1</sup> and administered atorvastatin (Lipitor, Pfizer) in an initial dose of 10 mg, which was subsequently titrated at 2-week intervals to 20 mg, 40 mg, or 80 mg, if needed, to achieve a level of LDL cholesterol within 15 mg per deciliter (0.39 mmol per liter) of 100 mg per deciliter (2.59 mmol per liter). Patients who met the LDL cholesterol goal were randomly assigned to receive either a fixed combination of atorvastatin (at the dose established during the run-in period) with 60 mg of torcetrapib or atorvastatin monotherapy with corresponding placebo tablets. A committee whose members were unaware of treatment assignment centrally adjudicated major cardiovascular adverse events.

The lead academic investigator wrote the manuscript and vouches for the accuracy and completeness of the data and the analyses. The study contract specified that a copy of the study database be provided to the coordinating center for independent analysis and granted the academic authors the unrestricted rights to publish the results.

### INTRAVASCULAR ULTRASONOGRAPHY

After angiography, baseline intravascular ultrasonography was performed. The methods used for image acquisition and measurement in regression-progression studies have been described previously.<sup>10-15</sup> The results were screened for image

quality in the core laboratory, and only patients whose findings met prespecified requirements for image quality were eligible for randomization. After 24 months, patients underwent a second intravascular ultrasonographic examination of the same coronary segment. Using digitized images, personnel who were unaware of patients' clinical characteristics and treatment assignments performed manual planimetric measurements for cross sections spaced at 1.0-mm intervals. Measurements were performed in accordance with established standards.<sup>16</sup> For each analyzed cross section, the operator measured the area of the external elastic membrane and the lumen. The accuracy and reproducibility of this method have been reported previously.<sup>17</sup>

#### CALCULATION OF EFFICACY MEASURES

The primary efficacy measure, the change in percent atheroma volume, was calculated as follows:

$$\left( \frac{\sum (EEM_{CSA} - LUMEN_{CSA})}{\sum EEM_{CSA}} \right) \times 100,$$

where  $EEM_{CSA}$  is the cross-sectional area of the external elastic membrane and  $LUMEN_{CSA}$  is the cross-sectional area of the lumen. The change in percent atheroma volume was calculated as the percent atheroma volume at 24 months minus the percent atheroma volume at baseline.

A secondary measure of efficacy, normalized total atheroma volume, was also calculated. First, the average atheroma area per cross section was calculated as follows:

$$\frac{\sum (EEM_{CSA} - LUMEN_{CSA})}{n},$$

where  $n$  is the number of cross sections in the pullback. To compensate for pullbacks of differing lengths, the total atheroma volume for each patient was calculated as the average atheroma area multiplied by the median number of cross sections for all patients in the study. The efficacy measure of the change in normalized total atheroma volume was calculated as the total atheroma volume at 24 months minus the total atheroma volume at baseline.

An additional secondary measure of efficacy, the change in atheroma volume in the most diseased 10-mm subsegment, was calculated by first determining the 10 contiguous cross sections with the greatest atheroma volume at baseline, then comparing the atheroma volume at follow-up for these cross sections.

#### STATISTICAL ANALYSIS

The trial database was transferred from the sponsor to the Cleveland Clinic, permitting independent confirmation of analyses. For continuous variables with a normal distribution, the mean ( $\pm$ SD) is reported. For variables not normally distributed, the median and interquartile ranges are reported. Measures of the efficacy of intravascular ultrasonography were adjusted with use of analysis of covariance. Lipoprotein levels are reported as the least-square mean ( $\pm$ SE) with the use of a linear model that included treatment group, geographic region, dose of atorvastatin, and baseline values. All reported P values are two-sided and not adjusted for multiple testing. For the primary efficacy measure (the change in percent atheroma volume), 413 patients in each study group were required for a power of 90% at a two-sided alpha of 0.05 to detect a treatment difference of 1.1% with a 5.0% standard deviation. Assuming a dropout rate of 25%, a total of 1100 patients were required.

## RESULTS

#### PATIENTS

From October 30, 2003, to August 16, 2004, at 137 centers in North America and Europe, 1188 patients were randomly assigned to study groups — 597 to the atorvastatin-only group and 591 to the torcetrapib–atorvastatin group. After 24 months of treatment, 910 patients (77%) remained in the study and had results on intravascular ultrasonography that could be evaluated at both baseline and follow-up. Of these patients, 446 were in the atorvastatin-only group and 464 in the torcetrapib–atorvastatin group. Demographic characteristics and the use of medications at baseline were similar in the two treatment groups (Table 1). The titrated dose of atorvastatin averaged 23 mg in both groups.

#### LABORATORY RESULTS AND BLOOD PRESSURE

Table 1 summarizes laboratory values and blood pressure at baseline and during treatment for the 910 patients who completed the trial. After 24 months of treatment, HDL cholesterol levels in the atorvastatin-only group decreased from 45.2 to 43.9 mg per deciliter (1.17 to 1.14 mmol per liter), and levels of HDL cholesterol in the torcetrapib–atorvastatin group increased from 46.0 to 72.1 mg per deciliter (1.19 to 1.86 mmol per liter). After 24 months, LDL cholesterol levels in the atorvastatin-only group increased from 84.3 to 87.2 mg per deciliter (2.18 to 2.25 mmol per liter), and LDL

cholesterol levels in the torcetrapib–atorvastatin group fell from 83.1 to 70.1 mg per deciliter (2.15 to 1.81 mmol per liter). Patients in the torcetrapib–atorvastatin group had a 61% relative increase in HDL cholesterol levels and a 20% relative decrease in LDL cholesterol levels, as compared with patients in the atorvastatin-only group.

Baseline blood pressure was 120/73 mm Hg in both study groups. The average post-randomization systolic blood pressure increased by 2.0 mm Hg in the atorvastatin-only group and by 6.5 mm Hg in the torcetrapib–atorvastatin group, a least-square mean difference of 4.6 mm Hg (95% confidence interval [CI], 3.7 to 5.6;  $P < 0.001$ ). Median levels of high-sensitivity C-reactive protein were slightly higher in the torcetrapib–atorvastatin group at baseline ( $P = 0.04$ ) and at 24 months ( $P = 0.02$ ), but the change in C-reactive protein did not differ significantly between treatment groups (Table 1). Characteristics were similar in the 278 patients who did not complete the trial or undergo final intravascular ultrasonography.

#### INTRAVASCULAR ULTRASONOGRAPHY

Table 2 summarizes the change in the primary and secondary measures of efficacy, as measured by intravascular ultrasonography. The primary efficacy measure, the change in percent atheroma volume, increased by 0.19% in the atorvastatin-only group and by 0.12% in the torcetrapib–atorvastatin group ( $P = 0.72$ ). A secondary measure, normalized atheroma volume, showed a small favorable effect in the torcetrapib–atorvastatin group, a reduction of 9.5 mm<sup>3</sup>, as compared with a reduction of 6.3 mm<sup>3</sup> in the atorvastatin-only group ( $P = 0.02$ ). The other secondary efficacy measure, the change in 10 mm of the most diseased segment, showed no statistical difference, with a reduction of 3.3 mm<sup>3</sup> in the atorvastatin-only group and of 4.2 mm<sup>3</sup> in the torcetrapib–atorvastatin group ( $P = 0.12$ ). There was no heterogeneity in the treatment difference for nearly all prespecified subgroups (see the Supplementary Appendix, which is available with the full text of this article at [www.nejm.org](http://www.nejm.org)). However, for patients whose percent atheroma volume was equal to or greater than the median value, there was a nearly significant effect in the torcetrapib–atorvastatin group ( $P = 0.054$ ). For patients with a baseline percent atheroma volume that was below the median value, the results showed a trend in favor of atorvastatin monotherapy ( $P = 0.09$ ). The interaction  $P$  value for this dichotomization was 0.005.

#### CLINICAL OUTCOMES AND ADVERSE EVENTS

Table 3 shows centrally adjudicated clinical events, blood-pressure–related adverse events, laboratory abnormalities, and reasons for study discontinuation. The frequency of major adverse cardiovascular events was similar in the two study groups. However, patients in the torcetrapib–atorvastatin group had more investigator-reported hypertensive adverse events (23.7% vs. 10.6%) and more blood-pressure values greater than 140/90 mm Hg (21.3% vs. 8.2%). A sustained increase of more than 15 mm Hg in systolic pressure occurred in 9.0% of patients in the torcetrapib–atorvastatin group and in 3.2% of patients in the atorvastatin-only group. Changes in systolic blood pressure for the two study groups are shown in Figure 1.

#### DISCUSSION

A reduction in levels of LDL cholesterol represents the principal target for primary and secondary prevention of cardiovascular disease.<sup>18</sup> However, many patients die or have complications from cardiovascular events despite the lowering of LDL cholesterol levels.<sup>19</sup> Accordingly, research has focused on the development of agents that target other pathways in the pathogenesis of atherosclerosis. HDL cholesterol is an attractive target because epidemiologic evidence demonstrates a strong inverse relationship between HDL cholesterol levels and cardiovascular risk.<sup>1</sup> The biologic plausibility of raising HDL cholesterol levels as a therapeutic strategy is further supported by evidence of the lipoprotein's antiinflammatory properties, antioxidant effects, and ability to promote reverse cholesterol transport.<sup>20,21</sup> Drugs that raise HDL cholesterol are available but have limitations. Fibric acid derivatives, such as gemfibrozil and fenofibrate, only modestly raise HDL cholesterol levels, generally by 7 to 15%. Large doses of niacin can raise HDL cholesterol levels by 25% or more, but administration is difficult in some patients because of the troublesome side effects of cutaneous flushing, occasional hepatotoxicity, and an increase in blood glucose levels.

Inhibition of CETP emerged as an attractive pharmaceutical target after studies involving Japanese patients with CETP deficiency showed very high HDL cholesterol levels.<sup>22</sup> However, the potential value of this therapeutic strategy has generated considerable controversy.<sup>5,6,23,24</sup> Our study provides evidence that directly addresses this controversy. After 24 months, treatment with the CETP inhibi-

**Table 1. Baseline Characteristics, Blood Pressures, and Laboratory Values.\***

Variable	Atorvastatin Only	Atorvastatin plus Torcetrapib	P Value
<b>All patients</b>			
No. of patients	597	591	
Age — yr	57±9.2	56.9±9.1	0.96
Male sex — %	70.5	70.4	0.96
Body-mass index†	30.3±5.2	30.6±6.2	0.41
History of diabetes — no. (%)	133 (22.3)	119 (20.1)	0.37
History of hypertension — no. (%)	463 (77.6)	440 (74.5)	0.21
Current smoker — no. (%)	112 (18.8)	102 (17.3)	0.50
Medication use at baseline — no. (%)			
Aspirin	563 (94.3)	554 (93.7)	0.68
Beta-blocker	457 (76.5)	449 (76.0)	0.82
ACE inhibitor or ARB	392 (65.7)	392 (66.3)	0.81
Statin	543 (91.0)	536 (90.7)	0.88
<b>Baseline values of patients who completed trial</b>			
No. of patients	446	464	
Cholesterol — mg/dl			
Total	157.5±27.1	157.7±27.6	0.91
LDL	84.3±18.9	83.1±19.7	0.35
HDL	45.2±11.2	46.0±12.8	0.34
Ratio of LDL cholesterol to HDL cholesterol			0.39‡
Median	1.90	1.88	
Interquartile range	1.6 to 2.2	1.5 to 2.3	
Triglycerides — mg/dl			
Median	123.9	122.0	0.66‡
Interquartile range	89.0 to 170.0	88.5 to 179.0	
C-reactive protein — mg/liter			
Median	1.8	2.1	0.04‡
Interquartile range	0.9 to 3.4	1.1 to 4.3	
Blood pressure — mm Hg§			
Systolic	120.0±11.5	119.8±11.3	0.81
Diastolic	73.4±7.4	73.3±7.1	0.70
<b>Follow-up at 24 months</b>			
Cholesterol — mg/dl			
Total	157.2±31.2	167.5±37.4	<0.001
LDL	87.2±22.6	70.1±25.4	<0.001
HDL	43.9±12.1	72.1±24.9	<0.001
Ratio of LDL cholesterol to HDL cholesterol			<0.001‡
Median	2.0	0.9	
Interquartile range	1.7 to 2.4	0.7 to 1.4	

Table 1. (Continued.)			
Variable	Atorvastatin Only	Atorvastatin plus Torcetrapib	P Value
Triglycerides — mg/dl			0.10‡
Median	110.0	104.0	
Interquartile range	76.5 to 159.0	72.5 to 150.7	
C-reactive protein — mg/liter			0.02‡
Median	1.5	1.8	
Interquartile range	0.7 to 3.0	0.8 to 4.2	
Blood pressure — mm Hg§			
Systolic	122.0±10.1	126.4±11.0	<0.001
Diastolic	74.3±6.4	76.0±6.6	<0.001
<b>Change from baseline</b>			
Cholesterol — %¶			
Total	1.9±0.9	7.2±0.9	<0.001
LDL	6.6±1.3	-13.3±1.3	<0.001
HDL	-2.2±1.4	58.6±1.4	<0.001
Triglycerides — %			<0.001
Median	-8.2	-14.3	
Interquartile range	-26.3 to 16.7	-38.5 to 8.9	
C-reactive protein — mg/liter			0.19
Median	-0.2	-0.1	
Interquartile range	-1.0 to 0.5	-1.1 to 0.8	
Blood pressure — mm Hg§			
Systolic	2.0±8.7	6.5±10.1	<0.001
Diastolic	0.8±5.1	2.8±5.4	<0.001

\* Plus-minus values are means ±SD unless otherwise indicated. To convert values for cholesterol to millimoles per liter, multiply by 0.02586. To convert values for triglycerides to millimoles per liter, multiply by 0.01129. ACE denotes angiotensin-converting enzyme, ARB angiotensin-receptor blocker, LDL low-density lipoprotein, and HDL high-density lipoprotein.

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

‡ Comparisons were performed with use of the Wilcoxon rank-sum test.

§ Values are the averages of all post-randomization measurements (586 patients in the torcetrapib-atorvastatin group and 589 in the atorvastatin-only group), including 1 patient who did not undergo final ultrasonography.

¶ Values are least-square means ±SE.

|| P values were calculated from an analysis of covariance on rank-transformed data, with the last observation carried forward.

tor torcetrapib with atorvastatin increased HDL cholesterol levels by approximately 60% and lowered LDL cholesterol levels by 20%, as compared with atorvastatin monotherapy. After 24 months of treatment, HDL cholesterol levels were actually higher than LDL cholesterol levels in patients treated with torcetrapib. However, despite these favorable effects on lipoprotein levels, there was no significant reduction in the progression of coronary atherosclerosis according to percent

atheroma volume, the primary efficacy measure (Table 2).

The results of torcetrapib administration can be considered in relation to the achieved LDL cholesterol levels. The mean on-treatment LDL cholesterol level has been a robust predictor of the progression rate of coronary atherosclerosis in trials involving the use of intravascular ultrasonography, showing regression when LDL cholesterol levels fall below approximately 75 mg per

deciliter (1.94 mmol per liter) (Fig. 2). In our study, the atorvastatin-only group had a mean LDL cholesterol level of 87.2 mg per deciliter (2.25 mmol per liter), resulting in a net progression of 0.19%, which falls close to the expected result. Patients in the torcetrapib–atorvastatin group had a mean LDL cholesterol level of 70.1 mg per deciliter (1.81 mmol per liter), but the increase in percent atheroma volume was greater than would be expected (0.12%).

Estimating the benefits expected from a change in HDL cholesterol levels is more difficult. Although no trials involving intravascular ultrasonography have directly examined the effects of therapies to increase HDL cholesterol levels, a small study examined the effects of short-term infusions of an HDL-like agent, apolipoprotein A-I Milano, and showed significant regression, with a reduction in percent atheroma volume of 1.06%.<sup>10</sup>

A single secondary efficacy measure, the change in total atheroma volume, showed a favorable effect associated with torcetrapib. However, the treatment difference was relatively small (least-square mean, 3.2 mm<sup>3</sup>), particularly considering the long duration of the trial. Other studies using intravascular ultrasonography have shown larger treatment effects for therapies with a favorable effect on clinical outcomes. A trial comparing moderate versus intensive statin therapy showed a treatment difference for total atheroma volume of 5.5 mm<sup>3</sup> after 18 months.<sup>11</sup> A more recent study using very intensive statin therapy for 24 months resulted in a regression of 14.7 mm<sup>3</sup> in total atheroma volume.<sup>14</sup> The infusion of apolipoprotein A-I Milano reduced total atheroma volume by 14.1 mm<sup>3</sup>. Accordingly, the totality of the data, with no benefit observed for the primary end point and one secondary end point and a small favorable effect for another secondary end point, supports the conclusion that the lipoprotein effects of torcetrapib failed to provide the anticipated antiatherosclerotic benefits. Accordingly, it seems likely that other drug effects prevented the slowing of atherosclerosis expected from the seemingly favorable lipid-modulating benefits of torcetrapib.

Several potential mechanisms could explain the lack of antiatherosclerotic efficacy observed in the torcetrapib–atorvastatin group. The increase

in systolic blood pressure observed in this group averaged 4.6 mm Hg, with 21.3% of patients exceeding 140/90 mm Hg and 9.0% having a sustained increase of more than 15 mm Hg (Fig. 1). These increases in blood pressure may have counterbalanced any benefits derived from the increases in HDL cholesterol levels and decreases in LDL cholesterol levels. Previous trials using intravascular ultrasonography have shown a relationship between a change in blood pressure and the progression of atherosclerosis.<sup>12,26</sup> The administration of amlodipine for 24 months lowered systolic blood pressure by 4.9 mm Hg and reduced percent atheroma volume by 0.8%, as compared with placebo.<sup>12</sup> Accordingly, it seems plausible that a mean increase in blood pressure of 4.6 mm Hg in the torcetrapib–atorvastatin group (as compared with the atorvastatin-only group) might increase percent atheroma volume by a similar amount (0.8%).

The possibility that the HDL cholesterol produced by torcetrapib might be dysfunctional also deserves careful consideration. There are conflicting data on the prevalence of atherosclerosis in patients with CETP deficiency or genetic polymorphisms. Some studies show protection, whereas others show increased susceptibility to atherosclerotic disease.<sup>27</sup> Proponents of CETP inhibition have proposed that the complete absence of this enzyme and associated abnormalities in homozygotes might produce dysfunctional HDL cholesterol, whereas partial inhibition would yield functional HDL particles.<sup>7,28</sup> In transgenic animal models of atherosclerosis, CETP inhibition has produced mixed results, with both proatherogenic and antiatherogenic effects, depending on the species studied.<sup>5</sup> Studies showing a proatherogenic effect were often performed in animals that do not naturally express CETP. In cholesterol-fed rabbits that express CETP, torcetrapib provided protection against the development of aortic atherosclerosis.<sup>29</sup>

The functionality of HDL cholesterol produced through CETP inhibition remains uncertain. Figure 3 illustrates the metabolism of HDL cholesterol, its role in reverse cholesterol transport, and the expected effects of CETP inhibition. Lipid-poor apolipoprotein A-I circulates as a discoidal particle, which is the preferred acceptor of cholesterol effluxed from macrophages through the

**Table 2. Primary and Secondary Study End Points as Evaluated on Intravascular Ultrasonography at Baseline and at 24-Month Follow-up with Changes from Baseline.**

Variable	Atorvastatin Only (N = 446)	Atorvastatin plus Torcetrapib (N = 464)	P Value
<b>Baseline</b>			
Percent atheroma volume*			0.88
Mean $\pm$ SD	37.1 $\pm$ 8.5	37.0 $\pm$ 8.6	
Median	36.5	36.8	
Interquartile range	31.2–42.7	31.3– 42.8	
Normalized total atheroma volume (mm <sup>3</sup> ) †			0.66
Mean $\pm$ SD	198.7 $\pm$ 86.2	196.1 $\pm$ 90.8	
Median	185.1	177.3	
Interquartile range	134.8–252.2	133.9–238.2	
Atheroma volume of most diseased 10-mm segment (mm <sup>3</sup> ) †			0.46
Mean $\pm$ SD	58.2 $\pm$ 25.7	56.8 $\pm$ 28.7	
Median	55.8	54.0	
Interquartile range	(39.5–74.2)	(35.9–72.6)	
<b>Follow-up at 24 months</b>			
Percent atheroma volume			0.78
Mean $\pm$ SD	37.3 $\pm$ 8.8	37.1 $\pm$ 8.6	
Median	36.3	37.0	
Interquartile range	31.1–43.4	31.4–42.7	
Normalized total atheroma volume (mm <sup>3</sup> )			0.32
Mean $\pm$ SD	192.4 $\pm$ 85.7	186.7 $\pm$ 87.6	
Median	176.4	169.7	
Interquartile range	129.2–242.8	127.3–226.5	
Atheroma volume of most diseased 10-mm segment (mm <sup>3</sup> )			0.22
Mean $\pm$ SD	54.9 $\pm$ 24.7	52.7 $\pm$ 26.5	
Median	53.4	50.5	
Interquartile range	37.4–69.7	34.5–65.3	
<b>Change from baseline</b>			
Percent atheroma volume			0.72
Mean $\pm$ SD	0.19 $\pm$ 2.83	0.12 $\pm$ 2.99	
Least-square mean $\pm$ SE	0.19 $\pm$ 0.14	0.12 $\pm$ 0.13	
Normalized total atheroma volume (mm <sup>3</sup> )			0.02
Mean $\pm$ SD	-6.3 $\pm$ 22.2	-9.4 $\pm$ 21.0	
Least-square mean $\pm$ SE	-6.3 $\pm$ 1.0	-9.5 $\pm$ 1.0	
Atheroma volume of most diseased 10-mm segment (mm <sup>3</sup> )			0.12
Mean $\pm$ SD	-3.3 $\pm$ 9.1	-4.1 $\pm$ 8.6	
Least-square mean $\pm$ SE	-3.3 $\pm$ 0.4	-4.2 $\pm$ 0.4	

\* This variable was the primary efficacy measure.

† This variable was a secondary efficacy measure.

**Table 3. Adverse Events, Clinical End Points, and Reasons for Discontinuation.\***

Variable	Atorvastatin Only (N = 597)	Atorvastatin plus Torcetrapib (N = 591)
	number (percent)	
<b>Cardiovascular event†</b>		
Death		
All causes	6 (1.0)	8 (1.4)
Coronary heart disease	1 (0.2)	1 (0.2)
Nonfatal myocardial infarction	16 (2.7)	13 (2.2)
Fatal or nonfatal stroke	8 (1.3)	2 (0.3)
Hospitalization for unstable angina	34 (5.7)	47 (8.0)
Coronary revascularization	95 (15.9)	114 (19.3)
Peripheral vascular disease	13 (2.2)	10 (1.7)
Transient ischemic attack	0	2 (0.3)
Hospitalization for congestive heart failure	4 (0.7)	9 (1.5)
Composite of death from coronary heart disease, nonfatal myocardial infarction, nonfatal stroke, and hospitalization for unstable angina	57 (9.5)	62 (10.5)
Composite of death from coronary heart disease, nonfatal myocardial infarction, nonfatal stroke, hospitalization for unstable angina, and coronary revascularization	117 (19.6)	124 (21.0)
<b>Blood pressure–related event</b>		
Investigator-reported hypertensive adverse event	63 (10.6)	140 (23.7)
Blood pressure >140/90 mm Hg	49 (8.2)	126 (21.3)
Blood pressure increase >15 mm Hg	19 (3.2)	53 (9.0)
<b>Abnormality in laboratory value</b>		
Aspartate aminotransferase >3× ULN	2 (0.3)	4 (0.7)
Alanine aminotransferase >3× ULN	5 (0.8)	8 (1.4)
Creatine phosphokinase		
>5× ULN	4 (0.7)	1 (0.2)
>10× ULN	1 (0.2)	0
<b>Discontinuation</b>		
No. of patients	140	135
Reason for discontinuation		
Preference of patient	57	48
Adverse event	64	66
Lack of efficacy	0	1
Death	6	6‡
Unspecified	13	15

\* ULN denotes upper limit of normal.

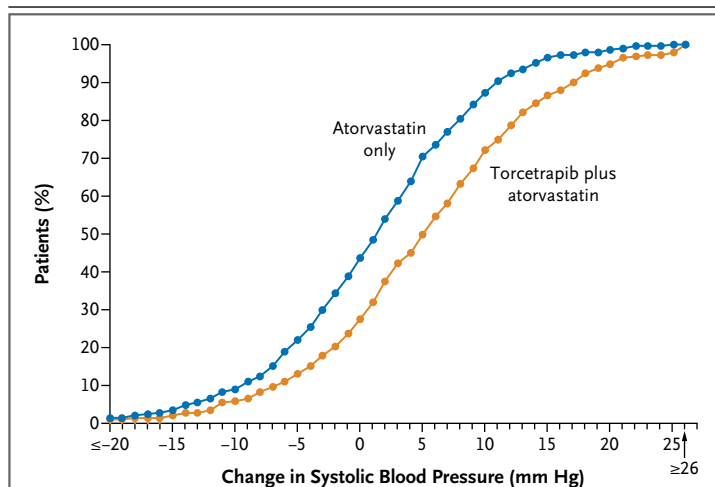
† Data on adverse events for each patient were collected for 28 days after the administration of the last dose of study medication and were adjudicated by a central committee. The results exclude three events that remain to be adjudicated.

‡ Number includes an additional patient who died after completing the study.

transmembrane ATP-binding cassette transporter A1 (ABCA1). CETP inhibition, however, increases the concentration of mature, cholesterol-laden alpha HDL particles, which are not optimal acceptors of ABCA1-mediated efflux, although they may facilitate reverse cholesterol transport mediated by ATP-binding cassette transporter G1 (ABCG1) or scavenger receptor class B1 (SR-B1) (Fig. 3). Recent evidence suggests that in vivo modification of HDL cholesterol can result in an abnormal particle with proinflammatory, pro-atherogenic properties.<sup>30,31</sup>

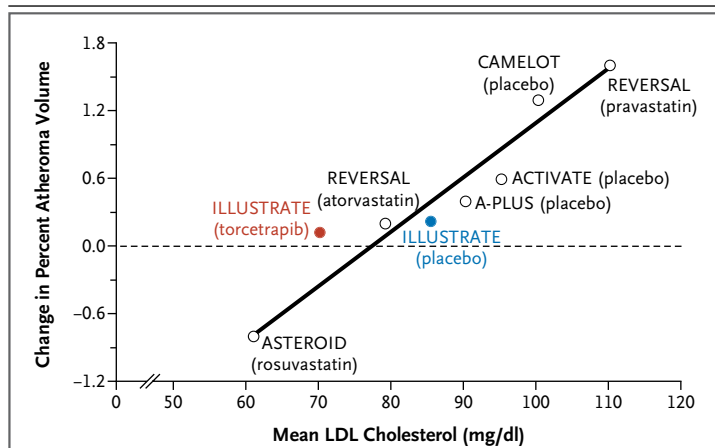
It is also possible that toxic effects unique to the torcetrapib molecule may have adversely affected the progression rate. The increase in blood pressure observed in torcetrapib-treated patients may reflect more generalized vascular toxicity, effects that could have counterbalanced any anti-atherosclerotic benefits derived from an increase in HDL cholesterol. In our study, a greater number of adverse cardiovascular events were observed in the torcetrapib–atorvastatin group than in the atorvastatin-only group (Table 3). Although these differences were not statistically significant, the study was not powered to evaluate cardiovascular outcomes. These results are consistent with the observation of worse clinical outcomes among patients who received torcetrapib in the prematurely terminated morbidity–mortality trial.

The possibility must be considered that CETP inhibition, regardless of specific molecular toxicity, will not provide antiatherosclerotic benefits. A critical question is whether the failure of torcetrapib precludes the possibility that other drugs in this class might be successfully developed as effective antiatherosclerotic agents. It is difficult to determine the extent to which the failure of torcetrapib was the result of dysfunctional HDL cholesterol, properties that increased blood pressure, or other toxic effects specific to this agent. Other CETP inhibitors do not appear to have a pressor effect.<sup>32</sup> Future post hoc analyses from our study and from other torcetrapib trials will attempt to elucidate the effect of changes in HDL cholesterol, LDL cholesterol, and blood pressure on trial results. Given the potential importance of developing therapies to raise HDL cholesterol levels, it would seem imprudent to abandon studies of CETP inhibition because of the failure of



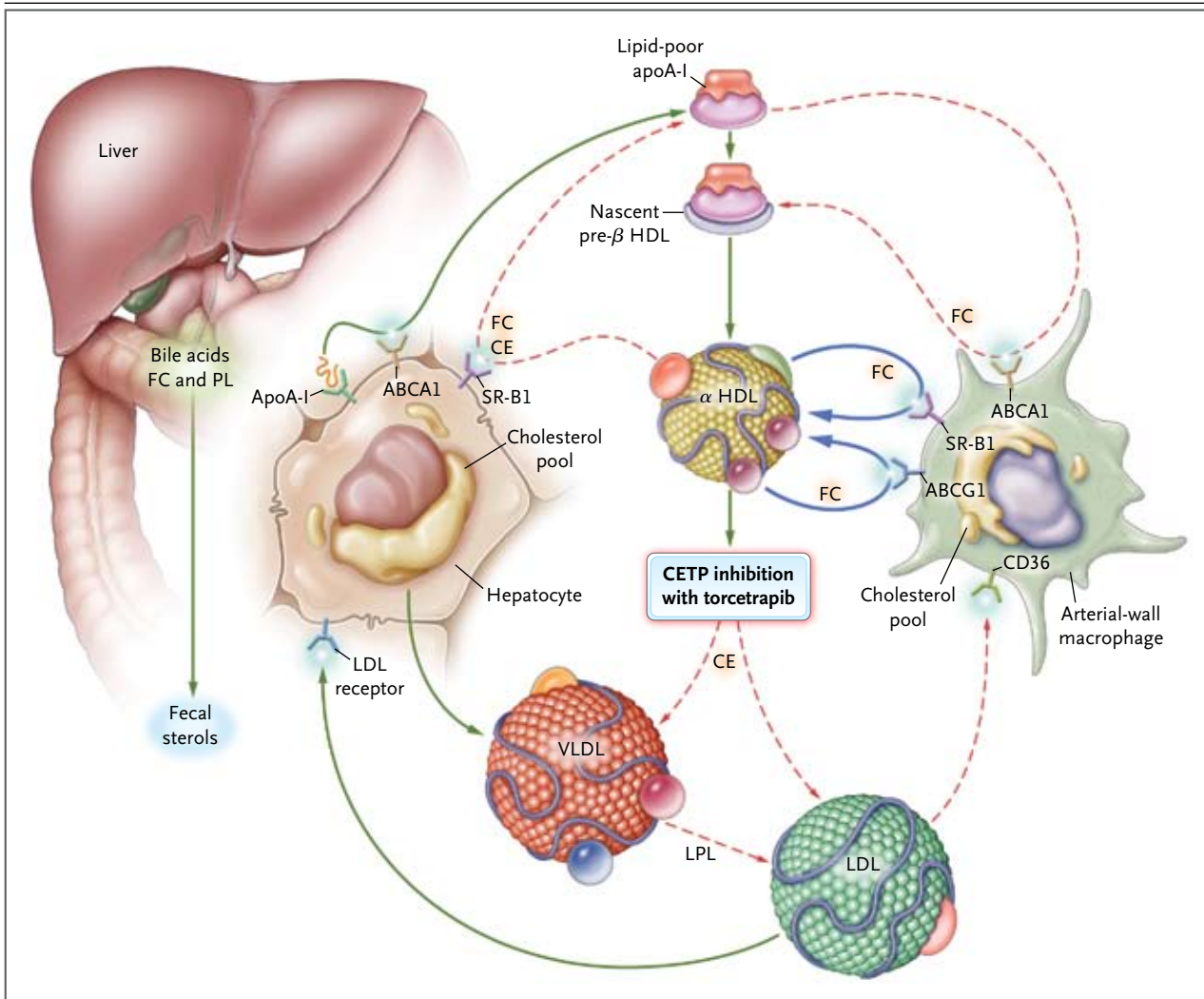
**Figure 1. Changes in Systolic Blood Pressure in the Two Study Groups.**

The graph shows data for all patients for whom blood pressure measurements were available — 586 in the atorvastatin-only group and 589 in the atorvastatin–torcetrapib group — regardless of whether the patients underwent final intravascular ultrasonography.



**Figure 2. Relationship between the Change in Percent Atheroma Volume and LDL Cholesterol in Regression–Progression Trials Using Intravascular Ultrasonography.**

Values for percent atheroma volume represent the prespecified measures in the cited studies: mean values, medians, or least-square means. ILLUSTRATE denotes Investigation of Lipid Level Management Using Coronary Ultrasound to Assess Reduction of Atherosclerosis by CETP Inhibition and HDL Elevation (ClinicalTrials.gov number, NCT00134173), REVERSAL the Reversal of Atherosclerosis with Aggressive Lipid Lowering,<sup>11</sup> CAMELOT Comparison of Amlodipine vs. Enalapril to Limit Occurrences of Thrombosis,<sup>12</sup> A-PLUS Avasimibe and Progression of Lesions on Ultrasound,<sup>25</sup> ACTIVATE ACAT Intravascular Atherosclerosis Treatment Evaluation<sup>15</sup> (NCT00268515), and ASTEROID A Study to Evaluate the Effect of Rosuvastatin on Intravascular Ultrasound-Derived Coronary Atheroma Burden<sup>14</sup> (NCT00240318).



**Figure 3. Schematic Representation of the Metabolism of HDL Cholesterol.**

Apolipoprotein A-I (ApoA-I) is secreted by the liver as a discoidal particle containing protein and phospholipid. This lipid-poor protein interacts with ATP-binding cassette transporter A1 (ABCA1) in macrophages, removing intracellular free cholesterol. When these lipid-poor HDL particles accept additional cholesterol, they mature into larger, spheroidal particles that do not actively interact with the ABCA1 transporter. However, the mature HDL particle can participate in reverse cholesterol transport through uptake in the liver by the scavenger receptor class B1 (SR-B1), potentially regenerating lipid-poor discoidal HDL cholesterol. Alternatively, mature HDL particles can also accept additional free cholesterol through the ATP-binding cassette transporter G1 (ABCG1). Mature HDL particles can also efflux free cholesterol from macrophages through the SR-B1 receptor. Cholesteryl ester transfer protein (CETP) inhibitors increase concentrations of the larger, mature alpha-HDL particles by blocking transfer of cholesteryl ester to particles of very-low-density lipoprotein (VLDL) and low-density lipoprotein (LDL) cholesterol. Pathways shown in blue represent the potentially beneficial effects of CETP inhibition, those shown with dashed lines have potentially reduced activity after CETP inhibition. FC denotes free cholesterol, PL phospholipids, CE cholesteryl ester, and LPL lipoprotein lipase.

a single agent in the class, particularly an agent with adverse effects on blood pressure.

The results of our study also have important implications for the use of imaging methods in the development of novel antiatherosclerotic therapies. Intravascular ultrasonography has been in-

creasingly proposed as one of several imaging methods for determining the potential of new agents.<sup>33</sup> Our results would have predicted neither benefit nor harm from the administration of torcetrapib. Although this finding may appear to be incongruent with the failed clinical out-

comes trial for torcetrapib, intravascular ultrasonography and other imaging techniques would not be sensitive to detect nonatherosclerotic vascular toxicity or other safety problems with any new drug. It is reassuring that even in the absence of a failed clinical outcomes trial for torcetrapib, our study would not have supported regulatory approval. Ultimately, any novel antiatherosclerotic therapy must demonstrate favorable results in clinical events trials, and atherosclerosis imaging will probably not replace the need for such outcomes studies. However, our results support the cautious use of intravascular ultrasonography and other imaging methods in the initial assessment of new antiatherosclerotic agents to select candidate therapies for large-scale clinical trials.

Finally, our findings demonstrate the great difficulty in developing therapies to interrupt the

atherosclerotic disease process. Twenty years after the introduction of statins, we are still waiting for the next breakthrough.

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