Effect of Torcetrapib on Carotid Atherosclerosis in Familial Hypercholesterolemia

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*Investigators and committees of the Rating Atherosclerotic Disease Change by Imaging with a New CETP Inhibitor (RADIANCE 1) trial are listed in the Appendix.

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ABSTRACT

BACKGROUND
Torcetrapib, an inhibitor of cholesteryl ester transfer protein, may reduce atherosclerotic vascular disease by increasing levels of high-density lipoprotein (HDL) cholesterol.

METHODS
A total of 850 patients with heterozygous familial hypercholesterolemia underwent B-mode ultrasonography at baseline and at follow-up to measure changes in carotid intima–media thickness. The patients completed an atorvastatin run-in period and were subsequently randomly assigned to receive either atorvastatin monotherapy or atorvastatin combined with 60 mg of torcetrapib for 2 years.

RESULTS
After 24 months, in the atorvastatin-only group, the mean (±SD) HDL cholesterol level was 52.4±13.5 mg per deciliter and the mean low-density lipoprotein (LDL) cholesterol level was 143.2±42.2 mg per deciliter, as compared with 81.5±22.6 mg per deciliter and 115.1±48.5 mg per deciliter, respectively, in the torcetrapib–atorvastatin group. During the study, average systolic blood pressure increased by 2.8 mm Hg in the torcetrapib–atorvastatin group, as compared with the atorvastatin-only group. The increase in maximum carotid intima–media thickness, the primary measure of efficacy, was 0.0053±0.0028 mm per year in the atorvastatin-only group and 0.0047±0.0028 mm per year in the torcetrapib–atorvastatin group (P=0.87). The secondary efficacy measure, annualized change in mean carotid intima–media thickness for the common carotid artery, indicated a decrease of 0.0014 mm per year in the atorvastatin-only group, as compared with an increase of 0.0038 mm per year in the torcetrapib–atorvastatin group (P=0.005).

CONCLUSIONS
In patients with familial hypercholesterolemia, the use of torcetrapib with atorvastatin, as compared with atorvastatin alone, did not result in further reduction of progression of atherosclerosis, as assessed by a combined measure of carotid arterial-wall thickness, and was associated with progression of disease in the common carotid segment. These effects occurred despite a large increase in HDL cholesterol levels and a substantial decrease in levels of LDL cholesterol and triglycerides. (ClinicalTrials.gov number, NCT00136981.)
GUIDELINES FOR THE PREVENTION AND management of cardiovascular disease focus on reducing levels of low-density lipoprotein (LDL) cholesterol by means of hydroxy-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors (collectively referred to as statins). However, recent meta-analyses have shown that even with the most aggressive treatment, these drugs reduce the risk of a major coronary event by only 30%. This finding, combined with an estimation that mortality from cardiovascular causes will increase worldwide by 90% by the year 2020, as compared with that in 1990, illustrates the need for new efficacious treatments. A review of four large, prospective epidemiologic studies has shown that an increase of 1 mg per deciliter (0.03 mmol per liter) in high-density lipoprotein (HDL) cholesterol was associated with a 2 to 3% reduction in the risk of cardiovascular disease. Moreover, HDL cholesterol levels remain predictive of the risk of recurrent cardiovascular disease in patients who have reached LDL cholesterol levels below 70 mg per deciliter (1.8 mmol per liter) with intensive statin treatment.

During the past few years, attempts to raise HDL cholesterol levels have been particularly successful with small-molecule inhibitors of cholesteryl ester transfer protein (CETP). By blocking the CETP-mediated transfer of cholesteryl ester from HDL cholesterol to apolipoprotein-B-containing lipoproteins and the simultaneous transfer of triglycerides in the opposite direction, torcetrapib is very effective at raising HDL cholesterol levels. Indeed, elevated CETP levels were shown to be associated with an increased risk of future coronary artery disease in apparently healthy subjects. Furthermore, the inhibition of CETP in rabbit models of atherosclerosis dramatically reduced the extent of disease. It is not known, however, whether CETP inhibition attenuates atherosclerosis in humans. Since new lipid-modulating drugs will be primarily used in addition to evidence-based lowering of LDL cholesterol, torcetrapib has been developed for use in combination with atorvastatin. In this setting, torcetrapib not only increased levels of HDL cholesterol and apolipoprotein A-I but also decreased levels of LDL cholesterol and apolipoprotein B-100 (the latter especially at higher doses) and also showed favorable effects on increasing the size of both HDL and LDL particles.

In our study, we used a combination of torcetrapib and atorvastatin in patients with heterozygous familial hypercholesterolemia. The rationale for studying this target population was that mutations in the LDL-receptor gene are associated with decreased levels of HDL cholesterol, smaller HDL particle size, and increased levels of CETP. Also, the progression of atherosclerosis in familial hypercholesterolemia is related to levels of both HDL cholesterol and CETP. Therefore, it was hypothesized that the use of torcetrapib would have distinct favorable effects in this group of patients. The aim of our study was to evaluate the effects of torcetrapib on carotid intima–media thickness, a surrogate marker for end points of cardiovascular disease in patients with familial hypercholesterolemia.

The results of this study need to be considered in light of the recent discontinuation of the large Investigation of Lipid Level Management to Understand Its Impact in Atherosclerotic Events (ILLUMINATE) trial (ClinicalTrials.gov number, NCT00134264), which showed an increase in all-cause mortality associated with torcetrapib.

STUDY DESIGN
The Rating Atherosclerotic Disease Change by Imaging with a New CETP Inhibitor (RADIANCE 1) trial was a prospective, double-blind, randomized, multicenter, parallel-group study. The trial was designed by the academic investigators in collaboration with the study sponsor. The institutional review board at each participating center approved the protocol, and patients provided written informed consent. Patients were eligible for entry into the study if they had received a diagnosis of heterozygous familial hypercholesterolemia either by genotyping or by having met the diagnostic criteria outlined by the World Health Organization.

During a run-in phase of 6 to 14 weeks, patients were counseled on therapeutic lifestyle changes and were administered atorvastatin at a dose of 20, 40, or 80 mg, titrated at 4-week intervals, for up to three visits to reach target LDL cholesterol levels, as recommended by guidelines from the National Cholesterol Education Program, or to reach the patient’s maximum tolerated dose. At study entry, patients who were taking cholesterol absorption inhibitors or bile-acid binders were permitted to continue taking these medications, provided that the dose was not changed during

METHODOLOGY
the course of the study. At the conclusion of the run-in period, patients were randomly assigned to receive either atorvastatin (at a dose established during the run-in period) with 60 mg of torcetrapib daily or atorvastatin monotherapy with corresponding placebo tablets. Patients and study personnel were unaware of study-group assignments, laboratory measurements, and carotid-imaging findings.

This article was written by the lead academic author, who vouches for the accuracy and completeness of the data and 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 right to publish the results. The analyses have been confirmed by an independent center.

Table 1. Baseline Characteristics, Values at 24-Month Follow-up, and Changes from Baseline.*

<table>
<thead>
<tr>
<th>Variable</th>
<th>Atorvastatin Monotherapy</th>
<th>Atorvastatin plus Torcetrapib</th>
<th>P Value</th>
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</thead>
<tbody>
<tr>
<td>All patients who underwent randomization</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of patients</td>
<td>454</td>
<td>450</td>
<td></td>
</tr>
<tr>
<td>Age — yr</td>
<td>45.2±12.9</td>
<td>46.8±12.0</td>
<td>0.06</td>
</tr>
<tr>
<td>Male sex — no. (%)</td>
<td>232 (51.1)</td>
<td>214 (47.6)</td>
<td>0.29</td>
</tr>
<tr>
<td>Body-mass index</td>
<td>26.7±4.4</td>
<td>26.7±4.3</td>
<td>1.00</td>
</tr>
<tr>
<td>Risk factors — no. (%)</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>History of diabetes</td>
<td>19 (4.2)</td>
<td>12 (2.7)</td>
<td>0.21</td>
</tr>
<tr>
<td>History of hypertension</td>
<td>114 (25.1)</td>
<td>110 (24.4)</td>
<td>0.82</td>
</tr>
<tr>
<td>Current smoker</td>
<td>95 (20.9)</td>
<td>86 (19.1)</td>
<td>0.50</td>
</tr>
<tr>
<td>Medication use — no. (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aspirin</td>
<td>133 (29.3)</td>
<td>138 (30.7)</td>
<td>0.65</td>
</tr>
<tr>
<td>Beta-blocker</td>
<td>92 (20.3)</td>
<td>83 (18.4)</td>
<td>0.49</td>
</tr>
<tr>
<td>ACE inhibitor or ARB</td>
<td>87 (19.2)</td>
<td>72 (16.0)</td>
<td>0.21</td>
</tr>
<tr>
<td>Ezetimibe</td>
<td>50 (11.0)</td>
<td>47 (10.4)</td>
<td>0.78</td>
</tr>
<tr>
<td>Baseline values for patients who completed the study</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>No. of patients</td>
<td>427</td>
<td>423</td>
<td></td>
</tr>
<tr>
<td>Cholesterol — mg/dl</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>213.5±42.1</td>
<td>213.0±39.3</td>
<td>0.86</td>
</tr>
<tr>
<td>LDL</td>
<td>138.9±37.6</td>
<td>138.4±35.5</td>
<td>0.84</td>
</tr>
<tr>
<td>HDL</td>
<td>51.8±12.8</td>
<td>52.9±12.7</td>
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<tr>
<td>Ratio of LDL to HDL</td>
<td></td>
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<tr>
<td>Median</td>
<td>2.7</td>
<td>2.5</td>
<td></td>
</tr>
<tr>
<td>Interquartile range</td>
<td>2.1 to 3.4</td>
<td>2.1 to 3.3</td>
<td></td>
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<tr>
<td>Triglycerides — mg/dl</td>
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<tr>
<td>Median</td>
<td>97.4</td>
<td>97.4</td>
<td></td>
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<tr>
<td>Interquartile range</td>
<td>75.2 to 141.6</td>
<td>70.8 to 132.8</td>
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<tr>
<td>C-reactive protein — mg/liter</td>
<td></td>
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<tr>
<td>Median</td>
<td>0.8</td>
<td>0.8</td>
<td></td>
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<tr>
<td>Interquartile range</td>
<td>0.4 to 1.9</td>
<td>0.4 to 1.9</td>
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<tr>
<td>Blood pressure — mm Hg</td>
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<tr>
<td>Systolic</td>
<td>116.6±10.9</td>
<td>115.9±11.7</td>
<td>0.42</td>
</tr>
<tr>
<td>Diastolic</td>
<td>73.5±7.0</td>
<td>72.9±7.5</td>
<td>0.17</td>
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</table>
Carotid Ultrasonography

All patients underwent carotid ultrasonography to assess carotid intima–media thickness. Replicate scans were performed within a week of each other at baseline and at 24 months, with interim follow-up scans at 6, 12, and 18 months. At each visit, a circumferential scan was performed with image acquisition at four predefined angles of the near and far walls of the right and left common carotid artery, carotid bifurcation, and internal carotid...
artery. All imaging centers used the same imaging hardware, Sequoia 512 scanners equipped with 8L5 transducers (Siemens), and protocols for imaging acquisition. Five-second image sequences were saved in Digital Imaging in Communications in Medicine (DICOM) format (National Electrical Manufacturers Association) and were written to magnetic optical disks for transfer to reading centers. Two reading centers (at the University Medical Center in Utrecht, the Netherlands, and at Wake Forest University Medical Center in Winston-Salem, NC) used standardized equipment and protocols to process stored images.

Semiautomated readings were analyzed with the use of automated measurement software (Image and Data Analysis). From each image sequence, the reader selected one frame in end diastole for measurement of carotid intima–media thickness. The leading edge (far wall) and trailing edge (near wall) of boundaries between the media and adventitia and between the lumen and intima were traced within the region of interest specified by the reader. Maximum carotid intima–media thickness was determined from a set of measurements perpendicular to the media–adventitia boundary. The readers were unaware of study-group assignments and of previous measurements of carotid intima–media thickness when reading an image.

Quality-assurance processes included central training and certification of all sonographers and readers on each continent, annual international meetings of sonographers and readers to reinforce protocol and standardized implementation, and regular site visits and performance reviews. Intraclass correlation coefficients for the mean maximum carotid intima–media thickness between replicate scans at baseline for 875 patients and at the end of the study for 814 patients were 0.96. These estimates include study-group assignments and of previous measurements of carotid intima–media thickness when reading an image.

Quality-assurance processes included central training and certification of all sonographers and readers on each continent, annual international meetings of sonographers and readers to reinforce protocol and standardized implementation, and regular site visits and performance reviews. Intraclass correlation coefficients for the monthly quality-assurance scans for 128 patients was 0.96. These estimates include differences within and between visits, within and between sonographers, and within and between reader-variability components.

The primary end point was annualized change in the maximum carotid intima–media thickness for the 12 carotid-artery segments (near and far walls of the right and left common carotid artery, the carotid bifurcation, and the internal carotid artery) based on all scans performed during the 2-year study period.

**RESULTS**

**PATIENTS**

From December 19, 2003, to November 22, 2004, a total of 904 patients underwent randomization...
at 37 centers in North America, Europe, and South Africa. Of these patients, 454 were assigned to the atorvastatin-only group and 450 to the torcetrapib–atorvastatin group. A total of 850 patients (427 in the atorvastatin-only group and 423 in the torcetrapib–atorvastatin group) remained in the study and underwent ultrasonography of the carotid artery at least once both at baseline and at follow-up (the full-analysis set). (Details of study-group assignments appear in the Supplementary Appendix, which is available with the full text of this article at www.nejm.org.) Demographic characteristics and baseline medications were similar in the two study groups (Table 1). The titrated daily dose of atorvastatin averaged 56.5 mg in both groups.

LABORATORY RESULTS AND BLOOD PRESSURE

Table 1 summarizes laboratory values and blood pressure at baseline and during the study period for the 850 patients in the full-analysis set who had post-baseline ultrasonographic results that could be evaluated. After 24 months, mean HDL cholesterol levels increased from 51.8 to 52.4 mg per deciliter (1.3 to 1.4 mmol per liter) in the atorvastatin-only group and from 52.9 to 81.5 mg per deciliter (1.4 to 2.1 mmol per liter) in the torcetrapib–atorvastatin group (Fig. 1). In the atorvastatin-only group, mean LDL cholesterol levels measured 165.5 mg per deciliter (4.3 mmol per liter) at screening and fell during the run-in period to 138.9 mg per deciliter (3.6 mmol per liter) at baseline. After 24

![Figure 1](https://example.com/figure1.png)

**Figure 1. Changes in Levels of High-Density Lipoprotein (HDL) and Low-Density Lipoprotein (LDL) Cholesterol in Patients Receiving Atorvastatin Alone or Atorvastatin plus Torcetrapib.**

Panels A and C show the levels of HDL and LDL cholesterol, respectively, in the study patients, and Panels B and D show the percent changes in HDL and LDL cholesterol, respectively, from baseline to 24 months, including a comparison of the percent change between the torcetrapib–atorvastatin group and the atorvastatin-only group for both HDL and LDL cholesterol (right-hand columns). To convert values for cholesterol to millimoles per liter, multiply by 0.02586.
months of treatment, mean LDL cholesterol levels in the atorvastatin-only group were 143.2 mg per deciliter (3.7 mmol per liter). In the torcetrapib–atorvastatin group, mean LDL cholesterol levels were 168.2 mg per deciliter (4.3 mmol per liter) at screening, 138.4 mg per deciliter (3.6 mmol per liter) at baseline, and 115.1 mg per deciliter (3.0 mmol per liter) at 24 months. As compared with atorvastatin alone, the net effect of torcetrapib was a 51.9% relative increase in HDL cholesterol and a 20.6% relative decrease in LDL cholesterol. Table 2 shows changes in lipoprotein subclasses in the two study groups. Baseline blood pressure was 116/73 mm Hg in the torcetrapib–atorvastatin group and 117/74 mm Hg in the atorvastatin-only group. During the study, mean systolic blood pressure increased by 1.3 mm Hg in the atorvastatin-only group and by 4.1 mm Hg in the torcetrapib–atorvastatin group, a least-square mean difference of 2.8 mm Hg (95% confidence interval [CI], 1.9 to 3.7; P<0.001).

**CAROTID ULTRASONOGRAPHY**

Table 3 summarizes the change in the primary and secondary efficacy measures as seen on carotid ultrasonography. The primary efficacy measure, annualized rate of change in maximum carotid intima–media thickness, was an increase of 0.0053 mm per year in the atorvastatin-only group and an increase of 0.0047 mm per year in the torcetrapib–atorvastatin group (P=0.87) (Fig. 2). However, the secondary efficacy measure, annualized change in the maximum and mean measures of carotid intima–media thickness for the common carotid artery, indicated regression in the atorvastatin-only group (a maximum decrease of 0.0042 mm per year and a mean decrease of 0.0014 mm per year) and progression in the torcetrapib–atorvastatin group (a maximum increase of 0.0040 mm per year [P=0.02] and a mean increase of 0.0038 mm per year [P=0.005]) (Table 3).

For nearly all prespecified subgroups, no heterogeneity in the difference between study groups was observed. Annualized change in maximum carotid intima–media thickness in patients with a history of diabetes was lower in the torcetrapib–atorvastatin group than in the atorvastatin-only group (P=0.05), although the number of patients with diabetes was limited (9 in the torcetrapib–atorvastatin group and 17 in the atorvastatin-only group). For patients with baseline HDL cholesterol levels of less than 40 mg per deciliter (1.0 mmol per liter), the results showed a trend in favor of atorvastatin monotherapy (P=0.09). However both of these results are probably due to chance.

**DISCUSSION**

The RADIANCE 1 trial showed that the addition of torcetrapib to atorvastatin did not provide incremental halting of the progression of atherosclerotic plaque in patients at high risk for cardiovascular disease.
sclerosis in the carotid arteries of patients with familial hypercholesterolemia, as has been previously shown with the use of atorvastatin alone.23 If anything, our data suggest a worsening of pathology conferred by this CETP inhibitor, despite a 52% increase in HDL cholesterol levels and a robust 21% decrease in LDL cholesterol levels in comparison with the results in the atorvastatin-only group. On the basis of extensive epidemiologic and various clinical-intervention studies, such lipoprotein changes were anticipated to render significant benefit.

To study atherosclerosis, we used ultrasonography to assess carotid intima–media thickness, a surrogate marker for cardiovascular disease.24 The annualized change in maximum carotid intima–media thickness, the primary end point of the study, did not differ significantly between patients with familial hypercholesterolemia who were treated with atorvastatin alone and those treated with a combination of atorvastatin and torcetrapib. In fact, carotid intima–media thickness of the common carotid artery, a secondary end point of our study, provided evidence of accelerated atherogenesis in the patients who were receiving torcetrapib. It is highly unlikely that

<table>
<thead>
<tr>
<th>Variable</th>
<th>Atorvastatin Monotherapy (N = 427)</th>
<th>Atorvastatin plus Torcetrapib (N = 423)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean ± SD</td>
<td>Median (IQR)</td>
<td>Mean ± SD</td>
</tr>
<tr>
<td>Baseline</td>
<td>maximum carotid intima–media thickness for each of the 12 carotid-artery sites</td>
<td>1.15±0.31 1.09 (0.93–1.33)</td>
<td>1.13±0.28 1.09 (0.94–1.27)</td>
</tr>
<tr>
<td></td>
<td>maximum carotid intima–media thickness for each of the 4 common carotid-artery sites</td>
<td>1.01±0.23 0.98 (0.83–1.17)</td>
<td>0.99±0.22 0.97 (0.82–1.14)</td>
</tr>
<tr>
<td></td>
<td>mean carotid intima–media thickness for each of the 4 common carotid-artery sites</td>
<td>0.72±0.15 0.70 (0.60–0.82)</td>
<td>0.71±0.15 0.70 (0.59–0.81)</td>
</tr>
<tr>
<td>24-Mo follow-up†</td>
<td>maximum carotid intima–media thickness for each of the 12 carotid-artery sites</td>
<td>1.16±0.33 1.09 (0.94–1.32)</td>
<td>1.14±0.29 1.10 (0.95–1.27)</td>
</tr>
<tr>
<td></td>
<td>maximum carotid intima–media thickness for each of the 4 common carotid-artery sites</td>
<td>1.00±0.22 0.97 (0.83–1.13)</td>
<td>1.00±0.21 0.99 (0.84–1.13)</td>
</tr>
<tr>
<td></td>
<td>mean carotid intima–media thickness for each of the 4 common carotid-artery sites</td>
<td>0.71±0.14 0.70 (0.61–0.80)</td>
<td>0.72±0.14 0.71 (0.60–0.81)</td>
</tr>
</tbody>
</table>

### Annualized change from longitudinal model

<table>
<thead>
<tr>
<th>Variable</th>
<th>Slope</th>
<th>SE</th>
<th>Slope</th>
<th>SE</th>
</tr>
</thead>
<tbody>
<tr>
<td>maximum carotid intima–media thickness for each of the 12 carotid-artery sites</td>
<td>0.0053</td>
<td>0.0028</td>
<td>0.0047</td>
<td>0.0028</td>
</tr>
<tr>
<td>maximum carotid intima–media thickness for each of the 4 common carotid-artery sites</td>
<td>-0.0042</td>
<td>0.0025</td>
<td>0.0040</td>
<td>0.0023</td>
</tr>
<tr>
<td>mean carotid intima–media thickness for each of the 4 common carotid-artery sites</td>
<td>-0.0014</td>
<td>0.0013</td>
<td>0.0038</td>
<td>0.0013</td>
</tr>
</tbody>
</table>

* Plus–minus values are means ±SD. IQR denotes interquartile range, and SE standard error.
† Number was calculated by the last-observation-carried-forward method.
the unanticipated outcome of this trial can be attributed to the measurement of carotid intima–media thickness itself. This marker has previously been shown to constitute a strong and accurate predictor of the risk of future vascular events in population studies. Furthermore, in evaluations of the efficacy of lipid-modifying medication, antioxidants, estrogen, and antihypertensive drugs, measurements of carotid intima–media thickness were successfully applied and were in line with the outcome of subsequent morbidity and mortality trials.

To account for the observed results, the potential benefit of the observed decrease in LDL cholesterol levels needs to be weighed against the detrimental effect of the rise in systolic blood pressure. The divergent effects of torcetrapib, as compared with atorvastatin alone, on LDL cholesterol and systolic blood pressure would favor the atorvastatin-only group by 0.014 mm at 2 years. The net opposing effect of the LDL cholesterol level and systolic blood pressure should have left a residual benefit for patients in the torcetrapib–atorvastatin group. The fact that none was observed leaves no possibility of any beneficial effect of the large increase in HDL cholesterol.

In line with the concept that elevation in levels of HDL cholesterol protects against atherosclerosis, small and moderate increases in HDL cholesterol levels, as achieved by the use of nicotinic acid (21%) and gemfibrozil (6%), have previously been reported to yield a significant reduction in the rate of progression of carotid intima–media thickness and in the risk of major cardiovascular events. The absence of an effect of a much greater increase in HDL cholesterol (52%) in our study indicates that torcetrapib either has an adverse vascular effect that negated the changes in lipoprotein levels or that CETP inhibition is not an effective therapeutic strategy. Although our study cannot determine which hypothesis is accurate, there are several possibilities that merit consideration.

With respect to the discrepancy between the remarkable effects of torcetrapib on lipid metabolism and its effects on carotid intima–media thickness, a direct vasculotoxic effect — as shown by a rise in blood pressure — appears to be a possible explanation. The natural ability of HDL to induce vasorelaxation, an effect that is thought to be mediated through scavenger receptor B1, may be adversely affected by torcetrapib.

Another possibility relates to the fact that in-
hibition of CETP by torcetrapib actually increases plasma levels of CETP. At a daily dose of 60 mg, torcetrapib continuously increases levels of CETP, a finding that is ascribed to an enhanced affinity of CETP for HDL.34 This complex formation (CETP–torcetrapib–HDL) is in turn associated with extreme elevations of large HDL particles, as exemplified by the substantial increase in levels of HDL2 cholesterol (157%). In this context, it is worrisome that HDL cholesterol levels were found to increase steadily over the duration of the trial (Fig. 1). It can be hypothesized that HDL cholesterol levels did not affect levels of C-reactive protein. In contrast, monotherapy with a similar dose of atorvastatin in patients with familial hypercholesterolemia resulted in a 45% decrease in levels of high-sensitivity C-reactive protein in a trial similar to ours in duration and size.35

In conclusion, the use of torcetrapib in patients with familial hypercholesterolemia did not result in regression of atherosclerosis, as assessed by a combined measure of thickness of the carotid-artery wall, and even caused progression of disease in the common carotid segment. These effects occurred despite an unparalleled increase in the HDL cholesterol level (52%) and a substantial decrease in the LDL cholesterol level (21%).

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APPENDIX

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