Inflammation and its echo in atherosclerosis
van Leuven, S.I.

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Chapter 11

Effect of Torcetrapib on Progression of Carotid Atherosclerosis in Heterozygous Familial Hypercholesterolemia

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Drs Kastelein and Bots share senior co-authorship.

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6Julius Center for Health Sciences and Primary Care, University Medical Center, Utrecht, the Netherlands (DEG, MLB).

*Investigators and committees of the Rating Atherosclerotic Disease change by Imaging with a new CETP inhibitor (RADIANCE 1) trial to assess reduction of atherosclerosis by CETP inhibition and HDL elevation are listed in the Appendix

Abstract

**Background:** Torcetrapib, an inhibitor of cholesteryl ester transfer protein (CETP), may reduce atherosclerotic vascular disease by virtue of its capacity to increase high-density lipoprotein-cholesterol (HDL-C).

**Methods:** Baseline and follow-up B-Mode ultrasound examinations were performed to obtain change in carotid intima-media thickness (CIMT) in 850 subjects with heterozygous familial hypercholesterolemia (FH). These subjects completed an atorvastatin run-in period and were subsequently randomized to blinded atorvastatin monotherapy (A) or atorvastatin combined with 60 mg torcetrapib (T/A) for a period of 2 years.

**Results:** After 24 months, HDL-C was 52.4 ± 13.5 mg/dL and LDL-C 143.2 ± 42.2 mg/dL in the atorvastatin group versus 81.5 ± 22.6 mg/dL and 115.1 ± 48.5 mg/dL in the T/A group, respectively. Average systolic blood pressure (SBP) during treatment increased 2.8 mmHg in the T/A group. The change in maximal CIMT, the primary efficacy parameter, was 0.0053±0.0028 mm/year in the atorvastatin group and 0.0047±0.0028 mm/year in the T/A group, p=0.87. The secondary efficacy parameter, annualized change in mean CIMT for the common carotid artery indicated increased progression of disease in the T/A group, -0.0014 vs. 0.0038 mm/year, p=0.005.

**Conclusions:** In FH patients, the use of torcetrapib with atorvastatin did not result in further reduction of progression of atherosclerosis as assessed by a combined measure of carotid arterial wall thickness and, when restricted to the common carotid segment, caused progression of disease. These effects occurred despite an unparalleled increase of HDL-C and a substantial additional decrease of LDL-C and triglyceride levels.

(ClinicalTrials.gov identifier - NCT00136981)
Introduction

The current guidelines for the prevention and management of cardiovascular disease (CVD) focus on reducing low density lipoprotein cholesterol (LDL-C) levels by means of HMG-CoA reductase inhibitors (statins). Recent meta-analyses have shown, however, that even with the most aggressive treatment these drugs reduce the risk of a major coronary event by only 30%. This combined with the estimation that worldwide cardiovascular mortality will increase by 90% in the year 2020 compared to 1990 illustrates the need for novel efficacious drugs. In that context it is important to note that several large prospective epidemiological studies showed that an increase of high-density lipoprotein cholesterol (HDL-C) by 1 mg/dl (0.026 mmol/L) is associated with a 2-3% reduction of CVD risk. Moreover, HDL-C levels remain predictive of recurrent CVD in patients with LDL-C levels below 70 mg/dL (1.8 mmol/L), as reached with intensive statin treatment.

Over the past few years, attempts to raise HDL-C 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-C to apolipoprotein B-containing lipoproteins and the simultaneous transfer of triglycerides in the opposite direction, torcetrapib is very effective in raising HDL-C. Indeed, elevated CETP levels were shown to be associated with an increasing risk of future coronary artery disease in apparently healthy individuals. Furthermore, inhibiting CETP in rabbit models of atherosclerosis dramatically reduces the extent of disease. It is not known, however, whether CETP inhibition attenuates atherosclerosis in humans. Since novel lipid-modulating drugs will be primarily used on top of evidence-based LDL-C lowering, torcetrapib has been developed in combination with atorvastatin. In this setting, torcetrapib not only increases HDL-C and apolipoprotein A-I but also decreases LDL-C levels and apolipoprotein B-100 (the latter especially at higher dosages) and also showed favourable effects on lipoprotein size (larger HDL and LDL size). In the current study, torcetrapib/atorvastatin was used in patients suffering from heterozygous familial hypercholesterolemia (FH). The rationale for
this target population consists of the fact that mutations in the LDL-receptor gene are associated with decreased levels of HDL-C, smaller HDL particle size as well as increased levels of CETP. Also, the progression of atherosclerosis in FH is related to both HDL-C and CETP concentration and thus it was hypothesized that the use of torcetrapib would have distinct favourable effects in this patient group. Here we present the results of a multi-centre, randomized, double-blind, placebo-controlled trial designed to evaluate the effects of torcetrapib on carotid intima-media thickness (CIMT), a surrogate marker for CVD endpoints in patients suffering from FH.

Methods

Study design

The RADIANCE 1 Trial (Rating Atherosclerotic Disease change by Imaging with a new CETP Inhibitor) was a prospective, double-blind, randomized, multicenter, parallel group study. The study was designed by the trial academic leadership in collaboration with the study sponsor. The Institutional Review Boards of participating centers approved the protocol and subjects provided written informed consent. Subjects were eligible for entry into the study if they had a diagnosis of heterozygous familial hypercholesterolemia either by genotyping or by meeting World Health Organization diagnostic criteria. During a 6-14 week run-in phase, subjects were counseled on therapeutic lifestyle changes and were administered atorvastatin in a dosage of 20, 40 or 80 mg, titrated at 4-week intervals, for up to three visits to reach an LDL-C target according to the National Cholesterol Education Program guidelines or to their maximally tolerated dose. Subjects who at screening, were on cholesterol absorption inhibitors or bile acid sequestrants, were permitted to remain on those medications provided that the dose was not changed during the course of the study. At the conclusion of the run-in period, subjects were randomized to receive either atorvastatin (at the dosage established during the run-in period) with torcetrapib 60 mg or atorvastatin monotherapy with corresponding placebo tablets. Subjects and
study personnel were blinded to treatment assignment, laboratory measurements and the carotid imaging findings.

This manuscript was written by the first author, who vouches for 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 rights to publish the results.

**Carotid ultrasound examinations and measurement**

Carotid ultrasonography was performed to assess CIMT. Replicate scans were performed within a week of each other at baseline and at 24 months, with interim follow-up scans at the 6, 12, and 18 month visits. At each visit a circumferential scan was performed with image acquisition at four pre-defined angles of the right and left common carotid, bifurcation, and internal carotid artery near and far walls. All imaging centers used the same imaging hardware (Sequoia 512 scanners equipped with 8L5 transducers, Siemens AG, Munich, FRG) and imaging acquisition protocol. Five-second image sequences were saved in Digital Imaging in Communications in Medicine (DICOM®) format (National Electrical Manufacturers Association, Rosslyn, VA, USA) and written to 640 MB magnetic optical disk for transfer to reading centers. Two reading centers (Vascular Imaging Center, University Medical Center, Utrecht, the Netherlands and Wake Forest University Medical Center, Ultrasound Reading Center, Winston-Salem, NC, USA) used standardized equipment and protocols to process stored images. Semi-automated readings were analyzed using Automated Measurement Software (AMS developed by Image and Data Analysis, Inc., Gothenburg, Sweden). From each image sequence, the reader selected one frame in end diastole from CIMT measurement. The leading edge (far wall) and trailing edge (near wall) of media-adventitia and lumen-intima boundaries were traced within the region of interest specified by the reader. Maximum CIMT was determined from a set of measurements perpendicular to media-adventitia boundary. The readers were blinded to the intervention and to previous CIMT measurements 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. Intra-class correlation coefficients
(ICC) for mean-max CIMT between replicate scans at baseline (n=875) and end of
study (n=814) were 0.90 and 0.88, respectively. ICC for the monthly QA scans (n=128)
was 0.96. These ICC estimates include within and between visits, within and between
sonographers, and within and between reader variability components.

The primary endpoint was annualized change in the maximum CIMT for the 12
carotid artery segments (near and far walls of the right and left CCA, carotid bulb, and
the ICA) based on all scans performed over the two-year study period.

**Statistical Methods**

A sample size of 304 subjects per treatment group was calculated to have 90% power
to detect a 0.020 mm/yr difference in the annualized rate of change of CIMT with a
two-sided alpha level of 0.05, assuming a common standard deviation of 0.076 mm/yr.
A linear mixed-effects model was used to analyze the annualized rate of change in
maximum CIMT including 84 maximum CIMT measurements (12 segments x 7
visits) for each subject as the dependent variables with random intercepts and slopes
as a function of time and fixed effects for geographic region, atorvastatin dose at run-in,
carotid segment, treatment, time, and time by treatment interaction. Testing was
two-sided and conducted with a 5% type I error rate. Laboratory parameters were
analyzed by analysis of covariance including terms for baseline value, treatment,
geographic region, and atorvastatin dose at run-in. Safety data were analyzed using a
linear model with terms for baseline value, hypertensive status, age, gender, smoking,
diabetes, BMI, creatine clearance, race, and treatment. With multiplicative interaction
terms, we studied whether treatment effects differed across subgroups. These pre-
specified analyses were performed for age (< and ≥ 65 years), gender, race (white
or non-white), HDL-C (< and ≥ 40 mg/dl), LDL-C (above and below the median),
triglycerides (< and ≥150mg/dL), smoking, history of diabetes mellitus, history of
hypertension, C-reactive protein (< and ≥ 3.0 mg/dl) and baseline maximum CIMT
(< and ≥ the median).
Results

Patient population
Between December 19th, 2003, and November 22nd, 2004, 904 patients were randomized at 37 centers in North America, Europe, and South Africa, 454 in the atorvastatin group and 450 in the torcetrapib-atorvastatin group. 850 patients had remained in the study and had at least one evaluable carotid ultrasound examination at both baseline and follow-up, 427 in the atorvastatin-only group and 423 in the torcetrapib-atorvastatin group (the full analysis set). Demographic characteristics and baseline medications were similar in both treatment groups (Table 1). The titrated dosage 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 treatment for the 850 subjects in the full analysis set who had evaluable post-baseline ultrasound studies. After 24 months treatment, HDL-C in the atorvastatin group, increased from 51.8 to 52.4 mg/dL. HDL-C in the torcetrapib group increased from 52.9 to 81.5 mg/dL (Figure 1). In the atorvastatin group, LDL-C levels measured 165.5 mg/dL at screening and fell during the run-in to 138.9 mg/dL at baseline. After 24 months of treatment, LDL-C levels in the atorvastatin group measured 143.2 mg/dL. Comparable LDL-C levels for the same timepoints in the torcetrapib-atorvastatin group measured 168.2, 138.4, and 115.1 mg/dL. The net effect of torcetrapib was a 51.9% relative increase in HDL-C and a 20.6% relative decrease in LDL-C compared with atorvastatin alone. Table 2 shows changes in lipoprotein subclasses between the treatment arms. Baseline blood pressure (BP) was 116/73 in the torcetrapib and 117/74 mmHg in the atorvastatin group. Average post-randomization systolic BP increased 1.3 mmHg in the atorvastatin group and 4.1 mmHg in the torcetrapib group, a LS mean difference of 2.8 mmHg, 95% confidence interval, 1.9-3.7, p<0.001.
Table 1. Baseline Characteristics, Blood Pressures and Laboratory Values

<table>
<thead>
<tr>
<th>All Randomized Subjects – Mean (SD) or Number (Percentage) of Subjects (n=904)</th>
<th>Atorvastatin Monotherapy (n=454)</th>
<th>Atorvastatin plus Torcetrapib (n=450)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age in years</td>
<td>45.2 (12.9)</td>
<td>46.8 (12.0)</td>
<td>0.06</td>
</tr>
<tr>
<td>Male Gender</td>
<td>232 (51.1%)</td>
<td>214 (47.6%)</td>
<td>0.29</td>
</tr>
<tr>
<td>Body mass index (kgs/height²)</td>
<td>26.7 (4.4)</td>
<td>26.7 (4.3)</td>
<td>1.00</td>
</tr>
<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 Smokers</td>
<td>95 (20.9%)</td>
<td>86 (19.1%)</td>
<td>0.50</td>
</tr>
<tr>
<td>Aspirin use at baseline</td>
<td>133 (29.3%)</td>
<td>138 (30.7%)</td>
<td>0.65</td>
</tr>
<tr>
<td>B-blocker use at baseline</td>
<td>92 (20.3%)</td>
<td>83 (18.4%)</td>
<td>0.49</td>
</tr>
<tr>
<td>ACE/ARB use at baseline</td>
<td>87 (19.2%)</td>
<td>72 (16.9%)</td>
<td>0.21</td>
</tr>
<tr>
<td>Ezetimibe use at baseline</td>
<td>50 (11.0%)</td>
<td>47 (10.4%)</td>
<td>0.78</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Subjects Completing the Trial (n=850): Mean (SD) or Median (IQR)</th>
<th>Baseline Values</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Total cholesterol (mg/dL)</td>
<td>213.5 (42.1)</td>
<td>213.0 (39.3)</td>
<td>0.86</td>
</tr>
<tr>
<td>LDL-C (mg/dL)</td>
<td>138.9 (37.6)</td>
<td>138.4 (35.5)</td>
<td>0.84</td>
</tr>
<tr>
<td>HDL-C (mg/dL)</td>
<td>51.8 (12.8)</td>
<td>52.9 (12.7)</td>
<td>0.24</td>
</tr>
<tr>
<td>LDL-C/HDL-C ratio</td>
<td>2.7 (2.1, 3.4)</td>
<td>2.5 (2.1, 3.3)</td>
<td>0.29</td>
</tr>
<tr>
<td>Triglycerides (mg/dL)</td>
<td>97.4 (75.2, 141.6)</td>
<td>97.4 (70.8, 132.8)</td>
<td>0.22</td>
</tr>
<tr>
<td>C-reactive protein (mg/L)†</td>
<td>0.8 (0.4, 1.9)</td>
<td>0.8 (0.4, 1.9)</td>
<td>0.70</td>
</tr>
<tr>
<td>Systolic Blood Pressure (mmHg)§</td>
<td>116.6 (10.9)</td>
<td>115.9 (11.7)</td>
<td>0.42</td>
</tr>
<tr>
<td>Diastolic Blood Pressure (mmHg)§</td>
<td>73.5 (7.0)</td>
<td>72.9 (7.5)</td>
<td>0.17</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>24 Month Follow-up Values: Mean (SD) or Median (IQR)</th>
<th>Baseline Values</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Total cholesterol (mg/dL)</td>
<td>218.8 (45.7)</td>
<td>216.9 (51.1)</td>
<td>0.58</td>
</tr>
<tr>
<td>LDL-C (mg/dL)</td>
<td>143.2 (42.2)</td>
<td>115.1 (48.5)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>HDL-C (mg/dL)</td>
<td>52.4 (13.5)</td>
<td>81.5 (22.6)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LDL-C/HDL-C ratio</td>
<td>2.7 (2.1, 3.4)</td>
<td>1.3 (1.0, 1.8)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Triglycerides (mg/dL)</td>
<td>97.4 (70.8, 141.6)</td>
<td>88.5 (70.8, 119.0)</td>
<td>0.001</td>
</tr>
<tr>
<td>C-reactive protein (mg/L)§</td>
<td>0.8 (0.4, 2.0)</td>
<td>0.9 (0.4, 2.2)</td>
<td>0.85</td>
</tr>
<tr>
<td>Systolic Blood Pressure (mmHg)§</td>
<td>117.9 (9.9) §</td>
<td>120.1 (12.2) §</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Diastolic Blood Pressure (mmHg)§</td>
<td>74.2 (6.3) §</td>
<td>74.7 (7.0) §</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Change from Baseline: Mean (SD), Median (IQR) or LS Mean Percentage Change (SE)</th>
<th>Baseline Values</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Total cholesterol</td>
<td>5.1 (0.9) †</td>
<td>3.8 (0.9) †</td>
<td>0.28</td>
</tr>
<tr>
<td>LDL-C</td>
<td>6.3 (1.3) †</td>
<td>-14.4 (1.3) †</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>HDL-C</td>
<td>2.5 (1.1) †</td>
<td>54.4 (1.1) †</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>2.1 (-17.6, 25.0)</td>
<td>-7.7 (-25.0, 20.0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>C-reactive protein (mg/L)§</td>
<td>0.0 (-0.3, 0.4)</td>
<td>0.0 (-0.3, 0.4)</td>
<td>0.95</td>
</tr>
<tr>
<td>Systolic Blood Pressure (mmHg)§</td>
<td>1.3 (6.9) §</td>
<td>4.1 (8.0) §</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Diastolic Blood Pressure (mmHg)§</td>
<td>0.6 (4.4) §</td>
<td>1.8 (4.8) §</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

§ Average of all post-randomization measurements. *p value from Wilcoxon rank sum test. † Least Square mean percentage change (SE) ‡ p value from analysis of covariance on rank transformed data, last observation carried forward. To convert cholesterol levels to millimoles per liter, multiply by 0.02586. To convert triglycerides to millimoles per liter, multiply by 0.01129. ACE = angiotensin converting enzyme inhibitor. ARB = Angiotensin receptor blocker. LDL-C = low density lipoprotein cholesterol. HDL-C = High density lipoprotein cholesterol LS = Least Squares. SE = Standard Error
Figure 1. Levels of HDL (mg/dL) (fig. 1A) with the percentage change from baseline (fig. 1B) and levels of LDL (mg/dL) (fig. 1C) with the percentage change from baseline (fig. 1D) in FH patients treated with atorvastatin monotherapy (A) or a combination of torcetrapib and atorvastatin (T/A) for a duration of 24 months.

Table 2. Changes in lipoprotein subclasses

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Treatment/comparison</th>
<th>LS Mean</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Apo-A Family</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Apo A-I</td>
<td>T/A vs A</td>
<td>+24.80%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>HDL-2-C</td>
<td>T/A vs A</td>
<td>+157.12%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>HDL-3-C</td>
<td>T/A vs A</td>
<td>+45.93%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>HDL size</td>
<td>T/A vs A</td>
<td>+0.88 nm</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Apo-B Family</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Apo B-100</td>
<td>T/A vs A</td>
<td>-16.71%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Non-HDL-C</td>
<td>T/A vs A</td>
<td>-19.38%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LDL particles small</td>
<td>T/A vs A</td>
<td>-376.31 nmol/L</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LDL size</td>
<td>T/A vs A</td>
<td>+0.45 nm</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>
**Carotid ultrasound results**

Table 3 summarizes the change in the primary and secondary carotid ultrasound efficacy parameters. The primary efficacy measure, annualized rate of change in maximum CIMT, was 0.0053 mm/year in the atorvastatin group and 0.0047 mm/year in the torcetrapib-atorvastatin group, p=0.87 (Figure 2). However, the secondary efficacy parameters, annualized change in the maximum (-0.0042 vs. 0.0040 mm/year, p=0.02) and mean (-0.0014 vs. 0.0038 mm/year, p=0.005) CIMT for the common carotid artery in fact indicated regression of CIMT in the atorvastatin group and progression of CIMT in the T/A group (Table 3). For nearly all prespecified subgroups no heterogeneity in the treatment difference was observed. Annualized change in maximum CIMT in subjects with a history of diabetes was lower in the torcetrapib group (p=0.05) although the number of diabetics was limited (T/A=9 vs. A=17). For subjects with baseline HDL-C<40 mg/dL, the results showed a trend in favor of atorvastatin monotherapy, p=0.09. Both these results, however, are likely chance findings.

![Figure 2. Maximum carotid intima-media thickness (CIMT) (mm) average over twelve carotid segments combined of FH patients treated with atorvastatin monotherapy (A) or a combination of torcetrapib and atorvastatin (T/A) for a duration of 24 months. Error bars represent standard deviation.](image-url)
Table 3. Baseline, Follow-up, and Change from Baseline in Maximum CIMT Endpoints

<table>
<thead>
<tr>
<th></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><strong>Baseline (mm)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Maximum CIMT for each of the 12 carotid artery sites</td>
<td>1.15 (0.31)</td>
<td>1.09 (0.93,1.33)</td>
<td>1.13 (0.28)</td>
</tr>
<tr>
<td>Maximum CIMT for each of the 4 CCA sites</td>
<td>1.01 (0.23)</td>
<td>0.98 (0.83,1.17)</td>
<td>0.99 (0.22)</td>
</tr>
<tr>
<td>Mean CIMT for each of the 4 CCA sites</td>
<td>0.72 (0.15)</td>
<td>0.70 (0.60,0.82)</td>
<td>0.71 (0.15)</td>
</tr>
<tr>
<td><strong>24 Month (LOCF) Follow-up (mm)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Maximum CIMT for each of the 12 carotid artery sites</td>
<td>1.16 (0.33)</td>
<td>1.09 (0.94,1.32)</td>
<td>1.14 (0.29)</td>
</tr>
<tr>
<td>Maximum CIMT for each of the 4 CCA sites</td>
<td>1.00 (0.22)</td>
<td>0.97 (0.83,1.13)</td>
<td>1.00 (0.21)</td>
</tr>
<tr>
<td>Mean CIMT for each of the 4 CCA sites</td>
<td>0.71 (0.14)</td>
<td>0.70 (0.61,0.80)</td>
<td>0.72 (0.14)</td>
</tr>
<tr>
<td><strong>Annualized Change from Longitudinal Model (mm/year)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Maximum CIMT for each of the 12 carotid artery sites</td>
<td>0.0053</td>
<td>0.0028</td>
<td>0.0047</td>
</tr>
<tr>
<td>Maximum CIMT for each of the 4 CCA sites</td>
<td>-0.0042</td>
<td>0.0025</td>
<td>0.0040</td>
</tr>
<tr>
<td>Mean CIMT for each of the 4 CCA sites</td>
<td>-0.0014</td>
<td>0.0013</td>
<td>0.0038</td>
</tr>
</tbody>
</table>

IQR=Interquartile range  
SD= Standard deviation  
SE=Standard error  
LOCF= last observation carried forward

Clinical adverse events  
The number of patients with at least one serious adverse cardiovascular event was 11 in the A treatment group (1 cardiovascular death, 0 non-fatal myocardial infarctions, 1 stroke, 9 ischemic or other cardiovascular events) and 24 in the T/A group (0 cardiovascular deaths, 3 non-fatal myocardial infarctions, 1 stroke, 23 ischemic or other events.)
cardiovascular events, 1 carotid stenosis and 1 blood pressure elevation considered a serious adverse event). Other cardiovascular events were mostly angina and chest pain not otherwise specified. Investigator-reported hypertensive adverse events were more common in the torcetrapib group, 8.9% vs. 3.7% and BP values >140/90 mmHg were recorded more frequently in the torcetrapib group, 7.8% vs. 3.1%. A sustained increase greater than 15 mmHg in systolic pressure occurred in 2.2% of torcetrapib-treated subjects versus 0.9% of subjects treated with atorvastatin alone.

Discussion

The RADIANCE 1 trial confirms that high dose atorvastatin therapy arrests the progression of atherosclerosis in the carotid arteries of FH patients. Surprisingly, the data also show that addition of torcetrapib to this therapeutic regimen did not provide further protection. If anything, our data suggest a worsening of pathology conferred by this CETP inhibitor, despite an unprecedented 52% increase of HDL-C levels and a robust 21% decrease of LDL-C levels. On the basis of extensive epidemiology and various clinical intervention studies, such lipoprotein changes are anticipated to render significant benefit. Nevertheless, when considered in light of the recent discontinuation of the large mortality and morbidity trial of torcetrapib (ILLUMINATE) that showed an increase in all-cause mortality, our findings are less surprising. Although these results could not have predicted the detrimental outcome of the ILLUMINATE trial, they may have significantly altered the course of further clinical research with this compound.

To study atherosclerosis, we employed ultrasonography to assess carotid intima-media thickness (CIMT), a surrogate marker for CVD. The annualized change in maximum CIMT, the primary end point of this study, did not differ for FH patients treated with atorvastatin alone (A) and those treated with the combination of atorvastatin and torcetrapib (T/A). In fact, CIMT of the common carotid artery, a
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secondary endpoint of this study, provided evidence of accelerated atherogenesis in
the patients using torcetrapib. It is highly unlikely that the unanticipated outcome
of this trial can be attributed to the measurement of CIMT per se. This marker has
previously been proven to constitute a strong and accurate predictor of future vascular
events in population studies. Furthermore, in studies in which the efficacy of lipid
modifying medication, anti-oxidants, and estrogens and antihypertensive treatment
was evaluated, CIMT measurements 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 LDL-C
decrease needs to be weighed against the detrimental effect of the rise in systolic blood
pressure. The divergent effects of torcetrapib on LDL-C (-21%) and SBP (+2.8 mm
Hg) are two prominent factors that may have affected CIMT. Focusing on LDL-C, in a
2-year pravastatin study (REGRESS), a comparable 28% decrease in LDL-C levels was
associated with a change of CIMT of 0.05 mm. In the ENHANCE trial, the addition
of ezetemibe to high dose simvastatin therapy was in fact powered to reduce LDL-C
levels by 18-23% and to detect a mean two year absolute CIMT difference of 0.05 mm
in a sample size of 650 FH heterozygotes. Extrapolating these findings to RADIANCE
1, the effect on LDL-C would translate into a CIMT difference of 0.03-0.05 mm in
favour of the torcetrapib arm.

In contrast, the observed increase of SBP can be expected to adversely affect CIMT. In
an attempt to account for this effect, we have used data from a recent meta-analysis on
the relationship between SBP and CIMT. That analysis would suggest that the effect
of the 2.8 mmHg increase in SBP would favour the atorvastatin arm by 0.014 mm
over two years. The net opposing impact of LDL-C and SBP should have left a residual
benefit of T/A: the fact that none was observed leaves no room for any beneficial effect
of the large HDL-C increase.

In line with the concept that elevation of HDL-C protects against atherosclerosis, small
and moderate increases of HDL-C as achieved by the use of nicotinic acid (+21%) or
gemfibrozil (+6%) have previously been reported to yield a significant reduction in
the rate of CIMT progression and risk of major cardiovascular events. The absence of
an effect of a much greater increase of HDL-C (+52%) in RADIANCE 1 indicates that
torcetrapib either has an adverse vascular effect that masked the changes in lipoprotein
levels or that CETP inhibition is not an effective therapeutic strategy. While the current
analysis does not inform which is the attributable cause, there are several possibilities
that merit consideration. With respect to the discrepancy between torcetrapib’s
remarkable effects on lipid metabolism and CIMT results, a direct vasculotoxic effect
of which a rise in blood pressure and peripheral resistance is only a biomarker, appears
possible. HDL’s natural ability to induce vasorelaxation, an effect that is thought to be
mediated via scavenger receptor B1, may be adversely affected by torcetrapib.

An adverse interaction of torcetrapib with atorvastatin is also a remote possibility,
however extensive preclinical and clinical work makes this highly unlikely (unpublished data on file, Pfizer). Another possibility relates to the fact that inhibition
of CETP by torcetrapib actually increases CETP plasma levels. At a daily dosage of 60
mg, torcetrapib increases CETP concentration continuously which is ascribed to an
enhanced affinity of CETP for HDL. This complex formation (CETP-Torcetrapib-
HDL) is in turn associated with extreme elevations of large HDL as exemplified by the
substantial increase of HDL2 cholesterol levels (157%). In this context, it is worrisome
that HDL-C levels were found to steadily increase over the entire duration of the
trial (see figure 1). It can be hypothesized that these effects may interfere with one
or more of HDL’s activities that include serving as an acceptor of cellular cholesterol,
inhibiting oxidation, thrombosis and vascular inflammation, promoting endothelial
repair and protecting against endothelial cell apoptosis. That HDL may have lost its
anti-inflammatory potential is illustrated by the observation that torcetrapib did not
affect CRP levels. In contrast, similar dose atorvastatin monotherapy resulted in a 45%
decrease of hsCRP levels in a FH trial of similar duration and size as RADIANCE 1.
The concept of inhibiting CETP to raise HDL-C and provide an anti-atherosclerotic therapy has been discussed in numerous reports and reviews for good reason since studies do not provide an unambiguous answer. Testing the hypothesis of CETP inhibition as a tool to reduce the burden of CVD requires careful further investigation of other small molecule inhibitors of CETP. However, in this quest, alternative strategies to reduce CETP-mediated neutral lipid transfer amongst plasma lipoproteins such as vaccination or strategies aimed at inhibition of the hepatic synthesis of CETP may also provide further insight.

In conclusion, the use of torcetrapib in FH did not result in regression of atherosclerosis as assessed by a combined measure of carotid arterial wall thickness and in fact caused progression of disease in the common carotid segment. These effects occurred despite an unparalleled increase of HDL-C (52%) and a substantial additional decrease of LDL-C (21%) levels. The torcetrapib driven increase in SBP alone does not appear to explain these results.

Disclosures
Dr. Kastelein reports having received consulting fees and lecture fees from Pfizer, AstraZeneca, Merck, and Schering-Plough and grant support from Pfizer and AstraZeneca. Dr. Evans has received consulting fees from AstraZeneca and grant support from the National Heart, Lung and Blood institute and Pfizer. Dr. Barter reports having received consulting fees from Pfizer, AstraZeneca, Merck and Abbott; lecture fees from Pfizer, AstraZeneca, Abbott and Merck; and grant support from Pfizer, Australian NHMRC. Drs. Revkin, Shear and Duggan are employees of Pfizer, Inc. Dr. Grobbee has received consulting fees and lecture fees from Pfizer, AstraZeneca, Servier and Organon and grant support from Pfizer, AstraZeneca, Servier and Organon. Dr Bots has received consulting fees and lecture fees from Pfizer, AstraZeneca and Servier and grant support from Pfizer, AstraZeneca and Servier.
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Listing of the investigators in the appendix.*

APPENDIX

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References


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