Cholesteryl Ester Transfer Protein Inhibitor Torcetrapib and Off-Target Toxicity

A Pooled Analysis of the Rating Atherosclerotic Disease Change by Imaging With a New CETP Inhibitor (RADIANCE) Trials

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Background—Torcetrapib, an inhibitor of cholesteryl ester transfer protein, has been shown to increase the cardiovascular event rate despite conferring a significant high-density lipoprotein cholesterol increase. Using data from the Rating Atherosclerotic Disease Change by Imaging with a New CETP Inhibitor (RADIANCE) trials, which assessed the impact of torcetrapib on carotid intima-media thickness (cIMT), we sought to explore potential mechanisms underlying this adverse outcome.

Methods and Results—Data from the RADIANCE 1 and 2 studies, which examined cIMT in 904 subjects with familial hypercholesterolemia and in 752 subjects with mixed dyslipidemia, were pooled. Subjects were randomized to either atorvastatin or torcetrapib combined with atorvastatin. Mean common cIMT progression was increased in subjects receiving torcetrapib plus atorvastatin compared with subjects receiving atorvastatin alone (0.0076 ± 0.0011 versus 0.0025 ± 0.0011 mm/y; P = 0.0014). Subjects treated with torcetrapib plus atorvastatin displayed higher postrandomization systolic blood pressure and plasma sodium and bicarbonate levels in conjunction with lower potassium levels. The decrease in potassium levels was associated with the blood pressure increase. Markedly, the use of renin-angiotensin-aldosterone system inhibitors tended to aggravate the blood pressure increase. Subjects receiving torcetrapib plus atorvastatin with the strongest low-density lipoprotein cholesterol reduction showed the smallest cIMT progression, whereas subjects with the highest systolic blood pressure increase showed the largest cIMT progression. High-density lipoprotein cholesterol increase was not associated with cIMT change.

Conclusions—These analyses support mineralocorticoid-mediated off-target toxicity in patients receiving torcetrapib as a contributing factor to an adverse outcome. The absence of an inverse relationship between high-density lipoprotein cholesterol change and cIMT progression suggests that torcetrapib-induced high-density lipoprotein cholesterol increase does not mediate atheroprotection. Future studies with cholesteryl ester transfer protein inhibitors without off-target toxicity are needed to settle this issue.

Key Words: cholesterol ▪ drugs ▪ imaging

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A low level of high-density lipoprotein cholesterol (HDL-C) is among the strongest predictors for cardiovascular disease. As a consequence, novel modalities to raise HDL-C as a means to reverse atherosclerosis have raised considerable interest. Small-molecule inhibitors of cholesteryl ester transfer protein (CETP) have been shown to increase HDL-C to unparalleled levels. On the basis of these findings, it has been suggested that CETP inhibition may further reduce the residual cardiovascular risk that persists during statin therapy. The impact of CETP inhibition by the novel small molecule torcetrapib has subsequently been addressed in intervention studies using atherosclerotic imaging as well as clinical end points. In December 2006, the mortality and morbidity study Investigation of Lipid Level Management to Understand Its Impact in Atherosclerotic Events (ILLUMINATE; www.clinicaltrials.gov number NCT00134264)
was prematurely terminated upon the revelation of a significant increase in all-cause mortality in the subjects using torcetrapib. At that time, 2 of the 3 studies investigating the efficacy of torcetrapib with the use of vascular imaging techniques had already been completed. Despite a significant improvement in lipid profiles, none of these imaging studies demonstrated any benefit of adding torcetrapib to atorvastatin therapy in terms of progression of carotid or coronary atherosclerosis. In fact, in the Rating Atherosclerotic Disease Change by Imaging With a New CETP Inhibitor (RADIANCE) 1 study, an increase of the common carotid intima-media thickness (cIMT) of the common carotid artery was observed.

Hypotheses have been put forward to explain these unanticipated results relating either to the mechanism of CETP inhibition per se or to off-target adverse effects of the torcetrapib molecule. An important argument favoring a causal role for the torcetrapib molecule rather than the CETP inhibition mechanism pertains to the observed increase in blood pressure (BP). Although safety data on other CETP inhibitors are scarce, this appears to be a unique consequence of the torcetrapib molecule because the use of other CETP inhibitors has not been associated with a rise in BP. In addition, in ILLUMINATE, torcetrapib use has been shown to cause electrolyte changes and elevations in plasma aldosterone, suggestive of a possible link with the unfavorable outcome of the studies with torcetrapib.

To gain more insight into the mechanisms underlying this adverse outcome, we merged the databases of the RADIANCE 1 and 2 studies and performed exploratory analyses into the parameters that were associated with cIMT progression and on-trial BP changes. In these analyses, we have focused primarily on parameters that are related to CETP inhibition as a mechanism (ie, on-trial high-density lipoprotein cholesterol [HDL-C] and low-density lipoprotein cholesterol [LDL-C] changes), as well as on parameters that are presumably connected to off-target toxicity (ie, on-trial BP and electrolyte changes).

Methods

Data Sources

The design and results of the RADIANCE 1 and RADIANCE 2 studies were published previously. Briefly, RADIANCE 1 enrolled subjects with heterozygous familial hypercholesterolemia, and RADIANCE 2 enrolled subjects with mixed dyslipidemia. In both studies, the atorvastatin dose was titrated to a target LDL-C level according to the patient’s cardiovascular risk based on the National Cholesterol Education Program Adult Treatment Panel III guidelines or to the maximally tolerated dose (20, 40, 80 mg/d in RADIANCE 1; 10, 20, 40, or 80 mg/d in RADIANCE 2). Next, subjects were randomly assigned to receive either atorvastatin monotherapy (atorvastatin group) or atorvastatin combined with 60 mg of torcetrapib (torcetrapib plus atorvastatin group) for 2 years. All subjects underwent B-mode ultrasonography at baseline, during follow-up, and at the end of the study to assess changes in cIMT. The ultrasound protocol and the procedures for offline cIMT reading were identical for RADIANCE 1 and RADIANCE 2. The primary end point of the original RADIANCE studies, the mean cIMT of 12 carotid segments, showed no significant difference between treatment arms and was therefore unlikely to provide insight into the potential mechanisms relating to the adverse outcome caused by torcetrapib. We therefore selected the annualized change in the mean common cIMT as the end point for the present article because previous results indicated harm as a result of torcetrapib use in relation to this outcome. This measure has been used as a primary efficacy outcome in a number of recent trials.

Risk Factor Information

At baseline, information was collected on cardiovascular risk factors, body mass index, medication use, lipid levels (total cholesterol, HDL-C, LDL-C, triglycerides), C-reactive protein, systolic BP (SBP) and diastolic BP (DBP), plasma electrolyte levels, and cIMT. After randomization, information was collected on lipid levels, BP, electrolyte levels, concomitant medication, and investigator-reported adverse events. Information on cIMT was collected every 6 months after baseline and in duplicate at the end of the study.

To study the changes from baseline in the different laboratory and BP values and to smooth out intraindividual and measurement variation, 8 postrandomization values were averaged, after which baseline values were subtracted. Thus, a positive data point represents an increase in the average postrandomization values.

Data Analyses

Baseline and on-trial characteristics of the subjects are presented by treatment arm in means and proportions. Student t tests and χ² tests were applied to examine differences between treatment arms in means and proportions, respectively. Mann-Whitney U tests were used for between-group comparisons when data were not normally distributed. Analyses of cIMT were performed in the full analysis set, consisting of 1533 subjects. For these subjects, at least 1 follow-up cIMT measurement was available. A linear mixed-effects model was used to analyze the annualized rate of change in mean common cIMT including the near and far wall measures of the right and left common carotid artery (4 segments×7 visits) for each participant as the dependent variables with random intercepts and slopes as a function of time and fixed effects for study, geographic region, atorvastatin dose at run-in, carotid segment, treatment, and time. A term for treatment by time interaction was included when appropriate. Testing was 2-sided and was conducted with a 5% type I error rate.

First, we evaluated which known risk factors were related to mean common cIMT progression to allow for adjustments in later analyses. These analyses were performed in strata of assigned treatment. Linear mixed-effects models were run with the risk factor and the interaction term of time multiplied by risk factor. The factors evaluated were baseline risk factors (age, gender, body mass index, smoking, history of diabetes, history of hypertension, HDL-C levels, LDL-C levels, triglyceride levels) and on-trial change in risk factors (HDL-C change, LDL-C change, triglyceride change, SBP change, DBP change). Those factors for which the interaction terms were statistically significant were entered into a multivariate model (factor and interaction term) to determine the independent relationship with cIMT progression.

The influences of CETP inhibition–related (HDL change and LDL change) and putative off-target (sodium change, potassium change, bicarbonate change, and SBP change) effects of torcetrapib on cIMT progression were further examined in a different set of analyses. To examine whether the increased cIMT progression in the torcetrapib plus atorvastatin arm could be (partly) explained by off-target effects, we calculated the difference in cIMT progression between treatment groups and then made additional adjustments for off-target effects to see whether the difference in cIMT progression would be attenuated. A similar analysis was performed for effects related to CETP inhibition.

To assess whether electrolyte changes were related to on-trial SBP change, a linear regression analysis was performed with the use of on-trial sodium, bicarbonate, and potassium change in 1 model. A similar analysis was performed for baseline use of different types of antihypertensive medication to assess their effect on SBP change.
the atorvastatin-only group and 0.0076 mm/y (95% CI, 0.0054 to 0.0097 mm/y) in the torcetrapib plus atorvastatin group, reflecting a highly statistically significant increased progression rate in the torcetrapib plus atorvastatin–treated individuals ($P=0.0014$).

**On-Trial Characteristics**

Compared with atorvastatin monotherapy, addition of torcetrapib treatment resulted in increased levels of HDL-C (+24.5 versus $-1.0$ mg/dL; $P<0.0001$) and lower levels of LDL-C ($-19.2$ versus $+4.3$ mg/dL; $P<0.0001$) as well as triglycerides ($-7.7$ versus $3.3$ mg/dL; $P<0.0001$). DBP (75.5 versus 74.7 mm Hg; $P=0.021$) and SBP readings (122.7 versus 119.3 mm Hg; $P<0.0001$) were higher in the group receiving torcetrapib plus atorvastatin (Table 2). The distribution of SBP changes in both treatment groups is depicted in Figure 1.

The average postrandomization values in the torcetrapib plus atorvastatin group compared with those for atorvastatin alone were significantly lower for potassium and higher for sodium and bicarbonate (Table 2). When analyses were restricted to those not receiving BP-lowering medication, similar findings were obtained. The change in potassium from baseline in the torcetrapib plus atorvastatin and atorvastatin groups ($-0.095$ versus $-0.055$ mEq/dL, respectively; $P=0.0004$) as well as postrandomization sodium and potassium levels (140.2 versus 139.9 mEq/dL, respectively; $P=0.0003$; and 4.20 versus 4.27 mEq/dL, respectively; $P=0.0004$) remained significantly different. These electrolyte changes were not associated with the torcetrapib-induced increase in HDL-C levels.

**(Changes in) Risk Factors Related to Common cIMT Progression**

We evaluated the effects of baseline risk factors and on-trial changes in risk factors on carotid atherosclerosis progression. In the atorvastatin-only group, apart from a history of diabetes mellitus ($P$ of interaction term $=0.004$), none of the baseline risk factors contributed to common cIMT progression. Furthermore, postrandomization changes in lipid levels (LDL-C [$P=0.78$], HDL-C [$P=0.50$], triglycerides [$P=0.65$]) did not relate to mean common cIMT progression. In this group, those with low postrandomization cIMT progression rates had higher baseline cIMT values, and those with larger postrandomization cIMT changes had lower baseline values, indicating regression to the mean. This is in agreement with the fact that all subjects were titrated to reach target LDL-C levels or to maximum tolerated statin dose during the run-in period.

In the torcetrapib plus atorvastatin group, age at baseline ($P=0.045$), history of hypertension ($P=0.06$), and postrandomization changes in LDL-C ($P=0.010$), triglycerides ($P=0.06$), SBP ($P=0.001$), and DBP ($P=0.007$) contributed to mean common cIMT progression. Notably, postrandomization changes in HDL-C did not predict mean common cIMT progression ($P=0.63$). In a multivariate linear mixed-effects model, baseline age, history of hypertension, and postrandomization change in LDL-C and in SBP remained significantly related to common cIMT progression. Relationships between postrandomization variables and common

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**Table 1. Baseline Characteristics of All Randomized Subjects (n=1656)**

<table>
<thead>
<tr>
<th></th>
<th>Atorvastatin Monotherapy (n=829)</th>
<th>Atorvastatin Plus Torcetrapib (n=827)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>50.4±12.4</td>
<td>51.8±11.9</td>
</tr>
<tr>
<td>Sex, male</td>
<td>477 (58)</td>
<td>451 (55)</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>28.2±7</td>
<td>28.1±4.61</td>
</tr>
<tr>
<td>History of diabetes</td>
<td>111 (13)</td>
<td>80 (10)</td>
</tr>
<tr>
<td>Current smokers</td>
<td>153 (18)</td>
<td>149 (18)</td>
</tr>
<tr>
<td>BP, mm Hg</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic</td>
<td>117.9±10.6</td>
<td>118.0±11.4</td>
</tr>
<tr>
<td>Diastolic</td>
<td>74.1±6.8</td>
<td>73.5±7.2</td>
</tr>
<tr>
<td>Medication use</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aspirin</td>
<td>337</td>
<td>347</td>
</tr>
<tr>
<td>β-Blocker</td>
<td>182</td>
<td>194</td>
</tr>
<tr>
<td>ACE inhibitor</td>
<td>158</td>
<td>137</td>
</tr>
<tr>
<td>ARB</td>
<td>46</td>
<td>67</td>
</tr>
<tr>
<td>Diuretic</td>
<td>133</td>
<td>136</td>
</tr>
<tr>
<td>Cholesterol, mg/dL</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>200.5±39.4</td>
<td>200.2±38.5</td>
</tr>
<tr>
<td>LDL</td>
<td>121.6±36.3</td>
<td>121.5±36.1</td>
</tr>
<tr>
<td>HDL</td>
<td>49.9±12.0</td>
<td>50.6±12.4</td>
</tr>
<tr>
<td>Triglycerides, mg/dL</td>
<td>127.0 (88.5 to 185.9)</td>
<td>129.0 (88.5 to 179.0)</td>
</tr>
<tr>
<td>C-reactive protein, mg/dL</td>
<td>0.3 (0.1 to 0.9)</td>
<td>0.4 (0.1 to 1.0)</td>
</tr>
<tr>
<td>Electrolytes, mEq/dL</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sodium</td>
<td>140.0±2.2</td>
<td>140.3±2.1</td>
</tr>
<tr>
<td>Potassium</td>
<td>4.2±0.4</td>
<td>4.2±0.4</td>
</tr>
<tr>
<td>Bicarbonate</td>
<td>24.6±2.7</td>
<td>24.7±2.6</td>
</tr>
<tr>
<td>cIMT, mm</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Maximum cIMT</td>
<td>1.22±0.31</td>
<td>1.22±0.32</td>
</tr>
<tr>
<td>Mean common cIMT</td>
<td>0.77±0.2</td>
<td>0.77±0.16</td>
</tr>
</tbody>
</table>

Data are given as mean±SD, number (%), or mean (interquartile range). Maximum cIMT is the average of the maximum intima-media thickness for each of the 12 carotid artery sites. Mean common cIMT is the average of the mean intima-media thickness for each of the 4 common carotid artery sites.

In this analysis, the use of angiotensin receptor blockers (ARBs), angiotensin-converting enzyme (ACE) inhibitors, diuretics, β-blockers, and calcium blockers was entered into 1 model. All linear regression analyses were done for the atorvastatin monotherapy arm and the torcetrapib plus atorvastatin arm separately and were weighted for cohort size.

**Role of the Funding Source**

All analyses were performed academically by the lead authors. The study data were analyzed independently by the study sponsor, Pfizer. The sponsor reviewed the manuscript and provided editorial comments to the lead authors.

The authors had full access to and take full responsibility for the integrity of the data. All authors have read and agree to the manuscript as written.

**Results**

Table 1 shows the baseline characteristics of all 1656 randomized subjects. The annualized change in mean common cIMT was 0.0025 mm/y (95% confidence interval [CI], 0.0003 to 0.0047 mm/y) in the atorvastatin-only group and 0.0076 mm/y (95% CI, 0.0054 to 0.0097 mm/y) in the torcetrapib plus atorvastatin group, reflecting a highly statistically significant increased progression rate in the torcetrapib plus atorvastatin–treated individuals ($P=0.0014$).
Table 2. On-Trial Characteristics and Adverse Events in Separate Treatment Arms

<table>
<thead>
<tr>
<th>Average postrandomization values</th>
<th>Atorvastatin Monotherapy</th>
<th>Atorvastatin Plus Torcetrapib</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total, mg/dL</td>
<td>204.6±1.4</td>
<td>203.8±1.4</td>
<td>0.68</td>
</tr>
<tr>
<td>LDL</td>
<td>126.1±1.3</td>
<td>102.1±1.3</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>HDL</td>
<td>49.0±0.4</td>
<td>75.1±0.7</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Triglycerides, mg/dL, median (interquartile range)</td>
<td>136.1 (96.2 to 184.6)</td>
<td>118.0 (86.3 to 159.3)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Electrolytes, mEq/dL</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sodium</td>
<td>139.9±0.1</td>
<td>140.4±0.1</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Potassium</td>
<td>4.26±0.01</td>
<td>4.17±0.01</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Bicarbonate</td>
<td>24.8±0.1</td>
<td>25.1±0.1</td>
<td>0.016</td>
</tr>
<tr>
<td>BP, mm Hg</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic</td>
<td>119.3±0.4</td>
<td>122.7±0.4</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Diastolic</td>
<td>74.7±0.2</td>
<td>75.5±0.3</td>
<td>0.021</td>
</tr>
<tr>
<td>Change from baseline</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total, mg/dL</td>
<td>3.9±0.9</td>
<td>3.7±1.1</td>
<td>0.85</td>
</tr>
<tr>
<td>LDL</td>
<td>4.3±0.7</td>
<td>−19.2±1.1</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>HDL</td>
<td>−1.0±0.2</td>
<td>24.5±0.4</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Triglycerides, mg/dL, median (interquartile range)</td>
<td>3.3 (−17.85 to 27.53)</td>
<td>−7.7 (−35.38 to 14.38)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Electrolytes, mEq/dL</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sodium</td>
<td>−0.111±0.063</td>
<td>0.058±0.067</td>
<td>0.067</td>
</tr>
<tr>
<td>Potassium</td>
<td>0.062±0.010</td>
<td>−0.014±0.011</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Bicarbonate</td>
<td>−0.055±0.088</td>
<td>0.131±0.086</td>
<td>0.130</td>
</tr>
<tr>
<td>BP, mm Hg</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic</td>
<td>1.5±0.2</td>
<td>5.2±0.3</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Diastolic</td>
<td>0.6±0.2</td>
<td>2.1±0.2</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

Data are mean±SE unless otherwise specified.

cIMT progression, as well as interactions between these variables, are depicted in Figure 2. The effects of LDL-C change and SBP change on cIMT progression oppose each other, whereas no interaction between HDL change and any of the other variables was observed.

CETP Inhibition–Related and Off-Target Effects on cIMT Progression

Next we looked specifically at the influence on cIMT progression of effects related to CETP inhibition (LDL change and HDL change) and of putative off-target effects (SBP change, sodium change, potassium change, and bicarbonate change). The mean difference in common cIMT progression between the atorvastatin/torcetrapib arm and the atorvastatin arm alone in the combined RADIANCE studies was 0.0050 mm (SE=0.0016) (P=0.0016). The difference in cIMT progression was attenuated by 20% after adjustment for off-target effects (on-trial changes in BP, bicarbonate, sodium, potassium): 0.0040 mm (SE=0.0016) (P=0.013). In contrast, the difference in cIMT progression became 28% more pronounced after adjustment for effects related to CETP inhibition (LDL change and HDL change): 0.0063 mm (SE=0.0028) (P=0.024).

Factors Related to BP Increase

Next we examined whether the observed electrolyte changes induced by torcetrapib were associated with SBP change. Of the studied variables (potassium change, sodium change, and bicarbonate change), only lower potassium levels were associated with an increase in SBP in subjects using torcetrapib and atorvastatin (Figure 3, top). A 1-mEq/dL difference in potassium change was associated with a 2.57-mm Hg change in SBP (95% CI, −4.54 to −0.60; P=0.01) in subjects in the torcetrapib plus atorvastatin group. In the atorvastatin monotherapy group, no such associations were found.

Effects of Antihypertensive Medication

To verify whether the use of antihypertensive medication at baseline influenced SBP readings in the torcetrapib plus atorvastatin group, we performed a linear regression analysis. The use of ACE inhibitors or ARBs at baseline was associated with a greater SBP increase in the torcetrapib plus atorvastatin group (2.81 mm Hg [95% CI, 0.43 to 5.18; P=0.02] and 1.81 mm Hg [95% CI, 0.05 to 3.57; P=0.04], respectively). Other antihypertensive drugs did not show this effect (Figure 3, bottom). Similarly, follow-up antihypertensive treatment with ACE inhibitors or ARBs did not result in lower end-of-study BP readings in the torcetrapib plus ator-
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oste volume. Higher plasma aldosterone levels, even within the
physiological range, already predispose to hypertension. The
production of aldosterone, which is accompanied by a concomitant increase in plasma
alcohol and aldosterone secretion. The difference in levels is associated with the
increase in cIMT progression between treatment groups was attenuated
by the largest BP increases. Conversely, the mineralocorticoid effect by torcetrapib contributing to a volume
overload. Our results agree with findings from the ILLUMI-
NATE study, in which torcetrapib use was associated with similar electrolyte changes and increased circulating aldosterone levels. The observed interrelation between the parameters mentioned in the present study strengthens the notion that an increased mineralocorticoid activity may be causally related to the adverse outcome associated with torcetrapib use.

Mineralocorticoid hormones have a proatherogenic effect
on the vasculature that can be attributed only partly to BP. Thus, aldosterone induces arterial stiffening through collagen deposition in the extracellular matrix, and subjects with hyperaldosteronism have been shown to have a thicker common cIMT compared with subjects with essential hypertension. These findings may explain why cardiovascular events in the torcetrapib plus atorvastatin group of the RADIANCE studies occurred across the entire spectrum of BP change and were not restricted to subjects characterized by the largest BP increases. Conversely, the mineralocorticoid excess may also be a marker of the effects of torcetrapib on the adrenals rather than the direct cause of the adverse outcomes associated with its use. Recently, Forrest et al reported that torcetrapib exerts direct pressor effects in animal models, depending on the presence of the adrenal glands, but is not completely inhibitable by the aldosterone receptor blocker eplerenone. In addition, torcetrapib can upregulate the expression of RAAS genes in endothelial cells of rat aorta. In view of the proatherogenic effects of tissue RAAS in the vessel wall, which may operate independently of the circulating RAAS, this could further add to adverse effects, independent of BP.

The exact mechanism by which torcetrapib elicits the
release of substances with mineralocorticoid effects remains to be established. Torcetrapib is known to form a stable complex with CETP, firmly attached to HDL particles. In this respect, it is interesting to note that HDL cholesterol also serves as a cholesterol-donating substrate for the adrenal gland, requiring cholesterol for the production of steroid hormones. On the basis of these data, it is tempting to speculate that torcetrapib enters the adrenals as part of the HDL particle, which may provide the basis of the mineralocorticoid release. Further studies are needed to test this hypothesis.

### Discussion

In the present study we confirmed that the use of torcetrapib induces electrolyte changes, increased BP, and increased cIMT progression. The BP changes were related to both the electrolyte changes and the increased cIMT progression. In contrast, torcetrapib-induced HDL increase was unrelated to electrolyte changes or cIMT progression. The difference in cIMT progression between treatment groups was attenuated after adjustment for off-target effects (BP and electrolyte changes) but not after adjustment for effects related to CETP inhibition (LDL-C and HDL-C changes). These findings suggest that off-target toxicity of the torcetrapib molecule has contributed to the adverse outcome in these patients.

### Mineralocorticoid Excess

Several arguments can be made in favor of a mineralocorticoid excess, elicited by torcetrapib, as a contributing factor to the observed adverse outcome. First, a mineralocorticoid excess can explain both the electrolyte changes as well as the BP increase. Aldosterone, produced in the adrenal gland, activates mineralocorticoid receptors on the principal cells of the distal tubule of the nephron, leading to increased sodium and bicarbonate reabsorption in exchange for potassium excretion, which is accompanied by a concomitant increase in plasma volume. Higher plasma aldosterone levels, even within the physiological range, already predispose to hypertension. The finding that potassium decrease was a significant predictor of the SBP increase after administration of torcetrapib further substantiates the mineralocorticoid hypothesis.

Second, we observed that the use of ACE inhibitors or ARBs at baseline was associated with an even greater SBP increase, whereas the use of diuretics, calcium blockers, or β-blockers was not. Treatment with renin-angiotensin-aldosterone system (RAAS) inhibitors leads to decreased aldosterone levels. Under these circumstances, a mineralocorticoid stimulus can be expected to have a more pronounced impact on BP. To corroborate this, we observed that the initiation of RAAS inhibitors for BP increase after the start of torcetrapib did not contribute to lower end-of-study BP readings. In contrast, the initiation of diuretics for the same indication resulted in reduced BP levels. These findings are consistent with a renin- and angiotensin-independent, direct mineralocorticoid effect by torcetrapib contributing to a volume overload. Our results agree with findings from the ILLUMI-
NATE study, in which torcetrapib use was associated with similar electrolyte changes and increased circulating aldosterone levels. In fact, the observed interrelation between the parameters mentioned in the present study strengthens the notion that an increased mineralocorticoid activity may be causally related to the adverse outcome associated with torcetrapib use.

Mineralocorticoid hormones have a proatherogenic effect on the vasculature that can be attributed only partly to BP. Thus, aldosterone induces arterial stiffening through collagen deposition in the extracellular matrix, and subjects with hyperaldosteronism have been shown to have a thicker common cIMT compared with subjects with essential hypertension. These findings may explain why cardiovascular events in the torcetrapib plus atorvastatin group of the RADIANCE studies occurred across the entire spectrum of BP change and were not restricted to subjects characterized by the largest BP increases. Conversely, the mineralocorticoid excess may also be a marker of the effects of torcetrapib on the adrenals rather than the direct cause of the adverse outcomes associated with its use. Recently, Forrest et al reported that torcetrapib exerts direct pressor effects in animal models, depending on the presence of the adrenal glands, but is not completely inhibitable by the aldosterone receptor blocker eplerenone. In addition, torcetrapib can upregulate the expression of RAAS genes in endothelial cells of rat aorta. In view of the proatherogenic effects of tissue RAAS in the vessel wall, which may operate independently of the circulating RAAS, this could further add to adverse effects, independent of BP.

The exact mechanism by which torcetrapib elicits the release of substances with mineralocorticoid effects remains to be established. Torcetrapib is known to form a stable complex with CETP, firmly attached to HDL particles. In this respect, it is interesting to note that HDL cholesterol also serves as a cholesterol-donating substrate for the adrenal gland, requiring cholesterol for the production of steroid hormones. On the basis of these data, it is tempting to speculate that torcetrapib enters the adrenals as part of the HDL particle, which may provide the basis of the mineralocorticoid release. Further studies are needed to test this hypothesis.
No Evidence for Antiatherosclerotic Effect of HDL Increase Mediated by CETP Inhibition

In the ILLUMINATE study, a post hoc analysis showed a trend toward fewer major cardiovascular events in those subjects who experienced an above-median HDL-C increase under torcetrapib treatment, suggestive of a positive impact of the lipid changes mediated by CETP inhibition. Similarly, in the present study, the mild LDL-lowering effect of torcetrapib was associated with a decreased cIMT progression. However, the absence of a relationship between HDL-C increase and decreased cIMT progression in this study could imply that CETP inhibitor–conferred HDL increase lacks an atheroprotective effect. Indeed, there has been concern that CETP inhibition might slow the recycling of HDL particles and reduce hepatic cholesterol uptake through the LDL receptor, thereby diminishing the flux of cholesterol through the reverse cholesterol transport pathway. Furthermore, studies examining the impact of CETP inhibition on inflammatory as well as oxidation markers have revealed mixed results. However, against the background of off-target toxicity, it is difficult to draw final conclusions on the atheroprotective capacity of HDL after CETP inhibition in the present study.

Study Limitations

Some aspects of this study merit caution. In the present study, the data from the RADIANCE 1 and 2 trials were merged, yielding a large sample size of >1600 subjects. This carries a potential limitation because the studied populations (ie, familial hypercholesterolemia and mixed dyslipidemia, respectively) are heterogeneous. Furthermore, although we gathered indirect evidence from a number of analyses, we did not directly quantify RAAS activity or mineralocorticoid levels in the RADIANCE studies. It should be stated explicitly that phase III studies are not intended to reveal mechanistic insights. Therefore, our results are hypothesis generat-
**Molecule or Mechanism?**

Despite a large increase in HDL-C and not related to this increase of HDL-C, torcetrapib use was strongly associated with adverse arterial wall changes. Although it cannot be excluded that the mechanism of CETP inhibition and its HDL effect was adverse by itself, torcetrapib-induced electrolyte changes and their association with BP elevations suggest that torcetrapib, as a molecule, resulted in an off-target mineralocorticoid excess. In turn, the association of the BP elevations with the cIMT changes suggests that the adverse intimal changes may be the result of this off-target effect. Other CETP inhibitors currently in clinical development (anacetrapib, dalce trapib) do not appear to raise BP.

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**Determination of whether the use of these agents will yield clinical benefit will have to wait until the results of a number of phase III trials are available in the future. Until then, the final verdict for CETP inhibition is still out.**

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**References**

The cholesteryl ester transfer protein (CETP) inhibitor torcetrapib has been shown to increase cardiovascular event rates despite conferring a significant high-density lipoprotein cholesterol increase. Hypotheses have been put forward to explain this unexpected result, relation either to the mechanism of CETP inhibition per se or to off-target adverse effects of the torcetrapib molecule. We pooled the data from 2 large vascular imaging trials with torcetrapib and confirmed that the use of torcetrapib induces electrolyte changes, increase in blood pressure, and increased carotid intima-media thickness progression. The blood pressure changes were related to both the electrolyte changes and the increased carotid intima-media thickness progression. In contrast, torcetrapib-induced high-density lipoprotein increase was unrelated to either electrolyte changes or carotid intima-media thickness progression. The difference in carotid intima-media thickness progression between treatment groups was attenuated after adjustment for off-target effects (blood pressure and electrolyte changes) but not after adjustment for effects related to CETP inhibition (low-density lipoprotein cholesterol and carotid intima-media thickness progression). In contrast, torcetrapib-induced high-density lipoprotein increase was unrelated to either electrolyte changes or carotid intima-media thickness progression. The difference in carotid intima-media thickness progression between treatment groups was attenuated after adjustment for off-target effects (blood pressure and electrolyte changes) but not after adjustment for effects related to CETP inhibition (low-density lipoprotein cholesterol and high-density lipoprotein cholesterol changes). Although it cannot be excluded that the mechanism of CETP inhibition was detrimental by itself, our findings suggest that off-target toxicity of the torcetrapib molecule has contributed to the adverse outcome seen with torcetrapib. Interactions with different types of antihypertensive medications suggest mineralocorticoid excess as a possible mechanism. Evidence is accumulating that other CETP inhibitors which are currently being developed do not display this type of off-target toxicity. Our study therefore supports a careful further development of these modalities, albeit with an unremittingly strong focus on their safety profile.

CLINICAL PERSPECTIVE

The cholesteryl ester transfer protein (CETP) inhibitor torcetrapib has been shown to increase cardiovascular event rates despite conferring a significant high-density lipoprotein cholesterol increase. Hypotheses have been put forward to explain this unexpected result, relating either to the mechanism of CETP inhibition per se or to off-target adverse effects of the torcetrapib molecule. We pooled the data from 2 large vascular imaging trials with torcetrapib and confirmed that the use of torcetrapib induces electrolyte changes, increase in blood pressure, and increased carotid intima-media thickness progression. The blood pressure changes were related to both the electrolyte changes and the increased carotid intima-media thickness progression. In contrast, torcetrapib-induced high-density lipoprotein increase was unrelated to either electrolyte changes or carotid intima-media thickness progression. The difference in carotid intima-media thickness progression between treatment groups was attenuated after adjustment for off-target effects (blood pressure and electrolyte changes) but not after adjustment for effects related to CETP inhibition (low-density lipoprotein cholesterol and high-density lipoprotein cholesterol changes). Although it cannot be excluded that the mechanism of CETP inhibition was detrimental by itself, our findings suggest that off-target toxicity of the torcetrapib molecule has contributed to the adverse outcome seen with torcetrapib. Interactions with different types of antihypertensive medications suggest mineralocorticoid excess as a possible mechanism. Evidence is accumulating that other CETP inhibitors which are currently being developed do not display this type of off-target toxicity. Our study therefore supports a careful further development of these modalities, albeit with an unremittingly strong focus on their safety profile.
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In the version of the article, “Cholesteryl Ester Transfer Protein Inhibitor Torcetrapib and Off-Target Toxicity: A Pooled Analysis of the Rating Atherosclerotic Disease Change by Imaging With a New CETP Inhibitor (RADIANCE) Trials,” by Menno Vergeer et al that was posted online on November 24, 2008 (DOI: 10.1161/CIRCULATIONAHA.108.772665), an error occurred.

In the Abstract, the full name of the RADIANCE trial was incorrect. It should be, “Rating Atherosclerotic Disease Change by Imaging With a New CETP Inhibitor.”

The error has been corrected in the current online version and in the final print version of the article in the December 9, 2008, issue of the journal (Circulation. 2008;118:2515–2522). The publisher regrets the error.

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