Efficacy and Safety of Torcetrapib, a Novel Cholesteryl Ester Transfer Protein Inhibitor, in Individuals With Below-Average High-Density Lipoprotein Cholesterol Levels

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OBJECTIVES This study was designed to evaluate the efficacy and safety of torcetrapib, a cholesteryl ester transfer protein (CETP) inhibitor, in subjects with low high-density lipoprotein cholesterol (HDL-C) levels.

BACKGROUND Evidence suggests HDL-C is atheroprotective. A proven mechanism for increasing the level of HDL-C is the inhibition of CETP.

METHODS A total of 162 subjects with below-average HDL-C (men <44 mg/dl; women <54 mg/dl) who were not taking lipid-modifying therapy were randomized to double-blind treatment with torcetrapib 10, 30, 60, or 90 mg/day or placebo (~30 subjects per group).

RESULTS The percent change from baseline to Week 8 with torcetrapib (least-squares mean difference from placebo) was dose-dependent and ranged from 9.0% to 54.5% for HDL-C (p = 0.0001 for 30 mg and higher doses) and from 3.0% to ~16.5% for low-density lipoprotein cholesterol (LDL-C) (p < 0.01 for 90-mg dose). Low-density lipoprotein cholesterol lowering was less in subjects with higher (>150 mg/dl) versus lower levels of baseline triglycerides; at 60 mg, the change in LDL-C was 0.1% versus −22.2% (p < 0.0001), respectively. Particle size for both HDL and LDL increased with torcetrapib. There were no dose-related increases in the frequency of adverse events. Significant blood pressure increases were noted in 2 of 140 subjects.

CONCLUSIONS Torcetrapib resulted in substantial dose-dependent elevations in HDL-C, accompanied by moderate decreases in LDL-C at the higher doses. Torcetrapib was generally well tolerated. (J Am Coll Cardiol 2006;48:1774 – 81) © 2006 by the American College of Cardiology Foundation

High-density lipoprotein cholesterol (HDL-C) is an independent inverse risk factor for coronary heart disease (CHD), and elevating HDL-C is a promising strategy for preventing cardiovascular events. However, the range of drugs for elevating levels of HDL-C is limited. Statins (1) and fibrates (2) provide only modest increases in HDL-C, and niacin (3), although more effective, is poorly tolerated.

The cholesteryl ester transfer protein (CETP) plays a pivotal role in cholesterol metabolism, exchanging cholesteryl esters (CEs) and triglycerides between lipoproteins (4). Typically, CETP transfers CEs from HDL to very low-density lipoprotein (VLDL) and low-density lipoprotein (LDL) in exchange for triglycerides and transfers triglycerides from VLDL to LDL and HDL in exchange for CEs (4). Thus, CETP activity is potentially pro-atherogenic, decreasing the CE content of atheroprotective HDL and increasing the CE content of atherogenic VLDL and LDL (4). Furthermore, by exchanging triglycerides in VLDL for CEs in HDL and LDL, CETP promotes the formation of small dense LDL and HDL by increasing the remodeling of triglyceride-enriched LDL and HDL particles by triglyceride lipases (4). Small dense LDL is particularly atherogenic (5). In individuals with elevated triglyceride levels, such as those with diabetes, the VLDL pool is typically enlarged, and CETP-driven triglyceride enrichment of HDL and LDL particles may be especially relevant in creating an atherogenic lipid profile (6,7).

Cholesteryl ester transfer protein inhibition is a potential strategy for elevating HDL-C and for treating cardiovascular disease (CVD) (4). In rabbit models, several techniques have been employed to suppress CETP activity, resulting in increases in HDL-C and atherosclerotic regression (8–11). Two CETP inhibitors, JTT-705 and torcetrapib, are in clinical development. In preliminary trials, torcetrapib has been shown to produce...
substantial elevations in HDL-C, modest decreases in LDL cholesterol (LDL-C), and increases in lipid particle size (12,13). This phase 2 study provides further data on the efficacy and safety of torcetrapib in a large group of individuals with below-average levels of HDL-C. A study of torcetrapib administered on a background of atorvastatin to similar subjects is reported in this issue of the Journal (see page 1782).

**METHODS**

**Study design.** This was a multicenter study (23 centers). Following screening, eligible participants were randomized to 8 weeks of double-blind treatment with either placebo or torcetrapib 10, 30, 60, or 90 mg once daily (Fig. 1).

**Participants.** Eligible participants were ages 18 to 65 years with low HDL-C levels (<44 mg/dl for men and <54 mg/dl for women) at screening (14). Exclusion criteria included major/unstable concurrent illnesses, lipid-altering therapy within 30 days of screening, and an LDL-C level of ≥1350 mg/dl or triglycerides ≥400 mg/dl during screening.

The protocol was approved by the Institutional Review Board or Independent Ethics Committee at each site and was conducted in compliance with the Declaration of Helsinki.

**Lipid assessments.** The primary end point was the percent change from baseline in the levels of HDL-C after 8 weeks. Absolute changes from baseline in HDL-C and percent changes and absolute changes in LDL-C, triglycerides, and total cholesterol were secondary end points. Additional lipid analyses included apolipoprotein concentrations; HDL particle type; HDL, VLDL, and LDL subclass composition; phospholipid concentrations; and nuclear magnetic resonance (NMR) lipoprotein.

**Analytical methods.** Biochemical analyses were performed by Medical Research Laboratories (Highland Heights, Kentucky). Total cholesterol and net triglycerides were quantified by a CDC-standardized enzymatic assay in an automated chemistry analyzer. High-density lipoprotein cholesterol was measured by separating HDL from LDL/VLDL by heparin/MnCl₂ chemical precipitation. Low-density lipoprotein cholesterol and VLDL cholesterol (VLDL-C) were estimated by the Friedewald formula (15). If total triglycerides were >400 mg/dl, LDL-C and VLDL-C were measured directly by beta-quantification using ultracentrifugation. Phospholipid was measured by an automated enzymatic colorimetric method. High-density lipoprotein sub-classes (HDL2 and HDL3) were separated by zonal ultracentrifugation. Apo A-I, A-II, and B-100 were analyzed by an automated immunoturbidimetric procedure. Lipoprotein subclasess where determined using proton NMR by Liposciences Inc. (Raleigh, North Carolina) (16).

**Safety assessments.** Safety assessments included a physical examination and measurement of vital signs, electrocardiograms, and standard laboratory safety tests. All adverse events (AEs) were recorded.

**Statistical analyses.** The primary statistical analysis for efficacy included all randomized participants who received at least 1 dose of study treatment with at least 1 before- and after-treatment end point measurement using the last-observation-carried-forward approach. The analysis of the primary end point (HDL-C percent change from baseline at week 8) employed analysis of covariance using a linear model that included a term for treatment group and baseline

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**Abbreviations and Acronyms**

| AE | adverse event |
| apo | apolipoprotein |
| CE | cholesteryl ester |
| CETP | cholesteryl ester transfer protein |
| CHD | coronary heart disease |
| CVD | cardiovascular disease |
| DBP | diastolic blood pressure |
| HDL-C | high-density lipoprotein cholesterol |
| LDL-C | low-density lipoprotein cholesterol |
| NMR | nuclear magnetic resonance |
| SBP | systolic blood pressure |
| VLDL-C | very low-density lipoprotein cholesterol |
value as a continuous covariate (SAS Proc Mixed). Study center was not included as an independent variable. Least-squares means (LS means) were computed and pairwise treatment comparisons of torcetrapib dose group versus placebo were assessed for statistical significance at the p = 0.05 level (2-sided) using a step-down procedure to preserve the type 1 error across the multiple comparisons (17). A 95% confidence interval (CI), unadjusted for multiplicity, was calculated for each pairwise comparison. Similar analyses were performed for secondary end points.

For lipid assessments, results are presented in figures as raw means for each time point. The percent changes in baseline observations was averaged and a change from baseline was calculated for each pairwise comparison. Similar analyses were performed for secondary end points.

For vital signs, each patient’s complement of after-baseline observations was averaged and a change from baseline was calculated. This measure was then analyzed in a manner analogous to the efficacy parameters discussed earlier; that is, ANCOVA was employed using SAS Proc Mixed with a linear model, including a term for treatment group and baseline value as a continuous covariate. Least-squares means were calculated and 95% CIs were computed for the within-treatment-group change from baseline.

**RESULTS**

**Baseline demographics.** Baseline demographic characteristics and lipid profiles of the randomized participants (n = 162) were well balanced across treatment groups (Table 1). Mean HDL-C levels for treatment groups ranged from 37 to 40 mg/dl.

**Efficacy: lipid parameters.** HDL AND HDL-RELATED APOLIPOPROTEINS. Torcetrapib dose-dependently increased HDL-C levels (Table 2, Fig. 2). Percent changes in HDL-C from baseline to Week 8 ranged from 9.0% to 54.5% with torcetrapib 10 to 90 mg/day (LS mean difference from placebo). Differences were significant at doses of 30, 60, and 90 mg/day (p ≤ 0.0001). Increases in HDL-C were accompanied by dose-dependent increases in the levels of apo A-I and apo A-II, with apo A-I being the dominant change (Table 3).

Ultracentrifugation/precipitation analysis showed that torcetrapib increased HDL particles of larger size (Table 3). High-density lipoprotein subclass changes determined by NMR spectroscopy were consistent with the findings from ultracentrifugation/precipitation analysis showing that torcetrapib produced dose-dependent increases in levels of the large HDL-C subclasses. At the 60-mg and 90-mg doses of torcetrapib, large HDL-C (8.3 to 13 nm) increased from 12.5 (SD ± 5.6) to 26.9 mg/dl (SD ± 11.3) (p < 0.05) and 13.2 (SD ± 6.3) to 35.0 mg/dl (SD ± 21.3) (p < 0.01), respectively. At these same doses of torcetrapib, mean HDL particle size also increased from 8.3 (±0.3) to 8.8 nm (±0.4) and 8.3 (±0.3) to 9.0 nm (±0.5), respectively (p ≤ 0.0001 for both).
observed with torcetrapib 60 mg (−8.1%) and 90 mg (−16.5%; p < 0.01) (Table 2, Fig. 3). At these doses, LDL-C decreases were accompanied by significant (p < 0.01) decreases in apo B-100 levels, suggesting a reduction in the concentration of circulating LDL particles (Table 3). Interestingly, LDL-C lowering with torcetrapib was less apparent in subjects with high baseline triglycerides (>150 mg/dl) compared with those with low baseline triglycerides <150 mg/dl (Table 4).

Nuclear magnetic resonance analysis demonstrated a trend to reduction in the concentration of the small LDL-C subclass. Torcetrapib 60 mg and 90 mg decreased small LDL-C (18.3 to 19.7 nm) from 35.6 (SD ± 39.5) to 11.9 mg/dl (SD ± 17.3) and from 42.1 (SD ± 44.2) to 10.3 mg/dl (SD ± 12.0), respectively (p = NS for both). Nuclear magnetic resonance spectroscopy showed LDL particle size was increased in a dose-dependent manner. Torcetrapib 60 mg and 90 mg increased mean LDL particle size from 20.4 (±0.7) to 21.2 nm (±0.6) and 20.4 (±0.7) to 21.3 nm (±0.6), respectively (p ≤ 0.0001 for both).

Very low-density lipoprotein cholesterol levels showed a dose-responsive decrease from baseline, with a maximal change of −25% with torcetrapib 90 mg at week 8. Very low-density lipoprotein cholesterol phospholipid levels, triglyceride levels, and subclass sizing patterns did not demonstrate any consistent dose-related trends.

Changes in non–HDL-C levels at week 8 were consistent with changes in apo B-100 levels (Table 3).

TOTAL CHOLESTEROL, TRIGLYCERIDES, AND LIPID RATIOS. There were no appreciable changes in total cholesterol.
levels. Total triglyceride levels were generally decreased in torcetrapib-treated subjects relative to placebo, although there was variability in response over course of the study (Table 2). Dose-related decreases in the LDL-C/HDL-C ratio (Table 2, Fig. 4) and the apo B-100/apo A-I ratio (Table 2) were consistent with the observed decreases in LDL-C and increases in HDL-C.

SAFETY AND TOLERABILITY. Torcetrapib was generally well tolerated (Table 5). Treatment-related discontinuations were rare. Two subjects withdrew from the study permanently: 1 because of severe diarrhea and vomiting that resolved following permanent discontinuation from treatment (torcetrapib 30 mg/day) and 1 because of mild asymptomatic abnormal liver function tests that resolved without intervention following discontinuation from treatment (placebo). Two subjects receiving torcetrapib 90 mg/day withdrew from the study temporarily because of treatment-related AEs (gastroesophageal reflux disease and rash) but resumed treatment and completed the study without recurrence of the AE.

The incidence of all-causality AEs was similar across placebo and torcetrapib treatment groups, with no evidence of a dose–related response (Table 5). Most treatment-
related AEs were mild or moderate, with headache, diarrhea, and flatulence being the most common. There were no treatment-related serious AEs or deaths.

Laboratory test abnormalities showed no dose-related trends. One subject receiving placebo demonstrated elevated liver transaminase levels (alanine aminotransferase/aspartate aminotransferase >3.0 × upper limits of normal [ULN]) and was withdrawn from treatment. No subject had creatine kinase elevations >10.0 × ULN (Table 5).

Although in some treatment groups at Week 8 there were elevations from baseline in systolic and diastolic blood pressure (SBP and DBP), over the course of the study, changes from baseline in SBP and DBP were highly variable in all treatment groups, with no evidence of a dose-response relationship with torcetrapib (Fig. 5). When all follow-up measures were averaged, mean SBP changes ranged from 0.2 mm Hg (placebo group) to 1.3 mm Hg (torcetrapib 60-mg group), with none of the changes in any group achieving statistical significance (all 95% CIs overlapped zero) (Table 6). Mean DBP changes ranged from −0.7 mm Hg (torcetrapib 10-mg group) to 0.9 mm Hg (torcetrapib 60-mg group); again, no change in any group was significant (Table 6).

Of the patients receiving torcetrapib, 1.6% (2 of 129) experienced elevations in blood pressure defined as 1) SBP ≥15 mm Hg or DBP ≥10 mm Hg from baseline at 3 consecutive visits or 2) SBP ≥180 mm Hg with a ≥20 mm Hg change from baseline or DBP ≥105 mm Hg with a ≥15 mm Hg change from baseline at a single visit. No subject permanently discontinued treatment because of elevated blood pressure.

**DISCUSSION**

This study provides further information about the lipid-modifying benefits and safety of torcetrapib. In individuals with low HDL-C levels, torcetrapib 30 to 90 mg/day resulted in substantial and significant dose-dependent elevations in HDL-C (54.5% at 90-mg dose). These changes in HDL and LDL are consistent with prior reports of torcetrapib (12,13).

Of importance, albeit post-hoc and in non-randomized subgroups, was the observation that LDL-C lowering with torcetrapib was almost completely lost in subjects with high baseline triglyceride levels. This suggests that CETP inhibition may be of limited utility as a monotherapy in those with high triglycerides (a highly prevalent concurrent presentation in those with low HDL and/or metabolic syndrome) requiring LDL lowering. One explanation may be that compositional changes in VLDL-1, in the presence of CETP inhibition, may lead to enhanced conversion of VLDL to LDL via lipoprotein lipase. Without corresponding up-regulation in LDL receptor activity, there may be an

<table>
<thead>
<tr>
<th>Torcetrapib (mg/day)</th>
<th>10</th>
<th>30</th>
<th>60</th>
<th>90</th>
</tr>
</thead>
<tbody>
<tr>
<td>TG ≤150 mg/dl</td>
<td>0.8 (−9.5, 11.1)</td>
<td>−2.9 (−14.0, 8.3)</td>
<td>−22.2 (−32.7, −11.6)*</td>
<td>−32.9 (−44.3, −21.4)*</td>
</tr>
<tr>
<td>n</td>
<td>13</td>
<td>10</td>
<td>12</td>
<td>9</td>
</tr>
<tr>
<td>TG &gt;150 mg/dl</td>
<td>−1.5 (−14.1, 11.0)</td>
<td>6.8 (−5.6, 19.2)</td>
<td>0.1 (−12.0, 12.2)</td>
<td>−10.3 (−22.2, 1.5)</td>
</tr>
<tr>
<td>n</td>
<td>19</td>
<td>20</td>
<td>22</td>
<td>24</td>
</tr>
</tbody>
</table>

*p ≤ 0.0001.

Abbreviations as in Table 2.
inability to clear the rapidly generated LDL. Statin therapy may resolve this issue, which would support strategies to administer torcetrapib with a statin.

Ultracentrifugation/precipitation analysis conducted during this study suggests that torcetrapib affects both the number and size of circulating HDL and LDL particles. Increases in the levels of apo A-I and A-II and increases in HDL2 and HDL3 cholesterol are indicative of increased numbers of the larger subspecies of HDL particles. This was confirmed by NMR HDL subclass analysis. Conversely, decreases in apo B are indicative of a reduction in the number of circulating LDL particles. Nuclear magnetic resonance analysis showed that torcetrapib also increased the size of LDL particles.

The effect of torcetrapib on LDL particle size may be particularly important in reducing atherosclerosis, as the characteristics of small dense LDL make it more atherogenic than larger, less dense LDL (5). Even if there was no significant effect of torcetrapib on HDL-C levels, the effects on LDL-C, including modest decreases in overall levels and a shift in particle size from small to large, might be expected to provide benefit.

In addition to further elucidating the beneficial effects of torcetrapib on lipid metabolism, this trial provides important safety data. Generally, torcetrapib was well tolerated, discontinuations from treatment were rare, there were no apparent dose-related trends in the incidences of AEs, and most AEs were mild or moderate in nature. Although previously published studies of torcetrapib have not reported effects on blood pressure (12,13), increases in blood pressure were observed in some individuals in this study. However, the lack of a consistent treatment-related pattern over time and dose suggests the effect to be of limited magnitude within this dose range. Further studies are underway to define the magnitude and clinical relevance of these blood pressure changes.

The link between lower LDL-C levels and decreased cardiovascular risk has been clearly demonstrated in CVD prevention trials with statins (18). Furthermore, recent statins trials provide evidence that aggressive versus moderate LDL lowering is associated with additional benefits (19,20). Yet there is less clinical trial data showing the benefits of increasing HDL-C levels and a distinct paucity of clinical trial data to show the impact of aggressively elevating HDL-C on clinical end points. This may partly be due to the current lack of well-tolerated drugs that can substantially increase HDL-C (21). Thus, although current

### Table 5. Summary of Safety—Number of Subjects (%)

<table>
<thead>
<tr>
<th>Treatment-related withdrawals</th>
<th>Placebo (n = 32)</th>
<th>10 mg (n = 32)</th>
<th>30 mg (n = 31)</th>
<th>60 mg (n = 34)</th>
<th>90 mg (n = 33)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subjects with AEs</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All-causality</td>
<td>24 (75)</td>
<td>19 (59)</td>
<td>19 (61)</td>
<td>22 (65)</td>
<td>18 (55)</td>
</tr>
<tr>
<td>Treatment related</td>
<td>6 (19)</td>
<td>8 (25)</td>
<td>6 (19)</td>
<td>4 (12)</td>
<td>7 (21)</td>
</tr>
<tr>
<td>Serious AEs</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All-causality</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>1 (3)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Treatment related</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
</tbody>
</table>

Both subjects were only temporarily discontinued from treatment and completed the study.

AEs = adverse events; ALT = alanine aminotransferase; AST = aspartate aminotransferase; CK = creatine kinase; ULN = upper limit of normal.

**Figure 5.** Least-squares mean change in systolic (A) and diastolic (B) blood pressure over the course of the study.
guidelines for CVD prevention recognize low HDL-C levels as a risk factor, they continue to place most emphasis on decreasing LDL-C levels (22). This fact, combined with the relatively modest decreases in LDL-C observed with torcetrapib and JTT-705, means that CETP inhibitors are likely to be used in combination with statin therapy. A separate phase 2 study evaluating the efficacy and safety of torcetrapib when administered on a background of atorvastatin to subjects with below-average HDL-C levels is reported in this issue of the Journal.

Acknowledgments
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