Cholesteryl Ester Transfer Protein Inhibition, High-Density Lipoprotein Raising, and Progression of Coronary Atherosclerosis: Insights From ILLUSTRATE (Investigation of Lipid Level Management Using Coronary Ultrasound to Assess Reduction of Atherosclerosis by CETP Inhibition and HDL Elevation)

Stephen J. Nicholls, E. Murat Tuzcu, Danielle M. Brennan, Jean-Claude Tardif and Steven E. Nissen

Circulation. 2008;118:2506-2514; originally published online November 24, 2008;
doi: 10.1161/CIRCULATIONAHA.108.790733
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231

Print ISSN: 0009-7322. Online ISSN: 1524-4539

Cholesteryl Ester Transfer Protein Inhibition, High-Density Lipoprotein Raising, and Progression of Coronary Atherosclerosis

Insights From ILLUSTRATE (Investigation of Lipid Level Management Using Coronary Ultrasound to Assess Reduction of Atherosclerosis by CETP Inhibition and HDL Elevation)

Stephen J. Nicholls, MBBS, PhD; E. Murat Tuzcu, MD; Danielle M. Brennan, MS; Jean-Claude Tardif, MD; Steven E. Nissen, MD

Background—Despite favorable effects on high-density lipoprotein cholesterol (HDL-C) and low-density lipoprotein cholesterol, the cholesteryl ester transfer protein inhibitor torcetrapib failed to slow atherosclerosis progression and increased mortality. We investigated the relationship between lipid changes and progression of coronary atherosclerosis.

Methods and Results—Intravascular ultrasound was performed at baseline and follow-up in 910 participants randomized to torcetrapib/atorvastatin or atorvastatin monotherapy. The relationship between changes in lipoprotein levels and the primary intravascular ultrasound end point, change in percent atheroma volume, was investigated. Compared with atorvastatin monotherapy, torcetrapib raised HDL-C by 61%, lowered low-density lipoprotein cholesterol by 20%, raised serum sodium (0.44±0.14 mmol/L, $P=0.02$), and lowered serum potassium (0.11±0.02 mmol/L, $P<0.0001$). Despite substantial increases in HDL-C, no effect was found of torcetrapib on percent atheroma volume. In torcetrapib-treated patients, an inverse relationship was observed between changes in HDL-C and percentage atheroma volume ($r=-0.17$, $P<0.001$). Participants with regression had greater increases in HDL-C (mean±SE, 62.9±37.4% versus 54.0±39.1%, $P=0.002$). Compared with the lowest quartile, torcetrapib-treated patients in the highest quartile of HDL-C change showed the least progression (−0.31±0.27 versus 0.88±0.27%, $P=0.001$). The highest on-treatment HDL-C quartile showed significant regression of percent atheroma volume (−0.69±0.27%, $P=0.01$). In multivariable analysis, changes in HDL-C levels independently predicted the effect on atherosclerosis progression ($P=0.001$).

Conclusions—The majority of torcetrapib-treated patients demonstrated no regression of coronary atherosclerosis. Regression was only observed at the highest HDL-C levels. Torcetrapib raised serum sodium and lowered potassium, consistent with an aldosterone-like effect, which may explain the lack of favorable effects in the full study cohort. Accordingly, other cholesteryl ester transfer protein inhibitors, if they lack this off-target toxicity, may successfully slow atherosclerosis progression. **(*Circulation*. 2008;118:2506-2514.)**

Key Words: atherosclerosis ■ high-density lipoprotein cholesterol ■ ultrasonics ■ torcetrapib

Although inhibition of cholesteryl ester transfer protein (CETP) substantially increases levels of high-density lipoprotein cholesterol (HDL-C) and has favorable effects on levels of low-density lipoprotein cholesterol (LDL-C), recent imaging studies failed to demonstrate that CETP inhibition with the investigational agent torcetrapib slows atherosclerosis progression in the coronary or carotid arteries.[1–3] A large morbidity–mortality trial studying torcetrapib was terminated prematurely after the data safety monitoring committee reported a significant increase in all-cause mortality.[4] Subsequently, the company developing torcetrapib discontinued all further studies.[5] Although the agent initially developed to inhibit CETP, torcetrapib, substantially increased blood pressure, the mechanism underlying the observed lack of benefit for torcetrapib has not been fully elucidated. Accordingly, uncertainty exists on whether the strategy of CETP inhibition is likely to yield a clinically useful pharmacological agent to raise HDL-C.

Continuing medical education (CME) credit is available for this article. Go to http://cme.ahajournals.org to take the quiz.

Received May 5, 2008; accepted September 12, 2008.

From the Departments of Cardiovascular Medicine (S.J.N., E.M.T., D.M.B., S.E.N.) and Cell Biology (S.J.N.), Cleveland Clinic, Cleveland, Ohio; and Montreal Heart Institute (J.-C.T.), Montreal, Quebec, Canada.

The online-only Data Supplement is available with this article at http://circ.ahajournals.org/cgi/content/full/CIRCULATIONAHA.108.790733/DC1.

Clinical trial registration information—URL: http://www.clinicaltrials.gov. Unique identifier: NCT00134173.

Correspondence to Stephen Nicholls, Department of Cardiovascular Medicine, Cleveland Clinic, Mail Code JJ-65, 9500 Euclid Ave, Cleveland, OH 44195. E-mail nichols1@ccf.org

Circulation **is available at http://circ.ahajournals.org** **DOI: 10.1161/CIRCULATIONAHA.108.790733**

Editorial p 2491
Clinical Perspective p 2514

Two principal explanations for the failure of torcetrapib have been proposed. One hypothesis suggests that the HDL particles generated by CETP inhibition do not participate in reverse cholesterol transport or possess other protective properties.[6] Alternatively, the specific agent tested in initial studies, torcetrapib, may have unique toxicity that counterbalances any antiatherosclerotic benefits arising from increasing HDL-C levels via CETP inhibition. The Investigation of Lipid Level management USing coronary ultrasound To assess Reduction of ATherosclerosis by CETP inhibition and HDL Elevation (ILLUSTRATE) trial assessed the effects of torcetrapib on the rate of progression of coronary atherosclerosis using intravascular ultrasonography (IVUS).[1] In the present post hoc analysis, we sought to characterize the relationship between changes in lipid parameters and changes in atheroma burden in the ILLUSTRATE trial. In particular, we sought to determine whether increasing HDL-C with torcetrapib was associated with a beneficial effect, a detrimental effect, or no effect on disease progression. An increase in disease progression at higher levels of HDL-C would support the concept that CETP inhibition has an adverse impact on the protective properties of HDL. In contrast, a reduction in disease progression at higher levels of HDL-C would support the concept that HDL particles retain some degree of functionality in the setting of CETP inhibition. The objective of the analysis was to help answer the question, was the failure of torcetrapib related to the "molecule" or the "mechanism of action?"

Methods

ILLUSTRATE Study Protocol

The details of the ILLUSTRATE protocol have been described previously.[1] After titration of atorvastatin to achieve a target LDL-C level $<100\pm15$ mg/dL (mean±SE; average dose 23 mg), patients were randomized to additional treatment with either torcetrapib 60 mg daily or placebo. IVUS images were acquired within a matched arterial segment at baseline and after 24 months of treatment. The leading edges of the external elastic membrane and lumen were defined by manual planimetry in images spaced precisely 1 mm apart. Atheroma area was calculated as the difference between areas occupied by the external elastic membrane and lumen. Percent atheroma volume (PAV) was determined as the sum of plaque areas for all cross sections divided by the sum of the external elastic membrane areas for these same cross sections.[7] Biochemical and blood pressure measurements were performed 1 month after baseline and then at 3-month intervals.

Statistical Analysis

For the purpose of the present analysis, only subjects who underwent ultrasonic imaging at both baseline and follow-up were included. Consistent with the primary report,[1] follow-up biochemical parameters were determined as the last observation carried forward, and blood pressure was reported as the average of all measures obtained during the treatment period. In the case of missing values (14% of samples), the nearest postbaseline result was used in the analysis. Student t tests (or Wilcoxon rank sum tests for nonnormally distributed data) and χ^2 tests were performed to assess differences across study groups for continuous and categorical variables, respectively. Changes from baseline to follow-up within each treatment group were compared by 1-sample t tests (or Wilcoxon signed rank tests for nonnormally distributed data). Locally weighted scatterplot smoothing (LOWESS) plots were used to depict the relationship between changes in PAV, after controlling for baseline values, and both achieved levels of and percentage change in HDL-C in each treatment group. Spearman correlation coefficients were calculated to assess the relationship between achieved levels or changes in levels of biochemical parameters and the change in PAV. Relationships between changes in imaging end points and changes in HDL-C were also described by quartiles within each treatment group. Linear regression models were used to calculate least squares means of changes in PAV, controlling for the baseline value, in patients stratified according to the level of achieved HDL or its percentage change.

A multivariable linear regression model was performed to determine the independent predictors of changes in PAV in patients treated with torcetrapib. This model incorporated all univariate predictors of changes in PAV (geographic region, atorvastatin dose, baseline PAV, percent change in HDL cholesterol, and black race). Changes in systolic blood pressure and potassium were also included in the multivariable model. All analyses were performed with SAS version 8.2 (SAS Institute, Inc, Cary, NC). $P<0.05$ was considered significant.

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.

Table 1. Baseline Characteristics

Parameter	Atorvastatin–Placebo (n=446)	Atorvastatin–Torcetrapib (n=464)
Age, y, mean±SE	57.4±9.0	56.8±9.1
Male, %	71.5	71.3
White race, %	92.2	91.6
Body mass index, kg/m^2, mean±SE	30.2±5.0	30.5±5.9
Diabetes mellitus, %	21.1	18.8
Hypertension, %	75.3	74.4
Metabolic syndrome, %	44.0	42.7
Current smoker, %	15.9	16.2
Previous myocardial infarction, %	24.4	26.5
Previous percutaneous intervention, %	26.9	27.4
Previous bypass grafting, %	4.9	2.4
Baseline statin use, %	91.0	91.4
β-Blocker use, %	74.7	75.9
ACE inhibitor use, %	51.8	55.6
Aspirin use, %	94.6	93.3

Baseline clinical characteristics and concomitant medications by treatment group. ACE indicates angiotensin-converting enzyme.

Results

Changes in Biochemical Parameters and Atheroma Burden

Clinical characteristics, biochemical parameters, and measures of atheroma burden at baseline and follow-up are summarized in Tables 1 and 2. In patients treated with torcetrapib plus atorvastatin, LDL-C decreased from 83.1 to 70.3 mg/dL ($P<0.001$), and HDL-C increased from 46.0 to 72.3 mg/dL ($P<0.001$). In patients treated with atorvastatin monotherapy, LDL-C increased from 84.3 to 88.1 mg/dL

Table 2. Biochemical Parameters and PAV at Baseline and 24-Month Follow-Up in Patients by Treatment Group

Parameter	Atorvastatin + Placebo (n=446)			Atorvastatin + Torcetrapib (n=464)			*P* Between Treatment Groups at Follow-Up
	Baseline	Follow-Up	*P*	Baseline	Follow-Up	*P*	
Total cholesterol, mg/dL	157.5±27.1	158.9±32.9	0.81	157.8±27.6	167.4±36.4	<0.001	0.001
LDL-C, mg/dL	84.3±18.9	88.1±23.2	<0.001	83.1±19.7	70.3±24.6	<0.001	<0.001
HDL-C, mg/dL	45.2±11.2	43.8±12.1	<0.001	46.0±12.8	72.3±24.4	<0.001	<0.001
Triglycerides, mg/dL*	123.9 (89.0–170.0)	116.5 (79.7–164.0)	<0.001	122.0 (88.5–179.0)	102.0 (73.0–150.2)	<0.001	0.005
LDL/HDL ratio*	1.9 (1.6–2.2)	2.1 (1.7–2.5)	<0.001	1.9 (1.5–2.3)	0.9 (0.7–1.3)	<0.001	<0.001
ApoB, mg/dL	73.0±15.2	74.2±17.1	0.51	73.5±15.6	64.1±15.8	<0.001	<0.001
ApoA-I, mg/dL	122.2±20.9	124.0±21.2	0.08	123.0±23.4	153.7±30.6	<0.001	<0.001
ApoB/A-I*	0.6 (0.5–0.7)	0.6 (0.5–0.7)	0.60	0.6 (0.5–0.7)	0.4 (0.3–0.5)	<0.001	<0.001
CRP, mg/L*	1.8 (0.9–3.4)	1.5 (0.7–3.0)	0.001	2.1 (1.0–4.1)	1.9 (0.8–4.2)	0.02	0.02
Potassium, mmol/L	4.25±0.41	4.27±0.30	0.08	4.22±0.37	4.14±0.32	<0.001	<0.001
Sodium, mmol/L	139.8±2.6	139.6±1.6	0.03	139.7±2.6	139.9±1.8	0.005	0.006
PAV	37.1±8.5	37.3±8.8	0.09	37.0±8.6	37.1±8.6	0.36	0.92

Values are expressed as mean±SE unless otherwise indicated. CRP indicates C-reactive protein.
*Median (interquartile range).

(*P*<0.001), and HDL-C decreased from 45.2 to 43.8 mg/dL (*P*<0.001). This resulted in a reduction in the LDL-C/HDL-C ratio from 1.9 to 0.9 in the torcetrapib-plus-atorvastatin treatment group (*P*<0.001) and an increase from 1.9 to 2.1 with atorvastatin monotherapy (*P*<0.001). Median levels of C-reactive protein decreased from 1.8 to 1.5 mg/L with atorvastatin monotherapy (*P*=0.001) and from 2.1 to 1.9 mg/L with torcetrapib plus atorvastatin (*P*=0.02). In patients treated with torcetrapib plus atorvastatin, sodium increased from 139.7 to 139.9 mmol/L (*P*=0.005), and potassium decreased from 4.22 to 4.14 mmol/L (*P*<0.001). In contrast, atorvastatin monotherapy was associated with a reduction in sodium from 139.8 to 139.6 mmol/L (*P*=0.03) and no change in potassium levels. Thus, compared with atorvastatin monotherapy, torcetrapib raised sodium (0.44±0.14 mmol/L, *P*=0.02) and lowered potassium (0.11±0.02 mmol/L, *P*<0.0001). Administration of torcetrapib plus atorvastatin did not have a beneficial impact on disease progression, with no significant changes in PAV from baseline to follow-up observed in either treatment group.

Relationship Between Changes in Biochemical Parameters and Atheroma Burden

The relationships between both baseline levels of and changes in biochemical parameters and changes in PAV are summarized in Table 3 and Figure 1. A significant correlation was observed between baseline levels of both triglycerides and apolipoprotein (apo) B and the change in PAV in both treatment groups. In patients treated with atorvastatin monotherapy, significant correlations were observed between the change in PAV and achieved levels of both triglycerides and the ratio of apoB to apoA-I. In contrast, patients treated with torcetrapib/atorvastatin showed significant correlations between the change in PAV and the achieved levels of HDL-C, change in HDL-C levels, apoA-I, and the LDL-C/HDL-C ratio (Table 3). Figure 1 shows the continuous relationship

Table 3. Correlation Coefficients Between Various Measures of Lipoprotein Levels and Change in PAV

Parameter	Baseline Levels				Absolute Change Levels				Percent Change Levels			
	Atorvastatin + Placebo (n=446)		Atorvastatin + Torcetrapib (n=464)		Atorvastatin + Placebo (n=446)		Atorvastatin + Torcetrapib (n=464)		Atorvastatin + Placebo (n=446)		Atorvastatin + Torcetrapib (n=464)	
	r	*P*	*r*	*P*	*r*	*P*	*r*	*P*	*r*	*P*	*r*	*P*
HDL-C	−0.04	0.47	−0.02	0.73	−0.03	0.54	−0.18	<0.001	−0.04	0.46	−0.17	<0.001
LDL-C	0.04	0.36	0.04	0.39	−0.03	0.59	0.05	0.34	−0.03	0.58	0.06	0.20
Triglycerides	0.12	0.009	0.16	<0.001	0.05	0.29	−0.02	0.63	0.07	0.12	0.01	0.92
Total cholesterol	0.06	0.19	0.13	0.007	0	0.95	−0.07	0.13	0	0.93	−0.08	0.11
LDL/HDL ratio	0.08	0.10	0.05	0.33	−0.01	0.88	0.09	0.05	−0.02	0.75	0.14	0.003
ApoB	0.09	0.05	0.17	<0.001	−0.01	0.83	−0.02	0.63	−0.01	0.89	−0.01	0.81
ApoA-I	0.02	0.67	0.01	0.83	−0.06	0.24	−0.16	<0.001	−0.05	0.29	−0.15	0.002
ApoB/apoA-I ratio	0.06	0.20	0.13	0.004	0.04	0.47	0.02	0.70	0.04	0.41	0.08	0.11
CRP	0.10	0.03	0.03	0.48	−0.03	0.54	−0.18	<0.001	0	0.93	0.02	0.68

CRP indicates C-reactive protein.

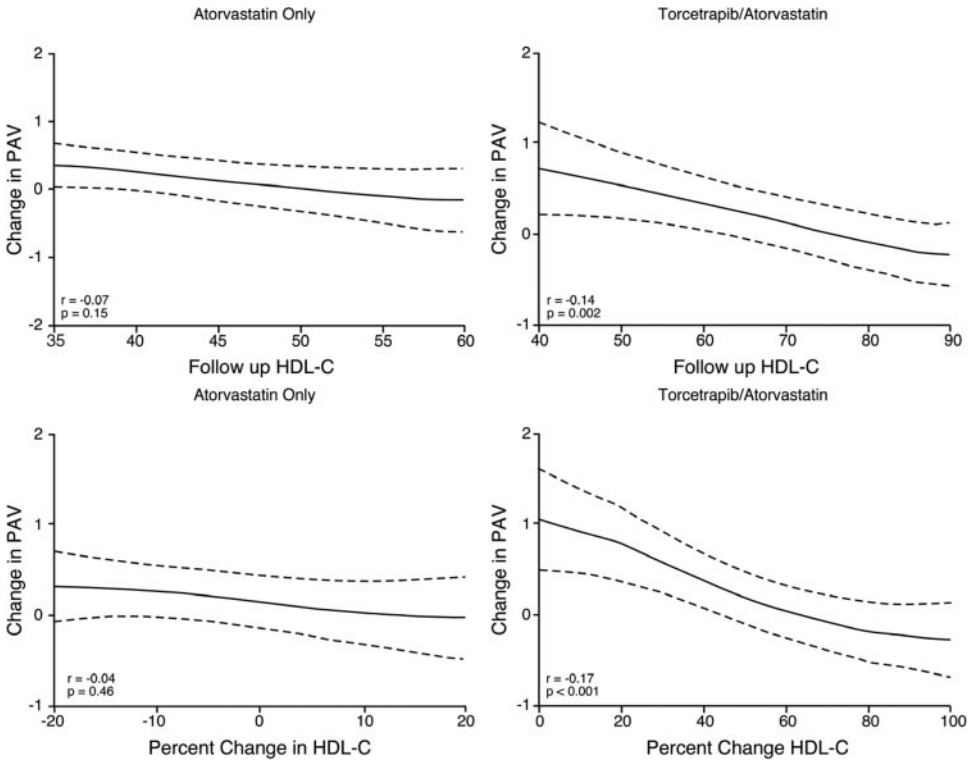


Figure 1. Locally weighted scatterplot smoothing (LOWESS) scatterplots illustrating the relationship between change in PAV, after controlling for the baseline value, and either follow-up level of HDL-C (top, in mg/dL) or percentage change in HDL-C (bottom), stratified according to treatment group.

between absolute HDL-C levels or change in HDL-C levels and the rate of disease progression by IVUS. This relationship is apparent in the torcetrapib-treated group but not the atorvastatin monotherapy group.

Biochemical Parameters and Regression Versus Progression

Biochemical parameters in patients experiencing regression or progression of atherosclerosis (decrease or increase in PAV, respectively) are summarized in Table 4. No significant differences were observed between regressors and progressors treated with atorvastatin monotherapy. In contrast, patients treated with torcetrapib plus atorvastatin who experienced regression had greater increases in HDL-C ($P=0.0002$) and apoA-I ($P=0.01$) and greater decreases in the LDL-C/HDL-C ratio ($P=0.02$) than patients who experienced progression. Lower baseline levels of triglyceride and greater increases in HDL-C were associated with an increase in the proportion of patients in the torcetrapib/atorvastatin group who underwent any degree of plaque regression (online-only Data Supplement Table). Changes in levels of apoB-containing lipoproteins did not predict the likelihood of regression or progression.

HDL-C and Changes in Atheroma Burden

The relationship between HDL-C and changes in atheroma burden is further illustrated in Figures 2 through 4. Despite considerable increases in HDL-C with torcetrapib, only patients who achieved the highest levels of HDL-C or the greatest percentage increase had regression of PAV (Figures 3 and 4). Interestingly, no relationship was observed between either achieved levels or percentage change in LDL-C and disease progression (online-only Data Supplement Figures I and II). No relationship between achieved levels ($P=0.57$ for trend) or changes ($P=0.26$ for trend) in HDL-C and cardiovascular events was observed in torcetrapib-treated subjects, although the study was not powered to assess clinical outcomes. The lack of efficacy of torcetrapib in the entire study population is further supported by the observation of a greater degree of disease progression at all but the highest levels of HDL-C when stratified according to HDL-C quartiles in the entire cohort (Figure 4). With multivariable analysis, independent predictors of the change in PAV in patients taking torcetrapib included the percentage increase in HDL-C ($P=0.001$), atorvastatin dose ($P=0.02$), baseline PAV ($P=0.0003$), and black race ($P=0.02$). Of interest, the change in systolic blood pressure was not a significant independent predictor of the change in PAV ($P=0.08$), nor were change in triglycerides ($P=0.51$) or change in potassium ($P=0.28$; Table 5). Multivariable analysis of both treatment groups combined revealed an interaction between treatment, percent change in HDL-C, and change in PAV ($P=0.08$) that was not affected by inclusion of baseline HDL-C in the model ($P=0.09$).

Discussion

Although torcetrapib treatment failed to slow the overall progression of coronary disease in the ILLUSTRATE trial, the current post hoc analysis demonstrated an inverse relationship between the extent of HDL-C increases with torce-

Table 4. Biochemical Parameters at Baseline and Follow-Up and Their Percentage Change in Patients Who Underwent Plaque Regression or Progression (Decrease or Increase in PAV, Respectively), Stratified According to Treatment Group

	Atorvastatin (n=446)			Atorvastatin + Torcetrapib (n=464)		
Parameter	Regression	Progression	*P*	Regression	Progression	*P*
Total cholesterol, mg/dL						
Baseline	156.7±27.2	158.2±27.1	0.58	154.4±27.0	161.1±27.7	0.007
Follow-up	157.9±31.2	159.7±34.3	0.73	165.8±35.2	169.0±37.5	0.57
Percentage change	1.9±18.7	1.9±17.8	0.96	8.4±21.6	6.1±20.8	0.25
LDL-C, mg/dL						
Baseline	84.6±20.0	84.1±17.9	0.77	82.2±19.3	84.0±20.1	0.34
Follow-up	88.0±23.8	88.1±22.7	0.92	69.4±25.8	71.2±23.4	0.17
Percentage change	6.1±26.0	6.4±24.1	0.85	−13.6±33.8	−12.4±31.6	0.23
HDL-C, mg/dL						
Baseline	45.7±11.9	44.8±10.6	0.51	45.7±11.7	46.3±13.8	0.92
Follow-up	44.7±12.4	43.0±11.7	0.10	74.1±23.5	70.5±25.3	0.02
Percentage change	−1.0±19.4	−3.0±18.0	0.19	62.9±37.4	54.0±39.1	0.002
Triglycerides, mg/dL*						
Baseline	117.5 (82.0, 165.0)	130.0 (92.0, 179.5)	0.11	111.0 (85.0, 161.0)	134.8 (96.5, 196.0)	0.001
Follow-up	105.0 (79.7, 152.0)	126.0 (81.0, 170.0)	0.05	92.0 (70.0, 141.0)	112.5 (79.7, 162.0)	0.001
Percentage change	−9.2 (−26.4, 14.3)	−5.9 (−25.3, 17.1)	0.41	−14.2 (−35.7, 7.6)	−15.1 (−40.6, 11.1)	0.82
LDL-C/HDL-C*						
Baseline	1.9 (1.6, 2.2)	2.0 (1.6, 2.2)	0.62	1.8 (1.5, 2.2)	1.9 (1.5, 2.3)	0.34
Follow-up	2.0 (1.7, 2.4)	2.1 (1.7, 2.6)	0.20	0.9 (0.7, 1.2)	1.0 (0.7, 1.5)	0.02
Percentage change	6.2 (−7.4, 25.7)	7.8 (−6.1, 25.9)	0.40	−51.3 (−61.5, −35.2)	−46.1 (−59.3, −25.0)	0.02
ApoB, mg/dL						
Baseline	72.1±14.8	73.8±15.6	0.26	71.2±15.1	75.8±15.8	0.004
Follow-up	73.3±16.1	74.9±17.8	0.50	62.3±15.6	65.9±15.8	0.01
Percentage change	3.2±21.5	3.4±24.0	0.77	−10.4±25.5	−11.4±21.0	0.56
ApoA-I, mg/dL						
Baseline	122.0±21.1	122.4±20.8	0.74	122.2±23.0	123.7±23.9	0.70
Follow-up	125.4±21.1	122.8±21.1	0.13	156.2±30.5	151.1±30.4	0.03
Percentage change	3.6±15.3	1.4±14.4	0.10	28.8±21.2	23.7±20.8	0.01
ApoB/A-I*						
Baseline	0.6 (0.5, 0.7)	0.6 (0.5, 0.7)	0.52	0.6 (0.5, 0.7)	0.6 (0.5, 0.7)	0.02
Follow-up	0.6 (0.5, 0.7)	0.6 (0.5, 0.7)	0.08	0.4 (0.3, 0.5)	0.4 (0.4, 0.5)	0.002
Percentage change	−2.3 (−12.8, 10.1)	−1.9 (−10.9, 13.6)	0.31	−34.0 (−41.8, −20.5)	−28.9 (−41.2, −17.2)	0.08

*Median (interquartile range). Values are expressed as mean±SE or % (interquartile values).

trapib treatment and the rate of atherosclerosis progression as determined by IVUS. In particular, regression, not accelerated progression, of atherosclerosis was observed in those patients who achieved the highest levels of HDL-C with torcetrapib. Furthermore, the majority of patients in the lowest 3 quartiles of HDL-C did not undergo disease regression. These post hoc exploratory data support the concept that despite the failure of torcetrapib to slow disease progression, the achievement of very high levels of HDL-C via CETP inhibition has the potential to generate functional HDL particles that participate in reverse cholesterol transport. Accordingly, the concept of CETP inhibition as a means to limit coronary atherosclerosis may remain a potentially viable strategy that requires further study. These findings provide useful insights into the failure of torcetrapib and suggest that the absence of benefit may reflect molecule-specific toxicity rather than a mechanism-based failure of this pharmacological approach to elevation of HDL-C levels. However, it remains to be demonstrated conclusively that inhibition of CETP does not result in either cardiac or noncardiac toxicity. Nonetheless, other CETP inhibitors may succeed where torcetrapib failed.

Although torcetrapib substantially increases blood pressure, this was not an independent predictor of the change in atheroma burden. Neither ILLUSTRATE nor the prematurely terminated clinical events trial reported an increased rate of stroke,[1,5] which is generally considered very sensitive to the effects of blood pressure changes. These observations suggest that the blood pressure increase is unlikely to be the principal explanation for the lack of an antiatherosclerotic benefit. It

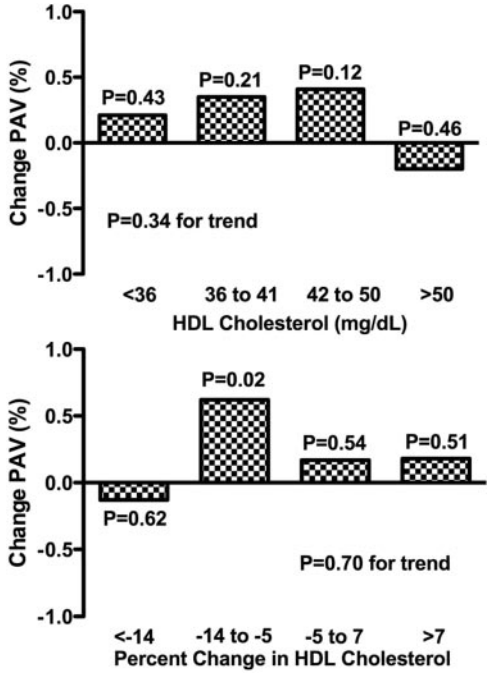


Figure 2. Least squares mean change in PAV, after controlling for the baseline value, in atorvastatin monotherapy–treated subjects according to quartile of achieved level (top) and percentage change (bottom) of HDL-C. *P* values above and below bars for comparison between baseline and follow-up.

appears more likely that torcetrapib has some other toxicity that mitigated any beneficial effect of substantial increases in HDL-C levels. This is further supported by the finding that the numerical rate of progression was greater in patients

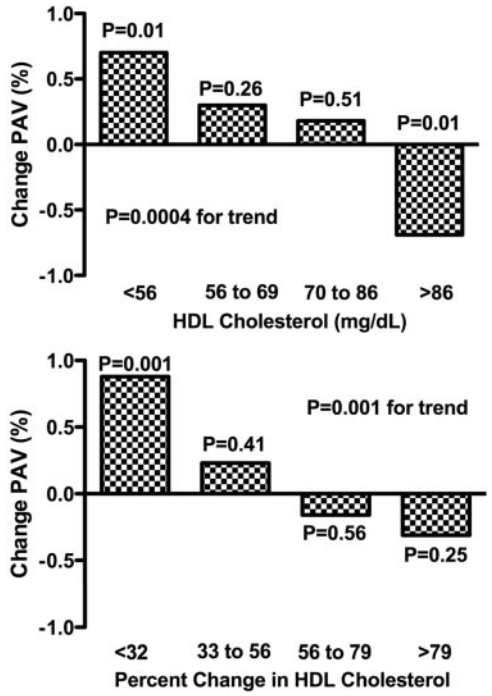


Figure 3. Least squares mean change in PAV, after controlling for the baseline value, in torcetrapib/atorvastatin-treated subjects according to quartile of achieved level (top) and percentage change (bottom) of HDL-C. *P* values above bars for comparison between baseline and follow-up.

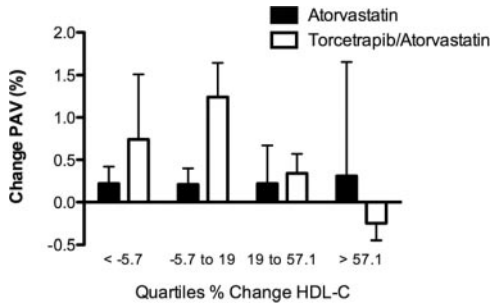


Figure 4. Least squares mean±SEM change in PAV, after controlling for the baseline value, in patients treated with either atorvastatin monotherapy (solid bars), or torcetrapib/atorvastatin (open bars), stratified according to quartiles of percentage change in HDL-C in the combined treatment groups.

treated with torcetrapib and atorvastatin, who achieved the least effective rise in HDL-C, and by the fact that the majority of patients at lower HDL-C levels did not regress (online-only Data Supplement Figure III). The observed increases in serum sodium and decreases in serum potassium levels, along with an increase in blood pressure, suggest an increase in aldosterone activity in response to torcetrapib treatment. Preclinical data have recently confirmed that torcetrapib functions as an aldosterone agonist, increasing systemic aldosterone levels.[8]

Increasing evidence implies a role of the renin-angiotensin-aldosterone system in atherosclerosis. Angiotensin II and aldosterone play a major role in blood pressure regulation and possess adverse oxidative and inflammatory effects.[9–13] Furthermore, inhibition of renin-angiotensin-aldosterone system activity retards lesion initiation and progression in animal models of atherosclerosis.[14] Given the observed changes in electrolytes and blood pressure, it now appears plausible that the aldosterone agonist effect of torcetrapib exerted a detrimental influence on atherosclerosis progression. Accordingly, this off-target toxicity may have counteracted any favorable effects derived from substantial increases in HDL-C produced by CETP inhibition.

After the initial description of genetic CETP deficiency,[15,16] the potential for pharmacological inhibition of CETP to benefit patients with atherosclerosis remained controversial. Although it has been long recognized that CETP inhib-

Table 5. Multivariable Analysis Indicating Independent Predictors of Changes in PAV in Patients Treated With the Combination of Torcetrapib and Atorvastatin

Parameter	Estimate (SE)	*P*
Atorvastatin dose	1.111 (0.537)	0.02
Baseline PAV	−0.057 (0.016)	0.0003
Change in HDL-C	−0.012 (0.004)	0.001
Change in LDL-C	0.001 (0.004)	0.74
Change in systolic blood pressure	0.025 (0.014)	0.08
Change in triglyceride	0.001 (0.001)	0.51
Change in potassium	−0.412 (0.384)	0.28
Previous stroke	−1.366 (0.706)	0.05
Black race	1.399 (0.616)	0.02

itors can substantially raise HDL-C levels,[17] considerable speculation has focused on the relative functionality of the HDL particles that are generated.[18] Despite the recent report that the combination of torcetrapib and a statin did not reduce the burden of atherosclerosis in apoE(Leiden)CETP transgenic mice,[19] beneficial effects of strategies that reduce CETP activity have been demonstrated in rabbits, a species that naturally expresses CETP.[20–22] In the present study, we observed that patients with the largest increases in HDL-C and those who achieved the highest systemic levels demonstrated plaque regression. Furthermore, although the plots in Figures 2 and 3 reveal a continuous relationship between changes in HDL-C and PAV in both treatment groups, they show a strong inverse slope only within the torcetrapib-treated subgroup. These data provide evidence that substantially raising HDL-C levels via CETP inhibition has the potential to slow or reverse coronary atheroma progression. Accordingly, the failure of torcetrapib to slow disease progression does not preclude the possibility that an alternative agent in this therapeutic class will result in benefit for patients with atherosclerosis.

The results of the present study have implications for understanding the potential impact of raising HDL-C via CETP inhibition on atherosclerosis in humans. Because the dosage of torcetrapib was limited by this agent's dose-dependent adverse effect on blood pressure, maximal increases in HDL-C could not be explored.[23] Greater CETP inhibition that results in higher HDL-C levels may produce more substantial antiatherosclerotic benefits. This is particularly important given that regression was not observed in the majority of patients in the lowest 3 quartiles of achieved HDL-C levels. Other CETP inhibitors that lack adverse effects on blood pressure or the vasculature can be used to explore greater levels of CETP inhibition. The finding of regression by IVUS for patients with the highest HDL-C elevations increases confidence that a potent CETP inhibitor may favorably affect clinical outcomes.

These observations provide useful insights into the impact of inhibiting CETP on potential HDL-mediated antiatherosclerotic effects in humans. Although some studies in patients with CETP deficiency have shown cardiovascular protection,[24,25] others have reported the presence of atherosclerotic disease in patients with reduced CETP activity,[26,27] although a low prevalence of CHD was observed when HDL-C levels were elevated.[27] Several groups have demonstrated that lipid-depleted forms of HDL are the preferred acceptor of cholesterol effluxed from cells via the ABCA1 transporter.[28,29] This observation raised the possibility that the generation of large, cholesterol-laden particles with CETP inhibition might result in impaired mobilization of cholesterol from macrophages within the vessel wall. However, the subsequent discovery that large HDL particles promote efflux via the ABCG1 transporter suggested that efflux would not be impaired after CETP inhibition.[30] This hypothesis is supported by observations that the efflux activity of HDL[31] and the excretion of fecal sterols[32] are not impaired after administration of torcetrapib in humans and that CETP inhibition does not impair reverse cholesterol transport in a rabbit model.[33] In addition, no evidence currently exists that CETP inhibition has an adverse impact on non–lipid-transporting functions of HDL. It is also of interest that greater disease progression was observed with the combination of torcetrapib and atorvastatin in patients with greater levels of apoB and triglyceride at baseline. This might suggest that CETP inhibition may be less effective or potentially detrimental in this clinical setting, although this requires further investigation with a CETP inhibitor that lacks any off-target toxicity.

Considerable evidence suggests that HDL can protect against the development of atherosclerosis. Observational studies consistently have demonstrated an inverse relationship between HDL-C levels and the subsequent risk of developing coronary heart disease.[34] In animal models of atherosclerosis, an increase in HDL-C levels produces favorable effects on lesion size and composition.[35–40] The greatest benefit of statin therapy typically is observed in patients with the lowest HDL-C levels.[41–43] Modest elevation of HDL-C with statins,[44] fibrates,[45,46] and niacin[47,48] is associated with reduced disease progression and morbidity. Two small studies in humans demonstrated that the infusion of reconstituted HDL promoted rapid regression of coronary atherosclerosis.[49,50] Because relatively modest elevations in HDL-C levels may have contributed to these clinical benefits, considerable interest exists in developing therapies that raise levels more substantially.

A number of limitations of the present exploratory analysis should be noted. Administration of torcetrapib in combination with atorvastatin did not have a beneficial impact on disease progression in the entire cohort. The present analysis is exploratory and describes the relationship between changes in levels of HDL-C and PAV. Although the analysis does not evaluate the functionality of HDL particles directly, the finding of regression and not accelerated progression of disease in patients with the highest level of HDL-C suggests that the ability of particles to mobilize lipids from the artery wall would appear to be preserved. All patients presented for a clinically indicated angiogram and had documented coronary artery disease. It is unknown whether the present findings are applicable in primary prevention. It is uncertain whether substantial elevation of HDL-C with CETP inhibitors has a favorable impact on plaque composition, which may represent an important determinant of atheroma rupture. The translation of beneficial changes on IVUS to improved clinical outcome remains to be defined. As a result, it cannot be assumed that regression associated with substantial HDL-C elevations will result in improved clinical outcome. Nonetheless, the findings highlight the ability of IVUS to provide mechanistic insights into the impact of medical therapies on both atherosclerotic plaque and associated arterial wall remodeling.

The results of this post hoc exploratory analysis have implications for further attempts to develop therapeutic agents that raise HDL-C levels. Although torcetrapib did not slow disease progression in the entire cohort, the finding of disease regression at the highest levels of HDL-C raises the possibility that another CETP inhibitor, without compound-specific toxicity, may be clinically efficacious. This potential should be explored in further well-designed, randomized clinical trials. There remains hope that new agents promoting

the protective properties of HDL will provide an adjunctive approach to achieve more effective prevention of cardiovascular disease.

Acknowledgments

We appreciate the technical expertise of the Intravascular Ultrasound Core Laboratory at the Cleveland Clinic.

Source of Funding

The ILLUSTRATE trial was sponsored by Pfizer Pharmaceuticals.

Disclosures

Dr Nicholls reports receiving honoraria from Pfizer, AstraZeneca, Takeda, and Merck Schering-Plough; consultancy fees from AstraZeneca, Roche, Novo-Nordisk, Pfizer, and Anthera Pharmaceuticals; and research support from LipidSciences. Dr Tuzcu reports receiving consultancy fees from Pfizer and honoraria from Pfizer and Merck. Dr Tardif holds the Pfizer and Canadian Institutes of Health Research chair in atherosclerosis. Dr Tardif has also received consultancy fees from Pfizer and AstraZeneca. Dr Nissen reports that the Cleveland Clinic Coordinating Center has received research support from Pfizer, AstraZeneca, Sankyo, Takeda, Novartis, Sanofi-Aventis, and Eli Lilly to perform clinical trials. Dr Nissen consults for many pharmaceutical companies but requires them to donate all honoraria or consulting fees directly to charity so that he receives neither income nor a tax deduction. D.M. Brennan reports no conflicts.

References

1. Nissen SE, Tardif JC, Nicholls SJ, Revkin JH, Shear CL, Duggan WT, Ruzyllo W, Bachinsky WB, Lasala GP, Tuzcu EM. Effect of torcetrapib on the progression of coronary atherosclerosis. *N Engl J Med*. 2007;356:1304–1316.
2. Kastelein JJ, van Leuven SI, Burgess L, Evans GW, Kuivenhoven JA, Barter PJ, Revkin JH, Grobbee DE, Riley WA, Shear CL, Duggan WT, Bots ML. Effect of torcetrapib on carotid atherosclerosis in familial hypercholesterolemia. *N Engl J Med*. 2007;356:1620–1630.
3. Bots ML, Visseren FL, Evans GW, Riley WA, Revkin JH, Tegeler CH, Shear CL, Duggan WT, Vicari RM, Grobbee DE, Kastelein JJ. Torcetrapib and carotid intima-media thickness in mixed dyslipidaemia (RADIANCE 2 study): a randomised, double-blind trial. *Lancet*. 2007;370:153–160.
4. Barter PJ, Caulfield M, Eriksson M, Grundy SM, Kastelein JJ, Komajda M, Lopez-Sendon J, Mosca L, Tardif JC, Waters DD, Shear CL, Revkin JH, Buhr KA, Fisher MR, Tall AR, Brewer B. Effects of torcetrapib in patients at high risk for coronary events. *N Engl J Med*. 2007;357:2109–2122.
5. In interests of patient safety, Pfizer stops all torcetrapib clinical trials; company has notified FDA and is in the process of notifying all clinical investigators and other regulatory authorities [press release]. New York, NY: Pfizer; December 2, 2006.
6. Tall AR, Yvan-Charvet L, Wang N. The failure of torcetrapib: was it the molecule or the mechanism? *Arterioscler Thromb Vasc Biol*. 2007;27:257–260.
7. Nissen SE, Nicholls SJ, Sipahi I, Libby P, Raichlen JS, Ballantyne CM, Davignon J, Erbel R, Fruchart JC, Tardif JC, Schoenhagen P, Crowe T, Cain V, Wolski K, Goormastic M, Tuzcu EM. Effect of very high-intensity statin therapy on regression of coronary atherosclerosis: the ASTEROID trial. *JAMA*. 2006;295:1556–1565.
8. Forrest MJ, Bloomfield D, Briscoe RJ, Brown PN, Cumiskey AM, Ehrhart J, Hershey JC, Keller WJ, Ma X, McPherson HE, Messina E, Peterson LB, Sharif-Rodriguez W, Siegl PK, Sinclair PJ, Sparrow CP, Stevenson AS, Sun SY, Tsai C, Vargas H, Walker M III, West SH, White V, Woltmann RF. Torcetrapib-induced blood pressure elevation is independent of CETP inhibition and is accompanied by increased circulating levels of aldosterone. *Br J Pharmacol*. 2008;154:1465–1473.
9. Griendling KK, Minieri CA, Ollerenshaw JD, Alexander RW. Angiotensin II stimulates NADH and NADPH oxidase activity in cultured vascular smooth muscle cells. *Circ Res*. 1994;74:1141–1148.
10. Keidar S, Kaplan M, Pavlotzky E, Coleman R, Hayek T, Hamoud S, Aviram M. Aldosterone administration to mice stimulates macrophage NADPH oxidase and increases atherosclerosis development: a possible role for angiotensin-converting enzyme and the receptors for angiotensin II and aldosterone. *Circulation*. 2004;109:2213–2220.
11. Mazak I, Fiebeler A, Muller DN, Park JK, Shagdarsuren E, Lindschau C, Dechend R, Viedt C, Pilz B, Haller H, Luft FC. Aldosterone potentiates angiotensin II-induced signaling in vascular smooth muscle cells. *Circulation*. 2004;109:2792–2800.
12. Rajagopalan S, Duquaine D, King S, Pitt B, Patel P. Mineralocorticoid receptor antagonism in experimental atherosclerosis. *Circulation*. 2002;105:2212–2216.
13. Virdis A, Neves MF, Amiri F, Viel E, Touyz RM, Schiffrin EL. Spironolactone improves angiotensin-induced vascular changes and oxidative stress. *Hypertension*. 2002;40:504–510.
14. Suzuki J, Iwai M, Mogi M, Oshita A, Yoshii T, Higaki J, Horiuchi M. Eplerenone with valsartan effectively reduces atherosclerotic lesion by attenuation of oxidative stress and inflammation. *Arterioscler Thromb Vasc Biol*. 2006;26:917–921.
15. Brown ML, Inazu A, Hesler CB, Agellon LB, Mann C, Whitlock ME, Marcel YL, Milne RW, Koizumi J, Mabuchi H. Molecular basis of lipid transfer protein deficiency in a family with increased high-density lipoproteins. *Nature*. 1989;342:448–451.
16. Inazu A, Brown ML, Hesler CB, Agellon LB, Koizumi J, Takata K, Maruhama Y, Mabuchi H, Tall AR. Increased high-density lipoprotein levels caused by a common cholesteryl-ester transfer protein gene mutation. *N Engl J Med*. 1990;323:1234–1238.
17. Brousseau ME, Schaefer EJ, Wolfe ML, Bloedon LT, Digenio AG, Clark RW, Mancuso JP, Rader DJ. Effects of an inhibitor of cholesteryl ester transfer protein on HDL cholesterol. *N Engl J Med*. 2004;350:1505–1515.
18. Barter PJ, Chapman MJ, Hennekens CH, Rader DJ, Tall AR. Cholesteryl ester transfer protein: a novel target for raising HDL and inhibiting atherosclerosis. *Arterioscler Thromb Vasc Biol*. 2003;23:160–167.
19. de Haan W, de Vries-van der Weij J, van der Hoorn JW, Gautier T, van der Hoogt CC, Westerterp M, Romijn JA, Jukema JW, Havekes LM, Princen HM, Rensen PC. Torcetrapib does not reduce atherosclerosis beyond atorvastatin and induces more proinflammatory lesions than atorvastatin. *Circulation*. 2008;117:2515–2522.
20. Sugano M, Makino N, Sawada S, Otsuka S, Watanabe M, Okamoto H, Kamada M, Mizushima A. Effect of antisense oligonucleotides against cholesteryl ester transfer protein on the development of atherosclerosis in cholesterol-fed rabbits. *J Biol Chem*. 1998;273:5033–5036.
21. Rittershaus CW, Miller DP, Thomas LJ, Picard MD, Honan CM, Emmett CD, Pettey CL, Adari H, Hammond RA, Beattie DT, Callow AD, Marsh HC, Ryan US. Vaccine-induced antibodies inhibit CETP activity in vivo and reduce aortic lesions in a rabbit model of atherosclerosis. *Arterioscler Thromb Vasc Biol*. 2000;20:2106–2112.
22. Okamoto H, Yonemori F, Wakitani K, Minowa T, Maeda K, Shinkai H. A cholesteryl ester transfer protein inhibitor attenuates atherosclerosis in rabbits. *Nature*. 2000;406:203–207.
23. Davidson MH, McKenney JM, Shear CL, Revkin JH. Efficacy and safety of torcetrapib, a novel cholesteryl ester transfer protein inhibitor, in individuals with below-average high-density lipoprotein cholesterol levels. *J Am Coll Cardiol*. 2006;48:1774–1781.
24. Barzilai N, Atzmon G, Schechter C, Schaefer EJ, Cupples AL, Lipton R, Cheng S, Shuldiner AR. Unique lipoprotein phenotype and genotype associated with exceptional longevity. *JAMA*. 2003;290:2030–2040.
25. Boekholdt SM, Sacks FM, Jukema JW, Shepherd J, Freeman DJ, McMahon AD, Cambien F, Nicaud V, de Grooth GJ, Talmud PJ, Humphries SE, Miller GJ, Eiriksdottir G, Gudnason V, Kauma H, Kakko S, Savolainen MJ, Arca M, Montali A, Liu S, Lanz HJ, Zwinderman AH, Kuivenhoven JA, Kastelein JJ. Cholesteryl ester transfer protein TaqIB variant, high-density lipoprotein cholesterol levels, cardiovascular risk, and efficacy of pravastatin treatment: individual patient meta-analysis of 13 677 subjects. *Circulation*. 2005;111:278–287.
26. Hirano K, Yamashita S, Kuga Y, Sakai N, Nozaki S, Kihara S, Arai T, Yanagi K, Takami S, Menju M, Ishigami M, Yoshida Y, Kameda-Takemura K, Hayashi K, Matsuzawa Y. Atherosclerotic disease in marked hyperalphalipoproteinemia: combined reduction of cholesteryl ester transfer protein and hepatic triglyceride lipase. *Arterioscler Thromb Vasc Biol*. 1995;15:1849–1856.
27. Zhong S, Sharp DS, Grove JS, Bruce C, Yano K, Curb JD, Tall AR. Increased coronary heart disease in Japanese-American men with mutation in the cholesteryl ester transfer protein gene despite increased HDL levels. *J Clin Invest*. 1996;97:2917–2923.

28. Wang N, Tall AR. Regulation and mechanisms of ATP-binding cassette transporter A1-mediated cellular cholesterol efflux. *Arterioscler Thromb Vasc Biol*. 2003;23:1178–1184.
29. Yancey PG, Bortnick AE, Kellner-Weibel G, de la Llera-Moya M, Phillips MC, Rothblat GH. Importance of different pathways of cellular cholesterol efflux. *Arterioscler Thromb Vasc Biol*. 2003;23:712–719.
30. Matsuura F, Wang N, Chen W, Jiang XC, Tall AR. HDL from CETP-deficient subjects shows enhanced ability to promote cholesterol efflux from macrophages in an apoE- and ABCG1-dependent pathway. *J Clin Invest*. 2006;116:1435–1442.
31. Yvan-Charvet L, Matsuura F, Wang N, Bamberger MJ, Nguyen T, Rinninger F, Jiang XC, Shear CL, Tall AR. Inhibition of cholesteryl ester transfer protein by torcetrapib modestly increases macrophage cholesterol efflux to HDL. *Arterioscler Thromb Vasc Biol*. 2007;27:1132–1138.
32. Brousseau ME, Diffenderfer MR, Millar JS, Nartsupha C, Asztalos BF, Welty FK, Wolfe ML, Rudling M, Bjorkhem I, Angelin B, Mancuso JP, Digenio AG, Rader DJ, Schaefer EJ. Effects of cholesteryl ester transfer protein inhibition on high-density lipoprotein subspecies, apolipoprotein A-I metabolism, and fecal sterol excretion. *Arterioscler Thromb Vasc Biol*. 2005;25:1057–1064.
33. Kee P, Caiazza D, Rye KA, Barrett PH, Morehouse LA, Barter PJ. Effect of inhibiting cholesteryl ester transfer protein on the kinetics of high-density lipoprotein cholesteryl ester transport in plasma: in vivo studies in rabbits. *Arterioscler Thromb Vasc Biol*. 2006;26:884–890.
34. Gordon T, Castelli WP, Hjortland MC, Kannel WB, Dawber TR. High density lipoprotein as a protective factor against coronary heart disease: the Framingham Study. *Am J Med*. 1977;62:707–714.
35. Badimon JJ, Badimon L, Fuster V. Regression of atherosclerotic lesions by high density lipoprotein plasma fraction in the cholesterol-fed rabbit. *J Clin Invest*. 1990;85:1234–1241.
36. Badimon JJ, Badimon L, Galvez A, Dische R, Fuster V. High density lipoprotein plasma fractions inhibit aortic fatty streaks in cholesterol-fed rabbits. *Lab Invest*. 1989;60:455–461.
37. Plump AS, Scott CJ, Breslow JL. Human apolipoprotein A-I gene expression increases high density lipoprotein and suppresses atherosclerosis in the apolipoprotein E-deficient mouse. *Proc Nat Acad Sci U S A*. 1994;91:9607–9611.
38. Rubin EM, Krauss RM, Spangler EA, Verstuyft JG, Clift SM. Inhibition of early atherogenesis in transgenic mice by human apolipoprotein AI. *Nature*. 1991;353:265–267.
39. Nicholls SJ, Cutri B, Worthley SG, Kee P, Rye KA, Bao S, Barter PJ. Impact of short-term administration of high-density lipoproteins and atorvastatin on atherosclerosis in rabbits. *Arterioscler Thromb Vasc Biol*. 2005;25:2416–2421.
40. Rong JX, Li J, Reis ED, Choudhury RP, Dansky HM, Elmalem VI, Fallon JT, Breslow JL, Fisher EA. Elevating high-density lipoprotein cholesterol in apolipoprotein E-deficient mice remodels advanced atherosclerotic lesions by decreasing macrophage and increasing smooth muscle cell content. *Circulation*. 2001;104:2447–2452.
41. MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in 20,536 high-risk individuals: a randomised placebo-controlled trial. *Lancet*. 2002;360:7–22.
42. Randomised trial of cholesterol lowering in 4444 patients with coronary heart disease: the Scandinavian Simvastatin Survival Study (4S). *Lancet*. 1994;344:1383–1389.
43. Downs JR, Clearfield M, Weis S, Whitney E, Shapiro DR, Beere PA, Largendorfer A, Stein EA, Kruyer W, Gotto AM Jr. Primary prevention of acute coronary events with lovastatin in men and women with average cholesterol levels: results of AFCAPS/TexCAPS: Air Force/Texas Coronary Atherosclerosis Prevention Study. *JAMA*. 1998;279:1615–1622.
44. Nicholls SJ, Tuzcu EM, Sipahi I, Grasso AW, Schoenhagen P, Hu T, Wolski K, Crowe T, Desai MY, Hazen SL, Kapadia SR, Nissen SE. Statins, high-density lipoprotein cholesterol, and regression of coronary atherosclerosis. *JAMA*. 2007;297:499–508.
45. Frick MH, Elo O, Haapa K, Heinonen OD, Heinsalmi P, Helo P, Huttunen JK, Kaitaniemi P, Koskinen P, Manninen V. Helsinki Heart Study: primary-prevention trial with gemfibrozil in middle aged men with dyslipidemia: safety of treatment, changes in risk factors and incidence of coronary heart disease. *N Engl J Med*. 1987;317:1237–1245.
46. Robins SJ, Collins D, Wittes JT, Papademetriou V, Deedwania PC, Schaefer EJ, McNamara JR, Kashyap ML, Hershman JM, Wexler LF, Rubins HB. Relation of gemfibrozil treatment and lipid levels with major coronary events: VA-HIT: a randomized controlled trial. *JAMA*. 2001;285:1585–1591.
47. Clofibrate and niacin in coronary heart disease. *JAMA*. 1975;231:360–381.
48. Brown BG, Zhao X-Q, Chait A, Fisher LD, Cheung MC, Morse JS, Dowdy AA, Marino EK, Bolson EL, Alaupovic P, Frohlich J, Albers JJ. Simvastatin and niacin, antioxidant vitamins, or the combination for the prevention of coronary disease. *N Engl J Med*. 2001;345:1583–1592.
49. Nissen SE, Tsunoda T, Tuzcu EM, Schoenhagen P, Cooper CJ, Yasin M, Eaton GM, Lauer MA, Sheldon WS, Grines CL, Halpern S, Crowe T, Blankenship JC, Kerensky R. Effect of recombinant ApoA-I Milano on coronary atherosclerosis in patients with acute coronary syndromes: a randomized controlled trial. *JAMA*. 2003;290:2292–2300.
50. Tardif JC, Gregoire J, L'Allier PL, Ibrahim R, Lesperance J, Heinonen TM, Kouz S, Berry C, Basser R, Lavoie MA, Guertin MC, Rodes-Cabau J. Effects of reconstituted high-density lipoprotein infusions on coronary atherosclerosis: a randomized controlled trial. *JAMA*. 2007;297:1675–1682.

CLINICAL PERSPECTIVE

Considerable interest has focused on the development of therapies that raise systemic levels of high-density lipoprotein (HDL) cholesterol. Despite substantial elevation of HDL cholesterol, the cholesteryl ester transfer protein inhibitor torcetrapib failed to slow progression of atherosclerosis and was associated with excess mortality in clinical trials. This has fueled speculation that the functionality of HDL is impaired in the setting of cholesteryl ester transfer protein inhibition. Although torcetrapib substantially elevated HDL cholesterol but had no effect on percent atheroma volume, in this post hoc analysis an inverse relationship was observed between changes in levels of HDL cholesterol and percent atheroma volume. Disease regression at the highest levels of HDL cholesterol suggests that HDL particles can retain their functional activity, in terms of lipid mobilization, in patients treated with cholesteryl ester transfer protein inhibitors. The lack of efficacy is likely to reflect some form of off-target toxicity, such as activation of the renin-angiotensin-aldosterone axis. As a result, additional cholesteryl ester transfer protein inhibitors that lack such adverse effects may have a beneficial influence on cardiovascular disease risk. This possibility requires confirmation in prospective randomized clinical trials.

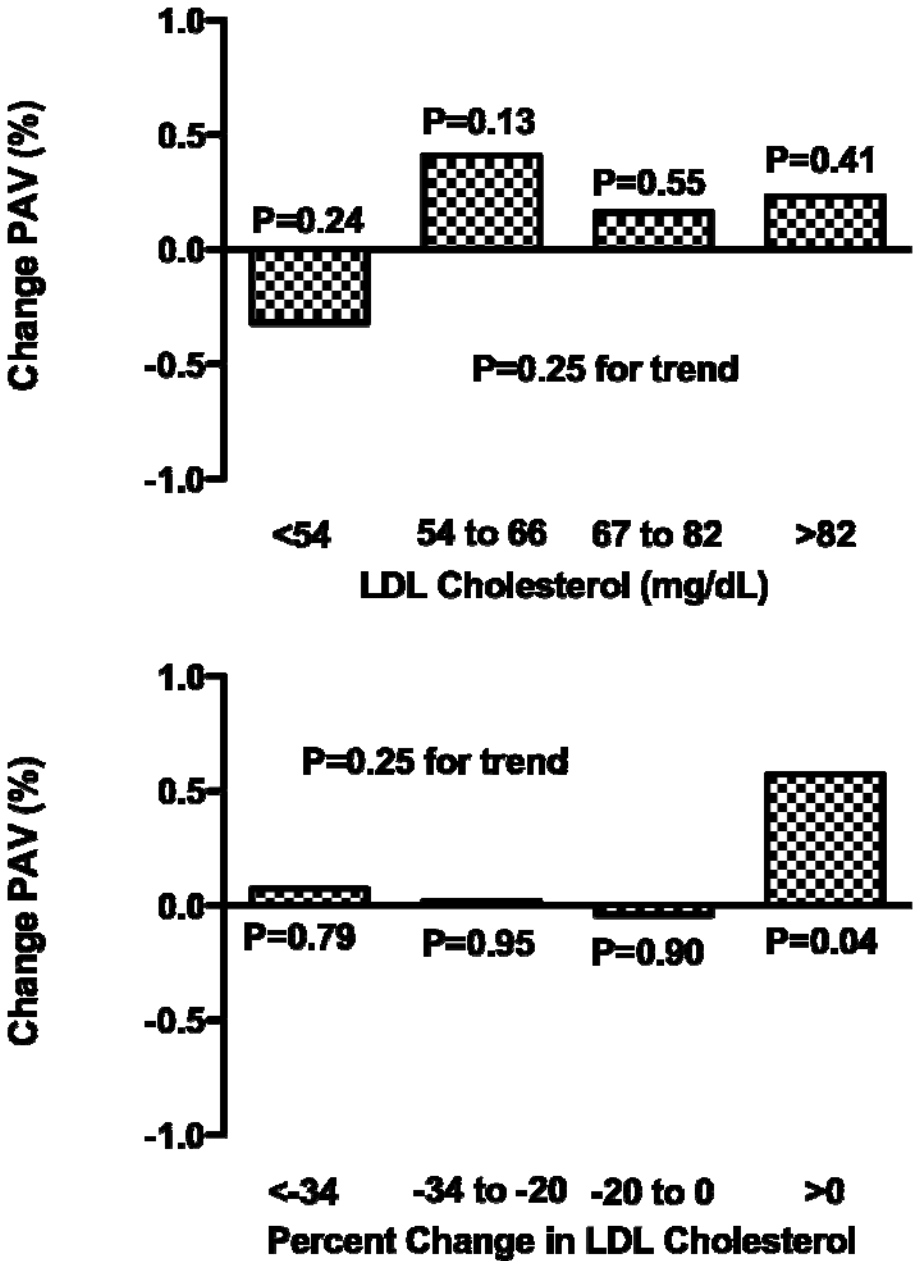
Go to http://cme.ahajournals.org to take the CME quiz for this article.

Supplementary Table 1.

	Atorvastatin + Placebo					Atorvastatin + Torcetrapib				
	Q1	Q2	Q3	Q4	P Value for trend	Q1	Q2	Q3	Q4	P Value for trend
HDL Cholesterol										
Baseline	44.3	42.0	46.2	45.5	0.93	44.8	54.1	53.0	47.8	0.46
Percentage Change	43.6	40.5	46.0	48.2	0.70	38.1	47.4	59.7	54.4	0.008
LDL Cholesterol										
Baseline	47.3	43.9	39.3	47.8	0.56	49.1	57.7	47.0	46.1	0.29
Percentage Change	47.3	39.6	45.1	46.4	0.67	53.1	53.5	48.3	44.7	0.49
Triglycerides										
Baseline	49.6	46.4	45.5	37.5	0.31	58.9	55.3	47.0	38.6	0.01
Percentage Change	44.8	48.4	44.3	41.7	0.83	45.5	51.5	52.5	49.5	0.76
CRP										
Baseline	50.9	40.6	42.1	45.8	0.42	53.9	49.1	41.5	55.8	0.13
Percentage Change	44.0	47.5	50.0	38.1	0.34	51.4	51.4	47.8	47.7	0.90

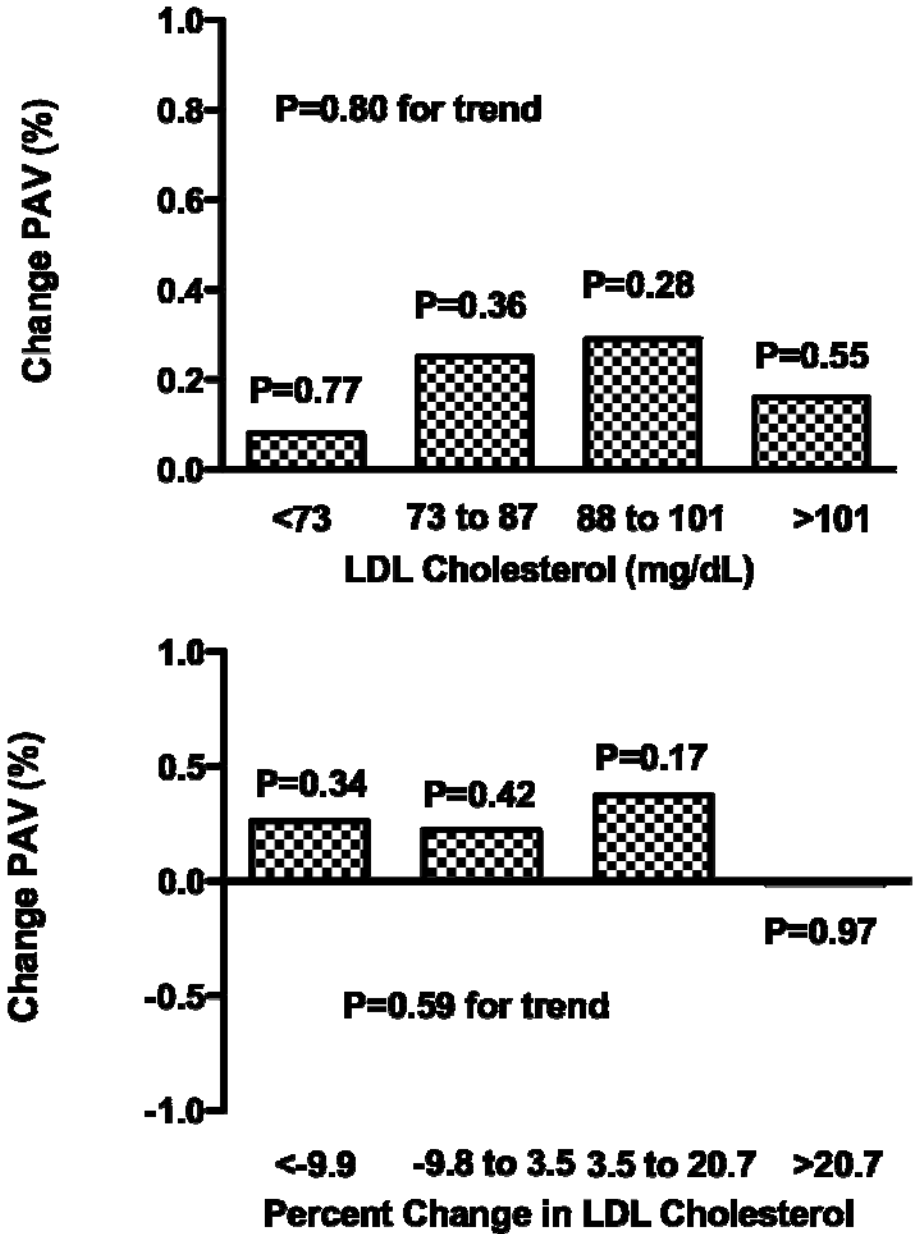
Supplementary Table 1. Percentage of subjects undergoing any degree of plaque regression (reduction in percent atheroma volume) according to quartiles of both baseline and percentage change in lipid and inflammatory markers, stratified by treatment group. CRP, C-reactive protein; HDL, high-density lipoprotein; LDL, low-density lipoprotein.

Supplementary Figure 1.



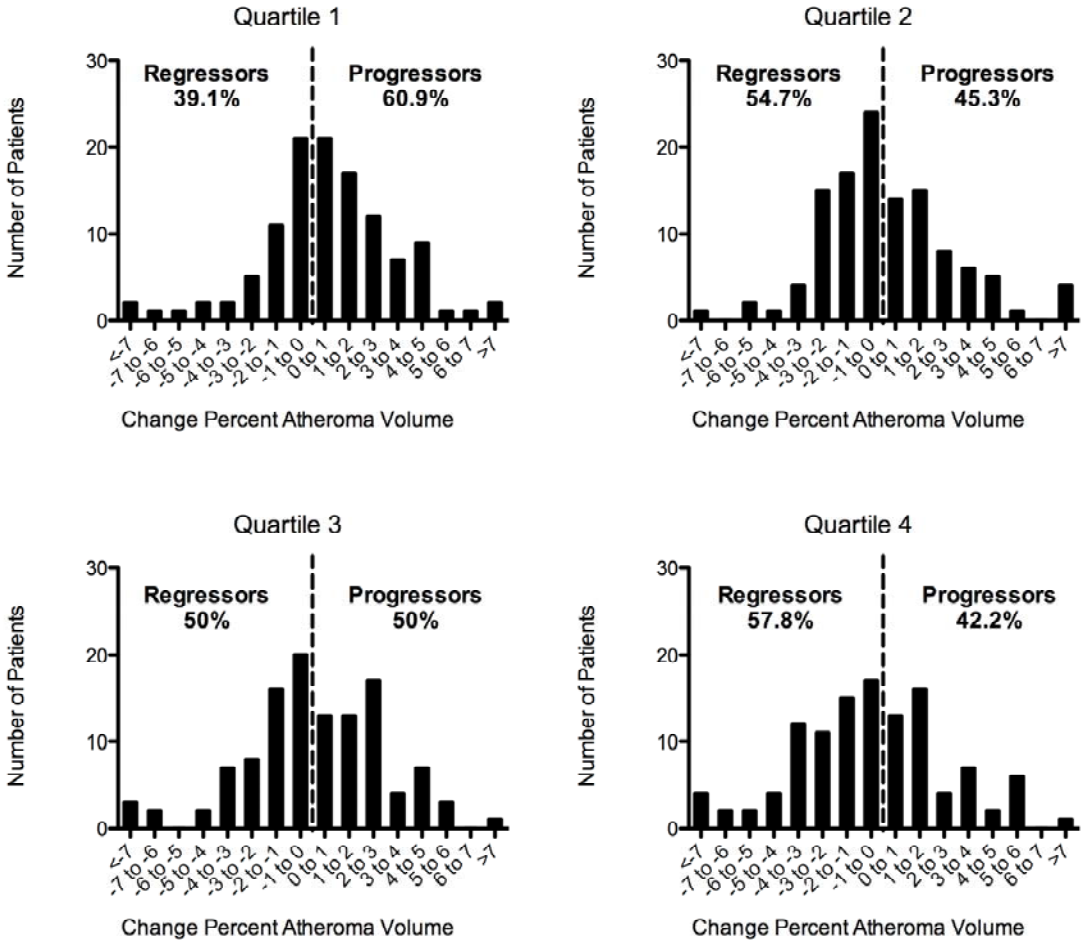
Supplementary Figure 1. Least square mean change in percent atheroma volume (PAV), after controlling for the baseline value, in torcetrapib/atorvastatin-treated subjects according to quartile of achieved level (upper panel) and percentage change (lower panel) of LDL cholesterol. P values above bars for comparison between baseline and followup.

Supplementary Figure 2.



Supplementary Figure 2. Least square mean change in percent atheroma volume (PAV), after controlling for the baseline value, in atorvastatin monotherapy-treated subjects according to quartile of achieved level (upper panel) and percentage change (lower panel) of LDL cholesterol. P values above bars for comparison between baseline and followup.

Supplementary Figure 3



Supplementary Figure 3. Histogram illustrating the number of torcetrapib/atorvastatin-treated patients stratified according to the degree of change of percent atheroma volume in each quartile of achieved level of HDL cholesterol. The dotted line represents no change, with regression to the left and progression to the right.