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Effects of Torcetrapib in Patients at High Risk for Coronary Events

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ABSTRACT

BACKGROUND

Inhibition of cholesteryl ester transfer protein (CETP) has been shown to have a substantial effect on plasma lipoprotein levels. We investigated whether torcetrapib, a potent CETP inhibitor, might reduce major cardiovascular events. The trial was terminated prematurely because of an increased risk of death and cardiac events in patients receiving torcetrapib.

METHODS

We conducted a randomized, double-blind study involving 15,067 patients at high cardiovascular risk. The patients received either torcetrapib plus atorvastatin or atorvastatin alone. The primary outcome was the time to the first major cardiovascular event, which was defined as death from coronary heart disease, nonfatal myocardial infarction, stroke, or hospitalization for unstable angina.

RESULTS

At 12 months in patients who received torcetrapib, there was an increase of 72.1% in high-density lipoprotein cholesterol and a decrease of 24.9% in low-density lipoprotein cholesterol, as compared with baseline ($P < 0.001$ for both comparisons), in addition to an increase of 5.4 mm Hg in systolic blood pressure, a decrease in serum potassium, and increases in serum sodium, bicarbonate, and aldosterone ($P < 0.001$ for all comparisons). There was also an increased risk of cardiovascular events (hazard ratio, 1.25; 95% confidence interval [CI], 1.09 to 1.44; $P = 0.001$) and death from any cause (hazard ratio, 1.58; 95% CI, 1.14 to 2.19; $P = 0.006$). Post hoc analyses showed an increased risk of death in patients treated with torcetrapib whose reduction in potassium or increase in bicarbonate was greater than the median change.

CONCLUSIONS

Torcetrapib therapy resulted in an increased risk of mortality and morbidity of unknown mechanism. Although there was evidence of an off-target effect of torcetrapib, we cannot rule out adverse effects related to CETP inhibition. (ClinicalTrials.gov number, NCT00134264.)

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EVIDENCE SUPPORTING THE PROPOSITION that high-density lipoprotein (HDL) cholesterol should be considered as a therapeutic target includes experimental models of atherosclerosis,¹ an inverse relationship to the risk of cardiovascular disease in humans,² clinical trials of drugs for which raising HDL cholesterol levels is a primary pharmacologic effect,³ and the residual risk of cardiovascular disease associated with a low HDL cholesterol level after effective statin therapy.⁴

Cholesteryl ester transfer protein (CETP) promotes the transfer of cholesteryl esters from HDL to other lipoproteins; the inhibition of this protein raises HDL cholesterol levels and decreases low-density lipoprotein (LDL) cholesterol levels. There is evidence supporting CETP inhibition as a therapeutic approach to the prevention of major cardiovascular events, although there is also evidence to the contrary.⁵⁻⁷

Torcetrapib is an inhibitor of CETP that has been shown to inhibit the development of atherosclerosis in rabbits.⁸ In early-phase studies in humans, the drug increased HDL cholesterol by 60 to 100% at the same time that it lowered LDL cholesterol by up to 20%.^{9,10} Torcetrapib was subsequently investigated in three large trials with the use of ultrasonography and other imaging techniques and was found to have no significant effect on coronary atheroma burden¹¹ or carotid intima-media thickness.^{12,13} Concurrent with these imaging studies, the Investigation of Lipid Level Management to Understand its Impact in Atherosclerotic Events (ILLUMINATE) trial tested the proposition that torcetrapib would decrease the risk of clinical cardiovascular events. This trial was terminated prematurely on December 2, 2006, in a decision made by the sponsor on the basis of the recommendation of the trial's independent steering committee, which was acting on advice from the independent data and safety monitoring board.¹⁴ This report describes the main results of the ILLUMINATE trial.

METHODS

STUDY DESIGN

We conducted a prospective, randomized, multicenter, double-blind clinical trial, using a centralized randomization strategy with a block size of four. The trial was designed by an independent

steering committee in collaboration with the sponsor, Pfizer. Data were collected by PharmaNet Development Group and analyzed independently by the Statistical Data Analysis Center at the University of Wisconsin, Madison; representatives of these organizations vouch for the completeness and veracity of the data and the analyses, respectively. An institutional review board at each center approved the protocol, and patients provided written informed consent. The original protocol was amended on November 28, 2006, a change that had not yet received institutional review board approval at the time of the trial's termination. The amendment included the addition of hospitalization for unstable angina to the primary outcome to increase the number of events and thus increase the statistical power to reject the null hypothesis.

Men and women between the ages of 45 and 75 years were eligible to participate in the study if they had a history of cardiovascular disease (including myocardial infarction, stroke, acute coronary syndrome, unstable angina, peripheral vascular disease, and cardiac revascularization) 30 days to 5 years before screening. Patients with type 2 diabetes without previous cardiovascular disease who met American Diabetes Association criteria or were receiving hypoglycemic agents were also eligible. Patients were excluded if they had evidence of an unstable medical condition, a life expectancy of less than 5 years, or an LDL cholesterol level of less than 100 mg per deciliter (2.6 mmol per liter) if the patient was not receiving a lipid-altering drug. Patients were also excluded if they had had a cardiovascular event during the run-in period or uncontrolled hypertension (defined as a systolic blood pressure of >140 mm Hg or a diastolic blood pressure of >90 mm Hg) or if the LDL cholesterol target level had not been reached at the end of the run-in period.

During a run-in period of 4 to 10 weeks, patients underwent lifestyle counseling and also received atorvastatin titrated (if needed) at 2-week intervals to achieve an LDL cholesterol level of less than 100 mg per deciliter. A variability tolerance of +15 mg per deciliter (0.4 mmol per liter) was allowed. Patients whose LDL level met the target were randomly assigned to receive either atorvastatin (at a dose established during the run-in period) plus 60 mg of torcetrapib or atorvastatin plus placebo. After termination of the trial,

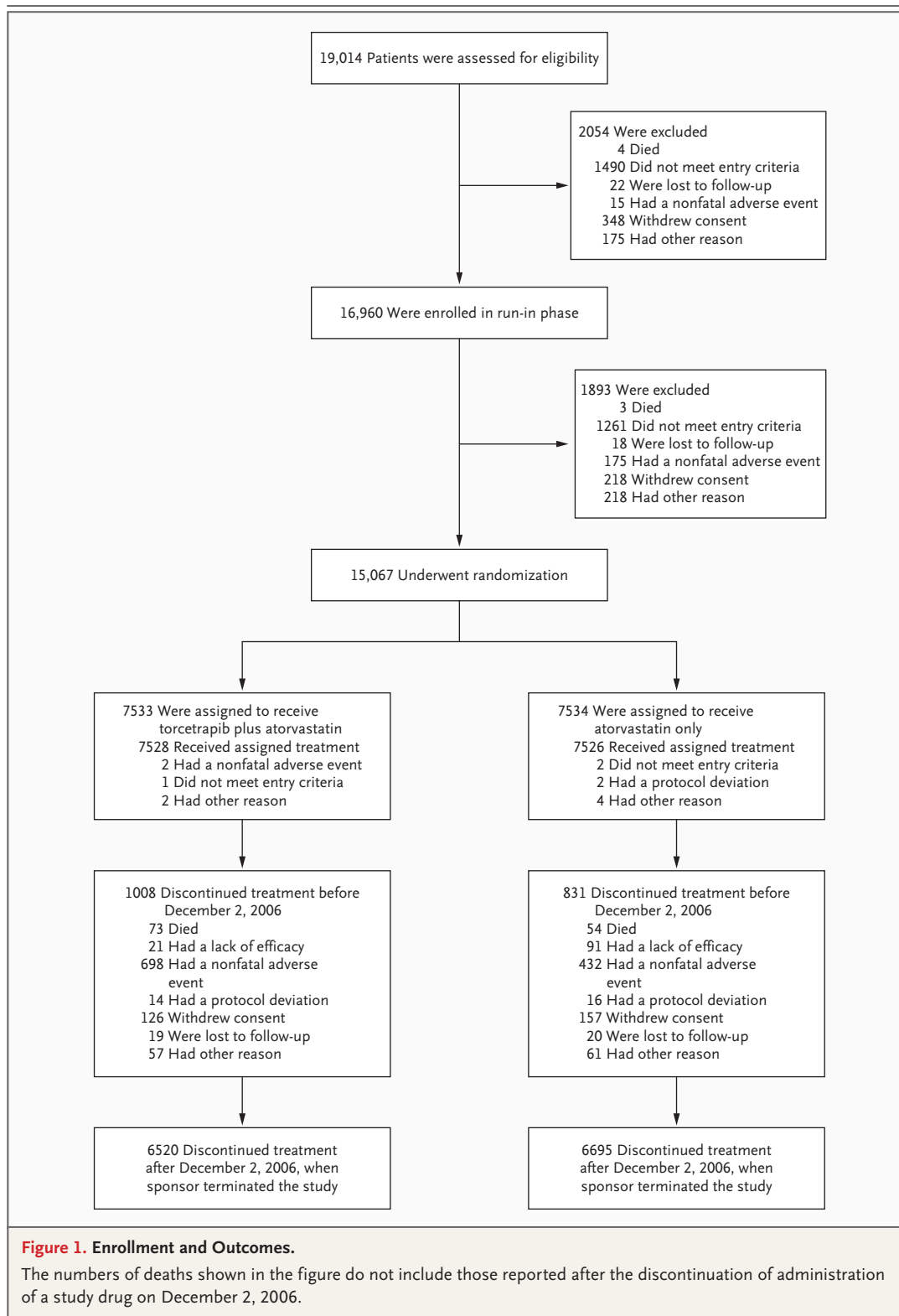


Table 1. Demographic and Clinical Characteristics of the Patients.*

Variable	Atorvastatin Only (N=7534)	Torcetrapib plus Atorvastatin (N=7533)	P Value
Male sex — no. (%)	5861 (77.8)	5854 (77.7)	0.90
White race — no. (%)†	7028 (93.3)	7019 (93.2)	0.82
Age — yr	61.3±7.6	61.3±7.6	0.82
Body-mass index	30.2±5.6	30.1±5.7	0.14
Smoking history — no. (%)			0.64
Current smoker	1047 (13.9)	1011 (13.4)	
Former smoker	4123 (54.7)	4167 (55.3)	
Nonsmoker	2364 (31.4)	2355 (31.3)	
Medical history — no./total no. (%)			
History of hypertension	5554/7515 (73.9)	5423/7504 (72.3)	0.02
Previous coronary revascularization	5133/7530 (68.2)	5188/7530 (68.9)	0.33
Previous myocardial infarction	3388/7472 (45.3)	3450/7463 (46.2)	0.28
History of angina	4497/7499 (60.0)	4581/7499 (61.1)	0.16
History of diabetes	3390/7504 (45.2)	3271/7517 (43.5)	0.04
Peripheral vascular disease	944/7417 (12.7)	930/7426 (12.5)	0.71
Congestive heart failure (class I or II)	523/7489 (7.0)	504/7494 (6.7)	0.53
Previous stroke	411/7513 (5.5)	394/7512 (5.2)	0.54
Previous transient ischemic attack	405/7477 (5.4)	311/7490 (4.2)	<0.001
Lipids			
Cholesterol — mg/dl			
Total	157.3±26.9	156.8±26.6	0.34
High-density lipoprotein	48.5±12.2	48.6±12.0	0.24
Low-density lipoprotein	79.9±20.4	79.7±20.4	0.45
Triglycerides — mg/dl			0.14
Median	128	127	
Interquartile range	93–179	92–177	
Apolipoprotein — mg/dl			
A-I	128.3±23.2	128.2±23.2	0.74
B	73.5±15.8	73.2±15.8	0.26
Vital signs			
Blood pressure — mm Hg			
Systolic	123.0±10.9	122.9±10.9	0.37
Diastolic	73.9±7.5	73.7±7.6	0.26
Heart rate — beats/min	65.4±9.5	65.4±9.6	0.82
Electrolytes — mmol/liter			
Potassium	4.40±0.39	4.40±0.39	0.54
Sodium	140.4±2.7	140.4±2.7	0.67
Chloride	102.7±2.9	102.8±2.9	0.21
Bicarbonate	24.3±3.1	24.3±3.0	0.81

Table 1. (Continued.)			
Variable	Atorvastatin Only (N=7534)	Torcetrapib plus Atorvastatin (N=7533)	P Value
Renal function			
Creatinine — mg/dl	1.0±0.22	1.0±0.22	1.00
Estimated glomerular filtration rate — ml/min/1.73 m ²	79.4±17.5	79.5±17.7	0.88
Liver function			
Aspartate aminotransferase — U/liter	23.1±8.2	23.0±8.1	0.70
Alanine aminotransferase — U/liter	26.2±12.7	26.1±13.2	0.43
Alkaline phosphatase — U/liter	80.5±24.8	80.8±24.2	0.28
Bilirubin — mg/dl			
Total	0.65±0.29	0.66±0.29	<0.001
Direct	0.180±0.069	0.183±0.071	<0.001
Creatine kinase — U/liter	125.7±99.7	126.8±136.3	0.47
Other selected measures			
QT interval (Bazett-corrected) — msec			
Median	410.3	409.8	0.53
Interquartile range	393.3–427.4	393.2–427.1	
C-reactive protein — mg/liter			
Median	1.40	1.30	0.003
Interquartile range	0.70–3.00	0.65–2.80	

* Plus-minus values are means ±SD. Complete data regarding demographic characteristics and medical history were not available for all patients; the minimum totals in each group were more than 95%. The body-mass index is the weight in kilograms divided by the square of the height in meters. To convert the values for cholesterol to millimoles per liter, multiply by 0.02586. To convert the values for triglycerides to millimoles per liter, multiply by 0.01129. To convert the values for creatinine to micromoles per liter, multiply by 88.4. To convert the values for bilirubin to micromoles per liter, multiply by 17.1.

† Race was self-reported by the patients.

the sponsor maintained support for independent oversight during the trial's closeout (which involved four of the academic authors) with continuing support from the Statistical Data Analysis Center, which performed the primary statistical analyses.

STUDY OUTCOMES

Patients' visits were scheduled at 1, 3, 6, 9, and 12 months after randomization. Thereafter, patients were to be seen twice yearly. An increase or decrease in the dose of atorvastatin was allowed at the 12-month visit on the basis of predefined LDL cholesterol levels. The level of HDL cholesterol was determined through enzyme analysis with the use of polyethylene glycol-modified cholesterol esterase, cholesterol oxidase, and dextran sulfate to generate peroxide that was mea-

sured calorimetrically. Total cholesterol and triglyceride levels were determined by standard enzymatic techniques. LDL cholesterol was quantified by the Friedewald formula, except when the triglyceride level was more than 400 mg per deciliter (4.5 mmol per liter), in which case the level was measured by direct beta quantification. Apolipoproteins A-I and B-100 were measured by means of immunoturbidimetric assay. High-sensitivity C-reactive protein (CRP) was measured with the use of a particle-enhanced immunoturbidimetric assay. All measurements were performed at a central laboratory (MDS). Blood pressure was measured in triplicate at each visit with the use of a standard calibrated measuring device with the patient seated after 5 minutes of rest. The first reading was not used, and the latter two readings were averaged for the visit measurement. The esti-

Table 2. Changes from Baseline at 3 Months and 12 Months in Selected Measures.*

Variable	Change at 3 Months			Change at 12 Months		
	Atorvastatin Only	Torcetrapib plus Atorvastatin	P Value	Atorvastatin Only	Torcetrapib plus Atorvastatin	P Value
Lipids (absolute change) — mg/dl						
Cholesterol						
Total	+1.6±20.5	+5.1±23.9	<0.001	+2.1±22.4	+9.3±26.3	<0.001
High-density lipoprotein	+0.5±6.2	+29.0±14.4	<0.001	+0.5±6.8	+34.2±17.0	<0.001
Low-density lipoprotein	+0.6±15.8	-20.5±20.8	<0.001	+0.9±17.1	-21.5±22.7	<0.001
Triglycerides						
Median	+1	-10	<0.001	+1	-10	<0.001
Interquartile range	-23 to 26	-38 to 12		-23 to 29	-38 to 14	
Apolipoprotein						
A-I	+0.4±16.0	+30.8±21.9	<0.001	NA	NA	NA
B	+0.6±11.1	-10.1±14.4	<0.001	NA	NA	NA
Lipids (percent change) — %						
Cholesterol						
Total	+1.7±13.3	+4.2±16.0	<0.001	+2.2±14.5	+7.0±17.7	<0.001
High-density lipoprotein	+1.7±12.7	+60.9±28.7	<0.001	+1.8±14.0	+72.1±34.7	<0.001
Low-density lipoprotein	+2.5±21.7	-24.0±25.1	<0.001	+3.0±23.7	-24.9±28.5	<0.001
Triglycerides						
Median	+1	-9	<0.001	+1	-9	<0.001
Interquartile range	-17 to 23	-26 to 11		-18 to 25	-27 to 13	
Apolipoprotein						
A-I	+1.3±18.6	+25.3±24.4	<0.001	NA	NA	NA
B	+2.0±16.6	-12.5±19.2	<0.001	NA	NA	NA
Vital signs (absolute change)						
Blood pressure — mm Hg†						
Systolic	+0.4±10.6	+4.4±11.8	<0.001	+0.9±11.5	+5.4±13.2	<0.001
Diastolic	+0.1±6.7	+2.1±7.2	<0.001	-0.1±7.4	+2.0±8.1	<0.001
Heart rate — beats/min	+0.4±7.2	+0.2±7.2	0.21	-0.1±7.7	-0.2±7.9	0.25
Electrolytes (absolute change) — mmol/liter						
Potassium	+0.02±0.37	-0.12±0.39	<0.001	+0.06±0.39	-0.08±0.42	<0.001
Sodium	0±3.14	+0.58±3.21	<0.001	+0.78±2.97	+1.39±3.12	<0.001
Chloride	-0.14±2.80	+0.10±2.92	<0.001	+0.01±2.78	+0.08±2.97	0.06
Bicarbonate	+0.55±3.54	+0.82±3.45	<0.001	+1.93±3.47	+2.28±3.48	<0.001
Renal function (absolute change)						
Creatinine — mg/dl	+0.002±0.115	-0.013±0.111	<0.001	+0.005±0.142	-0.008±0.140	<0.001
Estimated glomerular filtration rate — ml/min/1.73 m ²	-0.2±9.9	+1.0±9.6	<0.001	-0.3±10.8	+0.8±10.8	<0.001

ated glomerular filtration rate was calculated as described previously.¹⁵

The QT interval was calculated with the use of Bazett's correction. A decision to measure aldo-

sterone was made after termination of the trial after investigators observed a pattern of change in serum electrolytes and blood pressure. Stored serum samples that had been obtained from pa-

Table 2. (Continued.)

Variable	Change at 3 Months			Change at 12 Months		
	Atorvastatin Only	Torcetrapib plus Atorvastatin	P Value	Atorvastatin Only	Torcetrapib plus Atorvastatin	P Value
Liver function (absolute change)						
Aspartate aminotransferase — U/liter	-0.04±17.3	-0.70±7.3	<0.001	+0.08±9.03	-0.58±16.1	<0.001
Alanine aminotransferase — U/liter	+0.1±27.3	-0.6±11.5	<0.001	+0.1±12.5	-0.8±26.8	<0.001
Alkaline phosphatase — U/liter	+0.7±12.9	+0.1±14.6	<0.001	+0.3±16.4	+0.2±14.7	0.33
Bilirubin — mg/dl						
Total	-0.02±0.21	-0.04±0.21	<0.001	-0.04±0.21	-0.06±0.22	<0.001
Direct	-0.003±0.053	+0.009±0.057	<0.001	-0.002±0.055	+0.012±0.063	<0.001
Creatine kinase — U/liter	+1.3±114.7	-3.4±137.2	0.001	+1.2±93.7	-4.5±138.5	<0.001
Other selected measures (absolute change)						
QT interval (Bazett-corrected) — msec						<0.001
Median	NA	NA		-0.3	+3.3	
Interquartile range				-14.3 to 13.7	-10.3 to 17.3	
C-reactive protein — mg/liter			0.01			
Median	0	+0.04		NA	NA	
Interquartile range	-0.50 to 0.58	-0.40 to 0.60				

* Plus–minus values are means ±SD. Complete data were not available for all patients; for each measurement, baseline values were missing for less than 5% of patients, and values at 3 months or 12 months were missing for less than 10% of patients. To convert the values for cholesterol to millimoles per liter, multiply by 0.02586. To convert the values for triglycerides to millimoles per liter, multiply by 0.01129. To convert the values for creatinine to micromoles per liter, multiply by 88.4. To convert the values for bilirubin to micromoles per liter, multiply by 17.1. NA denotes not available.

† An increase of more than 15 mm Hg in systolic blood pressure was observed at 3 months in 7.6% of the atorvastatin-only group and 15.3% of the torcetrapib group and at 12 months in 9.4% of the atorvastatin-only group and 19.5% of the torcetrapib group (P<0.001 for both comparisons).

tients at baseline and at 3 months were used, with measurements made by means of liquid chromatography–tandem mass spectrometry (Mayo Central Laboratory for Clinic Trials).

EFFICACY MEASURES

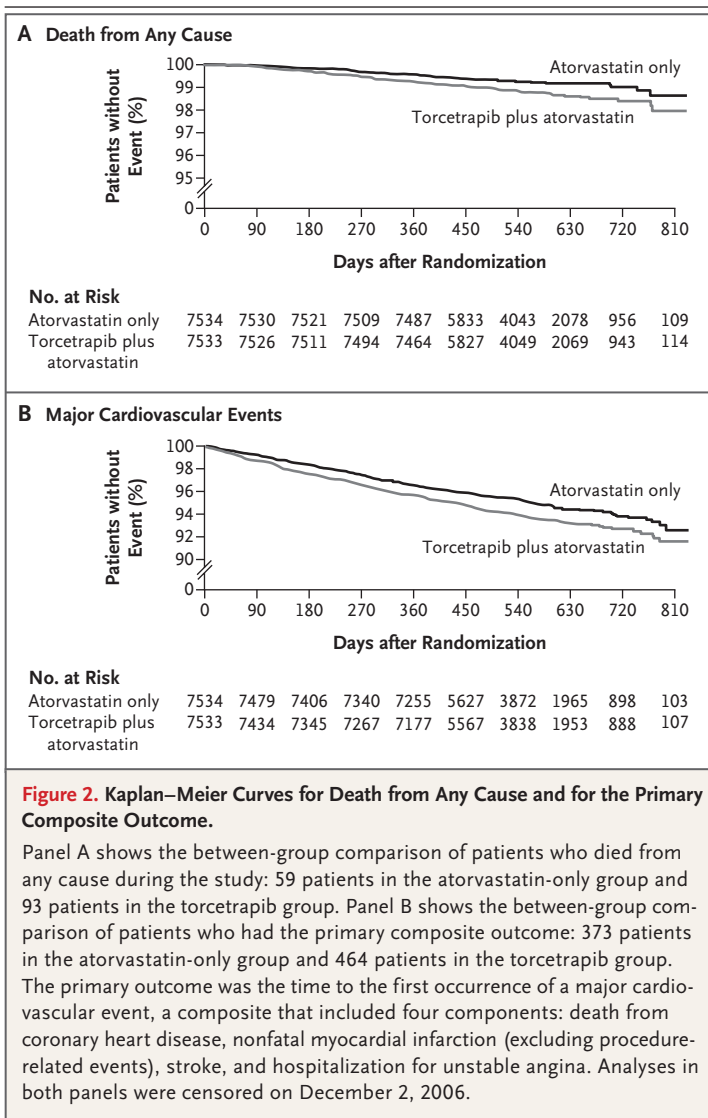
The primary outcome was the time to the first occurrence of a major cardiovascular event, a composite that included four components: death from coronary heart disease (defined as fatal myocardial infarction excluding procedure-related events, fatal heart failure, sudden cardiac death, or other cardiac death), nonfatal myocardial infarction (excluding procedure-related events), stroke, and hospitalization for unstable angina.

Secondary outcomes were the time to the first occurrence of each individual component of the primary outcome, the time to death from any cause, and the change from baseline in LDL and HDL cholesterol levels. Tertiary outcomes included further breakdowns in categories and composites of secondary outcomes.

Members of a central committee who were unaware of study-group assignments adjudicated potential outcomes as reported by the investigators. Adjudicated outcomes are not included in totals of adverse events and serious adverse events.

STATISTICAL ANALYSIS

The original design assumed a sample size of 13,000 patients (6500 per treatment group) to yield 551 primary outcomes in the atorvastatin-only group (8.48%) and 433 in the group receiving both atorvastatin and torcetrapib (6.66%) after an average of 4.5 years of follow-up — in other words, an absolute reduction of 1.82 percentage points or a relative reduction of 21% in the cumulative incidence. This number of patients would provide a statistical power of 90% to detect a treatment difference in the primary efficacy analysis at the two-sided level of 0.05 with the use of a log-rank test. A total of 15,067 patients underwent randomization, with overenrollment owing to an increase in screening activity after notification of



an upcoming closure in enrollment at each site. On the basis of the modified primary outcome in the amended protocol and on the increased number of patients, the number of primary outcomes at an average follow-up of 4.5 years was expected to be 1820.

The prespecified safety-monitoring boundary (a P value <0.01 , unadjusted for multiple comparisons) was based on a log-rank test for death from any cause. An efficacy-monitoring boundary (to be implemented after approximately 50% of the expected number of events had occurred in the primary outcome) was prespecified, but the requisite event count was never reached.

All treatment comparisons were performed with the use of an intention-to-treat analysis. All

data were censored for the primary analyses on December 2, 2006, when the trial was terminated. Events occurring after that date, in the period between termination of the study and the end of data collection, are also reported. These events were captured either at a final visit after the discontinuation of a study drug (active surveillance) or as a result of instructions to patients to report serious adverse events (passive surveillance). The last adjudicated outcome reported during this observation period occurred on July 15, 2007.

P values for continuous and ordered categorical data were computed with the use of a non-parametric Wilcoxon test. Pearson's chi-square test (without continuity correction) was used for dichotomous and unordered categorical data. The log-rank test was used for time-to-event analyses. Post hoc exploratory analyses were also performed; only descriptive statistics were used to identify patterns of association, since these analyses were not inferential in nature. No adjustments have been made for multiple comparisons.

RESULTS

PATIENTS

Between August 23, 2004, and December 28, 2005, a total of 15,067 patients underwent randomization at 260 centers in seven countries. Of these patients, 7534 were assigned to receive atorvastatin plus placebo (atorvastatin-only group), and 7533 were assigned to receive torcetrapib plus atorvastatin (torcetrapib group) (Fig. 1). At the end of the study on December 2, 2006, the median follow-up in each group was 550 days. Earlier discontinuation of treatment had occurred in 831 patients in the atorvastatin-only group (11.0%) and in 1008 patients in the torcetrapib group (13.4%). Higher rates of discontinuation owing to nonfatal adverse events in the torcetrapib group were associated mainly with a higher frequency of hypertension, nonspecific gastrointestinal symptoms, and headache. Follow-up was 99.7% complete, with 20 patients in the atorvastatin-only group and 19 patients in the torcetrapib group who were not followed until December 2, 2006. Baseline demographic and clinical characteristics of the two groups are presented in Table 1. Patients with a history of diabetes but no evidence of cardiovascular disease at study entry represented 18.8% of the atorvastatin-only group and 17.9% of the torcetrapib group (data not shown).

Table 3. Estimated Hazard Ratios for Protocol-Specified Cardiovascular Outcomes.*

Variable	Atorvastatin Only (N = 7534) <i>number (percent)</i>	Torcetrapib plus Atorvastatin (N = 7533) <i>number (percent)</i>	Hazard Ratio (95% CI)	P Value†
Primary composite outcome‡	373 (5.0)	464 (6.2)	1.25 (1.09–1.44)	0.001
Secondary outcome				
Death from coronary heart disease	33 (0.4)	40 (0.5)	1.21 (0.77–1.92)	0.41
Nonfatal myocardial infarction§	118 (1.6)	142 (1.9)	1.21 (0.95–1.54)	0.13
Stroke	40 (0.5)	43 (0.6)	1.08 (0.70–1.66)	0.74
Hospitalization for unstable angina	201 (2.7)	270 (3.6)	1.35 (1.13–1.62)	0.001
Death from any cause	59 (0.8)	93 (1.2)	1.58 (1.14–2.19)	0.006
Tertiary outcome				
Composite of death from coronary heart disease, nonfatal myocardial infarction, and stroke§	185 (2.5)	214 (2.8)	1.16 (0.95–1.41)	0.14
Stroke				
Hemorrhagic	2 (<0.1)	5 (0.1)	2.50 (0.49–12.91)	0.26
Ischemic	30 (0.4)	31 (0.4)	1.03 (0.63–1.71)	0.89
Embolic	9 (0.1)	7 (0.1)	0.78 (0.29–2.09)	0.62
Not classified	0	0	NA	NA
Coronary revascularization procedure	403 (5.3)	505 (6.7)	1.27 (1.11–1.44)	<0.001
Peripheral vascular disease¶	159 (2.1)	110 (1.5)	0.69 (0.54–0.88)	0.003
Transient ischemic attack	13 (0.2)	23 (0.3)	1.77 (0.90–3.50)	0.09
Hospitalization with primary diagnosis of congestive heart failure	50 (0.7)	84 (1.1)	1.69 (1.19–2.39)	0.003
Major coronary event	147 (2.0)	179 (2.4)	1.22 (0.98–1.52)	0.07
Major cardiovascular event and coronary revascularization procedure	589 (7.8)	738 (9.8)	1.27 (1.14–1.42)	<0.001
Major cardiovascular event, coronary revascularization procedure, and peripheral vascular disease	723 (9.6)	820 (10.9)	1.15 (1.04–1.27)	0.008
Stroke and transient ischemic attack	53 (0.7)	65 (0.9)	1.23 (0.85–1.77)	0.27
Major coronary event, stroke, and transient ischemic attack	197 (2.6)	234 (3.1)	1.19 (0.99–1.44)	0.07
Procedure-related myocardial infarction	8 (0.1)	11 (0.1)	1.38 (0.55–3.42)	0.49

* Data were censored on December 2, 2006, the date of the termination of the study. NA denotes not applicable.

† P values were calculated with the use of the log-rank test.

‡ The primary composite outcome was the time to the first occurrence of a major cardiovascular event, a composite that included four components: death from coronary heart disease, nonfatal myocardial infarction (excluding procedure-related events), stroke, and hospitalization for unstable angina.

§ Procedure-related myocardial infarction was excluded from this category.

¶ Peripheral vascular disease includes either first diagnosis or any procedure.

|| A major coronary event was the time to the first occurrence of death from coronary heart disease or nonfatal myocardial infarction (excluding procedure-related events).

BASELINE AND FOLLOW-UP LABORATORY AND CLINICAL ASSESSMENTS

Changes in lipids were evident within the first month after randomization (Fig. 1 of the Supplementary Appendix, available with the full text of this article at www.nejm.org). At 1 year, there were significant differences ($P < 0.001$) between the

torcetrapib group and the atorvastatin-only group. In the atorvastatin-only group, all lipid changes were minimal during the study; in the torcetrapib group, these changes included an increase of 72.1% in the HDL cholesterol, a decrease of 24.9% in LDL cholesterol, and a decrease of 9% in triglycerides (Table 2). Apolipoprotein measurements at

Table 4. Causes of Death.*

Event	Atorvastatin Only (N=59)	Torcetrapib plus Atorvastatin (N=93)
	<i>no. of patients</i>	
Any cardiovascular cause	35	49
Sudden death	25	26
Fatal myocardial infarction (not procedure-related)	6	8
Fatal stroke		
Hemorrhagic	0	4
Ischemic	0	2
Embolic	0	0
Not classified	0	0
Fatal heart failure	1	2
Other vascular-related cause	2	1
Fatal myocardial infarction (proce- dure-related)	0	2
Other cardiac-related cause	1	4
Any noncardiovascular cause	20	40
Cancer	14	24
Infection	0	9
Trauma	3	3
Suicide or homicide	1	0
Other cause	2	4
Reason unknown	4	4

* Data were censored on December 2, 2006, the date of the termination of the study.

3 months reflected the changes in lipids. The mean increase in systolic blood pressure from baseline to month 12 was 5.4 mm Hg in the torcetrapib group, as compared with 0.9 mm Hg in the atorvastatin-only group ($P<0.001$). The change in high-sensitivity C-reactive protein from baseline to month 3 differed significantly between the two groups ($P=0.01$), but the magnitude of the difference (0.04 mg per liter) was small.

Electrolyte levels were similar in the two groups at baseline (Table 1). At 12 months, there was a mean decrease in potassium of 0.08 mmol per liter in the torcetrapib group, as compared with an increase of 0.06 mmol per liter in the atorvastatin-only group ($P<0.001$). After 12 months, 2.3% of patients in the torcetrapib group and 0.6% of patients in the atorvastatin-only group had potassium levels of less than 3.5 mmol per liter ($P<0.001$). In the torcetrapib group, as com-

pared with the atorvastatin-only group, there were greater increases in levels of sodium (1.39 mmol per liter and 0.78 mmol per liter, respectively) and bicarbonate (2.28 mmol per liter and 1.93 mmol per liter, respectively; $P<0.001$).

At 12 months, the estimated glomerular filtration rate increased by 0.8 ml per minute per 1.73 m² of body-surface area in the torcetrapib group but decreased by 0.3 ml per minute per 1.73 m² in the atorvastatin-only group ($P<0.001$). The median change from baseline to month 12 in the QT interval was an increase of 3.3 msec in the torcetrapib group and a decrease of 0.3 msec in the atorvastatin-only group ($P<0.001$).

Post hoc measurements of aldosterone were performed for all patients for whom stored samples from both baseline and 3 months were available. One percent of samples submitted to the laboratory were of insufficient volume to permit analysis. Analysis was performed on baseline samples obtained from 6745 patients in the atorvastatin-only group (90.0%) and 6662 patients in the torcetrapib group (88.5%) and on samples obtained at 3 months for 6664 patients (88.4%) and 6562 patients (87.1%), respectively. Most analyzed samples (56.5% in the atorvastatin-only group and 52.7% in the torcetrapib group) had aldosterone levels below the lower limit of quantification for the test used (<4 ng per deciliter for samples with sufficient volume for undiluted testing and <8 ng per deciliter for samples with insufficient volume requiring dilution). Because of this, a direct comparison of median or mean values was not possible with these data. However, it was possible to calculate values in the 85th percentile and above, since this calculation depended only on the values of 8 ng per deciliter or more for which data were complete. At baseline, the 85th, 90th, and 95th percentiles were 8.5, 10.0, and 13.0 ng per deciliter, respectively, in the atorvastatin-only group and 8.3, 10.0, and 13.0 ng per deciliter, respectively, in the torcetrapib group ($P=0.21$). At 3 months, these percentiles were 8.6, 10.0, and 13.0 ng per deciliter in the atorvastatin-only group and 9.5, 11.0, and 14.0 ng per deciliter in the torcetrapib group ($P<0.001$). (The P values are Wilcoxon comparisons performed after truncating the data below 8 ng per deciliter.)

STUDY OUTCOMES

Figures 2A and 2B show Kaplan–Meier curves for death from any cause and the primary composite

Table 5. Relationship between Changes from Baseline to 1 Month in Key Measurements and Death from Any Cause or from Coronary Heart Disease and the Primary Outcome among 7533 Patients Who Received Torcetrapib.*

Variable	Change from Baseline to 1 Month		No. (%) with Missing Data
High-density lipoprotein cholesterol			
Change — mg/dl	Increase of ≤ 22	Increase of > 22	
No. of patients	3735	3663	135
Death — no. (%)			
Any cause	40 (1.1)	49 (1.3)	4 (3.0)
Coronary heart disease	20 (0.5)	18 (0.5)	2 (1.5)
Primary outcome — no. (%)	239 (6.4)	215 (5.9)	10 (7.4)
Low-density lipoprotein cholesterol			
Change — mg/dl	Decrease of ≥ 20	Decrease of < 20	
No. of patients	3826	3533	174
Death — no. (%)			
Any cause	43 (1.1)	46 (1.3)	4 (2.3)
Coronary heart disease	20 (0.5)	18 (0.5)	2 (1.2)
Primary outcome — no. (%)	217 (5.7)	234 (6.6)	13 (7.5)
Apolipoprotein A-I†			
Change — mg/dl	Increase of ≤ 30	Increase of > 30	
No. of patients	3650	3500	383
Death — no. (%)			
Any cause	38 (1.0)	32 (0.9)	23 (6.0)
Coronary heart disease	18 (0.5)	15 (0.4)	7 (1.8)
Primary outcome — no. (%)	234 (6.4)	198 (5.7)	32 (8.4)
Systolic blood pressure			
Change — mm Hg	Increase of ≤ 2.5	Increase of > 2.5	
No. of patients	3873	3562	98
Death — no. (%)			
Any cause	57 (1.5)	33 (0.9)	3 (3.1)
Coronary heart disease	28 (0.7)	11 (0.3)	1 (1.0)
Primary outcome — no. (%)	245 (6.3)	211 (5.9)	8 (8.2)
Serum potassium			
Change — mmol/liter	Decrease of ≥ 0.1	Decrease of < 0.1	
No. of patients	3709	3629	195
Death — no. (%)			
Any cause	54 (1.5)	35 (1.0)	4 (2.1)
Coronary heart disease	26 (0.7)	12 (0.3)	2 (1.0)
Primary outcome — no. (%)	240 (6.5)	211 (5.8)	13 (6.7)
Serum bicarbonate			
Change — mmol/liter	Increase of ≤ 0.7	Increase of > 0.7	
No. of patients	3695	3669	169
Death — no. (%)			
Any cause	35 (0.9)	54 (1.5)	4 (2.4)
Coronary heart disease	11 (0.3)	27 (0.7)	2 (1.2)
Primary outcome — no. (%)	214 (5.8)	239 (6.5)	11 (6.5)

* Data were censored on December 2, 2006, the date of the termination of the study. The primary outcome was the time to the first occurrence of a major cardiovascular event, a composite that included four components: death from coronary heart disease, nonfatal myocardial infarction (excluding procedure-related events), stroke, and hospitalization for unstable angina.

† The change in the measure of apolipoprotein A-I was between baseline and 3 months.

outcome. The hazard ratio for the primary outcome — major cardiovascular events — was 1.25 in the torcetrapib group, as compared with the atorvastatin-only group (95% confidence interval [CI], 1.09 to 1.44; $P=0.001$) (Table 3). The hazard ratio estimates for the individual components of the composite outcome ranged from 1.35 for hospitalization for unstable angina ($P=0.001$) to 1.08 for stroke ($P=0.74$).

At study termination, there were 93 deaths in the torcetrapib group and 59 in the atorvastatin-only group, for a hazard ratio of 1.58 in the torcetrapib group (95% CI, 1.14 to 2.19; $P=0.006$). The adjudicated causes of death are shown in Table 4. There was no significant interaction between study-group assignment and cause of death ($P=0.18$). In the torcetrapib group, as compared with the atorvastatin-only group, there was an increased risk of death from both cardiovascular causes (49 vs. 35) and noncardiovascular causes (40 vs. 20). No single cause of death explained the increased cardiovascular risks. For death from noncardiovascular causes, more patients in the torcetrapib group than in the atorvastatin-only group died from cancer (24 vs. 14) and infection (9 vs. 0). The primary sites of fatal cancers were similar in the two groups (Table 1 of the Supplementary Appendix). Seven of the nine deaths from infection were in patients with diabetes.

Numbers of reported major cardiovascular events and deaths occurring after the termination of the trial were similar in the two groups: 38 major cardiovascular events in each group, with 14 deaths in the torcetrapib group and 20 deaths in the atorvastatin-only group.

ADVERSE EVENTS

Adverse events were reported in 86.6% of patients in the torcetrapib group and in 83.3% of patients in the atorvastatin-only group ($P<0.001$). Among events that were significantly more frequent in the torcetrapib group than in the atorvastatin-only group were reported hypertension, which occurred in 1411 patients (18.7%) and 564 patients (7.5%, $P<0.001$), respectively; peripheral edema, in 467 (6.2%) and 353 (4.7%, $P<0.001$); angina pectoris, in 451 (6.0%) and 360 (4.8%, $P=0.001$); dyspnea, in 313 (4.2%) and 243 (3.2%, $P=0.003$); and headache, in 412 (5.5%) and 296 (3.9%, $P<0.001$). Serious adverse events were reported more frequently in the torcetrapib group than in the atorvastatin-only group (16.4% vs.

15.0%, $P=0.02$) (Table 2 of the Supplementary Appendix). Reported neoplasms (128 in the torcetrapib group and 136 in the atorvastatin-only group) and infections or infestations (182 and 177) were reported with similar frequencies in the two groups.

POST HOC EXPLORATORY ANALYSES

Post-randomization changes in selected measurements in the torcetrapib group were examined for their relationship to major cardiovascular events and death from any cause and from coronary heart disease (Table 5). The numbers and rates for these outcomes are given for subgroups whose change in the indicated measure from baseline to month 1 (or to month 3 for apolipoprotein A-I) was at or below the study-group median, as compared with above the median. The earliest time points were chosen to capture the maximum amount of information available before death. For death from any cause, higher rates were observed in association with greater decreases in potassium and greater increases in bicarbonate. For major cardiovascular events, lower rates were apparent in those with greater increases in HDL cholesterol and apolipoprotein A-I and for those who had smaller decreases in potassium and increases in bicarbonate. Paradoxically, there was an increased risk of death and major cardiovascular events in patients whose increase in systolic blood pressure was less than the median. It should be emphasized that the results shown in Table 5 were both exploratory and post hoc.

DISCUSSION

The increased mortality associated with the use of torcetrapib included increased risks of death from both cardiovascular and noncardiovascular causes. There was also a significant increase in the risk of major cardiovascular events in the torcetrapib-treated group. The question arises: By what mechanism did torcetrapib cause harm?

Clinical trials such as ours are not designed to elucidate mechanisms of either benefit or harm associated with the use of a drug. However, they may provide clues that have the potential to inform future research. To this end, we conducted a series of exploratory post hoc analyses in an attempt to gain some insight into what might have occurred.

There are at least two possible explanations for

the observation of increased mortality and morbidity associated with the use of torcetrapib in our study: an off-target effect of torcetrapib, unrelated to CETP inhibition, and an adverse effect of CETP inhibition per se, with the possible generation of dysfunctional or even proatherogenic HDL cholesterol.

A known off-target effect of torcetrapib is an increase in blood pressure. At 12 months in our study, systolic blood pressure increased by a mean of 5.4 mm Hg in the torcetrapib group from baseline, a greater effect than had been observed in earlier studies of shorter duration^{9,10} but consistent with the longer phase 3 imaging trials.^{11,13} The relationship between changes in blood pressure and clinical outcome in the torcetrapib group was counterintuitive, with an apparent increased risk of death in patients whose increase in systolic blood pressure was less than the median. However, it appeared that an increase in blood pressure above the median identified a group with lower baseline blood pressure levels, making it difficult to interpret the relationship without further analysis. The observed reduction in potassium and increases in sodium and bicarbonate in the torcetrapib group, as compared with the atorvastatin-only group, raised the possibility that the increase in blood pressure may have been a manifestation of mineralocorticoid excess. This proposition gained further support from post hoc findings of an increase in aldosterone levels in the torcetrapib group. The mechanism by which torcetrapib may have increased aldosterone levels is unknown.

Although cardiovascular events caused by a torcetrapib-induced increase in aldosterone is one possible explanation for the observed adverse outcomes, it does not rule out other unknown off-target effects of the agent. Nor does it rule out the possibility that CETP inhibition per se may have adverse effects. It has been suggested that the inhibition of CETP may generate HDL particles that are nonfunctional or even proatherogenic.¹⁶ Our study does not address the issue of how torcetrapib has a functional effect on HDL particles, although it was interesting to note that in the torcetrapib group, rates of cardiovascular events and death from coronary heart dis-

ease were lower in those whose increase in HDL cholesterol or apolipoprotein A-I was greater than the median. However, it must be emphasized that these post hoc observations are merely suggestive and do not rule out HDL dysfunctionality, nor do they rule out the possibility that other unknown effects of CETP inhibition may have contributed to a mechanism-related adverse outcome.

In conclusion, our study neither validates nor invalidates the hypothesis that raising levels of HDL cholesterol by the inhibition of CETP may be cardioprotective. Thus, the possibility that the inhibition of CETP may be beneficial will remain hypothetical until it is put to the test in a trial with a CETP inhibitor that does not share the off-target pharmacologic effects of torcetrapib.

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APPENDIX

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