

Effect of Intensive Compared With Moderate Lipid-Lowering Therapy on Progression of Coronary Atherosclerosis

A Randomized Controlled Trial

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IN A SERIES OF PIVOTAL CLINICAL trials, statin drugs have been shown to reduce both atherogenic lipoproteins and cardiovascular morbidity and mortality.¹⁻⁵ However, the optimal approach to lipid reduction with statins in patients with established coronary artery disease (CAD) remains uncertain. Although the efficacy of the various statins in reducing atherogenic lipoproteins and vascular inflammation varies significantly,⁶ the impact of these differences on clinical outcome is unknown. Because the large trials assessing morbidity and mortality were placebo controlled, they provide limited insight into differences between alternative strategies and target levels for lipid reduction. Accordingly, there is little scientific basis for

Context Statin drugs reduce both atherogenic lipoproteins and cardiovascular morbidity and mortality. However, the optimal strategy and target level for lipid reduction remain uncertain.

Objective To compare the effect of regimens designed to produce intensive lipid lowering or moderate lipid lowering on coronary artery atheroma burden and progression.

Design, Setting, and Patients Double-blind, randomized active control multicenter trial (Reversal of Atherosclerosis with Aggressive Lipid Lowering [REVERSAL]) performed at 34 community and tertiary care centers in the United States comparing the effects of 2 different statins administered for 18 months. Intravascular ultrasound was used to measure progression of atherosclerosis. Between June 1999 and September 2001, 654 patients were randomized and received study drug; 502 had evaluable intravascular ultrasound examinations at baseline and after 18 months of treatment.

Interventions Patients were randomly assigned to receive a moderate lipid-lowering regimen consisting of 40 mg of pravastatin or an intensive lipid-lowering regimen consisting of 80 mg of atorvastatin.

Main Outcome Measures The primary efficacy parameter was the percentage change in atheroma volume (follow-up minus baseline).

Results Baseline low-density lipoprotein cholesterol level (mean, 150.2 mg/dL [3.89 mmol/L] in both treatment groups) was reduced to 110 mg/dL (2.85 mmol/L) in the pravastatin group and to 79 mg/dL (2.05 mmol/L) in the atorvastatin group ($P < .001$). C-reactive protein decreased 5.2% with pravastatin and 36.4% with atorvastatin ($P < .001$). The primary end point (percentage change in atheroma volume) showed a significantly lower progression rate in the atorvastatin (intensive) group ($P = .02$). Similar differences between groups were observed for secondary efficacy parameters, including change in total atheroma volume ($P = .02$), change in percentage atheroma volume ($P < .001$), and change in atheroma volume in the most severely diseased 10-mm vessel subsegment ($P < .01$). For the primary end point, progression of coronary atherosclerosis occurred in the pravastatin group (2.7%; 95% confidence interval [CI], 0.2% to 4.7%; $P = .001$) compared with baseline. Progression did not occur in the atorvastatin group (-0.4%; CI -2.4% to 1.5%; $P = .98$) compared with baseline.

Conclusions For patients with coronary heart disease, intensive lipid-lowering treatment with atorvastatin reduced progression of coronary atherosclerosis compared with pravastatin. Compared with baseline values, patients treated with atorvastatin had no change in atheroma burden, whereas patients treated with pravastatin showed progression of coronary atherosclerosis. These differences may be related to the greater reduction in atherogenic lipoproteins and C-reactive protein in patients treated with atorvastatin.

JAMA. 2004;291:1071-1080

www.jama.com

For editorial comment see p 1132.

Author Affiliations, Financial Disclosures, and a List of the REVERSAL Investigators are listed at the end of this article.

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recommending treatment to reduce low-density lipoprotein cholesterol (LDL-C) levels below the current recommended guidelines.^{7,8}

We compared the effects of 2 statin regimens by using intravascular ultrasound. One of the regimens was designed to produce a moderate reduction in LDL-C level and the other was designed to produce an intensive (maximal) reduction in LDL-C level. Intravascular ultrasound provides detailed images of the vessel wall with a high-frequency (30 MHz), miniaturized, ultrasound transducer. Using a motorized pullback device, cross-sectional images are generated throughout the vessel length, enabling precise quantification of atherosclerotic disease burden. This study, the Reversal of Atherosclerosis with Aggressive Lipid Lowering (REVERSAL) trial, measured the rate of disease progression in patients treated with 2 different statins over an 18-month treatment period.

METHODS

The institutional review boards of all participating centers approved the REVERSAL protocol and all patients provided written informed consent. The protocol specified enrollment of patients aged 30 to 75 years who required coronary angiography for a clinical indication and demonstrated at least 1 obstruction with angiographic luminal diameter narrowing of 20% or more. The "target vessel" for intravascular ultrasound interrogation must not have undergone angioplasty or have a luminal narrowing of more than 50% throughout a "target segment" with a minimum length of 30 mm. Lipid criteria required an LDL-C level between 125 mg/dL (3.24 mmol/L) and 210 mg/dL (5.44 mmol/L) after a 4- to 10-week washout period.

Selection of Regimens

The study design sought to compare the effects on coronary disease progression of treatment regimens designed to produce an intensive lipid-lowering effect or a moderate lipid-lowering effect. For the moderate regimen, a

40-mg dose of pravastatin was selected because it was the highest approved dose at the time of study initiation and was one of the best-studied regimens in secondary prevention of coronary events.^{2,4} In addition, pravastatin carried a label approved by the Food and Drug Administration for reduction in atherosclerotic progression based on prior angiographic trials.^{9,10} Because a baseline LDL-C level of approximately 150 mg/dL (3.89 mmol/L) was anticipated, the regimen of 40 mg of pravastatin was expected to lower LDL-C to approximately 100 mg/dL (2.59 mmol/L). A dose of 80 mg of atorvastatin was selected as the more intensive agent because this dose was capable of producing the largest reduction in atherogenic lipoproteins of any available therapy.

Randomization and Allocation Concealment

Lipid-lowering medications were discontinued for at least 4 weeks. After a 2-week placebo run-in period, patients were randomized to receive either 80 mg of atorvastatin (2 × 40 mg) daily and a pravastatin placebo or 40 mg of pravastatin (1 × 40 mg) daily and 2 atorvastatin placebos (FIGURE 1). The patients and all study personnel were blinded to treatment assignment and lipid measurements. The intravascular ultrasound reading was performed by personnel who were blinded to treatment assignment. The randomization code was generated using a permuted block size of 4 (stratified by site) by a consulting statistician not otherwise involved in the trial. No other restrictions were used in the randomization procedure.

Catheterization and Intravascular Ultrasound

Following diagnostic angiography, intravascular ultrasound examination was performed in both the longest and least angulated target vessel meeting inclusion criteria. After administration of between 100 and 300 µg of intracoronary nitroglycerin, a 30 MHz, 2.6 F (0.87 mm) intravascular ultrasound catheter

(Ultracross, Boston Scientific Scimed Inc, Maple Grove, Minn) was advanced into the target vessel and the transducer was positioned distal to a side branch (distal fiduciary site). A motor drive progressively withdrew the transducer at a speed of 0.5 mm/s. During pullback, images were obtained at 30 frames/s and recorded on videotape. The intravascular ultrasound examination was screened for image quality in a core laboratory at the Cleveland Clinic Foundation. Only patients meeting prespecified image quality requirements were eligible for randomization.

The patients were examined during scheduled clinic visits every 3 months. A central laboratory performed all biochemical determinations (Medical Research Laboratory, Highland Heights, Ky).

After an 18-month treatment period, actively participating patients underwent repeat cardiac catheterization and intravascular ultrasound examination. The operator placed the intravascular ultrasound catheter in the vessel originally interrogated and positioned it distal to the original fiduciary site. A motorized pullback was repeated under conditions identical to the baseline study. (See VIDEO at <http://jama.com/cgi/content/full/291/9/1071/DC1>.)

Intravascular Ultrasound Core Laboratory Analysis

Videotapes containing the intravascular ultrasound pullbacks were analyzed in a blinded fashion by the core laboratory as previously reported.¹¹ The operator selected a distal fiduciary site, usually a branch site, as the beginning point for analysis. Subsequently, every 60th image was analyzed, generating a series of cross-sections spaced exactly 1.0-mm apart. The final cross-section analyzed was obtained at a proximal fiduciary site.

Intravascular Ultrasound Measurements

Intravascular ultrasound measurements were performed in accordance with the standards of the American College of Cardiology and the European So-

ciety of Cardiology.¹² Using the National Institutes of Health Image (version 1.62, National Institutes of Health public domain software, Bethesda, Md), the operator performed a calibration by measuring 1-mm grid marks encoded in the image. Manual planimetry was used to trace the leading edges of the luminal and external elastic membrane (EEM) borders. The accuracy and reproducibility of this method has been previously reported.¹³ In addition, intraobserver and interobserver variability were determined for a subset of patients in this trial. A total of 48 individually paired (baseline and follow-up) patient data sets were randomly chosen for evaluation by 6 intravascular ultrasound reviewers. Each reviewer reanalyzed 3 of his/her original intravascular ultrasound tapes—a total of 18 paired reviews for the analysis of intrareviewer variability. Each of the 6 reviewers also reanalyzed one of the other 5 reviewer's original intravascular ultrasound tapes—a total of 30 paired reviews for the analysis of interreviewer variability.

The primary end point (percentage change in total atheroma volume) was computed as:

$$\frac{TAV(\text{month } 18) - (\text{baseline})}{TAV(\text{baseline})} \times 100$$

where TAV is total atheroma volume. Total atheroma volume was calculated as the sum of the differences between EEM and lumen areas across all evaluable slices: total atheroma volume = $\Sigma(EEM_{CSA} - LUMEN_{CSA})$, where EEM_{CSA} = external elastic membrane cross-sectional area and $LUMEN_{CSA}$ = luminal cross-sectional area. A secondary efficacy parameter, change in percentage atheroma volume (PAV) was calculated as $PAV = PAV(\text{month } 18) - PAV(\text{baseline})$. PAV was calculated using the following formula:

$$PAV = \frac{\Sigma(EEM_{CSA} - LUMEN_{CSA})}{\Sigma(EEM_{CSA})} \times 100$$

Other prespecified secondary efficacy measures included the nominal change in atheroma volume for the 10 contiguous cross-sections with the greatest and least atheroma volume.

Statistical Methods

In the protocol, the assumptions used for power calculations required a sample size of 200 patients per treatment group to provide 90% power (assuming a SD of 23%) to detect a 7.4% difference in the primary end point with a 5% type I error rate for a 2-sided test. With an anticipated dropout rate of approximately 35%, enrollment of 300 patients per treatment group (total 600 randomized patients) was specified to provide an adequate number of evaluable patients.

Demographic and laboratory characteristics are summarized for all randomized patients completing the trial. The analysis of safety was performed in all patients who received at least 1 dose of drug. Categorical variables are described using frequencies, while continuous variables are reported as mean,

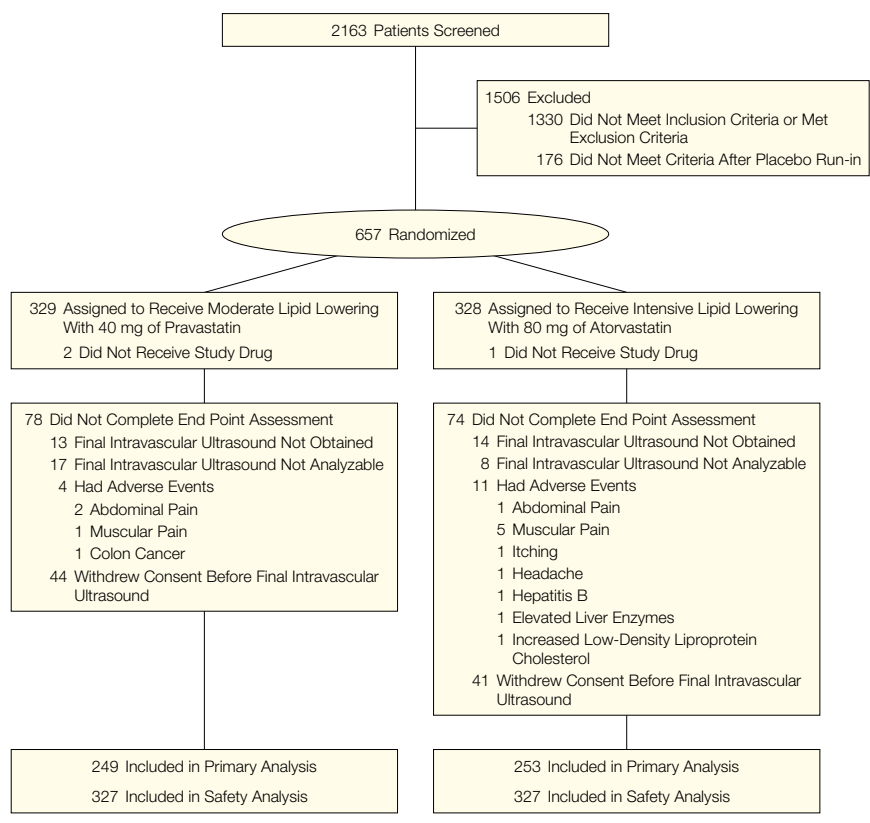
median (with 95% confidence intervals [CIs]), and SDs. For the efficacy analyses comparing treatment arms, an analysis of covariance model applied to rank-transformed data was used. For comparisons within treatment groups from baseline to follow-up, a Wilcoxon signed rank test was performed. Analysis of variance was used to analyze lipid parameters and log-transformed C-reactive protein (CRP) data. The relationship between reduction in LDL-C level and change in atheroma volume was assessed using linear regression analysis. Analyses were performed using SAS statistical software (version 8.12, SAS Institute Inc, Cary, NC).

RESULTS

Patient Population

Between June 1999 and September 2001, 2163 patients were screened, 657 were randomized, and 654 received study drug at 34 centers. A total of 502 patients had evaluable intravascular ul-

Figure 1. Disposition of Patients



trasound examinations at both baseline and 18-month follow-up (249 in the pravastatin group and 253 in the atorvastatin group). Of the 155 patients who were not included in the intravascular ultrasound analysis: 3 never received either study drug; 85 withdrew before a final intravascular ultrasound could be obtained; 15 were withdrawn for an adverse event; 27 did not have a final intravascular ultrasound; and 25 had an intravascular ultrasound examination that was not ana-

lyzable due to artifacts or pullbacks shorter than the prespecified minimum length of 30 mm. The distribution of these patients in the 2 study groups is summarized in Figure 1. Baseline demographic and laboratory characteristics are summarized in TABLE 1.

Laboratory Results

TABLE 2 summarizes laboratory values at trial completion for the 2 treatment cohorts. The mean (SD) LDL-C level was 79 (30) mg/dL (2.05 [0.78]

mmol/L) in the intensive (atorvastatin) group and 110 mg/dL (26) (2.85 [0.67] mmol/L) in the moderate (pravastatin) group ($P < .001$). Significant differences in the reduction in CRP were also observed: 36.4% in the atorvastatin group vs 5.2% in the pravastatin group ($P < .001$).

Efficacy Analyses

Primary Efficacy. TABLE 3 illustrates the results for the percentage change in atheroma volume, which is the primary efficacy parameter. Comparing the 2 regimens, the progression rate was significantly lower in the atorvastatin group ($P = .02$). The change in atheroma volume was positive in the pravastatin group (2.7%; 95% CI, 0.24-4.67), indicating net progression ($P = .001$ compared with baseline). In the atorvastatin group, the change was negative (-0.4%; 95% CI, -2.35 to 1.49), showing no disease progression ($P = .98$ compared with baseline).

Secondary Efficacy. Table 3 also illustrates the results for prespecified secondary efficacy analyses. Significant differences favoring intensive lipid lowering were observed for the nominal change in total atheroma volume ($P = .02$). Larger differences were observed for change in PAV ($P < .001$). Progression was observed in the pravastatin-treated group ($P < .001$ for both end points compared with baseline) and no progression occurred in the atorvastatin group (Table 3).

For the 10-mm subsegment with the greatest disease burden on intravascu-

Table 1. Baseline Demographic and Laboratory Characteristics

Characteristic	Type of Lipid-Lowering Regimen		P Value
	Moderate; 40 mg of Pravastatin (n = 249)	Intensive; 80 mg of Atorvastatin (n = 253)	
	Mean (SD)		
Age, y	56.6 (9.2)	55.8 (9.8)	.37
Weight, kg	91.4 (17.6)	90.9 (19.3)	.75
Body mass index*	30.5 (5.6)	30.5 (6.5)	.96
Cholesterol, mg/dL			
Total	232.6 (34.1)	231.8 (34.2)	.80
Low-density lipoprotein	150.2 (25.9)	150.2 (27.9)	.99
High-density lipoprotein	42.9 (11.4)	42.3 (9.9)	.51
Triglycerides, mg/dL	197.7 (105.6)	197.2 (95.7)	.96
Apolipoprotein B 100, mg/dL	153.0 (22.5)	152.4 (24.3)	.79
C-reactive protein, mg/L	3.0 (2.9)	2.8 (3.0)	.46
	No. (%)		
Men (n = 362)	182 (73)	180 (71)	.69
White (n = 444)	217 (87)	227 (90)	.54
Smoking status			
Current smoker (n = 132)	66 (27)	66 (26)	.97
Past or nonsmoker (n = 370)	183 (74)	187 (74)	.97
History of hypertension (n = 344)	173 (70)	171 (68)	.70
Prior statin use (n = 144)	81 (32)	63 (25)	.06
History of diabetes mellitus (n = 95)	45 (18)	50 (20)	.65
Metabolic syndrome (n = 203)	98 (39)	105 (42)	.65

SI conversion factors: To convert cholesterol to mmol/L, multiply by 0.0259; triglycerides to mmol/L, multiply by 0.0113. *Calculated as weight in kilograms divided by the square of the height in meters.

Table 2. Final Laboratory Results (n = 502)

Characteristic	Type of Lipid-Lowering Regimen				P Value*
	Moderate; 40 mg of Pravastatin (n = 249)		Intensive; 80 mg of Atorvastatin (n = 253)		
	Final Mean (SD)	Change From Baseline, %	Final Mean (SD)	Change From Baseline (%)	
Cholesterol, mg/dL					
Total	187.5 (32.2)	-18.4	151.3 (38.9)	-34.1	<.001
Low-density lipoprotein	110.4 (25.8)	-25.2	78.9 (30.2)	-46.3	<.001
High-density lipoprotein	44.6 (11.3)	5.6	43.1 (11.3)	2.9	.06
Triglycerides, mg/dL	165.8 (92.1)	-6.8	148.4 (94.9)	-20.0	<.001
Apolipoprotein B 100, mg/dL	118.1 (24.0)	-22.0	91.8 (27.9)	-39.1	<.001
C-reactive protein, mg/L	2.9 (3.0)	-5.2	1.8 (3.7)	-36.4	<.001

SI conversion factors: To convert cholesterol to mmol/L, multiply by 0.0259; triglycerides to mmol/L, multiply by 0.0113. *Analysis of variance was used to analyze lipid parameters and log-transformed C-reactive protein data.

lar ultrasound, differences between treatments were also significant ($P < .01$). There was net regression in both groups ($P < .001$ compared with baseline in the atorvastatin group and $P = .05$ compared with baseline in the pravastatin group). No differences between treatment groups were observed for the 10-mm subsegment with the least disease burden ($P = .20$).

Prespecified Subgroups. TABLE 4 illustrates the results for the primary end point (percentage change in atheroma volume) for 22 prespecified subgroups and 1 subgroup defined post-hoc. The results were similar for patients with baseline LDL-C levels above or below the mean. Compared with baseline, absence of progression was evident in the intensive lipid-lowering group (atorvastatin) for all 22 subgroups, whereas 15 of these subgroups showed statistically significant progression in the moderate lipid-lowering group (pravastatin).

Observer Variability. For the 18 patients included in the analysis for intraobserver variability, there were a total of 1177 images analyzed. The mean (SD) differences were negligible for both EEM (-0.16 mm^2 [0.68 mm^2]) and lumen areas (-0.02 mm^2 [0.75 mm^2]). Linear regression analysis showed close correlations between the original analysis and reanalysis ($r = 0.99$ for EEM; $r = 0.98$ for lumen areas). Of the 30 patients included in the analysis for interobserver variability, there were a total of 2151 images. The mean (SD) differences were negligible for both EEM (-0.07 [0.93] mm^2) and lumen areas (-0.07 [0.93] mm^2). Regression analysis showed close correlations between the original analysis and subsequent analyses ($r = 0.99$ for EEM; $r = 0.98$ for lumen areas).

Exploratory Analyses. We also compared the progression rates in the 2 treatment groups for patients attaining the guideline LDL-C level of less than 100 mg/dL (2.59 mmol/L) in post-hoc analysis. In the pravastatin group, 161 (65%) of 249 patients reached the guideline LDL-C level of less than 100 mg/dL (2.59 mmol/L) (mean [SD] level, 87.5 [9.8] mg/dL

[2.27 {0.25} mmol/L]). In the atorvastatin group, 246 (97%) of 253 patients achieved the guideline LDL-C level of less than 100 mg/dL (2.59 mmol/L) (mean [SD] level, 67.7 [16.1] mg/dL [1.75 {0.42} mmol/L]). When the 2 treatment regimens were compared, there was a strong trend toward a lower progression rate in the atorvastatin group ($P = .07$). In the subgroup attaining low LDL-C levels, there was progression in the pravastatin group

($P < .01$) and no progression in the atorvastatin group ($P = .93$) compared with baseline (Table 4).

Sensitivity Analysis. Because invasive regression-progression trials require patients to consent to a repeat catheterization for research purposes, all such trials have experienced a significant dropout rate during the course of the study. In REVERSAL, 78 pravastatin-treated patients and 74 atorvastatin patients did not complete the trial

Table 3. Change in Atheroma Volume, Change in Percentage of Atheroma Volume, and Atheroma Volume in 10-mm Subsegment With the Greatest Disease Severity

	Pravastatin (n = 249)	Atorvastatin (n = 253)	P Value Between Groups*
Atheroma Volume, mm³			
Baseline			
Mean (SD)	194.5 (114.8)	184.4 (115.7)	
Median (IQR)	168.6 (117.4 to 246.2)	161.9 (111.0 to 228.2)	.20
Follow-up			
Mean (SD)	199.6 (112.3)	183.9 (108.8)	
Median (IQR)	180.0 (125.5 to 255.3)	160.9 (107.4 to 240.3)	.05
Nominal change			
Mean (SD)	5.1 (31.4)	-0.4 (31.8)	
Median (95% CI)	4.4 (0.1 to 6.0)	-0.9 (-3.5 to 1.6)	.02†
P value compared with baseline‡	.01	.72	
Percentage change, %			
Mean (SD)	5.4 (20.1)	4.1 (29.6)	
Median (95% CI)	2.7 (0.2 to 4.7)	-0.4 (-2.4 to 1.5)	.02§
P value compared with baseline‡	.001	.98	
Percent Atheroma Volume, %			
Baseline			
Mean (SD)	39.5 (10.77)	38.4 (11.27)	
Median (IQR)	40.0 (32.5 to 46.3)	38.2 (31.7 to 45.8)	.18
Follow-up			
Mean (SD)	41.4 (10.0)	39.0 (10.8)	
Median (IQR)	41.8 (35.0 to 47.7)	38.7 (31.6 to 45.7)	.004
Nominal change			
Mean (SD)	1.9 (4.9)	0.6 (5.1)	
Median (95% CI)	1.6 (1.2 to 2.2)	0.2 (-0.3 to 0.5)	<.001†
P value compared with baseline	<.001‡	.18‡	
Atheroma Volume in 10-mm Vessel Subsegment With Greatest Disease Severity, mm³			
Baseline			
Mean (SD)	72.7 (29.0)	71.2 (29.8)	
Median (IQR)	69.4 (50.9 to 91.9)	67.2 (50.4 to 90.6)	.54
Follow-up			
Mean (SD)	71.0 (28.7)	67.0 (27.9)	
Median (IQR)	67.5 (49.3 to 91.9)	63.4 (47.2 to 83.7)	.16
Nominal change			
Mean (SD)	-1.7 (12.4)	-4.2 (12.8)	
Median (95% CI)	-1.2 (-2.63 to 0.20)	-4.2 (-5.2 to -2.9)	.01†
P value compared with baseline‡	.049	<.001	

Abbreviations: CI, confidence interval; IQR, interquartile range.

*Based on an analysis of covariance model applied to rank-transformed data.

†Prespecified secondary efficacy parameter.

‡Wilcoxon signed rank test for comparisons with baseline within groups.

§Prespecified primary efficacy parameter.

(and 3 patients never received either study drug). To examine the possibility that these patients might have altered the outcome, we performed 2 sensitivity analyses in which all 155 patients who did not complete the trial were imputed as showing no benefit from the more intensive regimen. In one of these analyses, all noncompleters in both treatment groups were assigned the median change observed for all pa-

tients. A second approach imputed all 155 noncompleters as showing no change from baseline in atheroma volume. For the imputed data, the mean and median values, SDs, and interquartile ranges are shown in TABLE 5. Because the imputed values are close to the central tendency for both treatment groups, the median values in Table 5 are identical for the 2 treatment groups and the *P* values for com-

parison with baseline cannot be readily interpreted. However, using both imputation methods, the primary efficacy analysis and both major secondary efficacy analyses (between-group comparisons) retained statistical significance.

TABLE 6 shows the adverse events and clinical end points encountered in the trial. Both regimens were well tolerated. The number of clinical events in this 18-month trial was too small for any meaningful analysis of morbidity and mortality.

Table 4. Median Percentage Change in Atheroma Volume in Prespecified Subgroups

Prespecified Subgroup	Pravastatin (n = 249)		Atorvastatin (n = 253)		<i>P</i> Value Between Groups†
	Median % Change in Atheroma Volume	<i>P</i> Value*	Median % Change in Atheroma Volume	<i>P</i> Value*	
Age, y					
≥Median (n = 231)	4.8	<.001	-1.5	.67	.01
<Median (n = 271)	-0.2	.31	0.5	.64	.75
Sex					
Male (n = 362)	2.3	.05	0.7	.72	.30
Female (n = 140)	3.9	.004	-2.3	.67	.03
Race					
White (n = 444)	3.1	.001	-0.8	.99	.03
Nonwhite (n = 58)	-1.4	.60	0.5	.81	.92
Smoking status					
Current smoker (n = 132)	0.4	.63	0.8	.88	.66
Past or nonsmoker (n = 370)	3.2	.006	-1.2	.96	.04
Body mass index‡					
≥30 (n = 234)	3.2	.008	-2.5	.59	.04
<30 (n = 268)	1.9	.06	1.5	.58	.34
History of diabetes mellitus					
Present (n = 95)	3.2	.03	0.7	.54	.35
Absent (n = 407)	2.5	.01	-0.8	.78	.06
History of hypertension					
Present (n = 344)	4.6	<.001	-0.3	.86	.03
Absent (n = 158)	1.7	.63	-1.6	.75	.86
The metabolic syndrome					
Present (n = 203)	2.1	.10	-1.2	.76	.19
Absent (n = 299)	3.2	.005	0.2	.73	.11
History of statin use					
Present (n = 144)	5.1	.003	-4.0	.91	.06
Absent (n = 358)	0.7	.06	0.3	.88	.26
Cholesterol, mg/dL					
Low-density lipoprotein					
>Mean (n = 221)	2.7	.04	1.9	.24	.66
<Mean (n = 281)	2.8	.01	-2.3	.26	.02
Patients reaching NCEP guideline level (<100 m/dL)§	1.9	.01	-0.9	.93	.07
High-density lipoprotein					
>Mean (n = 206)	4.4	.006	-1.5	.97	.07
<Mean (n = 296)	1.7	.05	0.1	.92	.24

Abbreviation: NCEP, National Cholesterol Education Program.

SI conversion factor: To convert cholesterol to mmol/L, multiply by 0.0259.

*Wilcoxon signed rank test for comparisons with baseline within groups.

†Based on an analysis of covariance model applied to rank-transformed data.

‡Calculated as weight in kilograms divided by the square of the height in meters.

§Post-hoc analysis (not prespecified). Of 249 patients receiving pravastatin, 167 achieved NCEP guideline level; and of 253 patients receiving atorvastatin, 246 achieved NCEP guideline level.

COMMENT

Although statin drugs are among the best-studied contemporary cardiovascular therapies, the optimal approach to cholesterol reduction in patients with established CAD remains controversial. Current US and European guidelines emphasize reducing LDL-C level to less than 100 mg/dL (2.59 mmol/L).^{7,8} The guidelines assume that different strategies for lipid lowering will provide similar benefits as long as patients attain the recommended LDL-C target level. Because major statin trials typically have used a uniform dose of a single statin in all patients, no comparative data exist to suggest a greater clinical benefit for more aggressive targets or alternative agents. We approached this knowledge gap by performing the first active-control statin trial of CAD progression.

In the current trial, patients with moderate cholesterol elevations received 18 months of intensive therapy with 80 mg of atorvastatin and showed significantly reduced progression of coronary atherosclerosis in comparison with patients who received a more moderate regimen consisting of 40 mg of pravastatin. For the primary and secondary efficacy measures, lower progression rates were observed in the intensively treated patients (*P* = .02 to *P* < .001). Numerically similar results were observed in prespecified subgroups (Table 4). Overall, these findings provide strong evidence that intensive treatment using the maximum approved dose of atorvastatin reduces

progression of atherosclerosis compared with a more moderate regimen consisting of 40 mg of pravastatin.

These findings have potential implications for treatment guidelines for patients with dyslipidemia and established CAD. Current recommendations are based on the principle of a recommended threshold for optimal benefit (established as a level of LDL-C of <100 mg/dL [<2.59 mmol/L]) for secondary prevention. The current study suggests that optimal benefits are achieved using a more intensive regimen (atorvastatin) designed to achieve LDL-C levels well below current guidelines. Differences between the 2 treatment regimens were evident for patients with baseline LDL-C and high-density lipoprotein cholesterol levels above and below the mean (Table 4). Thus, patients with entry LDL-C levels below the mean actually showed similar benefit when they received the more intensive (atorvastatin) regimen ($P = .02$; Table 4). This finding is consistent with other recent clinical trials, such as the Heart Protection Study, which demonstrated a further risk reduction when simvastatin was administered to patients with baseline LDL-C levels above and below 100 mg/dL (2.59 mmol/L).⁵ Although the current study does not provide sufficient evidence to modify guidelines, several ongoing trials are examining clinical outcomes following more intensive compared with less intensive treatment.

The REVERSAL trial suggests several potential mechanisms for the greater benefit observed with an intensive treatment regimen. Most atherogenic lipoproteins were reduced to a greater extent in the intensive treatment group (atorvastatin), including levels of LDL-C, total cholesterol, and triglycerides. However, factors other than greater LDL-C-reducing efficacy may also have influenced the results, including the differential effect of the 2 treatment regimens on inflammation. The 36.4% reduction in CRP in the atorvastatin group compared with the 5.2% reduction in the pravastatin group was larger than expected and signifi-

Table 5. Sensitivity Analyses Imputing Results for Patients Not Completing Trial

	Pravastatin (n = 329)	Atorvastatin (n = 328)	P Value Between Groups*
Median Imputation Method			
Nominal change in atheroma volume, mm ³			
Mean (SD)	4.2 (27.4)	0 (27.9)	
Median (95% CI)	1.38 (-2.4 to 5.2)	1.38 (-2.3 to 5.1)	.04
P value compared with baseline†	<.001	<.001	
Percentage change in atheroma volume, %			
Mean (SD)	4.3 (17.6)	3.4 (26.0)	
Median (95% CI)	0.9 (-2.6 to 4.4)	0.9 (-1.5 to 3.3)	.04
P value compared with baseline†	<.001	<.001	
Change in percentage atheroma volume, %			
Mean (SD)	1.7 (4.3)	0.7 (4.5)	
Median (95% CI)	0.9 (0.3 to 1.5)	0.9 (0.3 to 1.5)	<.01
P value compared with baseline†	<.001	<.001	
Zero Change Imputation Method			
Nominal change in atheroma volume, mm ³			
Mean (SD)	3.8 (27.4)	-0.3 (27.9)	
Median (95% CI)	0 (-3.8 to 3.8)	0 (-3.8 to 3.8)	.05
P value compared with baseline†	.13	.80	
Percentage change in atheroma volume, %			
Mean (SD)	4.1 (17.7)	3.2 (26.0)	
Median (95% CI)	0 (-3.6 to 3.6)	0 (-2.5 to 2.5)	.05
P value compared with baseline†	.13	.80	
Change in percentage atheroma volume, %			
Mean (SD)	1.4 (4.3)	0.5 (4.5)	
Median (95% CI)	0 (-0.6 to 0.6)	0 (-0.6 to 0.6)	<.01
P value compared with baseline†	<.001	.71	

Abbreviation: CI, confidence interval.

*Based on an analysis of covariance model applied to rank-transformed data.

†Wilcoxon signed rank test for comparison with baseline within groups.

Table 6. Adverse Events, Drug Discontinuations, and Clinical End Points (Safety Population)

	No. (%) of Patients	
	Pravastatin	Atorvastatin
Major adverse event	(n = 327)	(n = 327)
Death	1 (0.3)	1 (0.3)
Myocardial infarction	7 (2.1)	4 (1.2)
Stroke	1 (0.3)	1 (0.3)
Alanine aminotransferase >3*	(n = 316) 5 (1.6)	(n = 311) 7 (2.3)
Aspartate aminotransferase >3*	2 (0.6)	2 (0.6)
Creatine phosphokinase >10*	0	0
Drug discontinuation†	(n = 327) 22 (6.7)	(n = 327) 21 (6.4)
Musculoskeletal complaint‡	12 (3.4)	9 (2.8)
Abdominal complaint§	5 (1.5)	3 (0.9)
Cancer	2 (0.6)	0
Chest pain	2 (0.6)	0
Increased aspartate or alanine aminotransferase <3	0	4 (1.2)
Other	1 (0.6)	5 (1.5)

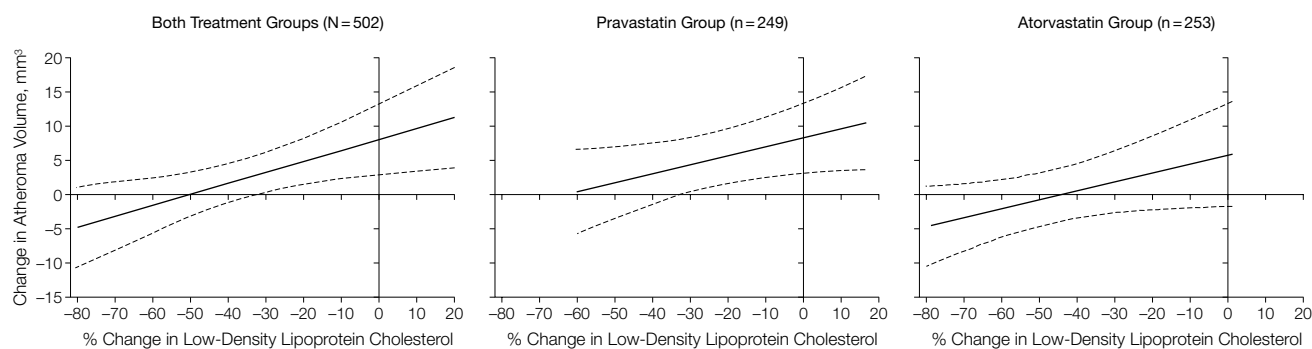
*Multiplied by the upper limit of normal.

†Regardless of whether the patient dropped out of the study.

‡Muscle pain or weakness, joint pain, or elevated creatinine phosphokinase (<10 times the upper limit of normal).

§Abdominal pain, cramping, or diarrhea.

||Flu-like symptoms, hot flashes, itching, headaches, or hepatitis B.

Figure 2. Comparison of Percentage of Low-Density Lipoprotein Cholesterol Reduction and Change in Atheroma Volume

The solid line indicates the relationship between mean change in low-density lipoprotein cholesterol and change in atheroma volume from linear regression analysis. The dashed lines indicate the upper and lower 95% confidence limits for the mean values.

cant ($P < .001$). Further analysis will be required to elucidate the relationship between the extent of reduction in CRP or other inflammatory markers and the effect on the progression of coronary atherosclerosis.

In addition to unpaired comparisons between the 2 treatment groups, the study prespecified paired analysis within groups to determine whether progression or regression had occurred from baseline to follow-up. Absence of measurable progression in the intensively treated cohort was evident for the primary end point, 3 prespecified secondary end points, and 22 prospectively defined subgroups (Tables 3 and 4). These subgroups included men and women, individuals with or without diabetes, and individuals with or without hypertension. In contrast, patients treated with a more moderate regimen of 40 mg of pravastatin showed significant progression ($P = .01$ to $P < .001$ compared with baseline) for all 4 prespecified efficacy parameters (Table 3) and 15 of 22 subgroups (Table 4).

An inverse relationship between percentage reduction in LDL-C level and atherosclerosis progression (change in atheroma volume) for both drugs was apparent from linear regression analysis (FIGURE 2). Expressed as percentage change, each 10% reduction in LDL-C level (15 mg/dL [0.39 mmol/L]) yielded approximately a 1% reduction in the change in atheroma volume after 18 months. However, LDL-C

level reductions alone did not explain all of the differences in efficacy. Although the 2 regression lines are parallel, the progression rate at any level of LDL-C reduction was lower with atorvastatin compared with pravastatin. The lower progression rate in the atorvastatin group was equivalent to an additional 20% (30 mg/dL [0.78 mmol/L]) reduction in LDL-C level. These data strongly suggest that other factors played an important role in the improved outcome in the group treated with atorvastatin. The most likely explanation is the larger reduction in CRP and other atherogenic lipoproteins, such as triglycerides, in the atorvastatin group. Supporting this observation, progression occurred even in the patients in whom pravastatin lowered LDL-C level below the recommended goal of 100 mg/dL (2.59 mmol/L) (mean [SD], 88 [9.8] mg/dL [2.27 {0.25} mmol/L]; Table 4). Importantly, the lower progression rate in the more intensive atorvastatin treatment group was achieved with a safety and tolerability profile similar to the more moderate pravastatin regimen (Table 6).

This is the first large randomized trial to directly compare the rate of CAD progression for patients treated with 2 different statins. All prior coronary regression-progression trials were placebo controlled and had a longer duration (2-3 years). Although a recent single center study using a combination of simvastatin and niacin showed reduc-

tion in angiographic stenosis severity, most prior trials have shown only slowing of the progression of the disease but neither regression nor an absence of progression.^{9-10,14-16} However, these studies used typical starting doses of statins and therefore did not explore the potential of more intensive therapy to delay or prevent progression. The current study had several important advantages over earlier studies. The actively tested agent, atorvastatin (80 mg dose), is a more potent lipid-lowering agent and produced both a reduction in LDL-C level approaching 50% and large reductions in CRP. The method (intravascular ultrasound) for assessing atherosclerosis is also relatively novel, allowing measurement of atheroma burden, not merely luminal narrowing.^{11,17,18} Interestingly, 2 other studies using an ultrasound method for imaging the vessel wall (measurement of carotid intimal medial thickness) also showed reduced progression with intensive treatment using 80 mg of atorvastatin.^{19,20}

Because different doses of the 2 statins were used, the potential impact of using a higher dose of pravastatin on the trial results must be considered. At the time of study initiation, the highest dose of pravastatin approved by the Food and Drug Administration was 40 mg. An 80-mg dose was approved midway through the trial. However, we deemed it undesirable to alter the dose of either study drug during an ongo-

ing clinical trial. Furthermore, the reduction in LDL-C level of all statins, including pravastatin, increases only moderately with an increased dose.²¹ The labeling approved by the Food and Drug Administration indicates only a 3% greater mean LDL-C reduction using 80 mg of pravastatin compared with the 40-mg dose. A meta-analysis of statin trials calculated only a 4% greater effect with 80 mg of pravastatin.²¹ Accordingly, we think it is unlikely that the use of the recently approved 80-mg dose of pravastatin would have significantly affected study results.

The importance of the progression rate of atherosclerosis as a clinical trial end point also requires additional comment. It is statistically challenging to perform actively controlled statin trials using morbidity and mortality end points because the differences in event rates are likely to be small. Such studies require enrollment of approximately 10 000 patients for 5 to 6 years of follow-up. The current study design enabled comparison of 2 active drugs with a sample size of about 500 patients and a duration of only 18 months. However, to accept this result as clinically meaningful, evidence of a relationship between progression rate and clinical outcome is important. Such a relationship has been demonstrated in prior angiographic trials with a high rate of adverse clinical outcomes in patients with more rapid disease progression.^{22,23} In these studies, small differences in progression rate of atherosclerosis were associated with significant differences in clinical outcome.

We believe that the current study has important implications for understanding the natural history of CAD. Previously, coronary atherosclerosis has been perceived as a progressive disease process in which most therapies are designed to slow the inexorable advancement of the disease. The present study suggests an impending paradigm shift, in which intensive lipid-modulating strategies can be used to stop and potentially reverse the atherosclerotic disease process. In some patients in the

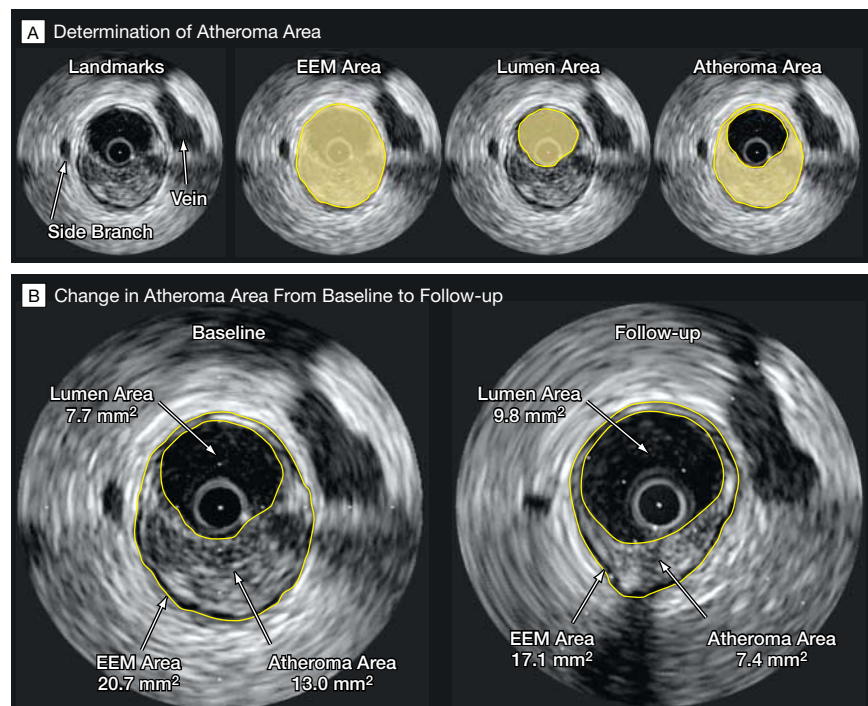
REVERSAL trial, substantial regression in atherosclerotic disease burden was observed (FIGURE 3). These observations confirm the potential of anti-atherosclerotic therapies to reverse the disease process. However, it also must be emphasized that many patients in both groups had significant progression despite statin treatment.

The current study has limitations. Intravascular ultrasound is a relatively new modality for assessment of atherosclerotic disease burden. Accordingly, the clinical implications of evidence of drug benefit derived from intravascular ultrasound remain uncertain. We also recognize that the major adverse clinical outcomes of death and myocardial infarction are the most important end points for secondary prevention trials. There were too few events for any meaningful analysis because 502 patients were followed up for only 18 months (Table 6). Therefore, our find-

ings must be confirmed in large outcome studies comparing morbidity and mortality using alternative lipid-lowering regimens. Several studies are under way comparing the effect of intensive with moderate lipid-lowering regimens on clinical events. These results will not be available for several years.

Despite these limitations, we believe the following conclusions are warranted. For secondary prevention, intensive treatment with 80 mg of atorvastatin in patients with moderate cholesterol elevations reduced progression of coronary atherosclerosis compared with a more moderate lipid-lowering regimen consisting of 40 mg of pravastatin. Compared with baseline, intensive treatment halted progression of atherosclerosis, whereas moderate therapy was associated with significant disease progression. The intensive regimen produced greater re-

Figure 3. Intravascular Ultrasound Images at Baseline and Follow-up



A, Atheroma area is calculated by subtracting the lumen area from the area of the external elastic membrane (EEM). B, Patient randomized to 80 mg of atorvastatin. There is substantial reduction in atheroma area (from 13.0 to 7.4 mm²). A lesser increase in lumen area is noted (from 7.7 to 9.8 mm²). See video at <http://jama.com/cgi/content/full/291/9/1071/DC1>.

ductions in atherogenic lipoproteins and CRP, which likely explain the improved outcome. A more intensive lipid-lowering therapy is required than is currently recommended by national and international guidelines to obtain maximal reduction in the progression of coronary atherosclerosis.

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Author Contributions: Dr Nissen had full access to all of the data in the study and takes responsibility for

the integrity of the data and the accuracy of the data analysis.

Study concept and design: Nissen, Tuzcu, Ganz, Vogel. **Acquisition of data:** Nissen, Tuzcu, Schoenhagen, Vogel, Howard, Cooper, Brodie, Grines, DeMaria. **Analysis and interpretation of data:** Nissen, Tuzcu, Schoenhagen, Brown, Ganz, Vogel, Crowe, Grines, DeMaria.

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Critical revision of the manuscript for important intellectual content: Nissen, Tuzcu, Schoenhagen, Brown, Ganz, Vogel, Crowe, Howard, Brodie, Grines, DeMaria. **Statistical expertise:** Nissen, Brown, Ganz.

Obtained funding: Nissen, Tuzcu.

Administrative, technical, or material support: Nissen, Tuzcu, Ganz, Vogel, Crowe, Howard.

Supervision: Nissen, Tuzcu, Schoenhagen, Ganz, Vogel, Cooper, Brodie, Grines.

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monary Associates (John Corbelli, MD); New York: Mount Sinai Hospital (Samin Sharma, MD). **North Carolina:** Chapel Hill: University of North Carolina (Sidney C. Smith, MD); Greensboro: LeBauer Cardiovascular Research Foundation (Bruce Brodie, MD); Greenville: East Carolina University (Michael Miller, MD); Winston-Salem: Wake Forest University (Michael A. Kutcher, MD). **Ohio:** Cleveland: Cleveland Clinic Foundation (E. Murat Tuzcu, MD); University Hospitals of Cleveland (Ravi Nair, MD); Columbus: Ohio State University Medical Center (Raymond Magorien, MD); Elyria: North Ohio Heart Care (Charles O'Shaughnessy, MD); Toledo: Medical College of Ohio (Christopher Cooper, MD). **Oklahoma:** Heart Institute, Tulsa (Wayne N. Leimbach, MD). **Pennsylvania:** Heart Care Group PC, Allentown (J. Patrick Kleaveland, MD). **Rhode Island:** Miriam Hospital, Providence (Paul Gordon, MD); Rhode Island Hospital, Providence (Barry Sharaf, MD). University of Texas, San Antonio (Steven R. Bailey, MD). University of Washington Medical Center, Seattle (David Linker, MD).

Funding/Support: This study was funded by Pfizer.

Role of the Sponsor: The sponsor, Pfizer, participated in discussions regarding study design and protocol development and provided logistical support during the trial. Monitoring of the study was performed by a contract research organization, Covalent, under contract with the sponsor, and maintained the trial database. The intravascular ultrasound end points were prepared by the Cleveland Clinic Cardiovascular Coordinating Center. Statistical analysis was performed by Averion Inc, under contract with the sponsor. The manuscript was prepared by the corresponding author and modified after consultation with the other authors. The sponsor was permitted to review the manuscript and suggest changes, but the final decision on content was exclusively retained by the authors.

Related Information: Online video available at <http://jama.com/cgi/content/full/291/9/1071/DC1>.

Acknowledgment: We acknowledge the contributions made by Brian Lyman, PhD, Kim Caswell, RN, Penny Sambrook, BS, Halit Silbershatz, PhD, Gary Palmer, MD, Lee Golden, MD, and John Tsai, MD.

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