

Effect of Very High-Intensity Statin Therapy on Regression of Coronary Atherosclerosis

The ASTEROID Trial

Steven E. Nissen, MD
Stephen J. Nicholls, MBBS, PhD
Ilke Sipahi, MD
Peter Libby, MD
Joel S. Raichlen, MD
Christie M. Ballantyne, MD
Jean Davignon, MD
Raimund Erbel, MD
Jean Charles Fruchart, PhD
Jean-Claude Tardif, MD
Paul Schoenhagen, MD
Tim Crowe, BS
Valerie Cain, MS
Kathy Wolski, MPH
Marlene Goormastic, MPH
E. Murat Tuzcu, MD
for the ASTEROID Investigators

ATHEROSCLEROSIS IS GENERALLY viewed as a chronic, progressive disease characterized by continuous accumulation of atheromatous plaque within the arterial wall. The last 2 decades have witnessed the introduction of a variety of antiatherosclerotic therapies, most notably the 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors (statins). Although statins rank among the most extensively studied therapies in contemporary medicine, the optimal target levels for low-density lipoprotein cholesterol (LDL-C) remain controversial. Recently, several active control trials have reported that more intensive statin

Context Prior intravascular ultrasound (IVUS) trials have demonstrated slowing or halting of atherosclerosis progression with statin therapy but have not shown convincing evidence of regression using percent atheroma volume (PAV), the most rigorous IVUS measure of disease progression and regression.

Objective To assess whether very intensive statin therapy could regress coronary atherosclerosis as determined by IVUS imaging.

Design and Setting Prospective, open-label blinded end-points trial (A Study to Evaluate the Effect of Rosuvastatin on Intravascular Ultrasound-Derived Coronary Atheroma Burden [ASTEROID]) was performed at 53 community and tertiary care centers in the United States, Canada, Europe, and Australia. A motorized IVUS pullback was used to assess coronary atheroma burden at baseline and after 24 months of treatment. Each pair of baseline and follow-up IVUS assessments was analyzed in a blinded fashion.

Patients Between November 2002 and October 2003, 507 patients had a baseline IVUS examination and received at least 1 dose of study drug. After 24 months, 349 patients had evaluable serial IVUS examinations.

Intervention All patients received intensive statin therapy with rosuvastatin, 40 mg/d.

Main Outcome Measures Two primary efficacy parameters were prespecified: the change in PAV and the change in nominal atheroma volume in the 10-mm subsegment with the greatest disease severity at baseline. A secondary efficacy variable, change in normalized total atheroma volume for the entire artery, was also prespecified.

Results The mean (SD) baseline low-density lipoprotein cholesterol (LDL-C) level of 130.4 (34.3) mg/dL declined to 60.8 (20.0) mg/dL, a mean reduction of 53.2% ($P < .001$). Mean (SD) high-density lipoprotein cholesterol (HDL-C) level at baseline was 43.1 (11.1) mg/dL, increasing to 49.0 (12.6) mg/dL, an increase of 14.7% ($P < .001$). The mean (SD) change in PAV for the entire vessel was -0.98% (3.15%), with a median of -0.79% (97.5% CI, -1.21% to -0.53%) ($P < .001$ vs baseline). The mean (SD) change in atheroma volume in the most diseased 10-mm subsegment was -6.1 (10.1) mm^3 , with a median of -5.6 mm^3 (97.5% CI, -6.8 to -4.0 mm^3) ($P < .001$ vs baseline). Change in total atheroma volume showed a 6.8% median reduction; with a mean (SD) reduction of -14.7 (25.7) mm^3 , with a median of -12.5 mm^3 (95% CI, -15.1 to -10.5 mm^3) ($P < .001$ vs baseline). Adverse events were infrequent and similar to other statin trials.

Conclusions Very high-intensity statin therapy using rosuvastatin 40 mg/d achieved an average LDL-C of 60.8 mg/dL and increased HDL-C by 14.7%, resulting in significant regression of atherosclerosis for all 3 prespecified IVUS measures of disease burden. Treatment to LDL-C levels below currently accepted guidelines, when accompanied by significant HDL-C increases, can regress atherosclerosis in coronary disease patients. Further studies are needed to determine the effect of the observed changes on clinical outcome.

Trial Registration ClinicalTrials.gov Identifier: NCT00240318

JAMA. 2006;295:1556-1565

www.jama.com

Author Affiliations and a complete list of the ASTEROID Investigators are listed at the end of this article.
Corresponding Author: Steven E. Nissen, MD,

Department of Cardiovascular Medicine, Cleveland Clinic Foundation, 9500 Euclid Ave, Cleveland, OH 44195 (nissens@ccf.org).

For editorial comment see p 1583.

therapy results in a greater reduction in adverse cardiovascular outcomes compared with more moderate treatment.¹⁻³ Accordingly, guidelines now recommend achieving more aggressive target levels (an LDL-C level of <70 mg/dL [1.8 mmol/L]) in certain very high-risk secondary prevention patients.⁴

In parallel to clinical outcomes trials, imaging studies have examined the effects of antiatherosclerotic therapies on the progression of atherosclerosis. Initial trials used quantitative coronary angiography or carotid ultrasound to determine the progression rates.⁵⁻¹⁰ More recently, intravascular ultrasound (IVUS) imaging has emerged as the predominant approach for evaluating the progression of coronary atherosclerosis.¹¹⁻¹⁹ IVUS provides a precise and reproducible method for determining the change in atheroma burden during treatment. Trials using IVUS have successfully investigated the effects of a variety of antiatherosclerotic therapies, including statins,^{12,16,17,19} blood pressure-lowering drugs,¹⁴ reduction of inflammatory markers,¹⁹ administration of a high-density lipoprotein (HDL) mimetic,¹¹ and novel investigative therapies.^{13,15,18}

The most positive IVUS trials to date have demonstrated a slowing or halting of progression of atherosclerosis during statin treatment. However, none of the major trials has provided convincing evidence of regression using rigorous IVUS measures of disease burden. We hypothesized that high-intensity statin therapy, designed to reach very low levels of LDL-C, particularly if achieved in conjunction with substantial elevation of HDL-C, might result in regression of coronary atherosclerosis. Accordingly, we designed the ASTEROID trial (A Study to Evaluate the Effect of Rosuvastatin on Intravascular Ultrasound-Derived Coronary Atheroma Burden) to examine the effects of high-intensity statin therapy on IVUS-derived measures of coronary disease progression. Rosuvastatin is the most recently introduced statin and typi-

cally produces greater reductions in LDL-C and larger increases in HDL-C than previously available agents.²⁰

METHODS

Selection of Study Patients

The institutional review boards of all participating centers approved the protocol and all patients provided written informed consent. The protocol specified enrollment of patients at least 18 years of age who required coronary angiography for a clinical indication, which typically consisted of stable or unstable ischemic chest pain syndromes or abnormal functional studies, such as exercise testing. Inclusion required demonstration of at least 1 obstruction with more than 20% angiographic luminal diameter narrowing in any coronary vessel. The target vessel for IVUS interrogation must not have undergone angioplasty nor have more than 50% luminal narrowing throughout a target segment with a minimum length of 40 mm.

All patients were statin-naïve, defined as receiving no statin therapy for more than 3 months during the previous 12 months. Patients treated with any lipid-lowering medication within the previous 4 weeks required a 4-week washout period before enrollment to obtain accurate baseline lipid values. Any baseline level of LDL-C was permitted; however, patients with uncontrolled triglyceride levels (≥ 500 mg/dL [5.7 mmol/L]) or poorly controlled diabetes (glycosylated hemoglobin levels $\geq 10\%$) were excluded.

Selection of Regimens

The study sought to determine the effects of high-intensity lipid lowering on coronary disease progression. Accordingly, we selected a regimen, rosuvastatin, 40 mg/d, that had previously demonstrated the largest reduction in LDL-C of any available statin therapy at the time of study initiation.²⁰ Rosuvastatin was also selected because previous studies had shown this agent to significantly increase HDL-C at the maximum therapeutic dosage.²⁰ Because all enrolled patients had estab-

lished coronary disease and because other trials had demonstrated substantially improved outcomes with intensive therapy, it was deemed ethically unacceptable to randomize patients in this high-risk group to low-intensity treatment. Accordingly, all patients received active treatment with rosuvastatin, 40 mg/d.

Baseline Catheterization and IVUS

Prior publications have thoroughly described the methods for IVUS interrogation.^{11,12,14,19} Following diagnostic angiography, the operator selected a target vessel for IVUS interrogation, defined as the longest and least-angulated vessel meeting inclusion criteria. After administration of 100 to 300 μ g of intracoronary nitroglycerin, a 40-MHz ultrasonography catheter (Atlantis, Boston Scientific Scimed Inc, Maple Grove, Minn) was advanced into the target vessel and the transducer was positioned distal to a side branch. The operator was instructed to select a starting point for interrogation as far distally as could be safely reached. This procedure was designed to provide the longest possible vessel segment for analysis. After selection of a starting point, the operator engaged a motor drive that progressively withdrew the transducer at a speed of 0.5 mm/s. During this pull-back, images were obtained at 30 frames per second and recorded on super-VHS videotape. The study was screened for image quality at a core laboratory at the Cleveland Clinic Foundation, Cleveland, Ohio, and only patients whose IVUS results met prespecified image quality requirements were eligible for inclusion in the study.

Clinic Visits and Laboratory Tests

Patients were examined during scheduled clinic visits every 3 months. A central laboratory performed all biochemical determinations (Medical Research Laboratory, Highland Heights, Ky). Lipid levels were obtained every 3 months and mean levels during treatment were computed from the time-weighted average of these values.

Follow-up Catheterization and IVUS

After a 24-month treatment period, actively participating patients underwent repeat IVUS examination. If a patient required coronary angiography between 18 and 24 months following enrollment, an end-of-study IVUS examination was performed then, to avoid subjecting patients to an additional invasive procedure at the 24-month visit. The operator placed the IVUS catheter in the vessel originally interrogated and positioned the transducer distal to the original branch site. A motorized pullback was repeated under conditions identical to the baseline study. This procedure was designed to obtain a series of cross-sectional images at sites identical to the original examination.

Randomization for Sequence Concealment

Videotapes containing baseline and follow-up pullbacks were analyzed in the Intravascular Ultrasound Core Laboratory at the Cleveland Clinic Foundation. All measurements were performed at the end of the study, after both the baseline and follow-up IVUS examinations were available. The baseline and follow-up pullbacks were reviewed as a pair. However, to conceal the imaging sequence, personnel not otherwise involved in the study performed blinding and randomization. As each baseline videotape was received, the images were digitized and the date imprinted on the videotape was removed from each image using digital processing. A similar procedure was performed for each follow-up videotape.

The 2 examination results were then resequenced using random assignments generated by an outside statistician. Personnel who were unaware of the coding and were therefore blinded to the sequence subsequently analyzed both videotapes. After the trial was concluded and all measurements were completed, the sequence coding was unblinded to enable calculation of changes from baseline to follow-up examination.

IVUS Analysis

A technician selected a distal branch site as the beginning point for analysis. Subsequently, every 60th image was analyzed, representing cross-sections spaced exactly 1.0 mm apart. IVUS measurements were performed in accordance with the standards of the American College of Cardiology and the European Society of Cardiology.²¹ Using customized public-domain software (ImageJ, version 1.29w, National Institutes of Health, Bethesda, Md), the technician performed a calibration by measuring 1-mm grid marks in the image. Manual planimetry was used to trace the leading edges of the luminal and external elastic membrane (EEM) borders. Previous reports have established the accuracy and reproducibility of this method.²²

Derived IVUS Measurements

The primary efficacy parameter of percent atheroma volume (PAV) was calculated as

$$\left(\frac{\sum (EEM_{CSA} - LUMEN_{CSA})}{\sum EEM_{CSA}} \right) \times 100$$

where EEM_{CSA} is the external elastic membrane cross-sectional area and $LUMEN_{CSA}$ is the luminal cross-sectional area. For each patient, the change in PAV was computed as PAV (end of treatment) – PAV (baseline).

The second prespecified primary efficacy parameter was the nominal change (end of treatment minus baseline) in total atheroma volume (TAV) in the 10-mm subsegment of the coronary artery with the largest plaque volume at baseline (the most diseased segment). The atheroma volume in the most diseased 10-mm segment was calculated as $\sum (EEM_{CSA} - LUMEN_{CSA})$, where EEM_{CSA} is the external elastic membrane cross-sectional area and $LUMEN_{CSA}$ is the luminal cross-sectional area, and the difference is summed over the 10-mm segment. For patients without 10 contiguous evaluable cross-sections, 8 or 9 cross-sections were used and the results were normalized to compensate for the missing cross-sections.

A secondary efficacy parameter, the change in normalized TAV, was calculated by first determining the average atheroma area per cross-section as

$$\frac{\text{Average Atheroma Area}}{\text{Area}} = \frac{\sum (EEM_{CSA} - LUMEN_{CSA})}{n}$$

where EEM_{CSA} is the external elastic membrane cross-sectional area, $LUMEN_{CSA}$ is the luminal cross-sectional area, and n is the number of evaluable cross-sections in the pullback.

Normalized TAV for each patient was calculated as the average atheroma area multiplied by the median number of comparable cross-sections in pullbacks for all patients completing the trial. The efficacy parameter of change in normalized TAV was calculated as normalized TAV (follow-up) – normalized TAV (baseline). This procedure adjusts for pullbacks of differing lengths, resulting in an equal weighting of each individual patient in computing the final efficacy results.

Statistical Analysis

To allow for 2 primary efficacy parameters, a Bonferroni correction was prespecified and a significance level of .025 was assigned for each end point. For the first primary efficacy parameter, change in PAV, a sample size of approximately 313 patients was specified for 80% power and a 2-sided α level of .025 to detect an expected change of –0.7%, assuming an SD of 4.0%. For the second primary efficacy parameter, change in the most diseased 10-mm subsegment at baseline, a sample size of approximately 171 patients was required for 80% power and a 2-sided α level of .025 to detect an expected change in normalized TAV of –3.0 mm³, assuming an SD of 12.6 mm³. If approximately 25% of patients discontinued early from the study, then 450 patients allocated to study medication would result in approximately 335 patients completing the study, which would provide sufficient power to assess both of the primary end points.

The statistical analysis plan defined tests of normality for the efficacy pa-

rameters and specified nonparametric testing if the data were not normally distributed. The efficacy results are presented as mean and SD and median and interquartile range for the change from baseline. If IVUS data were normally distributed, analysis of covariance, with baseline as a covariate and region as a factor, was specified. Otherwise, *P* values were to be calculated using the Wilcoxon signed rank test. Analysis of variance, with region as a factor, was used for analysis of the percentage of change in lipid values. Demographic and laboratory characteristics were calculated at baseline and follow-up for all patients completing the trial. A safety analysis was performed in all patients who received at least 1 dose of the study drug. Categorical variables are described using frequencies, while continuous variables are reported as means (with SDs) and medians (with 97.5% or 95% confidence intervals [CIs] or interquartile ranges). Analyses were performed using SAS software, version 8.2 (SAS Institute Inc, Cary, NC).

RESULTS

Patient Population

Between November 2002 and October 2003, 1183 patients were screened and 507 met all inclusion and exclusion criteria, including an acceptable baseline IVUS result, and received study drug at 53 centers. A total of 349 patients had evaluable IVUS examinations at both baseline and after 24 months of treatment (FIGURE 1). Of the 158 patients who were not included in the IVUS analysis, 14 were lost to follow-up, 2 were withdrawn per investigator discretion, 3 were withdrawn for protocol violations, 32 patients withdrew consent, 63 were withdrawn for an adverse event, and 11 withdrew for other reasons. Thirty-three patients did not have a final IVUS result analyzed, 13 of whom did not undergo a final IVUS examination and 20 of whom had IVUS results that were not analyzable because of artifacts or pull-backs shorter than the prespecified 40-mm minimum length.

Baseline demographic characteristics and concomitant medications for the 349 patients completing the trial and the 158 patients not completing the trial are summarized in TABLE 1. The characteristics of the 158 noncompleters were very similar to those of the 349 completers in terms of age, sex, weight, body mass index (calculated as weight in kilograms divided by the square of height in meters), and prevalence of hypertension and diabetes. Race/ethnicity was assessed by the investigator or study coordinator. This information was collected to determine whether the response to therapy (efficacy and safety) differed among individuals with different racial/ethnic backgrounds. The disposition of these patients is summarized in Figure 1.

Laboratory Outcomes

TABLE 2 summarizes laboratory values obtained during the study for patients completing the trial. The mean (SD) LDL-C level during treatment was 60.8 (20.0) mg/dL (1.6 [0.5] mmol/L), representing a 53.2% reduction from baseline (*P*<.001). Approximately 75% of patients achieved a mean LDL-C level of less than 70 mg/dL (1.8 mmol/L) during treatment. The mean (SD) HDL-C level during the trial was 49.0 (12.6)

mg/dL (1.3 [0.3] mmol/L), an increase of 14.7% from baseline (*P*<.001). The mean LDL-C/HDL-C ratio was re-

Figure 1. Flow of Patients Through the Trial

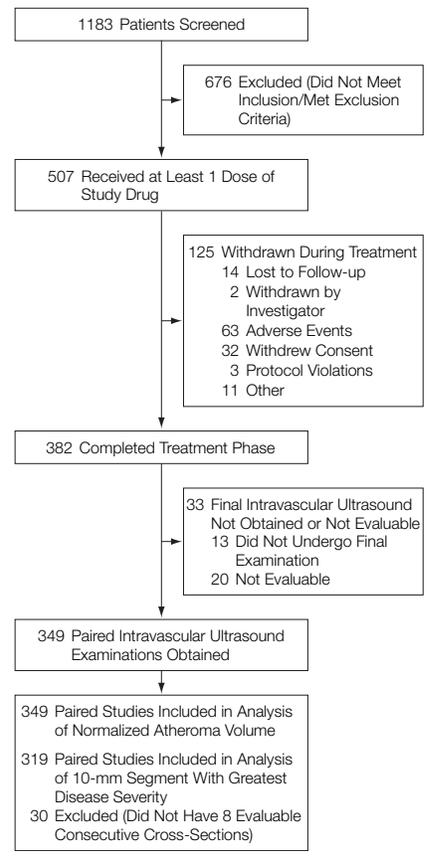


Table 1. Baseline Patient Characteristics*

Characteristics	Patients Completing the Trial (n = 349)	Patients Not Completing the Trial (n = 158)
Age, mean (SD), y	58.5 (10.0)	58.5 (10.3)
Male	245 (70.2)	115 (72.8)
White race	338 (96.8)	139 (88.0)
Weight, mean (SD), kg	85.5 (16.8)	86.2 (16.7)
Body mass index, median (IQR)†	28.4 (25.8-31.4)	28.9 (25.7-32.2)
History of hypertension	335 (96.0)	148 (93.7)
History of diabetes mellitus	46 (13.2)	18 (11.4)
History of acute coronary syndrome	60 (17.2)	24 (15.2)
History of prior myocardial infarction	86 (24.6)	35 (22.2)
Concomitant medications		
Aspirin	292 (83.7)	132 (83.5)
Angiotensin-converting enzyme inhibitors	186 (53.3)	72 (45.6)
Angiotensin receptor antagonists	64 (18.3)	21 (13.3)
Organic nitrates	297 (85.1)	138 (87.3)
β-Blockers	294 (84.2)	116 (73.4)

*Data are expressed as number (percentage) unless otherwise specified.
†Calculated as weight in kilograms divided by the square of height in meters.

duced from 3.2 to 1.3 ($P < .001$). Baseline lipid values for the 349 patients completing the trial and the 158 patients not completing the trial were very closely matched.

Efficacy Analyses

TABLE 3 shows the results for both the primary and the secondary efficacy parameters. All 3 efficacy parameters showed statistically significant regression. For the primary efficacy parameter of PAV, the mean (SD) decrease was -0.98% (3.15%) and the median was -0.79% (97.5% CI, -1.21% to -0.53%) ($P < .001$ compared with baseline). For the second

primary efficacy parameter, change in atheroma volume in the 10-mm subsegment with the greatest disease severity, the mean (SD) change was -6.1 (10.1) mm^3 , and the median change was -5.6 mm^3 (97.5% CI, -6.8 to -4.0 mm^3) ($P < .001$ compared with baseline). This change represents a median reduction of 9.1% in atheroma volume in the 10-mm segment with the greatest disease severity.

For the prespecified secondary efficacy parameter, normalized TAV, the mean (SD) change was -14.7 (25.7) mm^3 , with a median change of -12.5 mm^3 (95% CI, -15.1 to -10.5 mm^3) ($P < .001$ compared with baseline). This

change represents a median reduction of 6.8% in atheroma volume in the full arterial pullback.

For the primary efficacy parameter of PAV, 63.6% of patients showed regression and 36.4% showed progression. For the second primary efficacy parameter, change in the 10-mm subsegment with the greatest disease severity, 78.1% of patients demonstrated regression and 21.9% showed progression.

TABLE 4 shows the results for the primary end points for prespecified subgroups. There was no significant heterogeneity in the response to treatment for either of the 2 primary efficacy pa-

Table 2. Laboratory Results (n = 346)*

	Baseline		During Treatment		Percent Change, Least-Square Mean (95% CI)†
	Mean (SD)	Median (IQR)	Mean (SD)	Median (IQR)	
Total cholesterol, mg/dL	204 (41.2)	197 (179-224)	133.8 (25.4)	130 (116-148)	-33.8 (-35.6 to -31.9)
LDL-C, mg/dL	130.4 (34.3)	127 (109-148)	60.8 (20.0)	58 (47-72)	-53.2 (-55.6 to -50.9)
HDL-C, mg/dL	43.1 (11.1)	41 (35-49)	49.0 (12.6)	47 (41-54)	+14.7 (12.3 to 17.1)
Triglycerides, mg/dL	152.2 (81.7)	135 (97-187)	121.2 (56.8)	109 (84-144)	-14.5 (-19.4 to -9.6)
Apolipoprotein B ₁₀₀ , mg/dL	127.9 (29.2)	125 (107-144)	74.5 (22.3)	72 (58-85)	-41.5 (-43.7 to -39.3)
Apolipoprotein A-1	138.6 (27.1)	135 (119-153)	150.2 (31.3)	148 (129-164)	+8.9 (6.5 to 11.3)
Apolipoprotein B/A-1 ratio	0.95 (0.27)	0.93 (0.75-1.12)	0.51 (0.17)	0.49 (0.39-0.62)	-45.6 (-47.7 to -43.5)
LDL-C/HDL-C ratio	3.2 (1.1)	3.1 (2.5-3.8)	1.3 (0.5)	1.3 (0.9-1.6)	-58.5 (-60.7 to -56.2)
Non-HDL cholesterol, mg/dL	160.9 (40.2)	157 (134-181)	84.8 (23.2)	81 (69-97)	-47.2 (-49.4 to -45.1)

Abbreviations: CI, confidence interval; HDL-C, high-density lipoprotein cholesterol; IQR, interquartile range; LDL-C, low-density lipoprotein cholesterol. SI conversions: To convert total cholesterol, HDL-C, and LDL-C to mmol/L, multiply by 0.0259; to convert triglycerides to mmol/L, multiply by 0.0113. *Three of 349 patients completing the trial had missing baseline laboratory data. †From time-weighted average throughout the duration of therapy. Least-square means and 95% CIs were calculated by analysis of variance with region as a factor. $P < .001$ for all comparisons between baseline and treatment values.

Table 3. Baseline and Follow-up Intravascular Ultrasound Results

	Baseline	Follow-up	Change	Percent Change	No. (%) With Regression
Primary efficacy parameters					
Percent atheroma volume (n = 349)					222 (63.6)
Mean (SD)	39.6 (8.5)	38.6 (8.5)	-0.98 (3.15)	NA	
Median (IQR)	39.9 (33.8-45.3)	38.5 (32.6-44.3)	-0.79 (-1.21 to -0.53)*†	NA	
Atheroma volume in most diseased 10-mm subsegment, mm^3 (n = 319)					249 (78.1)
Mean (SD)	65.1 (27.0)	59.0 (24.5)	-6.1 (10.1)	-8.5 (13.7)	
Median (IQR)	65.1 (45.2-82.2)	58.4 (40.6-76.3)	-5.6 (-6.82 to -3.96)*†	-9.1 (-10.83 to -7.23)*†	
Secondary efficacy parameter					
Normalized total atheroma volume, mm^3 (n = 349)					272 (77.9)
Mean (SD)	212.2 (81.3)	197.5 (79.1)	-14.7 (25.7)	-6.7 (11.1)	
Median (IQR)	204.7 (146.0-259.8)	186.8 (135.1-243.8)	-12.5 (-15.08 to -10.48)*‡	-6.8 (-7.82 to -5.60)*‡	

Abbreviations: IQR, interquartile range; NA, not applicable. * $P < .001$ by Wilcoxon signed rank test for all comparisons between baseline and follow-up. †Data in parentheses are distribution-free 97.5% confidence intervals for the median. ‡Data in parentheses are distribution-free 95% confidence intervals for the median.

rameters for subgroups defined by age, sex, body mass index, history of diabetes mellitus, LDL-C levels, or HDL-C levels.

A post hoc sensitivity analysis was performed to assess the potential impact of patients not completing the trial on IVUS measures of efficacy. One approach imputed all 158 noncompleting patients as showing no change in atheroma burden (neither progression nor regression). Using this method, statistically significant regression was still observed for both PAV ($P<.001$) and change in atheroma volume for the most diseased 10-mm subsegment ($P<.001$). A second imputation method assigned the 22 patients who discon-

tinued the study because of ischemic events to a progression rate calculated from the median value for all patients completing the trial who showed progression. Using this method, regression was still observed for PAV ($P<.001$) and for the most diseased 10-mm subsegment ($P<.001$).

Adverse Events

TABLE 5 shows the treatment-emergent adverse events encountered in the trial. The regimen of 40 mg/d of rosuvastatin was well tolerated. Rates of elevation of hepatic enzymes were comparable with those reported in other recent trials using maximal statin dosages. There were no cases of rhabdo-

myolysis. Two patients experienced serious adverse events based on local, non-study-related laboratory values. A 79-year-old man had an elevated creatine kinase level following an episode of lower back pain that occurred after heavy lifting. After he received a nonsteroidal anti-inflammatory agent, renal failure developed, the family declined dialysis, and the patient died 5 days later. Postmortem examination revealed a fracture of the T11 vertebral body with local muscle hemorrhage. Multiple muscle biopsies found no evidence of rhabdomyolysis. A second patient had an elevated creatine kinase level after a seizure but continued taking the study drug, and creatine ki-

Table 4. Primary Efficacy Parameters in Prespecified Subgroups

Subgroup	Percent Atheroma Volume			Atheroma Volume in Most Diseased 10-mm Subsegment		
	No. of Patients	Median Change, % (IQR)	P Value*	No. of Patients	Median Change, mm ³ (IQR)	P Value*
Demographic characteristics						
Age						
≤Median	180	-0.8 (-3.0 to 0.4)	<.001	163	-6.1 (-11.3 to -1.1)	<.001
>Median	169	-0.6 (-2.8 to 1.1)	<.001	156	-4.4 (-10.8 to -0.4)	<.001
Sex						
Male	245	-0.8 (-2.8 to 0.8)	<.001	221	-6.1 (-11.2 to -0.4)	<.001
Female	104	-0.7 (-3.1 to 0.9)	<.001	98	-4.2 (-10.5 to -0.4)	<.001
Body mass index						
≤Median	174	-0.9 (-3.2 to 0.5)	<.001	161	-6.5 (-11.6 to -0.8)	<.001
>Median	173	-0.7 (-2.6 to 1.0)	<.001	156	-5.0 (-10.6 to -0.3)	<.001
History of diabetes						
Yes	46	-0.9 (-2.8 to 0.9)	.03	44	-6.4 (-11.1 to -1.5)	<.001
No	303	-0.8 (-3.0 to 0.8)	<.001	275	-5.4 (-10.9 to -0.3)	<.001
Subgroups by average LDL-C level during treatment, mg/dL						
≤Mean	192	-1.1 (-3.1 to 0.7)	<.001	177	-4.8 (-11.3 to -0.4)	<.001
>Mean	157	-0.6 (-2.3 to 1.0)	.001	142	-5.8 (-10.2 to -0.7)	<.001
<70	254	-0.9 (-3.1 to 0.7)	<.001	231	-5.6 (-11.4 to -0.4)	<.001
70-100	78	-0.3 (-2.2 to 1.2)	.09	72	-5.3 (-9.4 to 0.4)	<.001
≥100	17	-0.2 (-2.5 to 0.6)	.22	16	-6.9 (-11.9 to -1.5)	.004
Subgroups by average HDL-C level during treatment, mg/dL						
≤Mean	197	-0.9 (-2.9 to 0.9)	<.001	179	-6.2 (-11.0 to -0.7)	<.001
>Mean	152	-0.7 (-2.9 to 0.8)	<.001	140	-4.7 (-11.0 to -0.2)	<.001
>45	205	-0.7 (-2.9 to 0.7)	<.001	190	-5.3 (-11.5 to -0.4)	<.001
≤45	144	-0.8 (-2.9 to 1.1)	<.001	129	-5.9 (-10.6 to -0.4)	<.001
<40	80	-1.3 (-2.8 to 0.4)	<.001	71	-5.9 (-10.1 to -0.1)	<.001
≥40	269	-0.7 (-2.9 to 0.9)	<.001	248	-5.6 (-11.3 to -0.5)	<.001
<35	34	-1.5 (-2.6 to 0.1)	.008	29	-5.9 (-9.0 to -0.1)	<.001
≥35	315	-0.7 (-2.9 to 0.9)	<.001	290	-5.6 (-11.2 to -0.4)	<.001

Abbreviations: HDL-C, high-density lipoprotein cholesterol; IQR, interquartile range; LDL-C, low-density lipoprotein cholesterol.

SI conversions: To convert HDL-C and LDL-C to mmol/L, multiply by 0.0259.

*By Wilcoxon signed rank test for comparisons with baseline.

Table 5. Adverse Events, Drug Discontinuations, and Clinical End Points in the Safety Population (N = 507)

	No. (%)
Major treatment-emergent adverse events	
Death	4 (0.8)
Myocardial infarction	10 (2.0)
Stroke	3 (0.6)
Central laboratory abnormalities*	
ALT	
>3× ULN	9 (1.8)
>3× ULN on 2 consecutive visits	1 (0.2)
Creatine kinase	
>5× ULN	6 (1.2)
>5× ULN on 2 consecutive visits	1 (0.2)
>10× ULN	0
>10× ULN on 2 consecutive visits	0
Drug discontinuations†	
Musculoskeletal complaints‡	19 (3.7)
Gastrointestinal complaints§	2 (0.4)
Neoplasms	2 (0.4)
Increased creatine kinase	2 (0.4)
Increased ALT or bilirubin	2 (0.4)
Cardiovascular disorders	22 (4.3)
Total patients who discontinued	62 (12.2)

Abbreviations: ALT, alanine aminotransferase; ULN, upper limit of normal.

*Laboratory values were only collected once for 3 patients.

†Due to treatment-emergent adverse events.

‡Muscle pain or weakness.

§Abdominal pain or nausea.

||Include angina, congestive heart failure, arrhythmias, and other types of ischemic events.

nase levels returned to normal during therapy.

The number of clinical events in this 24-month trial was too small for any meaningful analysis of the relationship between progression rate and morbidity or mortality. Of the 3 remaining deaths, 2 were due to sudden cardiac death and 1 to gastric carcinoma.

COMMENT

For the past 2 decades, clinical trials of antiatherosclerotic drug therapies have sought to reduce coronary disease morbidity and mortality, presumably by decreasing the rate of progression of the underlying atherosclerosis. An implicit objective of these therapies is the regression of atherosclerotic plaque, defined as a statistically significant reduction in disease burden. Unfortunately, the goal of inducing actual regression of atherosclerosis has remained elusive. Most atherosclerosis trials have demonstrated that active lipid-modulating therapy, primar-

ily using statin drugs, can reduce the rate of disease progression.^{12-14,19} Two small, single-center trials have suggested that statins might induce regression, but methodological issues including small sample size have limited interpretation and generalization of results.^{16,17}

The current study, ASTEROID, sought to achieve atherosclerotic regression as an explicit goal in the design of the trial. Accordingly, the prespecified efficacy parameters were selected and the study was designed so that either frank progression or absence of progression would fail to meet the primary end point. Only regression, defined as a reduction in IVUS measures of atheroma burden with CIs not including zero, would yield a successful outcome. Despite the higher standard of evidence required, the current study demonstrated regression for all 3 prespecified IVUS end points with a high level of statistical significance (Table 3). FIGURE 2 shows a representative cross-section at baseline and follow-up for a patient who exhibited marked regression of disease.

Regression was achieved by reducing LDL-C levels to a mean of 60.8 mg/dL (1.6 mmol/L) (median, 57.6 mg/dL [1.5 mmol/L]), along with a significant increase in HDL-C levels (14.7%). The achieved LDL-C levels were the lowest values ever observed in a statin atherosclerosis progression trial, and the magnitude of the HDL-C increase also exceeded effects reported in previous statin trials.

Prior well-designed IVUS studies of statin therapy have not yielded compelling evidence for regression. Two small, single-center studies have suggested reduction in disease burden following statin therapy, but design limitations make interpretation difficult.^{16,17} The first, a study of 40 patients, showed a reduction in atheroma volume after 12 months of open-label simvastatin therapy, but the authors investigated an average arterial segment length of only 5.9 mm.¹⁶ The second study, in 24 patients with acute coronary syndromes, showed regression within a segment length of only 8.9 mm after 6

months of atorvastatin therapy.¹⁷ In both trials, the short segment length likely included only coronary lesions, making the studies vulnerable to the regression to the mean phenomenon. Moreover, arteries undergoing mechanical interventions were included, which could have affected atheroma measurements. Neither study used the most rigorous IVUS measure of global atherosclerosis burden, PAV. No large-scale IVUS trials in which patients received statins have demonstrated statistically significant regression.

In the current study, the choice of 2 primary efficacy parameters allowed testing of drug effects on regression using 2 different standards of evidence. The change in the 10-mm segment with the most severe disease is analogous to the methods used by investigators who examined only short segments with visible angiographic disease.¹⁶ This end point is a substantially less rigorous test for regression. Percent atheroma volume assesses drug effects within the full arterial pullback and represents the highest standard of evidence for regression. Using this more conservative end point, only a small study of patients administered an intravenous HDL-C mimetic (apolipoprotein A-I Milano phospholipid) has previously shown regression.¹¹

Designing a contemporary IVUS regression-progression trial creates major challenges that warrant further comment. Because contemporary guidelines and practice patterns require intensive treatment of secondary prevention patients, randomization of patients with established coronary disease to placebo or a low-intensity statin regimen was deemed ethically unacceptable.⁴ In the absence of a less intensively treated control group, special design considerations are required to avoid observer bias in an IVUS outcome study. In the current trial, each pair of baseline and follow-up IVUS images underwent digital processing to remove date identifiers, performed by technicians not otherwise involved in the study. The paired studies were then randomly

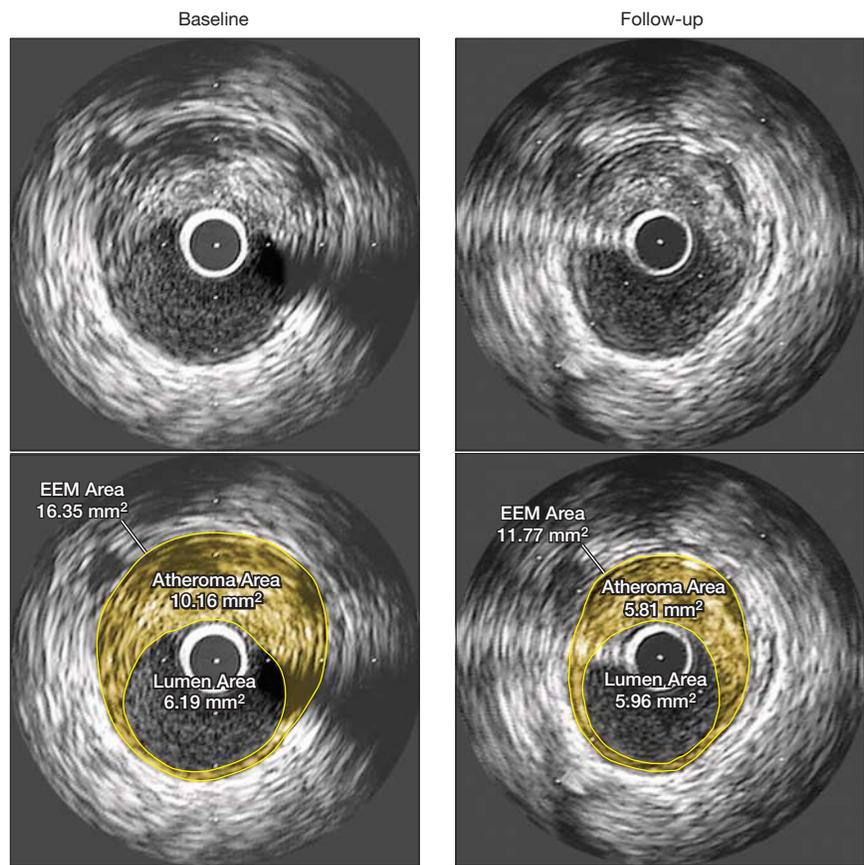
resequenced using codes provided by an outside statistician. This procedure blinded technicians from knowing whether an examination was obtained at baseline or follow-up and thereby eliminated any systematic bias in measurement of paired studies.

The magnitude and consistency of regression observed in the current trial are noteworthy. Table 4 demonstrates that regression occurred in virtually all subgroups, including men and women, older and younger patients, and most subgroups defined by lipid levels.

Despite the known limitations of cross-trial comparisons, many observers will likely compare these results with other recent IVUS regression-progression trials. The LDL-C levels achieved and the IVUS progression rates for several of these studies are shown in FIGURE 3. Linear regression analysis shows a high correlation between the mean LDL-C achieved in various trials and the mean progression rate for the most robust IVUS end point, PAV ($r^2=0.97$; $P<.001$). When viewed in this context, the results of the current study demonstrate that there exists no apparent threshold LDL-C level beyond which the benefits of statin therapy are no longer evident. If regression of disease is the desired outcome, then lower LDL-C is better.

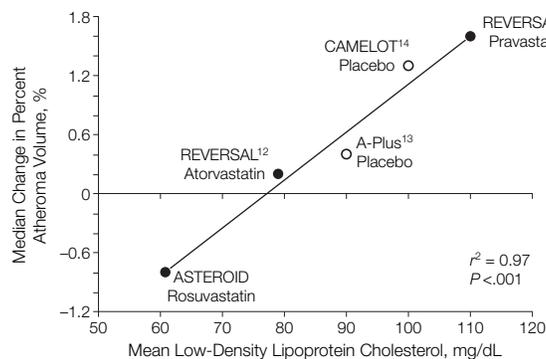
We believe that the current study has important implications for understanding the pathophysiology and optimal treatment of coronary artery disease. Traditional thinking has viewed atherosclerosis as an inexorably progressive disease for which even the most active therapies can merely slow advancement. The current study suggests that there is potential for a more optimistic strategy, in which aggressive lipid-modulating strategies can actually reverse the atherosclerotic disease process. The observed increases in HDL-C in the current study suggest that therapies designed to simultaneously lower LDL-C while raising HDL-C have the potential to substantially reduce lesion burden in patients with established disease. Clinical trials of combination therapies designed to both lower LDL-C

Figure 2. Example of Regression of Atherosclerosis in a Patient in the Trial



The top left panel illustrates the appearance of a single cross-section at baseline intravascular ultrasound examination, while the top right panel shows the same cross-section after 24 months of treatment. The bottom 2 panels illustrate the same cross-sections, but with measurements superimposed. Atheroma area was reduced from 10.16 mm² to 5.81 mm². EEM indicates external elastic membrane.

Figure 3. Relationship Between Mean Low-Density Lipoprotein Cholesterol Levels and Median Change in Percent Atheroma Volume for Several Intravascular Ultrasound Trials



There is a close correlation between these 2 variables ($r^2=0.97$). REVERSAL indicates Reversal of Atherosclerosis With Aggressive Lipid-Lowering¹²; CAMELOT, Comparison of Amlodipine vs Enalapril to Limit Occurrences of Thrombosis¹⁴; A-Plus, Avasimibe and Progression of Lesions on Ultrasound¹³; and ASTEROID, A Study to Evaluate the Effect of Rosuvastatin on Intravascular Ultrasound-Derived Coronary Atheroma Burden.

and raise HDL-C using novel antiatherosclerotic therapies are currently under way and will report results within the next 18 months.

We recognize the limitations of the current study. Because it was deemed ethically unacceptable to administer low-intensity statin therapy to patients with advanced coronary disease, we could not include a control group who received either placebo or a less active statin. We compensated for the absence of placebo controls by blinding date information on IVUS studies and resequencing the examinations to eliminate observer bias in interpretation. The 22 patients who were withdrawn for ischemic events may represent progressors, a potential source of bias in the trial. However, exploratory analyses imputing less favorable IVUS outcomes for these patients did not alter the conclusions. Despite the utility of IVUS demonstrated in several efficacy trials, the degree to which regression documented by IVUS will translate into a reduction in morbidity and mortality remains speculative. When feasible, clinical outcome trials to assess the effects of therapies on morbidity and mortality always provide more convincing evidence than intermediate end-point studies. However, randomized controlled trials of statins in this population are no longer ethically acceptable.

The current study supports several conclusions. For secondary prevention patients, very intensive statin therapy using 40 mg/d of rosuvastatin in patients with preexisting coronary disease reduced LDL-C to 60.8 mg/dL while raising HDL-C by 14.7%. These changes were larger in magnitude than has been observed in previous statin trials. The very low LDL-C levels and increase in HDL-C levels resulted in significant regression in atheroma burden for all 3 primary and secondary efficacy parameters. This very intensive statin regimen was well tolerated. These observations support the recommendation to administer very intensive statin therapy for high-risk patients with established coronary disease.

Published Online: March 13, 2006 (doi:10.1001/jama.295.13.jp60002).

Author Affiliations: Departments of Cardiovascular Medicine (Drs Nissen, Nicholls, Sipahi, Schoenhagen, and Tuzcu, Mr Crowe, and Mss Wolski and Goormastic) and Diagnostic Radiology (Dr Schoenhagen), Cleveland Clinic Lerner School of Medicine, Cleveland, Ohio; Donald W. Reynolds Cardiovascular Clinical Research Center, Department of Medicine, Brigham and Women's Hospital, and Harvard Medical School, Boston, Mass (Dr Libby); AstraZeneca, Wilmington, Del (Dr Raichlen and Ms Cain); Section of Atherosclerosis and Lipoprotein Research, Department of Medicine, Baylor College of Medicine, and Center for Cardiovascular Disease Prevention, Methodist DeBakey Heart Center, Houston, Tex (Dr Ballantyne); Hyperlipidemia and Atherosclerosis Research Group, Clinical Research Institute of Montreal, Montreal, Quebec (Dr Davignon); Department of Cardiology, Universität Duisburg-Essen, Duisburg, Germany (Dr Erbel); Département de Recherche sur les Lipoprotéines et l'Atherosclérose, Pasteur de Lille, Inserm U545 et Faculté de Pharmacie, Université du Droit et de la Santé de Lille 2, Lille, France (Dr Fruchart); and MHI Research Center, Montreal Heart Institute, Montreal, Quebec (Dr Tardif).

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, Nicholls, Libby, Raichlen, Ballantyne, Davignon, Erbel, Tardif, Schoenhagen, Goormastic, Tuzcu.

Acquisition of data: Nissen, Nicholls, Tardif, Schoenhagen, Crowe, Tuzcu.

Analysis and interpretation of data: Nissen, Nicholls, Sipahi, Libby, Raichlen, Davignon, Erbel, Fruchart, Tardif, Schoenhagen, Crowe, Cain, Wolski, Goormastic, Tuzcu.

Drafting of the manuscript: Nissen, Libby, Fruchart, Tuzcu.

Critical revision of the manuscript for important intellectual content: Nissen, Nicholls, Sipahi, Libby, Raichlen, Ballantyne, Davignon, Erbel, Tardif, Schoenhagen, Crowe, Cain, Wolski, Goormastic, Tuzcu.

Statistical analysis: Nissen, Nicholls, Sipahi, Cain, Wolski, Goormastic.

Obtained funding: Nissen.

Administrative, technical, or material support: Nissen, Nicholls, Schoenhagen, Crowe, Tuzcu.

Study supervision: Nissen, Raichlen, Erbel, Tardif, Tuzcu.

Financial Disclosures: Dr Nissen has received research support from AstraZeneca, Eli Lilly, Pfizer, Takeda, Sankyo, and Sanofi-Aventis. He has consulted for a number of pharmaceutical companies without financial compensation. All honoraria, consulting fees, or other payments from any for-profit entity are paid directly to charity, so that neither income nor any tax deduction is received. Dr Libby has received honoraria for lectures and consulting on behalf of AstraZeneca. Dr Ballantyne has received grants or research support from AstraZeneca, diaDexus, Gene Logic, GlaxoSmithKline, Integrated Therapeutics, Kos, Merck, Novartis, Pfizer, Roche, Sankyo Pharma, Sanofi-Synthelabo, and Schering-Plough; has consulted for AstraZeneca, Bayer, Merck, Novartis, Pfizer, Reliant, Roche, Sanofi-Synthelabo, and Schering-Plough; and has served on the speakers' bureaus for AstraZeneca, Kos, Merck, Pfizer, Reliant, and Schering-Plough. Dr Davignon has received research support and consulting fees from AstraZeneca. Dr Tardif holds a Pfizer and Canadian Institute of Health Research Chair in Atherosclerosis, partially funded by Pfizer, and has received honoraria from Pfizer and AstraZeneca. No other financial disclosures were reported.

Funding/Support: This study was funded by AstraZeneca.

Role of the Sponsor: The sponsor participated in discussions regarding study design and protocol development and provided logistical support during the trial. Monitoring of the study and maintenance of the trial database was performed by a contract research organization, Omnicare, under contract to the sponsor. The IVUS end points were verified by the Cleveland Clinic Cardiovascular Coordinating Center. Statistical analysis was performed by the sponsor and the contract research organization 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.

Independent Statistical Analysis: An independent statistical analysis was conducted by Kathy Wolski, MPH, and Marlene Goormastic, MPH, both from the Department of Cardiovascular Medicine at the Cleveland Clinic Foundation. These statisticians received the trial database simultaneously with the sponsor, which included all raw data, not just derived data sets, and independently computed the IVUS efficacy parameters and confirmed the lipid level outcomes and basic demographic variables. Mss Wolski and Goormastic are employed by the Cleveland Clinic Cardiovascular Coordinating Center, which received compensation for conducting the trial, including reimbursement for statistical services.

ASTEROID Investigators: *Australia:* John Hunter Hospital, New Lambton, New South Wales (G. Bellamy, MD); Wesley Medical Center, Auchenflower, Queensland (D. Colquhoun, MD); Austin and Repatriation Medical Center, Heidelberg, Victoria (M. Horrigan, MD). *Belgium:* Hôpital de la Citadelle, Liege (P. Materne, MD); Onze Lieve Vrouw Ziekenhuis, Aalst (G. Heyndrickx, MD); University Hospital Saint-Luc, Bruxelles (J. Renkin, MD); Antwerp University, Antwerp (C. Vrints, MD). *Canada:* Queen Elizabeth II Health Sciences Center, Halifax, Nova Scotia (M. Love, MD); Hospital Laval-Quebec Heart-Lung Institute, Ste-Foy (O. Bertrand, MD); Hospital Maisonneuve-Rosemont Polyclinique Research, Montreal, Quebec (C. Constance, MD); Montreal Heart Institute, Montreal, Quebec (J. Tardif, MD); Notre Dame Hospital, Montreal (F. Reeves, MD). *France:* Purpan University Hospital, Toulouse (J. Puel, MD); Georges Pompidou European Hospital, Paris (A. Lafont, MD); Hôpital Haut Léveque, Pessac (P. Coste, MD); Institut Jacques Cartier, Massy (M. Morice, MD). *Italy:* Cardiologia Ospedale Civile, Venezia (B. Reimers, MD); Divisione di Cardiologia Policlinico San Mateo, Pavia (E. Bramucci, MD); Unità di Emodinamica e Cardiologia Interventistica, Milan (A. Colombo, MD); Unità Operativa Distrettuale Cardiologia Invasiva e Emodinamica, Milan (P. Presbitero, MD); Unità Operativa Distrettuale Cardiologia-Laboratorio di Emodinamica, Rome (F. Prati, MD); Unità Operativa Distrettuale Emodinamica Haemodynamic Unit, Siena (A. Bravi, MD); Struttura Operativa Complesso di Cardiologia- Sezione Emodinamica, Udine (G. Bernardi, MD). *The Netherlands:* Isala Kliniek, Zwolle (M. Gosselink, MD); Onze Lieve Vrouwe Gasthuis Department of Cardiology, Amsterdam (J. Herrman, MD); St Antonius Ziekenhuis-Department of Cardiology, Nieuwegein (B. Rensing, MD). *United Kingdom:* Edinburgh Royal Infirmary Cardiology Department, Edinburgh, Scotland (N. Uren, MD). *Spain:* Hospital de Bellvitge, Barcelona (E. Esplugas Oliveras, MD); Hospital Clinic i Provincial, Barcelona (A. Betriu Gilbert, MD); Hospital Clínico de San Carlos, Madrid (C. Macaya Miguel, MD); Hospital Gregorio Marañón, Madrid (J. Botas Rodriguez, MD); Hospital Universitario de Malaga, Malaga (J. Hernandez Garcia, MD). *United States:* University of Alabama Hospital,

Birmingham (B. Brott, MD); Sutter Medical Center, Santa Rosa, Calif (P. Coleman, MD); University of Colorado Health Sciences Center, Denver (J. Messenger, MD); Littleton Medical Center, Denver, Colo (I. Dauber, MD); Hartford Hospital, Hartford, Conn (P. Thompson, MD); JFK Medical Center, Atlantis, Fla (M. Rothenberg, MD); Rush Medical Center, Chicago, Ill (R. Snell, MD); Iowa Heart Center, Des Moines (M. Ghali, MD); University of Michigan Health System, Ann Arbor (S. Chetcuti, MD); McLaren Regional Medical, Flint, Mich (J. Harris, MD); Cardiac and Vascular Research Center of Northern Michigan, Petoskey (L. Cannon, MD); St Mary Medical Center, Duluth, Minn

(A. Deibele, MD); United's John Nasseff Heart Hospital, St Paul, Minn (K. Baran, MD); Buffalo Heart Group, Buffalo, NY (J. Gelormini, MD); Millard Fillmore Hospital, Williamsville, NY (J. Corbelli, MD); Moses Cone Health System, Greensboro, NC (B. Brodie, MD); Medical College of Ohio, Toledo (C. Cooper, MD); Geisinger Clinic, Danville, Pa (J. Blankenship, MD); Miriam Hospital, Providence, RI (P. Gordon, MD); Houston Northwest Medical Center, Houston, Tex (B. Lachterman, MD); Aurora Sinai Medical Center, Milwaukee, Wis (Y. Shalev, MD).

Acknowledgment: We thank Nadine Juran, RN, project manager, and Craig Balog, BS, statistician, Cleveland

Clinic Cardiovascular Coordinating Center; Helena Melezinkova, MD, AstraZeneca, who monitored adverse events in Europe and Australia and reviewed an earlier version of the manuscript; Joseph Neubauer, AstraZeneca, who provided administrative support of the trial and study supervision; Rohini Chitra, PhD, and Richard Caplan, PhD, AstraZeneca, who provided statistical support in the design of the study; and the Intravascular Ultrasound Core Laboratory staff: Aaron Loyd, William Magyar, Tammy Churchill, Jay Zhitnik, Jordan Andrews, Teresa Fonk, Anne Colagiovanni, Andrea Winkhart, Jessica Fox, Troy Schweitzer, and Paula Shalling.

REFERENCES

1. Cannon CP, Braunwald E, McCabe CH, et al. Intensive versus moderate lipid lowering with statins after acute coronary syndromes. *N Engl J Med.* 2004;350:1495-1504.
2. LaRosa JC, Grundy SM, Waters DD, et al; Treating to New Targets (TNT) Investigators. Intensive lipid lowering with atorvastatin in patients with stable coronary disease. *N Engl J Med.* 2005;352:1425-1435.
3. Pedersen TR, Faergeman O, Kastelein JJ, et al; Incremental Decrease in End Points Through Aggressive Lipid Lowering (IDEAL) Study Group. High-dose atorvastatin vs usual-dose simvastatin for secondary prevention after myocardial infarction: the IDEAL study: a randomized controlled trial. *JAMA.* 2005;294:2437-2445.
4. Grundy SM, Cleeman JJ, Merz CN, et al; Coordinating Committee of the National Cholesterol Education Program. Implications of recent clinical trials for the National Cholesterol Education Program Adult Treatment Panel III Guidelines. *J Am Coll Cardiol.* 2004;44:720-732.
5. Blankenhorn DH, Azen SP, Krams DM, et al; MARS Research Group. Coronary angiographic changes with lovastatin therapy: the Monitored Atherosclerosis Regression Study (MARS). *Ann Intern Med.* 1993;119:969-976.
6. Waters D, Higginson L, Gladstone P, et al. Effects of monotherapy with HMG-CoA reductase inhibitor on the progression of coronary atherosclerosis as assessed by serial quantitative arteriography: the Canadian Coronary Atherosclerosis Intervention Trial (CCAIT). *Circulation.* 1994;89:959-968.
7. Jukema JW, Bruschke AV, van Boven AJ, et al. Effects of lipid lowering by pravastatin on progression and regression of coronary artery disease in symptomatic men with normal to moderately elevated serum cholesterol levels: the Regression Growth Evaluation Statin Study (REGRESS). *Circulation.* 1995;91:2528-2540.
8. Pitt B, Mancini GB, Ellis SG, Rosman HS, Park J-S, McGovern ME. Pravastatin limitation of atherosclerosis in the coronary arteries (PLAC I): reduction in atherosclerosis progression and clinical events. *J Am Coll Cardiol.* 1995;26:1133-1139.
9. Brown G, Albers JJ, Fisher LD, et al. Regression of coronary artery disease as a result of intensive lipid-lowering therapy in men with high levels of apolipoprotein B. *N Engl J Med.* 1990;323:1289-1298.
10. MAAS Study Group. Effect of simvastatin on coronary atheroma: the Multicentre Anti-atheroma Study (MAAS). *Lancet.* 1994;344:633-638.
11. Nissen SE, Tsunoda T, Tuzcu EM, et al. Effect of recombinant ApoA-I Milano on coronary atherosclerosis in patients with acute coronary syndromes: a randomized controlled trial. *JAMA.* 2003;290:2292-2300.
12. Nissen SE, Tuzcu EM, Brown BG, et al. Effect of intensive compared with moderate lipid-lowering therapy on progression of coronary atherosclerosis: a randomized controlled trial. *JAMA.* 2004;291:1071-1080.
13. Tardif JC, Gregoire J, L'Allier PL, et al; Avasimibe and Progression of Lesions on Ultrasound (A-PLUS) Investigators. Effects of the acyl coenzyme A:cholesterol acyltransferase inhibitor avasimibe on human atherosclerotic lesions. *Circulation.* 2004;110:3372-3377.
14. Nissen SE, Tuzcu EM, Libby P, Thompson PD, et al. Effect of antihypertensive agents on cardiovascular events in patients with coronary disease and normal blood pressure: the CAMELOT study: a randomized controlled trial. *JAMA.* 2004;292:2217-2226.
15. Eisen HJ, Tuzcu EM, Dorent R, et al; RAD B253 Study Group. Everolimus for the prevention of allograft rejection and vasculopathy in cardiac-transplant recipients. *N Engl J Med.* 2003;349:847-858.
16. Jensen LO, Thayssen P, Pedersen KE, Stender S, Haghfelt T. Regression of coronary atherosclerosis by simvastatin: a serial intravascular ultrasound study. *Circulation.* 2004;110:265-270.
17. Okazaki S, Yokoyama T, Miyauchi K, et al. Early statin treatment in patients with acute coronary syndrome: demonstration of the beneficial effect on atherosclerotic lesions by serial volumetric intravascular ultrasound analysis during half a year after coronary event: the ESTABLISH study. *Circulation.* 2004;110:1061-1068.
18. Tardif JC, Gregoire J, Schwartz L, et al; Canadian Antioxidant Restenosis Trial (CART-1) Investigators. Effects of AGI-1067 and probucol after percutaneous coronary interventions. *Circulation.* 2003;107:552-558.
19. Nissen SE, Tuzcu EM, Schoenhagen P, et al. Statin therapy, LDL cholesterol, C-reactive protein, and coronary artery disease. *N Engl J Med.* 2005;352:29-38.
20. Davidson M, Ma P, Stein EA, et al. Comparison of effects on low-density lipoprotein cholesterol and high-density lipoprotein cholesterol with rosuvastatin versus atorvastatin in patients with type IIa or IIb hypercholesterolemia. *Am J Cardiol.* 2002;89:268-275.
21. Mintz GS, Nissen SE, Anderson WVD, et al. American College of Cardiology Clinical Expert Consensus Document on Standards for Acquisition, Measurement and Reporting of Intravascular Ultrasound Studies (IVUS): a report of the American College of Cardiology Task Force on Clinical Expert Consensus Documents. *J Am Coll Cardiol.* 2001;37:1478-1492.
22. Schoenhagen P, Sapp SK, Tuzcu EM, et al. Variability of area measurements obtained with different intravascular ultrasound catheter systems: impact on clinical trials and a method for accurate calibration. *J Am Soc Echocardiogr.* 2003;16:277-284.