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

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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 therapy could regress coronary atherosclerosis as determined by IVUS imaging.

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) mm³, with a median of −5.6 mm³ (97.5% CI, −6.8 to −4.0 mm³) (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) mm³, with a median of −12.5 mm³ (95% CI, −15.1 to −10.5 mm³) (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

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therapy results in a greater reduction in adverse cardiovascular outcomes compared with more moderate treatment. 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. 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. More recently, intravascular ultrasound (IVUS) imaging has emerged as the predominant approach for evaluating the progression of coronary atherosclerosis. 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, blood pressure–lowering drugs, reduction of inflammatory markers, and novel investigative therapies. 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 typically produces greater reductions in LDL-C and larger increases in HDL-C than previously available agents.

**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-naive, 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 ≥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. Rosuvastatin was also selected because previous studies had shown this agent to significantly increase HDL-C at the maximum therapeutic dosage. Because all enrolled patients had established 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 rosvastatin, 40 mg/d.

**Baseline Catheterization and IVUS**

Prior publications have thoroughly described the methods for IVUS interrogation. Following diagnostic angiography, the operator selected a target vessel for IVUS interrogation, defined as the longest and least-angled vessel meeting inclusion criteria. After administration of 100 to 300 μg 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 pullback, 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. Using customized public-domain software (Image), 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.

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

$$\left( \frac{\sum (\text{EEM}_{\text{CSA}} - \text{LUMEN}_{\text{CSA}})}{\sum \text{EEM}_{\text{CSA}}} \right) \times 100$$

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 \(\Sigma (\text{EEM}_{\text{CSA}} - \text{LUMEN}_{\text{CSA}})\), 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

$$\text{Average Atheroma Area} = \frac{\sum (\text{EEM}_{\text{CSA}} - \text{LUMEN}_{\text{CSA}})}{n}$$

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 \(\alpha\) 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 \(\alpha\) 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-
Concomitant medications

| History of prior myocardial infarction | 86 (24.6) | 35 (22.2) |
| History of acute coronary syndrome | 60 (17.2) | 24 (15.2) |
| History of diabetes mellitus | 46 (13.2) | 18 (11.4) |
| History of hypertension | 335 (96.0) | 148 (93.7) |

Body mass index, median (IQR)†

28.4 (25.8-31.4) 28.9 (25.7-32.2)

White race

338 (96.8) 139 (88.0)

Male

245 (70.2) 115 (72.8)

Age, mean (SD), y

58.5 (10.0) 58.5 (10.3)

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.

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 pullbacks 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-
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). 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 atheroma volume 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-
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 discontinued 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 4 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 rhabdomyolysis. 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

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Percent Atheroma Volume</th>
<th>Atheroma Volume in Most Diseased 10-mm Subsegment</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. of Patients</td>
<td>Median Change, % (IQR)</td>
</tr>
<tr>
<td><strong>Demographic characteristics</strong></td>
<td></td>
<td><strong>No. of Patients</strong></td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤Median</td>
<td>180</td>
<td>−0.8 (−3.0 to 0.4)</td>
</tr>
<tr>
<td>&gt;Median</td>
<td>169</td>
<td>−0.6 (−2.8 to 1.1)</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>245</td>
<td>−0.8 (−2.8 to 0.8)</td>
</tr>
<tr>
<td>Female</td>
<td>104</td>
<td>−0.7 (−3.1 to 0.9)</td>
</tr>
<tr>
<td>Body mass index</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤Median</td>
<td>174</td>
<td>−0.9 (−3.2 to 0.5)</td>
</tr>
<tr>
<td>&gt;Median</td>
<td>173</td>
<td>−0.7 (−2.6 to 1.0)</td>
</tr>
<tr>
<td>History of diabetes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>46</td>
<td>−0.9 (−2.8 to 0.9)</td>
</tr>
<tr>
<td>No</td>
<td>303</td>
<td>−0.8 (−3.0 to 0.8)</td>
</tr>
<tr>
<td><strong>Subgroups by average LDL-C level during treatment, mg/dL</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤Mean</td>
<td>192</td>
<td>−1.1 (−3.1 to 0.7)</td>
</tr>
<tr>
<td>&gt;Mean</td>
<td>157</td>
<td>−0.6 (−2.3 to 1.0)</td>
</tr>
<tr>
<td>&lt;70</td>
<td>254</td>
<td>−0.9 (−3.1 to 0.7)</td>
</tr>
<tr>
<td>70–100</td>
<td>78</td>
<td>−0.3 (−2.2 to 1.2)</td>
</tr>
<tr>
<td>≥100</td>
<td>17</td>
<td>−0.2 (−2.5 to 0.6)</td>
</tr>
<tr>
<td><strong>Subgroups by average HDL-C level during treatment, mg/dL</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤Mean</td>
<td>197</td>
<td>−0.9 (−2.9 to 0.9)</td>
</tr>
<tr>
<td>&gt;Mean</td>
<td>152</td>
<td>−0.7 (−2.9 to 0.8)</td>
</tr>
<tr>
<td>≥45</td>
<td>205</td>
<td>−0.7 (−2.9 to 0.7)</td>
</tr>
<tr>
<td>≤45</td>
<td>144</td>
<td>−0.8 (−2.9 to 1.1)</td>
</tr>
<tr>
<td>&lt;40</td>
<td>80</td>
<td>−1.3 (−2.8 to 0.4)</td>
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<tr>
<td>≥40</td>
<td>269</td>
<td>−0.7 (−2.9 to 0.9)</td>
</tr>
<tr>
<td>&lt;35</td>
<td>34</td>
<td>−1.5 (−2.6 to 0.1)</td>
</tr>
<tr>
<td>≥35</td>
<td>315</td>
<td>−0.7 (−2.9 to 0.9)</td>
</tr>
</tbody>
</table>

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

S1 conversions: To convert HDL-C and LDL-C to mmol/L, multiply by 0.0259.

*By Wilcoxon signed rank test for comparisons with baseline.

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

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

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.

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, primarily using statin drugs, can reduce the rate of disease progression. 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.

The current study, ASTEROID, sought to achieve atherothrombotic 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 regression 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. 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. 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. 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 largescale 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. 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.

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. 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 assigned for central digital processing and review.
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 and raise HDL-C should be undertaken.

**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 mm$^2$ to 5.81 mm$^2$. 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-Lowering; CAMELOT, Comparison of Amlodipine vs Enalapril to Limit Occurrences of Thrombosis; A-Plus, Avasimibe and Progression of Lesions on Ultrasound, and ASTEROID, A Study to Evaluate the Effect of Rosuvastatin on Intravascular Ultrasound-Derived Coronary Atheroma Burden.
VERY HIGH-INTENSITY STATIN THERAPY AND CORONARY ATHEROSCLEROSIS


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Inclusion Criteria for the ASTEROID Study: 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 investigators queried 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 levels and basic demographic variables. Miss Wolski and Goormastic are employed by the Cleveland Clinic Cardiovascular Coordinating Center, which received compensation for conducting the trial, including reimbursement for statistical services.

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Esplugas Oliveras, MD); Hôpital Clinique i Provincial, Barcelona (A. Betriu Gilbert, MD); Hospital Clinico de San Carlos, Madrid (C. Macaya Miguel, MD); Hospital Gregorio Mara- nón, Madrid (J. Botas Rodriguez); Università di Milano, MalagA (J. Hernandez Garcia, MD); United States: University of Alabama Hospital, and raise HDL-C using novel antithrombotic therapies are currently un- der 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 pa- tients with advanced coronary dis- ease, 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 binding data information on IVUS studies and resequencing the exami- nations to eliminate observer bias in in- terpretation. The 22 patients who were withdrawn for ischemic events may rep- resent progressors, a potential source of bias in the trial. However, explor- atory analyses imputing less favorable IVUS outcomes for these patients did not alter the conclusions. Despite the utility of IVUS demonstrated in sev- eral 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 mor- bidity and mortality always provide more convincing evidence than inter- mediate end-point studies. However, randomized controlled trials of statins in this population are no longer ethi- cally 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 raise HDL-C using novel antithrombotic therapies are currently un- der 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 pa- tients with advanced coronary dis- ease, 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 binding data information on IVUS studies and resequencing the exami- nations to eliminate observer bias in in- terpretation. The 22 patients who were withdrawn for ischemic events may rep- resent progressors, a potential source of bias in the trial. However, explor- atory analyses imputing less favorable IVUS outcomes for these patients did not alter the conclusions. 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This very intensive statin regimen was well tolerated. These observations support the recommenda- tion to administer very intensive statin therapy for high-risk patients with established coronary disease.
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