Effect of Rosuvastatin Therapy on Coronary Artery Stenoses Assessed by Quantitative Coronary Angiography

A Study to Evaluate the Effect of Rosuvastatin on Intravascular Ultrasound-Derived Coronary Atheroma Burden

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Background—Previous studies using quantitative coronary angiography have demonstrated that statin therapy slows the progression of coronary stenoses in proportion to average low-density lipoprotein cholesterol levels during therapy. However, no major statin monotherapy study has demonstrated either halted progression or regression of angiographic disease. A Study to Evaluate the Effect of Rosuvastatin on Intravascular Ultrasound-Derived Coronary Atheroma Burden (ASTEROID) assessed whether rosuvastatin could regress coronary atherosclerosis by intravascular ultrasound and quantitative coronary angiography. Intravascular ultrasound showed atheroma volume regression in a single coronary artery with <50% angiographic luminal narrowing.

Methods and Results—ASTEROID treated 507 coronary disease patients with rosuvastatin 40 mg/d for 24 months. Blinded quantitative coronary angiography analyses of percent diameter stenosis and minimum lumen diameter were performed for up to 10 segments of coronary arteries and major branches with >25% diameter stenosis at baseline. For each patient, the mean of all matched lesions at baseline and study end was calculated. There were 292 patients with 613 matched stenoses. Rosuvastatin reduced low-density lipoprotein cholesterol by 53.3% to 61.1±20.3 mg/dL and increased high-density lipoprotein cholesterol by 13.8% to 48.3±12.4 mg/dL. Mean±SD percent diameter stenosis decreased from 37.3±8.4% (median, 35.7%; range, 26% to 73%) to 36.0±10.1% (median, 34.5%; range, 8% to 74%; $P<0.001$). Minimum lumen diameter increased from 1.65±0.36 mm (median, 1.62 mm; range, 0.56 to 2.65 mm) to 1.68±0.38 mm (median, 1.67 mm; range, 0.76 to 2.77 mm; $P<0.001$).

Conclusions—Rosuvastatin treatment for 24 months to average low-density lipoprotein cholesterol levels well below 70 mg/dL, accompanied by significant increases in high-density lipoprotein cholesterol, produced regression by decreasing percent diameter stenosis and improving minimum lumen diameter as measured by quantitative coronary angiography in coronary disease patients. **(*Circulation*. 2008;117:000-000.)**

Key Words: angiography ■ atherosclerosis ■ cholesterol ■ coronary disease ■ drugs

A Study to Evaluate the Effect of Rosuvastatin on Intravascular Ultrasound-Derived Coronary Atheroma Burden (ASTEROID) was designed to determine the effects of rosuvastatin treatment on the progression of coronary atherosclerosis in patients who had a clinically indicated cardiac catheterization that showed angiographic evidence of coronary artery disease (CAD). In ASTEROID, the methods used to evaluate the effect of rosuvastatin in the coronary vasculature were intravascular ultrasound (IVUS), to measure changes in plaque volume (which was the primary end point),

Clinical Perspective p ●●●

and quantitative coronary angiography (QCA), to measure changes in the lumen (which was a secondary end point). Previous studies using both of these imaging modalities have established that the natural history of coronary atherosclerosis is characterized by progression of disease. In particular, both placebo and statin treatment groups consistently demonstrated progression in QCA parameters, with an increase in the severity of coronary luminal narrowing as indicated by

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increases in percent diameter stenosis and decreases in minimum lumen diameter (MLD). The ability of statins to reduce the progression of atherosclerotic lesions or to result in the regression of atherosclerotic lesions has been evaluated in several previous studies.[1–6] These studies reported smaller increases in percent diameter stenosis and/or smaller decreases in coronary MLD, as assessed by QCA, in patients treated with fluvastatin, pravastatin, lovastatin, or simvastatin compared with those treated with placebo. Fewer patients treated with a statin developed new lesions compared with patients treated with placebo,[2,3,5,6] and statin-treated patients were more likely to have categorical regression and less likely to have categorical progression than placebo-treated patients.[1–6] However, no major statin monotherapy study has achieved either a halting of progression or regression of angiographic disease.

QCA has important limitations. Only the lumen, not the vessel wall itself, is visualized with angiography. The extent of atheroma within the vessel wall is not reliably ascertained by standard angiographic techniques,[7] and there may be extensive atheromatous involvement with only minimal impingement on the lumen. Furthermore, lumen size is a relatively crude measure of atherosclerotic disease, especially in patients with only mildly stenotic lesions. It has been known for 20 years that there is a compensatory adaptive enlargement or "remodeling" of atherosclerotic human coronary arteries with preservation of the cross-sectional area of the lumen in the early stages of the disease process. This knowledge is based on the findings of autopsy studies that demonstrated that the coronary lumen did not decrease in size until the atheroma occupied >40% of the area encompassed by the outside wall of the artery.[8]

IVUS provides images of the wall as well as the lumen, allowing accurate assessment of atheroma volume, but it is limited to larger, proximal segments with a smaller range of stenosis that will safely accommodate the relatively large-bore IVUS catheter. As such, prospective IVUS studies focus on the examination of the low end of the spectrum of diseased coronary arteries in regard to luminal narrowing or obstruction. QCA, by providing lumen information throughout the coronary tree, including more diseased segments, branch vessels, and distal stenoses, complements the detailed imaging data provided by IVUS for larger vessels. ASTEROID was designed to assess the effects of 2 years of therapy with 40 mg/d rosuvastatin on coronary atherosclerosis measured with both IVUS and QCA. The IVUS assessment of 1 major coronary artery in each patient, which was the primary objective of ASTEROID, has been previously reported.[9] Here, we broaden the assessment of the ASTEROID patients, reporting on the effects of rosuvastatin on discrete coronary stenoses by QCA, which was a secondary end point of the study.

Methods

Patients and Treatment

ASTEROID (4522IL/0076) was a prospective, multicenter, international open-label trial.[9] The institutional review board or ethics committee of all participating centers approved the protocol, and all patients provided written informed consent. This study included men and women ≥18 years of age with a clinical indication for coronary catheterization and angiographic evidence of CAD who met specific angiographic and IVUS criteria. Use of lipid-lowering medication for >3 months within the previous 12 months was not allowed. Patients who received lipid-lowering therapy in the 4 weeks before enrollment had a 4-week washout period to obtain accurate baseline lipid values. Any baseline level of low-density lipoprotein cholesterol (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. Inclusion required demonstration of at least 1 stenosis of >20% angiographic luminal diameter narrowing by visual estimation in any coronary vessel. The left main coronary artery had to have ≤50% reduction in lumen diameter, and the target vessel for IVUS interrogation could not have undergone angioplasty or bypass surgery or have >50% luminal narrowing throughout a target segment with a minimum length of 40 mm. Similarly, segments for QCA analyses could not have undergone bypass surgery or percutaneous coronary intervention. Patients were treated with rosuvastatin 40 mg/d for 24 months. They then underwent a second angiography and IVUS measurement.

Quantitative Coronary Angiography

Measurement of change in percent diameter stenosis for all stenoses >25% at baseline was defined as a prespecified outcome variable for ASTEROID. This is similar to the baseline stenoses examined in other QCA studies such as the Canadian Coronary Atherosclerosis Intervention Trial[2] and the Lipoprotein and Coronary Atherosclerosis Study.[6] For consistency with the prespecified percent diameter stenosis analysis, we also examined MLD in the same segments with >25% stenosis at baseline. Centers performed coronary angiography as part of the entry criteria for patients to be enrolled in the study, and follow-up angiography was performed at the end of the study. After administration of intracoronary nitroglycerin (100 to 300 μg), standard angiographic images were obtained so that each coronary segment was recorded in at least 2 orthogonal views. Images were recorded either on a DICOM-formatted CD (>99% of studies) or on cine film. Cine film images were subsequently digitized for analysis. Ten segments of the coronary arteries and their major branches were analyzed using end-diastolic frames with the Cardiovascular Angiography Analysis System-II (CAAS-II, Pie Medical Imaging BV, Maastricht, the Netherlands) applying an automated edge detection algorithm.[10]

The Angiography Core Laboratory at the Cleveland Clinic made all measurements. Each measurement was made by 2 technicians and reviewed by the medical director. All measurements were performed at the end of the study, after both baseline and follow-up examinations were available. Baseline and follow-up recordings were resequenced using random assignments, and the paired baseline and follow-up images were analyzed by personnel blinded to the sequences.

The reference diameter and most narrow point (ie, the MLD) were defined in each segment. Percent stenosis was defined as follows: [(reference diameter−MLD)/reference diameter]×100. The average of all lesions with >25% and <100% stenosis at baseline that also had posttreatment measurements in the corresponding segments was calculated for each patient. From these values, the change from baseline was calculated for each patient.

The diameter of the catheter tip was measured with digital calipers and used for image calibration. The MLD values for each patient at baseline for all segments in which the reference vessel size was ≥1 mm and the percent stenosis was >25% were calculated. The MLD on treatment was then calculated for the matching segments. The average change in MLD from baseline was calculated for each patient using these values. Clinically relevant regression or progression was defined as a nominal change (from baseline to 2 years) of ≥10% for percent diameter stenosis[11] and ≥0.2 mm (prespecified) for MLD.

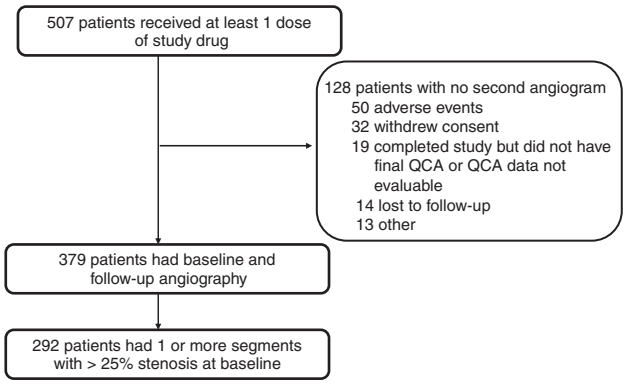

Figure 1. Flow of study patients.

The quality assurance process in the Angiography Core Laboratory was as follows. Images from 6 randomly selected patients were provided quarterly to each reviewer for measurement. The mean and SD across reviewers were determined, and the coefficient of variation (coefficient of variation=[SD/mean]×100) was calculated to assess the degree of interreviewer variability. The set limit for the coefficient of variation was 15%. This analysis was performed on a quarterly basis in the Angiography Core Laboratory on randomly selected images from multiple trials. These data have been reported previously, with intraobserver correlations for reference diameter and MLD of 0.996 and 0.997, respectively.[12] For these data, the mean differences between measurements for MLD and percent diameter stenosis were 0.0195 mm (SD, 0.22) and 1.42% (SD, 8.25), respectively. Quarterly reviews of quality assurance data by the study physician and statistician did not identify any notable inconsistencies in the QCA data used in the ASTEROID analyses.

Statistical Analysis

Regression of CAD was evaluated for the analysis set for the 2 QCA end points—percent diameter stenosis and MLD—for all lesions with >25% stenosis at baseline. Results are presented in terms of mean and median change from baseline, along with associated SD or 25th and 75th percentile values. Because the assumption of normality was not met for the data in these analyses, the change from baseline was tested with the Wilcoxon signed-rank test. The proportion of patients categorized as regressors versus progressors was tested using a 2-sided binomial test. ANOVA (including a factor for geographic region) was used to analyze the percent change from baseline in time-weighted average on-therapy values for lipids and lipoproteins. Least-squares linear regression analysis was applied to the mean QCA results for multiple trials, weighted by the number of patients in each arm, similar to that performed previously.[13]

The authors had full access to and take full responsibility for the integrity of the data. All authors have read and agree to the manuscript as written.

Results

Of the 507 patients enrolled in ASTEROID, 379 (75%) had baseline and follow-up angiograms. Of these 379 patients, 292 (77%) had ≥1 segment with >25% diameter stenosis at baseline that were matched with angiograms at the end of the study, permitting measurement of the change in the severity of stenosis (Figure 1). A total of 613 coronary segments in the 292 patients (median, 2 segments per patient) met the criterion of >25% stenosis at baseline and had stenosis measurements at both baseline and the end of the study. Of these patients, 11 had valid stenosis measurements but lacked calibrated MLD measurements at either baseline or the end of the study; thus, MLD analyses are based on 586 segments from 281 patients.

Patient demographics for the enrolled population are presented in Table 1 for both those with stenoses analyzed in this study and those who were not included in the analysis. The baseline demographics were very similar for both groups. For the QCA group, most patients were male and overweight, and the average age was 59 years. Almost all patients were hypertensive and white; 27% had a previous myocardial infarction; and 13% were diabetic.

Table 1. Baseline Characteristics

Baseline Patient Characteristics	Patients With Baseline Stenoses >25% and Matched Angiograms (n=292)	Patients Not Qualified for Analysis* (n=215)
Age, mean (SD), y	58.9 (9.8)	58.0 (10.3)
Male, n (%)	214 (73.3)	146 (67.9)
White, n (%)	283 (97.0)	194 (90.2)
Weight, mean (SD), kg	85.1 (16.1)	86.5 (17.5)
Body mass index, median (Q1 to Q3), kg/m^2	28.3 (25.9 to 31.4)	28.7 (25.7 to 32.1)
History of hypertension, n (%)	286 (98.0)	197 (91.6)
History of diabetes mellitus, n (%)	38 (13.0)	26 (12.1)
History of prior myocardial infarction, n (%)	78 (26.7)	43 (20.0)
History of acute coronary syndrome, n (%)	52 (17.8)	32 (14.9)
Concomitant medications		
Angiotensin-converting enzyme inhibitors, n (%)	160 (54.8)	98 (45.6)
Angiotensin receptor antagonists, n (%)	56 (19.2)	29 (13.5)
β-Blockers, n (%)	251 (86.0)	159 (74.0)
Organic nitrates, n (%)	248 (84.9)	187 (87.0)
Aspirin, n (%)	244 (83.6)	180 (83.7)

Q1 indicates quartile 1 (25th percentile); Q3, quartile 3 (75 percentile).
*Those without baseline stenoses >25% or without matched angiograms.

Table 2. Change in Lipids and Lipoproteins During Treatment, Analyzed by Patient

	Baseline Mean (SD) (n=290)	On-Treatment Mean (SD) (n=292)	LSM Percent Change (95% CI) (n=290)
Total cholesterol, mg/dL	204.7 (42.2)	133.9 (26.0)	−33.9 (−36.0 to −31.8)
LDL-C, mg/dL	131.5 (35.2)	61.1 (20.3)	−53.3 (−56.0 to −50.6)
HDL-C, mg/dL	42.8 (10.8)	48.3 (12.4)	13.8 (11.0 to 16.6)
Non–HDL-C, mg/dL	161.9 (41.2)	85.6 (23.5)	−47.0 (−49.4 to −44.5)
Triglycerides, mg/dL	151.8 (82.5)	123.5 (58.4)	−12.3 (−18.1 to −6.5)
Ratio of LDL-C to HDL-C	3.24 (1.08)	1.33 (0.51)	−58.2 (−60.8 to −55.5)
ApoB,* mg/dL	129.1 (30.1)	76.0 (22.9)	−40.9 (−43.3 to −38.4)
ApoA-I,* mg/dL	138.2 (27.1)	149.6 (31.5)	8.80 (5.95 to 11.66)
Ratio of ApoB to ApoA-I*	0.96 (0.27)	0.52 (0.17)	−44.8 (−47.2 to −42.5)

LSM indicates least-squares mean; Apo, apolipoprotein. On-treatment and percent change from baseline values were based on time-weighted average lipid and lipoprotein values.

*On-treatment and LSM percent change, n=287.

The baseline and on-treatment lipid data shown in Table 2 are similar to the results for the full ASTEROID intention-to-treat group reported previously.[9] Rosuvastatin treatment resulted in a 53.3% reduction in LDL-C, producing a mean of 61.1 mg/dL. High-density lipoprotein cholesterol (HDL-C) increased by 13.8% to a mean of 48.3 mg/dL. The ratio of LDL-C to HDL-C decreased by 58.2% to 1.33.

The baseline percent diameter stenosis and MLD and the changes with 24 months of rosuvastatin treatment are summarized in Table 3. Mean±SD percent diameter stenosis decreased from 37.3±8.4% (median, 35.7%; range, 26% to 73%) to 36.0±10.1% (median, 34.5%; range, 8% to 74%; $P<0.001$). Mean±SD MLD increased from 1.65±0.36 mm (median, 1.62 mm; range, 0.56 to 2.65 mm) to 1.68±0.38 mm (median, 1.67 mm; range, 0.76 to 2.77 mm; $P<0.001$).

Most patients showed a reduction in the percent diameter stenosis (regression), as shown in Table 4. By the clinical definition of regression or progression for percent diameter stenosis (≥10% change from baseline), 22 patients (7.5%) showed regression. Changes of <10% were seen in 261 patients (89.4%), and 9 patients (3.1%) showed progression.

Most patients showed a measurable increase in MLD (regression; Table 4). By the prespecified definition of clinical regression or progression (change of ≥0.2 mm in MLD from baseline to follow-up), 34 patients (12.1%) showed regression. Changes of <0.2 mm were seen in 230 patients (81.9%), and 17 patients (6.0%) showed progression.

There were no significant correlations between the on-therapy lipid levels and changes in the QCA parameters. There was, however, a trend toward an effect of the modification of the lipid profile if one examined the extremes of the lipid responses. For on-therapy LDL-C and on-therapy HDL-C, the highest quartile of lipid responses was, on average, associated with more beneficial effects on percent diameter stenosis and MLD than the lowest quartile of those lipid responses.

The safety profile of the study has been reported previously.[9] Among the 507 patients who received drug therapy in ASTEROID, there were 4 deaths (0.8%). Myocardial infarctions occurred in 10 patients (2.0%), 5 of whom had QCA analysis. Strokes occurred in 3 patients (0.6%), 2 of whom had QCA analysis.

Discussion

QCA and IVUS are 2 methods to quantify changes in the coronary arteries over time, and both have been used in clinical trials as surrogate measures to examine the effects of therapies on the progression of CAD. This analysis from ASTEROID examined the effects of intensive statin therapy on the lumen of the coronary artery measured as percent

Table 3. Baseline and Change in Measures of Stenosis by QCA During Treatment, Analyzed by Patient

	Mean (SD)	Median (Range)	Mean Change From Baseline (SD)	Median Change From Baseline (Q1 to Q3)
Percent diameter stenosis (n=292), %				
Baseline	37.3 (8.4)	35.7 (26.0–73.0)		
End of study	36.0 (10.1)	34.5 (8.0–74.0)	−1.3 (8.00)	−0.50 (−4.0 to 2.0)
P				<0.001*
MLD (n=281), mm				
Baseline	1.65 (0.36)	1.62 (0.56–2.65)		
End of study	1.68 (0.38)	1.67 (0.76–2.77)	0.03 (0.20)	0.02 (−0.04 to 0.11)
P				<0.001*

Q1 indicates quartile 1 (25th percentile); Q3, quartile 3 (75th percentile).

*Wilcoxon signed-rank test.

Table 4. Progression Versus Regression in Measures of Stenosis by QCA During Treatment, Analyzed by Patient

	n	Percent of Total
Percent diameter stenosis (total=292)		
Nominal changes		
Stenosis reduced (regression*)	156	53.4
No change	17	5.8
Stenosis increased (progression*)	119	40.8
Clinically relevant changes		
Stenosis reduced by ≥10% (regression*)	22	7.5
Stenosis changed by <10%	261	89.4
Stenosis increased by ≥10% (progression*)	9	3.1
MLD (total=281)		
Nominal changes		
MLD larger (regression*)	155	55.2
No change	12	4.3
MLD smaller (progression*)	114	40.6
Clinically relevant changes†		
MLD larger by ≥0.2 mm (regression*)	34	12.1
Change <0.2 mm	230	81.9
MLD smaller by ≥0.2 mm (progression*)	17	6.0

*Indicates that the proportion of regressors was significantly greater than the proportion of progressors, all $P<0.03$.

†Progression and regression predefined as absolute changes ≥0.2 mm in MLD.

diameter stenosis and MLD assessed by QCA in lesions causing >25% and <100% stenosis in any major coronary segment at baseline. In the primary ASTEROID results previously reported,[9] IVUS was used to measure the change in percent atheroma volume, change in atheroma volume in the 10-mm subsegment with the greatest disease severity at baseline (both primary efficacy parameters), and change in normalized total atheroma volume for the entire artery (secondary efficacy parameter) in a single coronary artery that was angiographically normal or had <50% stenosis at baseline. IVUS showed regression of all 3 measures of atheroma volume in the examined coronary arteries. In this analysis, intensive statin therapy led to a significant change in the coronary artery lumen in areas with luminal narrowing at baseline, with a reduction in percent diameter stenosis, a prespecified analysis, and an improvement in MLD in the same segments. The mean percent diameter stenosis was reduced by 1.3% (median change, 0.5%) during the study, and the mean MLD increased by 0.03 mm (median, 0.02 mm). These changes were in the same direction as and complement the IVUS findings of a decrease in percent atheroma volume (mean, 0.98%; median, 0.79%), reduction in atheroma volume of the most diseased segment (mean, 6.1 mm^3; median, 5.6 mm^3), and reduction in total atheroma volume (mean, 14.7 mm^3; median, 12.5 mm^3) that were previously reported.[9]

In the present trial, we show that 2 imaging modalities, which clearly measure different parameters and focus on different segments of the coronary arteries, demonstrated concordant improvements in angiographic measurements of lumen dimension and IVUS measurements of atheroma volume consistent with regression of atherosclerosis with intensive statin therapy in ASTEROID. Whereas IVUS focuses on the portion of the coronary tree with the least luminal narrowing, QCA focuses on the portion with the greatest luminal narrowing. A previous trial showed that changes in lumen dimension over time correlated weakly with IVUS parameters but that patients with angiographic progression over time had greater increases in plaque volume over time.[14] Another study found no correlation between IVUS and QCA parameters.[12]

QCA measures the lumen and therefore focuses on lesions that narrow the lumen, and progression of CAD as measured by QCA has been shown to predict clinical cardiovascular events such as nonfatal myocardial infarction, CAD mortality, and the need for revascularization in the Program for the Surgical Control of the Hyperlipidemias,[15] the Montreal Heart Institute study of nicardipine,[16] and the Cholesterol Lowering Atherosclerosis Study.[17] The change in MLD was the only measure to be independently associated with risk of coronary events in the Cholesterol Lowering Atherosclerosis Study.[17] Larger changes in the progression of CAD measured by QCA may reflect plaque instability and thrombosis, which led to luminal narrowing, that is, silent atherothrombotic events. The clinical significance of regression of CAD as measured by QCA has not been well studied; although previous QCA trials with statins consistently showed fewer patients with progression and more patients with regression than placebo, on average, patients continued to have progression of atherosclerosis in all the multicenter trials with statin monotherapy.[13] Perhaps the most important finding in this trial is that aggressive lipid-modifying therapy arrested progression or stabilized coronary stenoses during the 2 years of the study, as evidenced by the fact that 97% of patients remained stable or had regression in terms of percent diameter stenosis and that 94% of patients remained stable or had regression in terms of MLD (Table 4). Plaque stabilization may be more important than gross anatomic changes as a mechanism for the clinical benefits of statin therapy on CAD event reduction observed in clinical trials.[18]

One of the key clinical questions in the treatment of atherosclerotic CAD is the determination of clinical targets to optimize therapy. Although the National Cholesterol Education Program Adult Treatment Panel III guidelines focus on achieving a target LDL-C level,[19] others have argued that achieving a large percent reduction in LDL-C with intensive statin therapy may be a valid alternative approach,[20] and the recent American Heart Association/American College of Cardiology secondary prevention guidelines suggest that it is reasonable to achieve an LDL-C goal of <70 mg/dL or a reduction in LDL-C of >50%.[21] We performed an analysis, weighted by sample size, of multicenter angiographic trials with statins to explore the relationship between angiographic changes and LDL-C levels achieved or percent reduction in LDL-C achieved. As shown in Figure 2A and 2B, the change in percent diameter stenosis had a similar association with either LDL-C level achieved or the percent reduction in LDL-C. The change in MLD also was similarly associated

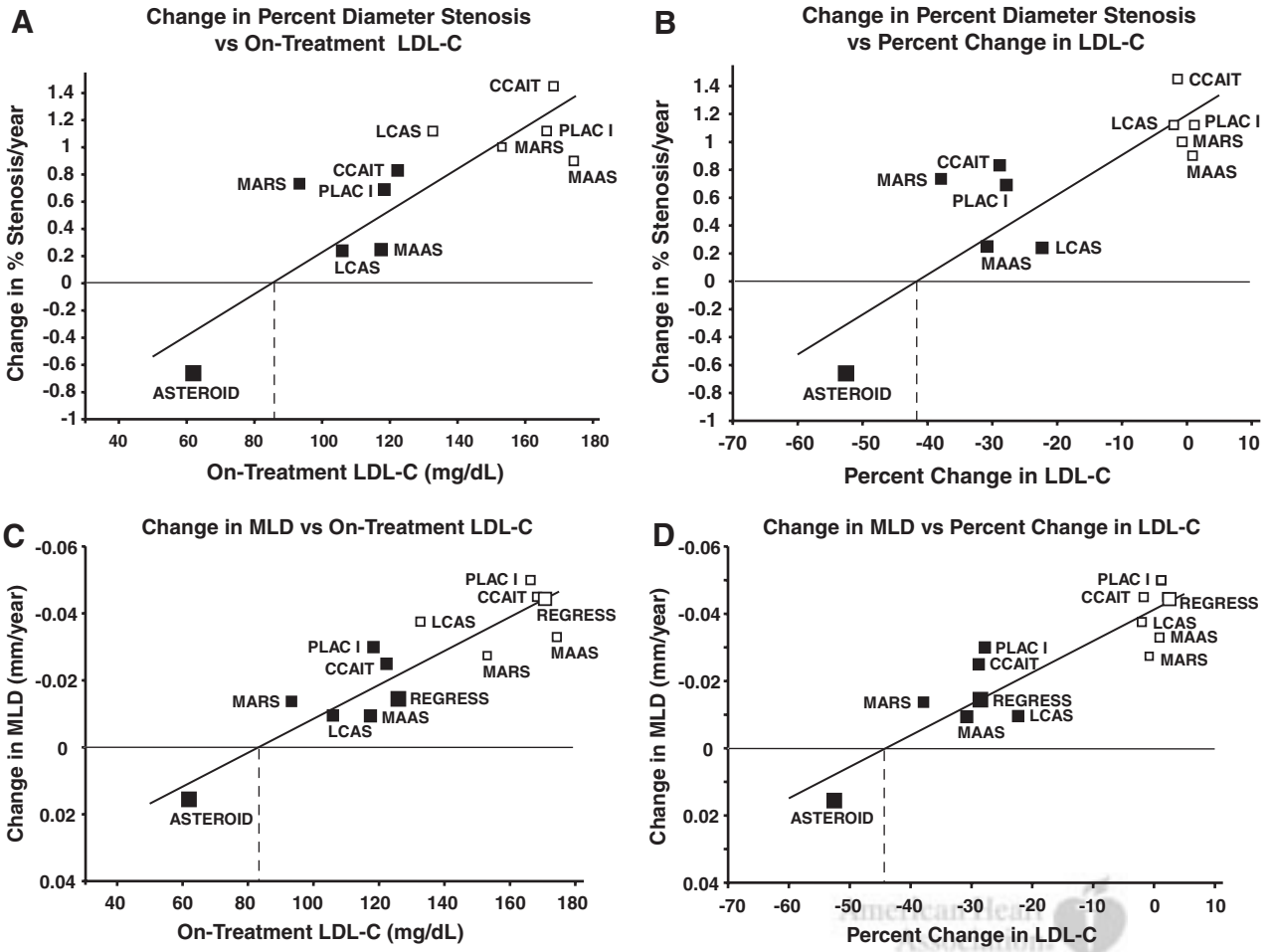

Figure 2. Association of effects on LDL-C with measures of stenosis by QCA in large trials of statin therapy. Regression analysis was based on data in the following publications and was weighted by the number of patients in each trial: the Multicentre Anti Atheroma Study[3] (MAAS; placebo=166, simvastatin=175); Canadian Coronary Atherosclerosis Intervention Study[2] (CCAIT; placebo=153, lovastatin=146); Regression Growth Evaluation Statin Study[4] (REGRESS; placebo=330, pravastatin=323); Pravastatin Limitation of Atherosclerosis in the Coronary Arteries[5] (PLAC I; placebo=157, pravastatin=163); Lipoprotein and Coronary Atherosclerosis Study[6] (LCAS; placebo monotherapy=163, fluvastatin monotherapy=156); Monitored Atherosclerosis Regression Study[1] (MARS; placebo=124, lovastatin=123); and ASTEROID (rosuvastatin=292 for change in percent diameter stenosis, 281 for change in MLD). A, Association between change in percent diameter stenosis and on-treatment LDL-C. B, Association between change in percent diameter stenosis and percent change in LDL-C. C, Association between change in MLD and on-treatment LDL-C. D, Association between change in MLD and percent change in LDL-C. □ Indicates placebo; ■, statin. The predicted value for zero net change is indicated by the dashed line on each panel. C and D, Adapted with permission from Reference 13.

with both LDL-C level achieved and the percent reduction in LDL-C as shown in Figure 2C and 2D.

Statins have other effects on lipids and lipoproteins besides reducing LDL-C, including lowering triglycerides and apolipoprotein B and raising HDL-C. The change in percent diameter stenosis had similar associations with on-treatment HDL-C level or percent change in HDL-C (Figure 3A and 3B), whereas the change in MLD had a closer association with percent change in HDL-C than on-treatment HDL-C level. Interestingly, a previously published analysis, which combined raw data from 4 IVUS trials in which 1455 patients had serial IVUS examinations on statin therapy, found that patients who achieved an LDL-C level of <87.5 mg/dL and had an increase in HDL-C of >7.5% had, on average, regression of atherosclerosis as measured by percent atheroma volume or total atheroma volume.[22] Although ASTEROID was 1 of the 4 studies in this analysis of IVUS data, the other 3 trials that made up the IVUS assessment were not a part of the QCA analyses in Figures 2 and 3. The hypothesis that the beneficial effects of statins on coronary atherosclerosis are related to reductions in LDL-C and increases in HDL-C, which is supported by these retrospective analyses of both angiographic and IVUS trials, is being prospectively tested in the Study of Coronary Atheroma by Intravascular Ultrasound: Effect of Rosuvastatin Versus Atorvastatin, which will compare high doses of 2 statins, atorvastatin 80 mg and rosuvastatin 40 mg, which differ in the LDL-C reductions and HDL-C increases they provide.

Limitations of the present study include the absence of a control group. However, it was considered unethical to treat patients with advanced CAD with placebo or a less effective statin. We compensated for the lack of a control group by blinding date information on the angiograms and resequencing them using random assignments to eliminate observer

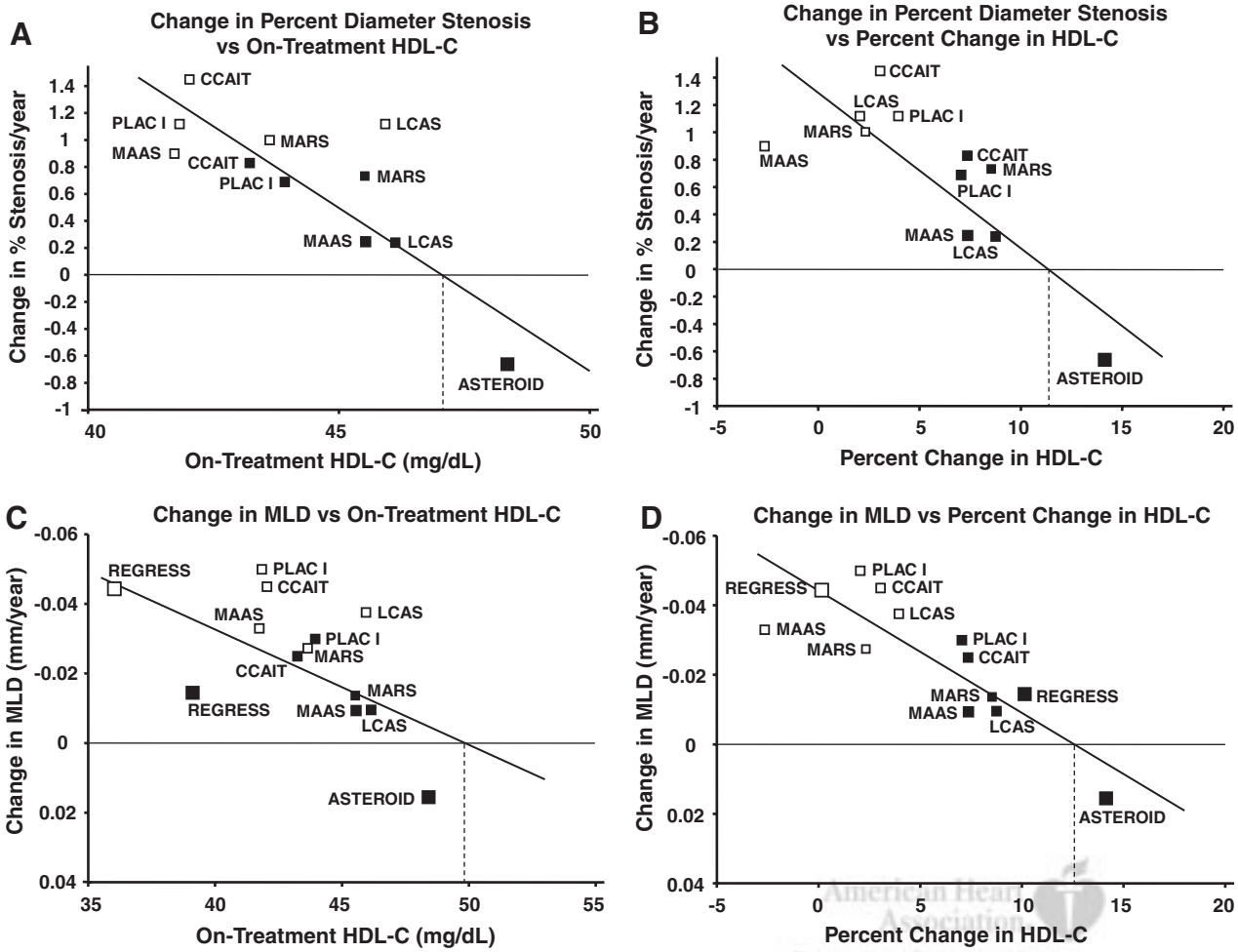

Figure 3. Association of effects on HDL-C with measures of stenosis by QCA in large trials of statin therapy. Source data and analysis methods were as in Figure 1. A, Association between change in percent diameter stenosis and on-treatment HDL-C. B, Association between change in percent diameter stenosis and percent change in HDL-C. C, Association between change in MLD and on-treatment HDL-C. D, Association between change in MLD and percent change in HDL-C. □ Indicates placebo; ■, statin. The predicted value for zero net change is indicated by the dashed line on each panel. Abbreviations as in Figure 2.

bias in the interpretation of the angiograms. Another limitation is the dropout rate of 25%; however, this rate is comparable to the dropout rate in similar populations in recent IVUS studies such as the Reversal of Atherosclerosis With Aggressive Lipid Lowering[23] (24% dropout rate) and Investigation of Lipid Level Management Using Coronary Ultrasound to Assess Reduction of Atherosclerosis by CETP Inhibition and HDL Elevation[24] (23% dropout rate) and in prior QCA studies such as the Lipoprotein and Coronary Atherosclerosis Study[6] (21% dropout rate). A limitation of the analyses comparing lipid changes and QCA parameters in statin trials is that the lipid changes, particularly reductions in LDL-C, may simply reflect more effective inhibition of HMG-CoA reductase; thus, the beneficial effects of statin therapy on coronary atherosclerosis may not be related solely to the changes in lipoproteins. Indeed, there are examples of therapies with mechanisms other than inhibition of HMG-CoA reductase that had marked benefits on both LDL-C and HDL-C levels but did not lead to improved outcomes on either coronary atherosclerosis or clinical events.[24,25] An additional limitation is that neither QCA nor IVUS as used in ASTEROID provides any information on the impact of statins or lipid changes on plaque composition, which, at least theoretically, may correlate more closely with event reduction. Of interest will be future studies that focus on how therapies both affect anatomic parameters and modify plaque composition, which may beneficially affect the vulnerability of patients to future clinical events.

Conclusions

Rosuvastatin treatment for 24 months resulted in mean LDL-C levels well below 70 mg/dL accompanied by significant increases in HDL-C and produced regression by decreasing percent arterial stenosis and improving MLD as measured by QCA in patients with CAD.

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CLINICAL PERSPECTIVE

Previous angiographic studies of statin therapy have shown reduced progression of coronary stenoses in proportion to average low-density lipoprotein cholesterol levels during therapy. However, no major statin monotherapy study has demonstrated either halted progression or regression of angiographic disease. A Study to Evaluate the Effect of Rosuvastatin on Intravascular Ultrasound-Derived Coronary Atheroma Burden (ASTEROID) tested whether intensive treatment by rosuvastatin for 24 months could modify the course of coronary atherosclerosis measured by either intravascular ultrasound of the artery wall (reported previously) or by quantitative coronary angiography of the artery lumen (the present report). Therapy reduced mean low-density lipoprotein cholesterol to 61 mg/dL and increased mean high-density lipoprotein cholesterol by 13.8% to 48 mg/dL in these patients. Quantitative coronary angiography showed significant net improvement in the 2 measures of stenosis: percent diameter stenosis and minimum lumen diameter of the stenoses. These improvements complement the intravascular ultrasound results from ASTEROID of the decrease in atheroma volume that was previously reported. This indicates that 2 imaging methods that measured different parameters and focused on different segments of the coronary arteries demonstrated concordant improvements consistent with regression of atherosclerosis with intensive statin therapy. In particular, rosuvastatin treatment for 24 months, resulting in mean low-density lipoprotein cholesterol levels well below 70 mg/dL and significant increases in high-density lipoprotein cholesterol, decreased coronary artery percent stenosis and improved minimum lumen diameter in patients with coronary artery disease. Both imaging and outcome studies suggest that intensive statin treatment seems warranted in high-risk coronary artery disease patients. The relative importance of low-density lipoprotein cholesterol reduction and high-density lipoprotein cholesterol elevation with statin therapy in producing these results on atherosclerosis requires further investigation.

Effect of Rosuvastatin Therapy on Coronary Artery Stenoses Assessed by Quantitative Coronary Angiography. A Study to Evaluate the Effect of Rosuvastatin on Intravascular Ultrasound-Derived Coronary Atheroma Burden

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