ILKE SIPAHI, MD*
Department of Cardiovascular Medicine, Cleveland Clinic; investigator, ASTEROID trial

STEPHEN J. NICHOLLS, MBBS, PhD†
Department of Cardiovascular Medicine, Cleveland Clinic; investigator, ASTEROID trial

E. MURAT TUZCU, MD‡
Vice chairman, Department of Cardiovascular Medicine, Cleveland Clinic; investigator, ASTEROID trial

STEVEN E. NISSEN, MD§
Chairman, Department of Cardiovascular Medicine, Cleveland Clinic; president, American College of Cardiology; principal investigator, ASTEROID trial

CME CREDIT

INTERPRETING THE ASTEROID TRIAL

Coronary atherosclerosis can regress with very intensive statin therapy

ABSTRACT

The ASTEROID trial (JAMA 2006; 295:1556–1565) showed that very intensive statin therapy with rosuvastatin 40 mg once daily results in highly significant regression of coronary atherosclerosis as assessed by serial intravascular ultrasonography (IVUS). The mean low-density lipoprotein cholesterol (LDL-C) level achieved with this regimen was 61 mg/dL, and the mean high-density lipoprotein cholesterol (HDL-C) level increased by 15%. While the merits of concomitant LDL-C-lowering and HDL-C-raising therapies remain to be determined, the results of the ASTEROID and other recent trials suggest that the optimal strategy for lipid-lowering in patients with coronary artery disease is to try for the lowest LDL-C level that can be attained without adverse effects.

KEY POINTS

Coronary IVUS is inherently a more sensitive method of monitoring atheroma progression and regression than coronary angiography.

In recent clinical trials, the relationship between LDL-C levels and progression of atherosclerosis was strong and linear.

The optional LDL-C goal of less than 70 mg/dL is likely to be applicable not only for patients at very high risk, but for all patients with coronary disease.

*Dr. Sipahi has received an educational grant from Pfizer.
†Dr. Nicholls has received lecture honoraria from AstraZeneca and Pfizer.
‡Dr. Tuzcu received grant support from Pfizer and Takeda and lecture honoraria from Pfizer.
§Dr. Nissen has received research support from AstraZeneca, Eli Lilly, Pfizer, Takeda, Sankyo, and Sanofi-Aventis. He has also consulted for a number of pharmaceutical companies without financial compensation. All his honoraria, consulting fees, or other payments from any for-profit entity are paid directly to charity, so that neither income nor tax deduction is received.

MANY PATIENTS who are found to have atherosclerotic plaques on coronary angiography ask whether it is possible to make the plaques regress. Until recently, we could only give them a vague answer and talk about decreasing symptoms and preventing coronary events, since we really did not have clear evidence of regression in most patients.

Now we can give them a more definite answer—yes—in view of the findings of the large-scale ASTEROID (A Study to Evaluate the Effect of Rosuvastatin on Intravascular Ultrasound-derived Coronary Atheroma Burden) trial,[1] in which we were investigators.

What the ASTEROID trial showed us and how we should apply its findings in the care of patients with coronary artery disease are the topics of this article.

BEFORE ASTEROID

Although some earlier studies suggested that atherosclerosis can regress with medications or lifestyle changes, many others did not.[2–8]

Of importance, these studies used conventional angiography, which basically shows the silhouette of the coronary lumen, not the plaques themselves. Changes in lumen size on angiography generally do not reflect the changes in the size of the plaques, due to vascular remodeling.[9,10] Thus, one can argue that "regression of atherosclerosis means regression of what we *don't* see on angiography."[11]

Given this crucial limitation of angiography, trials of atherosclerosis progression and regression have begun to use other imaging tests that can directly image the plaque such as magnetic resonance imaging, computed

TABLE 1

Glossary of study names

ACTIVATE—ACAT Intravascular Atherosclerosis Treatment Evaluation[14]

A-PLUS—Avasimibe and Progression of Lesions on Ultrasound[13]

ASTEROID—A Study to Evaluate the Effect of Rosuvastatin on Intravascular Ultrasound-derived Coronary Atheroma Burden[1]

CAMELOT—Comparison of Amlodipine Versus Enalapril to Limit Occurrences of Thrombosis[15]

CORONA—Controlled Rosuvastatin Multinational Trial in Heart Failure[24]

ESTABLISH—Early Statin Treatment in Patients with Acute Coronary Syndrome[20]

IDEAL—Incremental Decrease in End Points Through Aggressive Lipid Lowering[28]

JUPITER–Justification for the Use of Statins in Primary Prevention: an Interventional Trial Evaluating Rosuvastatin[23]

PROVE IT/TIMI 22—Pravastatin or Atorvastatin Evaluation and Infection Therapy-Thrombolysis in Myocardial Infarction[26]

REVERSAL—Reversal of Atherosclerosis With Aggressive Lipid Lowering[12]

TNT—Treating to New Targets[27]

tomography, and intravascular ultrasonography (IVUS). Of these, IVUS has become increasingly popular owing to its high resolution, which allows accurate assessment of the volume of atherosclerotic plaque.

Previous major IVUS trials were the REVERSAL,[12] A-PLUS,[13] and ACTIVATE[14] trials and the IVUS substudy of CAMELOT[15] (see TABLE 1 for the full names of these trials). Each tested the hypothesis that one medication would be superior to another or to placebo in its ability to retard progression of coronary atherosclerosis. While the results of these trials provided invaluable information about progression of atherosclerosis, none of them showed compelling evidence for regression of disease.

ASTEROID was the first large IVUS study to test if atherosclerosis could regress

In contrast, ASTEROID was the first large-scale IVUS study to test whether coronary atherosclerosis could actually regress.[1]

ASTEROID STUDY DESIGN

ASTEROID, performed in 53 community and tertiary-care hospitals in the United States, Canada, Europe, and Australia, was sponsored by AstraZeneca, the maker of rosuvastatin (Crestor).

All patients had coronary disease

The ASTEROID study enrolled patients aged 18 to 75 years who required coronary angiography for a clinical indication and in whom angiography had shown coronary artery disease (at least one obstruction with > 20% narrowing of the luminal diameter).

There was no low-density lipoprotein cholesterol (LDL-C) criterion for enrollment; however, patients with very high triglyceride levels (≥ 500 mg/dL) or poorly controlled diabetes (hemoglobin A_{1c} levels ≥ 10%) were excluded.

All patients were required to be "statin-naive," defined as receiving no statin therapy for more than 3 months during the previous 12 months. A total of 507 patients were enrolled, of whom 349 had evaluable IVUS examinations at both baseline and follow-up.

Treatment was maximal for all

Because we wanted to determine whether maximally intensive lipid-lowering can induce regression of coronary atherosclerosis, we chose rosuvastatin 40 mg as the study treatment—the regimen that had reduced LDL-C levels the most in previous clinical trials.

Because all the patients had established coronary disease and other trials had demonstrated that outcomes are better with intensive therapy, it was deemed unacceptable to randomize some of the patients to receive low-intensity statin treatment or placebo. Therefore, we gave everyone rosuvastatin 40 mg/day. Since there was no control group, we instead randomized the order in which we analyzed the IVUS studies (see below).

IVUS at baseline and after 24 months

After performing coronary angiography, the operator chose the longest and least angulated coronary artery for IVUS interrogation. After intracoronary nitroglycerin was given to prevent vasospasm, a high-frequency ultrasound catheter was advanced into the target vessel and the transducer was positioned distal to a

TABLE 2

Measures of efficacy in the ASTEROID trial

Primary measures

Percent atheroma volume =

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

where EEM_{CSA} is the external elastic membrane cross-sectional area and $LUMEN_{CSA}$ is the luminal cross-sectional area. Percent atheroma volume corresponds to the proportion of the total vessel volume occupied by the atherosclerotic plaque.

Atheroma volume in the most diseased 10-mm subsegment =

$$\sum_{1}^{10}(EEM_{CSA} - LUMEN_{CSA})$$

This corresponds to the sum of the atheroma areas in the most diseased 10-mm subsegment of the coronary artery.

Secondary measure

Normalized total atheroma volume =

$$\left[\frac{\sum(EEM_{CSA} - LUMEN_{CSA})}{\text{number of frames in a patient}}\right] \times \text{median number of frames for all patients}$$

Normalized total atheroma volume corresponds to the total volume of atherosclerotic plaque corrected for the differences in the lengths of the imaged segments.

side branch. Then the operator engaged a motor drive that progressively withdrew the transducer at 0.5 mm/second. During this pullback, images were obtained at 30 frames per second and recorded on videotape. Therefore, every 60th frame was exactly 1 mm apart.

IVUS was repeated after 24 months of treatment, and images were obtained at the same sites as in the original examination.

IVUS analysis at the core laboratory

All the videotapes were analyzed at a core laboratory at Cleveland Clinic. All measurements were performed at the end of the study after both the baseline and follow-up IVUS examinations were completed.

To conceal the imaging sequence, the dates on the IVUS images were removed and the two examinations were then resequenced using random assignments. Therefore, the technicians analyzing the IVUS tapes did not know which interrogation was baseline and which one was follow-up.

Subsequently, the distal branch site was identified as the beginning point for analysis and every 60th image (ie, every 1 mm from distal to proximal) was analyzed using computerized planimetry and according to the current standards.[16]

Three measures of efficacy

There were two primary measures of efficacy: change in percent atheroma volume and change in atheroma volume in the most diseased 10-mm subsegment. A secondary measure of efficacy was the change in normalized total atheroma volume in the whole imaged segment (TABLE 2).

Because the study tested whether rosuvastatin would induce regression of coronary atherosclerosis, all of the outcome measures were analyzed to see if they were significantly less than 0; the hypothesis was that all of the efficacy variables would be lower at follow-up.

STUDY RESULTS

Plasma lipids improved

The mean LDL-C level decreased from 130 mg/dL at baseline to 61 mg/dL during the study, a 53% reduction. The mean HDL-C level increased from 43 mg/dL to 49 mg/dL, a 15%

On therapy, LDL-C levels decreased from 130 to 61 mg/dL

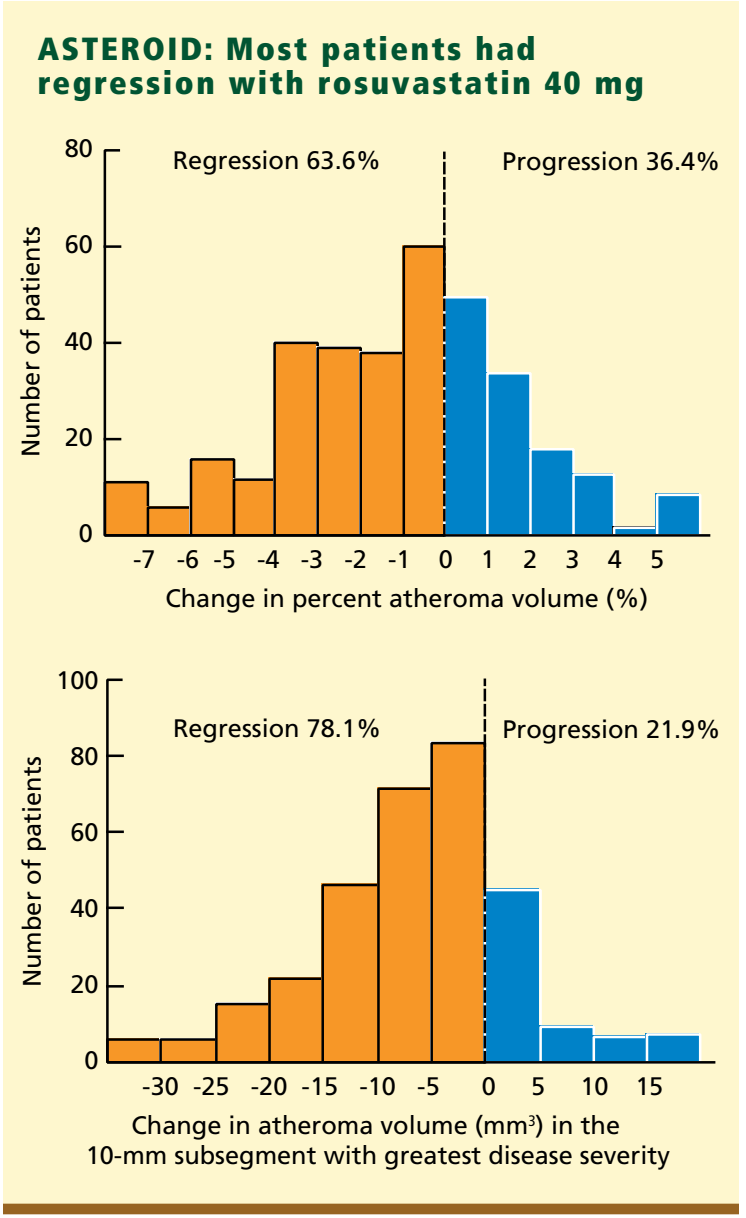


FIGURE 1. Disease regression in the ASTEROID trial.

improvement. The mean LDL-C to HDL-C ratio decreased dramatically, from 3.2 to 1.3.

Lesions regressed

All three measures of efficacy showed statistically significant regression, and most patients showed significant regression of disease:

- The percent atheroma volume decreased from a median of 39.9% at baseline to 38.5% at follow-up ($P < .001$). The median change from baseline was –0.79%. Using this measure of efficacy, regression was noted in 63.6% of patients and progression in 36.4% (FIGURE 1).
- The atheroma volume in the 10-mm subsegment with the greatest disease severity decreased from a median of 65.1 mm³ at baseline to 58.4 mm³ at follow-up ($P < .001$). The median change from baseline was –5.6 mm³. Using this measure of efficacy, regression was noted in 78.1% of patients and progression in 21.9%.
- The normalized total atheroma volume decreased from a median of 204.7 mm³ at baseline to 186.8 mm³ at follow-up ($P < .001$). The median change from baseline was –12.5 mm³. Using this measure of efficacy, regression was noted in 77.9% of patients and progression in 22.1%.

FIGURE 2 depicts a representative example of disease regression with rosuvastatin.

Adverse events

Rosuvastatin 40 mg/day was well tolerated. Rates of elevation of hepatic enzymes were comparable with those in other trials of statins in high doses (< 2%). There were no cases of rhabdomyolysis.

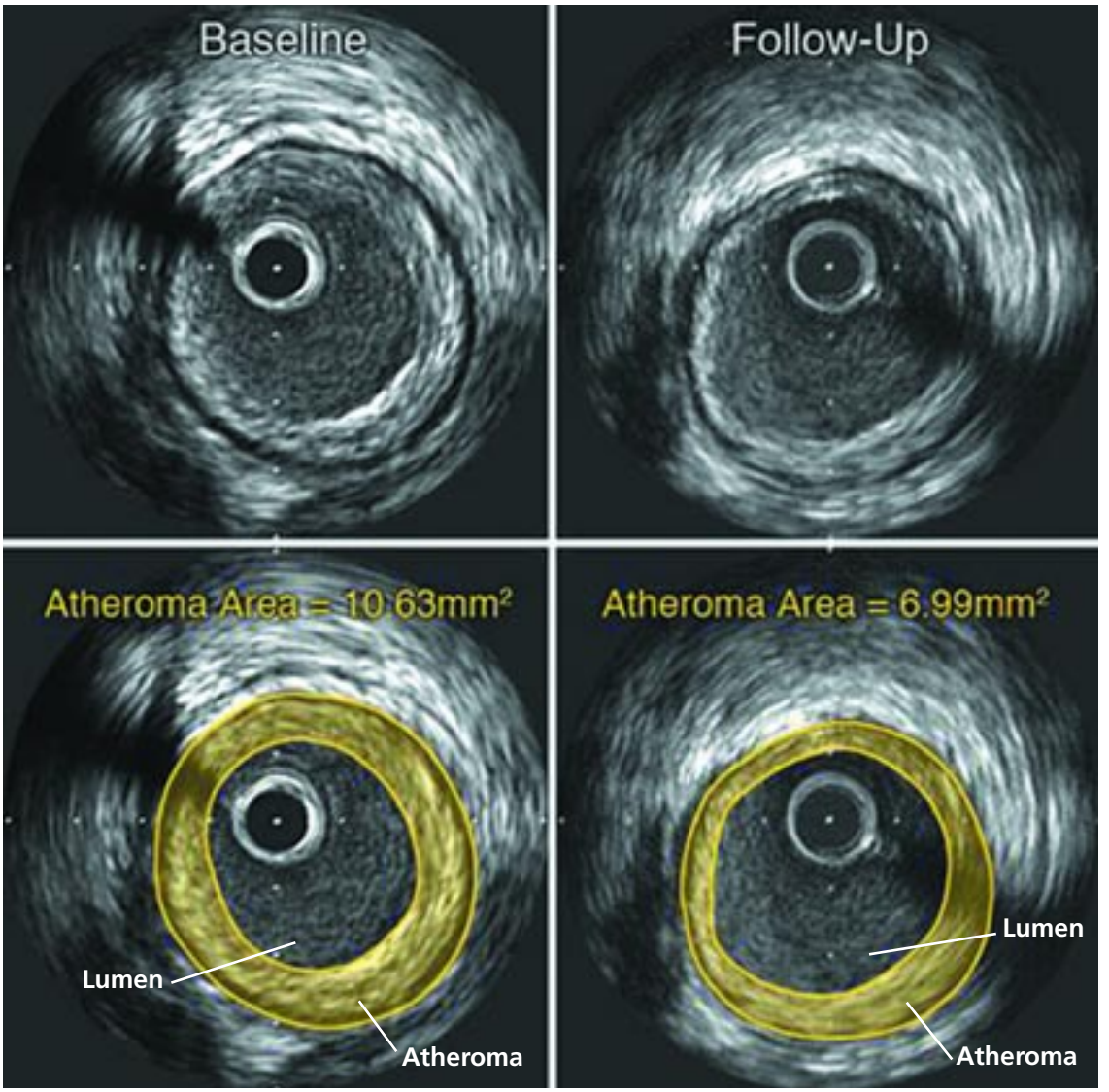
WHAT DOES THIS MEAN?

Convincing evidence for regression

The ASTEROID trial provides convincing evidence that very intensive statin therapy with rosuvastatin 40 mg daily can induce regression of coronary atherosclerosis. Depending on the outcome measure, 64% to 78% of the patients showed regression of disease, significantly more than in the older angiographic progression-regression trials, in which the fraction of patients with regression was between 7% and 41%.[17]

The remarkably more common occurrence of regression in the ASTEROID trial compared with the angiographic trials is probably explained by two factors:

- Rosuvastatin 40 mg/day was extremely efficacious, lowering LDL-C by 53%. In contrast, the lipid-lowering agents used in previous trials lowered LDL-C by only 16% to 46%.
- Coronary IVUS is inherently a more sensitive method of monitoring atheroma progression and regression than coronary angiography. Indeed, before the ASTEROID trial, a



IVUS is more sensitive than angiography for tracking atherosclerosis

FIGURE 2. Intravascular ultrasound examination at baseline (left) and after 24 months of statin therapy (right) in a patient in the ASTEROID trial.

few small, single-center IVUS studies had suggested that lipid-lowering medications could induce regression of coronary atherosclerosis.[18–20] However, these studies used only two-dimensional measurements, were very small, or were restricted to certain ethnic groups with relatively lower baseline LDL-C levels (ie, the Japanese ESTABLISH study[20]), thus limiting their impact.

Comparison to previous large-scale IVUS trials

The REVERSAL trial[12] was the first large-scale IVUS trial to evaluate the effect of statins on the progression rate of coronary atherosclerosis. In this study, plaque volume increased significantly in patients receiving a moderate lipid-lowering regimen of pravastatin (Pravachol) 40 mg/day but remained the same in patients receiving a more intensive regimen of atorvastatin (Lipitor) 80 mg/day.

TABLE 3 compares the patients in the REVERSAL and ASTEROID trials. Although cross-trial comparisons are prone to mistakes, and the relative benefits of different regimens can only be delineated in a head-to-head clinical trial, the following observations are noteworthy.

TABLE 3

Comparison of the REVERSAL and ASTEROID trials

	REVERSAL		ASTEROID
	PRAVASTATIN 40 MG (N = 249)	ATORVASTATIN 80 MG (N = 253)	ROSUVASTATIN 40 MG (N = 349)
Mean age, years	56	56	59
Male (%)	73	71	70
Mean body mass index, kg/m^2	30.5	30.5	28.4
History of hypertension (%)	70	68	96
History of diabetes (%)	18	20	13
Baseline lipids			
Total cholesterol, mg/dL	233	232	204
LDL cholesterol, mg/dL	150	150	130
HDL cholesterol, mg/dL	43	42	43
Triglycerides, mg/dL	198	197	152
Follow-up lipids			
Total cholesterol, mg/dL	188	151	133
LDL cholesterol, mg/dL	110	79	61
HDL cholesterol, mg/dL	45	43	49
Triglycerides, mg/dL	166	148	121
Percent change in lipids			
Total cholesterol, mg/dL	–18	–34	–34
LDL cholesterol, mg/dL	–25	–46	–53
HDL cholesterol, mg/dL	6	3	15
Triglycerides, mg/dL	–7	–20	–15
IVUS findings			
Median change in			
Percent atheroma volume, %	1.6	0.2	–0.8
Total atheroma volume, mm^3	4.4	–0.9	–5.6

The baseline demographic characteristics of the pravastatin and atorvastatin groups in REVERSAL and ASTEROID were similar, although ASTEROID patients had a slightly lower mean body mass index, fewer of them had diabetes, and more of them had hypertension. Because REVERSAL patients had to have LDL-C levels between 125 and 210 mg/dL to enroll, their baseline LDL-C level was about 20 mg/dL higher than in ASTEROID, which had no LDL-C criterion for enrollment.

The follow-up LDL-C level was highest in the REVERSAL pravastatin group, intermediate in the REVERSAL atorvastatin group, and lowest in ASTEROID. Strikingly, the outcome measures of disease progression had the same order: significant progression in the pravastatin group of REVERSAL, no change in the atorvastatin group of REVERSAL, and significant regression in ASTEROID. FIGURE 3 shows the relationship between the LDL-C level during treatment and the progression rate of coronary atherosclerosis in REVERSAL, ASTEROID, and the placebo groups of other large IVUS trials not specifically studying the effects of statins, such as the CAMELOT[15] and ACTIVATE[14] trials.

There is a very strong linear relationship between achieved LDL-C levels and the course of atherosclerosis. On the average, at an LDL-C level of about 80 mg/dL, atherosclerosis neither progresses nor regresses, and values below this, as achieved in the ASTEROID trial, can lead to significant disease regression. However, further investigation is required to elucidate the relative contributions of HDL-C-raising and modulation of non-lipid measures such as C-reactive protein on atheroma progression and regression.

Limitations of the ASTEROID study

Like every study, the ASTEROID trial had

some limitations, the most important of which was the lack of a control group receiving placebo or less-intensive lipid-lowering therapy. We deemed it ethically unacceptable to give a less-effective regimen or placebo to patients with angiographically documented coronary disease. This was partially overcome by randomly resequencing the order of the IVUS interrogations to eliminate observer bias.

Concomitant medications might have contributed to the results of this study. Of note, 84% of the patients received a beta-blocker during the study, which may have some antiatherosclerotic effects.[21]

Additionally, although some indirect evidence supports the use of IVUS as a valid surrogate end point for coronary outcomes,[22] there is currently no information on the prognostic significance of progression or regression demonstrated with this imaging test.

Finally, while rosuvastatin was well tolerated, ongoing larger trials with clinical end points, eg, JUPITER[23] (comparing rosuvastatin and placebo as primary prevention in 15,000 patients) and CORONA[24] (comparing rosuvastatin and placebo in 5,000 patients with ischemic heart failure) are likely to provide more robust information about its safety.

The lower the LDL-C level, the less atherosclerosis tends to progress

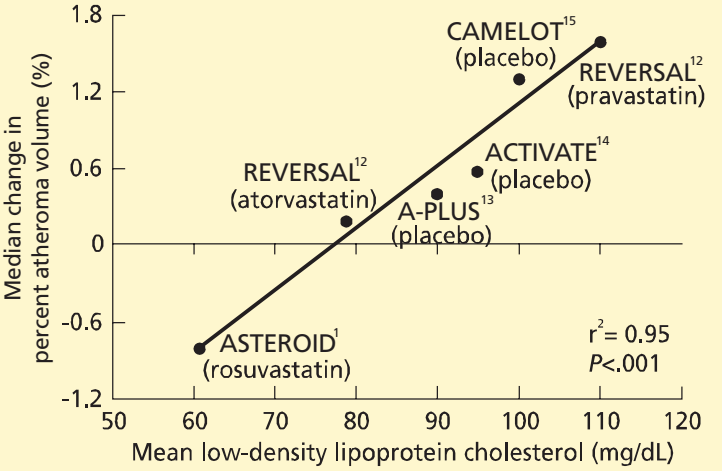


FIGURE 3. Mean low-density lipoprotein cholesterol (LCL-C) levels and median change in percent atheroma volume in recent clinical trials. The follow-up period was 24 months in ASTEROID, A-PLUS, and CAMELOT, and 18 months in the REVERSAL and ACTIVATE trials.

MODIFIED FROM NISSEN SE, NICHOLLS SJ, SIPAHI I, ET AL. EFFECT OF VERY HIGH-INTENSITY STATIN THERAPY ON REGRESSION OF CORONARY ATHEROSCLEROSIS: THE ASTEROID TRIAL. JAMA 2006; 295:1556–1565.

IMPLICATIONS FOR MANAGEMENT

For the secondary prevention of atherosclerotic disease, the revised version of the Adult Treatment Panel III (ATP III) of the National Cholesterol Education Program[25] recommends a target LDL-C level of less than 100 mg/dL, with an optional target of less than 70 mg/dL for patients at very high risk, such as those with a recent acute coronary syndrome event (according to the results of PROVE-IT[26]) or multiple uncontrolled risk factors.

After these guidelines were published, the results of two important clinical trials studying intensive lipid-lowering in patients with coronary artery disease became available.

The TNT trial[27] randomized patients with stable coronary artery disease to receive atorvastatin 10 mg/day or atorvastatin 80 mg/day; the mean on-treatment LDL-C levels during the study period were 101 mg/dL and 77 mg/dL, respectively. The composite end point of fatal coronary heart disease, nonfatal myocardial infarction, resuscitation after cardiac arrest, and stroke was reduced by 22% ($P < .001$) in the atorvastatin 80-mg group, while the total mortality rate was unchanged.

The IDEAL trial[28] randomized patients with a history of myocardial infarction (mostly remote) to receive simvastatin 20 mg/day or atorvastatin 80 mg/day; the mean on-treatment LDL-C levels were 104 mg/dL and 81 mg/dL, respectively. The composite end point of coronary death, nonfatal myocardial infarction, or cardiac arrest with resuscitation was reduced by 11% ($P = .07$), and nonfatal myocardial infarction by itself was reduced by 17% ($P = .02$) in the atorvastatin 80-mg group, while the total mortality rate was unchanged.

Both of these studies show that in patients with coronary artery disease who are not necessarily at very high risk, lipid-lowering to target LDL-C levels well below 100 mg/dL is associated with better outcomes. Therefore,

the optional goal of less than 70 mg/dL is likely to be applicable not only for patients at very high risk, but for all patients with coronary disease. In this context, the ASTEROID trial showed that with even lower levels of LDL-C (61 mg/dL), coronary atherosclerosis could regress, a finding not demonstrated with other, less effective regimens.

While the clinical merits of lowering LDL-C levels to the range of the 60s or 50s remains to be determined, accumulating evidence suggests that the optimal lipid-lowering strategy in patients with coronary disease can be to reduce LDL-C to lowest possible levels without causing adverse effects.

Acknowledgment. *We thank Timothy Crowe from the Cleveland Clinic Intravascular Ultrasound Core Laboratory for his assistance in the preparation of this manuscript.*

REFERENCES

1. **Nissen SE, Nicholls SJ, Sipahi I, et al.** Effect of very high-intensity statin therapy on regression of coronary atherosclerosis: the ASTEROID trial. JAMA 2006; 295:1556–1565.
2. **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.
3. **Kane JP, Malloy MJ, Ports TA, Phillips NR, Diehl JC, Havel RJ.** Regression of coronary atherosclerosis during treatment of familial hypercholesterolemia with combined drug regimens. JAMA 1990; 264:3007–3012.
4. **Blankenhorn DH, Azen SP, Kramsch DM, et al.** Coronary angiographic changes with lovastatin therapy. The Monitored Atherosclerosis Regression Study (MARS). Ann Intern Med 1993; 119:969–976.
5. **Haskell WL, Alderman EL, Fair JM, et al.** Effects of intensive multiple risk factor reduction on coronary atherosclerosis and clinical cardiac events in men and women with coronary artery disease. The Stanford Coronary Risk Intervention Project (SCRIP). Circulation 1994; 89:975–990.
6. **Waters D, Higginson L, Gladstone P, et al.** Effects of monotherapy with an HMG-CoA reductase inhibitor on the progression of coronary atherosclerosis as assessed by serial quantitative arteriography. The Canadian Coronary Atherosclerosis Intervention Trial. 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. **Brown BG, Zhao XQ, Chait A, et al.** Simvastatin and niacin, antioxidant vitamins, or the combination for the prevention of coronary disease. N Engl J Med 2001; 345:1583–1592.
9. **Glagov S, Weisenberg E, Zarins CK, Stankunavicius R, Kolettis GJ.** Compensatory enlargement of human atherosclerotic coronary arteries. N Engl J Med 1987; 316:1371–1375.
10. **Sipahi I, Tuzcu EM, Schoenhagen P, et al.** Paradoxical increase in lumen size during progression of coronary atherosclerosis: Observations from the REVERSAL trial. Atherosclerosis 2006 (e-pub ahead of print).
11. **Fuster V, Badimon JJ.** Regression or stabilization of atherosclerosis means regression or stabilization of what we don't see in the arteriogram. Eur Heart J 1995; 16(suppl E):6–12.
12. **Nissen SE, Tuzcu EM, Schoenhagen P, 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.** Effects of the acyl coenzyme A:cholesterol acyltransferase inhibitor avasimibe on human atherosclerotic lesions. Circulation 2004; 110:3372–3377.
14. **Nissen SE, Tuzcu EM, Brewer HB, et al.** Effect of ACAT inhibition on the progression of coronary atherosclerosis. N Engl J Med 2006; 354:1253–1263.
15. **Nissen SE, Tuzcu EM, Libby P, 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; 292:2217–2225.
16. **Mintz GS, Nissen SE, Anderson WD, 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.
17. **Brown BG, Zhao XQ, Poulin D, Albers JJ.** Regression of atherosclerosis. Does it occur and does it have clinical meaning? Eur Heart J 1995; 16(suppl E):2–5.
18. **Takagi T, Yoshida K, Akasaka T, Hozumi T, Morioka S, Yoshikawa J.** Intravascular ultrasound analysis of reduction in progression of coronary narrowing by treatment with pravastatin. Am J Cardiol 1997; 79:1673–1676.
19. **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.
20. **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.
21. **Sipahi I, Tuzcu EM, Nicholls SJ, et al.** Use of beta-blockers and progression of coronary atherosclerosis: an intravascular ultrasound analysis from the CAMELOT study. J Am Coll Cardiol 2006; 47(suppl A):320A–321A.
22. **Topol EJ.** Intensive statin therapy—a sea change in cardiovascular prevention. N Engl J Med 2004; 350:1562–1564.
23. **Mora S, Ridker PM.** Justification for the Use of Statins in Primary Prevention: an Interventional Trial Evaluating Rosuvastatin (JUPITER)—can C-reactive protein be used to target statin therapy in primary prevention? Am J Cardiol 2006; 97:33A–41A.
24. **Dunselman P, Hjalmarson A, Kjekshus J, McMurray J, Waagstein F; Executive Committee of the CORONA trial.** The statin wars [letter]. Lancet 2003; 362:1854.
25. **Grundy SM, Cleeman JI, Merz CN, et al.** Implications of recent clinical trials for the National Cholesterol Education Program Adult Treatment Panel III Guidelines. J Am Coll Cardiol 2004; 44:720–732.
26. **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.
27. **LaRosa JC, Grundy SM, Waters DD, et al.** Intensive lipid lowering with atorvastatin in patients with stable coronary disease. N Engl J Med 2005; 352:1425–1435.
28. **Pedersen TR, Faergeman O, Kastelein JJ, et al.** 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.

ADDRESS: *Ilke Sipahi, MD, Department of Cardiovascular Medicine, JJ65, Cleveland Clinic, 9500 Euclid Avenue, Cleveland, OH 44195; e-mail sipahii@ccf.org.*