ORIGINAL ARTICLE

Effect of Two Intensive Statin Regimens on Progression of Coronary Disease

Stephen J. Nicholls, M.B., B.S., Ph.D., Christie M. Ballantyne, M.D., Philip J. Barter, M.B., B.S., Ph.D., M. John Chapman, Ph.D., D.Sc., Raimund M. Erbel, M.D., Peter Libby, M.D., Joel S. Raichlen, M.D., Kiyoko Uno, M.D., Marilyn Borgman, R.N., Kathy Wolski, M.P.H., and Steven E. Nissen, M.D.

ABSTRACT

BACKGROUND

Statins reduce adverse cardiovascular outcomes and slow the progression of coronary atherosclerosis in proportion to their ability to reduce low-density lipoprotein (LDL) cholesterol. However, few studies have either assessed the ability of intensive statin treatments to achieve disease regression or compared alternative approaches to maximal statin administration.

METHODS

We performed serial intravascular ultrasonography in 1039 patients with coronary disease, at baseline and after 104 weeks of treatment with either atorvastatin, 80 mg daily, or rosuvastatin, 40 mg daily, to compare the effect of these two intensive statin regimens on the progression of coronary atherosclerosis, as well as to assess their safety and side-effect profiles.

RESULTS

After 104 weeks of therapy, the rosuvastatin group had lower levels of LDL cholesterol than the atorvastatin group (62.6 vs. 70.2 mg per deciliter [1.62 vs. 1.82 mmol per liter], P<0.001), and higher levels of high-density lipoprotein (HDL) cholesterol (50.4 vs. 48.6 mg per deciliter [1.30 vs. 1.26 mmol per liter], P=0.01). The primary efficacy end point, percent atheroma volume (PAV), decreased by 0.99% (95% confidence interval [CI], −1.19 to −0.63) with atorvastatin and by 1.22% (95% CI, −1.52 to −0.90) with rosuvastatin (P=0.17). The effect on the secondary efficacy end point, normalized total atheroma volume (TAV), was more favorable with rosuvastatin than with atorvastatin: −6.39 mm^3 (95% CI, −7.52 to −5.12), as compared with −4.42 mm^3 (95% CI, −5.98 to −3.26) (P=0.01). Both agents induced regression in the majority of patients: 63.2% with atorvastatin and 68.5% with rosuvastatin for PAV (P=0.07) and 64.7% and 71.3%, respectively, for TAV (P=0.02). Both agents had acceptable side-effect profiles, with a low incidence of laboratory abnormalities and cardiovascular events.

CONCLUSIONS

Maximal doses of rosuvastatin and atorvastatin resulted in significant regression of coronary atherosclerosis. Despite the lower level of LDL cholesterol and the higher level of HDL cholesterol achieved with rosuvastatin, a similar degree of regression of PAV was observed in the two treatment groups. (Funded by AstraZeneca Pharmaceuticals; ClinicalTrials.gov number, NCT00620542.)

From the Department of Cardiovascular Medicine, Cleveland Clinic (S.J.N., K.U., S.E.N.), and Cleveland Clinic Coordinating Center for Clinical Research (S.J.N., K.U., M.B., K.W., S.E.N.) — both in Cleveland; the Section of Cardiovascular Research, Baylor College of Medicine, and the Methodist DeBakey Heart and Vascular Center — both in Houston (C.M.B.); Heart Research Institute, Sydney (P.J.B.); INSERM Dyslipidemia and Atherosclerosis Research Unit, Hôpital de la Pitié, Paris (M.J.C.); the Department of Cardiology, West German Heart Center Essen, Essen, Germany (R.M.E.); the Cardiovascular Division, Brigham and Women's Hospital, Boston (P.L.); and AstraZeneca, Wilmington, DE (J.S.R.). Address reprint requests to Dr. Nicholls at the Department of Cardiovascular Medicine, Mail Code JJ-65, Cleveland Clinic, 9500 Euclid Ave., Cleveland, OH 44195, or at nichols1@ccf.org.

This article (10.1056/NEJMoa1110874) was published on November 15, 2011, at NEJM.org.

N Engl J Med 2011;365:2078-87.

Randomized clinical trials have consistently shown that inhibitors of 3-hydroxy-3-methylglutaryl coenzyme A reductase (statins) reduce cardiovascular event rates.[1-9] The favorable effects of statins extend across a range of levels of low-density lipoprotein (LDL) cholesterol, with no apparent lower threshold for a benefit.[3,9,10] In parallel, imaging trials have shown that intensive statin regimens slow the progression of coronary atherosclerosis and may even result in disease regression in some patients.[11,12] Accordingly, guidelines for cardiovascular disease prevention have increasingly emphasized that lowering LDL cholesterol levels with statins is the primary goal of lipid-modulating therapy.[13,14]

Available statins differ considerably in their ability to reduce atherogenic lipid levels and raise the level of high-density lipoprotein (HDL) cholesterol. Atorvastatin and rosuvastatin are the most effective statins for lowering LDL cholesterol levels, yielding average reductions that approach 50% for atorvastatin and exceed 50% for rosuvastatin.[15,16] Direct comparisons have shown greater reductions in LDL cholesterol levels and greater increases in HDL cholesterol levels with rosuvastatin,[15-17] but the clinical consequences of these differences remain unclear. Although studies comparing lipid lowering by these two statins have been carried out, to our knowledge, no randomized clinical trials have directly compared their effects on disease progression or cardiovascular event rates.

Intravascular ultrasonography can be used to obtain precise and reproducible serial measurements of atherosclerotic plaques in the coronary arteries.[18] The use of intravascular ultrasonography in clinical trials permits examination of the effects of antiatherosclerotic therapies on the course of coronary artery disease.[11,12,19-26] A meta-analysis of the results of such trials suggested that the combined effects of statins — lowering LDL cholesterol levels and increasing HDL cholesterol levels — slow the progression of coronary plaques.[27] We compared the highest doses of two intensive statin regimens to determine whether there were discernible differences in their effects on the progression of coronary atherosclerosis.

METHODS

STUDY DESIGN

The Study of Coronary Atheroma by Intravascular Ultrasound: Effect of Rosuvastatin versus Atorvastatin (SATURN) was a prospective, randomized, multicenter, double-blind clinical trial.[28] Randomization was stratified according to geographic region. The trial was designed by the Cleveland Clinic Coordinating Center for Clinical Research in collaboration with the sponsor (AstraZeneca Pharmaceuticals). The institutional review board at each site approved the protocol (available with the full text of this article at NEJM.org), and all patients provided written informed consent.

Patients 18 to 75 years of age were eligible if they had at least one vessel with 20% stenosis on clinically indicated coronary angiography and a target vessel for imaging with less than 50% obstruction. Patients who had not been treated with a statin in the preceding 4 weeks were required to have an LDL cholesterol level at entry that was higher than 100 mg per deciliter (2.6 mmol per liter); those who had received such treatment were required to have a level higher than 80 mg per deciliter (2.1 mmol per liter). Patients were excluded if they had received intensive lipid-lowering therapy for more than 3 months in the previous year or had uncontrolled hypertension, heart failure, renal dysfunction, or liver disease (see the Supplementary Appendix, available at NEJM.org).

Patients who met the inclusion criteria underwent preliminary randomization by means of an interactive voice-response system and were randomly assigned in a 1:1 ratio to receive either atorvastatin, at a dose of 40 mg daily, or rosuvastatin, at a dose of 20 mg daily, for 2 weeks to ascertain side effects and compliance. Patients with an LDL cholesterol level of less than 116 mg per deciliter (3.0 mmol per liter) and a triglyceride level of less than 500 mg per deciliter (5.6 mmol per liter) after 2 weeks again underwent randomization in a 1:1 ratio, this time to full-dose treatment with atorvastatin (80 mg daily) or rosuvastatin (40 mg daily) for 104 weeks. A clinical events committee whose members were unaware of the treatment assignments adjudicated cardiovascular events at a central location.

All the academic authors collected, held, and analyzed the data and made the decision to submit the manuscript for publication. The first academic author wrote the manuscript and vouches for the accuracy and completeness of the data and the analyses. The study was conducted in accordance with the protocol. Although the steering committee and coordinating center had confidentiality agreements with the sponsor, the study contract specified that a copy of the study database be pro-

vided to the coordinating center for independent analysis and granted the academic authors unrestricted rights to publish the results.

ACQUISITION AND ANALYSIS OF ULTRASONOGRAPHIC IMAGES

Intravascular ultrasonography was performed at baseline, after coronary angiographic assessments had been completed. Previous reports have described the methods used for image acquisition and analysis.[11,12,19-24] Imaging was performed in a single artery, and the results were screened by a core laboratory. Patients who met prespecified requirements for image quality were then eligible for randomization. After 104 weeks of treatment, patients underwent a second ultrasonographic examination of the same artery. Using digitized images, personnel who were unaware of the treatment assignments and the temporal sequence of paired images measured the lumen and external elastic membrane within a matched arterial segment. The accuracy and reproducibility of this method have been reported previously.

The primary efficacy end point, percent atheroma volume (PAV), was calculated as follows:

$$\text{PAV} = \frac{\Sigma\,(\text{EEM}_{\text{area}} - \text{lumen}_{\text{area}})}{\Sigma\,\text{EEM}_{\text{area}}} \times 100,$$

where EEM_{area} is the cross-sectional area of the external elastic membrane, and $\text{lumen}_{\text{area}}$ is the cross-sectional area of the lumen. For PAV, the summation of the EEM area minus the lumen area is performed first. This value is then divided by the summation of the EEM area, which is finally multiplied by 100. The change in PAV was calculated as the PAV at 104 weeks minus the PAV at baseline. A secondary efficacy end point, normalized total atheroma volume (TAV), was calculated as follows:

$$\text{TAV}_{\text{normalized}} = \frac{\Sigma\,(\text{EEM}_{\text{area}} - \text{lumen}_{\text{area}})}{\text{no. of images in pullback}} \times \text{median no. of images in cohort.}$$

For TAV, the summation of the EEM area minus the lumen area is performed first. This value is divided by the number of images in the pullback and then multiplied by the median number of images in the cohort. The average plaque area in the pullback was multiplied by the median number of images analyzed in the entire cohort to compensate for differences in segment length between subjects. The efficacy end point of change in normalized TAV was calculated as the TAV at 104 weeks minus the TAV at baseline. Regression was defined as a decrease in PAV or TAV from baseline.

BIOCHEMICAL ASSESSMENTS

During treatment, levels of HDL and LDL cholesterol and triglycerides were measured at 6, 12, 18, and 24 months. Levels of C-reactive protein were measured at 12 and 24 months.

STATISTICAL ANALYSIS

For continuous variables with an approximately normal distribution, means (±SD) are reported. For variables not distributed normally, medians and interquartile ranges are reported. Intravascular ultrasonographic efficacy end points are reported as medians, with distribution-free 95% confidence intervals, and treatment groups were compared with the use of analysis of covariance on rank-transformed data after adjustment for baseline values and geographic region. Lipoprotein levels during treatment are reported as least-squares means (±SE) from analyses of covariance controlled for treatment group and geographic region. For the change in the primary efficacy end point, PAV, a sample of 450 patients in each treatment group was required for 90% power at a two-sided alpha level of 0.05 to detect a nominal treatment difference of 0.65%, assuming a standard deviation of 3.0%. On the basis of an assumed withdrawal rate of 30%, 1300 patients were required for randomization. All reported P values are two-sided. The statistical-analysis plan is available, along with the protocol, at NEJM.org.

RESULTS

CHARACTERISTICS OF THE PATIENTS

From January 22, 2008, through June 12, 2009, a total of 1578 patients at 208 centers were randomly assigned to 2 weeks of treatment with half-maximal doses of either atorvastatin or rosuvastatin. After this run-in period, 1385 patients were randomly assigned to full-dose treatment: 691 to the atorvastatin group and 694 to the rosuvastatin group. After 104 weeks of treatment, 1039 patients (75%) remained in the study and underwent repeat intravascular ultrasonography, so that the findings on follow-up imaging could be compared with the baseline findings. Of these patients, 519 were in the atorvastatin group, and 520 were in the rosuvastatin group. There were no significant differences in demographic characteristics or in baseline medication use or laboratory values

between the two treatment groups (Table 1). Similarly, demographic and baseline characteristics did not differ significantly between patients who completed the study and those who did not.

BIOCHEMICAL MEASUREMENTS

It was deemed ethically inappropriate to discontinue statin treatment in the patients who were receiving statin treatment before randomization. Accordingly, the percentage changes in lipid levels could not be calculated. Table 2 shows the laboratory values during treatment for the 1039 patients who completed the trial. During 104 weeks of treatment, time-weighted least-squares mean LDL cholesterol levels were 70.2±1.0 mg per deciliter (1.82±0.03 mmol per liter) in the atorvastatin group and 62.6±1.0 mg per deciliter (1.62±0.03 mmol per liter) in the rosuvastatin group (mean difference, 7.5 mg per deciliter; P<0.001). The mean HDL cholesterol levels were 48.6±0.5 mg per deciliter (1.25±0.01 mmol per liter) in the atorvastatin group and 50.4±0.5 mg per deciliter (1.30±0.01 mmol per liter) in the rosuvastatin group (mean difference, 1.8 mg per deciliter [0.05 mmol per liter]; P=0.01). These values resulted in a lower ratio of LDL cholesterol to HDL cholesterol during treatment with rosuvastatin (1.30±0.02, vs. 1.50±0.02 with atorvastatin; P<0.001), a greater proportion of rosuvastatin-treated patients in whom LDL cholesterol levels below 70 mg per deciliter (1.81 mmol per liter) were achieved (72.1%, vs. 56.1% with atorvastatin; P<0.001), and a smaller proportion of rosuvastatin-treated patients whose LDL cholesterol levels remained higher than the current treatment goal of 100 mg per deciliter (2.6 mmol per liter) (4.6%, vs. 7.7% with atorvastatin; P=0.04). Median C-reactive protein levels during treatment were 1.0 mg per liter (interquartile range, 0.5 to 2.0) in the atorvastatin group and 1.1 mg per liter (interquartile range, 0.5 to 2.4) in the rosuvastatin group (P=0.05).

EFFICACY END POINTS

Table 3 summarizes the changes in the intravascular ultrasonographic efficacy end points. The primary efficacy end point, PAV, decreased by 0.99% (95% confidence interval [CI], −1.19 to −0.63) in the atorvastatin group and by 1.22% (95% CI, −1.52 to −0.90) in the rosuvastatin group (P<0.001 for the change from baseline in each group; P=0.17 for the between-group comparison). For TAV, a secondary efficacy end point, the effect was more favorable with rosuvastatin than with atorvastatin (a reduction of 6.39 mm³ [95% CI, −7.52 to −5.12] vs. a reduction of 4.42 mm³ [95% CI, −5.98 to −3.26]; P=0.01). For PAV, there was a nonsignificant trend toward a greater percentage of rosuvastatin-treated patients with disease regression (68.5%, vs. 63.2% with atorvastatin; P=0.07). For TAV, a significantly greater proportion of rosuvastatin-treated patients had disease regression (71.3%, vs. 64.7% with atorvastatin; P=0.02). There was statistical heterogeneity between prespecified subgroups for the primary end point, with greater regression of PAV with rosuvastatin, as compared with atorvastatin, in women (−1.76% vs. −0.71%, P=0.01) and in patients with higher baseline levels of HDL cholesterol (−1.41% vs. −0.61%, P=0.02) and those with higher baseline levels of LDL cholesterol (−1.47% vs. −1.00%, P=0.02) (Fig. 1). Greater regression was also observed with rosuvastatin in patients who had HDL cholesterol levels above the mean (−1.44%, vs. −0.63% with atorvastatin; P=0.03).

Table 1. Baseline Characteristics of Patients in the Intention-to-Treat Population.*

Characteristic	Atorvastatin (N=519)	Rosuvastatin (N=520)
Age — yr	57.9±8.5	57.4±8.6
Male sex — no. (%)	386 (74.4)	379 (72.9)
White race — no. (%)†	500 (96.3)	496 (95.4)
Body-mass index‡	29.2±5.5	28.9±5.0
Diabetes — no. (%)	87 (16.8)	72 (13.8)
Hypertension — no. (%)	367 (70.7)	364 (70.0)
Current smoking — no. (%)	157 (30.3)	179 (34.4)
Previous MI — no. (%)	137 (26.4)	117 (22.5)
Previous PCI — no. (%)	112 (21.6)	131 (25.2)
Prior statin use — no. (%)§	319 (61.5)	303 (58.3)
Concomitant medications — no. (%)		
Antiplatelet agent	508 (97.9)	507 (97.5)
Beta-blocker	317 (61.1)	315 (60.6)
ACE inhibitor	231 (44.5)	226 (43.5)
Angiotensin-receptor blocker	82 (15.8)	87 (16.7)

* Plus–minus values are means ±SD. ACE denotes angiotensin-converting enzyme, MI myocardial infarction, and PCI percutaneous coronary intervention. There were no significant differences between the treatment groups.
† Race was self-reported.
‡ The body-mass index is the weight in kilograms divided by the square of the height in meters.
§ Prior statin use was defined as use of a statin within 30 days before enrollment in the trial.

Table 2. Biochemical Values and Blood Pressure at Baseline and during Treatment in the Intention-to-Treat Population.*

Variable	At Baseline			During Treatment†		
	Atorvastatin (N=519)	Rosuvastatin (N=520)	P Value	Atorvastatin (N=519)	Rosuvastatin (N=520)	P Value
Cholesterol						
Total (mg/dl)	193.5±34.2	193.9±34.1	0.86	144.1±1.2	139.4±1.2	<0.006
LDL (mg/dl)	119.9±28.9	120.0±27.3	0.94	70.2±1.0	62.6±1.0	<0.001
HDL (mg/dl)	44.7±10.7	45.3±11.8	0.41	48.6±0.5	50.4±0.5	0.01
Non-HDL (mg/dl)	148.8±33.1	148.6±33.0	0.91	95.4±1.1	88.9±1.2	<0.001
LDL:HDL	2.8±0.9	2.8±0.9	0.81	1.5±0.1	1.3±0.1	<0.001
Triglycerides (mg/dl)						
Median	130	128	0.55	110	120	0.02
Interquartile range	97–177	91–181		87–150	91–159	
Apolipoprotein						
B (mg/dl)	104.9±21.7	105.4±21.2	0.68	75.1±0.9	72.5±0.9	0.03
A-I (mg/dl)	126.2±23.3	128.0±25.2	0.23	137.7±1.0	146.8±1.0	<0.001
B:A-I	0.9±0.2	0.9±0.3	0.72	0.6±0.1	0.5±0.1	<0.001
C-reactive protein (mg/liter)‡						
Median	1.5	1.7	0.29	1.0	1.1	0.05
Interquartile range	0.8–3.3	0.8–3.8		0.5–2.0	0.5–2.4	
Glucose (mg/dl)‡						
Median	97	97	0.74	99	97	0.49
Interquartile range	90–110	88–108		92–112	90–110	
Glycated hemoglobin (%)‡§	6.2±0.8	6.2±1.1	0.45	6.3±0.1	6.3±0.1	0.82
Blood pressure (mm Hg)						
Systolic	130.6±18.4	130.2±18.1	0.72	131.2±0.7	129.7±0.7	0.16
Diastolic	77.2±11.3	76.6±10.7	0.39	77.8±0.4	77.0±0.4	0.18

* Plus–minus values are means ±SD for baseline values and are least-squares means ±SE for values obtained during treatment. Medians and interquartile ranges for variables that were not distributed normally were calculated with the use of the Wilcoxon rank-sum test. To convert the values for cholesterol to millimoles per liter, multiply by 0.02586. To convert the values for triglycerides to millimoles per liter, multiply by 0.01129. To convert the values for glucose to millimoles per liter, multiply by 0.05551. LDL denotes low-density lipoprotein, and HDL high-density lipoprotein.

† Unless otherwise noted, laboratory values obtained during treatment are the time-weighted averages of all post-baseline values, and estimates are derived from an analysis-of-variance model, with factors for treatment group and geographic region.

‡ Final measurements were used for values obtained during treatment.

§ Both initial and final glycated hemoglobin values were available for 348 patients in the atorvastatin group and 361 patients in the rosuvastatin group.

CLINICAL ADVERSE EVENTS AND LABORATORY ABNORMALITIES

Table 4 shows centrally adjudicated clinical events, laboratory abnormalities, and reasons for study discontinuation. The frequency of cardiovascular events was similar in the two groups. The rate of abnormal laboratory values was low. A higher incidence of elevated alanine aminotransferase levels was observed in the atorvastatin group (2.0%, vs. 0.7% with rosuvastatin; P=0.04), and a higher incidence of proteinuria was observed in the rosuvastatin group (3.8%, vs. 1.7% with atorvastatin; P=0.02). Glycated hemoglobin levels did not change significantly in either group.

DISCUSSION

This study compared the effects on the progression of coronary atherosclerosis of the highest doses of atorvastatin and rosuvastatin, two of the most intensive statin regimens used in clinical practice today. Very low LDL cholesterol levels were

Table 3. Primary and Secondary End Points, as Evaluated on Intravascular Ultrasonography.*

End Point	Atorvastatin (N=519)	Rosuvastatin (N=520)	P Value
At baseline			
PAV — %			
Mean	36.0±8.3	36.7±8.2	0.33
Median (95% CI)	36.2 (30.6 to 41.4)	36.2 (31.4 to 42.0)	
TAV — mm^3			
Mean	144.2±63.8	144.1±60.8	0.99
Median (95% CI)	136.6 (95.8 to 182.9)	133.4 (95.9 to 180.1)	
At 104 weeks			
PAV — %			
Mean	34.9±8.1	35.4±8.2	0.64
Median (95% CI)	34.9 (29.6 to 40.3)	34.8 (29.5 to 40.2)	
TAV — mm^3			
Mean	138.5±63.2	135.7±57.7	0.67
Median (95% CI)	127.6 (91.0 to 176.1)	124.9 (93.4 to 167.7)	
Median change from baseline			
PAV — % (95% CI)	−0.99 (−1.19 to −0.63)	−1.22 (−1.52 to −0.90)	0.17†
TAV — mm^3 (95% CI)	−4.42 (−5.98 to −3.26)	−6.39 (−7.52 to −5.12)	0.01†
Disease regression — % of patients			
Based on change in PAV	63.2	68.5	0.07
Based on change in TAV	64.7	71.3	0.02

* Plus–minus values are means ±SD. CI denotes confidence interval, PAV percent atheroma volume, and TAV total atheroma volume.

† The P value for the between-group comparison of the change from baseline was calculated with the use of analysis of covariance, with the rate of change in PAV or in TAV as the independent variable and the rank of the corresponding baseline value as a covariate and treatment group as a factor.

achieved in both treatment groups, with mean values of less than or equal to 70 mg per deciliter (1.81 mmol per liter) — the most aggressive target specified by current lipid-lowering guidelines. During treatment, HDL cholesterol concentrations in both groups approached 50 mg per deciliter — levels currently considered acceptable for the secondary prevention of cardiovascular events. Both regimens had striking effects on coronary disease progression, resulting in significant regression of atherosclerosis. These data indicate that coronary artery disease can regress if the favorable levels of LDL and HDL cholesterol that were attained with statin therapy in this study are achieved.

As compared with the atorvastatin regimen, the rosuvastatin regimen resulted in lower LDL cholesterol levels (a difference of −7.5 mg per deciliter [−0.19 mmol per liter]) and slightly higher HDL cholesterol levels (a difference of 1.8 mg per deciliter [0.05 mmol per liter]). These differences did not result in a significant incremental effect on disease regression, as assessed according to the primary intravascular ultrasonographic end point (PAV). These results may have been influenced by smaller-than-anticipated differences between the two groups with respect to HDL cholesterol levels. Rosuvastatin did show a significant benefit with respect to disease regression as assessed according to TAV, a secondary intravascular ultrasonographic end point, but the difference between the two regimens was relatively modest. These data show that the two regimens are similar in their ability to limit progression or induce regression of coronary disease, although a small difference in efficacy cannot be ruled out on the basis of the significant differences observed for the change in TAV. Our study shows that in appropriately selected patients, either regimen can be used to reduce the atheroma burden for the purpose of secondary prevention.

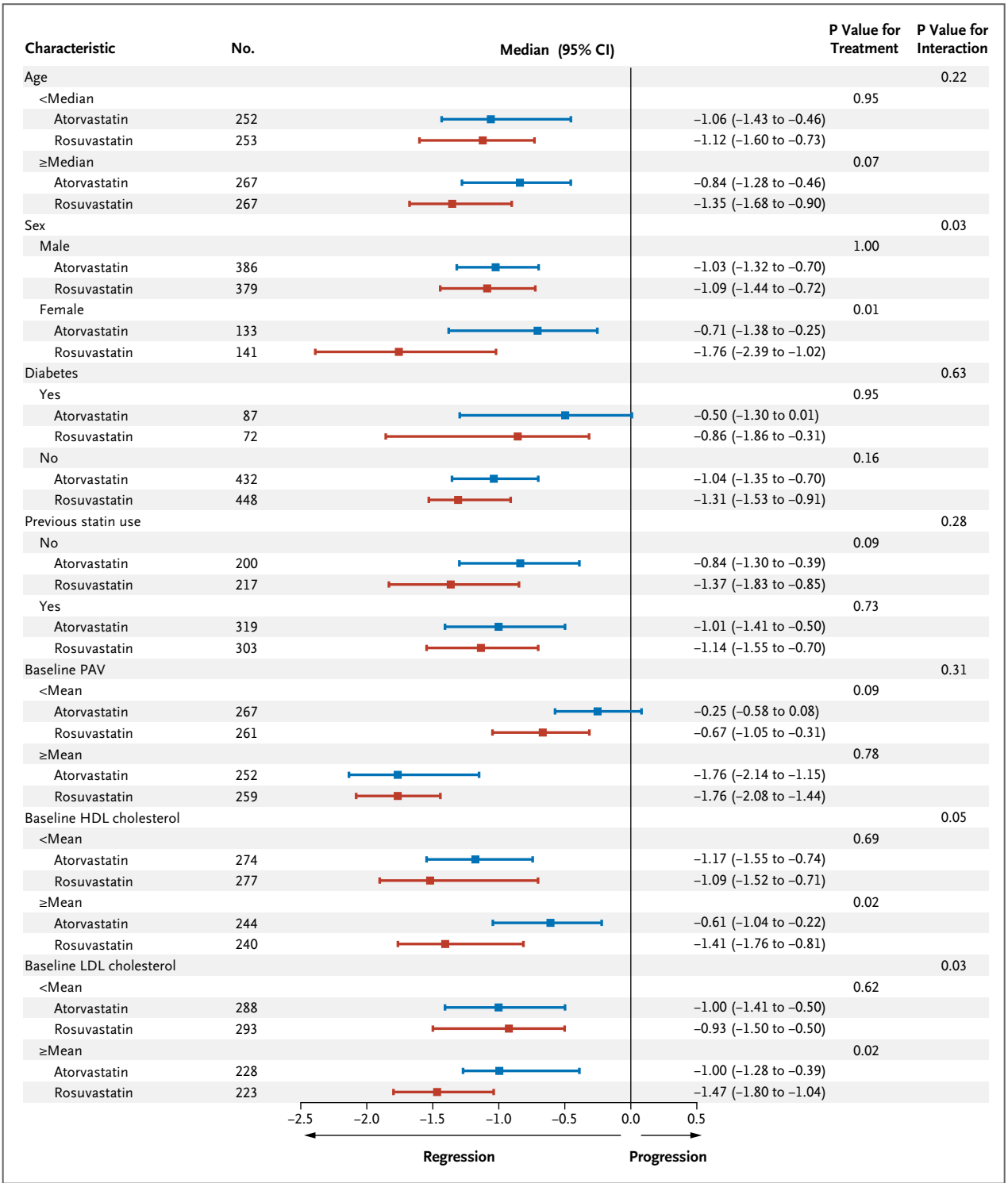

Figure 1. Prespecified Subgroup Analysis of Change in Percent Atheroma Volume from Baseline to Follow-up at 104 Weeks.

The P value for treatment applies to differences between treatment groups. HDL denotes high-density lipoprotein, LDL low-density lipoprotein, and PAV percent atheroma volume.

Overall, regression of atherosclerosis was observed in approximately two thirds of the study patients during 104 weeks of statin therapy. For the primary end point (PAV), a numerically higher percentage of rosuvastatin-treated patients had regression (68.5%, vs. 63.2% with atorvastatin), with a trend toward significance (P=0.07). The frequency and extent of regression in both groups were unprecedented, as compared with the results of prior intravascular ultrasonographic studies. Previous studies have suggested an association between progression rates and cardiovascular outcomes,[29,30] but the precise nature of the relationship remains a subject of ongoing research. Theoretically, regression involves reductions of the lipid, inflammatory, and necrotic components of plaque, each of which has been implicated in plaque rupture. Yet intravascular ultrasonography remains a surrogate end point, and a reduction in plaque volume should not be interpreted as equivalent to a clinical benefit in terms of preventing cardiovascular events. Furthermore, the clinical significance of regression or of observed differences in the secondary end point remains to be established. Despite these limitations, we consider the current evidence showing that the growth of atherosclerotic plaques can be reversed to be promising and deserving of further study in clinical trials.

The incidence of adverse effects accompanying the benefits observed in this trial was low. Increases in liver enzyme levels were more common in the atorvastatin group, with alanine aminotransferase levels that were more than 3 times the upper limit of the normal range in 14 patients, as compared with 5 patients in the rosuvastatin group (2.0% vs. 0.7%). Creatine kinase levels were more than 10 times the upper limit of the normal range in 4 atorvastatin-treated patients and in 1 rosuvastatin-treated patient, but in neither treatment group were there two consecutive increases in creatine kinase levels that were more than 5 times the upper limit of the normal range. Rhabdomyolysis was not observed in any patient. Proteinuria was more common in the rosuvastatin group than in the atorvastatin group (3.8% vs. 1.7%). Although the effect of statins on the incidence of diabetes has received considerable attention recently, neither treatment group had an increase in glycated hemoglobin levels. Taken as a whole, our findings indicate that intensive statin treatment led to disease regression with few adverse events.

Table 4. Clinical and Biochemical Adverse Events and Reasons for Discontinuation of Treatment.

Event	Atorvastatin (N=689)	Rosuvastatin (N=691)
Cardiovascular event — no. (%)		
Death from cardiovascular causes	2 (0.3)	2 (0.3)
Nonfatal myocardial infarction	11 (1.6)	11 (1.6)
Nonfatal stroke	2 (0.3)	3 (0.4)
Hospitalization for unstable angina	13 (1.9)	16 (2.3)
Arterial revascularization	41 (6.0)	42 (6.1)
First major adverse cardiovascular event	49 (7.1)	52 (7.5)
Abnormal laboratory value — no./total no. (%)*		
Aspartate aminotransferase >3× ULN	11/668 (1.6)	3/668 (0.4)
Alanine aminotransferase >3× ULN	14/668 (2.1)	5/668 (0.7)
Creatine kinase		
>5× ULN	5/668 (0.7)	2/668 (0.3)
>5× ULN on two consecutive visits	0/654 (0)	0/668 (0)
>10× ULN	4/668 (0.6)	1/668 (0.1)
New proteinuria†	11/654 (1.7)	25/652 (3.8)
Creatinine >ULN	20/668 (3.0)	22/668 (3.3)
Discontinuation of treatment — no. (%)		
Total	142 (20.6)	145 (21.0)
Reason for discontinuation		
Preference of patient	53 (7.7)	54 (7.8)
Adverse event	48 (7.0)	45 (6.5)
Loss to follow-up	9 (1.3)	20 (2.9)
Noncompliance	16 (2.3)	13 (1.9)
Other	16 (2.3)	13 (1.9)

* Laboratory data were missing for 44 patients. ULN denotes upper limit of the normal range.

† New proteinuria was defined as 2+ or greater protein on urinalysis during the follow-up period in patients with a negative finding or trace protein at baseline.

Although the study was not powered to detect between-group differences in major adverse clinical events, these outcomes were adjudicated at a central site. The overall incidence of myocardial infarction was 1.6% during 24 months of follow-up, and the incidence did not differ significantly between the treatment groups. The rate of stroke was 0.4% and the rate of cardiovascular death was 0.3%, with no significant between-group differences in these rates. Only 0.5% of patients underwent coronary-artery bypass grafting, but 5.4% of patients underwent percutaneous coronary intervention, in most cases for restenosis involving lesions initially treated at the time of enrollment.

These event rates are extremely low for a population with angiographically documented coronary disease and affirm that very intensive lipid-lowering with statins is associated with favorable clinical outcomes in a patient population at high risk.

Although subgroup analyses do not furnish definitive evidence of benefit or harm, they may provide hypothesis-generating insights. Statistical evidence of heterogeneity showing benefit with rosuvastatin, the most useful measure of subgroup differences, was observed among women and among patients with higher baseline levels of LDL cholesterol. The greater benefit noted among patients with higher HDL cholesterol levels may reflect improved functional activity of HDL. The better response of patients with higher LDL cholesterol levels seems biologically plausible, since these patients may have greater benefits from a more effective LDL cholesterol–lowering regimen. Future analyses may yield useful insights into which of the effects of statin therapy — reductions in LDL cholesterol levels, increases in HDL cholesterol levels, nonlipid antiinflammatory effects, or a combination of effects — is associated with plaque regression.

Our findings have implications for the development of novel antiatherosclerotic therapies. The LDL cholesterol levels seen in this study are lower than those endorsed by current guidelines, providing a biologic foundation for future trials that target very low LDL cholesterol levels. The levels of LDL and HDL cholesterol observed in the current study cannot be achieved with statins alone in all patients with atherosclerotic coronary disease; however, LDL cholesterol–lowering therapies currently under development may result in these lipid levels in more patients. Furthermore, about one third of patients in our study had disease progression despite maximally intensive statin therapy. This finding suggests a potentially important role for novel agents designed to reduce LDL cholesterol levels, increase HDL cholesterol levels, or modify disease activity by means of other pathways. Indeed, a substantial residual risk of clinical events remains in most secondary-prevention populations despite the use of the most effective current medical therapies, affirming the need for new antiatherosclerotic agents.

This study has important limitations. It was not ethically possible to measure disease progression in placebo-treated patients. The trial involved patients undergoing clinically indicated coronary angiography. It remains uncertain whether our findings apply to primary prevention in asymptomatic patients. In trials that use intravascular ultrasonographic assessment of regression–progression, some patients elect not to undergo follow-up cardiac catheterization and therefore cannot be considered in the calculation of intravascular ultrasonographic end points. In the current trial, 25% of patients did not have intravascular ultrasonographic imaging that could be evaluated at follow-up, which was a smaller percentage than that reported in most contemporary trials. Patients who did not complete the trial may have had rates of progression that were different from those among patients who completed the trial. This study used intravascular ultrasonography to examine disease progression, but some newer analytic methods may permit the characterization of plaque constituents. Alternative therapies might have differing effects on plaque composition.

Statins have been among the most extensively studied classes of pharmacologic therapies. The findings have elucidated how these agents work and have expanded their potential clinical usefulness. Although the current comparative study does not show a significant difference between the treatment groups with regard to the primary end point, it does show that high-dose, intensive statin therapy can be administered safely and can promote regression of atherosclerotic plaque to a greater extent than has previously been reported. These findings represent a useful step forward in the effort to prevent the devastating clinical sequelae of atherosclerotic cardiovascular disease.

Supported by AstraZeneca.

Dr. Nicholls reports receiving consulting fees from Roche, Esperion, Merck, Omthera, Sanofi-Aventis, and Boehringer Ingelheim, serving as an unpaid consultant for Abbott, Pfizer, LipoScience, Novo Nordisk, AtheroNova, and CSL Behring, receiving grant support from Eli Lilly, AstraZeneca, Novartis, Anthera, LipoScience, Roche, and Resverlogix and lecture fees from AstraZeneca and Roche; Dr. Ballantyne, receiving grant support from Abbott, AstraZeneca, Bristol-Myers Squibb, Genentech, GlaxoSmithKline, Kowa, Merck, Novartis, Roche, Sanofi-Synthelabo, and Takeda, consulting fees and honoraria from Abbott, Adnexus, Amarin, Amylin, AstraZeneca, Bristol-Myers Squibb, Esperion, Genentech, GlaxoSmithKline, Idera, Kowa, Merck, Novartis, Omthera, Resverlogix, Roche, Sanofi-Synthelabo, and Takeda and lecture fees from Abbott, AstraZeneca, GlaxoSmithKline, and Merck; Dr. Barter, holding an advisory board position for AstraZeneca, Merck, Roche, CSL Behring, and Pfizer, receiving grant support from Merck, consulting fees from CSL Behring, and lecture fees from AstraZeneca, Kowa, Merck, Pfizer, and Roche; Dr. Chapman, receiving grant support from Merck and Kowa, consulting fees from Merck and Pfizer, and lectures fees from Merck and Kowa; Dr. Erbel, receiving grant support from the Heinz Nixdorf Foundation and the German Research Foundation and support for travel, accommodations, or meeting expenses from Biotronik, Sanofi, and Novartis; Dr. Libby, serving as an unpaid consultant for Novartis, Johnson & Johnson,

Amgen, and Roche, serving in unpaid leadership roles for clinical trials sponsored by AstraZeneca, GlaxoSmithKline, Novartis, Pfizer, Pronova, and Sigma Tau, and having previously received royalties from Roche for the patent on CD40L in cardiovascular risk stratification; Dr. Raichlen, being an employee of and owning stock in AstraZeneca; and Dr. Nissen, receiving consulting fees from Eli Lilly, grant funding from AstraZeneca, Pfizer, Novartis, Karo Bio, Novo Nordisk, Takeda, Resverlogix, and Omthera, and support for travel, accommodations, or meeting expenses from Novo Nordisk, Takeda, Karo Bio, Eli Lilly, Pfizer, Novartis, and Amgen. No other potential conflict of interest relevant to this article was reported.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

We thank Craig Balog for statistical programming; C5Research for statistical support; Eileen Doherty, AstraZeneca Global Study Leader, SATURN Clinical Operations, Study Management and Operations, for providing study supervision and administrative support of the trial; and the staff of the intravascular ultrasound laboratory, William Magyar, Jordan Andrews, Eva Balazs, Anne Colagiovanni, Teresa Fonk, Karilane King, Erin Mayock, Roman Poliszczuk, Rhiannon Regal, and Jill Rusticelli.

REFERENCES

1. Randomised trial of cholesterol lowering in 4444 patients with coronary heart disease: the Scandinavian Simvastatin Survival Study (4S). Lancet 1994;344:1383-9.
2. The Long-Term Intervention with Pravastatin in Ischaemic Disease (LIPID) Study Group. Prevention of cardiovascular events and death with pravastatin in patients with coronary heart disease and a broad range of initial cholesterol levels. N Engl J Med 1998;339:1349-57.
3. MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in 20,536 high-risk individuals: a randomised placebo-controlled trial. Lancet 2002;360:7-22.
4. Downs JR, Clearfield M, Weis S, et al. Primary prevention of acute coronary events with lovastatin in men and women with average cholesterol levels: results of AFCAPS/TexCAPS: AirForce/Texas Coronary Atherosclerosis Prevention Study. JAMA 1998;279:1615-22.
5. Sacks FM, Pfeffer MA, Moye LA, et al. The effect of pravastatin on coronary events after myocardial infarction in patients with average cholesterol levels. N Engl J Med 1996;335:1001-9.
6. Shepherd J, Cobbe SM, Ford I, et al. Prevention of coronary heart disease with pravastatin in men with hypercholesterolemia. N Engl J Med 1995;333:1301-7.
7. 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;294:2437-45. [Erratum, JAMA 2005;294:3092.]
8. LaRosa JC, Grundy SM, Waters DD, et al. Intensive lipid lowering with atorvastatin in patients with stable coronary disease. N Engl J Med 2005;352:1425-35.
9. Ridker PM, Danielson E, Fonseca FAH, et al. Rosuvastatin to prevent vascular events in men and women with elevated C-reactive protein. N Engl J Med 2008;359:2195-207.
10. Baigent C, Blackwell L, Emberson J, et al. Efficacy and safety of more intensive lowering of LDL cholesterol: a meta-analysis of data from 170,000 participants in 26 randomised trials. Lancet 2010;376:1670-81.
11. 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;291:1071-80.
12. 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;295:1556-65.
13. Grundy SM, Cleeman JI, Merz CN, et al. Implications of recent clinical trials for the National Cholesterol Education Program Adult Treatment Panel III guidelines. Circulation 2004;110:227-39. [Erratum, Circulation 2004;110:763.]
14. Reiner Z, Catapano AL, De Backer G, et al. ESC/EAS guidelines for the management of dyslipidaemias: the Task Force for the management of dyslipidaemias of the European Society of Cardiology (ESC) and the European Atherosclerosis Society (EAS). Eur Heart J 2011;32:1769-818.
15. Jones PH, Davidson MH, Stein EA, et al. Comparison of the efficacy and safety of rosuvastatin versus atorvastatin, simvastatin, and pravastatin across doses (STELLAR Trial). Am J Cardiol 2003;92:152-60.
16. Nicholls SJ, Brandrup-Wognsen G, Palmer M, Barter PJ. Meta-analysis of comparative efficacy of increasing dose of atorvastatin versus rosuvastatin versus simvastatin on lowering levels of atherogenic lipids (from VOYAGER). Am J Cardiol 2010;105:69-76.
17. Barter PJ, Brandrup-Wognsen G, Palmer MK, Nicholls SJ. Effect of statins on HDL-C: a complex process unrelated to changes in LDL-C: analysis of the VOYAGER database. J Lipid Res 2010;51:1546-53.
18. Nicholls SJ, Sipahi I, Schoenhagen P, Crowe T, Tuzcu EM, Nissen SE. Application of intravascular ultrasound in antiatherosclerotic drug development. Nat Rev Drug Discov 2006;5:485-92.
19. Nissen SE, Nicholls SJ, Wolski K, et al. Comparison of pioglitazone vs glimepiride on progression of coronary atherosclerosis in patients with type 2 diabetes: the PERISCOPE randomized controlled trial. JAMA 2008;299:1561-73.
20. Nissen SE, Nicholls SJ, Wolski K, et al. Effect of rimonabant on progression of atherosclerosis in patients with abdominal obesity and coronary artery disease: the STRADIVARIUS randomized controlled trial. JAMA 2008;299:1547-60.
21. Nissen SE, Tardif J-C, Nicholls SJ, et al. Effect of torcetrapib on the progression of coronary atherosclerosis. N Engl J Med 2007;356:1304-16. [Erratum, N Engl J Med 2007;357:835.]
22. Nissen SE, Tsunoda T, Tuzcu EM, et al. Effect of recombinant ApoA-I Milano on coronary atherosclerosis in patients with acute coronary syndromes: a randomized controlled trial. JAMA 2003;290:2292-300.
23. Nissen SE, Tuzcu EM, Brewer HB, et al. Effect of ACAT inhibition on the progression of coronary atherosclerosis. N Engl J Med 2006;354:1253-63. [Erratum, N Engl J Med 2006;355:638.]
24. 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;292:2217-25.
25. Tardif JC, Grégoire J, L'Allier PL, et al. Effects of the acyl coenzyme A:cholesterol acyltransferase inhibitor avasimibe on human atherosclerotic lesions. Circulation 2004;110:3372-7.
26. Tardif JC, Grégoire J, L'Allier PL, et al. Effects of reconstituted high-density lipoprotein infusions on coronary atherosclerosis: a randomized controlled trial. JAMA 2007;297:1675-82.
27. Nicholls SJ, Tuzcu EM, Sipahi I, et al. Statins, high-density lipoprotein cholesterol, and regression of coronary atherosclerosis. JAMA 2007;297:499-508.
28. Nicholls SJ, Borgman M, Nissen SE, et al. Impact of statins on progression of atherosclerosis: rationale and design of SATURN (Study of Coronary Atheroma by InTravascular Ultrasound: Effect of Rosuvastatin versus Atorvastatin). Curr Med Res Opin 2011;27:1119-29.
29. von Birgelen C, Hartmann M, Mintz GS, Baumgart D, Schmermund A, Erbel R. Relation between progression and regression of atherosclerotic left main coronary artery disease and serum cholesterol levels as assessed with serial long-term (> or = 12 months) follow-up intravascular ultrasound. Circulation 2003;108:2757-62.
30. Nicholls SJ, Hsu A, Wolski K, et al. Intravascular ultrasound-derived measures of coronary atherosclerotic plaque burden and clinical outcome. J Am Coll Cardiol 2010;55:2399-407.