Antiatherosclerotic Effects of Long-Term Maximally Intensive Statin Therapy After Acute Coronary Syndrome

Insights From Study of Coronary Atheroma by Intravascular Ultrasound: Effect of Rosuvastatin Versus Atorvastatin

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Objectives—Patients with acute coronary syndromes (ACS) display diffuse coronary atheroma instability and heightened risk of early and late recurrent coronary events. We compared the long-term antiatherosclerotic efficacy of high-intensity statins in patients with ACS when compared with stable disease.

Approach and Results—Study of Coronary Atheroma by Intravascular Ultrasound (SATURN) used serial intravascular ultrasound measures of coronary atheroma volume in patients treated with rosuvastatin 40 mg or atorvastatin 80 mg for 24 months. The overall effect of high-intensity statins on the change in coronary percent atheroma volume and major adverse cardiovascular events (death/nonfatal myocardial infarction/ coronary revascularization) were evaluated in this post hoc analysis. When compared with non-ACS patients (n=678), patients with ACS (n=361) were younger, actively smoking, and had a previous myocardial infarction (all P<0.001).

At baseline, patients with ACS exhibited lower high-density lipoprotein cholesterol (43.5±11 versus 45.8±11 mg/dL; P=0.002), a higher apolipoprotein B: apolipoprotein A-1 ratio (0.90±0.24 versus 0.83±0.24; P=0.001) and greater percent atheroma volume (37.3±8.5% versus 35.9±8.1%; P=0.01) when compared with non-ACS patients. Despite similar achieved levels of lipid and inflammatory markers after high-intensity statin therapy, patients with ACS demonstrated greater percent atheroma volume regression than non-ACS patients (−1.46±0.14 versus −0.89±0.13; P=0.003). After propensity-weighted multivariable adjustment, baseline percent atheroma volume (P<0.001) and an ACS clinical presentation (P=0.02) independently associated with plaque regression. The 24-month major adverse cardiovascular events–free survival was similar between patients with ACS and non-ACS (90.6 versus 92.9%; P=0.25).

Conclusions—Long-term high-intensity statin therapy caused greater plaque regression and comparable major adverse cardiovascular events rates in ACS when compared with non-ACS patients. Despite a higher clinical risk profile, patients with ACS harbor a more modifiable disease substrate and seem to benefit the most from potent statin therapy. (Arterioscler Thromb Vasc Biol. 2014;34:2465-2472.)

Key Words: acute coronary syndrome ◼ atherosclerosis ◼ statins, HMG-CoA

Each year in the United States alone, there are >1.5 million hospital admissions for acute coronary syndromes (ACSs), whereas in Europe, the estimated annual incidence of ACSs is thought to vary between 1 per 80 and 1 per 170 of the population. Despite widespread use of proven treatment approaches, patients with ACS remain at considerable risk for subsequent cardiovascular events. The finding that culprit lesion revascularization after ACS reduces the relative risk of mid- to long-term cardiovascular events by only 20% suggests that many of these events are likely to arise from sites remote to the original culprit lesion. Such observations underscore the systemic nature of atherosclerosis and plaque instability. Therefore, systemic antiatherosclerotic therapies may add considerably to the local treatment of the culprit lesion in preventing recurrent events in patients with ACS.

Lipid-lowering treatment guidelines in the United States now broadly recommend high-intensity statin therapy for all patients with atherosclerotic cardiovascular disease.
whereas European guidelines advocate lowering low-density lipoprotein cholesterol (LDL-C) levels to either <70 mg/dL or to at least achieve a 50% reduction from baseline levels in patients considered to be at high cardiovascular risk.11 Indeed those receiving intensive versus moderate statin therapy after ACS seemingly derive the greatest clinical benefit.12–16 Yet despite the effectiveness and established tolerability of potent statin therapy,17 there remains a considerable gap between guideline recommendations and real-world practice for treating ACS. Not only are a majority of patients with ACS not prescribed intensive statin therapy18 but also of those prescribed statins, few achieve LDL-C levels of ≤70 mg/dL.19

Although there seems to be an early clinical benefit when initiating intensive versus moderate statin therapy acutely after ACS,20–22 to date no study has documented the longer term antiatherosclerotic efficacy of this treatment approach in the ACS population. Study of Coronary Atheroma by Intravascular Ultrasound: Effect of Rosuvastatin Versus Atorvastatin (SATURN; ClinicalTrials.gov number, NCT000620542) was the largest imaging trial comparing the antiatherosclerotic efficacy of 2 of the most potent statin regimens, by measuring the change in coronary atheroma volume on serial intravascular ultrasonography (IVUS).23 No appreciable difference of the primary efficacy end point of change in percent atheroma volume (PAV), safety, or clinical event rates was found between the 2 treatment groups. Thus, we undertook a post hoc analysis of the total SATURN cohort to ascertain that the long-term (24 months) antiatherosclerotic efficacy of maximally intensive statin therapy differs between patients presenting with or without an ACS at enrollment.

Materials and Methods
Materials and Methods are available in the online-only Supplement.

Results
Patient Characteristics
Table 1 presents baseline demographics, clinical characteristics, and concomitant medications in patients with ACS (n=361) and without ACS (n=678). Figure 1 describes absolute standardized differences in baseline covariates between patients with ACS and non-ACS before and after inverse probability of treatment weight adjustment. Of those presenting with ACS at baseline, 140 patients had a confirmed myocardial infarction and the remaining 221 had unstable angina. When compared with patients without ACS, those with an ACS were younger (55.9±8.6 versus 58.6±8.4 years; \( P < 0.001 \)), more likely men (77.3% versus 71.7%; \( P = 0.05 \)), had a previous myocardial infarction (35.5% versus 18.6%; \( P < 0.001 \)), were actively smoking (40.7% versus 27.9%; \( P < 0.001 \)), were receiving concomitant aspirin (72.9% versus 55.3%; \( P < 0.001 \)), β-blocker (78.1% versus 51.6%;
Table 2 describes baseline, follow-up, and changes of lipid and C-reactive protein levels. When compared with patients without ACS, those who presented with ACS had lower high-density lipoprotein cholesterol (43.5±11.2 versus 45.8±11.3 mg/dL; P=0.002), lower apolipoprotein (apo) apoA-1 (123.1±23.6 versus 129.3±24.4 mg/dL; P<0.001), and a higher apoB:apoA-1 ratio (0.90±0.24 versus 0.83±0.24; P<0.001) at baseline. At follow-up, there were no differences in lipid and C-reactive protein values between the groups. This was a result of the ACS group experiencing a significantly greater increase in high-density lipoprotein cholesterol (15.7±19.0% versus 9.0±17.5%; P=0.001) and apoA-1 levels (17.2±18.3% versus 11.4±17.3%; P=0.001) but a greater decrease in the apoB:apoA-1 ratio (−38.8±15.0% versus −34.6±16.7%; P<0.001) when compared with those without ACS.

Atheroma Burden, Calcification, and Vascular Dimensions

Table 3 describes the baseline and change in IVUS measurements in patients stratified according to presentation with or without ACS. At baseline, the ACS population demonstrated numerically greater PA V (37.3±8.5% versus 35.9±8.1%; P=0.01) and total atheroma volume (TAV; 148.2±64 versus 141.9±61.2 mm³; P=0.12) when compared with the non-ACS population. After controlling for baseline atheroma volume, greater PA V regression (−1.46±0.14 versus −0.89±0.13%; P=0.003) and TAV regression (−9.43±0.66 versus −6.18±0.62 mm³; P<0.001) was achieved in the ACS population when compared with the non-ACS population. Changes in lumen and external elastic membrane volumes did not differ between the ACS and the non-ACS populations. At baseline, the degree of plaque calcification across the entire pullback did not differ significantly between patients with non-ACS and ACS.

Discussion

The present analysis indicates that patients with ACS demonstrated significantly greater disease regression after maximally intensive statin therapy when compared with patients with stable coronary disease, highlighting the antiatherosclerotic benefits of long-term potent statin therapy in patients with ACS who are typically at greater cardiovascular risk.
These findings provide further insight into the dynamic nature of disease-modifying therapies in patients thought to harbor the most vulnerable form of coronary disease. Across several trials evaluating serial changes in coronary atheroma volume, the baseline extent of disease was independently associated with greater plaque regression in response to disease-modifying therapies, such that those with greater baseline plaque burden invariably demonstrated the most disease regression. However, despite the current multivariable analysis adjusting for the greater disease burden in ACS when compared with stable patients, an ACS clinical disposition remained independently associated with greater plaque regression. Findings of the present analysis are consistent with those of a recent meta-analysis evaluating the effect of statins on the IVUS-derived progression of coronary atherosclerosis, which uncovered a 2-fold greater decrease in coronary...
atheroma volume in patients with ACS when compared with those with stable coronary disease after statins.25 An explanation of these findings may relate to underlying differences in coronary atheroma composition in patients with ACS when compared with chronic stable coronary disease, who more likely harbor greater degrees of less modifiable fibrocalcific plaque. Furthermore, given the extended duration of the use of high-intensity statins in SATURN, this could have magnified both the delipidating and the pleiotropic actions of statins on plaque.

In addition to highlighting significant coronary atheroma regression after 6 weeks of recombinant apoA-1 Milano infusions in patients with ACS,27 2 small serial coronary IVUS studies demonstrated similar acute to short-term (6 weeks to 6 months) plaque regression when statins were administered to statin naïve patients with ACS.28,29 Yet, the significant degree of atheroma regression with high-intensity statins measured acutely after ACS in these studies contrasts with the lack of corresponding magnitude of disease regression measured within similar time frames in those with stable coronary disease.30,31 In the Early Statin Treatment in Patients With Acute Coronary Syndrome (ESTABLISH) study, moderate-intensity statin therapy was associated with disease regression...
This goal may, however, be simply to implement high-intensity statin therapy regardless of the baseline LDL-C level. Routine institution of high-intensity statin therapy, as recommended by the latest US guidelines, rather than targeting a specific LDL goal, may thus be a more appropriate and more readily implemented strategy for preventing recurrent MACE after an ACS. In addition, given that the mean achieved LDL-C levels in both patient groups were 65 to 66 mg/dL, the present findings further demonstrate the antiatherosclerotic efficacy of achieving LDL-C <70 mg/dL in high-risk patients.

This was a nonprespecified post hoc analysis of SATURN, with some limitations requiring consideration. SATURN was not prospectively powered for detecting differences in MACE. Furthermore, a majority of MACE in SATURN were driven by coronary revascularization, known to be influenced by differing clinical strategies across various regions. However, all coronary revascularizations in SATURN were adjudicated by a centralized clinical events committee. Despite the inherent risk attributable to coronary revascularization per se, revascularization improves the morbidity and mortality of these patients. The 2.3% absolute difference in event-free survival at 24 months might have become more pronounced, had a greater number of patients been studied, and followed up for a longer duration. Plaque composition was not available for this analysis, which may have provided further mechanistic insight into the reasons why plaque regression was greater in patients with ACS when compared with non-ACS patients. A recent prespecified post hoc analysis of serial plaque composition changes in SATURN uncovered that atheroma regression to high-intensity statins was mediated mostly by significant reductions in the fibrofatty (lipidic) component of plaque. However, the serial radiofrequency backscatter analysis of plaque composition still possesses inherent limitations and warrants further investigation. Although sophisticated statistical techniques were used to account for baseline differences between the ACS and non-ACS groups, propensity-weighting may not have eliminated the effects of unknown confounding variables that could have biased this analysis. For example, patients with ACS could have a greater tendency for behavior modification when compared with their stable coronary disease counterparts. Behavioral modification data (ie, smoking cessation, exercise, and dietary modification) and its potential affect on disease progression were not collected in SATURN. Furthermore, we cannot exclude a type-1 error rate because of the multiple statistical tests performed, and no further adjustments were made on the large number of multiple comparisons.

In conclusion, long-term high-intensity statin therapy provided superior antiatherosclerotic effects in higher-risk patients with ACS when compared with SATURN participants who presented with more stable disease. This systemic treatment seemed to alter the natural history and clinical expression of coronary atherosclerosis. These findings support the long-term use of high-intensity statin therapy in patients after an ACS.

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References


**Significance**

Study of Coronary Atheroma by Intravascular Ultrasound: Effect of Rosuvastatin Versus Atorvastatin (SATURN) was the largest coronary plaque imaging trial evaluating the effects of 2 high-intensity statin regimens on coronary atheroma >24 months; the primary efficacy end point between the 2 statins was not significantly different. Yet the long-term coronary antiatherosclerotic effects of high-intensity statins in patients with acute coronary syndromes compared with their stable counterparts is poorly understood. In this post hoc SATURN analysis, patients with acute coronary syndrome demonstrated greater disease regression when compared with stable patients. Adjusted survival curves also outlined similar major adverse cardiovascular events–free survival between the 2 patient groups. Despite greater cardiovascular risk, multivariable analysis revealed an acute coronary syndrome disposition to associate with plaque regression independently. These novel observations outline the modifiable nature of the coronary disease substrate in a patient population considered to harbor the most vulnerable form of coronary atheroma. Such findings have important implications for the acute and long-term management of patients with acute coronary syndrome, supporting recommendations of recent US-based lipid-lowering guidelines.
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METHODS

Patient selection
The design of SATURN has been previously described.1 Briefly, patients with angiographically demonstrable coronary disease and LDL-C <116 mg/dL following a 2-week treatment period with atorvastatin 40 mg or rosuvastatin 20 mg daily were re-randomized and treated for 24-months with atorvastatin 80 mg or rosuvastatin 40 mg daily. Subjects underwent IVUS imaging of a coronary artery at baseline and after 104 weeks of treatment. Patients undergoing a baseline IVUS, during the clinical investigation and treatment of a myocardial infarction [with evidence of a diagnostic troponin or creatine kinase (CK) rise] or unstable angina pectoris, were classified as presenting with an ACS.2 Patients with ST-segment elevation myocardial infarction were eligible for enrollment in SATURN if their CK had fallen below 3x the upper normal reference limit, at the time of screening.

Acquisition and analysis of intravascular coronary imaging
The presence of at least a single lumen stenosis of >20% angiographic diameter stenosis severity in an epicardial coronary artery at the time of a clinically indicated coronary angiogram was necessary for enrollment. IVUS was performed at baseline in a single, native coronary artery with no lumen stenosis of ≥50%, which had not undergone revascularization and was not considered to be the culprit vessel of a prior myocardial infarction. Images were screened by the Atherosclerosis Imaging Core Laboratory at the Cleveland Clinic Coordinating Center for Clinical Research for image quality, and those patients whose baseline imaging was acceptable were eligible for randomization. Following 104 weeks of treatment, patients underwent repeat IVUS of the same artery. Anatomically matched arterial segments were selected for analysis on the basis of proximal and distal side branches (fiduciary points). Cross-sectional images spaced 1-mm apart were selected for analysis, with lumen and external elastic membrane (EEM) leading edges defined by manual planimetry. Plaque area was determined as the area between these leading edges. PAV and total atheroma volume (TAV, the secondary efficacy endpoint in SATURN) were calculated, as previously described.3 Briefly, PAV was calculated as the proportion of the entire vessel wall occupied by atherosclerotic plaque, throughout the segment of interest. This is derived by first calculating the atheroma area (EEM-lumen) for each cross-sectional image and multiplying by the distance to the next image (1-mm), and summing across the entire segment to approximate the total volume of plaque in the vessel. Similarly, the total vessel volume is calculated by multiplying the EEM area measurement by the distance to the next image (1-mm) and summing across the entire segment. The ratio of the sum of plaque areas (essentially plaque volume) to vessel volume is then multiplied by 100 to represent the percentage of vessel occupied by atheroma, as follows:

$$PAV = \frac{\sum (EEM \text{ area} - \text{Lumen area}) \times 1\text{mm}}{\sum EEM \text{ area} \times 1\text{mm}} \times 100$$
The total atheroma volume (TAV) was calculated by summating each of the plaque areas multiplied by distance to the next image (1-mm) in all measured images. To account for heterogeneity of segment length in individual subjects, the TAV was normalized by multiplying the mean atheroma area in each pullback by the median segment length for the entire SATURN population cohort as follows:

\[
TAV_{\text{normalized}} = \frac{\sum (\text{EEM area} - \text{Lumen area}) \times 1\text{mm}}{\text{No. of images in pullback}} \times \text{Median no. of images in SATURN}
\]

The primary end point of SATURN, change in PAV, was calculated as the PAV at 104 weeks minus the corresponding PAV at baseline. Similarly, change in TAV was defined as the TAV at 104 weeks minus the corresponding TAV at baseline.

A calcium grade was assigned for each measured image, which reflected the presence of calcium and degree of acoustic shadowing that resulted (0 = no calcium, 1 = calcium with shadowing <90°, and 2 = calcium with shadowing >90°). In images containing multiple calcium deposits, the grade represented the summation of all angles of acoustic shadows present. A baseline calcium index was thus derived for each pullback by determining the average grade of all measured images.4

Statistical analysis
Continuous variables were reported as mean ± SD if normally distributed and as median (interquartile range) if non-normally distributed. Two-sample t-tests were used for normally distributed continuous variables, Wilcoxon rank-sum tests for non-normally distributed continuous variables, and chi-square tests for categorical variables. Because of significant differences in various baseline characteristics between ACS and non-ACS patients, a propensity score weighting method was applied. The propensity score model was developed by constructing a logistic regression model in which ACS vs. non-ACS was regressed on baseline characteristics related to the ACS status and/or the outcome variables. The estimated propensity score was obtained as the predicted probability of having an ACS in each subject. Inverse probability of treatment weight (IPTW) was then calculated as the inverse of the propensity score for ACS patients and as the inverse of (1 – propensity score) for the non-ACS patients. To assess bias reduction achieved by the propensity score weighting, standardized differences of the 10 covariates that were included for estimating propensity scores were compared before and after weighting, with a value of <10% indicating between-group balance (Figure 1).5 All subsequent analyses were weighted by IPTW.

Serial changes in IVUS measurements were analyzed by ANOVA adjusting for their baseline counterparts and were reported as least-squares mean ± SE. A multivariable linear regression model was undertaken to identify factors associated with change in PAV or TAV. To create the multivariable model, demographic data and clinical characteristics were entered into a multivariable linear model (with baseline IVUS variables, ACS status and the randomization group of SATURN forced into this model) for variable selection with bootstrap re-sampling (1000 iterations and a P value
criterion of 0.05 for retention). Those variables that had a 40% or higher probability of retention were entered into a second linear regression model with the stepwise model selection procedure. The significance level to enter and keep a variable was set at 0.05. The selected covariates formed the covariate set for the final multivariable linear regression model. All clinical events in SATURN were adjudicated by an independent committee. A survival analysis was further performed to assess for the effect of ACS on time to first major adverse cardiovascular event (MACE: defined as death, non-fatal myocardial infarction, coronary revascularization), and corresponding weighted survival curves were plotted. This was conducted on the 1380 patients (N= 478 with ACS) in SATURN with evaluable clinical data censored at the 24 month follow-up period. A 2-sided p-value of 0.05 was considered statistically significant. All analyses were performed using SAS software version 9.2 (SAS Institute Inc, Cary, North Carolina).

REFERENCES