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

Rishi Puri, Steven E. Nissen, Mingyuan Shao, Christie M. Ballantyne, Philip J. Barter, M. John Chapman, Raimund Erbel, Peter Libby, Joel S. Raichlen, Kiyoko Uno, Yu Kataoka, Stephen J. Nicholls

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: Effect of Rosuvastatin Versus Atorvastatin (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 higher 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 lipids 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 event–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

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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 early and late recurrent coronary events 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 with statins 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. Indeed those receiving intensive versus moderate statin therapy after ACS seemingly derive the greatest clinical benefit. Yet despite the effectiveness and established tolerability of potent statin therapy, 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 therapy but also of those prescribed statins, few achieve LDL-C levels of ≤70 mg/dL. Although there seems to be an early clinical benefit when initiating intensive versus moderate statin therapy acutely after ACS, 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). 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%; P<0.001), and were more likely to be receiving dual antiplatelet therapy (59.0% versus 34.5%; P<0.001).

Table 1. Baseline Demographics, Patient Characteristics, and Concomitant Medications*

<table>
<thead>
<tr>
<th>Variable</th>
<th>Total (n=1039)</th>
<th>No ACS (n=678)</th>
<th>Yes ACS (n=361)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>57.6±8.6</td>
<td>58.6±8.4</td>
<td>55.9±8.6</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Men</td>
<td>765 (73.6)</td>
<td>486 (71.7)</td>
<td>279 (77.3)</td>
<td>0.051</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>29.0±5.2</td>
<td>29.3±5.3</td>
<td>28.5±5.0</td>
<td>0.049</td>
</tr>
<tr>
<td>Previous MI</td>
<td>254 (24.4)</td>
<td>126 (18.6)</td>
<td>128 (35.5)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>History of PCI</td>
<td>243 (23.4)</td>
<td>160 (23.6)</td>
<td>83 (23.0)</td>
<td>0.83</td>
</tr>
<tr>
<td>Hypertension</td>
<td>731 (70.4)</td>
<td>489 (72.1)</td>
<td>242 (67.0)</td>
<td>0.09</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>159 (15.3)</td>
<td>112 (16.5)</td>
<td>47 (13.0)</td>
<td>0.14</td>
</tr>
<tr>
<td>Active smoker</td>
<td>336 (32.3)</td>
<td>189 (27.9)</td>
<td>147 (40.7)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Rosuvastatin</td>
<td>520 (50.0)</td>
<td>338 (49.9)</td>
<td>182 (50.4)</td>
<td>0.86</td>
</tr>
<tr>
<td>Aspirin</td>
<td>638 (61.4)</td>
<td>375 (55.3)</td>
<td>263 (72.9)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Dual antiplatelet therapy†</td>
<td>447 (43.0)</td>
<td>234 (34.5)</td>
<td>213 (59.0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>β-Blockers</td>
<td>632 (60.8)</td>
<td>350 (51.6)</td>
<td>282 (78.1)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>ACE inhibitors</td>
<td>457 (44.0)</td>
<td>258 (38.1)</td>
<td>199 (55.1)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Angiotensin receptor blocker</td>
<td>170 (16.4)</td>
<td>109 (16.1)</td>
<td>61 (16.9)</td>
<td>0.73</td>
</tr>
<tr>
<td>Nitrate</td>
<td>859 (82.7)</td>
<td>568 (83.8)</td>
<td>291 (80.6)</td>
<td>0.20</td>
</tr>
</tbody>
</table>

All medications listed are concomitant. Values of continuous variables are reported as mean±SD if normally distributed and median (interquartile range) if non-normally distributed. Categorical variables are reported as n (%). ACE indicates angiotensin-converting enzyme inhibitor; MI, myocardial infarction; and PCI, percutaneous coronary intervention.

*Data represented before inverse probability of treatment weight adjustment.
†Dual antiplatelet therapy comprises concomitant aspirin and clopidogrel.
Table 1 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 PAV (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 mm\(^3\); \( P=0.12 \)) when compared with the non-ACS population. After controlling for baseline atheroma volume, greater PAV 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 mm\(^3\); \( P<0.001 \)) 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.

### Multivariable Model of Factors Associated With Changes in Coronary Atheroma Volume

Table 4 summarizes a multivariable linear regression model of factors associated with changes in PAV and TAV, following inverse probability of treatment weight adjustment. A clinical presentation with an ACS was independently associated with PAV regression (\( \beta=−0.51; P=0.007 \)) and TAV regression (\( \beta=−2.65; P=0.004 \)). In addition, greater baseline PAV and TAV each associated with the likelihood of both PAV and TAV progression (\( \beta<0.001 \) and \( \beta<0.001 \), respectively). However, a higher average follow-up LDL-C level was associated with a greater likelihood of both PAV and TAV progression (\( \beta=−0.49; P<0.001 \) and \( \beta=−0.94; P<0.001 \), respectively). Rosuvastatin (compared with atorvastatin) was associated with greater TAV regression (\( \beta=−2.57; P=0.005 \)). However, there was no significant interaction between type of statin and ACS presentation on changes in TAV (\( P=0.15 \); Figure 1).

### Survival Analysis Between Patients

ACS Versus Non-ACS

Figure 2 shows a weighted survival curve analysis, comparing the event-free major adverse cardiovascular events (MACE) survival between patients with ACS and non-ACS. In SATURN, there were 4 cardiovascular deaths, 22 nonfatal myocardial infarctions, and 83 coronary revascularization procedures. After 24 months of maximally intensive statin therapy, 92.9% of patients with non-ACS and 90.6% of patients with ACS were free of MACE, respectively (\( P=0.25 \)). Furthermore, there was no significant treatment effect on MACE (\( P=0.32 \)).

### 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. An explanation of these findings may relate to underlying differences in coronary atheroma composition in patients with ACS when compared with stable patients. Pathological and imaging studies have demonstrated the coronary tree of patients with ACS to contain greater amounts of lipid-laden plaque and inflammatory infiltrate, occurring diffusely, when compared with non-ACS patients. High-intensity statins possess not only potent LDL-C–lowering properties but also significant anti-oxidant and anti-inflammatory effects. Such properties may have rendered patients with ACS more susceptible to the antiatherosclerotic effects of these potent statins when compared with patients 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.

### Table 3. Baseline Values for IVUS Measures and Change in Values From Baseline Between Patients With ACS and Non-ACS

<table>
<thead>
<tr>
<th>IVUS Parameter</th>
<th>Total (n=1039)</th>
<th>No (n=678)</th>
<th>Yes (n=361)</th>
<th>P Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Percent atheroma volume, %</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>36.3±8.3</td>
<td>35.9±8.1</td>
<td>37.3±8.5</td>
<td>0.01</td>
</tr>
<tr>
<td>Change from baseline</td>
<td>-1.16±0.10</td>
<td>-0.89±0.13</td>
<td>-1.46±0.14</td>
<td>0.003</td>
</tr>
<tr>
<td>P value for test of change from baseline</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>...</td>
</tr>
<tr>
<td>Total atheroma volume, mm³</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>144.1±62.2</td>
<td>141.9±61.2</td>
<td>148.2±64.1</td>
<td>0.12</td>
</tr>
<tr>
<td>Change from baseline</td>
<td>-7.69±0.45</td>
<td>-6.18±0.62</td>
<td>-9.43±0.66</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>P value for test of change from baseline</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>...</td>
</tr>
<tr>
<td>Lumen volume, mm³</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>248.3±88.6</td>
<td>250.0±91.3</td>
<td>245.1±83.5</td>
<td>0.39</td>
</tr>
<tr>
<td>Change from baseline</td>
<td>0.81±0.93</td>
<td>0.37±1.26</td>
<td>1.31±1.36</td>
<td>0.62</td>
</tr>
<tr>
<td>P value for test of change from baseline</td>
<td>0.38</td>
<td>0.77</td>
<td>0.34</td>
<td>...</td>
</tr>
<tr>
<td>EEM volume, mm³</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>392.4±135.8</td>
<td>391.9±138.1</td>
<td>393.3±131.4</td>
<td>0.88</td>
</tr>
<tr>
<td>Change from baseline</td>
<td>-6.90±1.14</td>
<td>-5.60±1.56</td>
<td>-8.41±1.68</td>
<td>0.22</td>
</tr>
<tr>
<td>P value for test of change from baseline</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>...</td>
</tr>
<tr>
<td>Baseline Calcium Index†</td>
<td>0.26 (0.08, 0.50)</td>
<td>0.25 (0.08, 0.49)</td>
<td>0.29 (0.10, 0.52)</td>
<td>0.07</td>
</tr>
</tbody>
</table>

Changes in ultrasonographic parameters are following inverse probability of treatment weight adjustment. Baseline and follow-up values are reported as mean±SD, and change values are reported as least-squares mean±SE. ACS indicates acute coronary syndrome; EEM, external elastic membrane; and IVUS, intravascular ultrasound.

*P value reflects comparisons between patients with ACS and non-ACS.

†Calcium index is represented as median (interquartile range).

### Table 4. Multivariable Linear Regression Model for Changes in Coronary Atheroma Volume

<table>
<thead>
<tr>
<th>Covariate</th>
<th>Estimated β-Coefficient (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>PAV</td>
<td>Baseline PAV</td>
<td>-0.57 (-0.75, -0.38)</td>
</tr>
<tr>
<td></td>
<td>ACS (vs no ACS)</td>
<td>-0.51 (-0.88, -0.14)</td>
</tr>
<tr>
<td></td>
<td>Average follow-up LDL-C</td>
<td>0.49 (0.41, 0.92)</td>
</tr>
<tr>
<td>TAV</td>
<td>Baseline TAV</td>
<td>-4.07 (-4.96, -3.18)</td>
</tr>
<tr>
<td></td>
<td>ACS (vs no ACS)</td>
<td>-2.65 (-4.44, -0.87)</td>
</tr>
<tr>
<td></td>
<td>Rosuvastatin (vs atorvastatin)</td>
<td>-2.57 (-4.35, -0.80)</td>
</tr>
<tr>
<td></td>
<td>Average follow-up LDL-C</td>
<td>0.94 (0.09, 1.80)</td>
</tr>
<tr>
<td></td>
<td>History of PCI</td>
<td>3.23 (1.16, 5.30)</td>
</tr>
<tr>
<td></td>
<td>BMI</td>
<td>0.96 (0.10, 1.82)</td>
</tr>
</tbody>
</table>

Following inverse probability of treatment weight adjustment. Randomization group of the trial (rosuvastatin vs atorvastatin) was forced into the model. PAV, TAV, BMI, and follow-up LDL-C are per SD. Average follow-up LDL-C values represent time-weighted average values. ACS indicates acute coronary syndrome at baseline clinical presentation in Study of Coronary Atheroma by Intravascular Ultrasound: Effect of Rosuvastatin Versus Atorvastatin (SATURN); BMI, body mass index; CI, confidence interval; LDL-C, low-density lipoprotein cholesterol; PAV, percent atheroma volume; PCI, percutaneous coronary intervention; and TAV, total atheroma volume.
high-risk coronary disease.11,37 This goal may, however, be
achieved at 6 months, even in individuals with low baseline LDL-C lev-
els. However, IVUS analysis in this study was undertaken in coronary segments <10 mm in length28 when compared with
>50 mm in SATURN. Nevertheless, these previous observations further underscore the postulate that, although patients with ACS harbor high-risk coronary atheroma, their disease substrate seems to be more susceptible to plaque stabilization and regression acutely, and that this stability can be maintained during the longer term in concert with the maintenance of potent statin therapy. Although the data collected from these previous studies, including SATURN, do not establish a direct link between coronary atheroma regression and lower clinical event rates, accumulating data suggest an association between IVUS-derived coronary atheroma volume6,24,32,33 and its rate of progression24,32 with incident clinical events, albeit driven largely by repeat coronary revascularization procedures.

Despite numerous guidelines suggesting the use of high-
intensity statins after ACS, real-world prescribing patterns of physicians seem not to reflect these recommendations. Such findings seem common to many regions of the world.18,19,34–36 Until recently, clinical guidelines tentatively recommended target LDL-C levels ≤70 mg/dL in those with established high-risk coronary disease.11,37 This goal may, however, be confusing for practitioners when managing patients with ACS. No randomized controlled trials have tested the hypothesis that achieving an LDL-C of ≤70 mg/dL, irrespective of the nature and intensity of statin therapy after an ACS, is equivalent to simply the broad implementation of 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,10 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,38 revascularization improves the morbidity and mortality of these patients.3 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.39 However, the serial radiofrequency backscatter analy-
sis of plaque composition still possesses inherent limitations and warrants further investigation.40 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 effect 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 pro-
vided 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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Disclosures

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10. AstraZeneca and Lipid Sciences. The other authors report no conflicts.


**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. 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. 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. 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:

\[
PAV = \frac{\sum (\text{EEM area} - \text{Lumen area}) \times 1\text{mm}}{\sum \text{EEM area} \times 1\text{mm}} \times 100
\]
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:

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

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