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Impact of statins on progression of atherosclerosis: rationale and design of SATURN (Study of Coronary Atheroma by InTravascular Ultrasound: Effect of Rosuvastatin versus Atorvastatin)

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Abstract

Background:
Previous imaging studies have demonstrated that the beneficial impact of high-dose statins on the progression of coronary atherosclerosis associates with their ability to lower levels of low-density lipoprotein cholesterol (LDL-C) and C-reactive protein (CRP) and to raise high-density lipoprotein cholesterol (HDL-C). The Study of Coronary Atheroma by InTravascular Ultrasound: Effect of Rosuvastatin versus Atorvastatin (SATURN, NCT00620542) aims to compare the effects of high-dose atorvastatin and rosuvastatin on disease progression.

Methods:
A total of 1385 subjects with established coronary artery disease (CAD) on angiography were randomized to receive rosuvastatin 40 mg or atorvastatin 80 mg for 24 months. The primary efficacy parameter will be the nominal change in percent atheroma volume (PAV), determined by analysis of intravascular ultrasound (IVUS) images of matched coronary artery segments acquired at baseline and at 24-month follow-up. The effect of statin therapy on plasma lipids and inflammatory markers, and the incidence of clinical cardiovascular events will also be assessed. The study does not have the statistical power to directly compare the treatment groups with regard to clinical events.

Conclusion:
Serial IVUS has emerged as a sensitive imaging modality to assess the impact of treatments on arterial structure. In this study, IVUS will be used to determine whether high-dose statins have different effects on plaque progression.

Introduction

Over the last two decades, pharmacological inhibitors of 3-hydroxy-3-methylglutaryl coenzyme reductase A (statins) have become the predominant therapeutic approach to lowering levels of atherogenic low-density lipoprotein cholesterol (LDL-C). Large placebo-controlled trials in both primary and secondary prevention settings have consistently demonstrated reductions in cardiovascular events with statin therapy. Accordingly, statins have become widely used in risk-reduction regimens and have profoundly impacted the burden and natural history of cardiovascular disease in developed nations.
The finding that more than half of the cardiovascular events in clinical trials are not prevented by statin use supports an ongoing need to understand the factors that are likely to result in their optimal effects.

**Evaluation of statins and atherosclerotic plaque**

Considerable interest has focused on characterizing the effects of statin therapy on the underlying arterial disease. Early animal studies demonstrated that statins reduce the extent of atherosclerosis as do interventions that lower LDL-C by dietary intervention. Subsequent investigations reported that statins also had favorable effects on plaque features implicated in fibrous cap rupture and acute ischemic events. The ability of statins to modify inflammatory, oxidative, and thrombotic pathways in cellular studies may contribute to their impact on the natural history of atherosclerosis. Advances in arterial wall imaging permit serial visualization of atherosclerotic plaque in anatomically matched segments, allowing evaluation of the effect of medical therapies on disease progression in vivo in humans.

**Findings from early generation imaging modalities**

Coronary angiography has been the primary tool for the diagnosis and quantification of coronary artery disease (CAD) for more than 50 years. In addition to guiding therapy in practice, clinical trials have employed quantitative coronary angiography extensively to evaluate the effect of medical interventions. Clinical trials of LDL-C-lowering therapies, including statins, have demonstrated a direct relationship between the achieved level of LDL-C and the rate of progression of lumen obstruction. But while many angiographic studies evaluated the impact of statin therapy in the 1990s, none were able to demonstrate disease regression. In fact, the only robust evidence of angiographic regression in that time frame was observed in the HDL-Atherosclerosis Treatment Study (HATS), in which the combination of a statin and niacin was associated with a significant reduction in percent diameter stenosis, and decreased cardiovascular events. This finding supported the incremental benefit obtained using combination regimens that lower levels of atherogenic lipids, while also raising high-density lipoprotein cholesterol (HDL-C).

Non-invasive B-mode ultrasonic imaging of the carotid arteries permits measurement of intimal-medial thickness (IMT). Population studies have demonstrated that a greater carotid IMT associates with cardiovascular risk factors, prevalence of coronary atherosclerosis, and prospective risk of cardiovascular events. Clinical trials of statin therapy have demonstrated a direct relationship between the degree of LDL-C lowering and slowing of carotid IMT progression. Serial evaluation of carotid IMT provided the first direct comparison of intensive and moderate statin regimens. In the Atorvastatin Simvastatin Atherosclerosis Project (ASAP), patients with familial hypercholesterolemia received either atorvastatin (80 mg; 51% reduction in LDL-C) or simvastatin (40 mg; 41% reduction in LDL-C). Carotid IMT increased in simvastatin-treated patients and decreased in atorvastatin-treated patients, a result that is consistent with regression of very early changes in the arterial wall. A similar finding was observed in the Arterial Biology for the Investigation of the Treatment Effects of Reducing Cholesterol (ARBITER) study, in which dyslipidemic patients were treated with atorvastatin (80 mg) or pravastatin (40 mg). IMT increased with the moderate strategy (LDL-C, 110 mg/dL) and decreased in the intensively treated patients (LDL-C, 76 mg/dL).
The Measuring Effects on Intima-Media Thickness: an Evaluation of Rosuvastatin (METEOR) study evaluated the impact of statin therapy on carotid IMT progression in low risk patients. Subjects with hypercholesterolemia, Framingham risk less than 10%, and maximum carotid IMT 1.2–3.5 mm, were treated with rosuvastatin (40 mg) or placebo for 24 months. Lowering LDL-C to 78 mg/dL with rosuvastatin slowed progression of carotid IMT, suggesting that statin therapy could be beneficial at the level of the arterial wall in patients who would not typically be candidates for lipid-lowering therapy²⁶. This provided an imaging correlate of the Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin (JUPITER) study, in which rosuvastatin 20 mg was associated with reduced cardiovascular events in lower-risk patients with elevated high-sensitivity C-reactive protein (hsCRP)²⁷.

Carotid IMT has also been employed to evaluate the potential impact of alternative strategies to lower LDL-C. In the Ezetimibe and Simvastatin in Hypercholesterolemia Enhances Atherosclerosis Regression (ENHANCE) study, patients with familial hypercholesterolemia were treated with simvastatin (80 mg) alone or in combination with the cholesterol absorption inhibitor ezetimibe (10 mg). Despite greater lowering of LDL-C in the combination group (58% vs. 41%), no significant difference was observed with regard to serial change in carotid IMT²⁸. While the reason underlying the lack of efficacy of combination therapy on carotid IMT progression remains unknown, the finding of a relatively low IMT at baseline suggested that previous lipid-lowering therapy might have modified the natural history of the intima-media thickening in these patients²⁸. Findings from other clinical trials suggest that ezetimibe based strategies may have a beneficial impact on IMT progression. A posthoc analysis of the Stop Atherosclerosis in Native Diabetics (SANDS) trial revealed that patients treated with ezetimibe had less IMT progression²⁹. Furthermore, the Vytorin and Carotid Intima-Media Thickness on Overall Arterial Rigidity (VYCTOR) study demonstrated IMT regression in a small number of patients treated with simvastatin/ezetimibe who achieved a very low LDL-C level (48 mg/dL)³⁰. While a study in patients with kidney disease demonstrated a reduction in vascular events with combination therapy including simvastatin and ezetimibe³¹, ultimately, an ongoing large clinical trial should clarify the effect on cardiovascular outcomes of a lipid-lowering strategy incorporating ezetimibe³².

Additional evidence beyond statin therapy suggests that the combination of lowering levels of atherogenic lipids and raising HDL-C likely has an incremental impact on the progression of carotid IMT. In the ARBITER 2 study, males with established vascular disease treated with a statin were treated for 12 months with either niacin 1000 mg or placebo. The addition of niacin to background statin therapy was associated with reduced IMT progression³³. Further open-label administration of niacin 1000 mg to all patients in the ARBITER 3 study demonstrated IMT regression with longer-term duration of niacin treatment³⁴. More recently, the ARBITER-6 HALTS study provided further evidence supporting the incremental benefit of niacin therapy in combination with statin therapy. In patients with vascular disease treated to goal (baseline LDL-C 82 mg/dL), additional treatment with niacin was associated with reduced IMT progression, compared with the addition of ezetimibe. Given that the LDL-C on-treatment was comparable in two groups (66 mg/dL vs. 70 mg/dL with ezetimibe and niacin, respectively), the incremental benefit in the niacin group likely reflected its other properties³⁵. The degree to which raising HDL-C underlies the benefit of niacin on disease progression remains undefined.

Findings from intravascular ultrasound
Intravascular ultrasound (IVUS) generates high-resolution imaging of the entire thickness of the arterial wall by placing a high-frequency ultrasound transducer within the lumen. Visualization of the whole vessel wall permits precise quantitation of the volumetric extent of atherosclerosis within a segment of coronary artery. In the earliest assessment of statin therapy, the German Atorvastatin Investigators Network (GAIN) employed serial IVUS to monitor the effects of open-label atorvastatin in patients randomized to an LDL-C goal of 100 mg/dL or to usual care. Despite lowering LDL-C to 86 mg/dL, there was no benefit in terms of slowing disease progression. In contrast, an increase in echogenicity (proposed to reflect a reduction in lipid content and increase in fibrous content of plaque) in atorvastatin-treated patients was proposed to support a potentially beneficial effect on plaque composition³⁶.

More recently, high-dose statin therapy has shown a beneficial effect on the progression of coronary atherosclerosis with IVUS. The Reversal of Atherosclerosis with Aggressive Lipid Lowering (REVERSAL) study compared intensive (atorvastatin, 80 mg) and moderate (pravastatin, 40 mg) lipid-lowering strategies in patients with angiographic CAD. While an increase in atheroma volume consistent with disease progression was observed in the moderately treated patients (LDL-C 110 mg/dL), no change in disease burden was demonstrated in the intensively treated group (LDL-C 79 mg/dL)³⁷. A direct relationship was observed between the degree of LDL-C lowering and the rate of disease progression, but patients treated with pravastatin required additional lowering of LDL-C to achieve the same impact on disease progression as observed in patients treated with atorvastatin. This finding suggested that atorvastatin’s benefit was likely not due exclusively to its effects on LDL-C.
The greater reduction of CRP with atorvastatin suggested that anti-inflammatory properties might have contributed to the benefit. These findings supported the additive benefit of lowering LDL-C and CRP, underlying the reduc
tion of clinical events with atorvastatin in the Pravastatin or Atorvastatin Evaluation and Infection Therapy (PROVE-IT) study.

A Study to Evaluate the Effect of Rosuvastatin on Intravascular Ultrasound-Derived Coronary Atheroma Burden (ASTEROID) evaluated the impact of treatment with rosuvastatin 40 mg for 24 months on the progression of coronary atherosclerosis. Reduction in LDL-C by 53% to 61 mg/dL, and elevation in HDL-C by 14.7% to 49 mg/dL, was associated with significant reductions in every measure of coronary atherosclerosis, consistent with disease regression. Subsequent analysis of major IVUS studies revealed that there was a direct relationship between the level of LDL-C achieved and the rate of disease progression, with regression observed when LDL-C was less than 70 mg/dL. Quantitative coronary angiography performed in ASTEROID demonstrated significant reductions in the percent diameter stenosis and an increase in minimum lumen diameter in segments containing at least 25% stenosis at baseline, consistent with angiographic regression. Pooled analysis of all major angiographic studies of lipid-modifying therapies revealed reduced progression of obstructive disease at lower levels of LDL-C and higher levels of HDL-C. Several other groups have confirmed the association between statin therapy and slowing of disease progression on IVUS. The Early Statin Treatment in Patients with Acute Coronary Syndrome (ESTABLISH) study compared the effects of atorvastatin (20 mg) and placebo for 6 months in 70 patients following an acute coronary syndrome. A significant reduction in plaque burden by 13.8%, consistent with regression, was observed in a relatively short, but diseased, segment of coronary artery. Similar findings were reported with a 6.3% reduction in plaque burden with treatment with simvastatin 40 mg in 40 Danish men with angiographic disease. In the Coronary Atherosclerosis Study Measuring Effects of Rosuvastatin Using Intravascular Ultrasound in Japanese Subjects (COSMOS), relatively low doses of rosuvastatin, 2.5–20 mg per day, administered for 76 weeks as open-label therapy was associated with a 38.6% reduction in LDL-C, a 19.8% increase in HDL-C, and a 5.1% decrease in plaque burden in 126 Japanese patients with stable CAD.

More recently, pitavastatin – the newest statin to reach clinical practice – has been evaluated with regard to its effect on plaque using IVUS. In the Japan Assessment of Pitavastatin (4 mg per day) and Atorvastatin (20 mg per day) in Acute Coronary Syndrome (JAPAN-ACS), plaque regression was observed with 8–12 months of open-label treatment with either agent in 302 patients undergoing percutaneous coronary intervention for an acute coronary syndrome. Contrast, the TOGETHER trial (Stabilization and Regression of Coronary Plaques Treated With Pitavastatin Proven by Angioscopy and Intravascular Ultrasound) of 52 weeks of treatment with pitavastatin (2 mg), with a 34.5% reduction in LDL-C and a 17.8% increase in HDL-C, did not associate with any reduction in plaque burden, but did result in a reduction in yellow grade observed on angioscopy – suggesting a beneficial effect on plaque composition.

The potential contribution of raising HDL-C to the benefit of statins in slowing disease progression was investigated in a pooled analysis of four clinical trials that employed IVUS. Analysis of 1455 statin-treated patients revealed that lowering LDL-C (by an average of 23.5%) and raising HDL-C (by an average of 7.5%) independently associated with slowed disease progression. Achieving low levels of LDL-C and modest elevations in HDL-C was associated with the greatest degree of disease regression, suggesting an incremental effect of modifying both atherogenic and protective lipid parameters. The strongest predictor of progression in these patients was the change in the ratio of apolipoprotein B/A-I, which is consistent with pathological observations of the relative importance of atherogenic and protective lipid particles in determining propagation of atherosclerotic plaque, and supports evidence from clinical cohorts that the apolipoprotein B/A-I ratio strongly predicts myocardial infarction.

Benefit at the level of the vessel wall with relatively modest changes in HDL-C is consistent with observations that infusing delipidated forms of HDL reduces disease burden. In combination, these studies suggest that a therapeutic strategy targeting both atherogenic and protective lipid parameters may have a greater impact on the amount of plaque in the artery wall.

**Implications of findings from imaging studies**

The clinical relevance of positive findings on imaging studies lies in the premise that the atherosclerotic plaque represents the cause of ischemic events and the need for revascularization. Considerable evidence demonstrates a relationship between plaque burden and outcome. Reports from autopsy series reveal the presence of more extensive atherosclerotic plaque within the coronary arteries in association with sudden cardiac death, compared with individuals who die of non-cardiac causes. Application of coronary angiography and carotid IMT across a large spectrum of cardiovascular risk has demonstrated a relationship between both the extent and progression of disease on imaging and the likelihood of clinical events.

Recent analysis from cohorts studied with IVUS has also demonstrated a relationship between atheroma
burden and outcome. In a small cohort of individuals who underwent serial imaging of the left main coronary artery over an 18-month period, greater plaque progression at the most diseased site was observed in patients who experienced a clinical event. This relationship was observed regardless of the culprit vessel deemed responsible for the event. The relationship between the volumetric extent of plaque on IVUS and outcome has been explored recently. A pooled analysis of six clinical trials, involving more than 4000 patients with coronary disease, showed a direct relationship between both the baseline extent and subsequent progression of plaque and the likelihood of clinical events. Patients who experienced a clinical event demonstrated an increase in percent atheroma volume that was 0.5% greater than individuals who were event free. Reports that therapies to slow disease progression typically reduce event rates in large clinical trials provide further support for the clinical relevance of positive findings on imaging. Nevertheless, the ultimate fate of novel anti-atherosclerotic therapies will be determined by their ability to reduce event rates in large clinical trials.

SATURN protocol

Study rationale and objectives

SATURN (Study of Coronary Atheroma by InTravascular Ultrasound: Effect of Rosuvastatin versus Atorvastatin, NCT00620542) will aim to compare directly the rate of progression of coronary atherosclerosis in patients treated with either rosvastatin 40 mg or atorvastatin 80 mg. Given the effect of altering levels of both LDL-C and HDL-C on disease progression, SATURN will seek to determine whether the greater impact on both these lipid parameters with rosvastatin will translate to a greater benefit at the level of the vessel wall. The primary objective of SATURN is to compare the effects of rosvastatin 40 mg with those of atorvastatin 80 mg on the progression of atherosclerosis in a matched segment of coronary artery following 104 weeks of treatment in patients with coronary disease. The primary efficacy parameter is the change in percent atheroma volume (PAV) measured by IVUS imaging, performed at baseline and at the end of the 104-week treatment period. Secondary end points include the change in total atheroma volume (TAV), on-therapy lipid and lipoprotein values and a safety evaluation, which will include analysis of adverse events and laboratory data. An exploratory objective of SATURN will be to characterize changes in measures of plaque burden and composition as a function of on-therapy values of lipid, lipoprotein, and inflammatory markers. The incidence of major adverse cardiovascular events will also be explored in the total patient cohort as a function of changes in IVUS variables.

Study population

A total of 1385 subjects aged ≥18 years with at least one >20% lumen stenosis in a native epicardial coronary artery, on visual estimation of a clinically indicated coronary angiogram, and meeting the entry criteria (Tables 1 and 2) were randomized in the trial. Randomization of patients occurred between February 2008 and June 2009. The clinical characteristics of patients enrolled in SATURN are summarized in Table 3. In general, the cohort is similar to that of previous clinical trials that employed serial IVUS imaging, in terms of age and predominance of males and whites, with a high prevalence of cardiovascular risk factors and a high rate of use of established medical therapies at baseline. Table 4 summarizes baseline measures of lipid and inflammatory parameters in patients stratified according to use of statins at baseline (defined as within 4 weeks of consent date). In general, LDL-C levels were above the level currently recommended by contemporary treatment guidelines, while average triglyceride and HDL-C levels were within the normal range.

Table 1. Inclusion criteria.

<table>
<thead>
<tr>
<th>Criteria</th>
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<tbody>
<tr>
<td>Men or women, 18 to 75 years of age</td>
</tr>
<tr>
<td>Clinical indication for coronary angiography</td>
</tr>
<tr>
<td>No statin therapy in the past 4 weeks: LDL-C &gt;100 mg/dL</td>
</tr>
<tr>
<td>Statin therapy in the past 4 weeks: LDL-C&lt;80 mg/dL</td>
</tr>
<tr>
<td>Triglycerides &lt;500 mg/dL</td>
</tr>
<tr>
<td>Angiographic evidence of coronary artery disease (at least one lesion &gt;20% reduction in lumen diameter)</td>
</tr>
<tr>
<td>Left main coronary artery with no reduction in lumen diameter &gt;50%</td>
</tr>
<tr>
<td>Target coronary artery for imaging that contains no stenosis ≥50%, has not sustained a myocardial infarction, has not undergone percutaneous coronary intervention or bypass surgery, and is not considered a candidate for intervention</td>
</tr>
</tbody>
</table>

Table 2. Exclusion criteria.

<table>
<thead>
<tr>
<th>Criteria</th>
</tr>
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<tbody>
<tr>
<td>Use of potent lipid-lowering therapy for more than 3 months in the last year (any dose of rosuvastatin; 40–80 mg of atorvastatin; 80 mg of simvastatin; Vitorin; ezetimibe in combination with any statin)</td>
</tr>
<tr>
<td>Use of fibrates, niacin (dose ≥250 mg), or omega-3 fatty acids (dose &gt;1000 mg) for more than 3 months in the last year</td>
</tr>
<tr>
<td>Left ventricular dysfunction (NYHA class III/IV or LVEF &lt;35%)</td>
</tr>
<tr>
<td>Heart disease requiring surgical or percutaneous intervention</td>
</tr>
<tr>
<td>Uncontrolled diabetes (HbA1c &gt;10%)</td>
</tr>
<tr>
<td>Liver disease (ALT, AST, or bilirubin ≥1.5 × ULN)</td>
</tr>
<tr>
<td>Hypothyroidism (TSH ≥10 × ULN)</td>
</tr>
<tr>
<td>Uncontrolled hypertension (systolic pressure ≥160 mmHg or diastolic pressure ≥100 mmHg)</td>
</tr>
<tr>
<td>Nephrotic syndrome or renal dysfunction (serum creatinine ≥2.0 mg/dL)</td>
</tr>
<tr>
<td>Malignancy unless disease free for &gt;5 years</td>
</tr>
<tr>
<td>History of statin hypersensitivity</td>
</tr>
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</table>

ALT, alanine transaminase; AST, aspartate transaminase; HbA1c, glycated hemoglobin; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; TSH, thyroid stimulating hormone; NYHA, New York Heart Association; TSH, thyroid stimulating hormone; ULN, upper limit of normal.
Study design

Study drug administration and visit schedule
After providing informed consent, patients undergoing a clinically indicated coronary angiogram entered a screening period (duration up to 4 weeks). Patients meeting the inclusion criteria were randomized to treatment with either rosuvastatin 20 mg or atorvastatin 40 mg for 2 weeks. After 2 weeks of therapy, blood will be drawn for lipid evaluation. Patients with a LDL-C less than 116 mg/dL and triglycerides less than 500 mg/dL will enter the full dose randomization phase of the study. This run-in phase at half dose was included to insure that patients would be likely to achieve the treatment goal for LDL-C (less than 100 mg/dL) at the highest doses and therefore not require additional lipid lowering therapy beyond statins. At that point, patients underwent further randomization to either rosuvastatin 40 mg or atorvastatin 80 mg for the 104 week treatment period of the study. Use of any lipid modifying agent, except for the study medication, is prohibited during the study.

Patients are seen every 13 weeks for monitoring of adverse events, study drug compliance, concomitant medication use, dietary counseling and collection of blood and urine samples for biochemical and safety analysis. After 104 weeks of treatment with the highest dose of either statin patients return for a repeat IVUS examination in the same coronary artery imaged at baseline and complete the study. Patients who require a clinically indicated coronary angiogram after 78 weeks of treatment are to undergo early repeat IVUS imaging and complete the study at that time. If percutaneous coronary intervention of the target artery is required then IVUS imaging should be performed first, where clinically appropriate.

Acquisition and analysis of intravascular ultrasound imaging
Ultrasonic imaging will be acquired and analyzed in the same manner as applied in previous IVUS studies of atherosclerosis progression. IVUS examinations will be performed in the longest and least angulated coronary artery that contains no lumen stenosis greater than 50% throughout a target segment of at least 40 mm in length, has not undergone revascularization, and was not the culprit vessel responsible for a previous myocardial infarction. The target vessel for imaging had also to be considered unlikely to require revascularization during the course of the study. Following anticoagulation and

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Statin Naive (n = 774)</th>
<th>Statin Treated (n = 611)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total cholesterol (mg/dL)</td>
<td>193.4 (172.1, 218.1)</td>
<td>177.9 (160.3, 204.4)</td>
</tr>
<tr>
<td>HDL-C (mg/dL)</td>
<td>119.9 (103.6, 141.1)</td>
<td>104.4 (91.3, 125.7)</td>
</tr>
<tr>
<td>Triglycerides (mg/dL)</td>
<td>44.5 (37.5, 52.2)</td>
<td>42.5 (36.7, 48.3)</td>
</tr>
<tr>
<td>Apolipoprotein B (mg/dL)</td>
<td>125.8 (92.1, 173.6)</td>
<td>132.0 (94.8, 184.2)</td>
</tr>
<tr>
<td>Apolipoprotein A-I (mg/dL)</td>
<td>125.0 (111.0, 142.0)</td>
<td>122.0 (108.0, 139.0)</td>
</tr>
<tr>
<td>Non-HDL-C (mg/dL)</td>
<td>148.9 (129.5, 173.2)</td>
<td>133.4 (116.4, 157.0)</td>
</tr>
<tr>
<td>Apolipoprotein B/A-I</td>
<td>0.9 (0.7, 1.0)</td>
<td>0.8 (0.7, 1.0)</td>
</tr>
<tr>
<td>Triglyceride/HDL-C</td>
<td>2.8 (1.9, 4.3)</td>
<td>3.2 (2.0, 4.7)</td>
</tr>
<tr>
<td>CRP (mg/L)</td>
<td>1.6 (0.8, 3.7)</td>
<td>1.8 (0.9, 3.9)</td>
</tr>
<tr>
<td>Glucose (mg/dL)</td>
<td>97.2 (88.2, 111.6)</td>
<td>95.4 (88.2, 108.0)</td>
</tr>
<tr>
<td>Systolic blood pressure (mmHg)</td>
<td>130.0 (120.0, 142.0)</td>
<td>130.0 (119.0, 140.0)</td>
</tr>
<tr>
<td>Diastolic blood pressure (mmHg)</td>
<td>80.0 (70.0, 84.0)</td>
<td>77.0 (70.0, 83.0)</td>
</tr>
</tbody>
</table>

Data presented as median (interquartile range).
CRP, C-reactive protein; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol.
administration of intracoronary nitroglycerin (dose, 100–300 μg), the imaging catheter is advanced as distally as possible within the vessel. Patients are imaged with either a 40 MHz Atlantis SR Pro (Boston Scientific Scimed, Inc., Maple Grove, MN, USA) or a 45 MHz Revolution (Volcano Corporation, San Diego, CA, USA) catheter. Continuous images are acquired while the catheter is withdrawn back to the aorta by a motor drive at a constant speed of 0.5 mm per second. Images are burned on DVD and sent to the core laboratory at the Cleveland Clinic for analysis.

Technicians blinded to the treatment status of the patient and the timing of each individual pullback will perform the analysis. A matched arterial segment will be determined for measurement that contains the same proximal and distal side branch. Cross-sectional images, spaced 1 mm apart, will be selected for measurement. The leading edges of the lumen and the external elastic membrane (EEM) will be defined by manual planimetry (Figure 1). In each image, the plaque area will be calculated as the area between the two leading edges. Additional measurements recorded for each image include the maximum and minimum plaque thickness and the degree of calcification.

Two measures of atheroma burden will be calculated for each patient. The percent atheroma volume (PAV) is calculated as the proportion of the EEM volume occupied by atherosclerotic plaque.

\[
\text{Percent Atheroma Volume} = \frac{\sum (\text{EEM}_\text{area} - \text{Lumen}_\text{area})}{\sum \text{EEM}_\text{area}} \times 100
\]

The total atheroma volume (TAV) is calculated as the summation of plaque areas in each measured cross-sectional image within the segment, and subsequently normalized by the median number of images analyzed in the entire cohort to account for heterogeneity in segment length between subjects.

\[
\text{TAV}_\text{Normalized} = \frac{\sum (\text{EEM}_\text{area} - \text{Lumen}_\text{area})}{\text{Number of Images in Pullback}} \times \frac{\text{Median number of images in cohort}}{\text{Number of Images in Pullback}}
\]

This adjustment allows for each subject to be equally represented in the statistical analysis. In addition to absolute changes in measures of atheroma burden, the percentage of subjects that demonstrate plaque regression, defined as any reduction in PAV from baseline, will be calculated.

Sample size determination and statistical analysis

Based on the assumption of a standard deviation for mean nominal change in PAV of 3.0, it was determined that a sample size of 900 subjects would be required to provide 90% power, at a 5% significance level, to demonstrate a difference between the treatment groups of 0.65 in terms of change in PAV. Subjects will be analyzed with a modified intention-to-treat approach, defined as all randomized subjects who received at least one dose of study drug and had evaluable IVUS measurements obtained at baseline and at follow-up. Anticipating that 30% of patients would discontinue from the study or have non-evaluable IVUS imaging at follow-up, approximately 1300 patients were required to achieve a total of 900 patients completing the study.

Potential insights from SATURN

SATURN will represent the largest clinical trial in which serial IVUS imaging will be employed to evaluate the impact of statin therapy on progression of coronary...
atherosclerosis. While the primary objective is to determine whether the highest doses of the two most efficacious statins have a differential effect on disease progression, SATURN may provide a number of additional insights with regard to the effects of statin therapy on atherosclerotic plaque. The relationship between on-treatment levels of lipid, lipoprotein and inflammatory markers with changes in measures of plaque burden and composition will be investigated in the total patient cohort. In addition, while the study lacks statistical power to directly compare cardiovascular event rates in the treatment groups, SATURN will enable characterization of the relationship between systemic and arterial wall factors and clinical outcome in patients with angiographic CAD treated with statins. Accordingly, SATURN will provide additional biological insights into the mechanism of action underlying protection from cardiovascular events observed with statin therapy.

Future directions of imaging studies beyond SATURN

Ongoing technological advances in arterial wall imaging could provide the opportunity to characterize the natural history of disease progression with other imaging modalities. While determination of coronary calcification by computed tomography can predict cardiovascular risk, the finding that intensive lipid lowering has no benefit on slowing progression of calcium in clinical trials and in meta-analyses of preventive therapies suggests that this modality is not likely ideal for evaluating novel anti-atherosclerotic agents. Computed tomography also has been developed to provide a non-invasive angiographic evaluation. While incremental improvements in image resolution have enhanced its ability to visualize the coronary arteries, its strength lies in its negative predictive value, with the ability of a normal study to stratify an intermediate-risk patient to a lower-risk category. Its resolution remains a limiting factor to detect small changes in atheroma burden with the precision required in clinical trials.

Magnetic resonance imaging provides high-resolution images of atherosclerotic plaque in larger arteries (e.g., aorta, carotid artery) and has been increasingly employed to study vascular biology. Early studies have demonstrated that statin therapy reduces the size of bulky lesions on serial evaluation. The additional potential to characterize plaque composition with magnetic resonance imaging could enable further characterization of the impact of medical therapies. High resolution magnetic resonance imaging has demonstrated reduced size of the necrotic core in carotid lesions of patients treated with rosvastatin. Whether the resolution of coronary imaging with magnetic resonance will improve enough to employ it in these clinical trials remains undetermined.

Molecular imaging reflects the ability to visualize specific biological processes or structures within the atherosclerotic plaque implicated in subsequent rupture and precipitation of ischemic events, by use of a range of non-invasive imaging modalities. Its use may provide additional information on the functional activity of plaque. While preliminary reports, primarily in experimental animals, suggest that such an approach may demonstrate benefits of statin therapy on the degree of inflammatory activity within carotid and aortic plaques, these techniques require ongoing development and validation.

While there is considerable interest in the development and potential clinical application of non-invasive imaging modalities, there continues to be significant advances in catheter-based imaging of coronary atherosclerosis from the perspective of plaque composition. Conventional IVUS imaging has limited ability to characterize plaque components other than calcium mineral. Radiofrequency analysis of ultrasound backscatter, however, can distinguish plaque components and potentially could classify various plaque subtypes. Preliminary studies using these approaches demonstrate that statin therapy has favorable effects on the amount of fibrous and lipid components within atherosclerotic plaque, confirming histological observations on carotid endarterectomy specimens and abundant experimental studies. The ability to determine the amount of lipid in the vessel wall with near-infrared (NIR) spectroscopy, and to quantify the thickness of the fibrous cap with optical coherence tomography (OCT), also may provide complimentary information on the efficacy of new therapies.

Conclusion

Intravascular ultrasound has provided important insights into the effects of statin therapy on the natural history of progression of coronary atherosclerosis. Early clinical studies have demonstrated that the combination of intensive lowering of LDL-C and relatively modest elevations in levels of HDL-C likely has an incremental effect on the amount of disease within the arterial wall. SATURN will seek to explore if differences in the level and ratio of atherogenic and protective lipid parameters with two of the most efficacious statins currently employed in clinical practice will have a differential effect on the pathological substrate of cardiovascular events.

Transparency

Declaration of funding

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Declaration of financial/other interest

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