Another Telescope for Examining Statins: the SATURN Trial

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STUDY

SUMMARY
Objective. The purpose of the Study of Coronary Atheroma by Intravascular Ultrasound: Effect of Rosuvastatin Versus Atorvastatin (SATURN) trial was to compare the effects of two intensive statin regimens on the progression of coronary atherosclerosis and to assess their safety and side-effect profiles.

Design. Serial intravascular ultrasonography was performed in 1,039 patients with coronary disease at baseline and after 104 weeks of treatment with either atorvastatin, 80 mg daily, or rosuvastatin, 40 mg daily. The primary efficacy endpoint was percent atheroma volume (PAV) and the secondary efficacy endpoint was total atheroma volume (TAV).

Results. At the end of 104 weeks of therapy, the rosuvastatin group had lower LDL cholesterol levels (62.6 vs. 70.2 mg/dl, P < 0.001) and higher HDL cholesterol levels (50.4 vs. 48.6 mg/dl, P = 0.01) than the atorvastatin group. The two regimens had a similar degree of regression of PAV, and rosuvastatin had a more favorable effect on TAV. Both agents induced regression in the majority of patients: 63.2% with atorvastatin and 68.6% 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.

Conclusion. Maximal doses of either rosuvastatin or atorvastatin resulted in significant regression of coronary atherosclerosis. Although rosuvastatin therapy resulted in lower LDL and higher HDL cholesterol levels than atorvastatin therapy, the two regimens brought about a similar degree of regression of PAV.

COMMENTARY
Before specifically commenting on the SATURN trial, it is important to briefly review the pathophysiology and intravascular ultrasound (IVUS) study of atherosclerosis. As humans age, the development of atherosclerosis is almost inevitable. However, the rate of its progression is highly variable and dependent on multiple other factors, including, but not limited to, genetic predisposition, environmental effects, and other individual cardiovascular risk factors (e.g., diabetes, hypertension, and dyslipidemia).

A chronic disease, atherosclerosis can remain asymptomatic for decades, but with time, lesions can silently evolve from stable to unstable (or vulnerable) plaque, predisposing to plaque rupture, which results in clinical vascular events. Stable atherosclerotic lesions in asymptomatic patients have increased amounts of extracellular matrix and smooth muscle cells, whereas unstable, vulnerable plaques have increased numbers of macrophages (inflammatory elements) and foam cells within a thin fibrous cap. These cells link hyperlipidemia and the pathogenesis of atherosclerosis because macrophages ingest elevated levels of oxidized lipoproteins, which accumulate within the vessel wall and subsequently within foam cells, leading to the formation of gross fatty streaks in the vessel wall.

The development of IVUS has been crucial to better visualization and analysis of atheroma formation and progression, as well as to understanding the benefits of lifestyle and pharmacological interventions on atherosclerosis. Although IVUS cannot separate plaque from media at the internal elastic membrane because of the limits of its resolution (170 μm), areas of plaque plus media together with external elastic membrane are accepted for measurement of atheroma (Figure 1).

IVUS studies have identified a decrease in adaptive remodeling of atheroma in patients with diabetes compared to those without diabetes. Moreover, pathology at autopsy has also demonstrated that, compared to patients without diabetes, those with type 2 diabetes have a significant increase in coronary plaque area and distal plaque burden. Overall, IVUS improves our characterization of atherosclerotic plaque formation and response to risk factor modification and pharmacological treatments.
The SATURN trial (sponsored by AstraZeneca Pharmaceuticals) compared the effect of maximum daily doses of atorvastatin (80 mg) to rosuvastatin (40 mg) on PAV (determined through IVUS) at 104 weeks, peaking interest in not only plaque regression, but also the biochemical effects and safety of high-dose statin regimens. In this prospective, randomized, double-blind trial, ~70% of the patients had hypertension, and 15% had diabetes with an average BMI of 29 kg/m², average HDL cholesterol of 45 mg/dl, and median fasting glucose of 97 mg/dl. Not far from meeting criteria for metabolic syndrome, the trial population typifies a growing U.S. population at risk for obesity and cardiometabolic syndrome.

The study investigators report that both regimens resulted in significant reductions in atheroma volume in >60% of patients and in LDL cholesterol levels ≤70 mg/dl in most patients. Additionally, both groups demonstrated an increase in HDL cholesterol, although the increase was slightly greater with rosuvastatin (45.3–50.4 mg/dl compared to 44.7–48.6 mg/dl with atorvastatin, \(P = 0.01\)). Interestingly, patients in both treatment arms also had a concomitant decrease in C-reactive protein and apolipoprotein B levels. Although many of the primary and secondary endpoint results are statistically significant for high-dose statin therapy, the clinical relevance and benefit of atheroma regression and the aforementioned numerical reductions remain unclear.

This study was not designed to assess hard clinical endpoints (e.g., mortality or myocardial infarction [MI]). However, it was still plagued by weaknesses inherent to IVUS-based trials. As mentioned earlier, the limits of resolution prevent better morphological analysis and characterization of plaque. More importantly, there are few clinical data directly linking changes in atheroma by IVUS to alterations in medical therapy and clinical outcomes. Although the SATURN study reports TAV as one surrogate marker of atherosclerosis, the Glagov phenomenon (positive remodeling) may also play a role in progression of atherosclerosis. The coronary artery remodels to accommodate plaque without affecting lumen size, allowing for delay in functionally important luminal stenosis until lesions occupy 40% of the internal elastic lamina area (Figure 2).

Statins have demonstrated a beneficial change in remodeling of the coronary artery. In patients with diabetes, the adaptive positive remodeling often fails, and it remains uncertain whether statin therapy can offset this failure and result in improved clinical outcomes.

As described earlier, atherogenesis is an intricate, multi-step process involving a variety of cell types and biochemical pathways. Statins reduce LDL particle numbers, thereby reducing lipid loading of macrophages (which form the necrotic core) and oxidative stress, ultimately leading to reductions in atheroma volume and stabilization...
of the vulnerable plaque, possibly by increasing fibrous cap thickness.17,18 Thin-cap fibroatheroma, plaque burden > 70%, and increased necrotic core have been additionally identified as independent predictors for future cardiovascular events (among other factors) in nonobstructive coronary lesions (Figure 3).19 However, the vulnerable plaque is subject to a host of genetic factors, wall stress, and vulnerable hematological variables, including glucose, other lipids, and inflammatory and prothrombotic factors.20 These other factors are clinically important to the evaluation of soft plaque because clinical data suggest that only 14% of MIs occur from artery closure at plaques initially producing stenosis of ≥75% before rupture and closure.21,22

In addition to atheroma volume and hematological factors, the associated endothelium plays a crucial role in atherosclerosis as an intermediary between the necrotic core of vulnerable plaque, blood products, wall stress, and cellular signaling pathways for acute and chronic endovascular changes. At the most basic level, endothelial dysfunction and nitric oxide production are associated with oxidative stress, which is a major source of atherogenesis.3

Ultimately, statins have demonstrated significant reduction in clinical events and remain one of the best therapies in combating coronary artery disease. However, at best, this class has only reduced the absolute risk of cardiovascular events by 1–2% in primary and 4–5% in secondary prevention trials. Even with current medical therapy, > 70% of cardiovascular events are not prevented with statin therapy.23–28 Clearly, statin therapy plays a role in medical therapy for atherogenesis. However, overall event rates suggest that multiple other factors discussed above are potential therapeutic targets that also warrant further investigation.

Finally, the SATURN trial provided a unique insight regarding the safety of high-dose statin regimens, which is of particular relevance after the recent U.S. Food and Drug Administration warning to limit the use of high-dose simvastatin because of the risk of myopathy.29 In a recent retrospective, pooled analysis of >14,000 patients treated with varying doses of atorvastatin,30 there was no evidence of a relationship between the dose of atorvastatin and the incidence of myopathy. The overall safety profiles of low- (10 mg) and high-dose (80 mg) atorvastatin were similar.30 Early data from phase III studies of high-dose rosuvastatin (40–80 mg) have raised concerns about increased dose-dependent proteinuria not readily evident with other statins.31

Although the SATURN trial was not designed or powered to detect differences in adverse events, the results were notable for slightly more frequent elevations in liver enzyme and creatine kinase levels in the atorvastatin group and more frequent proteinuria in the rosuvastatin group. Overall, adverse events were reassuringly infrequent and similar in both groups. However, the lack of an adequate comparator (low-dose regimens) and power in the analysis means that further study is needed.

In conclusion, the SATURN trial expands current knowledge of the morphological impact of high-dose statin therapy on atheroma volume by IVUS, while highlighting the call for better correlation between clinical, imaging, and biomarker endpoints and the need to resolve concerns surrounding high-dose statin therapy.
Figure 3. Multiple plaque characteristics are predictive of risk for future cardiovascular events (up to 22% in plaques with large atheroma volume and increased necrotic core). Statins have demonstrated reduction in atheroma volume and increase in fibrous cap thickness.18-19

REFERENCES


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