

## SATURN Study

By **Genevieve Salman, PharmD; Michael E. Stuart, MD; and Sheri A. Strite**

### Introduction

The Study of Coronary Atheroma by Intravascular Ultrasound: Effect of Rosuvastatin versus Atorvastatin (SATURN) was a prospective, randomized, multicenter, double-blind clinical trial. The study analyzed the intravascular ultrasonography of 1039 patients with coronary artery disease at baseline and then after 104 weeks of either taking atorvastatin 80 mg daily or rosuvastatin 40 mg daily. The study was sponsored by AstraZeneca, the manufacturer of rosuvastatin.

### Results

Percent atheroma volume (PAV), which was the primary efficacy point of the study, was decreased by a statistically non-significant amount in the rosuvastatin group as compared to the atorvastatin group (1.22 percent versus 0.99,  $P=0.17$ ). The secondary efficacy point, normalized total atheroma volume (TAV), also had a more statistically significant decrease in the rosuvastatin group compared to the atorvastatin group ( $-6.39 \text{ mm}^3$  versus  $-4.42 \text{ mm}^3$ ,  $P=0.01$ ). However,

in terms of the clinical application, cardiovascular events were the same for both groups. In addition, the rosuvastatin group had a higher incidence of proteinuria (3.8 percent vs. 1.7 percent).

### Conclusion

Although SATURN found that rosuvastatin decreased the primary and secondary endpoints, PAV and TAV to a greater extent than atorvastatin, the number of cardiovascular events was similar

Element	Criteria	Comments
Study Design Assessment	<p>Is the design appropriate to the research question? Is the research question useful?</p> <ul style="list-style-type: none"> <li>For efficacy, use of experimental study design (meaning study subjects and others were not allowed choice in determining interventions)</li> <li>Clinically significant area for study (morbidity, mortality, symptom relief, functioning and health-related quality of life) and reasonable definitions for clinical outcome such as response, treatment success or failure</li> <li>If composite endpoints used, reasonable combination used - and used for safety if used for efficacy</li> </ul>	<p>The purpose and design of the SATURN, a prospective, randomized, double-blinded, was appropriate and useful, as cardiovascular events are a leading cause of death in the United States. Although the study reported that the patients taking rosuvastatin 40 mg resulted in lower percent atheroma volume (PAV) and normalized total atheroma volume (TAV) than the patients taking atorvastatin 80 mg, the clinical outcome, number of cardiovascular events, were similar in both groups.</p>
Internal Validity Assessment	<p>Can bias, confounding or chance explain the study results?</p> <ul style="list-style-type: none"> <li>Ensure prespecified and appropriate 1) research questions, 2) populations to analyze, 3) outcomes, 4) group assignment methods, 5) study conduct methods, 6) analysis methods, and 7) level for statistical significance</li> </ul>	<p>1578 participants were present at the start of the trial, and only 1039 participant (65.8%) remained. An explanation as to why these participants did not complete the trial was not given.</p>
Selection Bias	<ul style="list-style-type: none"> <li>Groups are appropriate for study, of appropriate size, concurrent and similar in prognostic variables</li> <li>Methods for generating the group assignment sequence are truly random, sequencing avoids potential for anyone affecting assignment to a study arm and randomization remains intact</li> <li>Concealment of allocation strategies are employed to prevent anyone affecting assignment to a study arm</li> </ul>	<p>Baseline characteristics differ in terms number of patients with diabetes, current smoking, prior MI, prior PCI, and prior history of statin use. During the preliminary randomization, when patients were started at a lower dose of the respective statin, the concealment of allocation was achieved via an interactive voice system. However, the generation of the randomization sequence was not mentioned. During the second phase of the trial, when patients were instructed to take the maximum dose of the respective statin, the details regarding the concealment of allocation of the randomization sequence was not mentioned.</p>
Performance Bias	<p>Double-blinding methods employed (i.e., subject and all working with the subject or subject's data) and achieved Reasonable intervention and reasonable comparator used (e.g., placebo)</p> <p>No bias or difference, except for what is under study, between groups during course of study (e.g., intervention design and execution, co-interventions, concomitant medication use, adherence, inappropriate exposure or migration, cross-over threats, protocol deviations, measurement methods, study duration, etc.)</p>	<p>Although the study claimed to use double-blinded methods, the process was not explained in detail. Thus, the claim of the study being double-blinded is unclear. In particular, the study did not provide information regarding how the clinicians were blinded.</p> <p>The study did mention that use of any lipid-lowering medication was prohibited during the study.</p> <p>Since rosuvastatin 40 mg is inherently more potent than atorvastatin 80 mg, the comparison is biased toward rosuvastatin having the more lipid lowering effects. Also, although the study mentioned that patient adherence to the medication was assessed, the process by which this was done was not mentioned.</p>

Attrition Bias	Zero or minimal missing data points or loss from randomization (e.g., approximately 5% with differential loss, or approximately 10% without differential loss) unless good ITT analysis (see ITT below)	1578 participants were present at the start of the trial, and only 1039 participant (65.8%) remained. However, the authors did state that the patients remaining at the end of the trial did not differ in terms of their baseline characteristics.
Assessment Bias	Assessors are blinded	According to the study, a clinical events committee was designated to adjudicate cardiovascular events at a central location. This committee did not also did not know the treatment assignments of the patients. The data pertaining to the 34.2% of the patients that did not complete the study was not accounted for.
	Low likelihood of findings due to chance, false positive and false negative outcomes (judgment call on statistical significance, including confidence intervals)	
	Non-significant findings are reported, but the confidence intervals include clinically meaningful differences	
	Intention-to-Treat Analysis (ITT) performed (all people are analyzed as randomized + reasonable method for imputing missing values which puts the intervention through a challenging trial or reasonable sensitivity analysis)	
	Use of modeling only with use of reasonable assumptions	
Usefulness Assessment	Clinically significant area + sufficient benefit size = meaningful clinical benefit (consider efficacy vs effectiveness)	See conclusion.
External Validity	How likely are research results to be realized in the real world considering population and circumstances for care?	Rosuvastatin 40 mg is not as commonly prescribed. Therefore, clinical relevance of this study may not be as significant. Further, the study excluded patients with certain co-morbid conditions such as left ventricular dysfunction, heart disease requiring surgical intervention, and uncontrolled hypertension. These patients may be more at risk for cardiovascular conditions, which makes clinical applicability unclear. Also, the study mentioned that rosuvastatin resulted in higher rates of proteinuria. Proteinuria itself is associated with increased cardiovascular events, which may counteract the beneficial effects of rosuvastatin.
	Review n, inclusions, exclusions, baseline characteristics and intervention methods ? this is a judgment call.	
Patient Perspective	Consider benefits, harms, risks, costs, uncertainties, alternatives, applicability to which patients, adherence issues, potential for abuse, dependency issues and patient satisfaction	The clinical outcome of using either medication, rosuvastatin or atorvastatin, was similar in terms of cardiovascular events. However, the rosuvastatin had a higher incidence of proteinuria, and this adverse effect might impact renal patients especially.
Provider Perspective	Satisfaction, acceptability, likely appropriate application and actionability (e.g., FDA approval, affordability, external relevance, circumstances of care, able to apply, tools available)	Due to the limitations described above and the lack of clinical application, this study does not provide ample evidence that rosuvastatin is more efficacious than atorvastatin in terms of reducing cardiovascular effects.

\*Chart taken from the DelfiniGroup,LLC. Short Critical Appraisal Checklist: Updated 02/19/08  
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in both groups. Also, a significant number of the patients in SATURN (34.2 percent) were unaccounted for, making the results presented unreliable. The rosuvastatin group also had higher number of patients with proteinuria, and proteinuria itself can lead to cardiovascular complications.

### Overall Grade: B-U

Study quality is such that it appears likely that the evidence is sufficient to use in making health care decisions. However, there are some study issues that raise continued uncertainty. Health care decision-

makers should be fully informed of the evidence quality

### Delfini Comment

The SATURN trial as noted in the above critique contains significant threats to validity. But even if it didn't, it would be very difficult to determine how to apply the study findings to patient care. The primary endpoint of percent atheroma volume as measured by intravascular ultrasound was not significantly different in the two drugs. Useful information would require huge, long-term trials reporting differences in cardiovascular outcomes such as myocardial infarction

and mortality. This is an example of a clinical trial that provides difficult-to-use surrogate outcome information. Comparing drugs with different lipid-lowering potencies is problematic when lipid-lowering is one of the outcomes. Another difficult-to-interpret safety signal was the higher incidence of proteinuria in the rosuvastatin group (3.8%, vs. 1.7% with atorvastatin; P = 0.02). In summary, the SATURN trial reports intermediate marker results that are difficult to interpret and weakened by threats to both internal and external validity. The likely result of this trial is to add additional time for healthcare professionals to try and

explain what these findings mean to themselves, their patients and their colleagues.

### About the Authors

Genevieve Salman, PharmD is a clinical pharmacist on Surgery Unit at Riverside County Regional Medical Center. Michael E. Stuart, MD and Sheri A. Strite of Delfini Group are

experts at systematic literature reviews. The chart template is adapted from "Delfini Group, LLC, Short Critical Appraisal Checklist: U."

### References

1. Nicholls SJ, Ballantyne CM, Barter PJ, Chapman MJ, Erbel RM, Libby P, Raichlen JS, Uno K, Borgman M, Wolski K, and Nissen SE. "Effects of two intensive statin

regimens on progression of coronary disease." *The New England Journal of Medicine*. 365;22(2011): 2078-2087.

2. Nicholls SJ, Borgman M, Nissen SE, et al. "Impact of statins on progression of atherosclerosis: rationale and design of SATURN (Study of Coronary Atheroma by Intravascular Ultrasound Effect of Rosuvastatin versus Atorvastatin)". *Current Medical Research & Opinion*. 27;6(2011):1119-29.

## Delfini Evidence Grading Scale

### Grade A Evidence: Useful

The evidence appears strong and sufficient to use in making health care decisions - no significant threats to validity were ascertained.

### Grade B Evidence: Possibly Useful

The evidence appears potentially strong and is probably sufficient to use in making health care decisions - some threats to validity were identified

### Grade B-U Evidence: Possible to uncertain usefulness

The evidence might be sufficient to use in making health care decisions; however, there remains sufficient uncertainty that the evidence cannot fully reach a Grade B and the uncertainty is not great enough to fully warrant a Grade U. Health care decision-makers should be fully informed of the evidence quality.

### Grade U Evidence: Uncertain

There is sufficient uncertainty that caution is urged regarding its use in making health care decisions. Delfini does not use such information to inform clinical decisions regarding efficacy.



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