



Sex-Related Differences of Coronary Atherosclerosis Regression Following Maximally Intensive Statin Therapy

Insights From SATURN

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ABSTRACT

OBJECTIVES The study sought to explore sex-related differences in coronary atheroma regression following high-intensity statin therapy.

BACKGROUND Guidelines now recommend high-intensity statins in all individuals with atherosclerotic cardiovascular disease.

METHODS SATURN (Study of Coronary Atheroma by Intravascular Ultrasound: Effect of Rosuvastatin Versus Atorvastatin) employed serial intravascular ultrasound measures of coronary atheroma volume in patients treated with rosuvastatin 40 mg or atorvastatin 80 mg for 24 months. The treatment groups did not differ significantly in change from baseline of percent atheroma volume (PAV) or total atheroma volume (TAV) on intravascular ultrasound, nor in safety or clinical outcomes.

RESULTS Compared with men (n = 765), women (n = 274) were older (p < 0.001) and more likely to have hypertension (p < 0.001), diabetes (p = 0.002), and higher low-density lipoprotein cholesterol (LDL-C) (p = 0.01), high-density lipoprotein cholesterol (p < 0.001), and C-reactive protein (CRP) (p = 0.004) levels. At follow-up, women had higher high-density lipoprotein cholesterol (p < 0.001) and CRP (p < 0.001), but similar LDL-C (p = 0.46) levels compared with men. Compared with men, women had lower baseline PAV (34.0 ± 8.0% vs. 37.2 ± 8.2%, p < 0.001) and TAV (122.4 ± 55 mm³ vs. 151.9 ± 63 mm³, p < 0.001), yet demonstrated greater PAV regression (-1.52 ± 0.18% vs. -1.07 ± 0.10%, p = 0.03) and TAV regression (-8.27 ± 0.9 mm³ vs. -6.59 ± 0.50 mm³, p = 0.11) following treatment. Greater PAV regression in women versus men occurred with rosuvastatin (p = 0.004), those with diabetes (p = 0.01), stable coronary disease (p = 0.01), higher baseline LDL-C (p = 0.02), and higher CRP (p = 0.04) levels. On multivariable analysis, female sex was independently associated with PAV regression (p = 0.01), and a sex-treatment interaction was found (p = 0.036). For participants with on-treatment LDL-C levels <70 mg/dl, women achieved greater PAV regression (-1.81 ± 0.22% vs. -1.12 ± 0.13%, p = 0.007) and TAV regression (-10.1 ± 1.1 mm³ vs. -7.16 ± 0.65 mm³, p = 0.023) than men, whereas PAV and TAV regression did not differ by sex, with LDL-C levels ≥70 mg/dl.

CONCLUSIONS Women with coronary disease demonstrate greater coronary atheroma regression than men when empirically prescribed guideline-driven potent statin therapy. This benefit appears in the setting of lower on-treatment LDL-C levels. (CRESTOR Athero Imaging Head to Head IVUS Study [SATURN]; [NCT000620542](https://doi.org/10.1016/j.jcmg.2014.04.019)) (J Am Coll Cardiol Img 2014;7:1013-22) © 2014 by the American College of Cardiology Foundation.

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ABBREVIATIONS AND ACRONYMS

CRP = C-reactive protein

EEM = external elastic membrane

IVUS = intravascular ultrasound

HDL-C = high-density lipoprotein cholesterol

LDL-C = low-density lipoprotein cholesterol

PAV = percent atheroma volume

TAV = total atheroma volume

Over the course of the last 2 decades, randomized clinical trials and meta-analyses demonstrated the unequivocal benefits of statin-mediated cholesterol lowering in the prevention of cardiovascular events (1-3). Recent guidelines have shifted emphasis away from targeting specific low-density lipoprotein cholesterol (LDL-C) goals, and now endorse the broad use of high-intensity statins in all individuals with atherosclerotic cardiovascular disease (4). Despite the enrollment of both sexes in clinical trials employing statins, the anti-atherosclerotic effects of high-intensity statins

in women compared with men remains relatively unexplored. Moreover, some continue to question the merits of statins in women (5,6), particularly in the primary preventative setting. Much of this controversy stems from the consistent under-representation of women in randomized clinical trials (7). Although

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cardiovascular events are a leading cause of death in women, debate regarding the benefits of statins, in addition to other therapeutic strategies, may contribute to a sex disparity in the implementation of evidence-based strategies for the treatment of cardiovascular disease (8,9).

Intravascular ultrasound (IVUS) enabled characterization of factors promoting coronary atheroma

progression and for quantifying the ability of antiatherosclerotic strategies to slow disease progression. Although high doses of potent statins can regress coronary atheroma (10,11), and lower clinical event rates (12,13), there are currently no reports of differential sex-related effects of high-intensity statin therapy. The SATURN (Study of Coronary Atheroma by Intravascular Ultrasound: Effect of Rosuvastatin Versus Atorvastatin) study was a randomized controlled trial employing serial IVUS to evaluate the antiatherosclerotic efficacy of rosuvastatin and atorvastatin, each prescribed at their highest approved doses during a 24-month study period (11). By performing a post-hoc subgroup analysis of the SATURN study, we tested the hypothesis that there would be sex-specific variations in the effects of maximally intensive statin therapy on coronary atheroma progression.

METHODS

PATIENT SELECTION. The design of the SATURN study has been previously described (14). 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

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imaging of a coronary artery at baseline and after 104 weeks of treatment.

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 eligibility. IVUS was performed at baseline in a single, native coronary artery with no lumen stenosis of $\geq 50\%$ angiographic diameter stenosis severity, 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 of the Cleveland Clinic Coordinating Center for Clinical Research for quality, and patients whose baseline imaging met these requirements were eligible for randomization. Following 104 weeks of treatment, patients underwent a second IVUS of the same artery. Anatomically-matched arterial segments were selected for analysis on the basis of proximal and distal landmarks. 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. Percent atheroma volume (PAV) (a measure of plaque burden representing the percent of the EEM volume occupied by atheroma), the primary efficacy endpoint in the SATURN study, was calculated as previously described (15). Total atheroma volume (TAV) (simply the gross volume of atheroma normalized for length), the secondary efficacy endpoint in the SATURN study, was also calculated as previously described (15). Change in plaque burden was calculated as the PAV (or TAV) at 104 weeks minus the corresponding PAV (or TAV) at baseline. Plaque regression was defined as any decrease in PAV (or TAV) from baseline. The post-hoc analyses presented here pooled results from both treatment groups, as in the SATURN study, rosuvastatin and atorvastatin did not differ in the primary efficacy endpoint of the change in PAV from baseline.

STATISTICAL ANALYSES. Continuous variables were reported as mean \pm SD if normally distributed and as median (interquartile range) if not normally distributed. Demographics, baseline clinical characteristics, follow-up medications, laboratory biochemical data, and baseline IVUS parameters were compared between men and women. 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. Serial changes in IVUS measurements were analyzed by an analysis of variance adjusting for their baseline counterparts and were reported as least-squares mean \pm SE. Given the apparent sex-related differences of change in PAV, subgroup analyses were performed to analyze effects of various clinical characteristic subgroups as well as their interaction effects with sex upon change in PAV. Because the treatment showed a significant interaction effect with sex, a 2-way analysis of variance was performed to assess for a sex by treatment effect upon change in PAV adjusting for covariates. To identify covariates, a bootstrap resampling (1,000 iterations and a *p* value criterion of 0.05 for retention) was undertaken for demographic and clinical characteristics. Those variables having at least a 40% 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 model. The same multivariable model selection procedure was repeated for changes in TAV. Furthermore, the relationships between change in PAV and average (on-treatment) LDL-C and between change in TAV and average (on-treatment) LDL-C, were compared between sexes using local regression via the LOESS (Locally Weighted Scatter plot Smoothing) method. A 2-sided *p* value of 0.05 was considered statistically significant. All analyses were performed using SAS software version 9.2 (SAS Institute, Cary, North Carolina).

TABLE 1 Demographics, Baseline Characteristics, and Concomitant Medications

	Total (N = 1,039)	Women (n = 274)	Men (n = 765)	p Value
Age, yrs	57.6 \pm 8.6	59.2 \pm 8.5	57.1 \pm 8.5	<0.001
Body mass index, kg/m ²	29.0 \pm 5.2	29.4 \pm 5.9	28.9 \pm 5.0	0.66
Previous MI	254 (24.4)	50 (18.2)	204 (26.7)	0.005
Hypertension	731 (70.4)	220 (80.3)	511 (66.8)	<0.001
Diabetes mellitus	159 (15.3)	58 (21.2)	101 (13.2)	0.002
Current smoker	336 (32.3)	89 (32.5)	247 (32.3)	0.95
ACS at presentation	361 (34.7)	82 (29.9)	279 (36.5)	0.051
Rosuvastatin	520 (50.0)	141 (51.5)	379 (49.5)	0.59
Aspirin	638 (61.4)	153 (55.8)	485 (63.4)	0.03
Beta-blockers	632 (60.8)	152 (55.5)	480 (62.7)	0.03
ACE inhibitors	457 (44.0)	111 (40.5)	346 (45.2)	0.18
Angiotensin receptor blocker	170 (16.4)	54 (19.7)	116 (15.2)	0.08
Nitrates	859 (82.7)	215 (78.5)	644 (84.2)	0.03

Values are mean \pm SD, median (interquartile range), or n (%). All medications listed are concomitant.
 ACE = angiotensin-converting enzyme inhibitor; ACS = acute coronary syndrome; MI = myocardial infarction.

RESULTS

PATIENT CHARACTERISTICS. Table 1 presents baseline demographics, clinical characteristics, and concomitant medications in men (n = 765) and

women (n = 274). Compared with men, women were older (59.2 ± 9.0 years of age vs. 57.1 ± 9.0 years of age, p < 0.001), more likely to be hypertensive (80.3% vs. 66.8%, p < 0.001) or diabetic (21.2% vs. 13.2%, p = 0.002), and less likely to have had a prior myocardial infarction (18.2% vs. 26.7%, p = 0.005) or receive concomitant aspirin (55.8% vs. 63.4%, p = 0.03), beta-blocker (55.5% vs. 62.7%, p = 0.03), or nitrate therapy (78.5% vs. 84.2%, p = 0.03).

LABORATORY MEASUREMENTS. Table 2 describes baseline, follow-up, and changes of biochemical measurements. At baseline, compared with men, women had higher LDL-C (123.8 ± 31 mg/dl vs. 118.6 ± 27 mg/dl, p = 0.01), high-density lipoprotein cholesterol (HDL-C) (49.9 ± 12 mg/dl vs. 43.2 ± 10 mg/dl, p < 0.001), apolipoprotein (Apo) A-1 (137.6 ± 27 mg/dl vs. 123.4 ± 22 mg/dl, p < 0.001), and C-reactive protein (CRP) (1.8 [IQR: 1.0 to 4.1] mg/l vs. 1.5 [IQR: 0.8 to 3.3] mg/l, p = 0.004) levels, but a lower ApoB:A-1 ratio (0.81 ± 0.23 vs. 0.87 ± 0.24, p < 0.001). Following study treatment, LDL-C levels became similar across both sexes (66.8 ± 24 mg/dl vs. 65.1 ± 22 mg/dl, p = 0.46), but women continued to demonstrate higher HDL-C (54.3 ± 12 mg/dl vs. 47.6 ± 11 mg/dl, p < 0.001), ApoA-1 (152.0 ± 23 mg/dl vs. 138.3 ± 22 mg/dl, p < 0.001), and CRP (1.3 [IQR: 0.7 to 3.2] mg/l vs. 1.0 [IQR: 0.5 to 2.0] mg/l, p < 0.001) levels, but a lower ApoB:A-1 ratio (0.51 ± 0.17 vs. 0.54 ± 0.16, p = 0.001) compared with their male counterparts.

UNIVARIATE SEX-RELATED DIFFERENCES OF BASELINE AND CHANGE IN ULTRASONIC PARAMETERS. Table 3 describes the baseline and change of IVUS measurements. Compared with men at baseline, women had lower plaque burden (PAV: 34.0 ± 8% vs. 37.2 ± 8.2%, p < 0.001; TAV: 122.4 ± 55.2 mm³ vs. 151.9 ± 62.8 mm³, p < 0.001) and smaller lumen (231.0 ± 74 mm³ vs. 254.5 ± 93 mm³, p = 0.001) and EEM (353.4 ± 116 mm³ vs. 406.4 ± 140 mm³, p < 0.001) volumes. However, women demonstrated greater PAV regression than men (-1.52 ± 0.18% vs. -1.07 ± 0.10%, p < 0.001). TAV regression did not significantly differ between women and men (-8.27 ± 0.90 mm³ vs. -6.59 ± 0.53 mm³, p = 0.11). There were no sex-related differences for changes in lumen (0.74 ± 1.8 mm³ vs. 1.04 ± 1.1 mm³, p = 0.89) or EEM (-7.01 ± 2.28 mm³ vs. -5.74 ± 1.35 mm³, p = 0.63) volumes.

FACTORS ASSOCIATED WITH CHANGES IN CORONARY PLAQUE BURDEN. Given the significant univariate PAV regression in favor of women compared with men, Table 4 summarizes factors associated with sex-related differences of changes in PAV. Compared with men, women demonstrated

TABLE 2 Laboratory Findings

	Total (N = 1,039)	Women (n = 274)	Men (n = 765)	p Value
Baseline				
LDL-C	120.0 ± 28.1	123.8 ± 30.6	118.6 ± 27.0	0.01
HDL-C	45.0 ± 11.3	49.9 ± 12.1	43.2 ± 10.4	<0.001
Non-HDL-C	148.7 ± 33.1	152.6 ± 35.5	147.3 ± 32.1	0.02
Triglycerides	129 (94 to 180)	134 (100 to 167)	128 (92 to 182)	0.55
ApoB	105.1 ± 21.4	107.2 ± 23.5	104.4 ± 20.6	0.07
ApoA-1	127.1 ± 24.3	137.6 ± 26.9	123.4 ± 22.1	<0.001
ApoB:A-1	0.86 ± 0.24	0.81 ± 0.23	0.87 ± 0.24	<0.001
CRP	1.6 (0.8 to 3.5)	1.8 (1.0 to 4.1)	1.5 (0.8 to 3.3)	0.004
Follow-up*				
LDL-C	65.6 ± 22.6	66.8 ± 24.8	65.1 ± 21.8	0.46
HDL-C	49.3 ± 11.9	54.3 ± 11.9	47.6 ± 11.3	<0.001
Non-HDL-C	91.0 ± 25.9	92.4 ± 27.2	90.5 ± 25.3	0.27
Triglycerides	114.6 (89.5 to 154.3)	118.3 (92.9 to 154.7)	113.3 (87.7 to 154.3)	0.23
ApoB	73.7 ± 18.8	75.4 ± 21.1	73.1 ± 17.9	0.25
ApoA-1	141.9 ± 23.1	152.0 ± 22.6	138.3 ± 22.1	<0.001
ApoB:A-1	0.53 ± 0.16	0.51 ± 0.17	0.54 ± 0.16	0.001
CRP	1.0 (0.5 to 2.2)	1.3 (0.7 to 3.2)	1.0 (0.5 to 2.0)	<0.001
Change from baseline				
LDL-C				
Mean	-54.4 ± 30.1	-56.8 ± 32.8	-53.5 ± 29.1	0.12
% change	-43.7 ± 19.7	-44.0 ± 20.4	-43.6 ± 19.4	0.51
HDL-C				
Mean	4.3 ± 7.7	4.3 ± 8.6	4.4 ± 7.4	0.84
% change	11.3 ± 18.3	10.6 ± 18.6	11.6 ± 18.2	0.26
Non-HDL-C				
Mean	-57.8 ± 34.0	-60.2 ± 36.9	-56.9 ± 32.9	0.16
% change	-37.2 ± 18.4	-37.5 ± 19.0	-37.1 ± 18.1	0.56
Triglycerides				
Median (IQR)	-11.9 (-46.6 to 18.2)	-11.6 (-41.4 to 18.0)	-12.8 (-48.9 to 18.9)	0.80
Median of % change	-10.3	-9.2	-10.9	0.71
ApoB				
Mean	-31.5 ± 20.8	-31.8 ± 22.5	-31.4 ± 20.2	0.77
% change	-28.6 ± 18.2	-27.9 ± 22.3	-28.9 ± 16.4	0.97
ApoA-1				
Mean	14.6 ± 20.2	14.1 ± 21.6	14.8 ± 19.8	0.71
% change	13.4 ± 17.9	12.3 ± 17.5	13.8 ± 18.0	0.26
ApoB:A-1				
Mean	-0.32 ± 0.19	-0.30 ± 0.18	-0.33 ± 0.19	0.01
% change	-36.1 ± 16.2	-35.4 ± 17.1	-36.3 ± 15.9	0.61
CRP				
Median (IQR)	-0.4 (-1.6 to 0.2)	-0.5 (-1.8 to 0.2)	-0.4 (-1.5 to 0.1)	0.74
Median of % change	-33.3	-30.0	-33.3	0.44

Values are mean ± SD and median (interquartile range [IQR]). *Laboratory values obtained during treatment are the average on-treatment of all post-baseline values. All lipoprotein measurements are in mg/dl, and C-reactive protein (CRP) measurements are mg/l.

Apo = apolipoprotein; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol.

greater PAV regression if they had diabetes mellitus ($-1.91 \pm 0.36\%$ vs. $-0.77 \pm 0.27\%$, $p = 0.01$), had stable coronary disease at initial presentation ($-1.52 \pm 0.21\%$ vs. $-0.83 \pm 0.13\%$, $p = 0.01$), received rosuvastatin ($-1.90 \pm 0.25\%$ vs. $-1.06 \pm 0.15\%$, $p = 0.004$), and had higher baseline LDL-C levels ($-1.61 \pm 0.23\%$ vs. $-0.99 \pm 0.14\%$, $p = 0.02$) or higher baseline CRP levels ($-1.72 \pm 0.25\%$ vs. $-1.11 \pm 0.16\%$, $p = 0.04$). Further analysis revealed statistical heterogeneity with greater regression in women treated with rosuvastatin versus atorvastatin ($p = 0.03$).

MULTIVARIATE SEX-RELATED DIFFERENCES OF CHANGES IN PLAQUE BURDEN ACCORDING TO TREATMENT.

Based on these observations, a multivariable linear regression analysis sought to assess if there was a sex-treatment interaction upon change in atheroma volume after controlling for important covariates. Table 5 outlines the sex-related differences of baseline and multivariable-adjusted changes in PAV and TAV according to treatment groups. Women consistently demonstrated lower PAV and TAV compared with men at baseline across both treatment groups. In the atorvastatin-treated group, women demonstrated a similar degree of PAV regression ($-1.17 \pm 0.25\%$ vs. $-1.13 \pm 0.15\%$, $p = 0.87$) and TAV regression ($-7.70 \pm 1.29 \text{ mm}^3$ vs. $-5.62 \pm 0.74 \text{ mm}^3$, $p = 0.17$) compared with men. In the rosuvastatin-treated group, however, women demonstrated greater PAV regression ($-1.88 \pm 0.25\%$ vs. $-0.98 \pm 0.15\%$, $p = 0.002$), but not TAV regression ($-9.68 \pm 1.24 \text{ mm}^3$ vs. $-7.21 \pm 0.75 \text{ mm}^3$, $p = 0.09$) compared with men. Among the covariates, baseline PAV ($p < 0.001$) and female sex ($p = 0.002$) independently associated with plaque regression, whereas baseline nitrate use ($p = 0.003$) and increasing LDL-C ($p = 0.04$) each associated with plaque progression. Following adjustment for these covariates, a significant sex-treatment interaction persisted ($p = 0.036$) (Figure 1), suggesting that the treatment specification influenced the effect of sex on change in PAV. Following adjustment for baseline TAV, there was no significant sex-treatment interaction ($p = 0.51$), suggesting that the treatment specification failed to influence the effect of sex on change in TAV.

SEX-RELATED DIFFERENCES OF PLAQUE REGRESSION VERSUS ON-TREATMENT LDL-C LEVELS.

Figure 2 illustrates the relationship between change in PAV and average on-treatment LDL-C levels for men and women. For on-treatment LDL-C levels ≥ 70 mg/dl, women had similar PAV regression rates compared with men ($-1.05 \pm 0.28\%$ vs. $-0.97 \pm 0.18\%$, $p = 0.81$), whereas for on-treatment LDL-C levels

TABLE 3 Univariate Sex-Related Differences of Baseline and Change of Ultrasonic Parameters

IVUS Parameter	Total (N = 1,039)	Women (n = 274)	Men (n = 765)	p Value
Percent atheroma volume				
Baseline	36.3 ± 8.3	34.0 ± 8.0	37.2 ± 8.2	<0.001
Change from baseline	-1.19 ± 0.09	-1.52 ± 0.18	-1.07 ± 0.10	0.03
p value for change from baseline	<0.001	<0.001	<0.001	
Total atheroma volume, mm³				
Baseline	144.1 ± 62.2	122.4 ± 55.2	151.9 ± 62.8	<0.001
Change from baseline	-7.0 ± 0.45	-8.27 ± 0.90	-6.59 ± 0.53	0.11
p value for change from baseline	<0.001	<0.001	<0.001	
Lumen volume, mm³				
Baseline	248.3 ± 88.6	231.0 ± 74.0	254.5 ± 93.0	0.001
Change from baseline	0.96 ± 0.93	0.74 ± 1.81	1.04 ± 1.08	0.89
p value for change from baseline	0.30	0.68	0.34	
EEM volume, mm³				
Baseline	392.4 ± 135.8	353.4 ± 116.0	406.4 ± 140.0	<0.001
Change from baseline	-6.07 ± 1.16	-7.01 ± 2.28	-5.74 ± 1.35	0.63
p value for change from baseline	<0.001	0.002	<0.001	

Baseline values are reported as mean ± SD, and change values are reported as least-squares mean ± SE after controlling for the respective baseline value. All p values reflect comparisons between women and men. EEM = external elastic membrane; IVUS = intravascular ultrasound.

<70 mg/dl, women demonstrated significantly greater PAV regression than men ($-1.81 \pm 0.22\%$ vs. $-1.12 \pm 0.13\%$, $p = 0.007$). Figure 3 illustrates the relationship between change in TAV and average on-treatment LDL-C levels for men and women. For on-treatment LDL-C levels ≥ 70 mg/dl, women had similar TAV regression rates compared with men ($-5.26 \pm 1.43 \text{ mm}^3$ vs. $-5.55 \pm 0.89 \text{ mm}^3$, $p = 0.87$), whereas for on-treatment LDL-C levels <70 mg/dl, women demonstrated significantly greater TAV regression than men ($-10.1 \pm 1.13 \text{ mm}^3$ vs. $-7.16 \pm 0.65 \text{ mm}^3$, $p = 0.023$).

DISCUSSION

Although sex-related differences of cardiovascular outcomes exist (16), this may relate to a sex-specific clustering of risk factors (17). Yet, differential treatment patterns for cardiovascular disease in men and women may also contribute to differences in clinical outcome between the sexes (18-20). Statins comprise the cornerstone of our current antiatherosclerotic armamentarium, yielding widespread clinical benefits. A consistent under-representation of women in randomized clinical trials, however, has led to the publication of meta-analyses reporting conflicting results regarding the efficacy of statins in women (21,22). This inconsistency has created confusion and controversy among physicians, resulting in some openly questioning the merits of prescribing statins to women (5,23,24), despite clinical trials that enrolled both men and women reporting benefit (25).

TABLE 4 Subgroup Analysis for Between-Sex Comparisons of Changes in PAV

Clinical Characteristics (Women, Men)	p Value for Change From Baseline (Women)		p Value for Change From Baseline (Men)		p Value for Men Versus Women	p Value for Interaction
	Women	Men	Women	Men		
Age, yrs < median (102, 403)	-1.74 ± 0.30	<0.001	-1.18 ± 0.15	<0.001	0.10	0.83
Age, yrs ≥ median (172, 362)	-1.39 ± 0.21	<0.001	-0.94 ± 0.15	<0.001	0.08	
Diabetes (58, 101)	-1.91 ± 0.36	<0.001	-0.77 ± 0.27	0.006	0.01	0.06
No diabetes (216, 664)	-1.43 ± 0.20	<0.001	-1.11 ± 0.11	<0.001	0.17	
Hypertension (220, 511)	-1.49 ± 0.20	<0.001	-1.10 ± 0.13	<0.001	0.11	0.56
No hypertension (54, 254)	-1.69 ± 0.38	<0.001	-0.99 ± 0.17	<0.001	0.09	
Current smoker (89, 247)	-1.69 ± 0.32	<0.001	-1.08 ± 0.19	<0.001	0.11	0.61
Current nonsmoker (185, 518)	-1.44 ± 0.21	<0.001	-1.06 ± 0.12	<0.001	0.13	
Acute coronary syndrome (82, 279)	-1.51 ± 0.32	<0.001	-1.48 ± 0.17	<0.001	0.94	0.15
Stable coronary syndrome (192, 486)	-1.52 ± 0.21	<0.001	-0.83 ± 0.13	<0.001	0.01	
Rosuvastatin (141, 379)	-1.90 ± 0.25	<0.001	-1.06 ± 0.15	<0.001	0.004	0.03
Atorvastatin (133, 386)	-1.12 ± 0.25	<0.001	-1.07 ± 0.14	<0.001	0.88	
Baseline LDL-C < median (121, 385)	-1.34 ± 0.27	<0.001	-1.14 ± 0.15	<0.001	0.53	0.24
Baseline LDL-C ≥ median (151, 375)	-1.61 ± 0.23	<0.001	-0.99 ± 0.14	<0.001	0.02	
Baseline HDL-C < median (89, 421)	-1.72 ± 0.31	<0.001	-1.20 ± 0.14	<0.001	0.13	0.91
Baseline HDL-C ≥ median (184, 341)	-1.36 ± 0.21	<0.001	-0.92 ± 0.15	<0.001	0.09	
Baseline triglycerides < median (123, 390)	-1.45 ± 0.27	<0.001	-1.03 ± 0.15	<0.001	0.18	0.70
Baseline triglycerides ≥ median (150, 372)	-1.55 ± 0.23	<0.001	-1.10 ± 0.15	<0.001	0.10	
Baseline CRP < median (117, 365)	-1.36 ± 0.26	<0.001	-1.08 ± 0.14	<0.001	0.36	0.40
Baseline CRP ≥ median (148, 362)	-1.72 ± 0.25	<0.001	-1.11 ± 0.16	<0.001	0.04	
Baseline PAV < median (165, 354)	-0.82 ± 0.20	<0.001	-0.44 ± 0.14	0.002	0.12	0.49
Baseline PAV ≥ median (109, 411)	-2.24 ± 0.30	<0.001	-1.70 ± 0.15	<0.001	0.11	

Values are least-squares mean ± SE. Coronary syndrome was designated as the mode of presentation for the initial coronary angiogram during the time in which baseline intravascular ultrasound (IVUS) and study enrollment occurred.
PAV = percent atheroma volume; other abbreviations as in Table 2.

This analysis reports the novel finding of sex-related differences of the serial response of coronary atheroma following 2 years of maximally intensive statin therapy. Female sex was independently associated with coronary atheroma regression to this treatment, and more likely occurred in women

with diabetes mellitus, stable angina pectoris, and higher baseline LDL-C and CRP levels. A significant interaction emerged between sex and treatment specification, with rosuvastatin-treated women demonstrating the greatest degree of plaque regression compared with all other treatment groups. Both

TABLE 5 Multivariable-Adjusted Sex-Related Differences Between Baseline and Changes in Plaque Volume According to Treatment

IVUS Parameter	Atorvastatin			Rosuvastatin		
	Women (n = 133)	Men (n = 386)	p Value*	Women (n = 141)	Men (n = 379)	p Value†
Percent atheroma volume						
Baseline	33.3 ± 8.2	36.9 ± 8.2	<0.001	34.7 ± 7.7	37.4 ± 8.2	0.001
Adjusted change from baseline‡	-1.17 ± 0.25	-1.13 ± 0.15	0.87	-1.88 ± 0.25	-0.98 ± 0.15	0.002
p value for change from baseline	<0.001	<0.001		<0.001	<0.001	
Total atheroma volume, mm ³						
Baseline	117.6 ± 56.5	153.2 ± 63.6	<0.001	127.0 ± 53.7	150.4 ± 62.1	<0.001
Adjusted change from baseline§	-7.70 ± 1.29	-5.62 ± 0.74	0.17	-9.68 ± 1.24	-7.21 ± 0.75	0.09
p value for change from baseline	<0.001	<0.001		<0.001	<0.001	

Values are mean ± SD for baseline values and least-squares mean ± SE for change values. *Reflects comparisons between men and women within the atorvastatin-treated group. †Reflects comparisons between men and women within the rosuvastatin-treated group. ‡Multivariable adjustment for factors influencing change in PAV (controlling for baseline PAV, sex, baseline nitrate use, and change in LDL-C). Interaction p value for sex by treatment = 0.036. §Multivariable adjustment for factors influencing change in TAV (controlling for baseline TAV, sex, change in LDL-C, baseline non-HDL-C, age, baseline beta-blocker use, and concomitant ACE inhibitor use). Interaction p value for sex by treatment = 0.51.
TAV = total atheroma volume; other abbreviations as in Tables 1, 2, 3 and 4.

sexes demonstrated similar plaque regression rates when on-treatment LDL-C values were ≥ 70 mg/dL. For on-treatment LDL-C levels < 70 mg/dL, however, women demonstrated significantly greater coronary atheroma regression than their male counterparts. Although the biological mechanisms underlying this observation need further exploration, these findings highlight the efficacy of high-intensity statins in women with coronary artery disease, supporting the latest guideline recommendations of potent statin therapy in individuals with proven atherosclerotic cardiovascular disease. These data also provide novel insights into possible influences of sex on the natural history of coronary atherosclerosis and subsequent cardiovascular risk.

Vascular imaging, particularly serial coronary IVUS, has proven pivotal in defining factors promoting the progression, and regression, of atherosclerosis. In serial studies of coronary atheroma volume, the baseline extent of disease has consistently and independently predicted plaque regression to disease-modifying therapies, such that those with greater baseline plaque burden invariably demonstrate more disease regression (15), particularly in response to high-intensity statins (26). In the SATURN study, despite harboring less baseline coronary atheroma volume than their male counterparts, women still demonstrated greater atheroma regression than men, a finding that reinforces the significance of this observation in the present analysis. A prior pooled analysis of 978 patients from 3 trials employing serial coronary IVUS assessment of plaque progression showed that despite a greater cardiovascular risk-factor profile, women displayed less baseline plaque burden than men (27). Following a variety of risk-modifying therapies, the serial plaque response of women mirrored that of men. Meta-analyses, however, are subject to the possibility of confounding by inclusion of studies with differing treatments and entry criteria. These analyses imply that although women typically present with a lower disease burden than men, their disease appears more susceptible to the antiatherosclerotic effects of disease-modifying therapies.

Other advanced imaging techniques have elucidated sex-specific differences in plaque character and composition. High-resolution cardiac magnetic resonance of carotid plaques found intraplaque hemorrhage and lipid core to more frequently occur in men than in women (28). A post-hoc analysis from the PROSPECT (Providing Regional Observations to Study Predictors of The Events in the Coronary Tree) study (29) found sex-related differences of nonculprit vessel coronary plaque composition in

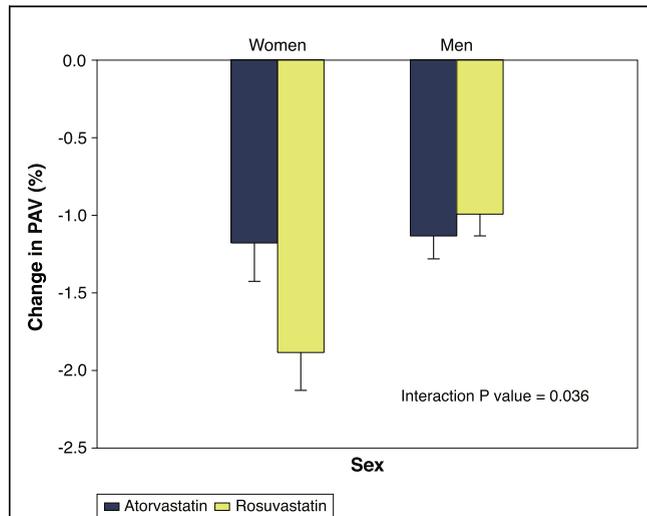


FIGURE 1 Interaction Between Sex and Treatment Upon Change in PAV

The interaction between sex and treatment specification upon change in coronary atheroma volume. PAV = percent atheroma volume.

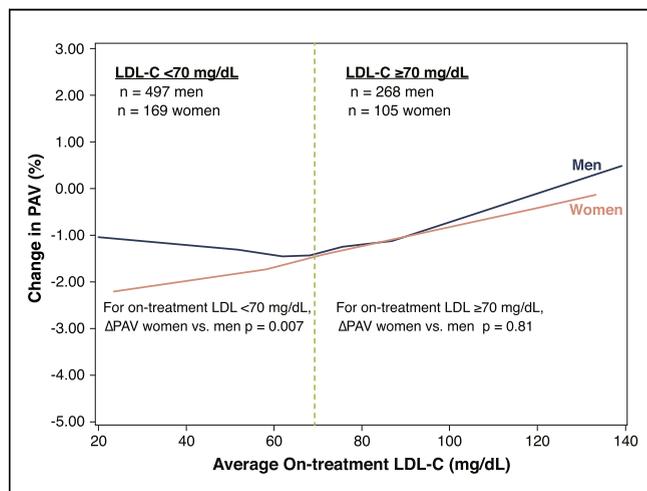


FIGURE 2 Sex-Related Variations of Changes in PAV Versus Average On-Treatment LDL-C Levels

Locally weighted (moving average) plot outlining the relationship between predicted changes in percent atheroma volume (PAV) from baseline versus average on-treatment low-density lipoprotein cholesterol (LDL-C) levels stratified according to sex. The average on-treatment LDL-C values on the x-axis reflect the first to 99th percentile LDL-C values in the SATURN (Study of Coronary Atheroma by Intravascular Ultrasound: Effect of Rosuvastatin Versus Atorvastatin) study; **blue** represents men, **pink** represents women. The **dotted green line** represents an on-treatment LDL-C value of 70 mg/dL. For on-treatment LDL-C < 70 mg/dL, the least-squares mean (LSM) changes in PAV for women versus men are $-1.81 \pm 0.22\%$ versus $-1.12 \pm 0.13\%$ ($p = 0.007$). For on-treatment LDL-C ≥ 70 mg/dL, the LSM changes in PAV for women versus men are $-1.05 \pm 0.28\%$ versus $-0.97 \pm 0.18\%$ ($p = 0.81$).

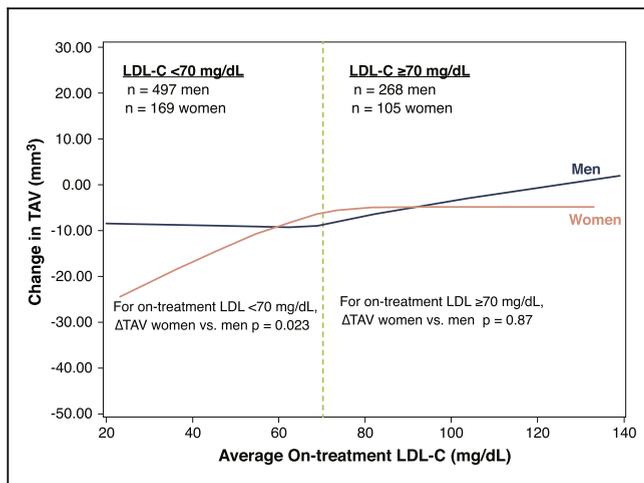


FIGURE 3 Sex-Related Variations of Changes in TAV Versus Average On-Treatment LDL-C Levels

Locally weighted (moving average) plot outlining the relationship between predicted changes in total atheroma volume (TAV) from baseline versus average on-treatment LDL-C levels stratified according to sex. The average on-treatment LDL-C values on the x-axis reflect the first to 99th percentile LDL-C values in the SATURN (Study of Coronary Atheroma by Intravascular Ultrasound: Effect of Rosuvastatin Versus Atorvastatin) study; **blue** represents men, **pink** represents women. The **dotted green line** represents an on-treatment LDL-C value of 70 mg/dL. For on-treatment LDL-C <70 mg/dL, the least squares mean (LSM) changes in TAV for women versus men are $-10.1 \pm 1.13 \text{ mm}^3$ vs. $-7.16 \pm 0.65 \text{ mm}^3$ ($p = 0.023$). For on-treatment LDL-C ≥ 70 mg/dL, the LSM changes in PAV for women versus men are $-5.26 \pm 1.43 \text{ mm}^3$ versus $-5.55 \pm 0.89 \text{ mm}^3$ ($p = 0.87$).

individuals less than, but not greater than, 65 years of age (30). Women younger than 65 years had less fibroatheromas, considered a more advanced form of atheroma, than similarly-aged men. In parallel to this, a pre-specified post-hoc serial plaque composition analysis of the SATURN study revealed significant reductions in the number of lipid-rich pathological intimal thickening lesions, yet static numbers of fibroatheromas, following high-intensity statin therapy (31). Collectively, this may explain why women in the SATURN study, with a mean age of 59.2 ± 8.5 years, demonstrated a greater benefit than men in terms of plaque regression. Younger women may simply possess a more modifiable (lipid-rich) atheromatous substrate than similarly-aged men and thus, derive a greater antiatherosclerotic benefit from aggressive statin-mediated LDL-C lowering.

The most recent treatment guidelines now recommend high-intensity statin therapy in all individuals with proven atherosclerotic cardiovascular disease (4), and do not advocate a specific LDL-C target following commencement of this therapy. However,

the present analysis demonstrates the novel finding of an incremental antiatherosclerotic benefit in women compared with men, when achieving on-treatment LDL-C levels <70 mg/dL; a cutoff level endorsed by previous treatment guidelines (32). A post-hoc analysis of the PROVE IT-TIMI 22 (Pravastatin or Atorvastatin Evaluation and Infection Therapy-Thrombolysis In Myocardial Infarction 22) trial revealed that women achieved less LDL-C reduction than men following high-intensity statin therapy, yet derived equal clinical benefit. This suggests superior risk-reduction in women compared with men per unit of LDL-C lowered (33), which appears consistent with the findings of the present analysis. However, these collective post-hoc findings will ultimately need testing in a prospective randomized controlled trial. Therefore, at present, it remains unclear if women derive greater clinical benefit than men with further LDL-C lowering. Furthermore, the SATURN study was not powered to detect differences in clinical outcomes. A prior pooled analysis of over 4,100 patients from 6 clinical trials, inclusive of nearly 1,300 women, however, demonstrated a significant association between the rate of coronary atheroma progression and incident clinical events, driven chiefly by rates of repeat coronary revascularization procedures (15). A recent pooled analysis of serial left main coronary atheroma progression demonstrated a similar association (34).

This analysis of the SATURN study found a significant sex-treatment interaction, suggesting a greater antiatherosclerotic effect in women treated with rosuvastatin. The reasons for this finding are unclear, and warrant further investigation. Nevertheless, one may speculate on the mechanistic basis of these observations. Various statins may exert different biological effects upon the vessel wall, further influenced by a sex-specific milieu. The more significant regression of PAV compared with TAV found in women (compared with men) may simply reflect a more potent effect of rosuvastatin upon the arterial wall. This finding may also be a reflection of the magnitude of achieved LDL-C levels. Indeed, **Figures 2 and 3** highlight significantly greater PAV and TAV regression in women compared with men when achieved LDL-C levels are <70 mg/dL. Lipidomic profiling has uncovered differential effects of atorvastatin and rosuvastatin on the detailed plasma lipoprotein subcompartments (35). Further pharmacogenomic- and metabolomic-based analyses may uncover sex-specific differences of various statins on the arterial wall, particularly regarding the delipidation of atherosclerotic plaque.

STUDY LIMITATIONS. This analysis has some limitations. Common to the limitations of many contemporary, large-scale randomized controlled trials, the SATURN study enrolled relatively fewer women than men, comprising 26% of the study population. In addition, the post-hoc findings of significantly greater plaque regression in rosuvastatin-treated women compared with men and in women with LDL-C <70 mg/dl requires replication in a larger cohort of women evaluated prospectively and should therefore be considered as hypothesis generating. However, the SATURN study comprises the largest cohort of women who have undergone serial coronary IVUS evaluation in a single trial, with the longest duration of follow-up compared with previous coronary imaging trials. These features provided enough statistical power to explore sex-related differences of serial plaque responses following maximally intensive statin therapy. The present analysis does not apply directly to a primary prevention setting. IVUS is invasive, and is thus inappropriate for evaluating asymptomatic, low-risk individuals. The present analysis did not evaluate plaque composition. Baseline differences in coronary plaque composition, and their potential influence on serial responses, may have provided additional mechanistic insight into the observed sex-specific differences of serial plaque behavior following high-intensity statin treatment. Data regarding menopausal status and use of hormone replacement therapy were not collected in the SATURN study. This data may have also provided additive mechanistic insight into the observed

sex-specific differences in serial plaque responses to potent statin therapy.

CONCLUSIONS

Long-term maximally intensive statin therapy resulted in women experiencing greater coronary atheroma regression than men, particularly below on-treatment LDL-C levels of 70 mg/dl, and especially in rosuvastatin-treated women. Female sex independently associated with plaque regression to high-intensity statins. The finding of a sex-treatment interaction in the degree of plaque regression should provide impetus for future research to probe mechanisms accounting for sex-specific variations of atheroma progression. These data support the use of high-intensity statin therapy in women with atherosclerotic cardiovascular disease, affirming recent treatment guidelines endorsing the use of potent statin therapy. In addition, dedicated clinical trials involving women may foster the development of personalized medicine.

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