High-Intensity Statin Therapy Alters the Natural History of Diabetic Coronary Atherosclerosis: Insights From SATURN

DOI: 10.2337/dc14-1121

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OBJECTIVE

Although statins can induce coronary atheroma regression, this benefit has yet to be demonstrated in diabetic individuals. We tested the hypothesis that high-intensity statin therapy may promote coronary atheroma regression in patients with diabetes.

RESEARCH DESIGN AND METHODS

The Study of Coronary Atheroma by Intravascular Ultrasound: Effect of Rosuvastatin Versus Atorvastatin (SATURN) used serial intravascular ultrasound measures of coronary atheroma volume in patients treated with rosuvastatin 40 mg or atorvastatin 80 mg for 24 months. This analysis compared changes in biochemistry and coronary percent atheroma volume (PAV) in patients with (*n* = 159) and without (*n* = 880) diabetes.

RESULTS

At baseline, patients with diabetes had lower LDL cholesterol (LDL-C) and HDL cholesterol (HDL-C) levels but higher triglyceride and CRP levels compared with patients without diabetes. At follow-up, diabetic patients had lower levels of LDL-C (61.0 ± 20.5 vs. 66.4 ± 22.9 mg/dL, *P* = 0.01) and HDL-C (46.3 ± 10.6 vs. 49.9 ± 12.0 mg/dL, *P* < 0.001) but higher levels of triglycerides (127.6 [98.8, 163.0] vs. 113.0 mg/dL [87.6, 151.9], *P* = 0.001) and CRP (1.4 [0.7, 3.3] vs. 1.0 [0.5, 2.1] mg/L, *P* = 0.001). Both patients with and without diabetes demonstrated regression of coronary atheroma as measured by change in PAV (−0.83 ± 0.13 vs. −1.15 ± 0.13%, *P* = 0.08). PAV regression was less in diabetic compared with nondiabetic patients when on-treatment LDL-C levels were >70 mg/dL (−0.31 ± 0.23 vs. −1.01 ± 0.21%, *P* = 0.03) but similar when LDL-C levels were ≤70 mg/dL (−1.09 ± 0.16 vs. −1.24 ± 0.16%, *P* = 0.50).

CONCLUSIONS

High-intensity statin therapy alters the progressive nature of diabetic coronary atherosclerosis, yielding regression of disease in diabetic and nondiabetic patients.

Diabetes currently affects over 200 million people worldwide (1). Given the global obesity epidemic, this number will likely continue to rise, placing substantial pressure on health care systems throughout the world (1–3). Diabetic patients with known coronary artery disease (CAD) invariably display accelerated disease

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Received 5 May 2014 and accepted 12 August 2014.

Clinical trial reg. no. NCT000620542, clinicaltrials.gov.

This article contains Supplementary Data online at http://care.diabetesjournals.org/lookup/suppl/doi:10.2337/dc14-1121/-/DC1.

progression and a significantly greater risk of fatal and nonfatal cardiovascular events compared with patients without diabetes (4–6). Moreover, the management of atherosclerotic disease in diabetic patients remains challenging, as intensive glycemic control fails to curb the incidence of macrovascular events (7–9).

Aggressive LDL cholesterol (LDL-C) lowering with high-intensity statin therapy can regress coronary atheroma and reduce the incidence of cardiovascular events in patients with established CAD (10–13). Although the clinical benefits of high-intensity statins have not yet undergone prospective evaluation in patients with diabetes, meta-analyses suggest that reductions in cardiovascular event rates parallel the degree of LDL-C lowering (14). Despite recent guidelines advocating the use of high-intensity statins in higher-risk diabetic individuals (15), there has been no prospective evaluation of the antiatherosclerotic effects of potent statin therapy on diabetic coronary atherosclerosis in humans in vivo.

SATURN (Study of Coronary Atheroma by Intravascular Ultrasound: Effect of Rosuvastatin Versus Atorvastatin; clinicaltrials.gov reg. no. NCT000620542) directly compared the effect of two high-intensity statin regimens (atorvastatin 80 mg vs. rosuvastatin 40 mg) on coronary atherosclerosis progression using serial intravascular ultrasound (IVUS) over 24 months (11). No appreciable difference of the primary efficacy end point of change in percent atheroma volume (PAV), safety, or clinical event rates was found between the two treatment groups. We tested the hypothesis that maximally intensive statin therapy exerts significant antiatherosclerotic effects in patients both with and without diabetes in SATURN.

RESEARCH DESIGN AND METHODS

Patient Selection

The design of SATURN has been previously described (16). In brief, patients with angiographic evidence of CAD and an LDL-C $<$116 mg/dL following a 2-week treatment period with atorvastatin 40 mg or rosuvastatin 20 mg daily were rerandomized and treated for 24 months with rosuvastatin 40 mg or atorvastatin 80 mg daily. Coronary IVUS imaging was obtained at baseline and following 24 months of treatment. The population of patients with diabetes was defined by provided medical history and patient reporting on initial trial enrollment.

Acquisition and Analysis of Intravascular Coronary Imaging

Previous reports have described, in detail, the acquisition and analysis of IVUS images (10). 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. Imaging was performed on a single coronary artery with no luminal stenosis $>$50% that had not required revascularization and was not considered to be a culprit vessel for a previous myocardial infarction. Images were screened by the Atherosclerosis Imaging Core Laboratory of the Cleveland Clinic Coordinating Center for Clinical Research for quality, and those patients whose baseline imaging was acceptable were eligible for randomization. Repeat IVUS imaging was obtained of anatomically matched segments of the same artery following 24 months of treatment.

Anatomically matched arterial segments were defined from baseline and follow-up imaging based on location of proximal and distal side branches. Images spaced 1 mm apart were selected for analysis by personnel blinded to treatment assignment and temporal sequence of image acquisition. The lumen and external elastic membrane (EEM) were defined by manual planimetry, with the plaque area defined as the difference in area between the borders of lumen and EEM. Changes in atheroma volume from baseline to 24 months were quantified using change in PAV and total atheroma volume (TAV). PAV was calculated by using the equation below to determine the proportion of vessel volume occupied by atherosclerotic plaque (17).

$$PAV = \frac{\sum(EEM_{area} - Lumen_{area})}{\sum EEM_{area}} \times 100$$

TAV was calculated using the equation below to determine the summation of plaque area calculated for each image and subsequently normalized to account for differences in segment length between subjects (17).

$$TAV_{normalized} = \frac{\sum(EEM_{\text{area}} - Lumen_{\text{area}})}{Number\ of\ images\ in\ pullback} \times Median\ number\ of\ images\ in\ cohort$$

EEM and lumen volumes were calculated by summation of their respective areas in each measured image and subsequently normalized to account for differences in length of arterial segments between subjects. The post hoc analyses presented here pooled results from both treatment groups; as in SATURN, rosuvastatin and atorvastatin did not differ in the primary efficacy end point of the change in PAV from baseline (11).

Statistical Analysis

All analyses were conducted on the modified intent-to-treat population, which included all patients with both baseline and follow-up IVUS measurements (n = 1,039). Continuous variables were reported as mean $\pm$ SD if normally distributed and as median (interquartile range [IQR]) if not normally distributed. Baseline clinical characteristics, concomitant medications, laboratory biochemical data, and baseline IVUS parameters were compared between patients with diabetes (n = 159) and without diabetes (n = 880). Two-sample Student t tests were used for normally distributed continuous variables, Wilcoxon rank-sum tests for nonnormally distributed continuous variables, and χ^2 tests for categorical variables.

Serial changes in IVUS measures were analyzed by ANOVA adjusting for their baseline counterparts and were recorded as least-squares mean $\pm$ SE. Due to the imbalance of baseline characteristics between patients with and without diabetes, propensity score adjustment was applied. In a multivariable logistic regression model, the outcome comprised the binary variable of diabetes versus nondiabetes, and the independent variables were baseline characteristics related to diabetes. Inverse probability of treatment weight (IPTW) was then calculated from the propensity scores and was placed into the ANOVA model as a weighting factor (18). To assess the improvement of baseline data imbalance through the application of IPTW, absolute standardized

differences of the 11 covariates that were included for calculating IPTW were compared before and after IPTW weighting, with all being <10%, which is deemed an appropriate degree of between-group balance (18,19). Furthermore, the IVUS data, weighted by IPTW, was analyzed per stratification of diabetes status and lower versus higher level of on-treatment LDL-C, with a cutoff value of 70 mg/dL. The effect of LDL-C lowering on change in PAV was further examined by plotting change in PAV against percent change in LDL-C (stratified by diabetes status). In addition, the relationship between achieved LDL-C levels and changes in PAV was assessed using the local regression smoothing (LOESS) method in diabetic and nondiabetic patients, respectively. A two-sided *P* value <0.05 was considered statistically significant. All analyses were performed using the SAS software version 9.2 (SAS Institute, Inc., Cary, NC).

RESULTS

Baseline Characteristics

Table 1 describes demographics, clinical characteristics, and concomitant medications in patients with diabetes (*n* = 159) and without diabetes (*n* = 880). Compared with patients without diabetes, patients with diabetes were older (59.4 ± 7.7 vs. 57.3 ± 8.7 years, *P* = 0.006) and less likely to be male (63.5 vs. 75.5%, *P* = 0.002), had higher BMI (31.3 ± 5.1 vs. 28.6 ± 5.2 kg/m^2, *P* < 0.001), and were more likely to have hypertension (84.3 vs. 67.8%, *P* < 0.001). Patients with diabetes were also less likely to be taking aspirin (53.5 vs. 62.8%, *P* = 0.03) but more likely to be treated with an angiotensin receptor blocker (27 vs. 14.4%, *P* < 0.001) compared with patients without diabetes. Use of other cardiovascular medications was similar. At baseline, 43 (27%) patients with diabetes were on insulin and 116 (73%) were taking oral antidiabetic drugs. Baseline HbA_{1c} measurements were not available for all patients with diabetes; thus baseline glycemic control could not be assessed.

Laboratory Measurements

Table 1 also describes risk factor control in patients with and without diabetes at baseline and at follow-up. Compared with patients without diabetes, patients with diabetes at baseline had lower levels of LDL-C (112.9 ± 25.1 vs. 121.2 ± 28.4 mg/dL, *P* < 0.001) and HDL cholesterol (HDL-C) (43.1 ± 9.5 vs. 45.3 ± 11.5 mg/dL, *P* = 0.03) but higher levels of triglycerides (139 [106, 187] vs. 128 mg/dL [92, 178], *P* = 0.03) and CRP (2.0 [1.0, 4.0] vs. 1.5 mg/L [0.8, 3.4], *P* = 0.01). Following high-intensity statin therapy, patients with diabetes had lower levels of LDL-C (61.0 ± 20.5 vs. 66.4 ± 22.9 mg/dL, *P* = 0.01) and HDL-C (46.3 ± 10.6 vs. 49.9 ± 12.0 mg/dL, *P* < 0.001) but higher levels of triglycerides (127.6 [98.8, 163.0] vs. 113.0 mg/dL [87.6, 151.9], *P* = 0.001) and CRP (1.4 [0.7, 3.3] vs. 1.0 mg/L [0.5, 2.1], *P* = 0.001).

Baseline and Changes in Atheroma Burden and Vessel Dimensions

Table 2 describes adjusted baseline and changes of indices of atheroma burden and vessel dimensions. Compared with patients without diabetes, patients with diabetes had greater baseline PAV (38.2 ± 8.8 vs. 36.0 ± 8.1%, *P* = 0.002) and TAV (155.1 ± 66 vs. 142.2 ± 61.4 mm^3, *P* = 0.02). Patients with and without diabetes had similar lumen and EEM volumes at baseline.

Both patients with and without diabetes demonstrated regression of atheroma as measured by change in PAV and TAV (ΔPAV: −0.83 ± 0.13 vs. −1.15 ± 0.13%, *P* = 0.08; ΔTAV: −5.7 ± 0.7 vs. −7.0 ± 0.7 mm^3, *P* = 0.19, respectively). Similarly, in patients with and without diabetes, no significant difference was noted for changes in lumen and EEM volumes. A similar proportion of patients with diabetes demonstrated regression of coronary atherosclerosis as compared with those without diabetes (64.8 vs. 66.0%, *P* = 0.76).

Intensive Lowering of LDL-C and Atheroma Progression

Figure 1*A* describes the degree of plaque regression achieved according to diabetes status stratified according to whether achieved LDL-C levels were ≤ vs. >70 mg/dL. Lowering of LDL-C to ≤70 mg/dL resulted in equivalent degrees of PAV regression (−1.09 ± 0.16 vs. −1.24 ± 0.16%, *P* = 0.50) and TAV regression (−6.2 ± 0.9 vs. −7.8 ± 0.9 mm^3, *P* = 0.16), irrespective of the presence or absence of diabetes. When achieved LDL-C levels were >70 mg/dL, nondiabetic patients achieved greater PAV regression compared with those with diabetes (−0.31 ± 0.23 vs. −1.01 ± 0.21%, *P* = 0.03), but similar TAV regression (−4.9 ± 1.2 vs. −5.5 ± 1.1 mm^3, *P* = 0.70). An LDL-C level of ≤70 mg/dL was obtained in 67% of patients with diabetes and 63% of patients without diabetes (*P* = 0.36). Figure 1*B* illustrates the comparative relationships between percent reduction in LDL-C and changes in plaque volume in both patients with and without diabetes. A figure demonstrating the relationship between the achieved LDL-C level and change in PAV for patients with and without diabetes is available in the Supplementary Data.

CONCLUSIONS

Statin therapy unequivocally reduces cardiovascular event rates in patients with CAD (20). However, CAD patients with concomitant diabetes represent a particularly high-risk population demonstrating accelerated disease progression and suffering its deadly complications (5). Although statins appear to benefit diabetic patients (14), prospective trials have generally involved the use of moderate-intensity statin regimens, and clinical event rates in these studies have remained relatively high (21,22). High-intensity statins regress coronary atheroma and significantly reduce major adverse cardiovascular events in patients at elevated cardiovascular risk (10,12,13,20,23). In diabetic patients, however, coronary atheroma regression has not been previously demonstrated, nor have high-intensity statin regimens been specifically tested in diabetic patients within a randomized, controlled clinical trial setting. The present analysis establishes the distinct antiatherosclerotic capacity of high-intensity statins, which significantly altered the progressive nature of diabetic coronary atherosclerosis.

In a pooled analysis of 2,237 patients from five trials that used serial coronary IVUS, Nicholls et al. (6) described the markedly progressive nature of coronary atherosclerosis in diabetic subjects accompanied by constrictive remodeling, despite the use of established medical therapies. Achieved LDL-C levels in the diabetic population were 80 mg/dL in this prior analysis, compared with achieved LDL-C levels of 61 mg/dL in SATURN (Fig. 2). The latest American

Table 1—Baseline demographics, patient characteristics, concomitant medications, and laboratory findings*

Variable	Total (n = 1,039)	Baseline diabetes status: Diabetes (n = 159)	Baseline diabetes status: No diabetes (n = 880)	P value
Age (years)	57.6 ± 8.6	59.4 ± 7.7	57.3 ± 8.7	0.006
Male	765 (73.6)	101 (63.5)	664 (75.5)	0.002
BMI (kg/m^2)	29.0 ± 5.2	31.3 ± 5.1	28.6 ± 5.2	<0.001
Previous MI	254 (24.4)	37 (23.3)	217 (24.7)	0.71
Hypertension	731 (70.4)	134 (84.3)	597 (67.8)	<0.001
Current smoker	336 (32.3)	42 (26.4)	294 (33.4)	0.08
ACS at presentation	361 (34.7)	47 (29.6)	314 (35.7)	0.14
Prior PCI	243 (23.4)	32 (20.1)	211 (24.0)	0.29
Rosuvastatin	520 (50.0)	72 (45.3)	448 (50.9)	0.19
Aspirin	638 (61.4)	85 (53.5)	553 (62.8)	0.03
Beta-blockers	632 (60.8)	92 (57.9)	540 (61.4)	0.41
ACE inhibitors	457 (44.0)	63 (39.6)	394 (44.8)	0.23
Angiotensin receptor blocker	170 (16.4)	43 (27.0)	127 (14.4)	<0.001
Nitrates	859 (82.7)	134 (84.3)	725 (82.4)	0.56
Insulin	N/A	43 (27.0)	N/A	N/A
OAD	N/A	116 (73.0)	N/A	N/A
Baseline				
LDL-C	120.0 ± 28.1	112.9 ± 25.1	121.2 ± 28.4	<0.001
HDL-C	45.0 ± 11.3	43.1 ± 9.5	45.3 ± 11.5	0.03
Non−HDL-C	148.7 ± 33.1	143.7 ± 29.8	149.6 ± 33.6	0.048
Triglycerides	129 (94, 180)	139 (106, 187)	128 (92, 178)	0.03
ApoB	105.1 ± 21.4	103.2 ± 19.1	105.5 ± 21.8	0.26
ApoA-1	127.1 ± 24.3	125.8 ± 22.5	127.4 ± 24.6	0.46
ApoB:A-1	0.86 ± 0.24	0.85 ± 0.22	0.86 ± 0.24	0.60
CRP	1.6 (0.8, 3.5)	2.0 (1.0, 4.0)	1.5 (0.8, 3.4)	0.01
Follow-up**				
LDL-C	65.6 ± 22.6	61.0 ± 20.5	66.4 ± 22.9	0.01
HDL-C	49.3 ± 11.9	46.3 ± 10.6	49.9 ± 12.0	<0.001
Non−HDL-C	91.0 ± 25.9	88.3 ± 23.1	91.5 ± 26.3	0.38
Triglycerides	114.6 (89.5, 154.3)	127.6 (98.8, 163.0)	113.0 (87.6, 151.9)	0.001
ApoB	73.7 ± 18.8	73.0 ± 16.7	73.9 ± 19.2	0.88
ApoA-1	141.9 ± 23.1	136.4 ± 23.6	142.9 ± 22.8	<0.001
ApoB:A-1	0.53 ± 0.16	0.55 ± 0.16	0.53 ± 0.16	0.08
CRP	1.0 (0.5, 2.2)	1.4 (0.7, 3.3)	1.0 (0.5, 2.1)	0.001
Change from baseline				
LDL-C				
Mean	−54.4 ± 30.1	−51.7 ± 29.4	−54.8 ± 30.2	0.16
% change	−43.7 ± 19.7	−44.1 ± 19.9	−43.6 ± 19.6	0.74
HDL-C				
Mean	4.3 ± 7.7	3.2 ± 7.2	4.6 ± 7.8	0.02
% change	11.3 ± 18.3	8.8 ± 17.4	11.8 ± 18.4	0.046
Non−HDL-C				
Mean	−57.8 ± 34.0	−55.4 ± 32.8	−58.2 ± 34.2	0.26
% change	−37.2 ± 18.4	−36.9 ± 18.1	−37.3 ± 18.4	0.60
Triglycerides				
Median (IQR)	−11.9 (−46.6, 18.2)	−13.3 (−44.2, 21.2)	−11.8 (−47.1, 17.9)	0.94
Median of % change	−10.3	−10.8	−10.3	0.74
ApoB				
Mean	−31.5 ± 20.8	−30.2 ± 19.7	−31.7 ± 21.0	0.40
% change	−28.6 ± 18.2	−28.1 ± 16.0	−28.7 ± 18.6	0.39
ApoA-1				
Mean	14.6 ± 20.2	10.6 ± 20.7	15.4 ± 20.1	0.005
% change	13.4 ± 17.9	9.9 ± 17.7	14.0 ± 17.8	0.004
ApoB:A-1				
Mean	−0.32 ± 0.19	−0.30 ± 0.19	−0.33 ± 0.19	0.03
% change	−36.1 ± 16.2	−33.1 ± 17.1	−36.6 ± 16.0	0.02
CRP				
Median (IQR)	−0.4 (−1.6, 0.2)	−0.5 (−1.7, 0.3)	−0.4 (−1.5, 0.1)	0.93
Median of % change	−33.3	−30.4	−33.3	0.53

All lipoprotein measurements are in mg/dL. CRP measurements are in mg/L. ACS, acute coronary syndrome; apoA-1, apolipoprotein A-1; MI, myocardial infarction; OAD, oral antidiabetic drug; PCI, percutaneous coronary intervention. *Values of continuous variables are reported as mean ± SD if normally distributed, and median (IQR) if not normally distributed. Categorical variables are reported as n (%). **Unless otherwise noted, laboratory values obtained during treatment are the time-weighted averages of all postbaseline values.

Table 2—Baseline values for intravascular ultrasonic measures and change in values from baseline between diabetic and nondiabetic patients with IPTW adjustment

IVUS parameter	Total (n = 1,039)	Baseline diabetes status: Diabetes (n = 159)	Baseline diabetes status: No diabetes (n = 880)	P value†
PAV (%)				
Baseline	36.3 ± 8.3	38.2 ± 8.8	36.0 ± 8.1	0.002
Change from baseline	−1.00 ± 0.09	−0.83 ± 0.13	−1.15 ± 0.13	0.08
P value for test of change = 0	<0.001	<0.001	<0.001	
TAV (mm^3)				
Baseline	144.1 ± 62.2	155.1 ± 66.0	142.1 ± 61.4	0.02
Change from baseline	−6.4 ± 0.5	−5.7 ± 0.7	−7.0 ± 0.7	0.19
P value for test of change = 0	<0.001	<0.001	<0.001	
Lumen volume (mm^3)				
Baseline	248.3 ± 88.6	248.0 ± 90.6	248.3 ± 88.3	0.91
Change from baseline	0 ± 0.9	−0.7 ± 1.2	0.6 ± 1.2	0.44
P value for test of change = 0	0.96	0.56	0.62	
EEM volume (mm^3)				
Baseline	392.4 ± 135.8	403.1 ± 138.5	390.4 ± 135.2	0.21
Change from baseline	−6.4 ± 1.1	−6.5 ± 1.6	−6.4 ± 1.6	0.96
P value for test of change = 0	<0.001	<0.001	<0.001	

Baseline values are reported as mean ± SD, and change values are reported as least squares mean ± SE. †P value reflects comparisons between diabetic and nondiabetic groups.

Heart Association/American College of Cardiology lipid treatment guidelines recommend high-intensity statins in diabetic individuals (without clinically evident atherosclerotic cardiovascular disease) who have an estimated 10-year risk of a cardiovascular event of >7.5%. These guidelines have now shifted emphasis away from specifically recommending target LDL-C levels (15). Previous U.S. guidelines (24), coupled with the present European guidelines (25), however, recommended lowering LDL-C to ≤70 mg/dL in patients with CAD, particularly those at greater cardiovascular risk (26). The present analysis, comprising the largest serial coronary imaging study of patients treated with high-intensity statins, suggests that lowering LDL-C to ≤70 g/dL in diabetic patients significantly modulates the progressive nature of diabetic coronary atherosclerosis. In contrast, diabetic patients not achieving LDL-C levels ≤70 mg/dL demonstrated significantly less disease regression compared with those without diabetes. This observation suggests that the threshold of achieving disease regression in diabetic patients likely requires a lower LDL-C level compared with nondiabetic individuals. As a consequence, the concept of targeting specific LDL-C levels in higher-risk patient subsets (such as those afflicted with diabetes) may ultimately require reappraisal in future clinical trials. Also noteworthy was the finding of intensive lipid lowering resulting in epicardial lumen volume preservation, with evidence of reverse arterial remodeling outlined by a reduction of EEM volumes (27).

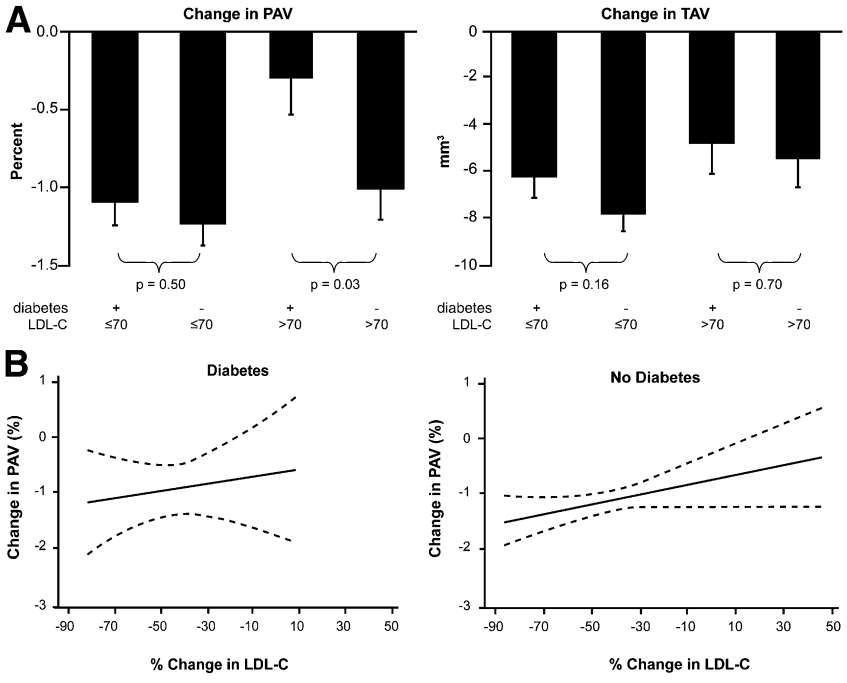

Figure 1—Intensive LDL-C lowering and atheroma progression. *A*: Changes in PAV and TAV in patients with and without diabetes according to average on-treatment LDL-C ≤ or >70 mg/dL. *B*: The relationship between percent change in LDL-C and change in PAV (solid line) with the upper and lower 95% CIs (dashed lines) for patients with and without diabetes.

Necropsy studies demonstrate diabetic coronary atheromas to contain a greater inflammatory component compared with nondiabetic coronary atheromas (28). Diabetic patients also displayed increased activation of proinflammatory pathways, increased free radical production, and larger necrotic cores (29). Along with LDL-C

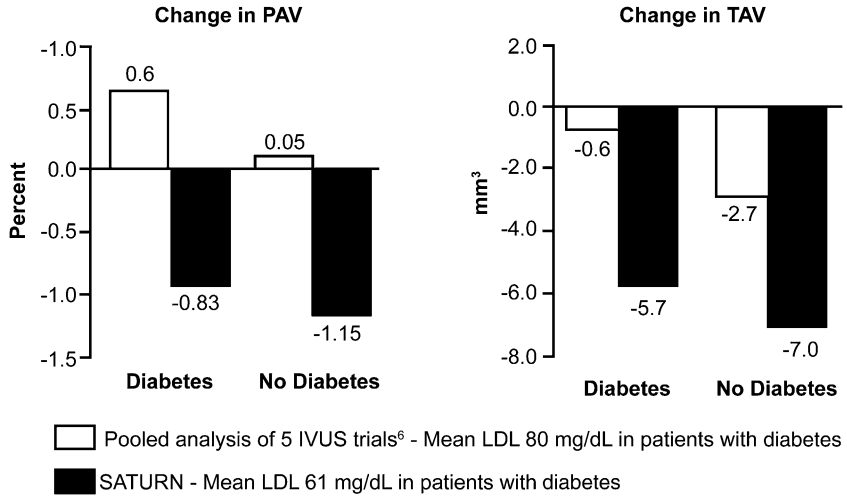

Figure 2—Comparison between current SATURN analysis and previous pooled analysis of five serial IVUS trials. Comparison of change in PAV and TAV seen in the current analysis of SATURN (black bars) in which the mean LDL-C in patients with diabetes was 61 mg/dL and a previous pooled analysis of five IVUS trials (6) (white bars) in which mean LDL-C in patients with diabetes was 80 mg/dL. Of note, statistical methods for the current analysis and previous analysis represented on this figure were different; thus no direct statistical comparisons between these analyses can be made.

reduction, statins also possess both anti-inflammatory and antioxidant effects that may enhance their antiatherosclerotic effect. The extended duration of high-intensity statin therapy in SATURN may have intensified these pleiotropic effects dose dependently, further promoting atheroma regression in these patients.

Although serial changes in coronary atheroma volume constitute a surrogate rather than clinical end point, previous studies have demonstrated significant associations between baseline and changes in coronary PAV with adverse cardiovascular events (17,30–32). Although not a substitute for a clinical outcomes trial, the present SATURN analysis demonstrates similar degrees of atheroma regression between patients with and without diabetes following maximally intensive statin therapy. These findings represent an important indicator of clinical benefit in this high-risk diabetic population.

This analysis has some limitations. This is post hoc analysis of a randomized trial. Consequently, there were differences in baseline characteristics and numbers of patients in each group. To correct for this, IPTW propensity matching was used to control for differences in baseline characteristics, which may not have entirely mitigated potential confounding. Changes in coronary atheroma volume measured on serial IVUS remains a surrogate end point. However, prior analyses have uncovered significant associations between IVUS-derived measures of coronary disease progression and incident coronary events (31,33). Moreover, there is unlikely to be a randomized clinical trial testing the efficacy of high-intensity statins in diabetic patients, and these SATURN insights serve as the only current direct evidence of the long-term antiatherosclerotic effects of intensive lipid modification in diabetic patients in vivo. The diagnosis of diabetes was recorded upon study enrollment. We were not able to establish whether the duration of diabetes or extent of glycemic control could have affected the response to high-intensity statin therapy. Lastly, this is an analysis of diabetic patients with known CAD, and hence these results may not apply to a diabetic population without known atherosclerotic disease.

In conclusion, high-intensity statin therapy is associated with coronary atheroma regression in both diabetic and nondiabetic patients, thus altering the progressive nature of diabetic atherosclerosis. This regression in diabetic individuals appears optimized when achieved LDL-C levels are below a 70 mg/dL threshold. These findings support the use of high-intensity statin treatment in diabetic patients with atherosclerotic disease. However, further research is required to elucidate if specific LDL-C targets are required to achieve plaque regression and lower clinical event rates in these high-risk diabetic patients with and without clinical atherosclerotic disease.

Acknowledgments. The authors appreciate the technical expertise of the Atherosclerosis Imaging Core Laboratory personnel at the Cleveland Clinic Coordinating Center for Clinical Research who performed all IVUS measurements.

Duality of Interest. SATURN was sponsored by AstraZeneca Pharmaceuticals. C.M.B. has received grant support from Abbott, AstraZeneca, Bristol-Myers Squibb, Genentech, GlaxoSmithKline, Kowa, Merck, Novartis, Roche, Sanofi-Synthelabo, and Takeda, consulting fees and honoraria from Abbott, Adnexus, Amarin, Amylin, AstraZeneca, Bristol-Myers Squibb, Esperion, Genentech, GlaxoSmithKline, Idera, Kowa, Merck, Novartis, Omthera, Resverlogix, Roche, Sanofi-Synthelabo, and Takeda, and lecture fees from Abbott, AstraZeneca, GlaxoSmithKline, and Merck. P.J.B. holds an advisory board position for AstraZeneca, Merck, Roche, CSL Behring, and Pfizer and receives grant support from Merck, consulting fees from CSL Behring, and lecture fees from AstraZeneca, Kowa, Merck, Pfizer, and Roche. M.J.C. receives grant support from CSL, GlaxoSmithKline, Pfizer, Randox, and Merck, consulting fees from Merck and Pfizer, lectures fees from Genzyme, Merck, Eli Lilly and Company, Roche, and Kowa, and equity interests in Wiley Inc. R.E. receives grant and travel support from the Heinz Nixdorf Foundation, German Research Foundation and accommodations/meeting expenses from Biotronik, Sanofi, and Novartis. P.L. serves as an unpaid consultant for Novartis, Johnson & Johnson, Amgen, and Roche, serves in unpaid leadership roles for clinical trials sponsored by AstraZeneca, GlaxoSmithKline, Novartis, Pfizer, Pronova, and Sigma Tau, and previously received royalties from Roche for the patent on CD40L in cardiovascular risk stratification. J.S.R. is an employee and owns stock in AstraZeneca. S.E.N. has received research support to perform clinical trials through the Cleveland Clinic Coordinating Center for Clinical Research from Pfizer, AstraZeneca, Novartis, Roche, Daiichi-Sankyo, Takeda, Sanofi, Resverlogix, and Eli Lilly and Company and is a consultant/advisor for many pharmaceutical companies but requires them to donate all honoraria or consulting fees directly to charity so that he receives neither income nor a tax deduction. S.J.N. has received speaking honoraria from AstraZeneca, Pfizer, Merck/Schering-Plough, and Takeda, consulting fees from AstraZeneca, Pfizer, Merck/Schering-Plough, Takeda, Roche, Novo Nordisk, LipoScience, and Anthera, and research support from AstraZeneca and Lipid Sciences. No other potential conflicts of interest relevant to this article were reported.

Author Contributions. B.S. and R.P. were involved in the initial study design, data analysis, and drafting of the manuscript. L.C. was involved in the initial study design and editing of the final manuscript. M.S. was responsible for all statistical analyses and drafting of the manuscript. C.M.B., P.J.B., M.J.C., R.E., P.L., J.S.R., K.U., and Y.K. formed part of the SATURN executive committee and were involved in the study design and provided edits, comments, and suggestions of content for the current manuscript. S.E.N. and S.J.N. were the principal investigator and study chairman, respectively, of SATURN and were involved in initial study design, data analysis, determining final content of the manuscript, and editing of the manuscript. All authors reviewed manuscript drafts and provided edits and comments. All authors reviewed and approved of the current version of the manuscript. S.J.N. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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