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Effect of Statin Treatment on Modifying Plaque Composition

A Double-Blind, Randomized Study

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ABSTRACT

BACKGROUND How statins alter the natural course of coronary atherosclerosis with compositional changes remains unclear.

OBJECTIVES This study aimed to determine the effect of statin therapy on modifying plaque composition.

METHODS The STABLE (Statin and Atheroma Vulnerability Evaluation) prospective, single-center, double-blind, randomized study evaluated the effect of statins on functionally insignificant coronary stenoses. We randomly assigned 312 patients with a virtual histology (VH) intravascular ultrasound–defined fibroatheroma-containing index lesion to rosuvastatin 40 mg versus 10 mg (2:1 ratio). In 225 (72%) patients, grayscale- and VH-intravascular ultrasound were completed at baseline and 12 months. The primary endpoint was the change in VH-defined percent compositional volume within the target segment from baseline to follow-up in the per-protocol analysis set.

RESULTS Percent necrotic core (NC) volume within the target segment significantly decreased from 21.3 ± 6.8% to 18.0 ± 7.5% during 1-year follow-up, whereas the percent fibrofatty volume increased (11.7 ± 5.8% vs. 14.8 ± 9.3%; all $p < 0.001$). Percent fibrous (59.4 ± 7.8% vs. 59.2 ± 8.6%) and dense calcium (7.6 ± 5.1% vs. 7.8 ± 5.6%) volumes were unchanged. Frequencies of VH (55% vs. 29%) decreased significantly. Normalized total (202.9 ± 72.3 mm^3 vs. 188.5 ± 67.8 mm^3; $p = 0.001$) and percent (51.4 ± 8.3% vs. 50.4 ± 8.8%; $p = 0.018$) atheroma volumes decreased. Independent predictors of percent NC volume change were body mass index ($\beta = 0.37$; 95% confidence interval [CI]: 0.05 to 0.70), high sensitivity C-reactive protein ($\beta = -3.16$; 95% CI: −5.64 to −0.69), and baseline percent NC volume ($\beta = -0.44$; 95% CI: −0.68 to −0.19; all $p < 0.05$). VH-defined percent compositional volume changes in the rosuvastatin 40- and 10-mg groups were similar.

CONCLUSIONS Rosuvastatin reduced NC and plaque volume and decreased thin-cap fibroatheroma rate. There were no significant differences between high- versus moderate-intensity rosuvastatin. (Statin and Atheroma Vulnerability Evaluation [STABLE]; NCT00997880) (J Am Coll Cardiol 2016;67:1772–83) © 2016 by the American College of Cardiology Foundation.

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Clinical benefits of lipid-lowering with 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors (statins) are well established (1-3). Intravascular ultrasound (IVUS) data have shown that statins may halt or even reverse the progression of coronary atherosclerosis, a presumed contributor to reduced cardiac mortality and morbidity (4-9). Although statins affected atheroma reduction in proportion to the ability to lower low-density lipoprotein (LDL) cholesterol (4-8), it has remained unclear whether the change in plaque composition is mediated by LDL lowering or is a pleiotropic effect. In addition, the optimal dose of intensive statin therapy for Asians has been indeterminate.

The appropriate treatment of nonischemia-producing coronary artery lesions with unstable plaque morphology is still under debate. The PROSPECT (Providing Regional Observations to Study Predictors of Events in the Coronary Tree) study demonstrated that a large plaque burden ≥70%, a small minimal lumen area ≤4.0 mm^2, and the presence of virtual histology (VH)-IVUS-defined thin-cap fibroatheroma (TCFA) are predictors of target lesion revascularization and recurrent events (10). However, the lack of serial follow-up imaging data has limited our understanding as to how statins alter the natural course of coronary atherosclerosis.

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Thus, the aims of this study in a prospective cohort of deferred coronary artery lesions were: 1) to assess the effect of statin therapy on the serial change in plaque composition within a fibroatheroma-containing target coronary artery segment; and 2) to compare the efficacy of high- versus moderate-intensity statins (rosuvastatin 40 mg vs. 10 mg) on plaque modification assessed by serial multimodality intravascular imaging at baseline and at 12-month follow-up.

METHODS

STUDY DESIGN. The STABLE (Statin and Atheroma Vulnerability Evaluation) trial was a prospective, single-center, double-blind, randomized study to assess the effect of high- and moderate-dose rosuvastatin on coronary plaque modification (**Central Illustration**). The principal investigator designed the trial, and the institutional review board approved the protocol. Funders did not participate in patient selection or management or in data collection and analysis. The funders assisted in the design of the protocol, but had no role in the conduct of the trial or in analysis or interpretation of the data. The principal investigator (S.J.P) had unrestricted access to the data after the database was locked and made the decision to submit the paper for publication. The principal investigator vouches for the completeness and accuracy of the analyses and the reported data. No agreements exist regarding confidentiality of the data among the funding company, sponsors, and the investigators. All patients provided written informed consent.

STUDY POPULATION. Consecutive patients 18 to 75 years of age who required clinically indicated coronary angiography or percutaneous coronary intervention were eligible if they had at least 1 deferred and untreated native coronary artery lesion with: 1) a visually-estimated angiographic diameter stenosis 20% to 50%; or 2) a diameter stenosis >50% without any evidence of inducible ischemia (fractional flow reserve ≥0.8 or no perfusion defect in the target vessel territory on thallium scan).

Anatomically comparable distal and proximal fiduciary points (such as side branches, calcium, or other imaging landmarks) were used for evaluating identical segments using multiple modalities at baseline and at follow-up. After clinical screening (Online Table 1), patients underwent VH-IVUS imaging of the target segment to identify an "index lesion" eligible for the study (see flow chart in Online Figure 1 for performance of VH-IVUS). Patients were eligible for randomization only if the index lesion contained a VH-identified fibroatheroma (see VH-IVUS in the Online Appendix). If so, patients were randomly assigned to receive high- (40 mg) or moderate-dose rosuvastatin (10 mg) once daily (2 tablets: 1 active drug [40 mg vs. 10 mg] plus 1 placebo) in a 2:1 ratio for 12 months. Serial angiography, grayscale- and VH-IVUS, and optical coherence tomography (OCT) were performed at baseline and at 12 months. Data analysis was performed in the per-protocol analysis set.

Clinical follow-up was also done after 1, 6, and 12 months to ascertain side effects and compliance. A clinical events committee whose members were unaware of the treatment assignments adjudicated cardiovascular events. Major adverse cardiac events were defined as the composites of death from any cardiac causes, myocardial infarction, and revascularization of the target lesions. Target lesion revascularization was considered clinically driven when the deferred vessels had stenosis of at least 50% in the presence of symptoms and objective evidence of ischemia in the target vessel territory. On the basis of follow-up angiography, major adverse cardiac events were attributed to a nonculprit lesion if the

ABBREVIATIONS AND ACRONYMS

EEM = external elastic membrane

hs-CRP = high-sensitivity C-reactive protein

IVUS = intravascular ultrasound

LDL = low-density lipoprotein

MLA = minimal lumen area

NC = necrotic core

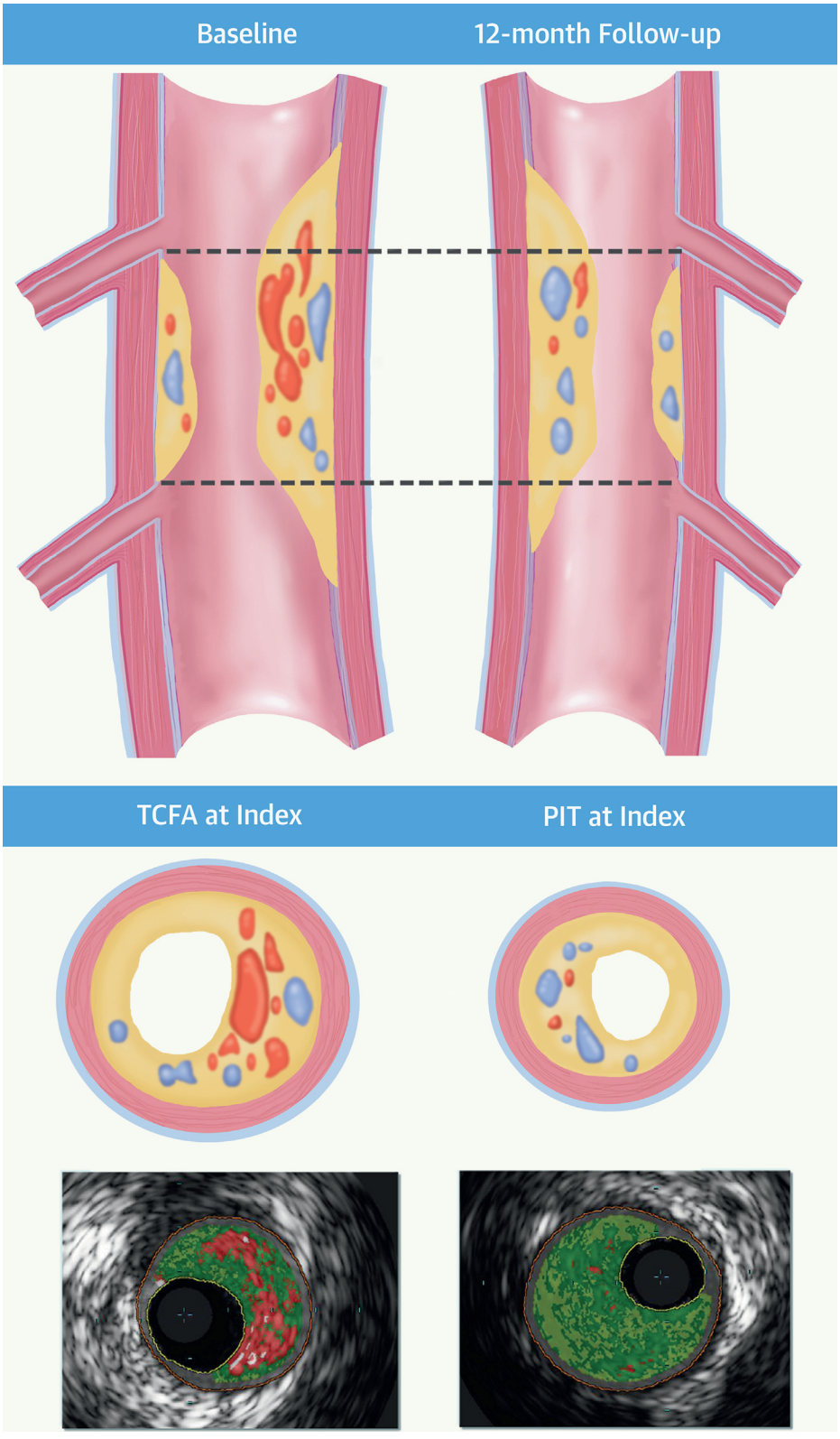
PAV = percent atheroma volume

TAV = normalized total atheroma volume

TCFA = thin-cap fibroatheroma

VH = virtual histology

CENTRAL ILLUSTRATION **Effect of Statin on Modifying Plaque Composition: The STABLE Trials**



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site associated with an event was previously untreated.

QUANTITATIVE CORONARY ANGIOGRAPHY. Quantitative coronary angiography was performed using standard techniques with automated edge-detection algorithms (CAAS-5, Pie-Medical, Maastricht, the Netherlands) in the angiographic analysis center of the CardioVascular Research Foundation (Seoul, Korea). Angiographic diameter stenosis, minimal lumen diameter, lesion length, and reference lumen diameter were measured at baseline and at follow-up (11).

GRAYSCALE IVUS. At baseline and at 12-month follow-up, grayscale-IVUS imaging of the same artery was performed using motorized transducer pullback (0.5 mm/s) and a commercial scanner (Boston Scientific/SCIMED, Minneapolis, Minnesota), consisting of a rotating, 40-MHz transducer within a 3.2-F imaging sheath. Using computerized planimetry (EchoPlaque 3.0, Indec Systems, Santa Clara, California), offline quantitative IVUS analysis was performed in accordance with the standards of the American College of Cardiology and the European Society of Cardiology in a core laboratory at the CardioVascular Research Foundation (12).

Minimal lumen area (MLA) and the external elastic membrane (EEM) area at the MLA site were measured. Plaque + media area was calculated as: EEM − lumen area. Plaque burden was calculated as: (plaque + media)/EEM × 100 (%) (12). For volumetric analysis, every 60th image within the target segment, beginning with the distal fiduciary site and ending with the proximal fiduciary site, was measured. All volumes were calculated using Simpson's rule and then normalized for analysis length.

Normalized total atheroma volume (TAV) and percent atheroma volume (PAV) were calculated as previously described (see grayscale IVUS in the Online Appendix) (4-8). The change in normalized TAV was calculated as: (normalized TAV at follow-up) − (normalized TAV at baseline). The change in PAV was calculated as: (PAV at follow-up) − (PAV at baseline).

The investigators were blinded to the assigned statin treatment and to whether a study was acquired at baseline or at follow-up. When there was discordance between the observers, a consensus reading was obtained.

VIRTUAL HISTOLOGY IVUS. VH-IVUS was obtained using a synthetic aperture array, 20-MHz, 2.9-F catheter (Eagle Eye, In-Vision Gold, Volcano Corporation, San Diego, California) with motorized catheter pullback (0.5 mm/s) after intracoronary administration of 0.2 mg nitroglycerin. VH-IVUS analyses were performed using pcVH version 2.1 software (Volcano Corporation). Using the same distal and proximal fiduciary points, the same coronary artery segment was imaged and assessed for the VH-IVUS analysis as for the grayscale IVUS analysis. EEM and luminal borders were contoured for each frame (median interslice distance, 0.40 mm).

Plaque components (13-16) and plaque types (10,14,15) were assessed as previously described (see VH-IVUS in the Online Appendix). If target segment had TCFA, the worst plaque type was TCFA. Without any TCFA within target segment, the worst plaque type was classified at the maximal percent necrotic core (NC) site. The worst plaque type within the target segment was assessed at baseline and at follow-up. At follow-up, plaque type was assessed at the corresponding site where the worst type of plaque was located at baseline (index lesion).

The pre-specified primary efficacy endpoint was the change in VH-defined percent compositional volume within the target segment from baseline to follow-up. The pre-specified secondary endpoint was the change in percent compositional volume comparing the rosuvastatin 40-mg versus 10-mg groups.

The investigators were blinded to the assigned statin treatment and also to whether a study was at baseline or follow-up. When there was discordance between the observers, including plaque type classification, a consensus reading was obtained.

OPTICAL COHERENCE TOMOGRAPHY. OCT was performed at the index lesion selected on the basis of VH-IVUS criteria using the same distal and proximal fiduciary points, (see OCT evaluation in the Online Appendix). Calcification, lipid pool, TCFA, plaque

CENTRAL ILLUSTRATION Continued

A total of 312 patients with a VH-IVUS–defined fibroatheroma-containing index lesion were randomly allocated to rosuvastatin 40 mg versus 10 mg. Data were analyzed in 225 patients in the per-protocol analysis set. At 1-year follow-up, all segmental volumes of EEM, lumen, and plaque decreased, which was associated with a constrictive remodeling. The frequency of VH-defined TCFA decreased from 55% at baseline to 29% at follow-up. Dashed lines refer to the target segment between fiduciary sites. EEM = external elastic membrane; IVUS = intravascular ultrasound; PIT = pathological intimal thickening; STABLE = Statin and Atheroma Vulnerability Evaluation; TCFA = thin-cap fibroatheroma; VH = virtual histology.

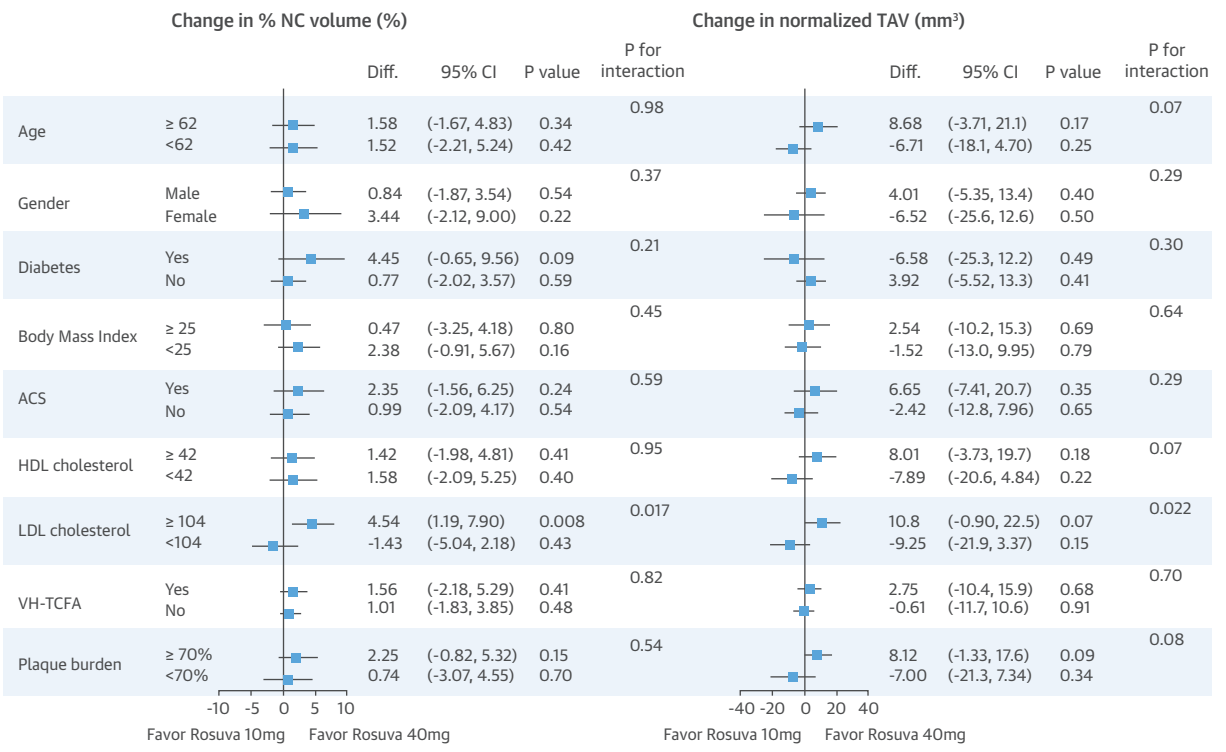
rupture, and thrombus were defined as previously described (17-20). An OCT-TCFA had a fibrous cap thickness at the thinnest part ≤65 μm and an angle of lipidic tissue ≥90°.

OCT images were analyzed by 2 independent investigators (S.-J.K. and J.-M.A.) who were blinded to the assigned statin treatment and to whether a study was at baseline or follow-up. When there was discordance between the observers, a consensus reading was obtained.

BIOCHEMICAL ASSESSMENT. Serial changes of high-sensitivity C-reactive protein (hs-CRP) and serum lipids (total cholesterol, triglycerides, high-density lipoprotein cholesterol, and LDL cholesterol) were assessed at baseline, 6 months, and 12 months.

STATISTICAL ANALYSIS. Sample size was calculated as described in the Online Appendix. All statistical analyses were performed using SAS release 9.2 (SAS Institute, Inc., Cary, North Carolina). Continuous variables were expressed as mean ± SD; categorical variables were shown as counts and percentages. Continuous variables were compared using unpaired Student *t* tests or nonparametric Mann-Whitney *U* tests; categorical variables were compared using chi-square statistics or the Fisher exact test. Changes in variables at 1-year follow-up from baseline were made using paired Student *t* tests for continuous and McNemar's test for categorical data. We constructed linear regression models to evaluate predictors of the changes in percent NC volume and in normalized TAV. Variables with a p value ≤0.20 in univariable analyses were candidates for entry into the multiple linear regression models. A stepwise selection method was used to develop the final multivariable models with a p value <0.1 to be included in the models. Residual diagnostic plots were used to detect features of concern in the model. Exploratory analyses of the residuals suggested that the chosen models were not inappropriate for the changes in percent NC volume and the change in normalized TAV. The results of the pre-specified subgroup

FIGURE 1 Pre-Specified Subgroup Analysis



(A) A significant interaction between LDL cholesterol at baseline and reduction in percent NC volume (p for interaction = 0.017) by rosuvastatin 40 mg (vs. 10 mg). **(B)** A significant interaction between LDL cholesterol at baseline and decrease in normalized TAV (p for interaction = 0.022) by rosuvastatin 40 mg (vs. 10 mg). *Subgroups were classified by median values. ACS = acute coronary syndrome; CI = confidence interval; HDL = high-density lipoprotein; LDL = low-density lipoprotein; NC = necrotic core; TAV = normalized total atheroma volume; VH-TCFA = virtual histology-defined thin-cap fibroatheroma.

analysis in Figure 1 were on the basis of the linear regression model, but an additional interaction p value was provided to quantify the evidence that change was different between the groups. We used the Bonferroni test for multiplicity correction of the change in each of 4 compositions (fibrous, fibrofatty, necrotic core, and dense calcium). All reported p values were 2-sided, and a value of $p < 0.05$ was considered statistically significant.

RESULTS

PATIENT POPULATION. Between May 2010 and December 2013, a total of 312 patients who met all clinical and VH-IVUS screening enrollment criteria were randomly assigned to rosuvastatin 40 mg (n = 209) versus 10 mg (n = 103). During treatment, 87 (28%) patients withdrew. Reasons for study discontinuation are shown in Online Table 2. Of 17 patients with adverse statin effects, 15 (88%) patients had been allocated to the rosuvastatin 40-mg group. Finally, paired baseline and follow-up grayscale- and VH-IVUS data were available in 225 patients in the per-protocol analysis set.

Clinical and laboratory characteristics of both the overall cohort of 225 patients and in the 2 dosing groups are shown in Table 1. Overall, 72 (32%) patients had a history of statin exposure before admission, whereas 153 (68%) patients were statin-naïve. Discharge medications were beta-blockers in 62%, calcium antagonists in 74%, angiotensin-converting enzyme inhibitors or angiotensin receptor blockers in 28%, aspirin in 99%, clopidogrel in 77%, and cilostazol in 2%.

Although LDL cholesterol and hs-CRP decreased with statin therapy, there was no significant relationship between the change in LDL cholesterol and the change in hs-CRP (r = 0.017; p = 0.85).

QUANTITATIVE CORONARY ANGIOGRAPHIC DATA. Lesion location was the left anterior descending artery in 88 patients (39%), the right coronary artery in 94 (40%), and the left circumflex artery in 43 (19%). Between baseline and 1-year follow-up, there was an

TABLE 1 Clinical and Laboratory Data

	Total (n = 225)	Rosuvastatin 40 mg (n = 152)	Rosuvastatin 10 mg (n = 73)	p Value
Age, yrs	62.3 ± 9.2	62.6 ± 9.3	61.8 ± 8.9	0.561
Male	164 (73)	108 (71)	56 (77)	0.425
Diabetes	56 (25)	40 (26)	16 (22)	0.762
Hypertension	142 (63)	103 (68)	42 (58)	0.180
Current smoking	71 (32)	46 (30)	25 (34)	0.465
Hyperlipidemia	132 (59)	84 (55)	28 (65)	0.390
Previous statin use	72 (32)	47 (31)	25 (34)	0.805
Previous PCI	15 (7)	11 (7)	4 (6)	0.779
Previous MI	4 (2)	2 (1)	2 (3)	0.597
Body mass index, kg/m^2	25.1 ± 2.9	24.9 ± 2.8	25.7 ± 3.0	0.070
Acute coronary syndrome	94 (42)	61 (40)	33 (45)	0.281
hs-CRP at baseline, mg/dl	0.22 ± 0.38 0.08 (0.04–0.21)	0.21 ± 0.38 0.08 (0.04–0.19)	0.23 ± 0.39 0.09 (0.05–0.23)	0.203*
hs-CRP at 12 months, mg/dl	0.10 ± 0.15†	0.10 ± 0.15†	0.12 ± 0.15†	0.240*
Lipid profiles at baseline, mg/dl				
Total cholesterol	173.1 ± 39.6	170.8 ± 34.8	177.9 ± 48.0	0.207
LDL cholesterol	106.6 ± 35.6	105.3 ± 32.8	109.3 ± 40.9	0.514*
HDL cholesterol	43.4 ± 11.9	44.9 ± 12.9	40.5 ± 9.3	0.011
Triglycerides	145.7 ± 81.8 126.0 (91.5–175.0)	133.4 ± 68.7 120.5 (87.0–165.3)	170.9 ± 99.4 143.5 (102.3–204.7)	0.006*
Lipid profiles at 12 months, mg/dl				
Total cholesterol	126.9 ± 31.3†	119.3 ± 26.9†	142.9 ± 35.4†	<0.001
LDL cholesterol	66.0 ± 26.1†	59.1 ± 22.2†	78.8 ± 27.8†	<0.001*
HDL cholesterol	49.1 ± 11.8†	49.7 ± 12.3	47.7 ± 10.6†	0.241
Triglycerides	114.8 ± 65.6† 103.0 (75.0–135.5)	104.1 ± 52.3† 92.0 (70.0–130.0)†	137.1 ± 83.3† 112.5 (83.0–155.5)†	0.004*

Values are mean ± SD, n (%), or median (interquartile range). *p values using nonparametric Mann-Whitney *U* test. †p value <0.05 vs. at baseline.

HDL = high-density lipoprotein; hs-CRP = high-sensitivity C-reactive protein; LDL = low-density lipoprotein; MI = myocardial infarction; PCI = percutaneous coronary intervention.

overall decrease in minimal lumen diameter (2.1 ± 0.5 mm vs. 2.0 ± 0.5 mm; p < 0.001) and an increase in diameter stenosis (36.5 ± 12.2% vs. 38.4 ± 12.9%; p < 0.001). In addition, there were significant decreases in proximal (3.6 ± 0.5 mm vs. 3.5 ± 0.5 mm) and distal (3.1 ± 0.5 mm vs. 3.0 ± 0.5 mm) reference lumen diameters (all p < 0.001).

GRAYSCALE AND VH-IVUS FINDINGS. For the overall cohort of 225 lesions, grayscale- and VH-IVUS data are summarized in Tables 2 and 3. Between baseline and 1-year follow-up, there were significant overall decreases in normalized TAV (202.9 ± 72.3 mm^3 vs. 188.5 ± 67.8 mm^3; p = 0.001) and PAV (51.4 ± 8.3% vs. 50.4 ± 8.8%; p = 0.018).

The primary efficacy parameter, changes in VH-defined percent compositional volumes within the target segment, is shown in Table 2. Segmental percent NC volume significantly decreased from 21.3 ± 6.8% to 18.0 ± 7.5% during the 1-year follow-up, whereas the percent fibrofatty volume increased (11.7 ± 5.8% vs. 14.8 ± 9.3%; all p < 0.001). The change in percent NC volume significantly correlated with the change in hs-CRP (r = 0.184; p = 0.015), but not with the change in LDL (r = −0.054; p = 0.43). VH-defined TCFA-containing lesions at baseline showed a greater change in percent NC volume at follow-up compared with those without a VH-TCFA (−5.2 ± 9.6% vs. −0.9 ± 6.8%; p = 0.001). The change in percent NC volume did not correlate with the change in normalized TAV (r = 0.067; p = 0.316).

As the secondary efficacy parameter, the change in VH-defined percent compositional volume within the target segment was not significantly different between the rosuvastatin 40- and 10-mg groups (Table 3).

Although statin-naïve patients (vs. patients with a history of stain exposure before admission) showed a greater decrease in LDL cholesterol levels, there was no significant difference in the changes in percent NC

TABLE 2 Grayscale- and VH-IVUS Data in the Overall Cohort of 225 Lesions

	Baseline	Follow-Up	95% CI	p Value	p Value by Bonferroni Test
Grayscale IVUS data					
Lesion length, mm	25.4 ± 8.9	25.5 ± 8.9	+0.1 (0.0 to 0.1)	0.117	
MLA, mm^2	4.3 ± 1.9	4.2 ± 2.0	−0.1 (−0.3 to 0.0)	0.030*	
EEM area at the MLA, mm^2	13.7 ± 4.7	12.7 ± 4.4	−0.9 (−1.3 to −0.6)	<0.001*	
P + M area at the MLA, mm^2	9.4 ± 3.9	8.6 ± 3.6	−0.8 (−1.1 to −0.5)	<0.001*	
Plaque burden at the MLA, %	67.7 ± 10.9	66.4 ± 12.1	−1.3 (−2.3 to −1.2)	0.026	
Normalized lumen, mm^3/mm	7.8 ± 3.3	7.6 ± 3.5	−0.2 (−0.5 to 0.0)	0.001*	
Normalized EEM, mm^3/mm	16.0 ± 5.3	15.2 ± 5.4	−0.8 (−1.1 to −0.6)	<0.001*	
Normalized P + M, mm^3/mm	8.2 ± 2.9	7.6 ± 2.7	−0.6 (−0.7 to −0.4)	<0.001*	
Remodeling index	0.89 ± 0.18	0.86 ± 0.19	−0.02 (−0.04 to 0.0)	0.034	
VH-IVUS segmental data (primary endpoint)					
Fibrous volume, %	59.4 ± 7.8	59.2 ± 8.6	−0.2 (−1.1 to 0.8)	0.744	0.999
Fibrofatty volume, %	11.7 ± 5.8	14.8 ± 9.3	+3.1 (1.9 to 4.2)	<0.001*	<0.001
Necrotic core volume, %	21.3 ± 6.8	18.0 ± 7.5	−3.2 (−4.4 to −2.1)	<0.001*	<0.001
Dense calcium volume, %	7.6 ± 5.1	7.8 ± 5.6	+0.3 (−0.3 to 0.8)	0.368*	0.999
VH-IVUS index lesion data					
% fibrous, %	47.3 ± 11.3	55.7 ± 12.3	+8.4 (6.7 to 10.2)	<0.001	<0.001
% fibrofatty, %	5.2 ± 4.7	9.9 ± 9.4	+4.6 (3.4 to 5.9)	<0.001*	<0.001
% necrotic core, %	36.4 ± 9.5	24.3 ± 11.3	−12.1 (−13.7 to −10.4)	<0.001*	<0.001
% dense calcium, %	11.1 ± 8.0	10.0 ± 8.4	−1.0 (−2.1 to 0.0)	0.051*	0.204
Maximal % necrotic core, %	37.2 ± 9.2	33.1 ± 9.3	−4.1 (−5.6 to −2.6)	<0.001	
Worst plaque type					
VH-TCFA	123 (54.7)	66 (29.3)		<0.001	
Thick-cap fibroatheroma	102 (45.3)	159 (70.7)			
Plaque type at index					
VH-TCFA	123 (54.7)	44 (19.6)			
Thick-cap fibroatheroma	102 (45.3)	159 (70.7)			
Pathological intimal thickening	0 (0)	19 (8.4)		<0.001	
Fibrous	0 (0)	3 (1.3)			
Fibrocalcific	0 (0)	0 (0)			

Values are mean ± SD or n (%), unless otherwise indicated. *p values using nonparametric Mann-Whitney *U* tests.

CI = confidence interval; EEM = external elastic membrane; IVUS = intravascular ultrasound; MLA = minimal lumen area; P + M = plaque plus media; VH-IVUS = virtual histology-intravascular ultrasound; VH-TCFA = virtual histology-defined thin-cap fibroatheroma.

TABLE 3 Changes in Efficacy Endpoints and Laboratory Values

	Total (N = 225)	Rosuvastatin 40 mg (n = 152)	Rosuvastatin 10 mg (n = 73)	Difference (95% CI)	p Value	p Value by Bonferroni Test
Change in normalized TAV	−14.36 ± 2.44	−14.72 ± 2.40	−13.63 ± 2.56	−1.08 (−9.53 to 7.37)	0.717*	
Change in PAV	−0.87 ± 0.39	−0.88 ± 0.40	−0.85 ± 0.38	−0.03 (−1.39 to 1.38)	0.735*	
VH-IVUS segmental data (secondary endpoint)						
Change in % fibrous volume	−0.15 ± 0.58	−0.07 ± 0.58	−0.34 ± 0.60	0.26 (−1.75 to 2.29)	0.793*	0.999
Change in % fibrofatty volume	3.11 ± 0.72	3.80 ± 0.71	1.69 ± 0.74	2.11 (−0.38 to 4.61)	0.097*	0.388
Change in % necrotic core volume	−3.22 ± 0.71	−3.72 ± 0.71	−2.17 ± 0.70	−1.55 (−3.99 to 0.89)	0.223*	0.892
Change in % dense calcium volume	0.25 ± 0.36	−0.02 ± 0.35	0.82 ± 0.37	−0.84 (−2.07 to 0.39)	0.197*	0.788
VH-IVUS index lesion data						
Change in % fibrous at index	−3.71 ± 0.98	−2.75 ± 0.97	−5.68 ± 0.99	2.72 (−0.43 to 6.29)	0.088*	0.352
Change in % fibrofatty at index	4.67 ± 0.76	5.10 ± 0.76	3.79 ± 0.78	1.31 (−1.33 to 3.95)	0.329*	0.999
Change in % necrotic core at index	−12.05 ± 1.05	−12.08 ± 1.02	−11.98 ± 1.13	−0.11 (−3.75 to 3.53)	0.877*	0.999
Change in % dense calcium at index	−1.02 ± 0.65	−1.34 ± 0.66	−0.35 ± 0.64	−0.98 (−3.25 to 1.27)	0.391*	0.999
Change in maximal % necrotic core	−4.14 ± 0.92	−4.20 ± 0.90	−4.00 ± 0.98	−0.19 (−3.39 to 2.99)	0.902*	
Change in hs-CRP, mg/dl	−0.12 ± 0.03	−0.12 ± 0.03	−0.12 ± 0.03	0.10 (−0.11 to 0.13)	0.868*	
% change in total cholesterol, mg/dl	−24.01 ± 1.88	−28.22 ± 1.54	−15.22 ± 2.29	−13.01 (−19.36 to −6.65)	<0.001*	
% change in LDL cholesterol, mg/dl	−31.71 ± 2.97	−38.71 ± 2.53	−16.87 ± 3.46	−21.84 (−32.12 to −11.54)	<0.001*	
% change in HDL cholesterol, mg/dl	16.32 ± 1.89	14.36 ± 1.89	20.39 ± 1.88	−6.03 (−12.72 to 0.66)	0.077*	
% change in triglyceride, mg/dl	−12.04 ± 3.40	−13.16 ± 3.27	−9.69 ± 3.68	−3.47 (−15.56 to 8.62)	0.572*	

Values are mean ± SE, unless otherwise indicated. *p values using nonparametric Mann-Whitney *U* test.
PAV = percent atheroma volume; TAV = total atheroma volume; other abbreviations as in Tables 1 and 2.

volume, normalized TAV, and PAV between the 2 groups (Online Table 3).

Table 4 summarizes subgroup-specific effects of rosuvastatin on the changes in plaque volume and composition, according to MLA ≤4.0 mm^2, plaque burden ≥70%, and the presence of VH-TCFA. The effect of rosuvastatin was shown according to angiographic diameter stenosis ≥50% (Online Table 4).

Table 5 compares the effects of rosuvastatin 40 mg versus 10 mg in patients with stable and unstable angina. There was a greater reduction in normalized TAV in stable versus unstable angina patients (−19.4 ± 2.8 mm^3 vs. −10.7 ± 2.8 mm^3; p = 0.027), whereas no significant difference in the change in percent NC volume was found between the 2 groups (−3.5 ± 0.9% vs. −3.0 ± 0.8%; p = 0.66).

PREDICTORS OF CHANGE IN NC AND PLAQUE VOLUMES. Table 6 shows univariable analysis for the baseline clinical and morphological factors

TABLE 4 Subgroup-Specific Effects of Statins According to Minimal Lumen Area, Plaque Burden, and VH-TCFA

	Minimal Lumen Area			Plaque Burden			VH-TCFA		
	≤4.0 mm^2 (n = 117)	>4.0 mm^2 (n = 108)	Difference (95% CI)	≥70% (n = 105)	<70% (n = 120)	Difference (95% CI)	Presence (n = 123)	Absence (n = 102)	Difference (95% CI)
Rosuvastatin 40 mg	76 (65%)	76 (70%)		71 (68%)	81 (68%)		86 (70%)	66 (65%)	
Rosuvastatin 10 mg	41 (35%)	32 (30%)		34 (32%)	39 (32%)		37 (30%)	36 (35%)	
Change in normalized TAV, mm^3	−11.2 ± 2.6	−17.7 ± 3.2	6.5 (−1.3 to 14.4)	−9.8 ± 2.5	−19.5 ± 3.2	9.7 (1.9 to 17.6)*	−15.1 ± 2.6	−13.4 ± 3.2	−1.8 (−9.7 to 6.2)
Change in PAV, %	−1.0 ± 0.5	−0.7 ± 0.5	−0.3 (−1.5 to 1.0)	−0.3 ± 0.5	−1.5 ± 0.4	1.3 (0.0 to 2.5)*	−1.0 ± 0.4	−0.7 ± 0.5	−0.3 (−1.6 to 1.0)
Change in % fibrous volume, %	−0.1 ± 0.7	−0.2 ± 0.7	0.1 (−1.7 to 2.0)	−1.2 ± 0.7	1.1 ± 0.7	−2.3 (−4.2 to −0.5)	0.8 ± 0.8	−1.4 ± 0.6	2.2 (0.3 to 4.1)†
Change in % fibrofatty volume, %	3.3 ± 0.8	2.9 ± 0.9	0.5 (−1.8 to 2.8)	1.8 ± 0.8	4.6 ± 0.8	−2.9 (−5.2 to −0.6)†	4.4 ± 0.9	1.6 ± 0.8	2.8 (0.4 to 5.1)
Change in % necrotic core volume, %	−3.2 ± 0.9	−3.2 ± 0.8	0.0 (−2.3 to 2.3)	−1.6 ± 0.8	−5.1 ± 0.8	3.5 (1.2 to 5.7)†	−5.1 ± 0.9	−0.8 ± 0.7	−4.3 (−6.5 to −2.1)†
Change in % dense calcium volume, %	−12.1 ± 1.2	−11.9 ± 1.3	−0.6 (−1.7 to 0.6)	1.1 ± 0.4	−0.7 ± 0.4	1.8 (0.6 to 2.9)†	−0.1 ± 0.4	0.6 ± 0.4	−0.7 (−1.8 to 0.5)

Values are mean ± SE, unless otherwise indicated. *p < 0.05 using nonparametric Mann-Whitney *U* test. †p < 0.05 using nonparametric Mann-Whitney *U* test (with Bonferroni method for multiplicity correction).
Abbreviations as in Tables 2 and 3.

TABLE 5 Changes in Efficacy Endpoints Between Patients With Stable Versus Unstable Angina

	Stable Angina				Unstable Angina				
	Rosuvastatin				Rosuvastatin				
	40 mg (n = 91)	10 mg (n = 40)	Difference (95% CI)	p Value	40 mg (n = 61)	10 mg (n = 33)	Difference (95% CI)	p Value	Interaction p Value
Change in normalized TAV, mm^3	−9.9 ± 2.4	−12.3 ± 5.7	2.4 (−7.9 to 12.8)	0.865	−21.7 ± 4.7*	−15.1 ± 4.3	−6.7 (−20.7 to 7.4)	0.320	0.287
Change in PAV, %	−0.6 ± 0.5	−0.7 ± 0.8	0.4 (−1.6 to −1.7)	0.649	−1.3 ± 0.7	−1.1 ± 0.8	−0.2 (−2.5 to 2.1)	0.821	0.867
Change in % fibrous volume, %	−0.1 ± 0.7	−0.1 ± 1.2	0.0 (−2.5 to 2.5)	0.996	0.0 ± 1.0	−0.6 ± 1.3	0.6 (−2.7 to 3.9)	0.718	0.772
Change in % fibrofatty volume, %	3.3 ± 0.7	1.6 ± 1.7	1.7 (−1.3 to 4.7)	0.268	4.6 ± 1.4	1.9 ± 1.3	2.7 (−1.5 to 7.0)	0.204	0.682
Change in % necrotic core volume, %	−3.3 ± 0.8	−2.3 ± 1.4	−1.0 (−4.2 to 2.2)	0.378	−4.3 ± 1.2	−2.0 ± 1.4	−2.3 (−6.2 to 1.6)	0.394	0.586
Change in % dense calcium volume, %	0.1 ± 0.4	0.9 ± 0.5	−0.7 (−2.3 to 0.9)	0.368	−0.2 ± 0.6	0.7 ± 0.8	−1.0 (−2.9 to 0.9)	0.308	0.828

Values are mean ± SE, unless otherwise indicated. p values using nonparametric Mann-Whitney *U* test. *p < 0.05 vs. stable angina patients with rosuvastatin 40 mg.
Abbreviations as in Tables 2 and 3.

affecting the changes in percent NC volume and the changes in normalized TAV. On multivariable analysis, the predictors of the change in percent NC volume were body mass index (β = 0.37; 95% confidence interval [CI]: 0.05 to 0.70; p = 0.025), hs-CRP (β = −3.16; 95% CI: −5.64 to −0.69; p = 0.012), and baseline percent NC volume (β = −0.44; 95% CI: −0.68 to −0.19; p = 0.001). Independent predictors of the changes in normalized TAV included age (β = 0.42; 95% CI: 0.02 to 0.83; p = 0.039), diabetes mellitus (β = 8.78; 95% CI: 0.26 to 17.2; p = 0.043), and normalized TAV at baseline (β = −0.15; 95% CI: −0.19 to −0.10; p < 0.001).

EFFECT OF HIGH- VERSUS MODERATE-DOSE STATIN. Online Table 5 shows baseline and follow-up grayscale and VH-IVUS data in patients treated with rosuvastatin 40 and 10 mg. Even though rosuvastatin 40 mg was associated with a greater reduction in total cholesterol, LDL cholesterol, and the low- to high-density lipoprotein ratio compared with rosuvastatin 10 mg, the changes in atheroma volume and composition were not significantly different between the 2 dosing groups (all p > 0.05) (Online Table 6). Between rosuvastatin 40 mg versus 10 mg, there were no significant differences in the frequency of normalized TAV reduction (69.1% vs. 63.0%; p = 0.224) or the frequency of percent NC volume reduction (64.5% vs. 58.9%; p = 0.253). In contrast, the pre-specified subgroup analysis showed a significant interaction between higher LDL cholesterol at baseline (≥104 mg/dl vs. <104 mg/dl as the median) and a greater reduction in percent NC volume (p for interaction = 0.017) by rosuvastatin 40 mg (vs. 10 mg) (Figure 1).

TABLE 6 Univariable Analysis for the Prediction of Changes in % NC and Normalized TAV

	Change % NC Volume			Change in Normalized TAV		
Variables at Baseline	Beta	SE	p Value	Beta	SE	p Value
Age	0.013	0.064	0.836	0.481	0.217	0.027
Male	1.212	1.308	0.355	−5.220	4.506	0.248
Diabetes mellitus	1.741	1.342	0.196	8.869	4.608	0.056
Body mass index	0.314	0.203	0.124	0.910	0.703	0.196
Acute coronary syndrome	−0.539	1.181	0.648	−8.742	4.031	0.031
Statin 10 mg (vs. 40 mg)	1.548	1.240	0.213	1.083	4.291	0.801
LDL cholesterol	−0.002	0.017	0.890	0.003	0.058	0.964
hs-CRP	−3.904	1.512	0.011	−7.594	5.266	0.151
Plaque burden at MLA	−0.103	0.053	0.053	−0.442	0.181	0.016
Normalized TAV	−0.009	0.008	0.251	−0.146	0.026	<0.001
% NC volume	−0.715	0.070	<0.001	−0.080	0.293	0.784
TCFA at index site	−4.308	1.134	<0.001	−1.770	4.034	0.661

NC = necrotic core; other abbreviations as in Tables 2 and 3.

OCT DATA. Except for 72 patients with a large vessel (>4.0 mm) or 16 patients with proximal lesion location, 224 patients were enrolled in the substudy. Follow-up OCT was performed in 147 patients. After excluding 18 patients with poor-quality images and 40 patients with mismatched OCT and IVUS target segments, both baseline and follow-up images could be analyzed in 89 patients (62 patients with rosuvastatin 40 mg and 27 patients with rosuvastatin 10 mg). Overall, the frequency of TCFA decreased from 44% at baseline to 20% at follow-up (p < 0.001), whereas there were no significant differences in the frequency of plaque rupture (16% vs. 12%), thrombi (17% vs. 11%), and calcium (67% vs. 73%) during follow-up (all p > 0.05). Online Figure 2 shows an example with serial changes in the multimodality imaging parameters.

CLINICAL OUTCOMES AT 12 MONTHS. During 12 months of follow-up, there was no cardiac death. Nonculprit-related major adverse cardiac events occurred in 8 (3.6%) patients (7 target lesion revascularizations and 1 myocardial infarction). There

was no significant difference in nonculprit-related event rates between rosuvastatin 40 mg versus 10 mg (3.9% vs. 2.7%; $p > 0.05$). Among the 175 patients whose culprit lesions were treated with stent implantation, 12-month culprit-related events occurred in 4 (2.3%) patients (3 target lesion revascularizations and 1 stent thrombosis).

DISCUSSION

Using baseline and follow-up multimodality intravascular imaging analysis, we observed changes in individual atherosclerotic plaque components that have been validated as high risk in the PROSPECT study (10). In this current study evaluating fibroatheroma-containing nonculprit target segments, rosuvastatin therapy reduced percent NC volume, total atheroma volume, and the frequency of VH-TCFA, which indicates that the amount and composition of atherosclerotic plaques can be modified by statin therapy. Rosuvastatin seemed to be effective in reducing percent NC volume irrespective of previous statin exposure or clinical presentation. Although high-dose rosuvastatin was associated with a greater decrease in LDL cholesterol levels, intravascular imaging effects at 1 year of follow-up were equivalent between the 2 groups (40 mg vs. 10 mg). The overall rate of plaque regression in the current analysis (67%) was consistent with those in the SATURN (Coronary Atheroma by Intravascular Ultrasound: Effect of Rosuvastatin versus Atorvastatin) (68.5% by rosuvastatin 40 mg/day) and the ASTEROID (A Study to Evaluate the Effect of Rosuvastatin on Intravascular Ultrasound-Derived Coronary Atheroma Burden) trials (63.6% by rosuvastatin 40 mg/day) (5,6). Independent predictors of percent NC volume reduction were a lower body mass index, a higher hs-CRP at baseline, and a larger percent NC volume at baseline. Unlike other studies in which patients with mild to intermediate angiographic stenosis were included irrespective of underlying plaque morphology, the current double-blinded, randomized trial only enrolled patients with index lesions identified as fibroatheromas by VH-IVUS.

The lack of association between the change in percent NC volume and the change in normalized TAV suggested that rosuvastatin could modify plaque compositions irrespective of its effect on atheroma reduction. The direct correlation between the reduced percent NC volume and the change in hs-CRP (not LDL cholesterol) implied that the anti-inflammatory effect of rosuvastatin might be an important mechanism underlying the plaque compositional changes. A previous study showed that 3-hydroxy-3-methylglutaryl coenzyme A reductase was present in coronary atherosclerotic plaques and was commonly expressed in TCFA (21). In the current analysis, the frequency of VH-TCFA decreased from 55% to 29%; and VH-TCFA-containing lesions at baseline had a greater reduction in percent NC volume compared with those without. Thus, patients with elevated hs-CRP levels, large percent NC, and the presence of VH-TCFA appeared to be more responsive to statin therapy.

In our study, there were no significant differences in the primary and secondary efficacy endpoints between rosuvastatin 40 mg versus 10 mg. This may be explained by ethnic differences. Previous trials in Japan demonstrated that moderate-intensity statin (atorvastatin 20 mg/day) reduced serum LDL cholesterol level and atheroma volume as effectively as high-intensity statins in Caucasians (8,21,22). In the Korean ARTMAP (Atorvastatin vs. Rosuvastatin Therapy With Equivalent Potency on Mild Coronary Atherosclerotic Plaques) study, both atorvastatin 20 mg/day and rosuvastatin 10 mg/day led to similar percent changes in LDL cholesterol level (−47% and −49%, respectively) and PAV (−0.3% and −1.0%, respectively) (23). Thus, moderate-dose statins (atorvastatin 20 mg/day or rosuvastatin 10 mg/day) in Asians with a smaller body size may be as effective as high-dose statins in Caucasians. Although 40- and 10-mg rosuvastatin doses resulted in similar reductions in percent NC volume, pre-specified subgroup analyses showed a significant interaction between the initial LDL cholesterol level (≥104 mg/dl vs. <104 mg/dl as the median) and the reduction in percent NC volume and normalized TAV. Indeed, there was a greater change in the 40-mg rosuvastatin group, especially in the setting of a higher baseline LDL cholesterol level.

The PROSPECT study suggested that MLA ≤4.0 mm^2, plaque burden ≥70%, and the presence of VH-TCFA were associated with an increased risk of nonculprit-related cardiac events (10). This current study showed that the reduction in percent NC volume was greater in the setting of plaque burden ≥70% (vs. <70%) and the presence (vs. absence) of VH-TCFA, whereas the changes were similar according to the baseline MLA ≤4.0 mm^2 or angiographic diameter stenosis ≥50%. In fact, the change in percent NC volume was affected not by the degree of stenosis, but by plaque burden and the presence of TCFA. Considering the low major adverse cardiac event rate (3.6% over 12 months, mostly target lesion revascularization), our study suggested that advanced atherosclerotic plaques containing VH-defined fibroatheroma could regress with statin treatment.

STUDY LIMITATIONS. First, it is not clear if the results can be applied to either primary prevention in asymptomatic patients or more advanced, ischemia-producing lesions. Second, 28% of patients dropped out and did not undergo follow-up imaging studies. Third, the sample size may be insufficient to prove an incremental effect of greater LDL cholesterol lowering on the changes in plaque composition and to perform more detailed subgroup-specific analysis. Including only 82% of the calculated sample size (N = 276 on the basis of the secondary endpoint), the lack of difference in imaging parameters between the 2 doses might be affected by the underpowered sample. Fourth, because this study only enrolled patients with fibroatheroma-containing lesions, these results cannot be extended to either nonfibroatheroma-containing lesions or more advanced ischemia-producing lesions. Fifth, the absence of a placebo group is another limitation. In this study, the 12-month follow-up duration was relatively short to observe the natural history of coronary atheroma formation and to differentiate the effects of high- versus moderate-intensity statin therapy. In addition, statin-naïve patients were <70% of the studied patients. Nevertheless, this study demonstrated significant effects of statin on plaque regression and compositional changes. Because paired OCT images were analyzed in only a small subset, the reduction of OCT-defined TCFA cannot be considered definitive. Finally, the poor resolution of VH-IVUS limits the identification of histologically-defined TCFA (<65 μm of fibrous cap thickness). Moreover, there is a validation issue of electrocardiogram-gated VH-IVUS imaging in serial follow-up studies.

CONCLUSIONS

Serial multimodality intravascular imaging demonstrated that rosuvastatin treatment could change plaque composition (decrease in percent NC and frequency of VH-TCFA) and plaque volume in nonculprit coronary lesions.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: In patients with nonculprit coronary lesions defined by VH-IVUS, rosuvastatin significantly reduced total atheroma volume, proportionate NC volume, and the frequency of TCFA.

TRANSLATIONAL OUTLOOK: Additional studies are needed to define the mechanisms of plaque stabilization and determinants of the optimum intensity of statin therapy for individual patients with coronary atherosclerosis.

REFERENCES

1. Sacks FM, Pfeffer MA, Moye LA, et al., for the Cholesterol and Recurrent Events Trial Investigators. The effect of pravastatin on coronary events after myocardial infarction in patients with average cholesterol levels. N Engl J Med 1996;335:1001–9.

2. Ridker PM, Danielson E, Fonseca FA, et al., for the JUPITER Study Group. Rosuvastatin to prevent vascular events in men and women with elevated C-reactive protein. N Engl J Med 2008;359:2195–207.

3. Tung P, Wiviott SD, Cannon CP, et al. Seasonal variation in lipids in patients following acute coronary syndrome on fixed doses of pravastatin (40 mg) or atorvastatin (80 mg) (from the Pravastatin or Atorvastatin Evaluation and Infection Therapy-Thrombolysis In Myocardial Infarction 22 [PROVE IT-TIMI 22] Study). Am J Cardiol 2009;103:1056–60.

4. Nissen SE, Tuzcu EM, Schoenhagen P, et al., for the REVERSAL Investigators. Effect of intensive compared with moderate lipid-lowering therapy on progression of coronary atherosclerosis: a randomized controlled trial. JAMA 2004;291:1071–80.

5. Nissen SE, Nicholls SJ, Sipahi I, et al., for the ASTEROID Investigators. Effect of very high-intensity statin therapy on regression of coronary atherosclerosis: the ASTEROID trial. JAMA 2006;295:1556–65.

6. Nicholls SJ, Ballantyne CM, Barter PJ, et al. Effect of two intensive statin regimens on progression of coronary disease. N Engl J Med 2011;365:2078–87.

7. Nissen SE, Tuzcu EM, Schoenhagen P, et al., for the Reversal of Atherosclerosis with Aggressive Lipid Lowering (REVERSAL) Investigators. Statin therapy, LDL cholesterol, C-reactive protein, and coronary artery disease. N Engl J Med 2005;352:29–38.

8. Hiro T, Kimura T, Morimoto T, et al., for the JAPAN-ACS Investigators. Effect of intensive statin therapy on regression of coronary atherosclerosis in patients with acute coronary syndrome: a multicenter randomized trial evaluated by volumetric intravascular ultrasound using pitavastatin versus atorvastatin (JAPAN-ACS [Japan assessment of pitavastatin and atorvastatin in acute coronary syndrome] study). J Am Coll Cardiol 2009;54:293–302.

9. Smith SC Jr., Grundy SM. 2013 ACC/AHA guideline recommends fixed-dose strategies instead of targeted goals to lower blood cholesterol. J Am Coll Cardiol 2014;64:601–12.

10. Stone GW, Maehara A, Lansky AJ, et al., for the PROSPECT Investigators. A prospective

natural-history study of coronary atherosclerosis. N Engl J Med 2011;364:226–35.

11. Ryan TJ, Faxon DP, Gunnar RM, et al. Guidelines for percutaneous transluminal coronary angioplasty. A report of the American College of Cardiology/American Heart Association Task Force on Assessment of Diagnostic and Therapeutic Cardiovascular Procedures (Subcommittee on Percutaneous Transluminal Coronary Angioplasty). J Am Coll Cardiol 1993;22:2033–54.

12. Mintz GS, Nissen SE, Anderson WD, et al. American College of Cardiology clinical expert consensus document on standards for acquisition, measurement and reporting of intravascular ultrasound studies (IVUS): a report of the American College of Cardiology Task Force on Clinical Expert Consensus Documents. J Am Coll Cardiol 2001;37:1478–92.

13. García-García HM, Mintz GS, Lerman A, et al. Tissue characterisation using intravascular radiofrequency data analysis: recommendations for acquisition, analysis, interpretation and reporting. EuroIntervention 2009;5:177–89.

14. Kubo T, Maehara A, Mintz GS, et al. The dynamic nature of coronary artery lesion morphology assessed by serial virtual histology intravascular ultrasound tissue characterization. J Am Coll Cardiol 2010;55:1590–7.

15. Maehara A, Cristea E, Mintz GS, et al. Definitions and methodology for the grayscale and radiofrequency intravascular ultrasound and coronary angiographic analyses. J Am Coll Cardiol Img 2012;5 3 Suppl:S1–9.

16. Yun KH, Mintz GS, Farhat N, et al. Relation between angiographic lesion severity, vulnerable plaque morphology and future adverse cardiac events (from the Providing Regional Observations to Study Predictors of Events in the Coronary Tree Study). Am J Cardiol 2012;110:471–7.

17. Prati F, Regar E, Mintz GS, et al., for the Expert's OCT Review Document. Expert review document on methodology, terminology, and clinical applications of optical coherence tomography: physical principles, methodology of image acquisition, and clinical application for assessment of coronary arteries and atherosclerosis. Eur Heart J 2010;31:401–15.

18. Jang IK, Tearney GJ, MacNeill B, et al. In vivo characterization of coronary atherosclerotic plaque by use of optical coherence tomography. Circulation 2005;111:1551–5.

19. Tearney GJ, Regar E, Akasaka T, et al., for the International Working Group for Intravascular Optical Coherence Tomography (IWG-IVOCT). Consensus standards for acquisition, measurement, and reporting of intravascular optical coherence tomography studies: a report from the International Working Group for Intravascular Optical Coherence Tomography Standardization and Validation. J Am Coll Cardiol 2012;59:1058–72.

20. Kume T, Akasaka T, Kawamoto T, et al. Assessment of coronary arterial thrombus by Optical Coherence Tomography. Am J Cardiol 2006;97:1713–7.

21. Komukai K, Kubo T, Kitabata H, et al. Effect of atorvastatin therapy on fibrous cap thickness in coronary atherosclerotic plaque as assessed by optical coherence tomography: the EASY-FIT Study. J Am Coll Cardiol 2014;64:2207–17.

22. Okazaki S, Yokoyama T, Miyauchi K, et al. Early statin treatment in patients with acute coronary syndrome: demonstration of the beneficial effect on atherosclerotic lesions by serial volumetric intravascular ultrasound analysis during half a year after coronary event: the ESTABLISH Study. Circulation 2004;110:1061–8.

23. Lee CW, Kang SJ, Ahn JM, et al. Comparison of effects of atorvastatin (20 mg) versus rosuvastatin (10 mg) therapy on mild coronary atherosclerotic plaques (from the ARTMAP trial). Am J Cardiol 2012;109:1700–4.

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APPENDIX For supplemental Methods as well as figures and tables, please see the online version of this article.