Comparison of Rosuvastatin Versus Atorvastatin for Coronary Plaque Stabilization

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Statins are widely used to lower cholesterol and to reduce cardiovascular events. Whether all statins have similar effects on plaque stabilization is unknown. We aimed to investigate coronary plaque response to treatment with different statins that result in similar lipid reduction using serial multimodality intracoronary imaging. Patients with de novo coronary artery disease requiring intervention were randomized to rosuvastatin 10 mg (R10) or atorvastatin 20 mg (A20) daily. Optical coherence tomography and intravascular ultrasound were performed at baseline, 6 months, and 12 months. Untreated nonculprit plaques were analyzed by optical coherence tomography for thin-cap fibroatheroma, minimum fibrous cap thickness, lipid arc, and lipid length. Total and percent atheroma volume, respectively were analyzed by intravascular ultrasound. Forty-three patients completed the protocol (R10: 24 patients, 31 plaques; A20: 19 patients, 30 plaques). The decrease in serum lipids was similar. From baseline to 6 months to 12 months, minimum fibrous cap thickness increased in the R10 group (61.4 ± 15.9 μm to 120.9 ± 57.9 μm to 171.5 ± 67.8 μm, p <0.001) and the A20 group (60.8 ± 18.1 μm to 99.2 ± 47.7 μm to 127.0 ± 66.8 μm, p <0.001). Prevalence of thin-cap fibroatheroma significantly decreased in the R10 and A20 groups (−48% and −53%, respectively, p <0.001 for intragroup comparisons). Only the R10 group had a decrease in macrophage density (−23%, p = 0.04) and microvessels (−12%, p = 0.002). Total atheroma volume decreased in the R10 group (109.2 ± 62.1 mm^3 to 101.8 ± 61.1 mm^3 to 102.5 ± 62.2 mm^3, p = 0.047) but not in the A20 group (83.3 ± 48.5mm^3 to 77.6 ± 43.0 mm^3 to 77.9 ± 48.6 mm^3, p = 0.07). In conclusion, although both statins demonstrated similar reductions in lipid profiles, the rosuvastatin group showed more rapid and robust plaque stabilization, and regression of plaque volume compared to the atorvastatin group. **(Am J Cardiol 2019;123:1565−1571)**

The majority of acute coronary syndromes (ACS) are due to the rupture of vulnerable atherosclerotic plaques.[1,2] Features of plaque vulnerability include thin fibrous cap, large necrotic core, increased macrophages, positive remodeling, and vasa vasorum. Using imaging modalities such as intravascular ultrasound (IVUS) or optical coherence tomography (OCT), most of these vulnerable features can be visualized. Of these features, thin fibrous cap is one of the most important determinants of vulnerability.[3−5] It is believed that statins reduce cardiovascular morbidity and mortality through reduction of low-density lipoprotein (LDL) cholesterol. However, pleiotropic effects of statins have also been proposed.[6,7] So far, there has been no head-to-head comparison of plaque stabilization using different statins that result in similar lipid profile changes. The aim of this study was to compare serial changes in plaque characteristics between rosuvastatin and atorvastatin at doses that result in similar levels of lipid reduction.

Methods

In this prospective single-center randomized clinical trial (NCT01023607), 120 patients presenting with *de novo* coronary artery disease undergoing percutaneous coronary intervention and who had ≥1 unstented nonculprit lipid-rich plaque were randomized to rosuvastatin 10 mg daily (R10), atorvastatin 20 mg daily (A20), or atorvastatin 60 mg daily (A60).[8] Patients had clinical assessment, OCT, and IVUS imaging during the index procedure (baseline), 6 months, and 12 months (Figure 1). Nonculprit lipid-rich plaques, defined by OCT as having fibrous cap thickness (FCT) ≤120 μm and lipid arc ≥100°,[9] were evaluated at each timepoint. Comparison of the A20 and A60 groups was previously published, however the R10 group was not included in the previous report.[8]

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See page 1570 for disclosure information.

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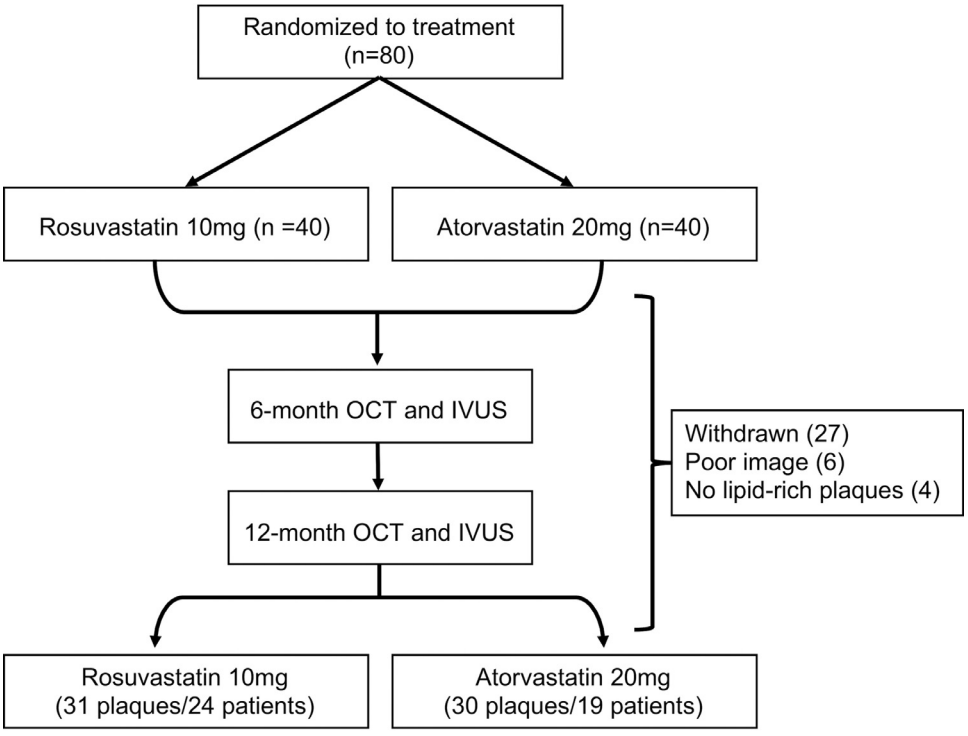


Figure 1. Study design. 80 patients were randomized to rosuvastatin 10 mg or atorvastatin 20 mg daily. Patients had IVUS and OCT imaging at baseline, 6 months, and 12 months. IVUS = intravascular ultrasound; OCT = optical coherence tomography.

Coronary angiography, IVUS, and OCT imaging were performed as previously described.[8] The study protocol was approved by the institutional review board of Harbin Medical Hospital and all patients provided informed consent. All images were independently analyzed by a core laboratory at Massachusetts General Hospital (Boston). Offline quantitative coronary angiography (QCA), OCT, and IVUS analysis were performed by 2 experienced investigators blinded to the patient study group and time point. Minimal lumen diameter, reference vessel diameter, and percent diameter stenosis were measured by QCA (CAAS QCA, Pie Medical Imaging, Maastricht, the Netherlands). OCT images were analyzed at the frame-level in 1 mm intervals and at the lesion-level (Lightlab Imaging, Westford, Massachusetts). Frame-level end points were lipid arc and categorical assessment of microvessels, macrophages, cholesterol crystals, and calcifications.[10–12] Lesion-level endpoints included lipid length, mean lipid arc, and maximum lipid arc. Minimum FCT was measured at the thinnest point 3 times and averaged. Mean lipid index was calculated as the product of the mean lipid arc and lipid length. Lesions were also categorically assessed for thin-cap fibroatheroma (TCFA) morphology. TCFA was defined as a plaque with lipid present in $\geq$2 quadrants and FCT $<$65 μm. Baseline and follow-up OCT pullbacks were then matched using fiduciary landmarks (side branches and stent edges) to compare interval changes. Interval changes in each measure were also expressed as the magnitude of the difference and as percent difference.

IVUS analysis was performed offline according to standard guidelines[13] using EchoPlaque (Indec Systems, Mountain View, California). Lumen area and external elastic membrane (EEM) area were analyzed in 1 mm intervals. Plaque area was calculated as EEM area−−lumen area in each image. Plaque burden was calculated as plaque area/EEM area $\times$ 100. Total atheroma volume (TAV) was calculated as the sum of all plaque areas per patient. Since pullback length varied between patients, TAV was normalized by the median number of cross sections in the study cohort and expressed as normalized TAV (nTAV). Percent atheroma volume (PAV) was calculated as the sum of all cross-sectional plaque burden values. All interval changes were calculated as follow-up minus baseline.

Outcomes are reported as mean and standard deviation or counts and percentages. Categorical outcomes were evaluated using the chi-square test whereas continuous measures were evaluated using a student's t Test. Comparison of changes in plaque composition and morphology was accomplished through generalized linear modeling using the generalized estimating equations to account for within-patient clustering of multiple plaques over multiple timepoints. All comparisons were 2-sided with an α-level of 0.05 indicating statistical significance. Statistical analysis was performed in MATLAB 2017b (Mathworks, Natick, Massachusetts) with the GEEQBOX Statistical Toolbox.[14]

Results

In total, 43 patients (61 plaques) randomized to R10 (24 patients, 31 plaques) or A20 (19 patients, 30 plaques) completed IVUS and OCT imaging at all 3 time points. The mean age was 56.1 years and 63% of patients were male.

Table 1
Baseline characteristics

Variable	R10 (n = 24 patients, 31 plaques)	A20 (n = 19 patients, 30 plaques)	p Value
Age (years)	57.5	54.2	0.22
Men	14 (58%)	13 (68%)	0.72
Hypertension	18 (75%)	12 (63%)	0.61
Dyslipidemia	6 (25%)	5 (26%)	0.80
Diabetes mellitus	14 (58%)	9 (47%)	0.68
Smoker	10 (42%)	8 (42%)	0.77
Previous MI	4 (17%)	4 (21%)	0.98
Previous CABG	0	0 (0%)	1.00
Clinical presentation			
Stable angina pectoris	0	3 (16%)	0.18
Unstable angina pectoris	2 (8%)	1 (5%)	
Non-ST-elevation myocardial infarction	18 (75%)	10 (53%)	
ST-elevation myocardial infarction	4 (17%)	5 (26%)	
Medications			
ACE-I/ARB	11 (46%)	7 (37%)	0.55
Beta-blocker	13 (54%)	11 (58%)	0.81
Calcium channel blocker	8 (33%)	4 (21%)	0.37
Nitrates	15 (63%)	11 (58%)	0.76
Aspirin	24 (100%)	19 (100%)	1.00
Clopidogrel	24 (100%)	19 (100%)	1.00

Dyslipidemia was defined as low-density lipoprotein cholesterol >140 mg/dl.

There were no statistically significant differences in the baseline clinical characteristics of the 2 groups (Table 1). Lumen dimensions did not significantly differ between the groups at any timepoint, nor did they change within each group over the study period (Supplemental Table 1).

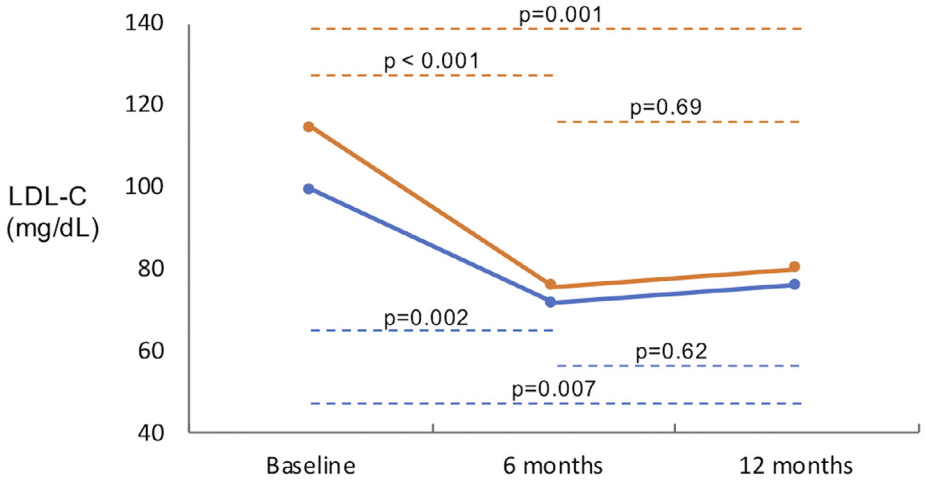
Baseline LDL cholesterol was significantly lower in the R10 group, but otherwise there were no significant differences between the R10 and A20 groups in any other lipid measure or timepoint (Table 2). In both groups, total cholesterol and LDL cholesterol significantly decreased between baseline and 6 months, but did not significantly change between 6 and 12 months (Figure 2). High-density lipoprotein did not change significantly during the study period, and there was no difference between the treatment groups at any time point.

From baseline to 6 months to 12 months, minimum FCT consistently and significantly increased in both groups (Figure 3, Table 3). Between baseline and 6 months, the R10 group had a significantly greater increase in FCT in terms of magnitude and percent (Supplemental Tables 2 and 3). Although both groups continued to show increases in FCT between 6 and 12 months, the R10 group had a higher magnitude and percent increase in FCT (Table 3). Overall, whereas FCT doubled by 12 months in the A20 group, it doubled by 6 months and tripled by 12 months in the R10 group.

Mean lipid arc, maximum lipid arc, and mean lipid index significantly decreased in both groups, but there were no significant differences between the treatment groups (Table 3). These observations were maintained upon considering the magnitude and percent changes in each measure (Supplemental Tables 2 and 3). Neither lipid length nor magnitude of change in lipid length changed significantly in either group, but the percent change was significant in each group between baseline and 12 months.

Table 2
Lipid profile at each time point

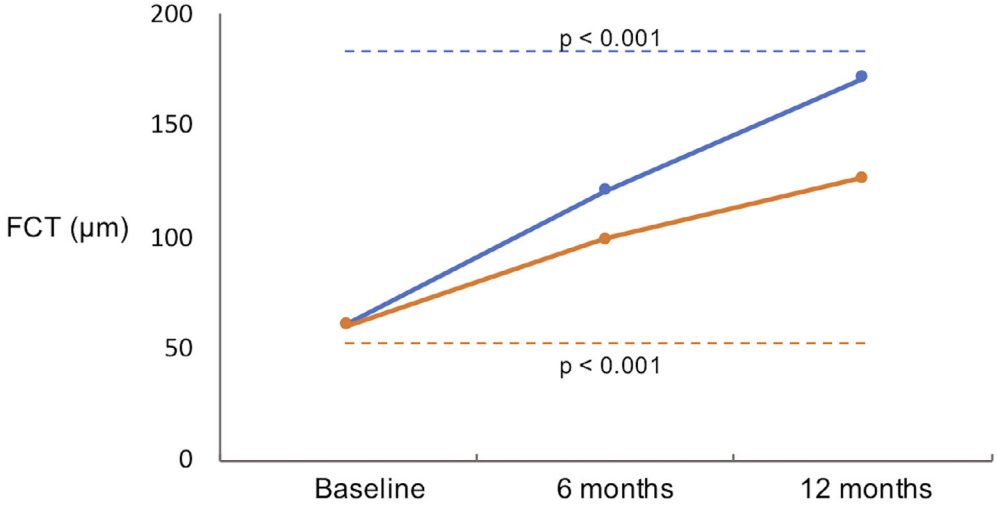
Variable	Time point	R10	A20	p Value
Total cholesterol (mg/dl)	*Baseline*	190 ± 44	203 ± 40	0.35
	6 months	148 ± 39	144 ± 35	0.70
	12 months	154 ± 45	153 ± 49	0.93
	$p\ value_{0\ to\ 6\ months}$	<0.001	<0.001	
	$p\ value_{6\ to\ 12\ months}$	0.63	0.50	
	$p\ value_{0\ to\ 12\ months}$	0.002	<0.001	
Triglycerides (mg/dl)	*Baseline*	245 ± 214	183 ± 83	0.24
	6 months	168 ± 122	135 ± 67	0.30
	12 months	158 ± 70	124 ± 59	0.10
	$p\ value_{0\ to\ 6\ months}$	0.06	0.08	
	$p\ value_{6\ to\ 12\ months}$	0.82	0.64	
	$p\ value_{0\ to\ 12\ months}$	0.05	0.04	
LDL Cholesterol (mg/dl)	*Baseline*	100 ± 21	115 ± 28	0.05
	6 months	72 ± 29	76 ± 28	0.64
	12 months	76 ± 34	80 ± 32	0.70
	$p\ value_{0\ to\ 6\ months}$	0.002	<0.001	
	$p\ value_{6\ to\ 12\ months}$	0.62	0.69	
	$p\ value_{0\ to\ 12\ months}$	0.007	0.001	
HDL Cholesterol (mg/dl)	*Baseline*	51 ± 15	50 ± 12	0.83
	6 months	54 ± 15	49 ± 14	0.26
	12 months	52 ± 13	50 ± 18	0.69
	$p\ value_{0\ to\ 6\ months}$	0.29	0.48	
	$p\ value_{6\ to\ 12\ months}$	0.65	0.79	
	$p\ value_{0\ to\ 12\ months}$	0.62	0.65	



Rosuvastatin 10mg	99.58 ± 20.99	71.69 ± 29.11	76.21 ± 33.46
Atorvastatin 20mg	114.73 ± 27.94	75.80 ± 27.71	80.13 ± 32.26
p-value	0.048	0.64	0.70

Figure 2. LDL cholesterol at baseline, 6 months, and 12 months. Serum LDL cholesterol decreased significantly in both groups between baseline and 6 months, however there was no significant change between 6 and 12 months. LDL cholesterol levels were similar between the 2 groups at 6 and 12 months.

The prevalence of TCFA significantly decreased in both the R10 and A20 groups (Table 4). However, between baseline and 12 months, only the R10 group demonstrated a significant decrease in the prevalence of macrophages and microvessels. In contrast, the A20 group showed no significant reduction in either macrophages or microvessels (Table 4). The prevalence of cholesterol crystals or calcifications did not significantly decrease in either group.



Rosuvastatin 10mg	61.35 ± 15.88	120.87 ± 57.89	171.52 ± 67.76
Atorvastatin 20mg	60.80 ± 18.09	99.23 ± 47.68	127.03 ± 66.84
p-value	0.90	0.12	0.012

Figure 3. Minimum fibrous cap thickness at baseline, 6 months, and 12 months. While both treatment groups demonstrated significant increases in minimum FCT, the rosuvastatin group showed significantly greater FCT than the atorvastatin group considering all time points (p = 0.03). Further analysis showed that this difference was significant specifically at 12 months (p = 0.012). FCT = fibrous cap thickness.

Table 3
OCT fibrous cap thickness and lipid content at each time point

Variable	Time point	R10	A20	p Value
FCT (μm)	*Baseline*	61.4 ± 15.9	60.8 ± 18.1	0.03
	6 months	120.9 ± 57.9	99.2 ± 47.7	
	12 months	171.5 ± 67.8	127.0 ± 66.8	
	p value	<0.001	<0.001	
Mean lipid arc (°)	*Baseline*	162.4 ± 43.1	174.5 ± 53.8	0.28
	6 months	153.2 ± 48.3	169.5 ± 50.8	
	12 months	141.1 ± 48.4	152.4 ± 62.2	
	p value	<0.001	0.005	
Maximum lipid arc (°)	*Baseline*	235.3 ± 68.4	230.8 ± 72.1	0.79
	6 months	220.9 ± 71.9	229.7 ± 66.9	
	12 months	191.6 ± 70.0	196.2 ± 83.0	
	p value	<0.001	0.003	
Lipid length (mm)	*Baseline*	10.5 ± 4.6	8.1 ± 3.2	0.06
	6 months	10.0 ± 4.6	8.6 ± 3.6	
	12 months	9.8 ± 4.7	7.8 ± 3.5	
	p value	0.08	0.46	
Mean lipid index (°mm)	*Baseline*	1752.8 ± 982.5	1448.6 ± 740.1	0.57
	6 months	1587.8 ± 980.4	1474.4 ± 831.9	
	12 months	1416.9 ± 899.8	1254.9 ± 877.8	
	p value	<0.001	0.005	

FCT = fibrous cap thickness.

In the R10 group, significant decreases were observed for TAV and nTAV, but PAV remained unchanged (Table 5). The A20 group showed no significant changes in TAV, nTAV, or PAV. There were no significant differences in TAV, nTAV, or PAV between the treatment groups at any time point. Furthermore, there was no significant change in the magnitude and percent difference in TAV, nTAV, and PAV over time or between the treatment groups (Supplemental Tables 4 and 5).

Table 4
OCT plaque characteristics at each time point

Variable	Time point	R10	A20	p Value
TCFA	*Baseline*	18 (58%)	21 (70%)	0.25
	6 months	8 (26%)	12 (40%)	
	12 months	3 (10%)	5 (17%)	
	p value	<0.001	<0.001	
Macrophages	*Baseline*	22 (71%)	23 (77%)	0.047
	6 months	19 (61%)	23 (77%)	
	12 months	15 (48%)	23 (77%)	
	p value	0.04	0.76	
Microvessels	*Baseline*	15 (48%)	11 (37%)	0.59
	6 months	10 (32%)	11 (37%)	
	12 months	8 (26%)	9 (30%)	
	p value	0.002	0.23	
Cholesterol crystals	*Baseline*	7 (23%)	7 (23%)	0.40
	6 months	0	0	
	12 months	3 (9.7%)	4 (13%)	
	p value	0.13	0.17	
Calcifications	*Baseline*	14 (45%)	11 (37%)	0.37
	6 months	14 (45%)	11 (37%)	
	12 months	17 (55%)	8 (27%)	
	p value	0.09	0.32	

ns = not significant; TCFA = thin-cap fibroatheroma.

Table 5
IVUS atheroma volume at each time point

Variable	Time point	R10	A20	p Value
TAV (mm^3)	*Baseline*	109.2 ± 62.1	83.3 ± 48.5	0.12
	6 months	101.8 ± 61.1	77.6 ± 43.0	
	12 months	102.5 ± 62.2	77.9 ± 48.6	
	p value	0.047	0.07	
nTAV (mm^3)	*Baseline*	99.0 ± 39.8	89.2 ± 37.7	0.61
	6 months	92.9 ± 40.3	83.8 ± 33.7	
	12 months	92.1 ± 37.2	86.0 ± 33.8	
	p value	0.02	0.20	
PAV (%)	*Baseline*	52.5 ± 9.2	54.5 ± 9.5	0.24
	6 months	52.0 ± 9.1	54.9 ± 9.7	
	12 months	51.3 ± 8.1	54.4 ± 9.5	
	p value	0.13	0.88	

TAV = total atheroma volume; nTAV = normalized total atheroma volume; PAV = percent atheroma volume.

Discussion

In our study, both treatment groups had a similar level of LDL cholesterol reduction, but there was a differential vascular response to each statin in terms of the speed and overall degree of fibrous cap thickening. Although both the R10 and A20 groups had a similar minimum FCT at baseline and similar levels of cholesterol reduction, the R10 group had a more rapid and robust increase that was maintained at 12 months, as evidenced by a nearly 300% average increase from baseline (Figure 4). Essentially, the increase in minimum FCT achieved by the A20 group by 12 months was achieved in 6 months by the R10 group. Furthermore, in both groups, LDL reduction was greatest in the first 6 months and, in fact, did not change further between 6 and 12 months. Yet, in the absence of concomitant LDL reduction, both groups continued to manifest an increase in FCT along with reductions in mean lipid arc, maximum lipid arc, and lipid index. In other words, plaques continued to stabilize in the absence of concurrent LDL reduction. Given that statin-induced plaque changes are more accentuated with higher baseline LDL levels,[15] we hypothesize that the lower baseline LDL level in the R10 group may have led to an underestimation of the differences between the 2 statins.

In addition to lowering LDL cholesterol, in vitro and animal studies suggest pleiotropic effects of statins include vascular endothelial protection,[7,16] antioxidant effects,[6] reduction in coagulation factor activity,[17] and a variety of anti-inflammatory properties.[17–20] Rosuvastatin may also decrease activity of endothelial[21] and monocyte-derived matrix metalloproteinases (MMPs),[22] an effect postulated to reduce fibrous cap thinning, thereby stabilizing atheromatous plaques. Interestingly, we demonstrated a significant decrease in the prevalence of macrophages in the R10 group only. This may be related to decreases in monocyte activation associated with rosuvastatin.[18] We, therefore, postulate that rosuvastatin-induced inhibition of MMPs and monocytic inflammation may play a role in our findings.

In contrast with previous IVUS findings, in our study only the R10 group had a significant reduction in TAV and nTAV, but the percent change in any of the atheroma volume measures was not significant in either group. Patients

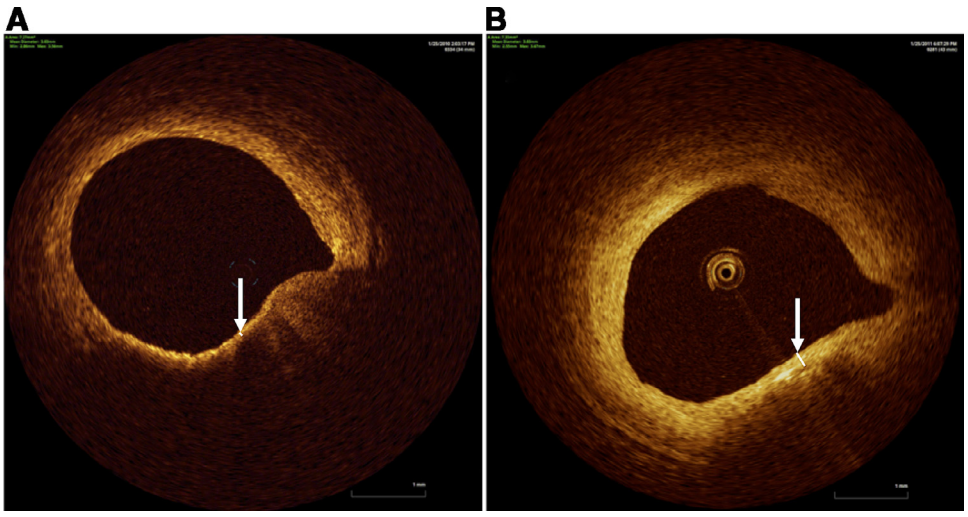


Figure 4. Interval increase in fibrous cap thickness. (*A*) Baseline OCT imaging, minimum FCT is approximately 50 μm (*white arrow*). (*B*) 12-month OCT imaging, minimum FCT has increased to approximately 300μm (*white arrow*). This patient was randomized to rosuvastatin. FCT = fibrous cap thickness; OCT = optical coherence tomography.

with ACS have shown substantially higher percent change in plaque volume: −16.9% and −18.1% in pitavastatin- and atorvastatin-treated patients, respectively, at 8 to 12 months in JAPAN-ACS, and −13.1% at 6 months in the atorvastatin group of ESTABLISH.[23,24] Larger trials in a broader group of patients, however, demonstrated more modest changes. In REVERSAL, at 18 months, the percent change in TAV was +2.7% in the pravastatin group and −0.4% in the atorvastatin group.[25] In SATURN, at 2 years, the change in PAV was −0.99% in the atorvastatin group and −1.22% in the rosuvastatin group.[26] Our results may be explained by use of relatively low statin doses, shorter treatment interval than REVERSAL and SATURN, inclusion of non-ACS patients, and a smaller study cohort, and therefore should not be interpreted as refuting previous studies.

There are several limitations of this study. First, the study cohort was small, primarily due to the invasive nature of serial imaging and related patient attrition. However, imaging at 3 timepoints provided a more comprehensive picture of vascular response to statin therapy over time. Second, this was a single center study performed in an Asian cohort, therefore the results may be less applicable to other populations. Third, we originally designed a 3-arm study investigating 3 groups: rosuvastatin 10 mg, atorvastatin 20 mg, and atorvastatin 60 mg daily. In the previous publication,[8] only analysis of the 2 atorvastatin groups was reported due to the sheer number and complexity of the results. The current work sought to investigate differences in plaque features in the setting of 2 different statins that resulted in similar lipid reduction, providing insight into potential nonlipid mediated effects of statin therapy. Fourth, although there were no significant differences in patients' clinical presentation, only the A20 group had patients presenting with stable angina. Theoretically, this could have played a role in the less-brisk vascular response to atorvastatin therapy. Finally, although we assume that faster and more significant fibrous cap thickening in the rosuvastatin group is morphologically beneficial in terms of plaque stabilization, we do not know if these differences persist beyond 12 months, or whether such differences translate to clinical outcomes.

In conclusion, patients treated with atorvastatin 20 mg or rosuvastatin 10 mg daily showed plaque stabilization even in the absence of continued LDL cholesterol reduction between 6 and 12 months, suggesting nonlipid mediated effects of statin therapy or that vascular structural changes require a sustained low LDL level. Further, despite similar lipid reduction in both groups, the rosuvastatin group had significantly faster and greater increase in FCT, and only the rosuvastatin group demonstrated a significant reduction in prevalence of macrophage density and microvessels as well as TAV. Our results suggest that rosuvastatin has more rapid and potent effects on plaque stabilization and that not all statins have similar effects on plaque stabilization. Whether these observations translate to clinical benefit, warrant larger scale studies with longer term follow-up.

Disclosures

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Supplementary materials

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.amjcard.2019.02.019.

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