

Serial Coronary CT Angiography–Verified Changes in Plaque Characteristics as an End Point

Evaluation of Effect of Statin Intervention

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OBJECTIVES This study sought to assess, by serial computed tomography angiography (CTA), the effect of statin treatment on coronary plaque morphology.

BACKGROUND In addition to the assessment of luminal stenosis, CTA also allows characterization of plaque morphology. Large, positively remodeled plaques with large necrotic cores have been reported as indicators of plaque instability.

METHODS CTA was performed in 32 patients (26 men, ages 64.3 ± 8.5 years). Of these, 24 received fluvastatin after the baseline study; 8 subjects who refused statin treatment were followed as the control subjects. Serial imaging was performed after a median interval of 12 months. All vessels were examined in every subject, and a 10-mm-long segment was identified for comparison before and after intervention. Total plaque volume, low attenuation plaque (LAP) volume, lumen volume, and remodeling index were calculated.

RESULTS In the statin-treated patients, the total plaque volume (92.3 ± 37.7 vs. 76.4 ± 26.5 mm³, $p < 0.01$) and LAP volume (4.9 ± 7.8 vs. 1.3 ± 2.3 mm³, $p = 0.01$) were significantly reduced over time; however, there was no change in the lumen volume (63.9 ± 25.3 vs. 65.2 ± 26.2 mm³, $p = 0.59$). On the other hand, no change was observed in the CTA characteristics in the control subjects, including total plaque volume (94.4 ± 21.2 vs. 98.4 ± 28.6 mm³, $p = 0.48$), LAP volume (2.1 ± 3.0 vs. 2.3 ± 3.6 mm³, $p = 0.91$), and lumen volume (80.5 ± 20.7 vs. 75.0 ± 16.3 mm³, $p = 0.26$). The plaque volume change (-15.9 ± 22.2 vs. 4.0 ± 14.0 mm³, $p = 0.01$) and LAP volume change (-3.7 ± 7.0 vs. 0.2 ± 1.5 mm³, $p < 0.01$) were significantly greater in the statin than the control group. The lumen volume (1.3 ± 15.6 vs. -5.5 ± 13.1 mm³, $p = 0.24$) and remodeling index ($-2.4 \pm 6.8\%$ vs. $-0.3 \pm 6.5\%$, $p = 0.53$) did not show the significant differences between the 2 groups. The decrease in the plaque volume was due to reduction in the LAP volume ($R = 0.83$, $p < 0.01$), and was not related to any changes in the lumen volume ($R = 0.21$, $p = 0.24$).

CONCLUSIONS This preliminary study suggests that serial CTA evaluation of coronary plaques allows for the assessment of interval change in the plaque morphology. Statin treatment results in decreases in the plaque and necrotic core volume. The features known to be associated with plaque instability. (J Am Coll Cardiol Img 2010;3:691–8) © 2010 by the American College of Cardiology Foundation

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In numerous clinical trials, various 3-hydroxy-3-methyl-glutaryl coenzyme A (HMG-CoA) reductase inhibitors, or statin drugs, have been shown to reduce both the circulating levels of atherogenic lipoproteins and acute cardiovascular events (1–5). Employing coronary angiographic and intravascular imaging techniques for serial examinations, it has been demonstrated that statins retard plaque progression, or even induce regression (6–10). The intravascular ultrasound (IVUS) examination has demonstrated the feasibility of actual diminution of the lipid cores in the atherosclerotic plaques. These favorable effects of statins mirror the experimental data wherein plaque stabilization becomes obvious after statin administration (11,12); the effect of statin administration is reported to be more effective than dietary modification (12,13). The statins also reduce intraplaque inflammation, neoangiogenesis, apoptosis, and metalloproteinase expression, all of which indicate plaque stabilization (12–15). Recent improvements in computed tomography angiography (CTA) technology have allowed characterization of plaque morphology noninvasively (16,17), and described positive remodeling and large plaque and low attenuation plaque (LAP) volumes as indicators of plaque instability (18,19). In the present study, we evaluated the feasibility of using serial coronary CTA studies for the assessment of the changes in plaque morphology. As an example, we assessed the efficacy of statin treatment on alterations in coronary plaque morphology.

ABBREVIATIONS AND ACRONYMS

CTA = computed tomography angiography

HDL-C = high-density lipoprotein cholesterol

IVUS = intravascular ultrasound

LAP = low attenuation plaque

RI = remodeling index

METHODS

Patients. In this prospective, nonrandomized study, we enrolled 32 patients who underwent coronary CTA with suspected coronary artery disease. Coronary arteries were segment-wise analyzed for each patient; the lesions with severe calcification on CTA (which precluded plaque characterization) were excluded. In addition, all segments with $\geq 75\%$ luminal stenosis were not included for they would not be available for comparison if subjected to intervention. Plaques with prior percutaneous coronary intervention were also excluded for the loss of natural vascular architecture. All 32 patients were statin naive and were never treated with other lipid-lowering drugs. Twenty-four patients were started on a fixed dose of fluvastatin (20 mg) regardless of their cholesterol levels and received fluvastatin for more than 6 months after the base-

line coronary CTA image acquisition (statin group). Eight patients who refused to accept fluvastatin treatment were enrolled as the control group. Serial CTA imaging was performed at least 6 months after the baseline CTA. The lipid profile including total cholesterol, triglyceride, and high-density lipoprotein cholesterol (HDL-C) levels were obtained at baseline and follow-up. The study was approved by the institutional review board, and all patients consented voluntarily to participate in the study protocol.

Coronary CTA. Sixty-four-slice multidetector computed tomography was used in this study in 15 patients, and 16-slice in the remaining 17 patients. Follow-up images were acquired by the same machine in every subject. Sixty-four-slice computed tomography (CT) (Aquilion 64, Toshiba Medical Systems, Otawara, Japan) angiography was performed with a collimation of 64×0.5 mm; detector pitch of 9.8 to 11.2; pixel size of 0.39×0.39 mm; rotation time of 350, 375, or 400 ms; tube current of 400 or 450 mA; and voltage of 135 kV. For the contrast-enhanced scan, 60 ml of contrast media was injected at 4.0 ml/s followed by 20 ml at 2.0 ml/s. Sixteen-slice CT (Aquilion 16, Toshiba Medical Systems) angiograms were performed with a collimation of 16×0.5 mm, detector pitch of 3.2 to 3.6, pixel size of 0.39×0.39 mm, rotation time of 400 ms, tube current of 360 mA, and voltage of 135 kV. For the contrast-enhanced scan, 60 ml of contrast media was injected at 3.0 ml/s followed by 40 ml at 1.5 ml/s with biphasic injection of a 40-ml saline chaser at 1.5 ml/s. Scanning was manually initiated based on the density of contrast enhancement in the left ventricle. All scans were performed during a single breath-hold. Patients received a beta-blocker 1 h before the CTA if the heart rate was more than 60 beats/min. The raw data of the scans were reconstructed using algorithms optimized for retrograde ECG-gated multislice spiral reconstruction in diastole. R-R interval was determined by the absolute number (milliseconds) from R wave to reconstruct the images at the optimal phase. The reconstructed image data of CTA was transferred to a computer workstation for post-processing (ZIO M900, Amin/ZIO, Tokyo, Japan). The reconstructed image data of CTA were also transferred to Sure Plaque software (Toshiba Medical Systems) to measure the plaque volume based on CTA density.

Plaque assessment. All vessels were examined in every patient, and a 10-mm-long vascular segment was identified for comparison; caution was exer-

cised to exclude severely calcified lesions. The CT angiograms were pooled, and 2 observers who were blinded to the patient identity, clinical history, and the sequence of imaging evaluated the scans together. Lesions at baseline and follow-up study were synchronized by using the branch points as the landmarks. Plaque and lumen volume measurements were performed using attenuation-based automated (Sure Plaque [Toshiba Medical Systems]) software. Planimetry of the lumen and external vessel area was performed in the first step, and in a second step, plaque characterization based on Hounsfield units (HU). The coronary plaques were color coded based on HU. The software color codes coronary plaques based on HU into LAP (<30 HU), intermediate attenuation plaque (30 to 150 HU), calcified plaque (350 to 1,000 HU), and lumen (150 to 350 HU), and measures the volume of each component. These HU ranges were defined by our previous study based on IVUS-verified plaque components, and the 30-HU threshold for the detection of LAP offered a sensitivity and specificity of 91% and 100%, respectively (19,20). As described previously, the remodeling index (RI) was calculated for all lesions. The outlines were confirmed by observers and readjusted manually if necessary. Although the subjective variation was not estimated for this study, we have previously reported excellent interobserver and intraobserver variability for plaque component characterization, including plaque attenuation and positive remodeling (19). The vessel was analyzed for LAP, total plaque and lumen volume, and RI. All parameters were compared between baseline and follow-up. We have previously described the plaque characteristics that are associated with subsequent vascular events. The plaques with $\geq 110\%$ positive remodeling index (PR) and ≤ 30 -HU attenuation (LAP) were described as 2-feature positive plaques, which are associated with $>22\%$ likelihood of an acute coronary event over the next 2 years. One-feature positive plaques (either PR or LAP) were associated with $>3\%$ 2-year risk, and 2-feature negative plaques were associated with $<0.5\%$ likelihood of an acute event. As such, the vulnerability could be defined on the scale of 0 to 2 (2-feature positive plaques being 2) for comparison of baseline and follow-up CTA plaque characteristics.

Statistical analyses. Categorical variables were expressed as percentages, and the Fisher exact probability test was used for comparisons between the statin group and the control group at baseline

characteristics. Continuous variables such as age, lipid profile, and plaque or lumen volume were expressed as mean \pm SD. Age and lipid profile were compared between the statin group and the control group by the analysis of unpaired Student *t* test, and between baseline and follow-up by the analysis of paired Student *t* test. The paired *t* test was used to compare lipid profiles between baseline and follow-up. Since plaque lumen and LAP volumes, and RI were not normally distributed at baseline, nonparametric test was used for plaque and lumen comparison. A Wilcoxon signed rank test was used to compare the baseline-to-follow-up changes of plaque lumen and LAP volumes, and RI between the statin and control groups. To compare the baseline CTA data and the change over time, the Mann-Whitney *U* test was employed. Correlation between the change of plaque volume and each LAP volume or lumen volume were analyzed by linear regression analysis and correlation coefficient. The presence of 0-, 1-, and 2-feature positive plaques was also compared between the statin group and the control group at baseline using the Mann-Whitney *U* test, and between baseline and follow-up using the Wilcoxon signed rank test. All *p* values were 2-sided, and a *p* value of <0.05 was considered statistically significant. All analyses were performed with SPSS-11 software (SPSS Japan Inc., Tokyo, Japan).

RESULTS

Thirty-two patients (26 men, 6 women, ages 64.3 ± 8.5 years) were enrolled in the current study and underwent clinical risk profiling and a CTA examination. Of these 32 patients, 24 received fluvastatin, and 8 served as the control group. The baseline clinical and CTA characteristics of both groups are shown in Table 1. There were no significant differences in patient characteristics and lipid profiles between the statin and control groups at baseline. Similarly, no difference was seen in the CTA characteristics. Total plaque volume (92.3 ± 37.7 vs. 94.4 ± 21.2 mm³, *p* = 0.38) and LAP volume (4.9 ± 7.8 vs. 2.1 ± 3.0 mm³, *p* = 0.19) at the baseline were similar in the 2 groups (Fig. 1). Lumen volume (63.9 ± 25.3 vs. 80.5 ± 20.7 mm³, *p* = 0.02) was significantly smaller in the statin group. RI ($102.0 \pm 7.9\%$ vs. $109.9 \pm 9.5\%$, *p* = 0.05) was similar in the 2 groups at baseline.

Post-treatment follow-up was undertaken at a median of 12 months (mean \pm SD: 14.3 ± 7.5 months; range 6 to 32 months) after the initial

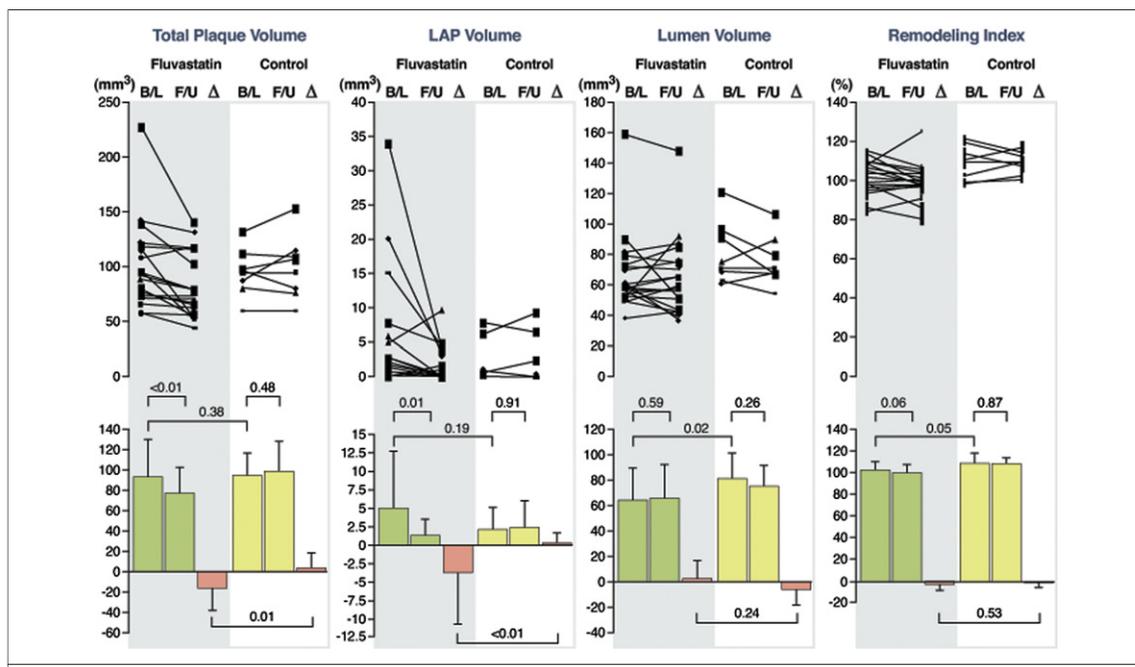
Table 1. Baseline Characteristics of 32 Participants

	Fluvastatin (n = 24)	Control (n = 8)	p Value
Age (yrs)	63.4 ± 9.5	66.9 ± 4.0	0.33
Men	19 (79%)	7 (88%)	0.99
Hypertension	11 (46%)	5 (63%)	0.69
Hyperlipidemia	4 (17%)	1 (13%)	0.99
Diabetes mellitus	5 (21%)	1 (13%)	0.99
Obesity (BMI >25)	3 (13%)	0 (0%)	0.55
Smoking	4 (15%)	3 (38%)	0.33
Previous MI	13 (50%)	2 (25%)	0.23
Time of follow-up (months)	15.8 ± 8.4	14.0 ± 7.4	0.59
Lipid profile			
Total cholesterol (mg/dl)	203.3 ± 31.1	181.6 ± 33.5	0.12
Triglyceride (mg/dl)	158.6 ± 74.9	181.4 ± 128.5	0.55
HDL-C (mg/dl)	53.2 ± 15.4	51.3 ± 12.9	0.77

BMI = body mass index; HDL-C = high-density lipoprotein cholesterol; MI = myocardial infarction.

study and statin therapy; neither side effects of statin treatment were observed nor were statins discontinued in any patient. In the statin-treated patients, total cholesterol (203.3 ± 31.1 vs. 189.5 ± 46.2 mg/dl, $p = 0.17$) and triglyceride (158.6 ± 74.9 vs. 149.4 ± 114.8 mg/dl, $p = 0.62$) decreased by the end of follow-up and HDL-C (53.2 ± 15.4

vs. 55.7 ± 15.6 mg/dl, $p = 0.29$) increased, but the levels were not statistically significantly different from the baseline (Table 2). Although the lipid profile was not significantly altered, a significant change was observed in the CTA-verified plaque morphology (Fig. 1). Total plaque volume (92.3 ± 37.7 vs. 76.4 ± 26.5 mm³, $p < 0.01$) and LAP

**Figure 1. Serial Change in Plaque Characteristics by CTA**

The top half of the figure shows changes in the plaque characteristics in individual patients. The bottom half demonstrates changes in the plaque volume, LAP volume, lumen volume, and remodeling index in the statin (green bars) and control (yellow bars) groups; the pink bars show the net difference between the first and second CTA images. At baseline, there is no significant difference in total plaque volume, LAP volume, lumen volume, or remodeling index between the statin and control groups. Upon follow-up, total plaque volume is significantly reduced in the statin group, as is the LAP volume. Luminal volume remains unchanged. B/L = baseline; CTA = computed tomography angiography; F/U = follow-up; LAP = low attenuation plaque.

Table 2. Lipid Profile at Baseline and Follow-Up

Lipid Profile	Baseline	Follow-Up	p Value
Statin group			
Total cholesterol (mg/dl)	203.3 ± 31.1	189.5 ± 46.8	0.17
Triglyceride (mg/dl)	158.6 ± 74.9	149.4 ± 114.8	0.62
HDL-C (mg/dl)	53.2 ± 15.4	55.7 ± 15.6	0.29
Control group			
Total cholesterol (mg/dl)	181.6 ± 33.5	188.0 ± 37.5	0.60
Triglyceride (mg/dl)	181.4 ± 128.5	151.1 ± 121.9	0.62
HDL-C (mg/dl)	51.3 ± 12.9	56.9 ± 17.0	0.06

HDL-C = high-density lipoprotein cholesterol.

volume (4.9 ± 7.8 vs. 1.3 ± 2.3 mm³, $p = 0.01$) showed significant regression at follow-up compared with baseline (Fig. 1). RI decreased, albeit not significantly, in the statin treatment group ($102.0 \pm 7.9\%$ vs. $100.3 \pm 8.0\%$, $p = 0.06$). The lumen volume did not change significantly (63.9 ± 25.3 vs. 65.2 ± 26.2 mm³, $p = 0.59$) after statin treatment. A CTA case example is presented in Figure 2.

On the other hand, in the control subjects, neither the lipid profile (total cholesterol: 181.6 ± 33.5 vs. 188.0 ± 37.5 mg/dl, $p = 0.60$, triglyceride: 181.4 ± 128.5 vs. 151.1 ± 121.9 mg/dl, $p = 0.62$, HDL-C: 51.3 ± 12.9 vs. 56.9 ± 17.0 mg/dl, $p = 0.06$), nor the CTA characteristics (total plaque volume: 94.4 ± 21.2 vs. 98.4 ± 28.6 mm³, $p = 0.48$; LAP volume: 2.1 ± 3.0 vs. 2.3 ± 3.6 mm³, $p = 0.91$; lumen volume: 80.5 ± 20.7 vs. 75.0 ± 16.3 mm³, $p = 0.26$; RI: 109.9 ± 9.5 vs. $109.6 \pm 6.0\%$, $p = 0.87$) changed. The plaque volume change (-15.9 ± 22.2 vs. 4.0 ± 14.0 mm³, $p =$

0.01) and LAP volume change (-3.7 ± 7.0 vs. 0.2 ± 1.5 mm³, $p < 0.01$) were significantly greater in the statin than the control group. The lumen volume (1.3 ± 15.6 vs. -5.5 ± 13.1 mm³, $p = 0.24$) and RI (-2.4 ± 6.8 vs. $-0.3 \pm 6.5\%$, $p = 0.53$) did not show significant differences between 2 groups. There was a significant correlation between the plaque volume change and LAP volume change ($R = 0.83$, $p < 0.01$) (Fig. 3). On the other hand, no significant correlation was found between the plaque volume change and lumen volume change ($R = 0.21$, $p = 0.24$). The prevalence of 0- to 2-feature positive plaques (based on positive remodeling and LAP) was not significantly different between the statin group and the control group (1.0 ± 0.4 vs. 1.3 ± 1.0 , $p = 0.28$) at baseline. In the statin group, plaque characteristics suggestive of instability were significantly reduced after statin treatment (0.6 ± 0.5 , $p = 0.01$). On the other hand, plaque characteristics did not change significantly in the control group (1.0 ± 0.5 , $p = 0.32$).

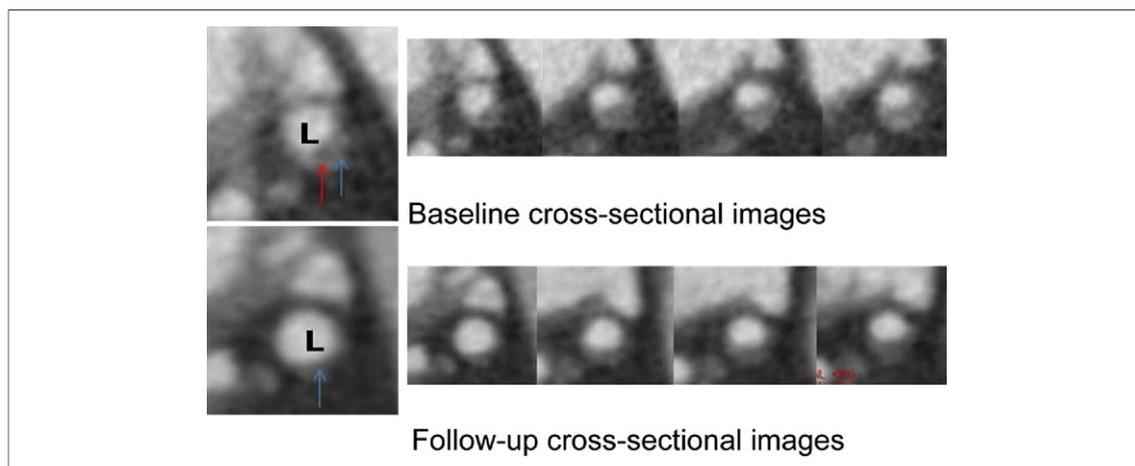


Figure 2. Serial CTA and Plaque Characteristics Before and After Statin Treatment

The upper panel shows baseline cross-sectional images of CTA, and the lower panel shows follow-up cross-sectional images. Note that the plaque (blue arrow) and low attenuation plaque (red arrow) size are reduced and the lumen (L) size enlarged after fluvastatin treatment.

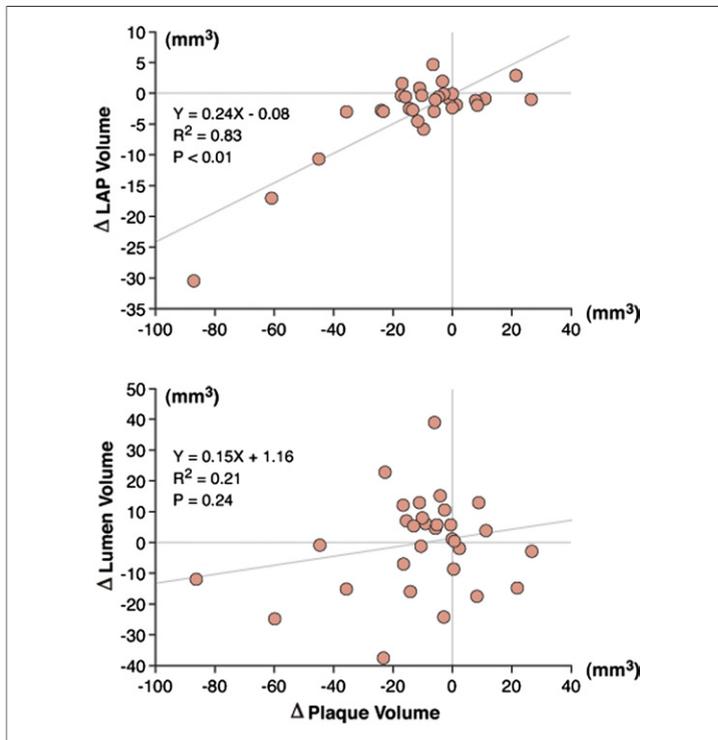


Figure 3. Correlation Between the Change in Plaque Volume or LAP Volume and Lumen Volume

The reduction in plaque volume is almost entirely driven by a decrease in LAP volume. **Upper panel**, there is a significant correlation between the plaque volume change and LAP volume change ($Y = 0.24X - 0.08$, $R^2 = 0.83$, $p < 0.01$). **Lower panel**, no significant correlation is found between the plaque volume change and lumen volume change ($Y = 0.15X + 1.16$, $R^2 = 0.21$, $p = 0.24$). LAP = low attenuation plaque.

DISCUSSION

This pilot study demonstrates the feasibility of employing serial CTA examinations for clinical trials designed to assess progression and regression of atherosclerotic coronary artery disease. This preliminary study also suggests that the use of statins even at a low dose may result in significant changes in plaque morphology. Statin treatment results in significant reduction of LAP volume and in turn an absolute decrease in plaque volume. These changes in LAP and total plaque volume occurred when no significant change was observed in the lumen size, and when the changes in lipid profile were not statistically significant. Lack of change in lipid profile may be due to near-normal baseline total cholesterol and triglyceride levels, lower statin dose, and relatively short duration of follow-up. This suggests that the changes in the plaque morphology may even occur with relatively less robust changes in the lipid profile, and may occur early after statin use.

The observed plaque changes in response to statin intervention represent resolution of morphological features associated with plaque instability. Plaques susceptible to rupture are typically voluminous, contain large necrotic cores, are positively remodeled, and often covered by thin and inflamed fibrous caps (20,21). It is expected that the intact plaques revealing similar characteristics would be vulnerable to rupture and acute coronary syndrome. In a prospective IVUS study, the plaques subsequently developing acute coronary events had initially exhibited a large eccentric plaque containing an echolucent zone (22). The efficacy of statin treatment has also been reported by serial IVUS examinations (4–10). The CTA noninvasively provides the qualitative and quantitative information (16–18,23,24). Our CTA follow-up study has also demonstrated that the coronary lesions comprising large plaque volume, large LAP or necrotic cores, and positive remodeling were at significantly higher risk of subsequent acute coronary syndrome as compared with the plaques that were neither positively remodeled nor contained LAP (19). The larger the positive remodeling and the greater the LAP volume, the higher was the likelihood of an acute event. It is reasonable to accept that a substantial reduction in LAP volume and total plaque volume should translate into plaque stability. The present study proposes that CTA could potentially be employed for the comparison of plaque size and plaque morphology at different time points and may allow the assessment of efficacy of therapeutic intervention. However, the current guidelines do not recommend CTA for plaque assessment alone and certainly not for serial plaque assessment. Although it is not possible to recommend serial scans to monitor the therapeutic efficacy of a medical intervention based on the present study, it at least indicates that plaque modulation, as a part of risk modification, is a feasible strategy. Such a strategy may also be justified in a clinical trial setting.

Study limitations. The current data only offer a preliminary feasibility study, and a larger multicenter, multireader, multisession outcomes study will be needed for defining the role of imaging strategy for demonstration of efficacy of statins in plaque stabilization. In addition, since this study was not a randomized clinical trial, although there were no differences in the baseline factors in the statin and control groups we studied, we cannot exclude the possibility of unknown confounders that we were unable to adjust for. It is especially important because the IVUS studies and carotid intima-media thickness evaluation, despite

larger populations, longer follow-up, and higher spatial resolution, have demonstrated smaller changes in plaque burden. Since plaque measurement was performed semiautomatically, there is a likelihood of measurement error, and it will be helpful to develop more robust automated software. Furthermore, more potent statins or larger doses of statins would need to be employed for better demonstration of efficacy of statin intervention. Similarly, follow-up scan duration would need to be longer and at more uniform intervals. Finally, demonstration of change in plaque morphology by serial CTA adds significant radiation exposure (25). In our present study, tube voltage was 135 kV, and radiation dose modulation software was not installed yet. For the serial CTA studies, radiation dose is one of the most important issues to be resolved. At the tube voltage of 135 kV, cutoff for LAP was ≤ 30 HU. Current low-dose protocols are performed at 120 kV or even at 100 kV. CTA plaque density, as well as the lumen density or spatial

resolution, may be affected by tube voltage and may need to be confirmed in each methodology. Furthermore, the reduction in radiation dose by voltage/current modulation (26), prospective gating (27,28), or limited volume scanning (29) would render serial imaging more acceptable.

CONCLUSIONS

This preliminary study suggests that serial CTA evaluation of the coronary plaques allows for the assessment of interval changes in the plaque morphology. Statin treatment results in a decrease in the plaque and necrotic core volumes; such features are associated with plaque instability.

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