Relationship Between Serum Inflammatory Marker Levels and the Dynamic Changes in Coronary Plaque Characteristics After Statin Therapy

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Background—The mechanism of statin for atheroma stabilization remains unclear. We aimed to assess the relationship between on-treatment changes in serum inflammatory biomarker levels and plaque composition in differed nonculprit coronary lesions.

Methods and Results—The changes in serum biochemical values, and intravascular ultrasound data were evaluated in 218 patients with virtual histology (VH)-intravascular ultrasound—defined fibroatheroma-containing segments after 12-month rosuvastatin treatment. When stratifying patients into quartiles according to the change in high-sensitivity C-reactive protein (hsCRP), there was a significant positive linear relationship for the changes in %necrotic core (coefficient, 1.31; standard error, 0.54) and %dense calcium volumes (coefficient, 0.80; standard error, 0.27), but a negative linear relationship for the changes in %fibrous (coefficient, −0.94; standard error, 0.45) and %fibrofatty volumes (coefficient, −1.17; standard error, 0.56; all $P<0.05$). The decrease in hsCRP (−1.2±3.9 versus 0.5±3.4 mg/L; $P=0.02$) was greater in those without VH-defined thin-cap fibroatheroma (TCFA, defined as >30° of necrotic core abutting the lumen in 3 consecutive slices) than those with VH-TCFA at follow-up. Diabetes mellitus, a larger normalized total atheroma volume, and the presence of VH-TCFA at baseline predicted the presence of VH-TCFA at follow-up (odds ratio, 4.01, 1.18, and 9.21, respectively; all $P<0.05$), whereas the change in hsCRP showed a trend (odds ratio, 1.19; $P=0.07$). The change in low-density lipoprotein-cholesterol had no relationship with the changes in hsCRP or plaque compositions.

Conclusions—With 12-month rosuvastatin therapy, a greater hsCRP reduction (not low-density lipoprotein-cholesterol) was associated with a greater decrease in %necrotic core volume and the absence of VH-TCFA, indicating a link between the anti-inflammatory action of statin and plaque stabilization by reducing NC and reinforcing fibrous cap.

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It has been suggested that statin therapy not only attenuates coronary atheroma progression but also modifies plaque composition,[1] which may consequently lead to a decrease in the risk of adverse cardiovascular events.[2] Although the mechanism of action of statin remains unclear, the pleiotropic effect of statin regardless of its low-density lipoprotein (LDL)-cholesterol–lowering effect has been considered to play a pivotal role in plaque regression and stabilization.[3] Serial intravascular imaging studies demonstrated the effects of statin on plaque volume reduction and compositional changes.[4,5] Previous studies showed the changes in the levels of serum inflammatory biomarkers, such as high-sensitivity C-reactive protein (hsCRP), homocysteine, fibrinogen, and lipoprotein(a) after statin treatment,[6,7] as well as better clinical outcomes in the presence of hsCRP lowering.[8,9] In particular, the relationship between baseline hsCRP levels and plaque morphology was previously demonstrated using a cross-sectional approach.[10] However, the interrelations between on-treatment changes in serum biomarkers and the dynamic nature of coronary lesion morphology have not been fully elucidated. Hence, in the present study of a prospective cohort of

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deferred coronary artery lesions, we aimed to link the changes in serum inflammatory biomarker levels after 1-year rosuvastatin therapy with the modification of plaque characteristics within fibroatheroma-containing target coronary artery segments using serial multimodality intravascular imaging at baseline and at follow-up.

Methods

Study Design and Population

This study represents a post hoc analysis of the STABLE trial (Statin and Atheroma Vulnerability Evaluation), which was a prospective, single-center, randomized double-blinded trial conducted to determine the effect of rosuvastatin 10 versus 40 mg in modifying plaque composition. The study design and population were described previously in detail.[11] In brief, a total of 312 patients aged 18 to 75 years who required clinically indicated coronary angiography or percutaneous coronary intervention with at least 1 deferred and untreated native coronary artery lesion were initially enrolled. Only 1 target lesion with the worst plaque type per patient was included in the analysis.

All patients received 10 or 40 mg rosuvastatin (1:2 randomization) once daily for 12 months. Serial angiography, grayscale-intravascular ultrasound (IVUS) were performed at baseline and after 12 months. Finally, 225 patients completed the follow-up at 12 months, whereas 87 (28%) patients withdrew. Of 225 patients, 218 patients with 218 lesions with complete data of grayscale-IVUS, virtual histology (VH)-IVUS, and blood laboratory tests were included in the present analysis. All patients provided written informed consent, and the institutional review board of Asan Medical Center approved the study.

Acquisition and Analysis of Grayscale- and VH-IVUS

At baseline and at the 12-month follow-up, grayscale-IVUS imaging was performed using motorized transducer pullback (0.5 mm/s) and a commercial scanner (Boston Scientific/SCIMED, Minneapolis, MN), consisting of a rotating, 40-MHz transducer within a 3.2-F imaging sheath. Offline quantitative IVUS analysis was performed using computerized planimetry (Echoplaque 3.0; Indec systems, Santa Clara, CA) 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]

VH-IVUS image acquisition was performed by using a synthetic-aperture array, 20-MHz, and 2.9-F catheter (Eagle Eye; In-Vision Gold; Volcano Corporation, San Diego, CA), with motorized catheter pullback (0.5 mm/s), after intracoronary nitroglycerin injection. VH-IVUS data analyses were performed using pcVH version 2.1 software (Volcano Corporation), using the same distal and proximal fiduciary points as for the grayscale-IVUS analysis. The external elastic membrane (EEM) and luminal borders were contoured for each frame (median interslice distance, 0.40 mm). The plaque components were categorized as dense calcium (DC, white), fibrous tissue (green), fibrofatty plaque (greenish yellow), or necrotic core (NC, red) and were reported as percentages of the total plaque area and volume.[13,14]

The change in plaque composition volume was calculated as the %plaque composition volume at the 12-month follow-up minus the baseline value. Fibroatheroma was defined as ≥10% confluent NC (spotty red color was not considered as confluent NC) and was classified into a VH-defined thin-cap fibroatheroma (VH-TCFA) or thick-cap fibroatheroma.[13,14] If there was >30° of NC abutting the lumen in 3 consecutive slices, the fibroatheroma was classified as a VH-TCFA; otherwise, it was classified as thick-cap fibroatheroma.[13,14]

The site of VH-TCFA with the maximal %NC was preferentially selected as the index site. In cases with only a thick-cap fibroatheroma (ie, no VH-TCFA), the index site was classified at the maximal %NC site within the target segment. The worst plaque type was selected for the index site. At follow-up, the plaque type was evaluated at the corresponding site in which the worst type of plaque was located at baseline.

The minimal lumen area and the EEM area at the minimal lumen area site were assessed. The plaque plus 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 evaluated. All the volumes were calculated using Simpson rule and then normalized for analysis length.

The normalized total atheroma volume (TAV) and percent atheroma volume were calculated as described previously; normalized TAV=(∑EEM−lumen)/n (n, the number of evaluable cross sections in the pullback), percent atheroma volume=(∑EEM−lumen)/∑EEM×100.[4] The change of atheroma volumes was calculated as volume at follow-up−volume at baseline. The investigators (S.-J.K. and J.-M.A.) 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.

Blood Biochemical Parameters

Blood samples were obtained after an overnight fast at baseline and at the 12-month follow-up before performing coronary angiography, in accordance with the standard institutional guidelines. The analysis methods of each blood biochemical parameter were summarized in Table I in the Data Supplement. In the laboratory, technically, the hsCRP level was measured and reported up to 30.0 mg/L and thus the hsCRP level ranged from 0.0 to 30.0 mg/L for the present analysis.

Statistical Analysis

Categorical variables are summarized using number and percentage and were compared using the χ^2 or Fisher exact tests. Continuous variables are summarized using mean±SD and were compared using Student *t* test or the paired *t* test as indicated, in the case of a normal distribution. If continuous variables were not normally distributed, the Mann–Whitney *U* test or Wilcoxon signed-rank test was used, as indicated. We performed Pearson correlation analysis to evaluate the association of biochemical parameters with atheroma volume change. As the distribution of continuous variables for biochemical parameters exhibited a sharp peak with long-range, low-intensity tails, the variables were grouped into 4 range quartiles. For quartile analysis according to the change in hsCRP levels, the first (lowest), second, third, and fourth (highest) quartiles were separated by 0.3, −0.2, and −1.1 mg/L, respectively. For quartile analysis according to the changes in LDL-cholesterol levels, the first (lowest), second, third, and fourth (highest) quartiles were separated by −14, −41, and −66 mg/dL, respectively. To assess the relationship between blood biochemical parameters and plaque composition changes, we used linear regression after subjects were stratified into 4 groups, based on a quartile split of each biochemical parameter. The linear regression analysis was performed after strictly testing linear and additivity of predictive relationships, independence of errors, constant variance of errors, and normality of the error distribution and confirming no violation of these assumptions. Moreover, multivariate logistic regression with backward elimination was performed to determine the independent predictors of the presence of TCFA at follow-up, using conventional cardiovascular risk factors, blood parameters, and morphological variables, with $P<0.1$ on univariate analysis. The statistical assumptions for binary logistic regression were also satisfied. The α value was set at 0.05 for all statistical tests. Data were analyzed using the SPSS package, version 21.0 (SPSS Inc., Chicago, IL).

Results

Baseline Characteristics

Table 1 summarizes the baseline characteristics of the 218 study patients. Using 1:2 randomization, rosuvastatin 10 and

40 mg were prescribed to 70 (32%) and 148 (68%) patients, respectively. The lesions were located in the left anterior descending artery in 87 (39.9%), right coronary artery in 89 (40.8%), and left circumflex artery in 42 (19.3%) patients. Angiographic diameter stenosis >50% was observed in 27 (12.4%) lesions.

Laboratory Data

The lipid profile and serum biomarker values at baseline and follow-up are described in Table 2. After 12-month statin therapy, there was a significant decrease in the total, LDL-cholesterol, and triglyceride levels, along with a decrease in the apolipoprotein (Apo) B100 levels. In contrast, the high-density lipoprotein-cholesterol and ApoA1 levels had increased. The levels of both hsCRP and homocysteine significantly declined, whereas those of fibrinogen and lipoprotein(a) increased at follow-up. The leukocyte count decreased, but not statistically significant. There was no significant correlation between the changes in hsCRP and LDL-cholesterol levels (r=0.01; P=0.88).

Table 1. Baseline Characteristics

	Total (n=218)
Age, y	62.4±9.2
Men	162 (74.3)
Body mass index, kg/m^2	25.2±2.9
Current tobacco use	69 (31.7)
Hypertension	138 (63.3)
Diabetes mellitus	54 (24.8)
Hyperlipidemia	128 (58.7)
Previous myocardial infarction	4 (1.8)
Previous PCI	15 (6.9)
Previous CABG	1 (0.5)
Clinical presentation	
Silent or stable angina	128 (58.7)
Acute coronary syndrome	90 (41.3)
No. of narrowed coronary arteries	
None	34 (15.6)
1	104 (47.7)
2	63 (28.9)
3	17 (7.8)
Medication at discharge	
Aspirin	218 (100.0)
Clopidogrel	182 (83.5)
β-blocker	139 (63.8)
Calcium-channel blocker	178 (81.7)
ACE inhibitor or ARB	61 (28.0)
Nitrate	22 (10.1)
Rosuvastatin 10 mg	70 (32.1)
Rosuvastatin 40 mg	148 (67.9)

Variables are presented as a mean±SD or n (%). ACE indicates angiotensin-converting enzyme; ARB, angiotensin-receptor blocker; CABG, coronary artery bypass grafting; and PCI, percutaneous coronary intervention.

Grayscale- and VH-IVUS Data

Table 2 summarizes the grayscale- and VH-IVUS data. After 12-month statin treatment, there were significant reductions in the percent atheroma volume and normalized TAV (−0.8±4.6%; P=0.01 and −0.6±1.2 mm^3; P≤0.001, respectively) and %NC volume, but an increase in the %fibrofatty volume (−3.0±8.5%; P≤0.001 and 2.9±8.9%; P=0.01, respectively). At baseline, the plaque types at the index site were TCFA in 119 (54.6%) lesions and thick-cap fibroatheroma in 99 (45.4%) lesions. At follow-up, the plaque types were TCFA in 43 (19.7%) lesions (P<0.001 versus baseline), thick-cap fibroatheroma in 154 (70.6%) lesions, pathological intimal thickening in 18 (8.3%) lesions, and fibrous plaque in 3 (1.4%) lesions.

Correlation Between the Changes in Serum Biomarker Levels and Plaque Morphology

When stratifying patients into quartiles according to the change in the hsCRP level, there were significant positive linear relationship for the changes in %NC (coefficient, 1.31; standard error [SE], 0.54; P=0.02) and %DC volumes (coefficient, 0.80; SE, 0.27; P=0.003), but negative linear relationship for the changes in %fibrous (coefficient, −0.94; SE, 0.45; P=0.04) and %fibrofatty volumes (coefficient, −1.17; SE, 0.56; P=0.04; Figure 1A). In particular, the differences in the absolute values of plaque compositional changes were significant only between the first (smallest degree of hsCRP reduction) and the fourth (largest degree of hsCRP reduction) quartiles according to the change in the hsCRP level. The fourth hsCRP quartile group showed the greatest reduction in %NC volume, whereas the first hsCRP quartile group was associated with increases in the %NC and %DC volumes. In contrast, there was no significant correlation between the change in LDL-cholesterol level and changes in the %NC and %DC volumes (Figure 1B). Consistent results were observed when we analyzed the correlation between the changes in the absolute volume in the target segment and changes in hsCRP or LDL-cholesterol levels (Figure I in the Data Supplement). Examples of regression or progression of vulnerable plaque feature after rosuvastatin change of the plaque characteristics on VH-IVUS after 12-month rosuvastatin therapy are depicted in Figure 2. Changes in the homocysteine, fibrinogen, lipoprotein(a), and leukocyte levels had no correlations with plaque compositional changes (Table II in the Data Supplement). Moreover, contrary to the change in hsCRP levels, the baseline hsCRP level did not have any correlation with the change in %NC volume (Table III in the Data Supplement).

Correlation analysis of atheroma volumes showed that the homocysteine levels at baseline were correlated with the normalized TAV at baseline (r=0.22; P=0.001) and with the normalized TAV at follow-up (r=0.27; P≤0.001; Figure II in the Data Supplement). Moreover, the change in lipoprotein(a) levels was significantly correlated with the change in normalized TAV (r=0.16; P=0.05). However, no other serum biomarker was correlated with atheroma volume changes (Table IV in the Data Supplement).

Table 2. Blood Biochemical Values and Intracoronary Imaging Study Parameters

	Baseline	Follow-Up at 12 mo	Change (Follow-Up−Baseline)	*P* Value
Lipid profiles, mg/dL				
Total cholesterol	172.3±39.6	127.2±31.6	−45.3±42.5	<0.001
HDL-cholesterol	43.5±12.0	49.2±11.9	5.8±9.1	<0.001
LDL-cholesterol	105.7±35.4	67.1±28.1	−38.8±40.3	<0.001
LDL/HDL-cholesterol (ratio)	2.6±1.1	1.4±0.7	−1.2±1.1	<0.001
Triglyceride	145.4±81.9	115.6±66.1	−30.0±69.3	<0.001
Serum biochemical markers				
ApoA1, mg/dL	125.0±22.1	137.7±23.9	14.0±18.5	<0.001
$ApoB_{100}$, mg/dL	87.7±25.2	61.9±19.3	−25.1±26.8	<0.001
$ApoB_{100}$/ApoA1 (ratio)	0.7±0.2	0.5±0.2	−0.3±0.2	<0.001
Leukocyte count, $\times 10^3/\mu L$	6.8±2.0	6.6±2.0	−0.1±1.9	0.15
hsCRP, mg/L	2.2±3.7	1.2±2.0	−0.9±3.9	<0.001
Homocysteine, mg/dL	12.5±3.5	11.9±3.3	−0.8±3.4	0.002
Fibrinogen, mg/dL	258.1±52.7	278.4±55.1	16.1±65.3	0.001
Lipoprotein(a), μmol/L	23.8±23.3	30.5±32.0	8.9±15.7	<0.001
Grayscale-IVUS				
MLA, mm^2	4.4±2.0	4.3±2.1	−0.1±1.1	0.03
EEM area at the MLA, mm^2	13.7±4.7	12.8±4.4	−0.9±2.6	<0.001
P+M area at the MLA, mm^2	9.4±3.9	8.6±3.7	−0.8±2.5	<0.001
Plaque burden at the MLA, %	67.4±10.9	66.2±12.2	−1.7±8.4	0.06
Percent atheroma volume, %	51.3±8.3	50.4±8.8	−0.8±4.6	0.01*
Normalized lumen, mm^3/mm	7.9±3.3	7.6±3.6	−0.3±1.6	0.001
Normalized EEM, mm^3/mm	16.1±5.4	15.3±5.4	−0.8±2.1	<0.001
Normalized total atheroma volume, mm^3	8.2±2.9	7.6±2.8	−0.6±1.2	<0.001
Virtual histology-IVUS				
Percent volume, segment, %				
Fibrous	59.4±7.8	59.1±8.7	−0.3±7.0	0.88
Fibrofatty	11.7±5.8	14.6±9.2	2.9±8.9	0.01
Necrotic core	21.3±6.7	18.4±7.4	−3.0±8.5	<0.001
Dense calcium	7.6±5.1	8.0±5.6	0.4±4.3	0.67

Values are presented as a mean±SD. Apo indicates apolipoprotein; EEM, external elastic membrane; HDL, high-density lipoprotein; hsCRP, high-sensitivity C-reactive protein; IVUS, Intravascular ultrasound; LDL, low-density lipoprotein; MLA, minimal lumen area; and P+M, plaque plus media.

**P* values were obtained using the paired *t* test, otherwise the Wilcoxon signed-rank test was used, as indicated.

Predictors of the Presence of TCFA at Follow-Up

VH-TCFA was noted at follow-up (combination of persistent and newly developed VH-TCFA) in 43 of 218 (19.7%) lesions. Table 3 compares the baseline clinical, biochemical, and morphological features between patients with and without VH-TCFA at follow-up. The patients with VH-TCFA at follow-up were more likely to have diabetes mellitus, as well as lower baseline levels of total and LDL-cholesterol and $ApoB_{100}$. Despite the lack of any significant difference in the baseline hsCRP levels, the increase in hsCRP level (−1.2±3.9 versus 0.5±3.4 mg/L; *P*=0.02) was greater in those with VH-TCFA than those without VH-TCFA at follow-up.

Table 4 shows the results of logistic regression for predicting the presence of VH-TCFA at follow-up. By multivariate analysis, diabetes mellitus, a greater normalized TAV, and the presence of VH-TCFA at baseline were independent predictors of the presence of VH-TCFA at follow-up (odds ratio, 4.01; 95% confidence interval, 1.62–9.97; *P*=0.001; odds ratio, 1.18; 95% confidence interval, 1.04–1.35; *P*=0.01; and odds ratio, 9.21; 95% confidence interval, 3.04–27.92; *P*≤0.001). Moreover, the change in the hsCRP level showed a trend for the presence of VH-TCFA at follow-up (odds ratio, 1.19; 95% confidence interval, 0.98–1.44; *P*=0.07), whereas the change in LDL-cholesterol had no relationship with the change in the hsCRP level or plaque composition.

Discussion

The major findings of the present study are as follows: (1) the decrease in %NC and %DC volumes and the absence of VH-TCFA at follow-up were associated with a greater reduction in hsCRP levels, but not with the change in the lipid profile and (2) a less reduction of hsCRP levels showed a trend toward the presence of TCFA at follow-up.

Although the benefits of statins are primarily attributed to its lipid-lowering effect, plaque regression and the reduced clinical event rate have also been associated with statin-mediated CRP level reduction.[8,15] However, it is unclear whether such statin-mediated CRP level reduction occurs in parallel with the change in LDL-cholesterol levels or occurs via a separate mechanistic pathway.[16] Moreover, the role of statin-mediated CRP reduction in the antiatherosclerotic effect and the clinical outcomes remains unclear. In several large trials, the on-treatment change in CRP levels was negligibly correlated with the change in LDL-cholesterol levels.[4,9] In the present study, we found that the decline in hsCRP levels occurred independently of the LDL-cholesterol level reduction.[17] A post hoc analysis of the SATURN trial (Atheroma by Intravascular Ultrasound: Effect of Rosuvastatin Versus Atorvastatin)[18] showed that elevated on-treatment CRP level, but not on-treatment LDL-cholesterol level, was independently associated with adverse cardiac events, thus indicating that systemic inflammation may contribute to cardiovascular risk even in optimally treated individuals. Nevertheless, the evidence that directly links statin-mediated CRP reduction, plaque modification, and clinical outcome improvement is lacking.

Although cross-sectional observations have supported the relationship between hsCRP and plaque morphology, the dynamic change in coronary atheroma was rarely predicted by the baseline hsCRP alone. Similarly, our current data showed

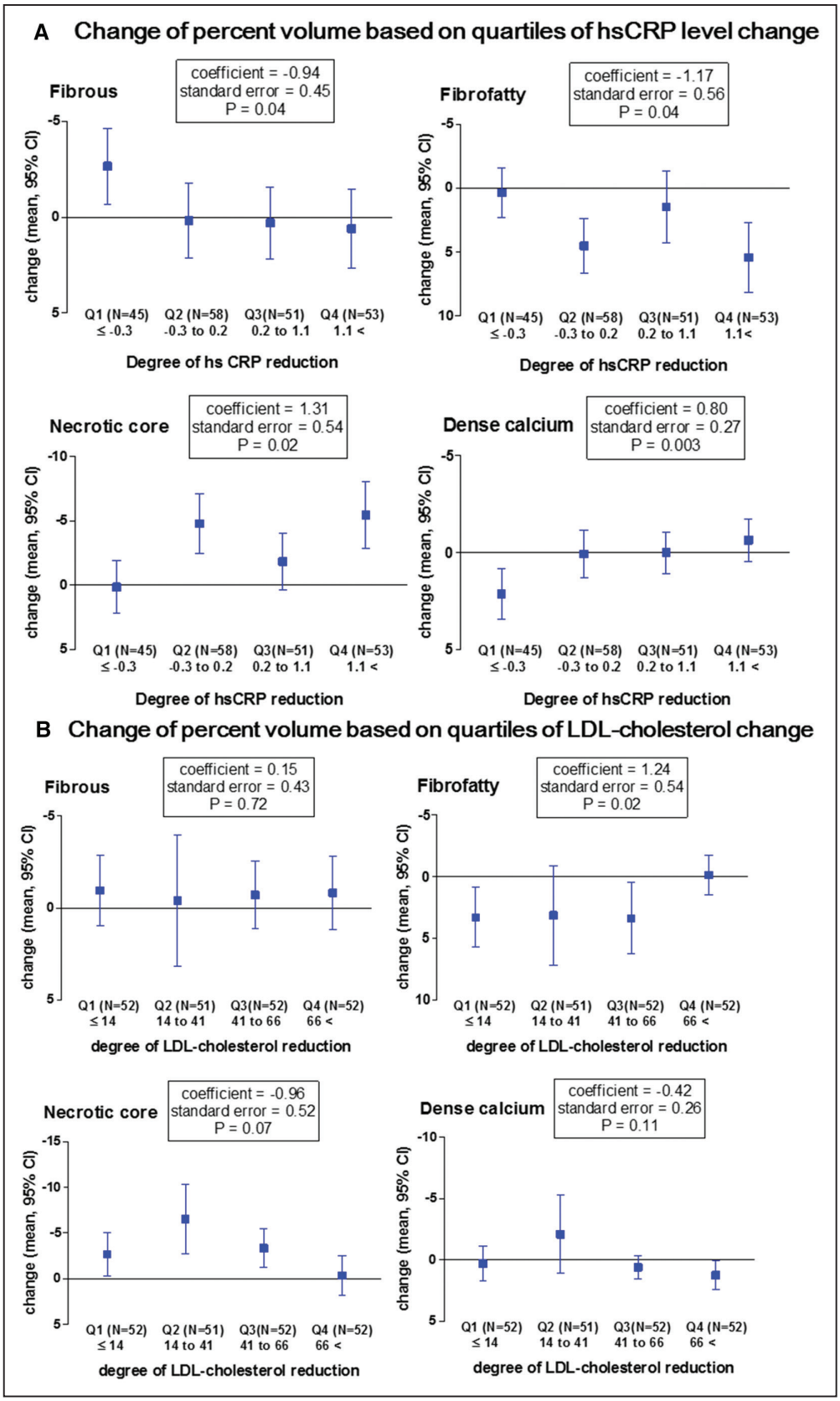

Figure 1. Serial changes in the percent volume in the target segment (plaque composition) across the quartiles of high-sensitivity C-reactive protein (hsCRP) level change (**A**) and of low-density lipoprotein (LDL)-cholesterol level change (**B**) >12 mo. Q1 refers to the lowest quartile (smallest degree of hsCRP reduction) and Q4 refers to the highest quartile (largest degree of hsCRP reduction). Reported values are coefficient, standard error by linear regression.

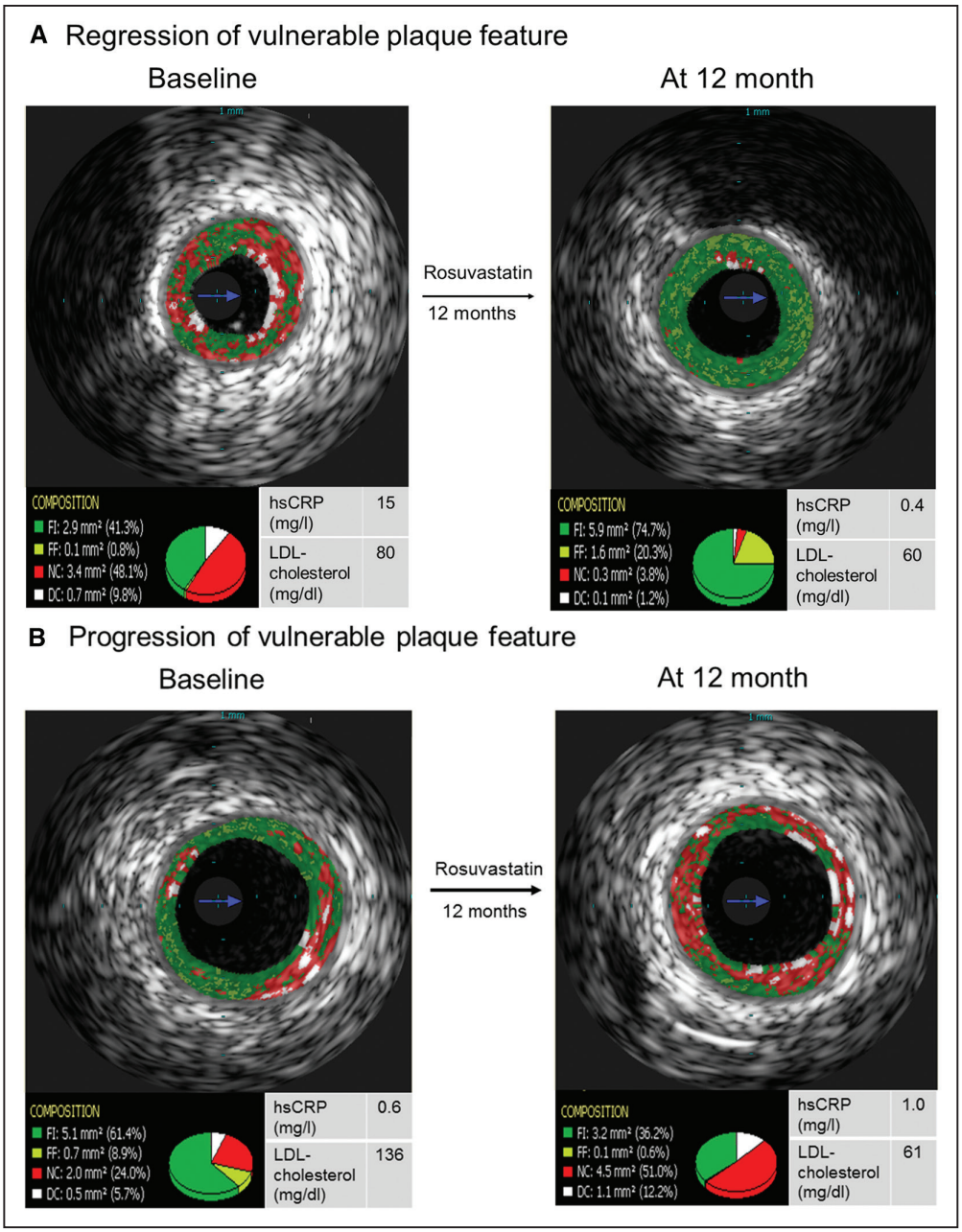

Figure 2. Examples of change of the plaque characteristics on virtual histology intravascular ultrasound after rosuvastatin therapy. **A**, Regression of vulnerable plaque feature along with decrease in the high-sensitivity C-reactive protein (hsCRP) level after 12-mo rosuvastatin treatment. **B**, Progression of vulnerable plaque feature along with increase in the hsCRP level despite 12-mo rosuvastatin treatment. DC indicates dense calcium; FB, fibrous; FF, fibrofatty; NC, necrotic core; and LDL, low-density lipoprotein.

no significant correlation between baseline hsCRP levels and the change in %NC volume. In addition, there was no difference in the baseline hsCRP level between patients with and without VH-TCFA at follow-up.

In a recent substudy of the IBIS-4 (Integrated Biomarker Imaging Study), which included 44 patients with ST-segment–elevation myocardial infarction patients with serial hsCRP measurement after high-intensity statin therapy, the change in hsCRP levels and on-treatment levels of hsCRP, but not LDL-cholesterol, was correlated with the change in %NC volumes.[19] In 71 patients from the SATURN trial, the change in the %NC volume was also correlated with on-treatment CRP level.[20] Similarly, our current study on 218 patients showed that a greater reduction in the hsCRP levels, but not LDL-cholesterol reduction, was associated with a greater reduction in the %NC volume and the absence of VH-TCFA at follow-up. These findings provide a link between the statin-mediated hsCRP level reduction and plaque stabilization via %NC volume reduction. Although the mean change in the %NC volume is subtle overall, the changes were individually variable. Because the effect of statins on atheroma modification was confined to the subset of patients with the greatest hsCRP level reduction, surveillance of the on-treatment hsCRP level may identify the progression of high-risk plaque composition,

Table 3. Clinical Characteristics, Blood Biochemical Values, and Grayscale-Intravascular Ultrasound Parameters Stratified According to the Presence of TCFA at Follow-Up

At 12-mo Follow-Up (n=218)	Absence of TCFA (n=175)	Presence of TCFA (n=43)	*P* Value
Clinical characteristics			
Age, y	62.3±9.2	62.9±9.3	0.79*
Male	131 (74.9%)	31 (72.1%)	0.86
Body mass index, kg/m^2	25.0±2.9	25.8±2.6	0.10
Rosuvastatin 40 mg	120 (68.6%)	28 (65.1%)	0.80
Hypertension	107 (61.1%)	31 (72.1%)	0.25
Diabetes mellitus	35 (20.0%)	19 (44.2%)	0.002
Hyperlipidemia	108 (61.7%)	20 (46.5%)	0.10
Current tobacco use	57 (32.6%)	12 (27.9%)	0.69
Acute coronary syndrome	72 (41.1%)	18 (41.9%)	1.00
TCFA at baseline	81 (46.3%)	38 (88.4%)	<0.001
Blood biochemical values, baseline			
Total cholesterol, mg/dL	174.5±41.5	163.3±29.3	0.04
HDL-cholesterol, mg/dL	44.0±12.4	41.5±10.3	0.18*
LDL-cholesterol, mg/dL	107.9±37.3	97.2±25.5	0.03
LDL/HDL-cholesterol (ratio)	2.6±1.1	2.5±0.9	0.54*
Triglyceride, mg/dL	143.9±80.8	151.7±86.8	0.74*
ApoA1, mg/dL	125.6±22.7	122.6±19.9	0.58*
$ApoB_{100}$, mg/dL	89.6±26.4	80.1±17.8	0.006
$ApoB_{100}$/ApoA1 (ratio)	0.7±0.3	0.7±0.2	0.22*
Leukocyte count, ×10^3/μL	6.8±2.1	6.6±1.6	0.50*
hsCRP, mg/L	2.3±3.8	1.6±3.1	0.69*
Homocysteine, mg/dL	12.4±3.3	12.8±4.0	0.96*
Fibrinogen, mg/dL	261.0±53.6	246.7±47.8	0.19*
Lipoprotein(a), μmol/L	24.7±24.0	19.8±20.0	0.12*
Blood biochemical values, change over the 12 mo			
Total cholesterol, mg/dL	−46.4±41.1	−40.9±48.2	0.84*
HDL-cholesterol, mg/dL	5.3±8.9	7.8±9.6	0.12
LDL-cholesterol, mg/dL	−39.0±40.3	−38.2±40.7	0.98*
LDL/HDL-cholesterol (ratio)	−1.2±1.1	−1.2±1.0	0.81
Triglyceride, mg/dL	−27.8±68.6	−38.8±71.8	0.28*
ApoA1, mg/dL	13.5±17.9	15.3±20.7	0.63
$ApoB_{100}$, mg/dL	−26.3±25.7	−21.1±30.1	0.86*
$ApoB_{100}$/ApoA1 (ratio)	−0.3±0.2	−0.2±0.2	0.99*
Leukocyte count, ×10^3/μL	−0.1±1.9	0.04±1.6	0.45*
hsCRP, mg/L	−1.2±3.9	0.5±3.4	0.02*
Homocysteine, mg/dL†	−0.7±3.3	−1.3±3.5	0.42*
Fibrinogen, mg/dL†	13.7±64.5	24.6±68.3	0.39
Lipoprotein(a), μmol/L†	8.0±14.7	12.1±18.4	0.25*

Values are presented as a mean±SD or number (%). Apo indicates apolipoprotein; HDL, high-density lipoprotein; hsCRP, high-sensitivity C-reactive protein; LDL, low-density lipoprotein; and TCFA, thin-cap fibroatheroma.

**P* values were obtained using the Mann–Whitney test; otherwise, the student's *t* test was used, as indicated.

†Values at follow-up were available in 146 (67%) for homocysteine, 152 (70%) for fibrinogen, and 148 (68%) for lipoprotein(a).

Table 4. Logistic Regression for the Prediction of the Presence of TCFA at Follow-Up, With Multivariate Analysis of the Variables With a *P*<0.1 on Univariate Analysis

	Univariate			Multivariate		
	OR	95% CI	*P* Value	OR	95% CI	*P* Value
Diabetes mellitus	3.17	1.55–6.43	0.001	4.01	1.62–9.97	0.003
Hyperlipidemia	0.54	0.27–1.06	0.07	…	…	…
Total cholesterol at baseline	0.99	0.98–1.00	0.10	…	…	…
HDL-cholesterol < median level of 42.0 mg/dL at baseline	2.02	1.00–4.09	0.05	2.24	0.96–5.24	0.06
$ApoB_{100}$ at baseline	0.98	0.97–1.00	0.03	0.99	0.97–1.00	0.09
Change hsCRP	1.18	1.03–1.35	0.02	1.19	0.98–1.44	0.07
PAV at baseline	1.06	1.02–1.11	0.004	…	…	…
nTAV at baseline	1.21	1.09–1.37	0.001	1.18	1.04–1.35	0.01
TCFA at baseline	8.82	3.61–26.55	<0.001	9.21	3.04–27.92	<0.001

Apo indicates apolipoprotein; CI, confidence interval; HDL, high-density lipoprotein; hsCRP, high-sensitivity C-reactive protein; nTAV, normalized total atheroma volume; OR, odd ratio; PAV, percent atheroma volume; and TCFA, thin-cap fibroatheroma.

even in the setting of intensive statin therapy. Furthermore, the action of statins in decreasing the inflammatory burden and stabilizing vulnerable plaques may partly explain the clinical benefits of statin therapy as secondary prevention.

The dynamic changes in plaque composition are not consistently reported among various studies. Kubo et al[5] reported that VH-TCFAs in 75% of cases at baseline regressed into thick-cap fibroatheroma or fibrotic plaques at the 12-month follow-up. In contrast, a substudy of the HORIZONS-AMI (The Harmonizing Outcomes With Revascularization and Stents in Acute Myocardial Infarction Study) showed persistent VH-TCFA in 78% of ST-segment–elevation myocardial infarction patients and an increase in the %NC volume at 13 months.[21] The discrepancy in plaque compositional changes among the studies may be because of the different populations, including various clinical settings from stable angina to ST-segment–elevation myocardial infarction, biological activity, hemodynamic forces, thrombogenicity, VH-IVUS methodology, statin dose and duration, and the uneven effect of different statins with widely varying pharmacokinetic profiles. In addition, the heterogeneous changing patterns of plaque composition may be explained in part by the lipophilicity of statins. Hydrophilic statins tend to be more anti-inflammatory as compared with lipophilic statins,[22] which can promote oxidant-induced apoptosis in vascular smooth muscle cells.[23] Furthermore, clinical studies showed that hydrophilic (versus lipophilic) statins were more effective in

preventing new Q-wave infarction and cardiovascular events in patients with acute myocardial infarction.[24] In a recent meta-analysis that showed no %NC change, the majority of included studies used lipophilic statins.[25] In contrast, our present study using hydrophilic rosuvastatin apparently demonstrated a reduction in %NC volume, consistent with the other studies using rosuvastatin.[1,26] Thus, further studies are warranted to investigate the precise mechanism of statin-induced plaque stabilization and the effects based on statin types and dosage.

Our current small-sized post hoc analysis had some limitations of note. First, as the study evaluated fibroatheroma-containing nonculprit lesions, the findings cannot be extrapolated to more advanced, culprit lesions or lesions without fibroatheroma. Second, although this analysis was performed in the cohort of the well-designed STABLE trial, the absence of a placebo group with potential regression to the mean is another limitation. Third, the current analysis did not include active mediators of atherogenesis such as chemokine, oxidant stress markers, atherogenic lipoproteins, and other inflammatory biomarkers that may affect atherosclerotic progression and vascular remodeling.[27] Fourth, the results from this underpowered, small-sized study evaluating Asians cannot be generalized. In particular, the levels of serum inflammatory biomarkers, except for hsCRP, were available only for ≈70% of patients, which limited our ability to identify the relationship between inflammatory biomarker levels and plaque morphology changes. Fifth, we did not assess the clinical outcomes based on inflammatory activity, as defined by the inflammatory biomarkers. Finally, the poor resolution of VH-IVUS limits the ability to identify histologically defined TCFA (fibrous cap thickness, <65 μm). Moreover, there is a validation issue for ECG-gated VH-IVUS imaging in serial follow-up studies.

Conclusion

Serial intravascular imaging data show that a greater hsCRP level reduction (not LDL-cholesterol level reduction) is associated with a greater decrease in the %NC volume and the absence of VH-TCFA after 12-month rosuvastatin treatment. This provides a link between statin-mediated hsCRP level reduction and plaque stabilization.

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Disclosures

None.

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CLINICAL PERSPECTIVE

Even though statin therapy has been associated with plaque regression and stabilization, it still remains uncertain how the on-treatment changes in serum inflammatory biomarkers and low-density lipoprotein-cholesterol level link with the dynamic nature of plaque characteristics. In a prospective cohort of deferred fibroatheroma-containing coronary artery lesions, the quartile analysis based on the changes in high-sensitivity C-reactive protein level showed significant positive linear relationships for the reduction in %necrotic core and % dense calcium after 1-year rosuvastatin treatment, particularly evident between the lowest versus the highest quartiles. Additionally, the statin-mediated high-sensitivity C-reactive protein reduction was much greater in the absence (versus presence) of virtual histology-defined thin-cap fibroatheroma at follow-up. Not in parallel with the change in the low-density lipoprotein-cholesterol level, the association between the changes in high-sensitivity C-reactive protein and %necrotic core volume indicates the anti-inflammatory action of statin on plaque stabilization by reducing %necrotic core and reinforcing fibrous cap. By using serial multimodality intravascular imaging, the current study emphasizes that the pleiotropic effect of statin regardless of its low-density lipoprotein–lowering action may play a pivotal role in plaque regression and stabilization. Further large-scaled studies are required to elucidate the precise mechanism of statin-mediated atheroma modification and the effect of different type and dosage of statin. In a practical point of view, it needs to be clarified whether monitoring of the serum high-sensitivity C-reactive protein level can be useful to assess the local response to medical treatment and its prognostic values.

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Relationship Between Serum Inflammatory Marker Levels and the Dynamic Changes in Coronary Plaque Characteristics After Statin Therapy

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Supplemental Material

Relationship between Serum Inflammatory Marker Levels and the Dynamic Changes in Coronary Plaque Characteristics following Statin Therapy

Supplemental Table 1. The analysis methods of blood biochemical parameters.

	Technology	Analyzer	Manufacturer
Lipid profile; Total cholesterol, HDL-cholesterol, LDL-cholesterol, triglyceride	Chemiluminescence immunoassay	Cobas 8000 C702	Roche Diagnostics system, Switzerland
Apolipoprotein B100, apolipoprotein A1, hsCRP, lipoprotein (a)	Nephelometric technology	BN II system	Siemens, Erlangen Germany
Leukocyte count	Fluorescent flow cytometry	Sysmex XE-2100	Sysmex Corporation, Kansai, Japan
Homocysteine	Nephelometric technology	ADVIA Centaur XPT	Siemens, Erlangen, Germany
Fibrinogen	Photo-optical	Sysmex CA-7000	TOA Medical

	technology	Electronics Co., Kobe, Japan

Abbreviation: HDL, high-density lipoprotein; hsCRP, high-sensitivity C-reactive protein; LDL, low-density lipoprotein.

Supplemental Table 2. Correlation between serum biomarker level changes and changes in the percent volume (plaque composition)

	Change of % fibrous		Change of % fibrofatty		Change of % necrotic core		Change of % dense calcium	
	r	p value	*r*	p value	*r*	p value	*r*	p value
Lipid profiles								
Change in LDL-cholesterol	-0.04	0.58	0.14	0.04	-0.08	0.23	-0.06	0.37
Change in HDL-cholesterol	0.02	0.78	-0.03	0.67	0.01	0.85	0.002	0.97
Change in LDL/HDL ratio	0.01	0.91	0.07	0.34	-0.06	0.42	-0.04	0.62
Change in LDL-cholesterol quartile	0.03	0.72	0.16	0.02	-0.13	0.07	-0.11	0.11
Change in HDL-cholesterol quartile	0.05	0.52	-0.01	0.90	-0.002	0.98	-0.05	0.46
Change in LDL/HDL ratio quartile	0.03	0.68	0.08	0.23	-0.07	0.31	-0.08	0.27
Apolipoprotein profiles								
Chang in ApoA1	0.03	0.76	0.07	0.43	-0.07	0.41	-0.05	0.59

Change in ApoB100	-0.13	0.12	0.02	0.93	0.05	0.56	0.11	0.18
Change in ApoB100/ApoA1 ratio	-0.12	0.16	-0.02	0.78	0.07	0.44	0.12	0.15
Change in ApoA1 quartile	0.03	0.76	0.01	0.91	-0.03	0.76	-0.02	0.84
Change in ApoB100 quartile	-0.10	0.23	-0.01	0.89	0.05	0.51	0.09	0.29
Change in ApoB100/ApoA1 ratio quartile	-0.08	0.31	-0.02	0.81	0.05	0.53	0.09	0.30
Serum inflammatory biomarkers								
Change in leukocyte count	-0.03	0.67	-0.02	0.81	0.05	0.52	-0.004	0.96
Change in hsCRP	-0.06	0.38	-0.15	0.03	0.15	0.03	0.12	0.09
Change in homocysteine	0.05	0.59	0.01	0.92	-0.03	0.73	-0.04	0.66
Change in fibrinogen	0.03	0.74	0.01	0.92	-0.03	0.70	-0.002	0.98
Change in lipoprotein (a)	-0.003	0.98	-0.09	0.27	0.08	0.33	0.03	0.76
Change in leukocyte count quartile	-0.06	0.41	-0.06	0.41	0.08	0.23	0.05	0.49
Change in hsCRP quartile	-0.14	0.04	-0.14	0.04	0.17	0.02	0.21	0.003

Change in homocysteine quartile	0.12	0.16	0.06	0.48	-0.11	0.20	-0.11	0.20
Change in fibrinogen quartile	0.07	0.38	0.05	0.54	-0.16	0.20	-0.02	0.85
Change in lipoprotein (a) quartile	-0.03	0.72	0.00	1.00	0.02	0.79	0.003	0.97

Correlations were determined using Pearson's correlation analysis.

Abbreviations: Apo, apolipoprotein; HDL, high-density lipoprotein; hsCRP, high-sensitivity C-reactive protein; LDL, low-density lipoprotein.

Supplemental Table 3. Correlation analysis between plaque composition (percent volume in the segment) and hsCRP at baseline or change in hsCRP

	% Fibrous		% Fibrofatty		% Necrotic core		% Dense calcium	
	r	p value	*r*	p value	*r*	p value	*r*	p value
hsCRP at baseline	0.02	0.82	0.16	0.02	-0.13	0.06	-0.10	0.16
Change in hsCRP	-0.06	0.38	-0.15	0.03	0.15	0.03	0.12	0.09
hsCRP quartile at baseline	0.01	0.87	0.13	0.06	-0.08	0.25	-0.13	0.06
Change in hsCRP quartile	-0.14	0.04	-0.14	0.04	0.17	0.02	0.21	0.003

Supplemental Table 4. Correlation between serum biomarkers and atheroma volume changes

	Change in PAV		Change in nTAV	
	r	p value	*r*	p value
Baseline				
Total cholesterol	0.04	0.89	0.01	0.31
HDL-cholesterol	0.04	0.43	0.06	0.19
LDL-cholesterol	0.05	0.87	0.02	0.28
LDL/HDL ratio	0.01	0.42	0.01	0.08
Triglyceride	0.02	0.79	0.05	0.46
ApoA1	0.05	0.44	0.07	0.31
ApoB100	0.06	0.42	0.02	0.77
ApoB100/ApoA1 ratio	0.02	0.81	-0.02	0.74
Leukocyte count	0.17	0.01	0.003	0.97
hsCRP	-0.04	0.61	-0.07	0.31
Homocysteine	0.10	0.14	0.09	0.19
Fibrinogen	0.07	0.34	0.07	0.28
Lipoprotein	-0.04	0.59	0.12	0.08
Follow-up				
Total cholesterol	0.05	0.50	0.05	0.44
HDL-cholesterol	0.02	0.81	-0.03	0.64
LDL-cholesterol	0.01	0.90	0.04	0.56

LDL/HDL ratio	-0.01	0.85	0.03	0.67
Triglyceride	0.07	0.34	0.11	0.12
ApoA1	0.13	0.13	0.034	0.69
ApoB100	0.06	0.46	0.11	0.19
ApoB100/ApoA1 ratio	0.02	0.82	0.11	0.20
Leukocyte count	-0.03	0.69	0.03	0.65
hsCRP	-0.05	0.44	0.05	0.51
Homocysteine	0.03	0.77	0.09	0.31
Fibrinogen	0.01	0.87	0.11	0.17
Lipoprotein (a)	-0.07	0.37	0.17	0.04
Change				
Total cholesterol	-0.01	0.93	0.03	0.66
HDL-cholesterol	-0.01	0.85	-0.08	0.23
LDL-cholesterol	-0.03	0.70	0.003	0.97
LDL/HDL ratio	-0.02	0.75	0.001	0.98
Triglyceride	0.04	0.54	0.04	0.59
ApoA1	0.03	0.70	-0.08	0.36
ApoB100	-0.02	0.86	0.01	0.92
ApoB100/ApoA1 ratio	0.01	0.92	0.04	0.61
Leukocyte count	-0.21	0.003	0.02	0.82
hsCRP	0.02	0.80	0.08	0.26
Homocysteine	-0.14	0.10	-0.08	0.32

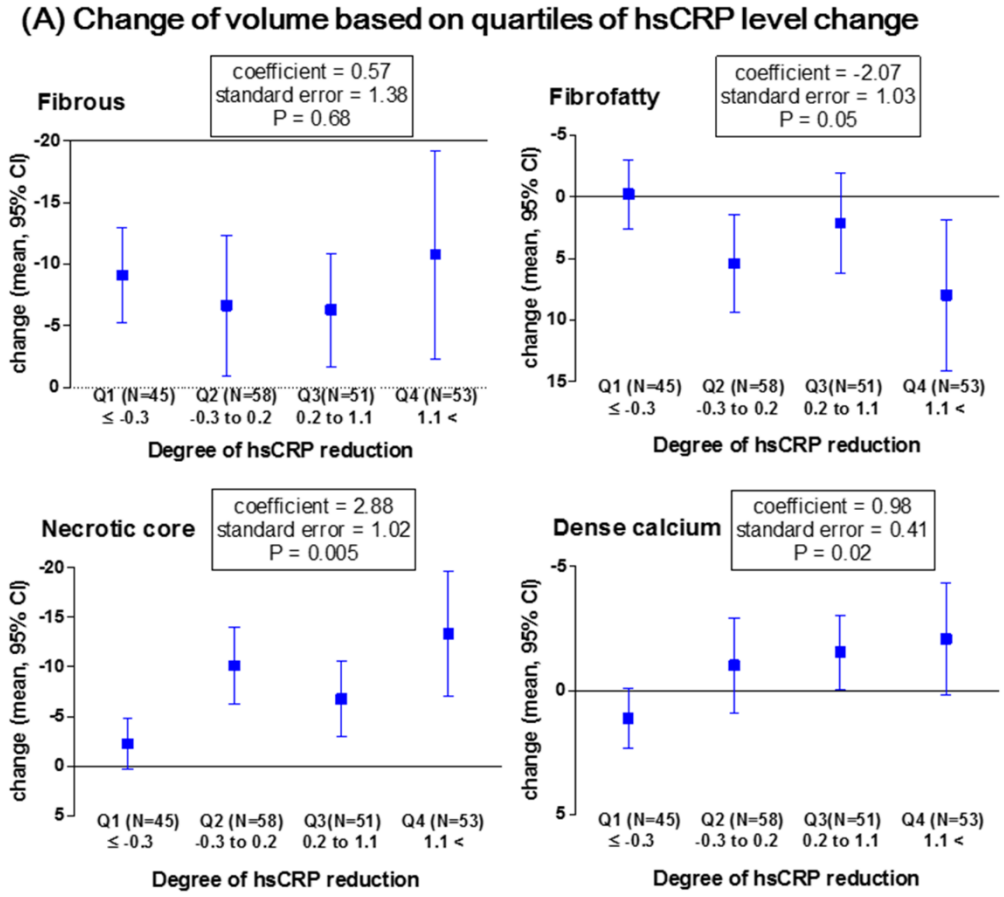
Fibrinogen	-0.03	0.72	0.05	0.56
Lipoprotein (a)	-0.05	0.52	0.16	0.05

Correlation is determined by using Pearson's correlation analysis.

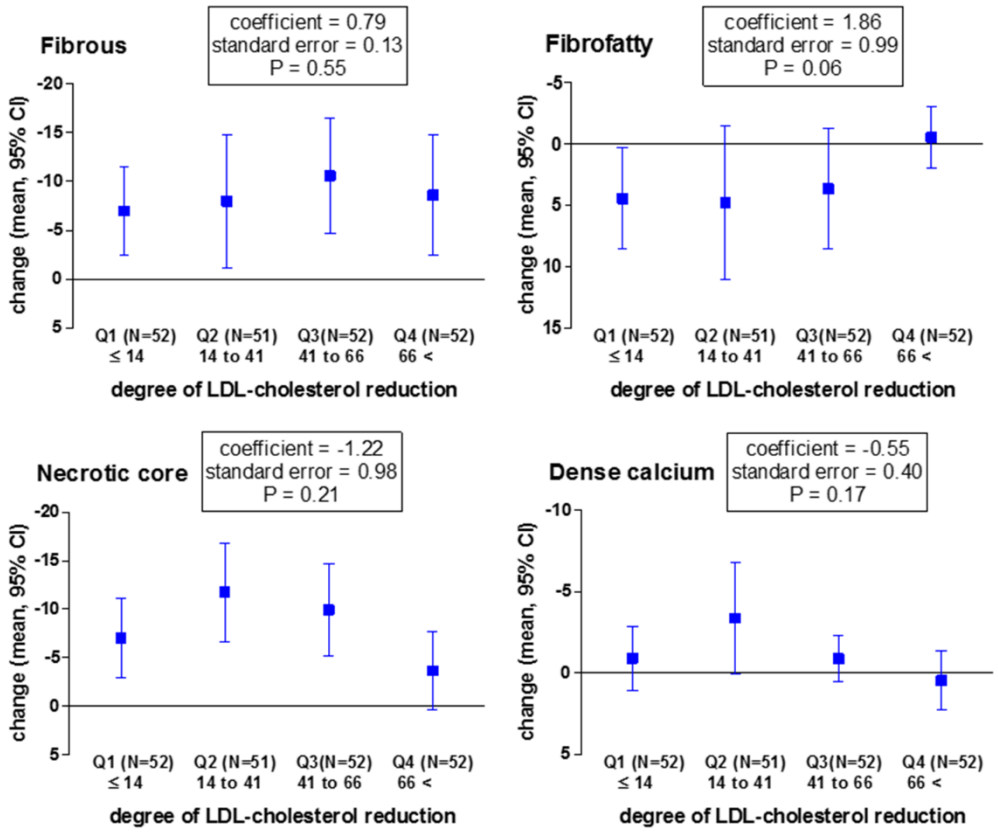
Abbreviations: Apo, apolipoprotein; HDL, high-density lipoprotein; hsCRP, high-sensitivity C-reactive protein; LDL, low-density lipoprotein; nTAV, normalized total atheroma volume; PAV, percent atheroma volume

Supplemental Figure 1. Serial changes in absolute volume in the target segment (plaque composition) across the quartiles of hsCRP level change (A) and of the serum LDL-cholesterol level change (B) during 12 months.

Q1 refers to the lowest quartile (smallest degree of hsCRP reduction) and Q4 refers to the highest quartile (largest degree of hsCRP reduction). Reported values are coefficient, standard error by linear regression; hsCRP, high-sensitivity C-reactive protein; LDL, low-density lipoprotein.



(B) Change of volume based on quartiles of LDL-cholesterol change



Supplemental Figure 2. Correlation between the homocysteine level at baseline and normalized total atheroma volume.