ORIGINAL RESEARCH

Clinical Predictors for Lack of Favorable Vascular Response to Statin Therapy in Patients With Coronary Artery Disease: A Serial Optical Coherence Tomography Study

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***Background*—**Previous studies have demonstrated that statin therapy improves cardiac outcomes, probably by stabilizing thin-cap fibroatheroma in patients with coronary artery disease. However, major adverse cardiac events still occur in some patients, despite statin therapy. The aim of this study is to identify clinical predictors for the lack of a favorable vascular response to statin therapy in patients with coronary artery disease.

***Methods and Results*—**A total of 140 nonculprit plaques from 84 patients with coronary artery disease who were treated with a statin and had serial optical coherence tomography imaging (median interval, 6.3 months) were included. Thin-cap area (fibrous cap thickness, <200 μm) was measured using a novel 3-dimensional computer-aided algorithm. Overall, the thin-cap area significantly decreased from baseline (median, 2.852 mm^2; 25^{th}–75^{th} percentile, 1.023–6.157 mm^2) to follow-up (median, 1.210 mm^2; 25^{th}–75^{th} percentile, 0.250–3.192 mm^2; $P<0.001$), and low-density lipoprotein cholesterol significantly decreased from baseline (mean±SD, 92.9±30.1 mg/dL) to follow-up (mean±SD, 76.3±23.3 mg/dL; $P<0.001$). The general linear model with multiple predictor variables revealed that the thin-cap area was significantly higher in patients with chronic kidney disease than in those without it (regression coefficient b, 1.691 mm^2; 95% confidence interval, 0.350–3.033 mm^2; $P=0.013$) and lower in patients with acute coronary syndrome (regression coefficient b, −1.535 mm^2; 95% confidence interval, −2.561 to −0.509 mm^2; $P=0.003$).

***Conclusions*—**Chronic kidney disease is an independent predictor for the lack of a favorable vascular response to statin therapy, whereas acute coronary syndrome is an independent predictor for favorable vascular response to statin therapy. These findings should be further warranted in future prospective studies.

***Clinical Trial Registration*—**URL: http://www.clinicaltrials.gov. Unique identifier: NCT01110538. **(*J Am Heart Assoc*. 2017;6: e006241. DOI: 10.1161/JAHA.117.006241.)**

Key Words: atherosclerosis • coronary artery disease • fibrous cap • optical coherence tomography • statin therapy

Fibrous-cap thickness (FCT) is one of the major determinants of coronary plaque vulnerability.[1–3] Thinning of the cap is a result of the degradation of collagen tissue by excessive release of matrix metalloproteinases from the accumulated macrophages.[4,5] The balance between degradation and synthesis of the fibrous cap might be influenced by several factors, including focal physical and biological stress,[6,7] patient clinical characteristics,[8,9] and therapeutic interventions. Recently, several studies using optical coherence tomography (OCT) demonstrated that therapy with statins (3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors) had the potential to increase the cap thickness[10,11]

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Accompanying Data S1, Tables S1 through S4 and Figures S1 through S4 are available at http://jaha.ahajournals.org/content/6/11/e006241/DC1/embed/inline-supplementary-material-1.pdf

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Clinical Perspective

What Is New?

- This is the first study to investigate the clinical predictors for the changes in fibrous cap area of nonculprit plaques in patients undergoing statin therapy.
- Chronic kidney disease is an independent predictor for the lack of a favorable vascular response to statin therapy, whereas acute coronary syndrome is an independent predictor for favorable vascular response to statin therapy.

What Are the Clinical Implications?

- Patients with chronic kidney disease with ischemic heart disease may need intensive therapy in addition to contemporary medical therapy, including statin, to achieve stabilization of nonculprit plaques.

in patients with coronary artery disease. However, major cardiac events still occur in patients receiving statin therapy,[12,13] and clinical predictors for these nonresponders have not yet been identified.

Therefore, we aimed to identify clinical factors contributing to less favorable vascular response to statins for stabilization of the fibrous cap in patients with coronary artery disease. To accomplish this purpose, we applied a novel computer-aided 3-dimensional method[14,15] to comprehensively measure the surface area of the thin fibrous cap[16] instead of a simple conventional measurement of the thinnest portion[17] of the fibrous cap.

Methods

Study Population

All study subjects had been enrolled in the image database of the Massachusetts General Hospital (Boston, MA) OCT Registry, which is a multicenter, prospective, all-comer registry including cases with coronary OCT imaging. All patients provided written informed consent, and this study was conducted in compliance with the Declaration of Helsinki. A total of 402 patients who underwent serial OCT procedures between August 2010 and February 2014 were enrolled. The registry contains data from several participating sites that supplemented repeated coronary angiography with OCT for routine follow-up catheterization at 6 to 9 months. Among these data, we identified serial images of 153 nonculprit plaques in 91 patients. After excluding patients with early (<6 months) or late (>14 months) follow-up (n=7), 140 nonculprit plaques in 84 patients were included in the final analysis. Nonculprit plaque was defined as plaque with >50% area stenosis compared with the reference segment, lipid arc ≥1 quadrant assessed by OCT, and not associated with the index event or presenting symptom, as evaluated by the treating physician. In all 84 patients, repeated OCT imaging was performed during the scheduled follow-up catheterization without any clinical event related to either the culprit or the nonculprit plaque. The study cohort included in this study was different from the one in our previous report.[18]

OCT Image Acquisition and Conventional Analysis

OCT images were acquired using frequency domain or time domain OCT after intracoronary administration of 100 to 200 μg of nitroglycerin. All images were analyzed using offline proprietary software at the Massachusetts General Hospital OCT Laboratory. Several landmarks, including stent edges, calcifications, and side branches, were used to identify the target plaque. Qualitative and quantitative analyses were performed at 1-mm intervals. All OCT plaque morphological features were analyzed using previously validated criteria[19,20] (Data S1). Macrophage infiltration was defined as signal-rich, distinct, or confluent punctuated regions that exceeded the intensity of background speckle noise and was semiquantitatively assessed using a previously described grading system.[11,21]

Three-Dimensional Thin-Cap Area Measurement

To volumetrically assess the 3-dimensional fibrous cap, we applied a computer algorithm that had been previously validated (Data S1 and Figure S1).[14] In this study, the thin-cap area was defined as the fibrous cap surface area with cap thickness <200 μm, in accordance with previous literature.[22] The secondary cutoff was defined as 80 μm. Intraobserver and interobserver reproducibility values of the area measurement were good (intraclass correlation coefficients, 0.942 and 0.927, respectively). All plaques were classified into 3 groups according to the tertile of absolute change in thin-cap area. The lower tertile, midtertile, and upper tertile were defined as the reduction group, mild reduction group, and no reduction group, respectively.

Definitions

Acute coronary syndrome (ACS) consisted of ST-segment elevation myocardial infarction, non–ST-segment elevation myocardial infarction, and unstable angina pectoris. Chronic kidney disease (CKD) was defined as estimated glomerular filtration rate (eGFR) of <60 mL/min per 1.73 m^2. The eGFR was calculated using the Modification of Diet in Renal Disease equation: eGFR (mL/min per 1.73 m^2)=175×(serum creatinine [mg/dL])$^{-1.154}$×(age)$^{-0.203}$×0.742 (if female)×1.210 (if black). Blood samples were obtained in the outpatient clinic or emergency department before OCT image acquisition at

baseline and follow-up. The analyses of cholesterol profiles and high-sensitivity hsCRP (C-reactive protein) values were available in 96.4% and 83.3% of patients, respectively, at follow-up. The intensity of statin treatment was classified as high, moderate, or low intensity, according to published guidelines.[23] Statin-naïve patients were defined as those receiving no statin therapy for >3 months before baseline OCT image acquisition.

Statistical Analysis

Categorical outcome data were summarized as counts (percentages), and between-group comparisons were performed using the Fisher exact test or χ^2 test, as appropriate, depending on the expected frequency distribution under the null hypothesis. Continuous outcome data were summarized by mean±SD or median (25th–75th percentile), as appropriate, depending on the normality of distribution tested by the Kolgormonov-Smirnov test. Between-group comparisons were performed using independent-sample *t* tests or Mann-Whitney *U* tests, and tests for the within-group longitudinal changes were performed using paired-sample *t* tests or Wilcoxon signed rank tests, accordingly. A general linear model with multiple predictor variables was used to determine independent clinical predictors of absolute change in thin-cap area. The generalized estimating equations approach was applied to account for within-subject correlation among the multiple plaques per single patient. Statistical significance was defined as $P<0.05$. All statistical analyses were performed using SPSS version 17.0.

Results

Clinical Characteristics

Baseline clinical characteristics and medications at discharge are shown in Table 1. The median (25^{th}–75^{th} percentile) follow-up duration was 6.3 (6.1–12.1) months. At baseline, 51 patients (60.7%) were seen with ACS, including 9 (10.7%) with ST-segment elevation myocardial infarction, whereas 33 patients (39.3%) were seen with stable angina. A total of 33 patients (39.3%) were statin naïve before baseline OCT image acquisition. All patients were prescribed a statin at discharge with high (n=2), moderate (n=71), or low (n=11) intensity treatment. Statin therapy was continued until the follow-up OCT image acquisition. During the follow-up period, no patients had a clinical event.

Table 1. Baseline Clinical Characteristics (n=84)

Characteristics	Value
Follow-up duration, median (25th–75th percentile), mo	6.3 (6.1–12.1)
Age, mean±SD, y	59.0±9.9
BMI, mean±SD, kg/m^2	24.7±2.4
Male sex, n (%)	65 (77.4)
Clinical presentation, n (%)	
STEMI	9 (10.7)
NSTEMI-ACS	42 (50.0)
Stable angina	33 (39.3)
Previous MI, n (%)	25 (29.8)
Previous PCI, n (%)	50 (59.5)
Hypertension, n (%)	53 (63.1)
Dyslipidemia, n (%)	68 (81.0)
Diabetes mellitus, n (%)	29 (34.5)
Chronic kidney disease, n (%)	7 (8.3)
Current smoker, n (%)	26 (31.0)
Family history of IHD, n (%)	4 (4.8)
LVEF, mean±SD, %	63.5±8.4
Discharge medication, n (%)	
DAPT	83 (98.8)
Statin	84 (100)
High intensity	2 (2.4)
Moderate intensity	71 (84.5)
Low intensity	11 (13.1)
β Blocker	35 (41.7)
ACEI/ARB	29 (34.5)
Statin naive	33 (39.3)

ACEI/ARB indicates angiotensin-converting enzyme inhibitor/angiotensin II receptor blocker; BMI, body mass index; DAPT, dual antiplatelet therapy; IHD, ischemic heart disease; LVEF, left ventricular ejection fraction; MI, myocardial infarction; NSTEMI-ACS, non–ST-segment elevation myocardial infarction–acute coronary syndrome; PCI, percutaneous coronary intervention; and STEMI, ST-segment elevation myocardial infarction.

Serial Change in Cholesterol Profile and Inflammatory Status

Results of laboratory testing at baseline and follow-up are shown in Table 2. Low-density lipoprotein cholesterol significantly decreased from baseline (92.9±30.1 mg/dL) to follow-up (76.3±23.3 mg/dL; $P<0.001$). Values of hsCRP also significantly decreased from baseline to follow-up (median, −1.0 mg/L; 25^{th}–75^{th} percentile, −3.0 to 0.0 mg/L; $P=0.006$).

Serial Change in Plaque Morphological Features by OCT

Thin-cap area became significantly smaller at follow-up (median, 2.852 [25th–75th percentile, 1.023–6.157] mm^2 at baseline versus 1.210 [25^{th}–75^{th} percentile, 0.250–3.192]

Table 2. Laboratory Findings at Baseline and Follow-Up

Findings	Baseline	Follow-Up	Change	*P* Value
Total cholesterol, mg/dL	170.6±39.7	151.1±34.3	−19.5±46.2	<0.001
LDL-C, mg/dL	92.9±30.1	76.3±23.3	−16.6±33.6	<0.001
HDL-C, mg/dL	45.0±12.2	45.9±13.5	0.92±13.6	0.545
LDL/HDL ratio	2.18±0.83	1.76±0.67	−0.42±0.83	<0.001
Triglyceride, mg/dL*	148.8 (102.7–195.7)	127.5 (88.6–168.0)	−15.1 (−66.9 to 13.8)	0.007
hsCRP, mg/L*	1.0 (1.0–3.0)	1.0 (0.0–2.0)	−1.0 (−3.0 to 0.0)	0.006
eGFR, mL/min per 1.73 m^2	83.4±19.2	80.8±20.1	−2.61±16.9	0.179
HbA1c, %	6.38±1.34	6.18±0.96	−0.03±0.57	0.154

Data are presented as mean±SD unless otherwise indicated (comparisons were made by paired-sample *t* test). eGFR indicates estimated glomerular filtration rate; HbA1c, glycosylated hemoglobin; HDL, high-density lipoprotein; HDL-C, HDL cholesterol; hsCRP, high-sensitivity C-reactive protein; LDL, low-density lipoprotein; LDL-C, LDL cholesterol.
*Median (25th–75th percentile) values are presented (comparisons were made by Wilcoxon signed-rank test).

mm^2 at follow-up; $P<0.001$). Other quantitative parameters of plaque morphological features at baseline, including thinnest FCT, lipid volume index, and macrophage grading, significantly improved during follow-up (Table 3). The absolute change in thin-cap area across individual cases is shown in Figure 1. Overall, plaques with larger thin-cap area at baseline had greater reduction at follow-up.

Thin-Cap Area According to the Baseline Statin Intake

The reduction of thin-cap area was significantly greater in statin-naïve cases (median, −1.906 [25th–75th percentile, −3.833 to −0.147] mm^2) compared with those already taking a statin at baseline (median, −0.515 [25th–75th percentile, −2.898 to 0.525] mm^2; $P=0.036$) (Figure 2).

Independent Predictors for the Change in Thin-Cap Area

Unadjusted effect estimates (via simple linear models) on the absolute change of thin-cap area revealed that the thin-cap area at baseline, follow-up duration, age, ACS, and low-intensity statin were the factors for the absolute change in thin-cap area (Table S1). Results of general linear modeling, with multiple covariate analyses determining clinical factors contributing to absolute change in thin-cap area, are shown in Figure 3. The general linear modeling revealed that CKD (effect estimate, 1.691; 95% confidence interval, 0.350–3.033; $P=0.013$), ACS (effect estimate, −1.535; 95% confidence interval, −2.561 to −0.509; $P=0.003$), and the thin-cap area at baseline (effect estimate, −0.368; 95% confidence interval, −0.478 to −0.259; $P=0.003$) were the independent predictors for the absolute change in thin-cap area. Similar results were obtained in the analysis using the cutoff of <80 μm for thin-cap area (Table S2). General linear modeling analysis of absolute change in thinnest 2-dimensional FCT showed that CKD and ACS are marginal predictors (Table S3).

Thin-Cap Area According to the Baseline Clinical Characteristics

A significant reduction of thin-cap area was observed in cases with ACS (median, −1.950 [25^{th}–75^{th} percentile, −4.605 to −0.171] mm^2; $P<0.001$) and non-CKD (median, −0.975 [25^{th}–75^{th} percentile, −3.447 to 0.057] mm^2; $P<0.001$), whereas no significant changes were observed in cases with stable angina (median, −0.297 [25^{th}–75^{th} percentile, −1.617 to 0.723] mm^2; $P=0.271$) or CKD (median, −0.006 [25^{th}–75^{th} percentile, −2.064 to 0.703]; $P=0.397$). There were no significant differences in follow-up duration between cases with and without CKD (median, 6.0 [25^{th}–75^{th} percentile, 6.0–6.7] months versus 6.3 [25^{th}–75^{th} percentile, 6.0–12.1] months; $P=0.20$) and between cases with ACS and with stable angina (median, 6.5 [25^{th}–75^{th} percentile, 6.1–12.2] months versus 6.1 [25^{th}–75^{th} percentile, 6.0–6.5] months; $P=0.06$). Representative 3-dimensional images of thin-cap areas in patients with CKD and ACS are shown in Figure 4.

Correlation Between Absolute Change in Thin-Cap Area and Changes in Other Parameters

Correlations between absolute change in thin-cap area, changes in laboratory findings, and changes in macrophage grade were assessed (Figure S2). Significant correlations were observed between the change in hsCRP values and the change in thin-cap area (Pearson $r=0.237$; $P=0.025$). No significant correlations were observed between the changes in low-density lipoprotein cholesterol values and the changes in thin-cap area across the whole cohort (Pearson $r=-0.060$; $P=0.493$), among patients receiving statin at baseline

Table 3. OCT Findings of Target Plaques at Baseline and Follow-Up (n=140)

Findings	Baseline	Follow-Up	Change	*P* Value
3D quantitative assessment				
Thin-cap area, mm^2*	2.852 (1.023–6.157)	1.210 (0.250–3.192)	−0.94 (−3.25 to 0.13)	<0.001
2D quantitative assessment				
Thinnest FCT, μm	117.2±63.1	145.9±66.6	28.7±67.3	<0.001
TCFA (<65 μm), n (%)	35 (25.0)	23 (16.4)	…	0.077
Mean lipid arc, °	164.0±58.3	148.5±56.7	−15.5±49.7	<0.001
Maximum lipid arc, °	232.1±70.0	215.1±76.6	−17.0±65.1	0.002
Lipid length, mm	7.91±3.63	7.27±3.99	−0.64±2.43	0.002
Lipid volume index	1346.9±835.0	1178.6±903.9	−179.2±644.2	0.002
Minimal lumen area, mm^2	3.08±1.29	3.05±1.49	−0.03±1.10	0.765
Area stenosis, %	59.9±9.1	56.3±14.7	−3.58±13.8	0.003
Macrophage grade*	4.0 (1.0–9.0)	3.0 (0.0–7.0)	−1.0 (−4.0 to 2.0)	0.012
Qualitative assessment, n (%)				
Cholesterol crystal	24 (17.1)	16 (11.4)	…	0.17
Microchannel	42 (30.0)	42 (30.0)	…	1.00
Calcium	74 (52.9)	73 (52.1)	…	0.91
Spotty calcium	63 (45.0)	65 (46.4)	…	0.81
Thrombus	4 (2.9)	4 (2.9)	…	1.00

Data are presented as mean±SD unless otherwise indicated (comparisons were made by paired-sample *t* test). 2D indicates 2 dimensional; 3D, 3 dimensional; FCT, fibrous-cap thickness; OCT, optical coherence tomography; and TCFA, thin-cap fibroatheroma.
*Median (25th–75th percentile) values are presented (comparisons were made by Wilcoxon signed-rank test).

(Pearson r=−0.256; P=0.065) or among patients who were statin naïve (Pearson r=−0.041; P=0.800). Significant correlations were also observed between the changes in macrophage grade and the change in thin-cap area (Pearson r=0.385; P<0.001). No significant correlations were observed between the changes in thin-cap area and changes in other plaque morphological features, including lipid volume index and percentage area stenosis (Figure S3).

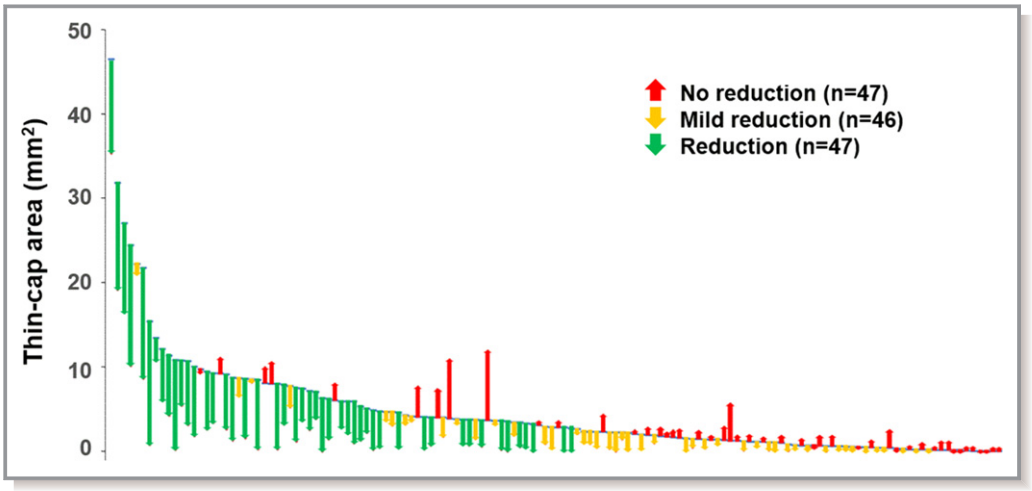

Figure 1. Absolute change in thin-cap area during follow-up in individual plaques. Absolute changes in thin-cap area in individual plaques are illustrated. The classification of 3 groups is based on the tertile of absolute change in thin-cap area. Green arrows (highest tertile) represent significant reduction of thin-cap area; yellow arrows, marginal reduction; and red arrows (lowest tertile), no reduction.

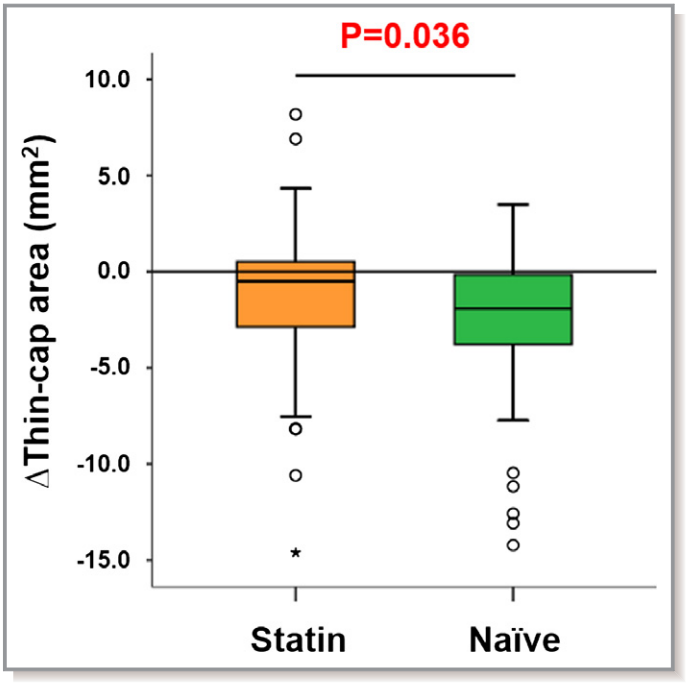

Figure 2. Absolute change in thin-cap area according to baseline statin intake. The reduction of thin-cap area was significantly greater in statin-naïve patients than in those who were already taking a statin at baseline.

Changes in Inflammation Status for Baseline Clinical Characteristics

Changes in inflammation status during follow-up were assessed for baseline clinical characteristics. Significant changes in hsCRP values and macrophage grades were observed in cases without CKD (median, −0.01 [25th–75th percentile, −0.03 to 0.00] mg/dL [*P*=0.001] and −1.0 [25th–75th percentile, −4.5 to 2.0] [*P*=0.012], respectively). No significant differences were observed in cases with CKD (median, −0.01 [25th–75th percentile, −0.01 to 0.01] mg/dL [*P*=0.317] and −1.0 [25th–75th percentile, −2.0 to 2.0] [*P*=0.555], respectively) (Figure S4A and S4B). In cases with ACS, hsCRP values and macrophage grades significantly decreased at follow-up (median, −0.01 [25th–75th percentile, −0.03 to 0.00] mg/dL [*P*<0.001] and −2.0 [25th–75th percentile, −5.5 to 2.0] [*P*=0.002], respectively), whereas no significant differences were observed in cases with stable angina (median, 0.00 [25th–75th percentile, −0.01 to 0.01] mg/dL [*P*=0.284] and 0.5 [25th–75th percentile, −3.0 to 3.0] [*P*=0.865], respectively) (Figure S4C and S4D).

Baseline Plaque Morphological Features According to the Change in Thin-Cap Area

Baseline plaque morphological features were compared between tertiles of absolute change in thin-cap area (Table S4). The reduction group had significantly larger thin-cap area and larger lipid index than the mild reduction (*P*<0.001 and *P*=0.006, respectively) and no reduction (*P*<0.001 and *P*<0.001, respectively) groups.

Discussion

To the best of our knowledge, this is the first study to investigate the clinical predictors for the changes in fibrous cap area in patients undergoing statin therapy using OCT. The main findings of this study include the following: (1) Overall, thin-cap area of nonculprit coronary plaques significantly decreased during a median 6.3 months of follow-up. (2) CKD was identified as an independent predictor for unfavorable thin-cap area reduction. (3) ACS was identified as an independent predictor for favorable thin-cap area reduction. (4) The improvement of inflammation status was significantly correlated with the reduction of thin-cap area.

Change in FCT

Plaque rupture is a major cause of ACS and sudden coronary death,[1,24] and a thin fibrous cap appears to be a marked precursor to plaque rupture.[2,3] Yet, the continuously changing nature of fibrous cap morphological features weakens its predictive and prognostic values.[25] Recently, several OCT studies demonstrated the impact of statin therapy on the improvement of FCT[10,11] as one of the potential underlying mechanisms for the improved clinical outcome in patients undergoing statin therapy.[13,26,27] Despite such improvements, major cardiac events still occur. Therefore, there is a need to identify clinical factors that predict unfavorable vascular responses to statin therapy.

To generate more practical cutoff values for FCT to detect rupture-prone plaque by OCT, Yonetsu et al assessed FCT in multiple points within the entire plaque.[22] They reported that the most representative FCT in ruptured plaques was 188 μm, which is thicker than the conventional pathology-based 65 μm, and that the thinnest portion was not matched with the ruptured site in most cases (78.9%). These findings suggest that cap thinning might occur diffusely in plaques and that a more comprehensive approach is needed to identify the true rupture-prone plaques and factors affecting changes in FCT. Therefore, in this study, we applied a recently introduced, computer-aided, 3-dimensional method[14,15] for the comprehensive analysis of FCT.[16]

Renal Function and FCT

In this study, baseline presentation with CKD independently predicted unfavorable thin-cap area reduction. This finding

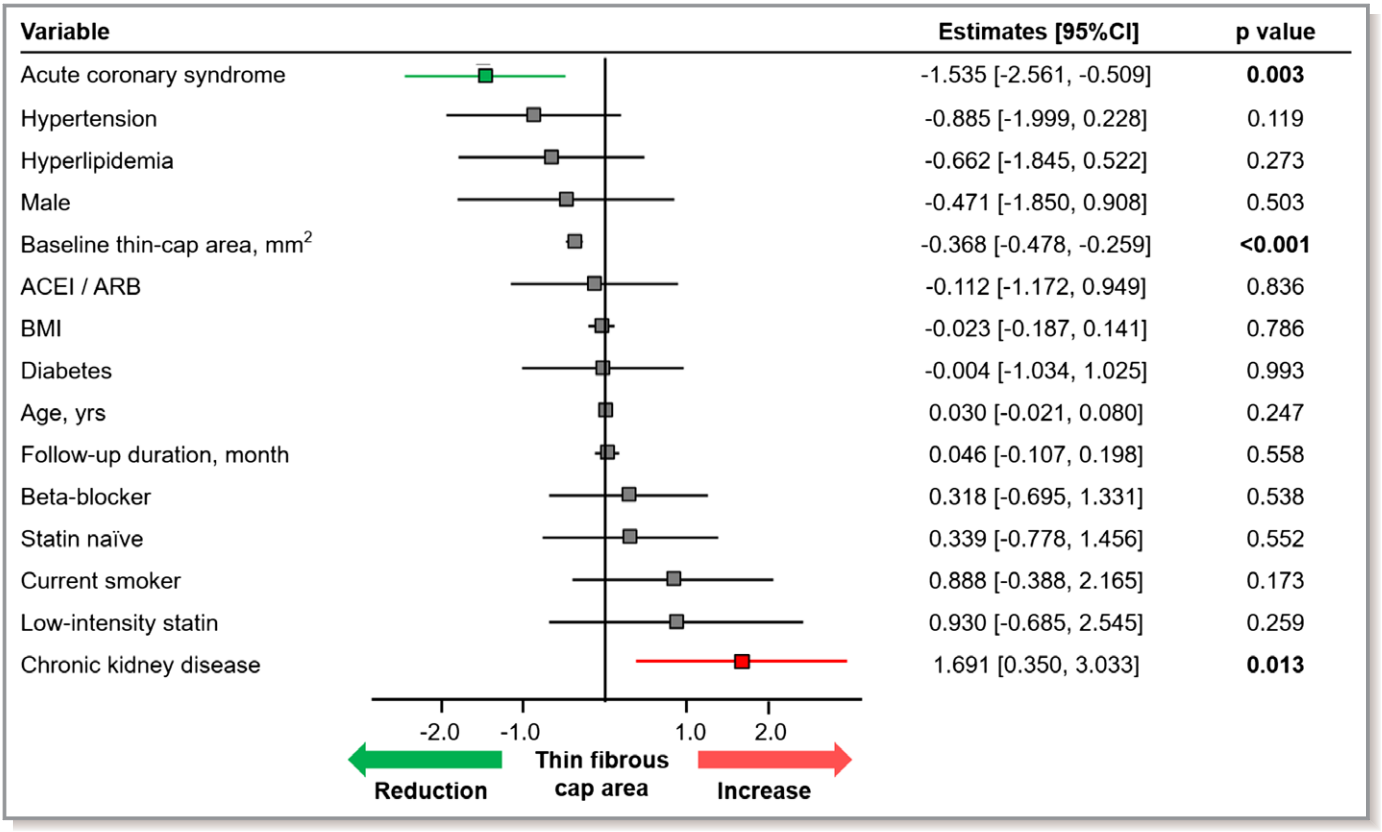

Figure 3. Clinical predictors for the response of thin-cap area to statin therapy. General linear modeling analysis for the absolute change in thin-cap area demonstrates that chronic kidney disease is a predictor for unfavorable response and acute coronary syndrome is a predictor for favorable response. ACEI/ARB indicates angiotensin-converting enzyme inhibitor/angiotensin II receptor blocker; BMI, body mass index; and CI, confidence interval.

indicates that there was a failure to thicken and stabilize fibrous tissue within the fibrous cap in patients with CKD. CKD is recognized as an independent predictor for cardiovascular events[28,29] and poor clinical outcomes.[30] A poor prognosis in patients with CKD is determined by the presence of more vulnerable features in coronary plaques. We previously demonstrated that patients with CKD had larger lipid profiles and a higher prevalence of plaque disruption compared with patients without CKD, although we found no significant difference in FCT at the thinnest portion across groups.[31] Using integrated backscatter intravascular ultrasonography, Miyagi et al demonstrated that coronary plaques in patients with CKD had greater lipid and less fibrous tissue volume in 89 patients with stable angina.[32] Hayano et al further demonstrated that lower eGFR levels were associated with greater lipid and lower fibrous content.[33] In addition, Baber et al reported in a substudy of the PROSPECT (Providing Regional Observations to Study Predictors of Events in the Coronary Tree) study that patients with CKD had plaques with a greater necrotic core, less fibrous volume, and worse clinical outcomes.[34] Although the exact causal relationship between vulnerability and renal dysfunction has not been thoroughly investigated, abundant factors, including the abnormalities of lipid metabolism,[35] activated gene expression of matrix metalloproteinases,[36] and impairment of macrophage emigration,[37] have been considered to interactively promote this vulnerability. In this study, we demonstrated that the inflammation status was not significantly stabilized by statin therapy in the CKD cohort during follow-up, thus suggesting impairment in the synthesis/degradation of fibrous tissue within the cap. It follows that the vulnerability of nonculprit plaques in patients with CKD would not be stabilized with contemporary medical therapy, including statins.

Changes in FCT and ACS

In the current study, ACS presentation at baseline was an independent predictor of greater reduction in thin-cap area. This result suggests that worsened clinical presentation and vulnerable plaque features at baseline may result in more favorable responses among nonculprit plaques to statin. Similar results were reported in several previous studies using intravascular ultrasonography and OCT.[10,38,39] Takarada et al demonstrated that the efficacy of statin therapy on improving FCT, assessed by serial OCT, was significantly greater in

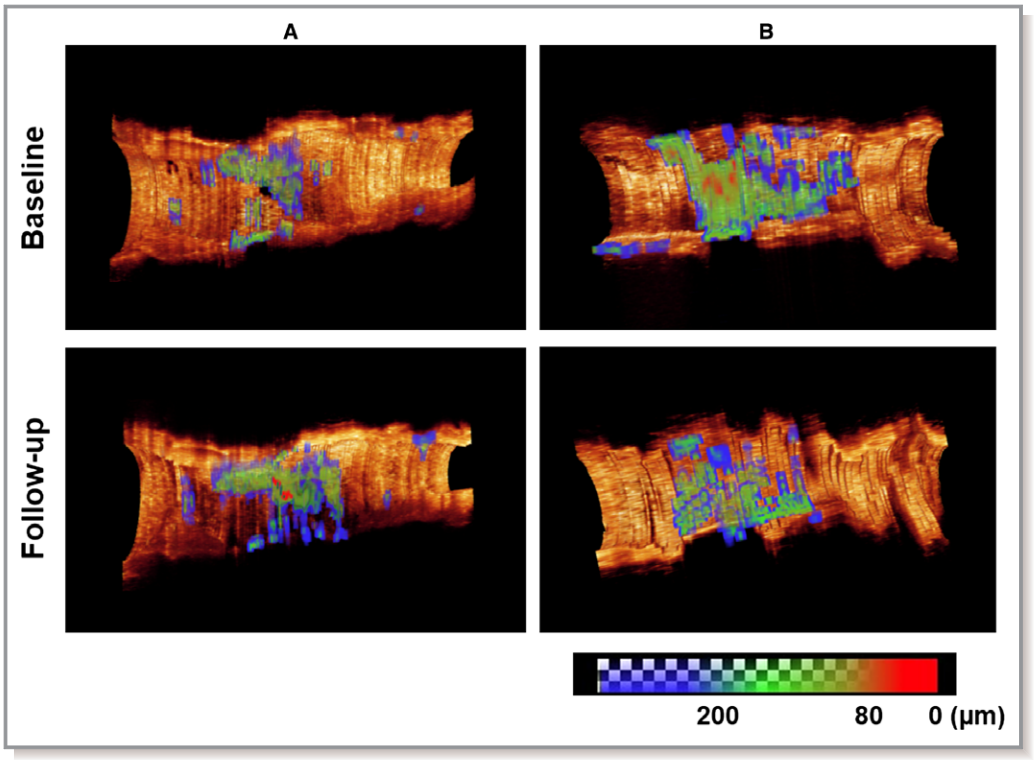

Figure 4. Representative 3-dimensional images of the change in thin-cap area during follow-up. The segmented fibrous cap was further rendered in a 3-dimensional model using a continuous color map on the basis of thickness. A, Chronic kidney disease: the thin-cap area (green to red) became bigger at follow-up. B, Acute coronary syndrome: the thin-cap area became smaller at follow-up.

plaques with thinner caps than in those with thicker caps.[10] In the SATURN (Study of Coronary Atheroma by Intravascular Ultrasound: Effect of Rosuvastatin Versus Atorvastatin) trial, which aimed to compare the efficacy of 2 different statins on the regression of plaque volume assessed by intravascular ultrasonography,[38] the greater change was observed in larger plaques than in smaller plaques. In addition, most studies that tested the efficacy of statin therapy on plaque stabilization in patients with ACS demonstrated improvement in plaque phenotype.[10,11,40,41] Recently, Tsujita et al conducted a randomized trial to investigate the efficacy of additional ezetimibe intake over atorvastatin alone on changes in plaque volume over 9 to 12 months of follow-up.[39] They reported that plaque regression in the group treated with additional ezetimibe was greater in the ACS cohort than in the stable angina cohort. In the above mentioned prospective randomized study using OCT,[11] the authors demonstrated a significant correlation between the changes in FCT and the changes in inflammation status, assessed by hsCRP and semiquantified macrophage values in patients with ACS treated with statins, similar to our results. Thus, in patients with ACS, plaque stabilization could be, at least in part, attributed to the stabilization of inflammatory status by interventions such as statins.

Limitations

Several limitations in this study require acknowledgment. First, the Massachusetts General Hospital OCT Registry is a multicenter, prospective registry for all comers without strict inclusion criteria or guidelines for OCT image acquisition. Follow-up OCT was not mandated in the registry. In this study, we retrospectively selected the cases that had a follow-up OCT study. Therefore, there was considerable variability in follow-up time. The differences in follow-up time might have affected the results. Second, different types and doses of statin were used, and the duration of statin therapy before baseline OCT was not recorded. Third, because our study data were obtained from Asian countries and, thus, all patients in the registry were Asian, most patients were treated in accordance with their respective domestic guidelines. Specifically, high-intensity dose statin is generally not recommended for the Asian population and, therefore, most patients were treated with moderate-intensity statin. Fourth, the number of cases with CKD was small, and the diagnosis of CKD was only based on the value of eGFR at 1 time point. In addition, there were no patients with CKD stage 4/5 (eGFR, <30 mL/min per 1.73 m^2) in this cohort. Fifth, we are still uncertain if our results can be adopted for a cohort with higher baseline

low-density lipoprotein cholesterol values and with a higher-intensity statin regimen. Finally, the direct impact of our results on clinical outcomes remains unknown. Larger studies with longer follow-up are warranted.

Conclusions

CKD is identified as an independent predictor for lack of favorable vascular response to statin therapy, whereas ACS is identified as a predictor for favorable vascular response to statin therapy. These findings should be confirmed by large-scale prospective studies.

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Disclosures

None.

References

1. Virmani R, Kolodgie FD, Burke AP, Farb A, Schwartz SM. Lessons from sudden coronary death: a comprehensive morphological classification scheme for atherosclerotic lesions. *Arterioscler Thromb Vasc Biol*. 2000;20:1262–1275.
2. Tian J, Ren X, Vergallo R, Xing L, Yu H, Jia H, Soeda T, McNulty I, Hu S, Lee H, Yu B, Jang IK. Distinct morphological features of ruptured culprit plaque for acute coronary events compared to those with silent rupture and thin-cap fibroatheroma: a combined optical coherence tomography and intravascular ultrasound study. *J Am Coll Cardiol*. 2014;63:2209–2216.
3. Burke AP, Farb A, Malcom GT, Liang YH, Smialek J, Virmani R. Coronary risk factors and plaque morphology in men with coronary disease who died suddenly. *N Engl J Med*. 1997;336:1276–1282.
4. Libby P, Ridker PM, Maseri A. Inflammation and atherosclerosis. *Circulation*. 2002;105:1135–1143.
5. Moreno PR, Purushothaman KR, Fuster V, Echeverri D, Truszczynska H, Sharma SK, Badimon JJ, O'Connor WN. Plaque neovascularization is increased in ruptured atherosclerotic lesions of human aorta: implications for plaque vulnerability. *Circulation*. 2004;110:2032–2038.
6. Chatzizisis YS, Baker AB, Sukhova GK, Koskinas KC, Papafaklis MI, Beigel R, Jonas M, Coskun AU, Stone BV, Maynard C, Shi GP, Libby P, Feldman CL, Edelman ER, Stone PH. Augmented expression and activity of extracellular matrix-degrading enzymes in regions of low endothelial shear stress colocalize with coronary atheromata with thin fibrous caps in pigs. *Circulation*. 2011;123:621–630.
7. Chatzizisis YS, Jonas M, Coskun AU, Beigel R, Stone BV, Maynard C, Gerrity RG, Daley W, Rogers C, Edelman ER, Feldman CL, Stone PH. Prediction of the localization of high-risk coronary atherosclerotic plaques on the basis of low endothelial shear stress: an intravascular ultrasound and histopathology natural history study. *Circulation*. 2008;117:993–1002.
8. Kato K, Yonetsu T, Kim SJ, Xing L, Lee H, McNulty I, Yeh RW, Sakhuja R, Zhang S, Uemura S, Yu B, Mizuno K, Jang IK. Nonculprit plaques in patients with acute coronary syndromes have more vulnerable features compared with those with non-acute coronary syndromes: a 3-vessel optical coherence tomography study. *Circ Cardiovasc Imaging*. 2012;5:433–440.
9. Kato K, Yonetsu T, Kim SJ, Xing L, Lee H, McNulty I, Yeh RW, Sakhuja R, Zhang S, Uemura S, Yu B, Mizuno K, Jang IK. Comparison of nonculprit coronary plaque characteristics between patients with and without diabetes: a 3-vessel optical coherence tomography study. *JACC Cardiovasc Interv*. 2012;5:1150–1158.
10. Takarada S, Imanishi T, Kubo T, Tanimoto T, Kitabata H, Nakamura N, Tanaka A, Mizukoshi M, Akasaka T. Effect of statin therapy on coronary fibrous-cap thickness in patients with acute coronary syndrome: assessment by optical coherence tomography study. *Atherosclerosis*. 2009;202:491–497.
11. Komukai K, Kubo T, Kitabata H, Matsuo Y, Ozaki Y, Takarada S, Okumoto Y, Shiono Y, Orii M, Shimamura K, Ueno S, Yamano T, Tanimoto T, Ino Y, Yamaguchi T, Kumiko H, Tanaka A, Imanishi T, Akagi H, Akasaka T. 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;64:2207–2217.
12. Mora S, Wenger NK, Demicco DA, Breazna A, Boekholdt SM, Arsenault BJ, Deedwania P, Kastelein JJ, Waters DD. Determinants of residual risk in secondary prevention patients treated with high- versus low-dose statin therapy: the treating to new targets (TNT) study. *Circulation*. 2012;125:1979–1987.
13. Sacks FM, Pfeffer MA, Moye LA, Rouleau JL, Rutherford JD, Cole TG, Brown L, Warnica JW, Arnold JM, Wun CC, Davis BR, Braunwald E; 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;335:1001–1009.
14. Galon MZ, Wang Z, Bezerra HG, Lemos PA, Schnell A, Wilson DL, Rollins AM, Costa MA, Attizzani GF. Differences determined by optical coherence tomography volumetric analysis in non-culprit lesion morphology and inflammation in ST-segment elevation myocardial infarction and stable angina pectoris patients. *Catheter Cardiovasc Interv*. 2015;85:E108–E115.
15. Nakamura D, Shimamura K, Capodanno D, Attizzani GF, Fineschi M, Musumeci G, Limbruno U, Sirbu V, Coccato M, De Luca L, Bezerra HG, Saia F, Guagliumi G. Fate of nonculprit plaques in patients with STEMI undergoing primary PCI followed by statin therapy: a serial optical coherence tomography analysis from the OCTAVIA study. *JACC Cardiovasc Imaging*. 2017;10:827–829.
16. Tenekecioglu E, Albuquerque FN, Sotomi Y, Zeng Y, Suwannasom P, Tateishi H, Cavalcante R, Ishibashi Y, Nakatani S, Abdelghani M, Dijkstra J, Bourantas C, Collet C, Karanasos A, Radu M, Wang A, Muramatsu T, Landmesser U, Okamura T, Regar E, Raber L, Guagliumi G, Pyo RT, Onuma Y, Serruys PW. Intracoronary optical coherence tomography: clinical and research applications and intravascular imaging software overview. *Catheter Cardiovasc Interv*. 2017;89:679–689.
17. Di Vito L, Yoon JH, Kato K, Yonetsu T, Vergallo R, Costa M, Bezerra HG, Arbustini E, Narula J, Crea F, Prati F, Jang IK; COICO Group (Consortium of Investigators for Coronary OCT). Comprehensive overview of definitions for optical coherence tomography-based plaque and stent analyses. *Coron Artery Dis*. 2014;25:172–185.
18. Hou J, Xing L, Jia H, Vergallo R, Soeda T, Minami Y, Hu S, Yang S, Zhang S, Lee H, Yu B, Jang IK. Comparison of intensive versus moderate lipid-lowering therapy on fibrous cap and atheroma volume of coronary lipid-rich plaque using serial optical coherence tomography and intravascular ultrasound imaging. *Am J Cardiol*. 2016;117:800–806.
19. Jang IK, Bouma BE, Kang DH, Park SJ, Park SW, Seung KB, Choi KB, Shishkov M, Schlendorf K, Pomerantsev E, Houser SL, Aretz HT, Tearney GJ. Visualization of coronary atherosclerotic plaques in patients using optical coherence tomography: comparison with intravascular ultrasound. *J Am Coll Cardiol*. 2002;39:604–609.
20. Tearney GJ, Yabushita H, Houser SL, Aretz HT, Jang IK, Schlendorf KH, Kauffman CR, Shishkov M, Halpern EF, Bouma BE. Quantification of macrophage content in atherosclerotic plaques by optical coherence tomography. *Circulation*. 2003;107:113–119.
21. Tahara S, Morooka T, Wang Z, Bezerra HG, Rollins AM, Simon DI, Costa MA. Intravascular optical coherence tomography detection of atherosclerosis and inflammation in murine aorta. *Arterioscler Thromb Vasc Biol*. 2012;32:1150–1157.
22. Yonetsu T, Kakuta T, Lee T, Takahashi K, Kawaguchi N, Yamamoto G, Koura K, Hishikari K, Iesaka Y, Fujiwara H, Isobe M. In vivo critical fibrous cap thickness for rupture-prone coronary plaques assessed by optical coherence tomography. *Eur Heart J*. 2011;32:1251–1259.

23. Stone NJ, Robinson JG, Lichtenstein AH, Bairey Merz CN, Blum CB, Eckel RH, Goldberg AC, Gordon D, Levy D, Lloyd-Jones DM, McBride P, Schwartz JS, Shero ST, Smith SC Jr, Watson K, Wilson PW, Eddleman KM, Jarrett NM, LaBresh K, Nevo L, Wnek J, Anderson JL, Halperin JL, Albert NM, Bozkurt B, Brindis RG, Curtis LH, DeMets D, Hochman JS, Kovacs RJ, Ohman EM, Pressler SJ, Sellke FW, Shen WK, Smith SC Jr, Tomaselli GF; American College of Cardiology/American Heart Association Task Force on Practice Guidelines. 2013 ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *Circulation*. 2014;129:S1–S45.
24. Farb A, Burke AP, Tang AL, Liang TY, Mannan P, Smialek J, Virmani R. Coronary plaque erosion without rupture into a lipid core: a frequent cause of coronary thrombosis in sudden coronary death. *Circulation*. 1996;93:1354–1363.
25. Kubo T, Maehara A, Mintz GS, Doi H, Tsujita K, Choi SY, Katoh O, Nasu K, Koenig A, Pieper M, Rogers JH, Wijns W, Bose D, Margolis MP, Moses JW, Stone GW, Leon MB. The dynamic nature of coronary artery lesion morphology assessed by serial virtual histology intravascular ultrasound tissue characterization. *J Am Coll Cardiol*. 2010;55:1590–1597.
26. Study of the Effectiveness of Additional Reductions in Cholesterol and Homocysteine (SEARCH) Collaborative Group, Armitage J, Bowman L, Wallendszus K, Bulbulia R, Rahimi K, Haynes R, Parish S, Peto R, Collins R. Intensive lowering of LDL cholesterol with 80 mg versus 20 mg simvastatin daily in 12,064 survivors of myocardial infarction: a double-blind randomised trial. *Lancet*. 2010;376:1658–1669.
27. Cannon CP, Braunwald E, McCabe CH, Rader DJ, Rouleau JL, Belder R, Joyal SV, Hill KA, Pfeffer MA, Skene AM; Pravastatin or Atorvastatin Evaluation and Infection Therapy-Thrombolysis in Myocardial Infarction 22 Investigators. Intensive versus moderate lipid lowering with statins after acute coronary syndromes. *N Engl J Med*. 2004;350:1495–1504.
28. Baigent C, Burbury K, Wheeler D. Premature cardiovascular disease in chronic renal failure. *Lancet*. 2000;356:147–152.
29. Go AS, Chertow GM, Fan D, McCulloch CE, Hsu CY. Chronic kidney disease and the risks of death, cardiovascular events, and hospitalization. *N Engl J Med*. 2004;351:1296–1305.
30. Anavekar NS, McMurray JJ, Velazquez EJ, Solomon SD, Kober L, Rouleau JL, White HD, Nordlander R, Maggioni A, Dickstein K, Zelenkofske S, Leimberger JD, Califf RM, Pfeffer MA. Relation between renal dysfunction and cardiovascular outcomes after myocardial infarction. *N Engl J Med*. 2004;351:1285–1295.
31. Kato K, Yonetsu T, Jia H, Abtahian F, Vergallo R, Hu S, Tian J, Kim SJ, Lee H, McNulty I, Lee S, Uemura S, Jang Y, Park SJ, Mizuno K, Yu B, Jang IK. Nonculprit coronary plaque characteristics of chronic kidney disease. *Circ Cardiovasc Imaging*. 2013;6:448–456.
32. Miyagi M, Ishii H, Murakami R, Isobe S, Hayashi M, Amano T, Arai K, Yoshikawa D, Ohashi T, Uetani T, Yasuda Y, Matsuo S, Matsubara T, Murohara T. Impact of renal function on coronary plaque composition. *Nephrol Dial Transplant*. 2010;25:175–181.
33. Hayano S, Ichimiya S, Ishii H, Kanashiro M, Watanabe J, Kurebayashi N, Yoshikawa D, Amano T, Matsubara T, Murohara T. Relation between estimated glomerular filtration rate and composition of coronary arterial atherosclerotic plaques. *Am J Cardiol*. 2012;109:1131–1136.
34. Baber U, Stone GW, Weisz G, Moreno P, Dangas G, Maehara A, Mintz GS, Cristea E, Fahy M, Xu K, Lansky AJ, Wennerblom B, Mathey DG, Templin B, Zhang Z, Serruys PW, Mehran R. Coronary plaque composition, morphology, and outcomes in patients with and without chronic kidney disease presenting with acute coronary syndromes. *JACC Cardiovasc Imaging*. 2012;5:S53–S61.
35. Vaziri ND. Dyslipidemia of chronic renal failure: the nature, mechanisms, and potential consequences. *Am J Physiol Renal Physiol*. 2006;290:F262–F272.
36. Perco P, Pleban C, Kainz A, Lukas A, Mayer G, Mayer B, Oberbauer R. Protein biomarkers associated with acute renal failure and chronic kidney disease. *Eur J Clin Invest*. 2006;36:753–763.
37. Ponda MP, Barash I, Feig JE, Fisher EA, Skolnik EY. Moderate kidney disease inhibits atherosclerosis regression. *Atherosclerosis*. 2010;210:57–62.
38. Nicholls SJ, Ballantyne CM, Barter PJ, Chapman MJ, Erbel RM, Libby P, Raichlen JS, Uno K, Borgman M, Wolski K, Nissen SE. Effect of two intensive statin regimens on progression of coronary disease. *N Engl J Med*. 2011;365:2078–2087.
39. Tsujita K, Sugiyama S, Sumida H, Shimomura H, Yamashita T, Yamanaga K, Komura N, Sakamoto K, Oka H, Nakao K, Nakamura S, Ishihara M, Matsui K, Sakaino N, Nakamura N, Yamamoto N, Koide S, Matsumura T, Fujimoto K, Tsunoda R, Morikami Y, Matsuyama K, Oshima S, Kaikita K, Hokimoto S, Ogawa H; PRECISE-IVUS Investigators. Impact of dual lipid-lowering strategy with ezetimibe and atorvastatin on coronary plaque regression in patients with percutaneous coronary intervention: the multicenter randomized controlled PRECISE-IVUS trial. *J Am Coll Cardiol*. 2015;66:495–507.
40. Okazaki S, Yokoyama T, Miyauchi K, Shimada K, Kurata T, Sato H, Daida H. 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;110:1061–1068.
41. Hiro T, Kimura T, Morimoto T, Miyauchi K, Nakagawa Y, Yamagishi M, Ozaki Y, Kimura K, Saito S, Yamaguchi T, Daida H, Matsuzaki M; 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.

SUPPLEMENTAL MATERIAL

Data S1.

Supplemental Methods

Study population

Treatment strategies for the culprit lesions, including dose and type of statin, were decided by the local physician. Among 84 patients, a total of 52 patients (61.9%) were treated with drug-eluting stents anddual anti-platelet drugs until follow-up.

OCT image acquisition and analysis

In this cohort, follow-up OCT image acquisition for non-culprit plaque was conducted after the routine follow-up angiography. All patients underwent follow-up OCT image acquisition without any adverse clinical events or recurrent symptoms.

OCT images were acquired using frequency domain (FD-OCT; C7-XR OCT Intravascular Imaging System; St. Jude Medical Inc., St. Paul, Minnesota) or time domain (TD-OCT; M2/M3 Cardiology Imaging System; LightLab Imaging Inc., Westford, Massachusetts) OCT. Although there are some differences, both systems use light sources with the same center wavelength (1300nm) and bandwidth, resulting in similar axial resolution (15μm). Therefore, it is unlikely that the evaluation of plaque components including fibrous cap thickness would have been affected by the differences between the two systems.

All OCT plaque morphologies were analyzed using previously validated criteria[1-3]. Fibrous cap thickness (FCT) was measured at its thinnest part 3 times and the average value was calculated. Thin-cap fibroatheroma (TCFA) was defined as a lipid plaque with the thickness of fibrous cap below 65 μm. Lipid arc and lipid length were measured on the cross-sectional image and longitudinal reconstructed view, respectively. Lipid volume index was

defined as the product of averaged lipid arc multiplied by lipid length [4, 5]. Cholesterol crystals were defined as thin linear regions of high light intensity without signal attenuation [6]. Microchannels were defined as small black holes of diameter 50-100 μm that were present on at least 3 consecutive cross-sectional frames [7]. Thrombus was defined as a mass > 250 μm [8] attached to the luminal surface or floating within the lumen. Calcifications were identified as low backscatter areas with sharp borders. Macrophage infiltration was defined as signal-rich, distinct, or confluent punctuated regions that exceeded the intensity of background speckle noise [9] and assessed semi-quantitatively using a previously described grading system [10]. In brief, macrophages were graded every 1mm interval along the entire plaque as follows: grade 0, no macrophage; grade 1, localized macrophage accumulation; grade 2, clustered accumulation <1 quadrant; grade 3, clustered accumulation ≥1 quadrant but <3 quadrants; and grade 4, clustered accumulation ≥3 quadrants. The summation of grades was reported as the macrophage grade of the plaque. Intra- and inter-observer reproducibility of measurement for calculating the macrophage grade was good (ICC=0.976 and 0.890, respectively).

3D thin-cap area measurement

To volumetrically assess the three-dimensional fibrous cap, we applied a previously validated computer algorithm (Figure S1). The fibrous cap and luminal boundary were semi-automatically segmented by the algorithm in all frames along the entire plaque. Two independent analysts who were blinded to the clinical information including timepoint adjusted the boundaries if there was a segmentation error. With the fully segmented fibrous cap, the algorithm quantified the thickness at each point of its luminal boundary. The fibrous cap area was calculated as the product of the frame interval and the arc length of fibrous cap summed over involved frames.

Definition

ST-segment elevation myocardial infarction (STEMI) was defined as continuous chest pain lasting >30 minutes, ST-segment elevation >0.1 mV in ≥2 contiguous leads or new left bundle-branch block on the 12-lead electrocardiogram (ECG), arrival to the hospital within 12 hours of symptom onset, and elevated cardiac markers (creatine kinase-MB or troponin T/I). Non STEMI (NSTEMI) was defined as ischemic symptoms with elevated cardiac markers in the absence of ST-segment elevation on the ECG. Unstable angina was defined as newly developed / accelerating chest symptoms on exertion / at rest within the past two weeks.

Statistical methods

To explore the independent clinical predictors of the change in the thin-cap area, we included the 'statin naïve' and 'low-intensity statin' covariates in the model in addition to the conventional clinical factors because previous studies reported that both statin intake [11] and dose [12] effected the chronological change of FCT. We also included the baseline thin-cap area inthe model because we observed a trend of greater change in plaques with larger baseline thin-cap area (Figure 1). Unadjusted values are described in Table S1. Intra- and inter-observer agreement of calculating the macrophage grade was evaluated by intraclass correlation coefficient (ICC) based on the random effects analysis of variance model.

Table S1. Unadjusted effect estimates on the absolute change of thin-cap area.

	Estimates	95% CI	p value
Baseline thin-cap area	-0.400	-0.505, -0.295	<0.001
Follow-up duration, month	-0.307	-0.527, -0.088	0.006
Age, yrs	0.089	0.033, 0.145	0.002
BMI	-0.090	-0.319, 0.139	0.441
Male	-0.835	-2.099, 0.429	0.196
Acute coronary syndrome	-2.115	-3.280, -0.950	<0.001
Hypertension	-0.778	-2.097, 0.542	0.248
Hyperlipidemia	-1.016	-2.457, 0.425	0.167
Diabetes	-0.745	-2.332, 0.842	0.357
Current smoker	-0.963	-2.422, 0.496	0.196
Chronic kidney disease	1.293	-0.344, 2.931	0.122
Statin naive	-1.270	-2.629, 0.089	0.067
Low-intensity statin	2.094	1.087, 3.102	<0.001
Beta-blocker	0.310	-1.006, 1.627	0.644
ACEI/ARB	-0.137	-1.666, 1.393	0.861

ACEI/ARB: angiotensin converting enzyme inhibitor/angiotensin II receptor blocker; BMI: body mass index; CI: confidential interval

Table S2. Unadjusted and adjusted effect estiamtes on the absolute change of thin-cap <80 μm area.

	Unadjusted Effects			Adjusted Effects		
	Estimates	**95% CI**	**p value**	**Estimates**	**95% CI**	**p value**
Baseline thin-cap <80μm area	-0.575	-0.776, -0.375	<0.001	-0.559	-0.708, -0.410	<0.001
Follow-up duration, month	-0.047	-0.089, -0.005	0.027	0.017	-0.006, 0.040	0.155
Age, yrs	0.017	0.005, 0.030	0.007	0.007	-0.001, 0.015	0.086
BMI	-0.004	-0.033, 0.025	0.784	0.001	-0.019, 0.020	0.927
Male	-0.207	-0.350, -0.064	0.004	-0.015	-0.122, 0.092	0.785
Acute coronary syndrome	-0.222	-0.409, -0.035	0.020	-0.093	-0.178, -0.007	0.034
Hypertension	-0.048	-0.258, 0.161	0.650	-0.162	-0.296, -0.028	0.018
Hyperlipidemia	-0.081	-0.270, 0.108	0.400	-0.132	-0.319, 0.055	0.168
Diabetes	-0.181	-0.468, 0.105	0.215	-0.059	-0.168, 0.050	0.287
Current smoker	-0.188	-0.462, 0.087	0.180	-0.008	-0.172, 0.155	0.921
Chronic kidney disease	0.159	-0.021, 0.339	0.083	0.227	0.001, 0.453	0.049
Statin naive	-0.201	-0.447, 0.045	0.110	0.024	-0.092, 0.140	0.685
Low-intensity statin	0.266	0.128, 0.403	<0.001	0.018	-0.140, 0.175	0.825
Beta-blocker	0.090	-0.117, 0.296	0.396	-0.002	-0.127, 0.123	0.971
ACEI/ARB	-0.026	-0.284, 0.232	0.842	0.011	-0.101, 0.122	0.851

ACEI/ARB: angiotensin converting enzyme inhibitor/angiotensin II receptor blocker; BMI: body mass index; CI: confidential interval

Table S3. Unadjusted and adjusted effect estiamtes on the absolute change of fibrous cap thickness.

	Unadjusted Effects			Adjusted Effects		
	Estimates	**95% CI**	**p value**	**Estimates**	**95% CI**	**p value**
Baseline FCT, μm	-0.510	-0.691, -0.330	<0.001	-0.524	-0.707, -0.341	<0.001
Follow-up duration, month	1.068	-3.358, 5.494	0.636	-1.910	-6.546, 2.725	0.419
Age, yrs	-0.622	-1.549, 0.306	0.189	-0.728	-2.109, 0.654	0.302
BMI	1.456	-4.409, 7.320	0.627	0.096	-5.068, 5.260	0.971
Male	23.169	-4.759, 51.096	0.104	2.116	-26.304, 30.536	0.884
Acute coronary syndrome	21.071	-2.770, 44.913	0.083	29.759	0.461, 59.056	0.047
Hypertension	33.139	10.503, 55.776	0.004	18.318	-8.993, 45.629	0.189
Hyperlipidemia	-3.839	-31.799, 24.120	0.788	1.801	-25.957, 29.560	0.899
Diabetes	4.842	-21.329, 31.013	0.717	0.615	-25.670, 26.899	0.963
Current smoker	24.744	-1.819, 51.308	0.068	14.111	-15.462, 43.683	0.350
Chronic kidney disease	-12.857	-43.479, 17.765	0.411	-25.717	-53.818, 2.383	0.073
Statin naive	4.505	-20.100, 29.109	0.720	-20.122	-48.524, 8.281	0.165
Low-intensity statin	-11.523	-36.219, 13.173	0.360	21.285	-16.038, 58.608	0.264
Beta-blocker	-20.628	-43.037, 1.782	0.071	-18.583	-38.600, 1.433	0.069
ACEI/ARB	-6.047	-29.543, 17.450	0.614	-21.088	-49.124, 6.948	0.140

ACEI/ARB: angiotensin converting enzyme inhibitor/angiotensin II receptor blocker; BMI: body mass index; CI: confidential interval; FCT: fibrous cap thickness

Table S4. Baseline plaque morphology according to the change of thin-cap area.

	Reduction	Mild reduction	No reduction	p value	R vs. M	R vs. N	M vs. N
Quantitative assessment							
Thin-cap area, mm^2*	7.137 [4.050, 10.691]	2.079 [0.720, 3.648]	1.119 [0.210, 2.272]	<0.001	<0.001	<0.001	0.020
Thinnest FCT, mm	89.4 ± 43.8	113.5 ± 61.8	148.7 ± 67.6	<0.001	0.010	<0.001	0.049
TCFA (<65μm), n (%)	20 (42.6)	7 (15.2)	8 (17.0)	0.003	0.004	0.007	0.813
Mean lipid arc, º	182.5 ± 57.7	167.0 ± 53.2	142.5 ± 57.7	0.003	0.038	0.002	0.095
Maximum lipid arc, º	259.8 ± 63.9	229.9 ± 57.8	206.7 ± 77.6	0.001	0.084	0.001	0.219
Lipid length, mm	9.38 ± 3.58	7.41 ± 3.28	6.94 ± 3.61	0.002	0.020	0.003	0.788
Lipid volume index	1744.3 ± 870.9	1234.5 ± 674.9	1067.0 ± 797.6	<0.001	0.006	<0.001	0.061
MLA, mm^2	3.25 ± 1.37	2.95 ± 1.14	3.04 ± 1.35	0.507	-	-	-
%Area stenosis	58.9 ± 8.25	60.1 ± 10.2	60.8 ± 8.97	0.614	-	-	-
Macrophage grade*	7.00 [2.00, 11.0]	3.00 [0.00, 8.00]	4.00 [1.00, 6.00]	0.053	-	-	-
Qualitative assessment							
Cholesterol crystal, n (%)	5 (10.6)	11 (23.9)	8 (17.0)	0.236	-	-	-
Microchannel, n (%)	13 (27.7)	15 (32.6)	14 (29.8)	0.873	-	-	-
Calcium, n (%)	25 (53.2)	22 (47.8)	27 (57.4)	0.648	-	-	-
Spotty calcium, n (%)	23 (48.9)	19 (41.3)	21 (44.7)	0.760	-	-	-
Thrombus, n (%)	1 (2.4)	3 (7.5)	0 (0)	0.170	-	-	-

R, M and N represent Reduction group, Mild reduction group and No reduction group, respectively. FCT: fibrous cap thickness; MLA: minimal lumen area; TCFA: thin-cap fibroatheroma. *Median (25^{th} – 75^{th} percentile) are presented and the comparisons were made by Wilcoxon's signed rank test, and all other continuous outcomes data are represented by mean ± SD and the comparisons were maded by paired sampels t-test.

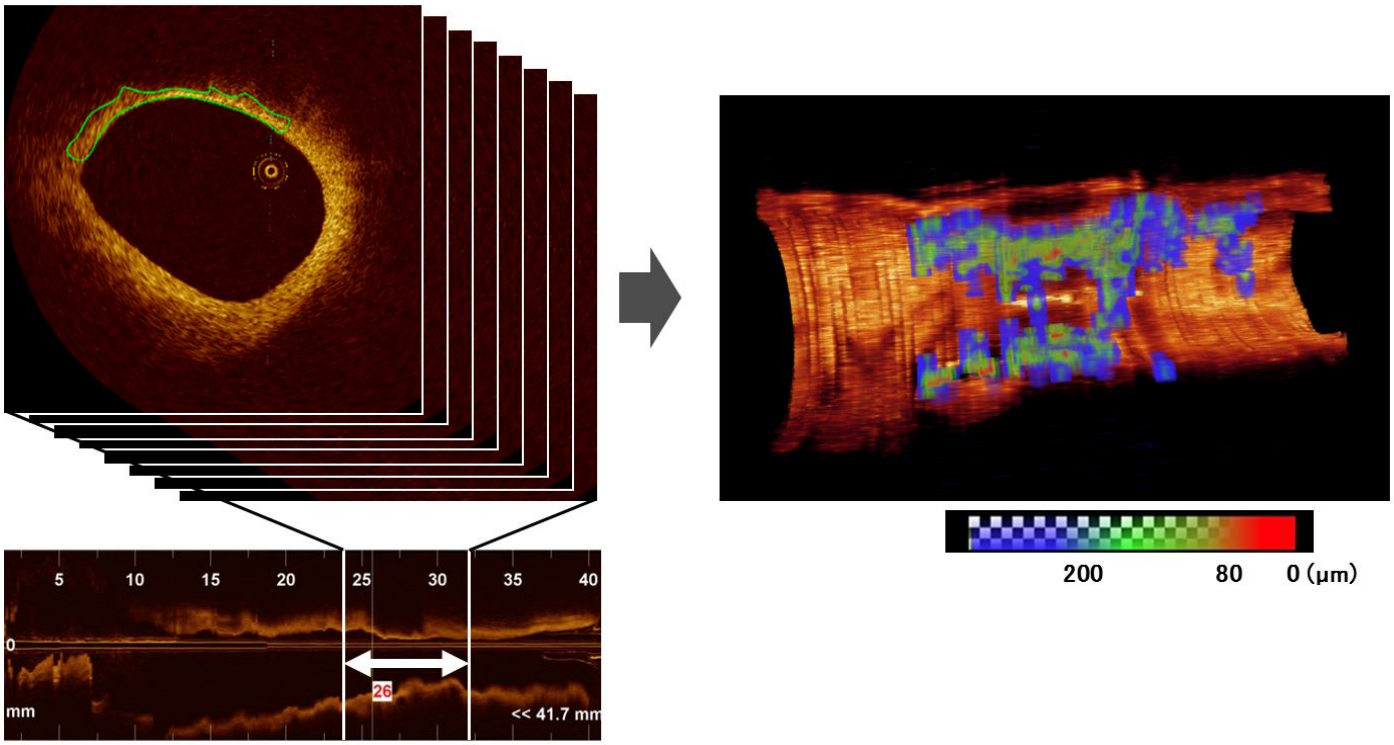

Figure S1. Three-dimensional thin-cap area measurement. The fibrous cap was semi-automatically segmented (green circle in left upper panel) by the validated computer algorithm in all frames along the entire plaque. With the fully segmented fibrous cap, the algorithm quantified the thickness at each point of its luminal boundary. The thin-cap area was calculated as the product of the frame interval and the arc length of thin fibrous cap (<200μm) summed over involved frames. A representative three-dimensional reconstructed image of thin-cap area is shown (right panel).

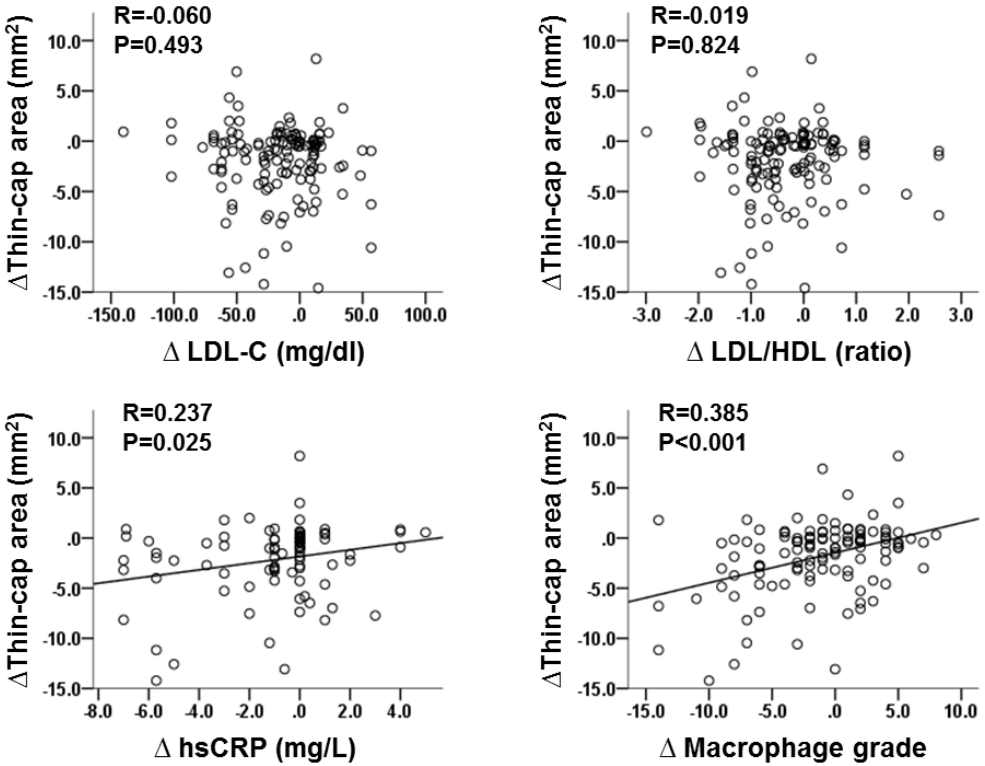

Figure S2. Correlation between the change of thin-cap area and changes of other parameters. Significant linear correlation was observed between the change of baseline hsCRP value and macrophage grade with the absolute change of thin-cap area.

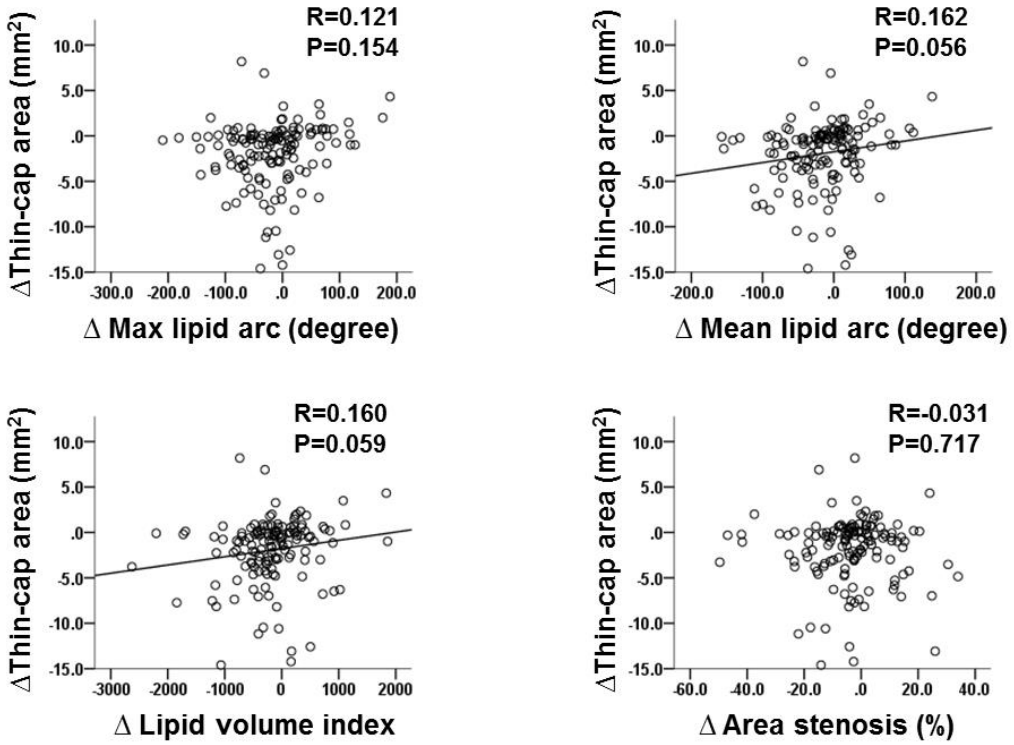

Figure S3. Correlation between the change of thin-cap area and changes of other plaque morphologies. Significant correlation was not observed between the absolute changes of thin-cap area and changes of other plaque morphologies including lipid volume index and %area stenosis.

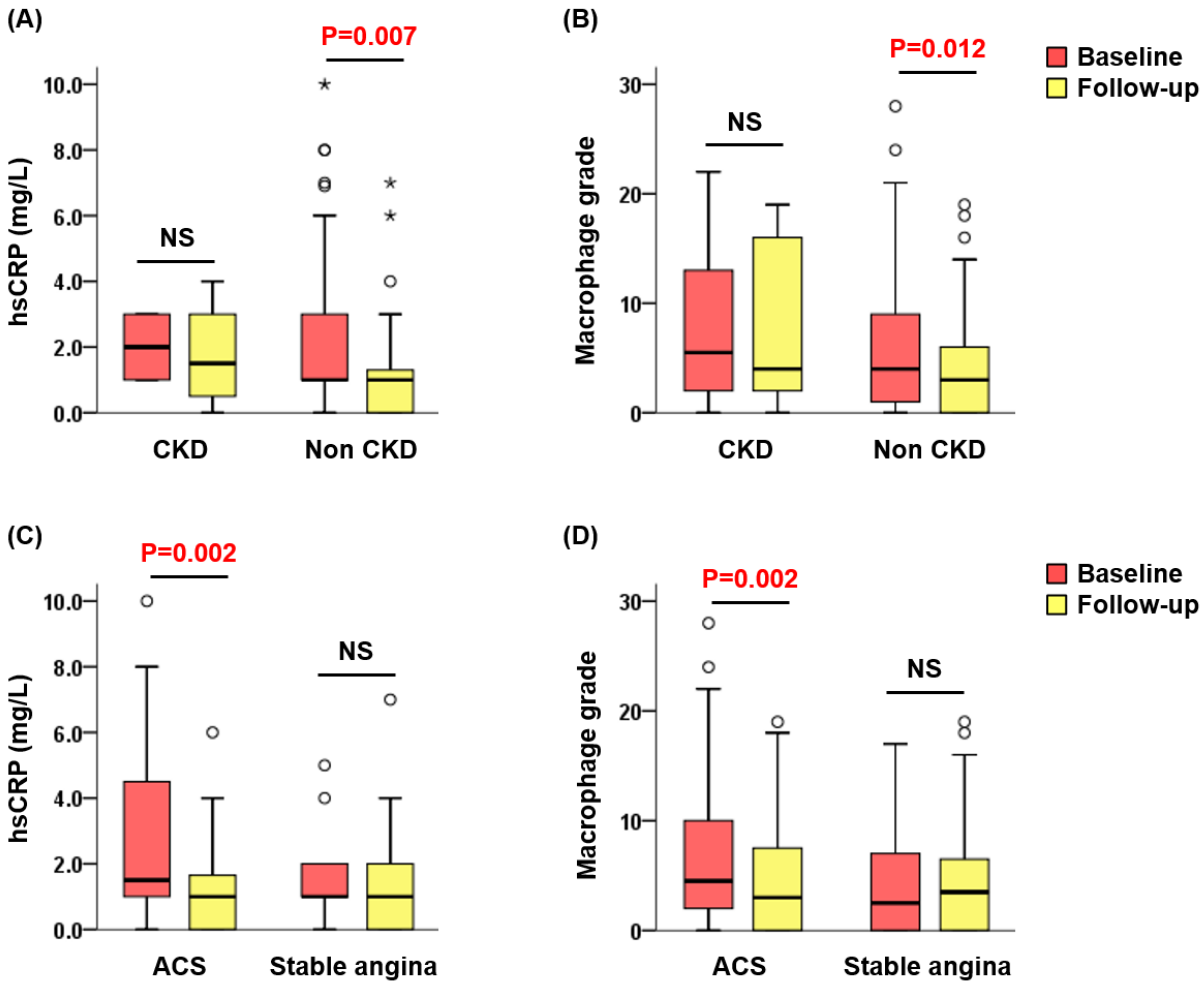

Figure S4. Change of inflammation status accoding to baseline clinical presentation. CKD patients failed to show significant reduction in hsCRP and macrophage grade at follow-up (A, B). Significant reduction of hsCRP values and macrophage grade at follow-up was observed only in ACS cases (C, D).

Supplemental References:

1. Jang IK, Tearney GJ, MacNeill B, Takano M, Moselewski F, Iftima N, Shishkov M, Houser S, Aretz HT, Halpern EF, Bouma BE. In vivo characterization of coronary atherosclerotic plaque by use of optical coherence tomography. *Circulation*. 2005;111:1551-1555.
2. Tearney GJ, Regar E, Akasaka T, Adriaenssens T, Barlis P, Bezerra HG, Bouma B, Bruining N, Cho JM, Chowdhary S, Costa MA, de Silva R, Dijkstra J, Di Mario C, Dudek D, Falk E, Feldman MD, Fitzgerald P, Garcia-Garcia HM, Gonzalo N, Granada JF, Guagliumi G, Holm NR, Honda Y, Ikeno F, Kawasaki M, Kochman J, Koltowski L, Kubo T, Kume T, Kyono H, Lam CC, Lamouche G, Lee DP, Leon MB, Maehara A, Manfrini O, Mintz GS, Mizuno K, Morel MA, Nadkarni S, Okura H, Otake H, Pietrasik A, Prati F, Raber L, Radu MD, Rieber J, Riga M, Rollins A, Rosenberg M, Sirbu V, Serruys PW, Shimada K, Shinke T, Shite J, Siegel E, Sonoda S, Suter M, Takarada S, Tanaka A, Terashima M, Thim T, Uemura S, Ughi GJ, van Beusekom HM, van der Steen AF, van Es GA, van Soest G, Virmani R, Waxman S, Weissman NJ, Weisz G, International Working Group for Intravascular Optical Coherence T. 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;59:1058-1072.
3. Yabushita H, Bouma BE, Houser SL, Aretz HT, Jang IK, Schlendorf KH, Kauffman CR, Shishkov M, Kang DH, Halpern EF, Tearney GJ. Characterization of human atherosclerosis by optical coherence tomography. *Circulation*. 2002;106:1640-1645..
4. Yonetsu T, Kato K, Uemura S, Kim BK, Jang Y, Kang SJ, Park SJ, Lee S, Kim SJ, Jia H, Vergallo R, Abtahian F, Tian J, Hu S, Yeh RW, Sakhuja R, McNulty I, Lee H, Zhang S, Yu B, Kakuta T, Jang IK. Features of coronary plaque in patients with metabolic syndrome and diabetes mellitus assessed by 3-vessel optical coherence tomography. *Circ Cardiovasc Imaging*. 2013;6:665-673
5. Kato K, Yonetsu T, Kim SJ, Xing L, Lee H, McNulty I, Yeh RW, Sakhuja R, Zhang S, Uemura S, Yu B, Mizuno K, Jang IK. Nonculprit plaques in patients with acute coronary

syndromes have more vulnerable features compared with those with non-acute coronary syndromes: A 3-vessel optical coherence tomography study. *Circ Cardiovasc Imaging*. 2012;5:433-440.

6. Liu L, Gardecki JA, Nadkarni SK, Toussaint JD, Yagi Y, Bouma BE, Tearney GJ. Imaging the subcellular structure of human coronary atherosclerosis using micro-optical coherence tomography. *Nat Med*. 2011;17:1010-1014.
7. Uemura S, Ishigami K, Soeda T, Okayama S, Sung JH, Nakagawa H, Somekawa S, Takeda Y, Kawata H, Horii M, Saito Y. Thin-cap fibroatheroma and microchannel findings in optical coherence tomography correlate with subsequent progression of coronary atheromatous plaques. *Eur Heart J*. 2012;33:78-85.
8. Matsumoto D, Shite J, Shinke T, Otake H, Tanino Y, Ogasawara D, Sawada T, Paredes OL, Hirata K, Yokoyama M. Neointimal coverage of sirolimus-eluting stents at 6-month follow-up: Evaluated by optical coherence tomography. *Eur Heart J*. 2007;28:961-967.
9. Tearney GJ, Yabushita H, Houser SL, Aretz HT, Jang IK, Schlendorf KH, Kauffman CR, Shishkov M, Halpern EF, Bouma BE. Quantification of macrophage content in atherosclerotic plaques by optical coherence tomography. *Circulation*. 2003;107:113-119.
10. Tahara S, Morooka T, Wang Z, Bezerra HG, Rollins AM, Simon DI, Costa MA. Intravascular optical coherence tomography detection of atherosclerosis and inflammation in murine aorta. *Arteriosclerosis, thrombosis, and vascular biology*. 2012;32:1150-1157.
11. Takarada S, Imanishi T, Ishibashi K, Tanimoto T, Komukai K, Ino Y, Kitabata H, Kubo T, Tanaka A, Kimura K, Mizukoshi M, Akasaka T. The effect of lipid and inflammatory profiles on the morphological changes of lipid-rich plaques in patients with non-st-segment elevated acute coronary syndrome: Follow-up study by optical coherence tomography and intravascular ultrasound. *JACC Cardiovasc Interv*. 2010;3:766-772.
12. Komukai K, Kubo T, Kitabata H, Matsuo Y, Ozaki Y, Takarada S, Okumoto Y, Shiono Y, Orii M, Shimamura K, Ueno S, Yamano T, Tanimoto T, Ino Y, Yamaguchi T, Kumiko H, Tanaka A, Imanishi T, Akagi H, Akasaka T. 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;64:2207-2217.