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# Does spotty calcification attenuate the response of nonculprit plaque to statin therapy?

## A serial optical coherence tomography study

Abigail Afolabi, MD, PhD[1*] | Irina Mustafina, MD, PhD[1,3*] | Linlin Zhao, MD[1*] | Lulu Li, MS[1] | Rong Sun, MD, PhD[1] | Sining Hu, MD, PhD[1] | Shaosong Zhang, MD, PhD[2] | Haibo Jia, MD, PhD[1] | Guagliumi Guilio, MD, PhD[4] | Bo Yu, MD, PhD, FACC[1]

[1]Department of Cardiology, The 2nd Affiliated Hospital of Harbin Medical University, The Key Laboratory of Myocardial Ischemia, Chinese Ministry of Education, Harbin, China

[2]Harbin Medical University, Harbin, China

[3]Bashkir State Medical University, Ufa, Republic Bashkortostan, Russian Federation

[4]Interventional Cardiology Unit, Azienda Ospedaliera Papa Giovanni XXIII, Bergamo, Italy

**Correspondence**
Bo Yu, MD, PhD, FACC; Department of Cardiology, The Second Affiliated Hospital of Harbin Medical University, The Key Laboratory of Myocardial Ischemia, Chinese Ministry of Education, Harbin 150086, China.
Email: yubodr@163.com
and
Haibo Jia, MD, PhD; Department of Cardiology, The Second Affiliated Hospital of Harbin Medical University, The Key Laboratory of Myocardial Ischemia, Chinese Ministry of Education, Harbin 150086, China.
Email: jhb101180@163.com

## Abstract

**Objectives:** The aim of this study was to determine if spotty calcification decreases the response of plaque progression to statin therapy.

**Background:** Previous studies showed that the presence of spotty calcification is a marker of vulnerable plaque. However, the relationship between spotty calcification and plaque progression is not clear.

**Methods:** Ninety-six nonculprit lipid-rich plaques in 69 patients who received serial optical coherence tomography (OCT) imaging were included. Plaques were divided into three groups: spotty calcification ($n = 38$), calcified ($n = 12$) and noncalcified ($n = 46$) plaques. Spotty calcification was identified by the presence of a lesion <4 mm in length with an arc of calcification <90°. Changes in plaque characteristics and fibrous cap thickness (FCT) at 6 and 12 months under statin therapy were analyzed by OCT.

**Results:** The increase of FCT was sustained from baseline to 6 and 12 months in three groups: spotty calcification (62.8 ± 20.9, 126.4 ± 84.9, and 169.2 ± 81.6 μm, respectively; $P < .001$), calcified (59.8 ± 17.0, 93.4 ± 51.4, and 155.2 ± 61.7 μm, respectively; $P < .001$) and noncalcified (60.0 ± 17.2, 125.5 ± 62.1, and 161.0 ± 80.5 μm, respectively; $P < .001$). Intensive statin induced a greater change in FCT at 12 months than moderate statin in the spotty calcification group ($P = 0.034$). The mean lipid arc decreased significantly at 12 months from baseline in the three groups ($P = 0.004$, $P = 0.023$, and $P < .001$, respectively).

**Conclusions:** Statin therapy was effective for plaque stabilization in plaques with and without spotty calcification. Patients with spotty calcification benefitted more from intensive statin than from moderate statin therapy.

KEYWORDS
lipid-rich plaque, optical coherence tomography, spotty calcification, statin therapy

## 1 | INTRODUCTION

Coronary artery calcification (CAC) is a dynamic process that is usually found in the presence of atherosclerotic plaque [1], and a high

*First three authors equally contributed to this study.

correlation exists between arterial calcification and plaque burden [2]. CAC plays an active role in plaque development by its action on macrophage activation, which places patients at higher risk for acute coronary events due to the increment of inflammation [3,4]. Previous studies detected arterial wall calcium deposits *in vivo* [5], and small calcium deposits were more significantly observed in the culprit lesion segment in acute coronary syndrome (ACS) patients using intravascular ultrasound (IVUS) [6]. Kataoka et al. studied atheroma progression in patients with spotty calcification using IVUS and showed that despite the use of medical therapies, spotty calcification was associated with accelerated disease progression and constructive positive modeling [7]. The high resolution of optical coherence tomography (OCT) allows the direct visualization of the plaque microstructure contributing to plaque vulnerability [8,9]. Recent OCT studies showed that lesions with spotty calcification had thinner fibrous cap thicknesses and demonstrated vulnerable plaque features [10]. In addition, spotty calcification is an independent predictor of plaque rupture in patients with ACS [11]. These findings implied that spotty calcification is a marker of plaque vulnerability in patients presenting with acute coronary syndrome.

Therefore, we sought to assess the relationship between spotty calcification and plaque progression at nonculprit lesions in response to statin therapy using OCT in patients with coronary artery disease.

## 2 | MATERIALS AND METHODS

### 2.1 | Study population

The current study population was from a prospective, randomized trial, which was performed to evaluate the progression of lipid-rich plaques treated with intensive versus moderate statin therapy at baseline and 6 and 12 month follow-ups [12] [ClinicalTrial.gov registered number: NCT01023607]. A total of 120 consecutive patients who underwent successful percutaneous coronary intervention (PCI) were enrolled in the study from September 2009 to March 2013 at the 2nd Affiliated Hospital of Harbin Medical University. The study criteria were reported previously [12].

All lipid-rich plaques were analyzed according to landmark at index and 6 and 12 month follow-ups. Fifty-one patients were excluded for the following reasons: (a) withdrawn ($n = 31$), (b) poor imaging ($n = 13$), and (c) image mismatch ($n = 7$). Finally, in our analysis, ninety-six lipid-rich plaques from sixty-nine patients who underwent serial OCT images (baseline, 6 months and 12 months) were divided into three groups based upon the distribution of the calcium: spotty calcification, calcified, and noncalcified group shown in Figure 1 All patients provided written informed consent, and this trial was approved by the Ethics Committee of the 2nd Affiliated Hospital of Harbin Medical University (Harbin, China).

### 2.2 | OCT image acquisition and analysis

All OCT procedures were performed after an intra-coronary administration of 100–200 mg of nitroglycerin. OCT imaging was performed using a time-domain (M3 Cardiology Imaging System; LightLab Imaging, Westford, Massachusetts) or frequency domain OCT system (C7-XR OCT Intravascular Imaging System, St. Jude Medical, St. Paul, Minnesota). Offline software (Light Lab Imaging) was used for OCT image analysis at an independent core laboratory of the 2nd Affiliated Hospital of Harbin Medical University. OCT images were analyzed at 1-mm intervals. All baseline and follow-up OCT images were analyzed by two independent reviewers who were blinded to clinical information. OCT images were analyzed according to the criteria previously reported [13]. A third professional investigator intervened when there was any discordance between the observers, and consensus was obtained.

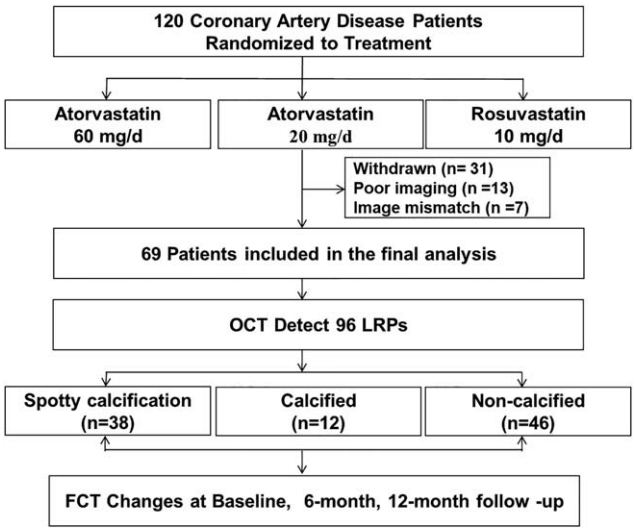


**FIGURE 1** Study flow chart of patient enrollment

The target lesions were determined according to coronary angiography. The corresponding segments at 6- and 12-month follow-ups were identified on the basis of reliable anatomic marks, such as the side branches, calcifications, and stent edges. All the enrolled plaques should be at least 5 mm away from either the distal or proximal stent edge.

All OCT images were analyzed using the previously validated criteria for plaque characterization [13–15]. Lipid-rich plaques were defined as plaques with lipid contents $>100°$ and FCTs $<120$ μm on the OCT image according to a previous study's definition [12]. The characteristic of a lipid core was a diffusely bordered, signal-poor region [15]. FCT covering the lipid core was measured at its thinnest part three times, and the average value of the three measurements was used for subsequent analysis. At follow-up, FCT was measured at the same site that it was measured at baseline, according to a landmark, using the same methodology. The lipid arc was measured on the cross-section with largest lipid core. Calcification was defined as an area with low backscattering signal and a sharp border [15]. Spotty calcification was defined as the presence of lesions $<4$ mm in length and containing an arc of calcification $<90°$ according to the definition of previous studies using gray-scale intravascular ultrasound [6,7]. Thin-cap fibroatheroma (TCFA) was defined as a plaque with lipid content in $\geq 2$ quadrants and the thinnest part of FCT $\leq 65$ μm on a cross-sectional image [13].

Macrophage infiltration was defined as signal-rich, distinct regions that exceeded the intensity of background speckle noise [16]. A microchannel was defined as signal-poor voids without a connection to the vessel lumen recognized on more than three consecutive cross-sectional OCT frames [8,13]. Thrombus was defined as a floating or protruding mass into the lumen with a dimension ≥25 μm [17]. Cholesterol crystals were defined as linear and highly backscattering structures within the lipid-rich plaques [13].

### 2.3 | Statistical analysis

SPSS version 19.0 (SPSS, IBM, Armonk, NY, USA) was used for data analysis. Continuous variables are presented as the mean ± standard deviation (SD) for normally distributed variables or median (interquartile range) for non-normally distributed variables. For the normality assessment of continuous variables, the Kolmogorov–Smirnov test was used. Categorical data were expressed as absolute number and percentage and were compared using either a chi-square test or Fisher's exact test, depending on the data, while for the comparison of continuous results in three groups over the three time points, 1-way ANOVA with Bonferroni correction for post hoc comparisons was applied. Generalized estimating equations approaches were used to take into account the intraclass correlation due to the multiple plaques analyzed within a single patient's data. A value of $P < .05$ was considered statistically significant.

## 3 | RESULTS

### 3.1 | Baseline patient clinical characteristics

Baseline characteristics of patients are summarized in Table 1. There was a significant difference in age ($P = 0.023$) and the treatment of nitrates at discharge ($P = 0.011$) between spotty calcification and noncalcified group. A history of hypertension was more common in patients with spotty calcification compared with noncalcified patients ($P = 0.029$). Similarly, more patients in calcified group had a history of

**TABLE 1** Baseline characteristics of patients

| Variables | Spotty ($n = 22$) | Calcified ($n = 12$) | Noncalcified ($n = 35$) | *P* value | | | |
|---|---|---|---|---|---|---|---|
| | | | | All | Spotty vs. Cal | Cal vs. non-Cal | Spotty vs. non-Cal |
| Age (years) | 58.6 ± 8.6 | 58.6 ± 6.3 | 52.8 ± 10.1 | 0.038 | 0.998 | 0.063 | 0.023 |
| Male | 13 (59.1%) | 9 (75%) | 21 (60.0%) | 0.607 | 0.354 | 0.351 | 0.581 |
| Hypertension | 17 (77.3%) | 10 (83.3%) | 17 (48.6%) | 0.027 | 0.676 | 0.036 | 0.029 |
| DM | 10 (45.5%) | 7 (58.3%) | 17 (48.6%) | 0.767 | 0.360 | 0.402 | 0.518 |
| Smoker | 9 (40.9%) | 5 (41.7%) | 19 (54.3%) | 0.552 | 0.966 | 0.337 | 0.239 |
| Prior MI | 5 (22.7%) | 1 (8.3%) | 9 (25.7%) | 0.448 | 0.293 | 0.204 | 0.529 |
| Prior PCI | 2 (9.1%) | 3 (25.0%) | 7 (20.0%) | 0.426 | 0.211 | 0.715 | 0.272 |
| Presentation | | | | | | | |
| STEMI | 2 (9.1%) | 2 (16.7%) | 8 (22.9%) | 0.186 | 0.530 | 0.838 | 0.070 |
| NSTEMI | 1 (4.5%) | 1 (8.3%) | 4 (11.4%) | | | | |
| UAP | 16 (72.7%) | 9 (75.0%) | 23 (65.7%) | | | | |
| SAP | 3 (13.6%) | 0 (0.0%) | 0 (0.0%) | | | | |
| Target coronary artery | | | | | | | |
| LAD | 14 (36.8%) | 3 (25.0%) | 13 (28.3%) | 0.854 | 0.73 | 0.835 | 0.646 |
| LCX | 7 (18.4%) | 3 (25.0%) | 8 (17.4%) | | | | |
| RCA | 17 (44.7%) | 6 (50.0%) | 25 (54.3%) | | | | |
| Medication at discharge | | | | | | | |
| AT60 | 7 (31.8%) | 6 (22.2%) | 14 (40.0%) | 0.837 | 0.505 | 0.699 | 0.822 |
| AT 20 | 8 (36.4%) | 4 (33.3%) | 11 (31.4%) | | | | |
| RT 10 | 7 (31.8%) | 2 (16.7%) | 10 (28.6%) | | | | |
| Aspirin | 22 (100.0%) | 11 (91.7%) | 35 (100.0%) | 0.090 | 0.169 | 0.084 | |
| Clopidogrel | 22 (100%) | 12 (100.0) | 34 (97.1%) | 0.611 | - | 0.554 | 0.424 |
| Beta-blocker | 16 (72.7%) | 7 (58.3%) | 19 (54.3%) | 0.374 | 0.391 | 0.539 | 0.133 |
| ACEI/ARB | 12 (54.5%) | 6 (50.0%) | 13 (37.1%) | 0.406 | 0.541 | 0.434 | 0.155 |
| CCB | 6 (27.3%) | 6 (50.0%) | 7 (20.0%) | 0.133 | 0.185 | 0.045 | 0.373 |
| Nitrate | 17 (77.3%) | 8 (66.7%) | 15 (42.9%) | 0.030 | 0.503 | 0.138 | 0.011 |

Continuous variables are expressed as the mean ± SD; categorical variables are expressed as number (percentage); $P < .05$ was considered significant.
Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; AT, atorvastatin; Cal, calcified; CCB, calcium channel blocker; LAD, left anterior descending; LCX, circumflex; MI, myocardial infarction; non-Cal, noncalcified; NSTEMI, non-ST-elevation myocardial infarction; PCI, percutaneous coronary intervention; RCA, right coronary artery; SAP, stable angina pectoris; RT, rosuvastatin; SD, standard deviation; Spotty, spotty calcification; STEMI, ST-elevation myocardial infarction; UAP, unstable angina pectoris.

hypertension compared to those in the noncalcified group ($P = 0.036$). Statin therapy at discharge and follow-up duration was comparable among the three groups.

## 3.2 | Changes in laboratory test

Serum levels of lipids and high-sensitivity C-reactive protein (hs-CRP) at baseline and follow-up are shown in Table 2. Low-density lipoprotein-cholesterol (LDL-C) significantly decreased from baseline to 6 months and 12 months in all three groups. Similarly, serum total cholesterol and triglycerides significantly decreased at 6 and 12 months compared with baseline in the three groups. Hs-CRP significantly decreased over time in both the spotty calcification group ($P = 0.002$) and the noncalcified group ($P = 0.028$). Serum levels of lipid and high-sensitivity C-reactive protein were comparable between the groups at each time point between the three groups. The absolute changes of laboratory data from baseline to 12 month follow-up were similar between the three groups (Supporting Information Table 1, Figure 2).

## 3.3 | Angiographic findings

Lesion length was significantly shorter in the spotty calcification group compared to that in the calcified group at baseline (10.6 ± 4.3 vs. 16.2 ± 5.8 mm, $P = 0.001$) and at the 6 month follow-up (11.4 ± 4.4 vs. 16.4 ± 5.6 mm, $P = 0.002$). The diameter stenosis was greater in the calcified group than in the noncalcified group at baseline ($P = 0.029$) and at the 6-month follow-up ($P = 0.026$), while the minimum lumen diameter and the reference vessel diameter were similar among the three groups (Supporting Information Table 2).

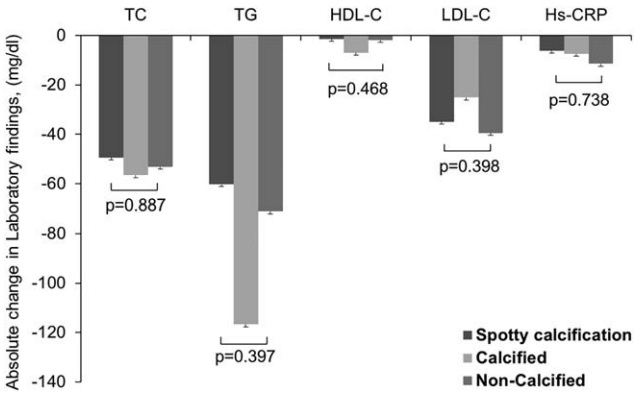


**FIGURE 2** Absolute changes of laboratory findings between the three groups from baseline to 12 months. Total cholesterol (TC), triglyceride (TG), high-density lipoprotein-cholesterol (HDL-C), low-density lipoprotein-cholesterol (LDL-C), high-sensitivity C-reactive protein (Hs-CRP). The absolute changes in the laboratory findings were comparable from baseline to 12 months between the three groups

## 3.4 | OCT findings

The changes in OCT findings are shown in Table 3. FCT significantly increased from baseline to 6 and 12 months in all three groups under statin therapy. In detail, an increase of FCT was significantly sustained in the three groups, as shown in Figure 3. The mean lipid arc decreased significantly from baseline to 12 months in the three groups. However, there was no significant difference in the absolute and percentage changes in FCT and the lipid arc at 6 and 12 months among the three groups. At baseline, the minimum lumen area (MLA), FCT, maximum lipid arc, and mean lipid arc were comparable

**TABLE 2** Laboratory findings

| Variables | BL | 6M Follow-up | 12M follow-up | *P* value All | BL vs. 6M | BL vs. 12M | 6M vs. 12M |
|---|---|---|---|---|---|---|---|
| Spotty calcification ($n = 22$) | | | | | | | |
| TC (mg/dl) | 193.9 ± 38.6 | 137.7 ± 38.8 | 144.5 ± 45.8 | <0.001 | <0.001 | <0.001 | 0.489 |
| TG (mg/dl) | 196.1 ± 88.2 | 132.4 ± 60.6 | 135.8 ± 52.4 | <0.001 | <0.001 | 0.001 | 0.633 |
| HDL (mg/dl) | 48.5 ± 12.9 | 46.1 ± 12.8 | 47.2 ± 15.8 | 0.748 | 0.435 | 0.687 | 0.736 |
| LDL (mg/dl) | 106.6 ± 25.6 | 69.6 ± 27.9 | 71.7 ± 30.0 | <0.001 | <0.001 | <0.001 | 0.780 |
| Hs-CRP (mg/dl) | 7.9 ± 11.5 | 1.4 ± 0.7 | 1.8 ± 2.0 | 0.002 | 0.013 | 0.016 | 0.217 |
| Calcified ($n = 12$) | | | | | | | |
| TC (mg/dl) | 221.8 ± 54.3 | 141.9 ± 35.1 | 165.3 ± 43.7 | <0.001 | <0.001 | 0.002 | 0.006 |
| TG (mg/dl) | 273.3 ± 260.6 | 146.4 ± 84.8 | 156.6 ± 80.1 | 0.021 | 0.043 | 0.062 | 0.524 |
| HDL (mg/dl) | 50.5 ± 11.1 | 45.6 ± 13.3 | 43.5 ± 12.9 | 0.067 | 0.089 | 0.067 | 0.417 |
| LDL (mg/dl) | 117.7 ± 23.3 | 71.4 ± 25.4 | 92.6 ± 32.3 | <0.001 | <0.001 | <0.001 | 0.018 |
| Hs-CRP (mg/dl) | 10.5 ± 14.5 | 3.4 ± 6.3 | 3.1 ± 6.9 | 0.181 | 0.164 | 0.165 | 0.913 |
| Noncalcified (n=35) | | | | | | | |
| TC (mg/dl) | 193.5 ± 38.1 | 142.7 ± 35.0 | 140.4 ± 33.6 | <0.001 | <0.001 | <0.001 | 0.598 |
| TG (mg/dl) | 208.4 ± 133.2 | 158.3 ± 111.8 | 137.4 ± 66.2 | <0.001 | 0.001 | <0.001 | 0.146 |
| HDL (mg/dl) | 49.4 ± 12.6 | 48.9 ± 13.9 | 47.6 ± 13.2 | 0.641 | 0.846 | 0.416 | 0.370 |
| LDL (mg/dl) | 108.3 ± 24.5 | 70.9 ± 26.5 | 68.8 ± 25.6 | <0.001 | <0.001 | <0.001 | 0.585 |
| Hs-CRP (mg/dl) | 12.5 ± 34.4 | 1.2 ± 0.8 | 1.0 ± 0.9 | 0.028 | 0.063 | 0.058 | 0.168 |

Continuous variables are expressed as the mean ± SD; categorical variables are expressed as number (percentage); $P < .05$ was considered significant. Abbreviations: 6M, 6 months; 12M, 12 months; BL, baseline; HDL-C, high-density lipoprotein cholesterol; Hs-crp, high-sensitivity C-reactive protein; LDL-C, low-density lipoprotein cholesterol; SD, standard deviation; TC, total cholesterol; TG, triglycerides.

**TABLE 3** Quantitative optical coherence tomography findings

| Variables | BL | 6M follow-up | 12M follow-up | *P* value All | BL vs. 6M | BL vs. 12M | 6M vs. 12M |
|---|---|---|---|---|---|---|---|
| Spotty calcification ($n = 38$) | | | | | | | |
| MLA ($mm^2$) | 3.2 ± 1.2 | 3.3 ± 1.2 | 3.4 ± 1.2 | 0.199 | 0.505 | 0.110 | 0.156 |
| FCT (μm) | 62.8 ± 20.9 | 126.4 ± 84.9 | 169.2 ± 81.6 | <0.001 | <0.001 | <0.001 | <0.001 |
| Mean lipid arc (°) | 180.5 ± 48.4 | 170.1 ± 57.6 | 158.8 ± 52.5 | 0.007 | 0.007 | 0.004 | 0.150 |
| Maximum lipid arc (°) | 245.5 ± 70.1 | 236.2 ± 78.2 | 210.2 ± 75.4 | 0.002 | 0.163 | 0.002 | 0.014 |
| Calcified ($n = 12$) | | | | | | | |
| MLA ($mm^2$) | 2.9 ± 1.4 | 3.3 ± 1.1 | 3.5 ± 1.2 | 0.256 | 0.049 | 0.220 | 0.614 |
| FCT (μm) | 59.8 ± 17.0 | 93.4 ± 51.4 | 155.2 ± 61.7 | <0.001 | 0.020 | <0.001 | 0.007 |
| Mean lipid arc (°) | 200.5 ± 50.2 | 185.9 ± 50.1 | 168.8 ± 51.8 | 0.018 | 0.077 | 0.023 | 0.025 |
| Maximum lipid arc (°) | 270.8 ± 60.6 | 238.4 ± 71.1 | 222.9 ± 71.2 | 0.054 | 0.123 | 0.012 | 0.499 |
| Noncalcified ($n = 46$) | | | | | | | |
| MLA ($mm^2$) | 3.4 ± 1.7 | 3.8 ± 2.1 | 3.6 ± 1.7 | 0.052 | 0.017 | 0.323 | 0.147 |
| FCT (μm) | 60.0 ± 17.2 | 125.5 ± 62.1 | 161.0 ± 80.5 | <0.001 | <0.001 | <0.001 | <0.001 |
| Mean lipid arc (°) | 163.4 ± 52.4 | 152.4 ± 49.5 | 137.1 ± 57.2 | <0.001 | 0.062 | <0.001 | 0.008 |
| Maximum lipid arc (°) | 229.9 ± 70.8 | 216.5 ± 67.9 | 185.3 ± 69.9 | <0.001 | 0.075 | <0.001 | <0.001 |

Continuous variables are expressed as the mean ± SD; Categorical variables are expressed as number (percentage); $P < .05$ was considered significant. Abbreviations: FCT, fibrous cap thickness; 6M, 6 months; 12M, 12 months; BL, baseline; MLA, minimum lumen area ($mm^2$); SD, standard deviation.

in the three groups (Table 4). The change patterns of OCT findings between moderate and intensive statin therapy were similar in the three groups. A continuous increase in FCT from baseline to 12 months was observed in the three groups (Supporting Information Tables 3 and 4). The absolute change of FCT at 12 months in the three groups according to statin dose is shown in Figure 4. Intensive statin therapy induced a significant increase in FCT at 12 months compared to moderate statin therapy in the spotty calcification group ($P = 0.034$).

The representative OCT images are shown in Figure 5. There was a significant difference in the presence of cholesterol crystals in spotty calcification compared to noncalcified group at the 6 and 12 months follow-ups ($P = 0.042$ and $P = 0.042$, respectively) (Table 5).

## 4 | DISCUSSION

This is the first study to evaluate the response of nonculprit lipid-rich plaques containing spotty calcification under statin therapy. The major findings of the present study are as follows: First, FCT, as primary determinant of plaque vulnerability, increased continuously over time in the three groups irrespective of the presence of spotty calcification. Furthermore, intensive statin therapy was more effective for increasing FCT in plaques containing spotty calcification. Second, patients with plaques containing spotty calcification were older and had a greater prevalence of hypertension.

In the present study, statin therapy was associated with a significant increase in FCT and smaller lipid arc at 12 months compared to baseline in the three groups. FCT is considered the most important determinant for plaque vulnerability and can be evaluated by OCT [13,18]. Using OCT, a recent prospective, randomized study (EASY-FIT) demonstrated a greater increase of FCT and the stabilization of lipid-rich plaques with higher dose of atorvastatin (20 vs. 5 mg/day) in a Japanese population. The effect of statin therapy on coronary plaques was also shown in a retrospective study, which reported the ability of statin therapy to increase FCT in nonculprit lesions of patients with acute coronary syndrome after 9 months [19,20]. This effect was evident in our study: fibrous cap thickness in plaques with spotty calcification, calcification and noncalcified increased after 12 months of statin therapy. In our study, we evaluated nonculprit lipid-rich plaques, and statin therapy effectively increased FCT and reduced the lipid arc in the three groups. Spotty calcification has recently been introduced as a marker of high-risk plaque and plaque progression [21]. Conventionally, we may think that plaques containing spotty calcification might not respond to statin therapy. However, the spotty calcification group benefitted from statin therapy, and plaque stability was achieved in our study. Three different statin regimes of intensive (AT60) and moderate (AT 20 or RT 10) statin therapies were used in the present study in a Chinese population. Intensive statin therapy was more effective in

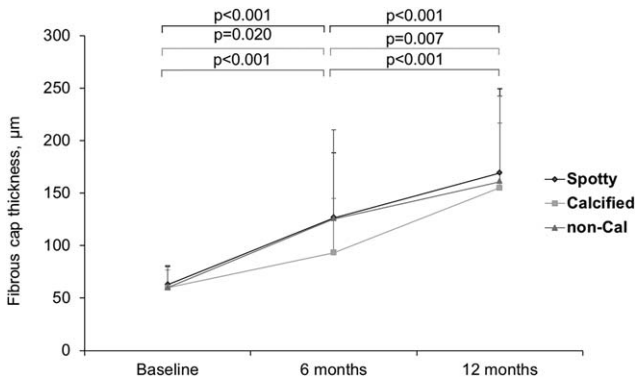


**FIGURE 3** Dynamic changes in fibrous cap thickness in the three groups. Fibrous cap thickness significantly increased from baseline to 6 and 12 months in the three groups. Spotty, spotty calcification; non-Cal, noncalcified

**TABLE 4** Optical coherence tomography findings: absolute and percentage change in fibrous cap thickness and lipid arc

| Variables | Spotty calcification ($n$ = 38) | Calcified ($n$ = 12) | Noncalcified ($n$ = 46) | $P$ value |
|---|---|---|---|---|
| At baseline | | | | |
| MLA ($mm^2$) | 3.2 ± 1.4 | 2.9 ± 1.4 | 3.4 ± 1.7 | 0.565 |
| FCT (μm) | 59.8 ± 17.0 | 62.8 ± 20.9 | 60.0 ± 17.2 | 0.774 |
| Mean lipid arc (°) | 200.5 ± 50.2 | 180.5 ± 48.4 | 163.4 ± 52.4 | 0.057 |
| Maximum lipid arc (°) | 270.8 ± 60.6 | 245.5 ± 70.1 | 229.9 ± 70.8 | 0.177 |
| Lipid length (μm) | 13.1 ± 5.99 | 9.0 ± 3.9 | 9.8 ± 4.7 | 0.030 |
| Change from baseline to 6 months | | | | |
| FCT (μm) | 63.7 ± 81.9 | 35.5 ± 43.1 | 66.4 ± 59.5 | 0.397 |
| Mean lipid arc (°) | −10.5 ± 32.8 | −33.3 ± 67.5 | −16.9 ± 47.4 | 0.333 |
| Maximum lipid arc (°) | −9.2 ± 45.4 | −32.9 ± 61.2 | −14.4 ± 45.9 | 0.378 |
| Percentage change from baseline to 6 months | | | | |
| FCT (%) | 108.8 ± 149.6 | 56.8 ± 64.4 | 119.2 ± 111.1 | 0.336 |
| Mean lipid arc (%) | −5.4 ± 21.7 | −15.2 ± 29.5 | −7.8 ± 25.1 | 0.504 |
| Maximum lipid arc (%) | −2.4 ± 25.1 | −11.6 ± 19.0 | −4.4 ± 22.1 | 0.538 |
| Change from baseline to 12 months | | | | |
| FCT (μm) | 106.2 ± 77.1 | 93.6 ± 49.4 | 101.7 ± 77.7 | 0.883 |
| Mean lipid arc (°) | −19.6 ± 36.5 | −22.2 ± 35.9 | −27.8 ± 35.5 | 0.601 |
| Maximum lipid arc (°) | −30.7 ± 55.5 | −42.1 ± 44.3 | −42.9 ± 47.4 | 0.549 |
| Percentage change from baseline to 12 months | | | | |
| FCT (%) | 185.4 ± 153.5 | 148.9 ± 65.4 | 180.7 ± 142.6 | 0.749 |
| Mean lipid arc (%) | −9.9 ± 20.11 | −10.8 ± 17.1 | −16.9 ± 19.7 | 0.273 |
| Maximum lipid arc (%) | −11.4 ± 24.5 | −13.3 ± 15.9 | −17.7 ± 19.8 | 0.414 |
| Change from 6 to 12 months | | | | |
| FCT(μm) | 39.8 ± 59.8 | 56.0 ± 51.3 | 32.1 ± 50.5 | 0.445 |
| Mean lipid arc (°) | −8.6 ± 33.9 | 8.4 ± 65.5 | −11.3 ± 44.2 | 0.464 |
| Maximum lipid arc (°) | −19.5 ± 44.2 | −8.2 ± 32.5 | −28.8 ± 41.9 | 0.371 |
| Percentage change from 6 to 12 months | | | | |
| FCT (%) | 54.1 ± 78.4 | 71.4 ± 70.1 | 32.9 ± 44.5 | 0.136 |
| Mean lipid arc (%) | −1.9 ± 20.1 | −7.5 ± 6.7 | −9.7 ± 21.8 | 0.257 |
| Maximum lipid arc (%) | −6.8 ± 18.9 | −2.9 ± 16.7 | −12.2 ± 19.6 | 0.303 |

Continuous variables are expressed as the mean ± SD; categorical variables are expressed as number (percentage); $P < .05$ was considered significant.
Abbreviations: FCT, fibrous cap thickness; MLA, minimum lumen area; SD, standard deviation.

increasing FCT than moderate statin therapy in plaques containing spotty calcification at the 12-month follow-up (Figure 4). Several patterns of calcification have been described to have different impacts on plaque stability. Spotty calcification has been shown to be involved in plaque vulnerability and play a key role in plaque stability supported by previous IVUS and OCT studies [22,23]. These observations may explain the difference observed between intensive and moderate statin therapy for increasing FCT in plaques containing spotty calcification. Calcifications are reported to support plaque stability [22]. Both statin therapy dosage increased FCT in plaques containing calcification. These findings might contribute to important therapeutic target, which requires a statin to stabilize lesions and potentially lead to the understanding of OCT features in patients with ACS.

Previous studies described spotty calcifications as a feature of high-risk plaques [23,24]. Using IVUS, Ehara et al. reported that the culprit lesions of patients with ACS were mostly specified by presence of spotty calcium associated with fibro-fatty plaques, while the culprit lesions were extensively calcified [6]. Fuji et al. discovered that ruptured plaques are associated with a larger number of calcium deposits within an arc of <90 degrees, a larger number of deep calcium deposits, and a remodeling index [25]. In the study, the term "spotty" refers to calcium deposits that are limited in size, whereas an IVUS study expanded the terms slightly by referring to small calcium deposits within the arc of <90°; we employed this definition in the present study [6,25]. Various studies have evaluated the relationship between different calcification patterns and plaque characteristics. However, no study has assessed the relationship between spotty calcification and plaque progression in nonculprit lipid-rich plaque after 12 months of statin therapy, using OCT, which is a high resolution imaging technique that could make our detection more accurate compared to previously used modalities.

Spotty calcification has been shown to be related to more unstable clinical presentation [6]. In our study, patients with spotty calcification at discharge used more nitrates, and it was assumed that patients had some clinical symptoms such as chest pain. Considering that there was a positive relationship between patients with acute myocardial infarction and spotty calcification in previous studies [25], we think that the clinical symptoms were caused by other mechanisms since the statin

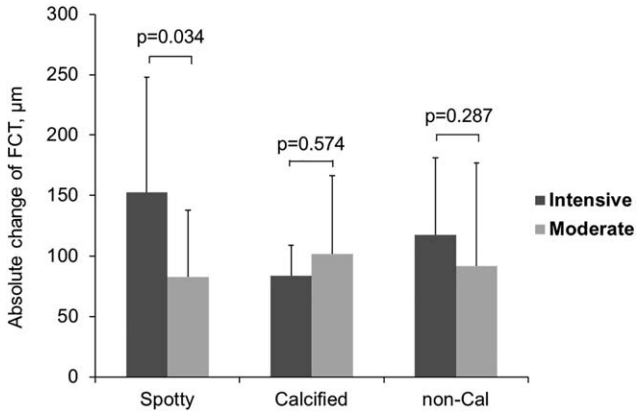


**FIGURE 4** Absolute change of FCT in the three groups from baseline to 12 months according to statin dose. In spotty calcification group, intensive statin treatment induced a significant increase in FCT at 12 months compared to moderate statin treatment ($P = 0.034$). In both the calcified and noncalcified groups, the increase in FCT was comparable at 12 months with intensive compared to moderate statin treatment. FCT, fibrous cap thickness; Spotty, spotty calcification; non-Cal, noncalcified; Intensive, intensive dose of statin; Moderate, moderate dose of statin

therapy strategy was able to reduce the lipid core and increase FCT. Detailing patients' clinical symptoms may be important for explaining the mechanical role of spotty calcification in clinical outcomes and is highly suggested for treatment. We admit that statin stabilizes the plaques containing spotty calcification; however, patients with spotty calcification may benefit from additional treatment. The risk factor of old age and history of hypertension observed in our patients in the spotty calcification group is in line with previous studies [7,26].

Spotty calcification has been demonstrated to be an active stage of atherosclerosis associated with inflammation [27]. Additionally, a positive feedback loop further stimulates macrophage activation, and prominent mineralization develops small calcification [3,4]. Thus, as macrophage apoptosis results in the release of cellular components and lipids that form necrotic cores, rendering the plaques vulnerable to rupture [28,29], and macrophage-triggered calcification would possibly cause plaque vulnerability. In the present study, spotty calcification was associated with the presence of macrophage at baseline, although OCT may not be the best imaging modality for the verification of macrophage. The presence of macrophages changed over time between the three groups.

The present study had several limitations. First, this was a post hoc, sub-analysis of a randomized study, and the study population was small. Second, due to the practical difficulties of OCT pullback length, some nonculprit lesions located in the distal segments were missed. Third, selection of the exact same site for FCT measurement was challenging at follow-up studies. However, all the identified markers were used to identify the same location. Fourth, according to OCT

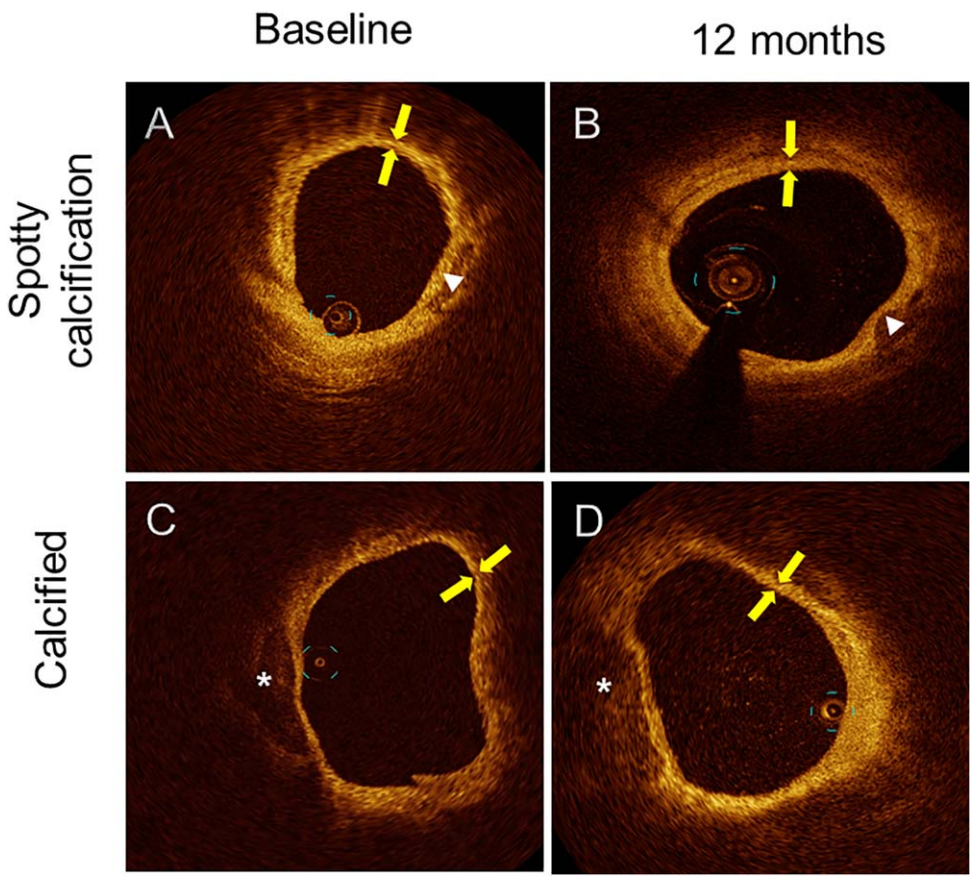


**FIGURE 5** The representative images of plaque containing spotty calcification (arrow head), calcified (*). The corresponding OCT imaging showed an increase in FCT (arrows) from baseline to 12 months in the spotty calcification (AB) and calcified (CD) groups

**TABLE 5** Qualitative optical coherence tomography findings

| Variables | Spotty ($n$ = 38) | Calcified ($n$ = 12) | Noncalcified ($n$ = 46) | *P* value | | | |
|---|---|---|---|---|---|---|---|
| | | | | All | Spotty vs. Cal | Cal vs. non-Cal | Spotty vs. non-Cal |
| Baseline | | | | | | | |
| Thrombus | 3 (7.9%) | 0 (0.0%) | 3 (6.5%) | 0.612 | 0.430 | 0.492 | 0.567 |
| TCFA | 24 (63.2%) | 8 (66.7%) | 30 (65.2%) | 0.968 | 0.556 | 0.605 | 0.845 |
| Macrophage | 35 (92.1%) | 8 (66.7%) | 27 (58.7%) | 0.002 | 0.048 | 0.438 | 0.001 |
| Microchannel | 21 (55.3%) | 7 (58.3%) | 16 (34.8%) | 0.112 | 0.852 | 0.125 | 0.060 |
| Cholesterol crystal | 11 (28.9%) | 3 (25.0%) | 9 (19.6%) | 0.602 | 0.552 | 0.475 | 0.315 |
| 6-month follow-up | | | | | | | |
| Thrombus | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | | | | |
| TCFA | 8 (21.1%) | 3 (27.3%) | 15 (34.1%) | 0.422 | 0.473 | 0.482 | 0.190 |
| Macrophage | 29 (76.3%) | 8 (66.7%) | 24 (52.2%) | 0.071 | 0.376 | 0.286 | 0.022 |
| Microchannel | 17 (44.8) | 4 (36.5) | 12 (26.7%) | 0.227 | 0.445 | 0.348 | 0.068 |
| Cholesterol crystal | 7 (18.4%) | 0 (0.0%) | 2 (4.3%) | 0.044 | 0.126 | 0.626 | 0.042 |
| 12-month follow-up | | | | | | | |
| Thrombus | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | | | | |
| TCFA | 5 (13.5%) | 2 (18.2%) | 5 (11.1%) | 0.813 | 0.513 | 0.418 | 0.500 |
| Macrophage | 26 (70.3%) | 7 (63.6%) | 23 (51.1%) | 0.205 | 0.471 | 0.455 | 0.078 |
| Microchannel | 10 (28.6%) | 5 (55.6%) | 10 (24.4%) | 0.176 | 0.130 | 0.077 | 0.680 |
| Cholesterol crystal | 7 (18.9%) | 0 (0.0%) | 2 (4.3%) | 0.044 | 0.126 | 0.626 | 0.042 |

Continuous variables are expressed as the mean ± SD; categorical variables are expressed as number (percentage); $P < .05$ was considered significant.
Abbreviations: Cal, calcified; non-Cal, noncalcified; SD, standard deviation; Spotty, spotty calcification; TCFA, thin-cap fibroatheroma.

definitions, TCFA was defined as LRPs with FCTs ≤ 65 μm. Macrophage accumulation was defined as signal-rich, distinct regions that exceeded the intensity of background shadow. Due to the limitation of the current OCT imaging system, some fibrous plaques might have been misdiagnosed as TCFA in the presence of macrophage accumulation on the surface of fibrous atherosclerotic plaque. Fifth, the relationship between spotty calcification and clinical outcomes is still unknown because of the small sample size and relatively short follow-up duration. Further studies with long-term follow-up and a large population are needed to test the clinical impact of increased FCT derived from lipid-lowering therapy.

## 5 | CONCLUSIONS

Statin therapy was equivalently effective on plaque stabilization in plaques with and without spotty calcification. Patients with spotty calcification benefitted more from intensive statin therapy than from moderate statin therapy. Intensive statin therapy may be important in plaques with spotty calcification.

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## SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article.

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