Spotty Calcification as a Marker of Accelerated Progression of Coronary Atherosclerosis

Insights From Serial Intravascular Ultrasound

Yu Kataoka, MD, Kathy Wolski, MPH, Kiyoko Uno, MD, Phip, Rishi Puri, MBBS, E. Murat Tuzcu, MD, Steven E. Nissen, MD, Stephen J. Nicholls, MBBS, Phip

Cleveland, Ohio

Objectives

The purpose of this study was to determine atheroma progression in patients with spotty calcification.

Background

Although extensively calcified atherosclerotic lesions have been proposed to be clinically quiescent, the presence of spotty calcification within plaque has been reported to be associated with an increased incidence of ischemic cardiovascular events. The relationship between spotty calcification and disease progression has not been investigated.

Methods

A total of 1,347 stable patients with angiographic coronary artery disease underwent serial evaluation of atheroma burden with intravascular ultrasound imaging. Patients with spotty calcification were identified based on the presence of lesions (1 to 4 mm in length) containing an arc of calcification of < 90°. Clinical characteristics and disease progression were compared between patients with spotty calcification (n = 922) and those with no calcification (n = 425).

Results

Patients with spotty calcification were older (age 56 years vs. 54 years; \( p = 0.001 \)), more likely to be male (68% vs. 54%; \( p = 0.01 \)), and have a history of diabetes mellitus (30% vs. 24%; \( p = 0.01 \)) and myocardial infarction (28% vs. 20%; \( p = 0.004 \)), and have lower on-treatment high-density lipoprotein cholesterol levels (48 ± 16 mg/dl vs. 51 ± 17 mg/dl; \( p = 0.001 \)). Patients with spotty calcification demonstrated a greater percent atheroma volume (PAV) (36.0 ± 7.6% vs. 29.0 ± 8.5%; \( p < 0.001 \)) and total atheroma volume (174.6 ± 71.9 mm³ vs. 133.9 ± 64.9 mm³; \( p < 0.001 \)). On serial evaluation, spotty calcification was associated with greater progression of PAV (+0.43 ± 0.07% vs. +0.02 ± 0.11%; \( p = 0.002 \)). Although intensive low-density lipoprotein cholesterol and blood pressure lowering therapy slowed disease progression, these efficacies were attenuated in patients with spotty calcification.

Conclusions

The presence of spotty calcification is associated with more extensive and diffuse coronary atherosclerosis and accelerated disease progression despite use of medical therapies. (J Am Coll Cardiol 2012;59:1592–7)

Calcification is a common finding in coronary arteries and has long been known to occur as a part of the atherosclerotic process (1). Traditionally, calcified plaque has been consid-
the presence of spotty calcification may influence not only plaque vulnerability but also atheroma progression. However, the natural history of atheroma burden in the setting of spotty calcified lesion remains to be fully characterized.

IVUS permits quantification of atheroma burden and imaging of coronary calcium with good histological correlation (9). IVUS has also enhanced the understanding of the factors that influence atheroma progression and its response to use of medical therapies (10–16). The present study investigated the extent and serial change of coronary atherosclerosis in patients with spotty calcification using antiatherosclerotic pharmacological therapies.

Methods

Study population. From the pooled data of 7 prospective atherosclerosis progression and/or regression IVUS trials, including 3,479 stable patients with established coronary artery disease (CAD), we selected 1,347 patients with spotty calcification only or without any calcium. Spotty calcification was defined as the presence of lesions 1 to 4 mm in length containing an arc of calcification of <90° (4). In the present analysis, we excluded patients who had extensive calcification only with an arc of calcification of ≥90° (n = 238) and patients with both extensive and spotty calcification (n = 1,469). These 7 studies were the REVERSAL (Reversal of Atherosclerosis With Aggressive Lipid Lowering) study (10), the CAMELOT (Comparison of Amlodipine Versus Enalapril to Limit Occurrences of Thrombosis) study (11), the ACTIVATE (Acylation: Cholesterol Acyltransferase Intravascular Atherosclerosis Treatment Evaluation) study (12), the ASTEROID (A Study to Evaluate the Effect of Rosuvastatin on Intravascular Ultrasound-Derived Coronary Atheroma Burden) trial (13), the ILLUSTRATE (Investigation of Lipid Level Management Using Coronary Ultrasound to Assess Reduction of Atherosclerosis by Cholesteryl Ester Transfer Protein Inhibition and High-Density Lipoprotein Elevation) study (14), the PERISCOPE (Efficacy Study of Pioglitazone Compared to Glimepiride on Coronary Atherosclerotic Disease Progression in Subjects With Type 2 Diabetes Mellitus) trial (15), and the STRADIVARIUS (Effect of Rimonabant on Progression of Atherosclerosis in Patients With Abdominal Obesity and Coronary Artery Disease) study (16). All patients were required to have CAD, which was defined as having at least 1 lumen narrowing >20% in a major epicardial coronary artery on a diagnostic coronary angiogram performed for clinical indication. Each study was approved by the institutional review boards of the participating clinical trial sites, and all participants in the trials provided informed written consent before enrollment.

Acquisition and analysis of IVUS images. The acquisition and analysis of ultrasonic images were previously described in detail (10–16). In brief, after anticoagulation therapy and administration of intracoronary nitroglycerin, an IVUS catheter (30 to 40 MHz) was inserted distally within the coronary artery. The target vessel for imaging was required to have a segment of at least 30 mm in length without lumen narrowing of >50%, a history of revascularization, and was not considered to be the culprit vessel for a previous myocardial infarction. Continuous ultrasonic imaging was acquired at a constant rate of 0.5 mm/s. Images were digitized for analysis in a single core laboratory by persons who were blinded to the clinical characteristics and treatment status of the patients. The matching arterial segment was defined from the images acquired at baseline and follow-up studies on the basis of the anatomic location of proximal and distal side branches (fiduciary points). Images spaced precisely 1 mm apart in the segment of interest were selected for analysis.

The plaque area was defined as the difference in area occupied by the lumen and external elastic membrane (EEM) borders. The total atheroma volume (TAV) was calculated by summation of the plaque area calculated for each measured image and subsequently normalized to account for differences in segment length between subjects. The percent atheroma volume (PAV) was calculated as the proportion of vessel wall volume occupied by atherosclerotic plaque: PAV (%) = [(ΣEEM_area − ΣLUMEN_area)/ΣEEM_area] × 100.

Volumes occupied by the lumen and EEM were similarly calculated by summation of their respective areas in each measured image and subsequently normalized to account for differences in segment length between subjects. The remodeling index at the most diseased site was calculated as the ratio of the EEM area at the diseased site compared with the least diseased site within the proximal 10 mm.

Statistical analysis. Continuous variables are expressed as mean ± SD or median, and categorical variables as percentages. The chi-square test was used to test for differences in categorical variables between groups, and continuous data were compared using unpaired t-tests, or Mann-Whitney log rank tests when the variable was not normally distributed. Serial change from baseline in atheroma burden and vessel dimensions was examined using analysis of covariance (ANCOVA), with the baseline value as a covariate and grouping variable (spotty calcium or no calcium) as a factor. Characteristics at baseline with an imbalance between groups were also included in an ANCOVA model. Results
are expressed as least significant mean ± SE. A p value <0.05 was considered significant. All statistical analyses were performed using SAS software, version 9.1.3 (SAS Institute, Cary, North Carolina).

Results

Clinical demographics in patients with spotty calcification. Spotty calcification was observed in 922 patients (27%), whereas 425 patients (12%) did not have any calcification evident on imaging. Baseline clinical characteristics and the use of antiatherosclerotic drugs are summarized in Table 1. Patients with spotty calcification were older, more likely to be male, have a history of diabetes mellitus, and previous myocardial infarction. These patients were also more likely to be treated with statins at baseline, whereas other medication use was similar between the 2 groups. Patients with spotty calcification had lower total cholesterol and high-density lipoprotein (HDL) cholesterol levels.

Baseline atheroma burden and vessel dimensions. The extent of atheroma burden at baseline is summarized in Table 2. Patients with spotty calcification had more atheromatous plaque, reflected by a higher PAV (36.0 ± 7.6% vs. 29.0 ± 8.5%; p < 0.001), TAV (174.6 ± 71.9 mm³ vs. 133.9 ± 64.9 mm³; p < 0.001), and percentage of images that contained plaque (68.5% vs. 43.4%; p < 0.001). The remodeling ratio at the site that contained the greatest amount of plaque was similar between the 2 groups. Vessel wall dimensions were summarized in Table 2. Patients with spotty calcification had larger vessels, demonstrated by a larger EEM (483.8 ± 167.1 mm³ vs. 455.8 ± 156.1 mm³; p = 0.004), but smaller lumen volume (309.2 ± 112.9 mm³ vs. 321.9 ± 112.8 mm³; p = 0.04), consistent with more extensive atherosclerosis.

Risk factor control. The use of antiatherosclerotic drugs and the degree of risk factor control at follow-up are summarized in Table 3. Beta-blockers were more likely to be used in patients with spotty calcification, although this difference failed to meet statistical significance. On therapy, patients with spotty calcification had significantly lower total cholesterol and HDL cholesterol levels. The groups did not differ with regard to the degree of other risk factor controls.

Serial change in plaque progression. The relationship between spotty calcification and plaque progression is summarized in Table 4. After controlling for baseline atheroma burden, patients with spotty calcification exhibited greater atheroma progression than patients without calcification.

<table>
<thead>
<tr>
<th>Table 2</th>
<th>Baseline Atheroma Burden</th>
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<tr>
<td><strong>No Calcium</strong> (n = 425)</td>
<td><strong>Spotty Calcium</strong> (n = 922)</td>
</tr>
<tr>
<td>Percent atheroma volume (%)</td>
<td>29.0 ± 8.5</td>
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<tr>
<td>Total atheroma volume (mm³)</td>
<td>133.9 ± 64.8</td>
</tr>
<tr>
<td>Lumen volume (mm³)</td>
<td>321.9 ± 112.7</td>
</tr>
<tr>
<td>EEM volume (mm³)</td>
<td>455.8 ± 156.0</td>
</tr>
<tr>
<td>Percentage of images containing plaque (%)</td>
<td>43.4</td>
</tr>
</tbody>
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<tr>
<th>Table 3</th>
<th>On-Treatment Medications and Risk Factor Control</th>
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</thead>
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<tr>
<td><strong>Concomitant medications</strong></td>
<td><strong>No Calcium</strong> (n = 425)</td>
</tr>
<tr>
<td>Statin use (%)</td>
<td>95.5</td>
</tr>
<tr>
<td>Beta-blocker use (%)</td>
<td>69.2</td>
</tr>
<tr>
<td>Aspirin use (%)</td>
<td>91.3</td>
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<tr>
<td>ACE inhibitor use (%)</td>
<td>50.1</td>
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Values are %, mean ± SD, or median (interquartile range).

Abbreviations as in Table 1.
demonstrated by a greater change in PAV (0.43 ± 0.07% vs. 0.02 ± 0.11%; p = 0.002). Furthermore, an ANCOVA model, including terms for baseline PAV, age, gender, diabetes mellitus, baseline low-density lipoprotein (LDL) cholesterol and HDL cholesterol levels, statin use and baseline atheroma burden, did not change the results, reflected by still greater progression of PAV in patients with spotty calcification (change in PAV: 0.68 ± 0.12% vs. 0.05 ± 0.17%; p = 0.002) (Table 4). No difference was observed with regard to changes in TAV (−0.77 ± 0.42 mm³ vs. −1.56 ± 0.62 mm³; p = 0.29), EEM (−6.73 ± 0.87 mm³ vs. −6.90 ± 1.28 mm³; p = 0.911), and lumen volume (−5.89 ± 0.71 mm³ vs. −5.49 ± 1.05 mm³; p = 0.76). The remodeling index at follow-up was lower in patients with spotty calcification (0.92 ± 0.19 vs. 0.95 ± 0.20; p = 0.02). This was consistent with the finding that patients with spotty calcification were more likely to show constrictive remodeling (55.1% vs. 49.5%; p = 0.04). Assigned treatment and measures of atheroma burden in each of the IVUS clinical trials are summarized in Table 5. There were no significant differences in assigned medical therapies of each trial between patients with and without spotty calcification. Patients with spotty calcification in each trial consistently exhibited a higher baseline PAV. In addition, a similar trend with greater progression of PAV was observed in these patients (Table 5).

The impact of intensive LDL cholesterol and blood pressure lowering therapy on coronary atherosclerosis was also investigated (Fig. 1). Intensive lowering of LDL cholesterol to <70 mg/dl had a beneficial impact on progression of PAV in both patients with spotty calcification (0.05 ± 0.13% vs. 0.57 ± 0.08%; p = 0.03) and patients without calcification (−0.49 ± 0.20% vs. 0.23 ± 0.12%; p = 0.01) (Fig. 1, left panel). However, patients without calcification were more likely to slow disease progression than patients with spotty calcification. With regard to achieving a systolic blood pressure level <130 mm Hg, a similar trend was observed in change in PAV at follow-up (Fig. 1, right panel).

Discussion

The present study shows that spotty calcification is related to a presence of greater atheromatous plaque and more disease progression. Although intensive control of LDL cholesterol and blood pressure slow plaque progression, this benefit was attenuated in patients with spotty calcification.
Our findings highlight the need for stricter risk factor control for the prevention of disease progression in these patients.

Considerable interest has focused on composition and morphological characteristics of individual atherosclerotic plaques, which are proposed to be related to plaque vulnerability. In postmortem studies, plaque ruptures and thin-capped atheromas, considered to represent vulnerable plaques, contain small calcium deposits (17,18). Recent studies also demonstrated that spotty calcification was frequently observed in the culprit atherosclerotic lesions associated with acute coronary syndrome (4,5). Thus, evidence has been accumulating that spotty calcification is closely related to vulnerable plaque. However, this calcium pattern has been evaluated only after the occurrence of acute coronary events in these studies, and it remains to be determined whether they are prevalent and how disease behaves in spotty calcified atheromas at nonculprit lesions in stable patients. The present analysis demonstrated that spotty calcification was observed in 27% of stable patients, and these lesions had larger atheromatous plaque volume with greater disease progression despite use of antiatherosclerotic medical therapies.

The finding that the presence of calcium is associated with greater atheroma burden is consistent with previous reports of a correlation between the amount of plaque and calcium in pathological studies and in small cohort studies by IVUS (19,20). Although calcified atherosclerotic lesions have been viewed conventionally as an advanced, stable, and quiet atherosclerotic form, spotty calcified lesions identify patients with more extensive and diffuse plaque. Plaque calcification represents a dynamic process that is related to oxidized lipids and inflammatory activity (6–8). At early-stage atherosclerosis, oxidized lipids, lipoproteins, and various inflammatory cytokines elaborated during atherogenesis stimulate the expression and activity of osteoblast-like cells within the arterial wall, resulting in the development of calcium deposit (6–8). Some in vitro and in vivo studies reported that macrophage and tumor necrosis factor-alpha preceded osteogenic activity and promoted plaque calcification (21,22). Considering that the process of plaque calcification is triggered by lipid oxidation and inflammatory response, spotty calcified plaque may contain more lipid and inflammatory materials than noncalcified lesions, and therefore, is likely to undergo greater atheroma progression. This calcium pattern does not seem to be degenerative, but reflects an active state that has extensive plaque volume and accelerated progression.

In the present study, constrictive remodeling was more commonly observed in patients with spotty calcification. The development of calcification has been considered an osteogenic process associated with inflammatory reactions (21,22). Therefore, this process may induce osteogenic differentiation and mineralization of vascular smooth muscle cell, resulting in the impaired vascular remodeling.

The benefits of LDL cholesterol and blood pressure lowering therapies on atheroma progression were diminished in patients with spotty calcification. Because calcium deposits are heavily infiltrated by macrophages, oxidized lipids, and inflammatory cytokines (21,22), stricter risk control may be needed for the prevention of disease progression in these patients. Our results have potential implications for the prediction of which patients are likely to derive benefit from aggressive risk factor intervention.
Study limitations. A number of caveats should be noted. This is an analysis of pooled data from 7 clinical IVUS trials to monitor atheroma progression. However, all images were analyzed in the same core laboratory using well-validated and standardized techniques. The ability to pool data from a number of clinical trials provided a database of a large number of patients with serial IVUS evaluation of plaque burden. Although our analysis reflects the relationship between spotty calcification and disease progression in patients with CAD, the resultant impact on clinical outcome remains to be determined. IVUS is limited in its ability to characterize plaque composition. Therefore, the plaque composition of spotty calcified lesions and its modification under medical therapies require further characterization.

Conclusions

In summary, spotty calcification is an important pattern identifying patients with diffuse, extensive atherosclerosis and accelerated disease progression. Although intensive risk factor control therapies are effective to slow plaque progression, these efficacies were attenuated in patients with spotty calcification. Our findings underscore stricter global risk control for the prevention of plaque progression in these patients.

Acknowledgments

The authors are grateful for the technical expertise of the Intravascular Core Laboratory of the Cleveland Clinic.

Reprint requests and correspondence: Dr. Stephen J. Nicholls, Department of Cardiovascular Medicine, Heart & Vascular Institute, Cleveland Clinic, 9500 Euclid Avenue, Cleveland, Ohio 44195. E-mail: nichols1@ccf.org.

REFERENCES


Key Words: disease progression • intravascular ultrasound • spotty calcification.