Prevalence, Distribution, Predictors, and Outcomes of Patients With Calcified Nodules in Native Coronary Arteries

A 3-Vessel Intravascular Ultrasound Analysis From Providing Regional Observations to Study Predictors of Events in the Coronary Tree (PROSPECT)

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Background—Pathological studies suggest that calcified coronary nodules are a rare cause of thrombotic events. The frequency, distribution, predictors, and outcomes of calcified nodules have never been described.

Methods and Results—After successful stenting in 697 patients (167 female; median age, 58.1 years) with acute coronary syndromes, 3-vessel gray-scale and virtual histology intravascular ultrasound was performed in the proximal-mid segments of all 3 coronary arteries as part of a prospective, multicenter study. On the basis of recent histological validation, an independent core laboratory identified calcified nodules as distinct calcification with an irregular, protruding, and convex luminal surface. Patients were followed up for 3 years (median). Overall, 314 calcified nodules were detected in 250 of 1573 analyzable arteries (185 of 623 patients). Thus, the prevalence of calcified nodules was 17% per artery and 30% per patient. Two or more calcified nodules were detected in 48 coronary arteries (3%) in 76 patients (12%). The calcified nodules were located <40 mm from the ostium of the coronary artery in 85% of left anterior descending arteries and 86% of left circumflex arteries, whereas calcified nodules within the right coronary arteries were evenly and more distally distributed. Patients with calcified nodules were significantly older and had more plaque volume, more thick-cap fibroatheroma, but fewer nonculprit lesion major adverse events on follow-up.

Conclusions—Calcified nodules in untreated nonculprit coronary segments in patients with acute coronary syndromes were more prevalent than previously recognized. Although their distribution mirrored the origin of most thrombotic events, calcified nodules caused fewer major adverse events during 3 years of follow-up. (Circulation. 2012;126:537-545.)

Key Words: acute coronary syndrome ■ atherosclerosis ■ calcification, physiologic ■ cardiac imaging techniques

The majority of acute coronary syndrome (ACS) events are the result of sudden luminal thrombosis, with 55% to 60% due to plaque rupture, 30% to 35% caused by plaque erosion, and a small portion resulting from a calcified nodule, an eruptive, dense, calcified mass often having an irregular surface appearance. Intravascular ultrasound (IVUS) provides detailed qualitative and quantitative cross-sectional coronary imaging and has a high sensitivity and specificity for detecting intracoronary calcium. To assess calcified nodules in vivo, a validation study was done using coronary arteries from human autopsied hearts. IVUS detected calcification in 285 frames in 856 pathological slices in 29 coronary arteries (11 left anterior descending [LAD], 5 left circumflex [LCx], and 13 right coronary [RCA] arteries) in 18 autopsy hearts; 17 (6.0%) were calcified nodules, and 268 (94.0%) were nonnodular calcium by histopathology. Calcified nodules were irregular and protruding with a convex luminal surface. The present analysis uses the 3-vessel IVUS data from the Providing Regional Observations to Study Predictors of Events in the Coronary Tree (PROSPECT) study to determine the frequency, distribution, angiographic appearance, virtual histology (VH—
IVUS appearance, predictors, and outcomes of nonculprit calcified nodules in ACS patients.

Clinical Perspective on p 545

Methods

Study Population
PROSPECT was a multicenter, multimodality imaging study that was performed at 37 sites in the United States and Europe to prospectively identify nonculprit vulnerable plaque after treatment of all culprit lesions in patients presenting with ACS. The primary PROSPECT analysis was reported previously. Briefly, patients had all culprit lesions treated (typically without preintervention IVUS) followed by gray-scale and VH-IVUS imaging of the left main coronary artery and the proximal 6 to 8 cm of all epicardial arteries. Clinical follow-up occurred at 30 days, at 6 months, and then yearly for at least 2 years. The prespecified primary end point was the incidence of major adverse cardiovascular events (the composite of death from cardiac causes, cardiac arrest, myocardial infarction, or rehospitalization resulting from unstable or progressive angina according to the Braunwald Unstable Angina Classification and the Canadian Cardiovascular Society Angina Classification). The primary end point was adjudicated by a clinical events committee that had no knowledge of other patient data and that used original source documents. On the basis of follow-up angiography, major adverse cardiovascular events were further adjudicated as occurring at initially treated sites (culprit lesions) or at previously untreated coronary segments (nonculprit lesions). If follow-up angiography was not performed, the site associated with the event was classified as indeterminate. Patient demographics, coronary risk factors, follow-up visits, and all relevant information were retrieved from the study database. The Institutional Review Board at each institution approved the study, and subjects gave written informed consent.

Coronary Angiography and Subsequent Qualitative Angiographic Analysis
Coronary angiograms were performed in at least 2 orthogonal views after intracoronary nitroglycerin. All angiograms were analyzed at the Angiographic Core Laboratory of the Cardiovascular Research Foundation (New York, NY). Qualitative analysis included thrombus, calcification (moderate or severe), and haziness. The longitudinal extension of each of these morphologies was recorded in relation to the distance from the coronary ostium. Nonculprit lesions were prespecified in the protocol as ≥30% visual diameter stenosis. All 3 epicardial vessels and all ≥1.5-mm-diameter side branches were divided into 29 Coronary Artery Surgery Study (CASS) segments. Each CASS segment was then subdivided into 1.5-mm-long subsegments and analyzed.

Gray-Scale and VH-IVUS Image Acquisition
After successful stenting of the culprit lesions in the 697 patients enrolled in the study, 3-vessel IVUS was performed with a synthetic-aperture-array, 20-MHz, 3.2F catheter (Eagle Eye, Volcano Corp, Rancho Cordova, CA) after intracoronary nitroglycerin. The IVUS catheter was advanced distally; the guiding catheter was disengaged; and the IVUS catheter was pulled back to the aorto-ostial junction with an R-100 motorized catheter pullback system at 0.5 mm/s. Because the left main was usually imaged during both LAD and LCx pullbacks, the run with better left main image quality was chosen for analysis. During pullback, gray-scale IVUS was recorded, raw radiofrequency data were captured at the top of the R wave, and reconstruction of the color-coded map by a VH-IVUS data recorder was performed (In-Vision Gold, Volcano Corp). IVUS studies were archived onto CD-ROM or DVD for offline analysis.

Gray-Scale IVUS Analysis
Of the 697 enrolled patients, 660 cases with complete IVUS data were sent to the independent IVUS core laboratory (Cardiovascular Research Foundation) for quantitative and qualitative analyses with validated QCU-CMS (Medis, Leiden, the Netherlands) software for contouring. Initial screening identified 623 patients with gray-scale IVUS images suitable for inclusion in the present analysis. The reasons for exclusion were dark images, too much noise, too short a segment of catheter pullback, or sudden jumping or sticking of the catheter during automatic pullback. In each patient, calcified nodules were classified as single (1 solitary nodule in 1 patient) or multiple (≥2 nodules in a single vessel or at least 1 nodule in ≥2 vessels). The diagnosis of a calcified nodule required independent review and agreement by 2 authors (Y.X. and A.M.). Interobserver and interobserver variability was examined in a randomly selected number of lesions. Each observer assessed the lesion independently on 2 separate occasions, 3 months apart, with blinding for earlier analysis. Intraobserver and interobserver variability yielded good concordance for the diagnosis of calcium nodule (κ=0.83 and κ=0.80, respectively).

When a calcified nodule was identified, the proximal and distal reference segments (the most normal-looking cross sections—ie, maximum lumen with least amount of plaque—within 5 mm proximal or distal to the calcified nodule but before any side branch) were also identified and selected for analysis. Between the proximal and distal reference segments, the slice with the smallest lumen and greatest amount of plaque was chosen as the minimum lumen area (MLA) site. Quantitative analysis included external elastic membrane (EEM), lumen, and plaque plus media (calculated as EEM minus lumen) cross-sectional area (CSA) at the site of the calcium nodules MLA site, and proximal and distal reference segments. Plaque burden (PB) was calculated as follows: PB=plaque+media CSA/EEM CSA×100. The remodeling index at the calcified nodule site and at the MLA site was the EEM divided by the average of the proximal and distal reference EEM. Lumen area stenosis at the calcified nodule site and at the MLA site was defined as 1 minus MLA divided by the average reference lumen CSA. Calcium analysis included calcium location (superficial, mixed, or deep) and maximum arc of calcium.

VH-IVUS Analysis
Of the 623 qualified gray-scale IVUS images, 573 cases had VH data available for analysis. The reasons for unavailable VH-IVUS images were failure to capture VH-IVUS data, too much noise, or segmental loss of VH images. VH-IVUS plaque components were color-coded as dense calcium (white), necrotic core (red), fibrofatty (light green), or fibrous tissue (dark green) and reported as absolute CSA and percentages of total plaque CSA with the use of pcVH 2.1 software (Volcano Corp) and proprietary qVH software (developed and validated at the Cardiovascular Research Foundation). Volumes were calculated with the Simpson rule and reported as total volume and normalized area (volume divided by length). Each lesion was classified by VH-IVUS into 1 of the following 5 phenotypes: (1) VH thin-cap fibroatheroma (VH-TCFA); (2) thick-cap fibroatheroma (ThCFA), divided into noncalcified thick-cap fibroatheroma or calcified thick-cap fibroatheroma, depending on whether the necrotic core did or did not contain superficial dense calcium; (3) pathological intimal thickening; (4) fibrotic plaque; and (5) fibrocalcific plaque. Although a lesion could contain features of >1 phenotype, in PROSPECT, a hierarchy of lesion phenotype was prespecified such that any fibroatheroma (VH-TCFA or ThCFA) took precedence over any nonfibroatheroma and VH-TCFA took precedence over ThCFA. Typical gray-scale and VH-IVUS pictures of a calcified nodule are shown in Figure 1.

Coregistration Between Angiogram and IVUS
Gray-scale and VH-IVUS analyses were coregistered to the angiographic roadmap through the use of fiduciary side branches for alignment with interpolation as necessary to account for different length measurements. Nonculprit lesions responsible for late events were identified with the follow-up angiogram; then, the corresponding segments and subsegments were matched side by side to the baseline angiograms and gray-scale and VH-IVUS studies. This
methodology has been reported as part of the primary PROSPECT analysis.4

Statistical Analysis
Statistical analyses were performed with SAS software, version 9.1.3 (SAS Institute, Cary, NC). Continuous variables were presented as the mean±SD or medians and interquartile ranges (IQRs); comparisons were conducted by the Student t test or the Kruskal-Wallis test. For comparison between calcium nodule site and the adjacent MLA site, a model with generalized estimating equations approach was used to compensate for any potential cluster effect of multiple calcium nodules in the same vessels or in the same patients. The generalized estimating equations model was developed by use of a working correlation structure of compound symmetry and a 2-level nested cluster effect for patient and vessel within patient using the PROC GENMOD code in SAS; the results are presented as least-square means with 95% confidential intervals. Discrete variables were presented as percentages and relative frequencies; comparisons were conducted by χ² statistics or the Fisher exact test as appropriate. Intraobserver and interobserver variability for the diagnosis of calcium nodule was measured by the κ test of concordance. Three-year outcomes are displayed as time-to-event curves, summarized by use of Cox regression model and hazard ratios. The proportional hazard assumptions for nonculprit major adverse cardiovascular events were checked by use of the graphical and numeric methods of Lin et al8 and the Kolmogorov-type supremum test. The P value from the supremum test is 0.08, indicating that proportional hazard assumptions are not being violated. A value of P<0.05 was considered statistically significant.

Results
Frequency and Distribution of Calcified Nodules
Among 623 patients with 1573 vessels imaged and qualified for analysis (574 LAD, 480 LCx, and 519 RCA), a total of 314 calcified nodules were detected in 250 arteries in 185 patients. Among these, there were 108 LAD nodules in 95 patients, 78 LCx nodules in 73 patients, and 118 RCA nodules in 82 patients. In addition, there were calcified nodules in the left main coronary artery in 10 patients. Thus, the prevalence of at least 1 calcified nodule was 16% per artery (250 of 1573) and 30% per patient (185 of 623). Overall, 17% of LAD, 15% of LCx, and 16% of RCA contained at least 1 calcified nodule. Two or more calcified nodules were detected in 48 coronary arteries (3%) in 76 patients (12%). Among them, 22 patients had >1 nodule in a single vessel, and 52 patients had nodules in >1 vessel. Overall, 3% of LADs, 1% of LCxs, and 5% of RCAs were found to have multiple nodules.

Comparison of Patients With and Without Calcified Nodules
Baseline clinical characteristics comparing 185 patients with at least 1 calcified nodule and 438 patients without any calcified nodules are shown in Table 1. Patients with at least 1 calcified nodule were significantly older, were more likely to have had prior cardiac interventions, and had better cholesterol profiles as indicated by a higher serum high-density lipoprotein cholesterol level and lower ratio of total cholesterol to high-density lipoprotein. Surprisingly, the frequency of diabetes mellitus, hypertension, smoking, and familial coronary artery disease was statistically similar between the 2 groups. There were also no differences between the group with single nodules and the group

Figure 1. Representative intravascular ultrasound (IVUS) and virtual histology (VH–IVUS) images of a calcified nodule and its adjacent fibroatheroma. Calcified nodule had a convex and irregular (nonsmooth and lumpy) luminal surface (white arrow in the lower row) on IVUS and its corresponding VH–IVUS images (middle row). There was a VH thin-cap fibroatheroma (double white arrows in the middle row) proximal to the calcified nodule with mild plaque burden. Angiographically, no significant abnormality was detected (white arrow).
Table 1. Clinical Characteristics of Patients With at Least 1 Calcified Nodule Versus Patients Without Any Calcified Nodules

<table>
<thead>
<tr>
<th></th>
<th>Calcium Nodule</th>
<th>No Calcium Nodule</th>
<th>P</th>
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</thead>
<tbody>
<tr>
<td>Patients, n</td>
<td>185</td>
<td>438</td>
<td></td>
</tr>
<tr>
<td>Age (IQR), y</td>
<td>61.1 (53.2–69.1)</td>
<td>57.0 (49.2–66.0)</td>
<td>0.0003</td>
</tr>
<tr>
<td>Male sex, % (n/N)</td>
<td>80.0 (148/185)</td>
<td>75.8 (332/438)</td>
<td>0.25</td>
</tr>
<tr>
<td>STEMI &gt;24 h, % (n/N)</td>
<td>31.4 (58/185)</td>
<td>29.5 (129/438)</td>
<td>0.64</td>
</tr>
<tr>
<td>BMI (IQR), kg/m²</td>
<td>27.6 (24.6–31.9)</td>
<td>28.1 (25.2–31.2)</td>
<td>0.52</td>
</tr>
<tr>
<td>HTN requiring medication, % (n/N)</td>
<td>49.7 (91/183)</td>
<td>44.9 (195/434)</td>
<td>0.28</td>
</tr>
<tr>
<td>DM, % (n/N)</td>
<td>17.3 (22/185)</td>
<td>16.7 (73/436)</td>
<td>0.87</td>
</tr>
<tr>
<td>Metabolic syndrome, % (n/N)</td>
<td>48.1 (87/181)</td>
<td>47.5 (201/423)</td>
<td>0.90</td>
</tr>
<tr>
<td>Prior MI, % (n/N)</td>
<td>11.4 (21/185)</td>
<td>9.9 (43/434)</td>
<td>0.59</td>
</tr>
<tr>
<td>Prior PCI, % (n/N)</td>
<td>13.5 (25/185)</td>
<td>8.9 (39/437)</td>
<td>0.09</td>
</tr>
<tr>
<td>Framingham score (IQR)</td>
<td>7.0 (5.0–9.0)</td>
<td>7.0 (5.0–9.0)</td>
<td>0.82</td>
</tr>
<tr>
<td>Estimated CrCl &lt;60 mL/min, % (n/N)</td>
<td>11.5 (20/174)</td>
<td>8.7 (36/414)</td>
<td>0.29</td>
</tr>
<tr>
<td>HDL, mg/dL</td>
<td>38.8 (37.0–51.0)</td>
<td>38.6 (33.0–45.0)</td>
<td>0.02</td>
</tr>
<tr>
<td>TC/HDL-C ratio</td>
<td>4.0 (3.3–5.0)</td>
<td>4.5 (3.8–5.5)</td>
<td>0.002</td>
</tr>
<tr>
<td>CRP level, mg/dL</td>
<td>1.9 (0.9–4.3)</td>
<td>1.6 (0.8–3.8)</td>
<td>0.25</td>
</tr>
</tbody>
</table>

IQR indicates interquartile range; STEMI, ST-segment-elevation myocardial infarction; BMI, body mass index; HTN, hypertension; DM, diabetes mellitus; MI, myocardial infarction; PCI, percutaneous coronary intervention; CrCl, creatinine clearance; HDL, high-density lipoprotein; TC, total cholesterol; HDL-C, HDL cholesterol; and CRP, C-reactive protein.

With multiple calcified nodules in terms of baseline clinical characteristics (data not shown). In addition, there was no significant difference in the rate of calcium nodules per patient among the clinical sites that enrolled patients in PROSPECT.

Angiographic Appearance of Calcified Nodules

Overall, only 35 calcified nodules (11%) had evidence of angiographic moderate calcium, 3 (1%) had angiographic severe calcium, and 19 (6%) had the appearance of angiographic haziness (Figure 2). The remaining 257 calcified nodules (82%) appeared normal on angiography. Patients with calcified nodules had the same number of angiographically calcified lesions as patients without calcified nodules (data not shown).

Qualitative and Quantitative Gray-Scale IVUS Findings of Calcium Nodules

The arc of nodular calcium measured 33.5° (IQR, 32.2–34.8); 91% were superficial and 9% were mixed, but none were only deep (leading edge of calcium closer to the EEM than to the lumen).

In 33% of calcified nodules (105 of 314), there was a branch near the calcified nodule site (47 proximal and 58 distal). The distance between the calcified nodule site and the branch measured 3.0 mm (IQR, 2.9–3.2).

The EEM CSA, lumen CSA, and remodeling index at the calcified nodule site were significantly larger than at the MLA site (lumen CSA: 8.6 mm² [IQR, 8.1–9.0 mm²] versus 7.0 mm² [IQR, 6.6–7.4 mm²]; P<0.0001), and the PB was correspondingly less (46.5% [IQR, 45.1%–47.9%] versus 54.4% [IQR, 53.1%–55.7%]; P<0.0001), as was area stenosis (31.4% [IQR, 30.0%–32.8%] versus 41.6% [IQR, 40.0%–43.1%]; P<0.0001; Table 2). Of all the calcified nodules analyzed, only 12 (of 314) had an MLA <4 mm², and only 8 had an area stenosis >50%.

Overall, 37% (118 of 314) of the calcified nodules were located distal to the MLA site, 55% (172 of 314) were located proximal to the MLA site, and 8% (24 of 314) were at the MLA site. Table 3 shows the location of the calcified nodules relative to the MLA site in the LAD, LCx, and RCA, separately.

Overall, 85% (95 of 114) of the calcified nodules were located within the first 40 mm of the LAD: 28 (25%) within the first 10 mm of the LAD, 28 (25%) from 11 to 20 mm, 20 (18%) from 21 to 30 mm, and 19 (17%) from 31 to 40 mm. The axial distribution of calcified nodules was similar in the LCx: 40% in the first 10 mm, 19% from 11 to 20 mm, 12% from 21 to 30 mm, and 13% from 31 to 40 mm. Conversely, calcified nodules within the RCA were evenly and more distally distributed. This analysis is shown in Figure 3.

VH-IVUS Appearance of Calcified Nodules

Overall, 276 of 314 calcified nodules had VH data available for analysis. Among them, 116 calcified nodules were contained in lesions classified as a fibroatheroma on the basis of their VH-IVUS appearance using the prespecified hierarchy in which a fibroatheroma took precedence over a nonfibroatheroma and VH-TCFA took precedence over ThCFA. Of the 116 calcium nodule–containing lesions classified as a fibroatheroma, 106 were a calcified ThCFA, 5 were a noncalcified ThCFA, and 5 were a VH-TCFA. Among the 160 calcified nodules that were in lesions not classified as a fibroatheroma, 56% were within lesions that had characteristics of pathological intimal thickening, 40% in fibrotic plaque, and 4% in fibrocalcific plaque. In addition, 82 of 276 calcified nodules had a fibroatheroma within the adjacent segment that was predefined as 5 mm proximal or distal to the calcified node: 12 were VH-TCFA, 29 were noncalcified ThCFA, and 41 were calcified ThCFA.

Volumetric IVUS Comparison of Patients With Versus Without Calcified Nodules

The volumetric gray-scale and VH-IVUS analyses of the entire length of all 3 coronary arteries imaged per patient (summing the LM, LAD, LCx, and RCA) are shown in Table 4. Patients with at least 1 calcified nodule had a larger total 3-vessel volumetric PB on gray-scale IVUS and more ThCFA, necrotic core, and dense calcium on total 3-vessel volumetric VH-IVUS.

Follow-Up Clinical Outcomes

Independent predictors of nonculprit events on a patient level were calculated by including the predictors previously reported in the main PROSPECT article (insulin-treated diabetes mellitus, prior percutaneous coronary intervention, MLA <4 mm², VH-TCFA, and PB >70%) and forcing into the model both a propensity score generated by age, high-density lipoprotein, and ratio of total cholesterol to high-density lipoprotein cholesterol.
(the variables that were statistically significant in Table 1) and the presence of at least 1 calcified nodule per patient versus no calcified nodules. The presence of at least 1 calcified nodule per patient was an independent predictor of freedom from nonculprit events (Table 5).

As shown in Figure 4, there were consistently fewer nonculprit lesion major adverse cardiac events in the calcified nodule group compared with the noncalcified nodule group at the 1-, 2-, and 3-year follow-up. The 3-year cumulative nonculprit lesion major adverse cardiovascular event rates were 7.1% versus 14.2%. Overall, there was no death, cardiac arrest, or myocardial infarction in the calcified nodules group. In the entire PROSPECT study, there were 54 nonculprit events associated with baseline IVUS-imaged lesions, but only 4 were associated with a nonculprit lesion calcified nodule, and they had a VH-TCFA within the same analysis segment and (therefore) were classified as VH-TCFA.

**Discussion**

In the present study using the 3-vessel IVUS data from PROSPECT, we report the prevalence, distribution, predictors, and outcomes of coronary artery calcified nodules in vivo. The major findings of our analysis are as follows. First, nonculprit calcified nodules were not unusual in patients with ACS; 314 calcified nodules were detected in 1573 arteries in 623 patients. Second, the axial location of calcified nodules was similar to previous reports of the location of plaque rupture, VH-TCFA, and acute coronary thrombosis. Third, calcified nodules were more common in older individuals. Finally, calcified nodules were, surprisingly, associated with fewer events during the 3-year follow-up.

**Table 2. Quantitative Intravascular Ultrasound Analysis of Calcified Nodules Versus the Adjacent Minimum Lumen Area (MLA) Site**

<table>
<thead>
<tr>
<th>Variables</th>
<th>Calcified Nodule Site*</th>
<th>MLA Site*</th>
<th>P†</th>
</tr>
</thead>
<tbody>
<tr>
<td>EEM CSA, mm²</td>
<td>16.2 (15.4–17.0)</td>
<td>15.7 (14.9–16.5)</td>
<td>0.0119</td>
</tr>
<tr>
<td>Lumen CSA, mm²</td>
<td>8.6 (8.1–9.0)</td>
<td>7.0 (6.6–7.4)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Plaque plus media CSA, mm²</td>
<td>7.7 (7.2–8.1)</td>
<td>8.7 (8.2–9.2)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Plaque burden, %</td>
<td>46.5 (45.1–47.9)</td>
<td>54.4 (53.1–55.7)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Remodeling index</td>
<td>0.98 (0.97–0.99)</td>
<td>0.96 (0.95–0.97)</td>
<td>0.0153</td>
</tr>
<tr>
<td>Area stenosis, %</td>
<td>31.4 (30.0–32.8)</td>
<td>41.6 (40.0–43.1)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

*MLA indicates minimum lumen cross-sectional area; EEM, external elastic membrane; and CSA, cross-sectional area.
†Generalized estimating equations least mean squares mean (95% confidence interval).

**Table 3. Calcified Nodule Location Relative to the Minimum Lumen Cross-Sectional Area Site**

<table>
<thead>
<tr>
<th></th>
<th>LAD</th>
<th>LCx</th>
<th>RCA</th>
</tr>
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<tbody>
<tr>
<td>Total calcified nodules, n</td>
<td>114</td>
<td>82</td>
<td>118</td>
</tr>
<tr>
<td>Proximal to the MLA site, n (%)</td>
<td>66 (58)</td>
<td>50 (61)</td>
<td>56 (47)</td>
</tr>
<tr>
<td>Distal to the MLA site, n (%)</td>
<td>36 (32)</td>
<td>29 (35)</td>
<td>53 (45)</td>
</tr>
<tr>
<td>At the MLA site, n (%)</td>
<td>12 (10)</td>
<td>3 (4)</td>
<td>9 (8)</td>
</tr>
</tbody>
</table>

LAD indicates left anterior descending artery; LCx, left circumflex artery; RCA, right coronary artery; and MLA, minimum lumen cross-sectional area.

*Overall P=0.10, LAD versus LCx versus CA.
Pathology and IVUS Assessment of Individual Calcified Nodules

The origin of calcified nodules in ACS patient is not precisely known. On histology, this lesion with element of fibrous layer has the greatest amount of calcification relative to plaque area among vulnerable plaque subtypes and is thought to be associated with a healed fibroatheroma and, potentially, frequent intraplaque hemorrhage. To assess calcified nodules in vivo, a calcified nodule validation study was done using coronary arteries from human autopsied hearts. IVUS detected calcification in 285 frames; 17 (6.0%) were calcified nodules and 268 (94.0%) were nonnodular calcium by histopathology. Two calcified nodules (11.8%) were solitary, and 15 (88.2%) were adjacent to nonnodular calcium. IVUS characteristics of calcified nodules were (1) protruding and convex shape of the luminal surface (94.1% in calcified nodule versus 9.7% in nonnodular calcium; P < 0.001), (2) convex shape of the luminal side of calcium (100% versus 16.0%; P < 0.001), (3) irregular luminal surface (64.7% versus 11.6%; P < 0.001), and (4) irregular leading edge of calcium (88.2% versus 19.0%; P < 0.001).

Burke et al. observed that healed plaque ruptures were associated with increased calcification and suggested that plaque disruption, via hemorrhage, may contribute to coronary calcification. Each calcified nodule is small, but calcified nodules tend to cluster in the present investigation, multiple calcified nodules were observed in 76 of 623 patients (12%), 22 in the same artery. Culprit calcified nodule has been reported by 1 pathology group to be a rare cause of coronary thrombosis. However, nonculprit calcified nodule may represent precursor lesions similar to thin-cap fibroatheromas; calcified nodules do not often lead to thrombosis (as suggest by the low event rate in the present study), just as thin-cap fibroatheromas do not always result in plaque rupture. Furthermore, in a computed tomographic angiography study, Thilo et al. reported that calcified nodules were rarely stenotic, similar to our present report, presumably because neither study evaluated culprit lesions.

Table 4. Volumetric Gray-Scale, Virtual Histology Intravascular Ultrasound, and Quantitative Coronary Angiography of the Entire Coronary Tree Comparing Patients With at Least 1 Calcified Nodule and Patients Without Any Calcified Nodules

<table>
<thead>
<tr>
<th>Variable</th>
<th>Calcified Nodule (n=185)</th>
<th>No Calcified Nodule (n=438)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>3-Vessel volumetric gray-scale IVUS*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total length analyzed, mm</td>
<td>213.1 (167.7–256.4)</td>
<td>202.8 (159.4–252.4)</td>
<td>0.21</td>
</tr>
<tr>
<td>NC lesions, n</td>
<td>5.0 (4.0–6.0)</td>
<td>5.0 (3.0–6.0)</td>
<td>0.006</td>
</tr>
<tr>
<td>Length of NC lesions, mm</td>
<td>88.9 (59.6–115.8)</td>
<td>67.6 (43.6–95.0)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Average EEM CSA, mm²/mm</td>
<td>16.1 (14.13–18.59)</td>
<td>16.1 (13.9–18.6)</td>
<td>0.71</td>
</tr>
<tr>
<td>Average lumen CSA, mm²/mm</td>
<td>8.0 (6.7–9.4)</td>
<td>8.1 (6.9–9.6)</td>
<td>0.37</td>
</tr>
<tr>
<td>Average P+M CSA, mm²/mm</td>
<td>8.2 (7.0–9.6)</td>
<td>7.8 (6.7–9.2)</td>
<td>0.10</td>
</tr>
<tr>
<td>Plaque burden, %</td>
<td>50.1 (46.9–53.0)</td>
<td>48.8 (46.4–51.6)</td>
<td>0.002</td>
</tr>
<tr>
<td>3-Vessel volumetric VH-IVUS*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total VH-TCFA lesions, n</td>
<td>1.0 (0.0–2.0)</td>
<td>1.0 (0.0–2.0)</td>
<td>0.92</td>
</tr>
<tr>
<td>Patients with ≥1 VH-TCFAs,* (n/N)</td>
<td>51.7 (89/172)</td>
<td>54.8 (234/427)</td>
<td>0.50</td>
</tr>
<tr>
<td>Total ThCFA lesions, n</td>
<td>2.0 (1.0–3.0)</td>
<td>1.0 (0.0–2.0)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>DC volume, %</td>
<td>6.2 (4.1–10.3)</td>
<td>4.4 (2.5–7.8)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Necrotic core volume, %</td>
<td>13.2 (8.9–18.0)</td>
<td>11.6 (6.9–17.3)</td>
<td>0.04</td>
</tr>
</tbody>
</table>

IVUS indicates intravascular ultrasound; NC, nonculprit lesion; EEM, external elastic membrane; CSA, cross-sectional area; P+M, plaque+media; VH, virtual histology; TCFA, thin-cap fibroatheroma; ThCFA, thick-cap fibroatheroma; and DC, dense calcium. Values in parentheses are interquartile ranges.

*Analysis performed by summing the volumes of all 3 coronary arteries on a per-patient basis.
Calcified Nodule as a Marker of Atherosclerosis

Previous pathological studies have shown a correlation between coronary calcium and atherosclerotic plaque volume. Mintz et al reported that the presence and magnitude of target lesion calcium paralleled the atherosclerotic plaque as assessed by IVUS. Similarly, Sangiorgi et al reported the relationship between the calcium area and plaque volume in a histopathological study of 723 coronary artery segments using nondecalcified methodology. Thus, these studies taken together imply that calcium is a reliable marker for extensive atherosclerosis. In the present study, plaque volume was greater in patients with at least 1 calcified nodule than in patients with no calcified nodules, along with more ThCFAs (but not more VH-TCFAs) and more necrotic core plaque and dense calcium. These findings suggested that calcified nodules might be a marker for atherosclerosis; however, they were associated with fewer future cardiac events, suggesting quiescence rather than ongoing activity.

Axial Distribution of Calcified Nodules

There are no pathology data on the location of nonculprit calcified nodules. Virmani et al reported that culprit calcified nodules were found predominantly in the mid-RCA, where coronary torsion stress was maximal. Interestingly, in the present study, coronary artery calcified nodules occurred in a limited, focal distribution similar to plaque ruptures, acute occlusions, and TCFAs. Calcified nodules in the present study were clustered mainly in the proximal segments of the LAD and LCx, whereas calcified nodules within the RCA were evenly and more distally distributed. In an angiographic study, Wang et al analyzed 208 consecutive patients with ST-segment–elevation myocardial infarction to determine the location of epicardial thrombosis and found that the occlusions tended to cluster within the proximal third of each coronary artery. In a 3-vessel IVUS study, Hong et al evaluated the axial location of plaque rupture in 392 patients. Plaque ruptures occurred mainly in the proximal segments of the LAD, the proximal and distal segments of RCA, and the entire LCx. Cheruvu et al also reported that TCFAs tended to cluster in predictable spots within the proximal third of the major coronary arteries in a pathological study.

Angiographic and VH Features of Calcified Nodule

The angiographic appearance of calcified nodules is not well established. One previous study reported a patient with an intracoronary angiographic filling defect that initially was diagnosed as intraluminal thrombus but whose preintervention IVUS imaging showed that the filling defect was, in fact, superficial calcification consistent with the appearance of a calcified nodule. However, in the present study, calcified nodules were an incidental finding, with 257 (82%) appearing normal on angiography, 38 (14%) having evidence of angiographic calcium, and 19 (6%) having the appearance of angiographic haziness. The reasons for the absence of any angiographic filling defects in the present analysis may be that we studied only nonculprit lesions, the calcium nodules in the present study were relatively small, and angiographic filling defects have been reported in culprit lesions of ACS patients, albeit rarely.

The VH-IVUS appearance of calcified nodules has never been reported. On pathology, calcified nodules appeared to be a mixture of calcified plate, bony spicules, and interspersed calcified nodule cohort

<table>
<thead>
<tr>
<th>At least 1 calcified nodule per patient vs no calcified nodules per patient</th>
<th>Coefficient</th>
<th>SE</th>
<th>P</th>
<th>Hazard Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Propensity score*</td>
<td>0.3870</td>
<td>1.5132</td>
<td>0.7982</td>
<td>1.47 (0.08–28.58)</td>
</tr>
<tr>
<td>History of cardiac intervention before the current event</td>
<td>0.8523</td>
<td>0.3426</td>
<td>0.0128</td>
<td>2.35 (1.20–4.59)</td>
</tr>
<tr>
<td>Presence of at least 1 lesion with a plaque burden &gt;70%</td>
<td>0.8983</td>
<td>0.2700</td>
<td>0.0009</td>
<td>2.46 (1.45–4.17)</td>
</tr>
<tr>
<td>Presence of at least 1 VH-TCFA</td>
<td>0.6464</td>
<td>0.2907</td>
<td>0.0262</td>
<td>1.91 (1.08–3.37)</td>
</tr>
</tbody>
</table>

Cl indicates confidence interval; VH-TCFA, virtual histology thin-cap fibroatheroma.

*Propensity score was generated by age, high-density lipoprotein, and ratio of total cholesterol to high-density lipoprotein cholesterol.
fibrin.12 We observed that a calcified nodule itself and its adjacent segment mostly had stable VH phenotype (calcified ThCFA or noncalcified ThCFA). The accuracy of VH-IVUS analysis behind calcium continues to be controversial and depends on the thickness, density, and amount of calcium analyzed. Sales et al20 reported that “adding” calcific elements to the atherosclerotic plaque led to a directly proportional increase in the area coded as necrotic core in VH-IVUS images and influenced the exact measurement of the amount and extent of necrotic core. Thus, in the present investigation, the necrotic core volume in the calcified nodule group might be overestimated by the influence of a greater amount of dense calcium. However, it is interesting to speculate that the presence of stable VH-IVUS lesion morphology may have contributed to the clinical outcomes in the present study.

Calcified Nodules and Cardiac Events
Virmani et al12 found calcified nodules in sudden coronary death victims and hypothesized that physical forces exerted by the nodules themselves might contribute to fibrous-cap disruption. However, other evidence indicated that calcific plaque may be stabilized as it evolves with decreased hard/soft interface area and thus less prone to rupture than noncalcified lesions.21 In the present study, we observed consistently fewer nonculprit lesion major adverse cardiac events in the calcified nodule group compared with the noncalcified nodule group at the 1-, 2-, or 3-year follow-up. More important, there was no death, cardiac arrest, or myocardial infarction in the calcified nodules group. Several explanations are possible. First, calcified nodules were rarely VH-TCFAs; the VH phenotype appearance of calcific nodules has not been associated with increased events.22,23 Second, calcified nodules were not associated with an increased frequency of VH-TCFAs elsewhere in the coronary tree, and VH-TCFAs were the only phenotype associated with increased events in PROSPECT.4 Third, calcified nodules may have been the end result of plaque rupture, thrombosis, and healing rather than being causative of events.

Limitations
The study cohort included nonculprit lesions in ACS patients, and it did not include culprit lesions and was not a study of a general patient population. Because vulnerable plaques tend to be clustered, the actual prevalence of calcified nodules might be lower than what we presented. Second, IVUS was performed after culprit lesion intervention; therefore, plaque tissue morphology at the culprit site could not be evaluated for the existence of calcified nodules. Third, pathological study has shown that a calcified nodule may be covered by a thin layer of fibrin or endothelium that is below the resolution of traditional IVUS. However, this should not affect the diagnostic accuracy of IVUS, although it might affect the likelihood that a calcified nodule would cause an event. In the future, tissue characterization of calcified nodules along with any overlying tissue should be detectable with optical coherence tomography. Fourth, the fact that relatively few events occurred during follow-up in the present study—both in patients with and in those without calcified nodules—attests to the benefits of intensive medical therapy in compliant patients and how closely these patients were followed up in this clinical trial (and expertly treated when severe angina did occur). Finally, calcification is a reflector for ultrasound, causing typical acoustic shadowing in the IVUS images. Ultrasound signals cannot penetrate or pass through the calcified layer and are reflected back toward the transducer. Therefore, accurate tissue characterization of the areas beneath calcification such as the interior of the calcified nodules in the present study is not possible as with conventional IVUS. The accuracy of VH-IVUS analysis behind calcium continues to be controversial and probably depends on the thickness, density, and amount of calcium analyzed.

Conclusions
Our findings demonstrated that calcified nodules in human coronary arteries were frequent and focally distributed. They were common in older patients and were unlikely to cause events during a 3-year follow-up.

Disclosures
Dr Xu has received a research grant from Boston Scientific, China. Dr Maehara has received research/grant support from Boston Scientific Corp and speaker’s honoraria from Volcano Corp. Dr Mintz has received research/grant support from and is a consultant for Volcano Corp and Boston Scientific Corp. Dr Stone is a consultant for Medtronic, Boston Scientific, Abbott Vascular, and The Medicines Company. Dr McPherson is a consultant for Abbott Vascular. The other authors report no conflicts.

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CLINICAL PERSPECTIVE

The majority of acute coronary syndrome events are the result of sudden luminal thrombosis, with 55% to 60% caused by plaque rupture, 30% to 35% resulting from plaque erosion, and a small portion due to a calcified nodule. In the present analysis using 3-vessel intravascular ultrasound and virtual histology imaging and comprehensive follow-up data from Providing Regional Observations to Study Predictors of Events in the Coronary Tree (PROSPECT), we describe the frequency of incidentally detected calcified nodules and the angiographic appearance, intravascular ultrasound and virtual histology intravascular ultrasound features, and natural history of patients whose arteries contain ≥1 calcified nodules. The incidence of calcified nodule was 17% per artery and 30% per patient. Two or more calcified nodules were detected in 48 coronary arteries (3%) in 76 patients (12%). The calcified nodules were located <40 mm from the ostium of the coronary artery in 85% of left anterior descending arteries and 86% of left circumflex arteries, whereas calcified nodules within the right coronary arteries were evenly and more distally distributed, similar to other vulnerable plaque types. Patients with calcified nodules were significantly older and had more plaque volume, more thick-cap fibroatheroma, but fewer events at follow-up that could be attributed to their calcified nodules. Therefore, although a culprit calcified nodule has been reported by 1 pathology group to be a cause (albeit rarely) of coronary thrombosis, incidentally detected nonculprit calcified nodules appear to be more benign and do not often lead to thrombosis as suggested by the low event rate in the present study.
Prevalence, Distribution, Predictors, and Outcomes of Patients With Calcified Nodules in Native Coronary Arteries: A 3-Vessel Intravascular Ultrasound Analysis From Providing Regional Observations to Study Predictors of Events in the Coronary Tree (PROSPECT)  
Yingjia Xu, Gary S. Mintz, Anthony Tam, John A. McPherson, Andrés Iñiguez, Jean Fajadet, Martin Fahy, Giora Weisz, Bernard De Bruyne, Patrick W. Serruys, Gregg W. Stone and Akiko Maehara

_Circulation_. 2012;126:537-545; originally published online June 28, 2012;  
doi: 10.1161/CIRCULATIONAHA.111.055004  
_Circulation_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231  
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

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석회결절을 보이는 관상동맥 병변은 오히려 안정적이다

권 준 교수 인하대병원 심장내과

Summary

배경
병리학적 연구 결과에서 관상동맥 석회결절이 혈전 발생의 드문 원인으로 제시된 바 있다. 하지만 관상동맥 석회결절의 빈도, 분포, 예측인자 그리고 임상적 결과에 대해서는 잘 알려진 것이 없다.

방법 및 결과
본 연구는 전향적, 다기관 연구로 급성 관상동맥증후군 환자 697명(여성: 167명, 연령 중앙값: 58.1세)을 대상으로 성공적인 스텐트 시술 후 3개 관상동맥 기시부에서 중간부까지 gray-scale 그리고 virtual histology intravascular ultrasound(VH-IVUS) 검사를 시행하였다. 최근의 조직학적 입증 자료에 근거하여 독립적인 코어 랩에서 불규칙하고 돌출된 그리고 볼록한 구멍 표면을 가지고 있는 분명한 관상동맥내 석회를 석회결절이라고 정의하였다. 모든 환자는 약 3년(중앙값) 동안 추적관찰하였다. 총 1,573개의 관상동맥(환자 623명 중 185명) 중 250개의 관상동맥에서 314개의 석회결절이 발견되었다. 따라서 관상동맥 석회결절이 단위 관상동맥으로는 17%, 단위 환자로는 30%의 유병률을 보였다. 환자 76명(12%) 의 48개 관상동맥(3%)에서는 2개 이상의 결절을 보였 다. 결절의 위치 분포를 보면 좌전하행지와 좌회선지에서 는 주로(85%, 86%) 개구부에서 40mm 이내 기시부에 분포한 반면에, 우관상동맥에서는 고르게 그리고 원위부 에 더 많이 분포하였다. 석회결절을 보인 환자들에서 나 이가 더 많았으며, 죽상반 용적은 더 컸고, VH-thick cap fibroatheroma(ThCFA)가 더 많이 관찰되었다. 반면에 3년 추적관찰 중 주요 심혈관사건 발생 빈도는 더 낮았다.

결론
급성 관상동맥증후군 환자 중 nonculprit 관상동맥에서 석회결절 병변이 의외로 많이 관찰되었다. 3년 추적 관찰 결과에서 관상동맥 혈전 발생 원인 중 하나로 여겨졌던 석회결절 병변에서 오히려 주요 심혈관사건이 적게 발생하였다.
관상동맥 석회결절은 관상동맥 죽상동맥경화증을 진단하는 데 있어 유용한 표식자로 알려져 있다. 1, 2 또한, 미국심장학회는 가이드라인을 통해 관상동맥질환 위험을 평가함에 있어 multidetector computed tomography로 평가한 관상동맥 석회화 점수(coronary artery calcium score)를 이용하도록 제시한 바 있다. 이처럼 관상동맥 석회결절은 관상동맥질환과 매우 밀접한 관계를 가지고 있다.

이러한 석회결절이 심혈관사건의 주범인 관상동맥 혈전 발생에 어떠한 연관성을 가지고 있는가? 대부분의 급성 관상동맥증후군은 갑작스러운 관상동맥내 혈전 발생에 의한 것으로 주로 죽상반 파열 또는 침식에 의한 것으로 설명되고 있다. Virmani 등은 급성 관상동맥증후군으로 사망한 환자의 관상동맥에서 석회결절을 관찰함으로써 석회결절이 죽상반 파열의 물리적 원인 가능성을 제시한 바 있다.

본 연구에서는 PROSPECT(Providing Regional Observations to Study Predictors of Events in the Coronary Tree) 연구 자료를 토대로 하였다. 3개 관상동맥에서 gray-scale과 VH-IVUS 영상자료 분석이 가능한 623명을 대상으로 3개 관상동맥에서의 석회결절 빈도를 조사하고, VH-IVUS 영상 소견을 통한 병리학적 분석과 함께 관상동맥조영검사 결과를 같이 비교하였다. 또한, 3년 동안의 추적관찰을 통해 1개 이상의 석회결절이 관찰된 250개 관상동맥에서의 석회결절의 주요 결과는 첫째, 환자 623명의 1,573개 관상동맥 중 185명(30%)의 250개 관상동맥(16%)에서 nonculprit 석회결절이 관찰되었으며, 이들 대부분은 ThCFA이며, 나머지 5개는 VH-ThCFA(VH thin-cap fibroatheroma)로 판명되었다. 또한, 82개의 석회결절은 5mm 내에 섬유족상반이 인접해 있었다. 이들 대부분은 ThCFA였으며 12개만은 VH-ThCFA였다.

VH-IVUS 영상을 이용한 이전 연구를 통해 ThCFA는 안정적인 병변인 반면, VH-TFCA는 혈전 발생의 원인으로 되는 불안정 병변과 관련이 높은 것으로 알려져 있다. 또한, PROSPECT 연구에서도 VH-TFCA만이 심혈관사건 발생을 증가시키는 유일한 표현형인 것으로 보고된 바 있다.6, 7 PROSPECT 연구에서는 3년간 총 54건의 nonculprit 병변에 의한 심혈관사건이 있었는데, 이 중에서 4건만이 석회결절이 있는 경우였으며, 그들 모두 VH-IVUS 영상분석 결과로 판명되었다.

따라서 석회결절 병변이 불안정한 VH-TFCA가 아닌 주로 안정적인 ThCFA인 것으로 나타난 본 연구 결과를 감안한다면 석회결절이 있는 병변에서 주요 심혈관사건 발생이 낮은 것은 어찌 보면 당연하다. 아마도 이전 보고에서 제시된 바와 같이 석회결절은 흉터와 같이 죽상반 파열이나 혈전증 후에 아물거나 침식 변환 후에 생긴 결과물이며, 그래서 오히려 식회병변에 비하여 파열되거나 침식될 위협이 적은 안정적인 병변이 아닌가 생각된다.6, 7 결론적으로, 비록 석회결절이 관상동맥 죽상동맥경화증을 진단하는 데 있어 유용한 표식자로 알려져 있으나, 석회결절의 섬유족상반 연결성에 대한 추가 연구가 필요하다.
증 진단에 예민한 표식자이며, 관상동맥 혈전증을 일으키는 하나의 드문 병리학적 원인군으로 분류되기도 하였지만, 본 연구 결과에서는 석회결절이 보이는 병변을 오히려 심혈관사건 발생 위험이 낮은 안정적인 병변으로 제시하고 있다. 단, 저자가 지적한 대로 석회결절을 제대로 통과할 수 없는 초음파를 이용하여 그 뒤의 구조를 영상화하고 분석했다는 점이 본 연구의 제한점으로 생각된다.

References
Prevalence, Distribution, Predictors, and Outcomes of Patients With Calcified Nodules in Native Coronary Arteries
A 3-Vessel Intravascular Ultrasound Analysis From Providing Regional Observations to Study Predictors of Events in the Coronary Tree (PROSPECT)

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Background—Pathological studies suggest that calcified coronary nodules are a rare cause of thrombotic events. The frequency, distribution, predictors, and outcomes of calcified nodules have never been described.

Methods and Results—After successful stenting in 697 patients (167 female; median age, 58.1 years) with acute coronary syndromes, 3-vessel gray-scale and virtual histology intravascular ultrasound was performed in the proximal-mid segments of all 3 coronary arteries as part of a prospective, multicenter study. On the basis of recent histological validation, an independent core laboratory identified calcified nodules as distinct calcification with an irregular, protruding, and convex luminal surface. Patients were followed up for 3 years (median). Overall, 314 calcified nodules were detected in 250 of 1573 analyzable arteries (185 of 623 patients). Thus, the prevalence of calcified nodules was 17% per artery and 30% per patient. Two or more calcified nodules were detected in 48 coronary arteries (3%) in 76 patients (12%). The calcified nodules were located <40 mm from the ostium of the coronary artery in 85% of left anterior descending arteries and 86% of left circumflex arteries, whereas calcified nodules within the right coronary arteries were evenly and more distally distributed. Patients with calcified nodules were significantly older and had more plaque volume, more thick-cap fibroatheroma, but fewer nonculprit lesion major adverse events on follow-up.

Conclusions—Calcified nodules in untreated nonculprit coronary segments in patients with acute coronary syndromes were more prevalent than previously recognized. Although their distribution mirrored the origin of most thrombotic events, calcified nodules caused fewer major adverse events during 3 years of follow-up. (Circulation. 2012;126:537-545.)

Key Words: acute coronary syndrome ■ atherosclerosis ■ calcification, physiologic ■ cardiac imaging techniques

The majority of acute coronary syndrome (ACS) events are the result of sudden luminal thrombosis, with 55% to 60% due to plaque rupture, 30% to 35% caused by plaque erosion, and a small portion resulting from a calcified nodule, an eruptive, dense, calcified mass often having an irregular surface appearance.1,2 Intravascular ultrasound (IVUS) provides detailed qualitative and quantitative cross-sectional coronary imaging and has a high sensitivity and specificity for detecting intracoronary calcium. To assess calcified nodules in vivo, a validation study was done using coronary arteries from human autopsied hearts. IVUS detected calcification in 285 frames in 856 pathological slices in 29 coronary arteries (11 left anterior descending [LAD], 5 left circumflex [LCx], and 13 right coronary [RCA] arteries) in 18 autopsy hearts; 17 (6.0%) were calcified nodules, and 268 (94.0%) were nonnodular calcium by histopathology. Calcified nodules were irregular and protruding with a convex luminal surface.3 The present analysis uses the 3-vessel IVUS data from the Providing Regional Observations to Study Predictors of Events in the Coronary Tree (PROSPECT) study to determine the frequency, distribution, angiographic appearance, virtual histology (VH)-
IVUS appearance, predictors, and outcomes of nonculprit calcified nodules in ACS patients.

**Clinical Perspective on p 80**

**Methods**

**Study Population**

PROSPECT was a multicenter, multimodality imaging study that was performed at 37 sites in the United States and Europe to prospectively identify nonculprit vulnerable plaque after treatment of all culprit lesions in patients presenting with ACS. The primary PROSPECT analysis was reported previously. Briefly, patients had all culprit lesions stented (typically without preintervention IVUS) followed by gray-scale and VH-IVUS imaging of the left main coronary artery and the proximal 6 to 8 cm of all epicardial arteries. Clinical follow-up occurred at 30 days, at 6 months, and then yearly for at least 2 years. The prespecified primary end point was the incidence of major adverse cardiovascular events (the composite of death from cardiac causes, cardiac arrest, myocardial infarction, or rehospitalization resulting from unstable or progressive angina according to the Braunwald Unstable Angina Classification and the Canadian Cardiovascular Society Angina Classification). The primary end point was adjudicated by a clinical events committee that had no knowledge of other patient data and that used original source documents. On the basis of follow-up angiography, major adverse cardiovascular events were further adjudicated as occurring at initially treated sites (culprit lesions) or at previously untreated coronary segments (nonculprit lesions). If follow-up angiography was not performed, the site associated with the event was classified as indeterminate. Patient demographics, coronary risk factors, follow-up visits, and all relevant information were retrieved from the study database. The Institutional Review Board at each institution approved the study, and subjects gave written informed consent.

**Coronary Angiography and Subsequent Qualitative Angiographic Analysis**

Coronary angiograms were performed in at least 2 orthogonal views after intracoronary nitroglycerin. All angiograms were analyzed at the Angiographic Core Laboratory of the Cardiovascular Research Foundation (New York, NY). Qualitative analysis included thrombus, calcification (moderate or severe), and haziness. The longitudinal extension of each of these morphologies was recorded in relation to the distance from the coronary ostium. Nonculprit lesions were prespecified in the protocol as ≥30% visual diameter stenosis. All 3 epicardial vessels and all ≥1.5-mm-diameter side branches were divided into 29 Coronary Artery Surgery Study (CASS) segments. Each CASS segment was then subdivided into 1.5-mm-long subsegments and analyzed.

**Gray-Scale and VH-IVUS Image Acquisition**

After successful stenting of the culprit lesions in the 697 patients enrolled in the study, 3-vessel IVUS was performed with a synthetic-aperture-array, 20-MHz, 3.2F catheter (Eagle Eye, Volcano Corp., Rancho Cordova, CA) after intracoronary nitroglycerin. The IVUS catheter was advanced distally; the guiding catheter was disengaged; and the IVUS catheter was pulled back to the aorto-ostial junction with an R-100 motorized catheter pullback system at 0.5 mm/s. Because the left main was usually imaged during both LAD and LCx pullbacks, the run with better left main image quality was chosen for analysis. During pullback, gray-scale IVUS was recorded, raw radiofrequency data were captured at the top of the R wave, and reconstruction of the color-coded map by a VH-IVUS data recorder was performed (In-Vision Gold, Volcano Corp.). IVUS studies were archived onto CD-ROM or DVD for offline analysis.

**Gray-Scale IVUS Analysis**

Of the 697 enrolled patients, 660 cases with complete IVUS data were sent to the independent IVUS core laboratory (Cardiovascular Research Foundation) for quantitative and qualitative analyses with validated QCU-CMS (Medis, Leiden, the Netherlands) software for contouring. Initial screening identified 623 patients with gray-scale IVUS images suitable for inclusion in the present analysis. The reasons for exclusion were dark images, too much noise, too short a segment of catheter pullback, or sudden jumping or sticking of the catheter during automatic pullback. In each patient, calcified nodules were classified as single (1 solitary nodule in 1 patient) or multiple (≥2 nodules in a single vessel or at least 1 nodule in ≥2 vessels). The diagnosis of a calcified nodule required independent review and agreement by 2 authors (Y.-K. and A.M.). Interobserver and intraobserver variability was examined in a randomly selected number of lesions. Each observer assessed the lesion independently on 2 separate occasions, 3 months apart, with blinding for earlier analysis. Intraobserver and interobserver variability yielded good concordance for the diagnosis of calcium nodule (κ = 0.83 and κ = 0.80, respectively).

When a calcified nodule was identified, the proximal and distal reference segments (the most normal-looking cross sections—ie, maximum lumen with least amount of plaque—within 5 mm proximal or distal to the calcified nodule but before any side branch) were also identified and selected for analysis. Between the proximal and distal reference segments, the slice with the smallest lumen and greatest amount of plaque was chosen as the minimum lumen area (MLA) site. Quantitative analysis included external elastic membrane (EEM), lumen, and plaque plus media (calculated as EEM minus lumen) cross-sectional area (CSA) at the site of the calcium nodule, MLA site, and proximal and distal reference segments. Plaque burden (PB) was calculated as follows: PB = (plaque + media CSA/EEM CSA) × 100. The remodeling index at the calcified nodule site and at the MLA site was the EEM divided by the average of the proximal and distal reference EEM. Lumen area stenosis at the calcified nodule site and at the MLA site was defined as 1 minus MLA divided by the average reference lumen CSA. Calcium analysis included calcium location (superficial, mixed, or deep) and maximum arc of calcium.

**VH-IVUS Analysis**

Of the 623 qualified gray-scale IVUS images, 573 cases had VH data available for analysis. The reasons for unavailable VH-IVUS images were failure to capture VH-IVUS data, too much noise, or segmental loss of VH images. VH-IVUS plaque components were color-coded as dense calcium (white), necrotic core (red), fibrofatty (light green), or fibrous tissue (dark green) and reported as absolute CSA and percentage of total plaque CSA with the use of qVH 2.1 software (Volcano Corp.) and proprietary qVH software (developed and validated at the Cardiovascular Research Foundation). Volumes were calculated with the Simpson rule and reported as total volume and normalized area (volume divided by length). Each lesion was classified by VH-IVUS into 1 of the following 5 phenotypes: (1) VH thin-cap fibroatheroma (VH-TCFA); (2) thick-cap fibroatheroma (THCFA), divided into noncalcified thick-cap fibroatheroma or calcified thick-cap fibroatheroma, depending on whether the necrotic core did or did not contain superficial dense calcium; (3) pathological intimal thickening; (4) fibrotic plaque; and (5) fibrocalcific plaque. Although a lesion could contain features of >1 phenotype, in PROSPECT, a hierarchy of lesion phenotype was prespecified such that any fibroatheroma (VH-TCFA or THCFA) took precedence over any nonfibroatheroma and VH-TCFA took precedence over THCFA. Typical gray-scale and VH-IVUS pictures of a calcified nodule are shown in Figure 1.

**Coregistration Between Angiogram and IVUS**

Gray-scale and VH-IVUS analyses were coregistered to the angiographic roadmap through the use of fiduciary side branches for alignment with interpolation as necessary to account for different length measurements. Nonculprit lesions responsible for late events were identified with the follow-up angiogram; then, the corresponding segments and subsegments were matched side by side to the baseline angiograms and gray-scale and VH-IVUS studies. This
methodology has been reported as part of the primary PROSPECT analysis.4

Statistical Analysis
Statistical analyses were performed with SAS software, version 9.1.3 (SAS Institute, Cary, NC). Continuous variables were presented as the mean ± SD or medians and interquartile ranges (IQRs); comparisons were conducted by the Student t test or the Kruskal-Wallis test. For comparison between calcium nodule site and the adjacent MLA site, a model with generalized estimating equations approach was used to compensate for any potential cluster effect of multiple calcium nodules in the same vessels or in the same patients. The generalized estimating equations model was developed by use of a working correlation structure of compound symmetry and a 2-level nested cluster effect for patient and vessel within patient using the PROC GENMOD code in SAS; the results are presented as least-square means with 95% confidential intervals. Discrete variables were presented as percentages and relative frequencies; comparisons were conducted by \( \chi^2 \) statistics or the Fisher exact test as appropriate. Intraobserver and interobserver variability for the diagnosis of calcium nodule was measured by the \( \kappa \) test of concordance. Three-year outcomes are displayed as time-to-event curves, summarized by use of Cox regression model and hazard ratios. The proportional hazard assumptions for nonculprit major adverse cardiovascular events were checked by use of the graphical and numeric methods of Lin et al8 and the Kolmogorov-type supremum test. The \( P \) value from the supremum test is 0.08, indicating that proportional hazard assumptions are not being violated. A value of \( P < 0.05 \) was considered statistically significant.

Results
Frequency and Distribution of Calcified Nodules
Among 623 patients with 1573 vessels imaged and qualified for analysis (574 LAD, 480 LCx, and 519 RCA), a total of 314 calcified nodules were detected in 250 arteries in 185 patients. Among these, there were 108 LAD nodules in 95 patients, 78 LCx nodules in 73 patients, and 118 RCA nodules in 82 patients. In addition, there were calcified nodules in the left main coronary artery in 10 patients. Thus, the prevalence of at least 1 calcified nodule was 16% per artery (250 of 1573) and 30% per patient (185 of 623). Overall, 17% of LAD, 15% of LCx, and 16% of RCA contained at least 1 calcified nodule. Two or more calcified nodules were detected in 48 coronary arteries (3%) in 76 patients (12%). Among them, 22 patients had >1 nodule in a single vessel, and 52 patients had nodules in >1 vessel. Overall, 3% of LADs, 1% of LCxs, and 5% of RCAs were found to have multiple nodules.

Comparison of Patients With and Without Calcified Nodules
Baseline clinical characteristics comparing 185 patients with at least 1 calcified nodule and 438 patients without any calcified nodules are shown in Table 1. Patients with at least 1 calcified nodule were significantly older, were more likely to have had prior cardiac interventions, and had better cholesterol profiles as indicated by a higher serum high-density lipoprotein cholesterol level and lower ratio of total cholesterol to high-density lipoprotein. Surprisingly, the frequency of diabetes mellitus, hypertension, smoking, and familial coronary artery disease was statistically similar between the 2 groups. There were also no differences between the group with single nodules and the group.
with multiple calcified nodules in terms of baseline clinical characteristics (data not shown). In addition, there was no significant difference in the rate of calcium nodules per patient among the clinical sites that enrolled patients in PROSPECT.

**Angiographic Appearance of Calcified Nodules**

Overall, only 35 calcified nodules (11%) had evidence of angiographic moderate calcium, 3 (1%) had angiographic severe calcium, and 19 (6%) had the appearance of angiographic hazy appearance (Figure 2). The remaining 257 calcified nodules (82%) appeared normal on angiography. Patients with calcified nodules had the same number of angiographically calcified lesions as patients without calcified nodules (data not shown).

**Qualitative and Quantitative Gray-Scale IVUS Findings of Calcium Nodules**

The arc of nodular calcium measured 33.5° (IQR, 32.2–34.8); 91% were superficial and 9% were mixed, but none were only deep (leading edge of calcium closer to the EEM than to the lumen).

In 33% of calcified nodules (105 of 314), there was a branch near the calcified nodule site (47 proximal and 58 distal). The distance between the calcified nodule site and the branch measured 3.0 mm (IQR, 2.9–3.2).

The EEM CSA, lumen CSA, and remodeling index at the calcified nodule site were significantly larger than at the MLA site (lumen CSA: 8.6 mm² [IQR, 6.1–9.0 mm²] versus 7.0 mm² [IQR, 6.6–7.4 mm²]; P < 0.0001), and the PB was correspondingly less (46.5% [IQR, 45.1%–47.9%] versus 54.4% [IQR, 53.1%–55.7%]; P < 0.0001), as was area stenosis (31.4% [IQR, 30.0%–32.8%] versus 41.6% [IQR, 40.0%–43.1%]; P < 0.0001; Table 2). Of the calcified nodules analyzed, only 12 (of 314) had an MLA <4 mm², and only 8 had an area stenosis >50%.

Overall, 37% (118 of 314) of the calcified nodules were located distal to the MLA site, 55% (172 of 314) were located proximal to the MLA site, and 8% (24 of 314) were at the MLA site. Table 3 shows the location of the calcified nodules relative to the MLA site in the LAD, LCx, and RCA, separately.

Overall, 85% (95 of 114) of the calcified nodules were located within the first 40 mm of the LAD: 28 (25%) within the first 10 mm of the LAD, 28 (25%) from 11 to 20 mm, 20 (18%) from 21 to 30 mm, and 19 (17%) from 31 to 40 mm. The axial distribution of calcified nodules was similar in the LCx: 40% in the first 10 mm, 19% from 11 to 20 mm, 12% from 21 to 30 mm, and 13% from 31 to 40 mm. Conversely, calcified nodules within the RCA were evenly and more distally distributed. This analysis is shown in Figure 3.

**VH-IVUS Appearance of Calcified Nodules**

Overall, 276 of 314 calcified nodules had VH data available for analysis. Among them, 116 calcified nodules were contained in lesions classified as a fibroatheroma on the basis of their VH-IVUS appearance using the prespecified hierarchy in which a fibroatheroma took precedence over a nonfibroatheroma and VH-TCF is took precedence over ThCFA. Of the 116 calcium nodule-containing lesions classified as a fibroatheroma, 106 were a calcified ThCFA, 5 were a noncalcified ThCFA, and 5 were a VH-TCF is. Among the 160 calcified nodules that were in lesions not classified as a fibroatheroma, 56% were within lesions that had characteristics of pathological intimal thickening, 40% in fibrotic plaque, and 4% in fibrocalcific plaque. In addition, 82 of 276 calcified nodules had a fibroatheroma within the adjacent segment that was predefined as 5 mm proximal or distal to the calcified nodule: 12 were VH-TCF is, 29 were noncalcified ThCFA, and 41 were calcified ThCFA.

**Volumetric IVUS Comparison of Patients With Versus Without Calcified Nodules**

The volumetric gray-scale and VH-IVUS analyses of the entire length of all 3 coronary arteries imaged per patient (summing the LM, LAD, LCx, and RCA) are shown in Table 4. Patients with at least 1 calcified nodule had a larger total 3-vessel volumetric PB on gray-scale IVUS and more ThCFA, necrotic core, and dense calcium on total 3-vessel volumetric VH-IVUS.

**Follow-Up Clinical Outcomes**

Independent predictors of nonculprit events on a patient level were calculated by including the predictors previously reported in the main PROSPECT article4 (insulin-treated diabetes mellitus, prior percutaneous coronary intervention, MLA <4 mm², VH-TCF is, and PB >70%) and forcing into the model both a propensity score generated by age, high-density lipoprotein, and ratio of total cholesterol to high-density lipoprotein cholesterol.
(the variables that were statistically significant in Table 1) and the presence of at least 1 calcified nodule per patient versus no calcified nodules. The presence of at least 1 calcified nodule per patient was an independent predictor of freedom from nonculprit events (Table 5).

As shown in Figure 4, there were consistently fewer nonculprit lesion major adverse cardiac events in the calcified nodule group compared with the noncalcified nodule group at the 1-, 2-, and 3-year follow-up. The 3-year cumulative nonculprit lesion major adverse cardiovascular event rates were 7.1% versus 14.2%. Overall, there was no death, cardiac arrest, or myocardial infarction in the calcified nodules group. In the entire PROSPECT study, there were 54 nonculprit events associated with baseline IVUS-imaged lesions, but only 4 were associated with a nonculprit lesion calcified nodule, and they had a VH-TCTA within the same analysis segment and (therefore) were classified as VH-TCTA.

### Discussion

In the present study using the 3-vessel IVUS data from PROSPECT, we report the prevalence, distribution, predictors, and outcomes of coronary artery calcified nodules in vivo. The major findings of our analysis are as follows. First, nonculprit calcified nodules were not unusual in patients with ACS; 314 calcified nodules were detected in 1573 arteries in 623 patients. Second, the axial location of calcified nodules was similar to previous reports of the location of plaque rupture, VH-TCTA, and acute coronary thrombosis.9–11 Third, calcified nodules were more common in older individuals. Finally, calcified nodules were, surprisingly, associated with fewer events during the 3-year follow-up.

### Table 2. Quantitative Intravascular Ultrasound Analysis of Calcified Nodules Versus the Adjacent Minimum Lumen Area (MLA) Site

<table>
<thead>
<tr>
<th>Variables</th>
<th>Calcified Nodule Site*</th>
<th>MLA Site*</th>
<th>Pt</th>
</tr>
</thead>
<tbody>
<tr>
<td>EEM CSA, mm²</td>
<td>16.2 (15.4–17.0)</td>
<td>15.7 (14.9–16.5)</td>
<td>0.0119</td>
</tr>
<tr>
<td>Lumen CSA, mm²</td>
<td>8.6 (8.1–9.0)</td>
<td>7.0 (6.6–7.4)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Plaque plus media CSA, mm²</td>
<td>7.7 (7.2–8.1)</td>
<td>8.7 (8.2–9.2)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Plaque burden, %</td>
<td>46.5 (45.1–47.9)</td>
<td>54.4 (53.1–55.7)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Remodeling index</td>
<td>0.98 (0.97–0.99)</td>
<td>0.96 (0.95–0.97)</td>
<td>0.0153</td>
</tr>
<tr>
<td>Area stenosis, %</td>
<td>31.4 (30.0–32.8)</td>
<td>41.6 (40.0–43.1)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

MLA indicates minimum lumen cross-sectional area; EEM, external elastic membrane; and CSA, cross-sectional area.

*Generalized estimating equations least mean squares mean (95% confidence interval).

†Corrected incorporating generalized estimating equations methods to account for clustering at the subject level and vessel level.

### Table 3. Calcified Nodule Location Relative to the Minimum Lumen Cross-Sectional Area Site*

<table>
<thead>
<tr>
<th></th>
<th>LAD</th>
<th>LCx</th>
<th>RCA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total calcified nodules, n</td>
<td>114</td>
<td>82</td>
<td>118</td>
</tr>
<tr>
<td>Proximal to the MLA site, n (%)</td>
<td>66 (58)</td>
<td>50 (61)</td>
<td>56 (47)</td>
</tr>
<tr>
<td>Distal to the MLA site, n (%)</td>
<td>36 (32)</td>
<td>29 (35)</td>
<td>53 (45)</td>
</tr>
<tr>
<td>At the MLA site, n (%)</td>
<td>12 (10)</td>
<td>3 (4)</td>
<td>9 (8)</td>
</tr>
</tbody>
</table>

LAD indicates left anterior descending artery; LCx, left circumflex artery; RCA, right coronary artery; and MLA, minimum lumen cross-sectional area.

*Overall P=0.10, LAD versus LCx versus CA.
Pathology and IVUS Assessment of Individual Calcified Nodules

The origin of calcified nodules in ACS patients is not precisely known. On histology, this lesion with an element of fibrous layer has the greatest amount of calcification relative to plaque area among vulnerable plaque subtypes and is thought to be associated with a healed fibroatheroma and, potentially, frequent intraplaque hemorrhage.\textsuperscript{12,13}

To assess calcified nodules in vivo, a calcified nodule validation study was done using coronary arteries from human autopsied hearts. IVUS detected calcification in 285 frames; 17 (6.0\%) were calcified nodules and 268 (94.0\%) were nonnodular calcium by histopathology. Two calcified nodules (11.8\%) were solitary, and 15 (88.2\%) were adjacent to nonnodular calcium. IVUS characteristics of calcified nodules were (1) protruding and convex shape of the luminal surface (94.1\% in calcified nodule versus 9.7\% in nonnodular calcium; \(P<0.001\)), (2) convex shape of the luminal side of calcium (100\% versus 16.0\%; \(P<0.001\)), (3) irregular luminal surface (64.7\% versus 11.6\%; \(P<0.001\)), and (4) irregular leading edge of calcium (88.2\% versus 19.0\%; \(P<0.001\)).\textsuperscript{3}

Burke et al\textsuperscript{14} observed that healed plaque ruptures were associated with increased calcification and suggested that plaque disruption, via hemorrhage, may contribute to coronary calcification. Each calcified nodule is small, but calcified nodules tend to cluster\textsuperscript{13}; in the present investigation, multiple calcified nodules were observed in 76 of 623 patients (12\%), 22 in the same artery.

Culprit calcified nodule has been reported by 1 pathology group to be a rare cause of coronary thrombosis.\textsuperscript{12,13} However, nonculprit calcified nodule may represent precursor lesions similar to thin-cap fibroatheromas; calcified nodules do not often lead to thrombosis (as suggest by the low event rate in the present study), just as thin-cap fibroatheromas do not always result in plaque rupture. Furthermore, in a computed tomographic angiography study, Thilo et al\textsuperscript{15} reported that calcified nodules were rarely stenotic, similar to our present report, presumably because neither study evaluated culprit lesions.

### Table 4. Volumetric Gray-Scale, Virtual Histology Intravascular Ultrasound, and Quantitative Coronary Angiography of the Entire Coronary Tree Comparing Patients With at Least 1 Calcified Nodule and Patients Without Any Calcified Nodules

<table>
<thead>
<tr>
<th>Variable</th>
<th>Calcified Nodule (n=185)</th>
<th>No Calcified Nodule (n=438)</th>
<th>(P)</th>
</tr>
</thead>
<tbody>
<tr>
<td>3-Vessel volumetric gray-scale IVUS*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total length analyzed, mm</td>
<td>213.1 (167.7–256.4)</td>
<td>202.8 (159.4–252.4)</td>
<td>0.21</td>
</tr>
<tr>
<td>NC lesions, n</td>
<td>5.0 (4.0–6.0)</td>
<td>5.0 (3.0–6.0)</td>
<td>0.006</td>
</tr>
<tr>
<td>Length of NC lesions, mm</td>
<td>88.9 (59.6–115.8)</td>
<td>67.6 (43.6–95.0)</td>
<td>(&lt;0.0001)</td>
</tr>
<tr>
<td>Average EEM CSA, mm(^2)/mm</td>
<td>16.1 (14.1–18.59)</td>
<td>16.1 (13.9–18.6)</td>
<td>0.71</td>
</tr>
<tr>
<td>Average aumen CSA, mm(^2)/mm</td>
<td>8.0 (6.7–9.4)</td>
<td>8.1 (6.9–9.6)</td>
<td>0.37</td>
</tr>
<tr>
<td>Average P+M CSA, mm(^2)/mm</td>
<td>8.2 (7.0–9.6)</td>
<td>7.8 (6.7–9.2)</td>
<td>0.10</td>
</tr>
<tr>
<td>Plaque burden, %</td>
<td>50.1 (46.9–53.0)</td>
<td>48.8 (46.4–51.6)</td>
<td>0.002</td>
</tr>
<tr>
<td>3-Vessel volumetric VH-IVUS*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total VH-TCFA lesions, n</td>
<td>1.0 (0.0–2.0)</td>
<td>1.0 (0.0–2.0)</td>
<td>0.92</td>
</tr>
<tr>
<td>Patients with (\geq 1) VH-TCFAs, * (n/N)</td>
<td>51.7 (89/172)</td>
<td>54.8 (234/427)</td>
<td>0.50</td>
</tr>
<tr>
<td>Total ThCFA lesions, n</td>
<td>2.0 (1.0–3.0)</td>
<td>1.0 (0.0–2.0)</td>
<td>(&lt;0.0001)</td>
</tr>
<tr>
<td>DC volume, %</td>
<td>6.2 (4.1–10.3)</td>
<td>4.4 (2.5–7.8)</td>
<td>(&lt;0.0001)</td>
</tr>
<tr>
<td>Necrotic core volume, %</td>
<td>13.2 (8.9–18.0)</td>
<td>11.6 (6.9–17.3)</td>
<td>0.04</td>
</tr>
</tbody>
</table>

*Analysis performed by summing the volumes of all 3 coronary arteries on a per-patient basis.

IVUS indicates intravascular ultrasound; NC, nonculprit lesion; EEM, external elastic membrane; CSA, cross-sectional area; P+M, plaque + media; VH, virtual histology; TCFA, thin-cap fibroatheroma; ThCFA, thick-cap fibroatheroma; and DC, dense calcium. Values in parentheses are interquartile ranges.

IVUS indicates intravascular ultrasound; NC, nonculprit lesion; EEM, external elastic membrane; CSA, cross-sectional area; P+M, plaque + media; VH, virtual histology; TCFA, thin-cap fibroatheroma; ThCFA, thick-cap fibroatheroma; and DC, dense calcium. Values in parentheses are interquartile ranges.

\(\text{LAD Calcified Nodules n=114}\)

\(\text{LCX Calcified Nodules n=82}\)

\(\text{RCA Calcified Nodules n=118}\)

Figure 3. Longitudinal distribution of calcified nodules. A total of 85\% of the calcified nodules in the left anterior descending artery (LAD) and 86\% of the calcified nodules in the left circumflex artery (LCX) were located between 0 and 40 mm from the coronary ostium. Conversely, calcified nodules within the right coronary artery (RCA) were evenly and more distally distributed.
Calcified Nodule as a Marker of Atherosclerosis

Previous pathological studies have shown a correlation between coronary calcium and atherosclerotic plaque volume. Mintz et al\textsuperscript{17} reported that the presence and magnitude of target lesion calcium paralleled the atherosclerotic PB as assessed by IVUS. Similarly, Sangiorgi et al\textsuperscript{18} reported the relationship between the calcium area and PB (but not luminal stenosis) in a histopathological study of 723 coronary artery segments using nondecalcified methodology. Thus, these studies taken together imply that calcium is a reliable marker for extensive atherosclerosis. In the present study, PB was greater in patients with at least 1 calcified nodule than in patients with no calcified nodules, along with more ThCFAs (but not more VH-TCFAs) and more necrotic core plaque and dense calcium. These findings suggested that calcified nodules might be a marker for atherosclerosis; however, they were associated with fewer future cardiac events, suggesting quiescence rather than ongoing activity.

Axial Distribution of Calcified Nodules

There are no pathology data on the location of nonculprit calcium. Virmani et al\textsuperscript{12} reported that culprit calcified nodules were found predominantly in the mid-RCA, where coronary torsion stress was maximal. Interestingly, in the present study, coronary artery calcified nodules occurred in a limited, focal distribution similar to plaque ruptures, acute occlusions, and TCFAs. Calcified nodules in the present study were clustered mainly in the proximal segments of the LAD and LCx, whereas calcified nodules within the RCA were evenly and more distally distributed. In an angiographic study, Wang et al\textsuperscript{9} analyzed 208 consecutive patients with ST-segment–elevation myocardial infarction to determine the location of epicardial thrombosis and found that the occlusions tended to cluster within the proximal third of each coronary artery. In a 3-vessel IVUS study, Hong et al\textsuperscript{10} evaluated the axial location of plaque rupture in 392 patients. Plaque ruptures occurred mainly in the proximal segments of the LAD, the proximal and distal segments of RCA, and the entire LCx. Cheruvu et al\textsuperscript{11} also reported that TCFAs tended to cluster in predictable spots within the proximal third of the major coronary arteries in a pathological study.

Angiographic and VH Features of Calcified Nodule

The angiographic appearance of calcified nodules is not well established. One previous study reported a patient with an intracoronary angiographic filling defect that initially was diagnosed as intraluminal thrombus but whose preintervention IVUS imaging showed that the filling defect was, in fact, superficial calcification consistent with the appearance of a calcified nodule.\textsuperscript{19} However, in the present study, calcified nodules were an incidental finding, with 257 (82%) appearing normal on angiography, 38 (14%) having evidence of angiographic haziness, and 19 (6%) having the appearance of angiographic calcium. The reasons for the absence of any angiographic filling defects in the present analysis may be that we studied only nonculprit lesions, the calcium nodules in the present study were relatively small, and angiographic filling defects have been reported in culprit lesions of ACS patients, albeit rarely.

The VH-IVUS appearance of calcified nodules has never been reported. On pathology, calcified nodules appeared to be a mixture of calcified plate, bony spicules, and interspersed...
fibron.12 We observed that a calcified nodule itself and its adjacent segment mostly had stable VH phenotype (calcified ThCFa or noncalcified ThCFa). The accuracy of VH-IVUS analysis behind calcium continues to be controversial and probably depends on the thickness, density, and amount of calcium analyzed. Sales et al.20 reported that “adding” calcific elements to the atherosclerotic plaque led to a directly proportional increase in the area coded as necrotic core in VH-IVUS images and influenced the exact measurement of the amount and extent of necrotic core. Thus, in the present investigation, the necrotic core volume in the calcified nodule group might be overestimated by the influence of a greater amount of dense calcium. However, it is interesting to speculate that the presence of stable VH-IVUS lesion morphology may have contributed to the clinical outcomes in the present study.

**Calcified Nodules and Cardiac Events**

Virmani et al.12 found calcified nodules in sudden coronary death victims and hypothesized that physical forces exerted by the nodules themselves might contribute to fibrous-cap disruption. However, other evidence indicated that calcific plaque may be stabilized as it evolves with decreased hard/soft interface area and thus less prone to rupture than noncalcified lesions.21 In the present study, we observed consistently fewer nonculprit lesion major adverse cardiac events in the calcified nodule group compared with the noncalcified nodule group at the 1-, 2-, or 3-year follow-up. More important, there was no death, cardiac arrest, or myocardial infarction in the calcified nodules group. Several explanations are possible. First, calcified nodules were rarely VH-TCFAs; the VH phenotype appearance of calcific nodules has not been associated with increased events.22,23 Second, calcified nodules were not associated with an increased frequency of VH-TCFAs elsewhere in the coronary tree, and VH-TCFAs were the only phenotype associated with increased events in PROSPECT.4 Third, calcified nodules may have been the end result of plaque rupture, thrombosis, and healing rather than being causative of events.

**Limitations**

The study cohort included nonculprit lesions in ACS patients, it did not include culprit lesions and was not a study of a general patient population. Because vulnerable plaques tend to be clustered, the actual prevalence of calcified nodules might be lower than what we presented. Second, IVUS was performed after culprit lesion intervention; therefore, plaque tissue morphology at the culprit site could not be evaluated for the existence of calcified nodules. Third, pathological study has shown that a calcified nodule may be covered by a thin layer of fibrin or endothelium that is below the resolution of traditional IVUS. However, this should not affect the diagnostic accuracy of IVUS, although it might affect the likelihood that a calcified nodule would cause an event. In the future, tissue characterization of calcified nodules along with any overlying tissue should be detectable with optical coherence tomography. Fourth, the fact that relatively few events occurred during follow-up in the present study—both in patients with and in those without calcified nodules—attests to the benefits of intensive medical therapy in compliant patients and how closely these patients were followed up in this clinical trial (and expertly treated when severe angina did occur). Finally, calcification is a reflector for ultrasound, causing typical acoustic shadowing in the IVUS images. Ultrasound signals cannot penetrate or pass through the calcified layer and are reflected back toward the transducer. Therefore, accurate tissue characterization of the areas beneath calcification such as the interior of the calcified nodules in the present study is not possible as with conventional IVUS. The accuracy of VH-IVUS analysis behind calcium continues to be controversial and probably depends on the thickness, density, and amount of calcium analyzed.

**Conclusions**

Our findings demonstrated that calcified nodules in human coronary arteries were frequent and focally distributed. They were common in older patients and were unlikely to cause events during a 3-year follow-up.

**Disclosures**

Dr Xu has received a research grant from Boston Scientific, China. Dr Maehara has received research grant support from Boston Scientific Corp and speaker’s honoraria from Volcano Corp. Dr Mintz has received research grant support from and is a consultant for Volcano Corp. Dr Stone is a consultant for Medtronic, Boston Scientific, Abbott Vascular, and The Medicines Company. Dr McPherson is a consultant for Abbott Vascular. The other authors report no conflicts.

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**CLINICAL PERSPECTIVE**

The majority of acute coronary syndrome events are the result of sudden luminal thrombosis, with 55% to 60% caused by plaque rupture, 30% to 35% resulting from plaque erosion, and a small portion due to a calcified nodule. In the present analysis using 3-vessel intravascular ultrasound and virtual histology imaging and comprehensive follow-up data from Providing Regional Observations to Study Predictors of Events in the Coronary Tree (PROSPECT), we describe the frequency of incidentally detected calcified nodules and the angiographic appearance, intravascular ultrasound and virtual histology intravascular ultrasound features, and natural history of patients whose arteries contain ≥1 calcified nodules. The incidence of calcified nodule was 17% per artery and 30% per patient. Two or more calcified nodules were detected in 48 coronary arteries (3%) in 76 patients (12%). The calcified nodules were located <40 mm from the ostium of the coronary artery in 85% of left anterior descending arteries and 86% of left circumflex arteries, whereas calcified nodules within the right coronary arteries were evenly and more distally distributed, similar to other vulnerable plaque types. Patients with calcified nodules were significantly older and had more plaque volume, more thick-cap fibroatheroma, but fewer events at follow-up that could be attributed to their calcified nodules. Therefore, although a culprit calcified nodule has been reported by 1 pathology group to be a cause (albeit rarely) of coronary thrombosis, incidentally detected nonculprit calcified nodules appear to be more benign and do not often lead to thrombosis as suggested by the low event rate in the present study.