EXPEDITED REVIEWS

Coronary Artery Calcification and Changes in Atheroma Burden in Response to Established Medical Therapies

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Objectives
This study sought to determine the relationship between coronary calcification and plaque progression in response to established medical therapies.

Background
Coronary calcification correlates with the extent of atherosclerosis and predicts clinical outcome.

Methods
Atheroma volume was determined in serial intravascular ultrasound pullbacks in matched arterial segments of 776 patients with angiographic coronary artery disease. A calcium grade at baseline was assigned for each image (0 = no calcium, 1 = calcium with acoustic shadowing < 90° and 2 = calcium with shadowing > 90°). Patients with a calcium index (average of calcium scores in a pullback) below versus above the median were compared with regard to plaque burden and progression.

Results
Patients with a high calcium index were older (59 vs. 54 years, p < 0.001), more likely to be male (80% vs. 68%, p < 0.001), and more likely to have a history of hypertension (71% vs. 64%, p = 0.03). These patients had a greater percentage atheroma volume (PAV) (45% vs. 34%, p < 0.001), total atheroma volume (TAV) (210 vs. 151 mm³, p < 0.001), and percentage of images with maximal plaque thickness ≥ 0.5 mm (93% vs. 72%, p < 0.001). The continuous rate of change in PAV (1.1 ± 0.4% vs. 0.8 ± 0.4%, p = 0.34) and TAV (1.7 ± 2.1% vs. -0.1 ± 2.2%, p = 0.37) was similar in patients with a lower and higher calcium index, respectively. A lower calcium index was associated with a higher rate of patients showing substantial change in atheroma burden (at least 5% change in PAV, 70% vs. 53%, p < 0.001).

Conclusions
Calcific plaques are more resistant to undergoing changes in size in response to systemic interventions targeting atherosclerotic risk factors. (J Am Coll Cardiol 2007;49:263–70) © 2007 by the American College of Cardiology Foundation

The significance of calcification in the genesis of atherosclerotic cardiovascular disease has received increasing attention. The calcified plaque has traditionally been regarded as the most established atheroma within the arterial tree (1). and often presents a challenge for percutaneous interventions (2). However, it has become apparent that plaque calcification represents a dynamic process that is intimately related to the degree of inflammatory activity (3). A number of inflammatory chemokines elaborated during atherogenesis stimulate the expression and activity of osteoblast-like cells within the arterial wall that produce calcium (4–9).

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The conventional view that calcified atheromas are less likely to undergo fibrous cap rupture has been modified to consider the extent, location, and morphologic appearance of calcification. In particular, microcalcification deposits in the shoulder region of atheroma are associated with an increased risk of fibrous cap rupture and subsequent ischemic events (10,11).
A number of imaging modalities have been reported to detect the degree of calcification within the coronary arterial tree. Increasing amounts of calcification, detected by computed tomography, has been reported to predict the presence and extent of atherosclerotic plaque (12–15), in addition to the likelihood of clinical events (16,17). Investigations are underway to understand how best the noninvasive quantification of coronary artery calcification can be integrated into clinical algorithms for cardiovascular risk stratification. Further, it remains unclear whether modifying the degree of progression of calcification in response to a number of systemic antiatherosclerotic therapies is associated with clinical benefit.

Intravascular ultrasound (IVUS) can image the entire arterial wall, is well validated to assess the volumetric extent of atheroma, and provides a limited characterization of its degree of calcification (18). A number of studies have used serial IVUS assessments of the arterial wall to show that intensive modification of atherosclerotic risk factors is associated with attenuation of plaque progression (19–21). The current study investigated the relationship between the degree of plaque calcification and both atheroma burden and its rate of progression in response to use of systemic interventions that target established risk factors.

Methods

Selection of patients. A retrospective analysis was performed of patients who participated in the REVERSAL (Reversal of Atherosclerosis with Aggressive Lipid Lowering Therapy) (21) and CAMELOT (Comparison of Amlodipine vs. Enalapril to Limit Occurrences of Thrombosis) (20) studies. These studies assessed the impact of intensive lipid-lowering and antihypertensive therapy on the rate of coronary atherosclerotic plaque progression. These studies involved serial assessment of a coronary arterial segment by IVUS using a standardized methodology and involved a high background rate of established medical therapies. Patients aged 30 to 75 years were identified as having coronary artery disease on angiography, performed for clinical indications, with at least one 20% diameter stenosis in a coronary artery. A target vessel was selected that had not undergone percutaneous intervention and had no luminal stenosis >50% throughout a target segment of at least 30 mm in length. A central laboratory performed all biochemical determinations (Medical Research Laboratory, Highland Heights, Kentucky).

Acquisition and analysis of IVUS images. The details of IVUS acquisition and analysis have been described in detail previously (19–21). An IVUS catheter was advanced into the target vessel after administration of between 100 and 300 μg of intracoronary nitroglycerin, and the transducer was positioned distal to a side branch. The catheter was withdrawn through the target vessel by a motor drive at a speed of 0.5 mm/s. Images were recorded on videotape at 30 frames/s. Cross-sectional images, spaced 1 mm apart in the pullback from a distal to proximal fiduciary site, were analyzed in a blinded fashion. Using the National Institutes of Health Image (version 1.62, National Institutes of Health public domain software, Bethesda, Maryland), manual planimetry was used to trace the leading edges of the luminal and external elastic membrane (EEM) borders. A segment was not measured if substantial artifact, presence of an arterial side branch, or extensive calcification precluded adequate planimetry of the EEM border. In the event that an image could not be analyzed, the corresponding image acquired at the other time point was not used for analysis.

ATHEROMA VOLUME. Total atheroma volume (TAV) was calculated as the average of the differences between EEM and lumen areas across all evaluable slices and then normalized to the length corresponding to the median number of comparable slices in the whole population.

The need to normalize atheroma volume reflects the heterogeneity in pullback length between patients because this is determined by the anatomical location of the side branches defining the proximal and distal fiduciary points. Percentage atheroma volume (PAV) representing the proportion of the vessel volume occupied by atheroma was calculated as the percentage of the sum of EEM areas occupied by TAV.

ARTERIAL REMODELING. Remodeling was calculated in 3 different ways: 1) Remodeling was characterized at the single cross-sectional site containing the greatest amount of plaque. A remodeling index (RI) was calculated at the site containing the greatest plaque area by calculating the ratio of the EEM area at that site (lesion) compared with the EEM area at a reference site containing the least amount of plaque in the 10 mm proximal to this site. Remodeling was categorized as expansive (RI >1.05), none (RI 0.95 to 1.05) or constrictive (RI <0.95) at that site. 2) Remodeling was characterized throughout the entire arterial segment by evaluating EEM and lumen volumes. 3) The serial change in remodeling was determined as the difference between RI, EEM, and lumen volumes at baseline and at completion of the study.

EXTENT OF CALCIUM. Calcification was assessed in 2 different ways: 1) A calcium grade was assigned for each measured image, which reflected the presence of calcium and degree of acoustic shadowing that resulted (0 = no calcium, 1 = calcium with acoustic shadowing <90°, and 2 = calcium with shadowing >90°). In images that contained multiple calcium deposits, the grade represented the summation of all angles of acoustic shadows present. A calcium index was derived for each pullback by determining the
average calcium grade of all measured images. For the purpose of the current analysis, patients were stratified according to having a calcium index less than or greater than the median (0.26). The atheroma area was not calculated for images containing calcium with an acoustic shadow $>$90° that precluded accurate planimetry of the EEM leading edge, resulting in exclusion of these images from volume calculations. However, the calcium grade for these images was included in the analysis. 2) The degree of calcification was also expressed as the percentage of images containing any detectable calcium.

**Statistical analysis.** Continuous variables are expressed as mean ± SD (median) and categorical variables as percentage. C-reactive protein is expressed as median (interquartile range). Groups were compared using unpaired t tests or Mann-Whitney log rank tests when the variable was not normally distributed. Correlations were assessed using Spearman rank-order correlation coefficients. To account for potential differences between the individual studies in this pooled analysis, a random-effects model was used to determine changes in atheroma volume in the groups. In addition to a volumetric analysis, patients were also classified as undergoing substantial change (at least 5% relative change in PAV from baseline) or no substantial change ($<$5% relative change in PAV from baseline). A value of p < 0.05 was considered significant. All statistical analyses were performed using SAS software, version 8.2 (SAS Institute Inc., Cary, North Carolina).

**Table 1 Clinical Characteristics of Subjects with a Calcium Index < or ≥ Median**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Calcium Index &lt; Median (n = 383)</th>
<th>Calcium Index ≥ Median (n = 393)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yrs)</td>
<td>$54.2 \pm 9.6$ (53)</td>
<td>$58.6 \pm 9.1$ (58)</td>
<td>$&lt;0.001$</td>
</tr>
<tr>
<td>Male (%)</td>
<td>68.1</td>
<td>80.4</td>
<td>$&lt;0.001$</td>
</tr>
<tr>
<td>Caucasian (%)</td>
<td>88.8</td>
<td>91.6</td>
<td>0.19</td>
</tr>
<tr>
<td>Body mass index (kg/m$^2$)</td>
<td>$30.3 \pm 5.5$ (29.3)</td>
<td>$30.4 \pm 5.9$ (29.5)</td>
<td>0.67</td>
</tr>
<tr>
<td>Hypertension (%)</td>
<td>63.7</td>
<td>71.0</td>
<td>0.03</td>
</tr>
<tr>
<td>Diabetes (%)</td>
<td>17.2</td>
<td>19.3</td>
<td>0.45</td>
</tr>
<tr>
<td>Metabolic syndrome (%)</td>
<td>37.3</td>
<td>37.2</td>
<td>0.96</td>
</tr>
<tr>
<td>Dyslipidemia (%)</td>
<td>96.6</td>
<td>95.2</td>
<td>0.31</td>
</tr>
<tr>
<td>Smoker (%)</td>
<td>23.8</td>
<td>27.2</td>
<td>0.29</td>
</tr>
<tr>
<td>Previous MI (%)</td>
<td>32.4</td>
<td>38.4</td>
<td>0.08</td>
</tr>
<tr>
<td>Previous CABG (%)</td>
<td>2.1</td>
<td>4.1</td>
<td>0.11</td>
</tr>
<tr>
<td>Previous PCI (%)</td>
<td>50.1</td>
<td>62.8</td>
<td>$&lt;0.001$</td>
</tr>
<tr>
<td>Statin (%)</td>
<td>32.6</td>
<td>33.6</td>
<td>0.78</td>
</tr>
<tr>
<td>Beta-blocker (%)</td>
<td>65.8</td>
<td>77.1</td>
<td>$&lt;0.001$</td>
</tr>
<tr>
<td>Aspirin (%)</td>
<td>90.6</td>
<td>93.9</td>
<td>0.09</td>
</tr>
<tr>
<td>ACE Inhibitor (%)</td>
<td>31.1</td>
<td>33.3</td>
<td>0.50</td>
</tr>
<tr>
<td>Calcium channel blocker (%)</td>
<td>27.4</td>
<td>32.6</td>
<td>0.12</td>
</tr>
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</table>

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Median (n = 393)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total cholesterol (mg/dl)</td>
<td>214.1 (214)</td>
<td>0.81</td>
</tr>
<tr>
<td>LDL cholesterol (mg/dl)</td>
<td>134.1 (136.5)</td>
<td>0.78</td>
</tr>
<tr>
<td>HDL cholesterol (mg/dl)</td>
<td>42.3 (40)</td>
<td>0.49</td>
</tr>
<tr>
<td>Triglycerides (mg/dl)</td>
<td>190.2 (168)</td>
<td>0.72</td>
</tr>
<tr>
<td>Systolic blood pressure (mm Hg)</td>
<td>130.5 (129)</td>
<td>0.001</td>
</tr>
<tr>
<td>Diastolic blood pressure (mm Hg)</td>
<td>78.0 (79)</td>
<td>0.07</td>
</tr>
<tr>
<td>C-reactive protein (mg/l)</td>
<td>2.90 (2.67)</td>
<td>0.72</td>
</tr>
</tbody>
</table>

Continuous variables expressed as mean ± SD (median) and categorical variables expressed as percentage. C-reactive protein expressed as median (interquartile range).

ACE = angiotensin-converting enzyme; CABG = coronary artery bypass graft; HDL = high-density lipoprotein; LDL = low-density lipoprotein; MI = myocardial infarction; PCI = percutaneous coronary intervention; SD = standard deviation.

**Results**

**Clinical characteristics.** Clinical characteristics, use of antiatherosclerotic therapies, and degree of risk factor control are summarized in Table 1; 64.7% of patients participated in the REVERSAL trial and 35.3% in the CAMELOT study. Patients with a calcium index greater than the median were older ($58.6 \pm 9.1$ years vs. $54.2 \pm 9.6$ years, $p < 0.001$), more likely to be male (80.4% vs. 68.1%, $p < 0.001$), and more likely to have a history of hypertension (71.0% vs. 63.7%, $p = 0.03$) or previous percutaneous intervention (62.8% vs. 50.1%, $p < 0.001$). Patients with a greater calcium index were more likely to have had a previous myocardial infarction (38.4% vs. 32.4%, $p = 0.08$), although this failed to meet statistical significance. Patients with a greater calcium index were more likely to receive a beta-blocker (77.1% vs. 65.8%, $p < 0.001$) and aspirin (93.9% vs. 90.6%, $p = 0.09$), although the latter failed to meet...
statistical significance. The degree of risk factor control did not differ between the groups, except for a higher systolic blood pressure (134.4 ± 17.7 mm Hg vs. 130.5 ± 16.3 mm Hg, p = 0.001) in the patients with a greater calcium index. **Baseline atheroma burden.** The relationship between coronary artery calcification and atheroma burden at baseline is summarized in Table 2. Patients with a calcium index above the median had a greater PAV (45.1 ± 8.7% vs. 34.2 ± 9.7%, p < 0.001), normalized TAV (210.0 ± 75.7 mm³ vs. 150.6 ± 67.0 mm³, p < 0.001), and percentage of images that contained plaque (defined as maximal plaque thickness >0.5 mm, 92.7 ± 12.7% vs. 71.9 ± 27.7%, p < 0.001). The percentage of images containing calcium correlated positively with PAV (r = 0.61, p < 0.0001) and normalized TAV (r = 0.47, p < 0.0001).

**Baseline arterial wall remodeling.** The relationship between arterial calcification and remodeling, at the site containing the greatest amount of plaque and throughout the pullback, is summarized in Table 3 and Figure 1. The RI at the most diseased site was lower in patients with a calcium index above the median (0.94 ± 0.21 vs. 0.97 ± 0.22, p = 0.03). This is consistent with the finding that patients with a greater calcium index were more likely to show constrictive remodeling (defined as an RI <0.95) at this site (51.4% vs. 43.5%, p = 0.03) at baseline. The degree of calcification was also associated with arterial wall dimensions throughout the pullback. Patients with a greater calcium index had a smaller lumen volume (253.8 ± 83.1 mm³ vs. 286.8 ± 101.8 mm³, p < 0.001) and a larger EEM volume (463.8 ± 137.8 mm³ vs. 437.4 ± 143.7 mm³ in high and low calcium groups respectively, p = 0.009). This is consistent with the finding that the percentage of images containing calcium correlated inversely with the lumen volume (r = −0.19, p < 0.0001) and directly with EEM volume (r = 0.12, p = 0.0007).

**Risk factor control with therapy.** The use of established antiatherosclerotic therapies and the degree of risk factor control are summarized in Table 4. Patients with a greater calcium index were more likely to be treated with a beta-blocker (81.7% vs. 70.0%, p < 0.001) and less likely to receive a statin (94.1% vs. 97.1%, p = 0.04). Apart from a higher systolic blood pressure in patients with a greater calcium index (131.5 ± 13.3 mm Hg vs. 128.0 ± 12.3 mm Hg, p < 0.001), the groups did not differ with regard to the degree of risk factor control on therapy.

**Serial plaque progression and remodeling.** The relationship between baseline coronary artery calcification and rate of change of plaque and remodeling, in response to use of established medical therapies, is summarized in Table 5 and Figure 2. There was no correlation between the percentage of images containing calcium at baseline and change in PAV (r = −0.06, p = 0.10) and normalized TAV (r = −0.06, p = 0.08) as continuous variables. As continuous variables, there was no difference between the low-calcium and high-calcium groups with regard to changes in PAV (1.1 ± 0.4% vs. 0.8 ± 0.4%, p = 0.34) and TAV (1.7 ± 2.1% vs. −0.1 ± 2.2%, p = 0.37). However, patients who showed evidence of substantial changes in PAV (>5% relative change in either direction) had lower baseline calcium indices (median 0.21 vs. 0.38, p < 0.001). A greater proportion of patients with a baseline calcium index below the median were likely to undergo a substantial change in atheroma burden (defined as at least a 5% change in PAV, 69.7% vs. 52.9%, p < 0.001) (Fig. 2). On multivariate analysis, controlling for differences in clinical characteristics, patients with a greater baseline calcium index remained less likely to undergo any substantial change in atheroma volume (odds ratio 0.48, 95% confidence interval 0.35 to 0.66, p < 0.0001). Similarly, patients with a lower calcium index were more likely to undergo substantial changes in atheroma volume.

### Table 2 Baseline Atheroma Burden of Subjects With a Calcium Index < or ≥ Median

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Calcium Index &lt; Median (n = 383)</th>
<th>Calcium Index ≥ Median (n = 393)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atheroma volume (%)</td>
<td>34.2 ± 9.7 (34.5)</td>
<td>45.1 ± 8.7 (44.6)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Total atheroma volume (mm³)</td>
<td>150.6 ± 67.0 (144.8)</td>
<td>210.0 ± 75.7 (197.2)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Abnormal images (%)†</td>
<td>71.9 ± 27.7 (80.6)</td>
<td>92.7 ± 12.7 (100)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Worst-least 10-mm volume†</td>
<td>2.32 ± 4.19 (1.44)</td>
<td>1.78 ± 2.18 (1.21)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Length of pullback (mm)</td>
<td>36 ± 14.2 (34)</td>
<td>38.4 ± 14.7 (37)</td>
<td>0.02</td>
</tr>
</tbody>
</table>

Results expressed as mean ± SD (median). *Abnormal image defined as containing a maximal plaque thickness >0.5 mm.
†Ratio of atheroma volume in the 10-mm segments containing the most and least amount of atheroma.

### Table 3 Baseline Remodeling Indices of Subjects With a Calcium Index < or ≥ Median

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Calcium Index &lt; Median (n = 383)</th>
<th>Calcium Index ≥ Median (n = 393)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Remodeling index</td>
<td>0.97 ± 0.22 (0.99)</td>
<td>0.94 ± 0.21 (0.94)</td>
<td>0.03</td>
</tr>
<tr>
<td>EEM volume (mm³)</td>
<td>437.4 ± 143.7 (419.1)</td>
<td>463.8 ± 137.8 (438.6)</td>
<td>0.009</td>
</tr>
<tr>
<td>Lumen volume (mm³)</td>
<td>286.8 ± 101.8 (272.4)</td>
<td>253.8 ± 83.1 (241.0)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Results expressed as mean ± SD (median). Remodeling index was calculated as the ratio of the EEM area at the site containing the most amount of plaque to the EEM area at a reference site containing the least amount of plaque in the proximal 10 mm.

EEM = external elastic membrane.
burden in response to intensive risk factor modification (Fig. 3). The groups did not differ with regard to the reduction in RI at the site containing the greatest amount of plaque. *p < 0.05 for comparison between groups.

Discussion

The findings of the current study show that patients with more plaque calcification are less likely to undergo changes in the amount of atheroma in response to use of medical therapies that target established cardiovascular risk factors. This occurred on the background of a positive relationship between the degree of calcification and both the extent and diffuse nature of coronary atherosclerosis. These results have potential implications for the prediction of which patients are likely to derive benefit from aggressive risk factor modification.

The finding that greater degrees of calcium are associated with more extensive atheroma burden is consistent with previous reports of a correlation between the amount of plaque and calcium on pathological studies (22) and a small cohort studied by IVUS (23). This supports the traditional view that older and more established plaques are more likely to calcify in response to a chronic pathological process (22). It also highlights the relationship between the degree of plaque calcification and the pattern of arterial remodeling. A large number of pathological and imaging studies have described the phenomenon whereby the arterial wall undergoes changes in size and shape, termed remodeling, in response to plaque accumulation (24,25). The typical response of the arterial wall is to undergo expansion in response to plaque deposition, in a process that initially preserves luminal dimensions. Contraction of the arterial wall with subsequent shrinkage of the lumen, constrictive remodeling, is more commonly seen in the presence of chronic coronary artery disease (26). This is supported by the current findings that patients with a greater amount of plaque calcium were more likely to show constrictive remodeling at the most diseased site, although contrasts with
a previous report that calcification did not differ between sites with compensatory enlargement or focal contraction (27). It has been reported that culprit lesions with constrictive remodeling are typically found in the setting of stable ischemic syndromes (26). This provides further support for the concept that calcified plaques might be more stable and less likely to rupture (28–31).

The current findings are in agreement with established reports showing that the degree of coronary arterial calcification, as determined by a range of noninvasive imaging modalities, correlates with the extent of atherosclerotic plaque in pathological specimens (12–15). The ability of IVUS to visualize the entire vessel wall provides a unique opportunity to precisely determine the correlation between these factors, in both a static and serial fashion, in vivo (18). The results of the current study suggest that in response to use of established medical therapies, the presence of greater degrees of calcium at baseline are associated with less change in the extent of atherosclerotic plaque. This is consistent with the finding from pathological studies that more calcified plaques contain less lipidic and inflammatory material (22). Given that flux of the lipidic, inflammatory, and necrotic components is likely to be more amenable to modification by use of antiatherosclerotic therapies, it is not surprising that more calcified lesions contain less of this material and are therefore less likely to undergo significant changes in morphology.

This has important implications for the use of imaging modalities that quantify coronary calcium in the assessment...
of antiatherosclerotic strategies. A number of reports have emerged describing the influence of lipid-lowering therapy on the rate of change of coronary calcium. Although lowering low-density lipoprotein cholesterol with cerivastatin was reported to reduce the annual rate of progression of coronary calcification (32), a number of groups have reported that intensive lowering of low-density lipoprotein cholesterol has no effect (33,34). Given that the current findings suggest that more calcified lesions are less likely to undergo changes in size, despite a similar degree of risk factor control with therapy, it must be questioned whether the serial assessment of coronary calcification is the most optimal method for determining which patients are likely to derive the greatest benefit from intensive risk factor modification or to assess the potential efficacy of experimental agents.

A number of limitations should be noted. This is an analysis of pooled patient cohorts from 2 randomized clinical trials that used serial IVUS evaluation of coronary atheroma by the primary end point. 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 provides a database of a large number of patients who have undergone serial assessments of plaque burden. The impact of a high, but not universal, use of established preventive medical therapies was assessed.

A number of analytical methods have been used to quantify the degree of calcification. These include direct measurement of the length and degree of arc of visualized calcification, the degree of acoustic shadowing behind the calcific deposit, and expression of the percentage of luminal surface occupied by calcium as determined by videodensitometry. The precision of each of these approaches is influenced by a number of factors, including the physical distance between the ultrasound transducer and site of calcification. Regardless, it is clear that patients who have more calcium are less likely to undergo substantial changes in the extent of coronary atherosclerosis.

It is not known whether the results can be applied to patients older than the patients who participated in these studies. However, given that the degree of calcification increases with age, the clinical utility of detecting calcium in elderly patients is questionable. It should be noted that a small number of images could not be analyzed because of extensive calcification that precluded adequate measurement of the EEM. Therefore, the difference in plaque burden between the 2 groups is likely to have been even greater. Further, patients with extensive calcification throughout the length of the pullback at baseline were excluded from participating in the studies if an accurate determination of atheroma volume was not possible. Therefore, these extreme levels of calcification were not included in the analysis. Given their small number, it is unlikely that they would have had a significant impact on the findings. However, it remains to be determined whether such heavily calcified lesions are also resistant to undergoing changes in size in response to established medical therapies.

Similarly, IVUS provides a very broad distinction of plaque composition, and in its current form it cannot reliably quantify changes in lipidic, inflammatory, and fibrotic components in response to systemic interventions. It also remains to be shown that changes in atheroma volume on serial IVUS directly correlate with clinical outcome. However, it is possible that substantial changes in atheroma are more likely to be clinically relevant for patients in terms of cardiovascular event rates. Investigating this hypothesis is beyond the scope of the current analysis.

In summary, patients with a greater amount of coronary atheroma calcification have more extensive plaque, which is less likely to undergo changes in response to intensive risk factor modification. This has important implications for the prediction of which patients are likely to derive the greatest benefit from implementation of aggressive risk factor modification strategies.

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