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Attenuated Plaque at Nonculprit Lesions in Patients Enrolled in Intravascular Ultrasound Atherosclerosis Progression Trials

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Objectives We investigated attenuated plaque (hypoechoic plaque with deep ultrasonic attenuation despite absence of bright calcium) in nonculprit lesions.

Background Recent intravascular ultrasound (IVUS) studies describe acoustic shadowing behind large, echolucent, acute culprit lesion sites in the absence of bright calcium. Such "attenuated plaque" is considered a characteristic of high-risk lesions, but its prevalence in stable nonculprit lesions is incompletely known.

Methods We reviewed IVUS pullback data from nonculprit vessels in 159 patients from the ASTEROID (A Study to Evaluate the Effect of Rosuvastatin on Intravascular Ultrasound-Derived Coronary Atheroma Burden) trial. We identified attenuated plaque and compared volumetric IVUS data in the segments with and without attenuation. In addition, we described plaque morphology in segments with attenuation at baseline and follow-up.

Results Attenuated plaque was found in 17 of 159 patients (10.7%, 95% confidence interval: 6% to 17%). At baseline, there were no significant differences in clinical presentation and cardiovascular risk factors between patients with and without attenuation. Other than a greater plaque eccentricity index ($p = 0.008$), there were no significant differences between segments with and without attenuation. In segments with attenuated plaque, expansive remodeling was observed in 53%, and calcified plaque adjacent to the attenuation site in 70% of patients. During follow-up, attenuation remained stable, and no events occurred in the patients with attenuation.

Conclusions Attenuated plaque is present in a significant number of nonculprit segments in patients enrolled in IVUS progression trials and remains stable during follow-up. There is a relationship with mixed calcified lesions. These findings challenge the prior assumption that attenuated plaque is a finding limited to culprit lesions associated with acute clinical presentation. (J Am Coll Cardiol Intv 2009;2:672–8) © 2009 by the American College of Cardiology Foundation

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Intravascular ultrasound (IVUS) allows limited characterization of atherosclerotic plaque morphology based on the echogenicity of the reflected signal. Accepted categories include echolucent, echodense, and echodense with shadowing ("calcified") plaque and reflect underlying plaque composition (1). Acoustic shadowing describes areas of signal void behind highly reflective or absorbent structures and is typically seen behind calcified plaque. However, very dense fibrous plaques may also produce sufficient attenuation to cause acoustic shadowing (1).

Recent observations at culprit lesions in patients with acute coronary syndromes have described acoustic shadowing behind large, echolucent plaques (Fig. 1). This finding has been termed "attenuated plaque" and has been considered an IVUS characteristic of high-risk lesions (2–4). The concept that attenuated plaque is an exclusive marker of lesion instability is supported by recent data showing absence of attenuation at the lesion sites causing stable coronary syndromes (5), and could have therapeutic implications in the setting of percutaneous coronary intervention (4). However, to understand the significance of "attenuation," it is important to investigate its presence and frequency in stable, nonculprit lesion sites.

We hypothesized that attenuated plaque can be present in vessel segments unrelated to clinical presentation. To test this hypothesis, we systematically evaluated the presence of attenuated plaque at nonculprit lesion sites in patients enrolled in an atherosclerosis progression trial.

Methods

Subject selection. We examined IVUS data from the ASTEROID (A Study to Evaluate the Effect of Rosuvastatin on Intravascular Ultrasound-Derived Coronary Atheroma Burden) trial (6). Similar to other IVUS progression trials, only patients with at least 1 obstructive lesion were included, and IVUS was performed in a vessel not containing the culprit lesion. Because attenuated plaque is typically described in larger plaques, we selected 159 patients with percent atheroma volume above the median for this study.

Standard IVUS acquisition and analysis data derived from the ASTEROID trial data. The acquisition protocol in the ASTEROID trial has been described in detail previously (6). In brief, after anticoagulation and administration of intracoronary nitroglycerin, a high-frequency ultrasound imaging catheter (40 MHz) was inserted in a nonculprit target vessel as far distally as possible. Continuous ultrasonic imaging was acquired during withdrawal of the catheter through the segment of artery at a constant rate of 0.5 mm/s. Images were stored on videotape and subsequently digitized for analysis in a single core laboratory by individuals who were blinded to the clinical characteristics and treatment status of the patients.

Images spaced precisely 1 mm apart in the segment of interest were selected for analysis. Using the National Institutes of Health Image public domain software (version 1.62, National Institutes of Health, Bethesda, Maryland), manual planimetry was used to trace the leading edge of the luminal and the external elastic membrane (EEM) borders. The EEM area, lumen area, minimal plaque thickness, maximal plaque thickness, maximal luminal diameter, and minimal luminal diameter were measured. The plaque area (defined as: EEM area − lumen area), percentage cross-sectional area reduction (defined as: plaque area/EEM area × 100%), and plaque eccentricity index (defined as: plaque and media thickness maximum/plaque and media thickness min >2.0) were calculated. Total atheroma volume 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 numbers of comparable slices in the whole population. Percentage atheroma volume, representing the proportion of the vessel volume occupied by atheroma, was calculated as the percentage of the sum of EEM areas occupied by total atheroma volume.

Calcification was identified as brighter echoes than adventitia with acoustic shadowing. The extent of calcification was described by the percentage of images containing calcium. 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.

Abbreviations and Acronyms

CI = confidence interval
EEM = external elastic membrane
IVUS = intravascular ultrasound
RI = remodeling index

Identification of attenuated plaques. For the current study, all IVUS pullbacks were reanalyzed by 2 independent observers (O.B. and P.S.). Attenuated plaque was defined as hypoechoic plaque with deep ultrasonic attenuation despite the absence of bright calcium. Plaques with attenuation were included in the analysis if the 2 observers agreed. The groups with and without attenuated plaque were compared with regard to clinical characteristics, overall vessel atheroma burden, and distribution at baseline based on the data derived from the ASTEROID trial database.

Dedicated plaque analysis in segments with attenuation at baseline. In segments with attenuated plaque at baseline, further analysis was performed at the cross section with attenuated plaque and adjacent images at 1-mm intervals, 5-mm proximally and 5-mm distally.

At the cross section with attenuated plaque, the lumen, plaque, and EEM area were measured by planimetry. If the EEM area could not be identified because of attenuation, we interpolated the EEM area. Plaque area and cross-sectional area stenosis were calculated. Remodeling was

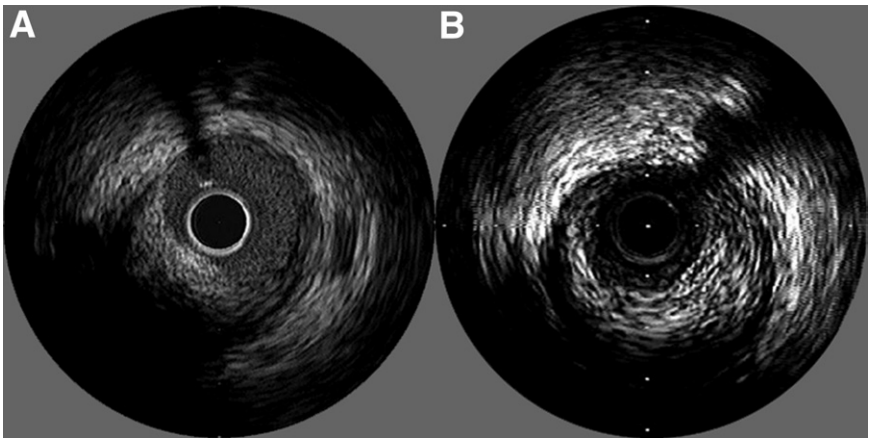

Figure 1. Two Examples of Plaques With Attenuation

Attenuated plaque was defined as plaque with deep ultrasonic attenuation despite absence of bright calcium. **(A)** Attenuation between 6 o'clock and 9 o'clock. **(B)** Attenuation between 5 o'clock and 8 o'clock.

defined by calculating the ratio of the EEM area at the site with attenuation, 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 (remodeling index [RI] >1.05), none (0.95 < RI <1.05) or constrictive (RI <0.95) at that site.

The distance of attenuated plaque from the respective coronary ostia was determined by multiplying motorized pullback speed rate (0.5 mm/s) by the time of the pullback.

For the 5-mm segments proximal and distal to the site with attenuation, the average EEM area, lumen area, plaque area, and cross-sectional area stenosis were calculated (6 for both proximal and distal segments). The presence of calcium in the proximal and distal segments was described by the percentage of images containing calcium.

Similar analysis was performed in matched segments at 2-year follow-up.

Statistical analysis. Results are expressed as mean ± SD for continuous variables and tested with the Student *t* test or Wilcoxon test if nonparametric. Percentages are presented for categorical variables and tested with the chi-square statistic. Fisher exact test was used for variables with low expected cell frequencies. A 95% confidence interval (CI) around the frequency of attenuated plaque was calculated using exact binomial probabilities. For the comparison of IVUS measurements between the cross section with attenuated plaque versus the proximal and distal sections, a 1-way analysis of variance was used with location used as a repeated factor. Student paired *t* test was used to test the differences between baseline and follow-up attenuated plaque cross sections. A value of $p < 0.05$ was considered significant. All analyses were conducted using SAS statistical software version 8.2 (SAS Institute, Cary, North Carolina).

Results

Prevalence of Attenuated Plaque

Attenuated plaque was found in 17 of 159 patients (10.7%, 95% CI: 6% to 17%) at baseline.

Table 1. Patient Characteristics at Baseline

Parameter	No Attenuated Plaque (n = 142)	Attenuated Plaque (n = 17)	p Value
Age, yrs	58.7 ± 9.72	59.8 ± 10.11	0.68
Female sex	25.4	5.9	0.12*
BMI	29.6 ± 4.8	27.9 ± 2.8	0.15*
Diabetes	11.3	5.9	0.70
Hypertension	94.4	100	0.60
Unstable angina	10.6	11.8	1.00*
Dyslipidemia	50	52.9	0.82
History of angina	54.2	76.5	0.08
History of MI	28.9	47.1	0.13
Baseline medications			
Beta-blocker	76.8	70.6	0.56*
Aspirin	93.7	100	0.60*
ACE inhibitor	48.6	41.2	0.56
Baseline parameters			
Total cholesterol	206.3 ± 41.9	213.7 ± 28.9	0.24
LDL-C	134.1 ± 33.1	137.7 ± 22.8	0.32
HDL-C	43.3 ± 10.8	45.6 ± 10.5	0.35
TG, median [IQR]	127 [90–166]	148 [116–191]	0.17
Systolic blood pressure	132.8 ± 20.3	135.4 ± 21.2	0.90
Diastolic blood pressure	75.4 ± 10.2	79.9 ± 11.2	0.07

Results are expressed as mean ± SD or %, unless otherwise indicated. *Fisher exact test.

ACE = angiotensin-converting enzyme; BMI = body mass index; HDL-C = high-density lipoprotein cholesterol; IQR = interquartile range; LDL-C = low-density lipoprotein cholesterol; MI = myocardial infarction; TG = triglycerides.

Table 2. IVUS Measurements in Segments With and Without Attenuated Plaque From the ASTEROID Trial Baseline Data

Parameter	No Attenuated Plaque (n = 142)	Attenuated Plaque (n = 17)	p Value
EEM volume	587.3 ± 157.7	572.8 ± 135.5	0.8
Lumen volume	342.7 ± 103.1	327.2 ± 73.0	0.9
PAV	41.6 ± 8.0	42.3 ± 7.7	0.6
TAV	244.6 ± 80.8	245.6 ± 84.8	0.7
Mean eccentricity index	4.4 ± 1.8	5.9 ± 2.4	0.008
% Images with calcium, median [IQR]	32.9 [8.8, 51.4]	34.5 [29.9, 36.0]	0.85

Results are expressed as mean ± SD unless otherwise indicated.
ASTERIOD = A Study to Evaluate the Effect of Rosuvastatin on Intravascular Ultrasound-Derived Coronary Atheroma Burden; EEM = external elastic membrane; IVUS = intravascular ultrasound; PAV = percent atheroma volume; TAV = total atheroma volume; other abbreviations as in Table 1.

Comparison of Clinical and IVUS Findings in Segments With and Without Attenuation at Baseline

Patient characteristics in patients with and without attenuated plaque. The patient characteristics of each group are summarized in Table 1. There were no differences in terms of age, sex, and cardiovascular risk factors between the 2 groups. There were no significant differences in clinical presentation, with 15 patients (10.7%) in the no-attenuated plaque group and 2 patients (11.2%) in the attenuated plaque group presenting with unstable coronary syndromes. There was a trend toward a more frequent history of angina in the patients with attenuated plaque (76.5% vs. 54.2%; p = 0.08).

IVUS measurements in segments with and without attenuated plaque. Volumetric IVUS findings in segments with and without attenuated plaque are summarized in Table 2. The EEM volume, lumen volume, and percent and total atheroma volumes were found to be similar. However, the mean plaque eccentricity index was significantly greater in the attenuated plaque group (4.4 ± 1.76 vs. 5.9 ± 2.40, p = 0.008).

IVUS Characteristics in Segments With Attenuation at Baseline

The IVUS characteristics at the attenuated plaque site and adjacent segments are summarized in Table 3. Plaque burden and eccentricity index were significantly higher in attenuated plaque cross sections. Nine of the 17 patients (53%) with attenuated plaque demonstrated expansive remodeling, 5 patients (29%) showed no remodeling, and 3 patients (18%) showed negative remodeling. By definition, there was no evidence of calcification at the attenuated plaque site. However, 35.3 ± 23.5% of slices in the proximal segment and 19.6 ± 34.0% of slices in the distal segment showed evidence of calcification (p <0.001). At least 1 calcified plaque was identified somewhere within the entire 10-mm segment in 70% of patients with attenuated plaque. When we classified these plaques according to their localization relative to the attenuated plaque site, 59% were observed in the proximal and 24% were observed in the distal 5-mm segments (Fig. 2).

The mean distances from the coronary artery ostia to the attenuated plaque cross section were shortest in the left anterior descending (24.4 ± 15.9 mm), followed by left circumflex (29.0 ± 21.9 mm) and then right coronary artery (34.2 ± 26.1 mm, p = 0.7).

Clinical and IVUS Data During 2-Year Follow-Up

During 2-year follow-up, 1 patient in the no attenuated plaque group developed a myocardial infarction and 1 patient developed a stroke. None of the 17 patients with attenuated plaque developed myocardial infarction, death, or stroke.

In these 17 patients the attenuated areas were unchanged at follow-up (Fig. 3). However, the atheroma areas at the sites of attenuated plaque were found smaller at the follow-up than at baseline. All other IVUS measurements were not significantly changed (Table 4).

Discussion

Examining nonculprit segments in patients enrolled in IVUS progression trials, we found attenuated plaque in about 11% of patients. Dedicated analysis of the site with attenuation demonstrated greater plaque burden and eccentricity than in the adjacent segments. The adjacent segments frequently demonstrated calcification in the vicinity of attenuated plaques. Comparison of clinical presentation and

Table 3. IVUS Measurements in Attenuated Plaque Segments at Baseline, Based on Dedicated Analysis

	Proximal Segment	Cross Section With AttP	Distal Segment	p Value*	p Value†
EEM area	17.1 ± 0.8	16.9 ± 0.8	15.9 ± 0.8	0.87	0.38
Plaque + media area	8.5 ± 0.4	10.15 ± 0.4	8.1 ± 0.4	0.01	0.002
Lumen area	8.6 ± 0.5	6.8 ± 0.5	7.8 ± 0.5	0.03	0.18
Average cross-sectional area stenosis	50.5 ± 1.7	60.4 ± 1.7	51.1 ± 1.7	<0.001	<0.001
Eccentricity index	6.2 ± 0.8	8.9 ± 0.8	6.3 ± 0.8	0.03	0.03

Results are expressed as least-square mean ± standard error. *The p value compares proximal segment to AttP segment; †the p value compares distal segment to AttP segment.
AttP = attenuated plaque; other abbreviations as in Table 2.

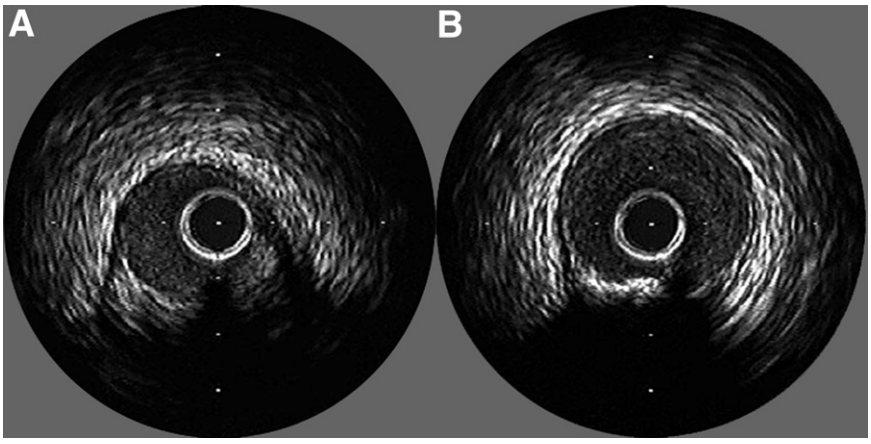

Figure 2. IVUS Cross Section at the Site With Attenuation and an Adjacent Image With IVUS Criteria of Calcification

This figure shows an intravascular ultrasound (IVUS) cross section at the site with attenuation **(A)** and an adjacent image with IVUS criteria of calcification **(B)**. Evidence of calcification was frequently present in the vicinity of attenuated plaques.

clinical characteristics in patients with and without attenuated plaque, as well as IVUS characteristics in segments with and without attenuation, showed no significant differences at baseline. During 2-year follow-up, lesion morphology remained stable, and no acute events occurred in the patient with attenuation.

Our results contribute to the understanding of plaque attenuation and its potential relationship to plaque vulnerability. In a previous study (4), attenuated plaque was observed at culprit lesions of patients presenting with acute coronary syndromes and was found to be associated with greater transient deterioration in coronary flow, larger infarct size, and higher incidence of fatal arrhythmia following percutaneous coronary intervention in patients with acute coronary syndromes. Importantly, in a recent study by Lee et al. (5) attenuated plaque was found in 25.6% of 293 patients presenting with acute coronary syndromes, but it was not present in 100 randomly selected patients with stable angina. Therefore, attenuation has been described as a characteristic marker of vulnerable lesions, with potential therapeutic implications in the setting of percutaneous coronary intervention. However, to understand the significance of attenuation, it is important to know its presence and frequency at nonculprit lesion sites and the natural history of such lesions. The presence of attenuation at nonculprit lesions in our data, regardless of clinical presentation, and the stability during follow-up challenge the previous assumption that attenuated plaque is a finding

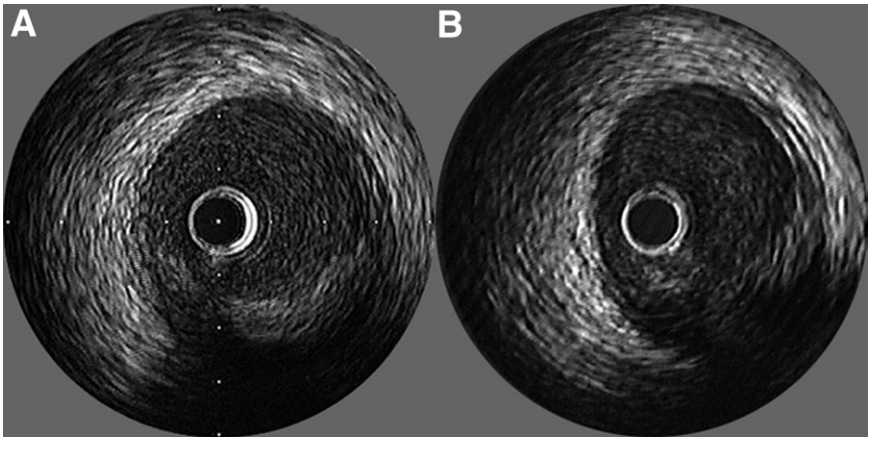

Figure 3. Plaque Site With Attenuation at Baseline and 2-Year Follow-Up

This figure shows a plaque site with attenuation at baseline **(A)** and 2-year follow-up **(B)**. Presence of attenuation and plaque morphology is not significantly changed.

Table 4. IVUS Measurements at the Cross Sections With Attenuation at Baseline and Follow-up

	Baseline	Follow-Up	p Value
EEM area	16.9 ± 3.2	15.3 ± 3.3	0.2
Plaque + media area	10.15 ± 1.89	8.7 ± 2.0	0.04
Lumen area	6.8 ± 2.1	6.6 ± 2.1	0.8
Average cross-sectional area stenosis	60.4 ± 7.2	57.5 ± 8.3	0.3
Eccentricity index	8.9 ± 4.2	7.6 ± 3.3	0.3

Results are expressed as mean ± SD.
Abbreviations as in Table 2.

limited to culprit lesions associated with acute clinical presentation.

The reasons for these discrepancies are unclear. However, it is important to consider that the presence of a plaque characteristic at a site remote from the culprit lesion is not definitive evidence refuting its association with plaque instability. Most notably, in literature regarding plaque rupture, investigators reported that the rupture can be identified distant from the lesion site, particularly in the setting of acute presentation (7–11). Similarly, the stability of such findings during follow-up could reflect the effect of the pharmacologic intervention, rather than natural history (8). Furthermore, in our study, dedicated analysis of the segments with attenuation demonstrates plaque characteristics previously associated with plaque vulnerability. These include expansive remodeling (12,13), lesion eccentricity (14,15), and the location/distribution in the coronary tree (16,17).

Intravascular ultrasound validation versus histology will be critical. Previous pathological studies have provided limited insight into the etiology of acoustic attenuation (18,19). In a series of 107 human cadaver coronary arteries, Yamada et al. (18) demonstrated that the percentage of fibrofatty and necrotic core plaque areas were significantly greater in plaques with attenuation than those without. Additionally, von Kossa staining indicated the presence of microcalcification within deep fibrotic tissue layers (19). Another histologic study found fibrofatty tissue components, extensive necrotic tissue containing cholesterol crystals, and microcalcification in close association with severe plaque calcification (20).

Taken together, these histological findings suggest that attenuated plaque may be related to an inhomogeneous calcification process, with multiple reflective surfaces associated with microcalcification in fibrofatty and necrotic tissue. Particularly in large plaques with these histologic findings, diminished power in the far field of the ultrasound may cause deep ultrasonic attenuation without the characteristic highly echogenic signal of more densely calcified plaque. Our finding of the frequent presence of calcification in the images adjacent to the image with attenuation is consistent with these findings, suggesting the presence of a homogeneous, mixed calcified plaque. Interestingly, such lesions have been associated with unstable lesions in both IVUS and computed tomography studies (21–23). Future advanced IVUS data analysis studies may provide further insights (22,24,25).

Study limitations. Our study is limited by the relatively small number of lesions with attenuated plaque and the lack of direct comparison of matched lesion sites with and without plaque attenuation. Matching individual lesions based on size and morphology is impractical due to selection bias. We, therefore, compared results of the entire vessel segment containing attenuation to segments without attenuation, based on data collected in the original clinical trial. Another limitation is based on the selection of patients with a plaque burden above the mean, which was done to ensure comparability to previous studies. It is likely that the prevalence of attenuation in patients with a smaller plaque burden is lower. The follow-up data is limited by the small number of lesions with attenuation, well-known limitations of matching individual lesions at different time points, and the likelihood that the pharmacological intervention caused plaque stabilization.

Conclusions

Our results demonstrate attenuated plaque in a significant percentage of nonculprit segments in patients enrolled in IVUS progression trials and relative stability during follow-up. The frequent presence of calcification adjacent to the cross section with attenuated plaque confirms a relationship with mixed calcified lesions. These findings challenge the previous assumption that attenuated plaque is an exclusive finding of culprit lesions associated with acute clinical presentation. Our data should caution against precocious use of this finding as a basis for interventional decision making until more data becomes available.

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Key Words: intravascular ultrasound ■ coronary artery disease ■ vulnerable plaque ■ imaging.