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The Relationship Between Attenuated Plaque Identified by Intravascular Ultrasound and No-Reflow After Stenting in Acute Myocardial Infarction

The HORIZONS-AMI (Harmonizing Outcomes With Revascularization and Stents in Acute Myocardial Infarction) Trial

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Objectives The aim of this study was to understand the impact of attenuated plaque on distal embolization during stent implantation in patients with acute myocardial infarction (AMI).

Background Attenuated plaques identified by grayscale intravascular ultrasound (IVUS) might predict transient deterioration in coronary flow and/or no-reflow during percutaneous coronary intervention (PCI).

Methods We analyzed clinical, angiographic, and IVUS data from 364 patients (n = 364 infarct-related arteries) enrolled in the randomized HORIZONS-AMI (Harmonizing Outcomes With Revascularization and Stents in Acute Myocardial Infarction) trial. No-reflow was final Thrombolysis In Myocardial Infarction (TIMI) flow grade ≤2 in the absence of mechanical obstruction. Attenuated plaque was hypoechoic or mixed atheroma with ultrasound attenuation without calcification. A mean attenuation score was created by measuring the angle of attenuation each 1 mm, scoring the angle as 1 to 4 (corresponding to <90°, 90° to 180°, 180° to 270°, or 270° to 360°, respectively), summing the scores, and normalizing for analysis length.

Results Overall, 284 (78.0%) patients had attenuated plaques; no-reflow occurred in 37 (10.2%). Patients with no-reflow had a higher mean attenuation score (median [interquartile range] 2.2 [0.0 to 2.8] vs. 1.3 [0.7 to 1.8], p < 0.001), lower baseline left ventricular ejection fraction (52.8% [43.2% to 61.5%] vs. 61.4% [52.2% to 68.1%], p = 0.002), and more baseline angiographic thrombus (89.2% vs. 74.1%, p = 0.043) with no differences in post-PCI stent expansion versus patients without no-reflow. Multivariate analysis indicated that mean attenuation score was the strongest predictor of no-reflow. The mean attenuation score that best predicted no-reflow was ≥2 points (90° to 180°, sensitivity of 81.5%, and specificity of 80.5%).

Conclusions Attenuated plaque was present in three-quarters of patients with AMI. The amount of attenuated plaque strongly correlated with no-reflow; the larger the attenuated plaque, the greater the likelihood of no-reflow. (Dual Arm Factorial Randomized Trial in Patients w/ST Segment Elevation AMI to Compare the Results of Using Anticoagulation With Either Unfractionated Heparin + Routine GP IIb/IIIa Inhibition or Bivalirudin + Bail-out GP IIb/IIIa Inhibition; and Primary Angioplasty with stent implantation with Either a Slow Rate-release Paclitaxel-eluting Stent [TAXUS™] or Uncoated Bare Metal Stent [EXPRESS2™]; NCT00433966) (J Am Coll Cardiol Intv 2011;4:495–502) © 2011 by the American College of Cardiology Foundation

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Percutaneous coronary intervention (PCI) with stent implantation is often performed to treat patients with acute myocardial infarction (AMI). However, PCI fails to achieve Thrombolysis In Myocardial Infarction (TIMI) flow grade 3 in 12% to 30% of cases, mainly because of the no-reflow phenomenon that is associated with poor functional and clinical outcomes (1–5). Retrospective intravascular ultrasound (IVUS) studies have shown that attenuated plaque (hypoechoic or mixed atheroma with ultrasound attenuation but without calcification) is common in acute coronary syndromes and is associated with a high rate of no-reflow or transient deterioration in coronary flow during PCI (6,7). The aim of the present study is to use the data from the HORIZONS-AMI (Harmonizing Outcomes With Revascularization and Stents in Acute Myocardial Infarction) trial to evaluate the impact of attenuated plaque on no-reflow in patients with AMI undergoing primary stent implantation.

Abbreviations and Acronyms

AMI = acute myocardial infarction
CK-MB = creatine kinase-myocardial band
CTFC = corrected Thrombolysis In Myocardial infarction frame count
IB = integrated backscatter
IVUS = intravascular ultrasound
LAD = left anterior descending coronary artery
LVEF = left ventricular ejection fraction
MLA = minimum lumen area
MLD = minimum lumen diameter
PCI = percutaneous coronary intervention
STEMI = ST-segment elevation myocardial infarction
TIMI = Thrombolysis In Myocardial Infarction
VH = virtual histology

Methods

Study population. The HORIZONS-AMI trial was a dual-arm, factorial, randomized trial in patients with ST-segment elevation myocardial infarction (STEMI). There were 2 randomization steps: 1) unfractionated heparin plus routine glycoprotein IIb/IIIa inhibition versus bivalirudin alone (1:1 randomization); and 2) paclitaxel-eluting TAXUS stents versus bare metal EXPRESS stents (Boston Scientific, Natick, Massachusetts) (3:1 randomization). A formal IVUS substudy enrolled 464 patients with baseline and 13-month follow-up imaging at 36 centers. The primary prespecified endpoint of the IVUS substudy has been reported previously (8).

This study was approved by the institutional review boards of the institutions in which the procedures were performed. Written informed consent was obtained from all patients before cardiac catheterization.

Clinical data were collected and included risk factors, left ventricular ejection fraction (LVEF) (evaluated by left ventriculography), and creatine kinase-myocardial band (CK-MB) levels.

Quantitative and qualitative coronary angiography. Coronary angiograms at baseline and immediately after PCI were performed in at least 2 orthogonal views after intracoronary nitroglycerin. Angiograms were analyzed at the Angiographic Core Laboratory of the Cardiovascular Research Foundation (New York, New York), which was blinded to the clinical and IVUS findings with the CMS-GFT algorithm (MEDIS, Leiden, the Netherlands). Minimum lumen diameter (MLD) and mean reference vessel diameter (RVD), obtained by averaging 5-mm segments proximal and distal to the target-lesion, were used to calculate diameter stenosis: ([1 − MLD/RVD] × 100%). Angiographic coronary blood flow was assessed at baseline and after PCI on the basis of TIMI flow grade (9) and corrected Thrombolysis In Myocardial infarction frame count (CTFC) (10). No-reflow was defined as final TIMI flow grade 0 and 1 or 2 in the absence of mechanical obstruction. Qualitative analysis was done with standard methods (11). Presence or absence of intracoronary thrombus (hazy, globular filling defect, or total occlusion) and calcification were evaluated.

IVUS imaging and analysis. The IVUS was performed after successful, uncomplicated stent implantation. Allowable IVUS systems included iLab, Galaxy, or Clearview (all with Atlantis SR Pro, 40-MHz catheters [Boston Scientific]) or In Vision Gold with 20-MHz EagleEye catheters (Volcano Therapeutics, Rancho Cordova, California). The IVUS imaging was performed with motorized pullback (0.5 mm/s) to include the stent and >5-mm segments proximal and distal to the stent. The IVUS studies were archived and sent to an independent, treatment-allocation-blinded IVUS core Laboratory (Cardiovascular Research Foundation, New York, New York) for quantitative and qualitative analyses with validated software (EchoPlaque, INDEC Systems, Inc., Mountain View, California).

Quantitative analysis included measurement of external elastic membrane, stent, lumen, and plaque + media (P+M

Foundation, with grant support from Boston Scientific and The Medicines Company. Drs. Mintz, Dressler, and Parise report being employed by the Cardiovascular Research Foundation. Dr. Stone is a member of the scientific advisory boards for and has received honoraria from Abbott Vascular and Boston Scientific and has served as consultant to Volcano Corporation. Dr. Mintz reports receiving honoraria and research support from Volcano Corporation; and honoraria and research fellowship support from Boston Scientific. Dr. Guagliumi reports receiving consulting fees from Volcano Corporation and Boston Scientific; and research grants from Medtronic Vascular, Boston Scientific, Lightlab, and Abbott Vascular. Drs. Mintz, Lansky, Guagliumi, Stone, and Maehara report receiving research grants from Boston Scientific. Drs. Mintz and Lansky report receiving research grants from Volcano Corporation. Dr. Witzenbicher reports receiving lecture fees from Boston Scientific, Abbott Vascular, and The Medicines Company. Dr. Brodie reports receiving lecture fees from The Medicines Company and MedRad/Possis. Dr. Mehran has served on the Advisory Board of and received consulting fees from Abbott Vascular, AstraZeneca, OrthoMcNeil, and Regado Biosciences, and has received a research grant from Bristol-Myers Squibb/Sanofi-Aventis. Dr. Maehara has relationships with Boston Scientific and the Volcano Corporation.

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= external elastic membrane − lumen) cross-sectional areas every 1 mm. Qualitative analysis included: 1) attenuation behind the plaque in the absence of calcification; 2) intra-stent plaque and/or thrombus protrusion (IVUS cannot reliably differentiate between plaque vs. thrombus that protrudes through stent struts); 3) intra-plaque echolucent zone (absence of ultrasound signal within the plaque); and 4) edge dissection (tangential tear in the plaque at the stent edge).

As previously reported, a mean attenuation score was created by measuring the angle of attenuation each 1 mm, scoring the angle as 1, 2, 3, or 4 points when the attenuation angle was <90°, 90° to 180°, 180° to 270°, or 270° to 360°, respectively; summing the scores to create an overall attenuation score; and finally, normalizing for analysis length (Fig. 1) (12). Plaque without attenuation was scored as 0 points. The presence of attenuation and the mean attenuation scores were analyzed by 2 independent, experienced observers (X.W. and A.M.), and consensus interpretation was included in the subsequent analysis.

Intraobserver and interobserver variability and reliability analysis. All lesions were analyzed 3 months apart to assess intraobserver and interobserver variability in the identification of attenuated plaque; both intraobserver (kappa = 0.96) and interobserver (kappa = 0.94) variability yielded good concordance. To assess the reproducibility of the mean attenuation score, 100 consecutive lesions were analyzed by 2 observers (X.W. and A.M.); the difference in the mean attenuation score after stenting was 0.08 ± 0.23 points, and the intraclass correlation coefficient for repeated measurement was 0.98.

Although only post-stent IVUS was pre-specified in the HORIZONS protocol, pre-PCI IVUS was performed in 40 patients at the discretion of the operator. We used images from these 40 patients to compare attenuation detection and mean attenuation score calculation between pre- and post-PCI IVUS studies. In these 40 lesions with both pre- and post-stenting IVUS, there were 29 attenuated plaques; there was complete agreement between the pre-stent and post-stent assessment of the presence of IVUS attenuation. The difference in the calculated mean attenuation score was 0.07 ± 0.12 points. Intraclass correlation coefficient comparing pre- versus post-stenting attenuation was 0.99. An example is shown in Figure 2.

Statistical analysis. Statistical analysis was performed with SAS software (version 9.1, SAS Institute, Inc., Cary, North Carolina). Categorical variables were compared with chi-square statistics or Fisher exact test. Continuous variables were compared with Wilcoxon rank-sum test and displayed as median (interquartile range). The cutoff of mean attenuation score was calculated by receiver-operator characteristic curve to predict no-reflow. The optimal cut-point was selected when the highest sum of sensitivity and specificity was available. We conducted a stepwise multivariate logistic regression analysis to identify independent predictors of no-reflow. The model included clinical, angiographic, and procedural characteristics and quantitative and qualitative IVUS findings with $p < 0.20$ in the univariate analyses. A p value <0.05 was considered to indicate statistical significance.

Results

Between March 25, 2005, and May 7, 2007, 402 patients (429 lesions) had analyzable post-PCI and follow-up IVUS studies. We excluded 11 lesions in saphenous venous

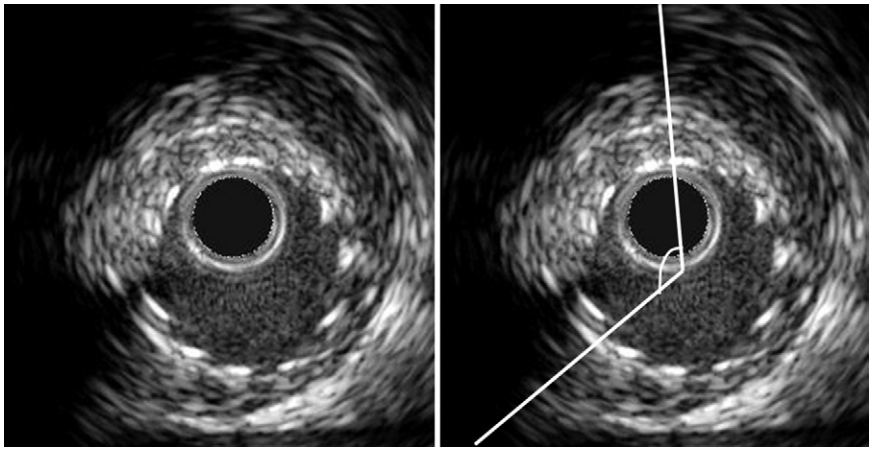

Figure 1. Attenuation Score

Attenuation score was 1, 2, 3, or 4 points when the attenuation angle was <90°, 90° to 180°, 180° to 270°, or 270° to 360°, respectively. In this picture, attenuation angle was 120°; therefore, attenuation score was 2 points.

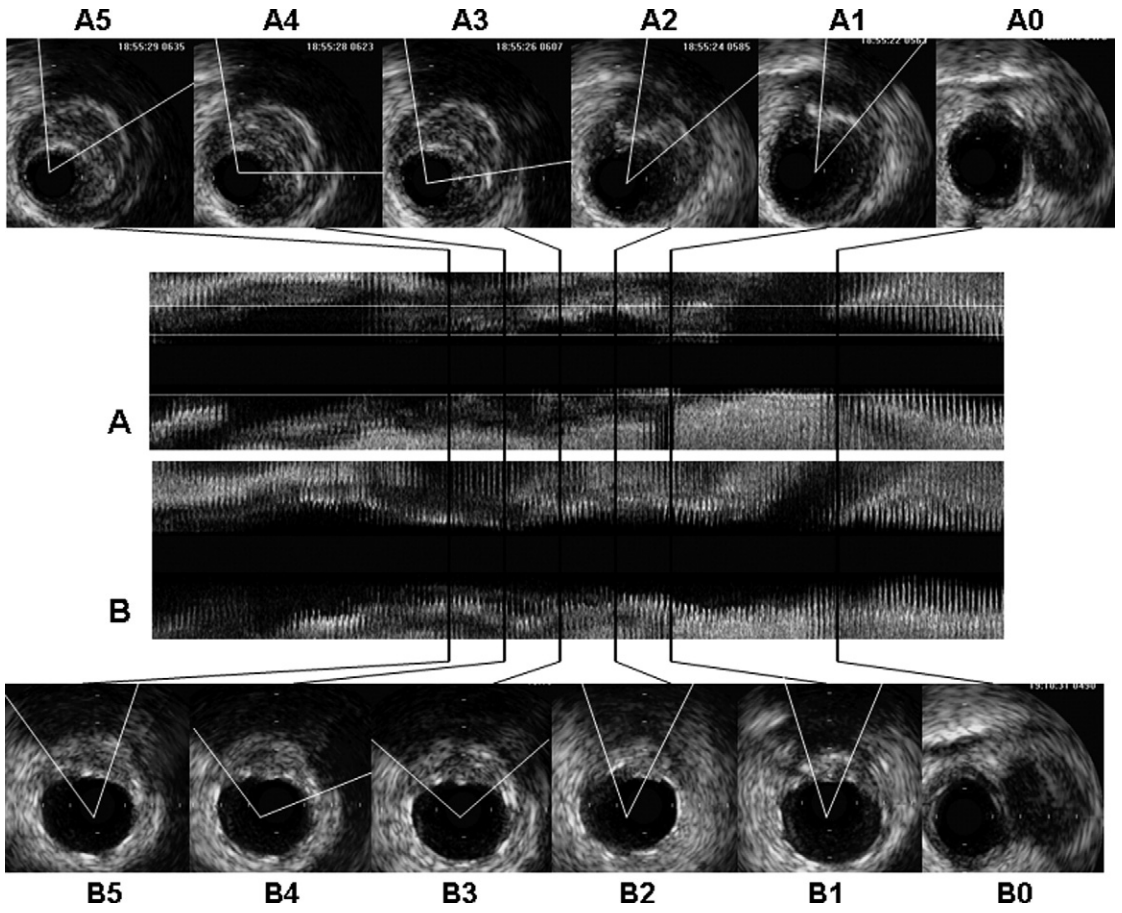

Figure 2. Mean Attenuation Score Before and After PCI

A and B were longitudinal sections through same lesion before and after percutaneous coronary intervention (PCI). Mean attenuation score was analyzed by measuring the attenuation angle each 1 mm (cross-section of lesion before PCI: **A0 to A5**; cross-section of lesion after PCI: **B0 to B5**), then summing the scores, and normalizing for analysis length. **A0 and B0** were bifurcation markers. Pre-PCI **(A)** attenuation angles of slices **A1 to A5** were 40°, 55°, 95°, 105°, and 60°, respectively. The corresponding attenuation scores were 1, 1, 2, 2, and 1 points; the mean attenuation score was 7/4.8 = 1.5. Post-PCI **(B)** attenuation angles of **B1 to B5** were 45°, 55°, 105°, 110°, and 55°, respectively; the corresponding attenuation score were 1, 1, 2, 2, and 1 points, yielding a mean attenuation score of 7/4.8 = 1.5.

grafts, 38 lesions in noninfarct-related arteries, and 16 lesions with unreliable pullback or zoom or gain not appropriate to evaluate attenuated plaque. Eventually, 364 de novo infarct-related coronary artery lesions in 364 patients were included.

Clinical characteristics. Overall, 78.8% (287) were men; the median patient age was 60.3 (51.3 to 68.9) years; 39.0% (n = 142) had infarct-related left anterior descending coronary artery (LAD) lesions; pre-intervention angiographic thrombus was present in 75.0% (n = 273); 73.1% (n = 266) had a pre-PCI TIMI flow grade ≤2; and pre-PCI LVEF was 61.0% (51.4% to 67.6%). As shown in Table 1, there were no statistically significant differences between patients with and without no-reflow except: 1) no-reflow was associated with lower CK-MB; 2) patients with no-reflow had higher CK-MB before and after PCI; and 3) there were fewer current smokers in the no-reflow group.

Angiographic and procedural findings. As shown in Table 2, patients with no-reflow more often had PCI of an LAD than a non-LAD lesion (59.5% vs. 36.7%, p = 0.026). Baseline angiographic thrombus was more frequent in patients with versus without no-reflow (89.2% vs. 74.1%, p = 0.043). Pre-PCI TIMI flow grade 0 to 2 was more common in patients with versus without no-reflow (86.5% vs. 71.2%, p = 0.047); similarly, pre-PCI CTFC was higher in no-reflow patients (41.0 [29.0 to 52.5] vs. 30.0 [20.0 to 40.0], p = 0.032). Final angiographic diameter stenosis was larger in patients with no-reflow (23.1% [16.6% to 27.3%] vs. 17.7 [12.6% to 23.8%], p = 0.004), whereas acute gain was similar between the 2 groups. The use of pre-dilation and post-dilation, balloon size, and balloon/artery ratio were similar between the 2 groups.

Table 1. Baseline Clinical Characteristics

	No-Reflow (n = 37)	Reflow (n = 327)	p Value
Age, yrs	63.6 (55.7–73.2)	59.1 (50.7–68.7)	0.105
Male	30 (81.1)	257 (78.6)	0.725
Hypertension	18 (48.6)	166 (50.8)	0.807
Hyperlipidemia	9 (24.3)	129 (39.4)	0.072
BMI, kg/m^2	27.3 (25.7–28.7)	27.0 (24.5–30.0)	0.538
Diabetes	2 (5.4)	45 (13.8)	0.199
Current smoking	11 (29.7)	167 (51.1)	0.014
Family history of CAD	11 (29.7)	126 (38.5)	0.295
LVEF, %	52.8 (43.2–61.5)	61.4 (52.2–68.1)	0.002
Baseline CK-MB, mg/dl	23.1 (9.5–91.5)	13.1 (4.4–32.5)	0.016
Peak CK-MB after PCI, mg/dl	323.0 (182.9–440.2)	215.0 (93.0–375.9)	0.025
ΔCK-MB, mg/dl	256.0 (109.5–354.9)	170.0 (55.2–348.9)	0.259
Bivalirudin	17 (45.9)	169 (51.7)	0.603

Values are median (interquartile range) or n (%).
BMI = body mass index; CAD = coronary artery disease; CK-MB = creatine kinase-myocardial band; LVEF = left ventricular ejection fraction; PCI = percutaneous coronary intervention.

Grayscale IVUS image analysis. As summarized in Table 3, there were no statistically significant quantitative differences between patients with and those without no-reflow. The frequency of plaque/thrombosis protrusion and echolucent plaque was also similar between the 2 groups.

Attenuated plaque and no-reflow. Overall, 78.0% (n = 284) of the patients had attenuated plaques, and 10.2% (n = 37) had no-reflow. There were 284 (78.0%) attenuated plaques in the stented segment and 122 (33.5%) in the proximal or distal unstented reference vessels, 115 of which (94.3%) were located both within the stented segment and in the reference segment, whereas 7 (5.7%) were located only in the reference segments ($p < 0.001$).

The mean attenuation score was significantly higher (2.2 [0 to 2.8] vs. 1.3 [0.7 to 1.8], $p < 0.001$), whereas the mere presence of attenuated plaque (73.0% vs. 78.4%, $p = 0.434$) and attenuation length (6.9 [0.0 to 16.9] mm vs. 8.0 [2.6 to 14.0] mm, $p = 0.874$) were similar in patients with versus without no-reflow. The mean attenuation score that best predicted no-reflow was ≥2 points (attenuation angle >90°) with a sensitivity of 81.5%, a specificity of 80.5%, and an area under the receiver-operator characteristic curve of 0.883. Final CTFC was significantly higher in patients with a mean attenuation score ≥2 points (24.0 [16.0 to 38.0]) versus patients with a mean attenuation score <2 points (19.0 [15.0 to 26.0], $p < 0.001$) versus patients without attenuation (20.0 [16.0 to 28.0], $p = 0.02$).

In 284 patients with attenuated plaques, no-reflow was associated with older patient age (66.1 [59.0 to 73.4] years vs. 60.4 [52.1 to 70.0] years, $p = 0.013$), lower LVEF (50.6% [43.0% to 61.6%] vs. 59.9% [50.6% to 67.4%], $p = 0.008$), and LAD lesion location (70.4% vs. 37.0%, $p = 0.004$). In 80 patients without attenuated plaques, no-reflow was only associated with angiographic thrombosis before PCI (20% vs. 0%, $p = 0.014$) as well as the frequency of pre-dilation (90.0% vs. 46.5%, $p = 0.015$) and post-dilation (70.0% vs. 28.2%, $p = 0.014$).

Independent predictors of no-reflow included mean attenuation score ≥2 (odds ratio: 6.586, 95% confidence interval: 2.680 to 16.188, $p < 0.001$) and angiographic thrombosis before PCI (odds ratio: = 9.143, 95% confidence interval: 1.182 to 70.732, $p = 0.034$). However, mean attenuation score ≥2 points had nearly 10 times the likelihood of no-reflow as mean attenuation score <2 points. Baseline TIMI flow grade and CTFC, target lesion length, infarct-related LAD lesion location, and echolucent plaque identified by IVUS did not correlate with no-reflow in this model.

Discussion

The major findings in the present study were that attenuated plaque was present in three-quarters of patients with

Table 2. Angiographic and Procedure Characteristics

	No-Reflow (n = 37)	Reflow (n = 327)	p Value
Infarct-related artery			0.026
Left anterior descending	22 (59.5)	120 (36.7)	
Left circumflex	5 (13.5)	53 (16.2)	
Right coronary artery	10 (27.0)	154 (47.1)	
Before PCI			
Lesion length, mm	12.8 (10.0–18.6)	16.0 (11.2–22.3)	0.036
RVD, mm	3.0 (2.7–3.4)	3.0 (2.7–3.3)	0.282
MLD, mm	0.0 (0.0–0.5)	0.0 (0.0–0.5)	0.697
DS, %	100 (85.0–100)	100 (81.6–100)	0.549
Thrombus	33 (89.2)	240 (74.1)	0.043
TIMI flow grade 0/1/2	32 (86.5)	232 (71.2)	0.047
CTFC	41.0 (29.0–52.5)	30.0 (20.0–40.0)	0.027
After PCI			
CTFC	45.5 (38.0–55.0)	19.0 (15.0–26.0)	<0.001
RVD, mm	3.1 (2.7–3.4)	3.1 (2.7–3.3)	0.445
MLD, mm	2.3 (2.1–2.8)	2.5 (2.1–2.8)	0.304
DS, %	23.1 (16.6–27.3)	17.7 (12.6–23.8)	0.004
Acute gain, mm	2.1 (1.9–2.5)	2.2 (1.8–2.6)	0.660
Thrombus	2 (5.4)	2 (0.6)	0.053
Procedure			
Time to reperfusion, h	4.8 (2.9–7.4)	3.5 (2.6–5.6)	0.048
Before dilation	28 (75.7)	206 (64.2)	0.164
After dilation	20 (54.1)	135 (42.1)	0.163
Aspiration	5 (13.5)	28 (8.8)	0.365
Maximum balloon diameter, mm	3.5 (3.3–4.0)	3.5 (3.0–3.8)	0.075
Maximum balloon: reference	1.16 (1.09–1.22)	1.17 (1.06–1.29)	0.982
Maximum pressure, atm	16.0 (14.0–18.0)	16.0 (14.0–18.0)	0.642
TAXUS use	29 (78.4)	244 (74.6)	0.617

Values are n (%) or median (interquartile range).
CTFC = corrected Thrombolysis In Myocardial Infarction frame count; DS = diameter stenosis; MLD = minimum lumen diameter; PCI = percutaneous coronary intervention; RVD = reference vessel diameter; TIMI = Thrombolysis In Myocardial Infarction.

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Table 3. Quantitative and Qualitative IVUS Analysis

	No-Reflow (n = 37)	Reflow (n = 327)	p Value
Reference*			
EEM CSA (mm^2)	15.6 (12.1–20.0)	15.1 (11.6–18.6)	0.254
Lumen CSA (mm^2)	9.7 (8.5–11.9)	9.2 (7.1–11.4)	0.113
P+M CSA (mm^2)	5.2 (3.0–7.9)	5.5 (4.0–7.4)	0.987
Plaque burden (%)	38.1 (23.9–44.3)	36.4 (29.2–43.8)	0.729
Stent segment			
EEM CSA at MLA site (mm^2)	14.5 (10.2–19.5)	15.6 (12.1–19.3)	0.653
Lumen CSA at MLA site (mm^2)	6.8 (5.3–8.5)	6.7 (5.2–7.8)	0.477
Stent CSA at MLA site (mm^2)	7.1 (5.5–9.0)	7.0 (5.5–8.4)	0.589
Focal stent expansion†	0.71 (0.60–0.86)	0.76 (0.66–0.88)	0.073
Diffuse stent expansion†	0.84 (0.79–0.98)	0.90 (0.79–1.02)	0.381
Mean EEM CSA, mm^3/mm	17.0 (13.1–20.2)	16.5 (13.8–20.0)	0.993
Mean lumen CSA, mm^3/mm	8.3 (7.2–10.5)	8.0 (6.7–9.9)	0.400
Mean stent CSA, mm^3/mm	8.8 (7.4–10.3)	8.0 (6.7–10.0)	0.236
Attenuation	27 (73.0)	257 (78.6)	0.434
Overall attenuation score	18.0 (0–43.0)	11.0 (2.0–24.0)	0.134
Attenuation length	6.9 (0–16.9)	8.0 (2.6–14.0)	0.873
Mean attenuation score	2.2 (0–2.8)	1.3 (0.7–1.8)	<0.001
Tissue protrusion	24 (64.9)	239 (73.1)	0.290
Echolucent plaque	11 (29.7)	64 (19.6)	0.148
Dissection at stent edge	7 (18.9)	42 (12.8)	0.277

Values are median (interquartile range) or n (%). *Average of proximal and distal (most normal-looking) reference sites. †Focal stent expansion was calculated as minimum stent area (MSA) divided by average reference lumen cross-sectional area (CSA); diffuse stent expansion was calculated as mean stent area divided by average reference lumen CSA.

EEM = external elastic membrane; IVUS = intravascular ultrasound; MLA = minimum lumen area; P+M = plaque + media.

STEMI. Because attenuated plaque was present in such a large percentage of STEMI patients, its mere presence did not predict no-reflow. Instead, the larger the attenuated plaque, the greater the likelihood of no-reflow; a mean attenuation score ≥2 points (attenuation angle ≥90°, indicative of a large, diffuse attenuated plaque) best-predicted no-reflow (sensitivity of 81.5%, specificity of 80.5%, area under the receiver-operator characteristic curve of 0.883).

No-reflow is related to capillary occlusion and microemboli to coronary resistance vessels (13–16). The capillary structure becomes disorganized in the no-reflow zone, because of endothelial swelling, tissue compression, myocyte edema, and neutrophil infiltration (17,18). This usually results from a large AMI but can be worsened by reperfusion. No-reflow is also attributed to thrombus and/or plaque embolization during PCI (19–22). These plaque components (including platelet-fibrin complex, macrophages, and cholesterol crystals) provoke arteriole spasm leading to further microvascular congestion, thrombosis, and sluggish coronary flow.

Previous studies have demonstrated that a greater pre-PCI plaque burden and a decreased plaque volume during PCI were related to CK-MB elevation after PCI (23–25). However, not only the size of the plaque but its composition is important in the pathogenesis of no-reflow. Specific grayscale IVUS plaque characteristics that have predicted no-reflow or CK-MB elevation after PCI have included a lipid pool-like image, positive remodeling, intracoronary mural thrombus, and now attenuated plaque (6,19,21,26). However, grayscale IVUS has only a limited ability to assess atherosclerotic plaque composition. Analysis of radiofrequency ultrasound backscatter signals known as integrated backscatter (IB)-IVUS or virtual histology (VH)-IVUS have been developed to improve on these limitations of grayscale IVUS. We have recently reported the strong relationship between attenuated plaque (grayscale IVUS) and a large amount of necrotic core indicative of a fibroatheroma (VH-IVUS) (27). This relationship is supported by histopathological studies demonstrating that attenuated plaque is composed of microcalcifications and cholesterol crystals (28,29). Acute coronary syndromes are most often caused by thrombosis superimposed on rupture of a thin-cap fibroatheroma containing a large necrotic core (30,31). Both IB-IVUS and VH-IVUS studies have suggested that lipid-rich plaque (IB-IVUS) or necrotic core-rich plaque (VH-IVUS) are associated with no-reflow (32–35). Thus, attenuated plaques represent a large amount of necrotic core containing fragile tissues such as lipid deposition with foam cells, cholesterol crystals, and microcalcifications that are easily embolized by mechanical fragmentation during coronary stenting.

However, the current study also shows that attenuated plaques are present in three-quarters of infarct-related lesions of STEMI patients. Thus, it is the size of the attenuated plaque and not its mere presence that is related to no-reflow. In a practical way, the current study suggests that culprit lesions containing a mean attenuation angle >90° have a higher risk of no-reflow. However, attenuation varies significantly over the length of the lesion. In the majority of infarct-related lesions, the arc of attenuated plaque is >180° (and sometimes circumferential) in the middle of the lesion and tapers closer to the reference segments. Therefore, the calculation of a mean attenuation score takes into account the severity of attenuation at its worst cross-section as well as its distribution (12,30). However, the frequency of attenuated plaque is higher in the current study than is reported by Lee et al. (6) but similar to the study by Okura et al. (7). The differences are not entirely clear, although patient selection might be an important explanation.

In the current analysis, attenuated plaque was also associated with reduced coronary flow before PCI; the incidence of pre-PCI TIMI flow grade 0/1 was 77.4% in patients with attenuated plaque versus 56.8% in patients without attenuated plaque. Previous studies have shown that spontaneous distal embolism of thrombus or atheromatous gruel from the epicardial culprit lesion was common in acute coronary syndromes and might be further triggered by PCI (36,37). The current study extends these previous observations to

suggest that large attenuated plaques might be more likely to embolize spontaneously before PCI as well as after balloon dilation and stent implantation.

Study limitations. This was a retrospective analysis. However, data were collected prospectively by independent monitors at each site. In most patients, IVUS was only performed after stenting (according to the established protocol). However, in the subset of patients with both pre- and post-stent IVUS, there were no significant differences in the presence or amount of attenuated plaque comparing pre- versus post-stenting studies; and reliability analysis showed excellent repeat measurements. There were 262 cases with a mechanical catheter (40 MHz, Boston Scientific) and 102 cases with a solid state catheter (20 MHz, Volcano Corporation). Although attenuated plaques were more common in patients with mechanical catheters versus solid state catheters (82.8% vs. 65.7%, $p < 0.001$), the frequency of no-reflow versus reflow was similar in mechanical catheters (72.2% vs. 70.3%) and in solid state catheters (27.8% vs. 29.7%) ($p = 0.807$). The number of variables included in our multivariate logistic regression analysis might lead to overfitting, due to the low number of events ($n = 37$). However the final model is parsimonious, because only 2 variables were selected. Finally, we did not assess the amount of attenuated plaque, per se, but the attenuation angle. The pre- versus post-stent comparison in the current analysis indicates that the angle of attenuation does not change, even though plaque was embolized as indicated by the CK-MB changes (in the current study) and changes in plaque mass reported in previous studies (7,38).

Conclusions

Attenuated plaque is present in three-quarters of patients with AMI. The extent of the attenuation rather than its mere presence is strongly correlated with no-reflow; the larger the attenuated plaque, the greater the likelihood of no-reflow.

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Key Words: acute myocardial infarction ■ intravascular ultrasound ■ no-reflow.