The incidence of periprocedural myocardial infarction (MI) after percutaneous coronary intervention (PCI) ranges from 2% to 50%, depending on the clinical presentation, type of procedure, choice of biomarker (creatine kinase [CK]-MB or troponin), and the threshold used to qualify the diagnosis.1 Because of this heterogeneity of definition, the prognostic implications of periprocedural MI are controversial.2 However, several studies have demonstrated that periprocedural MI is associated with worse in-hospital, short-term, and long-term clinical outcomes, including death, recurrent MI, and need for revascularization.3-5

Various mechanisms can lead to periprocedural MI, such as side branch occlusion or vessel spasm; however, distal embolization of atheroma or thrombus seems to be a dominant cause.6 In a cardiac MRI (cMRI) study of patients undergoing complex native coronary PCI, elevated troponin levels post-PCI correlated with new myocardial enhancement because of side branch occlusion in 43% of cases and in the apical myocardium distal to the stent in 57% of cases, as would be expected with distal embolization.7

Numerous studies have documented the occurrence of distal embolization during both elective and urgent PCI and have characterized its histopathologic substrate. In an analysis of catheter-retrieved materials from human studies of patients undergoing PCI for acute coronary syndrome (ACS),8 those with no-reflow had significantly higher amounts of visible atheroma and microscopic components such as platelet–fibrin complexes, cholesterol crystals, and macrophages.9 In another study of 37 lesions in 35 patients undergoing elective PCI, microscopic particles were captured by embolic protection devices (EPDs) in 28 (75.6%) lesions.9 Thrombotic components (fibrin strand–entrapped platelets, leukocytes, and red cells) accounted for the majority (≈75%) of captured debris, whereas plaque components (fibrous tissue, calcium spots, acellular amorphous material, macrophages, foam cells, and cholesterol clefts) accounted for the minority (≈25%).9 Similar findings were demonstrated among 33 patients undergoing either native or saphenous vein graft PCI.10 Supporting these in vivo findings, in a postmortem analysis of patients who died of ischemic heart disease, many had evidence of coronary microemboli, composed of cholesterol crystals, hyaline, and platelet aggregates.11

Clinically, distal embolization can result in asymptomatic biomarker elevation or symptomatic ischemia; angiographically, it can present as visually undetectable silent embolization, macroembolization resulting in epicardial coronary obstruction, or severe microvascular obstruction resulting in no-reflow.

Coronary angiography has limited capacity to assess the risk for distal macro- or microembolization. The development of advanced intracoronary imaging techniques and noninvasive imaging techniques, such as coronary computed tomography angiography (CCTA) and cMRI, provides an opportunity for detailed analysis of plaque composition, which can potentially identify lesions at high risk of causing distal embolization or periprocedural MI (Figures 1–4).12

In the present article, we review the association of intracoronary and noninvasive imaging findings with distal embolization and periprocedural MI. In addition, we compare these imaging findings with those used to identify vulnerable plaque.

**Grayscale Intravascular Ultrasound**

Intravascular ultrasound (IVUS), the most extensively studied intracoronary imaging modality, has an axial resolution of 150 to 200 μm and excellent tissue penetration.13 IVUS provides both qualitative and quantitative information about coronary plaques, suggesting its potential to identify plaques at risk of distal embolization. Several studies have characterized IVUS-detected features of plaques associated with an increased risk of distal embolization.

The qualitative features of IVUS associated with increased risk of distal embolization include plaque eccentricity, lipid pool–like images, presence of fissure, dissection or...
intracoronary thrombus, and, most importantly, presence or absence of deep ultrasound attenuation without calcification, referred to as attenuated plaque (Figure 1A and Figure 4B). In a study of 100 patients undergoing primary PCI for ST-segment elevation MI (STEMI), patients with no reflow more commonly had eccentric plaques (92% versus 51%; \( P<0.01 \)), fissure/dissection (92% versus 37%; \( P<0.01 \)), and lipid pool–like images (92% versus 25%; \( P<0.01 \)) compared with patients without no-reflow. Lipid pool–like images were the only qualitative IVUS finding independently predictive of no-reflow (odds ratio [OR], 118; 95% confidence interval [CI], 1.28–11008) (Table 1).

In another study of 140 patients with STEMI undergoing PCI, IVUS detection of an intracoronary mobile mass (which is usually suggestive of thrombus) was more common in patients with angiographic evidence of distal embolization compared with those without (75% versus 16%; \( P<0.001 \); adjusted OR, 53; 95% CI, 2.7–1040.7; Table 1). A larger study of 220 patients with ACS (49.5% with STEMI) found results similar to these 2 previous studies, demonstrating that patients with transient no-reflow were more likely to have eccentric plaque (60% versus 32%; \( P<0.01 \)), plaque rupture (25% versus 9%; \( P<0.05 \)), lipid pool–like images (65% versus 37%; \( P<0.05 \)), and thrombus (80% versus 33%; \( P<0.0001 \)).

The qualitative feature with most support in the literature is the presence of attenuated plaque. Attenuated plaque has been associated with adverse outcomes after PCI in several studies. Among 293 patients with ACS (36.2% with STEMI), no-reflow was more common in patients with attenuated plaque (26.7% versus 4.6%; \( P<0.001 \)) compared with those without (Table 1). In a similar study of 170 patients with STEMI, the odds of no-reflow were significantly higher (OR, 20.1; 95% CI, 5.87–69.0) in patients with attenuated plaque >5 mm in longitudinal length (Table 1). In a non-ACS study of 46 patients, the presence of attenuated plaque was an independent predictor of troponin T (TnT) elevation >3 times upper limit of normal (ULN; 95% CI, 1.60–8.94) after PCI. A large retrospective study evaluating ACS (n=336) and non-ACS (n=351) patients found that the presence of attenuated plaque was an independent predictor of no-reflow after PCI in both groups (OR, 5.93; 95% CI, 2.42–14.55 for ACS; OR, 6.62; 95% CI, 1.37–32.12 for non-ACS; Table 1). Although technically a qualitative feature, attenuated plaque can be quantitated by a total attenuation score, an integer-derived score based on the arc of attenuation for...
The total attenuation score can then be normalized to the length of vessel analyzed, providing a mean attenuation score. In an IVUS sub-study of 464 patients from the Harmonizing Outcomes with Revascularization and Stents in Acute Myocardial Infarction (HORIZONS-AMI) trial, a mean attenuation score ≥2 was a robust predictor of no-reflow after PCI (OR, 6.586; 95% CI, 2.680–16.188; Table 1).

In addition to the mean attenuation score, IVUS allows calculation of other unique quantitative parameters associated with increased risk for periprocedural MI or distal embolization after PCI. These include: (1) plaque area equal to the difference between external elastic membrane (EEM) cross-sectional area and lumen cross-sectional area, and (2) plaque burden or cross-sectional narrowing equal to the ratio of plaque area to EEM cross-sectional area. In 1 of the first and largest studies ever to examine the association between IVUS findings and post-PCI biomarker elevation, Mehran et al evaluated 2256 patients and found that plaque burden of the lesion site and reference segment (defined as the most normal-looking cross-section proximal and distal to the stenosis between major side branches) were independent predictors of post-PCI CK-MB elevation (OR, 1.14; 95% CI, 1.07–1.82, and OR, 1.01; 95% CI, 1.01–1.02, respectively; Table 1). Supporting this association between greater amount of plaque and adverse outcomes after PCI, 2 subsequent studies found independent associations with increasing plaque burden and plaque area with no-reflow after PCI (Table 1). Tanaka et al demonstrated a 1.55-fold increased odds (95% CI, 1.01–2.38) of developing no-reflow after PCI for STEMI with increasing plaque area, and Iijima et al demonstrated a 1.79-fold increased odds (95% CI, 1.1–3.23) of developing no-reflow after PCI for ACS (111 non–ST-segment myocardial infarction [NSTEMI] and 109 STEMI) with increasing plaque burden.

Radiofrequency Analysis IVUS

Grayscale IVUS can measure vessel and lumen dimensions and provide both quantitative and qualitative data about atherosclerotic plaque; however, its ability to provide information on plaque composition, which is another potentially important predictor of distal embolization, is limited. Cited reasons for this shortcoming include reliance on video images, which limits resolution; operator-dependent parameters, such as brightness and gain; and, importantly, use of only the amplitude of the radiofrequency signal to create images. Radiofrequency analysis of backscatter signals from a conventional IVUS catheter can be used to more reliably characterize plaque composition. Virtual histology (VH) IVUS, integrated backscatter (IB) IVUS, and iMAP IVUS are 3 available radio frequency (RF) analysis technologies that have been incorporated into conventional IVUS systems.
Although all 3 technologies were designed to improve plaque composition assessment, they are fundamentally different and cannot be considered interchangeable.

**Virtual Histology Intravascular Ultrasound**

VH IVUS, the first commercially available RF analysis tool, uses spectral analysis of radiofrequency backscatter signals from either a 20 MHz phased array or 45 MHz rotational IVUS catheter to allow real-time histopathologic classification of 4 different plaque components: fibrous, fibrofatty, dense calcium, and necrotic core. Two of these components, fibrofatty and necrotic core (Figure 1B), have been associated with increased risk for distal embolization or periprocedural MI.

Claessen et al performed a comprehensive review of previously published observational studies exploring the relationship of VH IVUS findings with distal embolization. Out of 11 previously published studies, 9 found an association with necrotic core plaque and distal embolization during PCI, whereas 2 found an association with fibrofatty plaque. These latter 2 studies found that patients who developed slow or no-reflow after PCI had higher fibrofatty plaque volume or percent fibrofatty plaque volume (Table 2).

One of the first studies to demonstrate the association between necrotic core and distal embolization used high-intensity transient signals seen on Doppler guidewire tracings. High-intensity transient signals have been shown to be a reliable method for the detection of distal embolization of small particles. Of 44 consecutive patients undergoing PCI for stable angina, those with the highest high-intensity transient signal counts had larger areas of dense calcium and necrotic core measured by VH IVUS. In multivariate analysis, necrotic core was the only independent predictor of higher high-intensity transient signal counts (OR, 4.41; 95% CI, 1.03–18.81; Table 2). The index of microcirculatory resistance can be reproducibly measured using a coronary pressure wire and is another method for detecting distal embolization. Yamada et al evaluated 29 patients undergoing elective PCI for the presence of thin cap fibroatheroma (TCFA), defined as >10% confluent necrotic core without a detectable overlying fibrous cap segment, pre-PCI. Patients without TCFA had significant improvement in index of microcirculatory resistance post-PCI, whereas patients with greater TCFA burden had higher post-PCI peak creatine kinase-MB levels and troponin I levels.

**Figure 3.** Case illustrating thrombus embolization during percutaneous coronary intervention of a thrombus-containing coronary lesion. A 65-year-old man with diabetes mellitus, hypertension, hyperlipidemia, systolic heart failure, and coronary artery disease with previous stenting presented with unstable angina. Coronary angiography demonstrated nonobstructive in-stent restenosis in the left anterior descending artery, chronic total occlusion of the left circumflex with poor collateral filling, and intermediate eccentric stenosis of the distal right coronary artery (RCA; arrows; A). Intravascular ultrasonography (IVUS) of the distal RCA lesion demonstrated plaque rupture, establishing it as the culprit lesion (arrows; B). Further evaluation with optical coherence tomography (OCT) demonstrated a large intracoronary thrombus (asterisk; C). Intracoronary eptifibatide and nicardipine were administered. Stenting resulting in no residual stenosis (arrows; D) and thrombolysis in myocardial infarction 3 flow. Postintervention IVUS demonstrated a well-expanded, well-apposed stent with tissue prolapse through the stent (arrows; E), and OCT demonstrated residual intrastent thrombus (arrows; F). The patient did not have any symptoms; however, postprocedural peak creatine kinase-MB increased to 23.4 ng/mL, and troponin I was 2.41 ng/mL. This case demonstrates that aggressive antiplatelet regimen and vasodilator administration may partially prevent or lessen the adverse consequences of distal embolization when treating thrombus-containing coronary lesions.
resistance measurements after PCI compared with those with TCFA (13.2 versus −4.4; 95% CI, −8.25–1.98). In a study of 71 STEMI patients by Kawaguchi et al, ST-segment re-elevation (suggestive of distal embolization) occurred in 16% of cases and had a strong association with necrotic core volume (area under the curve was 0.756) on receiver operating characteristics analysis. Necrotic core volume >33.4 mm³ was the optimal cutoff, providing a sensitivity of 81.7% and specificity of 63.6% for ST-segment re-elevation (Table 2). A similar study looking at 101 consecutive patients with STEMI found that necrotic core volume had the best diagnostic accuracy of VH IVUS parameters to predict ST-segment resolution <30% (area under the curve was 0.811). The optimal cutoff for necrotic core volume was 20.3 mm³, yielding a sensitivity of 75.0% and specificity of 74.1% (Table 2).

Although the aforementioned studies used surrogate markers of distal embolization, 2 subsequent studies looked at the association between VH IVUS findings and the occurrence of no-reflow during or after PCI. In 49 consecutive patients with ACS, Higashikuni et al found plaques with significantly lower percentage of fibrous component and higher percentage of necrotic core in patients with no-reflow compared with those without no-reflow at both the minimum lumen area site and the entire culprit lesion. The percent necrotic core of the entire culprit lesion was the only independent predictor of no-reflow during PCI (OR, 1.7; 95% CI, 1.1–2.5; Table 2). In a larger study of 190 consecutive patients with ACS examined with VH IVUS, Hong et al found plaques with higher percent necrotic core at the minimum lumen site (24.5% versus 16.1%; P=0.001) and higher percent necrotic core volume throughout the lesion (22% versus 14%; P<0.001) in patients with no-reflow compared with those without. In addition, patients with no-reflow had significantly more VH IVUS–detected TCFA (71% versus 36%; P<0.001), defined as ≥10% necrotic core area in 3 consecutive frames without overlying fibrous tissue in ≥40% plaque burden. After multivariate adjustment, percent necrotic core volume was the only independent predictor of no-reflow after stenting (OR, 1.126; 95% CI, 1.045–1.214; Table 2).

Finally, 3 studies have evaluated the association between cardiac biomarker rise after PCI with findings from VH IVUS. Böse et al prospectively demonstrated a linear relationship between plaque absolute necrotic core volume and percent necrotic core volume with post-PCI cardiac troponin I (TnI) elevation >0.1 ng/mL after PCI (Table 2). In a retrospective review of 80 consecutive patients without TnI elevation at admission, absolute necrotic core volume and percent necrotic core volume were higher in patients with elevated TnI after PCI compared with those without. The absolute necrotic core area at the minimum lumen site was the only independent predictor of elevated postprocedure TnI >3 times ULN (OR, 1.318; 95% CI, 1.090–1.594; Table 2), which occurred in 48% of the cohort. A third study evaluated the ability of Shin’s method of VH IVUS analysis to predict CK-MB elevation compared with the ULN in 112 consecutive patients with unstable angina undergoing PCI. Conventional RF IVUS analysis requires tracing the leading edge of the intima; in Shin’s method, the lumen contour is drawn around the IVUS catheter. Shin’s method allows accurate calculation of necrotic core, dense calcium, vessel

![Image](http://circimaging.ahajournals.org/content/1106/5/1327/F4.large.jpg)
areas, and vessel volumes, but does not allow quantification of fibrous or fibrofatty components, lumen areas, or plaque areas and volumes.44 Using Shin’s method, dense calcium volume and the ratio of necrotic core area to EEM in the most diseased 10 mm lesion segment were independent predictors of CK-MB elevation in multivariate analysis15,18 (Table 2).

Both attenuated plaque by grayscale IVUS studies and necrotic core by VH IVUS are consistent predictors of adverse outcomes after PCI. A recent multimodality imaging study suggested a strong correlation between these 2 findings.12 Out of 66 patients with stable angina or non-ST elevation ACS, 31 attenuated plaques were detected in 26 vessels.12 Nearly all of these plaques (93.5%) contained confluent necrotic core by VH IVUS.12 Furthermore, compared with control plaques (those without echolucency, attenuation, or calcification), attenuated plaques had a significantly higher percent necrotic core (P<0.001).12

### Integrated Backscatter Intravascular Ultrasound

In IB IVUS, average power in decibels can be calculated using a fast Fourier transformation of backscatter signals generated from a 40 MHz mechanically rotating IVUS catheter, allowing classification of coronary plaque into calcified, fibrous, and lipid components.45 Two studies have evaluated the association between IB IVUS findings and distal embolization after PCI.40,41 Shibuya et al41 examined the association between filter no-reflow and IB IVUS findings in 34 consecutive patients with unstable angina undergoing native coronary PCI with distal embolic protection using a filter EPD. Nine of 34 (26.4%) patients developed no-reflow after PCI.41 Percent lipid plaque content by IB IVUS was significantly higher (29.3% versus 26.1%; P=0.045) in patients with no-reflow compared with those without; however, in multivariate analysis only plaque volume detected by grayscale IVUS was independently predictive of no-reflow (OR, 6.157; P=0.049).41 Uetani et al40 studied 114 consecutive patients undergoing elective stent implantation, evaluating the association of IB IVUS findings with elevated cardiac biomarkers after PCI. Both lipid volume and fibrous volume were significantly higher in patients with post-PCI cardiac TnT levels ≥3 times ULN.40 Lipid fraction (percent lipid volume over total plaque volume) was also higher, whereas fibrous fraction was lower in patients with elevated TnT levels after PCI.40

### Table 1. Grayscale Intravascular Ultrasound Findings Associated with Distal Embolization and Periprocedural Myocardial Infarction

| First Author Year N Indication Primary Outcome Imaging Finding Odds Ratio 95% CI Comments |
|---------------------------------|---------------------------------|------------------|--------|--------|
| Mehran14 2000 2256 SA/UA CK-MB ≥1× ULN Plaque burden at reference segment 1.01 1.01–1.02 |
| Plaque burden at lesion site 1.14 1.07–1.82 |
| Tanaka15 2002 100 STEMI No-reflow Plaque area 1.55 1.01–2.38 |
| Lipid pool–like image 118 1.28–11008 |
| Fukuda19 2003 140 STEMI Angiographic distal embolization Intracoronary mobile mass 53 2.7–1040.7 |
| liiima16 2006 220 111 NSTEMI, 109 STEMI Transient no-reflow Thrombus 4.53 1.03–20 |
| Plaque burden, lesion site 1.79 1.01–3.23 |
| Lee16 2009 293 187 NSTEMI, 106 STEMI No-reflow Attenuated plaque n/a n/a 26.7% with vs 4.6% without (P<0.001) |
| Decreased antegrade flow post-PCI |
| Kimura20 2009 687 131 STEMI, 45 NSTEMI, 160 UA, 351 SA No-reflow Attenuated plaque 5.59 2.64–11.85 Overall population |
| 336 ACS |
| 351 SA |
| No-reflow Attenuated plaque 5.93 2.42–14.55 ACS population |
| Endo21 2010 170 STEMI No-reflow Attenuated plaque ≥5 mm long 20.1 5.87–69.0 |
| Wu17 2011 364 STEMI No-reflow Plaque rupture 5.94 1.64–21.5 |
| Lee22 2011 135 107 SA, 28 UA CK-MB>ULN Attenuated plaque 3.49 1.53–7.93 |
| Mitsuba23 2012 49 Non-ACS TnT ≥3× ULN Attenuated plaque Not reported 1.60–8.94 |

ACS indicates acute coronary syndrome; CI, confidence interval; CK, creatine kinase; n/a, not available; NSTEMI, non–ST-segment elevation acute myocardial infarction; PCI, percutaneous coronary intervention; SA, stable angina; STEMI, ST-segment elevation acute myocardial infarction; TnT, troponin T; UA, unstable angina; and ULN, upper limit of normal.
Lipid volume was the only independent predictor of post-PCI TnT elevation ($P<0.001$). Lipid volume showed excellent test characteristics to predict post-PCI TnT elevation (area under the curve, 0.889) with an optimal cutoff of 45.6 mm$^3$ (providing 100% sensitivity and 67.3% specificity; Table 2).

### iMAP Intravascular Ultrasound

iMAP IVUS, the newest IVUS technology, compares the RF spectral signal of a region of interest to that from a known database of histological subtypes. Using a pattern recognition algorithm, it has been shown to provide accurate ex vivo prediction of 4 histological subtypes: fibrotic, lipidic, necrotic, and calcified. Given its recent inception, limited in vivo human data from iMAP IVUS studies are available. In a study of 95 consecutive patients with stable angina or ACS, patients with slow flow after PCI had significantly higher absolute necrotic plaque volumes (43.3 mm$^3$ versus 20.1 mm$^3$; $P=0.0004$), as detected by iMAP IVUS. A necrotic core

<table>
<thead>
<tr>
<th>First Author</th>
<th>Year</th>
<th>N</th>
<th>Indication</th>
<th>Primary Outcome</th>
<th>Imaging Finding</th>
<th>Odds Ratio</th>
<th>95% CI</th>
<th>Comments</th>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Kawamoto28</td>
<td>2007</td>
<td>51</td>
<td>SA</td>
<td>High-intensity transient signals</td>
<td>Necrotic core area (minimum lumen site)</td>
<td>4.41</td>
<td>1.03–18.81</td>
<td></td>
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<td>Kawaguchi26</td>
<td>2007</td>
<td>71</td>
<td>STEMI</td>
<td>ST-segment re-elevation</td>
<td>Necrotic core (mm$^3$)</td>
<td>n/a</td>
<td>n/a</td>
<td>AUC, 0.756; &gt;33.4 mm$^3$ optimal cutoff; S/Sp, 81.7%/63.6%</td>
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<td>Nakamura25</td>
<td>2007</td>
<td>50</td>
<td>STEMI</td>
<td>No-reflow</td>
<td>Fibrofatty percent</td>
<td>n/a</td>
<td>n/a</td>
<td>23.1% with vs 17.0% without</td>
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<td>Higashikuni30</td>
<td>2008</td>
<td>49</td>
<td>16 UA, 33 NSTEMI/STEMI</td>
<td>No-reflow</td>
<td>Necrotic core percent (entire culprit lesion)</td>
<td>1.7</td>
<td>1.1–2.5</td>
<td></td>
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<tr>
<td>Böse37</td>
<td>2008</td>
<td>55</td>
<td>SA</td>
<td>Tnl</td>
<td>Necrotic core</td>
<td>n/a</td>
<td>n/a</td>
<td>Linear relationship with necrotic core and Tnl increase</td>
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<tr>
<td>Bae31</td>
<td>2008</td>
<td>57</td>
<td>47 STEMI, 10 NSTEMI</td>
<td>Slow flow</td>
<td>Fibrofatty volume (mm$^3$)</td>
<td>n/a</td>
<td>n/a</td>
<td>36.7 mm$^3$ with vs 18.0 mm$^3$ without</td>
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<tr>
<td>Hong39</td>
<td>2009</td>
<td>80</td>
<td>29 SA, 51 UA</td>
<td>Tnl ≥3× ULN</td>
<td>Necrotic core area (minimum lumen site)</td>
<td>1.318</td>
<td>1.090–1.594</td>
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<tr>
<td>Yamada38</td>
<td>2010</td>
<td>29</td>
<td>Elective</td>
<td>ΔIMR</td>
<td>TCFA</td>
<td>n/a</td>
<td>n/a</td>
<td>ΔIMR decreased with TCFA</td>
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<tr>
<td>Hong32</td>
<td>2011</td>
<td>190</td>
<td>111 UA, 34 NSTEMI, 45 STEMI</td>
<td>No-reflow</td>
<td>Necrotic core volume percent</td>
<td>1.126</td>
<td>1.045–1.214</td>
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<td>Shin33</td>
<td>2011</td>
<td>112</td>
<td>UA</td>
<td>CK-MB &gt;1× ULN</td>
<td>Necrotic core to EEM ratio (most diseased 10-mm lesion segment)</td>
<td>1.26</td>
<td>1.12–1.43</td>
<td></td>
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<td>Ohshima39</td>
<td>2012</td>
<td>101</td>
<td>STEMI</td>
<td>ST-segment elevation resolution &gt;30%</td>
<td>Necrotic core (mm$^3$)</td>
<td>n/a</td>
<td>n/a</td>
<td>AUC, 0.811; &gt;20.3 mm$^3$ optimal cutoff; S/Sp, 75.0%/74.1%</td>
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<td>Integrated backscatter IVUS</td>
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<td></td>
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<tr>
<td>Uetani40</td>
<td>2008</td>
<td>114</td>
<td>Elective</td>
<td>TnT ≥3× ULN</td>
<td>Lipid volume (mm$^3$)</td>
<td>n/a</td>
<td>n/a</td>
<td>AUC, 0.889; &gt;45.6 mm$^3$ optimal cutoff; S/Sp, 100%/67.3%</td>
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<tr>
<td>Shibuya41</td>
<td>2012</td>
<td>34</td>
<td>UA</td>
<td>Filter no-reflow</td>
<td>Lipid percent</td>
<td>n/a</td>
<td>n/a</td>
<td>29.3% with vs 26.1% without ($P=0.045$)</td>
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<td>iMAP IVUS</td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Utsonomiya42</td>
<td>2011</td>
<td>95</td>
<td>62 elective, 33 ACS</td>
<td>Slow flow</td>
<td>Necrotic plaque volume (mm$^3$)</td>
<td>n/a</td>
<td>n/a</td>
<td>AUC, 0.766; &gt;21.6 mm$^3$ optimal cutoff; S/Sp, 81.8%/61.9%</td>
</tr>
</tbody>
</table>

ACS indicates acute coronary syndrome; AUC, area under the curve; CI, confidence interval; CK, creatine kinase; CSN, cross-sectional narrowing; EEM, external elastic membrane; IMR, index of microcirculatory resistance; IVUS, intravascular ultrasound; n/a, not available; NSTEMI, non–ST-segment elevation acute myocardial infarction; S/Sp, sensitivity/specificity; SA, stable angina; STEMI, ST-segment elevation acute myocardial infarction; TCFA, thin cap fibroatheroma; Tnl, troponin I; UA, unstable angina; and ULN, upper limit of normal.
plaque volume cutoff of 21.6 mm³ yielded a sensitivity of 81.8% and specificity of 61.9% for predicting slow flow after PCI (Table 2).42

**Optical Coherence Tomography**

Optical coherence tomography (OCT) measures the amplitude of backscattered light, known as optical echoes, as a function of delay, allowing the creation of high-resolution (10–20 μm) images of intracoronary plaques47 and allowing identification of TCFA (Figure 1C), typically defined by a fibrous cap measuring <70 μm.34 Although OCT offers high-resolution images, it has poor tissue penetration, limiting its ability to quantify plaque volume,34 which was shown by the IVUS studies presented earlier to be correlated with the risk of adverse outcomes after PCI. To overcome this limitation, lipid content in plaque can be semiquantitated with a lipid arc (Figure 1C) measurement, defined as the number of circumferential degrees of lipid present in a given plaque segment. In a study of 83 patients with non-ST elevation ACS, Tanaka et al48 showed that those with no-reflow after PCI had higher measures of lipid arc (166 versus 44; P<0.001) and more often had TCFAs (50% versus 16%; P=0.005); however, lipid arc was the only independent predictor of no-reflow after PCI in multivariate analysis (OR, 1.018; 95% CI, 1.004–1.033; Table 3).22,46-52

In a study of 125 patients undergoing nonemergency stent implantation, Yonetsu et al49 did find an independent association of OCT-detected TCFA with elevated CK-MB levels after PCI. To overcome this limitation, lipid content in plaque can be semiquantitated with a lipid arc (Figure 1C) measurement, defined as the number of circumferential degrees of lipid present in a given plaque segment. In a study of 83 patients with non-ST elevation ACS, Tanaka et al48 showed that those with no-reflow after PCI had higher measures of lipid arc (166 versus 44; P<0.001) and more often had TCFAs (50% versus 16%; P=0.005); however, lipid arc was the only independent predictor of no-reflow after PCI in multivariate analysis (OR, 1.018; 95% CI, 1.004–1.033; Table 3).22,46-52

OCT has been shown to provide additional information regarding the risk of adverse outcomes after PCI when added to IVUS. In 135 patients undergoing PCI for stable or unstable angina, Lee et al50 found only 2 independent predictors of elevated CK-MB after PCI (IVUS-detected attenuated plaque: OR, 3.49; 95% CI, 1.53–7.93; Table 1; OCT-derived plaque rupture defined by fibrous cap disruption: OR, 2.92; 95% CI, 1.21–7.06; Table 3). In a separate study of the same population, Lee et al50 demonstrated the association between OCT-detected TCFA and TnI elevation >3 times ULN. TCFA was the strongest independent predictor of post-PCI troponin elevation (OR, 4.68; 95% CI, 1.88–11.64; Table 3). To overcome this limitation, lipid content in plaque can be semiquantitated with a lipid arc (Figure 1C) measurement, defined as the number of circumferential degrees of lipid present in a given plaque segment. In a study of 83 patients with non-ST elevation ACS, Tanaka et al48 showed that those with no-reflow after PCI had higher measures of lipid arc (166 versus 44; P<0.001) and more often had TCFAs (50% versus 16%; P=0.005); however, lipid arc was the only independent predictor of no-reflow after PCI in multivariate analysis (OR, 1.018; 95% CI, 1.004–1.033; Table 3).22,46-52

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**Near-Infrared Spectroscopy**

Near-infrared spectroscopy (NIRS) uses light in the near-infrared spectrum to determine the chemical composition of plaques, identifying lipids such as cholesterol and cholesteryl esters. NIRS has been validated for the detection of lipid core plaque (LCP) through comparison with histology44 and is highly reproducible.55 NIRS is currently combined with an IVUS catheter and produces a 2-dimensional map of the vessel, called a chemogram, in which each pixel is given a color based on the probability that LCP is present. High probability of lipid is assigned yellow color, and low probability, red color. A block chemogram represents the likelihood of LCP among 2 mm segments of the imaged coronary artery segment. NIRS also provides a quantitative measure of distribution of lipid burden, called the lipid core burden index (LCBI).

### Table 3. Optical Coherence Tomography Findings Associated With Distal Embolization and Periprocedural Myocardial Infarction

<table>
<thead>
<tr>
<th>First Author</th>
<th>Year</th>
<th>N</th>
<th>Indication</th>
<th>Primary Outcome</th>
<th>Imaging Finding</th>
<th>Odds Ratio</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tanaka49</td>
<td>2009</td>
<td>90</td>
<td>NSTEACS (including UA)</td>
<td>No-reflow</td>
<td>Lipid arc</td>
<td>1.018</td>
<td>1.004–1.033</td>
</tr>
<tr>
<td>Yonetsu49</td>
<td>2011</td>
<td>125</td>
<td>Nonemergency</td>
<td>CK-MB &gt;1× ULN</td>
<td>TCFA</td>
<td>4.68</td>
<td>1.88–11.64</td>
</tr>
<tr>
<td>Lee50</td>
<td>2011</td>
<td>131</td>
<td>24 UA, 107 SA</td>
<td>TnI &gt;3× ULN</td>
<td>TCFA (&lt;70 μm)</td>
<td>10.47</td>
<td>3.74–29.28</td>
</tr>
<tr>
<td>Lee50</td>
<td>2011</td>
<td>135</td>
<td>28 UA, 107 SA</td>
<td>CK-MB &gt;1× ULN</td>
<td>Ruptured plaque</td>
<td>2.92</td>
<td>1.21–7.06</td>
</tr>
<tr>
<td>Ozaki51</td>
<td>2011</td>
<td>59</td>
<td>22 NSTEACS, 37 STEMI</td>
<td>Microvascular obstruction assessed by MRI</td>
<td>TCFA (&lt;70 μm)</td>
<td>5.43</td>
<td>1.27–23.32</td>
</tr>
<tr>
<td>Porto52</td>
<td>2012</td>
<td>50</td>
<td>25 SA, 25 NSTEMI</td>
<td>TnI &gt;3 ULN</td>
<td>TCFA (≤ 65 μm)</td>
<td>29.79</td>
<td>1.36–32.08</td>
</tr>
</tbody>
</table>

CI indicates confidence interval; CK, creatine kinase; NSTEACS, non–ST elevation acute coronary syndrome; SA, stable angina; STEMI, ST-segment elevation acute myocardial infarction; TCFA, thin cap fibroatheroma; TnI, troponin I; UA, unstable angina; and ULN, upper limit of normal.
This is calculated as the fraction of pixels in a region of interest that have >0.6 probability of LCP multiplied by 1000.

PCI of a large LCP by NIRS (Figure 1F, Figure 2B, and Figure 4A and 4B) has been associated with no-reflow in several case reports. In a study of 30 patients undergoing native coronary PCI, postprocedural CK-MB level elevation >3 times the ULN was observed in 27% of patients with ≥2 2-mm yellow blocks on the block chemogram versus none with 0 to 1 yellow block within the stented lesion (P = 0.02). In a subset of 62 patients from the Chemometric Suspect none with 0 to 1 yellow block within the stented lesion patients with TnT elevation had greater low-attenuation (<50 HU) plaque volume (87.9 mm³ versus 47.4 mm³; P<0.01) and higher percentage of low-attenuation plaque (32.9% versus 29.0%; P<0.05). Three studies have demonstrated frequent occurrence of a ring-like high-attenuation signal surrounding low-attenuation plaques. Similar to IVUS, CCTA affords the ability to quantitatively characterize plaque by length, volume, and percentage. Noncalcified, low-density (<30 HU) plaque measuring >4.7 mm was an independent predictor of no-reflow among 78 patients undergoing PCI for either stable angina or ACS. In a study of 189 patients undergoing elective PCI for stable angina, postprocedural TnT elevation ≥0.1 ng/mL occurred in 59 (31.2%) patients. Those with TnT elevation had greater low-attenuation (<50 HU) plaque volume (87.9 mm³ versus 47.4 mm³; P<0.01) and higher percentage of low-attenuation plaque (32.9% versus 29.0%; P<0.05). Three studies have demonstrated frequent occurrence of a ring-like high-attenuation signal surrounding low-attenuation plaques. These studies have demonstrated an association between this ring-like enhancement and slow or no-reflow and elevated postprocedural TnT levels. The exact cause of this imaging phenomenon is unknown, but its presence is highly specific to OCT-detected TCFA and may be the CCTA morphological correlate. Finally, CCTA is able to provide an assessment of vessel remodeling, typically through the positive remodeling index (ratio of the average proximal and distal reference EEM area to lesion EEM area). The remodeling index was significantly higher in 40 patients with stable angina who experienced slow flow after PCI compared with 40

### Table 4. Noninvasive Imaging Findings Associated With Distal Embolization and Periprocedural Myocardial Infarction

<table>
<thead>
<tr>
<th>First Author</th>
<th>Year</th>
<th>N</th>
<th>Indication</th>
<th>Primary Outcome</th>
<th>Imaging Finding</th>
<th>Odds Ratio</th>
<th>95% CI</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kinohira</td>
<td>2007</td>
<td>26</td>
<td>SA</td>
<td>Transient slow flow</td>
<td>Plaque density &lt;50 HU</td>
<td>n/a</td>
<td>n/a</td>
<td>36.4% with vs 0% without</td>
</tr>
<tr>
<td>Nakazawa</td>
<td>2008</td>
<td>51</td>
<td>SA</td>
<td>Transient no-reflow</td>
<td>Plaque density in HU</td>
<td>0.96</td>
<td>0.91–0.99</td>
<td>55.6% with vs 16.7% without (P=0.013)</td>
</tr>
<tr>
<td>Kawasaki</td>
<td>2009</td>
<td>24</td>
<td>19 SA, 5 UA</td>
<td>Slow flow</td>
<td>HIP by cMRI</td>
<td>n/a</td>
<td>n/a</td>
<td>83% with vs 14% without (P&lt;0.01)</td>
</tr>
<tr>
<td>Uetani</td>
<td>2010</td>
<td>189</td>
<td>SA</td>
<td>TnT ≥0.1ng/mL</td>
<td>LA (&lt;50 HU) plaque volume</td>
<td>n/a</td>
<td>n/a</td>
<td>87.9 mm³ with vs 47.4 mm³ without (P&lt;0.01)</td>
</tr>
<tr>
<td>Hiragana</td>
<td>2011</td>
<td>78</td>
<td>35 SA, 43 ACS</td>
<td>No-reflow</td>
<td>LA (&lt;30 HU) plaque percent</td>
<td>n/a</td>
<td>n/a</td>
<td>32.9% with vs 29.0% without (P&lt;0.05)</td>
</tr>
<tr>
<td>Watabe</td>
<td>2012</td>
<td>107</td>
<td>SA</td>
<td>TnT ≥3×ULN</td>
<td>Remodeling Index</td>
<td>4.54</td>
<td>1.36–15.9</td>
<td>&gt;4.7 mm optimal cutoff; S/Sp 82%/86%</td>
</tr>
<tr>
<td>Kodama</td>
<td>2012</td>
<td>40</td>
<td>SA</td>
<td>Slow flow</td>
<td>Plaque density in HU</td>
<td>0.977</td>
<td>0.959–0.995</td>
<td></td>
</tr>
</tbody>
</table>

ACS indicates acute coronary syndrome; CI, confidence interval; cMRI, cardiac MRI; HIP, hyperintense plaque; HU, Hounsfield units; LA, low attenuation; n/a, not available; S/Sp, sensitivity/specificity; SA, stable angina; TnT, troponin T; and UA, unstable angina.
matched controls with normal postprocedure flow (1.5 versus 1.2; \( P < 0.001 \)).

In a larger study of 107 patients with stable coronary artery disease, the remodeling index was an independent predictor of postprocedural TnT elevation \( \geq 3 \) times ULN.

In addition to CCTA, cMRI may also provide a noninvasive assessment of the risk for distal embolization during PCI. Similar to carotid plaque imaging, coronary plaques detected by cMRI can be characterized as hyperintense plaques (HIP) or non-HIP based on the presence or absence of hyperintense signals on T₂-weighted imaging. A study of 24 patients with stable or unstable angina demonstrated a correlation between HIP and IVUS attenuation, lower HU density by CCTA, and positive remodeling by both IVUS and CCTA. Slow flow was significantly more common after PCI in patients with HIP compared with those with non-HIP (Table 4; 83% versus 14%; \( P < 0.01 \)).

### Imaging to Detect Vulnerable Plaque

In parallel to the research aiming to identify coronary plaques at high risk for post-PCI complications, numerous studies have used the same imaging modalities to identify plaques with a propensity to cause future cardiovascular events, or vulnerable plaques. Retrospective studies of culprit plaques have suggested that active inflammation, thin cap, large lipid core, and cap rupture are markers of vulnerable plaque. Several of these characteristics can be prospectively identified by the invasive and noninvasive imaging modalities presented above. For example, OCT provides sufficient resolution to detect lesions with thin fibrous caps or with cap rupture, whereas IVUS, RF IVUS, and NIRS can provide quantitative data regarding amount of lipid core within a plaque. The Providing Regional Observations to Study Predictors of Events in the Coronary Tree (PROSPECT) study was a natural history study in which patients with ACS undergoing coronary angiography also underwent grayscale and RF IVUS evaluation of all 3 major epicardial coronary arteries. PROSPECT demonstrated that nonculprit lesions with plaque burden \( \geq 70\% \) and lesions identified as TCFA by RF IVUS were associated with a higher risk of recurrent events. However, it is notable that only 26 (4.4%) of all 595 TCFAs progressed to cause a clinical event, and IVUS imaging caused 11 (1.6%) complications (10 dissections, 1 perforation).

### Clinical Implications

The ability of coronary angiography to predict post-PCI complications is limited. It has been described here that intravascular imaging can enhance detection of high-risk coronary plaque characteristics associated with increased risk for distal embolization and periprocedural MI, as well as detect plaque characteristics associated with vulnerable plaques. However, it is important to place the clinical implications of these findings in perspective by reflecting on the safety and feasibility of performing additional intracoronary imaging, the limitations of the existing evidence, and the uncertain ability to translate the existing data into practice changes that modify outcomes.

From a practical perspective, the 2 most important issues to address are the overall safety of intracoronary imaging and the relative merits of routine versus selective imaging strategies. Intracoronary imaging is generally a safe procedure. The most common acute procedural complication of IVUS imaging is vessel spasm, which occurs in \( \approx 2.9\% \) of cases and is readily reversible. Major complications such as dissection, vessel closure, thrombosis, or embolism occur in \( < 0.5\% \) of cases and are more common in patients with ACS.

Determining whether routine versus selective imaging is the optimal strategy is less straightforward. In favor of routine intracoronary imaging, angiography and clinical characteristics are poor predictors of distal embolization during PCI, and occurrences of no-reflow and periprocedural MI can be associated with major adverse events. Moreover, routine intracoronary imaging may allow PCI optimization to reduce the risk of periprocedural MI from causes other than distal embolization, such as side branch occlusion or incomplete lesion coverage. For example, the presence of significant plaque in the side branch ostium detected by IVUS is associated with an increased risk of side branch occlusion after PCI. An analysis of 75 lesions with NIRS demonstrated LCP extending beyond the angiographic margins in 16% of cases, which may potentially allow for more optimal selection of stent length and lesion coverage.

However, the low specificity of these modalities for the prediction of distal embolization and periprocedural MI, coupled with a measurable, albeit low, risk of complications with additional coronary instrumentation, suggests that routine intracoronary imaging may be a low-yield strategy. If a selective imaging strategy is chosen, patients presenting with ACS and those with long or thrombotic lesions represent the highest risk group for distal embolization or periprocedural MI, and hence the group is likely to derive the greatest benefit from coronary imaging. A tailored approach targeting these highest risk patients and lesions may optimize the risk/benefit ratio in favor of intracoronary imaging; however, further studies are needed to definitively answer this issue.

All studies included in this review were observational, making the results potentially subject to bias and confounding. Further, with the exception of grayscale IVUS, the majority of studies of each imaging modality were small, reporting data from less than a few hundred patients each, limiting the generalizability of their results. Finally, there was marked heterogeneity in the imaging predictors and end points evaluated in the individual studies. Some studies evaluated more clinically relevant end points, such as no-reflow, whereas others used low-level biomarker elevations, the clinical implications of which are uncertain.

Finally, the ability to detect lesions with a propensity for distal embolization or periprocedural MI a priori is most clinically compelling if it enables modification of the procedural strategy to decrease the risk of complications. Three embolization mitigation strategies can be used currently: vasodilators, glycoprotein IIb/IIIa inhibitors, and EPDs. In the absence of contraindications, such as high risk for bleeding, hypotension, or challenging coronary anatomy, we propose using a combination of all 3 strategies, as demonstrated in Figure 4. We think that this 3-strategy combination would likely provide the optimum protection, because EPDs would prevent debris from embolizing; glycoprotein IIb/IIIa inhibitors would prevent thrombus formation at the lesion site or within the filter; and vasodilators would allow preservation of brisk antegrade flow even if embolization occurs.
EPDs have thus far only shown benefit in saphenous vein graft interventions, but not in native coronary arteries. However, risk stratification of plaques at high risk for distal embolization may help identify patients who may benefit from EPD. In patients with angiographically defined plaque rupture, use of EPD was associated with less no-reflow, increased ST-segment resolution, and improved myocardial blush grade and left ventricular ejection fraction compared with patients treated without an EPD. Currently, no clear evidence exists to show that similar results can be achieved using newer intravascular and noninvasive imaging modalities. The ongoing Coronary Assessment by Near-infrared of Atherosclerotic Rupture-prone Yellow (CANARY; NCT01268319) trial is a prospective study that is randomizing patients with large LCPs in native coronary arteries undergoing clinically indicated PCI to use of a Filterwire (Boston Scientific, Natick, MA) or standard of care without an EPD.

Need for Future Research

The current state of knowledge in this field is limited by observational studies with small number of patients and heterogeneous end points. Randomized trials with consistent and clinically relevant end points are needed to test the utility of all available imaging modalities. Moreover, trials evaluating whether modification of current practice based on results of imaging can translate to improved outcomes are also important. Finally, careful analyses examining the net clinical benefit taking into account the upfront risks of additional imaging and the cost-effectiveness of these imaging modalities are needed before they are incorporated into routine clinical practice.

Conclusions

PCI can be complicated by distal embolization and periprocedural MI. Several currently available intracoronary and noninvasive imaging modalities can allow detection of LCP and other plaque characteristics that are associated with increased PCI risk (Figure 1). Incorporating the findings of intravascular imaging into practical treatment algorithms for the prevention of periprocedural MI is an area of active investigation.

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References


Intracoronary and Noninvasive Imaging for Prediction of Distal Embolization and Periprocedural Myocardial Infarction During Native Coronary Artery Percutaneous Intervention

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