This review updates the role of various intravascular imaging techniques (1) in the detection of vulnerable plaque and (2) during percutaneous coronary intervention (PCI), especially drug-eluting stent (DES) implantation and follow-up—including intravascular ultrasound (IVUS), virtual histology (VH-IVUS) and integrated backscatter (IB-IVUS), optical coherent tomography (OCT), near-infrared (NIR) spectroscopy, angioscopy, and MRI.

**IVUS, IB-IVUS, and VH-IVUS**

The current intracoronary ultrasound imaging frequency range of 20 to 45 MHz provides 70 to 200 μm axial resolution with >5 mm penetration. Grayscale IVUS allows robust quantitative measurements including lumen, vessel, and plaque area; qualitative assessment of lesions preintervention; and quantitative assessment and complications of lesions postintervention; however, it has poor sensitivity for detecting lipid-rich plaque (67%). High-frequency IVUS transducers can produce better resolution that should also improve plaque characterization but at the trade off of greater ultrasound reflection from blood. Blood speckle with >40 MHz ultrasound can cause confusion when identifying the lumen-tissue border, detecting in-stent neointimal tissue, etc; but it is easily solved by saline (negative contrast) injection through the guiding catheter.

Standard grayscale IVUS is limited, in part, because it uses only reflected ultrasound amplitude to formulate the image and requires significant postprocessing. In an effort to improve on the qualitative assessment of the reflected ultrasound signal, Kawasaki et al developed a plaque characterization algorithm called IB-IVUS using time domain information directly from the radiofrequency signal. This process has resulted in improved plaque characterization with a reported in vitro sensitivity of 90% and specificity or 92% for lipid-rich plaque.

In a similar effort to improve plaque characterization, spectral analysis (VH-IVUS) combined frequency and amplitude analysis and used an algorithm developed from known tissue types to detect fibrous plaque, fibrofatty plaque, necrotic core (NC), and dense calcium (Figure 1A', B'). Reported sensitivity and specificity of VH-IVUS are 91.7% and 96.6% for identification of the lipid-rich NC. VH-IVUS cannot detect thrombus formation (in fact, thrombus appears as either fibrotic or fibrofatty plaque depending on the age of the thrombus) and has not been validated for assessment of stent metal or intimal hyperplasia.

**OCT**

OCT uses a light source with a wavelength centered at 1.3 μm to "reflect" off the plaque and form an image analogous to the use of reflected ultrasound. Because of the short wavelength of OCT, it will reflect (and detect) very small objects including blood cells; therefore, in order for OCT to image the vessel wall, it requires a blood-free field. The original time-domain OCT technique requires continuous flushing with proximal balloon occlusion to displace the blood. Recently, faster data and image acquisition with optical frequency domain imaging (OFDI) allows rapid (ie, 15 to 30 mm/s) imaging with only a 3 to 5 second contrast or saline injection through the guiding catheter (without the need for proximal balloon occlusion). The major advantage of OCT is the very high spatial resolution (10 to 20 μm; Figure 1C). OCT tissue characterization includes lipid-rich plaque, fibrous plaque, calcium, red blood cell rich thrombus, platelet rich thrombus, and macrophages. The major disadvantage of OCT is limited tissue penetration and, therefore, inability to consistently image the adventitia and assess plaque burden.

**NIR Spectroscopy**

NIR spectroscopy uses a catheter that contains an optic fiber that emits diffuse reflectance NIR light (wave length 0.8 to 2.5 μm) into the tissue (Figure 2B). The pattern of absorption of the light in relation to the wavelength is unique for lipid and each of the other plaque elements. Although NIR spectroscopy uses light, transmission through blood has a high enough signal-to-noise ratio for adequate differentiation of lipid-rich plaque. Gardner et al reported NIR spectroscopy results for 212 coronary segments in 84 autopsied hearts. The first group of segments was used to develop the algorithm for lipid detection, and the second group of segments was used to validate the algorithm for detection of confluent (>0.2 mm thick and >60°) and relatively superficial NC with overlying mean fibrous cap thickness <0.45 mm (area under curve=0.8). A derived lipid burden index was well correlated to the histologically determined fibroatheroma volume. The major limitation of NIR spectroscopy is that it provides compositional information but not structural information.
Angioscopy
Like OCT, angioscopy requires a blood-free field and provides very high resolution (10 to 50 μm) images of the surface of the plaque through fiber optics rather than creating an image by reflecting light or sound. Angioscopy can assess plaque color and detect red and white thrombus and surface characteristics, such as ulcerations, fissures, and flaps. Histopathologic analysis of atherectomy specimens show that white plaques correlate with mainly fibrous plaque and yellow color plaques with atheromas with/without necrotic tissue. Using in vitro models and autopsy specimens, Miyamoto et al have demonstrated that the percent saturation of yellow color increases inversely with the thickness of the fibrous cap but not with the amount of lipid. Because color grading is subjective, quantitative colorimetry has been developed. For example, the yellow color intensity of culprit lesions in myocardial infarction (MI) is higher than that of lesions in patients with unstable angina.

Intravascular MRI
Plaque characterization by MRI is promising especially in the detection of NC and hemorrhage compared with other modalities. Saam et al have shown that the sensitivity or specificity for the detection of lipid-rich/NC and hemorrhage in the carotid artery were 92/65% and 82/77% using multiple sequences (time-of-flight, T1, proton density, and T2-
weighted images) in 31 patients who underwent endoatherectomy with histologic validation. Toussaint et al\textsuperscript{28} have shown that apparent water diffusion coefficient characterizing water molecule motion in tissue was much lower in lipid core compared with the other components. In 2005, a miniature (1.73 mm in diameter) MRI probe that contained both magnet and coil (ie, no need either external magnet or coil) was reported with an estimated resolution of 100 μm \textsuperscript{29,30} in vivo (Figure 2B, bottom).\textsuperscript{29,30} Lipid fraction was calculated based on diffusion coefficient of the tissue with depth information (0 to 100 μm or 100 to 250 μm from the surface of the plaque). However, long acquisition time with occlusion balloon was a technical limitation for in vivo patient evaluation.

Clinical Observations

Vulnerable Plaque Detection, Culprit and Nonculprit Ruptured Plaques, Erosions, and TCFAs

Pathologically, lesion substrates underlying thrombosis in patients who die suddenly are plaque ruptures in 55% to 60% and plaque erosions in 30% to 35%.\textsuperscript{31} When analyzing acute coronary syndrome (ACS) culprit lesions, the incidence of plaque rupture detected by IVUS (38% to 66%),\textsuperscript{32-34} OCT (47% to 73%),\textsuperscript{35,36} and angioscopy (47% to 55%)\textsuperscript{24,36} are similar. In 30 patients with acute MI studied using all 3 imaging modalities, OCT was better at detecting plaque erosion (23%) than angioscopy (3%) or IVUS (0%).\textsuperscript{36} Three-vessel imaging studies have shown that the incidence of secondary plaque rupture in ACS nonculprit lesions is fairly common, but not ubiquitous—17% (IVUS)\textsuperscript{33} and 31% (OCT)\textsuperscript{35}—to contradict an earlier report indicating that such findings occur in 79% of patients.\textsuperscript{32} Culprit and nonculprit-ruptured plaques occur in the proximal segments of the LAD and LCX and in the RCA down to its distal bifurcation.\textsuperscript{37} Two small serial IVUS studies (≈30 patients) have shown that nonculprit plaque ruptures do not lead to subsequent acute coronary events during 1.0 to 1.8 years of follow-up, although lack of statin treatment in these patients was associated with revascularization because of stenosis progression.\textsuperscript{38,39} An angiographic study reported that 50 nonculprit plaque ruptures in 30 patients slowly healed (defined as neointima covering and disappearance of thrombus); 23% healed within 1 year, and 55% healed after the first year (mean duration of follow-up was 13 ± 9 months).\textsuperscript{23}

However, the ultimate goal of many of these techniques is to identify vulnerable plaques before, not after, they rupture, ie, detection of the so-called thin-cap fibroatheroma (TCFA)—a fibroatheroma with a thin fibrous cap (<65 μm) and a large NC that may be the precursor of plaque rupture. Phenotype lesion classification using VH-IVUS is similar to pathology.\textsuperscript{40} Because the axial resolution of VH-IVUS is approximately 200 μm and the pathological definition of a thin fibrous cap is ≤65 μm (below the resolution of the 20 MHz IVUS transducer used to generate VH-IVUS), it is
impossible for VH IVUS to detect a pathologically defined TCFA. To overcome this spatial limitation, but still use plaque characterization information to detect likely TCFAs, the classification of a VH-TCFA has been developed to include >30° of the NC abutting to the lumen (ie, inferential evidence of <200 μm of fibrous cap). The ability of VH-IVUS to predict future coronary events is being tested in a prospective multicenter registry (PROSPECT [Providing Regional Observations to Study Predictors of Events in the Coronary Tree], an imaging study in patients with unstable atherosclerotic lesions) that collects VH-IVUS images and follows the patients clinically to determine whether the VH-IVUS has predictive information. The high resolution and sensitivity and specificity of OCT for lipid detection (85% to 94% and 90% to 94% in pathological ex vivo validation), measurement of a thin fibrous cap (comparable with histology), and macrophage detection suggest that optical imaging may be able to detect vulnerable plaques (TCFAs and erosions) in vivo; and phenotypic lesion classification using backscatter and attenuation coefficients of OCT has been reported. Using these various techniques, TCFAs have been found both at the culprit and at the nonculprit site in patients with ACS-61/69% (VH-IVUS), 77/77% (OCT), and 90/95% (yellow plaques, angioscopy). Hong et al reported that 83% of VH-TCFAs in patients withACS clustered within the 40-mm proximal coronary segments; the distribution of TCFAs in patients with ACS-61/69% (VH-IVUS), 77/77% (OCT), and 90/95% (yellow plaques, angioscopy). Hong et al reported that 83% of VH-TCFAs in patients with ACS clustered within the 40-mm proximal coronary segments; the distribution of TCFAs in patients with ACS was similar with patients with ACS. Using intravascular MRI, 16 of 18 lesions including 4 ulcerated plaque, 2 TCFAs and 2 thick-cap fibroatheroma, were correctly diagnosed (sensitivity, 100%; specificity, 89%).

Currently, the diagnosis of a TCFA must be made with caution. Sawada et al evaluated 126 plaques in 56 patients using both OCT and VH-IVUS. The positive predictive value to detect “definite TCFA” (defined as agreement by both OCT and VH-IVUS) was 78% by OCT but only 46% by VH-IVUS. False-positive VH-TCFAs were the result of misdiagnosing thick-cap fibroatheromas (a limitation of the poor spatial resolution of VH-IVUS). The main reason for misdiagnosis by OCT was that large amounts of dense calcium were misinterpreted as lipid-rich NCs (both appear as low-intensity images, differentiated only by an unclear border [lipid] versus a sharp border [calcium]). These various intravascular imaging modalities do not always agree in the prerupture diagnosis of vulnerable plaques.

Natural History of Vulnerable Plaque and Regression/Stabilization Studies

Among several IVUS plaque progression/regression trials, the greatest amount of plaque regression was observed in A Study to Evaluate the Effect of Rosuvastatin on Intravascular Ultrasound-Derived Coronary Atheroma Burden (ASTEROID) (rosuvastatin 40 mg/d, but without a placebo control); however, the net reduction within the worst segment was small (median, −5.6 mm3/10 mm [−6.82, −3.96]) in 2 years of follow-up. Although that study did not assess plaque vulnerability or individual plaque components, Serruys et al showed that an oral Lp-PLA2 inhibitor halted the increase of NC compared with conventional treatment (net change of VH-IVUS NC volume in the worst 10 mm was 0.5±13.9 mm3 in the treated group versus 4.5±17.9 mm3 in the control group, P=0.009) although there was no change in overall atheroma volume. Similar findings were seen in type-2 diabetic patients treated with pioglitazone. An angioscopic study in 31 patients showed that statin therapy decreased yellow color (mean yellow color value; 2.03 to 1.13) compared with a nonstatin group (1.67 to 1.99). Finally, statins increased fibrous cap thickness as assessed using OCT. Although none of these “vulnerability studies” or even grayscale plaque progression/regression studies related imaging findings to clinical events, they are consistent with the concept that pharmacological therapy stabilizes vulnerable plaque as much as it reduces plaque mass.

Percutaneous Coronary Intervention

Several studies associated IVUS use with a reduction in clinical events primarily by optimizing final post-DES procedure results. IVUS guidance may also be useful to identify high-risk lesions preintervention such as the ones that cause no-reflow or periprocedural MIs. There are 2 main mechanisms of no reflow: (1) capillary obstruction resulting from extensive myocardial cell damage and/or reperfusion injury and (2) distal embolization of plaque debris and thrombus in patients with ST-segment elevation myocardial infarction (STEMI) and non-STEMI ACS. In 100 patients with STEMI, a large plaque burden and a lipid pool, identified by grayscale IVUS as confluent hypoechoic area covered with a superficial hyperechoic layer, were predictors for no reflow. In another study of 106 patients with STEMI and 187 with non-STEMI, noncalcified attenuated plaque was associated with no reflow (Figure 3). Noncalcified attenuated plaque (likely associated with microcalcification, cholesterol crystals, or organized thrombus) is associated with no reflow during PCI of 26.7% versus 4.6% during PCI of nonattenuated plaques (P<0.001). Noncalcified attenuated plaque may be a grayscale indication of a larger NC and/or fibroatheroma (96% of attenuated plaques contained a fibroatheroma versus 52.3% on nonattenuated plaques, P<0.0001). In support of this, multiple VH-IVUS studies have shown that a larger NC is related to distal embolization during PCI in patients with both ACS and stable angina; these studies have shown relationships between VH-IVUS determined NC and high-intensity transient signals detected using the Doppler FloWire, CK-MB or TnT elevation post-PCI, or angiographic no reflow. Comparison of pre- versus post-PCI VH-IVUS have shown the disappearance of one third of the NC supporting the relationship between the size of the NC and distal embolization during PCI. However, it should be noted that VH-IVUS cannot detect thrombus formation that can also contribute to distal embolization and no-reflow post-PCI. It should also be mentioned that this finding is not unique to VH-IVUS; IB-IVUS and OCT studies have also shown a relationship between the amount of lipid and distal embolization during PCI. Mizote et al used angioscopy to evaluate 191 patients with STEMI and showed that distal protection was helpful with patients with plaque rupture as compared with those without rupture; patients with plaque rupture had increased ST-segment resolution (68±15% versus 40±21%, P<0.0001), better myocardial
blush scores (2.6 ± 0.2 versus 1.8 ± 0.3, \(P < 0.0001\)), and more plaque debris in aspirated samples (97.3% versus 78.5%) compared with patients without plaque rupture. Previous randomized trials using distal protection devices for STEMI failed to show the effectiveness of these mechanical protections, perhaps because of the failure to specifically identify lesions at high risk for distal embolization.\(^{72}\)

**DES Thrombosis, Restenosis, and Malapposition**

IVUS predictors of DES thrombosis or restenosis are stent underexpansion and residual edge “problems,” such as geographic miss or adjacent secondary plaques.\(^ {73–75}\) Roy et al\(^ {52}\) reported that IVUS guidance reduced stent thrombosis both within 1 month and from 1 to 12 months (0.7% versus 2.0% at 1 year, \(P = 0.014\)), supporting the use of IVUS during PCI procedures. This has been supported by results from studies by Park et al\(^ {53}\) (in unprotected left main-treated arteries), and the IVUS studies by Costantini et al\(^ {54}\) have documented late-acquired stent malapposition in \(\approx 5\% \) to 15% of DES in patients with non-MI and \(\approx 25\% \) to 30% of DES in patients with MI (Figure 4).\(^ {76–80}\) Late-acquired stent malapposition is typically the result of either positive vessel wall remodeling and/or thrombus dissolution behind the stent struts (especially in patients with MI). The clinical association of late-acquired stent malapposition and thrombosis remains controversial. Cook et al\(^ {79}\) reported that 10 of 13 patients with very late stent thrombosis (LST) (mean 1.8 years after stent implantation) had stent malapposition with a malapposition area twice as large as in patients with malapposition but without LST (mean, 8.3 versus 4.0 mm\(^2\)). Conversely, large single and multicenter studies have not shown an increased frequency of LST in patients with late-acquired stent-vessel wall malapposition, although most of these malappositions were small.\(^ {78,80}\) One meta-analysis, however, did suggest that there was an increased frequency of LST compared with what should have been expected in these studies.\(^ {81}\)

**Neointimal Coverage**

Finn et al\(^ {82}\) compared 23 DES-treated patients who died with LST with 23 DES-treated patients who did not have stent thrombosis (the duration between stent implantation and death was \(\approx 7\) months for both groups). The percentage of
endothelization in patients with LST was half that of the patients with non-LST (40% versus 80%). Notably, the distribution of endothelization was heterogeneous both within and among individual stent cross sections in the LST group.

OCT and angioscopy may be able to translate these histopathologic observations into living patients. Table 1 summarizes the OCT evaluation of neointimal stent coverage for sirolimus-eluting stents from 3 months to 2 years in patients who did not develop stent thrombosis.83–87 At 2 years, although the percentage of uncovered stent struts decreased from 15% to 5%, the percentage of patients with any uncovered strut decreased only from 95% at 3 months to 81% at 2 years. Similarly, optical coherence tomography for DES safety (ODEESSA) reported the frequency of uncovered stent struts at 6 months in overlap segments (Cypher, 8.7±13.3%; Taxus, 8.3±20.9%; Endeavor, 0.05±0.19%; bare metal stents, 1.8±4.0%) and in nonoverlap segments (Cypher, 7.9±11.3%; Taxus, 2.3±4.1%; Endeavor, 0.01±0.05%; bare metal stents, 0.5±2.2%). In the HORIZONS-AMI, OCT substudy uncovered stent struts were reported in 5.6% of Taxus stents and in 1.1% of bare metal stents (P<0.0001) at 13 months.

Compared with OCT, angioscopy is more qualitative. Neointimal coverage is graded as (1) absent neointima, (2) incomplete neointimal coverage (struts visible through thin neointima), and (3) well-covered neointima. Although there are variations among studies because of different definitions and follow-up periods, the incidence of patients with any uncovered struts by angioscopy seems to be less with bare metal stents than with DES and less with angioscopy than with OCT.88–93 Of interest, there is a consistent high (20% to 30%) incidence of coexistent, clinically silent mural thrombus in these OCT and angioscopic studies. Angioscopic neointimal coverage grade seems to be related to the presence of incidental thrombus (24% with incomplete coverage versus 0% with complete coverage, P=0.002)28 and correlated to better stent expansion assessed by IVUS.94

To date, there has not been pathological validation for endothelialization. In fact, endothelial thickness is below the resolution of even OCT or angioscopy. Finally, potential surrogates for stent thrombosis will require clinical correlation.

### Summary

Table 2 summarizes some of the strengths and weaknesses of the 6 discussed techniques. Grayscale IVUS is the current workhorse in the catheterization laboratory, especially, during percutaneous interventional procedures where lumen dimensions, plaque burden, and assessment of stent implantation and procedural complications are important. Grayscale IVUS substudies are now routinely used to assess new devices and techniques. However, grayscale IVUS has 2 main weaknesses: plaque characterization and resolution. VH-IVUS was developed to improve on the limited ability of grayscale IVUS to assess plaque composition, especially detection of the lipid-rich NC (Figure 1B'). However, VH-IVUS is even more limited than grayscale IVUS in thrombus identification; and the assessment of plaque composition behind calcium remains questionable.62,95,96 Angioscopy is the most reliable tool for detecting both red cell and platelet-rich thrombus, although recent studies have suggested that OCT may also be useful in thrombus

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**Table 1. OCT Detection of Neointimal Stent Strut Coverage and Incidental Thrombus Formation**

<table>
<thead>
<tr>
<th>Authors</th>
<th>Follow-up, mo</th>
<th>Stent type</th>
<th>ACS, %</th>
<th>Stents, n</th>
<th>Struts/stent, n</th>
<th>Exposed struts, %*</th>
<th>Thrombus, %</th>
</tr>
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<tbody>
<tr>
<td>Xie et al</td>
<td>3</td>
<td>Cypher</td>
<td>50</td>
<td>24</td>
<td>212</td>
<td>15</td>
<td>13</td>
</tr>
<tr>
<td>Matsumoto et al</td>
<td>6</td>
<td>BMS</td>
<td>NA</td>
<td>16</td>
<td>180</td>
<td>0.1</td>
<td>0</td>
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<tr>
<td>Kubo et al</td>
<td>9</td>
<td>Cypher</td>
<td>56</td>
<td>57</td>
<td>120</td>
<td>8</td>
<td>5</td>
</tr>
<tr>
<td>Zhu-Hua et al</td>
<td>12</td>
<td>Cypher</td>
<td>NA</td>
<td>55</td>
<td>137</td>
<td>9</td>
<td>8</td>
</tr>
<tr>
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<td>Cypher</td>
<td>NA</td>
<td>24</td>
<td>145</td>
<td>8</td>
<td>5</td>
</tr>
</tbody>
</table>

BMS indicates bare metal stent.

*Percentage was calculated as total exposed struts/total struts for all patients.

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**Table 2. The Difference of Strongest and Weakness**

<table>
<thead>
<tr>
<th></th>
<th>IVUS (40 MHz)</th>
<th>VH (20 MHz)</th>
<th>OCT</th>
<th>NIR Infrared Spectroscopy</th>
<th>Angioscopy</th>
<th>Intravascular MRI</th>
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<td>Axial resolution, μm</td>
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<td>200</td>
<td>10</td>
<td>NA</td>
<td>10 to 50</td>
<td>250 to 300</td>
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<tr>
<td>PCI (stent expansion and complications)</td>
<td>+ +</td>
<td>±</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Necrotic core</td>
<td>±</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>TCF A</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>±</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Thrombus</td>
<td>±</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Stent tissue coverage</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>-</td>
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</tbody>
</table>

++ indicates excellent; +, good; ±, possible; -, impossible.
detection. The resolution of IVUS (and VH-IVUS) limits its evaluation of surface structures such as (1) the thin fibrous cap of a TCFA with its macrophage infiltration, (2) neointimal stent coverage, and (3) plaque rupture and plaque erosion; all are better assessed using other techniques (Figure 1C). Despite widespread enthusiasm, the use of VH-IVUS to detect TCFA may be limited because the thickness of the thin fibrous cap is below the resolution of either grayscale or VH-IVUS and because thrombus appears as fibrotic or fibrofatty plaque. Similarly, the ability of OCT to detect a lipid-rich NC may need further validation. Conversely, near NIR and intravascular MRI were developed to detect lipid, and the algorithms are based on the confluent and relatively superficial lipid core; however, these 2 techniques do not provide other needed anatomic information. Although use of multiple techniques may not be practical during daily practice, these various techniques truly complement each other. Fortunately, early prototypes indicate the possibility to combine multiple modalities into 1 catheter and console.

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References


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