The past year was one of rapid development of novel intracoronary imaging methods with great potential to improve the care of patients. The impetus for the development of these new imaging methods has been a growing recognition of the limitations of coronary angiography—the dominant method for the assessment of coronary artery disease for the past 50 years. Examples of the remarkable images that can now be obtained in patients are shown in Figure 1 (1–3).

In most cases, the imaging techniques interrogate the coronary wall using either optical or acoustic signals delivered and retrieved by an intracoronary catheter. Although intravascular ultrasound (IVUS) and angioscopy have been used for decades, many of the methods under study are new, including optical approaches made possible by advanced lasers and optical detectors developed for use with the Internet (Table 1).

These new intracoronary imaging methods provide information often unobtainable by angiography that may improve treatment of both the culprit lesion and the nonculprit vulnerable plaques responsible for subsequent events (4).

**Intracoronary Imaging to Improve Outcomes at the Culprit Lesion Site**

Although the safety of coronary stenting has steadily improved the procedural complications of no or slow-reflow and peri-stenting infarction continue to occur in approximately 10% of patients. Within a year, restenosis is observed in 5% to 10% of patients, whereas stent thrombosis occurs in approximately 1% by 2 years. Intracoronary imaging may prove to be useful in reducing these complications by 1) improving the techniques of stent sizing and placement, 2) identifying the role of necrotic-core plaque as a cause of stent complications, and 3) assessing stent coverage and thrombosis.

**Imaging to Improve Stent Sizing and Placement**

Although angiographic guidance alone generally produces excellent outcomes, it has been proposed that the occasional complications (dissection, stent thrombosis, restenosis) result from a mismatch of vessel and stent size, failure to end the stent in an area of less plaque by IVUS, or failure to expand the stent leading to malapposition. Recently, Roy et al. (5) reported that IVUS guidance was an independent predictor of freedom from stent thrombosis, although there was no reduction in overall events. Doi et al. (6) demonstrated that reduced stent area determined by IVUS immediately after stenting is an independent predictor of subsequent in-stent restenosis. Gerber et al. (7) reported that IVUS-guided stent dilation led to larger lumen areas than did angiography-guided stenting. A randomized study of the value of IVUS guidance to optimize stenting has been initiated.
Necrotic Core Plaque as a Cause of Stenting Complications

Necrotic-core plaque and peri-stenting myocardial infarction (MI). Perhaps the greatest recent contribution of intracoronary imaging to understanding stenting complications has been the confirmation that balloon dilation of stenoses with necrotic cores produces emboli leading to peri-stenting MI. This phenomenon has been documented with the use of angioscopy (8), gray-scale IVUS (9), virtual histology (VH) IVUS (10), integrated backscatter (IB) IVUS (11), optical coherence tomography (OCT) (12) and near-infrared (NIR) spectroscopy (3).

Dilation of the necrotic core may also cause plaque shift that might in turn lead to side branch occlusion. Wei et al. (13) reported that balloon inflation led to a reduction in necrotic core (assessed by VH-IVUS), and a shift of plaque away from the ballooned area.

Intracoronary Imaging and Late Stent Thrombosis

Failure of endothelial coverage of stent struts is a cause of thrombus and may occur more frequently when stents are placed over a necrotic core (14–16). OCT studies show that the incidence of malaposed struts is higher with sirolimus-eluting stents (SES) than with bare metal stents (BMS) (17,18). Tanigawa et al. (19) found that use of an SES was a predictor of malapposition, as were overlap stenting, post-dilation type C lesions, diabetes mellitus, and inflation pressure (Fig. 2).

Murakami et al. (20) found a greater incidence of in-stent thrombus in paclitaxel-coated stents compared with SES. An OCT follow-up study demonstrated that uncovered struts persist up to 2 years after SES implantation, suggesting the need for further follow-up (21). Hassan et al. (22) found that the risk of acquired stent malapposition detected by IVUS was 4-fold higher with DES than BMS and the risk of very late stent thrombosis was higher in those with late malapposition. Takano et al. (23) observed a very high incidence of mural thrombus as detected by angioscopy 6 months after DES implantation despite angiographic evidence of stent coverage by neo-intima. The discordance between frequent mural thrombus and infrequent clinical stent thrombosis is presumably due to antiplatelet therapy (Fig. 3).

Finn et al. (14) suggested that BMS, because they endothelialize more readily than DES, may be preferred for a necrotic-core plaque when other factors favoring a BMS or a DES are equally balanced. These conclusions were based on autopsy findings not preceded by in vivo imaging. There is extensive clinical trial evidence supporting the safety of DES in acute coronary syndrome cases in which necrotic cores are likely to have been stented (24).

Abbott (25) noted that although both OCT and angioscopy can provide information about the presence of tissue over a stent, the tissue observed is not always thrombo-resistant endothelium. Higo et al. (26) found by angioscopy that neo-intima within an SES became increasingly yellow by 10 months and was associated with mural thrombus, whereas neo-intima within a BMS was more likely to be white and not associated with thrombus. Murakami et al. (27) also reported that neo-intima within an SES was yellow on angioscopy and showed OCT signs of a lipid-core plaque that were not observed in neo-intima over a BMS. Nakazawa et al. (28) noted that the angioscopic findings of yellow after SES placement and pathologic observations suggest that certain stents might create a “nouveau atherosclerosis” with unfavorable long-term consequences.

Intracoronary imaging, although not currently capable of detecting endothelial cells or measuring their function, is likely to play an important role in resolving the problem of late stent thrombosis because of its ability to identify thrombus and stent coverage. The intracoronary imaging findings that struts are often uncovered, that mural thrombus is frequent, and that even visible neo-intima may not be functional have implications for the duration of antiplatelet therapy and indicate the need for improved stent technology. It seems that the stent thrombosis rate may be lower with newer stents designed with less metal (leading to improved endothelialization) (29). Bioabsorable stents remove the problem of the prolonged presence of a thrombogenic substance requiring development of new thrombo-resistant endothelium (30,31). The new methods of intracoronary imaging may be useful in the evaluation of new types of stents designed to improve endothelial coverage and decrease stent thrombosis.

Identification of Vulnerable Plaque at Nonculprit Sites

Although detection of vulnerable plaque—the presumed cause of a subsequent coronary event from a
nonculprit lesion—is a major goal of intracoronary imaging, the term has been used with 4 different meanings (Table 2). The original definition described a concept (a plaque prone to disruption and thrombosis) (32), whereas angiographic studies indicated that such plaques are not necessarily stenotic at baseline (33,34). Autopsy data indicated that an inflamed thin cap fibroatheroma (TCFA) is likely to be a vulnerable plaque. The recent PROSPECT (Predictors of Response to Cardiac Resynchronization Therapy) study (37) used a broader definition that includes plaques likely to cause progressive angina. It could include a plaque not stented at the initial percutaneous coronary intervention (PCI) that caused angina with or without a minor nonthrombotic increase in stenosis during follow-up.

In September 2009, the results of the PROSPECT study, the first prospective, large-scale, long-term attempt to identify vulnerable plaques, were reported at the Transcatheter Cardiovascular Therapeutics (TCT) annual meeting (37). The study was conducted in 700 patients receiving PCI for an acute coronary syndrome. The PROSPECT study used the new, broad definition of a vulnerable plaque as a plaque, not the original culprit at the index event, likely to cause a major adverse cardiac event (MACE) after PCI. MACE was defined as cardiac death, cardiac arrest, MI, unstable angina, or increasing angina requiring revascularization or rehospitalization.

The primary findings were as follows: 1) by 3.4 years, 20.4% of the patients experienced a second event, only 4.9% of which were “hard” (cardiac death, cardiac arrest, and MI), leaving 15.5% with progressive angina or unstable angina (Fig. 4). 2) Approximately half of the events occurred at the previous culprit lesion site and half at sites not treated at the initial PCI. 3) Sites with a plaque burden of >70% as shown by IVUS, a VH-TCFA, and lumen area <4 mm² had a 17% risk of causing an event versus a risk of <2% for plaques without those 3 features (37).

These results are provocative. Although the rates of cardiac death and MI were lower than expected (presumably due to medical therapy including anti-thrombotic agents), the PROSPECT study demonstrated the ability of imaging to identify non-stented sites likely to cause MACEs after stenting of a culprit lesion. The PROSPECT study did not identify novel features of plaques prone to disruption and thrombosis—the original definition of vulnerable plaque—for 2 reasons. First, the broad definition of vulnerable plaque used—a plaque likely to cause an MACE event after stenting—including increasing angina that may not have been due to plaque disruption and thrombosis. Second, the successful predictors that included the finding of a lumen area <4 mm² provide relatively little new information because such narrowing is generally considered a sign of a flow-limiting stenosis in need of treatment regardless of future vulnerability.
Full interpretation of the PROSPECT study will not be possible until multiple publications are available describing the results of this extensive trial. For the present, the PROSPECT study investigators stated that the positive results of the trial did not support the routine performance of 3-vessel IVUS to identify vulnerable plaques.

Shear Stress to Identify Sites Vulnerable to Becoming Vulnerable

The plaques suspected to be vulnerable are not randomly distributed throughout the coronary tree. As would be expected from extensive vascular biology research showing the atherogenic effects of low endothelial shear stress (ESS), Chatzizisis et al. (38) found in swine that low ESS detected in vivo after 23 weeks of an atherogenic diet predicted the development by 30 weeks of lipid-laden high-risk plaques. Sites with low ESS also showed enhanced activity of matrix-degrading proteases—enzymes implicated in formation of plaques with necrotic cores (39). Conversely, Gijsen et al. (40) found that maximum plaque deformability was found at sites exposed to the highest ESS (40). The varied findings demonstrate the complex interactions among ESS, the stage of development of the plaque, expansive remodeling, and the development of stenosis.

Identification of TCFAs

Abundant pathologic and clinical data (36) indicate that TCFAs, which have many features attractive for imaging (Table 3), are likely to be vulnerable plaques. Different intracoronary imaging methods have different strengths and weaknesses for detecting the various features of interest. We focus mainly on those technologies capable of detection of the necrotic core, the largest feature of TCFA and perhaps the most attractive target for imaging.

Detection of the Necrotic Core

IVUS-based methods. IVUS, which is in widespread use to identify plaque structure and stent features, can also be used for plaque characterization. The 4 IVUS-based methods that have been used to identify necrotic core—gray-scale IVUS, VH-IVUS, IB-IVUS, and palpography—were reviewed recently (41).

Lee et al. (42) reported that attenuated plaque, defined as hypoechoic plaque not due to calcium shadowing and considered to represent necrotic core by gray-scale IVUS, was never found in stable patients, but was observed in 39.9% of patients with ST-segment elevation MI, supporting the association of attenuated plaque with necrotic-core plaque and/or a platelet thrombus. In contrast, Baytan et al. (43) found that attenuated plaques were found with equal frequency in stable and unstable patients and not associated with subsequent coronary events. As noted previously, patients with attenuated plaque were also more likely to experience a cardiac enzyme elevation after PCI, suggesting the presence of a necrotic core at the dilated site.

The limitations of gray-scale IVUS for tissue characterization led to the development of VH-IVUS and IB-IVUS, which use information in the radiofrequency backscattered IVUS signal not displayed on the gray-scale screen.
A VH-TCFA has been defined as a plaque that in 3 adjacent cross sections has a plaque burden >40% and a confluent necrotic core occupying ≥10% of the cross section of the artery that is in contact with the lumen (37). In studies of groups of patients, this definition has led to identification of plaques showing the expected features of necrotic cores. VH-TCFAs have been found to be more frequent in lesions causing acute coronary syndromes (44) and lesions causing embolization-related peri-stenting infarction (10). Similar studies are available for IB-IVUS. Okubo et al. (45) reported that IB-IVUS performed better than VH-IVUS in a correlation with a histologic gold standard.

The presence of a VH-TCFA is currently being used to select the plaques randomly assigned to standard care or treatment with a self-expanding stent designed for non-flow-limiting plaques suspected to be vulnerable (46).

Future improvements in IVUS technology include the possibility that higher frequency imaging will lead to improved spatial resolution and improved detection of lumen and external elastic membrane borders.

**Optical methods. INTRACoronARY ANGIOscopy.** In 1995, Uchida et al. (47) reported the first study linking plaque composition to patient outcome. Patients with glistening yellow plaques, presumably lipid-core plaques, had an increased incidence of future events. Later Ohtani et al. (48) linked the number of yellow plaques to the risk of future events, thereby detecting vulnerable patients. In 2009, Uchida (49) introduced fluorescence angioscopy for molecular imaging. Using

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**Table 2. Four Definitions of Vulnerable Plaque**

<table>
<thead>
<tr>
<th>Source (Ref. #)</th>
<th>Definition</th>
<th>Feature</th>
</tr>
</thead>
<tbody>
<tr>
<td>Studies of triggering of onset of coronary events (32)</td>
<td>A plaque prone to disruption and thrombosis after a triggering event.</td>
<td>A functional definition independent of histologic type</td>
</tr>
<tr>
<td>Angiographic studies (33,34)</td>
<td>As above, but the plaque need not be stenotic at baseline</td>
<td>This type of vulnerable plaque could not be detected by ischemia testing</td>
</tr>
<tr>
<td>Autopsy studies after coronary events (35,36)</td>
<td>An inflamed TCFA</td>
<td>A suspected vulnerable plaque and a good target for imaging</td>
</tr>
<tr>
<td>The PROSPECT study, a post-ACS and PCI natural history study (37)</td>
<td>A plaque likely to cause a new coronary event including cardiac death, MI, unstable angina, and progressive angina</td>
<td>A broader definition of vulnerable plaque that does not require disruption and thrombosis because increased angina is an end point</td>
</tr>
</tbody>
</table>

ACS = acute coronary syndrome; MI = myocardial infarction; PCI = percutaneous coronary intervention; TCFA = thin cap fibroatheroma.
Yamamoto et al. (50) found that the sensitivity, specificity, and accuracy of VH-IVUS for TCFA were 68%, 81%, and 75%, respectively.

OCT and Fourier domain OCT. OCT provides high-resolution (10 μm) images of arteries (51). Second-generation Fourier-domain OCT permits performance of OCT, which requires removal of blood from the field of view, with only a single flush (52). Using Fourier-domain OCT, Tearney et al. (1) were able to obtain microscopic images of the coronary wall including identification of macrophages in a cap covering a lipid pool. Kataiwa et al. (53) found that the new nonocclusive method is safe and provides image quality equal to that obtained with the balloon occlusion method.

Fujii et al. (54) found that OCT TCFAs were more frequent at the culprit site than at remote sites in MI patients and that MI patients were more likely than stable patients to have multiple TCFAs.

Xu et al. (55) demonstrated that a combination of backscattering and attenuation coefficient measurements could be used to improve tissue characterization by OCT. Additional future improvements include improved depth of penetration, which is currently limited to approximately 2 mm.

**Multimodality imaging. OCT and VH-IVUS.** Sawada et al. (2) interrogated plaques with both VH-IVUS and OCT to identify compositional and structural features. Of the 126 plaques examined, 61 showed TCFAs by VH-IVUS and 36 were classified as

**Table 3. Histologic Features of Suspected Vulnerable Plaques**

<table>
<thead>
<tr>
<th>Type</th>
<th>Features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inflamed thin-cap fibroatheroma, most frequent type and present in 60% to 70% of ACS cases</td>
<td>Necrotic core (lipid core)</td>
</tr>
<tr>
<td></td>
<td>Thin cap &lt;65 μm</td>
</tr>
<tr>
<td></td>
<td>Inflammation</td>
</tr>
<tr>
<td></td>
<td>Increased vasa vasorum</td>
</tr>
<tr>
<td></td>
<td>Expansive remodeling</td>
</tr>
<tr>
<td></td>
<td>Increased plaque burden</td>
</tr>
<tr>
<td></td>
<td>Intraplaque hemorrhage</td>
</tr>
<tr>
<td></td>
<td>Spotty calcification</td>
</tr>
<tr>
<td></td>
<td>Luminal narrowing</td>
</tr>
<tr>
<td>Erosion site, present in 20% to 30% of events, more frequent in women and younger patients with ACS</td>
<td>Increased proteoglycans</td>
</tr>
<tr>
<td>Calculated nodule, present in &lt;3% of patients with ACS</td>
<td>Extensive calcification protruding into lumen</td>
</tr>
<tr>
<td>Plaque with a mural thrombus not producing a significant stenosis</td>
<td>Considered to be a site of subsequent thrombosis because many plaques causing events show repeated episodes of disruption and thrombosis</td>
</tr>
</tbody>
</table>

Abbreviation as in Table 2.
TCFAs by OCT. In the combined analysis, 28 were diagnosed as TCFAs by both methods. During follow-up, 3 of these sites, which did not have a flow-limiting stenosis at the initial study, demonstrated stenosis progression requiring PCI (Fig. 1). The authors conclude that the combined use of OCT and VH-IVUS, preferably in a single catheter, might be a feasible approach for detecting TCFA.

Gonzalo et al. (56) also used both OCT and VH-IVUS to determine the frequency and distribution of high-risk plaques at bifurcations. This dual examination demonstrated that the proximal rim of the side branch ostium was the more likely region to contain a thin fibrous cap and a larger necrotic core.

**IVUS, OCT, AND ANGIOSCOPY.** Kubo et al. (57) used 3 methods—angioscopy, IVUS, and OCT—in patients with AMI. Intracoronary thrombus at the culprit site was observed in all cases by OCT and angioscopy, whereas IVUS identified thrombus in only 33% of cases. The incidence of plaque rupture was by 73% with OCT, 47% with angioscopy, and 40% with IVUS.

**Diffuse reflectance NIR spectroscopy.** A catheter-based NIR spectroscopy system has been developed to identify lipid-core plaque in coronary arteries (58). An NIR scan is performed through blood in a manner similar to that used for IVUS and is displayed as a map of the artery called a chemogram (59). The system, which was validated by comparison of NIR chemograms with histologic results in human coronary autopsy specimens and with a clinical study (59,60), has now been used in >700 patients. Although the chemogram provides accurate information about the presence of lipid-core plaque, it does not provide a structural image.

**Raman spectroscopy.** Raman spectroscopy is similar to diffuse reflectance NIR spectroscopy, but it relies on a more specific yet weaker signal created by photons that undergo a Raman shift within the tissue interrogated. A catheter-based system has obtained useful Raman signals from inside a human coronary autopsy specimen implanted in a living swine, but there are at present no reports of the use of the system in patients (61).

**Magnetic resonance imaging.** A catheter that contained both the device to generate the magnetic field and the coil to send and receive radiofrequency signals was able to identify lipid-core plaque in patients (62). However, the large size of the catheter and long processing time limited its clinical utility, and the system is no longer manufactured for this use.

**Intravascular thermography.** There have been attempts to identify necrotic-core plaque by measuring intracoronary temperature elevations. It was found, however, that the small thermal gradients associated with inflamed plaques are difficult to measure in flowing blood. A review of thermography was recently published (63).

**MEASUREMENT OF CAP THICKNESS.** The observation of thin caps in plaques that have ruptured has led to attempts to measure cap thickness in vivo. Cap thickness has been estimated by VH-IVUS, but the 100-µm limit of resolution of IVUS does
not permit exact measurement of the thin cap of interest. OCT and angioscopy, however, have greater resolution and have been used for more direct measurements of cap thickness. Takano et al. (64) found the expected inverse relationship between the intensity of yellow coloring (assessed by angioscopy) of the plaque and cap thickness as measured by OCT (Fig. 5). Plaques with the highest yellow color grade were found to have a cap thickness of only 40 ± 14 μm.

Identification of Other Plaque Morphologies Associated With Coronary Events

Although the effort to identify TCFAs has received the greatest attention in the quest for identification of vulnerable plaques, pathologic studies indicate that as many as 30% of clinical events occur at erosion sites and a much smaller number occur at the site of calcified nodules (Table 3).

In vivo identification of erosion sites lags behind the recent success in identifying necrotic cores. Fatal thrombi over erosion sites are more likely to be recurrent than thrombi over ruptured TCFAs (65). Although OCT may be able to identify some erosion sites, imaging of sites prone to erosion will require more detailed assessment of local molecular processes than is possible with current intracoronary imaging techniques (Fig. 6) (66).

Molecular Imaging of Coronary Atherosclerotic Plaques

A full understanding of the status of coronary atherosclerosis in a patient will require information about the molecular and cellular processes within plaques (67,68). Fortunately, progress in molecular and cellular imaging indicates that invasive and even noninvasive techniques offer promise for identification of molecular processes in the coronary plaques of patients (69–71).

### Table 4. Comparison of Intracoronary Imaging Modalities

<table>
<thead>
<tr>
<th></th>
<th>IVUS (40 MHz)</th>
<th>VH (20 MHz)</th>
<th>OCT</th>
<th>Near-infrared Spectroscopy</th>
<th>Angioscopy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Axial resolution, μm</td>
<td>100</td>
<td>200</td>
<td>10</td>
<td>NA</td>
<td>10–50</td>
</tr>
<tr>
<td>PCI (stent expansion and complications)</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>
</tr>
<tr>
<td>Detection of thin cap</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>
</tr>
<tr>
<td>Stent tissue coverage</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>+ +</td>
</tr>
<tr>
<td>Expansive remodeling</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Measurement through blood</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>-</td>
</tr>
</tbody>
</table>

Adapted from Maehara et al. (41)

++ = excellent; + = good; = possible; − = impossible; IVUS = intravascular ultrasound; NA = not available; VH = virtual histology; other abbreviations as in Tables 1 and 2.
Chang and Jaffer (71) injected an NIR fluorescence agent that is activated by proteases into atherosclerotic rabbits. Catheter interrogation of the iliac arteries then demonstrated activation of the agent, indicating the presence of protease activity in plaques. The agent colocalized with immunoreactive macrophages and cathepsin B, thereby identifying inflammation.

Conclusions

Intracoronary imaging is an active research field with great potential to improve patient care. In the effort to detect vulnerable plaque, the most significant development is the continued accumulation of evidence that certain plaques are more likely to cause clinical events and therefore deserve the term vulnerable; the evidence includes the early angioscopic study by Uchida (47), the recent observation that 3 patients with TCFAs by both VH-IVUS and OCT measures experienced events (2), and the finding in the PROSPECT study that certain sites were prone to cause clinical events (37).

As is apparent from Table 4, the various intracoronary imaging methods are complementary. Hence, extensive efforts are under way to build combined imaging devices. The improved characterization of coronary plaques with these new techniques has the potential to improve the selection of therapy for patients, reduce the complications of stenting, and identify vulnerable plaques so they may be treated before they cause an event. Multiple clinical studies are in progress to determine how these new diagnostic capabilities might be used to improve the daily care of patients with coronary artery disease.

Acknowledgments

We are grateful for the assistance of Ruth Potwin in preparation of the manuscript.

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REFERENCES


Key Words: imaging • intracoronary • plaque • vulnerable plaque.

APPENDIX
For a supplementary slide set, please see the online version of this article.