New Drugs and Technologies

Detection and Treatment of Vulnerable Plaques and Vulnerable Patients

Novel Approaches to Prevention of Coronary Events

Sergio Waxman, MD; Fumiyuki Ishibashi, MD; James E. Muller, MD

There is growing interest in the possibility that identification and treatment of vulnerable plaques and vulnerable patients can enhance the progress made against coronary artery disease. Innovations in medical therapy—statins and other agents—and novel interventional cardiology techniques—eg, drug-eluting stents—have significantly decreased the morbidity and mortality caused by coronary atherosclerosis. However, coronary events continue to be the leading cause of death in the United States, accounting for >479,000 deaths (1 in 5) in 2003.1

Improved preventive measures are needed because, for many individuals, sudden coronary death is the first sign of the disorder. And even those who survive an acute coronary syndrome remain at high risk. After successful treatment of the initial culprit lesion by a percutaneous coronary intervention (PCI), the risk of a coronary event from a new lesion is ≈10% in the following year and 5% in each of the subsequent 4 years.2,3 (Figure 1).

These substantial levels of ongoing morbidity and mortality have led to heightened interest in new methods to prevent coronary events. For primary prevention, the effort has focused on plasma markers and noninvasive testing to identify vulnerable individuals. For secondary prevention, interest has focused on vulnerable patients and the vulnerable plaques they may possess that might be identified and treated during the catheterization for their initial event.

Vulnerable Plaque

Definitions of the Vulnerable Plaque and the Vulnerable Patient

The terminology to describe vulnerability has become relatively standardized.4–10 The term “vulnerable plaque” is used to designate a plaque at high risk of disruption leading to thrombosis. “High-risk plaque” and “thrombosis-prone plaque” are used as synonyms for “vulnerable plaque.”

Although prospective evidence from natural history studies is not yet available, retrospective autopsy studies suggest that there are several histological types of vulnerable plaque.8 The most common type of suspected vulnerable plaque is an inflamed thin-cap fibroatheroma (TCFA), which is thought to account for 60% to 70% of coronary events (Figure 2). An additional 30% to 40% of events, particularly in younger women, occur at proteoglycan-rich erosion sites.11

Most vulnerable plaque detection devices in development are designed to detect TCFA. Because these devices will not detect erosion sites in advance, their sensitivity for predicting cardiac events will be limited. Specificity of a TCFA detector for predicting plaque rupture will also be limited because not all TCFA will rupture, nor will all ruptures lead to a cardiac event.

Hence, the term “vulnerable patient” has been introduced to indicate an individual with a high likelihood of experiencing a cardiac event. Such a patient is likely to have vulnerable blood (prone to thrombosis), vulnerable myocardium (prone to arrhythmia), and ≥1 vulnerable plaque. To enhance primary prevention, a search is underway for novel methods to identify vulnerable patients.7 Because a vulnerable plaque is likely to be the root cause of vulnerability of the patient and may be amenable to systemic or local therapy, the search for the vulnerable patient of necessity is closely linked to efforts to identify vulnerable plaques.

Systemic and Focal Manifestations of Atherosclerosis

There is considerable discussion about the relative effort that should be devoted to combating the systemic versus focal manifestations of atherosclerosis.7,12–16 If the systemic features of the disease are dominant, efforts to detect and treat vulnerable plaques are unlikely to yield significant benefits. In such a scenario, numerous vulnerable plaques would be present, and local treatment would not be feasible. Even if relatively few vulnerable plaques developed, they could appear rapidly, presumably in response to a systemic inflammatory stimulus, and thereby thwart attempts at local treatment, which could be administered only during cardiac catheterization.

The presence of plaques in many vascular beds as documented in autopsy studies, the diffuse inflammatory involvement sometimes observed in the coronary tree, and the appearance of >1 disrupted plaque in many patients with an acute coronary syndrome confirm the systemic nature of the disease.16

From the Department of Cardiovascular Medicine, Lahey Clinic, Burlington, Mass (S.W., F.I.); Tufts University School of Medicine, Boston, Mass (S.W.); and Cardiovascular Division, Massachusetts General Hospital and Harvard Medical School, Boston, Mass (J.E.M.).

Correspondence to Dr. Sergio Waxman, Lahey Clinic, 41 Mall Rd, Burlington, MA 01805. E-mail: Sergio.Waxman@lahey.org

Circulation. 2006;114:2390-2411. DOI: 10.1161/CIRCULATIONAHA.105.540013

Circulation is available at http://www.circulationaha.org

© 2006 American Heart Association, Inc.
However, there is also evidence that the lesions causing clinical events are focal. Interventional cardiologists generally find that a single location is responsible for an acute coronary event. Hence, most agree that atherosclerosis is a systemic disease with focal manifestations.

There is uncertainty, however, over the diffuse versus focal nature of risk in the coronary arteries. If TCFAs are considered to be precursors of culprit lesions, as many believe they are, then risk is quite focal because TCFAs are focal structures. Kolodgie et al\textsuperscript{17} found an incidence of only 1.3±1.4 TCFAs per heart in patients dying of sudden cardiac death despite the widespread presence of less advanced—and presumably lower-risk—atherosclerotic lesions. Hence, TCFAs, the sites suspected to be at highest risk, are often single, and when more than one is present, they are at most “oligofocal.” It has also been noted that risk is concentrated in the proximal portions of the coronary arteries\textsuperscript{18} where focal areas of low shear stress may predispose to formation of vulnerable plaques.\textsuperscript{19,20}

Thus, there is sufficient evidence supporting the focality of risk to test the hypothesis that local diagnosis and treatment of vulnerable plaques may be of clinical value. The importance of the local treatment of flow-limiting stenoses has already been demonstrated and is the basis for the millions of PCI and CABG procedures performed each year. The clinical value of its preventive counterpart, the local detection and treatment of vulnerable, noncritical stenoses, is currently unknown.

Pathophysiology of Vulnerable Plaque Formation

There has been considerable progress in the identification of the molecular and cellular processes causing atherosclerosis and its clinical sequelae.\textsuperscript{21,22} LDL cholesterol is central to the development of the disease. In addition, it is now clearly established that inflammation plays an important role in the initiation of lesions and is likely to be responsible for the activation of the disease in more than a single plaque or Atherosclerotic plaque. A, Cross section of a coronary artery from a patient who died of a MI. An occlusive thrombus overlies a ruptured (arrows) TCFA. B, High-power magnification. The contents of the atheromatous plaque have led to thrombosis. Courtesy of Dr E. Falk. C, Molecular and cellular inflammatory processes contributing to TCFA formation and rupture. T lymphocytes, macrophages, and mast cells all contribute to the inflammatory reaction associated with the accumulation of oxidized LDL and microvascular hemorrhage. Proteases may weaken the cap, leading to rupture and thrombosis. Modified from Hansson\textsuperscript{23} with permission from the Massachusetts Medical Society. Copyright 2005. D, TCFA detected in a longitudinal section of a human coronary artery autopsy specimen. A thin fibrous cap (small arrow) covers a relatively large lipid pool and necrotic core (large arrow). Courtesy of InfraReDx, Inc.
artery.23,24 Many of the processes leading to the formation of localized, inflamed TCFA are now understood23,24 (Figure 2C). These presumably dangerous, highly focal, and well-differentiated structures result from an interplay of the accumulation of oxidized LDL in the arterial wall and the actions of macrophages, which are strongly influenced by T lymphocytes.25

Studies in genetically engineered mice deficient in apolipoprotein E (apoE), which develop advanced plaques similar to those in patients, have increased our understanding of certain clinical observations. ACE inhibitors prevent myocardial infarction (MI) in patients, but the mechanism has been unclear. In the apoE mouse, it was found that increased levels of endogenous angiotensin II are associated with increased TCFA formation.26 An increase in T-helper type 1–like lymphocytes also promoted TCFA occurrence, indicating a possible role of the T-helper switch in the formation of these presumably vulnerable plaques.

Eriksson27 also used the apoE−/− mouse to study the mechanism of leukocyte recruitment into TCFAs. It was found that both platelet factor 4 and RANTES (a protein cytokine) play roles in leukocyte recruitment and that blockage of RANTES leads to decreased atherosclerosis.

The apoE−/− mouse has also been used to study apoptosis, which is a prominent feature of plaques that cause sudden coronary deaths in patients.28 ApoE−/− mice transfected with the Fas ligand, which promotes apoptosis, showed more frequent signs of vulnerability (ruptured plaques, intraplaque hemorrhages, buried caps, and iron deposits) than nontransfected mice.29 There was a 3-fold increase in the amount of hemorrhages, buried caps, and iron deposits) than nontransfected mice.30 Michowitz et al30 reported that the tumor necrosis factor–related apoptosis-inducing ligand also colocalized with oxidized LDL, suggesting that infiltration of LDL might increase cell death and lead to the formation of necrotic cores.

Sluijter et al31 studied matrix metalloproteinases, which can degrade cap constituents, and an extracellular matrix metalloproteinase inducer in carotid endarterectomy specimens. Increased activity of matrix metalloproteinases 8 and 9 was associated with an inflammatory plaque phenotype, and different glycosylation forms of extracellular matrix metalloproteinase inducer were associated with varying degrees of matrix metalloproteinase activity. It was concluded that extracellular matrix metalloproteinase inducer glycosylation may play a role in plaque destabilization.

Vascular and hemodynamic forces are also likely to play a role in the formation and rupture of TCFAs. Stone et al39 and Slager et al40 demonstrated that areas of low shear stress predispose to the formation of advanced plaques, presumably by creating conditions that favor transmigration of lipids and inflammatory cells into the vessel wall. High shear stress, on the other hand, can promote plaque rupture and platelet aggregability, leading to an occlusive thrombotic event.19,20

Moreno et al41 reported that, in human aortic plaques, microvessel density is increased in lesions with inflammation, intraplaque hemorrhage, and TCFA, suggesting that neovascularization contributes to TCFA formation and rupture. Kolodgie et al33 demonstrated increased hemorrhage, presumably from similar microvessels, in necrotic cores of coronary plaques of patients who died suddenly. Such hemorrhage would add to the lipid content of the plaque because erythrocytes are cholesterol rich.

**Plasma Markers of Vulnerability**

Increased understanding of the processes causing atherosclerosis has facilitated efforts to identify novel markers of risk that may be circulating in plasma and readily available for sampling. Plasma markers of risk that improve the accuracy provided by cholesterol determinations would enhance primary prevention in the general population by identifying individuals in need of further diagnostic testing and would improve secondary prevention by guiding therapy in patients known to have coronary disease.

High-sensitivity C-reactive protein (hs-CRP), the most extensively studied plasma marker of inflammation, identifies an increased risk of an acute coronary event independent of LDL cholesterol.34 Statin therapy, which prevents cardiac events, also decreases hs-CRP levels.35,36 A large randomized trial is in progress to determine whether statin therapy can prevent coronary events in patients with an elevated hs-CRP and normal LDL cholesterol levels.37

Lipoprotein-associated phospholipase A2, another plasma marker associated with inflammation, is an independent predictor of cardiac events.38 Nuclear factor-κB, which controls nuclear processes associated with inflammation, is increased in patients with unstable angina.39 Advances in genetics are already producing markers of vulnerability to coronary events. A markedly beneficial effect of a relatively rare mutation in the gene encoding a protease (proprotein convertase subtilisin/kexin type 9 serine protease) affecting plasma LDL levels was recently reported.40 The 2.6% of black subjects who had this beneficial mutation had an 88% reduction in coronary disease over a 15-year follow-up. Although this marker is useful for only a few, the finding supports the hypothesis that genetic plasma markers will eventually improve the identification of protected and vulnerable individuals in the general population.

**Methods to Image Vulnerable Plaques and Vulnerable Patients**

Although sampling of peripheral blood to assess vulnerability has the advantages of ease of use and low cost, imaging the actual extent of atherosclerosis in vessels provides improved risk stratification.41 For primary prevention, emphasis is on noninvasive imaging of vessels in those deemed to be at higher risk after initial assessment with demographic characteristics and plasma markers. For secondary prevention in patients already undergoing catheterization, invasive imaging can be performed with minimal added risk and cost and has considerable advantages over noninvasive imaging.

Although noninvasive imaging of coronary plaque would be of greatest value, it is quite challenging because of the small size, location, and motion of the coronary arteries. Hence, most efforts to perform noninvasive identification of
vulnerable plaques have focused on the carotid arteries, which are larger, closer to the surface, and not in motion.

Noninvasive Methods to Image Vulnerable Plaques in the Carotid Arteries

Four technologies are under study as methods to identify vulnerable carotid plaque: ultrasound, MRI, nuclear imaging, and x-ray multidetector computed tomography (MDCT). Such methods benefit from the accessibility of carotid plaques and the availability of tissue obtained after carotid endarterectomy to serve as the gold standard for the assessment of imaging results.

Ultrasonic imaging is the method most frequently used in clinical practice to evaluate carotid plaques. Although most clinical decision making is based exclusively on symptomatic status and the degree of stenosis detected, plaques that are hypoechoic or show signs of disruption have been reported to carry an increased risk of stroke.

Carotid ultrasound is also used as a research tool because individuals with increased intima-media thickness have been found to be at increased risk of coronary events. However, the predictive value of intima-media thickness findings is relatively limited for use in individual patients. This limitation, plus the inability of ultrasound to precisely identify different types of tissue, has led to research with other technologies.

MRI, which can readily identify lipid-rich tissue, has been used to identify potentially vulnerable carotid plaques. Four studies have identified a close relationship between MRI signs of vulnerability and histological findings. Ruberg et al used proton MR spectroscopy to enhance the ability of conventional MR to identify the chemical composition of tissue. Ex vivo spectroscopy was performed in carotid samples with an 11.7-T magnet. Peaks indicating the presence of cholesteryl esters were 5.5% of the signal obtained in a lipid-rich area (by MRI) versus 0.9% in a lipid-poor area. The authors conclude that image-guided proton MR spectroscopy may permit noninvasive detection and quantification of cholesteryl ester in atherosclerotic plaques in vivo.

Although the MRI results are promising, nuclear imaging methods have a greater ability to identify metabolic processes such as those associated with inflammation. Davies et al used PET to study fluorodeoxyglucose uptake as an index of macrophage activity in patients undergoing carotid endarterectomy for transient ischemic attacks. Fluorodeoxyglucose uptake was more likely to be increased at the site of a stenosis. Tuwakol et al demonstrated an excellent correlation between in vivo fluorodeoxyglucose-PET signals obtained preoperatively and the macrophage content of carotid plaques assessed by histological examination after carotid endarterectomy. The use of MDCT for plaque analysis is limited because of the lack of sufficient contrast between lipid and fibrotic components and because of the radiation exposure required. CT, which has been coupled with PET in the new PET/CT devices, is useful for providing anatomic orientation of the PET signal, which has poor spatial resolution.

Despite these advances in imaging, current clinical decision making for the management of carotid artery disease remains stenosis based and similar to that for coronary artery disease. Further studies are needed to confirm the linkage of findings suggesting vulnerability to cerebral events and to determine whether treatment (endarterectomy, stenting, or intensified systemic therapy) of plaques guided by supplemental information about vulnerability is superior to conventional management.

Noninvasive Methods to Image Vulnerable Plaques in the Coronary Arteries

As noted, significant obstacles must be overcome to reach the highly desirable goal of noninvasively identifying vulnerable plaques in the coronary arteries.

MDCT, with its rapid acquisition times (to overcome motion) and relatively high spatial resolution, has achieved the greatest success in noninvasive evaluation of coronary arteries. CT methods can assess the degree of coronary artery calcification, which adds prognostic information beyond that provided by the Framingham Risk Score. However, detection of calcification differs from detection of vulnerable plaques, which may not be calcified.

New MDCT instruments can detect coronary artery stenoses noninvasively, but characterization of the composition of plaques (beyond detection of calcium) is not yet possible (Figure 3). Identification of lipid-rich plaques is hampered by the lack of major differences in opacity between lipid-rich and fibrotic plaques. Nevertheless, Kunimasa et al were able to identify differences in the MDCT appearance of plaques in a group of patients with an acute coronary
syndrome compared with findings in a group of patients with stable angina. It seems likely that MDCT will identify "suspected" vulnerable plaque that will in many cases lead to more intensive study of the lesion at cardiac catheterization with one of the many invasive methods under development.

MRI has also been used for noninvasive characterization of coronary plaques (Figure 4). Unfortunately, the length of time required for study is considerable, and the resolution is insufficient for optimal characterization of coronary plaques. MRI capabilities may be enhanced with the use of agents to enhance contrast of macrophage presence. Novel agents have been developed for MR (and near-infrared [NIR]) molecular imaging that are activated by local enzymatic processes. Strauss et al have noted that the ability of nuclear studies to detect metabolic activity may eventually lead to successful noninvasive studies of vulnerable coronary artery plaques.

The development of methods to perform noninvasive characterization of coronary plaque will continue to be an active field of research that will be aided by results obtained by the invasive methods described below.

Invasive Imaging of Vulnerable Plaques in the Coronary Arteries

Invasive imaging methods have a great advantage over noninvasive methods in assessment of coronary plaques. Intracoronary catheters have an excellent vantage point close to the tissue of interest, and their movement is similar to that of their target. These advantages allow the invasive tools to provide more detailed information about coronary plaque composition, morphology, and extent than is possible with noninvasive approaches.

Numerous invasive approaches to characterize plaques are being evaluated. Coronary angiography can detect stenoses, but its limitations as a "lumenogram" have led to interest in imaging methods that provide information about the vessel wall.

Intravascular ultrasound (IVUS) can image the wall and thereby provide useful information on plaque volume and vessel remodeling. Novel IVUS methods have been developed to characterize the stiffness of plaques and to detect the presence of necrotic cores or fibrofatty tissue.

In addition to the acoustic techniques, optical methods can provide information about plaque characteristics. Angioscopy is the best method to detect intracoronary thrombus; it can also detect yellow plaque. Optical methods that can penetrate beyond the surface of the plaque are also under development. Optical coherence tomography (OCT) can provide high-resolution views of cap thickness, plaque microarchitecture, and macrophage infiltration. NIR spectroscopy is under development as a means to characterize the chemical composition of plaques.

Additional efforts include the development of a catheter-based MRI system that can identify lipid-rich tissue and catheters to measure thermal gradients associated with inflammation in the coronary arteries. Finally, molecular imaging agents may enhance identification of specific molecular processes within plaques.

The most versatile of these techniques can function through blood and scan the artery rapidly; others require removal of blood and/or can interrogate only a specific location.

There are varying levels of evidence that each technique can precisely measure its feature of interest (plaque composition, cap thickness, etc) in vivo (Table 1). As this evidence is strengthened, a second more difficult question must be answered: Does the feature identified indicate that a given plaque is more likely to rupture and cause a coronary event? Although it is possible that angiographic findings can predict coronary events, the natural history studies required to document predictive power for the novel techniques have only recently been initiated.

Coronary Angiography

Although the coronary angiogram fails to identify most of the atherosclerotic changes affecting the vessel, it has provided some information about plaque vulnerability. Ambrose et al, Little et al, and others used the angiogram to demonstrate that, in most cases, vulnerable plaques do not produce a significant stenosis before they rupture and cause a coronary event.

In addition to identifying stenosis, the angiogram, particularly in patients with acute coronary syndromes, may reveal a complex, irregular interface between the luminal surface of the plaque and the injected contrast material. (Figure 5). Angioscopic and autopsy studies have documented that these complex lesions are caused by plaque rupture, intraplaque hemorrhage, and intraluminal thrombosis.
<table>
<thead>
<tr>
<th>Invasive Diagnostic Method</th>
<th>Specific Use</th>
<th>Feature Detected</th>
<th>Highest Level of Development</th>
<th>Ability to Scan the Artery</th>
<th>Ease of Use</th>
<th>Level of Proof That Feature Is Accurately Detected</th>
<th>Level of Proof That Presence of the Feature Detected Predicts Coronary Events</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coronary angiography</td>
<td>Degree of stenosis</td>
<td>In standard clinical use for 50 y</td>
<td>Yes</td>
<td>Basic invasive skill required; requires only an injection of contrast material and x-ray imaging</td>
<td>Extensive</td>
<td>Linkage of complex lesions to clinical events in some studies, particularly in the absence of statin therapy$^{14,3}$</td>
<td></td>
</tr>
<tr>
<td>IVUS-based methods</td>
<td>Some plaque characteristics</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Standard IVUS</td>
<td>Plaque volume</td>
<td>In standard clinical use for &gt;10 y</td>
<td>Yes</td>
<td>Model for ease of use for invasive diagnostic devices</td>
<td>Extensive autopsy validation</td>
<td>Linkage of hypoechoic lesions to a small number of clinical events in a single study$^{107}$</td>
<td></td>
</tr>
<tr>
<td>Elastography</td>
<td>Deformability of plaque</td>
<td>In clinical trials</td>
<td>Yes</td>
<td>Complex data processing required</td>
<td>Autopsy validation and support from clinical findings</td>
<td>No data available</td>
<td></td>
</tr>
<tr>
<td>RF backscatter analysis</td>
<td>Necrotic core</td>
<td>In clinical trials</td>
<td>Yes</td>
<td>Autopsy and atherectomy validation</td>
<td>Preliminary linkage of RF IVUS findings to small number of clinical events$^{116}$</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(includes Virtual Histology)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Optical methods</td>
<td>Luminal and vessel dimensions</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Angioscopy</td>
<td>Yellow plaque</td>
<td>Extensive clinical and research use in Japan; no use in United States</td>
<td>Yes</td>
<td>Requires removal of blood and coronary occlusion</td>
<td>Yellow color requires objective determination</td>
<td>Linkage of glistening yellow plaque to small number of clinical events$^{22}$</td>
<td></td>
</tr>
<tr>
<td>Disruption and thrombus</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>OCT</td>
<td>Plaque microarchitecture</td>
<td>In clinical trials and available for clinical use in Japan</td>
<td>No</td>
<td>Requires removal of blood and coronary occlusion</td>
<td>Validated in autopsy specimens</td>
<td>No data available</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Accurate measure of cap thickness</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Macrophages</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NIR reflectance spectroscopy</td>
<td>Lipid pools, necrotic core</td>
<td>In clinical trials</td>
<td>Yes</td>
<td>Requires guidewire and pullback (similar to IVUS)</td>
<td>Validated in autopsy specimens</td>
<td>No data available</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Inflammation</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Other chemical constituents of plaque</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Raman spectroscopy</td>
<td>Precise chemical identification</td>
<td>Not yet in clinical trials</td>
<td>?</td>
<td>?</td>
<td>?</td>
<td>No data available</td>
<td></td>
</tr>
<tr>
<td>Thermography</td>
<td>Temperature of plaque</td>
<td>In clinical trials</td>
<td>Yes</td>
<td>May require temporary cessation of blood flow to prevent cooling of plaque</td>
<td>Validated in autopsy specimens; may be difficult to measure in patients</td>
<td>No data available</td>
<td></td>
</tr>
<tr>
<td>Intracoronary MRI</td>
<td>Lipid composition of plaque</td>
<td>In clinical trials</td>
<td>No</td>
<td>Requires apposition of detector to wall and cannot scan the artery</td>
<td>Validated in autopsy specimens</td>
<td>No data available</td>
<td></td>
</tr>
</tbody>
</table>
Goldstein et al\textsuperscript{16} demonstrated that additional angiographically complex lesions may occur at sites other than the culprit in \(\approx 40\%\) of patients with acute MI. However, the number of additional lesions was not large and hence in accord with the autopsy studies demonstrating the single and sometimes oligofocal distribution of ruptured plaques and TCFAs described above.

Complex lesions have a moderately increased likelihood (20\% to 40\%) of causing progression of stenosis within the year after their discovery, presumably because of organization of the initial thrombus followed by repeat rupture.\textsuperscript{79–83} Such lesions have also been linked to elevations in serum inflammatory markers and subsequent events.\textsuperscript{16,84–86} The finding of multiple complex lesions in an angiogram may be a sign that the patient (as opposed to the individual plaque) is vulnerable because of an active systemic inflammatory process that will produce numerous vulnerable plaques in the future. Statin therapy, which can decrease signs of inflammation, may have decreased the linkage between complex lesions and subsequent events demonstrated in prior studies.\textsuperscript{83}

The coronary angiogram has also been used to identify patients with paradoxical coronary vasoconstriction, which has been linked to future cardiovascular events.\textsuperscript{87–92} New angiographic systems permit the rapid display of 3D images that can serve as a scaffolding for display of findings of IVUS and other novel imaging methods.\textsuperscript{93}

**IVUS-Based Methods**

IVUS, which can be performed relatively easily and safely with a small catheter and does not require removal of blood, is used routinely in interventional cardiology and is being investigated as a means to identify vulnerable plaque.\textsuperscript{94,95} The primary routine uses of IVUS are to identify the amount of stenosis in borderline lesions and to assist in stent deployment.\textsuperscript{96} IVUS is also a valuable research tool for assessing the changes in plaque volume in response to novel antiatherosclerotic treatments.\textsuperscript{97–100}

**Use of IVUS for Plaque Characterization and Assessment of Vulnerability**

Standard IVUS is an excellent tool to determine whether plaques contain calcium, which produces a bright ultrasonic reflection. However, the association of calcification with plaque vulnerability is complex. Although calcification is associated with atherosclerosis, the plaques causing acute coronary syndromes have less calcium than those causing stable angina.\textsuperscript{101} Furthermore, stress analysis in autopsy specimens demonstrated that calcium does not increase fibrous cap stress and is less likely than a lipid pool to decrease mechanical stability of an atheroma.\textsuperscript{102} A spotty calcium pattern of calcification, which is more likely to be found in culprit lesions of patients with MI than in those of patients with stable angina, may be an indicator of vulnerability.\textsuperscript{103,104}

There have been efforts to use IVUS to identify other plaque components. Studies in autopsy specimens have shown that hypoechoic areas represent plaques with increased lipid content, low-intensity or ”soft” echoes represent fibromuscular lesions, and moderately hyperechoic areas are associated with fibrous plaques.\textsuperscript{105,106} A prospective study in a small number of patients found an increased risk of rupture and acute coronary syndrome caused by echolucent (presumably lipid-rich) plaques.\textsuperscript{107} Despite these data, the subjective nature of IVUS interpretations and questions about the limited sensitivity and specificity in vivo of the gray-scale images\textsuperscript{108,109} have led to attempts to improve the processing of the primary echo signal to enhance IVUS analysis of plaque composition.

These efforts have focused on novel methods to analyze the integrated backscatter of the radiofrequency (RF) signal to improve plaque characterization.\textsuperscript{110–112} Nair et al\textsuperscript{112} described an algorithm that could predict plaque composition of ex vivo human coronary plaques with an accuracy of \(\approx 90\%\). A commercially available system has been developed (Volcano, Inc, Rancho Cordova, Calif) using this analysis that assigns plaque to the categories of fibrotic, fibrofatty, calcific, and necrotic core and has been termed “virtual histology” (Figure 6).

A study by Kawasaki et al\textsuperscript{113} in patients with stable angina reported that 6 months of statin therapy causes changes in the RF IVUS signal consistent with a reduced lipid component indicating plaque stabilization. Fujii et al\textsuperscript{114} reported that positive (expansive) remodeling is more likely to occur in lesions that demonstrate fibrofatty plaque by IVUS. Sites with larger lipid cores by IVUS were more likely to be associated with expansive remodeling\textsuperscript{115} and to be located in the proximal portions of the coronary arteries.\textsuperscript{116} Patients with an acute coronary syndrome were more likely to have signs of a TCFA by virtual histology than were patients with stable angina.\textsuperscript{117}

Follow-up data after RF imaging are becoming available. Sano et al\textsuperscript{118} compared the baseline IVUS findings in 10 patients in whom a coronary syndrome occurred during follow-up with the baseline findings in 143 patients in whom
an event did not occur. Sites that led to an event were more likely to show an increased lipid area at baseline. The authors conclude that long-term, large-scale studies are needed to validate the approach. The Prospect Trial, which has already enrolled ~700 patients, is an example of the type of study needed to determine whether IVUS signals can prospectively identify plaques and/or patients vulnerable to the occurrence of coronary events.

**Detection of Ruptured Plaque by IVUS**

IVUS can frequently identify ruptured plaques because they have a distinctive anatomic structure. The findings are similar to those of angiographic and autopsy studies. Ruptured plaques are observed more frequently in patients with MI than in patients with stable angina and are associated with elevated hs-CRP. Patients with infarction are more likely to demonstrate a rupture site than are those with stable angina. Ruptured plaques that caused an acute coronary syndrome are associated with a smaller lumen and a greater plaque burden than are plaques that ruptured without causing a clinical event.

Although a ruptured plaque was by definition “vulnerable” before its rupture, it is also suspected to remain “vulnerable” to subsequent episodes of rupture and thrombosis. Hence, detection of a ruptured plaque by IVUS might be considered to be detection of a certain type of vulnerable plaque. The issue is not resolved. One IVUS-based study has reported that ruptured plaques causing mild stenosis were not associated with subsequent stenosis progression or recurrent acute coronary syndromes after MI in patients receiving adequate medical therapy. However, a second study demonstrated subsequent increases in stenosis at rupture sites in the absence of statin therapy.

The ability of IVUS to image deep into the wall of the artery has been used to evaluate remodeling in patients. Culprit lesions in patients with acute coronary syndromes demonstrate more expansive remodeling by IVUS than do the culprit lesions of patients with stable angina, suggesting that expansive remodeling might be associated with plaque vulnerability. Histological findings support this linkage because sites with expansive remodeling have larger lipid

---

**Figure 6.** Plaque characterization by IVUS. A, A traditional gray-scale cross-sectional IVUS image showing a plaque in the left anterior descending artery. B, Corresponding image using Virtual Histology (Volcano, Inc) to present tissue characterization information based on spectral analysis of backscatter data. White indicates calcification; green, fibrotic tissue; greenish-yellow, fibrolipidic tissue; and red, necrotic core. Modified from Rodriguez-Granillo et al with permission from The American College of Cardiology Foundation. Copyright 2005.

**Figure 7.** Ex vivo images of a coronary TCFA obtained by IVUS (A) and elastography (B), followed by macrophage (C) and collagen staining (D). In the elastogram, a soft plaque is indicated by deformability (yellow, arrow) with higher pressure. Macrophage presence (C) is increased and collagen is decreased (D) over a lipid pool. Modified from Schaar et al with permission from the American Heart Association. Copyright 2003.
cores and more macrophages than sites with constrictive remodeling. Hence, expansive remodeling, once thought to be beneficial because it reduced luminal narrowing, could be associated with a harmful predisposition to plaque rupture.130,131

IVUS after injection of microbubbles can also be used to detect the vasa vasorum present in advanced plaques that might be an additional feature of vulnerable plaques.132,133 Detection may be enhanced with the use of harmonic imaging after microbubble injection in which the signal is recorded at a higher frequency than that of the sonic waves directed to the plaque.134

**Elastography**

IVUS can also be used to assess the deformation of plaques during the changes in intracoronary pressure that occur during the cardiac cycle. This technique, called elastography, has been used to characterize the softness of plaques, which might be a sign of vulnerability.

Elastography has a high sensitivity and specificity for the detection of TCFA in postmortem coronary artery specimens.136 (Figure 7). Deformable plaques are more frequent in patients with acute MI and unstable angina than in patients with stable angina and are associated with higher levels of hs-CRP.137

Studies performed in MI patients at baseline and after 6 months showed a decrease in the deformability of plaques, presumably resulting from institution of lipid-lowering therapy.138 This promising technique is being tested in the Prospect Study and the Integrated Biomarker and Imaging Study (IBIS) 2 for its ability to predict coronary stenosis progression and events.

**Profiling of Shear Stress by IVUS**

IVUS has also been used to study shear stress produced by coronary artery blood flow, which may explain the localization of early plaque, TCFA, and culprit lesions.19,139,140 The technique uses 3D images of the vessel and computational fluid dynamics to calculate the forces directed along the endothelial surface of the vessel wall resulting from the friction associated with blood flow (Figure 8).

Plaque is more likely to originate at sites that have lower shear stress, which predisposes to inflammation and endothelial dysfunction.141 With such dysfunction, monocytes and lipids are more likely to penetrate the vessel wall, leading to TCFA formation, expansive remodeling, stenosis progression, and vulnerability.142 Hence, measurement of shear stress might be a method to identify sites that are “vulnerable” to becoming vulnerable. Detection of early steps in the process would be of considerable value, particularly if the time course of the appearance of vulnerable plaques, which is currently unknown, is relatively rapid.

**Optical Methods to Detect Vulnerable Plaque**

**Angioscopic Examination of the Coronary Artery**

Coronary angiography is currently the most precise clinical method available to identify the presence of thrombus, plaque disruption, and variations in color of the coronary arterial wall (Figure 9). During angioscopic examination, disruption appears as an irregular area, and thrombus is seen as a red, pink, or whitish mass. Nondisrupted plaques may be white, indicating a fibrotic composition, or yellow as a result of lipids that are rich in carotenoid pigments.143,144 The intensity of the yellow correlates inversely with cap thickness; a glistening yellow color indicates that a TCFA is present.72,145

Despite its capabilities, angioscopy is rarely used in clinical practice because it requires a blood-free field of view. The technique is valuable for research, with most use occurring in Japan.146,147

**Angioscopic Findings in Patients With Stable Angina the Acute Coronary Syndromes**

Angioscopic signs of both thrombus and disruption of the culprit site are more frequent in patients with unstable angina and MI than in patients with stable angina.148–150 Angioscopy has also confirmed the presence of disrupted and thrombotic plaques at sites other than the culprit lesion.151,152

Because ruptured plaques with thrombi may be prone to recurrent thrombosis,153 it is possible that these ruptured plaques detected by angioscopy may be a type of vulnerable plaque. Nonculprit lesions with disruption or thrombus detected by angioscopy tend to heal but may cause progression of angiographic stenosis.152 Healing was more likely to occur in patients with lower hs-CRP levels and more intensive statin therapy than in other patients.

**Angioscopic Assessment of Yellow Color**

Yellow plaques, which may be associated with vulnerability, are 5 times more likely to be associated with thrombus than are white plaques,154 and the culprit lesions in patients with MI are often yellow.155 Because visual assessment of yellow is subjective and affected by multiple variables, efforts are being made to develop quantitative colorimetry systems.145,156,157

Not all sites that are yellow by angioscopy are associated with acute coronary syndromes. Yellow plaque frequently occurs at nonculprit sites in patients with acute MI,158 and yellow plaques not associated with thrombosis occur in 50% to 60% of patients with stable angina.151 Although these
findings indicate the diffuse nature of atherosclerosis, it remains possible that the more locally occurring TCFAs, which are a subset of yellow plaques, might represent focal sites of vulnerability.

Uchida et al72 conducted one of the first reported studies of the natural history of lesions suspected to be vulnerable. Angioscopy was performed in 157 patients with stable angina. Over the subsequent 12 months, 68% of those with glistening yellow plaque experienced a coronary event as opposed to 8% in those with nonglistening yellow plaque and 3% in those with white plaques only. This important finding, which could represent the prospective identification of vulnerable plaque, requires replication in a larger study.

Angioscopy can also be used to assess the effect of preventive treatment.159 Therapy with atorvastatin changed lesions from yellow to white, suggesting plaque stabilization.160

Intravascular OCT

OCT uses the back-reflection of NIR light from optical interfaces in tissue to create high-resolution (10 μm), cross-sectional images.161 It provides a clearer picture of plaque structures than IVUS, which has a resolution of 100 μm.162 Autopsy studies have documented that OCT can accurately identify fibrous, fibrocalcific, lipid-rich plaques and macrophages and is the best technique to measure cap thickness163,164 (Figure 10).

The main limitation of intravascular OCT is the attenuation of the signal because of blood. Systems have been designed to remove blood from the field of view.165 These requirements limit the time for imaging and increase the complexity of use. A modification of OCT, called optical frequency domain imaging, is under development. It will permit much more rapid acquisition of the signal and may allow scanning of a considerable portion of the artery during a single flush.166

The promising features of OCT documented ex vivo can be obtained in the clinical setting. In 57 patients undergoing PCI, the OCT signs of lipid-rich plaques were observed in 90% of MI patients, 75% of acute coronary syndrome patients, and 59% of stable angina patients. The frequency of fibrous cap ≤65 μm was 72%, 50%, and 20% in the MI, acute coronary syndrome, and stable patients, respectively.167 The OCT sign of macrophage presence was higher in patients with acute coronary syndromes than in patients with stable angina.168 Pilot studies are underway to determine whether OCT can predict the progression of coronary stenosis.

Intracoronary NIR Spectroscopy

Diffuse reflectance NIR spectroscopy is in widespread use in many fields to identify the chemical composition of unknown substances.169 Because it appeared to be well suited for the identification of the composition of atherosclerotic plaques, several investigators tested its ability to identify lipids in ex vivo studies of autopsy or endarterectomy specimens.170–172 TCFAs and ruptured plaques could be readily identified by spectroscopy, even in the presence of up to 2 mm blood.173 There was doubt, however, as to whether NIR spectroscopy could be performed within the coronary arteries of patients in whom problems of cardiac motion, blood flow, and the need to scan entire arteries must be overcome.

Figure 9. A, Angioscopic image of a yellow plaque obtained in a human coronary autopsy specimen. B, Histology reveals that a TCFA is present. Image courtesy of Drs Ishibashi and Waxman.

Figure 10. OCT image of ruptured TCFA in a patient with acute MI (A). A lipid pool (L), intimal disruption (arrow), and guidewire artifact (asterisk) are visible. Macrophage density data are superimposed on the image (B). Modified from Tearney et al161 with permission from the International Society for Optical Engineering. Copyright 2006.
A catheter-based NIR spectroscopy device has now been constructed and successfully tested in 16 patients with stable angina and 10 with acute coronary syndromes. The device, which is similar in size and use to an IVUS catheter, was well tolerated and provided a full scan of the area of interest. High-quality spectra were obtained that are similar to those obtained in autopsy studies (Figure 11). Signals obtained from the wall of the coronary artery in vivo differed from those obtained from blood alone.

NIR studies have also been performed in a hypercholesterolemic swine model with extensive lipid-rich plaques. In this in vivo study in which coronary motion and blood flow were present, there was excellent reproducibility of NIR signals on repeat pullbacks and with different catheters (InfraReDx data on file).

Studies are underway in intact, perfused human coronary artery autopsy specimens to compare the NIR signals obtained with the scanning system with the gold standard of histology and create an advanced algorithm that will be used to interpret NIR signals obtained in patients. A registry has been established to determine the relationship of NIR findings to coronary events, as discussed below.

Raman NIR spectroscopy has also been studied for the assessment of coronary plaque composition. In this in vivo study in which coronary motion and blood flow were present, there was excellent reproducibility of NIR signals on repeat pullbacks and with different catheters (InfraReDx data on file).

Studies are underway in intact, perfused human coronary artery autopsy specimens to compare the NIR signals obtained with the scanning system with the gold standard of histology and create an advanced algorithm that will be used to interpret NIR signals obtained in patients. A registry has been established to determine the relationship of NIR findings to coronary events, as discussed below.

Raman NIR spectroscopy has also been studied for the assessment of coronary plaque composition. In this in vivo study in which coronary motion and blood flow were present, there was excellent reproducibility of NIR signals on repeat pullbacks and with different catheters (InfraReDx data on file).

Thermography
In 1996, Casscells et al studied the temperature of human atherosclerotic plaques in an ex vivo setting after a carotid endarterectomy. Inflamed plaques with increased macrophage density had a higher temperature than plaques that were not inflamed. These positive findings led to efforts by several groups to measure the temperature of plaques in patients undergoing catheterization.

It has been learned that coronary blood flow and catheter design features complicate measurement of plaque temperature in vivo. Blood flow is a coolant for the heart, which generates heat as a result of its contraction. This cooling effect makes it difficult to measure relatively small increases in plaque temperature without interrupting blood flow. In addition, catheters with increased sensitivity are needed to
measure the relatively small thermal signal. Prospective studies are planned to assess the feasibility of intracoronary temperature measurement and then test the ability of a temperature elevation to predict cardiac events.

**Intravascular MRI**

As noted, the noninvasive use of MRI to identify lipid in coronary plaques is limited by the small size of the target and cardiac motion. Two invasive MRI approaches are under development to overcome these problems. In the first, the patient is placed in a standard external MRI magnet, and an intravascular RF coil is used for local measurement. In the second, all the components required for the MRI measurement—magnets, RF coil, and detectors—are located in a single coronary catheter. Studies using the first approach in vivo in human iliac arteries obtained results similar to those of IVUS in the assessment of plaque size and signs of lipid. The method can also quantify components of atherosclerosis in human aortic autopsy specimens and in carotid endarterectomy specimens. The feasibility of accurate in vivo imaging has been demonstrated in rabbits and swine. This approach has the disadvantage of requiring that a patient must be studied in a suite containing an MRI magnet.

The second approach, in which the entire system is located on a catheter, has been validated ex vivo in aortic and coronary tissue (Figure 12). This approach showed significant differences in apparent diffusion coefficients between fibrous tissue, fatty streak, and lipid-rich necrotic cores. Data have now been collected in 61 coronary patients. Studies using the first approach in vivo in human iliac arteries obtained results similar to those of IVUS in the assessment of plaque size and signs of lipid. The method can also quantify components of atherosclerosis in human aortic autopsy specimens and in carotid endarterectomy specimens. The feasibility of accurate in vivo imaging has been demonstrated in rabbits and swine. This approach has the disadvantage of requiring that a patient must be studied in a suite containing an MRI magnet.

**Potential Treatment of Vulnerable Plaques**

It is likely that many agents already proven to prevent coronary events achieve their effect by reducing plaque vulnerability. Studies in animals have demonstrated that lipid-lowering diets and treatments convert fatty, presumably vulnerable plaques into fibrotic, presumably less vulnerable forms. Studies in patients in which the ability of lipid-lowering therapy to prevent events was far greater than its measurable effect on the degree of stenosis support such a concept.

Although plaque stabilizing therapies are a welcome addition, many events continue to occur in patients receiving the best currently available therapy. In the Prove-It Trial, 22.4% of patients experienced a coronary event during 2 years of intensive statin therapy.

The best long-term approach to prevention of coronary events is lifestyle changes supplemented by a fully effective systemic therapy, but such a regimen is not yet available. In addition, some patients will present with advanced disease, and others will not comply with such a regimen. Hence, it may be useful to supplement systemic therapy with effective local therapy for the most advanced lesions. Such an approach would be similar to the treatment of breast cancer with systemic chemotherapy plus local radiation.

**Systemic Therapy**

A number of newer systemic pharmacological approaches to coronary prevention are related to plaque vulnerability.

**Therapies to Lower LDL Cholesterol**

There is no doubt that intense lowering of LDL, which can be readily achieved by statin therapy, can prevent events resulting from complications from vulnerable plaques. Although direct evidence that such beneficial effects are due to plaque stabilization is not available, various imaging methods have been used to determine the effect of statins and other therapies on coronary and carotid artery plaques.

Nissen et al studied the effect of intensive lipid lowering with rosuvastatin on coronary atheroma in 507 patients undergoing IVUS examination at baseline and after 2 years of follow-up. The marked reduction in LDL was associated with an 11.1% decrease in coronary plaque volume as measured by IVUS. Although the study was not randomized and HDL increases also occurred, it is quite likely that the intense LDL lowering produced this beneficial decrease in plaque volume and stabilized plaques.

The effect of lipid lowering on calcification is complex. Noninvasive studies have shown that plaque calcification can actually increase during statin therapy.

The beneficial effects of statin therapy observed in the coronary circulation have also been observed in the carotid arteries and the aorta. Corti et al used noninvasive MRI measurement to document that statins caused regression of atherosclerotic carotid and aortic lesions in patients.

Animal studies have provided information about the mechanisms of plaque stabilization by statin therapy. A study of rabbits transferred from an atherogenic to a regression diet revealed that collagen content of the plaques increased. It has also been demonstrated in rabbits that statin therapy reduced macrophages and collagen breakdown products in lipid pools.

**Figure 12.** A self-contained intravascular MRI system with imaging areas superimposed on a human coronary artery (left). The arrowhead depicts 1 of 4 fields of view. The diagram (right) displays the lipid fraction in each quadrant in an ex vivo autopsy specimen. An increased lipid concentration is displayed in yellow. Reproduced from Schneiderman et al with permission from The American College of Cardiology Foundation. Copyright 2005.
Therapies to Increase HDL Cholesterol
It is likely that increases in HDL would increase plaque stability because such changes accelerate reverse cholesterol transport, lowers oxidation level, and decreases inflammation. Clinical studies have documented the prevention of coronary events with HDL raising by niacin and gemfibrozil therapy. A major National Institutes of Health study has been initiated to determine whether significant increases in HDL levels induced by niacin therapy can reduce coronary events.

Inhibitors of cholesteryl ester transport protein have emerged as promising agents to increase HDL levels. Torcetrapib and JTT-705 can produce elevations of ≥50% in HDL cholesterol. Clinical trials are in progress to determine whether such HDL elevations produce the expected clinical benefits.

The atheroprotective effects of apoA-1 Milano, a synthetic form of HDL, have received considerable attention. The agent was infused weekly for 5 weeks into patients recovering from an acute coronary syndrome. IVUS measurements demonstrated a small decrease in atheroma volume, supporting the transition to studies with clinical end points.

Additional approaches in this active field include the use of small molecules to increase HDL levels and a variety of nuclear hormone receptor agonists to increase ABC gene transcription and HDL levels and/or function. There are also efforts to evaluate systemic administration of unilamellar phospholipid vesicles and gene therapy involving HDL-related proteins.

Antiinflammatory Therapy for the Prevention of Coronary Events
The evidence that atherosclerosis is associated with inflammation has increased interest in the role of antiinflammatory agents in preventing coronary events. The concept is supported by the success of statin therapy, which may be due in part to antiinflammatory effects.

Lipoprotein-associated phospholipase A2 has emerged as a promising novel target for antiinflammatory therapy of atherosclerosis. This lipase circulates in plasma and can enter the vessel wall. Once in the wall, it interacts with macrophages and lymphocytes to intensify local inflammatory processes. A small-molecule inhibitor of lipoprotein-associated phospholipase A2 is under study.

An agent that can block endothelial cell signaling pathways that facilitate the movement of monocytes into the vessel wall is being studied. AGI-1067 blocks the production of vascular cell adhesion molecule 1 and has antioxidant and lipolytic activity. It has been shown to reduce restenosis after PCI and to increase the luminal dimensions of reference segments. A randomized study is underway in 6000 patients to determine whether AGI-1067 can reduce coronary events.

Summary of Systemic Therapy for Vulnerable Plaque
Ambrose and D’Agate have proposed a useful classification to assess the likelihood that a given systemic therapy is plaque stabilizing (Table 2). Therapies are grouped by the strength of the evidence that they prevent coronary events and the plausibility of a mechanism by which they might do so by stabilizing vulnerable plaques.

Although systemic therapy is clearly the preferred solution, current systemic therapy does not provide adequate protection, particularly for the very-high-risk group of patients whose disease activity has led to the need for a PCI. This situation leads to the following question: At the present time, is there a role for local preventive therapy as a supplement to systemic therapy in a patient already undergoing PCI?

Local Therapy for Vulnerable Plaque
The sine qua non of local therapy for vulnerable plaque is the existence and prospective detection of local areas of the vessel that are at increased risk of causing a coronary event. If the entire artery is found to be at high risk or if vulnerability rapidly emerges and resolves, there may be no role for local therapy. However, local diagnosis might still be of value as a guide to the intensity of systemic therapy, as is the case for cancer in which results of a local biopsy often guide systemic therapy.

In the context of uncertainty about the existence, detection, and timing of plaque vulnerability, it is not possible to recommend routine use of the promising local therapy options discussed below. Such therapy can be recommended only with the use of a vulnerability detector and the availability of data from a randomized trial demonstrating that the local therapy under consideration provides benefits greater than the complications associated with the intervention.

Evaluation of the promising local treatments for vulnerable plaque (stents, photodynamic therapy, and other options) is therefore being hindered by the absence of validated diagnostic devices. For the vulnerable plaque hypothesis, detection of risk appears to be a more formidable obstacle than availability of possible treatments.

![Modified from Ambrose and D’Agate with permission from the American College of Cardiology. Copyright 2005, Elsevier Inc.](http://circ.ahajournals.org/)

**TABLE 2. Classification of Systemic Therapy for Vulnerable Plaque**

<table>
<thead>
<tr>
<th>Therapies</th>
<th>Drug</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group 1: therapies with biological plausibility and positive clinical evidence</td>
<td>Statins, ACE inhibitors, β-blockers, aspirin</td>
</tr>
<tr>
<td>Group 2: therapies with biological plausibility but negative clinical evidence</td>
<td>Antioxidants, folic acid, antibiotics</td>
</tr>
<tr>
<td>Group 3: therapies with biological plausibility but conflicting or inconclusive clinical evidence</td>
<td>Angiotensin-receptor blockers, omega-3 fatty acids, other antihypertensive agents, cyclooxygenase-2 inhibitors, influenza vaccine, clopidogrel, metalloproteinase inhibitors</td>
</tr>
<tr>
<td>Group 4: therapies with biological plausibility but no clinical data available</td>
<td>Peroxisome proliferator–activated receptor antagonists, cholesterol ester transfer protein inhibitors</td>
</tr>
</tbody>
</table>
Treatment of Coronary Artery Risk Based on Location of Culprit Lesions

Although technologies to identify risk caused by an individual plaque are not yet validated, Wang et al.18 have identified regions of risk in arteries based on location of culprit lesions. It was found that most of the lesions causing the acute coronary syndromes occur within the proximal 30 mm of the major coronary arteries. These are also areas of decreased shear stress and increased numbers of TCFAs and ruptured plaques.17

Because the risk is associated with a relatively limited length of artery, it is possible that regional therapy (possibly with stents) might be useful for preventing subsequent events in patients undergoing PCI. Wang and colleagues18 have suggested that a randomized trial of such an approach might be conducted in high-risk patients. The trial might also use a vulnerability detector to identify patients with vulnerable arteries who would be the most likely to derive benefit.

Stents for the Treatment of Vulnerable Coronary Plaques and Arteries

Drug-eluting stents have been evaluated in an atherosclerotic rabbit model as a possible treatment for vulnerable plaques. Placement of a stent over lesions in the aorta reduced lipid core size and induced formation of an additional fibrous cap over the lipid pool (Figure 13). Although these results are encouraging, the benefits of stenting vulnerable plaques in patients must be shown in a randomized trial to exceed the complications, which include periprocedural infarction, restenosis, and stent thrombosis.213

Stenting for Intermediate Coronary Artery Stenoses That Are Not Flow Limiting

There is generally little difficulty with the decision to stent a culprit lesion. It is causing or has caused ischemia, and the need for the stent is relatively straightforward and indicated by guidelines.214 Unfortunately, many patients also have a second or third stenosis that is not producing ischemia but causes concern because it is suspected to be vulnerable. The concern is heightened if the lesion causes a 50% to 60% diameter stenosis, has a complex angiographic appearance, and is in a precarious location such as the proximal left anterior descending coronary artery.

In the absence of information about the likelihood that the plaque of concern might rupture, current guidelines call for the use of medical therapy. However, if the lesion were known to be vulnerable to rupture, stenting might be the better choice, depending on the balance of risks and benefits of stenting noted above.215

The use of stents or angioplasty for lesions causing an intermediate stenosis was examined in the Defier Trial. Patients with intermediate stenoses not causing a significant reduction in fractional flow reserve were randomly assigned to intervention (angioplasty or stenting) or medical therapy. In a 5-year follow-up, there was no difference in the low rate of cardiac death and MI between patients assigned to medical therapy and those treated with the intervention.216 It was concluded that the low risk of MI and cardiac death in this population (<1% per year) did not justify intervention for intermediate stenoses in this group of patients. However, the study excluded patients with more active disease who had sustained an MI or unstable angina and did not use a vulnerability detector. The possibility that stenting of intermediate lesions suspected to be vulnerable will be of value in acute coronary syndrome patients has led to a proposal to conduct the Prevail Trial, a randomized trial of the strategy.

Improvements in stent technology are likely to reduce the risks associated with stenting and thereby shift the risk-to-benefit ratio toward the stenting of intermediate stenosis. Bioabsorbable stents, which may reduce or eliminate the long-term risk of stent thrombosis, may be preferable for prophylactic stenting of nonstenotic vulnerable plaques.

Role of Vulnerability Detection in the Selection of Stenting Versus CABG as Optimal Therapy

In several commonly encountered clinical situations, knowledge of the vulnerability of the artery in question might be useful as a guide to treatment with stents or referral for surgery. For diabetics with stenosis in 3 vessels, the current standard of care is CABG because of documented reductions in cardiac events with surgery that are not achieved by multivessel stenting.217 The bypass graft, which is attached distal to much of the epicardial coronary artery, presumably bypasses nonstenotic vulnerable plaques that would otherwise be responsible for subsequent events. Stenting of flow-
limiting lesions, which is a focal treatment, would not provide such a benefit.

However, if it were possible to determine whether the arteries contained vulnerable nonstenotic plaques, the triage of such patients to stenting or CABG could be improved. Patients with stenoses and no evidence of nonstenotic vulnerable plaques could be treated with stenting, and those with extensive signs of vulnerability could be sent for CABG.

Multiple trials are in progress to compare the value of multivessel stenting with surgical treatment of patients with stenosis in 3 coronary vessels. Such trials would be aided by the detection of vulnerability and assessment of the degree of stenosis.

Similar considerations apply to therapy for patients with isolated left main coronary artery stenosis. If a localized left main stenosis is present and the remainder of the arteries show no evidence of significant stenosis or vulnerability, stenting might be the preferred therapy. Alternatively, if there were signs of diffuse vulnerability throughout the artery, CABG might be preferred.

### TABLE 3. Summary of Prospective Clinical Trials (in Progress or Planned) to Determine the Outcome Associated With Plaques Characterized by Intracoronary Diagnostic Devices

<table>
<thead>
<tr>
<th>Technique to Be Evaluated</th>
<th>Name of Trial</th>
<th>Trial Design</th>
<th>Types and Number of Patients to Be Enrolled</th>
<th>Principal Investigator</th>
<th>Sponsor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Shear stress profiling</td>
<td>Prediction</td>
<td>Changes in plaque morphology and remodeling at sites with low shear stress, plus major adverse cardiac events</td>
<td>500 PCI</td>
<td>Dr Peter Stone</td>
<td>Boston Scientific, Inc</td>
</tr>
<tr>
<td>IVUS-based plaque composition</td>
<td>Prospect</td>
<td>Natural history for coronary events</td>
<td>700 PCI</td>
<td>Dr Gregg Stone</td>
<td>Guidant, Inc, Volcano, Inc</td>
</tr>
<tr>
<td>IVUS-based plaque composition</td>
<td>Study of Prospective Events in Coronary Intermediate Atherosclerotic Lesions</td>
<td>Lesion progression and natural history for coronary events</td>
<td>2000 PCI, including 1000 with repeat IVUS measurements at 12 mo</td>
<td>Drs Etsuo Tsuchikane and Tadanori Aizawa</td>
<td>Volcano, Inc, Goodman Co, Fukuda Denshi Inc</td>
</tr>
<tr>
<td>Palpography</td>
<td>Substudy of Prospect</td>
<td>Natural history</td>
<td>200 PCI</td>
<td>Dr Gregg Stone</td>
<td>Guidant, Inc</td>
</tr>
<tr>
<td>Palpography</td>
<td>IBIS-2</td>
<td>Assessment of treatment with inhibitor of lipoprotein-associated phospholipase-2; End points are palpography and hs-CRP</td>
<td>450 PCI</td>
<td>Dr Patrick Serruys</td>
<td>GlaxoSmithKline, Inc</td>
</tr>
<tr>
<td>Thermography</td>
<td>Vulnerability Index Program 1</td>
<td>Feasibility and tolerability of thermal measurement</td>
<td>160 PCI stable angina</td>
<td>Drs William Wijns and Stephan Verhey</td>
<td>Bristol Myers Squibb Medical Imaging, Inc</td>
</tr>
<tr>
<td>Thermography</td>
<td>Vulnerability Index Program 2</td>
<td>Natural history for coronary events (after Vulnerability Index Program 1)</td>
<td>700 PCI ACS</td>
<td>Drs William Wijns and Stephan Verhey</td>
<td>Bristol Myers Squibb Medical Imaging, Inc</td>
</tr>
<tr>
<td>NIR spectroscopy</td>
<td>Spectroscopic Assessment of Coronary Lipid plus Registry</td>
<td>Spectra in patients, followed by natural history for coronary events</td>
<td>2000 PCI</td>
<td>Dr Sergio Waxman</td>
<td>InfraReDx, Inc</td>
</tr>
<tr>
<td>OCT</td>
<td>NIH-funded OCT Study</td>
<td>Stenosis progression on 18-mo restudy</td>
<td>100 PCI</td>
<td>Drs Guillermo Tearney and Brett Bouma</td>
<td>NIH</td>
</tr>
<tr>
<td>Diagnostic technique to be selected</td>
<td>Pilot Safety Study for Prevail</td>
<td>Randomization of intermediate stenoses to stenting or medical therapy, with possible use of a vulnerability detector</td>
<td>700 PCI</td>
<td>Dr Sheldon Goldberg</td>
<td>Cordis, Inc</td>
</tr>
</tbody>
</table>

ACS indicates acute coronary syndromes.
PTCA for the Treatment of Vulnerable Coronary Plaques
In 1995, Meier proposed that it might be of value to intentionally rupture presumably vulnerable intermediate stenoses with balloon angioplasty at the time of catheterization. Because the rupture would occur under controlled conditions and in the presence of intensive antithrombotic therapy, the procedure would not cause an acute coronary event. After the catheterization, the ruptured lipid-rich plaque would be expected to become a fibrotic plaque, and the danger of a coronary event would be eliminated. The procedure was called plaque sealing. The concept stimulated extensive debate but did not become an accepted practice.

Plaque sealing, however, could be reconsidered in light of new technical developments. The availability of stents provides an excellent treatment for the problems of subacute occlusion that limited the value of PTCA for preventive purposes. In addition, it is possible that a vulnerability detector might be able to identify the lesions most in need of therapy. The use of PTCA to intentionally rupture nonstenotic vulnerable plaques would not carry the long-term risks of stenting. Plaque sealing and all local therapies under discussion require evaluation in randomized trials.

Photodynamic Therapy for Vulnerable Coronary Arteries and Plaques
Photodynamic therapy has been proposed as a method to stabilize a specific plaque or a region of an artery by selective ablation of macrophages or other targeted cells. The photosensitizing agent metoxafin lutetium was tested in atherosclerotic rabbits. After photoactivation via an intra-aortic catheter, there was a marked reduction in the number of macrophages and a small decrease in atheroma burden without damage to normal tissue (Figure 14). The same agent has been administered to patients undergoing coronary stenting in a safety study and found to be well tolerated.

Using a different photodynamic agent, Waksman et al demonstrated that photodynamic therapy can reduce neointimal growth without suppressing reendothelialization of a stent in a porcine model. These early results suggest that photodynamic therapy might eventually have a role in the local or regional treatment of vulnerability.

Cooling, Heating, and Sonotherapy
Cryoenergy has been shown to reduce restenosis and increase the density of type III collagen in balloon-injured porcine arteries. It may be useful to stabilize vulnerable plaques because it can induce local apoptosis without causing excessive neointimal proliferation. Cryoenergy is currently being studied for the treatment of peripheral arterial disease.

Although heating and sonotherapy have also been considered as possible methods to treat vulnerable plaque, little supporting evidence is available.

Conclusions
The extensive activity described here has great promise to enhance the detection and treatment of vulnerability and thereby prevent coronary events. The net result of improved risk stratification will require increased attention because novel anti-atherosclerotic agents and treatments are likely to be costly and may carry unanticipated side effects.

As indicated in Table 3, many of the trials required to test the hypothesis that diagnosis and therapy of vulnerability are possible and beneficial are planned or in progress. In aggregate, the planned trials account for >6000 patients.

Although the efforts required to test the vulnerability hypothesis are considerable, they are justified by the benefits that could be achieved. Effective screening and treatment in the general population would decrease sudden death and initial MI, and success in the catheterization laboratory would decrease the high risk of recurrence that now follows PCI. Because the costly disorders of heart failure and arrhythmia would be prevented, economic analysis indicates that treatment of vulnerability would actually lower healthcare costs while decreasing morbidity and mortality resulting from coronary artery disease.

Source of Funding
Dr Waxman has received a grant from InfraReDx, Inc. to conduct clinical trials of a spectroscopy catheter.

Disclosure
Dr Muller is on leave of absence from his academic positions and is currently chief executive officer of InfraReDx, Inc, a company developing an NIR catheter. The other authors report no disclosures.

References


27. Mora S, Ridker PM. Justification for the Use of Statins in Primary Prevention: An Intervention Trial Evaluating Rosuvastatin (JUPITER): Can C-reactive protein be used to target statin therapy in primary prevention? Am J Cardiol. 2005;97:33A–41A.


93. Waxman et al New Devices to Assess and Treat Vulnerable Plaque...


Key Words: coronary disease ■ coronary imaging ■ prevention ■ plaque
Detection and Treatment of Vulnerable Plaques and Vulnerable Patients: Novel Approaches to Prevention of Coronary Events
Sergio Waxman, Fumiyuki Ishibashi and James E. Muller

_Circulation_. 2006;114:2390-2411
doi: 10.1161/CIRCULATIONAHA.105.540013
_Circulation_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2006 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/114/22/2390

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in _Circulation_ can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to _Circulation_ is online at:
http://circ.ahajournals.org//subscriptions/