The Editor's Roundtable: The Vulnerable Plaque

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Objectives

Upon completion of this activity, the physician should be able to:

1. Define "vulnerable plaque."
2. Better understand the benefits and limitations of coronary angiography and other invasive techniques in quantifying coronary atherosclerotic narrowing and atherosclerotic burden.
3. Better explain the mechanism of acute coronary events to patients as they relate to strategies for their prevention.

Target Audience: This activity is designed for cardiologists and all other health care specialists caring for patients with acute and chronic coronary artery disease.

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Introduction

The concept of vulnerable plaque originally evolved from studies of coronary atherosclerotic plaque in patients with unstable angina pectoris, acute myocardial infarctions, and sudden cardiac death.[1] Early descriptive features of vulnerable plaque included plaque rupture and fissuring,[2,3] occlusive thrombus formation,[4] and the involvement of noncritically stenotic plaque in the acute process.[5] In this Editor's Roundtable, the faculty members discuss the current state of knowledge about the relation between atherosclerotic plaque and acute coronary events, current clinical limitations in identifying plaque that place patients at risk, and ongoing research that may lead to the diagnosis and treatment of vulnerable plaque.

Dr. Friedewald: What is a *vulnerable plaque*?

Dr. Willerson: A *vulnerable plaque* is an atherosclerotic plaque in a coronary artery that is likely to rupture or fissure, leading to thrombosis, and then to acute coronary syndrome: myocardial infarction, unstable angina pectoris, or sudden cardiac death.[1] The histology of atherosclerotic plaque is generally comprised of a mixture of layer upon layer of cholesterol debris, calcium, and fibrous tissue.[6] Over time, the vulnerable plaque also may lead to *progressive* coronary artery disease, which is usually not included in the concept of vulnerable plaque.

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Dr. Roberts: You are referring to additional plaque formation and further arterial luminal narrowing?

Dr. Willerson: Yes. Sometimes coronary atherosclerosis progresses very rapidly, but progression also may be slow or absent. Key elements in atherosclerosis progression are fissuring and erosion of plaques and consequent thrombus, calcium, and fibrous tissue formation. Plaque erosion or fissuring may occur more often in women than in men.[7]

Dr. Stone: *Vulnerable plaque* is a clinical definition. Histologically, in most cases, a thin-capped fibroatheroma is present. In others, there are erosions of proteoglycan-rich plaques and, in a rare instance, there is only a calcified nodule. There is no way at present, however, to detect plaque phenotypes in living patients, and there have been no prospective natural history studies that help identify plaques that put patients at risk for acute coronary events. What Dr. Willerson describes is a *clinical* diagnosis of the vulnerable plaque for increased risk. While many plaques *do* progress very quickly, some of them progress slowly. The paradigm of vulnerable plaque can be expanded to include atherosclerotic lesions that put patients at risk for future morbidity and mortality.

Dr. Willerson: A histological definition of *vulnerable plaque* includes a plaque with a thin fibrous cap with associated cholesterol debris, a large number of inflammatory cells, and some smooth muscle cells at a site of plaque fissure, erosion, or rupture.[6] Inflammatory cells, especially macrophages and some activated T cells, release certain enzymes, such as proteases, specifically metalloproteases, which degrade collagen and cause plaque erosion.[8] In eroded or fissured plaques, inflammation is less common—present in only 20% to 30% of patients—whereas inflammatory cells are *always* present in ruptured plaques.[9] In eroded and fissured plaques, there are higher concentrations of hyaluronan, which promotes thrombosis by enhancing local adherence of platelets and white cells to the plaque.[10]

Dr. Friedewald: Do you believe that the vulnerable plaque can be detected clinically?

Dr. Willerson: Yes. I agree with Dr Stone's description of vulnerable plaque, but I caution that this is an evolving field. We do not yet know the natural history of atherosclerotic plaques that allows us to use imaging studies to detect vulnerable plaques, but this is an area of current research. For example, the inflamed plaque possesses *temperature heterogeneity*, in which 1 part of a plaque is warmer than the rest of the plaque.[11] Such heterogeneity can be detected with invasive catheters placed immediately adjacent to the plaque. Most plaques with temperature heterogeneity that rupture or fissure do not critically narrow the artery, usually causing $<$50% diameter narrowing of the lumen. Another type of study is *optical coherence tomography*, which provides microscopic examination of plaque cap thickness, lipid pool, and probably inflammation.[12] *Intravascular ultrasound* can provide a virtual histologic study of plaque fibrous tissue and calcium, but not cap thickness.[13] A technique termed *palpography* measures the tensile strength of the plaque by indentation with external pressure, helping to discern between lipid-rich plaques and those composed mainly of fibrous tissue and calcium.[14] The main problem with these techniques is that they are invasive, and we need noninvasive tests for detecting the vulnerable plaque. Kelly and colleagues[15] have developed nanotechnology techniques to identify inflammation in plaques using a peptide that binds to vascular cell adhesion molecule, the receptor for inflammatory cells in the plaque. There are other investigational approaches trying to identify some component of the vulnerable plaque that would allow using magnetic resonance imaging, computed tomography, or a combination of those imaging techniques.[16]

Many patients have *several* vulnerable plaques simultaneously.[17] Evaluations of patients with unstable angina pectoris in real time using *ultrasound virtual histology* have found that in about 35% of patients with a coronary thrombus and an acute myocardial infarction or unstable angina pectoris, there are 1 or more *additional* vulnerable plaques.

Dr. Stone: There are also *spectroscopic techniques* for studying the vulnerable plaque. Our institution has the first Food and Drug Administration–approved human spectroscopic device to characterize a plaque subtype, the InfraReDx LipiScan (InfraReDx, Inc., Burlington, Massachusetts), to detect lipid core. This has been validated histologically. Other devices for studying the vulnerable plaque are intravascular magnetic resonance imaging and measures of endothelial shear stress. Thus, many techniques are available to look at plaque phenotypes, metabolic activity characteristics, and physical properties, especially of thin-capped fibroatheromas. We have a harder time, however, detecting proteoglycan or hyaluronic-rich plaques that are likely to erode, although spectroscopy holds hope for those applications. Virtual histology also looks at the frequency domain and provides more information that has been correlated pathologically on a pixel-by-pixel basis with some of the different lesion types, including calcific, fibrotic, and fibrofatty lesions and the necrotic core. Second-generation *optical coherence tomography* (OCT) will soon be available in a form called *optical frequency-domain imaging* (OFDI), in which the pullback speeds are 10 to 20 times greater than with OCT. As a result, with OFDI flushing with saline, contrast, or another agent to clear the bloodstream, there is no need to occlude the coronary artery as in OCT, and therefore myocardial ischemia does not occur. Very rapid pullback over a 6 to 10 cm coronary artery segment length provides extraordinary resolution and allows measurement of the thickness of the fibrous cap.

Dr. Ambrose: There is confusion about the concept of the *vulnerable* plaque versus the *thrombosed* plaque. They are not the same.[18] The analogy often utilized is that the vulnerable plaque is the "volcano" that has yet to erupt, while the thrombosed plaque—the erupted "volcano"—is the immediate cause of the particular syndrome, and it is the disrupted or eroded plaque that leads to a coronary event.

Dr. Roberts: What do you mean by "thrombosed plaque"?

Dr. Ambrose: A plaque that is prone to thrombosis, fissuring, or erosion leading to a clinical event is often defined as a *vulnerable plaque*. The vulnerable plaque is a *preclinical* event. When thrombus forms it is then a *thrombosed* plaque, which is the immediate cause of most acute coronary syndromes.[19]

Dr. Stone: We are interested in detecting the *prerupture* or *prethrombosed* plaque, and there is morphologic confusion about this concept. Thin-capped fibroatheromas that do

not rupture may differ from those that rupture due to differences in hematologic parameters or systemic inflammation, factors outside the plaque itself. Thus, the entire patient must be scrutinized when assessing plaque vulnerability.

Although it is a systemic disease, atherosclerosis usually manifests itself *focally* in the coronary arterial tree. We need better understanding of the temporal course of these lesions. Are they constantly developing and regressing over time? What is the likelihood that any 1 lesion is going to rupture? Most investigators believe that it takes a long time for these lesions to develop and that they do not quickly go away. Data about their natural history, however, is lacking.

Dr. Willerson: Intensive lipid lowering with a statin often takes several weeks before there is risk reduction for acute myocardial infarction, unstable angina pectoris, or need for coronary artery revascularization. In animal models fed high-lipid diets causing atherosclerosis and inflammation, discontinuation of the lipid diet takes several weeks for the inflammation to subside and for the lesions to stabilize or regress even slightly. This process is not quickly affected by diet or statin therapy. When we can identify plaques with imminent risk, we will need quick-acting therapies like drug-eluting stents or drugs such as anti-inflammatory agents injected into the vulnerable plaque.

Dr. Ambrose: Discussions about vulnerable plaque tend to focus on the thin-capped fibroatheroma. Other types of vulnerable plaque are those that rupture without a clinical event and plaque erosion in which the plaque is not lipid rich, inflamed, or thin capped. These other types probably occur when systemic thrombogenicity of the blood is the main factor in converting asymptomatic vulnerable plaque to a thrombosed plaque and a resultant acute coronary event.[20]

Dr. Stone: Many vulnerable plaques probably rupture and are not followed by a clinical event. "Repair" of the ruptured plaque is likely a common mode of atherosclerosis progression. Histologically, this is manifest as layering of former ruptured plaques, 1 on top of the other, and we can envision that with each rupture the plaque impinges more on the coronary arterial lumen, making the lumen progressively stenotic. It is incorrect that only "mild" lesions rupture and become symptomatic vulnerable plaques. Among cases of sudden death and acute coronary thrombosis, there is usually about a 75% cross-sectional area of vascular luminal obstruction by a plaque with a very soft, lipid-rich core, accompanied by a large plaque burden. I believe that *truly* small plaques only infrequently cause clinical events.

Dr. Willerson: Whenever arterial endothelium is disrupted, the coronary artery at that location becomes at risk for thrombosis. Thus, if we could identify disrupted endothelium, intense antithrombotic therapy, which would prevent acute coronary events, could be provided. Endothelial healing is slow, taking at least weeks to occur because the vulnerable plaque has a paucity of smooth muscle cells, which, for unknown reasons, must first undergo apoptosis in the setting of endothelial disruption.

Dr. Ambrose: Myocardial infarcts often appear to be caused by "insignificant" lesions by coronary angiography. However a 75% cross-sectional area narrowing corresponds to about a 50% diameter narrowing angiographically.[21] These "insignificant lesions" are well-developed plaques, and there is a large plaque burden but without a large amount of luminal narrowing, due to remodeling. A lesion without significant luminal stenosis that suddenly occludes is more likely to cause an acute coronary event than a lesion with a prior ≥90% luminal stenosis.[19]

Dr. Willerson: Angiography underestimates the extent of true luminal narrowing and the atherosclerotic burden. Lesions with <50% luminal diameter narrowing should not be ignored. As many as 2/3 of all acute myocardial infarcts occur at sites of less than "critical" angiographic narrowing. Thus, we must look at the biology, the metabolism, and the functional status of atherosclerotic plaques and not focus solely on the degree of luminal narrowing.

Dr. Stone: Lesions causing <50% diameter narrowing are often of no concern. Those which are important are the vulnerable ones. Thus, how can we identify the vulnerable plaque? Angiography is not sensitive *enough*, and standard intravascular ultrasound is *too* sensitive. We need more accurate techniques to assess the morphologic and metabolic characteristics of the vulnerable plaque.

Dr. Friedewald: Dr. Roberts, how do you view the vulnerable plaque?

Dr. Roberts: I try to avoid the term "vulnerable plaque," and prefer "vulnerable *patient*," which I know Dr. Willerson has used.

Dr. Willerson: I believe in both.

Dr. Roberts: The cardiology community seems to focus primarily on which plaque is *vulnerable* rather than on the *quantity* of plaque in the coronary arteries. I put more importance on plaque quantity or "plaque burden," as some call it, than on plaque vulnerability. My colleagues and I through the years have spent much time performing detailed examinations of coronary arteries in patients with various forms of fatal coronary events.[22–64] In adults, the right coronary artery is about 10 cm long, the left main about 2 cm, the left anterior descending about 10 cm, and the left circumflex coronary artery about 6 cm (depending on whether it or the right coronary artery is dominant). That adds up to a total length of the 4 major coronary arteries of about 27 cm, or an average of 54 5-mm segments per adult heart. In patients with fatal coronary artery disease, regardless of the clinical subset, the quantity of plaque is enormous. There is not just 1 plaque here, another plaque there, with normal lumen between plaques. Plaques are *continuous*! Not a single 5-mm coronary segment is devoid of plaque in patients with fatal coronary disease, regardless of the clinical subset. About 35% of the 27 cm of coronary arteries in patients with acute myocardial infarction or sudden coronary death have >75% cross-sectional luminal narrowing by plaque alone.[22,23,32,40–42,46–50] Very few patients with unstable angina pectoris have been studied morphologically,[53] because most of those patients go on to have an acute myocardial infarction or they have coronary angioplasty or coronary artery bypass grafting, procedures which crack plaques. The most common causes of ruptured plaque in my experience are coronary angioplasty and coronary artery bypass grafting.[64]

I also have had the opportunity to study coronary endarterectomy specimens of the right coronary artery from patients with nonfatal coronary artery disease (removed at coronary bypass) and have found that the amount of nar-

rowing in them is similar, if not *greater*, than the degree of obstruction in the right coronary artery in patients with fatal coronary disease.[65] I have also been involved in studies examining plaque composition and found that the dominant component of atherosclerotic plaques in coronary arteries (maybe not in the aorta or carotid arteries) is *fibrous tissue*.[53–55,58–61] *Lipid* makes up about 10% of the average coronary plaque, *calcium* about 10%, and *other materials* the remaining 10%. In the patients that I have been involved in studying, those with unstable angina pectoris have the most coronary artery narrowing of any subset, and they have relatively normal left ventricular function. In my experience, ruptured plaque is not the cause of sudden coronary death.[63] The *quantity* of plaque in the sudden death patients is enormous. On average, 1/3 of the coronary tree is narrowed >75% in cross-sectional area by plaque alone in cases of sudden coronary death, whether it is the first coronary event or later after episodes of angina pectoris or acute myocardial infarction which healed.

Unstable angina pectoris is very difficult to study morphologically. Does ruptured plaque occur at the first episode of angina? If so, there is no proof of that thesis. Does ruptured plaque account for a patient shifting from stable angina to unstable angina? I am uncertain. In my experience with acute myocardial infarction, 70% of patients have a ruptured plaque with a thrombus superimposed on the plaque.[51] The other 30% do not. Every patient with acute myocardial infarction has an occlusive thrombus that has been demonstrated best in my view by coronary angiography, which has also demonstrated that such thrombi lyse in a few days.

Is atherosclerosis an inflammatory disease? It depends on how "inflammation" is defined. Morphologically, atherosclerosis is not an inflammatory disease. If inflammation is defined by elevation of certain cytokines, then inflammation is involved in atherogenesis.

There is *huge* variability in the amount of thrombus that may be present in coronary arteries in patients with fatal acute myocardial infarction. In a study by Brosius and me,[28] the average amount of thrombus was about 20% of the cross-sectional area of the plaque but ranged from to as much as 80% to as little as 2% of the plaque.

Dr. Friedewald: Are there certain plaque characteristics that you worry more about than others?

Dr. Roberts: I worry about the degree of coronary arterial luminal narrowing. It is actually *unfortunate* that every plaque is not "vulnerable," because vulnerability implies the presence of a lot of lipid in the plaque, and if all plaques were mostly lipid, the potential for plaque reversibility would be great.

Dr. Ambrose: Your analysis of plaque burden is consistent with the view that in patients with clinical coronary artery disease, up to 90% of "normal" areas in the coronary angiogram actually contain plaque as determined by intravascular ultrasound. I believe, however, that patients whom you have examined at autopsy with unstable angina pectoris are a very select group.

Dr. Roberts: Why do you think that?

Dr. Ambrose: Because at autopsy, you do not see individuals with unstable angina except for those who die. Among a consecutive series of patients with a clinical diagnosis of unstable angina pectoris referred for angiography, we found that 50% to 70% had suspected culprit lesions that were either ruptured plaque or thrombus.[66]

Dr. Roberts: The key word you used is "suspected."

Dr. Ambrose: Their angiographic characteristics suggested this diagnosis based on the postmortem histologic-angiographic analyses of Levin and Fallon.[67] Another pathologic view on the relation between cardiac sudden death and ruptured plaque came from Davies and Thomas[68] in 1984. Analyzing 3-mm coronary artery segments, they found an occlusive thrombus in most cases. Whether occlusive thrombus is present may depend on patient selection.

Dr. Roberts: Slicing coronary arteries at 3-mm segments is not easy. That's why I cut them into 5-mm segments. Those investigators did not look at the entire lengths of the 4 major coronary arteries, only selected segments.

Dr. Stone: There is a large body of evidence, much of it pathologic studies generated by Falk, Davies, and Virmani, showing about 70% of patients with sudden cardiac death have a ruptured thin-capped fibroatheroma. Some very elegant Japanese studies using angioscopy during acute myocardial infarction have shown the presence of thrombus in almost 100% of patients. I believe that we have good evidence for thrombus in most patients with acute coronary syndromes, but its appearance decreases with progression of the acute event. What is underestimated, however, is the overall plaque severity in these patients.

Dr. Roberts: By "plaque severity," you mean the degree of arterial luminal narrowing?

Dr. Stone: I refer to the greater degree of plaque burden, or cross-sectional area of the plaque, which ultimately encroaches on the arterial lumen itself. The more severe any individual lesion appears, as determined by coronary angiogram, the more likely it is to progress to total occlusion. Ambrose, Smith, and others have proposed that there are so many more angiographically mild to moderate lesions that, collectively, they are the ones that are more likely to occlude and cause cardiac events because they do not have collaterals that only form around hemodynamically significant lesions. Plaques most likely to rupture are those with positive remodeling, a large plaque burden with lipid-rich plaques, thin fibrous cores, few smooth muscle cells, a lot of macrophages and activated T cells—especially in the margins of the cap—and more type I collagen than type III collagen. Thus, with greater plaque burden, plaque vulnerability is increased.

Dr. Willerson: Bill Roberts's emphasis on plaque burden is accepted. I would like to add a "real-life" aspect. I believe that the *duration* of thrombosis and vasoconstriction are related to the clinical event. There is substantial evidence in both human and nonhuman models that endothelial injury of *any* type may cause transient thrombosis, which I believe characterizes unstable angina pectoris. Something has changed about the vascular endothelium: erosion, rupture, or some other reason for increased adherence of platelets in conjunction with white blood cells, transiently occluding or severely narrowing the coronary artery. With thrombus formation, there is always some vasoconstriction, because platelets release substances that dynamically constrict an artery, including thromboxane, serotonin, and adenosine phosphate. When this is brief—say 3 to 15 min-

utes—there is not likely to be myocardial injury. Platelet aggregation promotes this kind of cyclic flow phenomenon due to transient, dynamic reduction in flow based on transient thrombosis and coronary vasoconstriction, followed by dislodgement of the platelet plug and relief of vasoconstriction, which recurs over and over. I think that is what unstable angina pectoris is. When the thrombus remains a little longer, however—say 30 minutes or more—subendocardial injury occurs. This is a non-Q-wave myocardial infarction. When examined angiographically or by ultrasound, a lesser incidence of an occlusive thrombus is found with unstable angina and non-Q-wave non-ST-segment elevation myocardial infarction, which we used to call "nontransmural myocardial infarction." With progression to electrocardiographic ST-segment elevation, an occlusive thrombus is invariably present, along with persistent vasoconstriction, causing the injury to progress from the inner myocardial wall to the outer wall. That is an ST-segment elevation myocardial infarction, which is the target for acute thrombolytic therapy or percutaneous coronary intervention. Thus, it is not surprising that at postmortem examination, a coronary artery thrombus is not found in patients with unstable angina or the non-ST-segment elevation infarction, because both are evanescent events and findings at necropsy would depend on when the patient was necropsied relative to the time of death. It would not take long to occlude a coronary artery and cause death in a person with a heavy plaque burden, especially patients with prior cardiac injury and susceptibility to cardiac ventricular arrhythmias. Thus, I believe what Bill Roberts has found in his studies is entirely consistent with the observations of others.

Another intriguing aspect is the observation by Kolodgie and associates[10] of increased hyaluron concentration in the arteries of some of these patients, especially women, who have plaque erosions and die suddenly without thrombosis or with thrombosis but without frank rupture. There may be alterations in the coding of lipids, hyaluronan, and glycolipids that, in a setting of intense plaque burden and very narrow coronary arteries, might promote in situ thrombosis.

Dr. Ambrose: Blood thrombogenicity is probably an important determinant of whether plaque rupture or erosion leads to an acute coronary event. There are many ways in which inflammation and thrombosis are interrelated. While the end result is a thrombotic event, inflammation not only fuels what happens in the plaque, but through multiple mechanisms inflammation may promote thrombosis.

Dr. Roberts: There is no question that platelet aggregation is real, but I have difficulty diagnosing plaque erosion at autopsy. Clot formation may occur *all* the time, and I believe clotting plays a major role in plaque development in the first place. A vivid example is a patient with mitral stenosis who underwent surgery at the National Institutes of Health. He had a huge thrombus that filled the body of the left atrium. Twenty years later he died, and there was no thrombus in the left atrium, but there were atherosclerotic plaques covering the left atrial endocardial wall, pointing to a situation that started with a thrombus and ended with plaque.

Dr. Friedewald: What is the role of vasoconstriction?

Dr. Willerson: Thrombosis and vasoconstriction go together. Thrombus cannot develop without local enhanced vasoconstriction because as platelets aggregate, part of the initial nidus of the thrombus, they release several different substances, such as thromboxane, serotonin, and adenosine phosphate, which promote vasoconstriction. Thrombin is not platelet derived, but it accumulates at sites of vascular injury. These are powerful vasoconstrictors. The reason that clopidogrel adds to the protective effect of aspirin is that it inhibits adenosine phosphate, while aspirin inhibits only thromboxane and inflammation. The IIb/IIIa receptor antagonists inhibit most, but not all, of the platelet-derived vasoconstriction mechanisms. The important point is that thrombus cannot form without enhanced vasoconstriction.

Dr. Friedewald: Bill pointed out that most coronary plaques are very fibrotic, often calcified. Are areas of arteries containing such "hard" plaque capable of vasoconstriction?

Dr. Willerson: Much less, I think, although ruptured plaques associated with calcified nodules in plaques have been seen.

Dr. Stone: I believe that circumferential or heavily calcified coronary lesions are relatively protected from rupture and sudden rapid lesion progression. Calcified walls could be regarded as a "biological stent," although calcified plaques can slowly progress. Such calcified lesions develop after years of atherosclerosis, sometimes after multiple plaque ruptures with high shear stress. Low shear stress probably promotes plaque rupture, and high shear stress promotes atherosclerosis progression.

Dr. Friedewald: John, why do you place "vulnerable plaque" within quotations in your writings?[69,70]

Dr. Ambrose: Because I do not know what a vulnerable plaque really *is*. We *presume* a vulnerable plaque is, in most cases, a thin-capped fibroatheroma with a lipid or necrotic core and many inflammatory cells. Because we do not have natural history studies, we cannot be sure, and until we are certain, I recommend using either the phrase *presumed vulnerable plaque* or placing it within quotation marks.

Dr. Friedewald: Greg Stone, tell us about the PROSPECT (Providing Regional Observations to Study Predictors of Events in the Coronary Tree) study, which may provide us the natural history information about the vulnerable plaques.

Dr. Stone: PROSPECT is the first prospective multimodality imaging natural history study designed to identify vulnerable coronary plaques in patients who are at risk for acute cardiac events. PROSPECT involves 700 patients presenting with acute coronary syndrome, almost all of whom had a non-ST-segment elevation myocardial infarction or recent ST-segment elevation myocardial infarction and were treated with coronary angioplasty, "stabilizing" their entire coronary artery tree. Thus, all acute culprit lesions and hemodynamically significant lesions will be treated, so the patients will have been made stable and no further revascularization would be required. All patients are treated with aspirin, thienopyridine, and statins in high dose, as well as other usual standards of care therapies. The patients will be followed for 2 to 5 years.

This study is unique in that we have developed a methodology to analyze the coronary angiograms on a millimeter-by-millimeter basis. For every artery that is approximately $\geq$1 mm in diameter, we record complete quantitative and quali-

tative data regarding the reference vessel diameter, minimal lumen diameter, diameter stenosis, whether a lesion is present, the lesion length, and >30 qualitative characteristics of the lesions. We also perform 3-vessel intravascular ultrasound imaging of the proximal 6 to 8 cm of all 3 major coronary arteries after the stenting or angioplasty, so ultrasound was performed *after* the coronary artery tree was stabilized. Both grayscale intravascular ultrasound (IVUS) and radiofrequency IVUS—so-called virtual histology, which allows us to see the different plaque types—are utilized. These include thin-cap fibroatheromas, thick-cap fibroatheromas, fibrotic disease, fibrocalcific disease, intimal thickening, and minimal plaque. We also collect blood at 3 different time points (in hospital, 30 days, and 6 months) and assess several different biomarkers: soluble CD40 ligand, C-reactive protein (CRP), myeloperoxidase, and interleukin-6. We collect all the basic demographics as well as metabolic syndrome measurements: fasting glucose, insulin, hemoglobin A_{1c}, and waist circumference.

In PROSPECT, we follow patients to (1) see what percentage of them have the so-called rapid lesion progression leading to stable angina pectoris, unstable angina, acute myocardial infarction, or death and (2) correlate characteristics of lesions when first studied to determine which lesions place patients at increased risk for coronary events. Other baseline clinical, demographic, hematologic, angiographic, ultrasonic, and virtual histology data also will be correlated to events. In a subset of patients, palpography and multislice computed tomographic imaging will be employed. At this time, we have completed enrollment and the baseline analysis. We are not going to report the data until we see 100 events that are associated with nonculprit lesions (that is, not the original lesion that was treated but subsequent unanticipated lesions) and we have the complete analysis. We are in the follow-up phase now, and the 2-year follow-up will be complete in June 2008.

Dr. Friedewald: What have you found so far?

Dr. Stone: We are finding thin-cap fibroatheromas in approximately 1/3 of patients who have not been treated. We are finding a lot of plaque left behind, and about 40% of patients have severe stenosis using intravascular ultrasound criteria of a minimal luminal area of <4 mm, which strongly correlates with reduced coronary flow reserve and positive functional testing. It may be that some so-called vulnerable plaques are severe atherosclerotic lesions that progress to rupture because of shear stress or vasoconstriction or because of typical plaque rupture. There is some, but not complete, overlap between virtual histology thin cap fibroatheromas and the severe lesions.

Dr. Ambrose: This is the first big step in elucidating the natural history of these lesions.

Dr. Roberts: Who is sponsoring PROSPECT?

Dr. Stone: Abbott Vascular. Ultimately, we hope PROSPECT will provide the impetus for systemic, focal, or regional therapies, but those are a long way off. PROSPECT is mainly a fact-finding study.

Dr. Friedewald: Why do systemic factors, such as inflammation, cause only a *few* plaques to become "vulnerable" when, presumably, *all* plaques have similar exposure to systemic factors?

Dr. Stone: We do not have an answer to that question. It may have to do with shear stress and other environmental and hemodynamic factors that predispose thin-cap fibroatheromas to form in certain portions of the coronary tree. They tend to locate in the proximal 3 to 4 cm of the coronary tree near arterial branch points and bifurcations where there is a lot of nonlaminar flow, which may predispose to the formation of abnormal underlying microarchitecture. Those areas may be more prone to inflammation, which can lead to rupture of the thin cap. This thesis is speculative.

Dr. Ambrose: In some situations it has to do with the plaque itself. When blood comes into contact with the undersurface of a plaque that has eroded or ruptured, the ultimate result is determined by what is happening at that time in the patient. Is it in the early morning hours, when platelets are more sticky? Did the patient just smoke a cigarette, making his or her platelets sticky? Was the fibrinogen level elevated due to smoking or an inflammatory state? Thrombogenicity, or what is also referred to as "vulnerable blood"—the balance between the procoagulant, anticoagulant, antifibrinolytic, and profibrinolytic forces of the blood—is an important factor determining whether plaque rupture or erosion heals silently or progresses to an acute coronary event.

Dr. Friedewald: Does aspirin make plaques less "vulnerable"?

Dr. Ambrose: This alludes to the concept of "the vulnerable patient." As physicians, we do not treat plaques, we treat patients. In both primary and some secondary prevention trials, aspirin reduces the subsequent incidence of myocardial infarction.[71] The mechanism is probably related to a reduction of blood thrombogenicity due to reduced platelet activation or platelet aggregation and possibly an anti-inflammatory effect, so asymptomatic ruptures *remain* asymptomatic and do not lead to clinical events.

Dr. Friedewald: Does hypertension cause increased plaque vulnerability?

Dr. Ambrose: There are data suggesting that symptomatic plaque ruptures leading to clinical events tend to occur after stressful exercise and in people who are not athletic.[71] The presumed mechanism is that their blood pressure and heart rate—the double product—goes up rapidly, predisposing a vulnerable plaque to disruption.

Dr. Friedewald: Does plaque vulnerability differ between genders?

Dr. Stone: Among patients who die of either coronary thrombosis or sudden death, more women tend to have the erosive plaque subtype than the thin-cap fibroatheroma. Women tend to initially present with acute coronary events a decade or more later than men. There also are hormonal and genetic factors for plaque vulnerability. Cigarette smokers initially present with coronary events about a decade earlier than nonsmokers. They tend to have a more isolated, focal form of coronary atherosclerosis, a greater thrombus burden in general, and more erosive disease.

Dr. Roberts: In the quantitative studies in which I have been involved, the entire length of the right, left anterior descending, left circumflex, and left main coronary arteries were examined, and there was no difference among patients with fatal coronary events in degrees of luminal narrowing or in plaque composition between women and men.[61]

Dr. Ambrose: What intravascular ultrasound has taught is that what is believed to be angiographic "focal" disease is not truly isolated coronary artery disease.[13]

Dr. Roberts: Isolated coronary disease is a myth. There are no such things as "1-vessel disease" and "2-vessel disease."[72] Plaque is in *all* of the epicardial coronary arteries if it is in 1 of them. Furthermore, the quantity of plaque in patients with acute myocardial infarction is similar in *all* the major epicardial coronary arteries *regardless* which coronary artery contains a thrombus.[28]

Dr. Friedewald: Among persons with comparable severe artery coronary disease, why do some persons have acute myocardial infarction, some have sudden cardiac death, some develop chronic stable angina pectoris, and others do not have any coronary event? Does the concept of "vulnerable plaque" help address this heterogeneity of clinical manifestations of coronary artery disease?

Dr. Ambrose: There are few answers. If myocardial infarction or sudden death is caused by coronary thrombus, a focal manifestation of a systemic process, the concept of "vulnerable plaque" is reasonable. Whether a myocardial infarction leads to a fatal arrhythmia within the first 5 minutes after thrombosis occurs or 2 hours later may involve other factors. When coronary thrombosis is the cause of sudden death, ventricular fibrillation is usually the terminal event, but why this occurs is not necessarily addressed by the vulnerable plaque concept. A presentation with ventricular fibrillation versus coronary thrombosis presenting as acute myocardial infarction probably has much to do with what is happening in the myocardium at the time of the acute event. Ingestion of fish oil, for example, may raise the myocardial threshold for ventricular fibrillation. Epidemiologic data from societies with high fish oil consumption show a lower prevalence of sudden cardiac death and/or cardiovascular mortality in those populations.

Dr. Stone: I believe that the "vulnerable plaque" paradigm *partly* addresses the issue of variable presentations of coronary artery disease. It does not, however, address the questions of why vulnerable plaque develops in some patients and not in others, why it might develop early, and why it might simultaneously develop in 2 or more locations in the coronary arterial tree versus only 1 location. The answers may lie in genetic influences, hormonal factors, and other systemic perturbations that we do not understand. Many years ago, I read a letter to a medical journal describing a person who was a pathologic egg eater—30 to 40 eggs a day for >30 years—and he developed acute chest pain requiring coronary angiography. He had totally clean coronary arteries. This case may point to genetic influences that are very strong in the development of vulnerable plaque. Once a vulnerable plaque develops, however, what causes it to rupture? Is it just statistical phenomenology, or is it due to some secondary factor such as systemic inflammation? Some such secondary factors may be treatable with anti-inflammatory therapies, high-dose statins, or newer drugs that raise the high-density lipoprotein cholesterol.

Dr. Roberts: One of the reasons for the popularity of the "vulnerable plaque" concept is that we seek to explain acute coronary events. How do you explain a patient who has stable angina pectoris once a week for a couple of years and then suddenly has recurrent rest pain every few hours? Something has happened. The concept of ruptured plaque is inviting as an explanation. In *my* experience, however, ruptured plaque applies only to acute myocardial infarction, not to sudden coronary death or to unstable angina pectoris, and 70% of patients with acute myocardial infarction have thrombus superimposed on ruptured plaque. The other 30% have thrombus superimposed on plaque without underlying rupture. Maybe erosions were present, but I find erosions very difficult to be certain of by microscopy. What explains sudden death outside of the hospital? I have seen a lot of these cases, and *never* a ruptured plaque or a totally occluding thrombus.

Dr. Stone: What you are describing, Bill, is consistent with others' observations that about 70% have ruptured thin-cap fibroatheromas. In the other 30% of cases they are called *plaque erosions*, which require special stains to see. We have a lot more to learn about that 30% subset.

Dr. Roberts: Let us assume that there is plaque erosion. If thrombus does not form on top of it, does anything else happen? I have never seen an occlusive thrombus in a patient with sudden coronary death. Some say, "They died too soon to develop acute myocardial infarction." In the Seattle study, however, where they resuscitated many sudden cardiac arrest patients outside the hospital, only 50% proceeded to have an acute myocardial infarction in the hospital. I have never seen a ruptured plaque in unstable angina pectoris except in cases after coronary angioplasty or coronary artery bypass surgery. Acute myocardial infarction is the only coronary subset in my experience where the thrombus superimposed on a plaque actually totally occludes the lumen. It is likely that most of us in the high-cholesterol environment are forming small mural thrombi frequently and they organize into plaques.

Dr. Ambrose: The difference between sudden death and other acute syndromes is due to patient selection, the definition of the acute syndrome, and where the patient has been studied, at autopsy or at angiography. In our original angiographic work, we defined unstable angina pectoris according to the Braunwald classification that included patients with either a new onset of rest pain or an acute change in the frequency of angina.[73] Among these patients with unstable angina pectoris who had coronary angiography, we identified severe single lesions that had certain angiographic characteristics.[5] In another study involving patients who had coronary angiograms on 2 separate occasions, the first when they had stable angina pectoris and the second when they met the criteria for unstable angina, we found at least 1 new lesion by angiography (based on qualitative analysis) hypothesized as representing plaque rupture or thrombus.[74] This finding was subsequently corroborated in other angiographic studies and by other imaging modalities.[75]

Dr. Roberts: Patients who die suddenly outside the hospital have a *huge* amount of coronary artery narrowing. The *same* amount of coronary narrowing by plaque only occurs in patients with acute myocardial infarction, but in the latter cases thrombus is present. I believe that there is a fine line between adequate and inadequate myocardial oxygenation. A small increase in myocardial oxygen demand can tip the scales into an acute cardiac event. There does not have to be something "new" in a coronary artery for sudden death to occur.

Dr. Stone: Sudden cardiac death has a mix of causes. Some are primary arrhythmic events solely due to increased myocardial oxygen demand exceeding supply and others are due to plaque rupture with myocardial infarction and a ventricular arrhythmia.

Dr. Ambrose: What is found depends in part on patient selection. Patients with baseline significant left ventricular dysfunction should not be included in this group, as their terminal event does not require coronary thrombosis as a precipitating event.

Dr. Friedewald: Do you order a C-reactive protein on your patients who have had coronary events, and if so, how does that measurement influence your treatment?

Dr. Stone: I currently measure CRP mainly for research purposes. Whether drugs such as statins, which reduce CRP levels independent of their effects on serum cholesterol, have an additive effect in preventing cardiac events is unclear.

Dr. Friedewald: Where do we go from here with the "vulnerable plaque" concept?

Dr. Stone: This is an exciting time in the field of atherosclerosis because our understanding of the etiology and pathophysiology of atherosclerosis is advancing rapidly. We need to learn why atherosclerosis develops, why plaques rupture, underlying plaque phenotypes, genotypes, and systemic conditions that lead to rupture or development of coronary thrombosis for the non-rupture-prone plaques. Then we can develop more effective preventative strategies. We are in a time of a true technology explosion, both in imaging and therapeutic modalities. We have the *tools* to identify many of the individual components of vulnerable plaques, but we lack *validation*. Eventually, our therapies will have a high enough therapeutic-to-side-effect ratio that we can consider focal therapies such as stenting or regional therapies such as photodynamic therapy or cryotherapy or other newer investigational systemic therapies. The vulnerable plaque field has turned the corner, and in the next 5 to 10 years, we will see significant discoveries leading to true therapeutic advances.

Dr. Ambrose: What we also need is the ability to better identify the high-risk patient, especially in primary prevention. We stratify risk based on how many known risk factors an individual has, but we need additional information to identify the patients who are at highest risk for a first coronary event. Another issue is the future role of focal or regional treatment of the vulnerable plaque if it can be identified.

Dr. Willerson: We need to know more about the genetics and proteomics of patients at high risk for vascular events. Serum lipids are important, but there is a genetic risk that runs through this that is probably the major risk factor for premature heart attack. Recently, a region on chromosome 9 was identified—and it does not appear to be a standard gene—associated with a 40% increased risk of vascular events.[76] It is being studied carefully now, including ways to protect people who have this chromosomal alteration. There are at least 8 other genes that have been identified by people around the world—we have contributed 4—which, when present in a family member, add to the risk of heart attack and stroke. These are *additive* to the predictability of the chromosome 9 region. We do not, however, know anything about the proteins that are formed as a result of these genetic alterations. Ultimately, such genetic alterations will be measured clinically, and I believe there will be several different alterations that vary from family to family. The genetic approach will allow us to focus on high-risk patients much earlier. I also am optimistic that we are going to develop noninvasive ways to identify arterial inflammation. We have to get beyond just the catheter definition of a plaque and be able to noninvasively study all major arteries. I think we are going to reach a point where we can identify dangerous lesions and vulnerable patients. Finally, the "vulnerable *patient*" still needs attention as we assess the various risk factors.

Dr. Roberts: I believe in *preventing* plaques, so we do not have to worry about whether they are "vulnerable" or "nonvulnerable." The pharmaceutical industry has given us fantastic lipid-lowering drugs. The statin drugs are miracle drugs: they are to atherosclerosis what penicillin was and is to infectious disease. Yet, there are about 120 million Americans with low-density lipoprotein serum cholesterol levels $>$100 mg/dl, and only 13 million of those persons are being treated with statins. I see no reason not to start these drugs much earlier in life, at least in men, than is presently done, and if they were, fewer plaques would develop.

Dr. Friedewald: Thank you.

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