JACC: CARDIOVASCULAR IMAGING
VOL. 4, NO. 8, 2011

ISSN 1936-878X/$36.00
PUBLISHED BY ELSEVIER INC.
DOI:10.1016/j.jcmg.2011.06.006

EDITORIAL COMMENT

The Reality of Vulnerable Plaque Detection*

Gregg W. Stone, MD, Akiko Maehara, MD, Gary S. Mintz, MD
New York, New York

It is proposed that the initial step in the process leading directly to coronary thrombosis is the development, with advancing age, of what can be termed a "vulnerable atherosclerotic plaque."
—Muller et al. (1)

Coronary atherothrombosis is the leading single cause of death in the United States and Europe. Since the original description of angina by Heberden in 1772 (2), great strides have been made toward elucidating the processes that result in the development and progression of atherosclerosis.

See page 894

The lesion substrate prone to thrombosis was termed "vulnerable plaque," initially defined functionally as "the susceptibility of a plaque to rupture" (1). As described from human autopsy studies, atherosclerosis progresses from a benign phenotype (most typically pathological intimal thickening) to the more ominous fibroatheroma, characterized by a large necrotic core containing free cholesterol crystals and cholesterol esters (3). As the plaque becomes more inflamed and metabolically active, the fibrous cap becomes infiltrated with macrophages and T-lymphocytes, smooth muscle cells become depleted, the ratio of type I to type III collagen increases, and the fibrous cap thins, becoming a rupture-prone thin-cap fibroatheroma (TCFA). Less commonly, the vulnerable plaque phenotype may be represented by an erosion-prone proteoglycan-rich lesion or a calcific nodule. Regardless, the precipitating clinical event is arterial thrombosis, which, depending on the underlying plaque severity and the efficacy of the body's endogenous fibrinolytic system, results in a clinical spectrum of presentations ranging from sudden cardiac death due to coronary occlusion to an asymptomatic event with plaque progression.

A more clinically relevant definition of a vulnerable plaque is a lesion that places a patient at risk for future major adverse cardiac events (MACE), including death, myocardial infarction, or progressive angina. The identification of such plaques before they become symptomatic would afford prognostic stratification and facilitate primary prevention (e.g., aspirin, statins, and risk factor modification), perhaps one day including prophylactic focal or regional coronary therapy. Ironically, an advanced understanding of plaque vulnerability has been hindered for more than 2 decades by the very tool that until recently was considered the gold standard for the diagnosis of ischemic heart disease, namely, coronary arteriography. Intravascular ultrasound (IVUS) has exposed the major limitations of angiography, first and foremost the fact that the angiographic representation of the coronary lumen obscures the true plaque burden, leading to an underestimation of plaque severity (4). Because of this, serial retrospective angiographic studies suggested that most lesions that caused future myocardial infarctions were mild in severity (5), an observation at odds with earlier prospective studies showing that more severe angiographic stenoses were more likely to occlude (6), and pathological studies demonstrating that plaques that caused myocardial infarction and sudden death tended to have a large plaque burden (3).

*Editorials published in *JACC: Cardiovascular Imaging* reflect the views of the authors and do not necessarily represent the views of *JACC: Cardiovascular Imaging* or the American College of Cardiology.

From Columbia University Medical Center and the Cardiovascular Research Foundation, New York, New York. Dr. Stone is a consultant to Abbott Vascular, Medtronic, Boston Scientific, Volcano Corp., and InfraReDx. Dr. Maehara has received a research grant from Boston Scientific, and honoraria from Volcano Corp. Dr. Mintz is a consultant to Volcano Corp., Boston Scientific, and St. Jude.

In order to identify lesion and vessel characteristics that place patients at risk for future MACE, more than 2 dozen invasive and noninvasive technologies have been developed to characterize the compositional, physical, cellular, and biochemical signatures specific to pathological vulnerable plaque. Given their proximity to the plaque, intravascular catheters have the inherent advantage of a high signal-to-noise ratio, and 3 such imaging tools have emerged for clinical use: radiofrequency IVUS, optical coherence tomography, and near-infrared spectroscopy. Each imaging technique produces a graphical representation of the vessel wall with purported "vulnerable" characteristics, the accuracy of each having been validated to a greater or lesser degree against human histology. However, prior to clinical use of these tools, the image patterns that each generate must be validated to predict future MACE with reasonable sensitivity and specificity. In this regard, the PROSPECT (Providing Regional Observations to Study Predictors of Events in the Coronary Tree) study (7) was a multicenter, multimodality imaging study to prospectively characterize the coronary tree with 3-vessel intravascular imaging, and map subsequent events to untreated (nonculprit) lesions versus previously treated culprit lesions. Performed in 697 patients at 37 sites in the United States and Europe, the PROSPECT study prospectively characterized 3,160 nonculprit lesions, demonstrating by multivariable analysis that the 3 independent baseline predictors of future nonculprit-lesion–related MACE during a median follow-up of 3.4 years were a large plaque burden, a small lumen area, and a TCFA as classified by radiofrequency IVUS (VH-IVUS). Of note, the lesions fated to cause future MACE were mild at baseline by angiography (mean diameter stenosis of 32 ± 21%), but not by IVUS (mean plaque burden of 67 ± 10%), and progressed substantially to the time of the follow-up MACE (to an angiographic mean diameter stenosis of 65 ± 16%).

The ability to detect vulnerable plaque has significant implications for future research and clinical care, and the results from any single study, no matter how robust, should be replicated before being accepted. In this regard, the findings from the VIVA (VH-IVUS in Vulnerable Atherosclerosis) study are noteworthy. As reported by Calvert et al. (8) in this issue of *iJACC*, 3-vessel VH-IVUS was performed in the coronary arteries of 170 patients (1,096 lesions) with stable or unstable ischemic heart disease. At a median follow-up of 1.7 years, the strongest univariate correlates of future nonculprit-lesion–related MACE were large plaque burden, small lumen area, remodeling index, and a TCFA as classified by VH-IVUS. Although there are several important differences between PROSPECT and VIVA (multicenter vs. single center, 697 vs. 170 patients, inclusion of stable angina patients in VIVA, slightly different definitions of TCFA and MACE, different durations of follow-up, among others), the consistency of the findings with PROSPECT validate not only the clinical utility of VH-IVUS to detect vulnerable plaques, but also the concept itself, as a pathological and clinical entity, as linked by the imaging tool.

For certain, more information is required from VIVA, and several limitations deserve mention. Surprisingly, neither the clinical characteristics, angiographic findings, nor the pharmacological treatments of the patient cohort are reported in the paper. Greater details about the patient-level plaque characterization and adjudication processes are necessary. The number of nonculprit events is too few to support multivariable analysis without model overfitting, and although the frequency of death and myocardial infarction were comparable to PROSPECT, detailed data on the rates of rehospitalization and recurrent angina are not provided. Moreover, both VIVA and PROSPECT leave several important questions unaddressed:

1. What is the temporal stability of vulnerable plaque (9)? Neither study incorporated routine angiographic or intravascular imaging follow-up so as to not disrupt the natural history experiment.
2. How should VH-IVUS TCFAs be treated (and by corollary, should we screen for their presence)? Randomized trials to address these issues will be difficult and costly.
3. Can the findings from VH-IVUS be used to guide drug development? In this regard, the observation that the lipoprotein-associated phospholipase A2 (Lp-PLA2) inhibitor darapladib halted necrotic core expansion in patients with acute coronary syndromes and coronary artery disease was 1 of the motivating forces for the large-scale randomized STABILITY (Stabilization of Atherosclerotic Plaque by Initiation of Darapladib Therapy) trial (10).
4. Can the accuracy of core laboratory–based VH-IVUS lesion characterization be replicated at clinical sites? Automated edge-detection and pattern recognition software is required to reduce interobserver variability.
5. Is the accuracy of other imaging tools to detect vulnerable plaque as good as or better than

VH-IVUS? Optical coherence tomography and near-infrared spectroscopy each require their own natural history study for validation, ideally compared with each other and VH-IVUS.

6. And finally, what is the utility of noninvasive atherosclerosis imaging with multidetector computed tomography and magnetic resonance imaging? Such tools should be preferable for primary screening of high-risk, asymptomatic patients, reserving catheter-based plaque assessment for confirmation, and for secondary screening after symptomatic patient presentation (as applied in PROSPECT and VIVA).

In summary, although a complete understanding of the etiology and mechanisms of atherothrombosis remains an elusive goal, VH-IVUS has been validated as a tool capable of providing incremental discrimination to identify patients and lesions at risk for future MACE. It is our hope that this fundamental knowledge will provide the foundation to develop new therapies to prevent acute myocardial infarction and sudden cardiac death.

Reprint request and correspondence: Dr. Gregg W. Stone, Columbia University Medical Center, the Cardiovascular Research Foundation, 111 East 59th Street, 11th Floor, New York, New York 10022. *E-mail: gs2184@columbia.edu.*

REFERENCES

1. Muller JE, Tofler GH, Stone PH. Circadian variation and triggers of onset of acute cardiovascular disease. Clinical Progress Series. Circulation 1989;79:733–43.
2. Heberden W. Some account of a disorder of the breast. Med Trans Roy Coll Physicians 1772;2:59–67.
3. Virmani R, Kolodgie FD, Burke AP, Farb A, Schwartz SM. Lessons from sudden coronary death: a comprehensive morphological classification scheme for atherosclerotic lesions. Arterioscler Thromb Vasc Biol 2000;20:1262–75.
4. Topol EJ, Nissen SE. Our preoccupation with coronary luminology. The dissociation between clinical and angiographic findings in ischemic heart disease. Circulation 1995;92:2333–42.
5. Ambrose JA, Tannenbaum MA, Alexopoulos D, et al. Angiographic progression of coronary artery disease and the development of myocardial infarction. J Am Coll Cardiol 1988; 12:56–62.
6. Ellis S, Alderman E, Cain K, et al. Risk of anterior myocardial infarction by lesion severity and measurement method of stenoses in the left anterior descending coronary distribution: a CASS registry study. J Am Coll Cardiol 1988;11:908–16.
7. Stone GW, Maehara A, Lansky AJ, et al. A prospective natural-history study of coronary atherosclerosis. N Engl J Med 2011;364:226–35.
8. Calvert PA, Obaid DR, O'Sullivan M, et al. Association between IVUS findings and adverse outcomes in patients with coronary artery disease: the VIVA (VH-IVUS in Vulnerable Atherosclerosis) study. J Am Coll Cardiol Img 2011;4:894–901.
9. Kubo T, Maehara A, Mintz GS, et al. The dynamic nature of coronary artery lesion morphology assessed by serial virtual histology intravascular ultrasound tissue characterization. J Am Coll Cardiol 2010;55:1590–7.
10. White H, Held C, Stewart R, et al. Study design and rationale for the clinical outcomes of the STABILITY Trial (STabilization of Atherosclerotic plaque By Initiation of darapLadIb TherapY) comparing darapladib versus placebo in patients with coronary heart disease. Am Heart J 2010;160:655–61.

Key Words: acute coronary syndromes ■ acute myocardial infarction ■ atherosclerosis ■ vulnerable plaque.