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EDITOR'S PAGE

Vulnerable Plaques: From PROSPECT to Prospects…

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Modern cardiology can definitely pride itself for developing techniques designed to restore blood flow in coronary arteries with tight lesions that cause myocardial ischemia or in the aftermath of an acute myocardial infarction (MI). However, despite the advances in diagnosis and intervention, a substantial number of patients continue to suffer acute adverse events. This population of at risk patients, much larger than those presenting with overt ischemia, are at present a blind spot for cardiologists. We do not know which of the patients will suffer an event nor do we know when one will have one. While imaging has allowed us to see pathology and risk in fascinating detail, it has, however, not kept up as well for timely identification of near term risk or to be able to triage patients with need for prophylactic intervention. This is one area where technology, both for detection or treatment, has remained rather inadequate.

It was with this very intention that the PROSPECT (A Prospective Natural History of Coronary Atherosclerosis) study was designed; this study prospectively included nearly 700 patients presenting with acute coronary syndromes (ACS) who underwent a 3-vessel intravascular ultrasound (IVUS) imaging after uneventful 1- or 2-vessel percutaneous coronary intervention (PCI) to characterize both the originally-treated (culprit) lesions or unmanipulated (nonculprit) lesions (NCL) that might be associated with subsequent risk for major adverse cardiac events (MACE). From the proximal part of all 3 major coronary arteries, more than 3,000 NCL were identified by IVUS with a plaque burden of ≥40% (1). Patients were prospectively followed with the goal of determining the le-

sion characteristics predictive of future events. By 3 years, a new MACE had occurred in 20% of patients, nearly one-half of them arising from the NCL.

PROSPECT also collected a bounty of other clinically important data, beyond what was available at first publication. Some of these data were confirmed, for the first time in vivo, what was known or suspected from other sources, mainly postmortem pathology. Yet other data provided new insights into behavior of nonculprit vessel plaque. Because the ability to image and detect vulnerable plaque has significant implications in clinical care, PROSPECT deserves an in-depth analysis. This supplement, being sent with the current issue of *iJACC*, summarizes much of these additional insights from the PROSPECT study. While the supplement was supported by the Cardiovascular Research Foundation and publication of this supplement was made possible with unrestricted educational grants from Abbott Vascular and Volcano Corporation, the peer review process for these papers was exactly the same as for regular *iJACC* papers and completely independent from any input from these entities.

Can We Identify Vulnerable Plaques by Invasive Imaging?

Most NCL events arose from originally mild angiographic stenosis; a mean angiographic diameter stenosis of 30% at baseline evolved to 65% at the time of an event. Almost all MACE presented with severe progressive or unstable angina amenable to PCI, and not death or MI. Significant independent predictors of NCL-associated MACE included plaque burden ≥70% (hazard ratio [HR]: 5), thin-cap fibroatheroma (TCFA) by IVUS described as necrotic core abutting lumen (NCAL) (HR: 3), and a minimal lumen area ≤4.0 mm^2 (HR: 3); presence of 2 of 3 characteristics was asso-

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ciated with a 10% likelihood, and all 3 characteristics with an 18% likelihood of a 3-year MACE rate as compared to only 0.3% in NCL that lacked these 3 characteristics. In essence, the plaques likely to cause future coronary events were typically severe, with a large plaque burden and/or a small minimal lumen area and IVUS-verified NCAL (2). In fact, no events arose from coronary segments with <40% plaque area involvement.

Should We Routinely Image to Identify Vulnerable NCL During PCI?

At the first glance, the results of PROSPECT indicate that the criteria for vulnerable plaque detection were in fact identified and perhaps could be used to define plaques at risk for future events. While the combination of 3 characteristic NCL features conferred an HR of 11, almost 90% of patients with similar plaques did not have a MACE during the 3-year follow-up. Thus, even though these criteria offered the markers for overall coronary risk, their accuracy for identifying risk to the patient from any one particular plaque was not high enough. The overall hard event rates (death, MI) attributed to NCL were surprisingly low; most NCL events consisted of hospitalizations for progressive or unstable angina. Thus, an equally important message of PROSPECT pertains to the remarkable outcomes that can be achieved in coronary disease patients with optimal medical therapy. And that it is not advisable to intervene for high-risk lesions even if they can be identified.

This overall low NCL event rate must also be contrasted with the price of 3-vessel invasive interrogation. In PROSPECT, eleven patients (1.6%) had complications that were directly attributable to the 3-vessel imaging procedure. These complications resulted in 3 nonfatal MI (in 0.4% of patients). From following the PROSPECT results, it becomes important that any invasive imaging procedure must be safe enough to justify its use in patients whose hard event rate is 1% over 3 years. As such, these data reinforce that currently there may be no role for intravascular imaging for the detection of vulnerable plaque in patients with symptomatic coronary artery disease. Instead the focus must be on maximization of medical therapy in symptomatic coronary disease to reduce the risk of cardiovascular events. However, recent (unpublished) data from the HORIZONS-AMI

(Harmonizing Outcomes With Revascularization and Stents in Acute Myocardial Infarction) trial suggest that such plaques in patients with ACS may not typically regress, in contrast to TCFA in patients with stable ischemic heart disease (3). If proved to be true, for proposing a local therapy in PROSPECT (2 or 3 characteristics carrying) high-risk lesions it will be necessary to demonstrate that the MACE rates of the best current drug-eluting stents are <10% at 3 years, and randomized trials will need to be undertaken.

How Representative are the PROSPECT Criteria of Vulnerability?

From the view of vulnerable plaque detection, histopathological studies have provided valuable insight in proposing the criteria important for localization of high-risk lesions using imaging modalities and assessing the potential risk for rupture. These morphological criteria that support the definition of TCFA or vulnerable plaque results from a rather simple presumption that the lesion preceding rupture should bear strong resemblance in morphology to rupture itself. A necrotic core characterizes plaque rupture with an overlying thin-disrupted cap infiltrated by macrophages; there are few or no smooth muscle cells within the cap. The thickness of the fibrous cap near the rupture site measures <25 μm, with 95% of caps measuring <65 μm. It is precisely those lesions with intact fibrous caps of <65 μm observed at other (often times multiple) sites in the coronary vasculature, in patients dying of acute plaque rupture, that are designated vulnerable plaques or TCFA. Obviously important cause-and-effect data are missing from the current paradigm because of our inability to accurately detect vulnerable plaques in humans in vivo and because of the lack of a representative animal model. Therefore, a major limitation to the vulnerable plaque paradigm exists partly because the precise mechanisms of progression from an asymptomatic stable to high-risk plaque (TCFA) that lead to rupture and thrombosis are incompletely understood. Further complicating this paradigm is the observation that plaque progression beyond 50% cross-sectional area narrowing in a vast majority of cases occurs through repeated ruptures (and healing), which occur silently; luminal narrowing in essence increases with increasing number of healed plaque

ruptures. At autopsy, only 10% of cases with acute rupture had not had a previous rupture site. Therefore, it is not clear that even if pathologically inspired vulnerable plaque could be detected they would lead to clinical events.

This issue notwithstanding, how accurate a tool is IVUS for detecting the aforementioned vulnerable plaque criteria? Perhaps the most important criteria relating to vulnerable plaque detection is accurate measurement of the fibrous cap itself, which for vulnerable plaque should be <65 μm. Because the resolution of IVUS is 150 to 200 μm, it is incapable of identifying the fibrous cap thickness component of TCFA. Another problem with IVUS–virtual histology is its failure to distinguish "lipid pool" from "necrotic core." This separation is critical to calling a lesion "fibroatheroma" or TCFA, because necrotic core (not lipid pool) is a critical feature of the latter and not the former. In fact, the IVUS–virtual histology classification of plaque morphology into such terms of pathological intimal thickening and TCFA may in fact do the field a disservice because it implies that this technology has the ability to distinguish with high accuracy different plaque types.

What Are the PROSPECTS for Vulnerable Plaque Imaging?

Although PROSPECT has offered unprecedented details of the plaque characteristics by invasive imaging technology especially pertaining to the prognostic outcomes, it is important to speculate as to where our efforts for future investigation should be focused. As indicated above, the prognosis for patients with ACS after successful PCI who are medically compliant and closely followed is favorable and a mid term hard event rate does not justify an invasive imaging procedure of nonnegligible risk. However, hundreds of thousands of people who have not been diagnosed with coronary disease and are not receiving optimal medical therapy die, arrest, or develop MI every year. Therefore, the future investigation must focus on identifying asymptomatic or minimally symptomatic patients with large plaque burden, small luminal area (and TCFA if ever possible) through noninvasive screening (4,5) so that the advantage of the intensive medical therapy could be fully obtained (6,7). Similar to what PROSPECT has done with invasive imaging, even when a noninvasive imaging strategy is able to define the subjects who are at high risk for near term events, the final question will be to identify those subjects who would benefit from noninvasive imaging. It is expected that the emerging field of biomarker analysis may be able to refine risk categories and better define those patients worthy of noninvasive interrogation for a cost effective screening.

As any excellent investigation, the PROSPECT study has produced more questions than it has answered. A very important question will be—can we get PROSPECT level data from noninvasive imaging? Furthermore, what pieces of evidence will satisfy us that noninvasive imaging can identify patients at high risk of developing MACE? It will also behoove us to ponder how will therapy be different then? What level of risk for plaque rupture and risk reduction would be needed to claim benefit with intense therapeutic intervention should noninvasive imaging make such a diagnosis possible? These exciting questions should undoubtedly be answered in the next decade of imaging if we are to impact patient care and outcomes significantly.

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