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EDITORIAL VIEWPOINT

In Search of the Vulnerable Plaque

Is There Any Light at the End of the Catheter?*

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Plaque destabilization with consequent rupture (or erosion) and superimposed thrombosis is the proximate cause of acute coronary syndromes (ACS). Although ACS treatment has advanced considerably in the past decade, the ability to detect, predict, and prevent plaque vulnerability remains elusive.

Several imaging tools have been developed to characterize morphological determinants of plaque vulnerability (1). Among these, intravascular ultrasound (IVUS) is useful for characterizing stenosis severity, plaque burden (PB), remodeling, and calcification but has low resolution and limited ability to detect plaque erosion, rupture, and thrombus. Optical coherence tomography (OCT) can characterize plaques but possesses poor penetration, thereby limiting assessment of PB and overall plaque volume, and inadequate ability to characterize plaque composition beyond lipid deposits. Although OCT may define plaque rupture, thrombus, and thin cap, it requires a bloodless field and currently lacks a fully automated and validated method for detecting lipid components. Near-infrared spectroscopy (NIRS) identifies the chemical signature of the lipid component, specifically lipid core-containing coronary plaque (LCP), but provides no information on the lumen, plaque anatomy, and status of the fibrous cap or its attenuation. OCT and NIRS can image through calcified lesions, whereas IVUS cannot. Given that progression of coronary atherosclerosis depends on multiple factors that are cumulative, interactive, and nonlinear, a single imaging technique is unlikely to reliably detect all vulnerable plaques and predict outcomes.

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The TVC NIRS imaging system (Infraredx, Inc., Burlington, Massachusetts) is an intravascular imaging tool with 510(k) Food and Drug Administration clearance for LCP detection. In this issue of the *Journal*, Oemrawsingh et al. (2) present the results of the ATHEROREMO-NIRS study, part of the ATHEROREMO (European Collaborative Project on Inflammation and Vascular Wall Remodeling in Atherosclerosis) study. This single-center substudy is the first prospective, observational, natural history study designed to evaluate the prognostic implications of NIRS-detected increased lipid content in coronary plaques. Investigators analyzed data for 203 patients who underwent coronary angiography and percutaneous coronary intervention (PCI), if indicated, of the target lesion, and NIRS assessment in a nonculprit coronary segment. During 1-year follow-up, 28 sustained a major adverse cardiac and cerebrovascular event (MACCE), including 21 nonculprit lesion (NCL)-related events. Lipid core burden index (LCBI), as assessed by NIRS, independently predicted MACCE. The investigators acknowledge important study strengths and limitations. One notable limitation not addressed is whether LCBI offered incremental prognostic utility beyond the clinical variables of history of stroke and peripheral artery disease that were associated with MACCE. They appropriately characterize their findings as hypothesis-generating given that results from any single-center study, no matter how robust, must be replicated to be accepted.

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TABLE 1 Natural History Studies of Vulnerable Plaque Using Intracoronary Imaging Tools

Trial (Ref. #)	Tool	Cohort	Follow-Up	Primary Endpoint	Death (CV Death)*	MI*	NSTE-ACS*	Stroke	Hospitalization for Angina*	PCI/CABG*	MACE*
PROSPECT, multicenter (3) (N = 697)	VH-IVUS (3 vessel)	ACS	3.4 yrs	Cardiac death or arrest, MI, or rehospitalization for angina	0	6	NR	NR	69	67	74 (3.12)
VIVA, single center (4) (N = 170)	VH-IVUS (3 vessel)	ACS + SCAD	1.8 yrs	ACM, MI, or unplanned revascularization	2	2	NR	NR	NR	14	13 (4.2)
PREDICTION,† multicenter (5) (N = 506)	VH-IVUS + ESS (3 vessel)	ACS	1 yr	Lesion progression	7 (1)	2	2	0	10	53*	5 (0.10)
ATHEROREMO-IVUS, single center (6) (N = 581)	VH-IVUS (1 vessel)	ACS + SCAD	1 yr	ACM, nonfatal ACS, or unplanned revascularization	17 (7)	5	6	0	NR	17	45 (7.7)
ATHEROREMO-NIRS, single center (2) (N = 203)	NIRS (1 vessel)	ACS + SCAD	1 yr	ACM, nonfatal ACS, stroke, or unplanned revascularization	6 (6)	NR	4	3	NR	8	21 (10.3)

Values are n or n (%/year). *Only events attributable to nonculprit lesions (NCL) are shown. †PREDICTION was not powered for MACE but for assessment of lesion progression. Revascularizations were planned in PREDICTION, and most were related to clinically asymptomatic lesions that had progressed. Data shown for MACE in PREDICTION is cardiovascular (CV) death, myocardial infarction (MI), or acute coronary syndrome (ACS).

ACM = all-cause mortality; ATHEROREMO = European Collaborative Project on Inflammation and Vascular Wall Remodeling in Atherosclerosis; CABG = coronary artery bypass graft surgery; CAD = coronary artery disease; ESS = endothelial shear stress; IVUS = intravascular ultrasound; MACE = major adverse cardiac events; NIRS = near-infrared spectroscopy; NR = not reported; NSTE = non-ST- segment elevation; PCI = percutaneous coronary intervention; PREDICTION = Prediction of Progression of Coronary Artery Disease and Clinical Outcome Using Vascular Profiling of Shear Stress and Wall Morphology; PROSPECT = Providing Regional Observations to Study Predictors of Events in the Coronary Tree; SCAD = stable CAD; VH = virtual histology; VIVA = VH-IVUS in Vulnerable Atherosclerosis.

PROGNOSTIC UTILITY

Over the past decade, several prospective longitudinal studies utilizing intravascular imaging tools have yielded substantial insights into the natural history of culprit lesion formation (3–6) (**Table 1**). These trials have evaluated catheter-based plaque assessment for confirmation and secondary screening after symptomatic patient presentation. There are important differences among the trials in terms of patient population studied: ACS versus stable coronary artery disease (CAD), number of coronary vessels assessed (1 vs. 3), definition of large PB or thin-cap fibroatheroma (TCFA), outcome measures of major adverse cardiac events (MACE, different definitions), and reporting of lesion- or patient-specific outcomes. Thus, while their results cannot be directly compared, these studies have added to our understanding of the determinants of plaque vulnerability.

Table 2 summarizes the prognostic performance of currently available intravascular imaging tools for plaque phenotyping (PB or composition) in predicting MACE. For comparison, data also are shown for noninvasive coronary computed tomographic angiography (CTA) (7) and intracoronary fractional flow reserve (FFR) assessment (8). Although all lesion characteristics were significantly associated with outcomes (except for minimum lumen area [MLA] $\leq$4.0 mm^2 in the ATHEROREMO-IVUS study [6]), the positive predictive value (PPV) ranged from 4% for TCFA in the PROSPECT (Providing Regional Observations to Study Predictors of Events in the Coronary Tree) trial to 19% for PB >70%, also in the PROSPECT trial, reflecting the low prevalence (pretest likelihood) of outcomes (3). The C index, the only metric independent of prevalence, tracked with other outcomes with PB >70% in the PROSPECT trial yielding the highest discrimination (area under the curve [AUC]: 0.82). Lesions exhibiting all 3 IVUS-defined correlates of vulnerability (PB >70% + MLA $\leq$4.0 mm^2 + TCFA) yielded the highest hazard ratio (HR) and AUC for predicting future NCL-related events. However, the PPV was only 18% to 23%, reflecting MACE's low prevalence. Notably, NIRS-determined LCP, a measure of plaque necrotic core without PB, had comparable prognostic utility for MACE compared with all 3 IVUS-defined characteristics combined in the ATHEROREMO-IVUS study (HR: 4.2 vs. 3.7; PPV: 17% vs. 23%; AUC: 0.74 vs. 0.72). Furthermore, the predictive value of LCP for the occurrence of nonrevascularization MACE (composite of death, ACS, or stroke) or acute cardiac events (cardiac death or nonfatal ACS) was even stronger (unadjusted HR: 11.9 and 9.4; AUC: 0.85 and 0.82,