Coronary artery disease continues to intrigue with its multifactorial etiology and unpredictable clinical presentation. In most patients, the initial presentation is an acute coronary syndrome (ACS) frequently manifesting as an infarction, and in the most unfortunate cases, sudden cardiac death. However, for many patients who survive the acute event, coronary artery disease enters a quiescent or latent phase with a fairly benign course and favorable long-term outcome. It is reasonable to infer that a parallel process of dynamic disease activity at the tissue level underlies the unpredictable clinical course. Identification of such heightened disease activity and detection of vulnerable plaques before they lead to clinical events has been referred to as the “holy grail” of cardiology. We currently have multiple imaging modalities, each with differing strengths and weaknesses, capable of characterizing the morphologic features of coronary plaques. However, to bridge the knowledge gap between visualizing a plaque and predicting a future event, we need to accurately document the natural history of differing plaque types. In this issue of the Journal, Kubo et al. (1), present serial intravascular ultrasound virtual histology (IVUS-VH) images, showing differing patterns of longitudinal disease behavior and progression according to the baseline plaque composition.

Recurrent events after an acute coronary syndrome remain high for at least 12 months, and in approximately half the cases are due to new lesions, suggesting diffuse disease activation and progression (2). The presence of multiple vulnerable plaques and simultaneous plaque ruptures in patients with ACS has been documented, further supporting the notion of diffuse, multifocal disease activation (3,4). An active local inflammatory response is believed to be responsible for the rapid plaque growth, necrotic core formation, fibrous cap thinning, and plaque erosion associated with ACS. Systemic levels of inflammatory markers, such as C-reactive protein, seem to track disease activity and identify patients with an increased risk for a first coronary event as well as for a recurrent event after an ACS (5). Is it now possible to detect this activated disease state through accurate in vivo plaque characterization and provide personalized risk stratification?

IVUS ushered in the era of in vivo vessel wall visualization and the initial stages of plaque characterization, demonstrating the differing morphologies between culprit and nonculprit plaques (6). Two important limitations attributed to IVUS detection of vulnerable plaques include the inability to detect a thin fibrous cap (<65 μm) due to a spatial resolution >100 μm, and the inability to accurately distinguish specific plaque components. The addition of radiofrequency backscatter signal analysis—namely, virtual histology—has allowed for a more detailed plaque characterization according to the amount and location of fibrous, fibrofatty, fibrocalcific, dense calcium, and necrotic core components. Plaques are then characterized as pathological intimal thickening, thin-cap fibroatheroma (TCFA), thick-cap fibroatheroma (ThCFA), fibrotic, or fibrocalcific.

TCFA, the hallmark of a vulnerable plaque, is characterized by a large (>10% of plaque area) necrotic core component that is in extensive contact (>30° arc) with the lumen (7). Optical coherence tomography is also able to detect TCFA with its unmatched spatial resolution of 10 to 20 μm; however, its limited penetration (<2 mm) does not allow for plaque component determination (8). A direct comparison of IVUS-VH with optical coherence tomography for TCFA detection has concluded that neither modality may be sufficient and that a combined approach, which is feasible, may also be preferable for accurate TCFA detection (9). We are now capable of detecting TCFA in vivo, so the next important question is “What is the value of such information at a single point in time?”

The most notable contribution of the paper by Kubo et al. (1) is the serial IVUS-VH imaging that provides a glimpse (12 months) at the longitudinal behavior of nonobstructive coronary atheromas. The authors summarize their findings in 3 important conclusions. First, that approximately three-quarters of TCFA “heal” during the 12-month follow-up and evolve to less vulnerable plaque types. Second, that new TCFA may develop from pathological intimal thickening and ThCFA during this time. Finally, that disease progression relating to increasing plaque volume was noted among pathological intimal thickening, TCFA, and ThCFA, but was not seen in fibrotic and fibrocalcific plaques. Summarizing these central observations, one could conclude that the 5 plaque types interrogated serially in this study actually represent only 2 differing types of disease activity. Patho-
logical intimal thickening, TCFA, and ThCFA collectively represent the dynamic nature of an “active” disease state where plaques evolve, transform, and grow over time, whereas fibrotic and fibrocalcific plaques represent a dormant, more “stable” disease state without evidence of disease progression or plaque type modification. In this relatively small cohort, TCFA “healing” was not associated with the initial clinical presentation (ACS vs. non-ACS), statin, angiotensin-converting enzyme inhibitor, or angiotensin-receptor blocker treatment, change in low-density lipoprotein levels, or duration of follow-up. Baseline IVUS-VH characteristics were also not predictive of TCFA healing, and the only predictors of 12-month TCFA behavior were proximal plaque location, plaque burden, and vessel size. In a similar effort but in a larger sample (ACS, n = 700), the PROSPECT (Providing Regional Observation to Study Predictors of Events in the Coronary Tree) trial (2) recently reported 4 independent predictors of future events related to nonculprit atheromas according to baseline IVUS and IVUS-VH characteristics. These included plaque burden >70%, IVUS-VH TCFA determination, minimal lumen area <4.0 mm², and lesion length >11.6 mm. Notably, 3 of the 4 predictors were again not related to virtual histology information, and described bulky, long plaques with luminal narrowing as the ones more prone to lead to clinical events. Collectively, these insights suggest that screening for active disease rather than specific TCFA characterization may be sufficient for identification of vulnerable patients.

Is it possible that noninvasive imaging with a much wider clinical applicability is also capable of identifying vulnerable patients by utilizing the simpler “active versus stable” plaque classification scheme? Important data are accumulating for computed tomographic angiography as a possible modality for the detection of vulnerable plaques. Comparative studies with IVUS have defined attenuation <30 HU as 91% sensitive and 100% specific in detecting lipid rich plaques (10). In a recent report by Motoyama et al. (11), the detection of 2 plaque features, specifically low-attenuation signal (<30 HU) and positive vessel remodeling, proved very accurate in predicting a future ACS among 1,059 consecutive patients who underwent computed tomographic angiography. During a mean follow-up of 27 months, patients with plaques exhibiting both features had an event rate of 22.2%, compared with 3.7% for patients with either of the 2 features, and 0.5% for patients with neither feature. The hazard ratio associated with the presence of at least 1 feature was 22.79, with the second strongest predictor being hyperlipidemia, with a hazard ratio of 3.65 (11).

It is clear that technological advances have allowed us detailed in vivo plaque visualization previously only possible through autopsy studies. In our efforts to identify vulnerable patients, however, what is the value of measuring by optical coherence tomography a thin cap of <65μm when in all likelihood this will change over time? What is the value of color coding confluent necrotic core extensively abutting the lumen by IVUS-VH when proximal location, plaque burden, and lesion length are probably at least equally effective in predicting a future event? The major challenge is to incorporate all available knowledge gathered through the different imaging technologies and unify them in a single paradigm for the natural history of coronary artery disease. Clinical trials incorporating clinical risk profiles, biomarkers, and multimodality imaging are under way and will be critical in our efforts to define the coronary blueprint of a future event. An important first step may be our ability to classify patients as having “active” versus “stable” disease, utilizing an algorithm incorporating clinical data, biomarkers, and accurate noninvasive imaging.

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