The search for the vulnerable plaque has been a prolonged, circuitous journey that despite considerable investment and resource expenditure has hitherto failed to alter clinical practice. The rationale remains enticing. We have known for some time that plaques at risk of rupture and precipitating myocardial infarction and stroke have certain characteristics that extend beyond simple stenosis severity. These include inflammation, microcalcification, angiogenesis, positive remodeling, a thin fibrous cap, a large necrotic core, and plaque hemorrhage. Rapid recent advances now allow us to detect such features using both invasive and noninvasive imaging technologies. The hope has been that such technology might allow us to predict with accuracy the plaques and, more importantly, the patients at risk of rupture-related events. However, recent data have been somewhat disappointing, at least at the plaque level. The PROSPECT trial (Providing Regional Observations to Study Predictors of Events in the Coronary Tree) used virtual histology intravascular ultrasound to identify high-risk lesions (the virtual histology intravascular ultrasound defined thin capped fibroatheroma), demonstrating that such plaques were a predictor of events and offered good negative predictive value. However, of a total of 595 such lesions, only 26 caused an event and most of these were not myocardial infarctions. Although this, in part, may reflect the limitations of virtual histology intravascular ultrasound, it is increasingly being appreciated that high-risk plaques are in fact relatively common and only rarely go on to cause a clinical event. The positive predictive value is currently so low that questions have been raised about whether treatment to individual plaques will ever be justified. Faced with this fundamental issue, what then is the future of high-risk plaque imaging?

There is more hope at the patient level. When present high-risk plaques rarely exist in isolation but tend to form at multiple sites across the vasculature in patients with an active inflammatory disease process. Although the majority of these plaques will heal without consequence, it is believed that patients with active disease and a tendency to forming unstable lesions will be at increased risk of a clinical plaque rupture event. Recent data support this hypothesis. T1-weighted magnetic resonance imaging can identify plaques with intraplaque hemorrhage or intraluminal thrombus. Patients with evidence of such plaques in the carotid vasculature had a 3-fold increase in cardiac events. Similarly, patients with high-risk plaques in their coronary arteries detected using the same magnetic resonance approach and computed tomographic plaque characterization have also been found to have an adverse prognosis.

Although more encouraging, there remains an urgent need to improve the field of vulnerable plaque imaging so that it might at last make a useful contribution to clinical practice. This will require extensive scientific endeavor. In particular, improved understanding of what makes a plaque truly vulnerable, how the array of different high-risk features are related, which particular characteristics offer the best risk prediction, and how their presence evolves over time.

The article by Demeure et al in this issue of Circulation: Cardiovascular Imaging attempts to address some of these key issues. The authors investigated both carotid inflammation and angiogenesis using 18F-fluorodeoxyglucose positron emission tomography and contrast-enhanced ultrasound, respectively, performed in patients undergoing carotid endarterectomy (11 were symptomatic and 19 asymptomatic). The contrast-enhanced ultrasound used a contrast agent that remains intravascular and so informs about new vessel formation rather than vessel leakiness. Imaging data were then compared with histological analysis of the excised carotid atheroma. This provided both validation of the imaging findings and an alternative assessment of the presence of inflammation and angiogenesis in the different plaque types. A good correlation between 18F-fluorodeoxyglucose uptake and macrophage burden was observed as previously reported. Similarly, patients thought to have angiogenesis on ultrasound had a higher vessel density on histology than those that did not although the binary nature of this assessment does represent a limitation.

The key finding of the study was that inflammation (assessed using both 18F-fluorodeoxyglucose positron emission tomography and macrophage burden on histology) was increased in symptomatic versus asymptomatic patients, despite similar plaque burden. This supports previous data. The same, however, was not true of angiogenesis, whether assessed by imaging or histology. This suggests that inflammation and angiogenesis may not be as closely related as previously thought and that angiogenesis may not be such a high-risk marker, at least in the absence of associated plaque hemorrhage.

The authors are therefore to be congratulated on advancing our knowledge in the field. Moreover, they deserve credit for delivering such a trial. Performing complex imaging protocols in the increasingly narrow window between symptom
development and endarterectomy is a major logistical challenge that should be recognized. Such endeavors are nevertheless worth pursuing, providing a rare opportunity to directly correlate imaging findings with histology and to compare symptomatic with asymptomatic plaques.

So where next for the field? Prospective studies are now required to assess whether high-risk plaque imaging and measures of disease activity can provide incremental prognostic information and whether this might be cost effective. These should also address which patient populations would derive maximal benefit and whether combinations of different plaque characteristics add value. A recent study by Motoyama et al supported the latter notion demonstrating that coronary plaques with both positive remodeling and a large necrotic core on computed tomographic identified patients at increased future risk of cardiac events. Other positron emission tomography/computed tomographic trials underway will develop this theme further and examine whether positron emission tomographic measures of coronary disease activity are complementary to computed tomographic plaque characterization and associated measures of plaque burden (clinicaltrials.gov, NCT02278211).

Ultimately, atherosclerosis is a highly complex multifaceted disease process in which risk prediction is challenging. Combined assessments of plaque burden, plaque characteristic, and disease activity are likely to be required to accurately identify patients at imminent risk of myocardial infarction and stroke. Further innovative research of the kind presented by Demeure et al will be required if this concept is going to be translated in to clinical reality.

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