The ultimate goal of studies such as the one by Brown et al in this issue of Circulation: Cardiovascular Imaging is to provide the clinician with a diagnostic tool that identifies high-risk plaques prospectively to treat and prevent acute events. This tool must have a high positive predictive value and negative predictive value in the clinical setting and not require specific expertise or core-laboratory analysis to determine whether a plaque is vulnerable and should be treated pre-emptively—a yes/no, treat/don’t treat tool. Optical coherence tomography (OCT) has been proposed as that tool. OCT criteria for a thin-cap fibroatheroma (TCFA) include the presence and amount of lipid plaque and a thin fibrous cap with macrophage infiltration. However, in a core-laboratory study by Kim et al in which the intraobserver reproducibility was high, the interobserver intraclass correlation coefficient among 4 highly trained individuals (a better, but still idealized representation of what would happen clinically) was only 0.49 (95% confidence interval: 0.26–0.69) for fibrous cap thickness and 0.77 (95% confidence interval: 0.53–0.97) and 0.71 (95% confidence interval: 0.55–0.86) for maximum and average lipid arc, respectively. Quantification of lipid by OCT is problematic and is restricted to the arc of lipidic plaque because penetration through lipid or necrotic core (as well as assessment of plaque burden in high-risk plaques) is one of the limitations of OCT. Furthermore, limitations to the accurate OCT assessment of lipidic plaque include artifacts caused by shallow or tangential beam angulation and drop-put and confounders, such as the presence of macrophages, foam cells, microcalcifications, or hemosiderin, in the fibrous cap—all of which can produce the appearance of lipid, whether or not lipid is actually present.

Although the study by Brown et al is titled “Direct comparison of virtual-histology intravascular ultrasound and optical coherence tomography imaging for identification of thin-cap fibroatheroma,” in reality it is less of a direct comparison of 2 techniques than one of an increasing number of, albeit, small studies questioning the accuracy of OCT, as well as a rehabilitation of virtual histology (VH)—intravascular ultrasound (IVUS), suggesting that a combination of the 2 techniques is better than either alone.

IVUS was developed to improve on the limited tissue characterization of grayscale IVUS. Proposed criteria for a VH—fibroatheroma included >10% confluent necrotic core for 3 consecutive frames and confluent necrotic core >10% in contact with the lumen for 3 consecutive frames for VH-TCFA. Although used to good advantage in 3 important prospective studies—Providing Regional Observations to Study Predictors of Events in the Coronary Tree (PROSPECT), VH-IVUS in Vulnerable Atherosclerosis (VIVA), and European Collaborative Project on Inflammation and Vascular Wall Remodeling in Atherosclerosis - Intravascular Ultrasound (ATHEROREMO-IVUS)—VH-IVUS has fallen into disfavor (especially in the clinical setting) because of the relatively low resolution of VH-IVUS making it impossible to measure fibrous cap thinness consistent with TCFA; reproducibility issues, diagnostic reliability, and artifacts; and studies such as the animal study by Thim et al who found no correlation between the size of the necrotic core determined by VH-IVUS versus histopathology, as well as VH-IVUS necrotic cores in lesions lacking necrotic cores by histopathology.

In Brown et al’s histopathologic study, the positive predictive value and negative predictive value were 26.4% and 94.6%, respectively, for a VH-TCFA and 30.8% and 95.9%, respectively, for OCT-TCFAs. Thus, by themselves, both techniques were fundamentally flawed. Conversely, the highest diagnostic accuracy (89.0%) in predicting a histopathologic TCFA was seen when VH-IVUS necrotic core detection was combined with OCT fibrous cap thickness measurements. This approach used the strengths of each technology to compensate for the weaknesses of the other—quantification of necrotic core by VH-IVUS (that cannot identify a thin fibrous cap) and measurement of fibrous cap thickness by OCT (that cannot quantify lipid or necrotic core content).

Using 2 catheters and 2 machines is clinically cumbersome, unrealistic, and expensive, and it requires some method to coregister the 2 techniques. Although once a fantasy, combined imaging devices are now a reality. However, the 3 currently available radiofrequency IVUS technologies—VH-IVUS, integrated backscatter-IVUS, and iMAP—use different algorithms, are not interchangeable, and each, alone or in combination with OCT, requires validation. Conversely, the 2 frequency-domain OCT imaging devices—marketed as frequency-domain OCT and optical frequency-domain
imaging—merely represent different implementations of the same fundamental technology. However, issues of intellectual property may limit the commercialization of certain combinations. For example, VH-IVUS used in the study by Brown et al is owned by a company that was blocked from bringing frequency-domain OCT to market. Furthermore, combination devices must not sacrifice quality of each component technology for the sake of convenience and expediency.

But Does This Make Clinical Sense?
In PROSPECT, events attributable to each identified high-risk plaque were uncommon, suggesting that VH-IVUS in PROSPECT may have overestimated TCFAs prevalence despite the fact that prespecified 3-vessel VH-IVUS imaged only half of the lesions that caused events. According to the study by Brown et al, 3 quarters of the 600 VH-TCFAs identified in PROSPECT were likely to have been false positives; adding OCT to VH-IVUS would have halved the false-positive rate. Even so and especially in a setting of more complete 3-vessel imaging, the combination of OCT and VH-IVUS would still have identified mostly TCFAs that were either stable, developed thick fibrous caps when patients were treated with modern medical therapy, and ruptured silently and asymptptomatically. Serial OCT studies have documented an increase in fibrous cap thickness, especially with lipid-lowering agents. Studies by Mann and Davies showed that plaque rupture and healing were common and more often led to lesion progression than to acute events.

Second, in vivo OCT studies have indicated that ruptured plaques with thrombus formation may underlie only 50% of acute coronary syndromes. Thus, although the absence of a confluent necrotic core >10% (by VH-IVUS) or of a fibrous cap thickness <85 µm (by OCT) likely exclude a TCFA, they do not exclude other vulnerable plaque morphologies, such as precursors of erosions, spontaneous dissections, and calcified nodules.

Third, these issues become even more problematic in the context of asymptomatic individuals considering the large population at risk with an even lower rate of adverse events, complications associated with 3-vessel invasive imaging, however, low, and higher costs associated with combination versus single imaging technology devices. Although histopathologic correlations are important, imaging findings that reliably predict (or exclude) events are even more important than studies showing that one or another technology (or any combination of technologies) correlate better with histopathology. This is true even if the imaging technology is flawed when compared with histopathology; clinical data trumps histopathologic correlations, but it takes more time and resources.

Finally, and most importantly, vulnerable plaque imaging research must move beyond assessment of diagnostic accuracy in vitro and prediction of events in vivo and be linked to therapies that reduce events.

Disclosures
Dr Mintz is a consultant for and receives honoraria from BostonScientific, Volcano, Infraredx, ACIST, and St Jude. The Cardiovascular Research Foundation receives fellowship or research support from BostonScientific, Volcano, Infraredx, and St Jude.

References


**KEY WORDS:** Editorials • foam cells • intravascular ultrasound • macrophage • optical coherence tomography • vulnerable plaque
Optical Coherence Tomography and Virtual-Histology Intravascular Ultrasound: Strange Bedfellows? … or Not?
Gary S. Mintz

Circ Cardiovasc Imaging. 2015;8:e004045
doi: 10.1161/CIRCIMAGING.115.004045

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circimaging.ahajournals.org/content/8/10/e004045

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation: Cardiovascular Imaging can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation: Cardiovascular Imaging is online at:
http://circimaging.ahajournals.org//subscriptions/