Impact, the ability to have a long-lasting significant influence in the field, has become the focus not only of the National Institutes of Health and the National Science Foundation but also of science in general. An article in this issue, “Optical Coherent Tomographic Analysis of In-Stent Neointimal Hyperplasia After Drug-Eluting Stent Implantation,” deals with 2 high-impact areas of cardiology: extending the diagnostic capabilities of cardiovascular optical coherence tomography (OCT) and the cause of late drug-eluting stent failure.1 With respect to the latter, the article looks at atherosclerotic progression after drug-eluting stent placement and late development of different plaque morphologies, predominantly at the stent site. It suggests variability of plaque progression in the persistent area as a potential reason for failure. The article reviews the literature on this topic, so the cardiovascular OCT aspects of the paper, mainly the strengths and weaknesses of the technology, are the focus of the remainder of this editorial. The primary topic in particular is the effectiveness of OCT for plaque lipid identification.

As cardiovascular OCT now enters its 17th year, it is still widely held that its greatest potential for impact is in risk stratifying thin-cap fibroatheromas (TCFAs) and reducing stent placement failures.2,3 Kang et al1 address both these areas. More broadly, as with other studies done over the last several years, the article represents a new direction in the OCT field. With the recent commercialization of OCT imaging systems, we are seeing a new era of cardiovascular OCT studies directed by skilled clinical scientists at hypotheses that will affect patient outcomes (ie, high impact) and are not simply observational studies.4

The progress of OCT in the last 17 years has been dramatic from the original embodiment that had a penetration of <500 μm, a frame rate of 40 seconds per image, and an inability to be performed through a catheter.2 Kang et al, however, indirectly draw attention to 2 major obstacles facing OCT in cardiology. The first is that although recent studies have provided insight into why late occlusions occur, markers predicting poor outcomes at the time of intervention are essentially nonexistent.5,6 This is related in part to the paucity of studies in the previous decade designed to address this question.

However, Kang et al also draw attention to an issue I find even more critical: the limitations of current OCT embodiments for characterizing plaque.1 Although not significantly detracting from the conclusions of the article, the plaque characterizations at times overstate the abilities of current OCT, feeding off of misconceptions in the literature (or at least, in my opinion, poorly validated previous studies).

To prevent acute coronary syndromes, it is likely that the culprit plaques need to be identified and treated. Acute coronary syndromes occur secondary to the rupture of small, thin-walled, lipid-filled plaques in the coronary arteries. When these plaques rupture, they release thrombogenic factors into the blood, which leads to a cascading sequence of events, resulting in clot formation and vessel occlusion.7,8 These plaques are beyond the resolution of essentially all in vivo non-OCT imaging technologies. The American Heart Association classification of plaque uses broad criteria and has recently further subclassified plaque on the basis of the likelihood of rupture.8 The plaques most relevant to acute coronary syndromes are the TCFAs, which are characterized by a thin fibrous cap (<75-μm thickness), infiltration by macrophages/lymphocytes at some points, neovascularization into the intima, and few cap collagen bundles. The plaques leading to acute coronary syndromes are therefore structurally weak and vulnerable to mechanical pressure such as shear stress or rupture of intimal angiogenic vessels. The problem is further complicated by the fact that most TCFAs do not lead to acute coronary syndromes,7,8 which is consistent with results in the Kang et al article: “[M]any of the OCT neointimal ruptures and thrombi were small, … [but] were not responsible for clinical instability.” Kang et al confidently label plaques as having a lipid core, although the current ability of OCT to differentiate lipid from nonlipid has been highly questionable. This has implications for studies characterizing plaque with OCT in vivo, like the one in this issue.

The major TCFA marker examined effectively to date by OCT is intimal cap thickness, as was done by Kang et al. At autopsy, 95% of ruptured plaques have a thin fibrous cap. In our initial study of thin-walled plaques 17 years ago, we demonstrated the ability of OCT to identify in vitro plaque intimal cap thickness <40 μm with histological comparisons.9 These intimal cap measurements were confirmed ex
vivo a decade later ($r=0.90, P<0.001$). The ability to demonstrate intimal cap thickness is clearly the best demonstrated strength of OCT for identifying TCFA. However, the ability of OCT to identify lipid based on diffuse borders (or signal decay) comes from small data sets and, at the very least, needs to be confirmed (and, at worst, are incorrect). Aside from the thin intimal cap, it is critical to know when deciding on intervention if the plaque has a lipid core; if the plaque has a solid core, the likelihood of rupture would be small. Some groups have suggested that in an OCT image, a diffuse border (not sharp) between the intima and the core indicates lipid. This criterion was used extensively in the present article for plaque characterization and is being used in many clinical studies, making this a conclusion that should be well tested. However, we have previously suggested that the diffuse boundary was due to heavy scattering in the cap, likely from either calcium deposits or lipid crystals, and was not due to core composition. Consequently, this raises a concern regarding current interpretations of plaque during in vivo studies. In 1992, Yabushita et al measured the sensitivity and specificity of OCT in vitro, ranging from 71% to 98% for fibrous plaques, 95% to 97% for fibrocalcific plaques, and 90% to 94% for lipid-rich plaques among 2 OCT observers with good interobserver variability ($\kappa=0.83$ to 0.84). Similar results were obtained by a second group in 2006, but 2 additional studies performed the same year had less promising results; one of these studies reported only a 45% sensitivity and 83% specificity for identifying lipid-filled plaques. This study had difficulty in distinguishing between lipid and calcified plaque, which is consistent with our concern that intimal scattering rather than lipid is being measured.

Groups previously supporting the diffuse border have now suggested exponential signal decay at the intimal-cap boundary as a means of identifying lipid, emphasizing the concern about using diffuse borders as a marker. But again, this decay can be from high cap scattering of light and is therefore independent of the core composition. This problem of using diffuse borders to identify plaque lipid is illustrated in the Figure from our original OCT plaque characterization article (but is also seen in Figure 1 of the Kang et al article, as discussed in the legend).

There are few solid experimental data to support the use of diffuse boundaries to identify lipid accurately despite the fact that this criterion is being widely used in current in vivo human studies. However, this editorial is not suggesting that OCT ultimately will not be able to identify high-risk TFCAs. Much of the effort in vivo in the last decade focused on pushing OCT forward as a “clinically friendly,” high-resolution structural imaging technology. This made it available for studies like the Kang et al article. In parallel, however, adjuvant techniques were developed such as polarization-sensitive OCT for the assessment of collagen, elastography for assessing the tensile strength of intimal caps, image processing for improved contrast, Doppler for neovascularization, and absorption/dispersion analysis (such as second-order correlation approaches) for lipid detection.

These OCT techniques will likely greatly enhance plaque characterization. Polarization-sensitive OCT looks particularly promising for assessing intimal cap collagen and is being used successfully in other organ system in vivo (such as measuring cartilage collagen content).

Currently, cardiovascular OCT can neither reliably risk stratify plaque nor predict late occlusion after drug-eluting stent placement. The Kang et al article is part of a new era in which clinical scientists have access to commercial OCT systems and are producing hypothesis-driven studies with potentially high impact on patient management. This is critical, for example, in identifying markers of eminent stent failure. In addition, more in vitro and ex vivo work is needed for both interpreting OCT images of plaque in vivo and developing adjuvant techniques for plaque characterization. That being said, as someone in the field since the original article describing its utility, I believe that OCT has great potential to be a high-impact technology in the management of cardiovascular disease.

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References


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