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EDITORIAL COMMENT

Changing the Landscape of Secondary Prevention After Acute Coronary Syndrome

Morphology, Physiology, or Both?*

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Although detecting high-risk plaques for the prediction of future cardiovascular events has been long awaited, it remains an unsolved issue for researchers, physicians, and patients with coronary artery disease. Despite many attempts to identify high-risk plaques with invasive and noninvasive imaging modalities, detection with a high degree of accuracy remains challenging, especially when a single modality is used. Since their introduction into clinical practice, morphologic plaque evaluation and physiologic assessment using noninvasive or invasive imaging modalities have evolved independently by improving image quality and user-friendliness. However, vulnerable plaque development is a complicated biomechanical process influenced by the structure and constituents of the plaque as well as the physiologic forces across the plaque. Because morphologic plaque evaluation and physiologic assessment often complement each other, several previous studies have implied that a comprehensive evaluation of lesion geometry, plaque characteristics, and physiologic parameters could theoretically enhance the identification of high-risk plaques and enable accurate risk stratification of patients with acute coronary syndrome (ACS).[1] Nevertheless, this strategy is often difficult in daily clinical practice because of socioeconomic reasons that do not allow the use of multiple imaging modalities for one patient, longer analysis time, and poor reproducibility for plaque evaluation.

Recently, several investigators have tried to fill the gap between the morphologic and physiologic assessments by developing an application that estimates the image-based fractional flow reserve (FFR) using a single imaging modality (**Table 1**). Yu et al[2] developed a novel method for FFR computation using optical coherence tomography (OCT)–derived luminal information and reported high diagnostic accuracy of a new OCT-based FFR (OFR) using wire-based FFR as the reference standard. Based on their retrospective analysis of 118 patients, they reported that the accuracy, sensitivity, specificity, positive predictive value, and negative predictive value for OFR to identify FFR of ≤0.80 were 90% (95% CI: 84%-95%), 87% (95% CI: 77%-94%), 92% (95% CI: 82%-97%), 92% (95% CI: 82%-97%), and 88% (95% CI: 77%-95%), respectively.[2] They also showed that the OFR analysis time was 55 ± 23 seconds for each OCT pull back and that the intraobserver and interobserver variability in OFR analysis was very high (0.00 ± 0.02 and 0.00 ± 0.03, respectively).

One of the major advantages of this approach is that it offers one-stop evaluation for the comprehensive assessment of morphology and physiology, but its predictive accuracy for long-term clinical outcomes after percutaneous coronary intervention, particularly in patients with ACS, has not been reported. In this issue of *JACC: Asia*, Hong et al[6] examine for the first time the predictive accuracy of comprehensive morphofunctional assessment with OCT by evaluating a total of 604 patients with acute ACS who underwent OCT imaging in ≥1 nonculprit vessel during index coronary angiography. They also introduce the novel concept of the lipid-to-cap ratio (LCR), which is calculated taking into account the

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TABLE 1 Intravascular Imaging-Based Functional Evaluation

	Modality Used	Sensitivity	Specificity	Positive Predictive Value	Negative Predictive Value
Yu et al[2]	OCT	0.87	0.92	0.92	0.88
Lee et al[3]	OCT	0.750	1.00	1.00	0.929
Ha et al[4]	OCT	0.687	0.956	0.842	0.890
Bezerra et al[5]	IVUS	0.89	0.92	0.80	0.96

IVUS = intravascular ultrasound; OCT = optical coherence tomography.

lipidic burden of the plaque and the cap thickness over the diseased segment. They demonstrate that the LCR and OFR are the 2 most powerful predictors for non-culprit-vessel-related major adverse cardiovascular events at 2 years and also show that the combination of an LCR of >0.33 and OFR of ≤0.84 rendered the highest prognostic performance, detecting a subgroup of patients with a 43-fold higher risk of recurrent events at the 2-year follow-up. In a recent large-scale observational study with 1,378 patients who underwent OCT for 3,533 nonculprit plaques, Kubo et al[7] demonstrated that a larger maximum lipid arc and thinner minimum fibrous cap thickness were independently associated with ACS. They reported that ACS was more often associated with lipidic plaques characterized as both lipid rich and thin-cap fibroatheroma (TCFA) than lipidic plaques that did not have those characteristics (33% vs 2%; HR: 19.14; 95% CI: 11.74-31.20; $P < 0.001$). Thus, the novel index LCR is a reasonable parameter for predicting future ACS events that reflects 2 important morphologic features of the plaques.

Currently, FFR-guided decision making is the gold standard for treating patients with chronic coronary syndrome.[8] However, underestimation is a potential issue when used in the acute phase of ACS because of insufficient microcirculatory vasodilation during hyperemia.[9] On the other hand, OFR uses only quantitative luminal information obtained from OCT images; therefore, OCT-FFR offers a great advantage in evaluating the presence of ischemia in patients with ACS. In addition, because patients with ACS are often hemodynamically unstable, another important advantage could be the avoidance of hyperemia induction.

Another important benefit of this approach is that comprehensive morphofunctional evaluation with OFR and LCR could be obtained with a fully automatic process. In this way, this new approach improves the reproducibility, reduces the subjectivity of the assessment, and dramatically diminishes the time and effort required for the analysis. In contrast, OCT cannot measure lipid and plaque volumes accurately in plaques with large lipid angles because of the significant signal attenuation induced by lipid content. Thus, even experts and artificial intelligence cannot accurately measure lipid and plaque volumes in plaques with large lipid angles. Further investigation is necessary to evaluate the accuracy of artificial intelligence-based automatic quantitative evaluation of the lipidic burden of the plaques using pathologic assessment as a reference standard.

Although many ACS events result from the rupture of TCFA, the remaining events are caused by erosion of the intimal surface and calcified nodules with subsequent thrombus formation. We previously reported that among a total of 436 ACS patients, the incidences of plaque rupture, erosion, and calcified nodules in ACS culprit lesions were 46.1%, 39.9%, and 14.0%, respectively.[10] In this study, the presence of TCFA at the culprit lesion was independently associated with plaque rupture, whereas a lower incidence of TCFA was correlated with plaque erosion and calcified nodule. Furthermore, in a recent OCT study of ACS culprit lesions in 1,241 patients with ACS, Yamamoto et al[11] showed that the incidences of lipid-rich and TCFA plaques were 91.3% and 61.5% respectively, whereas those were 37.3% and 6.9% in plaque erosion and 15.3% and 3.2% in calcified nodules.[11] Indeed, in the present study, 49.7% of the enrolled patients did not undergo stent implantation, probably because of the OCT-based diagnosis of plaque erosion in the culprit lesions. Considering that acute coronary events caused by erosion and calcified nodules could occur via different mechanisms than plaque rupture, it remains unclear whether the current approach works for the prediction of ACS events attributable to erosions and calcified nodules. Actually, the majority of nonculprit vessel-related major adverse cardiovascular events during the follow-up period were cardiac death (n = 8; 31%) and revascularization (n = 16; 62%), and myocardial infarction was observed only in 2 patients (8%). Thus, whether the present approach is helpful in predicting subsequent ACS events requires further investigation. Nevertheless, the present study addresses contemporary unsolved issues of risk stratification after ACS events and opens up new possibilities for intravascular imaging in clinical practice. A prospective large-scale study is warranted to further confirm the potential benefit of the comprehensive

morphofunctional assessment with OCT in risk stratification after ACS events.

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