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EDITORIAL COMMENT

Moving Beyond Angiography

Integrating Physiology and Plaque Vulnerability, a Step Forward in Precision Medicine

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The landscape of cardiology and especially interventional cardiology is undergoing profound transformation with advances in new technologies.[1] We have long acknowledged the limitations of coronary angiography, which depicts only the vessel lumen,[2] and we are now embracing physiology-guided approaches, high-resolution imaging techniques, and new digital tools to improve patients' outcomes. The integration of computational physiology and advanced imaging is shifting the paradigm from treating visible stenosis to comprehensively managing patients' atherosclerotic risk. This includes assessing the functional significance of a stenosis, the biological morphology of the plaque, and its propensity to cause events, ushering in an era of precision medicine.

The advent of angiography-derived indexes, such as the Murray's law-based quantitative flow ratio (μFR), now enables rapid, single-projection, wire-free assessment with excellent diagnostic accuracy for identifying hemodynamically significant coronary stenosis.[3] High-resolution imaging techniques, such as optical coherence tomography (OCT), are known to accurately identify thin-cap fibroatheromas and morphologic characteristics associated with an increased risk for adverse events during long-term follow-up.[4-6] Concurrently, the development of biomechanical indexes that quantify arterial deformation, such as radial wall strain (RWS), may identify areas with features of vulnerability, acting as surrogate marker of plaque vulnerability and providing a noninvasive window into plaque biology. Indeed, RWS potentially identifies lesions harboring OCT-defined vulnerability features and may independently predict a higher risk for lesion-oriented adverse events.[7]

A multiparametric approach that combines these new technologies offers a complementary, dual assessment of ischemic and atherosclerotic risk. This may facilitate a tailored strategy that optimizes decision-making between intensified medical therapy and targeted revascularization. However, how this incremental information influences revascularization strategies for the management of intermediate coronary stenosis remains largely unexplored.

Li et al[8] should be congratulated for addressing, in this issue of *JACC: Asia*, this emerging aspect and for conducting a meticulous multicenter survey evaluating the influence of incremental information on coronary physiology and plaque vulnerability in guiding revascularization decision-making for intermediate coronary stenoses. They included 87 interventional cardiologists from 30 clinical centers across China and, assessing 25 angiographically intermediate lesions, analyzed 1,975 lesion-based decision sets. The study powerfully demonstrates that the sequential integration of angiography-derived computational physiology (μFR) and biomechanical plaque assessment (RWS), combined with OCT, altered revascularization decisions in nearly one-half (48.7%) of decision sets. In particular, adding μFR to angiography changed decisions in 21.1% of cases, with the vast majority (16.3%) representing a shift from planned revascularization to medical therapy. After adding RWS, revascularization decisions changed further in 15.9% of cases, with 11.3% shifting from medical therapy alone to revascularization. Finally, after optical coherence tomographic disclosure, revascularization decisions changed in 28.6% of

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cases, with the majority (26.6%) shifting from medical therapy alone to revascularization. If a novel quantitative optical coherence tomographic metric (lipid-to-cap ratio)[9] had been used instead of qualitative interpretation, the change after optical coherence tomographic disclosure would have been much smaller (16.1% vs 28.6%). Importantly, the discrepancy between qualitative optical coherence tomographic readings and the quantitative lipid-to-cap ratio metric suggests that subjective interpretation of OCT can lead to significant variability in decision-making.

These results offer several important insights. First, a significant proportion of initial angiogram-based decisions (31.1%) were discordant with the physiological significance of the lesion, confirming, once again, that visual assessment alone is unreliable for estimating ischemic burden. Second, the traditional reliance on subjective visual assessment is progressively modified by a multidimensional decision framework, in which interventionalists integrate functional significance with biological risk. This highlights the evolving clinical paradigm in which physicians consider both ischemic burden and plaque vulnerability in decision-making. This concept is further supported by the recent PREVENT (Preventive PCI or Medical Therapy Alone for Vulnerable Atherosclerotic Coronary Plaque) trial,[10] which demonstrated that performing preventive percutaneous coronary intervention (PCI) on non-flow-limiting lesions harboring vulnerable plaques reduced the incidence of adverse cardiac events compared with medical therapy alone.

Importantly, the inclusion of an "intensive medical therapy" option, distinct from standard medical therapy and revascularization, is a critical strength. It reflects the growing recognition that plaque vulnerability identified via RWS or OCT often warrants aggressive pharmacologic intervention (eg, potent lipid-lowering therapy) for significant plaque regression.[11,12] This underscores that modern interventional decision-making extends beyond the stent-vs-no-stent question and includes stratified medical management based on personalized risk assessment.

However, as we embrace a multiparametric approach, we must confront scenarios of discordant indexes, for example, a patient with a clearly non-ischemic μFR but a highly elevated RWS or a lesion with borderline physiology and ambiguous vulnerability signals. This reflects the complex, multifaceted nature of coronary artery disease and the need for an evidence-based integration of physiological and vulnerability data, probably within more sophisticated hierarchical framework aided by future artificial intelligence-powered software or artificial intelligence-driven risk stratification tools based both on imaging data and on patient-level clinical data.[13] Despite excellent correlations with their respective invasive gold standards, all these attractive angiographically derived physiological parameters have well-established limitations that should be kept in mind to ensure adequate interpretation in individual patients. Therefore, this is a call not for passive observation but for active, deeper comprehension; indeed, these potential algorithms should always be viewed as decision support tools, as clinicians must integrate objective data with the yet invaluable clinical context (patient age, comorbidities, functional status, etc).

From this perspective, the (understandable) absence of these clinical data in the study, compared with real-world practice, should be acknowledged as a limitation, along with the lack of clinical outcome assessment. Additional studies are required to confirm that the change in the decision-making process elicited by the additional information is indeed associated with superior clinical outcomes. Similarly, the fixed data sequence used in the study (angiography → μFR → RWS → OCT) may limit generalizability, as alternative sequences might yield different results. Nevertheless, this approach intentionally mirrors clinical practice, in which less invasive tools (μFR and RWS) are rationally used before more invasive ones (OCT). Evaluation of ischemia as the first approach remains appropriate in clinical practice, as it is the most evidence-based framework for guiding PCI, but plaque vulnerability assessment may provide complementary information, particularly in ischemia-negative but high-risk lesions, helping refine patient risk stratification. However, workflow and economic considerations, including procedural time and reimbursement, still limit the adoption of intracoronary imaging and physiological assessment in daily practice. Further data on cost-effectiveness and implementation pathways are warranted to facilitate the real-world adoption of multiparametric approach that combines these new technologies.

Interestingly, participants with longer experience in interventional cardiology were less likely to alter revascularization decisions with incremental data disclosure (OR: 0.39; 95% CI: 0.17-0.90; $P = 0.03$). This opens the debate as to whether clinical experience competes with emerging technology or whether the next generation of clinicians is simply more confident in the use of new tools and in applying them to patient management. In addition, the comprehensive lesion evaluation requires the use of

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relatively sophisticated technologies that require technical expertise and adequate interpretation. Implementing the use of noninvasive computational indexes and intravascular imaging is essential, and interventionalists should therefore become familiar with all these modalities. Indeed, although intravascular imaging has been strongly associated with improved PCI outcomes,[14] its use is still not widespread, with great variability across different countries and operators.[15]

The critical next step is to continue to validate these noninvasive computational indexes in prospective studies and to investigate these potential stepwise approaches in prospective randomized trials in order to demonstrate that the integrated use of coronary physiological indexes and vulnerable plaque characteristics does improve patient outcomes compared with actual standard of care. The incremental value of combining coronary physiology with intravascular imaging (OCT) to better guide PCI is being investigated in the COMBINE-INTERVENE (Combined Ischemia and Vulnerable Plaque Percutaneous Intervention to Reduce Cardiovascular Events) trial (NCT05333068). Hopefully, this will enhance personalized management strategies and support the transition to precision medicine in coronary artery disease.

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