JACC: ASIA VOL. 1, NO. 1, 2021

EDITORIAL COMMENT

The Multidimensionality of Coronary Artery Disease

Combining, Conflating and Changing*

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"Every now and then a man's mind is stretched by a new idea or sensation, and never shrinks back to its former dimensions."

—Oliver Wendell Holmes

In recent years in the field of noninvasive coronary artery disease (CAD) imaging, there has been a robust debate over the advantages and limitations of "anatomic" versus "physiologic" CAD assessment (1). Proponents of the physiologic approach have reasoned that ischemia evaluation represents the ideal method to identify at-risk patients and guide clinical decision making through selection of individuals who may benefit from coronary revascularization. Conversely, supporters of the "anatomic" approach to CAD evaluation have historically emphasized the presence of coronary luminal narrowing—most commonly reported as a 2-dimensional measure of diameter stenosis—as the standard on which to base CAD diagnosis and care.

While compelling, neither of these approaches has been proven in randomized controlled trials of stable populations of patients with suspected CAD undergoing noninvasive imaging to effectively guide clinical decision making in a manner that improves event-free survival. In the ISCHEMIA (International Study of Comparative Health Effectiveness With Medical and Invasive Approaches; NCT01471522) trial of 5,179 patients with moderate or severe ischemia, ischemia findings by an array of stress test modalities were inversely related to future adverse outcomes (ie, the worse the ischemia test, the better the outcome), and invasive treatment of ischemia did not improve patient outcomes (2). Although measures of coronary "anatomy" by stenosis in this trial were associated with adverse outcomes, treatment of severe stenoses by an invasive approach did not reduce the composite clinical end point. These findings in ISCHEMIA were nearly identical to those reported for the COURAGE (Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation; NCT00007657) trial more than a decade earlier (3). Both ISCHEMIA and COURAGE challenge the notion that assessment of stable patients with suspected CAD with ischemia testing followed by invasive angiography robustly improves outcomes, and strongly encourage us to identify more effective CAD metrics that can guide treatment decisions in a way that improves survival.

Recently, coronary CT angiography (CCTA) has emerged as a noninvasive modality which uniquely enables quantitative assessment of the primary CAD process (atherosclerosis), as well as the secondary anatomic consequence of atherosclerosis on the lumen (stenosis), and the late-stage tertiary physiologic consequence of both atherosclerosis and stenosis on flow properties (ischemia) (4). Understanding these temporally occurring features of CAD evokes the realization that we have focused CAD assessment in reverse order from later to earlier stages with the use of stress tests to determine ischemia and invasive angiograms to determine stenosis, with near-uniform neglect of atherosclerosis as the primary disease process itself. In short, our current approach identifies downstream sequelae of CAD rather than CAD itself. That the majority of myocardial infarctions occur in patients without ischemia or stenosis—along with the observed outcomes benefit for patients undergoing noninvasive CAD imaging stemming from

*Editorials published in *JACC: Asia* reflect the views of the authors and do not necessarily represent the views of *JACC: Asia* or the American College of Cardiology.

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Nathan Wong, PhD, served as Guest Editor-in-Chief for this paper.

The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

ISSN 2772-3747 https://doi.org/10.1016/j.jacasi.2021.05.008

improved medical treatment of atherosclerosis—emphasizes an urgent unmet clinical need to extend the definitions of CAD "anatomy" to incorporate measures of atherosclerosis, and to leverage CCTA's unique ability to noninvasively perform whole-heart atherosclerosis characterization and quantification.

In this issue of *JACC: Asia*, Yang et al (5) present the results of the CCTA Fractional Flow Reserve (FFR) registry, a substudy of the 3V FFR-FRIENDS (Clinical Implication of 3-Vessel Fractional Flow Reserve; NCT01621438) study of patients who underwent CCTA within 90 days of clinically indicated FFR. In this study of 643 patients for whom 1,013 vessels were directly interrogated by FFR, the authors sought to determine the relationship of high-risk plaque characteristics (HRPCs) and high-risk vessel characteristics (HRVCs) to ischemia as determined by FFR and to clinical outcome as determined by vessel-oriented composite outcome (VOCO). For the purposes of this paper, HRPC was defined as those with minimum lumen area <4 mm^2, plaque burden $\geq$70%, low-attenuation plaque, positive remodeling, spotty calcification, and napkin-ring sign. HRVCs were defined as those with total plaque volume (TPV) $\geq$306.45 mm^3, fibrofatty and necrotic core (FFNC) volume $\geq$4.46 mm^3, or percentage total atheroma volume (PAV) $\geq$32.2% in a target vessel. Finally, VOCO was defined as a composite of cardiac death, target vessel myocardial infarction, or target vessel revascularization at 2 and 5 years.

In brief, the study found that ischemic vessels exhibiting FFR $\leq$0.80 were associated with higher TPV and FFNC volume, as well as higher PAV, with generally weak correlations between these individual atherosclerosis findings and FFR continuous measurements. Together, however, HRPCs significantly improved discriminatory power of percentage stenosis to identify and exclude ischemic vessels, and, perhaps more importantly, HRVC was additive on top of HRPC. Similarly, for nonischemic vessels with FFR $>$0.80 deferred from revascularization, HRPC and HRVC findings improved identification of vessels at risk for VOCO, with stepwise increases of numbers of both HRPCs and HRVCs predicting VOCO. The contribution of HRPCs and HRVCs was temporally dependent, with HRPCs and HRVCs associated with VOCO at 2 years, but only HRVCs associated with VOCO at 5 years.

The authors should be congratulated for a well performed multicenter effort that extends the foundational knowledge of the complex relationships between atherosclerosis, stenosis, ischemia, and outcome. By performance of their study in a large multinational registry, they further authenticate the generalizability of the study findings, and highlight the complexity of CAD beyond a historically dichotomous categorization of "ischemic versus nonischemic" or "obstructive versus nonobstructive." The CAD measures described by the investigators underscore the complex multidimensional nature of the CAD process, and future validation of these study findings will allow us to develop clinical decision support tools that may improve diagnosis, risk stratification, clinical decision making, and disease tracking.

To this editorialist's knowledge, this study represents the first to dichotomize coronary vessels as ischemic or nonischemic according to FFR and then to examine the influence of noninvasive CCTA anatomic measures of atherosclerosis to ischemia in the FFR+ vessels and clinical outcomes in the FFR− vessels. In this regard, wonder whether there are actually 2 study questions rather than 1 being posed, that have been inadvertently conflated. For the first question, ie, ischemia identification, CCTA findings of atherosclerosis have been demonstrated in an array of clinical trials to be associated with ischemia by FFR, both by HRPCs as well as by HRVCs. The second question posed by the investigators is one of arguably much greater importance, ie, risk assessment in nonischemic vessels. Because the majority of myocardial infarctions occur from erosion or rupture of nonischemic and nonobstructive coronary lesions, improved clinical outcomes through lifestyle modifications and aggressive medical therapy may occur if we can effectively pinpoint the coronary lesions and vessels that connote the greatest risk (6). To put it simply, this approach may allow us to practice precision prevention in a way we were not capable of before.

A few notable findings should be considered when applying these study findings to daily clinical practice. Among the study population, $>$50% of the vessels interrogated by FFR exhibited a maximum stenosis $<$50%, suggesting a clinical reason to perform FFR beyond conventional angiographic measures of severe angiographic narrowing that may signal a bias of selection. Furthermore, the average PAV was 21.9%, which is consistent with high atherosclerotic burden. This PAV was accompanied by an FFNC PAV of 17.0%, which suggests a very high relative proportion of noncalcified plaque. Finally, $>$80% of VOCO events were driven by the most subjective composite end point—vessel-related ischemia-driven revascularization—with only a minority of events driven by myocardial infarction or cardiac death.

As with all well performed studies, this one is not immune to conjuring up many more questions than it answers: First, in the nonischemic vessel group, the relationship of CCTA atherosclerosis findings were related to downstream 2- and 5-year VOCOs. Because atherosclerosis is a highly dynamic process that is multifactorially influenced by lifestyle, medications, and other factors, it remains of high interest to understand the time-varying changes in atherosclerosis in relation to clinical outcome. Second, the cutoff points for HRVC measures of total plaque volume, FFNC volume, and PAV were derived empirically to maximize event prediction, and whether these thresholds can be effectively validated in an external cohort remains to be seen. Third, the authors make a valiant effort to examine dose-response relationships between HRPCs and HRVCs and outcome. The complexity of these dose-dependent phenomena are not fully explored, as it is unclear from the HRPC data listed whether an individual plaque with multiple HRPCs has the same diagnostic or prognostic contribution as multiple plaques with fewer HRPCs.

Despite the high quality of this study, its limitations should also be noted. First, numerous potential biases of selection are present, including choice of patients (a mix of stable and unstable patients), choice of vessels interrogated for FFR (majority of vessels <50% diameter stenosis), the clinical indications for performing CCTA, and others. Second, this study represents the first to introduce the concept of VOCO as a composite vessel-specific end point of cardiac death, target vessel myocardial infarction (TVMI), and target-vessel revascularization (TVR). This composite represents individual components that are: objective and vessel-specific (TVMI), subjective and vessel-specific (TVR), and nonvessel patient-specific (cardiac death). The mix of subjective and objective—as well as vessel- and patient-level—end points somewhat confounds clarity in interpretation. Third, while the authors are to be commended for extending the diagnostic paradigm beyond a single lesion to all of the atherosclerosis across a target vessel, it is likely that atherosclerosis in any given vessel is influenced by the atherosclerosis in other vessels. Thus, a high-risk patient-summary measure would have been highly illuminating and, in the absence of that measure, mixed-effects modeling would be valuable to better account for clusters of related elements whether in the same or different vessels.

The investigators of this study have appreciably "stretched" our minds by adding new ideas to diagnosis and prognostication of CAD through the integration of an array of atherosclerotic features that carry with them the potential to offer significant improvement over conventional measures of ischemia and stenosis. This approach is a novel one that broadens the traditional binarization of CAD as "ischemic versus nonischemic" or "stenotic versus nonstenotic." Given the highly complex multidimensional nature of CAD assessment as was done in this present study, the need becomes evident to develop multidimensional models that are likewise parsimonious enough that we can readily apply them in clinical practice to individual patients. Pericles said that "having knowledge but lacking the power to express it clearly is no better than never having any ideas at all." In this regard, technology solutions that can accurately and precisely analyze these atherosclerosis findings and, of equal import, convey them in a manner that clinicians can readily ingest serves as an urgent unmet need for development.

The present study results represent a large step forward in our understanding of CAD, and opens up an array of features that require further investigation toward improving CAD diagnosis and prognostication. As reminded by the words of Oliver Wendell Holmes, we must embrace this multidimensionality challenge, and be careful not to let our minds "shrink back to its former dimensions" of oversimplification of this complex disease (7).

FUNDING SUPPORT AND AUTHOR DISCLOSURES

Dr. Min serves as an employee of and holds equity in Cleerly; serves on the scientific advisory board of Arineta; and receives grant funding from the National Institutes of Health. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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JACC: ASIA, VOL. 1, NO. 1, 2021
JUNE 2021:49–52

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KEY WORDS atherosclerosis, coronary artery disease, ischemia