In this issue of Circulation: Cardiovascular Interventions, Kang et al1 compare intravascular ultrasound (IVUS) parameters against a gold standard of fractional flow reserve (FFR) for evaluating intermediate stenoses. Their work adds another piece of evidence to a debate whose outcome is fundamentally changing interventional cardiology. As encapsulated by the title of the “FFR versus Angiography for Multivessel Evaluation” (FAME) trial,2 the debate can be summarized simply: physiology versus anatomy. Its urgency and importance cannot be more clear, given recent skepticism toward the value of percutaneous coronary intervention (PCI): its ranking as 1 of the 10 most overused procedures in a consumer report3; litigation against an interventional cardiologist for allegedly implanting inappropriate stents4; and an editorial in a prominent medical journal calling to end ad hoc PCI.5 Therefore, the work by Kang et al1 is both timely and relevant.

The motivation to use anatomy when evaluating coronary lesions can be traced back to animal models developed more than 35 years ago. In chronically instrumented dogs with an external occluder, the coronary flow reserve fell as the lumen became progressively reduced.6 Experiments like this suggested that stenosis dimensions should be the criterion for PCI. However, a number of trials comparing outcomes in chronic angina found no survival benefit to anatomically driven PCI.7,8 Although selection bias in such studies remains a limiting factor for their generalization and may predispose the outcome toward the null hypothesis,9 it has led guidelines to recommend corroborating evidence from a functional study before PCI.10

Why do the animal models not translate better into human outcomes? Kang et al1 offer the correct explanation: “IVUS provides only a few anatomic parameters among numerous factors potentially affecting FFR.” Those factors include the complete geometric description of a stenosis (length, stenosis area, reference area), which determines its hemodynamic impact,11 diffuse atherosclerotic disease, which involves seemingly normal reference segments,12 outward remodeling, which compensates for the reduced lumen size,13 interactions between serial stenoses14 and between branches,15 and the variable size and resistance of the distal myocardial bed.16 Indeed, given these numerous effects, it might be considered remarkable that a focal IVUS measurement of minimum lumen area (MLA) performs as well as it does for predicting hemodynamic significance.

In contrast to anatomically driven treatment, physiology-guided selection of lesions for PCI reduces both major adverse cardiac events and cost in a randomized trial.2 FFR and IVUS have never been compared in a randomized fashion, but a nonrandomized, retrospective study showed that IVUS-guided lesion selection resulted in almost 3 times as many treated lesions without any difference in the event rate.17 Measuring FFR is technically no more complex or risky than IVUS and perhaps is even easier, given the 3.2F profile of the IVUS imaging sheath. FFR is more reproducible than IVUS, as demonstrated by the lower coefficient of variation reported by Kang et al.1 If the gold standard is as easy and inexpensive to measure as alternatives, then why not just perform the gold standard test?

Nevertheless, several groups have compared IVUS metrics to the gold standard of FFR in intermediate coronary lesions,18-22 the latest of which is the study by Kang et al.1 They report two key findings. First, several IVUS-based parameters predict an FFR <0.8, of which MLA <2.4 mm² produces the largest area under the receiver operating characteristic curve. Second, no IVUS parameter improves the accuracy in small-caliber vessels (MLA <2.4 mm²). For any prediction study, the number of “events” is critical, but only 49 of 236 lesions (21%) in the current study1 had an FFR <0.8. This contrasts to 63% in FAME2 but is similar to the positive FFR rates in prior work comparing IVUS against FFR: 25 of 51 (49%) lesions,18 12 of 53 (23%) lesions,19 14 of 55 (25%) patients,20 19 of 56 (34%) patients,21 and 38 of 94 (40%) patients.22 Although the majority of patients in the most recent study1 underwent PCI for stable angina, data on pre-PCI stress testing are not provided. It may be that in Korea a functional study was infrequently done before PCI, as is typical for the majority of patients here in the United States,23 which led to the observed low FFR-positive rate. Although Kang et al1 tout a high negative predictive value (NPV) for an MLA <2.4 mm², the NPV depends on the pretest probability (21%). Therefore, an IVUS parameter with no predictive power (area under the receiver operating characteristic curve =0.5, equivalent to a coin toss) would have...
an NPV of 79%.24 This comparison makes the reported NPV of 96% for MLA <2.4 mm² seem appropriately less dramatic.

A key subgroup explored by Kang et al1 examines lesions in small-caliber vessels (MLA <2.4 mm²). In this cohort, only plaque burden was an independent predictor of FFR <0.8 from the remaining IVUS-derived parameters but did not improve the accuracy. Two other groups have previously compared IVUS with FFR in small-caliber vessels: 60 patients with reference diameter <2.8 mm, 50% to 70% diameter stenosis, and lesion length <20 mm,21 and 94 patients with reference diameter <3 mm and 30% to 75% diameter stenosis.22 The first study found that no MLA cutoff could distinguish lesions with FFR ≥0.75.21 The second study found that plaque burden >79% and MLA ≥2.25 mm² identified 32 of the 38 patients (84%) with FFR <0.75 while misclassifying only 6 of the 56 patients (11%) with FFR ≥0.75. Applying this classification tree22 to the present study would provide additional insight into the question.

Taken together, these 3 studies1,21,22 suggest that lesions in small-caliber vessels prove especially difficult for IVUS evaluation. However, their findings also suggest that FFR-positive lesions are a minority in small vessels (44 of 119 [37%] lesions,1 19 of 56 [34%] patients,21 38 of 94 [40%] patients).22 Given the higher rates of restenosis in small vessels even with drug-eluting stents (for example, the in-segment restenosis rate of the sirolimus group was 8.9% for an average 2.8-mm diameter versus 18.4% for an average 2.3-mm diameter22), these studies strongly support FFR-selected PCI in small coronaries.

If FFR has compelling evidence to support lesion selection for PCI,2 carries no more risk or complexity, and works just as well for small-caliber vessels, then when should we use IVUS? The answer will allow us to prove the value of PCI to skeptics: Use FFR to determine when PCI is necessary; use IVUS to determine how PCI should be performed.26,27 Randomized trials have demonstrated that IVUS-directed PCI results in larger stent dimensions and lower rates of target vessel revascularization,28 although results have been heterogeneous, perhaps because of suboptimal incorporation of IVUS data by operators. Although not well represented in randomized trials, small-caliber vessels may provide an even better opportunity for IVUS-directed PCI to reduce restenosis. What are the percent diameter cutoffs that define an intermediate stenosis in need of FFR assessment? Data from the FAME trial suggest that a 50% to 70% stenosis still has a 35% chance of an FFR <0.8, whereas a 70% to 90% stenosis has a nonischemic FFR ~20% of the time.29 Therefore, a 50% to 90% diameter stenosis warrants investigation in a patient presenting for possible PCI if functional testing is discordant or not available. The study by Kang et al1 further supports reaching for a pressure wire instead of an IVUS catheter when evaluating intermediate lesions. Just as we should not judge a book by its cover, we should not judge a stenosis by its IVUS.

Disclosures

None.

References


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Don't Judge a Book by Its Cover: Don't Judge Stenosis Severity Solely by Intravascular Ultrasound
Nils P. Johnson and Charles J. Davidson

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