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## Paradigm Shift to Functional Angioplasty New Insights for Fractional Flow Reserve– and Intravascular Ultrasound–Guided Percutaneous Coronary Intervention

Seung-Jung Park, MD, PhD; Jung-Min Ahn, MD; Soo-Jin Kang, MD, PhD

Inducible myocardial ischemia during functional testing has crucial prognostic significance in determining whether or not to treat coronary artery stenosis.<sup>1–3</sup> In real-world practice, however, fewer than half of all patients are evaluated noninvasively for myocardial ischemia before revascularization therapy.<sup>4</sup> Thus, coronary angiograms are still frequently used as a cornerstone of decision making, despite the substantial discrepancy between the angiographic and functional severity of stenosis. Therefore, adjuvant technologies such as fractional flow reserve (FFR) and intravascular ultrasound (IVUS) are considered in daily practice to overcome the limitations of coronary angiography for diagnostic and interventional procedures. The present review evaluates the roles of FFR and IVUS in coronary stenosis and their incorporation into practice in contemporary catheterization laboratories.

### How Frequently Is Percutaneous Coronary Intervention Based on Objective Ischemia?

In contrast to the benefits of percutaneous coronary intervention (PCI) in patients with unstable angina and myocardial infarction, the benefits of PCI in patients with stable angina are less clear.<sup>5,6</sup> Nevertheless, recent advances in drug-eluting stents (DES) and adjuvant pharmacological agents may reduce the thresholds for revascularization therapy in the absence of firm evidence of objective ischemia. Thus, consideration is sometimes given to treating stenoses of intermediate degree without consideration of their functional significance.<sup>7</sup> In addition, although most surgical recommendations for patients with multivessel coronary artery disease are to bypass all lesions with diameter stenosis of  $>50\%$  for complete revascularization, the patency rate of vein grafts on vessels with functionally insignificant proximal stenosis has been in question.<sup>8</sup>

Because revascularization treatment based on ischemia may improve patient outcomes, guidelines have recommended noninvasive functional evaluation before revascularization treatment.<sup>3,9</sup> Despite these recommendations, however, noninvasive functional evaluations before revascularization are underutilized in real-world practice. Twenty years ago, Topol et al<sup>10</sup> reported that of a total of 2101 patients who underwent coronary angioplasty, only 29% had exercise testing before coronary angioplasty. Three years ago, Lin et al<sup>4</sup> demon-

strated that only 44.5% of 23 887 patients with stable angina underwent treadmill exercise or pharmacological stress testing and myocardial nuclear imaging within 90 days before elective PCI. Interestingly, high PCI volume ( $\geq 150$ ) and physician age 50 to 69 years (compared with physician age  $<40$  years) were found to be significant predictors of stress testing before elective PCI. Furthermore, in patients with acute coronary syndrome, nonculprit lesions with angiographic stenosis were frequently dilated, without consideration of objective ischemia.<sup>11</sup> Adding to the underuse of noninvasive functional studies, such studies are less sensitive and are limited in their ability to accurately localize ischemia-producing lesions in patients with multivessel coronary artery disease.<sup>12</sup>

Together, these findings indicate that the functional significance of target coronary artery stenosis is not evaluated in at least half of these patients, which potentially leads to the performance of PCI in patients who may not derive benefit from the procedure. In addition, unnecessary venous conduits may be anastomosed to the vessel with functionally insignificant stenosis, which carries a high risk of graft occlusion.<sup>8</sup> Conversely, it is possible that functionally significant stenosis remains unrevascularized.<sup>13–15</sup> Therefore, more lesion-specific alternatives to exercise stress testing or myocardial perfusion imaging during coronary angiography or PCI procedures are needed.

### Fractional Flow Reserve

Coronary pressure measurement is not a new concept. In the early days of PCI, the transstenotic pressure gradient was measured to evaluate the success of angioplasty.<sup>16</sup> By the 1990s, a novel pressure-derived index, FFR, was developed.<sup>17,18</sup> FFR is defined as the ratio of maximal hyperemic myocardial blood flow through a stenotic artery to the theoretical maximal hyperemic myocardial blood flow in the absence of stenosis and is calculated by measuring distal mean coronary and aortic pressures during maximal hyperemia with a 0.014-inch pressure-sensor angioplasty guide-wire. Therefore, it describes the influence of coronary stenosis on maximal perfusion of the subtended myocardium. For example, an FFR of 0.70 indicates a 30% reduction in maximal hyperemic blood flow due to a stenotic lesion. Normal FFR is 1.0, whereas an FFR  $<0.75$  is correlated with

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ischemia on noninvasive imaging in a variety of patient populations; an FFR  $>0.80$  excludes ischemia in 90% of cases. In a small gray zone of FFR between 0.75 and 0.80, the ischemic potential of the stenosis remains unclear.<sup>19,20</sup>

The achievement of maximal hyperemia is critical to functional lesion assessment. Both intracoronary and intravenous adenosine infusions safely produce maximal hyperemia; however, in a small percentage (8%) of patients, coronary hyperemia induced by the intracoronary administration of adenosine is suboptimal.<sup>21</sup> In addition, ostial or diffuse lesion assessment requires intravenous administration for disengagement of the guiding catheter (ostial lesion) and pressure-wire pull-back recording (diffuse lesion).<sup>19,22</sup> Therefore, intravenous administration of adenosine is preferred to achieve maximal steady state microvascular vasodilation.

Subsequent clinical studies have shown the superiority of this index, particularly in the selection of lesions appropriate for revascularization. However, although the use of FFR measurement has increased steadily over the past decade, FFR is not frequently used in current catheterization laboratory practice because of multiple factors, including habit, bias, training experience, practical pressures of patient throughput, financial incentives, misconceptions by patients, a perception by referring physicians of the need to stent coronary stenosis, cumbersome set-up time, and reimbursement for pressure wires.<sup>20</sup> Recently published results of the FAME (Fractional flow reserve versus Angiography for Multi-vessel Evaluation) randomized trial demonstrated that patient and lesion selection and treatment decisions based on systematic assessment of FFR may improve clinical outcomes in patients with coronary artery disease and save costs as well, particularly those associated with multivessel disease.<sup>23,24</sup> Because of the results of this pivotal trial, FFR measurement has gained considerable interest in the cardiology community. Furthermore, these results have been incorporated into the current guidelines for patients with coronary artery disease. US PCI guidelines now have a classification of recommendation IIa for FFR with level of evidence A, and European PCI guidelines have a classification of recommendation I with level of evidence A for FFR without objective evidence of ischemia.<sup>3,25</sup>

There are several reasons why FFR is unique and preferred in the accurate assessment of the functional significance of stenosis of individual coronary arteries. FFR has a sound mathematical basis and has been validated extensively in experimental conditions and in patients. In addition, FFR is not affected by hemodynamic conditions (eg, systemic pressure, heart rate, contractile state) and is lesion-specific, which makes it ideally suited to the assessment of multiple lesions in patients with multivessel disease. Furthermore, FFR can be determined easily during routine diagnostic workup and is quite reproducible.<sup>19</sup>

### Visual-Functional Mismatch

Several investigators have reported discrepancies between the severity of coronary angiographic stenosis and the severity of functional coronary stenosis. Of 143 patients with angiographic 3-vessel disease, 77 (54%) had no perfusion defect or only a 1-vessel disease pattern, as determined by myocardial perfusion imaging.<sup>12</sup> Another study that evaluated 67 patients with angiographic multivessel disease found that 26 patients

had no perfusion defects and 24 had 1 perfusion defect according to the myocardial perfusion imaging performed after coronary angiography.<sup>26</sup>

A recently published subanalysis of the FAME study thoroughly evaluated the “visual-functional mismatch” of coronary artery disease.<sup>27</sup> Of the patients with 3-vessel disease as assessed by visual estimation, only 14% had 3-vessel disease after FFR measurement, whereas 9% had no functionally significant stenoses. Of the 1329 target lesions ( $>50\%$  stenosis by visual estimation), only 816 (61%) had FFR  $\leq 0.80$ . Furthermore, among lesions with stenoses of 50% to 70%, 71% to 90%, and 91% to 99%, only 65%, 20%, and 4%, respectively, were found to have FFR  $>0.80$ . Of 509 patients with angiographically defined multivessel disease, only 235 (46%) had functional multivessel disease ( $\geq 2$  coronary arteries with an FFR  $\leq 0.80$ ). These findings indicated that in the absence of FFR, approximately 40% of procedures would have been performed in functionally insignificant stenotic lesions. Furthermore, a considerable proportion of patients who could have been treated by PCI underwent bypass surgery.<sup>28</sup> Therefore, coronary lesions with intermediate stenosis should be evaluated for their functional significance by FFR during PCI, particularly if no noninvasive tests are available.

The reason this phenomenon is so prevalent is that multiple factors, including lesion length, reference vessel size, and eccentricity of the lesion, contribute to flow resistance and abnormal FFR. In particular, the amount of myocardium supplied by the stenotic lesion influences its functional significance. A moderate stenosis in a vessel that supplies a large myocardial territory can be functionally significant, whereas a very severe stenosis in a vessel supplying a small myocardial territory may not be functionally significant.<sup>29</sup> Therefore, simple visual assessment via a coronary angiogram cannot predict the functional significance of coronary stenosis. Interventional cardiologists should overcome their personal visual bias that produces a suboptimal outcome option and use the option that produces the best treatment outcome.

### Natural Course of Lesions Deferred on Percutaneous Coronary Intervention-Based Fractional Flow Reserve Measurements

One of the barriers to the widespread use of FFR to guide therapy is concern about long-term safety if treatment of angiographically significant lesions is deferred. Nuclear imaging studies have suggested that treatment of nonischemic coronary lesions may be deferred and that patients with these lesions may be safe.<sup>1</sup> In a meta-analysis of thallium single-photon emission computed tomography (SPECT), the annual incidence of death or myocardial infarction was less than 1% per year in these patients.<sup>30</sup> Moreover, patients with lesions with insignificant FFR values were shown to have favorable outcomes.<sup>31,32</sup>

To date, the only randomized trial to address this concern is the DEFER (FFR to Determine Appropriateness of Angioplasty in Moderate Coronary Stenoses) study, in which 5-year outcomes were assessed in 325 patients assigned to 3 groups.<sup>31</sup> Patients with FFR  $\geq 0.75$  were randomly assigned to the deferral group ( $n=91$ , medical therapy for coronary artery disease) or the PCI group ( $n=90$ , PCI with stents), whereas patients in the reference group, with FFR  $<0.75$

**Table 1. Clinical Outcomes of Lesions Deferred on the Basis of FFR**

	Pijls et al <sup>32</sup>	Oud et al <sup>33</sup>	Legalery et al <sup>34</sup>	Mates et al <sup>35</sup>	Reczuch et al <sup>36</sup>	Meuwissen et al <sup>37</sup>	Bech et al <sup>38</sup>
Study design	Randomization	Observation	Observation	Observation	Observation	Observation	Observation
FFR cutoff value	≥0.75	≥0.75	≥0.80	≥0.75	>0.75	≥0.75	≥0.75
No. of patients	91	70	237	85	41	157	100
Age, y	61	64	60	61	61	61	61
Mean follow-up, mo	60	22	12	22.6	15	0.9	18
Clinical outcomes							
Death, n (%)			3 (1)				
Cardiac death	3 (3.3)	1 (1)	NA	2	0	0	0
Noncardiac death	3 (3.3)	3 (4)	NA	5	0	0	3
MI, n (%)	0	4 (6)	2 (1)*	0	1	2	1
TVR, n (%)	8 (8.9)	7 (10)	9 (4)	3	2	11	5

FFR indicates fractional flow reserve; NA, not available; MI, myocardial infarction; and TVR, target-vessel revascularization.

\*Acute coronary syndrome.

(n=144), underwent PCI as planned. The 5-year event-free survival rates were similar in the deferred and PCI groups (80% versus 73%,  $P=0.52$ ). The composite rates of cardiac death and acute myocardial infarction in the deferred, PCI, and reference groups were 3.3%, 7.9%, and 15.7%, respectively. Therefore, the annual risk of cardiac death or myocardial infarction in patients with normal FFR was <1%. These findings demonstrated that functionally nonsignificant coronary stenosis, regardless of angiographic stenosis, could be safely deferred for up to 5 years.

Recently, the 2-year clinical outcomes of patients with deferred lesions in the FFR-guided group from the FAME study were reported.<sup>32</sup> Among the 513 lesions in patients in whom treatment was deferred on the basis of FFR value, only 1 (0.2%) experienced an myocardial infarction and only 16 (3.2%) required repeat revascularizations. Other studies<sup>33–38</sup> have consistently shown that the rates of death and myocardial infarction in patients with deferred treatment of lesions are quite low (Table 1). In most of those studies, however, patient populations were small and follow-up periods were relatively short. Studies in larger populations with longer follow-up periods are needed to confirm the long-term safety of deferred PCI based on FFR.

### Can Intravascular Ultrasound Minimal Lumen Area Predict the Functional Significance of Coronary Artery Stenosis?

IVUS imaging provides a tomographic 360° sagittal scan of the vessel from the lumen through the media to the vessel

wall. IVUS has enriched the understanding of human coronary atherosclerosis and has contributed to understanding of the mechanisms of coronary angioplasty.

Although IVUS cannot directly estimate the functional significance of coronary stenosis, attempts have been made to determine the IVUS parameters that correspond to functionally significant coronary artery narrowing, thus integrating target-lesion anatomy and physiology.<sup>39–45</sup> Strong correlations have been observed between IVUS-measured minimal lumen area (MLA) and inducible ischemia as determined by myocardial SPECT imaging, coronary flow reserve, and FFR (Table 2).

Over the last 10 years, some interventionists have inserted stents into every lesion with MLA <4 mm<sup>2</sup> on IVUS; however, some argument against this approach has been raised recently as FFR was becomingly increasingly used in daily practice. Problems have centered around 2 questions: What IVUS-measured MLA truly corresponds to the ischemic threshold, and can IVUS predict the functional significance of coronary stenosis?

An IVUS MLA of 4 mm<sup>2</sup> is theoretically large enough to affect coronary blood flow. It is generally accepted that >50% diameter stenosis, which corresponds to >75% area stenosis, is significant. An MLA of 4 mm<sup>2</sup> is just equivalent to diameter stenoses of 24% and 43% for lesions with reference vessel diameters of 3 and 4 mm, respectively (Figure 1).

In addition, although IVUS MLA is important in determining coronary blood flow based on the Bernoulli equation,

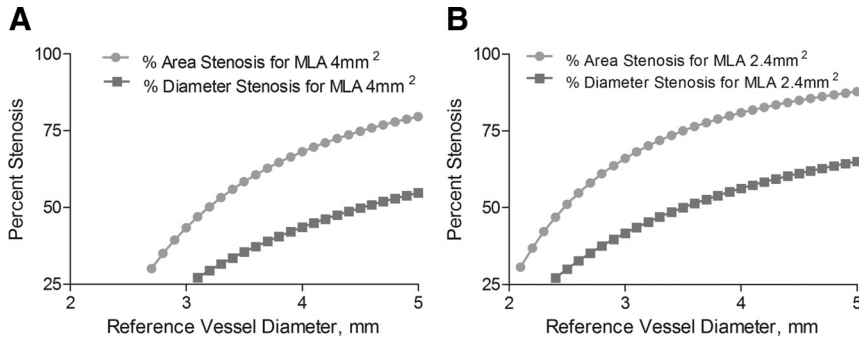
**Table 2. IVUS-Measured MLA Criteria for Functionally Significant Lesions**

	Nishioka et al <sup>39</sup>	Briguori et al <sup>40</sup>	Takagi et al <sup>41</sup>	Abizaid et al <sup>42</sup>	Jasti et al <sup>43</sup>	Lee et al <sup>44</sup>	Kang et al <sup>45</sup>
Functional study	Thallium (+)	FFR <0.75	FFR <0.75	CFR ≥2.0	FFR 0.75	FFR <0.75	FFR <0.8
No. of lesions	70	53	51	112	55	94	201
Cutoff MLA, mm <sup>2</sup>	≤4.0	≤4.0	<3.0	≥4.0	5.9*	≤2.0†	<2.4
Accuracy, %	NA	79	90.2	89	94	NA	68
Sensitivity, %	90	92	83.0	NA	93	82.4	90
Specificity, %	88	56	92.3	NA	95	80.8	60

IVUS indicates intravascular ultrasound; MLA, minimal lumen area; FFR, fractional flow reserve; CFR, coronary flow reserve; and NA, not available.

\*For left main coronary arteries.

†For small-vessel disease (<3 mm).

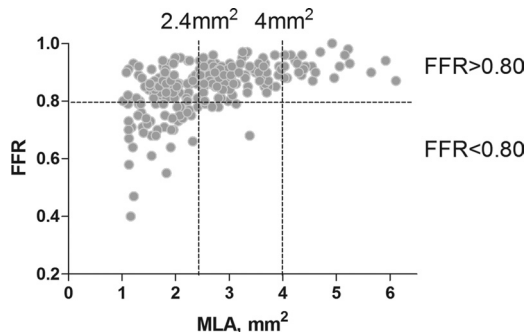


**Figure 1.** Theoretical relationships between reference vessel diameter and percentage diameter stenosis and percentage area stenosis for minimal lumen area (MLA) of (A) 4 mm<sup>2</sup> and (B) 2.4 mm<sup>2</sup>.

other important factors also affect coronary flow, including the degree of diameter stenosis, lesion length, plaque burden, vessel size, lesion morphology, plaque characteristics, blood viscosity, collateral circulation, and subtended myocardial perfusion bed.<sup>15</sup> Some of these factors can be measured as simply as MLA, but others cannot. Because the hemodynamic severity of coronary stenosis is influenced by the integration and spatial summation of the hemodynamic and anatomic aspects of a stenosis, IVUS MLA criteria alone are unlikely to predict the functional significance of coronary artery stenosis.

We recently addressed these issues in 201 patients with 236 coronary lesions who underwent preinterventional IVUS and FFR measurements to determine the best IVUS MLA criteria corresponding to FFR <0.80.<sup>45</sup> Multivariate analysis showed that MLA ( $\beta=0.020$ , 95% confidence interval 0.008 to 0.031,  $P=0.032$ ), plaque burden ( $\beta=-0.002$ , 95% confidence interval  $-0.003$  to 0.001,  $P=0.001$ ), lesion length with a lumen area <3 mm<sup>2</sup> ( $\beta=-0.003$ , 95% confidence interval  $-0.005$  to 0.001,  $P=0.005$ ), and left anterior descending artery location ( $\beta=-0.035$ , 95% confidence interval  $-0.055$  to 0.0016,  $P=0.001$ ) were independent predictors of FFR <0.80. In addition, using receiver operating characteristic analysis, we provided new IVUS MLA criteria that showed that the best cutoff value of IVUS MLA for predicting FFR <0.80 was 2.4 mm<sup>2</sup>, a figure smaller than reported previously.

Furthermore, a scatterplot (Figure 2) showed that the FFR values of lesions with MLA <4 mm<sup>2</sup> were widely scattered, and 66% of analyzed lesions had MLA <4 mm<sup>2</sup> but FFR >0.80. Using our new, stricter criteria of MLA, <2.4 mm<sup>2</sup>, 30% of analyzed lesions had MLA <2.4 mm<sup>2</sup> but FFR >0.80. Thus, the use of our new IVUS MLA criteria may



**Figure 2.** Scatterplot showing the relationship between intravascular ultrasound-determined minimal lumen area (MLA) and fractional flow reserve (FFR).

avoid unnecessary procedures in 36% of coronary lesions investigated. Nevertheless, regardless of cutoff values, use of IVUS MLA criteria alone cannot predict the result of FFR measurement and could still lead to the performance of unnecessary procedures in a considerable proportion of patients. Therefore, cardiologists should be aware of this disconnection between the visual (by IVUS) and functional relationship. In addition, MLA alone cannot replace noninvasive or invasive functional studies in clinical decision making about whether to dilate a coronary stenosis.

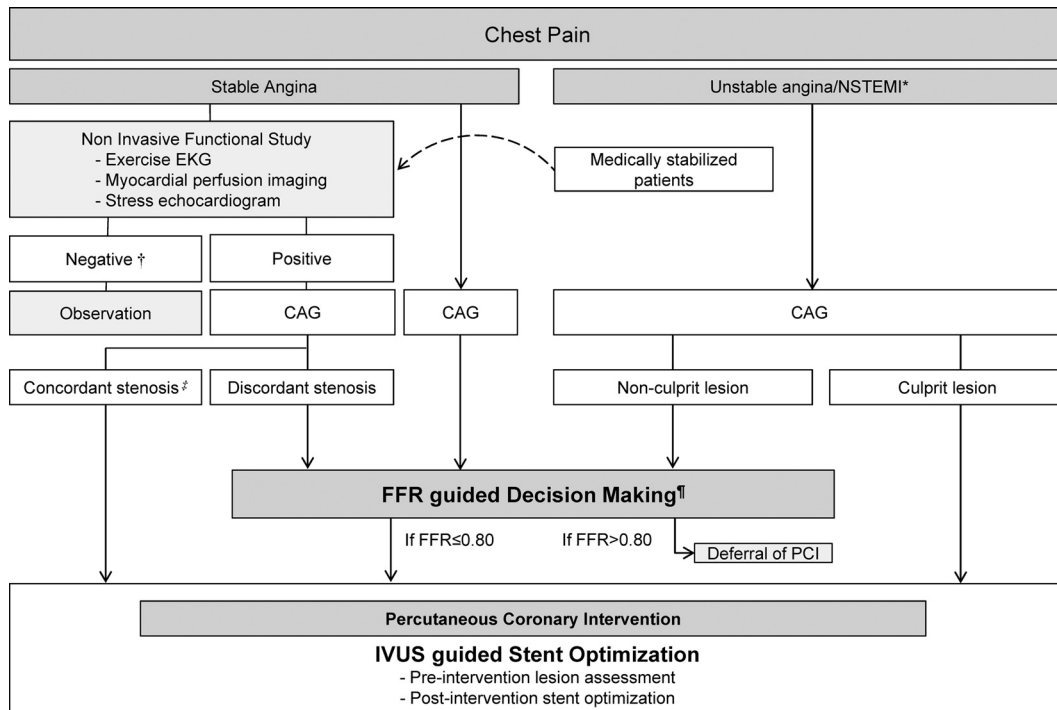
### Role of Intravascular Ultrasound in Percutaneous Coronary Intervention

In contrast to FFR, IVUS has provided valuable information on cross-sectional coronary vascular structure. IVUS has therefore played a key role in contemporary stent-based PCI in the accurate assessment of coronary anatomy, the selection of treatment strategy, and stent optimization.

The advent of DES, which have markedly reduced the rate of in-stent restenosis, may reduce the clinical utility of IVUS; however, contemporary PCI with DES is not totally free from in-stent restenosis and the need for subsequent repeat revascularization therapy.<sup>46</sup> Furthermore, the reduced risk of in-stent restenosis in patients undergoing DES implantation is offset by concerns about stent thrombosis.<sup>47</sup> The increased use of DES has increased the identification of complex lesions and the need for complicated procedures and has led to the treatment of more high-risk patients.<sup>48,49</sup>

Indeed, IVUS measurements of stent length and minimum stent lumen area have influenced the long-term outcomes of DES stenting.<sup>50</sup> In a study of 449 patients (543 lesions) who completed 6-month angiographic follow-up after implantation of sirolimus-eluting stents, the postprocedural minimum stent lumen area and stent length on IVUS emerged as the only predictors of stent restenosis. IVUS cutoff values that predicted restenosis were a minimum stent lumen of 5.5 mm<sup>2</sup> and a stent length of 40 mm.

Moreover, IVUS-guided DES implantation was found to significantly reduce the rates of definite stent thrombosis at 30 days and 12 months in 884 propensity-matched patients.<sup>51</sup> In that study, unselected patients undergoing DES implantation under IVUS guidance were identified and compared with those undergoing angiography-guided PCI. The IVUS-guided group showed significant reductions in definite subacute stent thrombosis (0.5% versus 1.4%,  $P=0.045$ ) and cumulative stent thrombosis (0.7% versus 2.0%,  $P=0.014$ ) at 12 months



**Figure 3.** Algorithm of functional angioplasty. CAG indicates coronary angiogram; EKG, electrocardiogram; FFR, fractional flow reserve; IVUS, intravascular ultrasound; NSTEMI, non-ST-segment elevated myocardial infarction; and PCI, percutaneous coronary intervention. \*Medically stabilized patients with unstable angina/NSTEMI may follow the algorithm of patients with stable angina. †In patients with a high likelihood of coronary artery disease based on patient's history and risk factors, multiple noninvasive functional studies or coronary angiogram despite negative noninvasive functional study is recommended. ‡Concordant (or discordant) stenosis indicates the stenosis in the same (or different) territory as ischemic territory of noninvasive functional study. Even in concordant stenosis, FFR measurement in a tandem lesion is recommended to identify the ischemia-producing specific lesion. ††FFR-guided decision making indicates FFR is measured first in all lesions, and only if it is  $\leq 0.80$  does the operator stent the lesion according to the particulars of the clinical situation, including myocardial ischemic burden, patient performance, and symptoms.

compared with the angiography-guided group.<sup>51</sup> Possible mechanisms were unclear, but poststenting IVUS surveillance might identify the factors associated with stent thrombosis, including stent underexpansion, malapposition, inflow/outflow disease, dissection, and thrombus, which could lead to treatment and subsequent reduction of the stent thrombosis.

We also reported the importance of IVUS-guided PCI in high-risk patients, including those with left main coronary artery stenosis and bifurcation stenosis.<sup>52,53</sup> Both studies demonstrated that compared with angiography-guided PCI, IVUS-guided PCI may reduce long-term mortality, probably by reducing the risk of stent thrombosis.

Together, these findings demonstrate that routine IVUS guidance may be important in optimizing DES implantation and in determining the safety of PCI procedures. Indeed, a randomized trial to compare IVUS-guided and angiography-guided PCI demonstrated that overall, 42% of patients in the IVUS-guided group received further treatment.<sup>54</sup> However, the lack of a proper study demonstrating the benefits of IVUS-guided PCI may be a barrier to the application of IVUS guidance in daily practice. This lack may be due to the updating of angiography-guided PCI by knowledge gained with the use of IVUS. That is, PCI procedures have been optimized according to IVUS findings, which prevents demonstration of the clinical benefits of IVUS-guided PCI.

### Functional Angioplasty: Incorporation of Fractional Flow Reserve and Intravascular Ultrasound Into Daily Practice

Although FFR-guided and IVUS-guided PCI have been compared,<sup>55</sup> the issue of superiority might be irrelevant. The FFR value and IVUS-measured parameters should not be considered an equivalent comparison, because these are complementary and not competitive.

FFR measurements, based on the objective determination of ischemia, can assist individual interventional cardiologists in making decisions about revascularization in patients with coronary artery disease, thereby helping to balance the risks and benefits of PCI in various clinical situations. Much clinical evidence indicates that use of this dedicated invasive functional method may help select appropriate patients and lesions for treatment, avoid unnecessary procedures, achieve reductions in medical costs, and improve patients' clinical outcomes. IVUS can be used to secure the PCI procedure by preintervention lesion assessment and postintervention stent optimization. In other words, FFR can be used to determine the functional significance of a stenotic lesion, whereas IVUS surveillance can be used to assess the anatomy of a lesion, including its size, the position of plaque, and the adequacy of stent deployment.

We propose an algorithm of functional angioplasty to incorporate FFR and IVUS into catheterization laboratory practice in Figure 3. This approach may include several

limitations of costs, procedural time, and availability of trained personnel. However, the simultaneous use of these 2 complementary modalities may result in optimization of PCI results and may indicate the future direction of interventional cardiology.

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### Disclosures

None.

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