Should we be using fractional flow reserve more routinely to select stable coronary patients for percutaneous coronary intervention?

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Purpose of review
To address the clinical benefit of fractional flow reserve (FFR) measurement in stable coronary artery disease (CAD) patients.

Recent findings
The efficacy of revascularization in patients with stable CAD has been debatable. However, there has been consensus that revascularization for ischemic-producing lesions may improve clinical outcomes. FFR is considered nowadays as the gold standard for the invasive assessment of ischemic potential of intermediate coronary artery stenosis. Intermediate stenosis with FFR of greater than 0.80 has been demonstrated to be safely deferred with annual event rate less than 1%. Recently, preliminary data of FAME II trial presented that revascularization for stenosis with FFR of 0.80 or less has clinical benefits over optimal medical treatment with respect to the reduction of unplanned hospitalization and urgent revascularization in stable CAD patients. A large randomized controlled trial demonstrated that FFR-guided percutaneous coronary intervention (PCI) improved clinical outcomes while reducing the medical costs in multivessel CAD. Therefore, current guidelines recommend the consideration of FFR measurements as level of evidence 'A' when the ischemic potential for specific target lesions is questionable.

Summary
Much clinical evidence indicates that use of this dedicated invasive functional method may help in selecting appropriate patients and lesions for treatment, avoiding unnecessary procedures, reducing medical costs, and improving each patient's clinical outcomes. Therefore, we should use FFR more routinely to select stable coronary patients for PCI.

Keywords
coronary disease, fractional flow reserve, revascularization

INTRODUCTION

During several decades, many physicians have assessed the severity of coronary artery stenosis by coronary angiography alone. However, multiple studies have reported the inaccuracy of conventional decision-making of revascularization based on angiography alone [1]. In addition, in stable coronary artery disease (CAD) patients, the benefit of revascularization has been in debate. By contrast, the use of objective ischemia-based percutaneous coronary intervention (PCI) may improve the functional status or clinical outcomes of patients [2–4]. Nevertheless, noninvasive functional evaluations are infrequently performed prior to PCI and suffer from relatively low sensitivity and low spatial resolution [5–7].

The fractional flow reserve (FFR) is a lesion-specific index reflecting the effect of coronary stenosis on myocardial perfusion and is considered as the gold standard for the invasive assessment of functional significance of the severity of coronary artery stenosis [8]. Previous studies have found superior clinical outcomes with FFR-based PCI

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KEY POINTS

- Ischemia-guided coronary revascularization may improve the clinical outcomes of stable coronary disease.
- The fractional flow reserve (FFR) is a lesion-specific index reflecting the effect of coronary stenosis on myocardial perfusion and is considered as the gold standard for the invasive assessment of functional significance of the severity of coronary artery stenosis.
- Revascularization for the stenosis of FFR of 0.80 or less may have benefit over optimal medical treatment regarding the reduction of urgent readmission and revascularization treatment, and the stenosis of FFR greater than 0.80 can be safely deferred to revascularization under optimal medical treatment.
- Therefore, FFR-guided revascularization in stable coronary disease results in avoiding unnecessary procedures, reducing medical costs, and improving each patient's clinical outcomes.

compared with conventional angiography-based treatment [9–14]. Therefore, current guidelines recommend the consideration of FFR measurements as level of evidence 'A' when the ischemic potential for specific target lesions is questionable [15,16]. However, despite the proven benefit of FFR measurement in assessing CAD, the FFR measurement was underutilized in daily practice for stable CAD patients. Therefore, we reviewed why we should use FFR more routinely to select lesions and patients for revascularization in stable CAD setting.

ISCHEMIA-GUIDED REVASCULARIZATION IN STABLE CORONARY ARTERY DISEASE PATIENTS

Revascularization for acute coronary syndrome has been considered as a life-saving procedure [17]. In contrast, the efficacy of revascularization in patients with stable CAD has been debatable. Large randomized clinical trials comparing revascularization and optimal medical treatment, such as the Clinical Outcomes Utilizing Revascularization and Aggressive drug Evaluation (COURAGE) or the Bypass Angioplasty Revascularization Investigation 2 Diabetes (BARI2D) trials, failed to demonstrate the benefit of stent implantation for the prevention of death, nonfatal myocardial infarction (MI), unplanned revascularization, or angina [18,19].

However, in a subgroup of stable CAD patients, particularly having poor exercise capacity or large ischemic burden, the benefit of revascularization has been observed. The clinical benefit of bypass surgery was evaluated in 5303 patients from the Coronary Artery Surgery Study (CASS) registry who underwent exercise test. Surgical benefit was observed only in patients who showed at least 1 mm of ST segment depression at stage 1 or less. However, among patients who were able to exercise into stage 3 or greater, survival benefit of surgical revascularization over medical treatment was not observed [20]. In addition, a large retrospective single photon-emission computed tomography study showed that the benefits of revascularization were confined to patients with greater than 10% of ischemic burden of left ventricle [21].

Recently, we evaluated the role of ischemia assessed by the traditional myocardial perfusion imaging (Fig. 1). Ischemia-guided PCI was defined as when revascularization was performed in the matched coronary artery with the perfusion abnormality on myocardial perfusion image. The incidence of major adverse cardiac and cerebrovascular events (MACCE) including death, MI, stroke, or repeat revascularization was significantly lower in the ischemia-guided PCI group than in the non-ischemia-guided PCI group (16.2 vs. 20.7%; adjusted hazard ratio, 0.73; 95% confidence interval, 0.60–0.88; $P = 0.001$), primarily driven by the lower repeat revascularization rate (9.9 vs. 22.8%; adjusted hazard ratio, 0.66; 95% confidence interval, 0.49–0.90; $P = 0.009$). Therefore, ischemia-guided revascularization using myocardial perfusion imaging appears to decrease the risk of repeat revascularization and MACCE for patients with multivessel disease [22▪▪].

Therefore, in stable CAD patients, ischemic targeting PCI may have the benefit over medical treatment. However, currently available noninvasive functional studies frequently failed to distinguish the specific ischemic territories and responsible stenosis. Hence, alternatives to traditional noninvasive functional study during PCI procedures are needed.

FRACTIONAL FLOW RESERVE

FFR is defined as the ratio of maximal blood flow achievable in a stenotic coronary artery relative to the maximal flow in the same vessel if it was normal [23,24]. A 0.014-inch pressure sensor-tipped coronary angioplasty guide wire is advanced across a stenosis, and the absolute distal pressure is recorded at rest and at maximal hyperemia induced with intracoronary or intravenous infusion of adenosine. Unlike coronary flow reserve, FFR is independent of changes in heart rate, blood pressure, or prior infarction, and takes into account the contribution of collateral blood flow. Therefore, FFR is a very specific

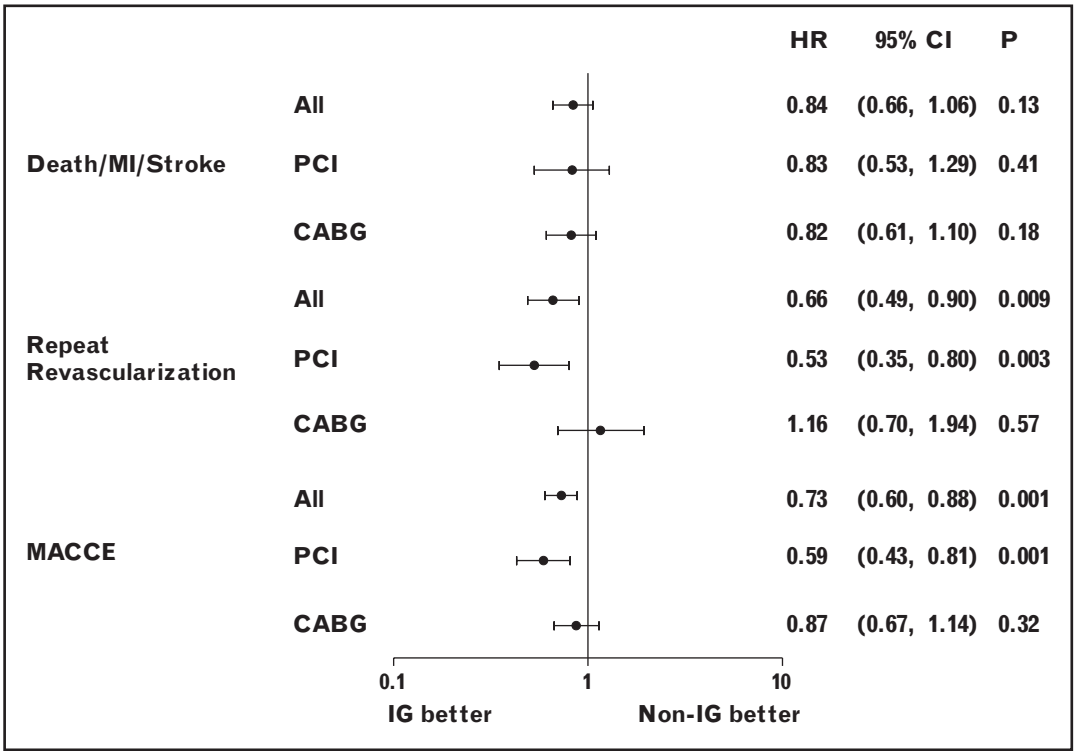

FIGURE 1. Adjusted hazard ratios of ischemia-guided revascularization for events. Image from [22▪▪].

index that describes the influence of coronary stenosis on maximal perfusion of the subtended myocardium. FFR values less than 0.75 are associated with stress testing in numerous comparative studies with high sensitivity (88%), specificity (100%), positive predictive value (100%), and overall accuracy (93%). FFR values of at least 0.80 are associated with negative ischemic results with a predictive accuracy of 95%. Reports from single stress-testing comparisons and variations in testing and patients have produced a small zone of FFR uncertainty (0.75–0.80), the use of which required clinical judgment. These lesion-specific values were already validated in a wide range of clinical situations. For example, an FFR of 0.70 simply indicates a 30% reduction in maximal hyperemic blood flow because of a stenotic lesion, which should be matched with clinical ischemia [25].

FRACTIONAL FLOW RESERVE GREATER THAN 0.80: STENTING NO MORE EFFECTIVE

The FFR to Determine Appropriateness of Angioplasty in Moderate Coronary Stenoses (DEFER) study, in which 5-year outcomes were assessed in 325 patients assigned to three groups [if FFR $\geq$0.75, the deferral group ($n=91$, medical therapy for CAD) or the PCI group ($n=90$, PCI with stents); if FFR less than 0.75, the reference group ($n=144$, PCI with stents)] [26]. The 5-year event rates of death or MI were 3.3 and 7.9% in the deferral group and the PCI group, respectively ($P=0.21$). Therefore, the annual risk of cardiac death or MI in patients with normal FFR is less than 1% per year and was not decreased by stent implantation, suggesting that functionally nonsignificant coronary stenosis, regardless of angiographic stenosis, could be safely deferred for up to 5 years [26].

From the 2-year clinical outcomes of the Fractional Flow Reserve Versus Angiography for Multivessel Evaluation (FAME) study, patients with deferred lesions in the FFR-guided group experienced the incidence of 2.0% of MI and of 3.2% of repeat revascularization [27]. In addition, recently, 5-year medical follow-up of functionally insignificant proximal left anterior descending artery stenosis (LAD) was reported. The 5-year survival estimate was 92.9% in the medical group (FFR $\leq$0.80) vs. 89.6% in the revascularized group (FFR $>$0.80; $P=0.74$). Therefore, they showed medical treatment of patients with a functionally nonsignificant stenosis (FFR $\geq$0.80) in the proximal LAD is associated with an excellent long-term clinical outcome.

Furthermore, stent implantation in functionally insignificant stenosis (FFR $>$0.80) can increase the risk of thrombotic events and restenosis to levels far exceeding the low risk associated with the deferral of

revascularization [26]. Even drug-eluting stent implantation cannot prevent the detrimental risk of adverse events when stents are implanted in multiple lesions [28]. Therefore, FFR measurement could avoid unnecessary PCI and its related complications, resulting in better clinical outcomes.

FRACTIONAL FLOW RESERVE 0.80 OR LESS: STENTING JUSTIFIED

The FAME II (Fractional Flow Reserve-Guided Percutaneous Coronary Intervention plus Optimal Medical Treatment versus Optimal Medical Treatment Alone in Patients with Stable Coronary Artery Disease) trial is a follow-up to the landmark FAME trial [29▪▪]. The goal of the FAME II trial is to compare the clinical outcomes, safety, and cost-effectiveness of PCI guided by FFR plus optimal medical treatment (OMT) with OMT alone in stable CAD. Prior to randomization, all patients will have an FFR measurement of affected arteries. Patients found to have one or more ischemic lesions (FFR $\leq$0.80) will be randomized 1 : 1 to PCI and OMT or OMT only. Standard of care for OMT includes the use of aspirin, beta blockers, antianginal medicine, and statin. Primary endpoint was major adverse cardiac event (MACE) rate, defined as all-cause death, documented MI, and unplanned hospitalization leading to urgent revascularization at 2 years. Preliminary results, presented recently, showed 7.6 times greater risk of hospital readmission with revascularization for patients who received OMT alone and 11.2 times greater risk in the need for unplanned hospital readmission with urgent revascularization. Therefore, revascularization for the stenosis of FFR 0.80 or less may have benefit over OMT regarding the reduction of urgent readmission and revascularization treatment.

CORONARY ANGIOGRAPHY OR INTRAVASCULAR ULTRASOUND CANNOT PREDICT THE FUNCTIONAL SIGNIFICANCE

During lesion assessment by FFR, some lesions appear significant on angiograms but are functionally nonsignificant; conversely, some lesions have benign-looking narrowing on angiograms but appear significant by FFR (Fig. 2).

Subanalysis of the FAME study thoroughly evaluated the 'visual-functional mismatch' of coronary artery disease [1]. Of the patients with three-vessel disease, as assessed by visual estimation, only 14% had three-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 of 0.80 or less. Furthermore, among lesions with stenoses of 50–70, 71–90%, and 91–99%, only 65, 20, and 4%, respectively, were found to have FFR greater than 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, about 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 [30].

We also demonstrated the discrepancy between coronary angiography and FFR in 1792 coronary stenoses in 1411 patients. Lesions with angiographic diameter stenosis (DS) of at least 50% and FFR greater than 0.80 were seen in 44% of intermediate coronary artery stenoses. Conversely, lesions with DS less than 50% and FFR less than 0.80 were found in 17% of the intermediate coronary artery stenoses (Fig. 3a, unpublished data).

Consistent findings were observed when minimal lumen area (MLA) measured by intravascular ultrasound was compared with FFR. During the last decade, some interventionists have inserted stents into a lesion with MLA less than 4 mm^2 [31]. However, we recently addressed these issues in 201 patients with 236 intermediate coronary stenoses who underwent preinterventional intravascular ultrasound (IVUS) and FFR measurement to determine the best IVUS MLA criteria corresponding to FFR less than 0.80 and its predictability. Using receiver operating characteristic analysis, IVUS MLA of 2.4 mm^2 was identified as the best cutoff value for predicting FFR less than 0.80. Despite stricter criteria than reported previously, among lesions with MLA less than 2.4 mm^2, only 37% had FFR of less than 0.80 (Fig. 3b) [32▪].

As functional significance of coronary stenosis was associated with various clinical and lesion specific factors, frequently unrecognizable in diagnostic coronary angiography or IVUS examination, anatomical assessment alone cannot predict the functional significance of coronary stenosis. Therefore, interventional cardiologists are supposed to employ the FFR measurement more frequently in decision making for revascularization, particularly in stable CAD patients.

FRACTIONAL FLOW RESERVE-GUIDED PERCUTANEOUS CORONARY INTERVENTION

FFR-guided PCI was considered when stents were placed in indicated lesions only if the FFR was 0.80 or less after FFR was measured in each diseased

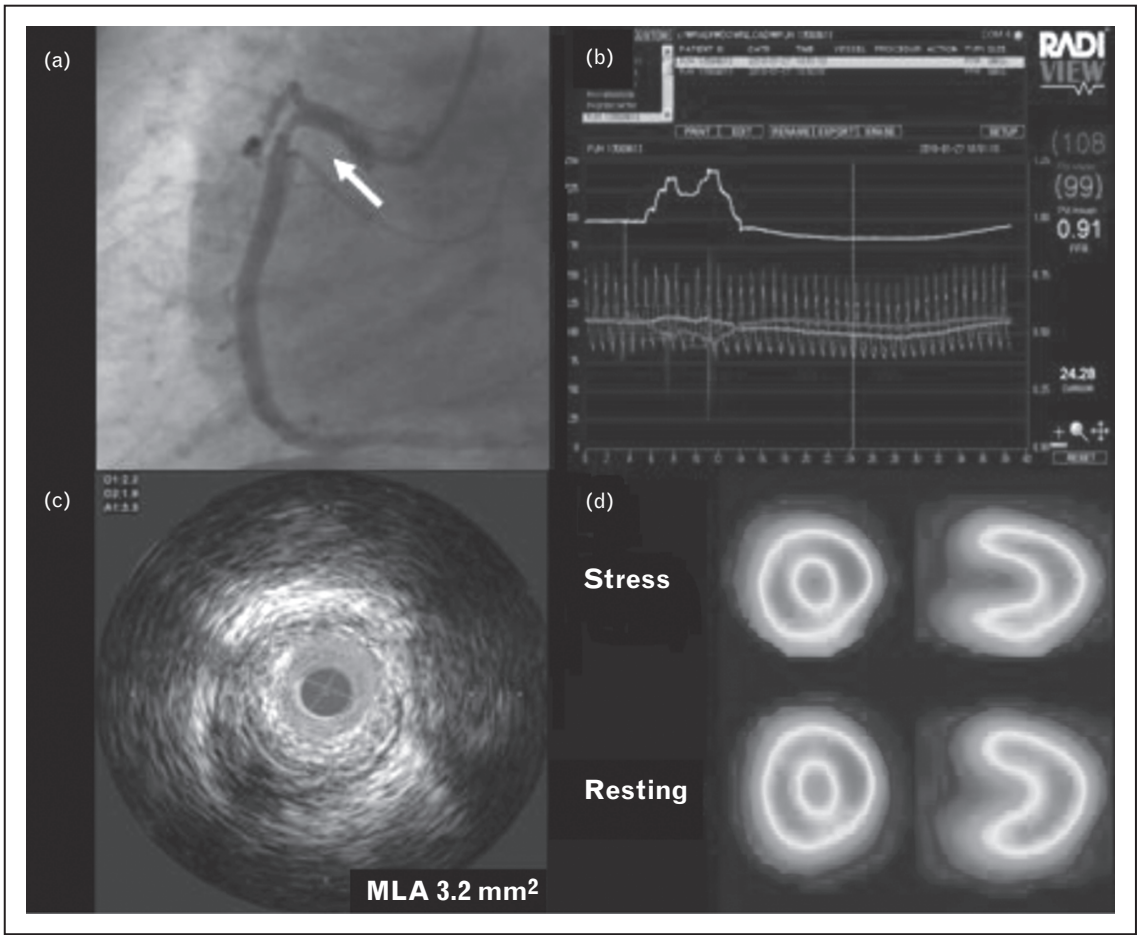

FIGURE 2. Examples of discrepancy between anatomical and functional assessments: 'Visual-Functional Mismatch': The results of (a) coronary angiography, (b) fractional flow reserve, (c) intravascular ultrasound, and (d) thallium SPECT are shown. Coronary angiography showed ≈70% diameter stenosis, but fractional flow reserve of 0.91, normal thallium SPECT was observed.

coronary artery. Clinical feasibility and benefits of FFR-guided PCI were firstly demonstrated in multivessel disease patients. Wongpraparut *et al.* [10] assessed the clinical outcomes of FFR-guided PCI in 137 patients with multivessel disease. The 30-month Kaplan–Meier event-free survival rate was significantly higher in the FFR-PCI than in the conventional PCI group (89 vs. 59%, $P < 0.01$).

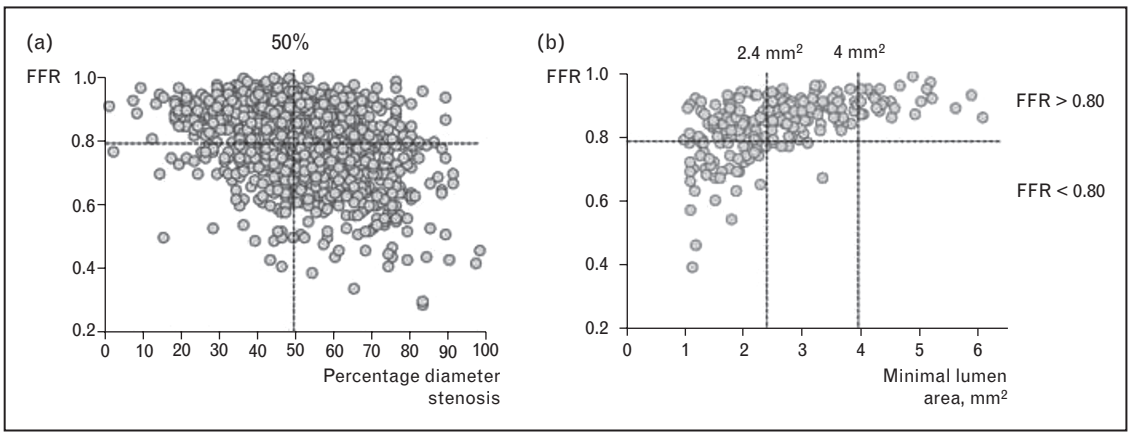

FIGURE 3. The scattered plot for the fractional flow reserve (FFR) and angiographic diameter stenosis (a) [unpublished data] and the FFR and minimal lumen area assessed by intravascular ultrasound (b) [32▪].

The FAME study was the only prospective, randomized trial designed to determine whether FFR-guided PCI was superior to angiography-guided PCI in a total of 1005 multivessel disease patients [12]. The rates of primary outcomes (13.2 vs. 18.4%, $P = 0.02$) and the combination of death or MI (7.3 vs. 11%, $P = 0.02$) at 1 year were significantly lower in the FFR-guided PCI than in the angiography-guided PCI group, which was maintained at 2-year follow-up. FFR-guided PCI strategy was also demonstrated to be beneficial in bifurcation disease and small vessel disease [11,14].

Another benefit of FFR-guided PCI is less use of stent implantation while achieving favorable clinical outcomes. Economic evaluation of the FAME study demonstrated that FFR-guided PCI in patients with multivessel coronary disease was associated with improvement of outcomes and saving resources [33]. This result was mainly derived from the more tailored use of stent implantation, thus avoiding procedure-related complications. Recently, stent overuse and appropriate use of PCI procedure have been an important issue in contemporary medical society [34]. FFR-guided PCI would be an important strategy to realize more appropriate stent procedure.

CONCLUSION

Much clinical evidence indicates that the use of this dedicated invasive functional method may help in selecting appropriate patients and lesions for treatment, avoiding unnecessary procedures, reducing medical costs, and improving each patient's clinical outcomes. Therefore, we should use FFR more routinely to select stable coronary patients for PCI.

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Conflicts of interest

There are no conflicts of interest.

REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as:

- ■ of special interest
- ■■ of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (pp. 694–695).

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