Landmark Fractional Flow Reserve Trials

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KEYWORDS

• Coronary artery disease • Coronary ischemia • Coronary physiology • Fractional flow reserve • Percutaneous coronary intervention

KEY POINTS

- Fractional flow reserve (FFR) has been validated using a true gold standard for noninvasive ischemia (a combination of 3 stress test modalities).
- The Fractional Flow Reserve to Determine Appropriateness of Angioplasty in Moderate Coronary Stenoses (DEFER) trial established the ability of FFR to identify intermediate lesions in which revascularization can safely be deferred.
- The Fractional Flow Reserve versus Angiography for Multivessel Evaluation (FAME) trial demonstrated the safety and feasibility of FFR-guided revascularization in stable and unstable patients with multivessel coronary disease.
- FAME 2 trial demonstrated higher rates of urgent revascularization, myocardial infarction (MI), and death in patients with stable angina (SA) who have functionally significant lesions based on FFR, which are treated with medical therapy.
- FFR has been shown to be cost effective through reduction in the number of unnecessary stents and reduction in adverse cardiac events.

INTRODUCTION

Historically, the gold standard for assessment of coronary disease was based on visual estimation of angiographic stenosis. The anatomic lumenogram information provided by coronary angiography is limited in its ability to assess physiologic significance of identified lesions and their likelihood of causing coronary ischemia. The clinical significance of a coronary lesion depends on the extent of viable myocardium supplied by the vessel. Approximately 39% of angiographically obstructive coronary stenoses have no functional significance.[1] Revascularization of nonhemodynamically significant coronary lesions may lead to worse clinical outcomes.

Several strategies have been used to identify and localize coronary ischemia. Noninvasive stress testing has been used as a first-line modality for diagnosis and risk stratification of patients with known or suspected coronary disease. Noninvasive techniques are useful from a population standpoint and have been implemented in appropriateness guidelines.[2] However, each of these imaging methods has limited spatial resolution and diagnostic accuracy, particularly in patients with multivessel coronary disease.[3] As shown in Fig. 1, myocardial perfusion imaging with single-photon emission computed tomography has poor correlation with FFR among patients with multivessel disease.[4]

Functional lesion testing using FFR has been validated in the assessment of intermediate coronary stenosis. FFR uses a coronary wire equipped with a miniaturized pressure transducer to measure the ratio of distal coronary pressure, distal to a coronary stenosis, to the proximal pressure during maximal coronary vasodilation.[5] Unlike coronary flow reserve, FFR is independent of variation in hemodynamic parameters,

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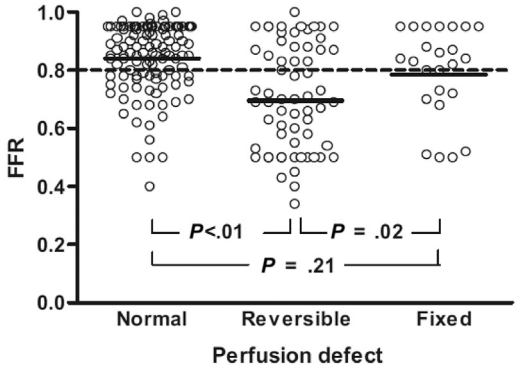

Fig. 1. Correlation of FFR and type of defect detected by myocardial perfusion imaging. (*From* Melikian N, De Bondt P, Tonino P, et al. Fractional flow reserve and myocardial perfusion imaging in patients with angiographic multivessel coronary artery disease. JACC Cardiovasc Interv 2010;3:311.)

such as heart rate, systemic blood pressure, and stroke volume. Importantly, FFR allows on-the-table hemodynamic assessment of coronary lesions overcoming many of the limitations of noninvasive evaluation modalities. An FFR value less than or equal to 0.80 has been validated for identification of ischemic lesions. Importantly, lesions with an FFR of greater than 0.80 can be managed safely without revascularization. Recent trials have demonstrated the superiority of FFR-based revascularization strategies over traditional angiography-guided revascularization. Herein, the authors review the landmark trials that validated FFR and its role in revascularization decisions.

VALIDATION IN COMPARISON TO NONINVASIVE ISCHEMIA ASSESSMENT

Pijls and colleagues[6] correlated FFR values with results of noninvasive stress test modalities (bicycle exercise testing, thallium scintigraphy, and stress echocardiography) among 45 patients presenting with chest pain and found to have moderate coronary lesions. Although there was no true gold standard for assessment of myocardial ischemia, the researchers used the combination of results of the 3 stress test modalities to establish a true noninvasive standard. The accuracy of any one stress test is 70% to 80%; however, the use of the combination of 3 test increases the accuracy to greater than 95% using Bayes theorem. Among the 21 patients with an FFR less than 0.75, myocardial ischemia was demonstrated on at least one of the stress tests. Following revascularization, the FFR values normalized. Among 21 of the 24 patients with FFR values greater than or equal to 0.75, there was no evidence of myocardial ischemia on any of the 3 stress test modalities. These patients were ultimately followed up for 14 months and remained free of revascularization during this time. Using a cutoff value of 0.75 for diagnosis of myocardial ischemia, this study demonstrated a sensitivity of 88% and specificity of 100% for FFR. This study also established early safety of deferral of revascularization for moderate coronary lesions with FFR values greater than or equal to 0.75.

SAFETY OF REVASCULARIZATION DEFERRAL WITH NORMAL FRACTIONAL FLOW RESERVE IN SINGLE-VESSEL CORONARY DISEASE

The long-term safety of deferring percutaneous revascularization of moderate coronary lesions with FFR values greater than or equal to 0.75 was subsequently demonstrated in the DEFER trial.[7] A total of 325 patients referred for elective percutaneous intervention of moderate de novo coronary lesions (defined as >50% diameter stenosis) with no documented myocardial ischemia within the prior 2 months were randomized to one of 2 groups based on the FFR value. All patients with FFR less than 0.75 underwent percutaneous transluminal coronary angioplasty (PTCA) as planned (reference group, n = 144). If the FFR was greater than or equal to 0.75, patients were randomized to either deferral of intervention (n = 91) or performance of PTCA as planned (n = 90). Among patients in the deferral and performance groups, event-free survival was similar at 24 months (89% vs 83%, P = .27). In contrast, patients in the reference group had a significantly lower event-free survival at 12 and 24 months of 80% and 78%, respectively, likely due to a greater burden of atherosclerosis. The proportion of patients with angina-free survival was similar between the deferral and PTCA groups at 1 year but was significantly higher among patients in the deferral group at 24 months (70% vs 51%, P = .02). This pivotal randomized trial established the short-term safety of deferring intervention for angiographically moderate lesions with nonischemic FFR values.

In a follow-up study from the DEFER trial,[8] event-free survival out to 5 years was not significantly different between the deferral and performance groups (80% vs 73%; P = .52). The combined rate of cardiac death and acute myocardial infarction (AMI) was 3.3% and 7.9% in the deferral and performance groups, respectively (P = .21), as shown in Figs. 2 and 3.