The importance of integrating coronary physiology into percutaneous coronary intervention (PCI) has been recognized since its inception. When Andreus Gruentzig first described percutaneous transluminal coronary angioplasty, he stressed the need to identify the translesional pressure gradient before and after intervention as a means of guiding a successful procedure.1 Subsequently, other investigators examined the use of the Doppler wire to measure coronary flow velocity reserve before and after PCI.2 Unfortunately, the lack of a low-profile pressure-monitoring device and the lack of appreciation of the importance of measuring hyperemic pressure gradients inhibited the full integration of coronary physiology into the PCI procedure. Additionally, with the advent of stents, the ease and safety of PCI improved dramatically. In conjunction with financial reimbursement for PCI and patient demand, these factors resulted in an inclination toward performing PCI, regardless of the functional significance of the stenosis.

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While this enthusiasm over PCI was occurring, Pijls and coworkers3 and De Bruyne and colleagues4 first described fractional flow reserve (FFR). Like any new technique, FFR has required time to mature. Over the ensuing 20 years since its introduction, improvements in the pressure wire-handling characteristics, the integration of data acquisition into the catheterization laboratory workflow, the completion of a number of multicenter, randomized studies, and the increased emphasis on appropriate use of PCI have contributed to FFR achieving its current status as an indispensable and critical component of PCI.

Concept of FFR

FFR is defined as the ratio of myocardial blood flow down a coronary artery in the presence of an epicardial stenosis compared with the flow down the same vessel in the theoretical absence of any stenosis.3 The derivation of FFR has been described in detail and is shown in brief in Figure 1.3,4 FFR can be calculated easily by measuring the mean distal coronary pressure with a coronary pressure wire and dividing it by the mean proximal coronary pressure, measured with a guiding catheter, during maximal hyperemia (Figure 2A and 2B).

FFR was first validated in a landmark study by Pijls, De Bruyne, and colleagues5 in which they measured FFR in 45 patients with single-vessel intermediate coronary disease. Because there is no true noninvasive reference standard for diagnosing myocardial ischemia and to improve the accuracy of existing tests, every patient underwent exercise testing, dobutamine stress echocardiography, and exercise thallium scintigraphy. According to the Bayes theorem and on the basis of the diagnostic accuracy of each individual stress test, the composite accuracy of these 3 consecutive tests for myocardial ischemia approaches 100%. In every patient with an FFR <0.75, myocardial ischemia was present on at least 1 test, and in 21 of 24 patients with FFR values of ≥0.75, myocardial ischemia was absent on all 3 tests, giving a sensitivity, specificity, and diagnostic accuracy of FFR for identifying lesions capable of inducing myocardial ischemia of 88%, 100%, and 93%, respectively. In the 24 patients with an FFR of ≥0.75, there were no ischemic events during 14 months of follow-up. This small study formed the cornerstone for a number of larger studies that validated...
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FFR has a number of unique aspects that distinguish it from other indexes of coronary physiology such as coronary flow velocity reserve (Table). FFR has an upper normal value of 1.0 in every patient and every vessel. In a study of 37 angiographically normal-appearing coronary arteries in patients without signs of myocardial ischemia, the average FFR was 0.97. FFR is extremely reproducible and independent of hemodynamic perturbations. In another study, the coefficient of variation of 2 repeated FFR measurements was 1.6%, and there was no significant difference in FFR after changing the heart rate with pacing, the blood pressure with sodium nitroprusside administration, or the left ventricular contractility with dobutamine administration.

FFR has a narrow cutoff range, distinguishing lesions capable of producing ischemia from lesions that are not hemodynamically significant. Multiple studies performed by numerous different groups in a variety of patient populations have shown that FFR values <0.75 to 0.80 have a very high specificity for identifying ischemia based on a variety of noninvasive imaging studies. If the FFR value is >0.80, it is very unlikely that the vessel or lesion interrogated is responsible for significant ischemia.

FFR has superb spatial resolution. By placing the pressure wire in the distal portion of an epicardial vessel, one can measure the FFR and determine whether the disease in that vessel is responsible for ischemia. If the FFR is abnormal, and particularly if the vessel has tandem areas of narrowing, one can slowly pull the pressure wire back to the proximal vessel during maximal hyperemia and identify which lesion is responsible for the greatest portion of the gradient. It is important to note that with the pressure sensor positioned between the 2 narrowings, distal to the proximal one, it is not possible to determine the “FFR” of the proximal narrowing. The reason is that each narrowing affects flow across the other and the removal of 1 narrowing, for example with PCI, can lead to an increase in flow down the vessel and a larger pressure gradient across the remaining lesion.

In the setting of tandem stenoses, equations have been described that allow the operator to determine the FFR of each lesion in the theoretical absence of the other lesion; however, the complexity of these equations and the requirement

**Derivation of Fractional Flow Reserve**

**FFR = Maximum Myocardial Flow (Stenosis) / Maximum Myocardial Flow (Normal)**

Myocardial Flow = \( \Delta \text{Pressure} / \text{Resistance} \)

\[ FFR = \frac{(P_d - P_v)}{P_{a} - P_{v}} / \text{Resistance at maximal hyperemia} \]

\[ FFR = \frac{P_d - P_v}{P_a - P_v} \]

\[ FFR = \frac{P_d}{P_a} \]

**Figure 1.** Derivation of fractional flow reserve (FFR). During maximal hyperemia, resistance is minimized and assumed to be unchanged in the presence and absence of an epicardial stenosis; therefore, it is removed from the equation. Venous pressure is generally negligible in relation to coronary pressure and assumed to equal zero. \( P_d \) indicates proximal coronary or aortic pressure; \( P_v \) distal coronary pressure; and \( P_a \) venous pressure.

FFR in a variety of patient populations and clinical scenarios, and it demonstrated the safety of deferring revascularization of lesions that are not functionally significant (nonischemic FFR).

**Practical Aspects of FFR**

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Unique Aspects of Fractional Flow Reserve

<table>
<thead>
<tr>
<th>Description</th>
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<tbody>
<tr>
<td>Normal value of 1.0 in every patient/vessel</td>
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<tr>
<td>Narrow ischemic threshold (0.75–0.80)</td>
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<tr>
<td>Highly reproducible</td>
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<tr>
<td>Independent of hemodynamic changes</td>
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<tr>
<td>Specific for epicardial artery stenosis</td>
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<td>Independent of the microvasculature</td>
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<td>Accounts for collateral flow</td>
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for measuring the coronary wedge pressure have limited their clinical utility.9

FFR is independent of the microvasculature, is specific for epicardial coronary artery disease, and accounts for both coronary and collateral flow. In patients with remote myocardial infarction (MI), for example, FFR still correlates with the presence or absence of ischemia on noninvasive stress imaging.10

In this setting, the flow across a given stenosis subtending infarcted myocardium will be less and the pressure gradient will be less, leading to a higher FFR value. The higher FFR is not falsely elevated but reflects the smaller amount of viable myocardium supplied by the vessel and still provides information on the expected gain in flow after PCI. On the other hand, if there is an intermediate lesion in a vessel supplying collaterals to viable myocardium subtended by a chronically occluded vessel, the flow down the collateral-supplying vessel will be greater than in the normal setting, the pressure gradient across the intermediate stenosis will be higher than expected, and the FFR will be lower. These scenarios help to explain why FFR is more accurate than angiography or intravascular anatomic methods such as intravascular ultrasound for identifying lesions capable of producing myocardial ischemia.

One of the limitations of FFR is that it is not reliable in the culprit vessel of a patient with an ST-segment–elevation MI. The reason is that FFR assumes that microvascular resistance will be minimized and fixed. In the culprit vessel of an ST-segment–elevation MI, there is a variable degree of reversible microvascular stunning, resulting in a lower maximum achievable flow, a lower pressure gradient, and a higher FFR. With time, the microvasculature may recover, maximum achievable flow may increase, and a larger gradient with a lower FFR may be measured across a given stenosis. For this reason, the FFR measured in the culprit vessel in the acute setting may be higher than the FFR measured in the same vessel 1 month later. However, in the setting of non–ST-segment–elevation acute coronary syndromes, in which the degree of reversible microvascular dysfunction is likely to be low, measuring FFR in the culprit and nonculprit vessels has been shown to be safe and effective.11 Moreover, in nonculprit vessels of patients with ST-segment–elevation MI, FFR remains accurate.12

Achieving maximal hyperemia is a prerequisite to measuring FFR accurately. A potential pitfall to FFR measurement is the lack of maximal vasodilation, which will result in lower maximal flow across a stenosis, a lower pressure gradient, and a falsely high FFR. In the validation studies and major clinical trials, FFR has been measured after administration of intravenous adenosine delivered via a central vein at 140 μg·kg−1·min−1. This method has been shown to be extremely safe and reliable.8 Most patients have symptoms of either chest pressure or dyspnea related to the infusion, but they are well tolerated in the vast majority of cases and resolve as soon as the infusion is discontinued. In one respect, these symptoms are reassuring because they inform the operator that hyperemia has occurred.

Why Do We Need FFR?

Myocardial ischemia is associated with symptoms and adverse cardiac outcomes. Noninvasive stress imaging identifies the presence and degree of myocardial ischemia and can predict death and MI.13 However, the spatial resolution (ie, the ability to identify the culprit lesion or even vessel) of noninvasive stress imaging is lacking, particularly in patients with multivessel coronary disease.14 The noninvasive test is a useful gatekeeper to decide which patients warrant invasive coronary angiography, but once the patient is in the cardiac catheterization laboratory, FFR is necessary to identify which lesion is responsible for the patient’s symptoms. This was recently highlighted in 2 studies comparing FFR and nuclear perfusion scanning in patients with multivessel disease, both of which demonstrated significant discordance between the 2 modalities and prompted the editorialists to conclude that FFR is the reference standard for identifying lesions capable of producing ischemia.15-17 Not only does the inaccuracy of noninvasive imaging make FFR necessary, but the fact that noninvasive stress imaging has not been performed in the majority of patients undergoing PCI further emphasizes the need for a cardiac catheterization laboratory–based technique for identifying lesions capable of producing ischemia.18

One might argue that the coronary angiogram is accurate enough to guide the decision about PCI once a patient makes it to the catheterization suite. However, in the Fractional Flow Reserve Versus Angiography for Multi-vessel Evaluation (FAME) trial, FFR was measured in >500 patients with multivessel coronary disease and compared with the visual interpretation of the angiogram.19 Approximately 35% of the lesions graded as being between 50% and 70% narrowed had an ischemic FFR, whereas roughly 20% of the lesions between 71% and 90% had nonischemic FFR values (Figure 3). Multiple smaller studies have asked experienced interventional cardiologists to predict which lesions will have an ischemic FFR value and which will not; in all cases, the diagnostic accuracy of the visual interpretation of the angiogram has been unacceptable for guiding decisions about the need for PCI.20-21 Quantitative coronary angiography has not improved the lack of concordance between the angiographic severity of a stenosis and its ischemic potential.22

Others might argue that FFR is not necessary because intravascular imaging techniques such as intravascular ultrasound or optical coherence tomography are available and can accurately identify which lesions warrant PCI. These techniques provide detailed visualization of coronary plaque and allow quantification of lumen area and other anatomic parameters such as...
lesion length that contribute to the ischemic potential of a stenosis. Unfortunately, they currently do not provide information on the viscous and separation forces or flow across a stenosis, all of which are accounted for by measuring the pressure gradient and all of which determine the functional significance of a stenosis. Most studies evaluating the accuracy of either intravascular ultrasound or optical coherence tomography for identifying lesions responsible for ischemia have compared the minimum lumen area assessed by either technique with FFR and have found poor correlations. The reason is that the cutoff for a significant minimum lumen area will vary, depending on where the measurement is made along the vessel, the size of the vessel, and the amount of viable myocardium subtended by the vessel. One of the advantages of FFR is that the same cutoff is applied in every patient and every vessel.

**Data Supporting FFR-Guided PCI**

Initially, FFR was promoted as a method for identifying which intermediate coronary lesions could be treated safely medically without PCI. At the 18-month follow-up of a retrospective cohort of 100 patients with chest pain, intermediate coronary stenoses, and nonischemic FFR values in whom PCI was deferred in favor of medical therapy, there were no cardiac deaths, 1 target vessel MI, and 3 target vessel revascularizations. These data were reassuring, but it was not until a multicenter, prospective, randomized trial was published by Bech and colleagues that FFR gained traction as a method for guiding PCI in patients with moderate left main disease in whom revascularization was deferred because the FFR was not in the ischemic range. More recently, Hamilos and colleagues reported 213 patients with moderate left main disease in whom FFR was measured. FFR was nonischemic in 138 of these patients, and revascularization was deferred. The 5-year survival rate was 90% in these patients compared with 85% in those with ischemic FFR values who underwent revascularization ($P=0.48$). The event-free survival also was similar between the 2 groups. In this study, as in previous ones, experienced interventional cardiologists were unable to predict accurately which lesions would have a significant FFR on the basis of their interpretation of the angiogram, further emphasizing the importance of an FFR-guided approach to PCI even when involving the left main coronary artery (Figure 4).

The DEFER trial and others like it established FFR as a method for deferring PCI, not necessarily as a technique to be embraced by the interventional cardiology community. Two studies evaluating FFR after stenting showed that it could be used to determine optimal stent deployment and to predict outcomes after PCI. However, it was not until the FAME trial was performed and published by Tonino and colleagues that FFR gained traction as a method for guiding PCI. In the FAME trial, 1005 patients with coronary lesions of >50% diameter stenosis in 2 or 3 major epicardial vessels that were amenable to PCI with drug-eluting stents were randomized either to the standard of care, angiography-guided PCI, in which case PCI was performed on the basis of the noninvasive clinical data and the angiographic appearance of the lesions, or to FFR-guided PCI, in which case FFR was measured across every stenosis and only if the FFR was ≤0.80 was PCI performed on the particular stenosis.

There were =3 lesions identified per patient in both groups, but the angiography-guided PCI group received significantly more stents per patient (2.7±1.2 versus 1.9±1.3; $P=0.001$). In addition, significantly more contrast media was administered to the angiography-guided PCI patients (302±127 versus 83.3% in the perform group ($P=0.27$). The cardiac death rate was 2.2% and the study lesion revascularization rate was 5.6%, without any MI in the deferral group. Angina relief also was similar between the 2 groups. Subsequently, the 5-year death and MI rates of the 2 groups have been reported. Although not statistically significant, the 3.3% rate in the deferral group was less than half the 7.9% rate in the perform group ($P=0.21$).

The findings from the DEFER trial established the safety of treating functionally nonsignificant intermediate epicardial coronary narrowings with medicine as opposed to PCI, but they did not address an important and often vexing subgroup of intermediate coronary lesions, those involving the left main coronary artery. The inadequacy of the angiogram alone for assessing the severity of moderate left main coronary disease has been appreciated for years. However, relying on a novel technique such as FFR to make the critical decision about revascularization in this setting has gained acceptance more slowly. Initially, a number of small, single-center studies demonstrated excellent short-term outcomes in patients with moderate left main disease in whom revascularization was deferred because the FFR was not in the ischemic range. More recently, Hamilos and colleagues reported 213 patients with moderate left main disease in whom FFR was measured. FFR was nonischemic in 138 of these patients, and revascularization was deferred. The 5-year survival rate was 90% in these patients compared with 85% in those with ischemic FFR values who underwent revascularization ($P=0.48$). The event-free survival also was similar between the 2 groups. In this study, as in previous ones, experienced interventional cardiologists were unable to predict accurately which lesions would have a significant FFR on the basis of their interpretation of the angiogram, further emphasizing the importance of an FFR-guided approach to PCI even when involving the left main coronary artery (Figure 4).

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Importantly, the hard end points of death and MI remained significant—appearing lesions (>50% diameter stenosis) that had deferred PCI of lesions that are not functionally significant. In the FFR-guided patients, there were 513 angiographically significant lesions that were treated medically without PCI. The 2-year rate of MI resulting from 1 of these lesions was 0.2% and the revascularization rate was 3.2%. This is particularly noteworthy given that approximately one fourth of these deferred lesions appeared >70% narrowed on visual interpretation of the angiogram. Data like these led the European Society of Cardiology to give FFR its highest recommendation, Class IA, in favor of FFR-guided PCI when objective evidence of ischemia is lacking. Older guidelines from the American cardiology societies give FFR a Class IIA recommendation for assessing the need for PCI of an intermediate lesion.

By demonstrating improved outcomes despite more judicious use of stents, the FAME trial validated the concept of “functional angioplasty,” stenting lesions responsible for ischemia and not hemodynamically significant. In this manner, the benefit of the stent is optimized and the risks are minimized. Although this approach results in a functionally complete revascularization, it does not result in an anatomically complete one. In patients with multivessel coronary disease, this is particularly relevant because many of our treatment decisions about revascularization are based on angiographic (or anatomic) assessment of the severity of coronary disease. For example, the Synergy between Percutaneous Coronary Intervention with Taxus can Cardiac Surgery (SYNTAX) score is an angiography-based scoring system designed to quantify the complexity of coronary disease. Patients with high SYNTAX scores tend to have better outcomes with coronary artery bypass graft surgery, whereas those patients with low scores appear to do equally well with PCI.

Because the SYNTAX score is based on visual interpretation of the angiogram, it is inherently limited by the inaccuracy of the angiogram. A substudy from the FAME trial asked whether incorporating FFR into the SYNTAX score and calculating a functional SYNTAX score (FSS) might convert patients with a higher-risk SYNTAX score to a lower risk and whether it might improve the risk stratification of patients with multivessel coronary disease undergoing PCI.

In the 497 patients in the FFR-guided arm of FAME, the SYNTAX score was calculated in the usual fashion, and the patients were divided into tertiles based on the SYNTAX score. The FSS was then determined by recalculating the SYNTAX score and taking into account only those lesions...
with an FFR ≤0.80. More than one third of patients moved from a higher-risk group to a lower-risk group after calculation of the FSS. In addition, the FSS was a significant predictor of death or MI, whereas the classic SYNTAX score was not (Figure 6). In this manner, the FSS simplifies the approach to PCI in many of these challenging patients with multivessel disease and may make PCI a more appropriate treatment than coronary artery bypass graft surgery. This hypothesis is now being tested prospectively in the FAME 3 trial, comparing FFR-guided PCI with coronary artery bypass graft surgery in patients with 3-vessel coronary disease.

The FAME trial also further established the safety and benefit of measuring FFR in patients with non–ST-segment-elevation acute coronary syndromes. A small study of 70 patients with unstable angina and non–ST-segment-elevation MI suggested that measuring FFR, even in the culprit vessel, was a safe and reliable method for triaging treatment decisions.38 The FAME trial, however, included a much larger cohort of 328 patients with unstable angina or non–ST-segment-elevation MI who underwent urgent angiography and were randomized to FFR-guided or to angiography-guided PCI, including FFR assessment of both the culprit vessel and nonculprit vessel. A substudy of this cohort revealed a relative risk reduction from FFR-guided compared with angiography-guided PCI in the patients with non–ST-segment-elevation acute coronary syndrome similar to that seen in the stable patients enrolled in the FAME trial.39

Although the FAME trial successfully demonstrated that decisions about PCI in patients with multivessel coronary disease should be based on FFR guidance and not the angiogram alone, one of the criticisms of the FAME trial was the use of the zotarolimus-eluting Endeavor stent in >40% of patients because of concern that it might be inferior to the 2 other drug-eluting stents available at the time of the study, the paclitaxel-eluting Taxus stent and the sirolimus-eluting Cypher stent. However, a subsequent study has demonstrated lower rates of periprocedural MI and similar rates of target lesion revascularization and target vessel failure with the Endeavor stent compared with the Taxus stent.40 Moreover, a longer-term comparison of the Endeavor and Cypher stents revealed significantly lower rates of mortality, MI, and major adverse cardiac events.41

Another criticism that has emerged is that the results of FAME would be different if the second-generation everolimus-eluting stent had been used because studies have shown that this stent is superior to first-generation drug-eluting stents.42 However, any improved outcome seen with the everolimus-eluting stent would occur in both the angiography- and FFR-guided patients, with the FFR-guided patients still having improved outcomes compared with the angiography-guided patients. For the angiography-guided patients to achieve results similar to or better than those achieved by the FFR-guided patients, the event rate after everolimus-eluting stenting would need to be similar to or lower than the event rate after medical treatment of nonischemic lesions. At the 2-year follow-up in FAME, the deferred lesions had a 0.2% MI rate and a 3.2% revascularization rate; at the 2-year follow-up after everolimus-eluting stenting, the MI rate was 2.5% and the target vessel revascularization rate was 6.8%.

A final criticism of FAME was the lack of a medical therapy arm in the randomization scheme, particularly in the patients with stable coronary artery disease. The Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation (COURAGE) trial randomized >2000 patients with stable single-vessel or multivessel coronary disease to best medical therapy alone or to PCI in addition to best medical therapy and found no difference in the rate of death or MI at a median follow-up of 4.6 years.44 On the basis of these results, some wondered what the event rate in FAME would have been if a medical therapy arm had been included in the two thirds of stable patients in FAME not presenting with an acute coronary syndrome.

One of the goals of the FAME 2 trial was to address this concern by comparing PCI of lesions with an abnormal FFR with best medical therapy in patients with stable single-vessel or multivessel coronary disease.45 One of the criticisms of the COURAGE trial is that low-risk patients without significant myocardial ischemia were enrolled. The FAME 2 trial was designed specifically to ensure the inclusion of patients with a large burden of ischemia. This was achieved by randomizing only patients with at least 1 lesion in 1 of the 3 major epicardial vessels with >50% narrowing and an FFR ≤0.80. Those patients with narrowings of >50% but with an FFR >0.80 were not included in the randomized portion of the study but were followed up in a registry and treated with best medical therapy. The goal was to randomize roughly 1600 patients and to follow them for 2 years with a primary composite end point of death, MI, or unplanned hospitalization requiring urgent revascularization.

After 888 patients had been randomized, recruitment into FAME 2 was stopped prematurely by the data and safety...
monitoring board because of a highly significant difference in the primary end point between the 2 groups. After a mean follow-up of only 7 months, the primary end point occurred in 12.7% of patients in the best medical therapy arm compared with 4.3% in the PCI plus best medical therapy arm. There was no significant difference in death (0.7% versus 0.2%; \( P=0.31 \)) or MI (3.2% versus 3.4%; \( P=0.89 \)), but there was a highly significant difference in the rate of unplanned hospitalization requiring urgent revascularization (11.1% versus 1.6%; \( P<0.001 \)) between the best medical therapy arm and PCI arm, respectively. The rate of any revascularization was also significantly higher in the best medical therapy arm (19.5% versus 3.1%; \( P<0.001 \)).

Both groups in FAME 2 received excellent medical therapy, with the vast majority prescribed aspirin, a statin, a β-blocker, and an angiotensin-converting enzyme inhibitor at rates similar to those seen in the COURAGE trial. The majority of patients in the best medical therapy arm also received a calcium channel blocker or nitrate for refractory angina. Despite this, the hospitalization rate for an acute coronary syndrome requiring urgent revascularization in the best medical therapy arm was 11.1% at just 7 months. In comparison, in the COURAGE trial, the rate of an acute coronary syndrome at a median follow-up of 4.6 years was only 11.8%. This difference likely resulted because, in the FAME 2 trial, in which FFR was measured first, patients with a larger burden of ischemia were randomized.

The concept of more severe ischemia resulting in worse outcomes is supported further by the fact that stratifying outcomes in FAME 2 on the basis of an FFR value of 0.65 demonstrated a significant interaction, meaning that those patients with more severe ischemia at baseline had even greater benefit with PCI compared with medical therapy alone.

Importantly, there were 332 patients in the FAME 2 trial with angiographic coronary disease that was not significant on the basis of the FFR assessment, and 166 of these patients were randomly assigned follow-up in a registry receiving best medical therapy alone. The primary end point occurred in only 3.0% of these registry patients with a 2.4% rate of urgent revascularization. This finding further emphasizes the importance of not only identifying angiographic evidence of coronary disease but also characterizing whether the disease is responsible for ischemia. Patients with these types of lesions benefit from PCI, whereas patients with angiographic disease that is not functionally significant as assessed by FFR respond well to medical therapy alone.

The FAME 2 trial has been criticized because it was stopped early, because there was no significant difference in the rate of death or MI, and because the primary end point included unplanned hospitalization requiring urgent revascularization, which some consider a subjective or “soft” end point. The data and safety monitoring board concluded that, from a scientific standpoint, the difference in the rate of the composite end point between the 2 groups was so statistically significant that it was extremely unlikely that completing enrollment would alter the results. Even though there was no difference in death and MI, the board considered unplanned hospitalization requiring urgent revascularization as an important safety outcome. Although this is a subjective end point compared with death and MI, it was adjudicated by an independent clinical events committee. Approximately one half of the unplanned hospitalizations requiring urgent revascularization were associated with biomarker elevation or ECG changes consistent with ischemia. With the use of this stricter and more objective definition of acute coronary syndrome, there was still a highly significant difference in the rate of unplanned hospitalization requiring urgent revascularization between the 2 groups (0.9% versus 5.2%; \( P<0.001 \); unpublished data).

The FAME 2 trial was not powered to detect a significant difference between the 2 randomized groups with respect to death and MI; however, a landmark analysis showed that, during the first 7 days after enrollment, there was a higher rate in the PCI arm (1.8% versus 0.2%; \( P=0.04 \)) resulting primarily from periprocedural MI in the PCI patients, whereas after 7 days, there was a higher rate of death and MI in the best medical therapy arm (1.6% versus 3.7%; \( P=0.05 \)) resulting primarily from spontaneous MI. Other studies have found that late spontaneous MI is a much stronger predictor of long-term mortality than peri-PCI MI. Longer-term follow-up of the FAME 2 trial will be important to evaluate this further.

Many accepted therapies that we provide our patients, for example, orthopedic procedures, do not reduce death or MI, but they improve quality of life and decrease the need for hospitalization. The fact that PCI guided by FFR has not yet been shown to decrease death or MI rates compared with medical therapy should not diminish its value.

Another important consideration in assessing the value of a new approach is the economic and quality-of-life implications of the approach compared with the standard of care. Both an early analysis using computer modeling and a randomized, single-center study suggested that measuring FFR was cost-effective in patients with intermediate single-vessel coronary disease compared with a noninvasive stress imaging strategy. In the FAME trial comparing FFR-guided PCI and angiography-guided PCI in patients with multivessel coronary disease, the FFR-guided approach significantly reduced costs both at the time of the procedure and during follow-up. Although the coronary pressure wire and adenosine cost approximately $800, by decreasing the number of drug-eluting stents necessary for revascularization, the FFR-guided approach resulted in roughly $700 savings in procedural costs. Because of the lower rate of adverse events in the FFR-guide group, the 1-year costs were reduced significantly by $2400.

Quality of life in the FAME trial was assessed with the EuroQual 5 dimension health survey at baseline, 1 month, and 1 year. The quality-adjusted life-years (QALYs) were numerically higher in the FFR-guided patients, although not statistically different at 1 year (0.853 versus 0.838; \( P=0.20 \)). Bootstrap simulation revealed that the FFR-guided strategy was cost-saving in >90% of cases and cost-effective (at a
Thus, compared with an angiography-guided approach, an FFR-guided strategy is a dominant one. More recently, the cost-effectiveness of an FFR-guided strategy for PCI has been compared with medical therapy in patients with stable coronary disease. In the FAME 2 trial,
performance of PCI on lesions with an abnormal FFR resulted in a roughly $6000 initial cost increase compared with best medical therapy. However, during the course of 1 year, this difference narrowed to just under $3000 because of increased revascularization costs in the best medical therapy arm. Quality of life improved significantly in the PCI group of patients, whereas there was no change in the best medical therapy arm. It was assumed, from previous data from the COURAGE trial and other studies, that this difference in quality of life would gradually dissipate over 3 years but that the cost difference between the 2 strategies would not narrow any further. From these assumptions, the cost-effectiveness of performing PCI on lesions with an abnormal FFR was $36000 per QALY gained compared with best medical therapy. Bootstrap simulation revealed that for 80% of cases the cost-effectiveness ratio was <$50000 per QALY gained and for 99.5% of cases it was <$100000 per QALY gained (Figure 7B).

Conclusions

Should FFR be measured in all cases of PCI? If a patient has typical angina and single-vessel coronary disease with a significant-appearing lesion in a vessel subtending myocardium that is ischemic on a noninvasive stress imaging study, then FFR measurement is not necessary. If a patient is having an acute MI with significant single-vessel coronary disease, FFR is not necessary. However, these 2 scenarios represent the minority of cases seen in the cardiac catheterization laboratory. The vast majority of cases involve patients with multivessel disease, lesions of indeterminate severity, or discordant or absent stress imaging data. In these scenarios, there is now a wealth of data supporting the routine measurement of FFR to guide PCI. Our primary goal in the catheterization laboratory should be to relieve the symptoms and to improve the prognosis of our patients. This is best accomplished by identifying and relieving stenoses responsible for myocardial ischemia. Measuring FFR is currently the most cost-effective and accurate method for achieving this goal.

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References


Response to Fearon

Armin Arbab-Zadeh, MD, PhD

Dr Fearon provides an excellent review of the studies supporting the use of fractional flow reserve (FFR) for guiding percutaneous coronary intervention (PCI). Although the review discusses some of the concerns in regard to the FFR-guided PCI concept, it does not address several key criticisms: (1) The benefit of FFR-guided PCI (including cost reductions) is merely due to a reduced number of PCIs compared with the standard approach; (2) there is no proof that the use of FFR guidance leads to a reduction in the number of PCIs more effectively than random omission of interventions for achieving the same effect; (3) the underlying assumption that reducing provokable myocardial ischemia independently of treating the underlying atherosclerotic disease reduces myocardial infarction or death in patients with stable coronary artery disease is congruent with neither our current understanding of cardiac event risk nor recent data from clinical trials; and (4) the differences in myocardial infarction definitions and the unmatched allocation of dual antiplatelet therapy led to exaggeration of differences among the treatment groups in the Fractional Flow Reserve Versus Angiography for Multivessel Evaluation (FAME) study and to considerable disadvantage of the medical arm in the FAME 2 trial, respectively. Unless these considerations can be adequately addressed, the validity of the FFR-guided PCI concept should be questioned and should be subjected to further critical review before the continued application of FFR can be unreservedly endorsed in a clinical setting.
Percutaneous Coronary Intervention Should Be Guided by Fractional Flow Reserve Measurement
William F. Fearon

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