The FAME Trial

Fractional flow reserve for target revascularization in multivessel PCI.

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Percutaneous coronary intervention (PCI) with balloon angioplasty and stenting is an effective means of reducing anginal symptoms,[1] and in acute coronary syndromes, early PCI of culprit lesions reduces mortality and morbidity.[2] Additionally, PCI is superior to medical therapy alone in reducing myocardial ischemic burden, which in turn may improve outcomes.[3] Recently published guidelines have underscored the importance of demonstration of ischemia when deciding between medical therapy and percutaneous revascularization.[4] Coronary angiography, with visual or computer-aided assessment of stenosis severity, has traditionally been the gold standard for determining the need for revascularization of a particular vessel, but as a purely anatomic metric, it is imperfect for several reasons. First, stenoses may be over- or underestimated, particularly when they are of intermediate severity.[5] Second, angiography does not take into account the amount of myocardium subtended by the diseased vessel or the presence of collateral circulation (Figure 1). Finally, in patients with multivessel disease, even if the ischemic territory has previously been determined, it may be difficult to accurately identify which stenosis is responsible for the ischemia and should be treated. Implantation of stents in lesions that do not cause ischemia should be discouraged, because adverse outcomes such as thrombosis and restenosis become more likely when more stents are deployed.[6]

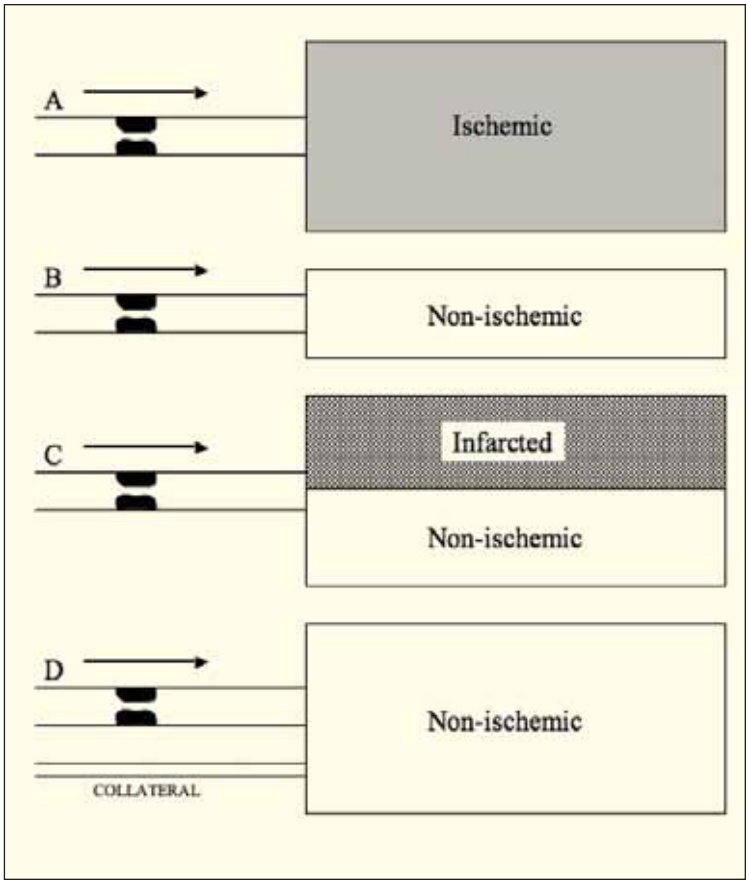

Figure 1. All stenoses are not equal. The diagram shows coronary arteries with the same diameter stenosis and their subtended myocardium. The territory served is large and flow through the stenosis is inadequate, resulting in ischemia (A). The flow is adequate for the smaller myocardial territory, and there is no ischemia (B). The territory is large but partially infracted (C). As scar tissue is metabolically inactive, flow is adequate to serve the remaining viable myocardium. The territory is large but also receives blood from collaterals (D). Total flow is adequate and there is no ischemia.[9]

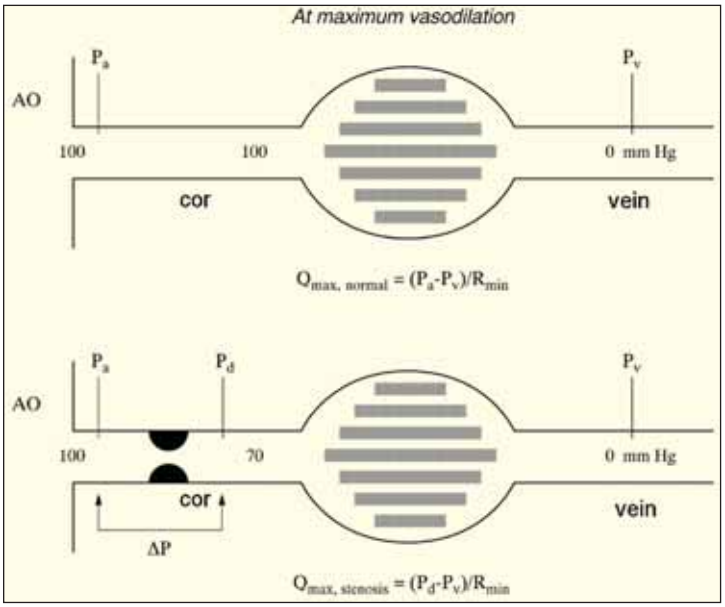

Figure 2. Schematic representation of FFR. The aorta (AO), epicardial coronary artery (cor), microcirculation (gray bars), and cardiac venous drainage are shown. The bottom diagram represents a system with an epicardial coronary stenosis. The top represents the same artery with no stenosis. Proximal coronary pressure (Pa) is easily measured through the guide catheter. Pressure distal to the stenosis (Pd) is measured by a pressure-tipped guidewire. Venous pressure (Pv) is assumed to be zero. Pressure is lower across the stenosis (Pd), so myocardial perfusion pressure can be calculated by Pd-Pv=Pd. The distal epicardial coronary pressure in the absence of stenosis is equal to Pa. Flow rates (Q) can be estimated by dividing perfusion pressure by resistance. Resistance at maximal hyperemia (Rmin), which is mainly determined by arteriolar and microvascular resistance, is minimal and constant irrespective of epicardial stenosis. Therefore FFR, the ratio of flow in a diseased system (Qmax, stenosis) to that in a normal system (Qmax, normal), can be estimated by Pd/Pa. (Reproduced from Pijls NH, De Bruyne B. Coronary pressure measurement and fractional flow reserve. Heart. 1998;80:539-542, with permission from BMJ Publishing Group Ltd.[11])

It is in this context that invasive coronary physiological assessment has been posited to have a role in assessing requirements for PCI. In 1993, Pijls et al described fractional flow reserve (FFR) as the ratio of hyperemic flow in the artery in the presence of a stenosis to the flow in the same artery in the absence of a stenosis (Figure 2).[7] FFR was measured in dogs by a pressure-tipped guidewire and correlated well with Doppler-derived FFR. Later, Pijls' group compared FFR to noninvasive measures of myocardial ischemia in humans (exercise electrocardiography, dobutamine echocardiography, and single photon emission computed tomography) and showed that FFR is a reliable substitute for stress testing when a cutoff of 0.75 is used.[8] The demonstration of equipoise between FFR and noninvasive tests for ischemia was furthered in the DEFER study, which examined outcomes after an FFR-guided approach to assess the need for revascularization.[10] In DEFER, patients who were found to have a stenosis at angiography but did not have a recent positive stress test underwent FFR measurement. All subjects with FFR < 0.75 underwent PCI (reference group), while those with FFR > 0.75 were randomized to PCI (perform group) or medical therapy (DEFER group). At 2 years, there was no advantage for PCI over medical therapy for lesions with FFR > 0.75 for the composite outcome of death, myocardial infarction (MI), revascularization, or procedure-related complications, and no additional symptomatic benefit with event-free survival of 89% for the DEFER group and 83.3% for the perform group. The results were similar with 5 years of follow-up.[12]

THE FAME TRIAL

The FAME (FFR Versus Angiography for Multivessel Evaluation) trial, published in 2009 in the *New England Journal of Medicine*,[13] investigated the utility of FFR in assessing the need for revascularization in subjects with multivessel disease. The FAME trial prospectively randomized 1,005 subjects with stable angina or acute coronary syndromes and multivessel disease, which was defined as visually estimated angiographic stenosis of > 50% in at least two major vessels; on the basis of angiographic and clinical data, the operator performed multivessel PCI. In the control, or angiographically guided arm, all lesions > 50% were treated with PCI. Subjects in the FFR-guided arm underwent FFR of all involved vessels, and only lesions with FFR ≤ 0.8 were treated. A cutoff of 0.8 was used because several studies have suggested increased sensitivity for ischemia at this level as compared to 0.75, perhaps at the expense of specificity. Drug-eluting stents were deployed in all lesions unless technical factors precluded their use (< 5% of lesions). Important exclusion criteria were left main stenosis, previous coronary bypass grafting, and recent moderate-to-large MI (non-ST-segment elevation MI with peak creatine kinase > 1,000 U/L or ST-segment elevation MI within 5 days of angiography). The primary endpoint was the rate of the composite endpoint of death, MI, and repeat revascularization at 1 year. Secondary endpoints examined symptoms as well as procedural characteristics

including length, volume of contrast used, and cost of materials.

The patients in the FAME trial were fairly representative of populations undergoing PCI in routine practice. The average patient was 64 years old and about three-fourths were male. One-third of the subjects were treated for unstable angina, and another third had a previous MI, although the article does not make clear how many of these had recent MI as opposed to chronic MI. The clinical and angiographic characteristics shown were indicative of a moderately, but not highly, complex group of patients: one-quarter were diabetic, one-quarter had low ejection fraction, vessel reference diameter of 2.5 mm and lesion length of approximately 12 mm. An average of 2.8 lesions was indicated per patient; 5% to 10% of lesions were total occlusions, and the SYNTAX score was 14.5. This is much lower than the scores in the recently presented SYNTAX study,[14] another contemporary trial of multivessel stenting, signifying an angiographically less complex patient group. Medical therapy was similar in the two arms and compatible with current management, although by no means ideal: subjects had been preloaded with aspirin in only 91% of cases and with clopidogrel in 60%; statins were used in 81%. Although there is no reason to suspect subsequent medical therapy differed between the patient groups, the article does not comment on the duration or intensity of antiplatelet therapy after PCI in this unblinded trial.

The angiographic characteristics of the two groups were similar. In each group, the operator indicated a similar number of lesions for PCI or FFR assessment, approximately three per patient. A large proportion of lesions, approximately 40%, were moderate by visual estimation (50%–70% diameter stenosis) and only 20% were > 90% stenosed or occluded. Notably, this pattern of lesion selection was also reflected in the quantitative coronary analysis (QCA) data, which demonstrated a mean lesion severity of approximately 60%. The QCA also showed that the lesions were short, with a mean length of 13 mm. Although this is not reported, the QCA data suggest a high percentage of type A/B1 lesions. The authors of the FAME trial also do not report on the proportion of subjects with at least one clearly severe lesion by angiography.

RESULTS

FFR was successfully performed for 94% of lesions, although this is likely an overestimate of the real-world utility of FFR because more than 10% of screened patients were excluded from the study due to vessel tortuosity or calcification. FFR was ≤ 0.8 in 63% and > 0.8 in 37% of lesions. Notably, 10.4 % of subjects in the FFR group did not have any lesions ≤ 0.8 and did not undergo intervention. The FFR-guided group had some clear intraprocedural advantages over the angiographically guided group. Fewer stents were placed (1.9 vs 2.7 stents; $P < .001$), resulting in a significantly lower total stent length. Also, less contrast medium was used. Procedure time was not longer in the FFR group, because the time taken to perform FFR was presumably offset by the extra interventions undertaken in the angiographically guided group. Additionally, an average of almost $700 was saved per procedure using the FFR-guided strategy, with a trend toward shorter hospital stays.

> "FFR gives interventional cardiologists a tool to make informed decisions while the patient is still on the table."

At 1-year follow-up, the primary endpoint occurred significantly less frequently in the FFR-guided group than in the angiographically guided group (13.2% vs 18.3%; $P = .02$). All components of the primary endpoint also favored FFR guidance, although they were not individually significant: 1.8% versus 3.0% for death ($P = .19$), 5.7% versus 8.7% for MI ($P = .08$), and 6.5% versus 9.5% for repeat revascularization ($P = .08$). The infarctions appeared to occur early (within 30 days) in both groups with little deviation in the Kaplan-Meier curves after this time; many of these infarctions may have been periprocedural but most were of at least moderate size (elevation of biomarkers to > 5 times normal). Although periprocedural infarctions may not have the same clinical significance as later events, they still predict outcomes[15] and should not be discounted. The survival curves for repeat revascularization continue to diverge over the 12-month follow-up; any difference between the groups is unlikely to reflect differences in the progression of nontarget lesions but rather increased target lesion revascularization for restenosis in the angiography arm due to increased stent numbers and length.[16] The almost-significant reduction in repeat revascularization is important because it indicates that FFR-guided angioplasty does not suffer consequence in terms of recurrent symptoms, at least in the medium term; this is also borne out by a lack of difference at 1 year in patient-reported symptoms or antianginal medication use.

LIMITATIONS OF THE FAME TRIAL

The FAME trial has several potential limitations related to the study design. Because the minimum visually estimated stenosis for inclusion was only 50%, participating centers may have recruited subjects with lesions that were

less severe than would otherwise be treated in routine angiography-based practice. If that is the case, the results from the angiography-only arm would be artificially poor, because many stents would have been placed without any benefit in terms of ischemia. The more than 10% of subjects with the FFR arm with no hemodynamically significant lesion and the suggestion of a preponderance of simple lesions present similar worries. However, almost two-thirds of tested lesions had FFR ≤ 0.8, which argues for rational lesion selection. A second limitation is the unblinded nature of this trial; treating clinicians were not blinded to the patients' randomization, therefore an element of bias favoring FFR and influencing softer endpoints like revascularization rates cannot be excluded. Finally, the decision to use a cutoff of 0.8 rather than 0.75 may have resulted in PCI of functionally nonsignificant lesions in the FFR arm. This would have reduced the benefit demonstrated by FFR.

CONCLUSION

The FAME trial is an important clinical trial for several reasons. First, it demonstrates conclusively that FFR can be used to guide stenting of multiple lesions "on the fly" in the catheterization laboratory and that with respect to outcomes after stenting, only physiologically significant lesions may be better than the usual strategy of stenting on the basis of visual estimation. Despite current guidelines,[4,17] angiography is frequently performed on patients without prior noninvasive testing for ischemia. In the FAME trial, this may have been reflected in the 10.4% of patients assigned to FFR in whom no lesions were ≤ 0.8 and who might not have undergone a prior stress test. Assuming the subjects in the FAME trial were representative of contemporary patients undergoing coronary angiography and that lesion selection was not biased by inclusion in the study, as many as 10% of patients in academic centers may be undergoing multivessel stenting when no PCI was indicated at all. Adherence to guidelines may be even worse in community hospitals.[18] FFR gives interventional cardiologists a tool to make informed decisions while the patient is still on the table. The second finding in the FAME trial is that in reducing unnecessary interventions, FFR reduces cost, which is an increasingly important endpoint considering the current state of health care spending. Also, FFR has been thought by some centers to be complicated and time-consuming. The FAME trial demonstrates that its use need not add to the length of the procedure and can reduce the patient's exposure to contrast medium.

Interventional cardiologists should actively heed the results of the FAME trial and incorporate FFR into their evidence-based practice. ■

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