

FFR for Decision Making in Complex PCI

The evidence to date supports fractional flow reserve guidance as a valuable imaging option during complex PCI.

BY AARON PEACE, MD, PhD, AND EMANUELE BARBATO, MD, PhD

Interventional cardiologists are increasingly faced with patients who have complex artery coronary disease such as multivessel disease, bifurcation disease, left main disease, or stenoses of calcified or tortuous vessels in elderly patients.¹ Management of these patients is even more difficult if we consider that previous noninvasive functional assessment is often inadequate to selectively guide the revascularization strategy.² Assuming optimal medical therapy is on board, it is often the case that we are then left with the conundrum of selecting the mode of revascularization that will be the most beneficial to the patient (ie, percutaneous coronary intervention [PCI] or coronary artery bypass graft surgery [CABG]).

The challenge for selection of best therapy is even more noteworthy in patients who have complex coronary artery disease because the risk of complications is significantly higher for these patients regardless of the revascularization strategy.³ As clinicians, we should have very robust, accurate, objective, and consistent evidence to show that our management of patients is correct and not based solely on the visual estimation obtained from coronary angiography.

Although intravascular ultrasound and optical coherence tomography provide us with very important anatomical information, it is difficult to glean information on the functional relevance of coronary stenoses to enable the clinician to provide the most appropriate revascularization. This is where fractional flow reserve (FFR) plays a vital role. FFR gives us crucial information on the ischemic burden of a coronary stenosis.⁴ In this article, we discuss the use of FFR in the setting of complex PCI based on the evidence available to date and then discuss the possible application of FFR guidance in managing complex interventions.

COMPLETE ANATOMICAL REVASCULARIZATION

Historically, complete anatomical percutaneous revascularization in patients with multivessel disease consists of either stenting (preferably with a drug-eluting stent [DES])

or CABG of all lesions that are deemed to be angiographically significant. Several pitfalls arise from our visual estimation of coronary stenoses during angiography. One may decide to apply the stringent definition of an angiographically significant stenosis of > 70% or a more conservative definition of > 50%. Either way, the application of such criteria is subjective and can affect the mode of revascularization chosen, as evidenced by the reclassification of the number of vessels that are actually diseased (ie, the number of vessels that are actually responsible for inducible ischemia).⁵

The clinical efficacy of an angiographically guided revascularization approach to patients with three-vessel or left main disease has been compared with CABG in the SYNTAX trial.⁶ The study did not meet the primary endpoint of noninferiority between the two revascularization strategies, resulting in a lower event rate in the group of patients who were treated with CABG. Interestingly, the greatest benefit from CABG arose largely in patients with more complex coronary artery disease. In fact, the rate of major adverse cardiovascular events in the group of patients treated with PCI progressively increased with greater severity and extension of coronary atherosclerotic disease (ie, with a SYNTAX score > 32).

This trend of increasing event rates was parallel to the increasing number of DES implanted. In addition to the SYNTAX score, the number of DES implanted seemed to be a good discriminatory index to predict outcomes, with the highest incidence of adverse events arising in patients receiving six stents or more.⁷

Overall, these results showed that in patients with more severe coronary atherosclerosis, where more complex interventions are applied, an angiographically guided PCI strategy is still affected by high failure rates in spite of the use of DES. Several reasons might account for these results. First, in the absence of functional evaluation of coronary artery disease, the risk exists for unnecessary stent implantation in nonischemic vessels, therefore inducing an additional iatro-

genic risk (eg, periprocedural myocardial infarction [MI], stent thrombosis, etc.). Second, some functionally significant lesions might remain undetected because of their mild angiographic appearance, in spite of being ischemia inducing.⁵ Third, patients with more extensive coronary artery disease have increased thrombotic risk due to limitations in the effectiveness of antiplatelet therapy.⁸ Last, the prolonged dual-antiplatelet therapy that is required after DES implantation exposes patients to potentially life-threatening bleeding complications. We can speculate that if an FFR-guided approach had been applied to guide the mode of revascularization, the results of the SYNTAX trial may well have been different.

USING FFR TO GUIDE THE REVASCLARIZATION STRATEGY

FFR is a well-validated diagnostic tool with excellent reproducibility and repeatability, which can selectively tailor revascularization on a lesion-to-lesion basis at the time of diagnostic angiography. Essentially, the combination of coronary angiography combined with FFR represents a “one-stop shop,” providing the clinician with crucial information on the presence or absence of ischemia, which we already know has important prognostic implications.

In brief, FFR is defined as the ratio of maximal myocardial blood flow in the presence of a stenosis to the maximal myocardial blood flow in the hypothetical case that the same artery would be normal.⁹ In other words, FFR tells us to what extent the myocardial blood flow can improve once the coronary stenosis is treated (eg, an FFR of 0.7 means that stenting the coronary lesion could result in up to a 30% improvement in maximal myocardial blood flow).

Practically, FFR is calculated as the ratio of the pressure distal to the lesion to be evaluated to the aortic pressure measured during maximal hyperemia. Whereas the aortic pressure is measured at the tip of the guiding catheter, the pressure distal to the lesion is measured with a dedicated pressure wire that is advanced into the target vessel distal to the stenosis of interest. Maximal hyperemia is reliably achieved with intravenous infusion of adenosine, although intracoronary bolus is used in the assessment of simple coronary anatomical settings (ie, focal intermediate stenosis). Cutoff values of FFR for the identification of myocardial ischemia have been investigated and validated extensively in several studies and head-to-head comparisons with noninvasive functional tests.¹⁰⁻¹²

An FFR value < 0.75 is consistently predictive of a stenosis responsible for myocardial ischemia (100% positive predictive value), whereas FFR values > 0.8 are typically not associated with inducible myocardial ischemia. Although a gray

zone exists, this is relatively narrow and accounts only for a minimal range of FFR values (between 0.75 and 0.8). A large body of evidence supports the use of FFR for guidance of revascularization in different anatomical lesion settings, such as intermediate stenoses, multivessel disease, left main disease, bifurcation lesions, sequential stenoses, diffuse atherosclerosis, and bypass grafts.¹³

COMPLETE FUNCTIONAL REVASCLARIZATION

A complete functional percutaneous revascularization strategy for patients with multivessel disease consists of stenting (preferably DES) all the physiologically significant lesions—those that are ischemia inducing—while treating the lesions that are not ischemia inducing with optimal medical therapy. In fact, the latter are better deferred with good long-term clinical outcome.

The DEFER study showed that the incidence of death and nonfatal MI at 5 years was not significantly different between patients who were deferred on the basis of nonfunctionally significant lesions and patients undergoing PCI despite negative FFR (3.3% vs 7.9%; $P = .21$).¹⁴ In addition, the percentage of patients who were free from angina at follow-up was not different between the two groups. These findings have also been confirmed in the setting of left main disease. In a registry of 213 patients with angiographically equivocal left main coronary artery stenosis, the 5-year survival rate of patients who were deferred on the basis of FFR > 0.8 and were treated with optimal medical therapy was favorable and comparable to that of patients with FFR < 0.8 who were treated with CABG (89.8% vs 85.4%; $P = .48$). In other words, patients with nonhemodynamically significant stenoses do not derive additional clinical benefit when undergoing revascularization.

In contrast, revascularization of ischemia-inducing lesions is associated with improvement of symptoms and better clinical outcomes.^{15,16} In patients with multivessel disease, a complete functional revascularization strategy guided by FFR measurement was compared with a complete anatomical revascularization strategy guided by angiography in the FAME (Fractional Flow Reserve Versus Angiography for Multivessel Evaluation) trial.¹⁷ Patients assigned to the angiography-guided PCI group underwent stenting of all indicated lesions, whereas patients assigned to the FFR-guided PCI group underwent stenting of indicated lesions only if the FFR was ≤ 0.8 .

Compared with the angiography-guided strategy, the FFR-guided strategy was associated with a significant reduction of major adverse cardiac events at 1 year (13.2% vs 18.3%; $P = .02$). This beneficial effect was also preserved at 2 years, with a significantly lower rate of MI (6.1% vs 9.9%; $P = .03$) and of the combined endpoint of death and MI (8.4% vs 12.9%; $P = .02$).¹⁸ Importantly, the FFR-guided strat-

egy was found to not only improve clinical outcome but also significantly reduce costs.¹⁹ It is important to note that the FAME population had a moderate level of CAD complexity, with a mean SYNTAX score of 14, compared to the SYNTAX study in which patients had more complex disease and a mean SYNTAX score of twice that level.

The beneficial effect of the FFR-guided strategy was also achieved thanks to a functional redefinition of coronary atherosclerosis severity. Among patients ($n = 115$) with angiographic three-vessel disease, only 14% had functional three-vessel disease, 43% had functional two-vessel disease, and 34% had functional single-vessel disease. In 9% of the cases, no functional severe stenosis could be detected.⁵ Changing the diagnosis from three vessels to two- or one-vessel disease could have a huge impact on the clinical decision making. According to the guidelines and/or local revascularization strategy, patients with three-vessel disease who are normally referred for surgery would be downgraded on the basis of the functional severity of the stenosis by FFR.

In extreme cases, the patient may be reclassified to single-vessel disease based on the FFR assessment and end up with a single stent. Avoidance of complex coronary intervention or CABG through FFR-guided reclassification is a very attractive scenario for the patient and the health service when we consider the potential risk exposure to the patient and the potential cost-saving exercise.

THE USE OF FFR IN BIFURCATION DISEASE

Atherosclerosis frequently occurs at branch points of coronary vessels, and for many cardiologists, the management of bifurcation disease remains a challenge. In addition, the existence of multiple techniques for treating bifurcation disease certainly does not simplify matters. Recent evidence suggests that provisional stenting is a more effective strategy than a two-stent strategy in the majority of cases when treating bifurcations.²⁰ Regardless of the strategy chosen, it is frequently the case that the ostium of the side branch is compromised either through plaque shift or carina shift. Trying to decide whether to treat or not to treat a side branch is not straightforward, and all of the anatomical applications we have, whether visual estimation, quantitative coronary analysis, or intravascular ultrasound, have not been found to be reliable in predicting the functional relevance of a jailed side branch and therefore determining the best strategy after the side branch has been jailed.

Although many operators have often proposed dilating the jailed side branch after plaque shift using final kissing balloons, the recently published NORDIC III trial suggests that a final kissing-balloon strategy is unnecessary because no clinical benefit was seen with this strategy out to 6 months.²¹ However, one possible explanation for this could be that in the side branches where a final kiss-

ing balloon was used, the stenosis was not functionally significant in the first place. In addition, when we consider the literature from Koo et al,²² showing that on average, approximately 32% of the jailed side branches were functionally significant, and apply it to the NORDIC III data, it could be argued that this study did not find a difference from final kissing balloons because it was not powered to answer this. One might speculate that had the strategy to dilate the side branch been based on the detection of inducible ischemia using FFR, the conclusion may have differed.

THE USE OF FFR IN LEFT MAIN STEM DISEASE

Left main coronary artery lesions are sometimes difficult to appreciate angiographically for several reasons: (1) the catheter obscures the angiographic image; (2) coexistent atherosclerosis makes it difficult to estimate the stenosis; (3) the mixing effect of blood and contrast at the ostium affects image quality; and (4) the left main artery can be remarkably short. Any one or a combination of these limitations makes it notoriously difficult to accurately evaluate the functional significance of a stenosed left main artery. In extreme cases, even an angiographically mild-to-moderate left main stenosis can provoke such a reflex action that patients undergo surgical revascularization of a functionally irrelevant lesion. The implications of this are far reaching because the patient may be subjected to sternotomy and bypass grafting. In addition, this strategy may be in vain because grafts anastomosed onto a vessel with no hemodynamically significant stenosis are at higher risk of early occlusion.²³

Again, FFR is invaluable in the assessment of left main disease because it eliminates many of the pitfalls that angiography presents. One thing that FFR has taught us is that the threshold to measure FFR in left main disease should be low (eg, in the presence of equivocal mild stenosis) because it supplies such a substantial myocardial mass. In terms of the safety of FFR to evaluate left main stem disease, we have several small studies supporting this practice and one more recent study evaluating 223 patients.²⁴ In each case, FFR was measured, and if the value was ≤ 0.8 , the patient was referred for surgery, whereas if the patient had an $\text{FFR} > 0.8$, the patient was prescribed optimal medical therapy alone.

The results of this study showed that the survival rates were comparable (89.8% vs 85.4%; $P = .48$), as were event-free survival estimates (74.2% vs 82.8%; $P = .5$) after 5 years of follow-up. Incidentally, in up to 23% of the patients, left main stenosis was deemed angiographically nonsignificant, whereas FFR showed a value of < 0.8 . In other words, revascularization was denied on the basis of the angiographic estimation of lesion severity; however, these patients actually had a functionally significant stenosis. These data support the role of FFR in left main disease.

FUTURE PERSPECTIVES: THE FAME II TRIAL

Despite the growing body of evidence supporting a revascularization strategy that is aimed at targeting the ischemic substrate, the data from the COURAGE trial raised several issues with regard to the merits of invasive revascularization strategies compared to a policy of aggressive optimal medical management of patients, particularly those with stable angina.²⁵

The COURAGE study showed that there was no difference in the primary endpoint of death and MI between a strategy of PCI plus optimal medical therapy and optimal medical therapy alone. Not surprisingly, these findings were met with criticisms questioning the real applicability of the COURAGE data to the real-world clinical practice. Having included only a small number of patients compared to all of those who were initially screened and the very high rate of noninvasive functional assessment (uncommon in clinical practice) raised the suspicion of a highly selected patient population.²⁶ In addition, it is very possible that nonfunctionally significant coronary lesions have been stented only on the basis of their angiographic appearance, which actually should have been left alone.

Based on the FAME trial and the results of COURAGE, the FAME II trial was designed. The purpose of the FAME II trial is simple in that it aims to compare the clinical outcomes, safety, and cost effectiveness of FFR-guided PCI plus optimal medical therapy versus optimal medical therapy alone in patients with stable coronary artery disease, including those who may necessitate complex PCI. This study is crucial and will undoubtedly address the question of which patient and which lesion subsets will benefit most from percutaneous coronary revascularization and optimal medical therapy.

CONCLUSION

There are still several question marks over the relative merits of PCI in the management of complex coronary disease. However, the one thing that seems clear is that as clinicians, we cannot continue to guide complex intervention solely on the basis of visual estimation. FFR measurement represents a valuable tool that enables the interventional cardiologist to base his decision making on the functional severity of the stenosis, therefore tailoring the treatment to those lesions and vessels that are responsible for the patient's symptoms. ■

Aaron Peace, MD, PhD, is with Cardiovascular Center, OLV-Clinic in Aalst, Belgium. He has disclosed that he holds no financial interest in any product or manufacturer mentioned herein.

Emanuele Barbato, MD, PhD, is with Cardiovascular Center, OLV-Clinic in Aalst, Belgium. He has disclosed that

he holds no financial interest in any product or manufacturer mentioned herein. Dr. Barbato may be reached at emanuele.barbato@olvz-aalst.be.

1. Hahalis G, Dargatzis G, Davlouros P, Alexopoulos D. Revascularization strategies for stable multivessel and unprotected left main coronary artery disease: From BARI to SYNTAX. *Int J Cardiol*. In press.
2. Lin GA, Dudley RA, Lucas FL, et al. Frequency of stress testing to document ischemia prior to elective percutaneous coronary intervention. *JAMA*. 2008;300:1765-1773.
3. Shishehbor MH, Topol EJ, Mukherjee D, et al. Outcome of multivessel coronary intervention in the contemporary percutaneous revascularization era. *Am J Cardiol*. 2006;97:1585-1590.
4. Uren NG, Melin JA, De Bruyne B, et al. Relation between myocardial blood flow and the severity of coronary-artery stenosis. *N Engl J Med*. 1994;330:1782-1788.
5. Tonino PA, Fearon WF, De Bruyne B, et al. Angiographic versus functional severity of coronary artery stenoses in the FAME study fractional flow reserve versus angiography in multivessel evaluation. *J Am Coll Cardiol*. 2010;55:2816-2821.
6. Serruys PW, Morice MC, Kappetein AP, et al. Percutaneous coronary intervention versus coronary-artery bypass grafting for severe coronary artery disease. *N Engl J Med*. 2009;360:961-972.
7. Gerber RT, Ielasi A, Al-Lamee R, et al. Long-term follow-up of multivessel percutaneous coronary intervention with drug-eluting stents for de novo lesions with correlation to the SYNTAX score. *Cardiovasc Revasc Med*. In press.
8. Mangiacapra F, De Bruyne B, Muller O, et al. High residual platelet reactivity after clopidogrel: extent of coronary atherosclerosis and periprocedural myocardial infarction in patients with stable angina undergoing percutaneous coronary intervention. *JACC Cardiovasc Interv*. 2010;3:35-40.
9. Pijls NH, van Son JA, Kirkeeide RL, et al. Experimental basis of determining maximum coronary, myocardial, and collateral blood flow by pressure measurements for assessing functional stenosis severity before and after percutaneous transluminal coronary angioplasty. *Circulation*. 1993;87:1354-1367.
10. De Bruyne B, Bartunek J, Sys SU, Heyndrickx GR. Relation between myocardial fractional flow reserve calculated from coronary pressure measurements and exercise-induced myocardial ischemia. *Circulation*. 1995;92:39-46.
11. Pijls NH, Van Gelder B, Van der Voort P, et al. Fractional flow reserve. A useful index to evaluate the influence of an epicardial coronary stenosis on myocardial blood flow. *Circulation*. 1995;92:3183-3193.
12. Pijls NH, De Bruyne B, Peels K, et al. Measurement of fractional flow reserve to assess the functional severity of coronary-artery stenoses. *N Engl J Med*. 1996;334:1703-1708.
13. De Bruyne B, Sarma J. Fractional flow reserve: a review: invasive imaging. *Heart*. 2008;94:949-959.
14. Pijls NH, van Schaardenburgh P, Manoharan G, et al. Percutaneous coronary intervention of functionally nonsignificant stenosis: 5-year follow-up of the DEFER study. *J Am Coll Cardiol*. 2007;49:2105-2111.
15. Davies RF, Goldberg AD, Forman S, et al. Asymptomatic Cardiac Ischemia Pilot (ACIP) study two-year follow-up: outcomes of patients randomized to initial strategies of medical therapy versus revascularization. *Circulation*. 1997;95:2037-2043.
16. Erne P, Schoenenberger AW, Burckhardt D, et al. Effects of percutaneous coronary interventions in silent ischemia after myocardial infarction: the SWISS II randomized controlled trial. *JAMA*. 2007;297:1985-1991.
17. Tonino PA, De Bruyne B, Pijls NH, et al. Fractional flow reserve versus angiography for guiding percutaneous coronary intervention. *N Engl J Med*. 2009;360:213-224.
18. Pijls NH, Fearon WF, Tonino PA, et al. Fractional flow reserve versus angiography for guiding percutaneous coronary intervention in patients with multivessel coronary artery disease: 2-year follow-up of the FAME (Fractional Flow Reserve Versus Angiography for Multivessel Evaluation) study. *J Am Coll Cardiol*. 2010;56:177-184.
19. Fearon WF, Bornschein B, Tonino PA, et al. Economic evaluation of fractional flow reserve-guided percutaneous coronary intervention in patients with multivessel disease. *Circulation*. 2010;122:2545-2550.
20. Hildick-Smith D, de Belder AJ, Cooter N, et al. Randomized trial of simple versus complex drug-eluting stenting for bifurcation lesions: the British Bifurcation Coronary Study: old, new, and evolving strategies. *Circulation*. 2010;121:1235-1243.
21. Niemela M, Kervinen K, Erglis A, et al. Randomized comparison of final kissing balloon dilatation versus no final kissing balloon dilatation in patients with coronary bifurcation lesions treated with main vessel stenting: the Nordic-Baltic Bifurcation Study III. *Circulation*. 2011;123:79-86.
22. Koo BK, Waseda K, Kang HJ, et al. Anatomic and functional evaluation of bifurcation lesions undergoing percutaneous coronary intervention. *Circ Cardiovasc Interv*. 2010;3:113-119.
23. Botman CJ, Schonberger J, Koolen S, et al. Does stenosis severity of native vessels influence bypass graft patency? A prospective fractional flow reserve-guided study. *Ann Thorac Surg*. 2007;83:2093-2097.
24. Hamlilos M, Muller O, Cuisset T, et al. Long-term clinical outcome after fractional flow reserve-guided treatment in patients with angiographically equivocal left main coronary artery stenosis. *Circulation*. 2009;120:1505-1512.
25. Boden WE, O'Rourke RA, Teo KK, et al. Optimal medical therapy with or without PCI for stable coronary disease. *N Engl J Med*. 2007;356:1503-1516.
26. Shaw LJ, Berman DS, Maron DJ, et al. Optimal medical therapy with or without percutaneous coronary intervention to reduce ischemic burden: results from the Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation (COURAGE) trial nuclear substudy. *Circulation*. 2008;117:1283-1291.