The FAME Trials: Impact on Clinical Decision Making

Guy R Heyndrickx¹ and Gábor G Tóth²

1. Cardiovascular Center Aalst, OLV-Clinic, Aalst, Belgium; 2. University Heart Center, Medical University of Graz, Graz, Austria

Abstract

Careful and stepwise evaluation of the fractional flow reserve (FFR) index has been performed over the years, culminating in the landmark Fractional Flow Reserve Versus Angiography for Multivessel Evaluation (FAME) and Fractional Flow Reserve-Guided Percutaneous Coronary Intervention Plus Optimal Medical Treatment Versus Optimal Medical Treatment Alone in Patients with Stable Coronary Artery Disease (FAME II) trials. Findings from these studies demonstrated unequivocally the overall inadequacy of angiography versus FFR to correctly assess stenosis severity. Thus, proof of concept and clinical applicability was established beyond debate and will be discussed here.

Keywords

Coronary artery disease, ischaemia, angiography, fractional flow reserve, FAME

Disclosure: The authors have no disclosures to make that are relevant to the present article.

Received: 2 May 2016 **Accepted:** 31 August 2016 **Citation:** *Interventional Cardiology Review*, 2016;**11**(2):116–9 DOI: 10.15420/icr.2016:14:3

Correspondence: Guy R Heyndrickx, Cardiovascular Center Aalst, OLV-Clinic, Moorselbaan, 164, B-9300 Aalst, Belgium. E: guy.heyndrickx@skynet.be

The presence as well as the extent of myocardial ischaemia are key to determining cardiovascular outcome,^{1–3} thus its identification is important. An endeavour to improve diagnostic accuracy in deciding which angiographic lesions are haemodynamically significant led to the development of the concept of fractional flow reserve (FFR). Based on pressure-flow analysis of a stenosis during maximum flow, the FFR indicates the impact of a coronary stenosis on the maximum inducible coronary flow and whether it would be susceptible to induce ischaemia during stress. In a landmark report, Pijls and co-workers validated the FFR index in a group of patients with single moderate coronary artery stenosis using three different non-invasive stress tests (exercise test, thallium scan and stress echocardiogram).⁴ Based on the findings of this study, the authors proposed a cut-off FFR value of 0.75 as a threshold for discrimination between ischaemia-inducible and ischaemia-non-inducible lesions (see for example *Figure 1*).

In the DEFER (Deferral versus Performance of Percutaneous Transluminal Coronary Angioplasty in Patients Without Documented Ischaemia) trial, the predictive value of this novel invasive index was tested for the first time in patients.⁵ The DEFER study was designed to investigate the safety and outcomes of deferring stenting in angiographic (FFR >0.75) stenoses. A total of 325 patients who were referred for percutaneous coronary intervention (PCI) due to an angiographic significant stenosis of >50 % were randomised to either the PCI group or PCI-deferral group. PCI was performed regardless of the FFR value in the PCI group. In the PCI-deferral group, PCI was undertaken only when the FFR was ≤0.75, and was deferred when the FFR was >0.75. At 12 months, event-free survival rates were similar in the deferral and PCI groups (89 versus 83 %, respectively; p=0.27). The results of this study indicate that a large number of patients referred for PCI on the basis of a coronary stenosis without objective proof of ischaemia had nonsignificant lesions as indicated by the FFR value. Stenting these patients did not reduce the rates of adverse cardiac events neither did it result in an improved functional class.⁵ Following on from the DEFER trial, the Fractional Flow Reserve Versus

Angiography for Multivessel Evaluation (FAME)⁶ and Fractional Flow Reserve-Guided Percutaneous Coronary Intervention Plus Optimal Medical Treatment Versus Optimal Medical Treatment Alone in Patients with Stable Coronary Artery Disease (FAME II)⁷ trials were designed to evaluate the superiority of FFR-guided revascularisation approaches compared with current medical practices in patients with stable coronary artery disease.

In this review we analyse why and to what extent the results of the FAME trials should influence our current decision-making process in the catheterisation laboratory.

FAME I Trial

The FAME trial compared two different revascularisation strategies in patients with stable coronary artery disease and multivessel disease (MVD): a standard angiographic-guided approach (revascularisation of lesions with >50 % stenosis) and an FFR-guided approach (revascularisation of lesions with an FFR ≤0.80).⁶

At 1 year follow-up, the primary endpoint (a composite of death, MI and repeat revascularisation) was significantly reduced in the FFR-guided group compared with the angiographic-guided group (13.2 versus 18.3 %; p=0.02). Regarding the secondary endpoints, while the reduction of all-cause mortality rates (1.8 versus 3.0 %; p=0.19), and reduction in MI rates (5.7 versus 8.7 %; p=0.07) were not significant, the reduction in the rates of the combined endpoints—a non prespecified secondary endpoint—(7.3 versus 11.1 %; p=0.04) was statistically significant. Collateral benefit of the FFR strategy was a decrease in the number of stents, a decrease in the amount of contrast and radiation time, resulting in a decrease in procedure-related costs. In addition, the functional status of the patients was similar between groups, if not improved in the FFR group.⁶

These results were maintained up to 2 years after the index procedure.⁸ Subsequently, from 2 to 5 years, the risks for both groups developed

similarly.⁹ Thus the FAME trial demonstrated, for the first time, the long-term safety and superiority of an FFR-guided approach, supporting the claim that functional rather than anatomical revascularisation should become the standard of care in this group of patients.

FAME II Trial

The FAME II trial was designed to clarify whether PCI of only haemodynamic significant stenoses (i.e. lesions with $\text{FFR} \leq 0.80$) combined with optimal medical therapy would be superior to optimal medical therapy alone as a first approach in patients with stable symptoms.⁷ Interestingly, recruitment in this trial was halted prematurely at the recommendation of the Data and Safety Monitoring Board after enrolment of 1220 patients due to observation of a highly significant difference in the incidence rates of the primary endpoint (cumulative incidence of death, MI or urgent revascularisation) between the PCI group and the medical-therapy group. The primary endpoint event rate at 1 year showed superiority of stenting with drug-eluting stents (DES) combined with optimal medical therapy over optimal medical therapy alone (4.3 versus 12.7 %; $p < 0.001$), with a significant decrease in the incidence of urgent revascularisation (1.6 versus 11.1 %; $p < 0.001$). However, the rate of death or MI did not differ between strategies.⁷ The premature stopping of recruitment may have influenced these latter data. The overall conclusion was that lesions with a positive FFR of ≤ 0.80 need to be revascularised upfront rather than started on optimal medical therapy.

FAMOUS-NSTEMI trial

As in the FAME trial, in the FAMOUS-NSTEMI trial, two decision strategies were compared here, in patients with non ST-elevation acute coronary syndromes referred for urgent invasive management either within 72 hours of the acute ischaemic event or with recurrent ischaemia within 5 days after the index ischaemic event.¹⁰ Patients were randomised after the initial treatment decision based solely on angiography was made. FFR measurements were performed in all patients but only disclosed in the FFR-guided group. The results showed that when FFR data were disclosed the initial treatment option was changed in 21.6 % of patients thereby reducing the revascularisation rate. Overall, health outcome and quality of life in both randomised groups were similar despite the finding that in the FFR-guided group the rate of procedure-related MI was lower, but the rate of spontaneous major adverse cardiac events was higher during the 12-month follow-up period.¹⁰ These observations will need to be confirmed but appear to support the results from the FAME trials, stressing the point that treatment of ischaemia-inducible lesions should be an important aim in this population of patients.

The Grey Zone: FFR Index of 0.75–0.80

As mentioned earlier, the seminal FFR validation study demonstrated in patients with a discrete coronary stenosis an FFR threshold value of 0.75, below which ischaemia was inducible as demonstrated in at least one of three different non-invasive stress tests.⁴ The authors reported a sensitivity of FFR to detect reversible ischaemia of 88 %, with a specificity of 100 %. Although this may appear to be a robust figure, it is not infallible. There are important reasons for the predictive value being < 100 %.

1. Maximal vasodilatation of the epicardial conduit vessels is a prerequisite for FFR measurements according to the proponents to avoid potential vasospasm during manipulation of the pressure wire.¹¹ Vasoconstriction of the epicardial conduit vessels is known

Figure 1: Coronary angiogram of right (R) and left (L) coronary artery (CA) together with FFR measurement of the L anterior descending artery (LAD)

(A) A diagnostic coronary angiogram in a 67-year-old man with typical exercise induced angina depicts two critical lesions on the RCA and L circumflex CA (LCx) with minor disease on the mid LAD. Stenting RCA and LCx with drug eluting stents (DES) did not result in alleviating all symptoms. A subsequent control angiogram revealed two patent stents on RCA and LCx and unchanged mild disease on the mid LAD. (B) FFR was then measured which revealed a hemodynamic significant lesion ($\text{FFR} = 0.67$) requiring stenting of the mid LAD as well. This example is a point in case disclosing the limitations and stressing the inaccuracy of angiography for assessing functional lesion severity.

to occur in cases of increased orthosympathetic drive, yet with no untoward effects on coronary flow as long as the coronary vessels are normal. In the presence of underlying atherosclerosis, the occurrence of vasoconstriction may further reduce the vessel diameter on top of an already fixed obstruction.¹² An FFR value of 0.75 during catheterisation with all vasomotion abolished by intracoronary nitrates may drop towards a value of 0.72 during exercise in cold weather due to some degree of superimposed alpha-mediated coronary vasoconstriction. Abolishing the vasomotion of epicardial conduit vessels before FFR measurements are taken may therefore sometimes mask the real FFR value occurring during daily activities.

2. The accuracy and reproducibility of the FFR measurement are based on maximum vasodilation following adenosine administration, which may not always be the case for a number of technical reasons such as the maximal used doses and the route of administration.¹³⁻¹⁵
3. Basic FFR metrics require simultaneous measurements of coronary venous or right atrial pressures, so as to integrate both maximum coronary flow and maximum collateral blood flow to

the subtended myocardium ($FFR_{myo} = [P_d - P_v] / [P_a - P_v]$). Because generally, central venous pressure is close to zero, the simplified equation $FFR = P_d / P_a$ has been advocated, which facilitates even more the routine use of this index.¹¹ However, in the following theoretical example with a hypothetical set of pressures during maximum coronary vasodilation (P_d : 75 mmHg; P_a : 100 mmHg; P_v : 0) the calculated FFR value of 0.75 will decrease to 0.71 if $P_v = 15$ mmHg. Therefore, omission of coronary venous pressure (P_v) measurements may result in overestimation of FFR index.¹⁶ In contrast, in a mathematical analysis with P_d and P_a values between 50 and 140 mmHg and P_v values of 0.5, 10 and 15 mmHg, only 2.87 % of the combinations tested would have resulted in inappropriate high estimate of FFR if P_v was not considered.¹⁷ A recent analysis of 1600 coronary stenoses revealed that the differences between FFR and FFR_{myo} was minimal even in patients with markedly increased P_v values.¹⁸ FFR values above the grey zone (i.e. >0.80) did not yield values below the grey zone (i.e. ≤ 0.75) confirming that the impact of venous pressure on FFR is negligible indeed.

4. Interpreting FFR values may be less straightforward under certain conditions such as in the presence of elevated left ventricular end-diastolic pressure¹⁹ in patients with left ventricular dysfunction or in the presence of unprotected left main stem lesions with large myocardial mass at risk distal to the index lesion.

The investigators of the FAME trial therefore decided that altering the FFR cut-off value towards 0.80 would eliminate the uncertainty of some stenosis with an FFR between 0.75 and 0.80. Accordingly, all the clinical trials and large registries demonstrating clinical benefit of FFR-guided revascularisation over angiographic-guided strategies have been based on the cut-off value of 0.80. In a recent survey, 16 % of lesions interrogated with FFR were considered to fall in the grey zone based on their FFR value.²⁰ Altering the FFR cut-off value towards 0.80 would increase its sensitivity, but at the cost of its specificity. By adhering strictly to the cut-off value of 0.75, a small number of patients might be denied the benefit of stenting. Were all lesions between 0.75 and with 0.80 to be stented, a larger number of patients would be denied the benefit of deferring stenting, with some, albeit small risk of procedural complications, restenosis, stent thrombosis or late-stent thrombosis.

Adjedj and co-workers reviewed a large dataset of 1459 patients with single-vessel disease and compared the long-term outcome of patients with an FFR value within the grey zone (0.75–0.80) who were treated either by revascularisation or medical therapy.²⁰ Rates

of major adverse cardiac events (death, MI and any revascularisation) up to 5 years were comparable between medical therapy and revascularisation groups (13.9 and 11.2%, respectively; $p=0.30$), whereas a trend towards a higher rate of death or MI was observed in the medical therapy group (9.4 versus 4.8 %, respectively; $p=0.06$).

Post-FAME Era

The overwhelmingly convincing data from the FAME and the FAMOUS-NSTEMI trials should not be ignored. The uniqueness of the FFR index as a marker of ischaemia-prone lesions in patients with coronary artery disease is well known.

However, despite the widely publicised results from the FAME trials, the extensive workshops on use and interpretation of FFR and the recommendation for FFR use as a diagnostic tool according to current guidelines,²¹ the actual rate of FFR use in clinical practice remains disappointingly low (<7 % in the United States).²² Several reasons for this low-level FFR use have been cited; however, cost and reimbursement issues are likely the most valid limitations that discourage people from routine FFR use. Such hindrance of a more liberal use of the pressure wires during diagnostic coronary angiography may be resolved in the future with the further development of non-invasive methods that allow FFR calculations derived from coronary computed tomographic angiography^{23,24} or from 3D quantitative coronary angiography.²⁵

Whether a cut-off value of 0.75 or 0.80 is used, there will be some risk of false-negative results. Where FFR values fall within the grey zone, treatment decisions should not be made based on a single index, but after having considered all of the clinical information available as well as the objective quantitative data, including risk assessment and patient preferences.

Conclusion

The FAME trials have lifted the last road blocks towards the general acceptance by the cardiology community of this novel paradigm in which the diagnostic focus of coronary lesions is shifted from anatomical characteristics to a functional impact on myocardial perfusion. This unique vision on how to evaluate severity and prognosis of coronary lesions should force us to rethink our current algorithm for the treatment of patients with chest pain where FFR measurements may supplant non-invasive stress tests, which are only being performed in <50 % of patients prior to elective PCI.²⁶ However, it will take some time to alter the current course of patient care. ■

1. Kaul S, Lilly DR, Gascho JA, et al. Prognostic utility of the exercise thallium-201 test in ambulatory patients with chest pain: comparison with cardiac catheterization. *Circulation* 1988;**77**:745–58. PMID: 3258193.
2. Beller GA, Zaret BL. Contributions of nuclear cardiology to diagnosis and prognosis of patients with coronary artery disease. *Circulation* 2000;**101**:1465–78. PMID: 10736294.
3. Hachamovitch R, Hayes SW, Friedman JD, et al. Comparison of the short-term survival benefit associated with revascularization compared with medical therapy in patients with no prior coronary artery disease undergoing stress myocardial perfusion single photon emission computed tomography. *Circulation* 2003;**107**:2900–7. DOI: 10.1161/01.CIR.0000072790.23090.41; PMID: 12771008.
4. 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**:1703–8. DOI: 10.1056/NEJM199606273342604; PMID: 8637515.
5. Bech GJW, De Bruyne B, Pijls NH, et al. Fractional flow reserve to determine the appropriateness of angioplasty in moderate coronary stenosis. *Circulation* 2001;**103**:2928–34. PMID: 11413082.
6. Tonino PAL, De Bruyne B, Pijls NH, et al. Fractional flow reserve versus angiography for guiding percutaneous coronary intervention. *N Engl J Med* 2009;**360**:213–24. DOI: 10.1056/NEJMoa0807611; PMID: 19144937.
7. De Bruyne B, Pijls NH, Kalesan B, et al. Fractional flow reserve-guided PCI versus medical therapy in stable coronary disease. *N Engl J Med* 2012;**367**:991–1001. DOI: 10.1056/NEJMoa1205361; PMID: 22924638.
8. 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**:177–84. DOI: 10.1016/j.jacc.2010.04.012; PMID: 20537493.
9. van Nunen LX, Zimmermann FM, Tonino PA, et al. Fractional flow reserve versus angiography for guidance of PCI in patients with multivessel coronary artery disease (FAME): 5-year follow-up of a randomised controlled trial. *Lancet* 2015;**386**:1853–60. DOI: 10.1016/S0140-6736(15)00057-4; PMID: 26333474.
10. Layland J, Oldroyd KG, Curzen N, et al. Fractional Flow reserve vs. angiography in guiding management to optimize outcomes in non-ST-segment elevation myocardial infarction: the British Heart Foundation FAMOUS-NSTEMI randomized trial. *Eur Heart J* 2015;**36**:100–11. DOI: 10.1093/eurheartj/ehu338; PMID: 25179764.
11. Pijls NH, De Bruyne B. Coronary Pressure. Second Edition. Kluwer Academic Publishers. Dordrecht / Boston / London. 2000. Chapter 5. Practical Set-up of coronary pressure measurements. pp.83–114.
12. Heusch G, Baumgart D, Camici P, et al. Alpha-adrenergic coronary vasoconstriction and myocardial ischemia in humans. *Circulation* 2000;**101**:689–94. PMID: 10673263.
13. Pijls NH, Tonino PA. The crux of maximum hyperemia: the last remaining barrier for routine use of fractional flow reserve. *JACC Cardiovasc Interv* 2011;**4**:1093–5. DOI: 10.1016/j.jcin.2011.08.007; PMID: 22017934.
14. Nair PK, Marroquin OC, Mulukutla SR, et al. Clinical utility of regadenoson for assessing fractional flow reserve. *JACC Cardiovasc Interv* 2011;**4**:1085–92. DOI: 10.1016/j.jcin.2011.07.011; PMID: 22017933.
15. De Luca G, Venegoni L, Iorio S, et al. Effects of increasing doses of intracoronary adenosine on the assessment of fractional flow reserve. *JACC Cardiovasc Interv* 2011;**4**:1079–84. DOI: 10.1016/j.jcin.2011.08.004; PMID: 22017932.
16. Layland J, Wilson AM, Whitbourn RJ, et al. Impact of right atrial pressure on decision-making using fractional flow

- reserve (FFR) in elective percutaneous intervention. *Int J Cardiol* 2013;**167**:951–3. DOI: 10.1016/j.ijcard.2012.03.087; PMID: 22475843.
17. Kumar GT. Letter to the editor: The influence of right atrial pressure on fractional flow reserve. *J Invasive Cardiol* 2012;**24**:A43–4. PMID: 23043042.
 18. Toth GG, De Bruyne B, Rusinaru D, et al. Impact of right atrial pressure on fractional flow reserve measurements. Comparison of fractional flow reserve and myocardial flow reserve in 1,600 coronary stenoses. *JACC Cardiovasc Interv* 2016;**9**:453–9. DOI: 10.1016/j.jcin.2015.11.021; PMID: 26896888.
 19. Leonardi RA, Townsend JC, Patel CA, et al. Left ventricular end-diastolic pressure affects measurements of fractional flow reserve. *Cardiovasc Revasc Med* 2013;**14**:218–22. DOI: 10.1016/j.carrev.2013.06.001; PMID: 23886870.
 20. Adedji J, De Bruyne B, Floré V, et al. Significance of intermediate values of fractional flow reserve in patients with coronary artery disease. *Circulation* 2016;**133**:502–8. DOI: 10.1161/CIRCULATIONAHA.115.018747; PMID: 26733607.
 21. Windecker S, Kolh PH, Alfonso T, et al. 2014 ESC/EACTS Guidelines on myocardial revascularization. The Task Force on Myocardial Revascularization of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS) Developed with the special contribution of the European Association of Percutaneous Cardiovascular Interventions (EAPCI). *Eur Heart J* 2014;**35**:2541–619. DOI: 10.1093/eurheartj/ehu278; PMID: 25173339.
 22. Riley RF, Don CW, Powell W, et al. Trends in coronary revascularization in the United States from 2001 to 2009: recent declines in percutaneous coronary intervention volumes. *Circ Cardiovasc Qual Outcomes* 2011;**4**:193–7. DOI: 10.1161/CIRCOUTCOMES.110.958744; PMID: 21304092.
 23. Wong DTL, Ko BS, Cameron JD, et al. Transluminal attenuation gradient in coronary computed tomography angiography is a novel noninvasive approach to the identification of functionally significant coronary artery stenosis: a comparison with fractional flow reserve. *J Am Coll Cardiol* 2013;**61**:1271–9. DOI: 10.1016/j.jacc.2012.12.029; PMID: 23414792.
 24. Nørgaard BL, Leipsic J, Koo BK, et al. Coronary computed tomography angiography derived fractional flow reserve and plaque stress. *Curr Cardiovasc Imaging Rep* 2016;**9**:2. DOI: 10.1007/s12410-015-9366-5; PMID: 26941886.
 25. Tu S, Barbato E, Köszegi Z, et al. Fractional flow reserve calculation from 3-dimensional quantitative coronary angiography and TIMI frame count: a fast computer model to quantify the functional significance of moderately obstructed coronary arteries. *JACC Cardiovasc Interv* 2014;**7**:768–77. DOI: 10.1016/j.jcin.2014.03.004; PMID: 25060020.
 26. Lin GA, Dudley RA, Lucas FL, et al. Frequency of stress testing to document ischemia prior to elective percutaneous coronary intervention. *JAMA* 2008;**300**:1765–73. DOI: 10.1001/jama.300.15.1765; PMID: 18854538.