

Fractional flow reserve as an aid to decision-making

The impact of FFR and iFR on current PCI strategies

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Summary

Fractional flow reserve (FFR) measurement has become the gold standard for assessing myocardial ischaemia and has been recommended in both American and European guidelines as an aid to deciding whether or not to perform myocardial revascularisation. Indeed, large clinical trials have demonstrated that an evaluation of stenoses guided by FFR reduced death, nonfatal myocardial infarction and repeat revascularisation (MACE) when compared with an evaluation guided by angiography only and that percutaneous coronary intervention (PCI) with optimal medical treatment was superior to optimal medical treatment alone to reduce MACE in the presence of a pathological FFR.

To measure an FFR, the use of a pharmacological vasodilator (usually adenosine) is necessary. To avoid adenosine administration, the instantaneous wave-free ratio (iFR) recently emerged with the identification of a “wave-free period” of resistances similar in both magnitude and variability to those observed during FFR measurement. Nevertheless, iFR overall accuracy is only 80.4% and therefore iFR should not currently be recommended as an alternative to FFR.

Key words: FFR; iFR; PCI; coronary artery disease

Introduction

The decision to revascularise a patient presenting with stable coronary artery disease (SCAD) is based on the identification, extent and location of epicardial coronary stenosis via angiography. However, several recent trials have shown a benefit of revascularisation over medical treatment in terms of the prognosis when epicardial coronary stenosis induces extensive myocardial ischaemia, whatever the severity of coronary artery stenosis identified at angiography [1, 2]. Fractional flow reserve (FFR) measurement has become the gold standard for assessing myocardial ischaemia and has been recommended to aid decision-making about myocardial revascularisation in the most recent American and European guidelines [3, 4].

What is fractional flow reserve?

FFR is a technique allowing physicians to assess the impact of epicardial stenosis on the maximum flow in a given coronary artery. In order to measure the FFR, a

guide wire must be inserted during coronary angiography to measure pressure distal from the stenosis during maximum hyperaemia. The calculated ratio of pressure distal and proximal to the lesion (FFR) indicates the degree of ischaemia that a stenosis is inducing at maximum vasodilatation. In other words, if FFR is 0.70, this means that maximum myocardial blood flow is only 70% of its normal value. An FFR of 0.70 implies that stenting the focal stenosis responsible for this abnormal ratio would have to improve maximum myocardial blood flow by 43% $([1.0-0.7]/0.7)$ to reach an FFR of 1.0 – the FFR in a normal coronary artery (fig. 2). An FFR of 0.80 or less identifies ischaemia-causing coronary stenoses with an accuracy of more than 90%, and this is the ratio currently used for clinical decision-making [5].

Importance of ischaemia in stable coronary artery disease management

Several trials have addressed the question of the benefits of revascularisation over medical treatment in patients presenting with SCAD. In particular, the randomised COURAGE trial, published in 2007, involved 2287 patients with SCAD [6]. The investigators assigned patients to undergo a percutaneous coronary intervention (PCI) with optimal medical therapy (OMT) or to receive OMT alone. The results demonstrated that PCI did not reduce the risk of death, myocardial infarction, or other major cardiovascular events when added to OMT. The COURAGE trial's important finding was that revascularisation based on coronary angiography (only one-third of patients had proven myocardial ischaemia) in a low-risk population had no added value, in terms of prognosis, over OMT. Furthermore, the COURAGE trial's nuclear substudy showed that the patients with the worst prognosis were those who had extensive myocardial ischaemia, whatever the treatment assigned (fig. 1) [1].

The value of coronary angiography in detecting myocardial ischaemia

Coronary angiography is the gold standard method for detecting epicardial coronary artery stenosis. However, it has several limitations in the detection of myo-

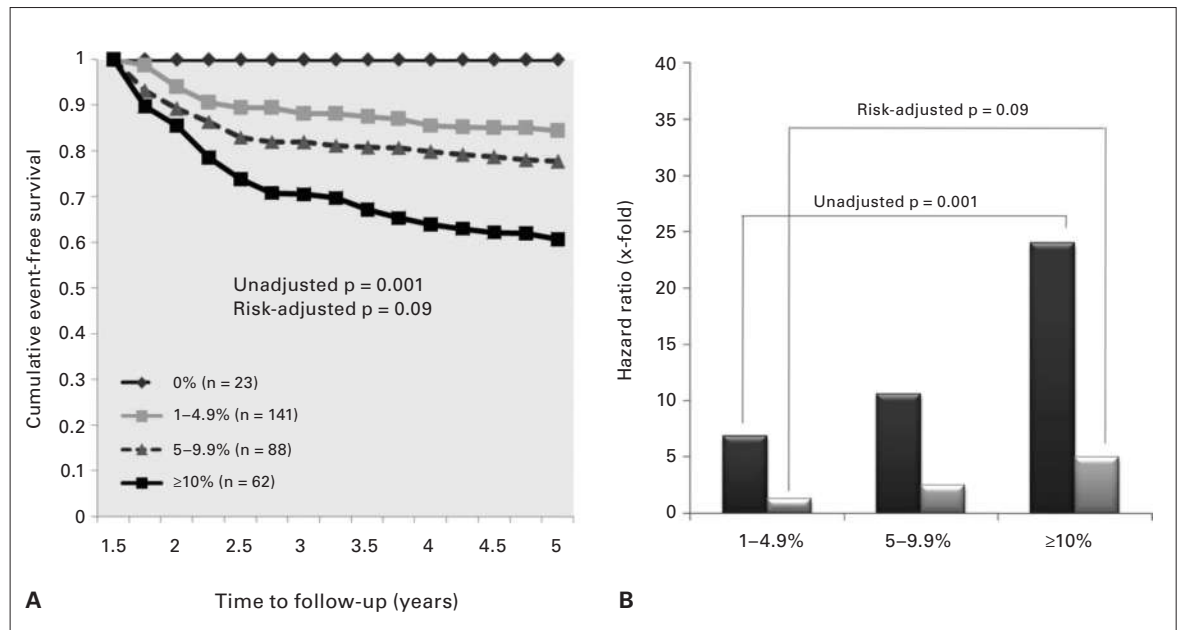


Figure 1: A. Kaplan-Meier survival plot for patients by residual ischaemia, including 0%, 1–4.9%, 5–9.9%, and ≥10% ischaemic myocardium, 6–18 months after PCI+OMT or OMT. Overall event-free survival was 100%, 84.4%, 77.7%, and 60.7%, respectively, for the groups with 0%, 1–4.9%, 5–9.9%, and ≥10% ischaemic myocardium ($p = 0.001$). In a risk-adjusted Cox model (controlling for randomised treatment), this difference was not significant ($p = 0.09$). B. Unadjusted (dark gray bars) and risk-adjusted (light gray bars) hazard ratios for the extent and severity of residual ischaemia at 6–18 months of follow-up. OMT = optimal medical treatment; PCI = percutaneous coronary intervention. Reprinted with permission from: Shaw LJ, Berman DS, Maron DJ, Mancini GBJ, Hayes SW, Hartigan PM, 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;117:1283–91. Promotional and commercial use of the material in print, digital or mobile device format is prohibited without the permission from the Publisher Wolters Kluwer Health. Please contact healthpermissions@wolterskluwer.com for further information.

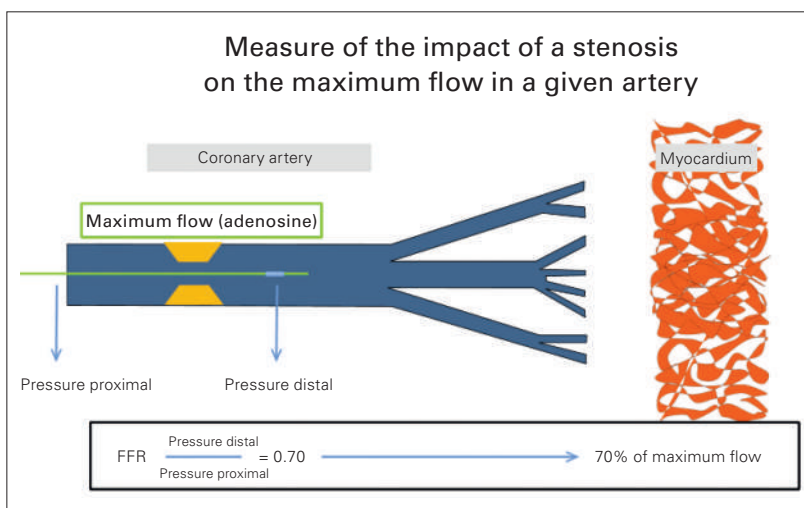


Figure 2: Principle of fractional flow reserve and its relation to myocardial ischaemia (see text).

cardial ischaemia, especially in intermediate stenosis, as it cannot account for all aspects of severity. A recent study addressed this issue in a large and unselected patient population; it examined the potential clinical and physiological significance of the discord-

ance between the severity of coronary artery disease seen on an angiogram and the FFR (fig. 3) [7]. The study compared a sample population of 4 086 patients with at least one stenosis of intermediate angiographic severity. The diagnostic accuracy of a stenosis of ≥50% of the normal vessel diameter predicting an FFR ≤0.80 was 0.64 (95% confidence interval [CI] 0.56–0.72). This study found that one-third of a large patient population showed a discordance in the diagnosis of severity thresholds between an angiogram showing stenosis ≥50% diameter and FFR ≤0.8.

What is the prognosis of patients revascularised on the basis of FFR measurement?

In the FAME trial, 1055 patients with stable angina and multivessel coronary artery disease were randomised to undergo PCI guided by angiography alone or PCI guided by angiography and FFR. The primary endpoint was a composite of death, nonfatal myocardial infarction and repeat revascularisation (MACE) at 1 year. The results were statistically significant for the primary endpoint at 1 year (18.3% in the angiography group versus 13.2% in the FFR group, $p = 0.02$) and also for the

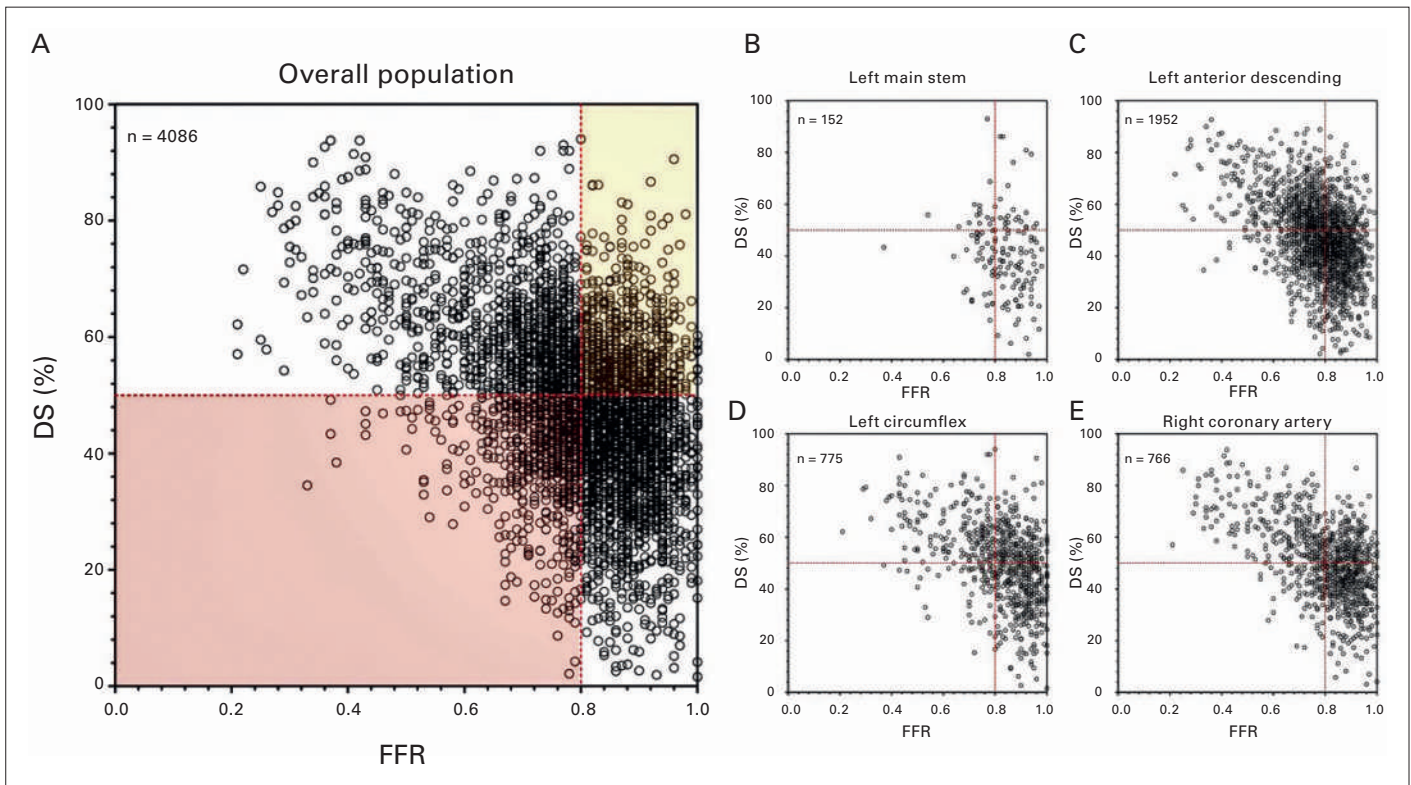


Figure 3: Correlation between diameter stenosis (DS) vs fractional flow reserve (FFR) in the overall population (A), and specifically in the left main stem (B) and the three major branches (C–F). The x-axes indicate the functional metric (FFR), and the y-axes indicate the angiographic metrics (DS).

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number of stents used per patient (2.7 ± 1.2 stents in the angiography group versus 1.9 ± 1.3 stents in the FFR group, $p < 0.001$). Thus, the FAME trial indicated that, among patients for whom a PCI was planned, an FFR-guided strategy was better than an angiography-guided strategy in terms of a MACE at 1 year. At 2 years, MACE occurred in 22.4% in the angiography group versus 17.9% in the FFR group ($p = 0.08$) but of importance, the 2-year rates of mortality or myocardial infarction were 12.9% in the angiography group versus 8.4% in the FFR group ($p = 0.02$) [8]. After 5 years, MACE occurred in 31% of patients in the angiography group versus 28% in the FFR group ($p = 0.31$) with an absolute difference which is not significant due to the smaller number of patients at risk and to the similar incidence of events in both groups beyond 2 years [9]. Nevertheless, the FAME trial did not give information on whether revascularisation (even based on a FFR strategy) was better than OMT in the context of SCAD.

This issue was addressed by the FAME II trial. In this study, patients with SCAD for whom PCI was being considered all had their stenoses evaluated with use of FFR measurement. If the FFR found at least one stenosis to be significant, then patients were randomised to PCI

with OMT or to OMT alone. The primary endpoint was a composite of death, myocardial infarction, or urgent revascularisation. After the inclusion of 1220 patients, significant differences between the two groups were observed in terms of the primary endpoint (4.3% in the PCI with OMT group and 12.7% in OMT group; $p < 0.001$) and, accordingly, the study was interrupted. It is of particular interest that the difference between the groups were driven by the rate of urgent revascularisation (1.6% in the PCI with OMT group and 11.1% in the OMT group; $p < 0.001$). These urgent revascularisations were triggered by an increase in biomarker levels, ischaemic changes on ECG, or both, in half of the patients and the awareness of the presence of a stenosis could be a bias, influencing decisions regarding revascularisation. However, the follow-up at 2 years [10] confirmed the statistically significant difference in term of urgent revascularisation rate between the OMT group and the PCI with OMT group. In addition, the follow-up at 2 years showed a statistically significant difference in terms of the rate of urgent revascularisation triggered by myocardial infarction or/and unstable angina with ECG modification between the OMT group and the PCI with OMT group (7.0 vs 3.4%, hazard ratio 0.22; 95% CI

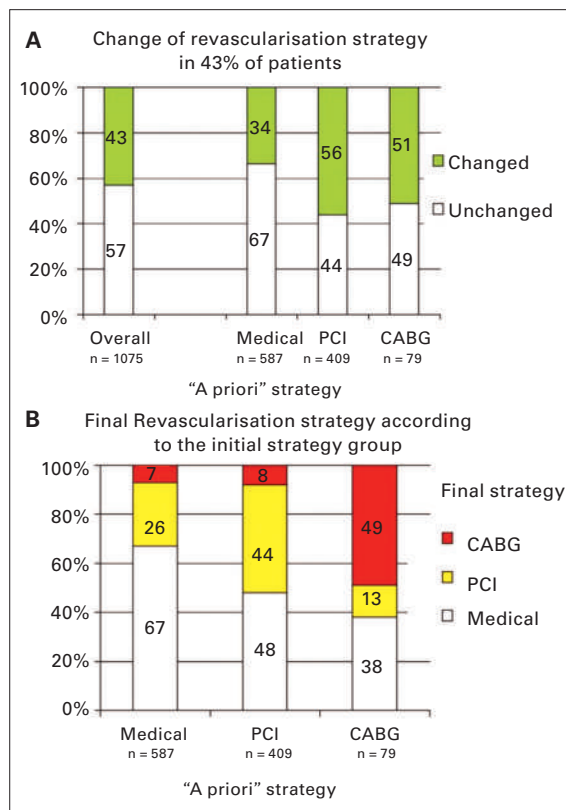


Figure 4: A. Reclassification of the revascularisation strategy according to the "a priori" strategy group. Despite minor overall changes, a change in strategy occurred for 43% of all patients (κ , 0.22; 95% confidence interval 0.17–0.27). B. Details of the final revascularisation strategy applied in each a priori strategy group. CABG = coronary artery bypass graft surgery. PCI = percutaneous coronary intervention. Reprinted with permission from: Van Belle E, Rioufol G, Pouillot C, Cuisset T, et al. Outcome impact of coronary revascularization strategy reclassification with fractional flow reserve at time of diagnostic angiography: insights from a large French multicenter fractional flow reserve registry. *Circulation*. 2014;129(2):173–85. Promotional and commercial use of the material in print, digital or mobile device format is prohibited without the permission from the Publisher Wolters Kluwer Health. Please contact healthpermissions@wolterskluwer.com for further information.

0.11–0.42; $p < 0.0001$). Even if the rate of death between the two groups were not statistically different, this study transformed the COURAGE paradigm: (PCI not

seen as indispensable in the treatment of patients with SCAD). Indeed FAME II demonstrated that patients with coronary artery disease and proven ischaemia should be treated with PCI if FFR measurement suggested it. Therefore, the 2013 European Society of Cardiology (ESC) guidelines on the management of SCAD established a class I recommendation (level of evidence A) in which the FFR should be used to identify haemodynamically relevant coronary lesion(s) when evidence of ischaemia is not available.

The impact of FFR measurement in current PCI strategies

The recent study by Van Belle et al. was based on 1075 patients from the French FFR registry. Interventional cardiologists had to prepare their initial therapy plan after an angiogram and a subsequent plan after the results of follow-up FFR measurement. A highly significant 43% of patients had their treatment plan changed on the basis of the FFR results (fig. 4). After FFR, 51% of the treatment plans initially set for a coronary artery bypass graft were changed; plans were changed for 56% of patients set to undergo PCI and 33% of patients meant to have OMT. This study showed a dramatic reclassification of patients following FFR measurement and confirmed the poor diagnostic accuracy of the coronary angiogram for detecting ischaemia.

iFR versus FFR

Hyperaemia is a fundamental aspect of FFR measurement. In order to facilitate maximum blood flow and microcirculation (and minimal resistance) during that measurement, the patient is given a pharmacological vasodilator, usually adenosine. Blood pressure is then measured proximal and distal to the stenosis, and their ratio is the FFR.

In April 2012, Sen et al. published the results of an alternative method of measurement known as the instantaneous wave-free ratio or iFR [11]. In order to avoid the administration of adenosine, the authors looked for a period in the cardiac cycle where resistance (at rest) is naturally minimised. They identified a "wave-free pe-

Table 1: Individual Data From Included Studies and Individual Study Sites.

Study/participating Site	No. of lesions	Cut-off point	AUC from ROC	Overall accuracy in %
Total	1523	0.9	0.81	80.4
ADVISE	432	0.91	0.82	81.9
VERIFY	654	0.89	0.8	79.4
Seoul National University	179	0.92	0.83	82.7
Stony Brook University	149	0.93	0.81	79.2
Columbia University	95	0.91	0.84	82.1
AMC/VUMC/KCL	84	0.9	0.78	78.6

riod” with resistances similar in both magnitude and variability to those observed during FFR measurement; this allowed them to calculate the ratio of pressures distal and proximal to the lesion without adenosine. Jeremias et al. recently compared iFR and FFR in a study of 1768 patients from 15 clinical sites (table 1) [12]. They observed that with an iFR of 0.90 (corresponding to an FFR \leq 0.80), the overall accuracy of this method was only 80.4% and, therefore, one patient in five was misdiagnosed. In our opinion, adenosine is neither a confounder in FFR measurement nor is it a danger to the patient, especially with intra-coronary administration. Accordingly, iFR should not currently be recommended as an alternative to FFR in routine clinical practice.

Conclusion

FFR measurement has become a validated diagnostic tool used in routine daily practice; it is easily reproducible, quick to measure, correlates very well with non-invasive tests, and has been extensively tested in different clinical trials. For these reasons, FFR measurement has a class I recommendation (level of evidence A) in the ESC and ACC/AHA guidelines for identifying haemodynamically relevant coronary lesions [3, 4]. The iFR, however, is a new diagnostic tool that has only been studied for the past 2 years; it is questionable conceptually and lacks clinical and experimental validation and cannot yet be recommended to be used in routine clinical practice.

Disclosure statement

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