

# Fractional flow reserve guided revascularization in daily practice: clinical judgment does not always meet science

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**Abstract:** Measurement of the fractional flow reserve (FFR) during invasive coronary angiography is the accepted “gold standard” for assessing the functional significance of coronary artery lesions by determination of the characteristics of blood flow proximal and distal to a coronary stenosis during pharmacologically-mediated hyperemia. Abnormal FFR is associated with higher cardiac event rate if the coronary lesion is left untreated. On the other hand, it was shown that patients derived no clinical benefit from revascularization of angiographically obstructive lesions which were hemodynamically insignificant according to FFR (>0.8).

This editorial comment refers to an observational cohort study which reported that in approximately 20% of real world patients the treatment strategy chosen was discordant with FFR findings.

Our comment discusses these findings and concludes that while the standard of care is to treat patients in accordance with their FFR results (when available), it should be recognized that there are some clinical scenarios that may require a treatment strategy that is discordant with FFR result.

**Key Words:** Fractional flow reserve (FFR); coronary artery disease (CAD); clinical decision making



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In current clinical practice, coronary angiography still plays an important role in invasive imaging of the coronary arteries despite rapid developments in noninvasive imaging. The temporal and spatial resolution of conventional invasive coronary angiography is higher than any alternative non-invasive method and therefore it remains the common anatomic gold standard for diagnosis of obstructive coronary artery disease (CAD) and for decision-making in patients who are candidates for revascularization. However, coronary angiography is of limited value in two major aspects related to coronary stenosis evaluation: the first is its limited ability to visualize atherosclerotic plaque, because angiography demonstrates the luminal contour but cannot define or quantify the amount and composition of coronary atherosclerotic plaque within the vessel wall (1). More importantly and relevant to the current review; Coronary angiography

is of very limited value in identifying hemodynamically significant coronary lesions that are associated with inducible myocardial ischemia (2).

Measurement of the fractional flow reserve (FFR) during invasive coronary angiography is the accepted “gold standard” for assessing the functional significance of coronary artery lesions by determination of the characteristics of blood flow proximal and distal to a coronary stenosis during pharmacologically-mediated microvascular hyperemia (3). FFR now has a class I-A indication from the European Society of Cardiology for identifying hemodynamically significant coronary lesions when non-invasive evidence of myocardial ischemia is unavailable (4). FFR is defined as the ratio of maximal coronary blood flow through a stenosed artery to the blood flow within a normal (non-stenosed) artery (abbreviated to a pressure ratio, distal/proximal). It provides a physiological

adjunct to invasive coronary angiography by accurately detecting flow-limiting coronary artery stenoses and improves decision-making for coronary revascularization (5). FFR is the only diagnostic method to date for ischemia detection that has been demonstrated to improve event-free survival (6,7). In the FAME study, patients with multivessel CAD who underwent FFR-guided revascularization experienced lower rates of adverse events with lower healthcare costs than patients undergoing angiography (alone)-guided revascularization (7,8). The results of the FAME study are in accordance with the 5-year follow-up of the DEFER (6) study which demonstrated that patients derived no clinical benefit from revascularization of angiographically obstructive lesions (>50% stenosis) which were hemodynamically insignificant according to FFR. In patients with stable CAD and a functionally significant stenosis, FFR-guided percutaneous coronary intervention (PCI) in combination with medical therapy decreased the need for urgent revascularization as compared with medical therapy alone (9). Despite these apparent benefits, less than 10% of coronary procedures use adjunctive intracoronary imaging or employ FFR to guide management (10). This is due to various practical limitations related to the measurement of FFR such as the added time and expense associated with the use of a coronary pressure wire and the need for intracoronary or intravenous administration of adenosine. Consequently, revascularization is frequently performed in patients with stable CAD and “innocent” lesions, who may not benefit from the intervention.

In the current issue of the journal, Orvin *et al.* (11) present a retrospective, observational cohort study which included a heterogeneous group of 189 patients who underwent a clinically indicated FFR evaluation of a coronary stenosis of uncertain significance and evaluated the treatment strategy chosen according to the FFR result. They also report mid-term (average 27 months, range 7-112 months) clinical outcome in relation to the FFR result and the treatment strategy chosen. The authors found that only 29% of patients had a functionally significant stenosis (FFR  $\leq$ 0.8), however, 36% of patients underwent immediate coronary intervention. Overall 35 (18.5%) of the 189 patients were actually treated in discordance with FFR results.

In analyzing the reasons for the clinical decision leading to a management strategy that was discordant from FFR result, the authors found that in about half of these patients (19/35), the FFR value was around the cutoff value (0.75-0.85). Overall, the tendency of clinical decision in this group of patients treated in discordant with FFR result was

toward a revascularization strategy as only 2 patients who had an FFR value of <0.75 were treated conservatively and 14 patients with FFR >0.85 underwent revascularization. The authors explain that in this group of patients who underwent revascularization despite a non-significant FFR, the decision was based on clinical judgment, positive stress test or high risk plaque morphology.

Not surprisingly, the authors observed that real time angiographic assessment of stenosis severity was often more severe than appreciated offline with quantitative coronary angiography and many times was discordant with the FFR measurement. Interestingly, the authors found that the adverse event rate was similar in both group of patients (those who were treated in accordance and those treated in discordance with FFR results). They therefore concluded that in everyday practice the operator's decision whether to intervene or not is sometimes (~20%) discordant with FFR results and clinical judgment continues to play a role in revascularization decisions.

While an evidence-based approach to coronary revascularization is important in the current era, especially when functional assessment of a coronary stenosis is available, it is important to recognize patient-specific and lesion-specific factors that may influence the clinical decision whether to perform revascularization or not. In real world scenarios, many factors may influence the physician's decision whether to perform revascularization including patient preference, compliance with medication, bleeding tendency, the complexity of the coronary lesion and various other factors which may all lead to a decision which can be discordant with the FFR result.

The authors should be commended for describing their real world experience with FFR and for presenting the reality and dilemmas of FFR-based clinical decision making where the imperative is to balance between the art and science of medicine. The similar event rate observed in both groups of patients regardless of adherence to FFR result is interesting and in disagreement with the landmark studies mentioned above but may be related to the low event rate observed in the current study.

In addition to patient-specific or lesion-specific factors that may influence treatment strategy and are discussed in the current study, FFR measurement may not always accurately reflect the true significance of a coronary stenosis. Common examples are when using sub-maximal hyperemia or when using a large guiding catheter that may obstruct the ostium of the coronary artery and interfere with maximal blood flow. Other possible causes are the presence

of abundant collaterals, severe left ventricular hypertrophy or cases of coronary spasm (which will not necessarily benefit from PCI) (2). However, despite those possible pitfalls in FFR measurement that may be considered by the physician and affect the clinical decision, the majority of FFR results in most clinical scenarios represent the true physiological significance of the lesion and should therefore guide coronary interventions.

Therefore, in agreement with the current study conclusions, and in view of FFR literature, the question of whether to “treat the patient or the FFR monitor” should probably be answered as: treat the patient according to the FFR result in most cases but recognize that there are some unusual scenarios where you may need to treat the patient and ignore the monitor. However, in these cases, just have a good reason for doing so.

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