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## Article

# Fractional Flow Reserve Implications for Clinical Decision Making in Coronary Artery Disease

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**Abstract:** Fractional flow reserve (FFR) is regarded as the gold standard for assessing the functional significance of coronary artery lesions, yet it remains underutilized in clinical practice. Our objective was to investigate whether FFR results have the potential to alter treatment decisions for coronary lesions compared to visual assessments of angiographic images made by three operators at a high-volume interventional center. In this retrospective study, we aimed to reassess the angiographic images of 63 patients presenting with chronic coronary syndrome (n=39, 61.9%) and acute coronary syndrome (n=24, 38.1%) who underwent FFR. Three experienced interventional cardiologists (with >300 PCI procedures per year) reevaluated, blinded to FFR results, 105 ambiguous lesions in 63 patients to determine angiographic significance and treatment strategy. The observers reached a concordant agreement ( $\geq 2$  operators made the same decision) to perform PCI in 60 (57.1%) of the lesions based on angiographic evaluation. Interestingly, 9 (15%) of these lesions were functionally non-significant (FFR >0.80). The observers agreed to defer PCI in 45 (42.9%) of the lesions; however, 4 (8.9%) of these were functionally significant (FFR  $\leq 0.80$ ) and required PCI. Thus, inter-observer concordance in visual-guided therapeutic decision-making is variable and not always confirmed by the functional significance of coronary lesions.

**Keywords:** fractional flow reserve; coronary artery disease; visual assessment variability; clinical decision making

## 1. Introduction

Precise evaluation of myocardial ischemia is crucial in the management of coronary artery disease (CAD) for making informed decisions about coronary revascularization [1]. Fractional flow reserve (FFR) is a pressure-derived estimate of coronary flow impairment and one of the most established invasive physiological tests in interventional cardiology. It is defined as the ratio between the mean hyperemic coronary artery pressure distal to the lesion and mean pressure in the aorta. FFR is an invasive index of hemodynamic significance of stenosis severity with a diagnostic accuracy similar to myocardial perfusion scintigraphy [2]. European guidelines recommend performing fractional flow reserve (FFR) measurements prior to revascularization, particularly when previous ischemia testing is inconclusive or absent [3]. However, despite the growing preference for physiologically guided revascularization, there remains a significant gap between guideline recommendations and the actual clinical use of functional assessment of the lesions [4,5].

The hemodynamic significance, as defined by an FFR  $\leq 0.80$ , shows a weak correlation with the visually assessed diameter of the stenosis. In the FAME trial (Fractional Flow Reserve versus Angiography for Guidance of PCI in Patients with Multivessel Coronary Artery Disease), only 35% of stenoses assessed by invasive quantitative coronary angiography (CA) in the 50-70% range were hemodynamically significant, and among stenoses in the 71-90% range, 20% were not significant. Only a stenosis diameter estimated at >90% was found to be hemodynamically significant with a high accuracy of 96% [6]. CA is the current gold-standard method of CAD assessment, but it fails to adequately determine lesion significance because lumen narrowing is just one of many variables influencing coronary flow limitation. Other critical factors that are not easily quantifiable by CA

include lesion length, collateral flow, and the amount and viability of the myocardium supplied downstream [7,8]. Several studies have shown that FFR-based evaluation at the time of CA led to the reclassification of revascularization strategies (PCI, coronary artery bypass grafting, or medical treatment) in a significant proportion of patients with intermediate-grade lesions (>40% of patients were reclassified) [9–11]. However, the impact of FFR on determining revascularization tactics may be of greater interest for patients with multivessel CAD, giving us the opportunity to minimally intervene on functionally significant lesions and safely defer insignificant ones [12].

Unlike FFR, which is an objective method for assessing lesions capable of inducing ischemia, CA is a subjective method for evaluating the degree of arterial lumen stenosis, dependent on the observer. The inter-observer agreement in visually guided therapeutic decision-making is variable [13], and not always confirmed by the functional significance of coronary lesions [14]. Therefore, we aimed to determine the variability in visual assessment of CAD and the impact of FFR on the clinical decision making. Angiographically guided therapeutic decisions were largely concordant with FFR results in our study. However, in 12.4% of cases, FFR impacted the treatment strategy, both by indicating PCI for hemodynamically significant lesions (8.9%) and by deferring PCI for non-significant lesions (15%).

## **2. Materials and Methods**

### *2.1. Patient Selection*

This was a retrospective observational study that included 63 patients with CAD assessed by CA, who underwent at the same time functional evaluation by FFR of 105 lesions (50-99% artery lumen stenosis) in 2023, in the Institute of Cardiology, Chisinau, Republic of Moldova. Patients were assessed for age, sex, traditional risk factors, clinical status at presentation (stable angina, unstable angina, or NSTEMI), clinical and paraclinical data serving as indications for CA (anginal symptoms, dyspnea, exercise test, prior myocardial infarction, low left ventricular ejection fraction). CA was performed using GE Innova IGS angiography machines, following standard protocol. The angiographic characteristics of CAD were assessed: number of diseased vessels, the location and severity of stenoses. Thus, inclusion criteria for the study group were patients with CAD, defined as 50-99% lumen narrowing, as assessed by CA, which were subsequently evaluated by FFR measurement (Figure 1). Patients with STEMI, left main CAD and those with chronic total occlusions were excluded from this study.

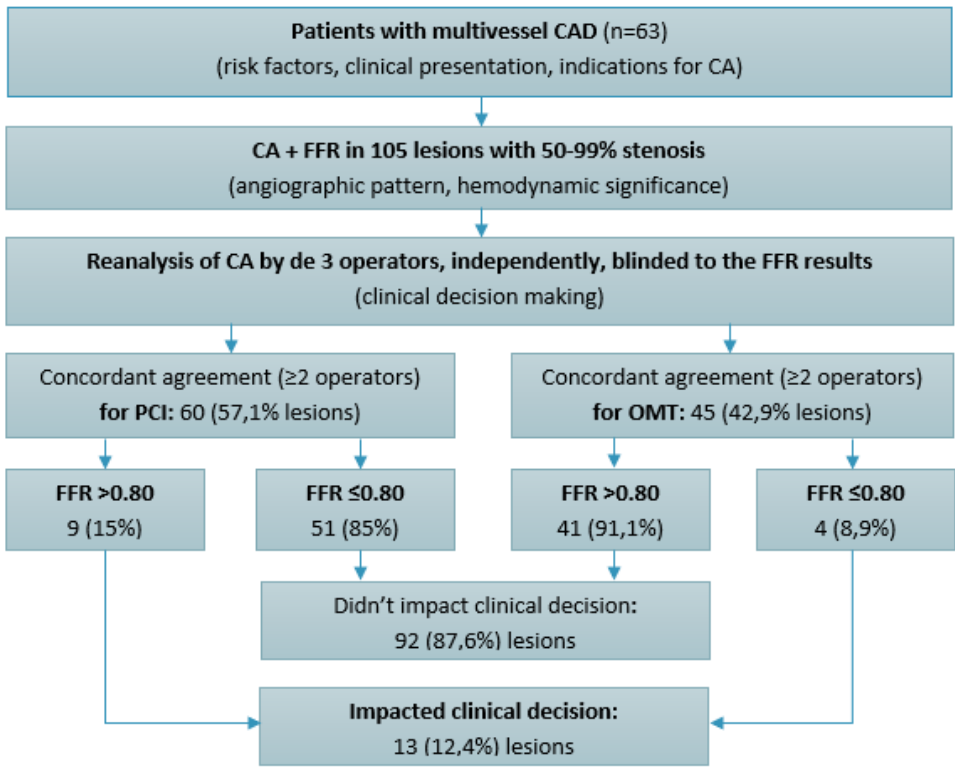


Figure 1. Study flowchart.

2.2. Fractional Flow Reserve

FFR assessment was performed for all 50-99% stenoses assessed by the primary operator at the time of CA. After intravenous administration of heparin (70 IU/kg), a 0.014" intracoronary pressure wire, 175 cm (PressureWire X, Abbott Medical, Minneapolis, USA) was advanced distal to the stenosis (Figure 2). After intracoronary administration of 100-200 mcg of isosorbide dinitrate (according to hemodynamics), reactive hyperemia was induced by intravenous adenosine (140–180 µg/kg/min) administration [15]. An FFR value of ≤0.80 was used as the cutoff to indicate functional significance of CAD [16]. Percutaneous coronary intervention (PCI) was performed for lesions with an FFR ≤0.80, while lesions with an FFR >0.80 were managed with optimal medical therapy (OMT), in accordance with current guideline recommendations [3]. If a patient had two or more functionally significant lesions in two or more arteries, staged PCI was preferred, with an interval of 2-4 weeks between the initial procedure and subsequent intervention. PCI was performed using standard percutaneous techniques, either via radial, brachial, or femoral approach.

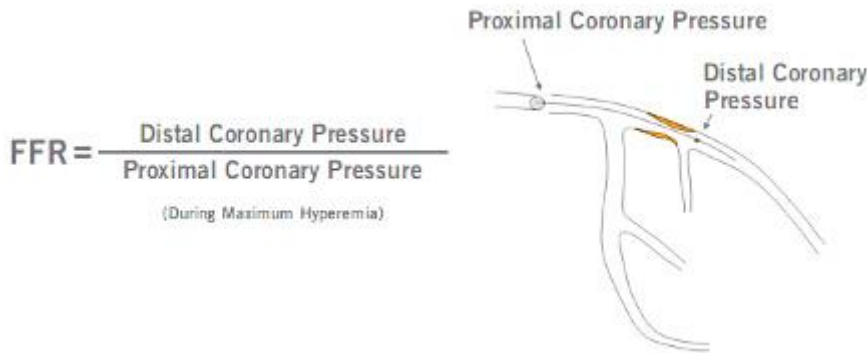


Figure 2. Fractional flow reserve assessment.

### 2.3. Visual Assessment Variability

Each CA was reanalyzed by three experienced interventional cardiologists (with a volume of >300 PCIs performed annually), independently of each other, to determine the angiographic severity of lesions and the need for revascularization based on visual assessment, clinical presentation, and blinded to FFR values. Concordant agreement was considered when at least two interventional cardiologists made the same decision - to treat or not treat a lesion. Complete agreement, when all three interventional cardiologists had the same treatment decision, was also assessed. These results were matched with FFR results to reveal where it had an impact to change clinical decision-making.

### 2.4. Statistical Analysis

Statistical analysis was conducted using the Statistical Package for Social Sciences (SPSS), version 16. Categorical variables were reported as frequencies and percentages, while continuous variables were presented as mean  $\pm$  standard deviation. The normality of data distribution was assessed using the Kolmogorov–Smirnov test.

## 3. Results

### 3.1. Study Population

The mean age of the study population of 63 patients was 63,55 years (range 34 to 78 years), with 48 (76,2%) males and 15 (23,8%) females (Table 1). The most prevalent risk factors in this study group were: hypertension – 60 patients (95,2%), dyslipidemia – 54 patients (85,7%), type 2 diabetes mellitus – 40 patients (63,5%), family history of cardiovascular disease – 11 patients (17,5%), and smoking 9 patients (14,3%). In total, there were identified 105 lesions of 50-99% stenosis in 63 patients, which were evaluated by FFR, averaging 1,67 lesions per patient.

**Table 1.** Demographic and clinical characteristics of the study population.

Patient Characteristics		N = 63 (100%)
Mean Age (years ± standard deviation) 63.55±8.7		63,55±8,7
Sex	Male	48 (76,2%)
	Female	15 (23,8%)
Risk Factors	Smoking	9 (14,3%)
	Type 2 Diabetes Mellitus	40 (63,5%)
	Hypertension	60 (95,2%)
	Dyslipidemia	54 (85,7%)
	Family history	11 (15,5%)
Clinical Presentation	Stable Angina	39 (61,9%)
	Unstable Angina	20 (31,7%)
	NSTEMI	4 (6,4%)
Indications for CA	Typical Angina	34 (53,9%)
	Dyspnea	12 (19%)
	Atypical Presentation	5 (7,9%)
	Positive Stress Test	7 (11,1%)
	Prior Myocardial Infarction	16 (25,4%)
	Left Ventricular Systolic Dysfunction (EF <50%)	13 (20,6%)
Stress Testing	No pre-procedural Stress Testing	56 (71,4%)
	Positive Stress Test	7 (11,1%)
Puncture Site	Radial Access	58 (92%)
	Femoral Access	4 (6,4%)
	Brachial Access	1 (1,6%)
Diseased Vessels	One-vessel disease	30 (47,6%)
	Two-vessel disease	23 (36,5%)
	Three-vessel disease	10 (15,9%)

Clinical presentation was diverse, including stable angina in 39 patients (61,9%), unstable angina in 20 patients (31,7%), and NSTEMI in 4 patients (6,4%). The indications for CA were predominantly the presence of typical angina pectoris: 34 patients (53,9%) and prior myocardial infarction 16 patients (25,4%). Most patients - 56 (88,9%) who underwent CA did not have exercise testing within the 90-day pre-procedural period, and only 7 (11,1%) of them had a positive exercise test for documenting ischemia. In 92% of cases, coronary angiography was performed via radial access, which implies minimal local complications at the puncture site.

3.2. Lesion Characteristics

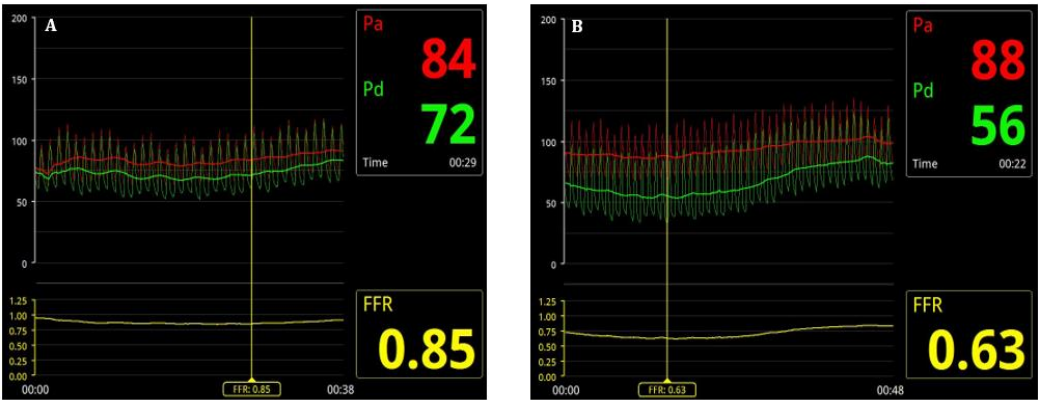
In terms of angiographic characteristics, 33 (52,4%) patients in the study group had multivessel CAD (two- or three- vessel disease), and the majority of lesions were located in the left anterior descending artery (LAD) - 53 (50,5%) (Table 2). The primary operator visually assessed 58 (55,2%) of lesions as being severe and 47 (44,8%) of lesions as being moderate. Nonsignificant FFR values (>0.8) were found in 50 of the lesions (47,6%), which did not undergo PCI, while significant FFR values (≤0.8) were found in 55 of the lesions (52,4%), which underwent PCI (Figure 3). Interestingly to mention that 21 of the hemodynamic significant lesions (38.2%) were found in patients presented with acute coronary syndrome (unstable angina or NSTEMI).



**Table 2.** Angiographic characteristics and hemodynamic significance of the lesions.

Angiographic Characteristics			Hemodynamic Significance	
105 (100%) lesions			FFR >0.8	FFR ≤0.8
			50 (47,6%) lesions	55 (52,4%) lesions
Lesion Location	LAD	53 (50,5%)	28 (52,8%)	25 (47,2%)
	RCA	28 (44,4%)	13 (46,4%)	15 (53,6%)
	LCx	24 (38,1%)	9 (37,5%)	15 (62,5%)
Stenosis	Moderate (50-74%)	47 (44,8%)	39 (83,0%)	8 (17,0%)
Severity	Severe (75-99%)	58 (55,2%)	11 (19,0%)	47 (81,0%)

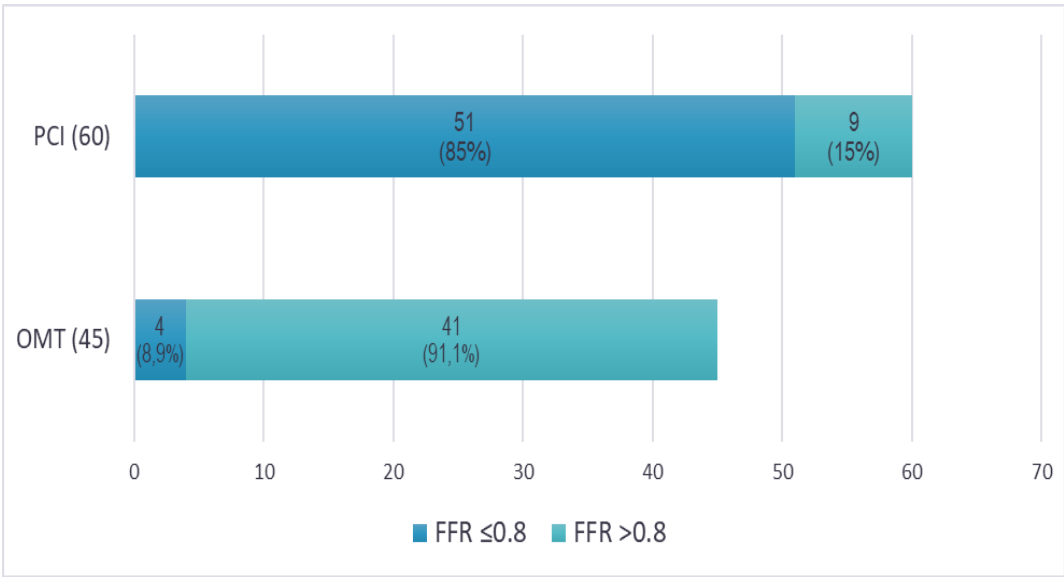
Lesions located in the LAD showed hemodynamic significance (FFR ≤0.8) in 25 (47,2%) of cases, those in the RCA – in 15 (53.6%) of cases, and those in the LCx – in 15 (62.5%) of cases. Moderate stenoses (50-74%) were hemodynamic significant (FFR ≤0.8) in 8 (17,1%) of cases, and the majority of severe stenoses (75-99%) were hemodynamically significant – in 47 (81,0%) of cases.



**Figure 3.** FFR measurement = Pd (distal pressure) /Pa (aortic pressure), during maximal hyperemia. Example of A. Non-significant FFR (>0.8) and B. Significant FFR (≤0.8).

3.3. Clinical Decision Making

Upon re-evaluating the angiographic images, three experienced interventional cardiologists (each performing over 300 PCIs annually) independently reviewed the cases, blinded to FFR results. Concordant agreement (at least two out of three cardiologists making the same decision) was reached to proceed with PCI for 60 lesions (57.1%) based on angiographic assessment and clinical presentation (Figure 4). Interestingly, 9 of these lesions (15%) had FFR values that were functionally insignificant. Conversely, there was concordant agreement to defer PCI in favor of OMT for 45 lesions (42.9%). However, 4 of these lesions (8.9%) had FFR values that were functionally significant and required PCI. As a result, FFR had an impact to change revascularization decision in 13 lesions (12.4%), both indicating PCI for 4 functionally significant lesions, and deferring 9 functionally non-significant lesions for OMT. Notably, complete agreement (all three cardiologists making the same decision to either perform PCI or defer to OMT) was achieved in only 82 lesions (78.1%).



**Figure 4.** Discrepancy of clinical decisions with FFR values.

**4. Discussion**

The current study evaluates the impact of FFR on revascularization decisions for atherosclerotic lesions with 50-99% stenosis in a group of 63 patients with CAD. The majority of patients with CAD are men, typically over the age of 60, with other traditional risk factors such as hypertension and dyslipidemia [17,18]. Most often, the indication for CA is driven by typical angina symptoms, and rarely have these patients undergone non-invasive stress testing to document inducible ischemia. On CA this population has predominantly multivessel disease and most frequently lesions involve the LAD. More than half of these lesions are functionally significant and require revascularization via PCI.

Despite the demonstrated benefits of FFR, less than 10% of coronary procedures utilize intracoronary imaging or FFR to guide patient management [19,20]. This is due to various practical limitations related to FFR measurement, such as the additional time and costs associated with using a coronary guidewire equipped with a distal pressure sensor and the need for intracoronary or intravenous adenosine administration. Consequently, PCI is sometimes performed on functionally insignificant lesions, where the intervention could be safely deferred in favor of optimal medical therapy [21].

The study cohort included a variety of clinical presentations, ranging from stable angina to unstable angina and NSTEMI. Previously, the diagnostic performance of FFR in patients with NSTEMI had been evaluated by others [22,23]. In the present study, one of the key findings was that significant FFR (≤0.8) was found in 55 (52.4%) lesions, and in more than one-third of them—21 (38.2%), patients presented with acute coronary syndrome (unstable angina or NSTEMI).

Another important finding from this study was that moderate stenosis, angiographically assessed at 50-79%, revealed hemodynamic significance (FFR ≤0.8) in 17% of cases, while the majority of severe stenosis, assessed at 75-99%, were hemodynamically significant - in 81% of cases. However, 19% of lesions with severe stenosis were found to be functionally non-significant, allowing the FFR-guided strategy to prevent unnecessary revascularization in these cases. The difference in visual and hemodynamic guidance was found in other studies, where it had reduced the need for stenting and flattened the added cost of the pressure wire [24,25].

Discrepancies between the visually and functionally estimated significance of intermediate stenoses are frequently encountered and can change the clinical decision-making in more than one third of cases, as reported in other studies [26]. In the present study, there was concordant agreement (≥2 out of 3 interventional cardiologists) to revascularize 60 (57.1%) of the lesions based on the angiographic appearance, while 9 (15%) of these were functionally non-significant according to FFR



measurements. On the other hand, a concordant agreement to defer PCI in favor of OMT was reached for 45 (42.9%) of the lesions, while 4 (8.9%) of these were functionally significant. Thus, FFR assessment of lesions has a significant clinical impact, leading to a change in treatment strategy in 13 lesions (12.4%).

Despite its well-established clinical value, the routine use of FFR in daily practice is not consistently cost-effective [24], making it important to identify the group of lesions where FFR can yield truly significant results. The clinical and cost implications of such a shift in the decision-making process, especially in resource-limited areas like the Republic of Moldova, require further evaluation in larger studies. In reality, many factors can influence the physician's decision to perform revascularization, including patient preference, treatment compliance, lesion complexity, the feasibility of achieving complete revascularization, and additional costs, all of which can lead to a decision that may be discordant with the FFR outcome.

## 5. Conclusions

Angiographically guided decision making on revascularization of CAD is largely aligned with FFR results. However, in 12.4% of cases, FFR influenced a change in treatment strategy, leading to the indication of PCI for hemodynamically significant lesions (8.9%) and the deferral of PCI for non-significant ones (15%).

**Author Contributions:** Involved in data curation, formal analysis, investigation, visualization and writing the original draft: MD, PhD candidate Andrei Grib. Ensure project administration and resources, as well as writing – reviewing & editing: MD, PhD Marcel Abras. Involved in data curation and software: MD, PhD Artiom Surev. Substantial contributions to conceptualization, methodology and supervision: Prof. Dr. Livi Grib. All authors have read and agreed to the published version of the manuscript.

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**Institutional Review Board Statement:** The study was conducted in accordance with the Declaration of Helsinki and approved by the Ethics Committee of Research at USMF “Nicolae Testemitanu”, nr. 00274RA from 12.09.2019.

**Informed Consent Statement:** Informed consent was obtained from all subjects involved in the study.

**Data Availability Statement:** The data presented in this study is available on request from the corresponding author. The data is not publicly available due to privacy and ethical restrictions.

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**Conflicts of Interest:** The authors declare no conflicts of interest.

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