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Coronary Physiology in the Management of CAD Patients: Position Paper Regarding the Current Scenario in India

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Abstract

Fractional flow reserve (FFR), a physiology-based diagnostic method, has emerged as an important decision-making tool in determining the borderline or intermediate coronary lesions requiring revascularization. As per the guidelines recommended by European and American cardiology associations, functional assessment of indeterminate lesions is to be considered strongly prior to PCI. However, in India, FFR continues to be a much-underutilized tool due to limited facilities, and many times, physicians are reluctant to advise FFR because of its time-consuming nature with additional cost implications of simple diagnostic tests. Notably, for stenoses ranging between 50% - 70% where the choice between revascularization and medication becomes ambiguous, FFR provides invaluable insight. Without such guidance, there is a risk of improper decisions and strategies while planning revascularization procedures, which might adversely influence clinical outcomes, escalation of the cost due to unnecessary procedures, and prolonged hospitalization as a result of simple vs complex procedures. Landmark studies have validated the efficacy of FFR in enhancing outcomes in coronary artery disease (CAD) patients, especially when paired with a coronary angiogram. This combination provides robust evidence of the functional significance of stenosis in stable CAD. Additionally, non-hyperemic pressure ratio indices correlate well with conventional FFR. Hence, adopting FFR-guided management can have transformative effects on the clinical and economic facets of treating severe CAD with intermediary lesions in Indian settings.

Keywords

Coronary Physiology, Fractional Flow Reserve, Percutaneous Coronary Intervention, Revascularization

1. Basics of Coronary Physiology

Coronary artery disease (CAD) is the most common type of cardiovascular disease, which affects millions of people in India. [1] The prevalence of CAD ranges from 1% to 2% in rural and 2% to 4% in urban Indians. [2] It was the third-most common cause of mortality in 2005 and became the most common cause of mortality in 2016. [3] [4] According to the Registrar General of India, a total of 17% of deaths and 26% of adult deaths were attributable to CAD during 2001-2003. The corresponding mortality increased to 23% and 32% in 2010-2013, respectively. [2] The Global Burden of Disease Study has underlined growing trends in disability-adjusted life years (DALYs) from CAD in India. [4] Further, the CAD poses a catastrophic economic and social burden among Indians. [5] The World Health Organization (WHO) estimates that the CAD epidemic has cost the Indian Government United States Dollar (USD) 237 million between the years 2005 and 2015. However, most of the expenses should be considered ineffectual, as about 80% of myocardial infarction cases can be prevented by adequate treatment and prevention strategies. [2] Thus, a rapid and precise diagnosis of CAD will improve the management of the disease and decrease its burden among patients.

The outcome of CAD depends on the degree of inducible ischemia. A coronary angiogram is traditionally used to examine the stenosis. However, it offers only anatomical information but does not provide information on the functional significance of the stenotic lesion. [6] The initial management with percutaneous coronary intervention (PCI) based on angiography only does not improve outcomes for patients with stable CAD. [7] The same is also confirmed by recent trials such as ISCHEMIA. [8] In healthy coronary vessels, blood flow maintains a linear pressure-flow relationship. However, the presence of stenosis disrupts this relationship by amplification of resistance due to hemodynamic challenges. Viscous friction, created by the blood's effort to navigate the narrowing, coupled with flow separation, turbulence, and the formation of eddies, compounds this resistance. As a result, there's an energy loss, leading to a significant pressure drop just after the stenotic region. This deviation from the typical linear pressure-flow relationship, resulting in a curvilinear one in vessels with stenosis, establishes a notable pressure gradient. Furthermore, the pressure loss relative to blood flow exhibits a quadratic relationship, meaning the pressure drop intensifies more rapidly as flow increases. Clinically, two angiographically similar stenoses can have divergent implications. One might severely restrict blood flow, leading to symptoms like angina, while another, though visibly apparent, may not be clinically significant. This underscores the importance of considering both anatomical and functional consequences when evaluating stenosis. [9] [10] Therefore, the coronary blood flow assessment helps detect hemodynamically relevant stenosis and is an essential element for determining the extent of obstructive coronary disease. Fractional flow reserve (FFR) correlates the distal coronary pressure and clinical significance of a stenosis. It quantifies the peak reduction in flow due to stenosis by measuring the ratio between mean distal coronary pressure (Pd) and mean aortic pressure (Pa) during maximal vasodilation. The FFR concept is based on the assumption that a proportional linear relationship exists between coronary perfusion pressure and flow, irrespective of the presence or absence of stenosis during maximum vasodilatation. [11]

Over the years, FFR emerged as a reliable and straightforward physiologic index over coronary angiography for the assessment of intermediate lesions, guiding multivessel PCI and stent deployment. [12] Currently, FFR continues to be the gold standard invasive diagnostic test in guiding revascularization in patients with CAD. It has a normal value of 1.0 for each coronary vessel and patient. An FFR of 0.75 (specificity 100%) indicates inducible ischemia, while 0.80 (sensitivity 90%) implies an absence of inducible ischemia in the majority of patients. Decision-making for revascularization should depend on the clinical judgment if FFR values fall between 0.75 and 0.80. [10] [11] Fractional flow reserve is measured usually after coronary angiography in the catheterization laboratory. It requires a pressure-sensor wire or a guiding catheter and a hyperemia-inducing agent. Several 0.014-inch pressure monitoring guide wires are available to record pressure distal to the target lesion. Fractional flow reserve is measured followed by the administration of intracoronary nitroglycerin (100 - 200 μg) for dilating the coronary vessel. This is subsequently followed by the administration of hyperemia-inducing agent in inducing maximum hyperemia and minimum microvascular resistance. Adenosine (IV 140 - 150 μg/kg/min; IC ≥ 80 μg [LCA] and ≥40 μg [RCA]) is the gold standard for FFR measurement, but other agents such as regadenoson, nicorandil, nitroprusside, papaverine, and dobutamine have also been used as a substitute for adenosine. [13] [14]

2. Clinical Application of FFR

The use of FFR has been recommended by the European (Class 1A) and US guidelines (Class 2A) for an evaluation of angiographic intermediate coronary lesions (50% to 70% stenosis) and for guiding revascularization decisions in patients with stable CAD (**Table 1**).

3. Clinical Evidence Related to the Benefits of FFR in CAD

Key trials related to FFR

Multiple prospective randomized controlled trials have established the benefits of FFR in deferring PCI (**Table 2**). The DEFER study, [18] which followed up patients for 15 years, has shown that PCI can be safely deferred based on a

Table 1. Indications and Recommendations for FFR.

Guidelines	Recommendations
2018 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) [15]	• FFR is the current standard of care for the functional assessment of lesion severity in patients with intermediate-grade stenosis (typically around 40% - 90% stenosis) without evidence of ischemia in non-invasive testing or those with multivessel disease. • FFR may also be useful for the selection of lesions requiring revascularization in patients with multivessel CAD.
2016 and 2017 ACC/AATS/AHA/ASE/ASNC/SCAI/SCCT/STS Appropriate Use Criteria for Coronary Revascularization in Patients With Stable Ischemic Heart Disease [16]	• Invasive measurements (such as FFR) may be very helpful in further defining the need for revascularization and may substitute for stress test findings. • FFR ≤ 0.80 is abnormal and is consistent with downstream inducible ischemia. • Appropriate use criteria advocate for expanded use of intracoronary physiologic testing. • In the presence of an asymptomatic intermediate-severity non-culprit artery stenosis, revascularization was rated as an "appropriate therapy," provided that the FFR was ≤0.80.
Society of Cardiovascular Angiography and Interventions: Expert consensus statement on the use of fractional flow reserve, intravascular ultrasound, and optical coherence tomography: A consensus statement of the Society of Cardiovascular Angiography and Interventions [17]	• In SIHD when noninvasive imaging is unavailable, nondiagnostic, or discordant, FFR should be used to assess the functional significance of intermediate-severe coronary stenosis (50% - 90%). • In SIHD, PCI of lesions with FFR < 0.80 improves symptom control and decreases urgent revascularization compared to medical therapy. • When FFR > 0.80 in angiographically intermediate lesions with SIHD, medical therapy is indicated.

CAD: Coronary artery disease; FFR: Fractional Flow Reserve; PCI: Percutaneous coronary intervention; SIHD: Stable ischemic heart disease.

nonsignificant FFR. Patients were assigned to either the deferral group (n = 91) or performance group (n = 90) if FFR was >0.75; PTCA was performed (reference group; n = 144) as if FFR was <0.75. Event-free survival was not different between the deferral and performance groups at 2-year follow-up (89% vs 83% months) but was significantly lower in the reference group (78%). At the 15-year follow-up, patients in the defer group had a significantly lower rate of myocardial infarction compared to the performance group (2.2% vs. 10%; relative risk [RR] 0.22, 95% confidence interval [CI] 0.05 - 0.99, P = 0.03). However, the rate of mortality was similar between defer, performance, and reference groups (Defer vs. Perform, RR 1.06, 95% CI 0.69 - 1.62, P = 0.79). Overall, patients with intermediate and functionally non-significant lesions deferred based on FFR had an excellent prognosis at 15-years follow-up. [19] The FAME trial demonstrated the importance of routine measurement of FFR during DES-stenting; patients with multiple-vessel disease with FFR-guided management have superior PCI outcomes compared to coronary angiography-guided treatment. At 1-year follow-up, the composite primary endpoint of death, nonfatal MI, and repeat revascularization event rate are significantly lower in the FFR-guided group than the angiography-guided group (13.2% vs 18.3% P = 0.02). [20] FFR-guided PCI

Table 2. Key physiology studies with FFR.

Study and Year	N	Design	Population	FFR cutoff	Outcomes
DEFER 2001 [19]	325	RCT	Stable CAD and intermediate stenosis without evidence of ischemia	0.75	No benefit stenting a non-ischemic stenosis
FAME 2009 [20]	1005	RCT	Multivessel CAD	0.80	Routine measurement of FFR in patients with multivessel CAD who underwent PCI with DES had a reduction in MACE at 1 year
FAME 2 2012 [22]	888	RCT	Stable CAD and hemodynamically significant stenoses	0.80	FFR-guided PCI with DES plus OMT vs OMT alone attenuated the rate of urgent revascularization. In negative FFR, OMT alone resulted in excellent outcomes, notwithstanding the angiographic assessment of the stenoses.
FAMOUS-NSTEMI 2014 [26]	350	RCT	NSTEMI referred for invasive management	0.80	FFR-guided management was associated with lower rates of revascularization versus angiography-guided management. Spontaneous MACE was more common in the FFR group during the 12-month follow-up.
DANAMI-3-PRIMULTI 2015 [27]	627	RCT	STEMI and multivessel disease who had undergone primary PCI of an infarct-related coronary artery	0.80	FFR-guided staged revascularization during index admission reduced the risk of future events and the need for revascularization.
Compare-Acute 2017 [28]	885	RCT	STEMI and multivessel disease who had undergone primary PCI of an infarct-related coronary artery	0.80	FFR-guided complete revascularization of non-infarct-related arteries in the acute setting resulted in lower MACE, including the need for revascularization.
IRIS-FFR 2017 [25]	5846	Prospective registry	At least one coronary lesion	0.75	Lesions with FFR ≤ 0.75: risk of MACE was significantly lower in revascularized lesions than deferred lesions. Lesions with FFR ≥ 0.76: risk of MACE was not significantly different between deferred and revascularized lesions.
Mayo Registry 2013 [30]	7358	Retrospective registry	PCI candidates without STEMI or cardiogenic shock	<0.75: PCI 0.75 - 0.80: Operator discretion >0.8: OMT	FFR-guided treatment was associated with a positive long-term outcome with a decreased reduction in MACE events.
RIPCORD 2014 [31]	200	Prospective observational study	Stable angina	0.80	Routine measurement of FFR at diagnostic angiogram affects the patient management approach.

CAD: Coronary artery disease; DES: Drug-eluting stent; FFR: Fractional Flow Reserve; MACE: Major adverse cardiovascular events; NSTEMI: Non-ST elevation myocardial infarction; OMT: Oral medical therapy; PCI: Percutaneous coronary intervention; RCT: Randomized controlled trial; STEMI: ST-elevation myocardial infarction.

resulted in a significant reduction in major cardiovascular events (MACE) at up to two years. At five year follow-up, the risk was similar between FFR-guided and angiography-guided groups (relative risk 0.91, 95% CI 0.75 - 1.10; P = 0.31). [21] The FAME 2 [22] [23] trial has shown that compared to the medical-therapy group, FFR-guided PCI significantly lowered composite of death, MI, or urgent revascularization at 1-year (4.3% vs 12.7%; HR 0.32; 95% CI 0.19 to 0.53; P < 0.00), 2-year (4.0% vs 16.3%; HR, 0.23; 95% CI, 0.14 to 0.38; P < 0.001) and 5-year follow-up (13.9% vs 27.0%; HR 0.46; 95% CI, 0.34 to 0.63; P < 0.001) in patients with stable coronary diseases. [24] The need for urgent revascularization was significantly reduced in the PCI group compared to the medical-therapy group (3.4% vs.7.0%, P = 0.01). Further, the rate of death of MI from 8 days to 2 years was significantly lower in the PCI group versus the medical-therapy group (4.6% vs 8.0%, P = 0.04). [22] [23] However, there were no significant differences in the mortality or MI between the groups at 5 years (5.1% and 5.2; HR 0.98; 95% CI 0.55 to 1.75 and 8.1% and 12.0%; HR 0.66; 95% CI, 0.43 to 1.00, respectively). [24] Both FAME 1 and 2 trials have demonstrated that FFR-guided PCI intervention was associated with prolonged clinical benefits with regard to death, MI, or urgent revascularization at 5 years. Overall, the FAME 1 and FAME 2 trials provide evidence for the benefits of FFR-guided multivessel angioplasty in myocardial infarction. These trials demonstrate that FFR-guided PCI can lead to better clinical outcomes, including a reduction in major adverse cardiac events and the need for urgent revascularization. By accurately assessing the functional significance of coronary artery stenosis, FFR-guided multivessel angioplasty allows for more targeted and effective interventions, improving patient outcomes and reducing the need for additional procedures.

IRIS-FFR, a prospective registry of the larger population, assessed the prognosis of deferred and revascularized coronary lesions based upon FFR value. This study showed a linear association between FFR values and the risk of cardiac events in deferred lesions (adjusted HR, 1.06; 95% CI, 1.05 - 1.08; P < 0.001). The use of FFR demonstrated significant benefits in the prognosis and management of coronary artery stenoses. The research confirmed that for lesions with FFR ≥ 0.76, deferring revascularization in favor of medical therapy was a reasonable and safe treatment strategy. In contrast, for lesions with FFR ≤ 0.75, revascularization was associated with improved outcomes. Especially noteworthy was the finding that medical treatment was a viable strategy within the gray zone (FFR values between 0.75 and 0.80), reinforcing the tool's precision and effectiveness in guiding coronary interventions. [25]

Recent evidence also suggests that FFR can have a beneficial role in the assessment of non-infarct–related arteries. In the FAMOUS-NSTEMI randomized trial, patients with NSTEMI in the FFR-guided group had a lower revascularization rate compared to angiography guidance alone (79.0% vs. 86.8%, difference 7.8% (−0.2%, 15.8%), P = 0.054). However, health outcomes and quality of life parameters were similar between the two groups. [26] Similarly, patients with STEMI had improved outcomes upon revascularization based on FFR values. [27] [28] Muller *et al.* demonstrated excellent long-term outcomes by deferring revascularization in patients with an angiographically intermediate left anterior descending coronary artery (LAD) based on FFR values. At 5-year follow-up, the medical treatment of patients with hemodynamically nonsignificant stenosis (FFR ≥ 0.80) in the proximal LAD was associated with low event-free survival estimates (death, MI, and target vessel revascularization) compared to revascularization group 89.7% vs. 68.5%, $P < 0.0001$) and similar survival rates (92.9% vs 89.6%). [29]

Clinical evidence in India

Though FFR was introduced in India in the early 2000s, there is limited published evidence in the Indian population.

FIND, a retrospective study, analysed clinical usefulness, cost-benefit, and medium-term outcomes of FFR-based intervention of intermediary CAD lesions ($N = 59$; 81 vessels). There was a concordance of about 58% between angiography alone and FFR-guided angiography. This indicated that >40% of the lesions would be classified as significant and might have undergone unnecessary PCI intervention. Further, for every two patients or three lesions, one stent was avoided with FFR added to angiography. In total, 26 stents were avoided when FFR was done. Similarly, the angiogram results showed six needed surgery, while additional FFR results suggested surgery only for three. [32] In a large ambispective study conducted at Christian Medical College (CMC) Vellore, in India ($N = 400$), about 80% of patients had a change in management strategy based on FFR assessment (cut-off of ≤0.80). The FFR assessment revealed hemodynamically significant lesions in only 29% of the total of 477 intermediate coronary lesions; this resulted in the avoidance of stenting strategy in almost one-third of patients referred for PCI (30.5%). Based on FFR measurement, several clinical management subsets were identified: stent avoidance: 30% of patients had stent avoidance (1.2 stents saved per patient); stent reduction: 31.3% of patients had a reduction in the number of stents implanted (1.07 stents saved per patient); PCI instead of CABG: 10% of patients had a change in decision from CABG to multivessel PCI; and CABG instead of PCI: 8.3 of patients had a change in decision from PCI to CABG. At 21-median follow-up, the composite endpoint of cardiac death, nonfatal MI, objective evidence of ischemia, and ischemia-driven revascularization in the vessels assessed by FFR occurred in 0.9% of patients in the stent avoidance subset compared to 6.9% in any stent group ($P = 0.04$). [13] A recent retrospective and prospective observational study ($N = 250$) found that FFR helps plan treatment for patients with acute or chronic coronary syndrome. [33] The initial treatment plan based on initial angiography versus the final treatment plan post-FFR was: medical management in 183 (56.5%) vs. 214 (66.0%); CABG 36 (11.1%) vs. 25 (7.7%); and PCI 105 (32.4%) vs. 85 (26.2%). For the subjects initially assigned to medical management based on angiography alone, 14% (26/183) were subsequently assigned to PCI following FFR disclosure, whereas for patients assigned to PCI and CABG, 44% (46/105) and 36% (13/36), respectively, were then assigned to medical therapy following FFR disclosure, reemphasizing the importance of FFR in decision making. The frequency of actual revascularization (CABG + PCI) following FFR disclosure changed from 43.5% to 34.2% per lesion, and the overall MACE rate for the study population of 250 patients at 24 months follow-up was 0.9%: death occurred in 3 patients including one patient who was changed to MM from PCI after FFR. There were no cases of TVR, TLR, MI, and cardiac death immediately after intervention or during the follow-up.

Safety concerns with Adenosine

Though intravenous or intracoronary administration of adenosine is commonly used for FFR assessment, it is associated with adverse events. In the study conducted at CMC Vellore, about 16% of patients reported adverse events with no significant difference between intracoronary and intravenous administration. Chest pain is the most common symptom reported in 3.8% of patients, and 5.8% of patients had bradycardia and underwent treatment. Ventricular fibrillation occurred in one patient with intracoronary administration, and three patients had atrial fibrillation. [13]

A prospective observational study conducted in South India has shown a good correlation of adenosine-free indices such as whole cycle Pd/Pa, instantaneous wave-free ratio (iFR), and contrast-induced submaximal hyperemia (cFFR) with FFR. However, further validation is needed for adenosine-free indices to be commonly used in clinical practice. [34]

Cost-effectiveness of FFR

The FIND study showed that the addition of FFR to angiogram led to the avoidance of unnecessary stent placements. By not deploring 26 stents, a total of INR 26 lakhs was saved. While the FFR procedure added an extra cost of INR 17.7 lakhs for 59 patients, the net benefit amounted to INR 8.3 lakhs. [32] Thomson *et al.* showed that the use of FFR resulted in a total of INR 51,847 (USD 746) cost-savings per patient. Post revision of stent and pressure wire pricing, the cost savings would be reduced by 36% to INR 18,613 (USD 268) per patient. A cost of INR 4531 (USD 65) per patient could be saved in private sector hospitals, where full FFR wire is charged without any subsidization. [13] Further, appropriate-based reimbursement of elective procedures could potentially save the medical costs per person. Considering the large volume of PCI being carried out in the country, significant patient-level cost reductions can be expected in both the private and public sectors. [13]

4. Perception and Concerns about Coronary Physiology in the Indian Scenario

Despite huge evidence showing the utility of FFR in the evaluation of intermediate coronary stenoses, it is used only in a minority of such cases. In India, this procedure is being used in limited tertiary care private and state-funded tertiary centres due to additional expenditure and time of the procedure. Logistical efforts that are required to perform FFR, concerns related to potential complications, the uncertainty concerning the optimal performance, and interpreting FFR measurements are the possible reasons for its low usage. Other major contributing factor for low use is the high cost of the FFR wire. The majority of patients have to pay from their own resources with inadequate or lack of reimbursement facility for the procedure. As FFR is an invasive procedure, therefore, by its nature, its use is restricted in an invasive setting. Further, the use of adenosine incurs additional complexity, time, side effects, and cost. [13] While preparing the patient for the FFR procedure, medicines or nutrition may inadvertently influence the outcomes of FFR. Since fasting is not mandatory in most centers, the effect of drugs or nutrition is of high relevance to the clinician. Additionally, FFR measurement has several technical limitations. Narrow ostium or proximal stenosis may obstruct catheter progression, resulting in inaccurate FFR measurements. Adequate calibration, complete disengagement of the catheter, and recalibration are to be considered while obtaining FFR to get optimal reading; otherwise, it may lead to false interpretation of lesions with less reliability of the study. Pressure signal drift is one of the key challenges during calibration. To achieve equal pressure between the pressure sensor and aortic pressure, it is advised to remove the introducer and completely close the hemostatic valve. Extreme tortuosity or small vessels may cause artefacts. The tip of the wire should be shaped appropriately with curvature, not exceeding 45˚, before introducing into the coronary vessel. It is recommended not to place the pressure sensor in extreme tortuous segments. Submaximal hyperemia is one of the most important pitfalls of FFR measurement. In such instances, reprogramming the injection rate or changing the stimulus is recommended to achieve maximum hyperemia. [35]

Wherever studies in a clinical setting, FFR resulted in a paradigm shift in managing CAD. Among Indians, FFR measurements have a significant effect on safety and clinical outcomes for patients with severe CAD. It provides a credible and objective evaluation of intermediate and uncertain stenosis prior to revascularization, to identify ischemia inducible lesions and aid the treatment decision-making process. [13] [32]

Cardiovascular disease, especially CAD, has a profound impact on the cost of health care. Reimbursement programmes are therefore key to decrease the economic and societal burden of CAD among Indians. The healthcare system in India includes several government health insurance schemes such as the Central Government Health Scheme (CGHS) (https://cghs.gov.in/) and National Rural Health Mission (https://nhm.gov.in/), Employees' State Insurance (ESI) Scheme (https://www.esic.nic.in/), etc. along with voluntary private health insurance schemes. Pradhan Mantri Swasthya Suraksha Yojana (PMSSY) has provisions for tertiary care. The National Programme for Prevention and Control of Cancer, Diabetes, Cardiovascular Diseases and Stroke (NPCDCS) aims to set up intensive cardiac care at district clinics and advanced cardiac care centres at tertiary-level hospitals. (https://dghs.gov.in/) The Ayushman-Bharat Pradhan Mantri Jan Arogya Yojana (AB-PMJAY) is a completely tax-funded scheme to provide secondary and tertiary care for up to 500,000 Indian rupees (INR) per year per household. It is aimed to benefit 50 crore beneficiaries in India. Cardiac interventions have topped the list of high-end medical procedures that most beneficiaries of Ayushman Bharat. Data from the National Health Agency, the Health Ministry body, revealed that angioplasty has been the most high-end procedure performed since its inception. (PM-JAY Annual Report)

Using the Rajiv Gandhi Jeevandayee Arogya Yojana (RGJAY), a public insurance scheme administered by the RGJAY Society (autonomous of the National Insurance Company), Karthikeyan *et al.* explored the feasibility of settling reimbursements for appropriate criteria based PCI or CABG surgeries conducted at tertiary centres in Maharashtra. A 12.3% reduction in the PCI procedures was observed one year after the introduction of appropriateness-based reimbursement. This reduction was similar for both public and private centers. With the use of appropriateness-based reimbursement, approximately 783 (95% CI 483 - 1099) PCI procedures would be avoided with potential annual savings of about INR 57 million (US$ 0.93 million; 95% CI 0.57 - 1.3) to the government scheme. [36] As of now, none of the health insurance schemes has provisions for physiology assessments of coronary lesions. Since informed clinical judgment for intermediate-severe lesions that are based upon FFR measurements might benefit Indian patients with severe CAD clinically, the inclusion of FFR under government or private schemes lessens the economic burden.

5. The Way Forward

Over two decades of clinical research and experience have positioned coronary physiology as an indispensable tool in catheter intervention. Hemodynamic evaluation of a coronary artery lesion is a crucial diagnostic step to gauge its functional impact. FFR has a class IA recommendation from the European Society of Cardiology for assessing angiographically moderate stenosis. [37] By guiding the therapeutic strategy, FFR helps in deferring unnecessary procedures for lesions showcasing an FFR > 0.8, thereby refining patient management and clinical outcomes. Studies such as the FAME have further highlighted the significance of FFR. The FAME study revealed that approximately 35% of visually evaluated lesions with 50% - 70% stenosis had an FFR below 0.80, suggesting potential benefits from revascularization. [20] In instances where stenosis is not angiographically significant despite compromised blood flow due to factors such as tandem/long or proximal lesions, FFR measurement becomes a potentially deciding factor for the need for revascularization. The long-term follow-up of DEFER and FAME studies has consolidated the rational and safe use of FFR-guided management in patients with stable CAD.

Fractional flow reserve continues to be the gold standard for the detection of myocardial ischemia in guiding revascularization in patients with CAD. In addition to FFR, several non-hyperemic pressure ratios (NHPR) indices have been developed to evaluate coronary physiology during rest without hyperemia. However, these indices are not backed up by the robust long-term data as for FFR. Although they may overestimate the hemodynamic relevance of some lesions, they remain instrumental when hyperemic agents aren't suitable. [37] Among these indices, the instantaneous wave-free ratio (iFR) is the most studied. It measures the wave-free diastolic pressure in which intracoronary pressure at rest is comparable to that calculated during FFR without hyperemia. [38] The iFR has been shown to provide non-inferior clinical outcomes compared to FFR. [39] A meta-analysis of 23 studies found a good correlation (correlation coefficient 0.80 (0.78 - 0.82), P = 0.001) between the iFR and FFR. [40] Further, newer NHPR indices, such as diastolic hyperemia-free ratio (DFR), resting full-cycle ratio (RFR), and diastolic pressure ratio (DPR/dPR), have also been compared to FFR and iFR and found to be equivalent. [38] [41] The reliability of NHPRs compared to FFR has been a topic of investigation. Studies have shown that NHPRs, including iFR, provide diagnostic classification equivalent to FFR. [42] However, it is important to note that approximately 20% of iFR and FFR measurements may be discordant. This discordance may be attributed to various pathophysiological factors, such as microcirculatory resistance and vasodilator response. Further research is needed to understand better the factors contributing to discordance and to improve the reliability of NHPRs. A recent study has shown that there is no significant difference in all-cause mortality, MI, or the need for revascularization at 5-year follow-up for 109/840 of lesions with FFR/iFR discordance, of which 40 lesions were negative FFR discordant. [43] Therefore, the negative measurements of any of these indices can be used to defer interventions for lesions with FFR/iFR discordance. For intermediate lesions (DFR 0.85 - 0.95), a hybrid approach can be adopted. [37] By leveraging both FFR and NHPR, clinicians can maximize their clinical decision-making potential. Advancements in imaging technology allow for non-invasive estimation of FFR using 3-D angiograms via quantitative flow ratios, offering a promising frontier for lesion assessment without invasive catheterization. NHPRs offer the advantage of not requiring the administration of hyperemic agents, which can reduce procedural costs. Additionally, NHPRs may decrease procedural time, leading to potential cost savings. However, it is vital to consider the initial investment required for the equipment and training necessary for performing NHPR measurements. Further economic evaluations are needed to determine the long-term cost-effectiveness of NHPRs compared to FFR.

Although published data on the Indian population are insufficient, extensive real-world experience from various high-volume centers and operators suggests similar outcomes. It would be prudent to consider that the data generated in the Western healthcare system have similar clinical applicability. Therefore, the treatment strategy should be based on existing global evidence and guidelines. The available evidence should be evaluated for applicability in Indian scenarios. Options of endorsement by cardiac societies and inclusion in Indian guidelines should be explored further. Since FFR-guided PCI has been in use for a long time in India, interventional cardiologists should make it a mandatory tool to document ischemia producing lesions/vessels prior to performing an intervention. Such practice would ensure patients get optimum clinical benefits through "Evidence-based Medicine" and could also save significant economic burden on the healthcare system, both private and government system.

6. Conclusion

Routine use of FFR for the management of severe CAD with intermediary stenosis may be associated with a high degree of treatment reclassification by distinguishing between functionally significant and insignificant lesions. This helps avoid unnecessary stenting, thereby reducing the risk of future stent-related MACE. Fractional flow reserve guided management strategies aid physicians in making the best treatment decisions and provide clinical and cost-effective benefits to the patients.

Author Contribution

All authors contributed equally to the conception, design, drafting, review, and finalization of the manuscript.

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Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

References

[1] Rao, M., Xavier, D., Devi, P., Sigamani, A., Faruqui, A., Gupta, R., Kerkar, P., Jain, R. K., Joshi, R., Chidambaram, N. and Rao, D.S. (2015) Prevalence, Treatments and Outcomes of Coronary Artery Disease in Indians: A Systematic Review. *Indian Heart Journal*, **67**, 302-310. https://doi.org/10.1016/j.ihj.2015.05.003

[2] Gupta, R., Mohan, I. and Narula, J. (2016) Trends in Coronary Heart Disease Epidemiology in India. *Annals of Global Health*, **2**, 307-315. https://doi.org/10.1016/j.aogh.2016.04.002

[3] Sharma, M. and Ganguly, N.K. (2005) Premature Coronary Artery Disease in Indians and Its Associated Risk Factors. *Vascular Health and Risk Management*, **1**, 217-225.

[4] India State-Level Disease Burden Initiative CVD Collaborators (2018) The Changing Patterns of Cardiovascular Diseases and Their Risk Factors in the States of India: The Global Burden of Disease Study 1990-2016. *Lancet Glob Health*, **6**, e1339-e1351.

[5] Kumar, L., Prakash, A. and Gupta, S.K. (2019) Assessment of Economic Burden and Quality of Life in Stable Coronary Artery Disease Patients. *Indian Journal of Medical Specialities*, **10**, 26-29. https://doi.org/10.4103/INJMS.INJMS_1_18

[6] Aye, T. and Graham, R. (2017) Risk Stratification in Stable Coronary Artery Disease. *Continuing Cardiology Education*, **3**, 37-43. https://doi.org/10.1002/cce2.49

[7] Boden, W.E., O'Rourke, R.A. and Teo, K.K. (2007) Optimal Medical Therapy with or without PCI for Stable Coronary Disease. *The New England Journal of Medicine*, **356**, 1503-1516. https://doi.org/10.1056/NEJMoa070829

[8] Maron, D.J., Hochman, J.S., Reynolds, H.R., *et al*. (2020) Initial Invasive or Conservative Strategy for Stable Coronary Disease. *The New England Journal of Medicine*, **382**, 1395-1407. https://doi.org/10.1056/NEJMoa1915922

[9] Stegehuis, V.E., Wijntjens, G.W., Murai, T., Piek, J.J. and van de Hoef, T.P. (2018) Assessing the Haemodynamic Impact of Coronary Artery Stenoses: Intracoronary Flow Versus Pressure Measurements. *European Cardiology Review*, **13**, 46-53. https://doi.org/10.15420/ecr.2018:7:2

[10] Kern, M.J., Lerman, A. and Bech, J.W. (2006) Physiological Assessment of Coronary Artery Disease in the Cardiac Catheterization Laboratory: A Scientific Statement from the American Heart Association Committee on Diagnostic and Interventional Cardiac Catheterization, Council on Clinical Cardiology. *Circulation*, **114**, 1321-1341. https://doi.org/10.1161/CIRCULATIONAHA.106.177276

[11] van de Hoef, T.P., Meuwissen, M., Escaned, J., Davies, J.E., Siebes, M., Spaan, J.A. and Piek, J.J. (2013) Fractional Flow Reserve as a Surrogate for Inducible Myocardial Ischaemia. *Nature Reviews Cardiology*, **10**, 439-452. https://doi.org/10.1038/nrcardio.2013.86

[12] Bishop, A.H. and Samady, H. (2004) Fractional Flow Reserve: Critical Review of an Important Physiologic Adjunct to Angiography. *American Heart Journal*, **147**, 792-802. https://doi.org/10.1016/j.ahj.2003.12.009

[13] Thomson, V.S., Varghese, M.J. and Chacko, S.T. (2020) Coronary Artery Disease Management and Cost Implications with Fractional Flow Reserve Guided Coronary Intervention in Indian Patients with Stable Ischemic Coronary Artery Disease. *Catheterization and Cardiovascular Interventions*, **97**, 815-824. https://doi.org/10.1002/ccd.28897

[14] Al-Obaidi, F.R., Fearon, W.F. and Yong, A.S.C. (2018) Invasive Physiological Indices to Determine the Functional Significance of Coronary Stenosis. *IJC Heart & Vasculature* **18**, 39-45. https://doi.org/10.1016/j.ijcha.2018.02.003

[15] Neumann, F.J., Sousa-Uva, M. and Ahlsson, A. (2019) 2018 ESC/EACTS Guidelines on Myocardial Revascularization. *European Heart Journal*, **40**, 87-165. https://doi.org/10.1093/eurheartj/ehy394

[16] Patel, M.R., Calhoon, J.H. and Dehmer, G.J. (2017) ACC/AATS/AHA/ASE/ASNC/SCAI/SCCT/STS 2016 Appropriate Use Criteria for Coronary Revascularization in Patients With Acute Coronary Syndromes: A Report of the American College of Cardiology Appropriate Use Criteria Task Force, American Association for Thoracic Surgery, American Heart Association, American Society of Echocardiography, American Society of Nuclear Cardiology, Society for Cardiovascular Angiography and Interventions, Society of Cardiovascular Computed Tomography, and the Society of Thoracic Surgeons. *Journal of the American College of Cardiology*, **69**, 570-591. https://doi.org/10.1016/j.jacc.2016.10.034

[17] Lotfi, A., Jeremias, A. and Fearon, W.F. (2014) Society of Cardiovascular Angiography and Interventions. Expert Consensus Statement on the Use of Fractional

Flow Reserve, Intravascular Ultrasound, and Optical Coherence Tomography: A Consensus Statement of the Society of Cardiovascular Angiography and Interventions. *Catheterization and Cardiovascular Interventions*, **83**, 509-518. https://doi.org/10.1002/ccd.25222

[18] Bech, G.J.W., De Bruyne, B., Pijls, N.H., De Muinck, E.D., Hoorntje, J.C., Escaned, J., Stella, P.R., Boersma, E., Bartunek, J., Koolen, J.J. and Wijns, W. (2001). Fractional Flow Reserve to Determine the Appropriateness of Angioplasty in Moderate Coronary Stenosis: A Randomized Trial. *Circulation*, **103**, 2928-2934. https://doi.org/10.1161/01.CIR.103.24.2928

[19] Zimmermann, F.M., Ferrara, A. anf Johnson, N.P. (2015) Deferral vs. Performance of Percutaneous Coronary Intervention of Functionally Non-Significant Coronary Stenosis: 15-Year Follow-Up of the DEFER Trial. *European Heart Journal*, **36**, 3182-3188. https://doi.org/10.1093/eurheartj/ehv452

[20] Tonino, P.A., De Bruyne, B. and Pijls, N.H. (2009) FAME Study Investigators. Fractional Flow Reserve versus Angiography for Guiding Percutaneous Coronary Intervention. *The New England Journal of Medicine*, **360**, 213-224. https://doi.org/10.1056/NEJMoa0807611

[21] van Nunen, L.X., Zimmermann, F.M., Tonino, P.A., Barbato, E., Baumbach, A., Engstrøm, T., Klauss, V., MacCarthy, P.A., Manoharan, G., Oldroyd, K.G. and Ver Lee, P.N., *et al.* (2015) 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. *The Lancet*, **386**, 1853-1860. https://doi.org/10.1016/S0140-6736(15)00057-4

[22] De Bruyne, B., Pijls, N.H., and Kalesan, B. (2012) Fractional Flow Reserve-Guided PCI versus Medical Therapy in Stable Coronary Disease. *The New England Journal of Medicine*, **367**, 991-1001. https://doi.org/10.1056/NEJMoa1205361

[23] De Bruyne, B., Fearon, W.F. and Pijls, N.H. (2014) Fractional Flow Reserve-Guided PCI for Stable Coronary Artery Disease. *The New England Journal of Medicine*, **371**, 1208-1217. https://doi.org/10.1056/NEJMoa1408758

[24] Xaplanteris, P., Fournier, S., Pijls, N.H., Fearon, W.F., Barbato, E., Tonino, P.A., Engstrøm, T., Kääb, S., Dambrink, J.H., Rioufol, G. and Toth, G.G. (2018) Five-Year Outcomes with PCI Guided by Fractional Flow Reserve. *The New England Journal of Medicine*, **379**, 250-259. https://doi.org/10.1056/NEJMoa1803538

[25] Ahn, J.M., Park, D.W. and Shin, E.S. (2017) Fractional Flow Reserve and Cardiac Events in Coronary Artery Disease: Data from a Prospective IRIS-FFR Registry (Interventional Cardiology Research Incooperation Society Fractional Flow Reserve). *Circulation*, **135**, 2241-2251. https://doi.org/10.1161/CIRCULATIONAHA.116.024433

[26] Layland, J., Oldroyd, K.G. and Curzen, N. (2015) 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. *European Heart Journal*, **36**, 100-111. https://doi.org/10.1093/eurheartj/ehu338

[27] Engstrøm, T., Kelbæk, H. and Helqvist, S. (2015) Complete Revascularisation versus Treatment of the Culprit Lesion Only in Patients with ST-Segment Elevation Myocardial Infarction and Multivessel Disease (DANAMI-3—PRIMULTI): An Open-Label, Randomised Controlled Trial. *Lancet*, **386**, 665-671. https://doi.org/10.1016/S0140-6736(15)60648-1

[28] Smits, P.C. and Boxma-de Klerk, B.M. (2017) Fractional Flow Reserve-Guided Multivessel Angioplasty in Myocardial Infarction. *The New England Journal of Medi-*

cine, **377**, 397-398. https://doi.org/10.1056/NEJMc1706275

[29] Muller, O., Mangiacapra, F. and Ntalianis, A. (2011) Long-Term Follow-Up after Fractional Flow Reserve-Guided Treatment Strategy in Patients with an Isolated Proximal Left Anterior Descending Coronary Artery Stenosis. *JACC*, **4**, 1175-1182. https://doi.org/10.1016/j.jcin.2011.09.007

[30] Li, J., Elrashidi, M.Y. and Flammer, A.J. (2013) Long-Term Outcomes of Fractional Flow Reserve-Guided vs. Angiography-Guided Percutaneous Coronary Intervention in Contemporary Practice. *European Heart Journal*, **34**, 1375-1383. https://doi.org/10.1093/eurheartj/eht005

[31] Curzen, N., Rana, O. and Nicholas, Z. (2014) Does Routine Pressure Wire Assessment Influence Management Strategy at Coronary Angiography for Diagnosis of Chest Pain? The RIPCORD Study. *Circulation*: *Cardiovascular Interventions*, **7**, 248-255. https://doi.org/10.1161/CIRCINTERVENTIONS.113.000978

[32] Sengottuvelu, G., Chakravarthy, B., Rajendran, R. and Ravi, S. (2016) Clinical Usefulness and Cost Effectiveness of Fractional Flow Reserve among Indian Patients (FIND Study). *Catheterization and Cardiovascular Interventions*, **88**, E139-E144. https://doi.org/10.1002/ccd.25517

[33] Kasturi, S., Singh, S. and Shanivaram, V.K.R. (2021) Usefulness of Fractional Flow Reserve during Routine Clinical Procedures in All-Comer Coronary Artery Disease Patients. *World Journal of Cardiovascular Diseases*, **11**, 509-522. https://doi.org/10.4236/wjcd.2021.1111048

[34] Raja, D.C., Subban, V., Mathew, R, and Abdullakutty, J. (2019) Comparison of Resting and Adenosine-Free Pressure Indices with Adenosine-Induced Hyperemic Fractional Flow Reserve in Intermediate Coronary Lesions. *Indian Heart Journal*, **71**, 74-79. https://doi.org/10.1016/j.ihj.2018.11.016

[35] Achenbach, S., Rudolph, T., and Rieber, J. (2017) Performing and Interpreting Fractional Flow Reserve Measurements in Clinical Practice: An Expert Consensus Document. *Interventional Cardiology*, **12**, 97-109. https://doi.org/10.15420/icr.2017:13:2

[36] Karthikeyan, G., Shirodkar, U., Lochan, M.R., and Birch, S. (2017) Appropriateness-Based Reimbursement of Elective Invasive Coronary Procedures in Low- and Middle-Income Countries: Preliminary Assessment of Feasibility in India. *The National Medical Journal of India*, **30**, 11-14. https://doi.org/10.4103/0970-258X.234389

[37] Boutaleb, A.M., Ghafari, C., Ungureanu, C., *et al.* (2023) Fractional Flow Reserve and Non-Hyperemic Indices: Essential Tools for Percutaneous Coronary Interventions. *World Journal of Clinical Cases*, **11**, 2123-2139. https://doi.org/10.12998/wjcc.v11.i10.2123

[38] Warisawa, T., Cook, C.M. and Howard, J.P. (2019) Physiological Pattern of Disease Assessed by Pressure-Wire Pullback Has an Influence on Fractional Flow Reserve/Instantaneous Wave-Free Ratio Discordance. *Circulation*: *Cardiovascular Interventions*, **12**, e007494. https://doi.org/10.1161/CIRCINTERVENTIONS.118.007494

[39] Westra, J., Tu, S., Winther, S., *et al.* (2018) Evaluation of Coronary Artery Stenosis by Quantitative Flow Ratio during Invasive Coronary Angiography: The WIFI II Study (Wire-Free Functional Imaging II). *Circulation*: *Cardiovascular Imaging*, **11**, e007107. https://doi.org/10.1161/CIRCIMAGING.117.007107

[40] De Rosa, S., Polimeni, A., Petraco, R., Davies, J.E. and Indolfi, C. (2018) Diagnostic Performance of the Instantaneous Wave-Free Ratio: Comparison with Fractional

Flow Reserve. *Circulation*: *Cardiovascular Interventions*, **11**, e004613. https://doi.org/10.1161/CIRCINTERVENTIONS.116.004613

[41] Jeremias, A., Maehara, A., and Généreux, P. (2014) Multicenter Core Laboratory Comparison of the Instantaneous Wave-Free Ratio and Resting P_d/P_a with Fractional Flow Reserve: The RESOLVE Study. *Journal of the American College of Cardiology*, **63**, 1253-1261. https://doi.org/10.1016/j.jacc.2013.09.060

[42] Sen, S., Asrress, K.N., Nijjer, S., *et al*. (2013) Diagnostic Classification of the Instantaneous Wave-Free Ratio Is Equivalent to Fractional Flow Reserve and Is Not Improved with Adenosine Administration. *Journal of the American College of Cardiology*, **61**, 1409-1420. https://doi.org/10.1016/j.jacc.2013.01.034

[43] Lee, S.H., Choi, K.H. and Lee, J.M. (2019) Physiologic Characteristics and Clinical Outcomes of Patients with Discordance between FFR and iFR. *JACC*: *Cardiovascular Interventions*, **12**, 2018-2031. https://doi.org/10.1016/j.jcin.2019.06.044