EFFECTIVENESS OF FFR VS. ANGIOGRAPHY GUIDED PERCUTANEOUS CORONARY INTERVENTIONS (PCIs) IN PATIENTS WITH STABLE CORONARY ARTERY DISEASE

Report

December, 2023

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ABBREVIATIONS

ACCF	American College of Cardiology Foundation
ACS	Acute Coronary Syndrome
AHA	American Heart Association
CA	Coronary Angiography
CABG	Coronary Artery Bypass Graft Surgery
CCS	Canadian Cardiovascular Society
CGHS	Central Government Health Scheme
COR	Culprit Only Revascularization
CR	Complete Revascularization
DALY	Disability Avoided Life Years
DAPT	Dual Antiplatelet Therapy
DES	Drug Eluting Stent
EACTS	European Association for Cardio-Thoracic Surgery
ESC	European Society of Cardiology
FFR	Fractional Flow Reserve
iFR	Instantaneous Wave-Free Ratio
IRA	Infarct Related Artery
ISR	In Stent Restenosis
IVUS	Intravenous Ultrasound
MACE	Major Adverse Cardiovascular Events
MI	Myocardial Infarction
PCI	Percutaneous Coronary Intervention
PTCA	Percutaneous Transluminal Coronary Angioplasty
QoL	Quality-of-Life
RCT	Randomized Controlled Trial
RR	Repeat Revascularization
SCAI	Society for Cardiovascular Angiography and Interventions
STEMI	ST Elevation Myocardial Infarction
TVR	Target Vessel Revascularization

EFFECTIVENESS OF FFR VS. ANGIOGRAPHY GUIDED PERCUTANEOUS CORONARY INTERVENTIONS (PCIs) IN PATIENTS WITH STABLE CORONARY ARTERY DISEASE

ABSTRACT

Fractional Flow Reserve (FFR) has been reported to provide more precise information about the severity of coronary lesions, especially in intermediate stenosis (50-70%) leading to more informed clinical decisions. We evaluated and compiled the existing evidence regarding the clinical-effectiveness of FFR guided PCI in comparison to angiography guided PCI in stable coronary artery disease (CAD) patients with intermediate stenosis (50-70%) and the cost implications of using FFR on stable CAD patients with intermediate stenosis and referred to undergo PCI. Long-term clinical outcomes, encompassing major adverse cardiac events (MACEs), mortality, and myocardial events (MI), were reported to be comparable between FFR-guided and angiography-guided PCI. Studies suggested FFR reduces number of unnecessary PCIs in intermediate stenosis by measuring the physiological significance of the coronary lesions. However, the actual fraction of this reduction in clinical practice was lacking. Only two Indian studies on FFR costing were found, showing cost savings by avoiding stents in intermediate stenosis. However, these studies were limited by a single private hospital setting, small sample size, and obsolete cost considerations for FFR wires and stents. Data on the actual reduction in PCIs using FFR in clinical practice in India was unavailable, which is crucial especially in a fee-for-service system. This is important given comparable clinical outcomes between FFR-guided and angiography-guided strategies. A cost-minimization analysis indicated no savings upon using FFR in stable CAD at current FFR wire and stent prices. Potential for savings may emerge if the cost of the FFR wire substantially decreases compared to the stent cost. It is crucial to evaluate how integrating FFR into routine practice may impact the number of deployed stents, before conducting a cost-effectiveness analysis.

1. INTRODUCTION

Coronary artery disease (CAD) stems from blockage of the coronary arteries due to plaque deposition, leading to insufficient blood and hence oxygen supply to the myocardium. CAD prevalence has risen in epidemic proportion in India during the last two decades (1–3). Although comprehensive nationwide data on CAD prevalence remains elusive, a series of smaller yet significant cross-sectional studies conducted across various regions of the country indicate a worrisome surge in the burden (2-3 folds) of this condition (4,5).

Furthermore, higher case fatality rates among Indians with acute coronary syndrome (ACS) may lead to an underestimation of CAD prevalence. CAD was the leading cause of DALYs in India in 2016, accounting for 17·8% of total deaths. Its prevalence has been reported to be the highest in Kerala, Punjab, Tamil Nadu and Maharashtra (Fig. 1) (3). CAD could be asymptomatic or present with complications such as acute coronary syndrome (ACS), cardiac arrhythmias, congestive heart failure, myocardial infarction and may cause sudden death (6).

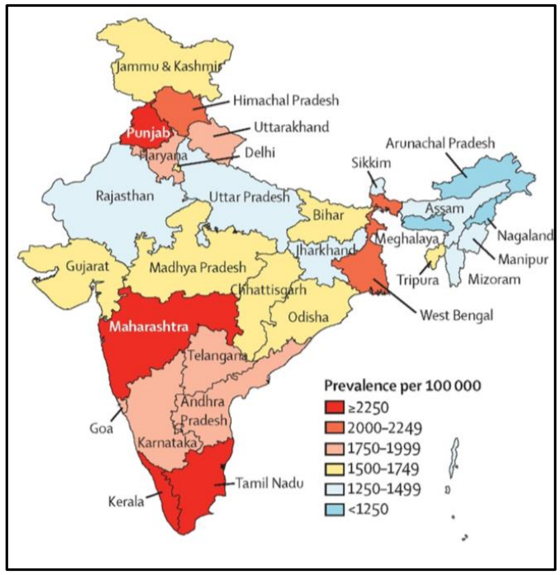

Figure 1: Crude prevalence of CAD in India, 2016 (3)

1.1. Coronary Artery Disease (CAD) its Treatment Modalities

Coronary artery disease (CAD) is a condition marked by the gradual buildup of plaque within the coronary arteries, which supply blood to the heart muscle. Two distinct manifestations of Coronary Artery Disease (CAD) are as follows (7):

(i) **Acute Coronary Syndrome**: characterized by either ST-Elevation Myocardial Infarction (STEMI) or Non-ST-Elevation Myocardial Infarction (NSTEMI), both resulting in myocardial tissue damage and, (ii) **Stable Coronary Artery Disease (CAD)** characterized by persistent, manageable symptoms such as angina during exertion or stress, distinct from acute coronary syndrome. The treatment approach of above conditions diverges depending on the specific condition.

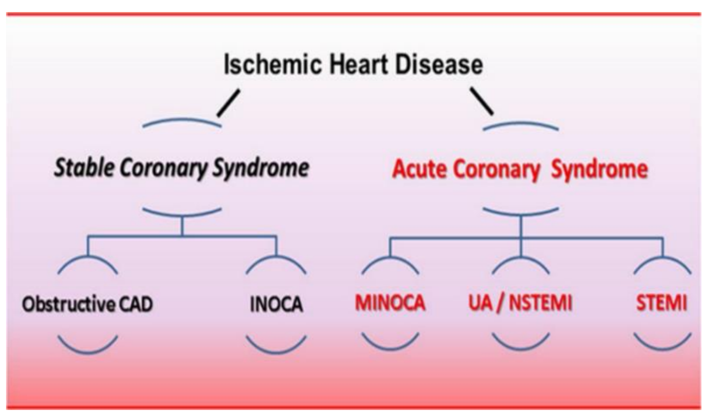

Figure 2: Coronary disease subgroups that cause ischemic heart disease (INOCA - Ischemia and No Obstructive Coronary Artery Disease; MINOCA - Myocardial Infarction and No Obstructive Coronary Artery Disease) (8).

In the former category, swift interventions are sought to enhance blood flow, employing thrombolytic agents or, where feasible, resorting to Invasive Coronary Angiography coupled with stent placement, heralding the preferred course of action for STEMI cases. For NSTEMI presentations, early coronary angiography, succeeded by potential stent deployment or Coronary Artery Bypass Grafting (CABG), stands as the favored therapeutic avenue (9). Managing Stable CAD requires a careful and prudent approach. Central to addressing this particular form of CAD is the essential need for determining ischemia, a mandate that can be accomplished through certain non-invasive testing methods such as stress testing (9). Stress testing involves subjecting individuals to physical stress on a treadmill or bicycle ergometer. For those unable to engage in physical exercise, pharmaceutical agents like Dobutamine or Adenosine are administered. Subsequently, Ischemia is detected through various imaging methods, including ECG (commonly used in TMT and Bicycle ergometry), Echocardiography (applied in Stress Echo or Dobutamine stress echo), and occasionally MRI, often paired with Dobutamine/Adenosine Stress using radioisotopes such as Technetium Setamibi/Thallium.

The global strategy for Acute Coronary Syndrome is widely accepted, but challenges arise in judiciously using Percutaneous Coronary Intervention (PCI) and Stenting for Stable Coronary Artery Disease (CAD). Trials like COURAGE (10) and BARI (11) support intensive oral medical therapy (OMT) and lifestyle interventions, delaying revascularization in single-vessel disease (without Left Main involvement) and favoring CABG over PCI in significant and multi-vessel disease. The ISCHEMIA (12) trial revealed no initial benefit from invasive strategies for stable CAD with moderate/severe ischemia on stress testing. A recent ORBITA trial (13) underscores that PCI does not provide superior outcomes compared to a placebo in stable angina patients with single-vessel CAD. Studies conducted in India align with these findings, endorsing OMT for single-vessel CAD without Left Main (LM) involvement (14), advocating CABG for LM-CAD over PCI for long-term cost-effectiveness (15), and favoring CABG for Multi-vessel CAD (16). Overall, conservative therapy or OMT is recommended as the initial treatment, with CABG preferred over PCI in case of non-responsiveness. Government of India guidelines (17) also recommend PCI for culprit lesions (followed by stress testing) and CABG for complex CAD.

1.2. Rationale of the Study

As previously mentioned, the treatment strategies for Acute Coronary Syndrome are widely accepted, but challenges persist in the careful use of PCI and stenting for Stable CAD. Despite studies and guidelines, there an upward trend in the utilization of PCI and stent placement have been reported across India. 2018 National Interventional Council (NIC) data indicated there were 438,351 PCIs conducted across 709 centers utilizing 578,164 coronary stents (13.14% increase from the previous year). Drug eluting stents (DES) accounted for 98.12% of stents, 48.81% domestically manufactured (18).

Furthermore, an analysis of healthcare utilization trends within the Ayushman Bharat Pradhan Mantri Jan Arogya Yojana (PM-JAY) revealed that cardiac care constituted 5% (4.8 lakhs claims) of the total claims submitted, contributing to 26% (32,235 crores) of the scheme's overall financial expenditure (Fig. 3). Within the 130 cardiac packages offered by PM-JAY, the five most frequently availed packages accounted for 70% of the total cardiac care utilization. And amongst those top five packages, PTCA-Single stent procedure held the highest utilization rate at 34%, followed closely by PTCA-Double stent at 29% (19).

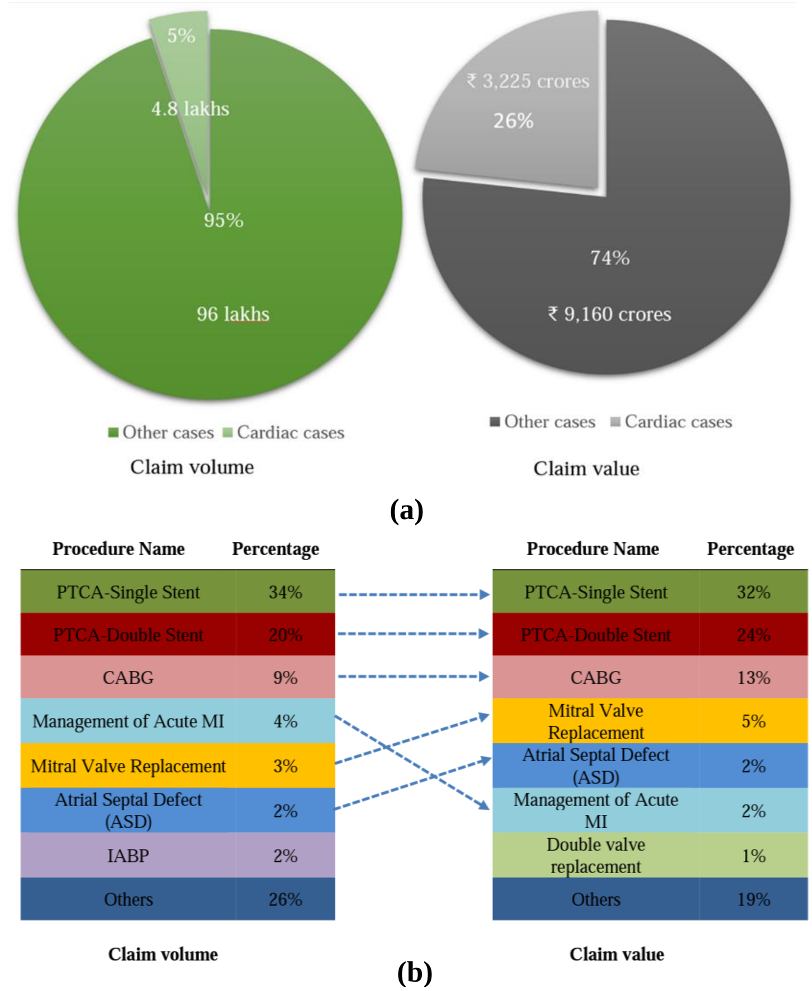

Figure 3: (a) Claim volume vs claim value across India (b) Top cardiac packages (19).

The rising trend in PCI and stent package utilization in India highlights the necessity for effective strategies to accurately diagnose ischemia and optimize PCIs and stenting in stable CAD patients. Currently, coronary angiography is recommended as a diagnostic tool for stable CAD patients with high-risk clinical conditions, guiding revascularization decisions (20). However, angiography is reported to have limitations, especially in intermediate-severity stenoses (40–70%), accurately predicting functional significance in less than 50% of cases (21). Therefore, decisions for revascularization in intermediate coronary lesions (50-70% stenosis) are recommended to be based on physiological significance of coronary lesions.

Fractional Flow Reserve (FFR) has been reported to provide more precise information about the physiological significance of coronary lesions, especially in cases stable CAD of intermediate severity (50%-70%), leading to more informed clinical decisions and tailored treatment depending upon the patients need (22–25).

While endorsed in some of the guidelines in high income countries such as American College of Cardiology Foundation (ACCF)/ American Heart Association (AHA) Task Force on Practice Guidelines and the Society for Cardiovascular Angiography and Interventions (SCAI), Task Force on Myocardial

Revascularization of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS) (26) and recommended as an optional investigation in Stable Angina in the Standard Treatment Workflows of Indian Council of Medical Research (ICMR) in India (27), the utilization of FFR remains limited (~1%) in India (18).

In India, FFR is reimbursed by a some private as well as public sector health insurance schemes such as Central Government Health Scheme (CGHS) (28), Ayushman Bharat Arogya Karnataka (ABAK) (29), Dr. YSR Aarogyasri Health Care Trust and EHS by Andhra Pradesh (30). However, FFR has not been included in the flagship healthcare scheme of the Government of India, Ayushman Bharat Pradhan Mantri Jan Arogya Yojana (PM-JAY).

In light of the above, we conducted an assessment and compilation of existing evidence on the clinical effectiveness of FFR-guided PCI compared to angiography-guided PCI in stable coronary artery disease patients with intermediate stenosis (50-70%). Additionally, we explored the cost implications of using FFR in stable coronary artery disease patients with intermediate stenosis referred for PCI.

The decision to exclude Fractional Flow Reserve Computed Tomography (FFR-CT) (31), Instantaneous Wave-Free Ratio (iFFR) (32), and Intravascular Ultrasound (IVUS) (33) as comparators was based upon – the differing principles of these procedures, limited clinical trials, and expert's opinion aligning with routine practices in interventional cardiology.

1.3. Fractional Flow Reserve – Principle and Function

FFR is used for the assessment of functional significance of coronary stenosis and obtaining improved clinical outcomes from revascularization (22,34). FFR is defined as the ratio of maximal achievable blood flow in coronary artery with stenosis to the hypothetical maximal achievable blood flow in the same artery in the absence of stenosis (23). It can be measured by the ratio of mean coronary pressures distal (P_D) and proximal (P_A) of the stenosis, i.e., $P_D^{(H)}/P_A^{(H)}$ (35).

$$FFR = \frac{F_{S_{MAX}}}{F_{N_{MAX}}} \approx \frac{P_D^{(H)}}{P_A^{(H)}}$$

FFR uses a coronary wire equipped with a miniaturized pressure transducer that is inserted through a guide catheter across the stenotic lesion to measure the ratio of coronary pressure distal to a coronary stenosis to the proximal pressure during maximal coronary vasodilation (Fig. 4) (25). Initial studies suggested that the. FFR cut-off value of 0.75 was reliable in the identification of ischemia-producing lesions but a cut-off value of 0.80 is widely accepted (23). Lesions with an FFR value greater than 0.80 have been reported to be managed safely without the need for revascularization.

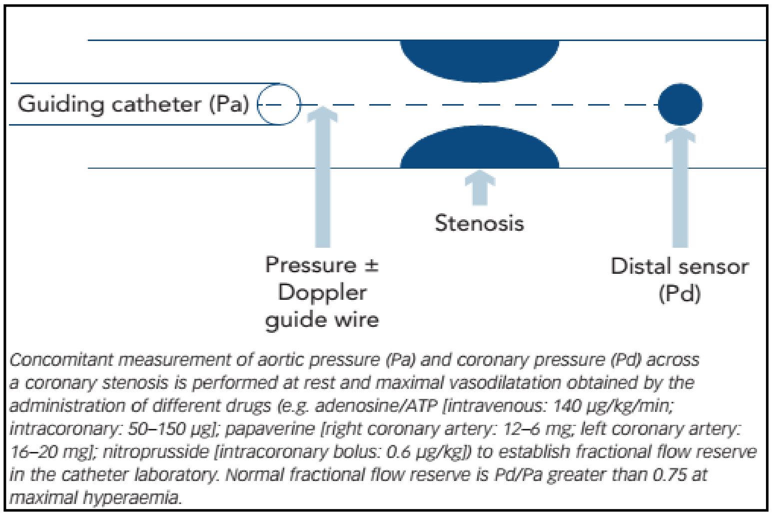

Figure 4: Schematic diagram of method used to measure Fractional Flow Reserve (25)

2. RESEARCH QUESTION

Is fractional flow reserve (FFR) more effective compared to angiography in guiding percutaneous coronary interventions (PCIs) in patients with stable coronary artery disease (CAD)?

3. OBJECTIVE

i. To compare the clinical effectiveness of FFR guided Vs. Angiography guided PCI in Stable CAD patients.

ii. To evaluate the cost implications of using FFR in stable CAD patient with intermediate stenosis (50-70%) who are referred to undergo PCI.

4. METHODOLOGY

4.1. Literature Review

i. **Comparing the Clinical-Effectiveness of FFR guided Vs. Angiography guided PCI:** We conducted a rapid literature review to compare the clinical effectiveness of FFR guided Vs. angiography guided PCI in patients with stable CAD. Studies included were systematic reviews, meta-analyses and clinical trials comparing the effect of effect of either strategy on Major Adverse Cardiac Events (MACE), Myocardial Infarction (MI), Cardiovascular Mortality (CM), All-cause Mortality ACM), Repeat Revascularization (RV), stent thrombosis, major bleeding, Change in Management Decisions etc.

ii. **Cost Implications of Using FFR:** A rapid review was conducted to evaluate the cost implications of using FFR in patients with stable CAD with intermediate stenosis (50-70%) and referred for PCI. Any Indian study reporting the costing of FFR guided revascularization was included.

4.1.1. *Study selection criteria*

Studies were screened and selected from the searched literature based upon the following selection criteria.

(i) Comparing the Clinical-Effectiveness of FFR vs. Angiography guided PCI

- ***Inclusion Criteria***

i. PICO Statement

- Population: Adult population with Stable Coronary Artery Disease.
- Intervention: FFR guided PCI.
- Comparator: Angiography Guided PCI.
- Outcome: MACEs, Myocardial Infarction (MI), Cardiac Mortality (CM), All-cause mortality (ACM), Revascularization (RV), Stent Thrombosis, Quality of Life etc.

ii. Study Design: Systematic Literature Review, Meta-Analysis. Network Meta-Analysis and Trials comparing FFR guided and Angiography guided revascularization. Network Meta-Analysis having at least one direct comparison of FFR vs. angiography guided revascularization.

- ***Exclusion Criteria***

i. Studies comparing FFR or Angiography with any other strategy such as FFT-CT, IVUS, iFR etc.

ii. Studies comparing FFR and angiography with other disease conditions [such as acute coronary syndrome (STEMI/NSTEMI)] or other treatment modality such as CABG.

iii. Studies in other than English language.

(ii) Cost Implications of Using FFR:

- ***Inclusion Criteria***

i. PICO:

- Population: Adult population with Stable CAD having Intermediate Stenosis (50-70%) and referred to undergo stenting.
- Intervention: FFR guided PCI or Stent placement.
- Comparator: Angiography Guided PCI or Stent placement.
- Outcome: Cost savings.

ii. Any study reporting the costing of using FFR in Indian context.

- ***Exclusion Criteria***

i. Costing of FFR conducted outside India.

ii. Studies comparing FFR and angiography with other disease condition [such as ACS (STEMI/NSTEMI)] or other treatment modality such as CABG.

iii. Studies in language other than English.

4.1.2. Data Source and Search Strategy

(i) Comparing the Clinical-Effectiveness of FFR Vs. Angiography guided PCI

PubMed and **Cochrane Library** were searched using the Key words "Fractional Flow Reserve" and "FFR" in titles and abstracts and the MeSH Term "Fractional Flow Reserve, myocardial" applying the filter "Meta-Analysis and Systematic Review, in the last 5 years, English". PubMed database was searched using the following search strings, till December, 2023:

Search: *(((Fractional Flow Reserve[Title/Abstract]) OR (FFR[Title/Abstract])) OR (fractional flow reserve, myocardial[MeSH Terms])) OR (myocardial fractional flow reserve[MeSH Terms]) Filters: Meta-Analysis, Systematic Review, in the last 5 years, English Sort by: Most Recent*

Date: 12.12.2023 (12:05 PM).

Similarly, Cochrane Library was searched using the following search strategy till December, 2023:

Cochrane Search *Name: Fractional Flow Reserve Trials/ Systematic Review*

Date Run: 12/12/2023 (03:20 PM)

ID	***Search***	***Hits***
#1	***(Fractional Flow Reserve):ti,ab,kw OR (FFR):ti,ab,kw with Cochrane Library publication date Between Jan 2023 and Dec 2023 (Word variations have been searched)***	***97***
#2	***MeSH descriptor: [Fractional Flow Reserve, Myocardial] explode all trees***	***231***
#3	***#1 OR #2***	***314***

(ii) Cost Implications of Using FFR:

PubMed Database was searched using the Key Words "Fractional Flow Reserve", "FFR" "Costing" and "India". PubMed database was searched using the following search strings:

Search: *(((Fractional Flow Reserve[Title/Abstract]) OR (FFR[Title/Abstract])) AND ((((cost) OR (costing)) OR (cost analysis)) OR (cost-analysis))) AND ((India) OR (Indian)) Sort by: Most Recent*

Date: 17.12.2023 (6:40 PM).

4.1.3. Literature Screening

All the searched articles were pooled and screened by titles followed by the abstracts and full text based upon the inclusion and exclusion criteria mentioned above. Two independent reviewers (AS and NSN) were involved in the screening process.

4.1.4. Data extraction and Synthesis

Information was collected from the chosen studies with the help of a Data Extraction Table. Subsequently, a comprehensive narrative data synthesis was performed based on the gathered information.

4.2. Cost Analysis Based upon Assumptions from the Literature.

A cost analysis was undertaken based upon assumptions derived from the literatures. These assumptions considered a 30% prevalence of multi-vessel coronary artery disease (CAD) (18), an average of 2 lesions per patient (as 3 or more stenoses are recommended for CABG), the latest stent cost ceiling as Rs. 38,265 (36), and an FFR wire cost of Rs. 40,000 (clinician's opinion and market survey). For simplicity, the procedure costs for both stenting and FFR were assumed to be the same in this model, considering they are performed concurrently. The cost benefit in using FFR was calculated based upon the assumptions that after applying the FFR data there was a stent avoidance in 30% cases, stent reduction in 30% patients, and no change in decision for 40% of the cases. All these percentages and subjects considered were from a group of patients having intermediate legions (50%-70%) and recommended for PCI based upon angiography (37,38).

4.3. Clinician's Opinion

Responses were gathered with the help of a questionnaire (Annexure – I) and online communication, from interventional cardiologists from the government medical hospitals as well as private hospitals, on the use of FFR and its advantages over angioplasty, if any, and approximate cost of performing FFR (in INR) per patient etc. Questions 1-3 of the questionnaire captured the respondent's details such as name, designation, affiliation and experience etc. Questions 4-9 focused on FFR such as conditions in which it was advised for CAD patients, their advantage, if any, its role in critical decision-making, approximate cost per patient and additional equipment required for performing FFR. Finally, the respondent was given the opportunity to share any other relevant information. The list of cardiologists was retrieved from hospital/medical academic institution webpages. The questionnaire link was sent to cardiologist via email and messages.

5. RESULTS

5.1. Rapid Literature Review

5.1.1. Selection and Screening

(i) Comparing the Clinical-Effectiveness of FFR vs, Angiography guided PCI in stable CAD.

Our search retrieved 124 articles from PubMed and 314 articles from Cochrane Library (Fig. 5).

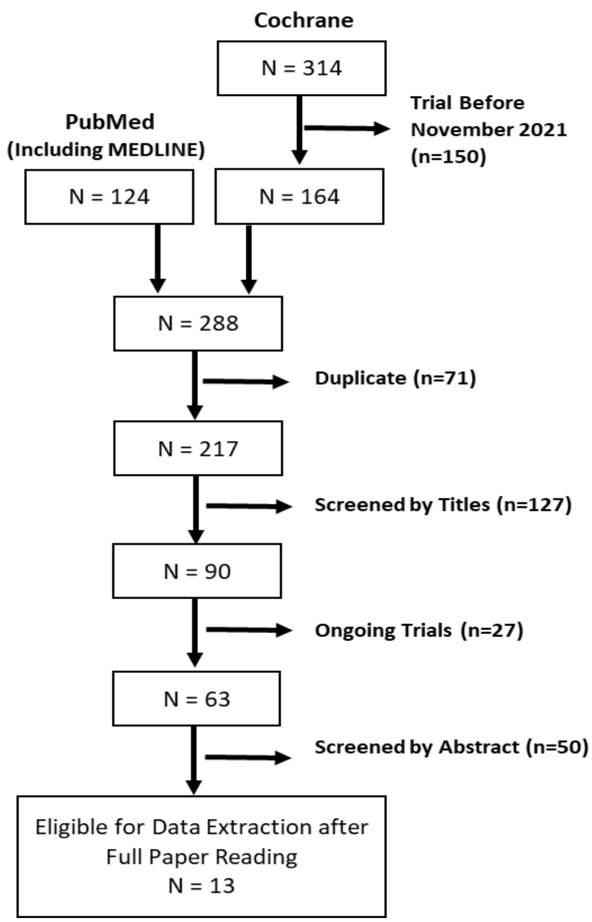

Figure 5. Flow Diagram for Literature Review for Comparing Clinical Effectiveness of FFR vs. angiography guided PCI.

Latest systematic review retrieved was by Elbadawi *et al.* (2022) that contained clinical trials data till November, 2021 (39). Thus, individual clinical trials before November 2021 were excluded. Combining the articles retrieved from PubMed and Cochrane Library we had a total number of 288 articles and after removing the duplicates 217 articles were screened by their titles. Thereafter, removing the ongoing trials, remaining 63 articles were screened by their abstract and finally 15 articles were found to be eligible for data extraction. However, full paper was not available for a clinical trial (40) and a network meta-analysis (41) so data available from their abstract were reported.

(ii) Cost Implications of Using FFR:

PubMed search retrieved 13 articles that were screened by their title and abstract and two articles were found to be eligible for data extraction (Fig. 7).

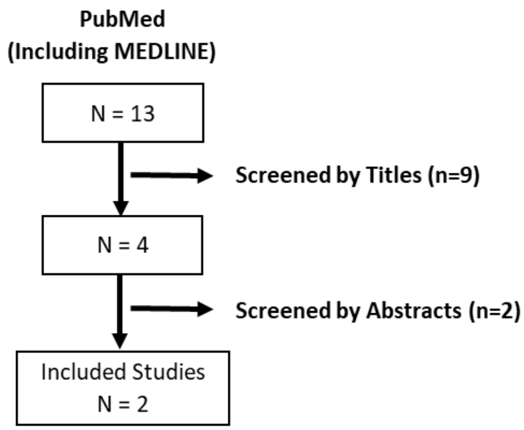

Figure 7: Flow Diagram for Literature Review for Cost Implications of Using FFR in india.

5.1.2. Data Extraction

Information was collected from the chosen studies with the help of a Data Extraction Table (Tables at Annexure II - III). Subsequently, a comprehensive narrative data synthesis was performed based on the gathered information.

5.1.3. Data Synthesis

(i) Comparing the Clinical-Effectiveness of FFR vs, Angiography guided PCI in stable CAD.

Most studies compared FFR-guided and angiography-guided strategies, with some additionally examining other approaches like oral medications and IVUS/iFR-guided management in network meta-analysis. Main outcomes focused on MACEs, MI, CM, ACM, RV. Secondary aspects included angina, major bleeding, stent placement, procedural costs (39,42–47) and patient's quality of life (37–39,48–51).

(a) Major Adverse Cardiovascular Events (MACE)

The definition of MACE varied between studies. It included any combination of all-cause mortality, MI, repeat target vessel revascularization, and stent thrombosis (46,52,53). Most systematic literature reviews showed that there was **no significant difference between FFR-guided and angiography-guided PCI** in long term MACE in patients with obstructive CAD (OR 0.86 95% CI 0.72–1.03, I2 = 72.3%) (54); (13.6% versus 13.9%, RR 0.97, 95% CI 0.85 to 1.11, I^2=0% (39); 14.6% versus 14.4%, HR: 0.97, 95% CI: 0.69-1.36; P = 0.85 (50); FFR (9.5%) vs. Angiography (8.7%) (51); Relative efficacy of CA vs. FFR - 0.86 (0.57, 1.20) (53). Two meta-analyses reported a **trend of reducing MACEs in-hospital with FFR** (OR 0.81, 0.64–1.02) (45) and **at follow up** (OR 0.63, 95% CI: 0.47 to 0.86, P=0.004) (47) compared to angiography. Similarly, a network meta-analysis indicated a lower risk of MACE with functionally guided PCI (41). However, the abstract did not provide specific numbers, and the full paper was inaccessible, with the risk of bias remaining unclear. A clinical trial on 305 patients whose full study and numerical values were inaccessible reported better optimal post-PCI FFR value in physiology-based PCI group (40).

(b) Myocardial Infarctions

No significant difference was observed towards reduction of MI in both the groups in a number of studies – FFR (5.66%) vs. angiography (5.43%)(51); in patients with Chronic Coronary Syndrome (CCS) without LM disease or reduced left ventricle ejection fraction (LVEF) (IRR 0.74, 95% CI 0.49–1.10) (55); (OR, 0.65; 95% CI, 0.37-1.1) (56); recurrent MI in patients with obstructive CAD (RR 0.92, 95% CI 0.74 to 1.14 (39); non-fatal MI in patients with multi-vessel CAD (4.8% vs 5.3%, RR 0.99, 95% CI 0.59 to 1.65, p = 0.96, I^2 = 61%) (43); among the groups (CA, fractional flow reserve, instantaneous wave-free ratio, and optical coherence tomography) (53). Two studies reported insignificant MI reduction in FFR group compared to angiography OR 0.74 (0.57–0.99) (45) and OR 0.65 (95% CI 1.01-0.44) (46)**.** A recent study reported lower **risk of MI in FFR-guided PCI** as compared to non-physiology-guided coronary revascularization (OR 0.74 95% CI 0.59–0.93, I^2 = 44.7%), though not much significant (54). It is to be mentioned that this study considered revascularization through PCI as well as CABG in a network meta-analysis comparing angiography-guided PCI and also with intracoronary imaging-guided (IVUS/ OCT) PCI. Similarly, another recent study was associated with **reduced risk of MI** compared with angiography-guided PCI (41). However, the full paper was inaccessible and the abstract did not provide specific numbers. Risk of bias was also unclear.

(c) Cardiovascular Mortality

No difference was reported for Cardiovascular Mortality between FFR-guided and angiography-guided revascularization (RR 1.27, 95% CI 0.50 to 3.26) in patients with obstructive CAD (39); 2.6% in the FFR vs. 1.1% in the control group (HR: 2.37; 95% CI: 0.83-6.76; P = 0.11) (50).

(d) All-Cause Mortality

Most of the studies reported **no impact of physiologically guided PCI** (IRR 0.95, 95% CI 0.57–1.58) **and angiography guided PCI** (IRR 0.95, 95% CI 0.84–1.08) strategies on all-cause mortality (ACM) in patients with Chronic Coronary Syndrome (CCS) without LM disease or reduced left ventricle ejection fraction (LVEF) (55); in obstructive CAD (3.5% vs 3.1%; RR 1.16, 95% CI 0.80 to 1.68) (39); 1-year All-cause mortality in multi-vessel CAD (2.3% vs 2.1%, RR 1.08, 95% CI 0.68 to 1.74, p = 0.74, heterogeneity [I^2] = 66%) (43); FFR group (3.7%) versus control group 1.5%, (HR: 2.34; 95% CI: 0.97-5.18; P = 0.06) (50); between FFR vs. non FFR guided group - (1.46%) vs. Angiography group (0.91%) (51) (OR, 0.85; 95% CI, 0.53-1.4) (56) and among different groups (CA, fractional flow reserve, instantaneous wave-free ratio, and optical coherence tomography) (53), **No difference was reported in in-hospital** (OR 0.58, 95% CI: 0.31 to 1.09, P 5 0.09) or **follow-up all-cause mortality** (OR 0.84, 95%CI: 0.59 to 1.20, P 5 0.34) (47). **Two studies reported potential reduction** in all-cause mortality with FFR compared to CA (OR 0.78; 0.63–0.98) (45) and reduction in composite of all-cause mortality compared to non-FFR-guided PCI and MT in patients with angina pectoris (AP) (56). Although, **no significant prognostic improvement was reported**. A recent study reported **lower risk of all-cause mortality** by FFR-guided PCI as compared to non-physiology-guided "coronary revascularization" (OR 0.79 95% CI 0.64–0.99, I2 = 53%) (54). This study considered revascularization through PCI as well as CABG in a network meta-analysis comparing angiography-guided PCI and also with intracoronary imaging-guided (IVUS/ OCT) PCI.

(e) Revascularization

In terms of revascularization the results were contrasting. **FFR was reported to be associated with reduction in the proportion of re-vascularized** patients compared to coronary angiography (CA), with **more patients referred to exclusively medical treatment** (P = 0.02) (50); decreased revascularization (IRR 1.93, 95% CI 1.29–2.91) in patients without LM disease or reduced left ventricle ejection fraction (LVEF) (55). **FFR (OR 1.4; 1.04–1.85) showed a better performance** compared with CA regarding (Target vest revascularization) TVR (OR 0.36 0.01–5.59) (45); (OR 0.68) (46). The FFR was also associated with lower in-hospital target lesion revascularization (TLR) compared to CA (OR 0.62, 95% CI: 0.40 to 0.97, P50.04) but not at follow-up (OR 0.83, 95% CI: 0.50 to 1.37 (47). However, **No difference** between FFR-guided versus angiography-guided revascularization was reported at 1 year (RR 0.95, 95% CI 0.79 to 1.13) or at 5 years (RR 0.90, 95% CI 0.75 to 1.08), **No difference was reported in repeat revascularization** (5.5% vs 6.8%, RR 0.81, 95% CI 0.60 to 1.10, p = 0.18, I^2 = 11%) (43); (OR 1 95% CI 0.82–1.20, I2 = 43.2%) (54), **repeat ischemia-driven revascularization** (RR 0.99, 95% CI 0.81 to 1.21) (39) and **Unplanned Revascularization** (FFR 9.49 vs. CA 8.7%) (51)**.**

(f) Number of PCIs, Stents Placed and Stent-Thrombosis

All studies reporting the number of stents used in revascularization consistently demonstrated that **FFR-guided revascularization was associated with a lower number of stents** compared to angiography-guided revascularization. (SMD=−0.80, 95% CI −1.33 to −0.27 (39). Reportedly, in patients with multi-vessel coronary artery disease (CAD), 40% of lesions initially classified as angiographically significant were reclassified as not physiologically significant by FFR. This reclassification contributed to a reduction in the pooled average number of stents in the FFR-guided arm (mean difference 0.5, 95% CI 0.8 to 0.1, p = 0.01) (43). **FFR was also associated with a reduced number of PCIs performed** (including number of stents placed) (OR 0.04, 95% CI: 0.01 to 0.15, P50.00001) (47). **Both FFR and iFR reported to reduce TVR compared to CA** (respectively OR 0.68 and OR 0.70) but the number of stents deployed did not differ between iFR and FFR (46). Regarding stent **thrombosis rates, no significant difference was reported** between FFR and angiography (RR 0.61, 95% CI 0.31 to 1.21 (39,45).

(g) Management Strategies, Hospitalization Cost and Procedural Details

In a prospective controlled trial (RIPCORD 2), it was reported that approximately 15% of patients assigned to the angiography-only group required further investigations. In contrast, for **98% of the patients in the angiography + FFR group, doctors were able to establish a definitive management plan.** However, **no significant difference in the management strategy** adopted or in the plan for number of segments or vessels to be treated (51). **Lower mean procedure cost was reported for FFR-PCI** due to non-increment on procedure time (Mean Difference 24.27, 95% CI: 26.61 to 21.92, P50.0004) (38). **However, there was no difference in total cost** (SMD=−0.09, 95% CI −0.45 to 0.26) (39) and **Median total hospital cost** (NHS) for the 2 groups (£4136 for angiography (IQR, £2613–£7015) versus £4510 (IQR, £2721– £7415; P=0.137) for angiography + FFR) (51)**. Hospital stay and number of OPD visits were also same in both the groups** [(5 (2-10) and 5 (2-11)] (51).

In terms of procedural details, a couple of systematic literature reviews and meta-analysis reported **no difference in procedure duration** (SMD=0.17, 95% CI −0.28 to 0.62), **volume of contrast agent** (SMD=0.08, 95% CI −0.29 to 0.45) (39) or **Mean Difference** 0.79, 95% CI: 22.41 to 3.99, P=0.63 (47), However, **one trial (RIPCORD 2) reported longer procedural duration in FFR** - 69.0 min. (SD 27.0) as compare to CA - 42.4 min. (SD 27.0), **greater use of contrast and radiation** in FFR - 206.0 mL (SD 96.2) vs CA - 146.3 (87.0) (51).

(h) Quality of Life (QoL)

Two trials (FUTURE and RIPCORD 2) reported the quality-of-life (QoL) and showed **no significant difference** between the two groups in QoL using the visual analog scale score of the EuroQol EQ-5D-5L in Median Quality of Life (Angiography: 75, interquartile range 60–87 and Angiography + FFR: 75, interquartile range, 60–90; P=0.88) (51); Visual scale = 71+/-19 in the FFR group vs 71+/-16 in the control group; P = 0.62) in multi-vessel CAD (50). However, RIPCORD 2 also reported that FFR contributed to better QoL in patients with more significant disease (P=0.03) (51).

5.1.4. <u>Cost implications and Clinical Outcomes of FFR in Indian Context</u>

A comprehensive Cost-Effectiveness Analysis (CEA) of FFR was not conducted due to the comparable clinical outcomes of FFR-guided PCI and angiography-guided PCI. Existing evidence was compiled, with a primary focus on the costing of the FFR strategy particularly in the Indian context. Only two studies from India were identified that addressed the costing of FFR in addition to clinical outcomes (37,38).

An ambient observational study carried out in CMC Vellore (37) observed that among 400 patients with 477 intermediate lesions scheduled for PCI based upon angiography, **FFR guided strategy resulted in stent avoidance** for 30% patients (saving 1.2 stents per patient) and reduced stent usage in 31% patients (1.07 stents saved per patient). FFR also prompted a revascularization strategy change in 10% of patients, shifting from CABG to multi-vessel PCI, and in 8.25% of patients, transitioning from PCI to CABG. (Fig. 8).

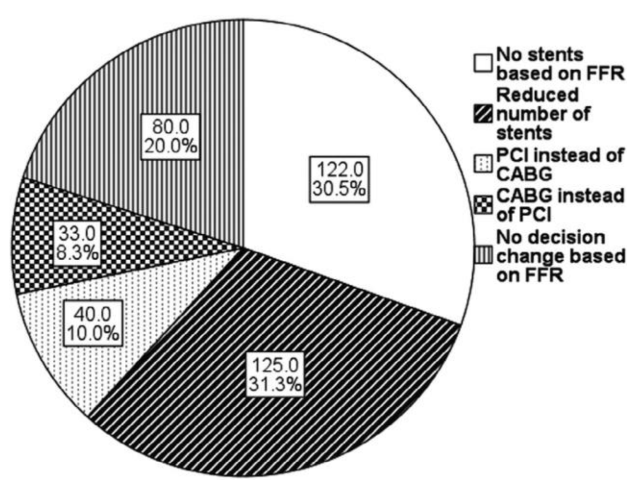

Figure 8: Clinical Management Decisions following FFR (37)

A similar trend of stent reduction was observed in the FIND study (38), which involved 59 patients with 81 lesion vessels and 67 intermediate stenosis. Out of the 45 patients recommended for PCI based on angiography, only 35.5% were deemed necessary for PCI upon FFR assessment. This led to a **38% reduction in stent usage, saving 26 stents out of the 66** initially recommended. Specifically, for every 2 patients or 3 vessels with intermediate stenosis, FFR resulted in the avoidance of one stent. Changes in revascularization decisions were also noted, with only 3 out of 6 patients suggested for CABG actually undergoing the procedure.

(i) Clinical Outcomes

a. <u>Primary End Points:</u>

The composite primary endpoint (cardiac death, non-fatal myocardial infarction (MI), ischemia, or ischemia-driven revascularization in the assessed vessel) **were lower (0.9% in stent avoidance group versus 6.9% in combined stented group)**, with a statistically significant difference (p =.04; 95% CI: −0.10 to −0.10) (Table 1) (37).

Table I: Clinical outcomes in the stented and non-stented group on the basis of fractional flow reserve (FFR) (37)

Outcomes	All patients *n* = 324	Stent avoidance group *n* = 108	Any stent group *n* = 216	*p* (95% CI)
Primary outcome (%)	16 (4.94)	1 (0.9)	15 (6.9)	.04 (–0.10, –0.01)
Cardiac death (%)	1 (0.3)	-	1 (0.5)	
Nonfatal MI (%)	1 (0.3)	-	1 (0.5)	
Objective ischemia (%)	7 (2.2)	-	7 (3.2)	
[a]Target vessel revascularization (%)	7 (2.2)	1 (0.9)	6 (2.8)	
Secondary outcomes (%)	20 (6.2)	4 (3.7)	16 (7.4)	.29 (–0.09,0.02)
Any death (%)	4 (1.2)	2 (1.9)	2 (0.9)	
Nonfatal MI (%)	1 (0.3)	-	1 (0.45)	
Objective ischemia (%)	6 (1.9)	-	6 (2.8)	
[b]Any revascularization (%)	9 (2.8)	2 (1.9)	7 (3.2)	

Note: Values presented as n (%).
[a]Revascularization in the vessel assessed by FFR.
[b]Revascularization of any vessel irrespective of the vessel assessed by FFR.

The Kaplan-Meier event-free survival curve (Fig. 9) also suggested a sustained divergence in outcomes.

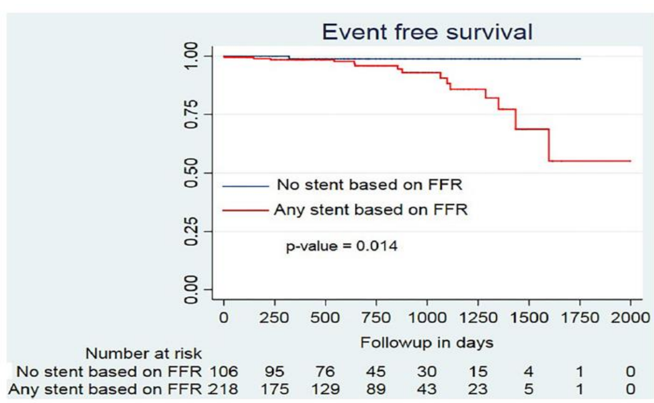

Figure 9: Kaplan- Meir Survival Curve for Stented and Non stented group (37).

b. <u>Secondary Outcomes:</u>

- **Extended MACE** (death, nonfatal myocardial infarction, and ischemia-driven revascularization) showed **no statistically significant difference** (p =.29) between the avoided and stented groups (Table I) (37). Adverse events related to adenosine were minimal, with no significant difference between intracoronary and intravenous administration (0.9% and 1.8%; p = .51).
- **Micro-Costing of FFR**

  Among a total of 400 patients, 305 were included in the cost analysis due to changes in treatment decisions (from PCI to CABG or vice-versa) and incomplete billing information. **Stent costs ranged from Rs. 25,000 to Rs. 1,40,000, with an average of Rs. 46,753,** while **FFR wire cost was Rs. 21,200.** The re-sterilized FFR wire was shared between two patients on average. Considering these factors, the FFR strategy led to cost savings, with a per-patient saving of INR 51,847 and a **total savings of INR 15,813,379** (Table II). The cost study was extended using the **2019 stent ceiling price of INR 30,080** (excluding taxes) (57), and the **pressure wire price was adjusted to INR 30,000.** Three pricing scenarios were explored, relevant for both public and government hospitals in developing countries (Table III):

Table II – Cost Savings Prior to DES Cost Ceiling and FFR Cost Revision (37)

FFR based decision (*n* = 305)	Angiogram charges in INR (USD)	PTCA charge in INR (USD)	FFR wire in INR (USD)	Medication charges in INR (USD)	Average nos. of lesions	Average nos. of stents saved with FFR	[a]Computed stent charges per patient in INR (USD)	[b]Stent charges saved per person in INR (USD)	[c]Nett savings per person in INR (USD)	Total savings for study cohort in INR (USD)
Stent avoidance (*n* = 107)	15,998 (230)	Nil	11,062 (159)	663 (9)	1.22	1.2	57,038 (820)	57,038 (820)	1,12,446 (1,617)	1,20,31,792 (173,119)
Reduced number of stents (*n* = 122)	Nil	83,131 (1,196)	11,062 (159)	663 (9)	2.6	1.07	1,21,558 (1,749)	50,025 (719)	38,300 (551)	46,72,686 (67,232)
No stent avoidance or reduction in the number of stents (*n* = 76)	Nil	83,131 (1,196)	11,062 (159)	663 (9)	2.2	0	1,02,857 (1,479)	0	−11,725 (−168)	−8,91,100 (−12,821)
Net savings in INR (USD)									[d]51,847 (746)	15,813,379 (227,530)

Abbreviations: FFR, fractional flow reserve; INR, Indian Rupees; PTCA, percutaneous coronary angioplasty; USD, United States Dollars.
[a]Average stent price was INR 46,753. Computed stent charges were calculated as (Avg stent price × Number of lesions).
[b]Average stent price × Average number of stents avoided by use of FFR.
[c]Net savings = Computed costs without FFR strategy (PTCA + Stent) − Cost using FFR strategy (Pressure wire cost + Angiogram cost + Medication cost − Stent saving - PTCA cost saving; if no stent was used).
[d]Total savings in the study divided by the total number of patients included in the cost analysis (*n* = 305).

i. **Category 1 -** A flat FFR procedural charge of INR 20,000 for all patients, regardless of FFR assessment outcome. This charge applied to both PCI patients and those in whom PCI was avoided based on FFR assessment.
ii. **Category 2 -** A FFR procedural charge of INR 20,000 for patients with negative FFR results, leading to avoided PCI. A subsidized charge of INR 10,000 was applied if PCI was performed.
iii. **Category 3 -** A FFR procedural charge of INR 20,000 for patients with negative FFR results, resulting in avoided PCI. If PCI was performed, the FFR procedural charges were waived.

In the above scenarios, costs were calculated using full or subsidized FFR wire prices to accommodate different cost practices in private and public hospitals. Once more, FFR was reported to offer a cost-saving, yielding **per-patient savings between INR 4,531 and INR 32,515**, although stent cost limits slightly diminished the cost benefits.

Table III - Cost Savings Post DES Cost Ceiling and FFR wire Cost Revision (37)

Patient categories	FFR procedural charges in INR	[a]FFR wire charged in full Saving per person in INR (USD)	[b]Subsidized FFR wire charges Saving per person in INR (USD)
[c]Category 1	Full	4,531 (65)	19,531 (281)
[d]Category 2	Subsidized	11,023 (159)	26,023 (375)
[e]Category 3	No charge	18,613 (268)	32,515 (468)

Note: PCI charges were taken as INR 80 000/– for all the cost computations.
Abbreviations: FFR, fractional flow reserve, INR, Indian rupees, USD, United States dollars.
[a]INR 30,000 (USD 432).
[b]INR 15,000 (USD 216).
[c]FFR procedural charges of INR 20 000/– for all patients irrespective of FFR outcome.
[d]Subsidized procedural charges of INR 10000 for patients with positive FFR who undergo PCI.
[e]No FFR procedural charges for patients with positive FFR who undergo PCI.

The second (FIND) study, conducted **before stent cost ceiling**, also highlighted FFR as a cost-saving strategy (38). Cost analysis was conducted on 59 patients in a Chennai-based private super specialty hospital from May 2011 to August 2013, with an **average stent cost of INR 1 lakh** and **FFR procedure cost of INR 30,000**. By avoiding 26 stents, a saving of INR 26 lakhs was achieved, while the FFR procedure for 59 patients incurred INR 17.7 lakhs. Overall, a net cost saving of INR 8.3 lakhs was reported. Furthermore, avoiding Dual Antiplatelet Therapy (DAPT) costs for stented patients resulted in an additional saving of INR 1200, leading to a total **net cost saving of INR 8,57,600 in one year**.

5.2. Cost Analysis Based upon Assumptions from the literature.

The cost benefit of using FFR was evaluated with assumptions that FFR resulted in stent avoidance 30% of cases, stent reduction in 30%, and no change in decision in 40% in patients having intermediate lesions (50%-70%) and recommended for PCI (37,38). Multi-vessel CAD prevalence was set at 30% (18), with an average of 2 lesions per patient. Stent cost was Rs. 38,265 (36), and FFR wire cost was Rs. 40,000, considering equal procedure costs for Stenting and FFR. It was found that FFR led to reduction of total stents from 130 to 82. With the specified costs of stents and FFR wire and no procedure cost differences, FFR strategy didn't show immediate cost savings. However, FFR could potentially be cost-saving if the FFR wire cost was below INR 17,500 for single use of FFR Or, INR 35,000, allowing reuse of FFR-wire on two patients after sterilization (37,38) (Annexure IV). Incorporating variations in procedure costs and guide wire use could lead to a more realistic FFR wire cost relative to Stent cost.

5.3. Clinicians' Opinions

Responses were collected from six interventional cardiologists, with 4 to 22 years of experience and consultations ranging from 500 to 1200 patients per month. Three were affiliated with government academic hospitals, two with private academic hospitals, and one with a private hospital. All respondents mentioned the positive aspects of FFR, acknowledging its role in assessing the physiological significance of lesions and determining patient suitability for revascularization. This was particularly noted in cases of intermediate coronary stenosis (50-70%) in straight lesions and up to 95% in acute bend lesions in ischemic heart disease (IHD). The utility of FFR in decision-making for bifurcation lesions was also highlighted. (see Annexure IA).

A key principle emphasized for the rational use of Stent or CABG in Stable CAD patients was the "evidence of ischemia", preferably obtained through non-invasive methods like Stress ECG, Echo, or MPI before angiography. FFR could serve as an alternative to provide evidence of ischemia if other methods are not feasible or inconclusive. Patients with FFR values above 0.80 could potentially be managed with medical therapy.

Regarding FFR costs, four respondents indicated a range of **INR 30,000 to INR 40,000** while another from a private hospital reported **INR 70,000**. One respondent mentioned a cost of **FFR wire as Rs. 39,760** including GST. Suggestions were also made to explore advanced techniques like CT-FFR, iFR, and RFR, which showed promising results. The survey also revealed that FFR wasn't routinely incorporated into diagnostic work-ups in three out of the six represented hospitals.

6. DISCUSSION

Most studies indicated no significant differences in the long-term MACE, MI, cardiovascular mortality, all-cause mortality or stent-thrombosis between FFR-guided and angiography-guided PCI (39,46,50–53). However, two studies reported reduced MACE in-hospital (45) and upon follow-up (47) with FFR. The data on revascularization outcomes were inconsistent, with reduction re-vascularization by FFR in patients involving LM (55) and TVR (45,46) while some reporting no difference in 1-5 years, repeat and unplanned revascularization (43,51). No significant difference was reported for procedural details, such as the duration of procedures and contrast volume used. Quality of Life (QoL) also showed no significant difference between FFR-guided and angiography-guided strategies. Existing evidence does not convincingly establish the clinical superiority of FFR-guided PCI and angiography-guided PCI in stable CAD. Notably, a decreased number of stents and PCIs was reported by FFR-guided strategies compared to angiography, based on the physiological significance of coronary lesions (37–39,43,45–47,55), thereby directing more patients toward medical management (50). Clinicians also favored FFR for guiding PCI, especially in instances of intermediate stenosis and multi-vessel CAD, to determine the physiological significance and necessity of stent placement. However, data was lacking on the proportion of PCI procedures actually avoided in actual clinical practice with the use of FFR, especially in Indian context.

In terms of cost, the total hospital costs (39), hospital stay and number of OPD visits were same (51) for the two approaches. There were only two studies providing insights into the clinical and cost implications of FFR in the Indian context (37,38), reporting FFR's role in stent avoidance, reduction, and transition in treatment modalities. Micro-costing, considering an average stent cost of INR 46,753 and FFR wire cost of INR 21,200, revealed that the FFR strategy resulted in per-patient savings of INR 51,847. When considering 2019 stent ceiling price of INR 30,080 and the pressure wire price as INR 30,000 and exploring three pricing scenarios, FFR showed cost savings, ranging from INR 4,531 to INR 32,515 per patient (37). The scenarios included a flat FFR procedural charge, a subsidized charge for patients with negative FFR results, and waived charges if PCI was performed after a negative FFR result. Another earlier FIND study, considering stent cost of INR 1 lakh and FFR procedure cost of INR 30,000 also supported FFR as a cost-saving strategy, reporting a net saving of INR 8.3 lakhs by avoiding 26 stents and associated therapy in 59 patients.

The abovementioned micro-costing studies had limitations of being conducted in a single private hospital setting, on a limited sample size, and obsolete cost considerations for stents and FFR wire. Furthermore, data on the actual proportion of avoided PCI procedures in clinical practice in India was lacking. This is important in a “fee-for-service systems” as both FFR usage and stent implantation contribute to revenue generation. This becomes crucial considering existing evidence indicating comparable clinical outcomes between FFR-guided and angiography-guided strategies.

Our costing exercise suggested that the FFR strategy does not yield cost savings at the current price point i.e. stent cost of Rs. 38,265 and FFR wire cost of Rs. 40,000. The potential for FFR to be cost-saving strategy may emerge if the FFR wire cost is substantially lower (below INR 17,500 for single use) than the stent cost. The current analysis relies on assumptions derived from above two Indian studies, emphasizing the need for a detailed cost study to accurately estimate the cost-saving impact of FFR wire.

Overall, FFR and angiography guided PCI has comparable clinical outcomes with FFR resulting in reducing the number of stents in patients with intermediate stenosis in stable CAD but data on the actual proportion of avoided PCI procedures in clinical practice in India was lacking. The potential for FFR to be cost-saving strategy may emerge if the FFR wire cost is substantially lower than the stent cost. A comprehensive cost study is required for the same. Assessing the potential impact of integrating FFR into routine practice is crucial to understand its effect on the number of deployed stents before initiating a cost-effectiveness analysis.

7. CONCLUSIONS

In conclusion, FFR-guided and angiography-guided strategies demonstrate similar clinical outcomes. Reportedly, FFR caused a reduction in PCIs in stable CAD patients with intermediate stenosis. However, data on the actual proportion of avoided PCI procedures in clinical practice was lacking. This is crucial in a "fee-for-service systems", as existing evidence indicates comparable clinical outcomes between FFR-guided and angiography-guided strategies, and both FFR and stent implantation contribute to revenue. The potential impact of using FFR in routine practice needs to be assessed for its effect on the number of stents deployed, before a cost-effectiveness analysis can be performed. Limited Indian studies on its clinical and cost implications prompt the need for comprehensive costing studies. The potential for FFR to be cost-saving strategy may emerge if the FFR wire cost is substantially lower than the stent cost. Evaluating the potential impact of integrating FFR into routine practice is essential to assess its effect on the number of deployed stents before conducting a cost-effectiveness analysis.

8. RECOMMENDATIONS

The potential impact of incorporating FFR into routine practice needs evaluation to assess its effect on the number of deployed stents in Indian context before conducting a cost-effectiveness analysis.

9. LIMITATIONS

i. The study used a rapid review for assessing FFR's clinical effectiveness and cost implications.
ii. Costing analysis was based upon some preliminary assumptions from the literature.

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ANNEXURE I

Questionnaire for the Cardiologists

Health Technology Assessment India (HTAIn) is a part of Department of Health Research (DHR), Ministry of Health & Family Welfare (MoHFW), Government of India. HTAIn facilitates the process of transparent and evidence-informed decision making in the field of healthcare. Indian Institute of Science (IISc), Bangalore is one of the Regional Resource Centers (RRC) of HTAIn, responsible for assessing and analyzing the health technologies viz. medicines, devices and health programs for its cost-effectiveness, clinical-effectiveness and equity issues by means of Health Technology Assessment (HTA), and in turn help in decision making for an efficient use of the limited health budget and provide people access to the quality health care reducing their out of pocket expenditures (OOPs) on health.

Analyzing technologies in the field of diagnostics is the current focus of our RRC. Currently, we are evaluating the effectiveness, feasibility, and advantages of using Fractional Flow Reserve (FFR) for coronary artery disease (CAD) patients. As part of the assessment, we are conducting an extensive literature review and consulting with cardiologists. We invite inputs from interventional cardiologists through this questionnaire. The results from this endeavor will find place in a report which will be submitted to HTAIn and will be used to inform healthcare policy.

Please note: The results will be anonymized before their use in the report. Kindly write to us at htain.rrc.iisc@gmail.com with any queries.

* Indicates mandatory questions.

1. Name*:
2. Email Address*:
3. Designation & Affiliation*:
4. Where are you currently practicing? * (More than one selection allowed)
   - Government hospital
   - Private hospital
   - Government academic hospital
   - Private academic hospital
   - Other (Details)
5. Are you an interventional cardiologist? *
   - Yes
   - No
6. On an average, how many patients visit you for consultations in a month?
7. How long have you been practicing as a cardiologist? (in years)
8. Is FFR regularly conducted as part of the work-up for patients with coronary artery disease (CAD) in your hospital? *
   - Yes
   - No
   - Other (Details)
9. Under what conditions is FFR advised? *
10. Are there any advantages of using FFR-Index before angioplasty? *
    - Yes
    - No
11. What are the critical clinical decisions made using FFR? *
12. What is the approximate cost of FFR (in INR) per patient? *
13. What additional equipment is required for conducting FFR? *
14. Any other relevant information would you like to share?

ANNEXURE IA

Questionnaire's Responses

Questions ► / Response ▼	Where Are You Currently Practicing?	Are You An Interventional Cardiologist ?	On An Average, How Many Patients Visit You For Consultations In A Month?	How Long Have You Been Practicing as a Cardiologist? (In Years)	Is FFR Regularly Conducted As Part Of The Work-Up For Patients With Coronary Artery Disease (CAD) In Your Hospital?	Under What Conditions Is FFR Advised?	Are There Any Advantages Of Using FFR-Index Before Angioplasty?	What Are The Critical Clinical Decisions Made Using FFR?	Any Other Relevant Information Would You Like To Share?	What Is The Approximate Cost Of FFR (In INR) Per Patient?	What Additional Equipment Is Required For Conducting FFR?
1.	Government Academic Hospital	Yes	500	10 YEARS	No	INTERMEDIATE CORONARY STENOSIS ON CORONARY ANGIOGRAPHY	Yes	USEFUL IN BIFURCATION LESIONS AND INTERMEDIATE STENOSIS	FFR IS AN OLDER TECHNIQUE, NEWER MODALITIES LIKE CT-FFR, IFR, RFR HAVE COME UP	40000	FFR WIRE AND CONSOLE
2.	Private Academic Hospital	Yes	1200	22	Yes	Moderate Stenosis	Yes	Lesion Significance		30000	Console
3.	Private Academic Hospital	Yes	200	12	No	Intermediate Stenosis	Yes	Lesion Significance		30000	FFR Wire And Console
4.	Government Academic Hospital	Yes	800	11 Years	No	Intermediate Coronary Stenosis	Yes	Useful In Lesion Significance		35000	Console
5.	Private Hospital	Yes	500-600	4	Yes	Intermediate Disease On Angiography	Yes	FFR >0.80 Left On Medical Therapy	Should Be Included as Part of Government Schemes Like AYUSHMAN BHARAT. Integral Part of Management. Without It , Correctness Of Procedure Is More Of Educated Guesswork Sometimes	70000	FFR Wire And FFR Console Machine
6.	Government Academic Hospital	Yes	1000	18 years	Yes	Intermediate coronary stenosis 50 to70 in straight lesions and upto 95% in acute bends for patients with Stable IHD	Yes	1. Is the lesion physiologically significant? 2. Does the patient benefit from revascularization?	CT-FFR and Angio FFR will be replacing wire based FFR in over 75% of cases in 5 yrs. The important principle for ensuring rational use of Stents or CABG among Stable CAD patients is "evidence of ischemia using an appropriate method (Stress ECG/ Echo/ MPI) before angiography is done and if that is not possible due to any valid reason, to put stent or send for CABG only if a lesion with stenosis of less than 90% has an FFR value of less than 0.8)	FFR wire was procured in 2023 at Rs. **39760** inclusive of all taxes per wire	Cardiac Cath lab with a hemodynamic recorder, FFR measuring unit either standalone (4 to 5 Lakh) or integrated with an intracoronary imaging unit like IVUS (40 to 60 Lakh Volcano or Boston) or OCT (85 to 120 Lakh St Jude Abbott)

ANNEXURE II

1. Effectiveness of FFR Guided Vs. Angiography Guided Angiography - Data Extraction Sheet

Sl. No.	Title	Author (First) and Year	Journal	Objective	Study Type, No. of Studies and No. of Patients included	Primary Outcomes	Secondary Outcomes	Conclusion	Risk of Bias
1.	Coronary Physiology Guidance vs. Conventional Angiography for Optimization of Percutaneous Coronary Intervention: the AQVA II Trial.	Biscaglia S. *et. al.* (2023)	Journal of the American College of Cardiology	First, demonstrating the superiority of physiology-guided PCI, using either angiography or microcatheter-derived FFR, over conventional angiography-based PCI in complex and high-risk procedures (CHIP). Second, establishing the non-inferiority of angiography-derived FFR guidance compared to microcatheter-derived FFR guidance.	• Clinical Trial. • 305 Patients	• Invasive post-PCI FFR value. • Physiology-based PCI was better (77%) than conventional angiography-based PCI (54%). • Whether using angiography or microcatheter-derived FFR, the outcomes were equally good (non-inferior), demonstrating both methods are effective.	• Unclear.	• In CHIP patients, procedural planning and guidance based on physiology (either through angiography-or microcatheter-derived FFR) are superior to conventional angiography for achieving optimal post-PCI FFR values.	• Unclear
2.	Fractional flow reserve use in coronary artery revascularization: a 78,897 patients systematic review and meta-analysis.	Sanz Sánchez J *et. al* (2023)	iScience	To conduct a systematic review and meta-analysis to compare the benefits of FFR -guided PCI with other revascularization strategies, including angiography-guided PCI, intracoronary imaging-guided (IVUS/ OCT) PCI, and CABG.	• Systematic review and meta-analysis. • 26 studies enrolling 78,897 patients • Follow Up-12-84 Months.	• All-cause mortality (ACM) • FFR-guided PCI as compared to non-physiology-guided coronary revascularization had **lower risk of all-cause mortality** (OR 0.79 95% CI 0.64–0.99, I2 = 53%)	• Myocardial infarction (MI), repeat revascularization and major adverse cardiac events (MACE). • FFR-guided PCI as compared to non-physiology-guided coronary revascularization had **lower risk of MI)**(OR 0.74 95% CI 0.59–0.93, I2 = 44.7%). • **No differences between groups were found in terms of MACEs** (OR 0.86 95% CI 0.72–1.03, I2 = 72.3%) **and repeat RV** (OR 1 95% CI 0.82–1.20, I2 = 43.2%)	• FFR-guided PCI in CAD patients had lower risks of ACM and MI compared to non-physiology-guided strategies. • No significant differences in MACE and repeat revascularization were observed, but caution is needed due to high heterogeneity and potential null effects on all-cause death and MI risks.	• Publication bias was detected for ACM
3.	Comparison of Intravascular Imaging, Functional, or Angiographically Guided Coronary Intervention.	Kuno T. *et al. (2023)*	Journal of the American College of Cardiology	To evaluate clinical outcomes with imaging-guided PCI or functionally guided PCI when compared with conventional angiography-guided PCI.	• Network Meta-Analysis • 32 trials and with a total of 22,684 patients. •	• MACE - a composite of cardiovascular death, myocardial infarction (MI), and target lesion revascularization (TLR) • functionally guided PCI was associated with reduced risk of MACE and MI compared with angiography-guided PCI,	• Unclear	• Intravascular imaging-guided and functionally guided PCI had better outcomes compared with Angiography-guided PCI. • Intravascular imaging-guided PCI was the best strategy to reduce the risk of cardiovascular events. • The results were consistent in the ACS and non-ACS cohorts.	• Unclear
4.	Revascularization strategies versus optimal medical	Galli M et al. (2022)	International Journal of Cardiology	Exploring the comparative effects of different	• Network Meta-Analysis	• Compared to OMT all revascularization therapies showed **reduction in primary end**	• **Angiography-guided PCI was associated with increased**	• Revascularization strategies were associated with a reduction	Majority (n = 13) of

	therapy in chronic coronary syndrome: A network meta-analysis.			revascularization strategies (in patients with Chronic Coronary Syndrome (CCS) without LM disease or reduced left ventricle ejection fraction (LVEF) .	18 RCTs • 26,625 patients • mean follow-up of 5.1 years.	**points - Modest with angiography-guided PCI** (IRR 0.86, 95% CI 0.75–0.99) and greater with physiology-guided PCI (IRR 0.60, 95% CI 0.47–0.77) and CABG (IRR 0.58, 95% CI 0.48–0.70). • **Angiography-guided PCI was associated with an increase of the primary endpoint** compared to physiology-guided PCI (IRR 1.43, 95% CI 1.14–1.79) and CABG (IRR 1.49, 95% CI 1.27–1.74). • CABG was the only strategy associated with reduced myocardial infarction (IRR 0.68, 95% CI 0.52–0.90), cardiovascular death (IRR 0.76, 95% CI 0.64–0.89), and all-cause death (IRR 0.87, 95% CI 0.77–0.99), but increased stroke (IRR 1.69, 95% CI 1.04–2.76).	**revascularization** compared with both CABG (IRR 2.88, 95% CI 2.18–3.82) and physiology-guided PCI (IRR 1.93, 95% CI 1.29–2.91) • **Physiology-guided PCI was associated with a non-significant trend towards reduced MI** (IRR 0.74, 95% CI 0.49–1.10), while there were no differences with angiography-guided PCI (IRR 0.95, 95% CI 0.75–1.20), compared with medical therapy. • There was **no impact** of Physiologically guided PCI and Angio guided PCI strategies **on all-cause death** (IRR 0.95, 95% CI 0.57–1.58 and IRR 0.95, 95% CI 0.84–1.08, respectively)(	of the primary endpoint (as defined in each trial), compared with medical therapy. • Physiology-guided PCI and CABG were associated with a reduction of the primary endpoint and of revascularizations, compared with angiography-guided PCI. • Among CCS patients without LM disease or reduced LVEF, physiology-guided PCI and CABG are associated with better outcomes than angiography-guided PCI • CABG was associated with a reduction of MI and of CV and all-cause mortality but at the cost of a higher risk of stroke, compared with medical therapy	RCTs - low risk for bias • 4 - some concerns • 1 - high risk.
5.	Routine Pressure Wire Assessment Versus Conventional Angiography in the Management of Patients With Coronary Artery Disease: The RIPCORD 2 Trial	Stables RH. et al. (2022)	Circulation	To test the hypothesis that systematic FFR assessment of all relevant coronary arteries at the stage of the diagnostic angiogram would provide superior resource use, quality of life (QoL), and clinical outcomes compared with the use of the angiogram alone.	• Open-label prospective randomised controlled trial	• **No significant difference in Clinical Events** in terms of both individual events and a composite of major adverse cardiac events. FFR vs. CA (MACEs-9.5 vs. 8.7%, MI- 5.66 vs. 5.43%, Stroke-2.19 vs. 1.45%, Death 1.46 vs. 0.91%, Unplanned Revascularization (9.49 vs. 8.7) • **Similar Median total hospital cost** (NHS) over the period for the 2 groups: £4136 for angiography (IQR, £2613–£7015) versus £4510 (IQR, £2721– £7415; P=0.137) for angiography+FFR. • **No significant difference in median quality of life** using the visual analog scale of the EuroQol EQ-5D-5L: angiography, 75 (interquartile range, 60–87); and angiography+FFR, 75 (interquartile range, 60–90; P=0.88).	• **Definitive management plan in >98% FFR** cases of cases. further test required in 14.7% CA patients. • **No significant differences in the broad management strategy** adopted (in terms of medical therapy, PCI, or CABG)	• Routine FFR assessment of all epicardial vessels of graftable or stentable diameter at the time of diagnostic angiography in patients with stable chest pain or after admission with non–ST-segment–elevation acute coronary syndromes is cost neutral (NHS)compared with angiographic guidance alone and is not associated with significant differences in QoL or angina status at 1 year. This strategy therefore has no overall advantage compared with angiography alone.	Potential Investigator Bias (No Blinding)
6.	Fractional flow reserve versus angiography alone in guiding myocardial revascularisation: a systematic review and meta-analysis of randomised trials	Elbadawi A. et al. (2022)	Heart	To examine the comparative efficacy and safety of FFR-guided versus angiography-guided revascularisation among patients with obstructive CAD.	• Systematic review and meta-analysis. • 7 Randomized Trials with total 5094 patients. • weighted mean follow-up duration was 38 months.	• **No significant difference** between FFR-guided and angiography-guided revascularisation in long-term **MACE** (13.6% vs 13.9%; RR 0.97, 95% CI 0.85 to 1.11, I^2=0%). • No difference between FFR-guided versus angiography-guided revascularization **at 1 year** (RR 0.95, 95% CI 0.79 to 1.13) or **at 5 years** (RR 0.90, 95% CI 0.75 to 1.08) • **No differences between both groups in rates of cardiovascular mortality** (RR 1.27, 95% CI 0.50 to 3.26)	• **No difference** in repeat ischaemia-driven **revascularization** (RR 0.99, 95% CI 0.81 to 1.21), **recurrent MI** (RR 0.92, 95% CI 0.74 to 1.14) or **stent thrombosis** (RR 0.61, 95% CI 0.31 to 1.21). • FFR-guided revascularisation was associated with **fewer number of stents** compared with angiography-guided revascularisation (SMD=−0.80, 95% CI −1.33 to −0.27), • **No difference in total cost** (SMD=−0.09, 95% CI −0.45 to 0.26), **procedural duration** (SMD=0.17, 95% CI −0.28 to	• FFR-guided revascularization did not reduce the long-term risk of MACE or any of the individual secondary outcomes compared with angiography-guided revascularization. • FFR guidance reduced the number of stents during revascularization procedure compared with angiographic guidance..	Low

							0.62) or **volume of contrast agent** (SMD=0.08, 95% CI −0.29 to 0.45) and **all-cause mortality** (3.5% vs 3.1%; RR 1.16, 95% CI 0.80 to 1.68).		
7.	Meta-Analysis Comparing Clinical Outcomes of Fractional-Flow-Reserve- and Angiography-Guided Multivessel Percutaneous Coronary Intervention	Connor Jack Matthews (2022)	The American Journal of Cardiology	RCTs comparing an FFR-guided PCI strategy versus angiography-guided PCI strategy in patients with multivessel CAD	• Meta-Analysis • 3 RCTs. • 3095 patients. • Follow-up time 1-year	**No significant difference in** - overall 1-year trial-defined **composite endpoint** in the pooled cohort (10.7% vs 11.8%, RR 0.94, 95% CI 0.68 to 1.30, p = 0.72, heterogeneity [^{I2}] = 60%), - overall 1-year **All-cause mortality** (2.3% vs 2.1%, RR 1.08, 95% CI 0.68 to 1.74, p = 0.74, heterogeneity [I^2] = 66%), - **nonfatal MI** (4.8% vs 5.3%, RR 0.99, 95% CI 0.59 to 1.65, p = 0.96, I^2 = 61%) or - **repeat revascularization** (5.5% vs 6.8%, RR 0.81, 95% CI 0.60 to 1.10, p = 0.18, I^2 = 11%).	• **40% of lesions** that are classified as angiographically significant were **reclassified as not physiologically significant** leading to reduction in Pooled avg. no. of stents in the FFR-guided arm (mean difference 0.5, 95% CI 0.8 to 0.1, p = 0.01).	• FFR-guided PCI is helpful to identify physiologically significant lesions in patients with multivessel CAD. • FFR-guided PCI leads to fewer stent placements but does not impact 1-year all-cause death, MI or repeat revascularization. Up to 40% of angiographically significant lesions can be safely deferred.	Potential Bias in one trial.
8.	Fractional Flow Reserve to Guide Treatment of Patients With Multivessel Coronary Artery Disease	Rioufol G. et al. (2021)	Journal of the American College of Cardiology	Evaluate whether a treatment strategy based on FFR was superior to a traditional strategy in the treatment of multivessel CAD	• Prospective randomized open-label superiority trial.	• The trial was stopped prematurely by the data safety and monitoring board after a safety analysis and 927 patients were enrolled. • At 1-year follow-up: - **No significant differences** in **MACEs** or cerebrovascular events rates between FFR grp. (14.6%) vs. control group (14.6%); HR: 0.97; 95% CI: 0.69-1.36; P = 0.85). - No significant difference in All-**cause mortality** in the FFR group (3.7%) versus control group 1.5%, (HR: 2.34; 95% CI: 0.97-5.18; P = 0.06). - No difference in **Cardiovascular mortality** - 2.6% in the FFR Vs. 1.1% in the control group (HR: 2.37; 95% CI: 0.83-6.76; P = 0.11). - **FFR significantly reduced the proportion of re-vascularized patients, with more patients referred to exclusively medical treatment** (P = 0.02).	• **No significant difference** between the 2 study groups in **quality-of-life** scores at 1 year (visual scale = 71+/-19 in the FFR group vs 71+/-16 in the control group; P = 0.62).	• In patients with MVD, FFR-guided strategy increased treatment by OMT alone and decreased revascularization rates but did not significantly influence clinical outcomes at 1 year. • FFR helps in deciding most appropriate revascularization strategy but does not per se influence clinical outcome.	Unclear
9.	How to guide PCI? A network meta-analysis	Pang J. et al. (2020)	Medicine	To determine whether the new techniques (FFR, iFR, IVUS, OCT) could improve the patients' mortality, major adverse cardiovascular events (MACEs) and myocaridial infarction (MI) compared to coronary angiography (CA)	• Network Meta-Analysis. • 18 Studies 10 RCTs (7822 patients), 4 prospective studies (1759 patients) and 4 retrospective studies (52,616 patients) • Total 62197 patients • Follow up – 5 Years	• **No significant difference** in reducing **all-cause mortality** among the groups. (CA, fractional flow reserve, instantaneous wave-free ratio, and optical coherence tomography showed no difference in reducing mortality.) • No significant difference in the incidence of **MACEs** among the groups Relative efficacy of CA vs. FFR 0.86 (0.57, 1.20). • IVUS-guided PCI was significantly superior to CA, but there was no significant difference among the other groups. • No significant difference **in MI** incidence among the groups.		• IVUS-guided PCI is an effective method to decrease all-cause death, MACEs.	Moderate

10.	Efficacy of Fractional Flow Reserve-Guided Percutaneous Cornary Intervention for Patients with Angina Pectoris A Network Meta-Analysis	Shinohara H. et al. (2020)	International Heart Journal	To clarify whether FFR-guided PCI improves the prognosis in patients with AP compared with non-FFR-guided PCI, CABG, and MT (medical treatment)	• Network Meta-Analysis. • 12 RCTs. • 18,093 patients • Follow up - >12 Months	• **All-cause mortality** of FFR-guided PCI was **not significantly different** from that of non-FFR-guided PCI: OR, 0.85; 95% CI, 0.53-1.4 • **No significant difference in MI** in the FFR-guided PCI group compared to non-FFR-guided PCI group (OR, 0.65; 95% CI, 0.37-1.1). • **FFR-guided PCI significantly reduced the composite endpoints** compared with non-FFR-guided PCI (OR, 0.66; 95% CI, 0.46-0.95). • **No Significant prognostic improvement with FFR**-guided PCI for AP compared with non-FFR-guided PCI, CABG, and MT. • **FFR-guided PCI may significantly reduce the composite** of all-cause mortality and myocardial infarction compared with non-FFR-guided PCI and MT.	• **No significant difference in All-cause mortality** in FFR-guided PCI group compared to non-FFR-guided PCI: OR, 0.85; 95% CI, 0.53-1.4;	• FFR-guided PCI did not show significant prognostic improvement compared with non-FFR guided PCI, CABG, and MT. • FFR-guided PCI may significantly reduce the composite of all-cause mortality and MI compared with non-FFR-guided PCI and MT.	Low
11.	Comparison between functional and intravascular imaging approaches guiding percutaneous coronary intervention: A network meta-analysis of randomized and propensity matching studies	Iannaccone M. et al, (2019)	Catheter Cardiovascular Intervention	Compare functional (FFR) vs imaging (Optical Coherence Tomography or OCT) vs standard angiography.	• Network meta-analysis • 33 Studies (16 RCTs, 17 studies were PSWMs. • CA was evaluated as control group in all the included studies (52,114 patients), FFR in 11 studies (5,484 patients), OCT in 4 studies (572 patients), and IVUS in 18 studies (10,777 patients). • Follow up – 1-3 yrs.	After 2 (1–3) years, • IVUS performed better for MACE than CA (odds ratio [OR] 0.75 0.52–0.88), whereas there was just a trend for FFR (OR 0.81, 0.64–1.02). • **FFR** (OR 0.78; 0.63–0.98) and IVUS (OR 0.75; 0.50–0.97) **reduced all-cause death** compared to CA • **FFR** (OR 0.74:0.57–0.99) and IVUS OR (0.82:0.54–0.94) but not OCT (OR 1.17; 0.03–89.23) **reduced subsequent MI** compared with CA • **FFR** (OR 1.4; 1.04–1.85) and IVUS (OR 1.49; 1.1–2.36) showed a **better performance** compared with CA regarding (Target vest revascularization) **TVR** but similar to OCT (OR 0.36 0.01–5.59)	• FFR evaluation may be at risk of false negative results due to diffuse vasoconstriction leading to higher levels of pressure distal to lesions	• The present results stress the need for a wider use of functional or imaging-driven PCI • These techniques are complementary in the management of CAD in different settings and the choice of the approach should be tailored on the patient	Potential aggregation bias or ecological fallacy in study level variables.
12.	Network meta-analysis comparing iFR versus FFR versus coronary angiography to drive coronary revascularization	Verardi R. et al. (2018)	Journal of Interventional Cardiology	To compare the efficacy and safety of iFR-guided versus FFR-guided versus CA-guided strategy.	• Network Meta-Analysis. • 8 Studies (7 RCTs. 1 propensity score adjusted observational study) • 4126 patients with FFR, 2160 with iFR, and 2214 with CA. • Follow up – 12 Months.	• Rates of **MACE and all-cause death did not differ** between iFR vs FFR (respectively OR1.04 and OR 0.86 for). • Reduction in **MI in FFR** versus CA, although **not significant** (OR 0.65 [95%CI 1.01-0.44]), • Both **FFR** and iFR **reduced** (Target vessel revascularization) **TVR** compared to CA (respectively OR 0.68 and OR 0.70). • Both **FFR** and iFR **reduced risk of subsequent MI** compared to CA (respectively OR 0.66 [95%CI 0.98-0.43] and OR 0.79 [95%CI 0.98-0.38])	• Vasodilatation test of FFR is able to establish safely which stenosis should be stented and which ones should be deferred. On the other hand, • Number of stents deployed did not differ between iFR and FFR.	• Compared to CA alone, both FFR and iFR are safe and effective in guiding coronary revascularization, reducing the number of invasive interventions without influencing MACE and all-cause-mortality at 12 months. • Both FFR and iFR-guided revascularization reduce the risk of subsequent MI at 12 months	Low

13.	Fractional flow reserve versus angiography guided percutaneous coronary intervention: An updated systematic review	Enezate et al. (2017)	Catheterization and Cardiovascular Interventions	To compare outcomes of fractional flow reserve (FFR) to angiography (ANGIO) guided percutaneous coronary intervention (PCI).	• Systematic Literature Review and Meta-Analysis • 11 Studies and 51,350 patients (7 prospective (5 RCTs and 2 non-RCTs) and 4 retrospective studies. • Follow-up: >9 Months (9-60 Months)	• FFR-PCI was associated with **lower in-hospital MACE** (OR 0.51, 95% CI: 0.37 to 0.70, P50.0001) and MACE at follow-up (OR 0.63, 95% CI: 0.47 to 0.86, P50.004, Figure 2A, B) compared with ANGIOPCI. • **Lower hospitalization MI** in FFR-PCI than ANGIO-PCI (OR 0.54, 95% CI: 0.39 to 0.75, P50.0003) and at follow-up (OR 0.53, 95% CI: 0.40 to 0.70, P50.00001) • The FFR-PCI group was associated with **lower in-hospital target lesion revascularization** (TLR) in comparison to ANGIO (OR 0.62, 95% CI: 0.40 to 0.97, P50.04) but not at follow-up (OR 0.83, 95% CI: 0.50 to 1.37, P50.46, • **No difference of in-hospital** (OR 0.58, 95% CI: 0.31 to 1.09, P 5 0.09) **or follow-up All cause mortality** (OR 0.84, 95%CI: 0.59 to 1.20, P 5 0.34)	• FFR-PCI was associated with a **lower number of PCIs (including number of stents)** performed (OR 0.04, 95% CI: 0.01 to 0.15, P50.00001) and **lower mean procedure cost** (Mean Difference 24.27, 95% CI: 26.61 to 21.92, P50.0004). • **No difference in mean procedural time** between FFR-PCI and ANGIO-PCI (Mean Difference 0.79, 95% CI: 22.41 to 3.99, P50.63, Figure 7), **or mean contrast volume** (Mean Difference 28.28, 95% CI: 224.25 to 7.68, P50.31) or **on fluoroscopy time** (Mean Difference 0.38, 95% CI: 22.54 to 3.31, P50.80)	• FFR guided PCI was associated with lower rates of MI and MACE rates, fewer unnecessary PCIs and reduced procedure cost without an increases in procedure time, contrast use or fluoroscopy time. • Further studies are needed to specify the clinical settings, lesions characteristics, and subgroups of patients who would benefit most from FFR evaluation and overcome the heterogeneity of available evidence.	Unclear

ANNEXURE III

2. Cost Implications of using FFR - Data Extraction Sheet

Sl. No.	Title	Author (First) and Year	Journal	Objective	Study Type, No. of Studies and No. of Patients included	Primary Outcomes	Secondary Outcomes	Conclusion	Risk of Bias (High, Moderate. Low)
1.	Coronary artery disease management and cost implications with fractional flow reserve guided coronary intervention in Indian patients with stable ischemic coronary artery disease	Thomson VS *et al.* 2020	Catheterization and Cardiovascular Interventions	To study the safety of stent avoidance, frequency of change in management decisions, and its cost implications while using a fractional flow reserve (FFR)-guided treatment strategy for intermediate-grade coronary artery stenosis.	• Ambispective Study • Study Period August 2013 to January 2017 • Total Patients - 5384 patients (FFR was used to guide management decisions in 400 patients with 477 lesions. • Median follow-up duration was 21 months • Lesion severity with intermediate range (50–70%). • FFR Cut off for RV ≤0.80	• **Composite primary endpoint** - Notably lower 0.9% in stent avoidance group versus 6.9% in combined stented group, with a statistically significant difference (p =.04; 95% CI: −0.10 to −0.10) • **Event-free survival** between the two groups persisted consistently until the end of the follow-up period	• **Extended MACE** - No statistically significant difference (p = .29) between the avoided and stented groups • **Adverse events related to adenosine** were minimal, • **Decision Change upon FFR:** - Stent avoidance in 30% patients - Stent reduction in 31% patients. - PCI to CABG -10% patients - CABG to PCI – 8.25% patients - No change in 20% patients • **Micro- Costing of FFR:** - Prior to Stent Cost Ceiling and Old FFR wire Cost: **Cost Saving** of INR 51,847 per patient and total cost saving of INR 15,813,379 - After Stent Cost Ceiling in 2019 and revised FFR wire cost – **Cost Savings** per patient (between INR 4,531 and INR 32,515)	FFR guidance in angioplasty brings about **changes in management decisions** in the majority of patients with SIHD resulting in stent avoidance or fewer stent implantations. The above strategy is **safe and results in significant patient-level cost savings.**	Not Clear
2.	Clinical Usefulness and Cost Effectiveness of Fractional Flow Reserve Among INDian Patients (FIND Study	Sengottuvelu *et al.* 2016	Catheterization and Cardiovascular Interventions	To study the clinical usefulness, cost benefit, and medium term outcome of fractional flow reserve (FFR) based management of coronary artery disease of intermediate severity.	• Retrospective study • 59 patients with 81 lesions • Stenosis: 50%-70% • May 2011 to August 2013 • Follow up - 12 months (Mean 11±5 Months)	•	• **Management Decision change** by FFR - 42% • **Stent avoidance –** 39% (26 stents were avoided out of 67) in 59 patients • **Reduction in PCI** - 35.5% patients. • **CABG to PCI** - 50% (3 out of 6 patients) • **Costing:** - Prior to stent cost ceiling - Net benefit of INR 8,57,600 (USD 15,600) at the end of 1 year.	Indians with lesions of intermediate severity on conventional coronary angiogram benefit both economically and clinically when FFR is added to angiography. The benefit would be most for those with multi vessel disease.	Not Clear

COSTING OF FFR

1. SINGLE AND MULTIVESSEL DISEASE PREVELANCE (From the Literature)

Assumptions	
Total Patient with Intermediate Stenosis	100
Patients with Single Stenosis (Prevalence of Single Vessel Disease = 70%)	70
Patients with multi-vessel Stenosis (Prevalence of Multi-Vessel Disease = 30%)	30
Average No. of Intermediate Stenosis in Multivessel Case	2

2. STENT UTILIZATION

Single Vessel CAD				
Decisions Based upon FFR	Fraction of Single Vessel Stenosis Avoided/ Reduced/ No Change	No. of Patients	No. of Stents utilized	No. of stents saved
Avoided	30% of 70 Patients	21	0	21
No Change	70% of 70 Patients	49	49	0
Total		70	49	21
Total Stents Utilized				
Total Stents without FFR		70	70 (1 stent per patient)	
Stents placed with FFR			49	

Multi-Vessel CAD				
Decisions Based Upon FFR	Fraction of Single Vessel Stenosis Avoided/ Reduced/ No Change	No. of Patients	No. of Stents utilized	No. of stents saved (Average 2 Stenosis Per Patient)
Avoided	30% of 30 Patients	9	0	18
Reduced	30% of 30 Patients	9	9	9
No Change	40% of 30 Patients	12	24	0
Total		30	33	27
Total Stents Utilized				
Total Stents without FFR		30	60 (2 stents per patient)	
Stents placed with FFR			33	

3. COST CONSIDERATIONS (From the Literature and Expert opinion)

Component	Costs
Stent Cost	38265
FFR Cost (Sterilized and Reused on average of 2 Patients)	40000
Medicine with FFR (Adenosine)	600
Post Stenting Medicine (DAPT)	1200

4. COST CALCULATION

i. Without FFR

Total Number of Stents without FFR	70 stents in 70 patients with Single Stenosis + 60 Stents in 30 Patients with multiple Stenosis (average 2 stents per patient)	= (70+60) =130
Total Cost Without FFR	**Total Number of Stents * (Cost of Stent + Post Stenting Medication)**	= 130 * (38265 + 1200) **= 5130450**

ii. With FFR

Total Number of Stents with FFR	Total Number of Stents Without FFR – (Total Stents Saved With FFR in single vessel stenosis + Total Stents Saved With FFR in Multi-vessel Stenosis)	= 130 – (21+27) = 82
Total Cost with FFR		
1. Scenario 1: Upon Reusing FFR Wire Twice After Sterilization (FFR Wire Cost = 40000/2)	**{Total patients *(FFR Charges + Adenosine Cost)} + (Total Stent Deployed with FFR * (Stent charges + Post Stenting Medication)}**	**= {**100 * (**20000**+600)} + (82 (38265+1200)} **= 5296130**
2. Scenario 2: FFR wire used only once (FFR Wire Cost = 40000)	**{Total patients *(FFR Charges + Adenosine Cost)} + (Total Stent Deployed with FFR * (Stent charges + Post Stenting Medication)}**	**= {**100 (**40000**+600)} + (82 (38265+1200)} **= 7296130**

<u>Conclusion:</u>

1. Total Cost without using FFR was calculated to be INR 5296130 in scenario 1 when FFR wire is used used on tw patients after sterilization and INR 7296130 in scenario 2 when FFR wire was used in single patient against total cost incurred without using FFR i.e. INR 5130450, hence FFR was not a cost saving strategy in both the scenarios.
2. FFR could potentially be cost saving when FFR Wire Cost will be below INR 17000 (For single use) Or below Rs. 34000 for Double Use following Sterilization).