DECLARATION

I, Dr Srinivasa Prasad, hereby declare that the project in this book was undertaken by me under the supervision of the faculty, Department of Cardiology, Sree Chitra Tirunal Institute for Medical Sciences and Technology.

Thiruvananthapuram
Date
Dr Srinivasa Prasad
DM Trainee

Forwarded

The candidate, Dr. Srinivasa Prasad, has carried out the minimum required project.

Thiruvananthapuram
Date
Prof. Dr Ajitkumar VK
Head of Department of Cardiology
Clinical Outcomes of patients with coronary artery disease who underwent FFR evaluation of intermediate coronary lesionS– COFFRS Study

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ACKNOWLEDGEMENT

At the outset I would like to thank my mentor, guide - Prof Harikrishnan S, to whom I am greatly indebted to, for his immense support, encouragement and inspiring attitude – not only for this project, but for many more projects, presentations and cath lab learning throughout my DM period.

I deeply thank Dr Sanjay G, for allowing me to pursue this project (originally his brainchild project) and for his constant guidance, valuable inputs and motivation throughout this project.

Special thanks to my co-guide -Dr Abhilash SP for his valuable suggestions.

My sincere thanks to technical staff of SCTIMST for their extreme co-operation and support.

Finally I express my gratitude to all my patients, and all those who directly and indirectly helped me do this study.

Srinivasa Prasad
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Abbreviations & Acronyms
**Abbreviations and Acronyms:**

- ACS: Acute Coronary Syndrome
- CABG: Coronary artery bypass graft
- CAD: Coronary artery disease
- COURAGE Trial: Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation (COURAGE) trial
- DEFER Trial: Measurement of fractional flow reserve to assess the functional severity of coronary-artery stenoses – DEFER Trial
- DS: Percent diameter stenosis
- ECG: Electrocardiogram
- FAME 2 Trial: Fractional flow reserve versus angiography for guidance of PCI in patients with multivessel coronary artery disease (FAME)
- FFR: Fractional Flow Reserve
- LVF: Left ventricular failure
- MACE: Major adverse cardiac events
- MLD: Minimum luminal diameter
- Non-STE-ACS: Non ST elevated acute coronary syndrome
- NSTEMI: Non-ST elevated myocardial infarction
- PCI: Percutaneous coronary interventions
- QCA: Quantitative Coronary Angiography
RD: Reference diameter,

STEMI: ST elevated myocardial infarction

TVR: Target vessel revascularization

UA: Unstable angina
Introduction
Invasive coronary angiography is known for its precision in delineating topographical anatomy of lumen of epicardial coronary arteries, but lacks the ability to determine the functional significance of coronary stenoses. Functional severity of coronary narrowing has been determined to be the most prominent prognostic factor among the individuals with documented coronary artery disease(1). Hence, combined assessment of anatomy and functional information with high accuracy would help in guiding the treatment strategy for patients with known or suspected coronary artery disease, particularly those with intermediate degree of stenosis(2).

Fractional Flow Reserve (FFR) is an invasive but ‘easy and simple to measure’ index of the functional significance of severity of coronary stenosis with a diagnostic precision of myocardial scintigraphy, albeit with a better spatial resolution(2). It is derived from the ratio between coronary (distal to stenosis) and aortic pressure measurements during maximal hyperemia(3). Hence FFR in combination with conventional angiography is rapidly emerging as an accurate approach of combining anatomy and physiology(4).

Role of FFR in determining the need for coronary stenting has been studied in various trials and has been recommended to assess the significance of intermediate coronary lesions.(2,3,5–7). FFR has been demonstrated to be an
useful index in patients referred for percutaneous revascularisation with intermediate stenosis, involving single coronary vessel (2,3,7,8) and also in those with multi-vessel disease(5,9). Additional concerns regarding the association between drug-eluting stents and late complications, continued exposure to dual anti-platelet therapy, and increased costs make appropriate use of these devices critical(10). This leaves FFR as a better choice to assess hemodynamic significance of intermediate lesion and to guide treatment strategy.

Clinical outcomes of the decision to intervene based on FFR has been addressed in various trials, being conducted in controlled environment (7,11–14). Availability of such data from routine clinical practice is limited(15). In India, routine clinical use of FFR is more or less limited to tertiary care centres and its utilization is probably confined to a small group of patients with CAD. Demographic, risk profile and natural history of coronary artery disease among Indian/ Asian patients are affected by some unique factors such as younger age group, predominant metabolic syndrome, exposure to lipid-rich diet and increasingly common sedentary life style(16–18) and there is data which discuss about smaller coronary artery diameters in Indian patients undergoing angiography(19). There is no data regarding the utility of FFR from India.
In this study, we intended to assess the clinical outcome of FFR based management strategies in Indian patients, results of which could serve to validate and re-emphasize the utility of this investigation in our setting.
Aims and Objectives
This study aims to evaluate the utility of FFR in those stable ischemic heart disease patients with intermediate coronary disease with the following objectives:

1. To study the clinical outcomes among the patients who underwent FFR as part of the evaluation of their coronary stenosis

2. To compare the outcomes among patients who underwent revascularisation versus those kept under medical follow up based on FFR assessment.
Materials and Methods
**Study Design**

This is a retrospective study (approved by the Institutional Ethics Committee, No: - SCT/IEC/778/ JUNE 2015) was conducted between June 2010 to June 2015 at Sree Chitra Tirunal Institute for Medical Sciences and Technology (SCTIMST), Trivandrum, a tertiary care hospital in India.

**Study Patients:**

Medical records of all patients who underwent FFR during the period between June 2010 to June 2015 were reviewed. All patients with stable ischemic heart disease or those patients who had acute coronary event a week or more prior to the procedure were included.

Study population were grouped into 3 groups:

- **Group 1** – FFR >0.8 and kept on medical followup;
- **Group 2** – FFR \(\leq 0.8\) and underwent revascularization by PCI or CABG; and
- **Group 3** – FFR \(\leq 0.8\) and did not undergo revascularisation as per patient preference.
**Exclusion criteria:**

1) Culprit Coronary vessel responsible for acute coronary syndrome within 7 days. (However if the FFR was studied in non-culprit coronary arteries in the same patient it was included)

2) Left Main Coronary artery lesion

3) Previous CABG

4) Contraindication to adenosine,

5) Conditions for which FFR has not been validated (tortuous coronary arteries, left ventricular hypertrophy)

6) Life-threatening comorbidity.

7) FFR assessment of a stenosis in a coronary artery supplying collaterals to the vascular bed subtended by a totally occluded artery.

**Coronary pressure measurement and calculation of FFR:**

FFR was measured in all intermediate stenoses for assessment of hemodynamic significance. Intracoronary pressure measurements were performed with a 0.014-inch pressure guidewire (PressureWire Aeris from St. Jude Medical or Prime wire PRESTIGE from Volcano Inc, Rancho Cordova, California, USA) introduced through a guide catheter. Hyperemia was induced by intravenous adenosine (140 μg/kg/min until a steady state was obtained or for at least 6 minutes) after a bolus dose of intracoronary nitroglycerin of
200 micrograms. The FFR was calculated from the ratio of mean hyperemic distal coronary pressure measured by the pressure-wire and the mean aortic pressure obtained by the coronary guide catheter. (RADIANALYZER, St Jude Medical OR VOLCANO, Volcano Corporation). As per the departmental protocol, FFR value of >0.80 was considered as a criteria to defer revascularisation at the time of procedure and the decision to revascularise was based on the cut-off value of FFR ≤ 0.80. If there were serial stenotic lesions, pressure gradient drop of > 10 mmHg was considered significant. All patients had received antiplatelets, statins and beta blockers. Those who underwent revascularization received aspirin and clopidogrel for at least 12 months after the procedure.

**Quantitative coronary arteriography:**

Angiograms were reviewed by two independent investigators to determine the severity. Quantitative assessment of lesions (QCA – Quantitative Coronary Angiography) was done using a validated software employing Siemens/Philips algorithm. Reference diameter (RD), minimum luminal diameter (MLD), and percent diameter stenosis (DS) were assessed in two orthogonal views.
**Follow-up and clinical events:**

All patients were evaluated at the outpatient intervention clinic for drug compliance, new / persistent/ worsening symptoms, ECG changes & any MACE events including repeat coronary angiogram and coronary revascularisation, if done.

**Primary end point**

The primary endpoint during the follow-up was major adverse cardiac events (MACE), defined as composite of cardiovascular death, non-fatal acute coronary syndrome, and any repeat revascularization of the vessel in which FFR was studied (target vessel revascularization – TVR). A repeat angiogram was performed only when indicated clinically. The culprit artery responsible for the recurrence of symptoms was based on the correlation of electrocardiographic changes, echocardiographic data (if available), and the diagnostic angiogram.

**Secondary end point**

The secondary endpoints were individual components of the MACE. Myocardial infarction was defined as (two out of three criteria): prolonged chest pain > 20 min; levels of serum creatine kinase (or the MB fraction) or troponin over two-fold higher than the upper normal limit; and ST-T segment changes or new Q waves on serial electrocardiogram indicative of myocardial
damage(20).

**Statistical analysis:**

The data was analysed with commercially available statistical software (SPSS) to study the percentage of patients who had clinical event, MACE, repeat angiogram and revascularization – PCI/CABG.

Continuous variables are expressed as mean with standard deviations and discrete variables as counts and percentage. For categorical variables, chi-square test and Fisher exact t test were used, and for continuous variables, student t test was used. Clinical, angiographic variables and FFR values between the deferred, revascularised and nonrevascularised groups were compared. Survival curves were determined by Kaplan and Meier method and compared by the log-rank test. A p value less than or equal to 0.05 was considered statistically significant.
Review of Literature
Several investigators have reported discrepancies between the severity of coronary angiographic stenosis and the severity of functional coronary stenosis. Lima et al. (21) showed that 54% (77 of 143) patients with angiographic 3-vessel disease, had either had no perfusion defect or a single vessel disease pattern on myocardial perfusion imaging. Similarly, Melikian et al. (22), found that 26 of 67 patients with angiographic multivessel disease had no perfusion defects and 24 had single perfusion defect by myocardial perfusion imaging performed after coronary angiography.

Visual – functional mismatch analysis was done from the landmark trial – FAME study (12), revealed that of 14% had significant three vessel disease on FFR assessment, among those who were labeled as having 3 vessel disease based on visual assessment and 46% had 2 or more coronary artery involvement with significant FFR of ≤0.80. And a significant 9% did not have any physiologically significant coronary lesions. Also only 61% (816 of 1329) target lesions (visually estimated to have >50% stenosis), had FFR ≤0.80. On further analysis, FFR was >0.80 in 65% of the lesions assessed as 50 to 70% stenosis severity, 20% among those estimated to have 71 to 90% stenosis and 4% among those with 91 to 99% severity.

These observations, highlighted that significant 40% of revascularization
procedures were uncalled for, more so without a physiological assessment by FFR. Also a considerable proportion would have benefitted by percutaneous revascularization, rather than undergoing coronary bypass graft surgery. Hence, it is recommended to have a physiological or functional assessment by FFR in those coronary lesions of intermediate stenosis severity during revascularization procedure, particularly when noninvasive tests are not available.

Several factors are implicated for the dissociation between angiographic and FFR severity. These include length of lesion, size of the reference vessel, and eccentricity of the lesion – all of which would affect resistance to the coronary blood flow and thereby yield an abnormal FFR. Myocardial area or mass being supplied by diseased coronary vessel is the major determinant of the functional significance of the given stenotic lesion. Thus, when an intermediate lesion of a coronary vessel that supply large myocardial territory could be functionally significant, wherein a lesion of severe stenosis, catering to small myocardial territory could be insignificant physiologically.

DEFER Study (“FFR to Determine Appropriateness of Angioplasty in Moderate Coronary Stenoses”) (7), the only randomized trial till date, addressed the issue of tailoring the management strategy comparing percutaneous revascularization with medical therapy in those with intermediate coronary stenosis. Study randomly assigned its 325 subjects with intermediate coronary
lesions into 3 groups: 1. Deferral group (n = 91, FFR was ≥0.75 , all were treated with optimal medical therapy), 2. PCI group (n = 90, FFR was ≥0.75 , and all these patients underwent PCI with stent implantation along with optimal medical therapy) and 3. Reference group (n = 144, FFR was <0.75, all underwent PCI as planned). On 5 year followup, it was noted that event-free survival were similar among deferred and PCI groups (80% versus 73%, P=0.52). The composite endpoints of cardiac cause of mortality and acute myocardial infarction were 3.3% in deferred group, 7.9% in PCI group, and 15.7% in the reference group , thereby yielding <1% annual risk of cardiac mortality or MI in those with normal FFR. Thus this study showed that functionally non-significant coronary lesion, can be managed safely with optimal medical therapy, deferring the PCI, regardless of angiographic stenosis, for a period of upto 5 years.

FAME study (“The Fractional Flow Reserve versus Angiography for Multivessel Evaluation (FAME) study ”)(12) pointed out the cost effectiveness of FFR-based revascularization strategy over one year of followup, with significantly low rate of composite endpoints of death, non-fatal myocardial infarction, and repeat revascularization.

A study by Alexandre Berger,et al(23) studied the outcome of patients with multivessel CAD (n = 102), who were grouped into those who underwent
PCI for at least one vessel based on FFR of $< 0.75$ (113 vessels), and those who were deferred revascularisation for at least one vessel based on FFR value of $\geq 0.75$. They found no significant difference in clinical cardiac events of new onset angina, MI, or target vessel revascularisation, between the two groups over a period of 3 years (MACE rate of 13%). Study did not have any mortality event. Authors conclusively showed the safety of deferring the PCI of functionally nonsignificant stenosis, and proceeding only with functionally significant stenosis in patients with multivessel disease, even if planned for multivessel PCI based on angiographic severity.

A retrospective study (24) of real life clinical patients from Mayo clinic, compared clinical outcomes of patients who underwent angiography guided PCI ($n = 6268$), FFR guided PCI ($n = 369$) and FFR based defer group ($n = 721$). Over a follow-up period of 7 years, MACE event rates were 57% in angiographic guided PCI group and 50% in those with FFR guided PCI group, ($p = 0.016$ between the groups); with lower rate of death or MI in FFR guided PCI group in comparison to angiographic guided group (Hazard Ratio 0.85, 95% confidence interval : 0.71 to 1.01, $p = 0.06$). Also, lower rate of MI was noted in the FFR-guided deferred-PCI group independently. (Hazard Ratio : 0.46, 95% Confidence Interval : 0.26–0.82, $P = 0.008$).

Study by Takafumi Yamane et al (25), compared clinical outcome
between patients with intermediate coronary lesion and FFR <0.75 who underwent PCI (n = 99) and patients with intermediate CAD and FFR between 0.75 and 0.79 who were kept on optimal medical therapy (n = 26). Kaplan meier survival analysis revealed that over a period of 82 months, there was poorer event-free survival of the patients with FFR between 0.75 to 0.79 and kept on medical therapy (p=0.0148). Study concluded and proposed to consider FFR cutoff of 0.80 among intermediate coronary lesions for deferring PCI.

Two-year clinical outcome study of patients with deferred lesions in the FFR-guided group from the FAME study(26) demonstrated that only 0.2% (1 of 513) had MI and only 3.2% (16 of 513) needed repeat revascularization.

Other smaller studies(27–32) also have consistently shown lower rates of death and MI in patients with FFR guided deferred treatment of intermediate coronary lesions.
Observations and Results
Observation and Results

Two hundred and eighty two patients with intermediate coronary lesions, (as assessed by quantitative coronary angiography), who underwent FFR to assess the functional severity of the lesion were included in the study. 239 of them were males (male : female ratio  4.6 : 1). Median age was 57 years (range = 28–78). 151 patients (53.3%) were diabetic, 117 (41.4%) were hypertensive and 157 (55.6%) patients used tobacco (all were males). Pre-angiography stress test result was available in 196 patients, of whom 94 (48%) tested positive for inducible ischemia, 74 (37.6%) had inconclusive test results and 28 (14.3%) had negative result but were advised coronary angiogram for assessment of their symptoms. The remaining 85 patients (30.2%) underwent coronary angiography without stress testing based on their clinical presentation.

Coronary angiogram revealed single vessel disease (SVD) in 68 (24.1%) , double vessel disease (DVD) in 122 (43.3%) and three vessel disease (TVD) in 92 (32.6%). 192 (68.1%) of patients had positive FFR value (FFR ≤ 0.8) with a mean FFR of 0.7 among these patients.

90 patients (31.9%) were in Group 1, 175 patients (62.1%) in group 2 (PCI in 141 & CABG in 29) and 17 (6%) in group 3. The baseline characteristics of each group are listed in table 1.
### TABLE 1: Profile of patients in the three groups

<table>
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<tr>
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<th>FFR &gt; 0.8</th>
<th>FFR ≤ 0.8</th>
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<tbody>
<tr>
<td></td>
<td>Group I Medial</td>
<td>Group II Revascularized</td>
</tr>
<tr>
<td><strong>Total Number</strong></td>
<td>90</td>
<td>144</td>
</tr>
<tr>
<td><strong>Number on follow up</strong></td>
<td>89 (98.8%)</td>
<td>144(100%)</td>
</tr>
<tr>
<td><strong>Mean Age (years)</strong></td>
<td>57.7</td>
<td>57.9</td>
</tr>
<tr>
<td><strong>Male (%)</strong></td>
<td>77</td>
<td>81</td>
</tr>
<tr>
<td><strong>Diabetes</strong></td>
<td>43 (47.7%)</td>
<td>78 (54.2%)</td>
</tr>
<tr>
<td><strong>Hypertension</strong></td>
<td>11 (12.2%)</td>
<td>82 (56.9%)</td>
</tr>
<tr>
<td><strong>Smoking</strong></td>
<td>6 (6.6%)</td>
<td>113 (78.4%)</td>
</tr>
<tr>
<td><strong>Dyslipidemia</strong></td>
<td>4 (4.4%)</td>
<td>48 (33.3%)</td>
</tr>
<tr>
<td><strong>Family history of CAD</strong></td>
<td>1 (1.1%)</td>
<td>29 (20.1%)</td>
</tr>
<tr>
<td><strong>≥ 2 CAD risk factors (%)</strong></td>
<td>11 (12.2%)</td>
<td>92 (63.9%)</td>
</tr>
<tr>
<td><strong>NYHA III / IV at presentation (%)</strong></td>
<td>7 (7.7%)</td>
<td>19 (13.2%)</td>
</tr>
<tr>
<td><strong>Stable IHD</strong></td>
<td>78 (86.6%)</td>
<td>124 (86.1%)</td>
</tr>
<tr>
<td><strong>Recent ACS</strong></td>
<td>12 (13.7%)</td>
<td>20 (13.9%)</td>
</tr>
<tr>
<td><strong>Mean EF %</strong></td>
<td>63.5%</td>
<td>61%</td>
</tr>
<tr>
<td><strong>SVD</strong></td>
<td>43 (47.8%)</td>
<td>25 (17.4%)</td>
</tr>
<tr>
<td><strong>DVD</strong></td>
<td>30 (33.3%)</td>
<td>70 (48.6%)</td>
</tr>
<tr>
<td><strong>TVD</strong></td>
<td>17 (18.9%)</td>
<td>49 (34.0%)</td>
</tr>
<tr>
<td><strong>Prox LAD &gt;50% (%)</strong></td>
<td>78 (86.7%)</td>
<td>138 (95.8%)</td>
</tr>
<tr>
<td><strong>Mean minimum stenosis diameter (mm)</strong></td>
<td>1.58</td>
<td>1.02</td>
</tr>
<tr>
<td><strong>Mean FFR</strong></td>
<td>0.91</td>
<td>0.68</td>
</tr>
<tr>
<td><strong>Median follow up (months)</strong></td>
<td>21.7 (6 to 56)</td>
<td>18 (5 to 50)</td>
</tr>
<tr>
<td><strong>MACE</strong></td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td><strong>Medications at last followup #</strong></td>
<td>Aspirin 89 (100%)</td>
<td>144 (100%)</td>
</tr>
<tr>
<td></td>
<td>Clopidogrel 15 (16.9%)</td>
<td>138 (95.8%)</td>
</tr>
<tr>
<td></td>
<td>Statins 76 (85.4%)</td>
<td>142 (98.6%)</td>
</tr>
<tr>
<td></td>
<td>Nitrates 04 (4.5%)</td>
<td>11 (7.6%)</td>
</tr>
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SVD = Single vessel disease, DVD = Double vessel disease, TVD = triple vessel disease. ACS = Acute coronary syndrome. Prox LAD = proximal left anterior descending artery, NYHA = New York Heart Association. CAD = Coronary artery disease. * includes patients at least a week after ACS. # Percentages calculated for patients available for followup. Percentages calculated for each group
All non-ACS patients with intermediate coronary lesions assessed by FFR

FFR > 0.8

n=89

FFR ≤ 0.8

n=192

OMT n=89

Underwent PCI / CABG

n=175

PCI 144; CABG 31

CV mortality n=0

Non fatal ACS n=4

Urgent revascularization n=0

Not willing for revascularization n=17

CV mortality n=3

Non fatal ACS n=4

Urgent revascularization n=1
Observation and Results

Table 2: MACE in the three groups

<table>
<thead>
<tr>
<th></th>
<th>Group I (n=89)</th>
<th>Group II PCI / CABG (n=175)</th>
<th>Group III (n=17)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MACE</td>
<td>3</td>
<td>4</td>
<td>7</td>
</tr>
<tr>
<td>% of MACE</td>
<td>3.41</td>
<td>2.28</td>
<td>41.17</td>
</tr>
<tr>
<td>CV Death</td>
<td></td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Nonfatal ACS</td>
<td>2</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>Urgent Revascularisation</td>
<td></td>
<td>1</td>
<td></td>
</tr>
</tbody>
</table>

Group I = FFR >0.8, Group II = FFR ≤0.8 and underwent revascularization, Group III = FFR ≤0.8 and did not agree for revascularisation

281 (99.6%) patients had regular follow up in our interventional clinic at 3 weeks, 3 months, 6 months, 1 year after the procedure and thereafter yearly. One patient was lost to followup in group 1. Mean follow up of patients was 17.9 months.

Three patients (3.4%) in Group 1 had MACE (1 STEMI who underwent primary PCI, 2 Unstable angina – one of them underwent elective revascularisation. 4 patients (2.3%) in Group 2 patients had admissions for Non-STE-ACS (2 – UA, 2 NSTEMI). 7 patients (41.17%) in Group 3 had MACE (3 death with acute LVF, 2 NSTEMI, 2 STEMI – of whom 1 needed urgent revascularisation following an STEMI (rescue PCI involving FFR assessed vessel), other was lysed, and later on underwent PCI electively involving non-FFR assessed vessel. MACE rates were low and were not significantly different in group 1 and group 2 (p=0.73).
Event–free survival analysis over the followup period by Kaplan–meier method showed no statistically significant difference (p=0.73) between the medical group (group 1) and revascularised group (group 2). Since non-revascularised group (group 3) was underpowered, statistical significance of event free survival of this group in comparison with other groups was not considered.

Figure: Kaplan Meier Curve showing event free survival
Discussion
Discussion

In this study, we compared the clinical outcomes of a FFR assessment based coronary revascularisation. The strategy of medical management of stenoses with FFR > 0.80 and treating only stenoses that are hemodynamically significant (≤ 0.8) with revascularization appears safe as evidenced by the similar MACE rates. Those patients who had coronary stenoses with FFR < 0.80 and refused to undergo revascularisation had higher MACE rates of 41.17%. Thus the results of the present study extend the usefulness of FFR in clinical decision making in Indian patients with intermediate single or multivessel disease.

In our observational study, we found a higher prevalence of patients with positive FFR (68.1%). In the DEFER study, where enrollment was based primarily on angiographic assessment of patients with negative stress test or without a stress test, the prevalence of positive FFR was about 55%.(3) However, in the all-comers FAME-2 study, which included consecutive patients who underwent angiography for their symptoms and were found to have at least 50% stenosis in coronary angiogram, 72% of the 1220 patients who were eligible were found to have FFR < 0.8. This is similar to what was found in our study, where the patients underwent angiogram for clinical indications, with about 60% of the entire study population having had a positive
or inconclusive stress test prior to angiography. The angiographic severity of the lesion was assessed using quantitative coronary angiography (QCA) algorithms, and it has been reported that QCA algorithms often yield lesser stenotic severity when compared to visual assessment (20). This too would have contributed to higher FFR positivity rates, unlike studies which mainly employed visual assessment for severity estimation of lesions.

The clinical outcomes in patients who were kept on medical management after negative FFR result were comparable to other studies. In DEFER trial (3,7), which randomised patients with FFR ≥ 0.75 into deferred group and PCI group showed that the 5-year event-free survival rates were statistically comparable among both groups (80% versus 73%, P=0.52). Among the deferred and PCI groups, composite rates of cardiac death and acute myocardial infarction were 3.3% and 7.9% respectively. Therefore, the annual risk of cardiac death or myocardial infarction in patients with normal FFR was <1%. The study demonstrated that functionally nonsignificant coronary stenosis could be safely deferred for up to 5 years, regardless of angiographic stenosis. Among the patients who had FFR > 0.8 in the FAME-2 study (registry group), the occurrence of MACE was 3% over one year (12,13,33,34). Many other smaller studies (26–32) similarly have demonstrated consistently low rates of death and myocardial infarction in patients with deferred treatment of lesions.
Those patients who were advised revascularization based on the FFR values and underwent the procedure in our study (group 2) had MACE rate of 2.3 % over 18 months. In the FAME-2 trial, the MACE rate was 4.3% at one year in patients who underwent PCI. Our patients were younger (mean age of 56.3 years vs 63.5 years in FAME 2) and had fewer acute coronary events before angiography (12% vs 37%). The definition of MACE in our study (cardiovascular death, non fatal ACS, target vessel revascularization) and in FAME 2 (any death, non fatal MI, any repeat revascularization ) was also different. While the mode of revascularization was only PCI in FAME 2, our patients underwent either PCI or CABG. These factors along with the shorter duration of follow up might have contributed to the apparent difference in the primary end point rates between the two studies.

There was remarkable difference in the MACE rates between patients who underwent revascularization and those who refused it initially (2.3% vs 41.17%) in our study than what was reported in the FAME 2 trial (4.3 % in the PCI group vs 12.7 % in the group with FFR $\leq$0.8 randomized to medical management). This appears to be driven by a high rate of events in the group of patients who refused revascularization initially in our study. The higher event rates could be explained by higher risk profile (Diabetes 41.2% – vs 25%) , more patients with extensive coronary involvement (Multivessel disease 100%
vs 22.3%), more symptomatic patients (NYHA FC III/ IV symptoms 41.2% vs 22.5%) in our study compared to FAME 2 trial.

To the best of our knowledge, this is the first Indian study of its nature. Despite the differences in clinical profile of patients when compared with those in randomised clinical trials, the data from this study which reflects real-world practice, helps in reassuring the utility of FFR-based clinical decisions in patients with CAD in this part of the world.

**Limitations:**

The study, being a retrospective and non-randomised one, limits comparison of competing strategies. The smaller sample size in the third group might have inflated the event rates.
Among patients with intermediate coronary artery disease having at least one stenosis with a FFR of \( \leq 0.80 \), FFR-guided PCI with drug eluting stents or CABG plus medical therapy, as compared with the patients with FFR of > 0.8 on medical therapy alone, had a similar rates of mortality, MI and need for urgent revascularization.

This study also highlights the importance of timely revascularisation in patients with ischemic FFR, as emphasized by higher MACE rate of 41% among the patients with FFR of 0.80 or less but did not undergo revascularisation.

Thus, we conclude that FFR based clinical decisions in the management of patients with coronary artery disease is safe.


25. Yamane T. Long-Term Follow-Up After Deferral of Percutaneous
Bibliography


27. Oud N, Marques KM, Bronzwaer JGF, Brinckman S, Allaart CP, de Cock CC, et al. Patients with coronary stenosis and a fractional flow reserve of ≥0.75 measured in daily practice at the VU University Medical Center. Neth Heart J]. 2010 Sep];18(9):402–7.


34. Van Nunen LX, Zimmermann FM, Tonino PAL, Barbato E, Baumbach
THESIS PROFORMA

NAME: Willing to participate in study :
Yes/ No

AGE / SEX: Informed Consent Obtained :
Yes/ No

HOSP NO:

Address:

Telephone No: 1. 2.

Diagnosis:

Relevant Details:

Case History Review:

Duration of Stable angina

Functional Class

Previous ACS

Previous CABG

Severe Valvular heart disease

Airway reactive disease

Renal Dysfunction

Other Major comorbidities

ECG:

ST – T changes: ST elevation/ ST depression/ T inversion/ T flat / T biphasic

Anterior / Lateral / Septal / Inferior

Q waves: Present / Absent,

if present : Anterior / Lateral / Septal / Inferior
ECHO:

RWMA: Anterior / Lateral / Septal / Inferior

Severe Valvular Heart disease

CAG Findings:

Date of procedure:

SVD/ DVD/ TVD

Left Main involvement : Yes/ No

Coronary lesions assessed:

<table>
<thead>
<tr>
<th></th>
<th>Visual assessment of Severity*</th>
<th>FFR (Findings)</th>
<th>IVUS/ OCT# (Findings)</th>
<th>Decision (PCI/ OMT)</th>
<th>Comments</th>
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<td>3</td>
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</tbody>
</table>

* Visual assessment of severity would be reviewed by 2 cardiologists
# if used for same vessel/ lesion
FOLLOW UP REVIEW

Date of Review:  

Procedure to review duration: _______ months

Death: Yes / No

If Yes, Date and time:

Cause: cardiac / Noncardiac

Details of cause of death

Myocardial Infarction: Yes/ No  Date and Time:

ECG: STEMI / NSTEMI

Details:

Cardiac Biomarker: Elevated/ Not elevated

Details:

Serial Levels:

<table>
<thead>
<tr>
<th>Date &amp; Time</th>
<th>Biomaker</th>
<th>Value</th>
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</table>

Repeat coronary angiogram/ revascularisation of study vessel

Date of procedure:

Revascularization: Done / Not needed

CAG Details:
CONSENT

Study on clinical outcomes in patients who underwent FFR study in borderline coronary lesions among stable angina patients is an observational study to assess the predictive role of FFR on subsequent clinical outcome in patients with chronic stable angina. This study aims to study the natural history of chronic stable angina patients who undergo FFR study for decision of revascularisation and correlate it to long term outcomes in patients with structural heart disease. The doctor performing the study has explained to me in detail about the scientific basis of this study. He has also explained to me about my role as a subject in the study. The doctor also explained that there is no risk involved as this is an observational study.

I realize that I am participating in a scientific study which I agree to after realizing the issues involved. I realize that there will be no differences in my treatment and it will not increase the cost of management of my disease if I participate in this study. I am voluntarily participating in this study and I am aware of the right to refuse the consent for participating in this study at any juncture. The doctor has assured me that my personal identity will be protected during the study.

I realize that I may not have any direct benefits from participating in this study. However the information collected during this study may be useful for other patients in future who will require management of arrhythmias in future. Being aware of the above mentioned facts, I agree to participate in this study.

Signature of patient/relative:

Name of patient:

Date:

Signature of doctor:

Name of doctor:

Date:

Contact address: Dr Srinivasa Prasad
SR, Dept of Cardiology
SCTIMST, Trivandrum
പ്രാവൃത്തികൾ

കൊടുക്കിയിരിക്കുന്ന സാങ്കേതിക പ്രധാനമാണ് താമസം നിർമ്മാണം. അതിനെ പ്രതിപാദിക്കാനുള്ള പ്രധാനമാണ് കൂടുതൽ സമരതയും അന്യമാണ്. കൊടും പ്രതിപാദം വഴിയും സമരം നിർമ്മാണം നടത്തിയിരിക്കുന്നതിന്റെ രീതിയിൽ അതിനെ പ്രതിപാദിക്കാനുള്ള പ്രധാനമാണ് കൂടുതൽ സമരതയും അന്യമാണ്. കൊടും പ്രതിപാദം വഴിയും സമരം നിർമ്മാണം നടത്തിയിരിക്കുന്നതിന്റെ രീതിയിൽ അതിനെ പ്രതിപാദിക്കാനുള്ള പ്രധാനമാണ് കൂടുതൽ സമരതയും അന്യമാണ്. കൊടും പ്രതിപാദം വഴിയും സമരം നിർമ്മാണം നടത്തിയിരിക്കുന്നതിന്റെ രീതിയിൽ അതിനെ പ്രതിപാദിക്കാനുള്ള പ്രധാനമാണ് കൂടുതൽ സമരതയും അന്യമാണ്.


txchvnm

kxv knabhjgdxjvñj

qmv

bhjgdxjvñj

knabhjgdxjvñj
മലയാളം രണ്ടു വിഭാഗങ്ങളാണ്, മലയാളം വിശ്വാസം വിശ്വാസം ഒന്നിച്ചാണ് മലയാളം വിശ്വാസം ഒന്നിച്ചാണ്.

മലയാളം രണ്ടു വിഭാഗങ്ങളും മലയാളം വിശ്വാസം ഒന്നിച്ചാണ്.

മലയാളം രണ്ടു വിഭാഗങ്ങളും മലയാളം വിശ്വാസം ഒന്നിച്ചാണ്.

മലയാളം രണ്ടു വിഭാഗങ്ങളും മലയാളം വിശ്വാസം ഒന്നിച്ചാണ്.

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മലയാളം രണ്ടു വിഭാഗങ്ങളും മലയാളം വിശ്വാസം ഒന്നിച്ചാണ്.
Institutional Ethics Committee
(IEC Regn No. ECR/189/Inst/KL/2013)

SCT/IEC/778/JUNE-2015

Dr. Srinivasa Prasad B.V
Senior Resident
Department of Cardiology
SCTIMST, Thiruvananthapuram

Dear Dr. Srinivasa Prasad B.V,

The Institutional Ethics Committee reviewed and discussed your application to conduct the study entitled "CLINICAL OUTCOMES IN PATIENTS WHO UNDERWENT FFR STUDY IN BORDERLINE CORONARY LESIONS AMONG STABLE ANGINA PATIENTS (IEC/778)" on 12th June, 2015.

The following documents were reviewed:

Original submission

1. Covering letter addressed to the Chairperson, IEC, SCTIMST dated 25.05.2015
2. TAC Approval Letter
3. IEC application form
4. Proposal for study
5. Proforma
6. Informed consent form in English and Malayalam
7. CVs of PI and Co-PIs

Revised submission

1. Covering letter addressed to the Chairman, IEC, SCTIMST dated 27.01.2016
2. Modified IEC Application form was submitted
3. TAC Approval letter
4. Project proposal
5. Modified Information Sheet in English and Malayalam was submitted.
6. CV of PI, and Co-PI's.
The following members of the Ethics Committee were present at the meeting held on 12th June, 2015 at G. Parthasarathi Board Room, AMCHSS, SCTIMST.

<table>
<thead>
<tr>
<th>SL. No.</th>
<th>Member Name</th>
<th>Highest Degree</th>
<th>Gender</th>
<th>Scientific /Non Scientific</th>
<th>Affiliation with Institution(s)</th>
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<tbody>
<tr>
<td>1</td>
<td>Justice Gopinathan. P.S</td>
<td>BSc. LLB</td>
<td>Male</td>
<td>Legal Expert (Chairperson)</td>
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<tr>
<td>2</td>
<td>Dr. J. M. Tharakan</td>
<td>MD</td>
<td>Male</td>
<td>Clinician (Cardiologist)</td>
<td>Yes</td>
</tr>
<tr>
<td>3</td>
<td>Shri. O.S. Neelakandan Nair</td>
<td>BE</td>
<td>Male</td>
<td>Engineer</td>
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<tr>
<td>4</td>
<td>Dr. R V G Menon</td>
<td>PhD</td>
<td>Male</td>
<td>Lay Person</td>
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<tr>
<td>5</td>
<td>Dr. Meenu Hariharan</td>
<td>DM</td>
<td>Female</td>
<td>Clinician (Gastro-Enterologist)</td>
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<tr>
<td>6</td>
<td>Dr. Rema M. N</td>
<td>MD</td>
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<td>Pharmacologist</td>
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<tr>
<td>7</td>
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<td>Female</td>
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<tr>
<td>8</td>
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<td>MD</td>
<td>Female</td>
<td>Pharmacologist</td>
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<tr>
<td>9</td>
<td>Dr. K R S Krishnan</td>
<td>ME, PhD</td>
<td>Male</td>
<td>Biomedical Scientist/Engineer (Surgeon)</td>
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<tr>
<td>10</td>
<td>Dr. K. Jayakumar</td>
<td>MS, MCh</td>
<td>Male</td>
<td>Ethicist/Social Scientist (Member Secretary)</td>
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<tr>
<td>11</td>
<td>Dr. Mala Ramanathan</td>
<td>MSc, PhD, MA</td>
<td>Female</td>
<td>Ethicist/Social Scientist (Member Secretary)</td>
<td>Yes</td>
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</tbody>
</table>

IEC Decision

The IEC approved the conduct of the study in the present form.

Remarks:

The Institutional Ethics Committee expects to be informed about the progress of the study, any SAE occurring in the course of the study, any changes in the protocol and patient information/informed consent and asks to be provided a copy of the final report.

There was no member of the study team who participated in voting / decision making process. The ethics committee is organized and operated according to the requirements of Good Clinical Practice and the requirements of the Indian Council of Medical Research (ICMR).

Sincerely,

Mala Ramanathan
Member Secretary, IEC