



## Original Article

# Clinical Outcomes of patients with coronary artery disease who underwent FFR evaluation of intermediate coronary lesionS– COFFRS study



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## ARTICLE INFO

## Article history:

Received 12 March 2016  
Accepted 12 December 2016  
Available online 29 December 2016

## Keywords:

Fractional flow reserve  
Clinical outcome  
Indian  
Coronary

## ABSTRACT

**Background:** We undertook this study to validate the impact of FFR-guided coronary interventions among Indian patients, which is not readily available as of date. Our patients differ from their western counterparts, both in terms of risk profile (younger, more metabolic syndrome, lipid rich diet) as well as their coronary size.

**Methods:** We retrospectively evaluated 282 patients with intermediate stenosis in their coronary arteries, who underwent FFR to assess the functional severity of the lesion. There were 3 groups: Group 1–FFR > 0.8 and kept on medical follow-up; Group 2–FFR ≤ 0.8 and underwent revascularisation; and Group 3–FFR ≤ 0.8 and refused to undergo revascularization. 281(99.6%) patients had regular follow-up in our clinic.

**Results:** Median age–57 years (range = 28–78). Males = 230, 90 patients were in Group 1, 175 in group 2 (PCI in 144 & CABG in 31) and 17 in group 3. Median follow-up of patients was 17.9 months (2 to 56 months). Three patients(3.4%) in Group 1 had MACE (1 STEMI, 2 UA); 4 patients (2.3%) in Group 2 had Non-STE-ACS; 7 patients (41%) in Group 3 had MACE (3 deaths with acute LVF, 2 NSTEMI, 2 STEMI)

**Conclusion:** In our experience, MACE events were not higher in patients with FFR > 0.8 and kept under medical therapy and were similarly lower in patients with FFR ≤ 0.8 and underwent revascularisation (p = 0.73). Also MACE events were higher in patients with FFR ≤ 0.8 and did not undergo revascularisation compared to other two appropriately treated groups (p = 0.03). FFR based revascularization decision appears to be a safe strategy in Indian patients.

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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.<sup>1</sup> 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.<sup>2</sup>

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.<sup>2</sup> It is derived from the ratio between coronary (distal to stenosis) and aortic pressure measurements during maximal hyperemia.<sup>3</sup> Hence FFR in combination with conventional angiography is rapidly emerging as an accurate approach of combining anatomy and physiology.<sup>4</sup>

**Abbreviations:** 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; IMR, Index of Microvascular Resistance; HMR, Hyperemic Microvascular Resistance; 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.

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<http://dx.doi.org/10.1016/j.ihj.2016.12.007>

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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<sup>2,3,5–7</sup>. FFR has been demonstrated to be a useful index in patients referred for percutaneous revascularisation with intermediate stenosis, involving single coronary vessel,<sup>2,3,7,8</sup> and also in those with multi-vessel disease.<sup>5,9</sup> 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.<sup>10</sup> This leaves FFR as a better choice to assess hemodynamic significance of intermediate lesion and to guide treatment strategy.

Clinical outcome of the decision to intervene based on FFR has been addressed in various trials, conducted in controlled environment.<sup>7,11–14</sup> Availability of such data from routine clinical practice is limited.<sup>15</sup> In India, 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 coronary artery disease (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<sup>16–18</sup> and there is data which discuss about smaller coronary artery diameters in Indian patients undergoing angiography.<sup>19</sup> Thus it is speculative that many Indian patients with borderline lesions undergo unwarranted revascularization without much clinical improvement. FFR, by assessing the ischemic profile, could benefit by helping to select a better revascularization strategy. 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, the results of which could serve to validate and re-emphasize the utility of this investigation in our setting.

## 1. 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 between patients who underwent revascularisation and those kept under medical follow up based on FFR assessment.

## 2. Methods

### 2.1. Study design

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

### 2.2. Study patients

Medical records of all patients who underwent FFR during the period between June 2010 to June 2015 were reviewed.

### 2.3. Inclusion criteria

- All patients with stable ischemic heart disease with denovo intermediate lesions or
- those patients who had acute coronary event a week or more prior to the procedure with denovo borderline lesions.

Study population were grouped into 3 groups:

- Group 1–FFR > 0.8 and kept on medical follow-up;
- Group 2–FFR ≤ 0.8 and underwent revascularization by PCI or CABG; and
- Group 3–FFR ≤ 0.8 and did not undergo revascularisation as per patient preference.

### 2.4. 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/ prior PCI
- 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.

A total of 8263 patients had undergone coronary angiography during the study period for evaluation of their coronary ischemic symptoms, of whom, 471 (5.7%) patients had undergone FFR for physiological severity assessment of coronary lesions. After reviewing these 471 patient medical records, 189 patients were excluded from the analysis (86 had associated valvular heart disease, 74 had significant left main disease, 9 had significant tortuous coronary anatomy, 4 had prior CABG, 12 had significant renal dysfunction, 2 had intracranial neoplasm, and 2 had incomplete data)

### 2.5. 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 (Pressure Wire Aeries 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 min) 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 hospital 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 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.

### 2.6. 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.

## 2.7. 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.

### 2.7.1. 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.

### 2.7.2. 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.

## 3. Statistical analysis

The data was analysed with a 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 test were used, and for continuous variables, student *t*-test was used. Clinical, angiographic variables and FFR values between the deferred, revascularised and non-revascularised 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.

## 4. 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

**TABLE 1**  
Profile of patients in the three groups.

	FFR>0.8		FFR ≤ 0.8	
	Group I Medical	Group II Revascularized	Group III Non-Revascularized	
			PCI	CABG
Total Number	90	144	31	17
Number on follow up	89 (98.8%)	144(100%)	31(100%)	17(100%)
Mean Age (years)	57.7	57.9	54.8	55.9
Male (%)	77	81	90	88
Diabetes	43 (47.7%)	78 (54.2%)	23 (74.2%)	7 (41.2%)
Hypertension	11 (12.2%)	82 (56.9%)	14 (45.1%)	10 (58.8%)
Smoking	6 (6.6%)	113 (78.4%)	26 (83.2%)	12 (70.5%)
Dyslipidemia	4 (4.4%)	48 (33.3%)	20 (64.5%)	8 (47.1%)
Family history of CAD	1 (1.1%)	29 (20.1%)	9 (29.0%)	5 (29.4%)
≥ 2 CAD risk factors (%)	11 (12.2%)	92 (63.9%)	22 (71%)	12 (70.6%)
NYHA III/IV at presentation (%)	7 (7.7%)	19 (13.2%)	11 (35.5%)	7 (41.2%)
Stable IHD	78 (86.6%)	124 (86.1%)	28 (90.3%)	16 (94.1%)
Recent ACS <sup>a</sup>	12 (13.7%)	20 (13.9%)	3 (9.7%)	1 (5.9%)
Mean EF%	63.5%	61%	51.9%	53.2%
SVD	43 (47.8%)	25(17.4%)	0	0
DVD	30 (33.3%)	70 (48.6%)	15 (48.4%)	7 (41.2%)
TVD	17 (18.9%)	49 (34.0%)	16 (51.6%)	10 (58.8%)
Prox LAD > 50% (%)	78 (86.7%)	138 (95.8%)	29 (93.5%)	16 (94.1%)
Mean minimum stenosis diameter (mm)	1.58 ± 0.12	1.02 ± 0.16	1.24 ± 0.29	1.07 ± 0.15
Mean reference vessel diameter (mm)	3.59 ± 0.21	2.75 ± 0.34	3.18 ± 0.51	3.05 ± 0.55
Mean percentage diameter stenosis (%)	56 ± 3	63 ± 6	61 ± 9	65 ± 5
Mean FFR	0.91 ± 0.07	0.68 ± 0.05	0.73 ± 0.03	0.70 ± 0.05
Median follow up (months)	21.7 (6 to 56)	18 (5 to 50)	15.8 (6 to 43)	14.1 (2 to 45)
MACE	3	4	0	7
Medications at last followup <sup>b</sup>				
Aspirin	89 (100%)	144 (100%)	31 (100%)	17 (100%)
Clopidogrel	15 (16.9%)	138 (95.8%)	07 (22.6%)	06 (35.3%)
Statins	76 (85.4%)	142 (98.6%)	31 (100%)	17 (100%)
Nitrates	04 (4.5%)	11 (7.6%)	01 (3.2%)	14 (82.3%)

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.

<sup>a</sup> Includes patients at least a week after ACS.

<sup>b</sup> Percentages calculated for patients available for followup. Percentages calculated for each group.

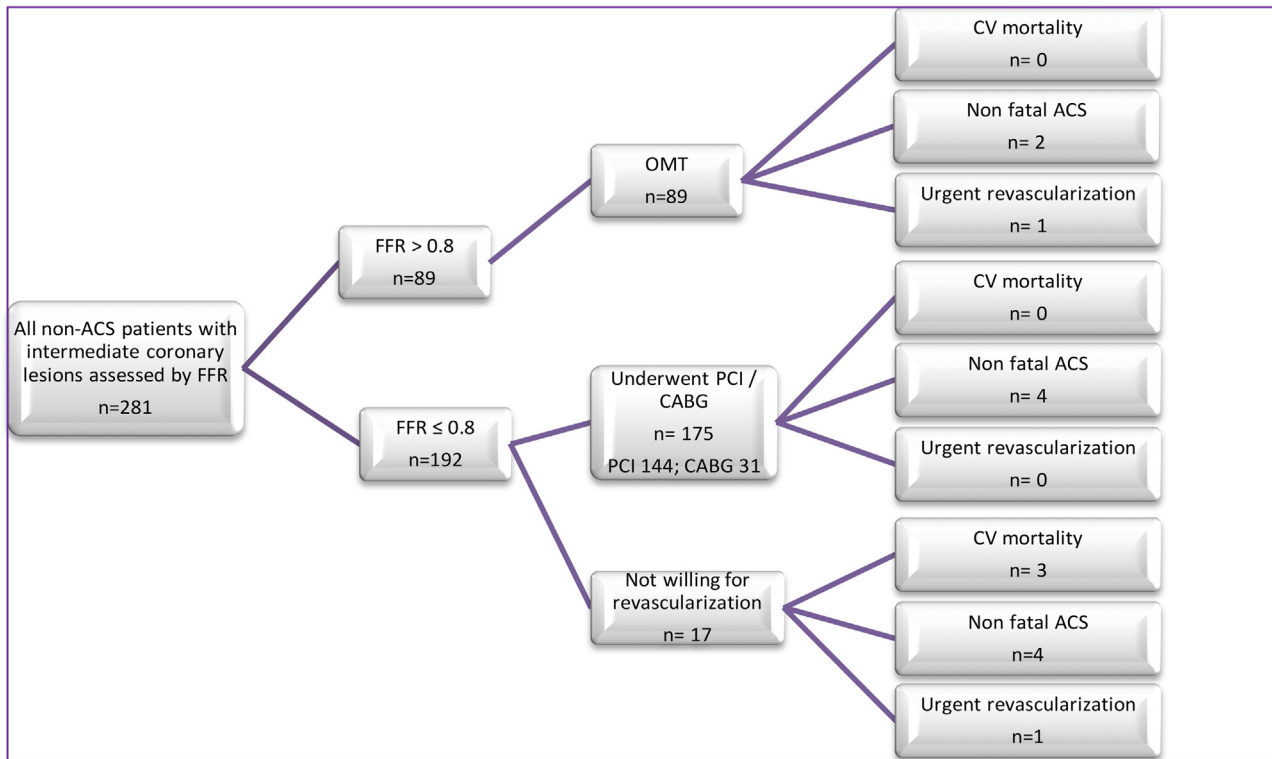


Fig. 1. Study flow.

disease (TVD) in 92 (32.6%). 192 (68.1%) of patients had positive FFR value ( $FFR \leq 0.8$ ) 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.

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 (2 to 56 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 ( $p=0.73$ ). Thus 11 patients had undergone repeat angiogram on followup for their coronary event. (3 in Group 1, 4 in Group 2, and 4 in group 3) (Fig. 1). 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 (Fig. 2), (Table 2).

## 5. Discussion

In this study, we compared the clinical outcomes of FFR assessment based coronary revascularisation. The strategy of medical management of stenoses with  $FFR > 0.80$  and treating only stenoses that are hemodynamically significant ( $\leq 0.8$ ) 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 retrospective 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%.<sup>3</sup> 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

Table 2  
MACE in the three groups.

	Group I (n = 89)	Group II PCI/CABG (n = 175)	Group III (n = 17)
MACE	3	4	7
% of MACE	3.41	2.28	41.17
CV Death			3
Nonfatal ACS	2	4	4
Urgent Revascularisation			1

Group I =  $FFR > 0.8$ , Group II =  $FFR \leq 0.8$  and underwent revascularization, Group III =  $FFR \leq 0.8$  and did not agree for revascularisation.

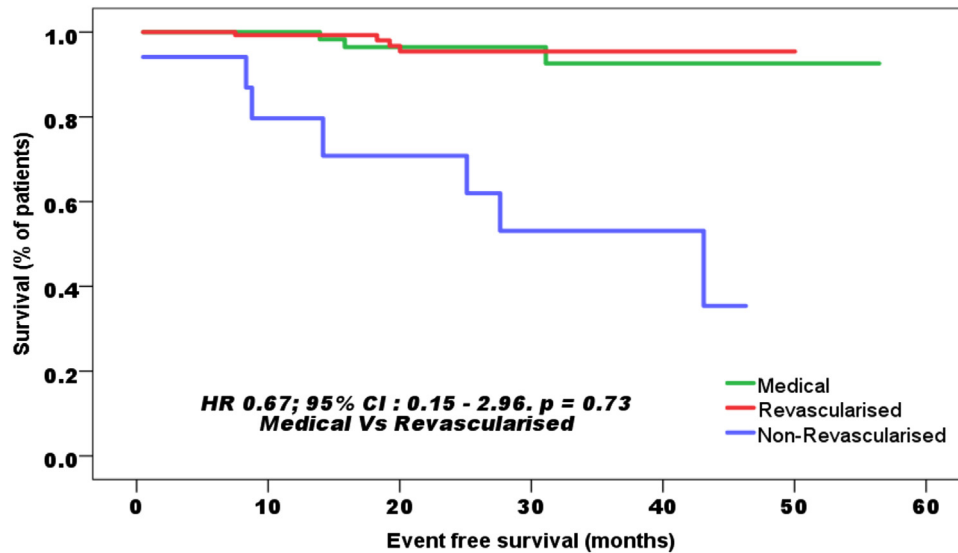


Fig. 2. Kaplan Meier Curve showing event free survival.

assessment.<sup>20</sup> 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,<sup>3,7</sup> which randomised patients with  $\text{FFR} \geq 0.75$  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  $\text{FFR} > 0.8$  in the FAME-2 study (registry group), the occurrence of MACE was 3% over one year.<sup>21,22</sup> Many other smaller studies<sup>23–29</sup> 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  $\text{FFR} \leq 0.8$  randomised 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. Though, not an objective of the study, we noted that size of coronaries in our study population were comparable to those enrolled in major randomised trials like FAME and DEFER, which is unlike the preexisting notion of smaller coronaries in Asians/Indians. (Mean reference vessel diameter measured by QCA was  $3.1 \pm 0.7$  mm in our study population compared to  $2.5 \pm 0.7$  mm in FAME and  $3.0 \pm 0.6$  mm in DEFER).

## 6. 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. Since diabetic patients are of significant proportion, assessment of microvascular status by IMR/HMR might have added to overall assessment.

## 7. Conclusion

Among patients with intermediate coronary artery disease having at least one stenosis with an  $\text{FFR}$  of  $\leq 0.80$ , FFR-guided revascularization (PCI with drug eluting stents or CABG) plus medical therapy, had similar rates of mortality, MI and need for urgent revascularization, as compared with the patients with  $\text{FFR}$  of  $> 0.8$  on medical therapy alone.

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  $\text{FFR}$  of 0.80 or less but did not undergo revascularisation.

Thus, we conclude that in our retrospective study, FFR based clinical decisions in the management of patients with coronary artery disease was safe over a period of 18 months follow-up.

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