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Usefulness of Fractional Flow Reserve during Routine Clinical Procedures in All-Comer Coronary Artery Disease Patients

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Abstract

Background: Fractional flow reserve (FFR)-guided interventions, though proved to be safe, continue to be a much-underutilized modality in determining treatment strategy, and data is lacking in Indian population. **Objective:** We aimed to determine the use of FFR-guided PCI and assess the overall impact on treatment decisions and clinical outcomes in patients with acute coronary syndrome (ACS) or chronic coronary syndromes (CCS). **Methods:** In this single-center retrospective and prospective observational study, FFR had been performed for the evaluation of treatment reclassification and clinical outcomes, as per physician's clinical practice. **Results:** Data was obtained for 250 subjects (mean age 60.45 ± 9.6 years) with 324 lesions. The treatment plan based on angiography alone changed in 28% of lesions post-hyperemic FFR. The initial treatment plan based on angiography vs. the final treatment plan post-FFR (>0.80) was medical management 56.5% vs. 66.0%; CABG 11.1% vs. 7.7%; and PCI 32.4% vs. 26.2%. In subjects initially assigned to medical management, 14% had changed to PCI, and for subjects initially assigned to PCI, 44% had changed to medical therapy. Receiver operating characteristics (ROC) curve analysis revealed a good correlation between a resting FFR value of <0.87 and hyperemic FFR value of <0.80. The rate of 2-year major adverse cardiovascular events (MACE) was 0.9%. **Conclusion:** This study supports the use of FFR in determining treatment strategy in ACS or CCS patients with low MACE. Resting FFR value of <0.87 may be an alternative to intracoronary nitroglycerine/adenosine/Nikorandil-induced FFR in predicting positive FFR particularly in hemodynamically unstable patients, and who are intolerant to hyperemic drugs.

Keywords

Angiogram, Fractional Flow Reserve, Percutaneous Coronary Intervention,

Coronary Physiology

1. Introduction

Coronary angiography (CA) is considered the standard technique for guiding percutaneous coronary intervention (PCI) in patients with myocardial ischemia. Myocardial ischemia is a crucial risk factor among patients with multi-vessel coronary artery diseases [1] [2]. Evidence shows that decisions pertaining to coronary stenoses revascularization should be taken not only based on angiographic results but also considering non-invasive or invasive indication of reversible myocardial ischemia [3]. Controversies still exist about performing PCI in angiographically significant but functionally non-significant stenosis [4].

Fractional flow reserve (FFR) has been considered an effective index and gold standard to assess the physiological lesions and detect myocardial ischemia [1]. It is defined as the ratio of maximum blood flow in a stenotic coronary artery to maximum blood flow in a normal artery without stenosis as measured using a coronary pressure wire during invasive coronary angiography [2]. The FFR value in a normal coronary artery is 1.0. An FFR value of 0.80 implies coronary stenosis probability to trigger myocardial ischemia with greater than 90% accuracy [5]. The FFR provides more specific information and has a better spatial resolution. In FFR, every artery is examined individually, and masking of one ischemic zone by another is avoided. Some observational studies have suggested that worse clinical outcomes associated with stenosis deferred revascularization with lower FFR values than higher FFR values [6] [7].

The European Society of Cardiology guidelines (2010) have incorporated FFR as a class I recommendation into current PCI techniques [8]. The American Heart Association/American College of Cardiology guidelines (2011) have given class IIa recommendation for FFR [9]. The American College of Cardiology (2017) has recommended FFR among patients with stable ischemic heart disease (SIHD) for revascularization [10]. In the FAME (Fractional Flow Reserve Versus Angiography in multi-vessel Evaluation) study, there was a significant reduction in the mortality and myocardial infarction (MI) rates at two years in the FFR-guided group (8.4%) compared with the angiography-guided group (12.9%) ($p = 0.02$) [1]. The RIPCORD study revealed that after FFR, there was a 26% change in the management plan (medical management, coronary artery bypass grafting [CABG], and percutaneous coronary intervention [PCI]) among stable coronary artery disease (CAD) population. Furthermore, the number of vessels with significant coronary disease changed in 32% of the cases after FFR disclosure [11].

For patients with multivessel disease (MVD), minimal use of stents through the PCI intervention needs to be achieved for complete relief of myocardial ischemic symptoms. Improved health and economic outcomes in terms of quality of life and treatment expenditure have been demonstrated in patients undergoing FFR by deferring PCI and other surgical revascularization treatments [12]. However, multiple studies have reported conflicting decisions between the usage of angiography and FFR-guided interventions with the significant reclassification of treatment plans in patients with MVD. Although FFR-guided revascularization is backed by a substantial body of evidence and is cost-effective, it remains underutilized due to a combination of factors such as added procedural time and operator unfamiliarity. In addition, limited studies have been published to understand the treatment plan changes using coronary angiography and FFR in India. The purpose of this study is to understand the routine use of FFR in clinical practice. The study aimed to determine the reclassification rates of coronary revascularization strategy after performing FFR in addition to diagnostic angiography. The study also assessed the impact of FFR-guided intervention on treatment decisions and clinical outcomes.

2. Material and Methods

2.1. Study Design and Population

This study was a single-center, open-label, retrospective and prospective observational study. The data were collected between October 2015 and March 2020 with a median follow-up of 27 months. Patients included in the study were as follows: 1) patients aged eighteen years or older at the time of procedure; 2) non-culprit vessel assessment of patients presenting with ST-elevation myocardial infarction (STEMI), non-ST-elevation myocardial infarction (NSTEMI), unstable angina, or stable coronary artery diseases; and 3) patients planned to undergo FFR for further PCI consideration, or those who underwent cardiac catheterization. Patients with extremely tortuous or calcified coronary arteries, and with a patent coronary artery bypass graft at the target vessel were not considered for analysis.

2.2. Procedure

Baseline characteristics, including demographics (age, gender), clinical parameters (comorbidities, clinical presentation), and routine laboratory tests before the procedures, were recorded.

Angiography was performed according to standard practices. The FFR procedure was performed after the recording of angiographic parameters. In the FFR procedure, a coronary pressure wire (Radi, St Jude Medical, Uppsala, Sweden) was advanced through the coronary artery, distal to the lesion, adequately. The pressure was equalized with the sensor at the tip of the guiding catheter. Maximal coronary hyperemia was triggered with adenosine (140 μg/kg per min) through a central venous infusion. For all participants, aspirin and clopidogrel were continued for one year.

The treating physicians recorded prior revascularization strategy on angiography before performing the FFR measurements. Then, the final patient revascularization strategy was recorded after performing FFR measurements. The treatment plan established was medical management (MM), coronary artery bypass surgery (CABG), and PCI. Medical management was considered for an FFR value of >0.80, and revascularization was recommended if FFR was less than 0.80. The cutoff value of 0.80 was selected in line with contemporary guidelines and previous findings [13] [14]. Reclassification of the treatment decision was regarded as "changed" if there was at least one decision change based on FFR for multiple lesions; if none of the decisions have been changed for multiple lesions, the treatment decision was defined as "unchanged".

2.3. Endpoints and Definitions

The endpoints determined in the present study were cardiac events, target vessel revascularization (TVR), and target lesion revascularization (TLR). Cardiac death was defined as any death because of a proximate cardiac cause, including cardiac arrest, myocardial infarction, low-output failure, or fatal arrhythmia. Both TVR and TLR were defined according to latest ARC consensus statement [15].

2.4. Statistical Analysis

Frequency and percentage change in treatment decisions were presented at the subject level and per lesion level. The following cutoff values were used to categorize a continuous variable into a binary variable. FFR group was defined as "low FFR" if it was equal to or below 0.80. Continuous variables were expressed as mean ± SD; categorical variables were expressed as absolute numbers and percentages (%). The receiver-operating characteristic (ROC) area under the curve analysis was used to estimate the diagnostic efficiency of resting FFR value of <0.87 in patients with resting FFR value of >0.80, and to identify the most appropriate cut-off value corresponding to hyperemic FFR value of <0.80. The diagnostic performance of resting FFR was assessed using sensitivity and specificity.

3. Results

3.1. Demographics and Baseline Characteristics

Two hundred and fifty subjects underwent FFR between October 2015 and March 2020. The mean age was 60.45 ± 9.6 years; and 199 (79.6%) were males. Majority (71.6%) of the population had a history of hypertension, and more than half were diabetic. Fifty-seven patients (22.8%) had a history of prior PCI, while 8 (3.21%) had a history of previous CABG and 11 (4.4%) had history of MI. The mean LVEF (%) was 55.82 ± 8.4. One hundred and thirty (52.0%) subjects presented with unstable angina. Of the 324 target lesions, 185 (57%) were located in the left anterior descending coronary artery, 41 (12.7%) in right coronary artery, and 50 (15.4%) in left circumflex artery. Key baseline and lesion characteristics are summarized in **Table 1**.

Table 1. Baseline and lesion characteristics.

Demographics	Patients (N = 250)
Age (years) (mean ± SD)	60.45 ± 9.6
Female	51 (20.4)
Male	199 (79.6)
Medical history	
DM	138 (55.2)
HTN	179 (71.6)
Cerebrovascular accident	5 (2)
Peripheral arterial disease	4 (1.6)
Smoking	33 (13.2)
Previous PCI	57 (22.8)
Previous CABG	8 (3.2)
Previous MI	11 (4.4)
LVEF% (mean ± SD)	55.82 (8.4)
Indication for PCI	
Unstable angina	130 (52.0)
STEMI	31 (12.4)
NSTEMI	30 (12.0)
Stable angina	11 (4.4)
Chest pain	48 (19.2)
Lesion characteristics (N = 324 lesions)	
Vessels treated	
LAD	185 (57.1)
RCA	41 (12.7)
LCX	50 (15.4)
LM	10 (3.1)
LMCA-LAD	12 (3.7)
LMCA-LCX	5 (1.5)
OM	13 (4.0)
Pre-procedure diameter stenosis (mean ± SD) mm	61.3 ± 10.91
SYNTAX 22 - 33	24 (9.6)
SYNTAX >33	8 (3.2)

*All data presented as n (%) unless otherwise indicated. BMI: body mass index; CABG: coronary artery bypass grafting; LAD: left anterior descending artery; LVEF: left ventricular ejection fraction; NSTEMI: non-ST-elevation myocardial infarction; LCX: left circumflex; LMCA: left main coronary artery; NTG: nitroglycerine; PCI: percutaneous coronary intervention; RCA: right coronary artery; STEMI: ST-elevation myocardial infarction; SD: standard deviation; DM: diabetes mellitus; HTN: hypertension.

3.2. Procedural Characteristics

Post angiography, medical management was planned in 183 cases, CABG and PCI was planned in 36 (11.1%) and 105 (32.4%) cases, respectively (Table 2). Non-hyperemic FFR was done in 229 (70.7%) cases, while adenosine-induced FFR was carried out in 302 (93.2%) cases, and nitroglycerine-induced FFR in 186 (57.4%) cases. For adenosine-induced hyperemia, intravenous approach was used in 128 (39.5%) patients and intracoronary approach in 92 (28.4%) patients, while both approaches were used in 93 (28.7%) patients. The mean adenosine-induced FFR was 0.83 ± 0.08, non-hyperemic FFR value was 0.91 ± 0.07, and nitroglycerine-induced FFR was 0.87 ± 0.08.

3.3. Change in Treatment Strategy

The treatment plan based on angiography alone changed following resting FFR

Table 2. Procedural characteristics.

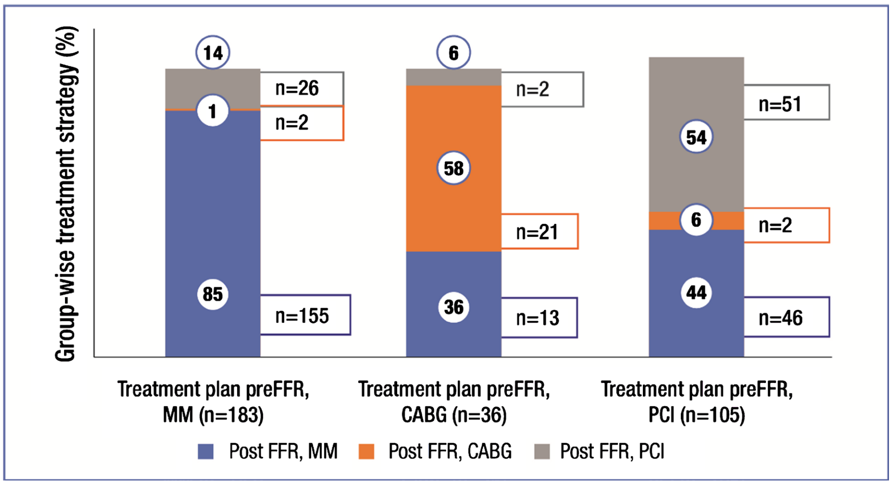
Post CAG plan (N = 324)	
Medical management	183 (56.5)
CABG	36 (11.1)
PCI	105 (32.4)
Number of stents (N = 105)	
1	87 (82.9)
2	12 (11.4)
Unknown	6 (5.8)
FFR performed	
Non-hyperemic FFR	229 (70.7)
Adenosine	302 (93.2)
NTG	186 (57.4)
Nikorandil	1 (0.3)
Non-hyperemic FFR value (n = 229)	
<0.89 (Positive)	63 (27.5)
≥0.89 (Negative)	166 (72.5)
Adenosine FFR value (n = 302)	
≤0.80 (Positive)	95 (31.5)
>0.8 (Negative)	207 (68.5)
NTG FFR value (n = 187)	
≤0.80 (Positive)	32 (17.1)
>0.8 (Negative)	154 (82.3)

*All data presented as n (%) unless otherwise indicated. CABG: Coronary artery bypass grafting; CAG: coronary angiogram; FFR: fractional flow reserve; NTG: nitroglycerine; PCI: percutaneous coronary intervention.

disclosure in 78 lesions (38%) hyperemic FFR in 90 lesions (29.8%), and both resting and hyperemic FFR in 88 lesions (27.2%). The initial treatment plan based on initial angiography versus the final treatment plan post-FFR was: medical management in 183 (56.5%) vs. 214 (66.0%); CABG 36 (11.1%) vs. 25 (7.7%); and PCI 105 (32.4%) vs. 85 (26.2%); as shown in **Figure 1**.

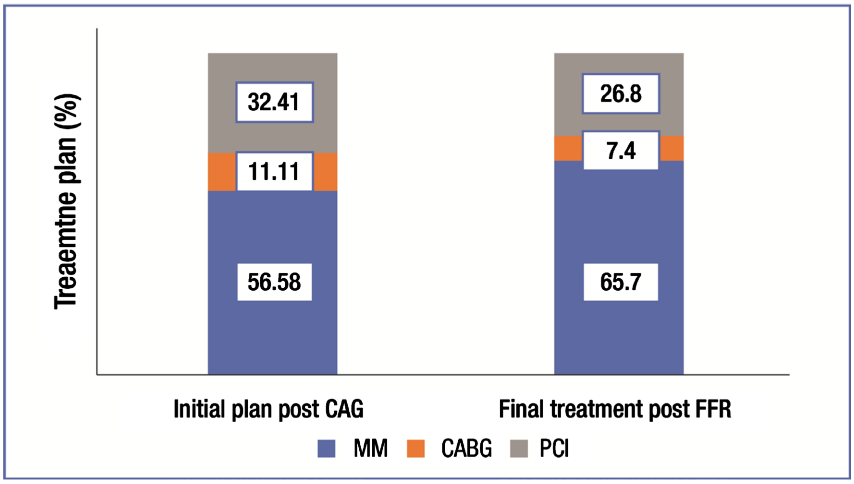
For the subjects initially assigned to medical management based on angiography alone, 14% (26/183) were subsequently assigned to PCI following FFR disclosure. For the subjects initially assigned to PCI and CABG, 44% (46/105) and 36% (13/36), respectively, were then assigned to medical therapy following FFR disclosure (**Figure 1**). The frequency of actual revascularization (CABG + PCI) following FFR disclosure changed from 43.5% to 34.2% per lesion (**Figure 2**).

After positive hyperemic FFR, 74% of lesions (82/111) underwent PCI; 21.6%



CABG: coronary artery bypass grafting; FFR: fractional flow reserve; MM: medical management; PCI: percutaneous coronary intervention.

Figure 1. Change in treatment plan per lesion in MM, CABG, and PCI groups (N = 324).



CABG: Coronary artery bypass grafting; CAG: coronary angiogram; FFR: fractional flow reserve; MM: medical management; PCI: percutaneous coronary intervention.

Figure 2. Overall change in treatment plan per lesion (N = 324).

of lesions (24/111) underwent CABG. Medical management was continued in 99% of lesions (209/211) in patients who had negative hyperemic FFR values (Table 3).

Table 4 provides a detailed breakdown of the distribution of coronary disease as determined by FFR. Disease status changed in a total of 186 lesions (74.4%) after FFR data were revealed compared with the assessment based on angiogram alone. The total number of mild CAD cases increased from none to 82 post FFR. There were 89 cases with SVD including 58 cases of mild CAD post FFR. Also, a higher number of number of lesions were redistributed to SVD from DVD post FFR; of 88 TVD lesions determined by CAG, 51 lesions were considered SVD and 14 cases were mild CAD post FFR.

Using an hyperemic FFR cut-off value of < 0.80 to assess treatment classification, a ROC curve revealed that the resting FFR cut-off value of <0.87 in patients with FFR value of >0.80 correlated with hyperemic FFR value of <0.80; the area

Table 3. Final treatment plan based on hyperemic FFR values.

Decision by CAG, n (%)	After hyperemic FFR						
	>0.80 (Negative)			≤0.80 (Positive)			No FFR value
	MM	CABG	PCI	MM	CABG	PCI	PCI
MM (n = 183)	154 (84)		1 (1)	1 (1)	2 (1)	24 (13)	1 (1)
CABG (n = 36)	13 (34)	1 (3)			20 (56)	2 (6)	
PCI (n = 105)	42 (40)			4 (4)	2 (2)	56 (53)	1 (1)
	209	1	1	5	24	82	2

*All data presented as n (%) unless otherwise indicated. CABG: Coronary artery bypass grafting; CAG: coronary angiogram; FFR: fractional flow reserve; MM: medical management; PCI: percutaneous coronary intervention.

Table 4. Distribution of CAD post FFR.

Vessel Disease (n = 250)	SVD	DVD	TVD	LM + SVD	LM + DVD	LM + TVD	MILD CAD	Pre FFR
SVD	22						58	80
DVD	51	23					14	88
TVD	12	21	19				6	58
LM + SVD	2			3				5
LM + DVD	1	1		4	2		3	11
LM + TVD	1	1			1	4		7
LMCA							1	1
Post FFR	89	46	19	7	3	4	82	250

CAD: Coronary artery disease; CAG: coronary angiogram; DVD: dual vessel disease; LMCA: left main coronary artery; LM: left main; FFR: fractional flow reserve; SVD: single vessel disease; TVD: triple vessel disease.

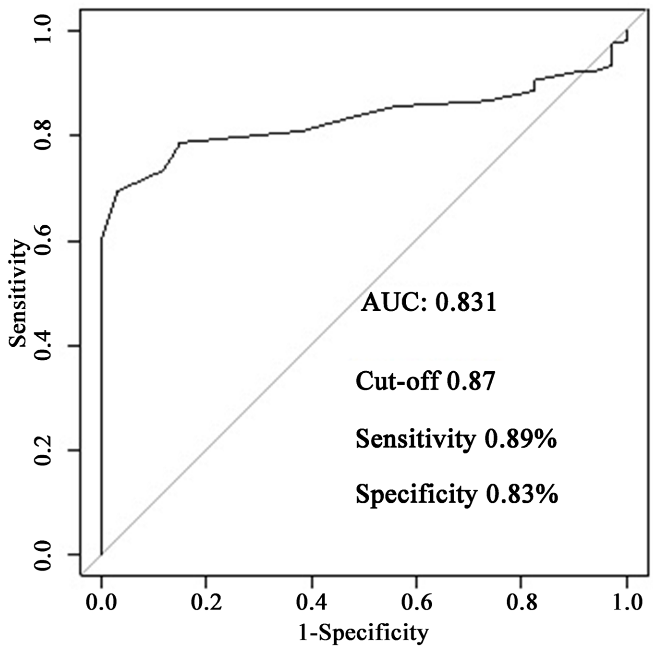


Figure 3. ROC curves of resting FFR values for an FFR cut-off value of 0.80.

under the ROC curve was 0.831, indicating good accuracy for the resting FFR cut-off value of <0.87. A total of 5/46 cases were found discordant for resting FFR < 0.87 and positive hyperemic FFR, and 30/180 cases were found discordant for resting FFR ≥ 0.87 and negative hyperemic FFR. The sensitivity and specificity of resting FFR for the detection of a cut-off FFR value of less than 0.80 were 0.89% and 0.83% in treated lesions (Figure 3).

3.4. Clinical Outcomes

Major adverse cardiac events (MACE) were defined as a composite, including all-cause death, non-fatal myocardial infarction, and TLR/TVR. The MACE for the overall population at 24 months was 0.9%: death occurred in 3 patients including one patient who was changed to MM from PCI after FFR. There were no cases of TVR, TLR, MI, and cardiac death immediately after intervention or during the follow-up.

4. Discussion

This retrospective study demonstrated the safety and feasibility of FFR-guided management in CAD patients with multiple vessel disease and intermediary lesions. Majority of the patients were ACS. The FFR-guided management resulted in a considerably higher change in treatment post FFR.

The use of FFR has been recommended by the European (Class 1A) [8] and US guidelines (Class 2A) [10] [16] for evaluation of angiographic intermediate coronary lesions (50% to 70% stenosis) and for guiding revascularization decisions in patients with stable CAD. According to the Society of Cardiovascular Angiography and Interventions, in SIHD, PCI of lesions with FFR < 0.80 improves symptom control and decreases urgent revascularization compared to medical therapy. When FFR > 0.80 in angiographically intermediate lesions with SIHD, medical therapy is indicated [17]. Accordingly, FFR in the current study was utilized in patients with features of both ACS and SIHD with mean stenosis of 61 mm.

Several single-country registries, such as R3F (French FFR Registry) POST-IT (Portuguese Study on the Evaluation of FFR-Guided Treatment of Coronary Disease), reported that FFR was associated with a high rate of change of the revascularization strategy (38% overall) [18] [19]. A similar revascularization rate was also observed in the recent IRIS-FFR study [20]. The RIPCORD registry determined the impact of routine FFR at the time of diagnostic CAG on management in stable chest pain patients. Overall, after disclosure of FFR data, management plan based on CA alone was changed in 26% of patients [11]. In the current study that included 20% patients with stable angina, an overall change in treatment strategy from initial plan was done in 28% of procedures post CAG.

A retrospective study in India, FIND, analyzed clinical usefulness, cost-benefit, and medium-term outcomes of FFR-based intervention of intermediary CAD lesions (N = 59; 81 vessels). Post FFR, about 40% of lesions have been spared from unnecessary PCI intervention. Further, for every two patients or three lesions, one stent was avoided with FFR added to angiography. In total, 26 stents were avoided when FFR was used. Similarly, post FFR, only three of six patients required surgery [21]. In a large ambispective study conducted at CMC institute Vellore [22], in India (N = 400), about 80% of patients had a change in management strategy based on FFR assessment (cut-off of ≤0.80). The FFR assessment revealed hemodynamically significant lesions in only 29% of the total of 477 intermediate coronary lesions; this resulted in the avoidance of stenting strategy in almost one-third of patients referred for PCI (30.5%). Based on FFR measurement, several clinical management subsets were identified: stent avoidance: 30% of patients had stent avoidance (1.2 stents saved per patients); stent reduction: 31.3% of patients had reduction in the number of stents implanted (1.07 stents saved per patient); PCI instead of CABG: 10% of patients had a change in decision from CABG to multivessel PCI; and CABG instead of PCI: 8.3 of patients had a change in decision from PCI to CABG [21]. In the current study, the percent of final revascularization was 34.2%, a decrease in 10% of revascularisations planned after initial CAG. Post FFR, total number of dual or more vessel disease reduced from 169 to 79. Importantly, 82 cases of mild CAD were newly determined post FRR, impacting the treatment strategy both pre and post PCI. The number of CABG reduced from 36 to 24, and the number of PCI procedures reduced from 105 to 87 post FFR. While change in CABG post CAG to medical management and PCI post FFR was observed in 36% and 6% of lesions, change in PCI post CAG to medical management and CABG was observed in 44% and 2% of lesions, respectively. The total number of stents saved was 24 post FFR (reduced from 105 post CAG to 81 post FFR).

Previous studies reported adverse events with adenosine with no significant difference between intracoronary and intravenous administration [11] [22]. We did not find any major clinically significant adverse events with adenosine except few minor side effects like bradycardia and hypotension which were managed with IV atropine, IV fluids and in some patients IV inotropes. Moreover, we found that whenever a resting FFR value is <0.87 it usually predicts hyperemic FFR value <0.80 with intracoronary nitroglycerine/adenosine/Nikorandil in majority of patients, and this may be considered as one of the indicators to predict positive FFR test. We feel this finding would be an additional parameter to make decision in patients with clinically unstable status, and who are intolerant to hyperemic drugs which might save time and cost. However, this should be confirmed in future multiple randomized trials.

Several real-world studies noted that FFR-guided treatment was associated with a positive long-term outcome with a decreased reduction in MACE events [23] [24]. The overall 24-month clinical outcome (MACE) rate is shown to be 4.7% which is comparable to the previous findings from historical studies [25] [26]. Similar to our study, an observational study in Indian setting showed that at 21-median follow-up, the composite endpoint of cardiac death, nonfatal MI, objective evidence of ischemia, and ischemia-driven revascularization in the vessels assessed by FFR occurred were observed in 0.9% of patients [21].

5. Conclusion

In conclusion, the use of FFR in this observational study considerably changed the treatment plan compared to only angiogram. Based on the outcomes, it can be suggested that FFR-guided management is safe and feasible to guide revascularization decisions of both ACS and stable CAD patients and might benefit Indian patients with multiple vessel disease and intermediate/borderline lesions. Further, long-term prospective studies are needed to establish the safety and feasibility of FFR-guided revascularization in ACS and stable CAD patients.

Limitations

Though our study included larger population with ACS compared to other studies in Indian settings, our study is limited by observational design without control arm.

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Conflicts of Interest

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

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