HUE UNIVERSITY
UNIVERSITY OF MEDICINE AND PHARMACY

CHAU DO TRUONG SON

APPLICATION OF FRACTIONAL FLOW RESERVE IN GUIDING NON-CULPRIT LESIONS PERCUTANEOUS CORONARY INTERVENTION IN ACUTE MYOCARDIAL INFARCTION

SUMMARY OF MEDICAL DOCTORAL DISSERTATION

HUE - 2024

The dissertation was completed at:
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INTRODUCTION

1. Rationale for the study

Coronary angiography remains the most widely used method to assess the degree of coronary stenosis. The Fractional Flow Reserve (FFR) is an index that evaluates the potential of a lesion to cause myocardial ischemia, which narrows the coronary lumen. It is less impacted by hemodynamic factors. FFR's effectiveness and safety in guiding the treatment of lesions with intermediate stenosis in chronic coronary artery disease is well-established when compared to coronary angiography. However, FFR's use in acute coronary syndrome settings, particularly acute myocardial infarction (AMI), remains contentious.

In Vietnam, most studies on FFR focus on patients with chronic coronary artery disease, with only Vu Quang Ngoc's study examining FFR on AMI. This leaves many questions unanswered: What are the characteristics of nonculprit lesions with intermediate stenosis in AMI? If FFR is used to investigate lesions not causing intermediate stenosis, how accurate and safe is it? When performing complete percutaneous coronary intervention (PCI) on lesions in AMI, which method should guide the treatment of non-culprit lesions with intermediate stenosis levels—relying solely on coronary angiography results, or should FFR also be measured to evaluate the physiological accuracy of blood vessels?

To address these inquiries, we conducted the study: "Application of Fractional Flow Reserve in guided non-culprit lesions percutaneous coronary intervention in acute myocardial infarction" with three objectives:

(1) Examine the clinical and paraclinical characteristics of non-culprit lesions with intermediate stenosis in patients with AMI.

(2) Evaluate the characteristics of FFR and resting full-cycle ratio (RFR) in intermediate non-culprit lesions in patients with AMI

(3) Compare the performance value of FFR versus quantitative coronary angiography (QCA) in guided intermediate non-culprit lesions PCI in patients with AMI.

2. Scientific and practical significance

This study presents the application of FFR and RFR measurements to guide non-culprit lesions PCI in patients with AMI. The findings shed light on the effectiveness and safety of the FFR and RFR measurement procedures for patients with AMI.

While there's a dearth of research and data on this topic, particularly in Vietnam, this study can equip clinicians with a wider perspective,

enabling them to determine the most effective intervention method for non-culprit injuries in AMI patients.

In clinical practice, it is a pressing concern to decide on a treatment strategy for guided PCI based solely on FFR or QCA. This approach helps to avoid overlooked lesions and prevents excessive intervention on lesions that haven't yet caused significant ischemia.

3. CONTRIBUTION OF THE THESIS

This dissertation presents one of first studies in Vietnam that applies FFR in the intervention of intermediate non-culprit lesions in patients with AMI. Guided FFR have helped increase medical treatment rates and decrease rates of PCI compared to QCA. The FFR group used fewer stents and less contrast agent, which was a statistically significant difference compared to the control group. Although not significantly, the FFR group also had lower rates of major cardiovascular events and mortality. Additionally, the RFR can be used in conjunction with FFR to investigate non-culprit lesions in patients with AMI, due to their strong correlation.

4. STRUCTURE OF THE THESIS

The thesis spans 130 pages, comprising a 3-page introduction, a 34-page literature review, a 25-page segment on study objects and methodology, a 28-page results section, a 32-page discussion, and a 4-page conclusion, limitations, and recommendations segment. The thesis integrates 52 tables, 9 charts, 14 figures, and 3 diagrams. It includes 149 references, 17 in Vietnamese and 132 in English, with 67 references from the past 5 years, representing 44,96% of the total.

Chapter 1
LITERATURE REVIEW

1.1. ACUTE MYOCARDIAL INFARCTION

1.1.1. Overview of acute myocardial infarction

A MI is the prolonged ischemic necrosis of a myocardial area in the ventricle, typically larger than 2 cm^2, caused by occlusion of the coronary artery. AMI is a cardiovascular disease that is becoming increasingly prevalent worldwide due to its complex pathophysiological mechanism, dangerous complications, and high mortality rate. In Vietnam, the incidence of AMI has been rising, and mortality rates remain high.

1.1.2. Pathophysiology of acute myocardial infarction

This includes two main types: ST-elevation myocardial infarction (STEMI), which involves complete obstruction of blood flow through

the epicardial coronary artery, and Non-ST-elevation myocardial infarction (NSTEMI), which involves incomplete obstruction of blood flow through the same artery.

1.1.3. Diagnosis of acute myocardial infarction

Acute STEMI is primarily diagnosed based on typical chest pain symptoms of acute coronary syndrome and electrocardiogram (ECG) images. NSTEMI is primarily diagnosed based on suspected symptoms.

1.1.4. Classification of coronary artery lesions

A culprit lesion is the one responsible for the current MI episode. Any remaining lesions on the coronary tree that are not the culprit lesion are considered non-culprit lesions.

1.2. RECANALIZATION TREATMENT FOR AMI

1.2.1. Emergency recanalization treatment of acute STEMI

Two methods exist: (1) Primary PCI and (2) Thrombolysis. Coronary artery bypass surgery is only used in certain cases when primary PCI is inappropriate or unsuccessful. Primary PCI, the preferred choice, is performed within 48 hours of symptom onset.

1.2.2. Recanalization treatment of NSTEMI

This follows the latest updated guidelines on recanalization treatment of NSTEMI from the ESC in 2023.

1.2.3. Intervention for Nonculprit Lesions with acute STEMI

The indications for interventions include those for non-culprit lesions intervention in patients with STEMI, according to the European Society of Cardiology (ESC) 2018, ACC/AHA 2021, and ESC 2023 guideline. While ample evidence supports the treatment of primary PCI of culprit lesions, the evidence for PCI of non-culprit lesions and the timing of intervention is somewhat less definitive.

1.2.4. Non-culprit lesion PCI in NSTEMI

For NSTEMI, there is limited strong evidence from prospective studies or randomized controlled trials. The 2023 ESC guidelines, which suggest complete coronary revascularization in patients with NSTEMI, are based on similar recommendations for patients with STEMI and stable chronic coronary artery disease.

1.3. FRACTIONAL FLOW RESERVE

1.3.1. Basics concepts of coronary circulation

Coronary circulation can increase from resting levels to maximum (coronary reserve), depending on an increase in myocardial oxygen demand or in response to neurological or pharmacological stimuli that induce hyperemia.

1.3.2. Concept of Fractional flow reverse

FFR is defined as the ratio of maximum achievable blood flow through a blockage to the maximum achievable blood flow in the same vessel in the hypothetical absence of the blockage. It is expressed as a fraction of the expected normal value if the artery were completely normal.

1.3.3. FFR Threshold for Myocardial Ischemia

Previous studies (Pijls NHJ et al, DEFER, FAME and FAME 2) strongly support the hypothesis that patients with stable coronary artery disease and an FFR > 0.80 have a good prognosis, especially without PCI. It is recommended that these lesions only receive optimal medical treatment. Chronic coronary artery disease treatment guidelines, such as those from the 2019 ESC or the 2021 American Heart Association, also use a cutoff of 0.80. For non-culprit lesions AMI, recent large studies also use the cutoff point of FFR ≤ 0.80.

1.4. ASSESSMENT OF NON-CULPRIT LESIONS

1.4.1. Principles for physiological assessment of the severity of of coronary artery stenosis

The most crucial factor in determining the treatment strategy for coronary artery disease is the patient's myocardial ischemia. The ESC 2019 treatment guidelines define intermediate stenosis levels from 40 to 90% in coronary stenosis. However, large FFR-guided studies on non-culprit injuries set the non-culprit injury threshold at 50 - 90%.

1.4.2. Imaging Exploration Methods

Coronary Angiography: The 2023 ESC recommendations suggest PCI for nonculprit lesions guided by coronary angiography. Current studies use stenosis ≥50% with vessels ≥2.0mm in diameter.

QCA (Quantitative Coronary Angiography): This is a method of measuring the degree of coronary stenosis using DSA software.

Intravascular Ultrasound (IVUS): A probe emitting ultrasound beams into the coronary artery is used to create images of the coronary artery wall, including both horizontal and vertical slices.

Optical Coherence Tomography (OCT): A probe with a fiber-optic cable, emitting light with a wavelength similar to infrared rays, is inserted into the coronary artery to create an image of the coronary artery wall.

1.4.3. Methods for Assessing Coronary Artery Stenosis

Intracoronary pressure indexes like the coronary flow reserve (CFR) and index of microvascular resistance (IMR) assess functional epicardial coronary stenosis depending on changes in hemodynamics. However, they have limited clinical application, especially in AMI settings.

FFR: This invasive method provides many advantages when assessing damage to each coronary artery branch feeding respective myocardial regions due to its high sensitivity, specificity, and accuracy. FFR has become a reference tool in research for other methods of assessing myocardial ischemia, such as selective coronary angiography and IVUS, for each lesion on each arterial branch.

Other methods related to FFR: contrast FFR, Quantitative Flow Ratio (QFR) and CT FFR.

Other Resting Indicators (without Microvascular Dilation): Pd/Pa ratio, instantaneous wave-free ratio (iFR), Diastolic Pressure Ratio (dPR), RFR, and Diastolic Pressure Ratio (dPR), resting distal coronary pressure to aortic pressure ratio (Pd/Pa).

1.5. RELEVANT RESEARCH IN VIETNAM AND ABROAD

1.5.1. Studies comparing FFR versus coronary angiography in guided PCI for non-culprit lesions in AMI

This includes the FLOWER-MI (2021), FRAME-AMI (2022) studies, and the meta-analyses by Wald et al. (2020) and Gallone et al. (2020).

1.5.2. Overview of FFR Research and Treatment Guidelines Globally

1.5.2.1. Acute STEMI

Culprit lesions: Main research in this area was conducted by De Bruyne et al. in 2001 and Tamita K et al. in 2002.

Non-culprit lesions: Important studies were done by Ntalianis et al. in 2010, DANAMI-3 PRIMULTI (2015), COMPARE ACUTE (2017), COMPLETE (2019), and FIRE (2023) highlight FFR's effectiveness in guiding complete treatment of nonculprit lesions in patients with STEMI. In Vietnam: Vu Quang Ngoc in 2021

1.5.2.2. Non-ST Elevation AMI

This is discussed in the FAMOUS-NSTEMI study 2014, study by Mehta et al. 2015, and the 2023 ESC treatment guidelines for acute coronary syndrome.

CHAPTER 2
STUDY SUBJECTS AND METHODOLOGY

2.1. STUDY SUBJECTS, RESEARCH PERIOD, AND SETTINGS

2.1.1. Study subjects

The subjects were hospitalized patients diagnosed with AMI who had successfully underwent culprit PCI.

Selection Criteria: Patients with STEMI within 48 hours who

had successful PCI, or those with NSTEMI

Exclusion Criteria: Patients with AMI accompanied by cardiogenic shock or acute pulmonary edema (Killip III – IV), or if the acute STEMI occurred more than 48 hours after symptom onset. Other exclusion criteria include severe accompanying medical conditions such as severe pneumonia, gastrointestinal bleeding, chronic obstructive pulmonary disease, and end-stage chronic renal failure. Patients with severe acute heart failure, hemodynamic instability following primary PCI, a history of MI in vascularly dominated areas as confirmed by other diagnostic methods. Segments distal to lesions with collateral circulation from the same or contralateral vessels, stenosis of the left main coronary artery ≥ 50%, chronic total occlusion (CTO), and contraindications to Adenosine are also excluded.

2.1.2. Research Period

The study was conducted from January 2020 to October 2023.

2.1.3. Research settings

The research was conducted at two hospitals: The Department of Interventional Cardiology and Department of Internal Cardiology at Gia Dinh People's Hospital, and the Department of Interventional Cardiology and Department of Cardiology at the University of Medicine and Pharmacy Hospital, both in Ho Chi Minh City.

2.2. RESEARCH METHODOLOGY

2.2.1. Study design: This is a longitudinal study.

2.2.2. Sample size

The sample size was estimated using the formula to estimate a proportion. Based on the study by Wong et al (2021), which reported a major cardiovascular event rate of 7.9%, the minimum sample size of this study was calculated to be 112 patients. The actual sample size was 130 patients, with 65 patients receiving intervention under FFR guidance and 65 patients not using FFR (guided by coronary angiography).

2.2.3. Sampling method

This study employed a non-probability, purposive sampling method.

2.2.3.1. Intervention group under FFR guidance

This group comprised patients who had FFR performed on non-culprit lesions with intermediate stenosis ranging from 50-90%. The patients were further classified into two groups:

(1) Acute STEMI patients who experienced the onset of chest pain within 48 hours of primary PCI successfully on the culprit lesion. These patients had nonculprit lesion FFR measured at least three days

after primary PCI.

(2) NSTEMI patients who were successfully intervened in the culprit lesion. These patients had their FFR measured during the same or subsequent procedures.

Treatment direction for non-culprit lesions: Stenosis less than 50% required no FFR examination and was considered FFR > 0.8, optimal medical treatment was applied. Stenosis between 50 - 90% required an FFR. If FFR ≤ 0.8, PCI was applied; if FFR > 0.8, optimal medical treatment was applied. Stenosis greater than 90% required no FFR, was considered FFR ≤ 0.8, and PCI was applied.

2.2.3.2. Control group (QCA group)

This group of patients had PCI performed on non-culprit lesions based on QCA. These patients had at least one nonculprit lesion with stenosis between 70 - 90%. We divided these patients into two groups:

(1) Acute STEMI: These patients experienced chest pain within 48 hours, with successful primary PCI on culprit lesions. This group was perfomed PCI on non-culprit lesions at least 03 days after the primary PCI.

(2) NSTEMI: successful PCI of the culprit lesion. Patients received PCI for nonculprit lesions during the same or subsequent procedure.

Treatment pla for non-culprit lesions: Stenosis 50 - 70%: medical treatment, stenosis 70 - 90%: PCI, stenosis > 90%: PCI. Patients would be followed for at least 12 months for major cardiovascular events (all-cause mortality, cardiovascular death, non-fatal MI, cerebral stroke, target vessel revascularization, composite events).

2.2.4. Research facilities

We use a DSA digital subtraction angiography machine from Siemens, Germany, as well as an FFR measuring apparatus, which includes two generations of machines: the Radi Analyzer Xpress and the Quantien machine from St. Jude Medical/Abbott. These machines also have integrated RFR measurement, so we can compare the RFR when we use them. For dilating the epicardial coronary artery, we use nitroglycerin via direct coronary artery pump. For microvascular dilation, we use Adenosine, also through a direct coronary artery pump. Other diagnostic tools we use include an Echocardiogram, Electrocardiogram, and blood tests.

2.2.5. Steps to conduct research

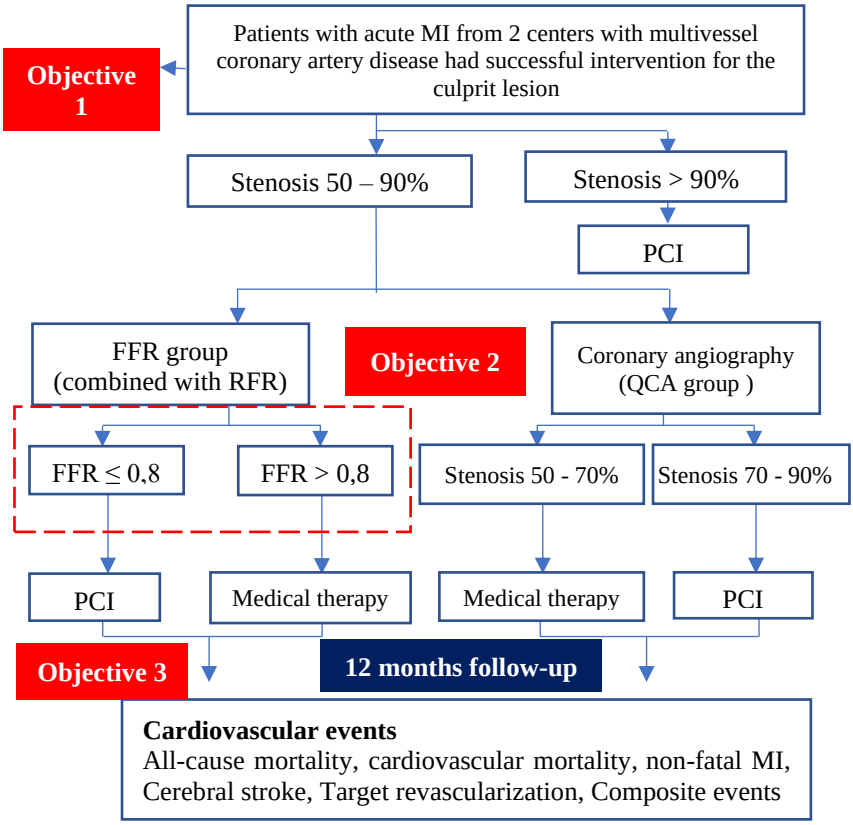

Figure 2.1. Research flowchart

2.2.6. Research variables

Clinical Features: patient's medical history, including symptoms of chest pain and the time of onset; personal history, such as hypertension (as defined by the Vietnam Heart Association 2022), Type 2 diabetes (as per the American Diabetes Association's 2023 definition), Dyslipidemia (according to the 3rd report of the National Cholesterol Education Program - ATP III), smoking, stroke, peripheral artery disease, and body mass index (BMI) classified according to Asian standards; clinical scales such as GRACE score, TIMI score, PRECISE-DAPT score, and the Killip classification.

Paraclinical Tests: hematological biochemistry, including cardiac markers (Troponin I - hs ng/L), creatinine (µmol/L), and a biland lipid (total cholesterol, triglycerides, HDL-C, LDL-C, units in mmol/L);

electrocardiogram as per the 4th global definition of AMI in 2018, and an echocardiogram following the 2017 guidelines of the American College of Cardiology, measured using the Simpson method.

Percutaneous Coronary Imaging and Intervention and FFR Measurement: Record parameters such as temporary pacing, thrombectomy, IVUS, balloon angioplasty before and after stent placement, direct stent placement, coronary flow before and after placement according to TIMI, and the type, quantity, and characteristics of stents placed. If possible, measure FFR before and after intervention and record Pd/Pa, RFR; Evaluating PCI outcomes: assess visual success and procedural success according to SCAI standards; Evaluating FFR Measurement Results: Determine technical and procedural success.

Post-procedure patient monitoring: Monitor patients for events related to the coronary intervention procedure or FFR measurement within 24 hours, such as death, reinfarction, severe bleeding, acute kidney injury due to contrast agent, or a new stroke.

Post-discharge patient monitoring: cardiovascular events by phone call or from medical records if the patient is readmitted to the hospital. Follow each patient for at least 12 months. If a patient experiences an event (as per figure 2.1), record it and conclude monitoring.

2.3. Data analysis

We used SPSS 20.0 software to analyze the data and draw correlation charts. Column charts and pie charts were created using Microsoft Excel 365 software.

In terms of descriptive statistics, we examined the distribution of quantitative variables. If a normal distribution was observed, we presented the mean value ± standard deviation. If not, we presented the median value, along with the 25% - 75% percentile range. For qualitative variables, we provided the frequency (n) and the percentage (%).

For the statistical inferences, we compared proportions using the Chi-square test (χ^2) and Fisher's exact test. We assessed the similarity between two diagnostic indices using the Cohen's Kappa consensus coefficient. When comparing two means, we used the t-test and the Mann-Whitney test. To compare more than two means, we used ANOVA and the Kruskal Wallis test. When comparing two average values before and after an intervention, we performed a paired t-test and a Wilcoxon signed-rank test. For survival analysis, we utilized the Log Rank test and created a Kaplan-Meier chart. To analyze factors related to major cardiovascular events and mortality in the FFR group and control group, we calculated the Odds ratio (OR) and 95%

confidence interval (CI). Lastly, we conducted a correlation analysis and provided a correlation coefficient (r) and correlation chart.

2.4. Research ethics

The study received approval from the ethics council of Hue University of Medicine and Pharmacy, Gia Dinh People's Hospital and the University of Medicine and Pharmacy Hospital in Ho Chi Minh City.

Indication for coronary angiography and PCI adhered to the treatment guidelines put forth by the American College of Cardiology, European Society of Cardiology, and the Vietnam Cardiology Association, current at the time of hospital admission.

This observation-based study does not disrupt the diagnosis and treatment process. Participants and/or their families in both the FFR group and control group were thoroughly briefed and gave their consent, promising to collaborate throughout the research process. Patients reserve the right to withdraw from the study at any time, and all patient information are kept confidential.

The procedures for imaging, coronary intervention and FFR measurement align with the Ministry of Health's "Guidelines for Technical Procedures of Internal Medicine Specialized in Cardiology", as per decision 3983/QD-BYT dated October 3, 2014.

CHAPTER 3
RESULTS

3.1. GENERAL CHARACTERISTICS OF STUDY POPULATION

3.1.1. Clinical features of the study population

General characteristics: The study involved 130 patients with an average age of 62.5 ± 10.4 years, 66.9% of whom were men. Most patients had hypertension (80.0%), hyperlipidemia (67.7%), and a BMI $\geq$ 23 kg/m^2 (50.8%). There was no difference in general characteristics between the two groups, except for a higher proportion of patients with dyslipidemia in the FFR group (p=0.003) (Table 3.1).

Clinical characteristics: The proportion of patients with Killip I was high at 96.2%. In the NSTEMI group, the median GRACE cardiovascular risk score was a respectable 130.5, under 140 points. The PRECISE DAPT score was also low at 16, under 25 points, showing a low risk of bleeding. Patients can safely use dual antiplatelet therapy for over 12 months. The median time from door-to-balloon was 95.5 minutes (Table 3.2).

Admission medications: In the FFR group, more patients used

low molecular weight heparin and proton pump inhibitors compared to the control group (58.5% vs. 40.0%, p=0.035 and 58.5% vs. 38.5%, p=0.023, respectively) (Table 3.3).

3.1.2. Pre-clinical features of the study population

Paraclinical characteristics: The median ejection fraction (EF) was 52.0%. Patients with EF <40% only accounts for a low rate of 16.9%. The average LDL-C value was high at 3.3 ± 0.9 mmol/L (Table 3.4).

Diagnosis of AMI: the rate of acute STEMI was higher than that of NSTEMI. In the group of acute STEMI, inferior MI accounted for the highest proportion with 43.4%. Most patients have 2-vessel coronary artery disease (61.5%), while 38.5% have 3-vessel disease (Table 3.5).

3.1.3. Characteristics of the culprit lesions primary PCI

Characteristics of the culprit coronary artery lesions include the most common being LAD (40.8%), with the majority having very severe stenosis over 90% (92.3%) (Table 3.6).

In terms of emergency intervention parameters for culprit coronary artery, the radial artery is the most common access route (83.1%). A large majority of lesions were completely occluded with TIMI flow 0: 71.1%. Thrombectomy was received by 38.2% of patients. Balloon dilation before and after stent placement was prevalent, at rates of 72.3% and 91.5% respectively (Table 3.7).

Regarding the characteristics of stents in the intervention of culprit coronary artery lesions, most patients received one stent (80.0%). The vessel with the most stents in the FFR group was the RCA, and in the control group it was the LAD, but this difference wasn't statistically significant. The average stent had a diameter of 3.0 mm and a length of 32 mm (Tables 3.8, 3.9, 3.10).

The results of the intervention for culprit lesions show that post-intervention TIMI was mostly TIMI III (98.5%). Imaging success was achieved in 96.2% of cases and procedural success was 100% (Table 3.11).

3.1.4. Characteristics of nonculprit lesions of intermediate stenosis in patients with AMI

3.1.4.1. Characteristics of nonculprit coronary artery lesion

The FFR group had a noticeably higher rate of 50 - 70% stenosis than the control group (41.9% vs. 23.4%). On the other hand, the control group had a significantly higher rate of 70-90% stenosis compared to the FFR group (72.3% vs. 40.7%), with p <0.001. The LAD was the most commonly affected non-culprit coronary artery branch, at 43.9%. Severe lesions (B2/C) made up the majority, standing at 60.0%. (Table 3.12).

3.1.4.2. Characteristics of nonculprit coronary artery lesion intervention

When treating nonculprit coronary artery lesions, we found 86 lesions in the FFR group. Among these, 41 received medical treatment and 45 underwent intervention. The control group had 94 lesions, with 22 treated medically and 72 via intervention. All vessels reached TIMI III flow post-treatment (Table 3.13).

In terms of discharge medication, every patient was prescribed Aspirin. In the P2Y12 group, around one third (32.3%) were given Clopidogrel, and the remaining two thirds (67.7%) were put on Ticagrelor. Two thirds of the patients were also on ACE inhibitors and beta blockers. Almost all patients (98.5%) were prescribed statins (Refer to Table 3.14).

3.2. CHARACTERISTICS OF FFR AND RFR IN INTERMEDIATE NON-CULPRIT LESION IN PATIENTS WITH AMI

3.2.1. Characteristics of FFR and RFR in non-culprit lesions of intermediate stenosis in patients with AMI

Characteristics of treated patients: Most procedures to investigate FFR were accessed through the radial artery (87.7%). The median time from primary PCI to FFR was 5 days (Table 3.15).

Table 3.16. Postive FFR and RFR assessment before and after intervention

Index		Before PCI		After PCI	
		n	%	n	%
FFR	Positive	27	39.1	0	0
	Negative	42	60.9	27	100.0
Total		69	100.0	27	100.0
RFR	Positive	26	56.5	4	19.0
	Negative	20	43.5	17	81.0
Total		46	100.0	21	100.0

Adenosine side effects: The two most common side effects were sinus bradycardia (23.2%) and temporary third-degree atrioventricular block (20.3%) (Chart 3.1).

Table 3.17. Average FFR and RFR values before and after intervention

Variable	Number of vessels	Before PCI	After PCI	p
General FFR	69	0.82 ± 0.11	N/A	N/A
General RFR	46	0.85 ± 0.10		
Pd/Pa	66	0.90 ± 0.10		
Positive FFR	27	0.71 ± 0.10	0.89 ± 0.04	<0.001
Positive RFR and RFR after PCI	20	0.77 ± 0.10	0.93 ± 0.05	<0.001

Before PCI, the parameters linked to FFR assessment showed that the non-culprit vessel with the highest FFR was LAD at 55.1%. Adenosine usage resulted in side effects for 49.3% of patients. In the group with positive lesions, all were classified as B2/C lesions (Table 3.18).

3.2.2. Correlation and concordance between FFR and RFR on non-culprit lesions of intermediate stenosis

Before PCI, the average RFR LCx was found to be lower than that of the LAD and RCA. However, following PCI, the average FFR and RFR LAD dropped below the RCA and LCx values. This change was significant, with a p-value < 0.05 (Table 3.19).

Table 3.20. Correlation between FFR and RFR before and after PCI

Stage	n	r	p
Before PCI	46	0.621	<0.001
After PCI	21	0.608	0.003

Before PCI, the concordance was observed in the assessment of both FFR and RFR indices in the same group of 46 patients. The concordance was confirmed with a Cohen's Kappa consensus coefficient of 0.654, p<0.001. However, no conclusion has been drawn about the concordance between FFR and RFR in the 21 patients after PCI (Table 3.21).

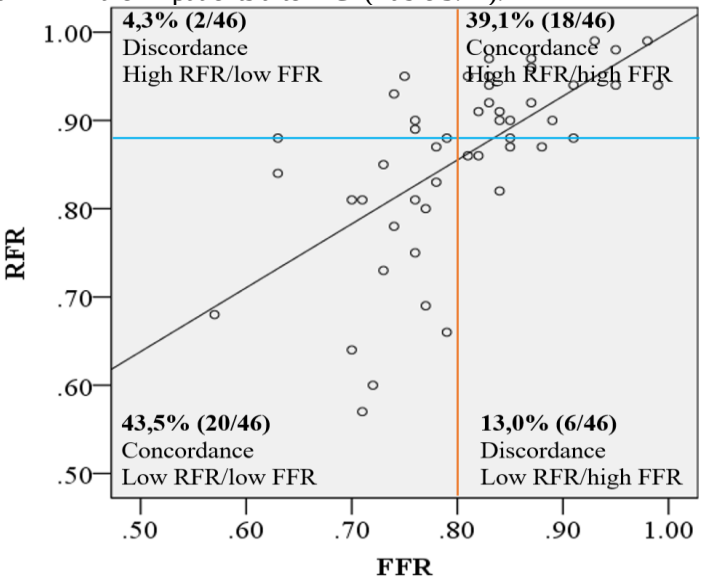

Chart 3.2. Correlation and concordance between FFR and RFR before PCI (n=46)

Comment: The FFR and RFR indexes are categorized into four groups, based on the results of FFR ⩽ 0.8 and RFR ⩽ 0.89. The group with discordant FFR makes up 17.3%, while the one with concordant FFR constitutes 82.7%. The former includes Group 1: high FFR (FFR>0.80)/low RFR (RFR⩽0.89), and Group 2: low FFR (FFR⩽0.80)/high RFR (RFR>0.89). The latter, on the other hand, consists of a group with low FFR (FFR⩽0.80)/low RFR (⩽0.89), and another group with high FFR (FFR>0.80)/high RFR (RFR >0.89).

3.3. PERFORMANCE VALUE OF FFR COMPARED TO QCA IN GUIDING INTERMEDIATE NON-CULPRIT LESIONS PCI IN PATIENTS WITH AMI

3.3.1. Changing the treatment strategy for non-culprit coronary artery lesions

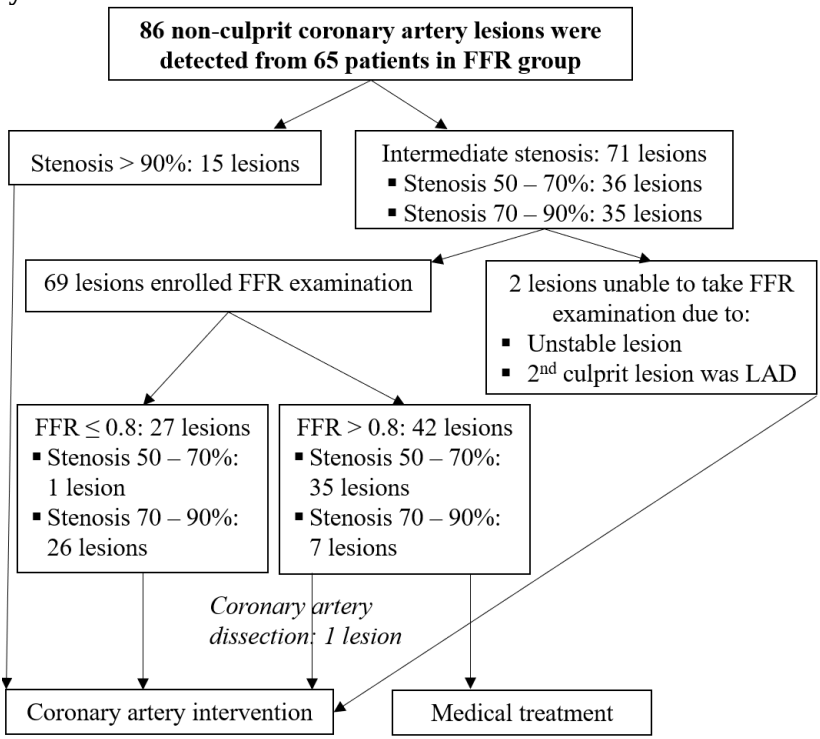

Figure 3.1. Treatment strategy for FFR guided PCI of nonculprit lesions

Treatment changes according to FFR results versus QCA in

intermediate stenosis groups: In the 50% - 70% stenosis group, compared to 100% medical therapy based on findings of coronary angiography, findings from FFR affected 7.7% for PCI. For patients with stenosis of 70% or more, the FFR group shifted 37.5% of patients to medical treatment in the 70%-90% stenosis group (Figure 3.4).

Treatment adjustments according to FFR group versus QCA in all intermediate stenotic lesions: In 69 lesions where FFR was used, FFR guidance increased the rate of medical treatment from 52.2% (if using QCA guidance) to 59.4% and lessened the rate of PCI from 47.8% to 40.6%. Among these, there was one case of negative FFR still requiring PCI due to coronary artery dissection (Figure 3.5).

3.3.2. Effectiveness of non-culprit coronary artery intervention according to FFR guidelines compared to the control group

Significant differences were observed in stent parameters in the FFR group and the control group for non-culprit lesions. The average number of stents per patient at intervention times was 2.28 ± 0.93 in the FFR group, which was statistically lower than the control group (1.97 ± 0.97 vs. 2.60 ± 0.77; 0.80 ± 0.83 vs. 1.34 ± 0.57; $p < 0.001$). However, the average amount of contrast agent per patient was not significantly different between the two groups ($p>0.05$). For non-culprit arteries, the FFR group had a significantly lower average number of stents than the control group, at 0.60 ± 0.66 vs. 0.93 ± 0.66 ($p=0.001$). Similarly, fewer patients in the FFR group had one or more stents compared to the control group, with percentages of 52.3% vs. 76.6% ($p=0.004$). The FFR group also used less contrast agent on non-culprit arteries, with a median amount of 65 ml vs. 130 ml in the control group ($p<0.001$). Interestingly, the stent length in the FFR group was significantly longer than in the control group, with median lengths of 32 mm vs. 25 mm ($p=0.001$) (Tables 3.22, 3.23, 3.24).

In terms of intervention results for non-culprit coronary artery lesions, both the FFR and control groups performed well. TIMI III was achieved 100% in both groups, and procedural success was high in both groups. The median hospital stay was 7 days, with no significant difference between the two groups (Table 3.25).

3.3.3. Main cardiovascular events in patients with non-culprit lesions

The frequency of major cardiovascular events was similar in both the FFR and control groups. There was one case of cardiac mortality in the control group. Both the FFR group and the control group each reported two non-cardiac deaths. The control group had three cases of non-fatal MI, which is 2.3% of the total. Kidney failure also occurred

in three cases in the control group, accounting for 2.3% of the total. The FFR group reported two cases of revascularization on previous lesions with negative FFR. Lastly, the control group reported one case of stroke, as shown in Figure 3.6.

Table 3.26. Comparison of major cardiovascular events in patients with nonculprit coronary artery injury in the FFR group and the control group

Events	Total (n=130)		FFR (n=65)		Control (n=65)		p
	n	%	n	%	n	%	
In-hospital	3	2.3	0	0	3	4.6	N/A
Post-discharge	11	8.5	4	6.2	7	10.8	0.344
Death	5	3.8	2	3.1	3	4.6	1.000
Follow-up time	15.35 ± 7.96		14.75 ± 8.90		15.95 ± 6.90		0.127

Table 3.27. Median event-free survival time after hospital discharge in the FFR group and control group

Group	n	Number of events	Event-free survival time (months)		p
			Mean	SE	
FFR group	65	4	24.3	0.5	0.364
Control group	65	7	22.9	0.7	
Total	130	11	23.6	0.5	

Table 3.28. Average survival time without death after hospital discharge in the FFR group and control group

Group	n	Number of events	Survival time (months)		p
			Mean	SE	
FFR group	65	2	24.4	0.4	0.667
Control group	65	3	24.1	0.5	
Total	130	5	24.3	0.3	

3.6.4. Association between major cardiovascular events, mortality and study group

The FFR group patients demonstrated a reduced likelihood of experiencing major cardiovascular events in comparison to the control group, with an OR = 0.54 (95% CI: 0.15 - 1.95). However, statistical significance was not achieved (p>0.05) (Table 3.29).

The FFR group patients showed a lower mortality risk compared to the control group, with an OR = 0.66 (95% CI: 0.11 - 4.06). This, however, was not statistically significant (p>0.05) (Table 3.30).

CHAPTER 4
DISCUSSION

4.1. GENERAL CHARACTERISTICS OF STUDY POPULATION

4.1.1. Clinical characteristics of patients with AMI

4.1.1.1. General characteristics of research subjects

Risk factors play a substantial role as follows: Hypertension 80.0%, Diabetes 37.7%, Dyslipidemia 67.7%, Smoking 43.8%, and a BMI ≥ 23 comprise 50.8%. According to research by José de Carvalho Cantarelli and colleagues involving 29,538 patients, independent prognostic factors for individuals with multivessel coronary artery disease include being over 40, being male, having hypertension, dyslipidemia, and type 2 diabetes.

4.1.1.2. Clinical characteristics of study subjects

Generally, our patient sample doesn't consist of high-risk subgroups. Existing studies examining PCI typically exclude patients with Killip III or IV statuses, or those experiencing cardiogenic shock or acute pulmonary edema.

4.1.1.3. Admission medication

The FFR group showed a noticeably higher usage of low molecular weight heparin and proton pump inhibitors when compared to the control group (58.5% vs. 40.0%, p=0.035 and 58.5% vs. 38.5%, p=0.023, respectively). The application of remaining drugs followed the recommended treatment guidelines for patients with AMI who had undergone stent placement.

4.1.2. Paraclinical characteristics of patients with AMI

4.1.2.1. Paraclinical characteristics of study subjects

The median EF was 52.5%. Only a small percentage (16.9%) had an EF less than 40%. An EF of ≤40% is linked with increased in-hospital and 1-year mortality rates in patients undergoing PCI. The median blood creatinine concentration (µmol/L) was 87.0 (25th - 75th percentiles: 75.3 - 99.1). Patients with normal kidney function can undergo the procedure multiple times. The mean LDL-C concentration (mmol/L) in our study was 3.3 ± 0.9 mmol/L, which was higher than in a recent study.

4.1.2.2. Diagnosis of acute myocardial infarction

The proportion of acute STEMI was higher than that of NSTEMI (58.5% vs. 41.5%). It's notable that over half of the patients presented with 2-vessel coronary disease (61.5%), and 3-vessel disease represented 38.5%. Sampling issues could potentially influence these findings.

4.1.3. Characteristics of the culprit lesion primary percutaneous intervention

4.1.3.1. Characteristics of culprit coronary artery lesions

The Left Anterior Descending artery (LAD) is most frequently affected, accounting for 40.8% of cases, closely followed by the Right Coronary Artery (RCA) at 34.6%. This is consistent with Vu Quang Ngoc's study, which found the LAD involved in 51.4% of cases. However, it differs from the FRAME AMI study which identified the RCA as the most commonly affected artery (42.2%) and the LAD as the second (34.7%). The prevalence of lesions in specific coronary artery branches may vary based on sample selection.

4.1.3.2. Parameters of emergency PCI for culprit lesions

The radial artery is the most common access route, used in 83.1% of cases. Thrombectomy was performed on 38.2% of patients. Most lesions were completely occluded, with a TIMI flow rating of 0 in 71.1% of cases.

4.1.3.3. Characteristics of stents in intervention of culprit coronary artery lesions

In the study, 80.0% of patients had a single stent placed on the culprit lesion, with an exceptional case in each group where 3 stents were deployed. All stents used were drug-eluting, adhering to the ESC treatment guidelines of 2023. The median volume of contrast medium used was 150ml per procedure.

The median stent diameter was 3.0mm, which is smaller compared to the 3.3 ± 0.4mm in Vu Quang Ngoc's research, and the 3.2mm in the FRAME AMI study. The average stent length in our study was 32.0 mm, which is less than both Vu Quang Ngoc's study (34 ± 10 mm) and the FRAME AMI study (35.5 ± 16.9 mm).

4.1.3.4. Outcomes of PCI for culprit lesions

After PCI, TIMI flow is predominantly TIMI III, accounting for 98.5%. The angiographic success rate is 96.2%, and the procedural success rate is 100%.

4.1.4. Characteristics of intermediate nonculprit lesions in patients with AMI

4.1.4.1. Characteristics of nonculprit coronary artery lesions

The LAD is the most commonly identified non-culprit coronary artery, accounting for 43.9%. This, of course, depends on the findings related to the culprit coronary artery. It's noteworthy that the rate of 50 - 70% stenosis was significantly higher in the FFR group than the control group (41.9% vs. 23.4%). Conversely, the rate of 70 - 90%

stenosis was significantly higher in the control group than the FFR group (72.3% vs. 40.7%), with p <0.001. The majority of injuries were severe, falling into type B2/C, at a rate of 60.0%.

4.1.4.2. Characteristics of PCI procedure for non-culprit coronary artery lesions

The FFR group had a higher rate of medical treatment at 47.7% compared to 23.4% in the control group, while the control group had a higher rate of PCI at 76.6% compared to the FFR group's 52.3%. In clinical practice, we typically treat and monitor lesions with 50 - 70% stenosis medically, hence we only performed PCI for lesions with stenosis between 70 - 90% and over 90% in our study.

Both study groups had similar medications upon discharge. All patients were given dual antiplatelet therapy: Aspirin was used in all patients, while in the P2Y12 group, Clopidogrel was used by a third of patients (32.3%) and Ticagrelor by two-thirds (67.7%). This treatment aligns with the 2023 ESC guidelines on Acute Coronary Syndrome.

4.2. CHARACTERISTICS OF FFR AND RFR IN INTERMEDIATE NON-CULPRIT LESIONS IN PATIENTS WITH AMI

4.2.1. Characteristics of FFR and RFR on intermediate non-culprit lesions

4.2.1.1. Characteristics of treated patients

Most FFR investigations are conducted via the radial artery (87.7%), a lower proportion than the 95.5% reported in Vu Quang Ngoc's study.

4.2.1.2. Characteristics of the FFR measurement procedure

FFR and RFR Values: Prior to the PCI, the average FFR of the positive FFR group was 0.71 ± 0.10. Post PCI, it increased significantly to 0.89 ± 0.04 (p<0.001). The mean RFR was 0.85 ± 0.10, with the positive group averaging 0.77 ± 0.10. The Pd/Pa averaged out at 0.90 ± 0.10.

Correlation of FFR and RFR: Before PCI, the correlation was r = 0.621, p < 0.001, indicating a strong positive relationship between these two indices. Previous studies have also shown a strong correlation between FFR and RFR, ranging from 0.727 - 0.822. Before PCI, the FFR and RFR indices had a high degree of agreement, as evidenced by Cohen's Kappa coefficient of 0.654 (p < 0.001). Post PCI, the correlation between FFR and RFR was r = 0.608, p = 0.003, again showing a strong positive relationship.

FFR and RFR concordance: Based on FFR ≤ 0.80 and RFR ≤

0.89, the FFR and RFR indices are categorized into four groups. The disconcordance FFR group made up 17.3% of the total, while the concordance FFR group comprised 82.7%. This is consistent with other studies, which have shown results ranging from 19.8% to 22.2%. Both FFR and RFR are proven indices for determining the physiological degree of coronary stenosis. FFR is an index that shows the level of epicardial coronary vasculature narrowing when inducing hyperemia with microvascular vasodilators such as Adenosine.

4.3. PERFORMANCE VALUE OF FFR COMPARED TO QCA IN GUIDED INTERMEDIATE NON-CULPRIT LESIONS IN PATIENTS WITH AMI

4.3.1. Changing the treatment strategy for non-culprit coronary artery lesions

The use of FFR increased the medical treatment rate in our study, compared to QCA-guided. This was observed in 7.7% of patients from the 50 - 70% stenosis group and in 7.2% across all intermediate stenosis lesions. Our findings align with those of the FAMOUS-NSTEMI studies, the FUTURE study, and the research by Vu Quang Ngoc et al. Utilizing FFR to steer patient interventions assists in minimizing unnecessary invasive procedures and surgeries.

4.3.2. Effectiveness of non-culprit PCI according to FFR-guided compared to the control group

4.3.2.1. Results of stent parameters in the FFR group and control group in PCI for non-culprit lesions

The average number of stents per patient during intervention and the result of non-culprit lesion intervention in the FFR group were both significantly lower than in the control group (1.97 ± 0.97 vs. 2.60 ± 0.77; 0.80 ± 0.83 vs. 1.34 ± 0.57; $p<0.001$). Additionally, the average number of stents in non-culprit arteries within the FFR group was significantly lower than the intervention group, 0.60 ± 0.66 vs. 0.93 ± 0.66 ($p=0.001$). The RCTs COMPARE-ACUTE and DANAMI-3-PRIMULTI consistently demonstrated the benefits of FFR-guided nonculprit lesion PCI in reducing the rate of urgent revascularization.

4.3.2.2. Evaluate the results of procedure for non-culprit coronary artery lesions in the FFR group and the control group

Results of procedures for non-culprit lesions: quite good: TIMI III reached 100% in both groups, procedural success was achieved in most patients in both groups. In the criteria for procedural success,

TIMI III flow is one of the most important factors.

Acute kidney injury: In the hospital, we only recorded patients with acute kidney injury due to contrast agents in the control group at a rate of 2.3%, a difference that was not statistically significant.

Hospital stay: In our study, the median number of hospital days was 7 days and was similar between the 2 groups.

Intervention outcomes for non-culprit lesions: The results were rather favorable, with a TIMI III level achieved by 100% of both groups, and the majority of patients in both categories experiencing procedural success. Among the factors for procedural success, achieving TIMI III flow is key.

Acute kidney injury: We observed a 2.3% occurrence of acute kidney injury caused by contrast agents during hospital stay, exclusively in the control group. However, this difference was not statistically significant.

Duration of hospital stay: The median duration of hospital stay in our study was 7 days, with no significant difference noted between the two groups.

4.3.3. Main cardiovascular events in patients with non-culprit lesions

4.3.3.1. Comparison of major cardiovascular events in patients with nonculprit coronary artery lesions in the FFR group and the control group

We observed 15 events in total, which included 3 in-hospital events and 11 post-discharge events. These events were more common in the control group, but the difference wasn't statistically significant. This could be due to the limitations in our study sample size.

The all-cause mortality rate in the control group was higher at 4.6% (3 out of 65 cases). This included one sudden death at home due to suspected heart failure, and two deaths in the FFR group. Out of the 65 cases, 3.1% were non-cardiac, showing no statistical difference between the two groups. Our study's population structure is similar to FRAME AMI. Despite the mortality rate in the FFR group being lower than in the control group, the difference doesn't yet have statistical significance due to the smaller sample size and shorter follow-up period.

Non-fatal recurrent MI occurred in 4.6% (3 out of 65) of the control group cases. No incidents were observed in the FFR group, but the difference wasn't statistically significant. Non-fatal MI typically occurs in two scenarios: peri-procedural MI and spontaneous MI during patient monitoring.

Target lesion revascularization rate was higher in the FFR group than in the control group, but the stenosis grade remained the same when angiography was performed again. However, the patient was still decided to perform PCI due to unstable chest pain symptoms.

One case of transient ischemic attack occurred in the control group, but the patient recovered on their own.

The cumulative event rate was 10.8% in the control group, higher than the FFR group's 6.2%. But, there was no statistically significant difference between the two groups ($p = 0.334$). The average duration of our study was 3.5 years, one year longer than the FLOWER MI study, which had a cumulative event rate of 5.5% in the FFR group and 4.2% in the QCA group.

The average event-free survival time in the FFR group was 24.3 months, compared to 22.9 months in the control group. The difference wasn't statistically significant ($p>0.05$). Similarly, the death-free survival time in the FFR group was 24.4 months, higher than the control group 24.1 months, but the difference wasn't statistically significant ($p>0.05$). Despite this, the event-free survival time in the FFR group was higher than the control group for most of the follow-up period.

4.3.3.2. Association between treatment according to FFR guidelines and major cardiovascular events

Patients in the FFR group had a lower likelihood of experiencing major cardiovascular events when compared to the control group. The rate of these events was 6.2% in the FFR group, which is less than the 10.8% observed in the control group. However, this difference was not statistically significant (OR=0.54, 95%CI: 0.15 - 1.95, $p>0.05$). Similar results were found in research by Maznyczka et al., where there was no difference in all-cause mortality rate between the FFR group (3.5%) and the angiography-guided group (3.7%). Nevertheless, it was noted that FFR significantly reduced the number of patients requiring stents or surgery.

CONCLUSION

1. Clinical and paraclinical characteristics of intermediate non-culprit lesions in patients with AMI

The proportion of 50 - 70% stenosis was significantly higher in the FFR group compared to the control group (41.9% vs. 23.4%, $p<0.001$). Conversely, the rate of 70-90% stenosis was significantly higher in the control group compared to the FFR group (40.7% vs.

72.3%, p<0.001). The most common non-culprit coronary artery was the LAD (43.9%). Severe stenotic lesions (B2/C) accounted for the majority of cases, at 60.0%.

2. Characteristics of FFR and RFR in intermediate non-culprit lesions in patients with AMI

The average FFR was 0.82 ± 0.11 in the positive group and 0.71 ± 0.10 in the negative group , while the average RFR was 0.85 ± 0.10 in the positive group and 0.77 ± 0.10 in the negative group. The average Pd/Pa amounted to 0.90 ± 0.10.

Arteries with a positive FFR (≤ 0.80) was 39.1%. After intervention, all were FFR negative (>0.80). Both FFR and RFR improved post-intervention (p<0.001). However, 49.3% experienced side effects from Adenosine.

The correlation between FFR and RFR was significant both before (r=0.621, p<0.001) and after intervention (r=0.608, p=0.003). The concordance between FFR and RFR before intervention was 82.7%, with the Cohen's Kappa of 0.654 (p < 0.001).

3. Performance value of FFR and QCA for interventional guidelines of intermediate non-culprit lesions in AMI

In the 50% - 70% stenosis group, compared to 100% medical therapy based on findings of QCA, findings from FFR shifted 7.7% to PCI. For patients with stenosis of 70% or more, the FFR guidelines shifted 37.5% of patients to medical treatment in the 70%-90% stenosis group.

In 69 lesions where FFR was used, FFR guidance increased the rate of medical treatment from 52.2% (if using coronary angiography guidance) to 59.4% and lessened the rate of PCI from 47.8% to 40.6%.

The average number of stents per patient and the result in non-culprit lesion intervention in the FFR group were lower than in the control group (1.97 ± 0.97 vs. 2.60 ± 0.77; 0.80 ± 0.83 vs. 1.34 ± 0.57; p<0.001).

The average number of stents in non-culprit coronary arteries in the FFR group was lower than the intervention group (0.60 ± 0.66 vs. 0.93 ± 0.66, p=0.001).

The volume of contrast agent in non-culprit arteries in the FFR group was significantly lower than in the intervention group, with a median of 65 ml vs. 130 ml (p<0.001).

The Kaplan-Meier curve demonstrated that the event-free survival time in the FFR group was higher than the control group for the majority of the follow-up period. However, it became similar at

the conclusion of a 25-month follow-up. The in-hospital event rate was higher in the control group than the FFR group (4.6% vs. 0%), but the difference was not statistically significant.

Post-discharge, the event rate and mortality rate were lower in the FFR group compared to QCA (6.2% vs. 10.8%, p = 0.344, and 3.1% vs. 4.6%, p = 1.000, respectively). However, these differences were not statistically significant.

In the FFR group, patients demonstrated a reduced probability of major cardiovascular events and mortality compared to the control group, with OR = 0.54 (95% CI: 0.15 - 1.95) and OR = 0.66 (95% CI: 0.11 – 4.06) respectively. However, these differences were not found to be statistically significant.

STUDY LIMITATION

Our research was conducted during the COVID-19 outbreak (2019-2021), a time that presented several challenges. These included restrictions on data sampling, and patient monitoring. Additionally, the relatively small size of our study, with 65 patients in both the FFR and control groups, led to a limited number of events, which made further analysis challenging. Furthermore, FFR was evaluated using two different types of wires in two distinct stages, causing minor tool non-uniformity, but its impact was minimal.

RECOMMENDATION

Interventional cardiologists may apply FFR to examine non-culprit lesions with intermediate stenosis in patients with AMI.

The RFR index, which strongly correlates with FFR, could be used in conjunction with FFR to investigate these non- culprit lesions.

Further larger sample size, multicenter studies with extended follow-up periods should be conducted for a precise assessment of using the FFR to guide PCI for non-culprit lesions in AMI patients.

LISTED OF RELATED SCIENTIFIC WORKS THAT HAD BEEN PUBLISHED

1. Chau Do Truong Son, Hoang Anh Tien, Truong Quang Binh, Nguyen Do Anh, Nguyen Dinh Dat, Le Manh Thong (2023) Characteristics of non-culprit lesions with intermediate stenosis and the correlation between FFR and RFR in patients with acute myocardial infarction. Journal of Medicine and Pharmacy 13(5).
2. Chau DTS, Truong QB, Nguyen DA, Le MT, Nguyen DD, Hoang AT (2023) Fractional flow reserve in assessment of intermediate nonculprit lesions in acute myocardial infarction. J Pharm Pharmacogn Res 11(5): 823–832. https://doi.org/10.56499/jppres23.1696_11.5.823