Original Article

Adverse Cardiac Events Compared between Instantaneous Wave-Free Ratio-Guided and Standard Angiography-Guided Revascularization in Thai Patients with Intermediate-Grade Stenosis Coronary Artery Disease

Ruampornpanu N, MD[1], Wongpraparut N, MD[1], Tresukosol D, MD[1], Chunhamaneewat N, MD[1], Towashiraporn K, MD[2], Pongakasira R, MSc[2]

[1] Division of Cardiology, Department of Medicine, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand

[2] Her Majesty's Cardiac Center, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand

Objective: To compare the rate of adverse cardiac events between instantaneous wave-free ratio (iFR)-guided and standard angiography-guided revascularization in Thai patients with intermediate coronary artery disease (CAD).

Materials and Methods: This retrospective cohort clinical study included patients with intermediate CAD who underwent revascularization at Siriraj Hospital, Thailand's largest national tertiary referral center, between January 2016 and June 2017. Enrolled patients underwent either iFR-guided or standard angiography-guided revascularization. Baseline demographic and clinical data, laboratory investigations, medications, intraprocedural findings, postprocedural outcomes, composite endpoint of death from any cause, non-fatal myocardial infarction, and repeat revascularization were compared between groups.

Results: Three hundred forty-three patients (98 iFR-guided, 245 angiography-guided) were included. The mean age was 67 years, and 218 were male. A primary endpoint event occurred in five patients in the iFR group, and in 21 patients in the angiography group. The rate of death from any cause, non-fatal myocardial infarction, repeat revascularization, and stent thrombosis did not differ significantly between groups, but each rate was lower in the iFR group. Fluoroscopic time, radiation dose, and procedure cost were all significantly lower in the iFR group.

Conclusion: For the patients with intermediate stenosis of CAD, the iFR guided treatment group had a trend toward lower rate of a composite of death, non-fatal myocardial infarction, and repeat revascularization than angiography guided group, but not statistically significant.

Keywords: Physiologic assessment, Angiography, Coronary artery disease

J Med Assoc Thai 2019;102(6):699-706
Website: http://www.jmatonline.com
Received 18 Apr 2019 | Revised 2 May 2019 | Accepted 6 May 2019

Coronary artery disease (CAD) is the leading cause of death among non-communicable diseases in Thailand. Coronary revascularization is indicated in patients with significant coronary artery stenosis that have Canadian Cardiovascular Society grading of angina pectoris of III or IV, or in patients with area of ischemia greater than 10%[1]. Stenosis of a coronary artery greater than 70% is well correlated with ischemia. Although 50% to 70% stenosis of a coronary artery (40% to 80% in some studies) was defined as an intermediate lesion in some prior studies, the results showed weak association between intermediate lesion and adverse physiologic effect[2-4]. In the Fractional Flow Reserve Versus Angiography for Multivessel Evaluation (FAME) study, physiologic ischemia occurred in 35% of patients with intermediate coronary artery stenosis[5]. Fractional flow reserve (FFR) measurement is a class IIa recommendation in intermediate coronary artery stenosis that results in decreased adverse cardiac

Correspondence to:

Wongpraparut N.

Division of Cardiology, Department of Medicine, Faculty of Medicine Siriraj Hospital, Mahidol University, 2 Wang Lang Road, Bangkoknoi, Bangkok 10700, Thailand.

Phone: +66-2-4196104, **Fax**: +66-2-4197412

Email: wongpraparut@yahoo.com

How to cite this article: Ruampornpanu N, Wongpraparut N, Tresukosol D, Chunhamaneewat N, Towashiraporn K, Pongakasira R. Adverse Cardiac Events Compared between Instantaneous Wave-Free Ratio-Guided and Standard Angiography-Guided Revascularization in Thai Patients with Intermediate-Grade Stenosis Coronary Artery Disease. J Med Assoc Thai 2019;102:699-706.

events after revascularization[2,3,6-14]. Instantaneous wave-free ratio (iFR), which measures the pressure and flow during the diastole in the wave-free period, was also used to assess significant physiologic stenosis in patients with intermediate lesion[15-17].

A large randomized controlled study published in 2017 compared the rate of adverse cardiac events between FFR and iFR[4]. In that study, an FFR value of 0.80 or less and an iFR value of 0.89 or less indicated significant physiological coronary artery stenosis. At the 1-year follow-up, there was no significant difference in adverse cardiac events. including the rate of composite death, non-fatal myocardial infarction, and unplanned revascularization within 12 months, between the FFR and iFR groups (6.7% versus 6.1%, 95% confidence interval 0.79 to 1.58, respectively; p=0.53)[4].

Even though physiologic testing is recommended in the current practice guidelines, it has not been widely adopted in routine clinical practice in Thailand due to budgetary restrictions. Moreover, although iFR was introduced in Thailand in 2016, most hospitals still use standard angiography as the main modality for evaluating significant CAD. However, there is no data comparing iFR-guided versus angiographic-guided revascularization in Thailand. Accordingly, the aim of the present study was to investigate the rate of adverse cardiac events compared between iFR-guided and standard angiography-guided revascularization in Thai patients with intermediate CAD.

Material and methods

Study design

This single-center retrospective cohort clinical study included patients with intermediate CAD who underwent revascularization at Siriraj Hospital, Thailand's largest national tertiary referral center, between January 1, 2016 and June 30, 2017. Enrolled patients underwent either iFR-guided or standard angiography-guided revascularization. The protocol for the present study was approved by the Siriraj Institutional Review Board (SIRB), Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand (certificate of approval no. Si013/2018).

Patient population

Patients eligible for inclusion in the present study had intermediate CAD with stenosis occupying 40% to 70% of vessel diameter based on angiographic appearance and as decided by a cardiac interventionist. Additional inclusion criteria were age greater than 18 years and having at least single-vessel intermediate CAD. In patients with stable CAD, any lesion could be assessed. However, in patients with acute coronary syndrome (not including ST-elevation myocardial infarction), non-culprit lesions were assessed. Patients were divided into either the iFR-guided revascularization group or the angiography-guided revascularization group. Data in both groups were recorded in a consecutive manner. Patients having a life expectancy of less than one year from underlying diseases or other diseases, a history of previous coronary artery bypass graft (CABG), contraindication to antiplatelet, and/or pregnancy were excluded.

Procedures

iFR measurements were performed using a coronary pressure wire (Philips Volcano, Amsterdam, The Netherlands). An iFR value lower than 0.89 indicated significant physiological stenosis. Re-vascularization (percutaneous coronary intervention [PCI] or CABG) was performed according to standard clinical practice. The type of antiplatelet (aspirin or P2Y12 inhibitors) administered before, during, and/or after revascularization was determined according to the discretion of the attending cardiologists.

Data collection, end points, and follow-up

Patient demographic, clinical, laboratory, medication, procedural, and outcome data were collected from hospital inpatient and outpatient medical records. An attempt was made to contact patients who were lost to follow-up by telephone to inquire about clinical outcome. The primary endpoint was the rate of composite death from any cause, non-fatal myocardial infarction, or repeat revascularization after procedure. The secondary endpoints included each of the individual component outcomes from the primary endpoint, and stent thrombosis, procedural time in catherization lab, radiation dose in the catherization lab, and any bleeding event after procedure.

Myocardial infarction was defined as any symptoms of chest pain or chest discomfort, or abnormal electrocardiogram (EKG) plus evidence of rising or falling pattern of cardiac enzymes. Any bleeding events were defined according to thrombosis in myocardial infarction (TIMI) bleeding criteria. All patients were followed for at least six months after the revascularization procedure.

Sample size calculation and statistical analysis

The primary objective was to determine whether

Table 1. Baseline demographic, clinical, lifestyle, and follow-up characteristics compared between the iFR and angiography groups

Characteristics	iFR group (n=98) n (%)	Angiography group (n=245) n (%)	p-value
Age (year), Mean±SD	66.86±11.23	67.27±10.73	0.751
Sex: male	58 (59.2)	160 (65.3)	0.287
Indication for angiography			0.014
Stable angina	82 (83.7)	174 (71.0)	
Unstable angina	4 (4.1)	26 (10.6)	
NSTEMI	9 (9.2)	43 (17.6)	
Other	3 (3.1)	2 (0.8)	
Diabetes mellitus	45 (45.9)	118 (48.2)	0.707
Hypertension	92 (93.9)	215 (87.8)	0.095
Dyslipidemia	62 (63.3)	175 (71.4)	0.139
Renal failure	21 (21.4)	58 (23.7)	0.656
Smoking status			0.761
Current	5 (5.1)	11 (4.5)	
Quit	11 (11.2)	26 (10.6)	
Not available	82 (83.7)	208 (84.9)	
Follow-up duration (month), Mean±SD	10.77±3.98	14.02±5.14	<0.001

iFR=instantaneous wave-free ratio; SD=standard deviation; NSTEMI=non-ST segment elevation myocardial infarction

A p-value <0.05 indicates statistical significance

the rate of major cardiac events (primary outcome) differed significantly between patients who received iFR-guided treatment and those who received angiography-guided treatment. Using an alpha level of 0.05, statistical power of 0.80, and assuming a 1-year rate of major cardiac events of 18.3% in the angiography group[14] and a 6.7% rate in the iFR group[4], a minimum sample size of 100 patients in the iFR group and 200 patients in the angiography group was calculated.

All endpoint analyses were performed using per-protocol analysis. Descriptive statistics were used to summarize demographic and clinical data. Categorical variables were compared using chi-square test or Fisher's exact test, and continuous variables were compared using independent t-test or Mann-Whitney U test. Categorical variables are presented as number and percentage, and continuous variables are shown as either mean ± standard deviation or median (interquartile range) depending on the distribution of data. SPSS Statistics version 19.0 (SPSS Inc., Chicago, IL, USA) was used for all statistical analyses. Statistical significance was assumed for all p-values less than 0.05.

Results

Baseline characteristics

Three hundred forty-three patients (98 iFR-guided and 245 angiography-guided) were included. The mean age was 67 years, and 218 were male. The baseline characteristics between groups are shown in Table 1 and 2. The iFR-guided group had more stable CAD patients than the standard angiography group (Table 1), and clopidogrel was more commonly used as a second antiplatelet in the standard angiography group than in the iFR-guided group (Table 2). Regarding angiographic findings, the numbers of coronary vessels affected were not different between groups, and most patients in both groups had single-vessel disease. In the iFR-guided group, 68.2% of patients had no stenosis lesion inducing ischemia, which meant that revascularization was deferred in those patients. Baseline left ventricular systolic function was not significantly different between groups (Table 3).

Primary endpoint

A primary endpoint event occurred in five (5.1%) patients in the iFR-guided group, and in 21 (8.6%)

Table 2. Laboratory investigations and medications compared between the iFR and angiography groups

Characteristics	iFR group (n=98) n (%)	Angiography group (n=245) n (%)	p-value
Creatinine (mg/dl), Mean±SD	1.39±1.33 (n=96)	1.55±1.65 (n=243)	0.406
CrCl (CKD-EPI equation) (ml/minute/1.73 m^2), Mean±SD	64.45±25.05 (n=96)	61.41±24.66 (n=243)	0.309
LDL (mg/dl), Mean±SD	89.81±41.95 (n=59)	96.93±35.73 (n=125)	0.235
AST (U/L), Median (IQ1, IQ3)	26.00 (19.00, 31.00) (n=30)	21.50 (17.50, 27.00) (n=64)	0.207
ALT (U/L), Median (IQ1, IQ3)	21.50 (16.50, 26.50) (n=32)	21.00 (15.00, 29.00) (n=67)	0.686
Hematocrit (g/dl), Mean±SD	37.95±5.53 (n=88)	39.10±6.68 (n=215)	0.159
Platelets (x10^3/ul), Mean±SD	240.184±68.87 (n=87)	244.33±79.42 (n=223)	0.670
Aspirin	90 (91.8)	243 (99.2)	0.001
Clopidogrel	62 (63.3)	214 (87.3)	<0.001
Ticagrelor	16 (16.3)	23 (9.4)	0.067
Prasugrel	7 (7.1)	2 (0.8)	0.003
Beta blocker	72 (73.5)	185 (75.5)	0.694
ACEI/ARB	55 (56.1)	118 (48.2)	0.183
Statin	88 (89.8)	223 (91.0)	0.725

iFR=instantaneous wave-free ratio; SD=standard deviation; CrCl=creatinine clearance; CKD-EPI=Chronic Kidney Disease Epidemiology Collaboration; LDL=low-density lipoprotein; AST=aspartate transaminase; IQ=interquartile; ALT=alanine aminotransferase; ACEI/ARB=angiotensin converting enzyme inhibitors/angiotensin receptor blockers

A p-value<0.05 indicates statistical significance

Table 3. Angiographic and iFR findings compared between the iFR and angiography groups

Characteristics	iFR group (n=98)	Angiography group (n=245)	p-value
Angiographic findings, n (%)			0.641
One-vessel CAD	41 (41.8)	105 (42.9)	
Two-vessel CAD	39 (39.8)	86 (35.1)	
Three-vessel CAD	18 (18.4)	54 (22.0)	
Left main involvement	4 (4.1)	12 (4.9)	1.000
Number of total lesions evaluated by iFR	129	NA	
Number of intermediate lesions per patient, Mean±SD	1.48±0.63	1.39±0.57	0.214
Number of significant stenoses (iFR ≤0.89) per total lesion after assessment by iFR, n (%)	41 (31.8)	NA	
Mean iFR, Mean±SD	0.91±0.09	NA	
Number of treated lesions guided by iFR per total lesion	38	NA	
LVEF (%), Mean±SD	54.51±17.27(n=59)	58.11±16.59(n=156)	0.162

iFR=instantaneous wave-free ratio; CAD=coronary artery disease; SD=standard deviation; LVEF=left ventricular ejection fraction; NA=not available

A p-value<0.05 indicates statistical significance

Table 4. Primary and secondary endpoints compared between the iFR and angiography groups

Endpoint	iFR group (n=98) n (%)	Angiography group (n=245) n (%)	p-value
Primary endpoint: death from any cause, nonfatal myocardial infarction, or repeat revascularization	5 (5.1)	21 (8.6)	0.273
Death from any cause	3 (3.1)	7 (2.9)	1.000
Non-fatal myocardial infarction	0 (0.0)	9 (3.7)	0.065
Repeat revascularization	2 (2.0)	9 (3.7)	0.735
Stent thrombosis	0 (0.0)	0 (0.0)	-
Fluoroscopic time (minute), Median (P25, P75)	16.33 (8.18, 24.46) (n=97)	17.80 (13.11, 25.39) (n=242)	0.022
Radiation dose (mGy), Median (P25, P75)	1,278 (492, 2,081) (n=97)	1,709 (1,100, 2,543) (n=243)	0.001
Any bleeding event	1 (1.0)	8 (3.3)	0.455
TIMI major bleeding	0 (0.0)	1 (0.4)	
TIMI minor bleeding	1 (1.0)	7 (2.8)	
Cost per person (Thai baht), Mean±SD	138,571±70,728	156,551±51,496	0.024

Ifr=instantaneous wave-free ratio; P=percentile; TIMI=thrombosis in myocardial infarction score; SD=standard deviation

A p-value<0.05 indicates statistical significance

patients in the angiography-guided group (p=0.273) (Table 4).

Secondary endpoints

Death from any cause occurred in three patients in the iFR group (3.1%), and in seven patients in the angiography group (2.9%) (p=1.000). Non-fatal myocardial infarction occurred in nine patients (3.7%), and those patients were in the angiography group (p=0.065). The rate of repeat revascularization was 2% in the iFR group, and 3.7% in the angiography group (p=0.735). No patients in either group had stent thrombosis. The median fluoroscopic time was 16.33 minutes (8.18, 24.46) in the iFR group, and 17.80 minutes (13.11, 25.39) in the angiography group (p=0.022). The radiation dose was significantly lower in the iFR group [1,278 mGy (492, 2,081)] than in the angiography group [1,709 mGy (1,100, 2,543)] (p=0.001). Any type of bleeding event occurred in 1% of patients in the iFR group, and in 3.3% of patients in the angiography group (p=0.455) (Table 4). The mean cost of the procedure was significantly lower in the iFR group (138,571±70,728 Thai baht) than in the angiography group (156,551±51,496 Thai baht) (p=0.024).

Discussion

The authors found that iFR-guided revascularization has similar outcome to angiography-guided revascularization in Thai patients with intermediate CAD; however, radiation dose, fluoroscopic time, and procedure cost were all found to be significantly lower in the iFR-guided group than in angiography-guided group.

The FAME study, which included 1,005 patients with multivessel CAD and coronary stenosis of 50% or more, found FFR-guided revascularization as an add-on to angiography to be associated with lower 1-year event rates of death, myocardial infarction, and repeat revascularization compared to angiography-guided revascularization alone (13.2% versus 18.3%, respectively; p=0.02)[14]. iFR demonstrated diagnostic accuracy similar to that of FFR[15-17]. The iFR was not found to be inferior to FFR relative to clinical event rates in patients with intermediate coronary stenosis (6.7% versus 6.1%, respectively; p=0.53)[4]. The iFR cutoff values used in many studies differed due to the acceptance of different levels of sensitivity, specificity, and accuracy. In 2012, 157 stenosis lesions were assessed in a pilot study for the ADVISE study[15]. Compared to an FFR cutoff value of 0.80, those authors decided upon an optimal iFR cutoff value of 0.83 with a diagnostic accuracy of 88%. Later in 2013, that same group included 339 more coronary lesions and identified a new iFR cutoff point (when compared to FFR) of 0.89 with a diagnostic accuracy of 94%[18].

Although iFR has demonstrated accuracy and efficacy similar to that of FFR for identifying physiologically significant coronary stenosis, iFR has not yet been included in the standard revascularization guidelines. The iFR demonstrated slightly greater advantage than FFR in patients with contraindications for adenosine. Based on previous findings, the authors hypothesized that iFR-guided treatment would be associated with a lower rate of adverse events than angiography-guided treatment. An iFR cutoff point of 0.89 or less was used in the present study.

The results of the present study revealed a lower rate of non-fatal myocardial infarction and repeat revascularization in the iFR-guided group, but the difference between groups was not statistically significant. This may be explained by the relatively low rate of clinical events in both study groups. Using data from previous studies to calculate the present study sample size, the primary endpoint was estimated to occur in approximately 6.7% of patients in the iFR-guided group[4], and in 18.3% of patients in the angiography-guided group[14]. However, and in contrast, the primary endpoint occurred in 5.1% of patients in the iFR group, and in 8.6% of patients in the angiography group in the present study. This lower percentage of adverse events would require a larger sample size to identify statistically significant differences and associations.

A comparison of baseline characteristics revealed no significant difference between groups, except indication for coronary angiography and the type of antiplatelet, both of which were higher in the angiography group. There were more patients with acute coronary syndrome in the angiography group, and most patients in the iFR group had stable CAD. Significantly more patients in the angiography group were prescribed aspirin and clopidogrel than were patients in the iFR group. The fact that the type of antiplatelet was selected at the discretion of the interventionist suggests platelet choice as a possible confounding factor that could have influenced a better outcome in the iFR group.

Regarding patient safety, fluoroscopic time and radiation dose were significantly lower in the iFR-guided treatment group. This finding may, in part, be because the patients in the iFR group had additional criteria to qualify for revascularization than patients in the angiography group. More specifically, patients that had an iFR value of greater than 0.89 did not receive inappropriate revascularization, and the incidence of adverse cardiac events in these patients did not increase in the present study. Regarding bleeding, there was no difference between groups for either TIMI major or TIMI minor bleeding events. Concerning cost, the mean procedure cost per patient was significantly lower in the iFR-guided group than in the angiography-guided group. Similar to previous studies, the authors found that iFR could distinguish physiologically significant stenosis of intermediate CAD, which resulted in a decrease in the number of unnecessary revascularization procedures[19,20].

Limitation

The major limitation of the present study is its retrospective design, which makes it vulnerable to missing and/or incomplete data. A second potential shortcoming is the relatively small size of the study population, especially in the iFR group. This factor may have given the present study insufficient statistical power to identify all significant differences and associations between groups. Third and last, although our data were collected from a single center, our hospital is a large university-based national tertiary referral hospital that is often referred complicated cases. As a result, the present findings may not be generalizable to other care settings. Further prospective study is needed to further clarify the differences between these revascularization guidance techniques in Thai patients with intermediate severity CAD.

Conclusion

Among Thai patients with intermediate CAD, the iFR-guided treatment group had significantly lower fluoroscopic time, radiation dose, and procedure-related cost than the angiography-guided treatment group. The iFR-guided group had a lower rate for the composite endpoint of death, non-fatal myocardial infarction, and repeat revascularization than the angiography-guided group, but the difference between groups was not statistically significant.

What is already known on this topic?

The iFR is a new tool for measuring physiological stenosis in patients with intermediate CAD (40% to 70%). Clinical outcome of iFR-guided PCI was not inferior to FFR in large clinical trials. There is no data comparing iFR versus angiography-guided revascularization in Thailand.

What this study adds?

In patients with intermediate CAD, the iFR-guided treatment group had a lower rate of composite death, non-fatal myocardial infarction, and repeat

revascularization than the angiography-guided revascularization group (all p>0.05).

Conflicts of interest

All authors declare no personal or professional conflicts of interest, and no financial support from the companies that produce and/or distribute the drugs, devices, or materials described in this report.

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