Visual-Functional Mismatch and Results of Fractional Flow Reserve Guided Percutaneous Coronary Revascularization

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Objective: *To identify mismatches in the significance of coronary artery stenosis determined by physician's visual estimation (VE) vs. quantitative coronary angiography (QCA), by VE vs. fractional flow reserve (FFR), and independent predictors for mismatch between VE and FFR. Second objective was to evaluate the clinical outcomes of patients receiving FFR-guided percutaneous coronary intervention (PCI).*

Material and Method: *Two hundreds eighty consecutive patients (338 coronary lesions including non-left main (non-LM) 316 lesions and left main (LM) 22 lesions) underwent coronary angiography, offline edge detection QCA, and FFR measurement between August 2011 and December 2013 were included in the present study. Baseline patient data, lesion characteristics, and clinical outcomes were recorded and analyzed. Coronary lesions were then divided into four groups according to FFR results and treatment (FFR <0.75 and PCI, FFR 0.75-0.80 and PCI, FFR 0.75-0.80 and defer PCI, FFR >0.80 and defer PCI). Mismatches in the significance of coronary artery stenosis determined by VE vs. QCA, VE vs. FFR, independent predictors of VE-FFR mismatch, and clinical outcomes after FFR-guided treatment were reported.*

Results: *Lesions with VE-QCA mismatch were seen in 64% of non-LM lesions and in 87% of the LM lesions. Conversely, lesions with VE-QCA reverse mismatch were seen in 13% of non-LM lesions and in 0% of the LM lesions. Lesions with VE-FFR mismatch were seen in 42% of non-LM lesions and in 53% of the LM lesions. Lesions with VE-FFR reverse mismatch were seen in 15% of non-LM lesions and in 14% of the LM lesions. The independent predictors for VE-FFR mismatch in non-LM lesions were shorter lesion and greater minimal lumen diameter. After FFR guided-treatment and dividing coronary lesions into four groups, all patients were followed-up for a median period of 11.6 (IQR; 7.3, 17.6) months. Major adverse cardiovascular events (excluded one death) of 338 lesions were not significantly different in the four groups (1.7% vs. 5.1% vs. 5.3% vs. 2.7%, p = 0.717). The median cost of procedure of lesions undergone FFR plus additional PCI was significantly higher than lesions undergone FFR only (140,000 vs. 137,000 vs. 45,000 vs. 45,000 Baht, p<0.001).*

Conclusion: *Mismatches between visually-estimated significance of angiographic coronary stenosis and QCA or FFR are frequently encountered. Visual estimation of coronary angiography alone cannot entirely predict functional significance of coronary stenosis. FFR measurement provides a helpful strategy for decision making before further revascularization.*

Keywords: *Fractional flow reserve, Percutaneous coronary intervention, Visual-functional mismatch, Quantitative coronary angiography*

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In routine clinical practice, a substantial proportion of patients undergo percutaneous coronary revascularization without an adequate prior non-invasive functional evaluation. Although there are several methods to determine significance of coronary luminal narrowing in cardiac catheterization lab, interventionists traditionally have been trained to assess and made a decision about further management of coronary stenotic lesion mostly on a visual estimation (VE) with an angiogram or their clinical judgments. However, using the coronary angiogram can be difficult to specify which lesions cause ischemia. Revascularization of coronary stenosis that causes ischemia improves patient's status and outcome. For stenoses that do not cause ischemia, however, the benefit of revascularization is less clear[1]. In fact, visual analysis generally leads to overestimate the lesions with severe stenosis, and to underestimate the lesions with more modest degrees of luminal narrowing[2]. In a prospective study, the potential for observer error

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with visual analysis from a coronary angiogram has been estimated to exceed 35%[3].

Quantitative coronary angiography (QCA) is another option to determine the significance of coronary artery stenosis. The rationale for performing QCA is based upon the limitation of visual coronary angiography. The greatest advantage of QCA is its theoretical freedom from observer influences and bias, minimizing significant potential intraobserver and interobserver variability[3-5]. Therefore, it is a method to provide more objective interpretation of the coronary lumenogram than standard visual estimation.

Currently, Fractional flow reserve (FFR) is considered the gold standard for invasive assessment of functional significant coronary stenosis[6-8]. Over the last decade, several studies have investigated methods for identifying patients that might benefit from FFR-guided percutaneous coronary intervention (PCI) including stable patients that elected treatment for single vessel coronary artery disease[9-12], multivessel coronary artery disease[13,14], equivocal left main coronary artery lesions, or bifurcation lesions[15-20]. Angiography alone is inaccurate in assessing the functional significance of a coronary stenosis when compared with the FFR, not only in the 50% to 70% stenotic lesions but also in the 70% to 90% angiographic severity category[1]. Normal FFR is 1.0, whereas an FFR <0.75 is correlated with ischemia on noninvasive imaging in a variety of patient populations; an FFR >0.80 excludes ischemia in more than 90% of cases. In a small gray zone of FFR between 0.75 and 0.80, the ischemic potential of the stenosis remains unclear[21,22].

The first objective of the present study was to identify mismatches in the significance of coronary artery stenosis determined by physician's visual estimation versus nonfunctional test (QCA), physician's visual estimation versus functional test (FFR), and the independent predictors of mismatch between visual estimation and FFR. Second objective was to evaluate the outcomes of patients receiving FFR-guided PCI.

Material and Method

Study designs

The present trial was a prospective, single-centered cohort study that was conducted at Central Chest Institute. Written informed consent was obtained from each patient before performing coronary angiography, FFR, and PCI procedure. The protocol was approved by the Institutional Review Board.

Patient population

Between August 2011 and December 2013, in a prospective cohort, 280 consecutive patients with 338 coronary lesions, underwent angiographic and invasive physiologic assessment by FFR before intervention, and were included in the current analysis. Study population included patients with stable ischemic heart disease (SIHD), unstable angina, and non-ST elevation myocardial infarction (NSTEMI). SIHD was defined as angina chest pain on exertion with a stable pattern for at least three months preceding coronary angiogram. Unstable angina and NSTEMI were defined according to Braunwald classification[23], and the universal definition of MI[24], respectively. All patients were 33 to 86 years of age and had at least one target vessel with 30 to 90% of coronary angiographic stenosis seen on physician's visual estimation.

Clinical definitions and endpoints

VE-QCA "mismatch" was defined as percent stenosis by physician's visual estimation ≥70% for non-left main (non-LM) lesion (or ≥50% for LM lesion) and percent diameter stenosis by QCA <50%, whereas VE-QCA "reverse mismatch" was defined as percent stenosis by physician's visual estimation <70% for non-LM lesion (or <50% for LM lesion) and percent diameter stenosis by QCA ≥50%. VE-FFR "mismatch" was defined as percent stenosis by physician's visual estimation ≥70% for non-LM lesion (or ≥50% for LM lesion) and FFR >0.80, whereas VE-FFR "reverse mismatch" was defined as percent stenosis by physician's visual estimation <70% for non-LM lesion (or <50% for LM lesion) and FFR ≤0.80.

Lesions with FFR <0.75 were treated with PCI, whereas lesions with FFR >0.80 were deferred PCI. In case FFR 0.75-0.80, treatment strategies were determined at the operator's discretion. Coronary lesions were then divided into four groups according to FFR and treatment (FFR <0.75 and PCI, FFR 0.75-0.80 and PCI, FFR 0.75-0.80 and defer PCI, FFR >0.80 and defer PCI). The primary end point was the rate of major adverse cardiovascular events (MACE). MACE was defined as a composite of death, recurrent myocardial infarction (MI), any repeated revascularization, stroke, and congestive heart failure (CHF). The secondary end point included angina class as assessed with the Canadian Cardiovascular Society (CCS) classification system, and the cost of material used in cardiac catheterization lab. After discharge, first follow-up assessment was performed approximately at one month. Then the further follow-up

was scheduled at out-patient department (OPD). If the patients discontinued the follow-up at the OPD, a contact by phone was made.

Visual estimation (VE)

Diagnostic left heart catheterization and coronary angiography were performed with standard percutaneous approach from either femoral or radial artery. Each vascular segment of the coronary artery was recorded in two orthogonal or nearly orthogonal views to avoid missing important diagnostic information about eccentric stenosis. The operator then estimated percent of coronary stenosis visually. As results of previous study regarding significant operator variability and systematic form of "stenosis inflation" that causes operators to estimate a diameter stenosis that is roughly 20% higher than that measured by QCA[25], a stenosis that visually measured 50% (diameter) stenosis was thus typically called 70% (area) stenosis, whereas a stenosis that visually measured 70% (diameter) stenosis was called 90% (area) stenosis[26]. Significant anatomical coronary stenosis was defined as ≥70% stenosis in non-LM and ≥50% stenosis in LM lesions[27].

Quantitative coronary angiography (QCA)

Measuring by an independent observer that was blinded to patient clinical outcome and FFR data, the severity of the coronary lesion was assessed by using offline edge detection QCA calculations with the Medcon analysis software (Horizon Cardiology version 12.2, McKesson Israel LTD., Tel-Aviv, Israel). The radiopaque catheter was used for calibration. The percent diameter stenosis, minimal lumen diameter, reference lumen diameter, and lesion length were measured, preferably, on end-diastolic images. The lesion segment was defined as proximal, mid, or distal. Significant angiographic diameter stenosis by QCA was defined as the presence of ≥50% stenosis on the coronary lesion segment.

Fractional flow reserve (FFR)

A 0.014-inch pressure monitoring guidewire (PrimeWire-Prestige, Volcano Corporation, San Diego, CA, USA) was calibrated and introduced into the guiding catheter. Subsequently, the pressure wire was advanced further into the target coronary artery, until the pressure sensor was located just distal to the lesion segment. For ostium left main, ostium right coronary artery, or diffuse-diseased segment, the maximal myocardial hyperemia was induced by intravenous adenosine 140 mcg/kg/min via large central vein, whereas all other lesions were used escalating intracoronary bolus doses of adenosine through the guiding catheter until steady-state hyperemia was achieved. During maximal hyperemia, FFR was calculated as the ratio between the simultaneously recorded mean distal coronary artery pressure and aortic pressure. Significant FFR was defined as ≤0.80[6,27].

Sample size calculation

From literature review, prevalence of angiographic FFR mismatch or reverse mismatch was seen in 32.59% of coronary lesions[28]. By using α error = 0.05 and Z (two-tailed test) = 1.96, the calculated sample size were at least 338 coronary lesions.

Statistical analysis

The categorical data were presented as frequency and percentage. The continuous variables were reported as a mean ± standard deviation. Differences between the patient groups were examined using Chi-square or Fisher's exact test. Differences in continuous variables between groups were assessed using the unpaired Student's t-test or the Mann-Whitney U-test. Correlation between two quantitative variables was used Spearman's rho analysis. Univariate analyses were used to examine the relationship between variables and VE-FFR mismatch or reverse mismatch. Multivariate analyses by Enter logistic regression analysis method were used to assess whether prognostic variables were still statistically significant when adjusted for other variables significantly associated with the mismatch or reverse mismatch in the univariate analyses. All tests were two-tailed. A p-value of <0.05 was considered statistically significant. All of the analyses were done using STATA/SE 11 software package (Stata Corp LP, College Station, TX, USA).

Results

Study population

After excluding four patients (unsuccessful FFR measurement in two patients, FFR performed only after PCI in one patient, and unrecorded FFR results in one patient), 280 patients (338 lesions) undergoing coronary angiogram, offline edge detection QCA, and FFR measurement were enrolled between August 2011 and December 2013. Their baseline clinical characteristics and lesion locations are provided in Table 1. The average patient age (± SD) was 62.2±10.1 years, 70.4% were men, 38.2% had diabetes, 90.4%

Table 1. Clinical characteristics and lesion locations in 280 patients (338 lesions)

Clinical characteristics (n = 280)	
Age (years)	62.2±10.1
Male	197 (70.4%)
Ejection fraction (%)	60.7±13.5
Diabetes	107 (38.2%)
Hypertension	226 (80.7%)
Hyperlipidemia	268 (95.7%)
Smoking	32 (11.4%)
Previous PCI	159 (56.8%)
Clinical manifestation	
Stable ischemic heart disease	253 (90.4%)
Unstable angina	9 (3.2%)
Non-ST elevation MI	18 (6.4%)
Lesion locations (n = 338)	
Left main coronary artery	22 (6.5%)
Proximal LAD	102 (30.2%)
Mid LAD	87 (25.7%)
Distal LAD	6 (1.8%)
Proximal LCX	23 (6.8%)
Mid LCX	22 (6.5%)
Distal LCX	2 (0.6%)
Proximal RCA	19 (5.6%)
Mid RCA	47 (13.9%)
Distal RCA	8 (2.4%)

PCI = percutaneous coronary intervention; LAD = left anterior descending artery; LCX = left circumflex; RCA = right coronary artery
Values are mean ± SD or n (%)

had clinical manifestation as stable ischemic heart disease, and 6.5% had isolated LM lesions. Percent stenosis by visual estimation ranged from 30% to 90%. Percent stenosis by visual estimation ≥70% was seen in 142 (44.9%) lesions for non-LM lesions, and ≥50% was seen in 15 (68.2%) lesions for LM lesions. Percent diameter stenosis by QCA ≥50% was seen in 73 (23.1%) lesions for non-LM lesions, and in two (9.1%) lesions for LM lesions. Two hundred twenty seven, 48, and five patients underwent FFR measurement for one, two, and three lesions, respectively. FFR results ranged from 0.44 to 1.0. The mean FFR (± SD) at maximal hyperemia was 0.82±0.09. FFR was not significantly higher in females than in males (0.84±0.10 vs. 0.82±0.09, p = 0.112) and no significant correlation with patient age (r = 0.024, p = 0.656). FFR ≤0.80 was seen in 108 (34.2%) lesions of non-LM lesions, and eight (36.4%) lesions for LM lesions. For non-LM lesions that visually estimated percent stenosis ≥70%, FFR ≤0.80 was seen in 82 (57.7%) lesions. For LM lesions that visually estimated percent stenosis ≥50%, FFR ≤0.80 was seen in seven (46.7%) lesions. After FFR measurement, patients were treated according to FFR value and were divided into four groups as mentioned previously (Fig. 1).

Diagnostic accuracy of visually estimated angiographic % stenosis and QCA

There was a significant correlation between visually estimated percent stenosis and QCA in the non-LM (r = 0.363, p<0.001), whereas this correlation was not statistically significant in the LM group (r = 0.246, p = 0.271). Among the 142 non-LM lesions with visually estimated percent stenosis ≥70%, QCA diameter stenosis <50% (VE-QCA mismatch) was seen in 91 (64%) lesions. Conversely, among the 174 non-LM lesions with visually estimated percent stenosis <70%, QCA diameter stenosis ≥50% (VE-QCA reverse mismatch) was found in 22 (13%) lesions (Fig. 2A). In the LM group, VE-QCA mismatch was observed in 13 (87%) lesions, whereas VE-QCA reverse mismatch was not seen (Fig. 2B). The LM group showed a trend of higher frequency of VE-QCA mismatch (87% vs. 64%, p = 0.079), and lower frequency of VE-QCA reverse mismatch (0% vs. 13%, p = 0.316) compared with the non-LM group. Comparing visual estimation with QCA in evaluation the significance of coronary stenotic lesion, visual estimation had a sensitivity of 70.7% (95% CI: 59 to 80.6), a specificity of 60.5% (95% CI: 54.3 to 66.4), a positive predictive value of 33.8% (95% CI: 26.4 to 41.7), and a negative predictive value of 87.8% (95% CI: 82.2 to 92.2).

Diagnostic accuracy of visually estimated angiographic % stenosis and FFR

There was also a significant correlation between visually estimated percent stenosis and FFR in the non-LM (r = -0.503, p<0.001), whereas this correlation was not statistically significant in the LM group (r = -0.346, p = 0.115). Among the 142 non-LM

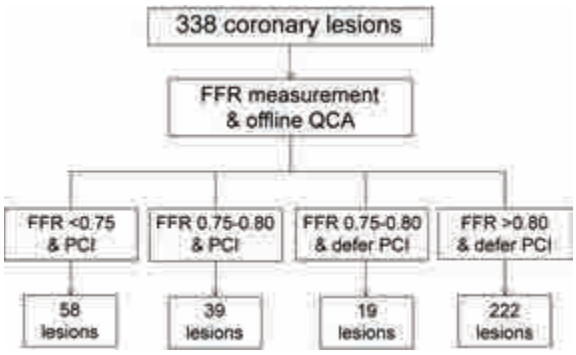

Fig. 1 Study flowchart.

lesions with visually estimated percent stenosis ≥70%, FFR >0.80 (VE-FFR mismatch) was seen in 60 (42%) lesions. Conversely, among the 174 non-LM with visually estimated percent stenosis <70%, FFR ≤0.80 (VE-FFR reverse mismatch) was found in 26 (15%) lesions (Fig. 3A). In the LM group, VE-FFR mismatch was observed in eight (53%) lesions, whereas VE-FFR reverse mismatch was seen in one (14%) lesions (Fig. 3B). The LM group showed a trend of higher frequency of VE-FFR mismatch (53% vs. 42%, $p = 0.410$), and nearly the same incidence of VE-FFR reverse mismatch (14% vs. 15%) compared with the non-LM group. Comparing visual estimation with FFR in evaluation the significance of coronary stenotic lesion, visual estimation had a sensitivity of 76.7% (95% CI: 68 to 84.1), a specificity of 69.4% (95% CI: 62.9 to 75.4), a positive predictive value of 56.7% (95% CI: 48.6 to 64.6), and a negative predictive value of 85.1% (95% CI: 79 to 89.9).

Comparison of the baseline characteristics, angiographic and QCA parameters according to visually estimated percent stenosis and FFR were summarized in Table 2 (for non-LM lesions) and in Table 3 (for LM lesions). For non-LM lesions, univariate analysis demonstrated seven factors that predicted VE-FFR mismatch, but could not demonstrate any factors predicting VE-FFR reverse mismatch. Multivariate analysis identified the independent predictors for VE-FFR mismatch for non-LM lesions as shorter lesion and greater minimal lumen diameter (Table 4). For LM lesions, the number of LM lesions was underpowered for predictor analysis.

Fig. 4 demonstrated the frequencies of VE-FFR mismatch and reverse mismatch relative to the involved vessel and lesion location. Examples of VE-FFR mismatch and reverse mismatch were presented in Fig. 5-8.

Results of clinical outcome

Median follow-up time in the present study was 11.6 (IQR; 7.3, 17.6) months. Twenty patients lost to follow-up at the OPD and received telephone follow-up instead. The mean left ventricular ejection fraction was 60.7±13.5%. At baseline, the Canadian Cardiovascular Society (CCS) angina class I, II, and III were developed in 48%, 48.2%, and 3.8% of

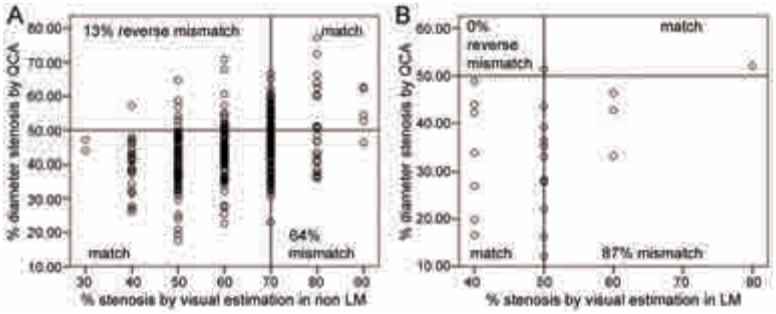

Fig. 2 Correlation between angiographic % stenosis by visual estimation and QCA: (A) non left main lesions, (B) left main lesions.
QCA = quantitative coronary angiography; LM = left main

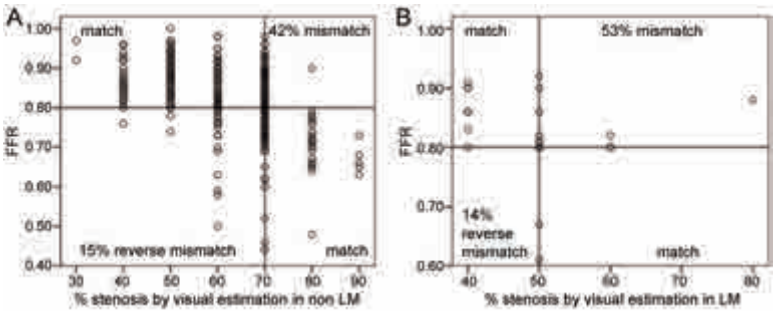

Fig. 3 Correlation between angiographic % stenosis by visual estimation and FFR: (A) non left main lesions, (B) left main lesions.
FFR = fractional flow reserve; LM = left main

Table 2. Clinical, angiographic, and QCA parameters in 316 non left main lesions

	% stenosis by VE ≥70%		% stenosis by VE <70%	
	FFR ≤0.80 n = 82	FFR >0.80 ("mismatch") n = 60	FFR ≤0.80 ("reverse mismatch") n = 26	FFR >0.80 n = 148
Age (years)	62.5±10.3	62.5±10.7	60.1±10.3	62.4±10.0
Male	62 (75.6%)	40 (66.7%)	19 (73.1%)	95 (64.2%)
Diabetes	33 (40.2%)	18 (30.0%)	13 (50.0%)	58 (39.2%)
Hypertension	73 (89.0%)	44 (73.3%)*	21 (80.8%)	121 (81.8%)
Hyperlipidemia	80 (97.6%)	54 (90.0%)	26 (100%)	144 (97.3%)
Smoking	6 (7.3%)	6 (10.0%)	5 (19.2%)	17 (11.5%)
SIHD	71 (86.6%)	55 (91.7%)	24 (92.3%)	135 (91.2%)
Ejection fraction	60.8±13.6	59.7±13.1	56.7±17.9	61.3±13.2
LAD	55 (67.1%)	27 (45.0%)*	20 (76.9%)	93 (62.8%)
LCX	12 (14.6%)	11 (18.3%)	2 (7.7%)	22 (14.9%)
RCA	15 (18.3%)	22 (36.7%)*	4 (15.4%)	33 (22.3%)
Proximal segment	39 (47.6%)	26 (43.3%)	13 (50.0%)	66 (44.6%)
Mid segment	32 (39.0%)	32 (53.3%)	13 (50.0%)	79 (53.4%)
Distal segment	11 (13.4%)	2 (3.3%)*	0 (0%)	3 (2.0%)
Type of lesion				
De novo	82 (100%)	58 (96.7%)	26 (100%)	136 (91.9%)
ISR	0 (0%)	2 (3.3%)	0 (0%)	12 (8.1%)
Lesion length (mm)	22.2±10.2	18.8±7.3*	19.0±9.6	19.7±8.3
QCA-DS (%)	48.6±9.4	46.4±7.4	41.2±7.4	42.1±8.5
QCA-MLD (mm)	1.2±0.3	1.5±0.4*	1.5±0.3	1.6±0.4
QCA-RLD (mm)	2.4±0.6	2.8±0.7*	2.6±0.6	2.8±0.6

QCA = quantitative coronary angiography; VE = visual estimation; FFR = fractional flow reserve; SIHD = stable ischemic heart disease; LAD = left anterior descending artery; LCX = left circumflex artery; RCA = right coronary artery; ISR = instent restenosis; DS = diameter stenosis; MLD = minimal lumen diameter; RLD = reference lumen diameter
Values are mean ± SD or n (%)
* *p*-value <0.05 versus 82 lesions with VE ≥70% and FFR ≤0.80

Table 3. Clinical, angiographic, and QCA parameters in 22 left main lesions

	% stenosis by VE ≥50%		% stenosis by VE <50%	
	FFR ≤0.80 n = 7	FFR >0.80 ("mismatch") n = 8	FFR ≤0.80 ("reverse mismatch") n = 1	FFR >0.80 n = 6
Age (years)	59.3±6.8	60.6±11.1	56.0	66.8±8.8
Male	7 (100%)	7 (87.5%)	1 (100%)	5 (83.3%)
Diabetes	3 (42.9%)	2 (25.0%)	0 (0%)	1 (16.7%)
Hypertension	6 (85.7%)	8 (100%)	1 (100%)	4 (66.7%)
Hyperlipidemia	6 (85.7%)	8 (100%)	1 (100%)	6 (100%)
Smoking	1 (14.3%)	3 (37.5%)	0 (0%)	0 (0%)
SIHD	7 (100%)	6 (75.0%)	1 (100%)	6 (100%)
Ejection fraction	64.9±7.0	65.5±12.7	67.0	58.7±9.0
Type of lesion				
De novo	7 (100%)	8 (100%)	1 (100%)	6 (100%)
ISR	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Lesion length (mm)	10.5±3.4	11.1±4.4	15.1	10.4±4.4
QCA-DS (%)	28.7±10.8	39.9±10.7	48.8	30.6±11.4
QCA-MLD (mm)	1.9±0.3	2.1±0.4	1.7	2.2±0.7
QCA-RLD (mm)	2.6±0.6	3.5±0.7	3.2	3.1±0.5

QCA = quantitative coronary angiography; VE = visual estimation; FFR = fractional flow reserve; SIHD = stable ischemic heart disease; ISR = instent restenosis; DS = diameter stenosis; MLD = minimal lumen diameter; RLD = reference lumen diameter
Values are mean ± SD or n (%)

Table 4. Multivariate analysis of independent factors predicting VE-FFR "mismatch" in 316 non left main lesions

	Crude odds ratio (95% confidence intervals)	Adjusted odds ratio (95% confidence intervals)	*p*-value
Hypertension	0.34 (0.14, 0.83)	0.52 (0.17, 1.59)	0.249
LAD	2.49 (1.25, 4.94)	0.28 (0.07, 1.07)	0.063
RCA	0.39 (0.18, 0.83)	0.82 (0.17, 4.05)	0.812
Distal segment	4.49 (0.96, 21.09)	0.25 (0.04, 1.63)	0.147
Lesion length (mm)	1.04 (1.00, 1.09)	0.94 (0.89, 0.99)	0.037*
QCA-MLD (mm)	0.07 (0.02, 0.25)	10.13 (1.03, 99.85)	0.047*
QCA-RLD (mm)	0.34 (0.19, 0.63)	0.31 (0.04, 2.84)	0.303

VE = visual estimation; FFR = fractional flow reserve; LAD = left anterior descending artery; RCA = right coronary artery; QCA = quantitative coronary angiography; MLD = minimal lumen diameter, RLD = reference lumen diameter

patients, respectively. The mean serum creatinine was 1.0±0.2 mg/dl. Most lesions undergone FFR measurement were in proximal and mid left anterior descending artery (LAD) locations. For lesions that the operator decided to perform PCI, drug-eluting stents (DESs) were used in 92% of the lesions (Biolimus, Zotarolimus, Everolimus, and Sirolimus DES). The numbers of stent used per lesions were 1.3±0.5 stents. The mean total stent length was 26.9±12.9 mm. The mean stent diameter was 2.9±0.4 mm.

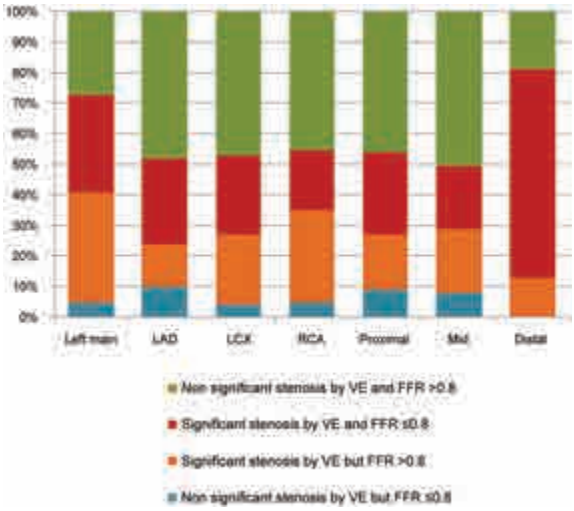

Fig. 4 Frequencies of VE-FFR mismatch and reverse mismatch according to vessel type and location (n = 22 for left main, n = 195 for LAD, n = 47 for LCX, n = 74 for RCA, n = 144 for proximal segments, n = 156 for mid segments, n = 16 for distal segments).
LAD = left anterior descending artery; LCX = left circumflex artery; RCA = right coronary artery; VE = visual estimation; FFR = fractional flow reserve

All patients undergone PCI had taken clopidogrel, whereas almost all patients had taken aspirin (95%) and statins (98.5%). The mean LDL cholesterol level was 101.9±33.6 mg/dl. Percentages of patients receiving beta-blockers and ACEI (or ARB) were 75% and 66%, respectively. One patient had cardiovascular death. This case was a 75-year-old woman with three vessel diseases and poor left ventricular ejection fraction of 30%. She underwent PCI with rotablator plus three DESs implanted at mid RCA, and was stented with one DES at distal left circumflex artery (LCX) one year ago. She underwent FFR measurement with intravenous adenosine infusion for evaluation mid LAD and proximal LAD lesions. FFR results of mid LAD lesion was 0.76, whereas proximal LAD lesion was 0.88. The interventionist decided to perform PCI with one DES to mid LAD, and deferred PCI to proximal LAD. During early period post PCI, she was in her stable condition. Unfortunately, she had cardiac arrest six months later. Her ECG from local hospital revealed asystole. She was immediately transferred back to this institute. However, she passed away sooner than emergency temporary pacemaker insertion or coronary angiogram could be done. Table 5 showed MACE (excluded death) of 338 lesions. There were no significant differences in MACE occurred in the four groups (1.7% vs. 5.1% vs. 5.3% vs. 2.7%, $p = 0.717$) (Fig. 9). CCS angina improvement in the four groups were not statistically different (43.1% vs. 46.2% vs. 47.4% vs. 47.7%, $p = 0.939$). In the FFR >0.80 & defer PCI group, there were two cases of CHF, one case of ischemic stroke, two cases of paroxysmal AF, and one case of warfarin overdose required admission. The median (Q1, Q3) cost of procedure of lesions undergone FFR plus additional PCI was significantly higher than lesions undergone

FFR only (140,000 (87,000, 181,000) vs. 137,000 (91,000, 156,500) vs. 45,000 (41,000, 77,000) vs. 45,000 (41,000, 73,000) Baht, $p<0.001$).

Discussion

The present study demonstrated two main findings. First, discordant results between VE and

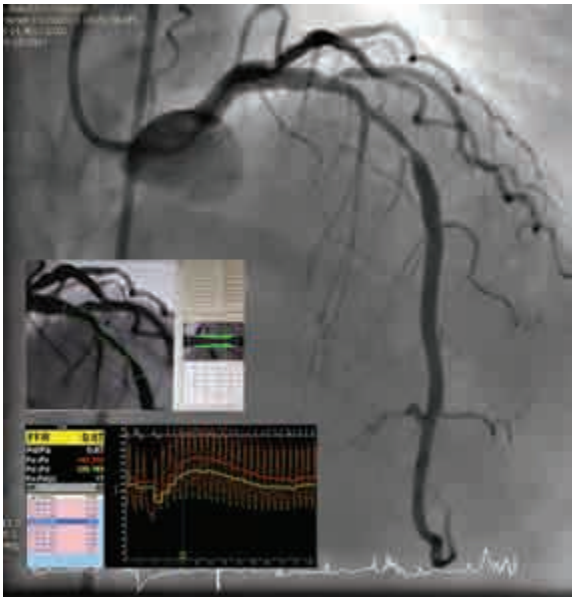

Fig. 5 A 58-year-old woman with stable ischemic heart disease. Percent stenosis of long lesion at mid LAD by visual estimation was approximately 80%, percent diameter stenosis by QCA was 51.6%, whereas FFR was 0.87 (VE-FFR mismatch).

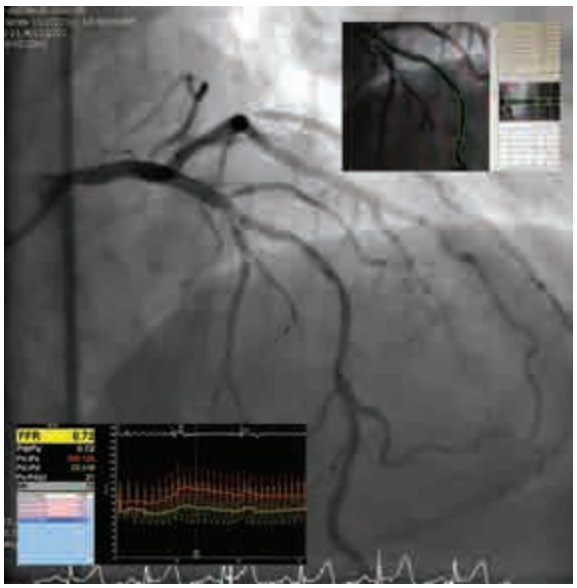

Fig. 6 A 64-year-old man with stable ischemic heart disease. Percent stenosis of diffuse long lesion at mid LAD by visual estimation was 60 to nearly 70%, percent diameter stenosis by QCA was 36.4%, whereas FFR was 0.72 (VE-FFR reverse mismatch).

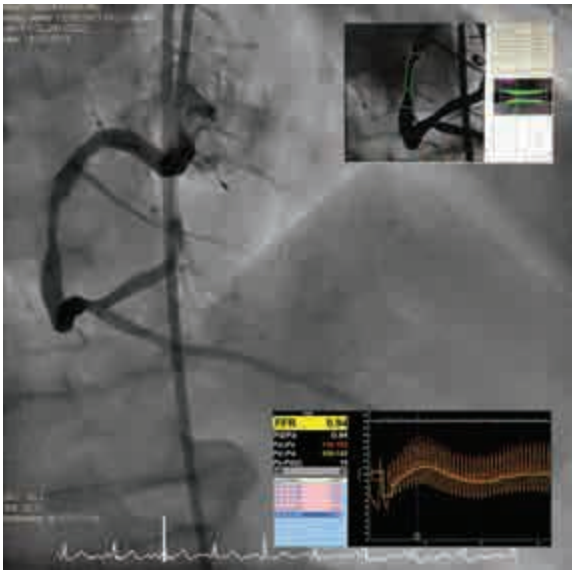

Fig. 7 A 72-year-old man with stable ischemic heart disease. Percent stenosis at mid RCA by visual estimation was approximately 70%, percent diameter stenosis by QCA was 57.5%, whereas FFR was 0.94 (VE-FFR mismatch).

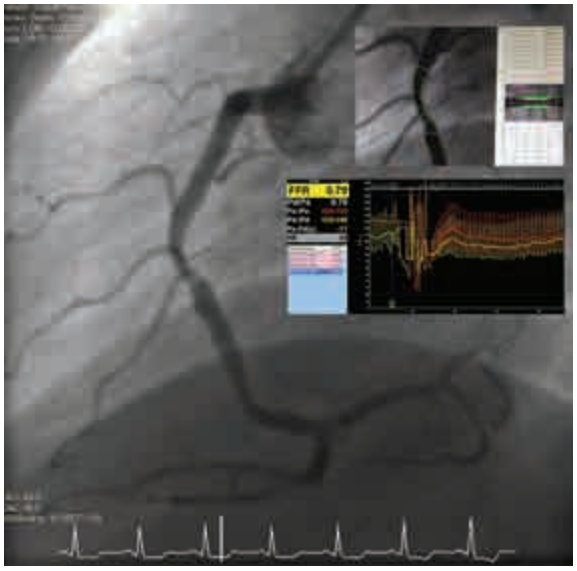

Fig. 8 A 47-year-old man with stable ischemic heart disease. Percent stenosis at mid RCA by visual estimation was approximately 60%, percent diameter stenosis by QCA was 43.9%, whereas FFR was 0.79 (VE-FFR reverse mismatch).

Table 5. Results of clinical outcome (338 lesions)

	FFR <0.75 & PCI (n = 58)	FFR 0.75-0.80 & PCI (n = 39)	FFR 0.75-0.80 & defer PCI (n = 19)	FFR >0.80 & defer PCI (n = 222)
PCI				
DES used	54 (93.1%)	35 (89.7%)	0 (0%)	0 (0%)
BMS used	2 (3.4%)	2 (5.1%)	0 (0%)	0 (0%)
POBA	2 (3.4%)	2 (5.1%)	0 (0%)	0 (0%)
MACE				
Recurrent MI	0 (0%)	1 (2.6%)	0 (0%)	0 (0%)
Any revascularization	1 (1.7%)	0 (0%)	1 (5.3%)	0 (0%)
CHF	0 (0%)	0 (0%)	0 (0%)	2 (0.9%)
Stroke	0 (0%)	1 (2.6%)	0 (0%)	1 (0.5%)
Others	0 (0%)	0 (0%)	0 (0%)	3 (1.4%)
CCS angina improvement	25 (43.1%)	18 (46.2%)	9 (47.4%)	106 (47.7%)
Median (Q1, Q3) costs of material (Baht)	140,000 (87,000, 181,000)	137,000 (91,000, 156,500)	45,000 (41,000, 77,000)	45,000 (41,000, 73,000)

FFR = fractional flow reserve; PCI = percutaneous coronary intervention; DES = drug eluting stent; BMS = bare metal stent; POBA = plain old balloon angioplasty; MACE = major adverse cardiovascular events; MI = myocardial infarction; CHF = congestive heart failure; CCS = Canadian Cardiovascular Society

QCA were almost 40%, whereas visual- functional mismatch between VE and FFR were as high as 30%. Second, the MACE outcomes of lesions underwent FFR-guided revascularization were quite low.

From previous report, visual analysis generally leads to overestimate lesions with severe stenosis, and to underestimate lesions with more modest degrees of luminal narrowing[2]. In the present study, overestimation of severe stenosis that leads to VE-QCA mismatch could occur in both non-LM and LM lesions, whereas underestimation of more modest degrees stenosis that led to VE-QCA reverse mismatch could be found only in non-LM lesions. The present cohort demonstrated that visual estimation tended to overestimate lesion severity compared to calculated QCA as previously reported in the literature[29]. Although QCA attempted to standardize the measurement of stenosis severity, it had only weak correlation to translesional functional assessment in the catheterization lab[30,31]. FFR, unlike QCA, was the gold standard for invasive functional significance of coronary stenosis. In the present study, both VE-FFR mismatch and reverse mismatch were found in both non-LM and LM lesions. Although the number of LM lesions was underpowered, it seemed that LM lesions had higher incidence of VE-FFR mismatch compared to non-LM lesions. As LM supplies a large myocardial territory, therefore, FFR measurement to assess significant severity of LM lesions should be performed before considering revascularization. The present study demonstrated the same predictors of VE-FFR mismatch in non-LM lesions that included shorter lesion and greater minimal lumen diameter, but could not demonstrate significant correlation with a predictor such as non-LAD location as in previous studies[28,32].

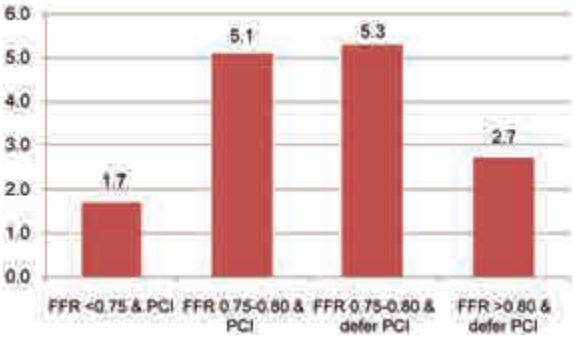

Fig. 9 Percent (%) of major adverse cardiovascular events in 4 groups of patients according to FFR value and treatment.
FFR = fractional flow reserve; PCI = percutaneous coronary intervention

FFR values less than 0.75 were associated with positive noninvasive stress testing in numerous comparative studies with high sensitivity (88%), specificity (100%), positive predictive value (100%), and overall accuracy (93%)[33,34]. FFR values of at least 0.80 were associated with negative ischemic results with a predictive accuracy of 95%[21]. In a small transitional zone of FFR between 0.75 and 0.80, reports from stress testing indicated that the ischemic potential

of the stenosis remains unclear[21,22], and required clinical judgment before further revascularization. In 2009, the FAME study group[13] that used FFR compared with angiography as a guide for PCI in multivessel diseases decided to take an FFR cutoff value of 0.80 in order to limit the number of ischemic lesions left untreated in that small transitional zone. The 2010 ESC guidelines for myocardial revascularization[6], and the 2012 ACC/AHA guidelines for the diagnosis and management of patients with stable ischemic heart diseases[27] have documented ischemia by a cutoff value of 0.80. In the present cohort, further management in this transitional zone was judged by individual operator. As 90% of the patients in the present study had a clinical presentation of stable ischemic heart disease, this might affect the operator's judgment to defer PCI in some asymptomatic cases.

From previous study, it is known that persons who have lesions with an FFR of more than 0.80, if optimally treated with best available medication, have an excellent prognosis, with the risk of cardiac death or myocardial infarction related to this stenotic lesions approximately 1% per year up to five years after measurement[10]. In the present study, although MACE occurred in lesions with FFR >0.80 & defer PCI was 2.7%, there was no cardiac death or myocardial infarction occurred in this group of patients.

In the present study, the strategic treatment in lesions with FFR <0.75 was followed contemporary guidelines. In terms of revascularization, all lesions with FFR <0.75 were received PCI, dual antiplatelet treatment, statins and other available medical treatment. The mean FFR in the present group was 0.67±0.07 suggested that there were large area of myocardium at risk for ischemia. Due to small number of patients with short period of follow-up, the relatively low rate of MACE in this group compared to contemporary FFR-guided PCI study, could not reached a valid conclusion regarding the outcome. By considering visual-functional mismatch and performing PCI only in ischemic stenotic lesions, in terms of economic standpoint, as well as previous study[35], FFR-guided PCI is a useful strategy to reduce inaccurate revascularization and total cost per patient.

Conclusion

First, the mismatches or discordant results between visually-estimated significance of angiographic coronary stenosis and QCA or FFR are frequently encountered. Second, visual estimation of coronary angiography alone cannot entirely predict functional significance of coronary stenosis. FFR measurement provides a helpful strategy in assessing coronary lesions for deciding whether to perform revascularization immediately or to defer intervention.

Limitations

The present study had some limitations. First, from a methodological standpoint of a cohort study, this study may have a bias. The decision to perform FFR and the choice of management afterwards were determined by each individual operator. Therefore, selection bias at the outset might have affected clinical outcomes. Second, the number of LM lesions was underpowered for predictor analysis. Finally, due to the relatively small event rate, attributed to a small population with a short-term follow-up period analyzed at a single center, may affect the outcome results. However, the small selected patient group represented the institute's everyday practice. Nevertheless, the current study's results should be further investigated and validated in larger cohort studies.

What is already known on this topic?

From clinical researches, there are increasing evidences of discrepancy results in evaluation of angiographic coronary artery stenotic lesions between physician's visual estimation and nonfunctional test (QCA) or functional test (FFR).

What this study adds?

The present study demonstrated mismatches in determination the significance of coronary artery stenotic lesions by visual estimation and QCA or by visual estimation and FFR in Thai patients. Included in this study were the clinical results of using functional test (FFR) as a guide to consider further revascularization and the difference in costs of procedure in Thai patients.

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Potential conflicts of interest

None.

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ความคลาดเคลื่อนของการประเมินนัยสำคัญของเปอร์เซนต์ความตีบของหลอดเลือดหัวใจจากภาพฉีดสี coronary angiogram และผลของการใช้fractional flow reserve เพื่อเป็นแนวทางในการพิจารณาทำการถ่างขยายหลอดเลือดหัวใจ

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วัตถุประสงค์: ข้อแรกเพื่อศึกษาถึงความคลาดเคลื่อนไม่สอดคล้องกัน (mismatch) ของการประเมินนัยสำคัญของความตีบของหลอดเลือดหัวใจโคโรนารี (the significance of coronary artery stenosis) ระหว่างวิธีการประเมินด้วยสายตาโดยแพทย์ (physician's visual estimation: VE) เทียบกับวิธีประเมินด้วย quantitative coronary angiography (QCA), ประเมินโดยวิธี VE เทียบกับวิธีวัด fractional flow reserve (FFR), และปัจจัยอิสระที่มีผลต่อการเกิดความคลาดเคลื่อนไม่สอดคล้องกันของการประเมินด้วยวิธี VE เทียบกับวิธี FFR ข้อที่สองเพื่อศึกษาผลทางคลินิกในผู้ป่วยที่ใช้การวัด FFR มาเป็นแนวทางบ่งชี้สำหรับการพิจารณาทำการถ่างขยายหลอดเลือดหัวใจ (percutaneous coronary intervention: PCI)

วัสดุและวิธีการ: การศึกษานี้เป็นการศึกษาแบบไปข้างหน้า (prospective cohort study) ประกอบด้วยผู้ป่วย 280 ราย ซึ่งมีรอยตีบของหลอดเลือดหัวใจ (coronary lesion) บริเวณที่ไม่ใช่ท่อเมน (non left main) 316 รอยตีบ และบริเวณท่อเมน (left main) 22 รอยตีบที่ได้รับการตรวจฉีดสีหลอดเลือดหัวใจ (coronary angiography), วัด offline edge detection QCA, และวัดค่า FFR ในช่วงระหว่างเดือนสิงหาคม พ.ศ. 2554 ถึงธันวาคม พ.ศ. 2556 โดยผู้ป่วยแต่ละรายจะได้รับการจดบันทึกข้อมูลพื้นฐาน, ลักษณะของรอยตีบที่หลอดเลือดหัวใจและผลทางคลินิกเพื่อมาทำการวิเคราะห์ โดยหลังจากที่ได้รับการตรวจวัด FFR แล้วจะทำการแบ่งกลุ่มของรอยตีบหลอดเลือดหัวใจตามค่า FFR และการรักษาที่ได้รับออกเป็น 4 กลุ่ม คือ กลุ่ม FFR <0.75 และได้รับการทำ PCI, กลุ่ม FFR 0.75-0.80 และได้รับการทำ PCI, กลุ่ม FFR 0.75-0.80 และไม่ได้รับการทำ PCI, กลุ่ม FFR >0.80 และไม่ได้รับการทำ PCI จากนั้นจะมีการรายงานความคลาดเคลื่อนไม่สอดคล้องกันของนัยสำคัญของความตีบของหลอดเลือดหัวใจจากการประเมินด้วยวิธี VE เทียบกับวิธี QCA, วิธี VE เทียบกับวิธี FFR รวมถึงปัจจัยอิสระที่มีผลต่อการเกิดความคลาดเคลื่อนไม่สอดคล้องกันของการประเมินด้วยวิธี VE เทียบกับวิธี FFR และผลทางคลินิกในผู้ป่วยที่ใช้ค่าที่ได้จากการวัด FFR มาเป็นแนวทางบ่งชี้สำหรับการพิจารณาทำการถ่างขยายหลอดเลือดหัวใจ

ผลการศึกษา: 1) รอยตีบของหลอดเลือดหัวใจที่มีความคลาดเคลื่อนไม่สอดคล้องกันแบบ mismatch ของการประเมินด้วยวิธี VE เทียบกับวิธี QCA พบได้ใน 64% ของรอยตีบที่ไม่ใช่ท่อเมน และพบใน 87% ของรอยตีบที่ท่อเมนตามลำดับ ในทางกลับกันรอยตีบของหลอดเลือดหัวใจที่มีความคลาดเคลื่อนไม่สอดคล้องกันแบบ reverse mismatch ของการประเมินด้วยวิธี VE เทียบกับวิธี QCA พบได้ใน 13% ของรอยตีบที่ไม่ใช่ท่อเมนแต่ไม่พบความคลาดเคลื่อนนี้ในรอยตีบที่ท่อเมน 2) รอยตีบของหลอดเลือดหัวใจที่มีความคลาดเคลื่อนไม่สอดคล้องกันแบบ mismatch ของการประเมินด้วยวิธี VE เทียบกับวิธี FFR พบได้ใน 42% ของรอยตีบที่ไม่ใช่ท่อเมน และพบใน 53% ของรอยตีบที่ท่อเมนตามลำดับ ในทางกลับกันรอยตีบของหลอดเลือดหัวใจที่มีความคลาดเคลื่อนไม่สอดคล้องกันแบบ reverse mismatch ของการประเมินด้วยวิธี VE เทียบกับวิธี FFR พบได้ใน 15% ของรอยตีบที่ไม่ใช่ท่อเมน และพบใน 14% ของรอยตีบที่ท่อเมนตามลำดับ 3) ปัจจัยอิสระที่มีผลต่อการเกิดความคลาดเคลื่อนไม่สอดคล้องกันแบบ mismatch ของการประเมินด้วยวิธี VE เทียบกับวิธี FFR ในรอยตีบที่ไม่ใช่ท่อเมนคือ รอยตีบที่สั้นกว่าและรอยตีบที่มีเส้นผ่านศูนย์กลางภายในที่โตกว่า 4) หลังจากที่ได้แบ่งรอยตีบของหลอดเลือดหัวใจตามค่า FFR และการรักษาแล้วได้ทำการตรวจติดตามผู้ป่วยเป็นระยะเวลาตามค่ามัธยฐาน 11.6 เดือน พบว่ามีผู้ป่วยเสียชีวิต 1 ราย ส่วนภาวะทางหัวใจและหลอดเลือดที่ร้ายแรง (major adverse cardiovascular event) อื่นๆ ที่เกิดขึ้นใน 4 กลุ่ม ไม่ได้แตกต่างกันอย่างมีนัยสำคัญทางสถิติ (1.7% vs. 5.1% vs. 5.3% vs. 2.7%, p = 0.717) ทั้งนี้พบว่ามัธยฐานของค่ารักษาในรอยตีบที่วัด FFR แล้วทำ PCI ร่วมด้วยมีค่าสูงกว่ามัธยฐานของค่ารักษาในรอยตีบที่วัด FFR อย่างเดียวอย่างมีนัยสำคัญทางสถิติ (140,000 vs. 137,000 vs. 45,000 vs. 45,000 บาท, p<0.001)

สรุป: ความคลาดเคลื่อนไม่สอดคล้องกันของการประเมินนัยสำคัญความตีบของหลอดเลือดหัวใจด้วยวิธีประเมินด้วยสายตาโดยแพทย์กับวิธี QCA หรือ วิธี FFR พบได้บ่อย การประเมินด้วยสายตาอย่างเดียวไม่สามารถทำนาย functional significance ของรอยตีบได้ทั้งหมด และการวัด FFR เป็นวิธีการที่สามารถช่วยในการประเมินประกอบการตัดสินใจได้ว่าควรทำการถ่างขยายรอยตีบที่หลอดเลือดหัวใจต่อไปหรือไม่