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Outcomes of Percutaneous Coronary Intervention in Intermediate Coronary Artery Disease

Fractional Flow Reserve–Guided Versus Intravascular Ultrasound–Guided

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Objectives This study sought to evaluate the long-term clinical outcomes of a fractional flow reserve (FFR)–guided percutaneous coronary intervention (PCI) strategy compared with intravascular ultrasound (IVUS)–guided PCI for intermediate coronary lesions.

Background Both FFR- and IVUS-guided PCI strategies have been reported to be safe and effective in intermediate coronary lesions.

Methods The study included 167 consecutive patients, with intermediate coronary lesions evaluated by FFR or IVUS (FFR-guided, 83 lesions vs. IVUS-guided, 94 lesions). Cutoff value of FFR in FFR-guided PCI was 0.80, whereas that for minimal lumen cross sectional area in IVUS-guided PCI was 4.0 mm^2. The primary outcome was defined as a composite of major adverse cardiac events including death, myocardial infarction, and ischemia-driven target vessel revascularization at 1 year after the index procedure.

Results Baseline percent diameter stenosis and lesion length were similar in both groups (51 ± 8% and 24 ± 12 mm in the FFR group vs. 52 ± 8% and 24 ± 13 mm in the IVUS group, respectively). However, the IVUS-guided group underwent revascularization therapy significantly more often (91.5% vs. 33.7%, $p < 0.001$). No significant difference was found in major adverse cardiac event rates between the 2 groups (3.6% in FFR-guided PCI vs. 3.2% in IVUS-guided PCI). Independent predictors for performing intervention were guiding device: FFR versus IVUS (relative risk [RR]: 0.02); left anterior descending coronary artery versus non-left anterior descending coronary artery disease (RR: 5.60); and multi- versus single-vessel disease (RR: 3.28).

Conclusions Both FFR- and IVUS-guided PCI strategy for intermediate coronary artery disease were associated with favorable outcomes. The FFR-guided PCI reduces the need for revascularization of many of these lesions. (J Am Coll Cardiol Intv 2010;3:812–7) © 2010 by the American College of Cardiology Foundation

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Because of the limitations of coronary angiography (1), adjunctive techniques to more accurately evaluate lesion severity are important in patients with intermediate coronary stenosis before percutaneous coronary intervention (PCI). Fractional flow reserve (FFR) has been the reference standard for the physiological assessment of coronary artery stenosis, particularly intermediate ones (2–4). Deferring intervention of intermediate coronary lesions with a FFR ≥0.75 or 0.80 is associated with favorable long-term clinical outcomes (5,6). An intravascular ultrasound (IVUS)–

See page 818

derived minimal lumen area (MLA) ≤4.0 mm^2, or minimal lumen diameter ≤1.8 mm have been shown to correlate with a FFR <0.75 (7), and deferring intervention in intermediate coronary lesions based on MLA ≥4.0 mm^2 results in favorable clinical outcomes (8). However, there are few studies that compared FFR- and IVUS-guided coronary intervention strategies in patients with de novo coronary intermediate lesions. The aim of this study was to evaluate the clinical outcomes of a FFR- versus IVUS-guided PCI strategy for intermediate coronary lesions.

Methods

Patient population and study design. The patient population consisted of 167 consecutive patients (177 lesions) who underwent FFR or IVUS assessment to decide whether to perform PCI or not for de novo intermediate coronary lesions between August 2006 and June 2008. An intermediate coronary lesion was defined as 40% to 70% diameter stenosis by visual assessment. For this study, the target vessel was a single lesion in the proximal or mid part of a major epicardial coronary artery with reference vessel diameter larger than 2.5 mm. The lesion had no documented evidence of ischemia by noninvasive tests (not performed, negative, inadequate, or not evaluable for a target lesion). Patients were not eligible for enrollment if they: 1) had undergone intervention in the setting of primary or emergent PCI for an acute coronary syndrome; 2) had prior coronary artery bypass graft surgery; 3) had multiple lesions in the same epicardial artery; 4) had left main disease, primary myocardial disease, or a major life threatening illness; or 5) had contraindications to adenosine, aspirin, or clopidogrel.

The use of FFR or IVUS was made based on operator preference. The cutoff value of FFR in the FFR-guided PCI group was 0.80 (6,9,10) and that of MLA in the IVUS-guided PCI was 4.0 mm^2 (7,8). Implanted stents were commercially available drug-eluting stents (DES) in all cases.

Procedural details. Coronary angiography was performed in multiple views after the intracoronary injection of 0.2 mg nitroglycerin. Percutaneous coronary intervention was performed following standard interventional techniques. Antiplatelet and antithrombotic agents were prescribed according to current PCI guidelines (3). All coronary angiograms were analyzed using standard definitions and measurements by quantitative coronary angiography (Quantcor QCA, version 4.0, Pie Medical Imaging, Maastricht, the Netherlands) by an experienced physician who was blinded to the type of PCI guidance.

Fractional flow reserve was defined as the ratio between mean distal coronary pressure and mean aortic pressure, both measured simultaneously at maximal hyperemia. Coronary pressure was measured using a 0.014-inch sensor-tipped PCI guidewire (Pressure Wire, Radi Medical Systems, Uppsala, Sweden). The wire was introduced through a 6- or 7-F guiding catheter, equalized, and advanced distal to the stenosis as previously described (9). The FFR value was checked after administration of adenosine to induce maximal hyperemia, either intravenously (140 μg/kg/min) or intracoronarily (40 μg in the right, 80 μg in the left coronary artery).

Abbreviations and Acronyms

DES = drug-eluting stent(s)
FFR = fractional flow reserve
IVUS = intravascular ultrasound
LAD = left anterior descending coronary artery
MACE = major adverse cardiac event
MLA = minimal lumen area
PCI = percutaneous coronary intervention
TVR = target vessel revascularization

Intravascular ultrasound guidance was performed using conventional 6- or 7-F guiding catheters and a 0.014-mm guidewire positioned distally, and IVUS catheters of 30 or 40 MHz (Boston Scientific Corp., Natick, Massachusetts) pulled back automatically at a constant speed of 0.5 mm/s. The lesion site selected for analysis was the image slice with MLA and minimal stent area, which were measured following the guidelines for IVUS measurements by the American College of Cardiology (11).

Definitions and study outcomes. The primary outcome was defined as a composite of major adverse cardiac events (MACE), defined as death, myocardial infarction, and ischemia-driven target vessel revascularization (TVR) at 12 months after the index procedure. Death was defined as all-cause mortality. The diagnosis of myocardial infarction was based on either the development of new pathological Q waves in ≥2 contiguous electrocardiogram leads and/or cardiac enzyme level elevation >3 times the upper limit of normal value. TVR included target lesion PCI and bypass surgery of the target lesion. TVR was performed only in the presence of symptoms and/or signs of ischemia. Stent thrombosis was defined according to the Academic Research Consortium guidelines (12).

Statistical analyses. Data are expressed as mean ± SD for continuous variables and as percentages for discrete vari-

ables. Continuous variables were compared using Student *t* test. Categorical variables were compared using chi-square tests or Fisher exact test, as appropriate. All calculated p values were 2-sided and differences were considered to be statistically significant when the respective p values were <0.05. Multivariate logistic regression analysis was used to assess independent predictors of performing PCI and of MACE. The parameters analyzed in multivariate analysis were selected when p value was lesser than 0.5 in univariate analysis. All statistical analyses were performed using SPSS version 15.0 for Windows (SPSS Inc., Chicago, Illinois).

Results

Baseline clinical, angiographic, and procedural characteristics are summarized in Tables 1 and 2. Among 167 consecutive patients (177 lesions), 83 lesions were assessed by FFR and 94 lesions by IVUS. Intracoronary adenosine was used in 79 lesions to induce maximal hyperemia. The resulting groups were well matched without significant differences in the frequency of clinical cardiovascular risk factors. The incidence of multivessel disease was significantly higher in the FFR group (66.3% vs. 48.9%, p = 0.02). The most common target lesion location was the left anterior descending coronary artery (LAD) in both groups (48.2% in the FFR group vs. 58.8% in the IVUS group, p = 0.18). There was no significant difference in clinical presentation. Both groups had similar percent diameter stenosis (51 ± 8% vs. 52 ± 8% in the FFR and IVUS groups respectively, p = 0.53). However, reference vessel diameter was larger in the IVUS-guided group (3.39 ± 0.49 mm vs. 3.23 ± 0.43 mm, p = 0.03). Although angiographic lesion length was similar between 2 groups, IVUS lesion length was slightly longer than angiographic lesion length in IVUS group (23.5 ± 12.7 mm in angiographic lesion length vs. 25.3 ± 11.0 mm in IVUS lesion length, p = 0.008). The incidence of performing PCI was much lower in the FFR-guided group (33.7% vs. 91.5%, p <0.001) as shown in Figure 1. The mean FFR value of deferred lesions was 0.87 ± 0.06 whereas that of revascularized lesions was 0.72 ± 0.07 in the FFR-guided group. The mean MLA of deferred lesions was 5.1 ± 1.5 mm^2 and that of lesions treated by PCI was 2.9 ± 0.9 mm^2 in the IVUS-guided group (Table 2). When evaluating LAD lesions alone, the frequency of PCI continued to be greater with IVUS guidance compared with FFR guidance (52.5% in FFR group vs. 90.9% in IVUS group, p < 0.001).

The 12-month clinical outcomes are summarized in Figure 2. There were no significant differences in TVR (3.6% in FFR group vs. 2.1% in the IVUS group, p = 0.67)

Table 1. Baseline Patient and Lesion Characteristics

	FFR-Guided (n = 83)	IVUS-Guided (n = 94)	p Value
Clinical			
Age, yrs	63 ± 9	62 ± 9	0.50
Men	55 (66.3)	55 (58.5)	0.35
Diabetes	18 (21.7)	24 (25.5)	0.60
Hypertension	35 (42.2)	48 (51.1)	0.29
Hypercholesterolemia	13 (15.7)	14 (14.9)	1.00
Current smoking	27 (32.5)	34 (36.2)	0.64
Previous PCI	17 (20.5)	12 (12.8)	0.22
Clinical presentation			0.22
Stable angina	38 (45.8)	34 (36.2)	
Acute coronary syndrome	45 (54.2)	60 (63.8)	
LVEF, %	61 ± 10	59 ± 10	0.14
Angiography			
Extent of disease			0.02
Single	28 (33.7)	48 (51.1)	
Multi	55 (66.3)	46 (48.9)	
Target vessel			0.18
LAD	40 (48.2)	55 (58.5)	
Non-LAD	43 (51.8)	39 (41.5)	
Lesion location			0.77
Proximal	40 (48.2)	43 (45.7)	
Mid	43 (51.8)	51 (54.3)	
Lesion type*			0.87
Simple	25 (30.1)	30 (31.9)	
Complex	58 (69.9)	64 (68.1)	
Lesion length, mm	24 ± 12	24 ± 13	0.92
Reference vessel diameter, mm	3.23 ± 0.43	3.39 ± 0.49	0.03
Minimal lumen diameter, mm	1.59 ± 0.32	1.61 ± 0.45	0.68
Percent diameter stenosis, %	51 ± 8	52 ± 8	0.53

Values are mean ± SD or n (%). *According to the American College of Cardiology/American Heart Association classification, type A and B1 lesions are simple, whereas type B2 and C lesions are complex.

FFR = fractional flow reserve; IVUS = intravascular ultrasound; LAD = left anterior descending coronary artery; LVEF = left ventricular ejection fraction; PCI = percutaneous coronary intervention.

Table 2. Procedural Results

	FFR-Guided		IVUS-Guided		
	Defer (n = 55)	PCI (n = 28)	Defer (n = 8)	PCI (n = 86)	p Value
FFR					
Pre-intervention	0.87 ± 0.06	0.72 ± 0.07			
Post-intervention		0.91 ± 0.05			
IVUS, mm^2					
Pre-interventional MLA			5.1 ± 1.5	2.9 ± 0.9	
Post-interventional MSA				7.3 ± 2.8	
Stent number		1.1 ± 0.5		1.1 ± 0.5	0.97
Stent length, mm		31 ± 13		28 ± 14	0.42
Stent size, mm		3.2 ± 0.4		3.3 ± 0.5	0.16
Post-intervention					
MLD, mm		2.89 ± 0.42		3.03 ± 0.47	0.19
DS, %		11 ± 4		11 ± 3	0.45

Values are mean ± SD.

DS = percent diameter stenosis; MLA = minimal lumen diameter; MLD = minimal lumen diameter; MSA = minimal stent area; other abbreviations as in Table 1.

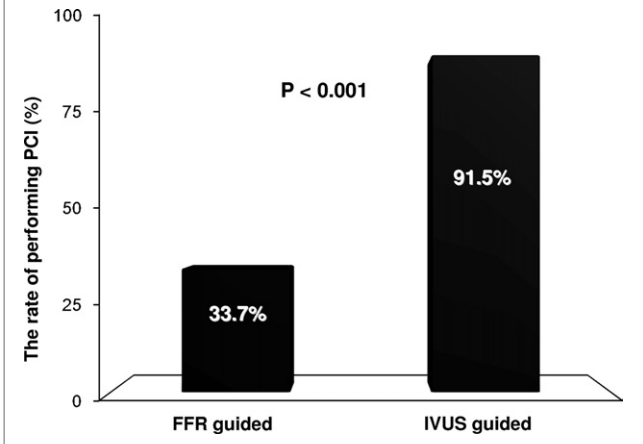

Figure 1. The Rate of Performing PCI According to Type of Guiding Device

The fractional flow reserve (FFR)–guided group showed significantly lower rates of performing percutaneous coronary intervention (PCI) compared to the intravascular ultrasound (IVUS)–guided group.

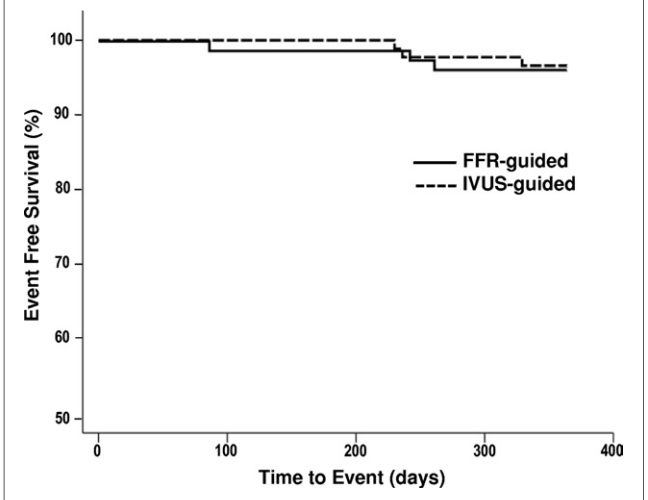

Figure 3. Kaplan-Meier Survival Curves for Freedom From Adverse Cardiac Events During 12 Months of Follow-Up

Kaplan-Meier survival curves for freedom from adverse cardiac events during 12 months of follow-up for both groups. p > 0.05. Abbreviations as in Figure 1.

and MACE (3.6% in FFR group vs. 3.2% in IVUS group, p = 1.00) between the 2 groups. The 3 TVR cases in the FFR-guided group were due to in-stent restenosis, deferred lesion aggravation, and progression of a nontarget lesion. The 2 TVR cases in the IVUS-guided group were secondary to in-stent restenosis. One noncardiac death was observed in the IVUS group, which was related to a respiratory infection. No myocardial infarction or stent thrombosis was observed in either group. Kaplan-Meier estimates of cumulative freedom from MACE during 12-month follow-up are shown in Figure 3.

In multivariate logistic regression analysis, performing intervention was significantly affected by FFR versus IVUS guidance (relative risk [RR]: 0.02, 95% confidence interval [CI]: 0.01 to 0.07), LAD versus non-LAD lesion (RR: 5.60, 95% CI: 1.98 to 15.80), and multi- versus single-vessel disease (RR: 3.28, 95% CI: 1.02 to 10.60) (Table 3). No variable was related to MACE in univariate analysis.

Discussion

The major findings in the current study are: 1) FFR- or IVUS-guided PCI in patients with intermediate coronary lesions was associated with favorable clinical outcomes; and 2) the rate of performed PCI in intermediate coronary

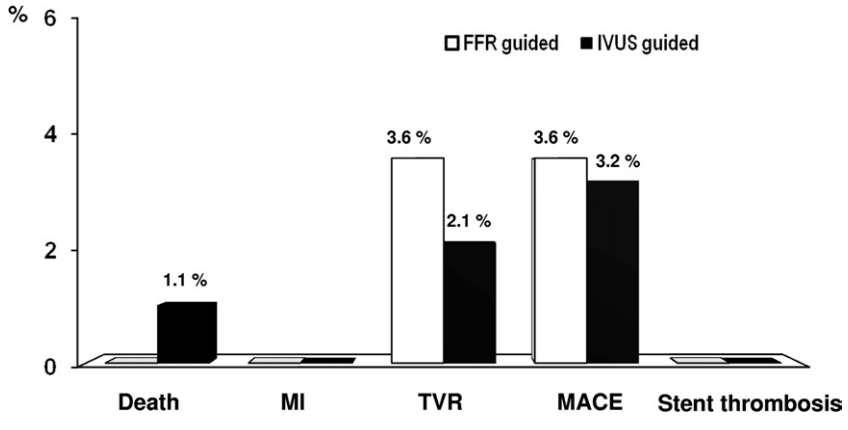

Figure 2. 1-Year Clinical Outcomes According to the Type of Guiding Device

The FFR- and IVUS-guided groups demonstrated excellent 12-month clinical outcomes without significant between-group differences. All p values were >0.05. MACE = major adverse cardiac event; MI = myocardial infarction; TVR = target vessel revascularization; other abbreviations as in Figure 1.

Table 3. Predictors of Performing PCI in the Intermediate Coronary Lesions

	Univariate Variables			Multivariate Variables		
	Relative Risk	95% CI	p Value	Relative Risk	95% CI	p Value
Age, yrs	0.98	0.95–1.02	0.30	0.97	0.92–1.03	0.30
Men	1.30	0.69–2.45	0.41	2.41	0.85–6.82	0.10
Diabetes	0.74	0.36–1.45	0.40	0.42	0.14–1.28	0.13
Current smoking	1.46	0.75–2.84	0.27	0.79	0.28–2.25	0.66
ACS	1.81	0.96–3.38	0.07	2.17	0.83–5.66	0.12
LVEF	0.98	0.94–1.01	0.12	0.98	0.94–1.03	0.49
FFR (vs. IVUS)	0.02	0.01–0.07	<0.001	0.02	0.01–0.07	<0.001
Multi (vs. single) VD	0.77.	0.41–1.44	0.41	3.28	1.02–10.60	0.047
LAD (vs. non-LAD) lesion	2.56	1.36–4.82	0.004	5.60	1.98–15.80	0.001
Lesion type	1.71	0.88–3.30	0.11	2.56	0.83–7.86	0.10
Lesion length	1.01	0.99–1.04	0.36	1.01	0.96– 1.05	0.85
Reference vessel diameter	1.77	0.87–3,61	0.11	1.80	0.61–5.32	0.29

All parameters described in this table did not have significant interactions with each other.
ACS = acute coronary syndrome; CI = confidence interval; VD = vessel disease; other abbreviations as in Table 1.

lesions was significantly lower in the FFR-guided compared with the IVUS-guided group without any increase of adverse event rates according to established criteria.

Assessment of a coronary lesion with intermediate severity remains challenging for interventional cardiologists. The clinical importance of a mild-to-moderate coronary stenosis has been increased by some who propose that acute myocardial infarctions originate from such lesions (13,14). Some argue that for this reason, PCI with DES might be beneficial for the patients with an intermediate coronary lesion (15,16). However, recent studies showed that stenting intermediate stenoses, without demonstrating their physiologic significance, does not improve outcome (5,6), and optimal medical treatment might result in similar outcomes (17). In this study, the overall incidence of MACE at 1 year was very low, namely 3.4% (6 of 177 lesions). Although 36% (63 of 177 lesions) of cases were deferred, the MACE rate was similar or lower than the results of recent DES clinical trials. The MACE rate of the deferral group was 3.2% (2 of 63) and similar to that of the PCI group, which was 3.5% (4 of 114). In a pooled analysis in which outcomes after DES were evaluated from 4 randomized trials (16), the MACE rate of DES is similar or even higher than that of FFR- or IVUS-guided deferral group in the current study. Therefore, FFR or IVUS measurements can be helpful in guiding the clinical decision process in patients with doubtful angiographic severity by reducing unnecessary stenting without increasing adverse clinical events.

By multivariate regression analysis, performing intervention was more frequent in the IVUS-guided group, in an LAD lesion, or in patients with multivessel disease. The last 2 factors seem intuitive, because the LAD territory has a large burden of myocardium compared with that of other major coronary arteries, and multivessel disease patients have a higher chance of having a significant lesion, whether assessed by IVUS or FFR. In the current study, the rate of PCI was 3 times higher in the IVUS-guided group than in the FFR-guided group. However, the MACE rate was not different between the 2 groups. Although there have been several studies reporting a good correlation between FFR- and IVUS-derived MLA for assessing coronary lesions (7,18), the cutoff point based on MLA <4.0 mm^2 does not reflect the location of a lesion or the amount of myocardium subtended by the vessel. When the rate of PCI was reanalyzed according to reference vessel diameter ($\geq$3.0 mm or $<$3.0 mm) or lesion location (proximal or mid), the results did not change. Therefore, IVUS can overestimate the clinical significance of intermediate coronary lesions (19) and likely explains the increased rate of PCI in this group. If MLA <3.0 mm^2 was applied for the cutoff point in the current study, as previously reported (20), the incidence of performing PCI might be decreased to 42.6%, similar to that of the FFR-guided group. When a cut-point was used that resulted in equal PCI rates of FFR group, MLA 2.5 mm^2 was the most indicated value. Unfortunately, this retrospective pilot study was not powered to detect a difference in clinical outcome. With larger numbers, one might anticipate that the excess PCI in the IVUS-guided group would translate into an increase in the adverse event rate. This study further confirms the safety of deferring PCI in nonischemia-producing lesions (21).

Study limitations. First, it was a retrospective study. There were several different baseline characteristics such as a higher incidence of single-vessel disease and larger reference vessel diameter in the IVUS group. Second, the decision to select IVUS or FFR was left at the discretion of the operators. Although there was no statistically significant

difference of selection of guided method between operators, this study's results are subject to selection bias. It is not a direct comparison of IVUS and FFR within the same patients, attempting to see which patients would be acceptable for PCI using each technology. Third, the number of patients included in the study was small and the duration of the follow-up was relatively short considering the low event rate at 1-year follow-up. Therefore, these results should be confirmed by larger randomized studies with a longer follow-up period. Fourth, the consequences of the multivariate test could be overfitted, because the parameters were selected when p value was <0.5 in univariate analysis.

Conclusions

Both FFR- and IVUS-guided PCI for intermediate coronary artery disease were associated with favorable outcomes. The FFR-guided PCI reduces the need for revascularization of many of these lesions.

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Key Words: coronary angiography ■ fractional flow reserve ■ intravascular ultrasound ■ outcome ■ percutaneous coronary intervention.