

## Clinical Outcomes of Deferred Lesions With Angiographically Insignificant Stenosis But Low Fractional Flow Reserve

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**Background**—Data are limited regarding outcomes of deferred lesions in patients with angiographically insignificant stenosis but low fractional flow reserve (FFR). We investigated the natural history of angiographically insignificant stenosis with low FFR among patients who underwent routine 3-vessel FFR measurement.

**Methods and Results**—From December 2011 to March 2014, 1136 patients with 3298 vessels underwent routine 3-vessel FFR measurement (3V FFR-FRIENDS study, ClinicalTrials.gov identifier NCT01621438), and this study analyzed the 2-year clinical outcomes of 1024 patients with 2124 lesions with angiographically insignificant stenosis (percentage of diameter stenosis <50%), in which revascularization was deferred. All lesions were classified according to FFR values, using a cutoff of 0.80 (high FFR >0.80 versus low FFR ≤0.80). The primary end point was outcome of major adverse cardiovascular events (a composite of cardiac death, myocardial infarction, and ischemia-driven revascularization) at 2 years. Mean angiographic percentage of diameter stenosis and FFR of total lesions were 32.5±10.3% and 0.91±0.08%, respectively. Among the total lesions with angiographically insignificant stenosis, 8.7% showed low FFR (185 lesions). The incidence of lesions with low FFR was 2.5%, 3.8%, 9.0%, and 15.1% in categories of percentage of diameter stenosis <20%, 20% to 30%, 30% to 40%, and 40% to 50%, respectively. At 2-year follow-up, the low-FFR group showed a significantly higher risk of major adverse cardiovascular events compared with the high FFR group (3.3% versus 1.2%, hazard ratio: 3.371; 95% CI, 1.346–8.442; *P*=0.009). In multivariable analysis, low FFR was the most powerful independent predictor of future MACE in deferred lesions with angiographically insignificant stenosis (adjusted hazard ratio: 2.617; 95% CI, 1.026–6.679; *P*=0.044).

**Conclusions**—In deferred angiographically insignificant stenosis, lesions with low FFR showed significantly higher event rates than those with high FFR. FFR was an independent predictor of future major adverse cardiovascular events in lesions with angiographically insignificant stenosis.

**Clinical Trial Registration**—URL: <http://www.clinicaltrials.gov>. Unique identifier: NCT01621438. (*J Am Heart Assoc.* 2017;6:e006071. DOI: 10.1161/JAHA.117.006071.)

**Key Words:** coronary artery disease • discordance • fractional flow reserve • prognosis • reverse mismatch • stents

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An accompanying Figure S1 is available at <http://jaha.ahajournals.org/content/6/8/e006071/DC1/embed/inline-supplementary-material-1.pdf>

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## Clinical Perspective

### What Is New?

- This study investigated the incidence and natural history of deferred angiographically insignificant but functionally significant lesions.
- Among angiographically insignificant stenosis, the lesions with low fractional flow reserve (8.7%) showed a higher risk of clinical events than those with high fractional flow reserve.

### What Are the Clinical Implications?

- Fractional flow reserve was an independent predictor of future clinical events, even in lesions with angiographically insignificant stenosis.
- These results suggest that the angiographic threshold for fractional flow reserve measurements may need to be lowered.

The presence of ischemia is a prerequisite for the improvement of clinical outcomes utilizing percutaneous coronary intervention.<sup>1</sup> It is well known that a discrepancy exists between angiographic stenosis severity and the presence of myocardial ischemia.<sup>2–10</sup> This discrepancy cannot be completely resolved, even with more precise invasive imaging modalities, such as intravascular ultrasound or optical coherence tomography.<sup>11–14</sup> Currently, fractional flow reserve (FFR) is regarded as a gold standard invasive method to define lesion-specific ischemia, and FFR-guided percutaneous coronary intervention has been proven to reduce unnecessary revascularization and to enhance the clinical outcomes of patients.<sup>15–19</sup> As a result, current guidelines recommend FFR measurement for intermediate coronary stenosis when there is no definite evidence of lesion-specific ischemia.<sup>20,21</sup> Nevertheless, it is well known that angiography can underestimate the functional significance of coronary artery stenosis.<sup>3,22</sup>

The RIPCORD (Does Routine Pressure Wire Assessment Influence Management Strategy at Coronary Angiography for Diagnosis of Chest Pain?) study evaluated the clinical implications of routine FFR measurement in all coronary arteries and demonstrated an important influence on planning patient management.<sup>23</sup> In the RIPCORD study, ≈16% of lesions with percentage of diameter stenosis (%DS) <50% showed FFR <0.80. However, there is a paucity of clinical outcome data for deferred angiographically insignificant stenosis with significant FFR, and these lesions have not been regarded as the target of FFR measurement or revascularization.<sup>19–21,24</sup>

In the current study, we investigated the incidence and natural history of angiographically insignificant stenosis with low FFR, called *reverse mismatch*, among patients who underwent routine 3-vessel FFR measurement.

## Methods

### Study Design and Patient Population

The study population was derived from the 3V FFR-FRIENDS study (3-vessel FFR for the assessment of total stenosis burden and its clinical impact in patients with coronary artery disease, ClinicalTrials.gov identifier NCT01621438), which was designed to investigate the clinical relevance of physiologic total stenosis burden assessed by routine 3-vessel FFR measurement. Patients were consecutively screened and enrolled at 11 centers in 3 countries (Korea, China, and Japan) between November 2011 and March 2014. This study included patients who were at least 18 years old and had >30% stenosis in major epicardial coronary arteries by visual estimation. The enrolled patients underwent FFR measurement in all major coronary arteries. Patients with depressed left ventricular systolic function (ejection fraction <35%), acute ST-segment elevation myocardial infarction within 72 hours, previous coronary artery bypass grafting, chronic renal disease, abnormal epicardial coronary flow (TIMI [Thrombolysis in Myocardial Infarction] flow <3), or planned coronary artery bypass grafting after diagnostic angiography were excluded.

The current study was performed to evaluate the incidence and clinical outcomes of deferred angiographically insignificant stenosis but with low FFR. Among the main study cohort, 2124 angiographically insignificant stenoses (1024 patients) for which revascularization was deferred were selected for the current analysis.

The study protocol was approved by the institutional review board or ethics committee at each participating center and was conducted in accordance with the Declaration of Helsinki. All patients provided written informed consent before enrollment and FFR measurement.

### Angiographic Analysis and Quantitative Coronary Angiography

Coronary angiography was performed using standard techniques. Angiographic views were obtained after administration of intracoronary nitrate (100 or 200 μg). All angiograms were analyzed at a core laboratory (Seoul National University Hospital) in a blinded fashion. Quantitative coronary angiography was performed in optimal projections with validated software (CAAS II, Pie Medical System). Minimum lumen diameter, reference vessel size, %DS, and lesion length were measured. Angiographically insignificant stenosis was defined as lesions with %DS <50% by quantitative coronary angiography.

### Coronary Physiologic Measurements

All coronary physiologic measurements were performed after diagnostic angiography. This study used preinterventional FFR in

case of percutaneous coronary intervention. Briefly, a 5- to 7-Fr guide catheter without side holes was used to engage the coronary artery, and a pressure-temperature sensor guide wire was used for FFR measurement. FFR measurement protocol was standardized among the participating centers before the beginning of the study. The pressure sensor was positioned at the distal segment of a target vessel, and intracoronary nitrate (100 or 200  $\mu$ g) was administered before each physiologic measurement. Continuous intravenous infusion of adenosine or ATP was used to induce hyperemia for FFR measurement. Hyperemic proximal aortic pressure and distal arterial pressure were obtained during sustained hyperemia, and FFR was calculated by means of distal arterial pressure/proximal aortic pressure during hyperemia.

### Patient Follow-up, Outcome Measurements, and Adjudication of Clinical Events

Clinical data were obtained at outpatient clinic visits or by telephone and/or medical questionnaire when needed. An independent clinical events committee adjudicated all events; the members were unaware of clinical, angiographic, and physiologic data. The primary outcome was major adverse cardiac events (MACE), including cardiac death, vessel-related myocardial infarction, and vessel-related ischemia-driven revascularization, during 2-year follow-up. The individual components of MACE were also evaluated. All clinical outcomes were defined according to the Academic Research Consortium, including the addendum to the definition of myocardial infarction.<sup>25,26</sup> All deaths were considered cardiac unless an undisputable noncardiac cause was present. Ischemia-driven revascularization was defined as a revascularization procedure with at least 1 of the following: (1) recurrence of angina, (2) positive noninvasive test, and (3) positive invasive physiologic test.

### Statistical Analysis

Categorical variables were presented as numbers and relative frequencies (percentages), and continuous variables were presented as means and standard deviations or median with interquartile range according to their distribution, which was checked by the Kolmogorov–Smirnov test. Data were analyzed on a per-patient basis for clinical characteristics and on a per-vessel basis for all other analyses. Linear regression analysis was used to estimate the correlation coefficient (Pearson or Spearman, according to the normality of the variables) between quantitative variables.

The cumulative incidence of clinical events was presented as Kaplan–Meier estimates and compared using the log-rank test. Hazard ratios (HRs) and 95% confidence intervals (CIs) were calculated using a marginal Cox proportional hazards regression model to adjust the clustering of multiple-vessel measurements in the same patient.<sup>27</sup> The proportion hazards assumptions in the

marginal Cox proportional hazards models were graphically inspected in the log–log plot and were confirmed with tests of nonzero slope in a generalized linear regression of the scaled partial residuals on survival time. All marginal Cox proportional hazards models for clinical outcomes presented in the study met the assumption of proportional hazards. To adjust for differences in baseline stenosis severity between high and low FFR groups, a marginal Cox regression model was adjusted with %DS. In addition, a multivariable marginal Cox model with penalized methods was used to identify independent predictors of MACE at 2 years. The included covariates were age, male sex, hypertension, current smoking, diabetes mellitus, hyperlipidemia, previous myocardial infarction, %DS, SYNTAX score, and acute coronary syndrome. C-statistics with 95% CI were calculated to validate the discriminant function of the model.

All probability values were 2-sided, and  $P < 0.05$  was considered statistically significant. The statistical packages SPSS version 18.0 (IBM Corp) and SAS version 9.3 (SAS Institute Inc) were used for statistical analyses.

## Results

### Characteristics of Patients and Lesions

Table 1 summarizes the baseline characteristics of 1024 patients. Of the total patient cohort, 77.9% underwent

**Table 1.** General Characteristics of Study Population (N=1024)

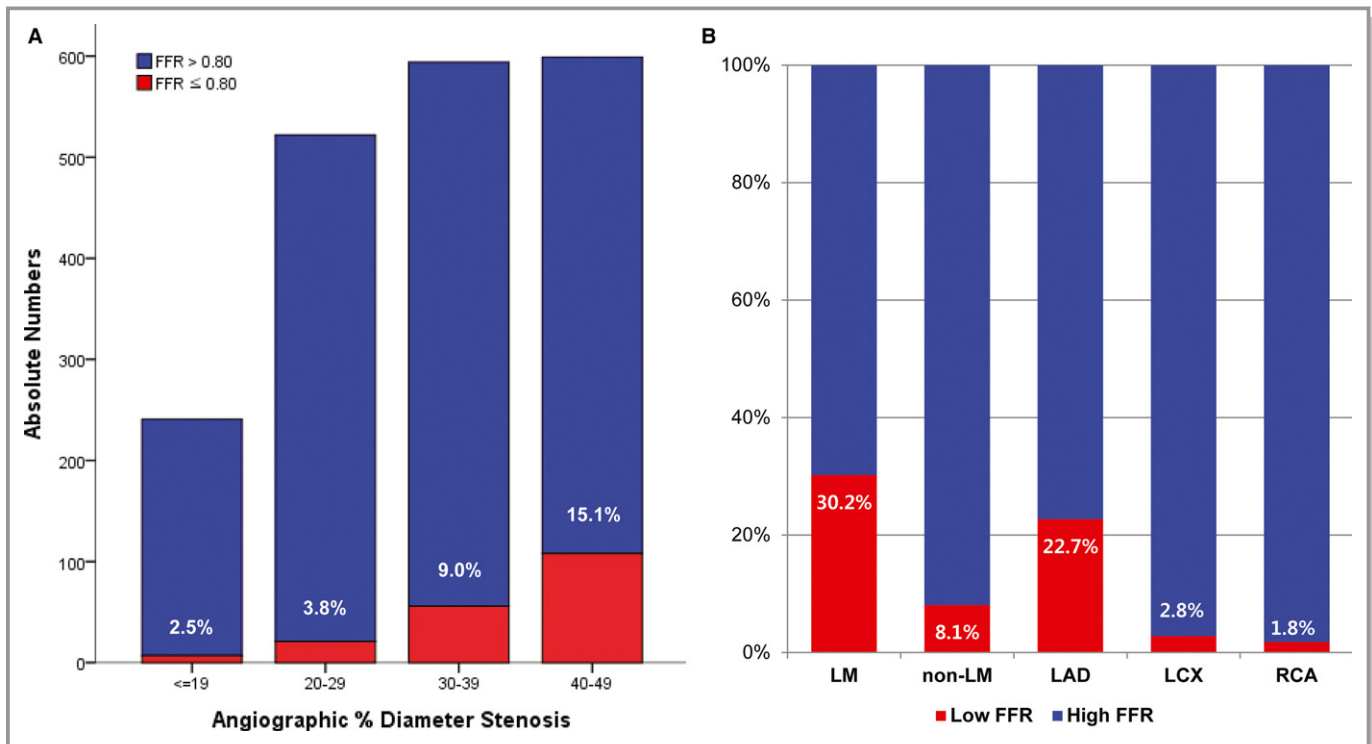
General characteristics	
Age, y	61.6 $\pm$ 9.9
Male sex	750 (73.2)
Ejection fraction, %	62.5 $\pm$ 7.3
Cardiovascular risk factors	
Hypertension	615 (60.1)
Diabetes mellitus	314 (30.7)
Hypercholesterolemia	532 (52.0)
Current smoker	294 (28.7)
Previous MI	97 (9.5)
Previous PCI	341 (33.3)
Clinical presentations	
Stable angina	798 (77.9)
Unstable angina	171 (16.7)
Myocardial infarction	55 (5.3)
NSTEMI	39 (3.8)
Recent STEMI	16 (1.6)

Values are mean $\pm$ SD or n (%). MI indicates myocardial infarction; NSTEMI, non–ST-segment elevation myocardial infarction; PCI, percutaneous coronary intervention; STEMI, ST-segment elevation myocardial infarction.

**Table 2.** Lesional Profiles of Angiographically Insignificant Lesions According to FFR

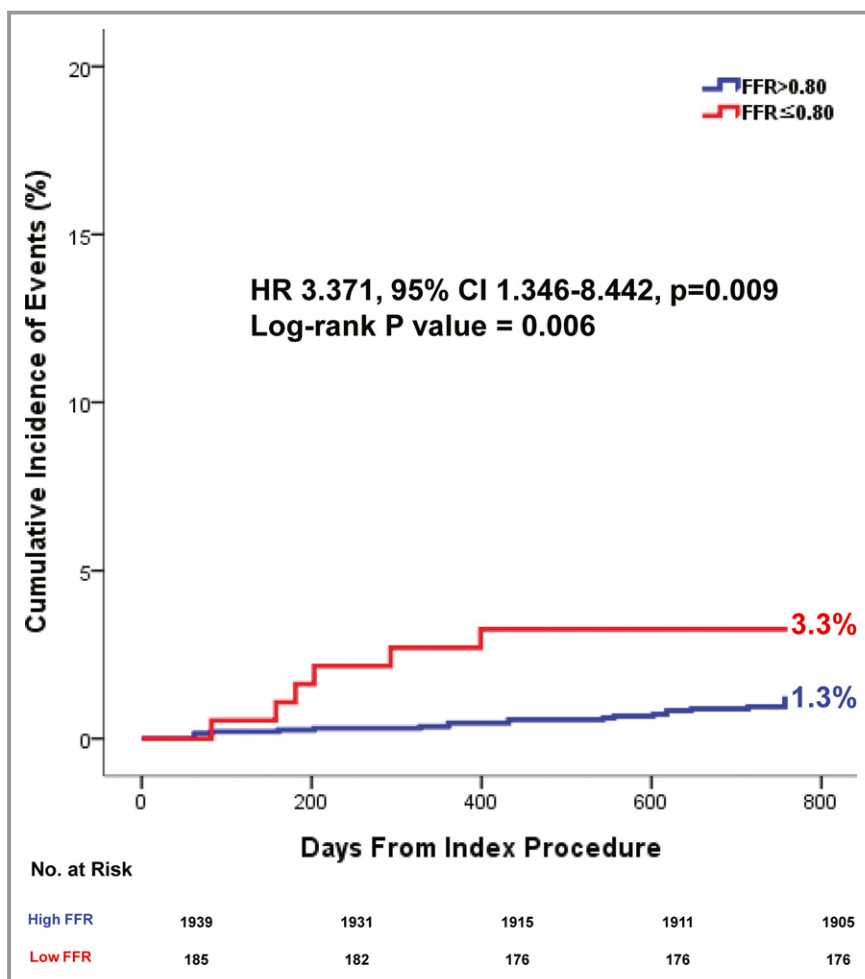
	Total (n=2124)	FFR >0.80 (n=1939)	FFR ≤0.80 (n=185)	P Value
Lesion location				<0.001
Left main	63 (3.0)	44 (2.3)	19 (10.3)	
LAD	670 (31.5)	518 (26.7)	152 (82.2)	
LCX	721 (33.9)	701 (36.2)	20 (10.8)	
RCA	733 (34.5)	720 (37.1)	13 (7.0)	
Lesion segment				<0.001
Proximal segment	872 (41.1)	818 (41.8)	62 (33.5)	
Mid segment	702 (33.1)	611 (31.5)	91 (49.2)	
Distal segment	550 (25.9)	518 (26.7)	32 (17.3)	
QCA				
RD, mm	3.04±0.61	3.08±0.61	2.66±0.46	<0.001
MLD, mm	2.06±0.54	2.10±0.54	1.64±0.35	<0.001
DS, %	32.5±10.3	31.7±10.2	38.3±8.5	<0.001
Lesion length, mm	8.4±5.7	8.3±5.5	9.8±7.3	<0.001
SYNTAX score	8.0 (3.0–12.0)	7.0 (2.0–12.0)	10.0 (6.0–14.0)	<0.001
FFR	0.91±0.08	0.93±0.06	0.77±0.04	<0.001

DS indicates diameter stenosis; FFR, fractional flow reserve; LAD, left anterior descending artery; LCX, left circumflex artery; MLD, minimum lumen diameter; QCA, quantitative coronary angiography; RCA, right coronary artery; RD, reference diameter.



**Figure 1.** Distribution of lesions according to angiographic percentage of diameter stenosis (%DS) and FFR. A, Distributions of total lesions are presented according to %DS and FFR values. The incidence of lesions with low FFR was 2.5%, 3.8%, 9.0%, and 15.1% in %DS categories <20%, 20% to 30%, 30% to 40%, and 40% to 50%, respectively. B, The proportions of lesions with low FFR are presented according to target vessels. LM and LAD showed the highest proportions of lesions with low FFR compared with non-LM or non-LAD. FFR indicates fractional flow reserve; LAD, left anterior descending artery; LCX, left circumflex artery; LM, left main vessel; RCA, right coronary artery.

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**Figure 2.** Comparison of 2-year clinical outcomes of deferred angiographically insignificant lesions classified according to fractional flow reserve. Kaplan–Meier curves are shown for deferred angiographically insignificant lesions, classified according to FFR values. HRs were calculated from a marginal Cox proportional hazards regression model. CI indicates confidence interval; FFR, fractional flow reserve; HR, hazard ratio.

coronary angiography due to stable coronary artery disease. Among the 2124 total lesions, 74.2% of stenoses were located in the proximal or middle portion of the interrogated vessels. Mean angiographic %DS and FFR were  $32.5 \pm 10.3\%$  and  $0.91 \pm 0.08\%$ , respectively (Table 2).

### Comparisons Between High- and Low-FFR Lesions

Among the total vessels, 8.7% of vessels (185/2124) showed low FFR despite an angiographic %DS <50%. The

**Table 3.** Cumulative Rates of Clinical Outcomes Among Deferred Lesions According to the Classification Using Percentage of Diameter Stenosis and FFR

	FFR >0.80 (n=1939)	FFR ≤0.80 (n=185)	Hazard Ratio (95% CI)	P Value
Major adverse cardiac events*	1.2% (19)	3.3% (6)	3.371 (1.346–8.442)	0.009
Cardiac death	0.6% (12)	1.1% (2)	1.759 (0.394–7.860)	0.460
Vessel-related myocardial infarction	0.3% (6)	0.0% (0)	NA	0.451
Vessel-related ischemia-driven revascularization	0.6% (7)	2.2% (4)	6.103 (1.786–20.851)	0.004

Cumulative incidences of clinical outcomes are presented as Kaplan–Meier estimates. The number of vessels that developed each event are presented. P values were log-rank P value in survival analysis. FFR indicates fractional flow reserve; NA, not available.

\*Defined as a composite of cardiac death, myocardial infarction, or ischemia-driven revascularization by percutaneous or surgical methods.

**Table 4.** Independent Predictors of Major Adverse Cardiac Events in Deferred Angiographically Insignificant Lesions

Variable	Adjusted HR	95% CI	P Value
Low FFR ( $\leq 0.80$ )	2.617	1.026–6.679	0.044
SYNTAX score	1.057	1.002–1.114	0.040
Age	1.028	0.984–1.073	0.217
Male sex	2.254	0.681–7.463	0.183
Hypertension	0.602	0.269–1.347	0.217
Current smoking	1.302	0.556–3.049	0.543
Diabetes mellitus	1.298	0.568–2.970	0.536
Hyperlipidemia	0.824	0.366–1.855	0.641
Previous myocardial infarction	0.994	0.257–3.846	0.993
Acute coronary syndrome	1.871	0.807–4.340	0.145
Diameter stenosis	1.012	0.969–1.057	0.579

C-index of the marginal Cox regression model was 0.756 (0.671–0.841). CI indicates confidence interval; FFR, fractional flow reserve; HR, hazard ratio.

incidence of lesions with low FFR was 2.5%, 3.8%, 9.0%, and 15.1% in %DS categories <20%, 20% to 30%, 30% to 40%, and 40% to 50%, respectively (Figure 1A). Among 185 lesions with low FFR, 171 lesions (92.4%) were located in the left main vessel (LM) or left anterior descending coronary artery (Table 2 and Figure 1B). Revascularization was deferred in all 185 lesions with low FFR due to angiographically insignificant stenosis.

The lesions with low FFR showed significantly higher %DS, lesion length, and SYNTAX score and significantly lower reference diameter and minimum lumen diameter compared with those with high FFR (Table 2). All target lesions were deferred despite low FFR, mainly because of angiographically insignificant stenosis.

### Comparison of Clinical Outcomes of Angiographically Insignificant Lesions, According to FFR

The estimated 2-year MACE risk was increased along with the decrease in FFR value (Figure S1). At 2-year follow-up, deferred lesions with low FFR showed a significantly higher risk of MACE compared with lesions with high FFR (3.3% versus 1.3%; HR: 3.371; 95% CI, 1.346–8.442;  $P=0.009$ ; Figure 2). These significant differences were mainly driven by higher risk of ischemia-driven revascularization in the low FFR group (2.2% versus 0.6%; HR: 6.103; 95% CI, 1.786–20.851;  $P=0.004$ ; Table 3). When %DS was adjusted, deferred lesions with low FFR also showed significantly higher risk of 2-year MACE compared those with high FFR (adjusted HR: 2.650; 95% CI, 1.081–6.498;  $P=0.033$ ).

In multivariable analysis, low FFR was the most powerful independent predictor of future MACE in deferred lesions with angiographically insignificant stenosis (adjusted HR: 2.617; 95% CI, 1.026–6.679;  $P=0.044$ ; Table 4).

## Discussion

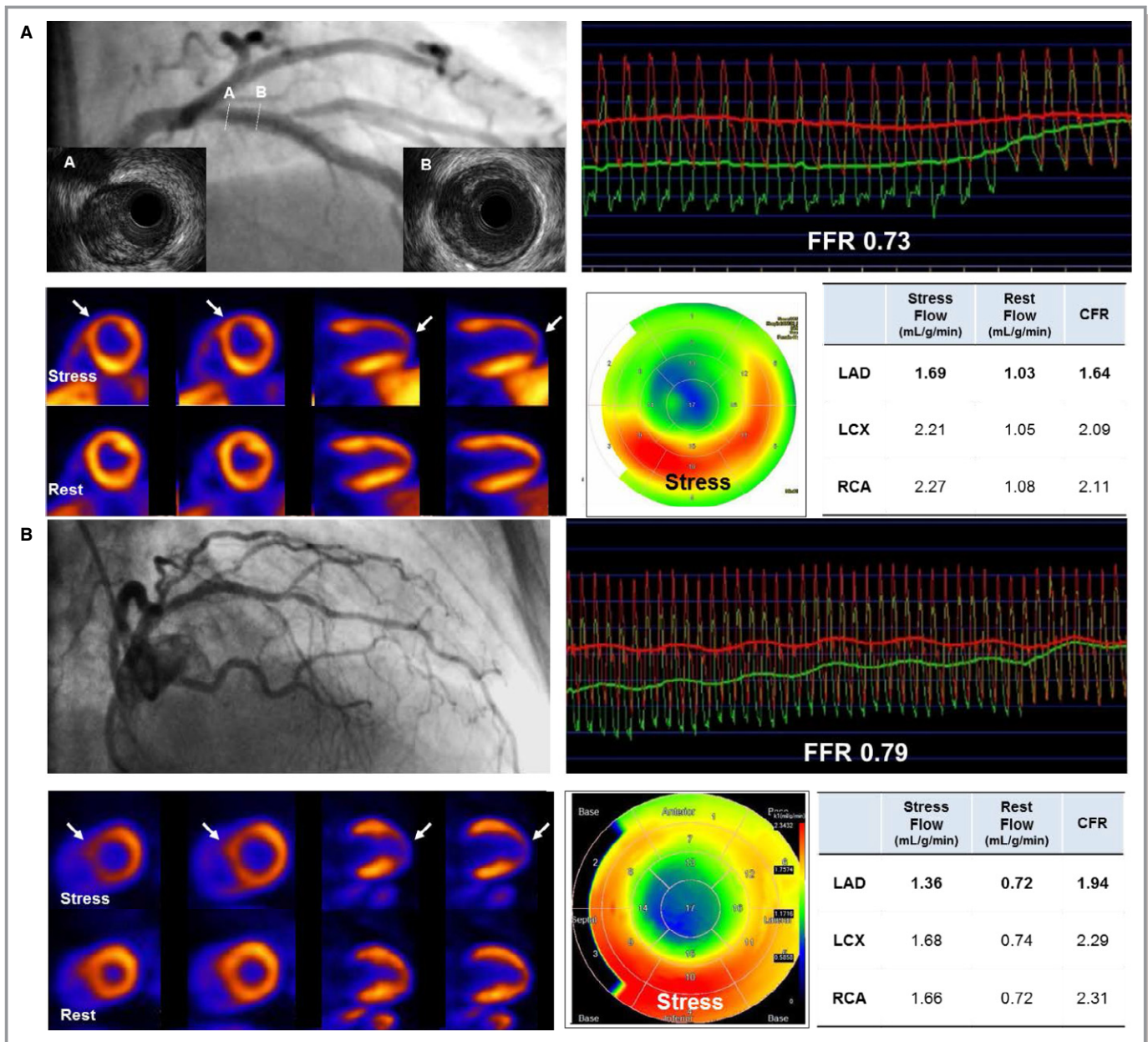
This study focused on the incidence and natural history of deferred angiographically insignificant stenosis and low FFR in patients who underwent routine 3-vessel FFR measurement. The main findings were as follows. First, despite angiographically insignificant stenosis, about 8.7% of lesions showed low FFR. Second, deferred lesions with low FFR showed a significantly higher risk of MACE compared with those with high FFR. Third, low FFR was independently associated with MACE in deferred lesions with angiographically insignificant stenosis.

### Low FFR in Angiographically Insignificant Lesions

Several previous studies revealed the discrepancy between anatomic severity and presence of myocardial ischemia.<sup>4–6,8–11</sup> This discrepancy can be classified into 2 categories, such as *angiographically significant but functionally insignificant* (mismatch) or *functionally significant but angiographically insignificant* (reverse mismatch).<sup>5</sup>

Although evidence has shown favorable clinical outcomes of deferred lesions with high FFR despite angiographically significant stenosis,<sup>17,18,28,29</sup> there remains a paucity of evidence evaluating lesions with low FFR despite angiographically insignificant stenosis. Current guidelines do not recommend FFR measurement in stenosis with %DS <40% to 50%.<sup>20,21</sup> These angiographically insignificant lesions have not been considered as a target for FFR measurement, or for percutaneous coronary intervention in general, and data are limited regarding the true incidence, predictors, mechanisms, and natural history of those lesions after deferral of revascularization. Although Park et al previously reported that 16% of non-LM stenoses and 40% of LM stenoses showed reverse mismatch, they did not evaluate the clinical implications of reverse mismatch.<sup>5</sup>

In the 3V FFR-FRIENDS study, FFR was measured in all major coronary arteries according to the study protocol. In the current study, mean angiographic %DS was  $32.5 \pm 10.3\%$ , and 70.3% and 39.7% of the lesions had %DS <40% and <30%, respectively. In angiographically insignificant lesions, about 8.7% (185/2124) showed low FFR, and most of those were located at the LM or left anterior descending artery, similar to previous studies.<sup>5,11,12</sup> This finding is consistent regarding the fundamental relationship between pressure and flow, as those locations are associated with high flow across the lesion.<sup>3,30</sup>



**Figure 3.** Representative case examples of angiographically insignificant stenosis with low FFR. Two representative cases of angiographically insignificant stenosis with low FFR are presented. The limitations of coronary angiography, such as hidden focal stenosis (A) and angiographically underestimated diffuse atherosclerosis (B), can cause the low FFR, despite angiographically insignificant stenosis. In both cases, N<sup>13</sup>-ammonia positron emission tomography showed a reversible perfusion defect in stress imaging (arrow), low-stress myocardial blood flow, and coronary flow reserve in LAD territory. CFR indicates coronary flow reserve; FFR, fractional flow reserve; LAD, left anterior descending artery; LCX, left circumflex artery; RCA, right coronary artery.

### Natural History of Deferred Lesions With Angiographically Insignificant Stenosis But Low FFR

Our study demonstrated higher risk of MACE in deferred lesions with low FFR, despite angiographically insignificant stenosis. Furthermore, low FFR itself was also an independent predictor of MACE among deferred lesions with

angiographically insignificant stenosis in a multivariable marginal Cox regression model. It should be noted that patients in the current study who had lesions with low FFR despite angiographically insignificant stenosis were closely followed and received optimal medical treatment. Overall, >97% of patients completed 2-year follow-up, and the percentage of patients using statins was 86.7% at discharge and 83.0% at 2-year follow-up. These findings suggest that

FFR measurement needs to be performed in patients with a lower degree of stenosis than those recommended in current guidelines when clinically indicated.

Several mechanisms may be involved in the presence of lesions with low FFR despite angiographically insignificant stenosis, such as hidden focal stenosis (Figure 3A) or diffuse stenosis (Figure 3B). In our study, the low-FFR group had higher SYNTAX scores and smaller reference vessel diameters compared with those with high FFR. These findings suggest an influence of diffuse disease on low FFR. Despite angiographically insignificant stenosis, lesions with low FFR are continuously exposed to high pressure gradient across the stenosis. Consequently, this pressure gradient, which represents the magnitude of external forces acting on the plaque (eg, wall shear stress), and the presence of myocardial ischemia may increase future risk of cardiovascular events.<sup>30–34</sup> Further study with a large sample size and a longer clinical follow-up period is warranted to clarify the natural history and optimal treatment strategy for those lesions.

## Limitations

Some limitations of this study should be noted. First, because the treatment strategy was determined at the discretion of operators, optimal treatment strategy for lesions with angiographically insignificant stenosis but low FFR could not be evaluated in our study. Second, the mechanism of reverse mismatch could not be fully assessed because intravascular ultrasound had not been systemically performed. Third, the event rates were generally lower than those of previous studies. This difference seems to be due to the unique design of this study and lower angiographic lesion severity than that of previous studies.<sup>19</sup> Fourth, noninvasive perfusion imaging and invasive imaging studies were not performed systematically. Fifth, although the current study performed the multivariable adjusted analysis, the possibility of additional confounding bias or bias from unmeasured confounders could not be completely excluded.

## Conclusions

Among deferred lesions in patients with angiographically insignificant stenosis, lesions with low FFR showed significantly higher event rates compared with those with high FFR. FFR itself was an independent predictor of future MACE, even in lesions with angiographically insignificant stenosis. These results suggest that the angiographic threshold for FFR measurements may need to be lowered, especially for lesions in the LM or the left anterior descending artery.

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## Disclosures

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**Supplementary Figure 1. Estimated 2-Year MACE Rates According to FFR**

