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Clinical Outcomes According to Fractional Flow Reserve or Instantaneous Wave-Free Ratio in Deferred Lesions

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ABSTRACT

OBJECTIVES The authors investigated 2-year clinical outcomes according to fractional flow reserve (FFR) and instantaneous wave-free ratio (iFR) values in deferred lesions.

BACKGROUND Invasive physiological indices such as FFR or iFR are used in clinical practice to select ischemia-causing stenosis and to guide the treatment strategy for patients with coronary artery disease.

METHODS From the 3V FFR-FRIENDS (3-Vessel Fractional Flow Reserve for the Assessment of Total Stenosis Burden and Its Clinical Impact in Patients With Coronary Artery Disease) study, 821 deferred lesions (n = 374) with both FFR and iFR available were included in this study. The primary outcome was major adverse cardiac events (MACE) (a composite of cardiac death, myocardial infarction, and ischemia-driven revascularization) at 2 years. The lesions were classified according to FFR and iFR cutpoints into concordant normal (Group 1: FFR >0.80 and iFR >0.89), high FFR and low iFR (Group 2: FFR >0.80 and iFR ≤0.89), low FFR and high iFR (Group 3: FFR ≤0.80 and iFR >0.89), and concordant abnormal (Group 4: FFR ≤0.80 and iFR ≤0.89).

RESULTS Deferred lesions with low FFR (≤0.80) or low iFR (≤0.89) showed significantly higher rates of 2-year MACE, compared with high FFR (>0.80) or high iFR (>0.89), respectively (7.2% in low FFR vs. 2.4% in high FFR; $p < 0.001$; 8.1% in low iFR vs. 2.4% in high iFR; $p < 0.001$). Both FFR and iFR showed significant association with occurrence of MACE as continuous values (hazard ratio [HR] of FFR: 0.570, 95% confidence interval [CI]: 0.337 to 0.963; $p < 0.001$; HR of iFR: 0.350, 95% CI: 0.217 to 0.567; $p < 0.001$). When comparing the discriminant ability between FFR and iFR, the c-index was comparable between FFR and iFR (c-index 0.677 vs. 0.685; $p = 0.857$). Among 4 groups classified according to FFR and iFR levels, only Group 4 with concordant abnormal results showed significantly higher risk of MACE, compared with group 1 (HR: 7.708, 95% CI: 2.621 to 22.667; $p < 0.001$).

CONCLUSIONS Both FFR and iFR showed significant association with future risk of MACE in deferred lesions. The discordant results between FFR and iFR were not associated with the increased risk of MACE. The risk of MACE was significantly increased only in lesions with abnormal results of both FFR and iFR. (J Am Coll Cardiol Intv 2017;10:2502-10) © 2017 by the American College of Cardiology Foundation.

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The presence of inducible myocardial ischemia is the prerequisite for the benefit of percutaneous coronary intervention (PCI). In this regard, a pressure-derived physiological index, fractional flow reserve (FFR), has been regarded as a standard invasive method to evaluate the functional significance of epicardial coronary artery stenosis (1,2). Recently, a physiological index that does not require hyperemia, instantaneous wave-free ratio (iFR), was introduced and is also used in clinical practice (3). Three large clinical studies investigated the diagnostic performance of iFR against FFR and reported various ranges of diagnostic accuracy, from 60% to 90% (3-5). However, the diagnostic performance of FFR and iFR were comparable when the other references were used to define the presence of myocardial ischemia (6-8). In addition, 2 recently published large-scale, randomized controlled trials (DEFINE-FLAIR [Functional Lesion Assessment of Intermediate Stenosis to Guide Revascularisation], iFR-SWEDEHEART [Evaluation of iFR vs FFR in Stable Angina or Acute Coronary Syndrome]) showed noninferiority of iFR-guided strategy compared with FFR-guided strategy in terms of 1-year clinical outcomes (9,10).

SEE PAGE 2511

Because iFR is measured during resting status and FFR during hyperemic status, each index may represent the different aspect of pathophysiology in patients with coronary artery disease. Furthermore, no previous study focused on clinical outcomes of deferred lesions with discordant results between FFR and iFR. Because both the DEFINE-FLAIR and iFR-SWEDEHEART trials adopted exclusive allocations between FFR- and iFR-guided strategy groups, the outcomes of deferred lesions with discordant results could not be investigated. The main purpose of the current study was to investigate 2-year clinical outcomes according to FFR and iFR values in deferred lesions.

METHODS

STUDY DESIGN AND PATIENT POPULATION. The study population was derived from the 3V FFR-FRIENDS (3-Vessel Fractional Flow Reserve for the Assessment of Total Stenosis Burden and Its Clinical Impact in Patients With Coronary Artery Disease; NCT01621438) study, which was designed to investigate the clinical relevance of total stenosis burden assessed by 3-vessel FFR measurement. Patients with depressed left ventricular systolic function (ejection fraction <35%), acute ST-segment elevation myocardial infarction within 72 h, previous coronary artery bypass graft surgery, chronic renal disease, abnormal epicardial coronary flow (Thrombolysis In Myocardial Infarction flow grade <3) or planned coronary artery bypass graft surgery after diagnostic angiography were excluded. When PCI was indicated, coronary interventions were performed using current standard techniques. For lesions with significant per-vessel FFR (≤0.80), PCI was recommended as per the current guideline. However, the decision for PCI was at the discretion of the operators.

This substudy was performed to investigate 2-year clinical outcomes according to FFR and iFR values in deferred lesions. Among the main study cohort, 821 deferred lesions (n = 374) with both FFR and iFR were included in the current study. The current study was conducted by 4 predefined centers with uniform protocol for both resting and hyperemic pressure recordings. The enrolled patients were not taking part in conflicting studies. The study protocol was approved by the institutional review board or ethics committee at each participating center, and all patients provided written informed consent.

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, version 5.7.1 (Pie Medical System, Maastricht, the Netherlands). Minimum lumen diameter, reference vessel size, percent diameter stenosis, and lesion length were measured. Angiographic disease severity was also assessed by SYNTAX score (10).

CORONARY PHYSIOLOGICAL MEASUREMENTS. All coronary physiological measurements were performed after diagnostic angiography. Briefly, a 5- to 7-F guide catheter without side holes was used to engage the coronary artery, and a pressure-temperature sensor guidewire (St. Jude Medical, St. Paul, Minnesota) was used for FFR measurement. The pressure sensor was positioned at the distal segment of a target vessel, and intracoronary nitrate (100 or 200 μg) was administered before each physiological measurement. iFR was calculated as the mean pressure distal to the stenosis divided by the mean aortic pressure during the diastolic wave-free period. The baseline tracing data with a duration of 5 heart beats

ABBREVIATIONS AND ACRONYMS

CI = confidence interval

FFR = fractional flow reserve

HR = hazard ratio

iFR = instantaneous wave-free ratio

IQR = interquartile range

MACE = major adverse cardiovascular event(s)

MI = myocardial infarction

PCI = percutaneous coronary intervention

TABLE 1 General Characteristics of Deferred Patients (N = 374)

General characteristics	
Age, yrs	63.9 ± 9.7
Male	287 (76.7)
Ejection fraction, %	61.6 ± 6.6
Cardiovascular risk factors	
Hypertension	242 (64.7)
Diabetes mellitus	133 (35.6)
Hypercholesterolemia	259 (69.3)
Current smoker	67 (17.9)
Chronic renal failure	13 (3.5)
Previous MI	29 (7.8)
Previous PCI	115 (30.7)
Clinical presentations	
Stable angina	276 (73.7)
Unstable angina	36 (9.6)
Myocardial infarction	18 (4.8)
NSTEMI	11 (2.9)
Recent STEMI	7 (1.9)
Multivessel disease	225 (60.2)
SYNTAX score	11.0 (7.0-17.6)

Values are mean ± SD, n (%), or median (interquartile range).

MI = myocardial infarction; NSTEMI = non-ST-segment elevation myocardial infarction; PCI = percutaneous coronary intervention; STEMI = ST-segment elevation myocardial infarction.

or longer were extracted from the FFR console platforms. The iFR was calculated using automated algorithms acting over the wave-free period over a minimum of 5 beats as previously described (3). Continuous intravenous infusion of adenosine was used to induce hyperemia for FFR measurement. Hyperemic proximal aortic pressure and distal arterial pressure were obtained, and FFR was calculated as the lowest average of 3 consecutive beats during adenosine infusion. After measurements, the pressure wire was pulled back to the guide catheter, and the presence of pressure drift was checked. All pressure readings were collected and validated at the core laboratory in a blinded fashion.

CUTOFF VALUES OF PHYSIOLOGICAL INDICES AND LESION CLASSIFICATIONS. The cutoff values of 0.80 (11) and 0.89 (4,9,10) were used for FFR and iFR, respectively. The lesions were classified according to FFR and iFR cutpoints into concordant normal (Group 1: FFR >0.80 and iFR >0.89), high FFR and low iFR (Group 2: FFR >0.80 and iFR ≤0.89), low FFR and high iFR (Group 3: FFR ≤0.80 and iFR >0.89) and concordant abnormal (Group 4: FFR ≤0.80 and iFR ≤0.89).

FOLLOW-UP OF THE PATIENTS, OUTCOME MEASUREMENTS, AND ADJUDICATION OF CLINICAL EVENTS. Clinical data were obtained at outpatient clinic visits or by telephone contact when needed. An independent clinical events committee whose members were unaware of clinical, angiographic, and physiological data adjudicated all events. The primary outcome was major adverse cardiac events (MACE) at 2 years, including cardiac death, vessel-related myocardial infarction (MI), and vessel-related ischemia-driven revascularization. All clinical outcomes were defined according to the Academic Research Consortium, including the addendum to the definition of MI. All deaths were considered cardiac unless an undisputable non-cardiac cause was present. Ischemia-driven revascularization was

TABLE 2 General Characteristics Deferred Vessels

	Total	High FFR	Low FFR	p Value*	High iFR	Low iFR	p Value†
Per-vessel analysis (N = 821)	821 (100.0)	738/821 (89.9)	83/821 (10.1)		746/821 (90.9)	75/821 (9.1)	
Measured vessel location				<0.001			<0.001
Left anterior descending artery	239 (29.1)	187 (25.3)	52 (62.7)		190 (25.5)	49 (65.3)	
Left circumflex artery	310 (37.8)	288 (39.0)	22 (26.5)		289 (38.7)	21 (28.0)	
Right coronary artery	272 (33.1)	263 (35.6)	9 (10.8)		267 (35.8)	5 (6.7)	
Quantitative coronary angiography							
Reference diameter, mm	2.98 ± 0.61	3.02 ± 0.61	2.57 ± 0.47	<0.001	3.02 ± 0.61	2.54 ± 0.46	<0.001
Minimum lumen diameter, mm	1.79 ± 0.68	1.86 ± 0.67	1.21 ± 0.45	<0.001	1.86 ± 0.67	1.18 ± 0.43	<0.001
Diameter stenosis, %	40.8 ± 15.9	39.3 ± 15.5	53.4 ± 14.3	<0.001	39.5 ± 15.5	53.7 ± 14.6	<0.001
Lesion length, mm	9.1 ± 6.3	8.8 ± 5.9	11.9 ± 7.9	<0.001	8.8 ± 5.9	12.1 ± 8.5	<0.001
Coronary physiological parameters							
FFR	0.90 ± 0.07‡	0.92 ± 0.06	0.75 ± 0.05	<0.001	0.91 ± 0.06	0.78 ± 0.08	<0.001
iFR	0.97 ± 0.05§	0.98 ± 0.04	0.88 ± 0.07	<0.001	0.98 ± 0.03	0.84 ± 0.06	<0.001

Values are n (%), n/N (%), or mean ± SD. Generalized estimating equation model or maximum likelihood chi-square tests were used for overall and between groups comparison in per-vessel analysis. *p Values for the comparison of variables between high and low FFR groups. †p Values for the comparison of variables between high and low iFR groups. ‡FFR: median 0.92 (interquartile range [IQR]: 0.85 to 0.96). §iFR: median 0.99 (IQR: 0.94 to 1.00).

FFR = fractional flow reserve; iFR = instantaneous wave-free ratio.

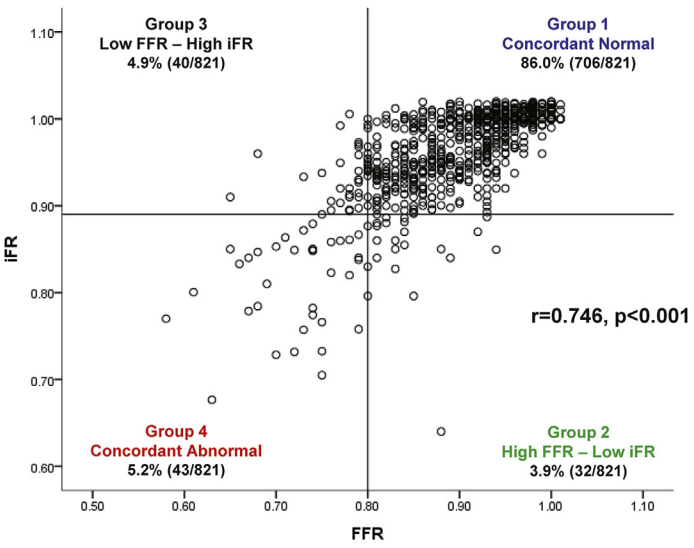
defined as a revascularization procedure with at least 1 of the following: 1) recurrence of angina; 2) positive noninvasive test; and 3) positive invasive physiological test.

STATISTICAL ANALYSIS. Categorical variables were presented as numbers and relative frequencies (percentages), and continuous variables were presented as mean ± SD or median with interquartile range (IQR) 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.

In order to compare clinical outcomes of deferred lesions, event rates were calculated based on Kaplan-Meier censoring estimates, and the log-rank test was used to compare survival curves between groups. Those clinical event data were compared using a marginal Cox proportional hazards regression model to calculate the hazard ratio (HR) and 95% confidence interval (CI) in order to adjust for intrasubject correlations among the interrogated vessels (12). In order to explore the prognostic impact of FFR or iFR as continuous values, estimated MACE rates derived from the marginal Cox proportional hazards regression model were plotted according to FFR or iFR values. The discriminant function of model with FFR or iFR was compared using Harrell's c-statistics.

A multivariable marginal Cox model with penalized methods was used to identify independent predictors of MACE. The discriminant function of the multivariable model was presented with Harrell's c-statistics with 95% CI. All analyses incorporated a participating center as a random effect.

FIGURE 1 Distribution of Lesions According to FFR and iFR



Among the total 821 deferred lesions, the FFR and iFR showed a significant correlation ($r = 0.746$; $p < 0.001$), and 8.8% of lesions showed discordant classifications according to FFR and iFR cutoff value of ≤0.80 and ≤0.89, respectively. FFR = fractional flow reserve; iFR = instantaneous wave-free ratio.

All probability values were 2-sided, and p values <0.05 were considered statistically significant. The SPSS version 18.0 (SPSS, Chicago, Illinois) and SAS version 9.3 (SAS Institute, Cary, North Carolina) statistical packages were used for statistical analyses.

RESULTS

CHARACTERISTICS OF PATIENTS AND LESIONS. Table 1 shows baseline clinical characteristics of the patients. About 60% of patients showed multivessel disease and median SYNTAX score was 11.0 (IQR: 7.0 to 17.6). Table 2 demonstrates lesion profiles. Mean

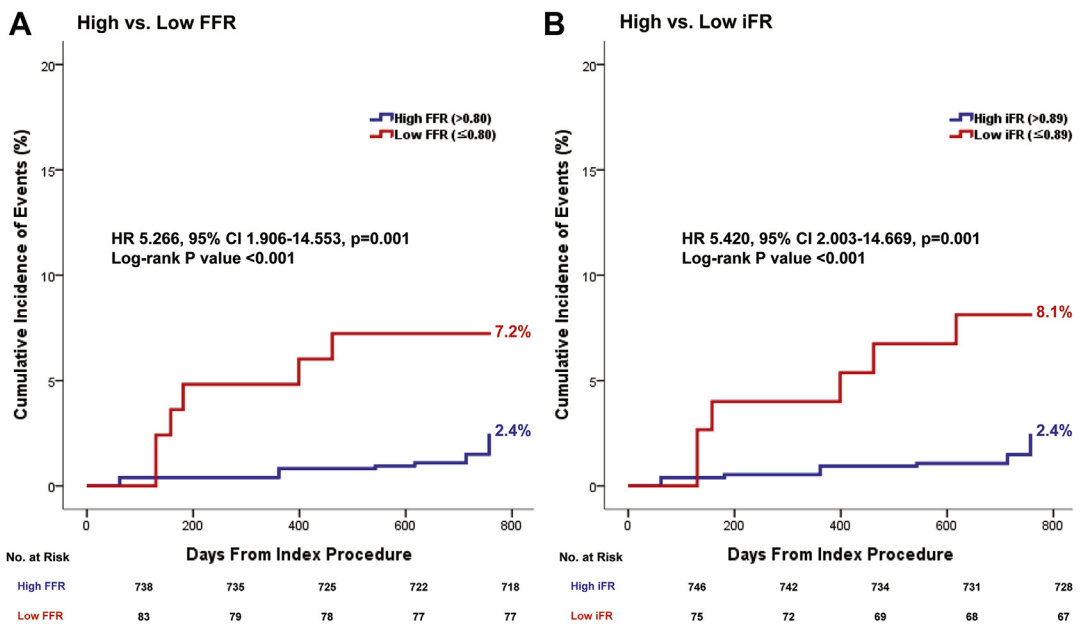
TABLE 3 Clinical Outcomes of Deferred Vessels According to FFR or iFR Values

	High FFR	Low FFR	p Value*	High iFR	Low iFR	p Value†
Per-vessel analysis (N = 821)	738/821 (89.9)	83/821 (10.1)		746/821 (90.9)	75/821 (9.1)	
Cardiac death	1.0 (7)	0.0 (0)	0.345	0.8 (6)	1.4 (1)	0.675
Vessel-related MI	0.8 (5)	1.2 (1)	0.683	0.8 (5)	1.4 (1)	0.541
Vessel-related ischemia driven revascularization	1.5 (4)	7.2 (6)	<0.001	1.6 (5)	6.7 (5)	<0.001
MACE‡	2.4 (11)	7.2 (6)	<0.001	2.4 (11)	8.1 (6)	<0.001

Values are n/N (%) or % (n). The cumulative incidences of clinical outcomes are presented as Kaplan-Meier estimates during the median follow-up of 729.0 (699.0 to 747.0) days. p Values are by log-rank or Breslow p value in survival analysis. *Log rank p values for the comparison of cumulative incidence of events between high and low FFR groups. †Log rank p values for the comparison of cumulative incidence of events between high and low iFR groups. ‡Major adverse cardiovascular events included cardiac death, myocardial infarction, and ischemia-driven revascularization.

MACE = major adverse cardiovascular events; other abbreviations as in Tables 1 and 2.

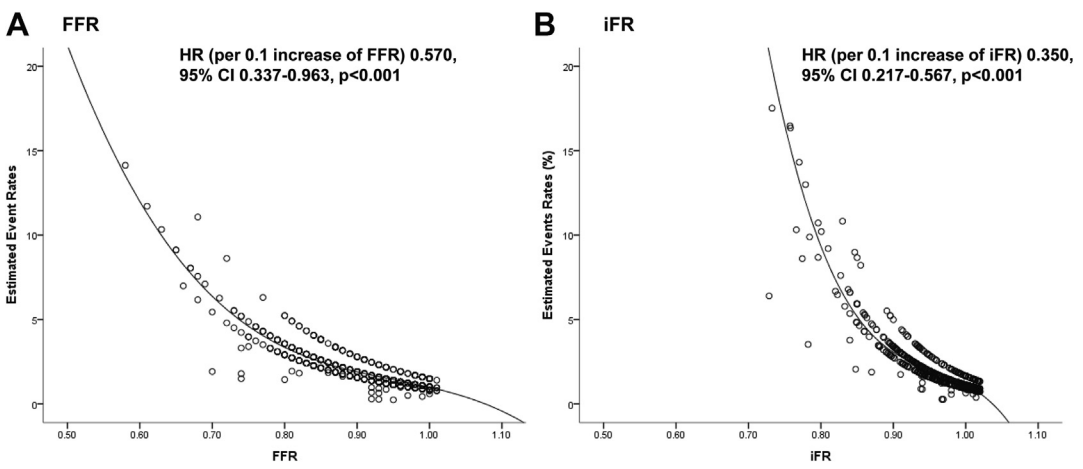
FIGURE 2 Comparison of 2-Year Clinical Outcomes of Deferred Lesions, Between Lesions with High or Low FFR, or Between Lesions With High or Low iFR



Kaplan-Meier curves are shown for the comparison of 2-year rates of MACE in deferred lesions according to **(A)** high versus low FFR, or according to **(B)** high- versus low-iFR values. CI = confidence interval; HR = hazard ratio; other abbreviations as in Figure 1.

angiographic percent diameter stenosis, FFR, and iFR were 40.8 ± 15.9% (median 42.8%; IQR: 28.1% to 51.6%), 0.90 ± 0.07 (median 0.92; IQR: 0.85 to 0.96), and 0.97 ± 0.05 (median 0.99; IQR: 0.94 to 1.00), respectively. In comparison between high- and low-FFR groups, the low-FFR group showed significantly higher stenosis severity and lesion length. Compared with high-iFR lesions, low-iFR lesions showed higher

FIGURE 3 The Associations Between Estimated MACE Rates and FFR or iFR Values in Deferred Lesions



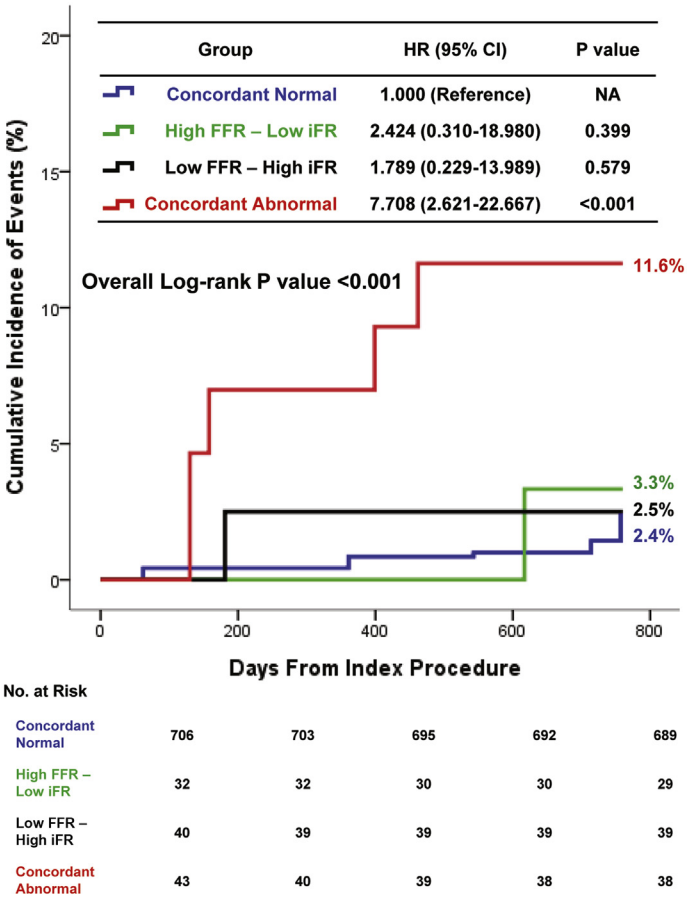
Both **(A)** FFR and **(B)** iFR as continuous values showed significant nonlinear relationship with the estimated risk of MACE, and lower FFR and iFR values showed exponentially increased risk of MACE. MACE = major adverse cardiac event(s); other abbreviations as in Figures 1 and 2.

stenosis severity and lesion length. Although the FFR and iFR showed a significant correlation ($r = 0.746$; $p < 0.001$), 8.8% (Group 2: 3.9% and Group 3: 4.9%) showed discordant results between FFR and iFR (Figure 1).

CLINICAL OUTCOMES ACCORDING TO FFR OR iFR VALUES. Deferred lesions with low FFR (≤0.80) or low iFR (≤0.89) showed significantly higher rates of 2-year MACE, compared with high FFR (>0.80) or high iFR (>0.89), respectively (7.2% in low FFR vs. 2.4% in high FFR; $p < 0.001$; 8.1% in low iFR vs. 2.4% in high iFR; $p < 0.001$), mainly driven by higher risk of ischemia-driven revascularization (Table 3, Figure 2). Both FFR and iFR as continuous values showed significant prognostic impact (HR of FFR [per 0.1 increase]: 0.570, 95% CI: 0.337 to 0.963; $p < 0.001$; HR of iFR [per 0.1 increase]: 0.350, 95% CI: 0.217 to 0.567; $p < 0.001$). The FFR and iFR showed a nonlinear relationship with the estimated risk of MACE, and lower FFR and iFR values showed exponentially increased risk of MACE (Figure 3). When comparing the discriminant ability between FFR and iFR, the c-index was comparable between FFR and iFR (c-index 0.677 in FFR vs. 0.685 in iFR; $p = 0.857$).

CLINICAL OUTCOMES OF GROUPS CLASSIFIED BY FFR AND iFR VALUES. Figure 4 demonstrates the comparison of 2-year MACE among 4 groups. Two-year MACE rates in Group 1 to Group 4 were 2.4%, 3.3%, 2.5%, and 11.6%, respectively ($p < 0.001$). Only Group 4 showed statistically significant hazard, compared with Group 1 (Figure 4, Table 4). Among high-FFR lesions, there was no significant difference in the rates of MACE between high- and low-iFR lesions (Online Figure 1). Similarly, among high-iFR lesions, high- and low-FFR lesions also showed comparable rates of MACE (Online Figure 2). In a multivariable model, Group 4 was independently associated with risk of MACE (Table 5).

FIGURE 4 Comparison of 2-Year Clinical Outcomes of Lesions Classified by FFR and iFR in Deferred Lesions



Kaplan-Meier curves are shown for the 4 groups of deferred lesions, classified by FFR and iFR. HRs and 95% CIs were calculated from a marginal Cox proportional hazard regression model. Abbreviations as in Figures 1 and 2.

DISCUSSION

The current study compared clinical outcomes according to FFR or iFR values in deferred lesions. The main findings were as follows. First, deferred lesions with low FFR or low iFR showed significantly higher risk of MACE than those with high FFR or high iFR, respectively. Second, both FFR and iFR showed significant nonlinear association with the MACE risk, that is, deferred lesions with lower FFR or iFR showed exponentially increased risk of MACE. Third, FFR and iFR showed comparable discriminant ability in the prediction of MACE. Last, discordant iFR/FFR results were not associated with increased MACE. The lesions with concordant abnormal results of both FFR and iFR showed significantly increased risk of MACE.

PHYSIOLOGY-BASED STRATEGY IN CONTEMPORARY PRACTICE. Physiology-based decision making according to the functional significance of stenotic lesions has become a standard approach for patients with coronary artery disease. Among the invasive physiological indices, FFR has been a reference standard and FFR-based decisions are proved to enhance patient's clinical outcome and cost-effectiveness (13–16). Recently, the concept of iFR was developed from insightful observation from wave-intensity analysis using both intracoronary pressure and flow velocity data (3). Despite the

TABLE 4 Clinical Outcomes of Deferred Vessels According to FFR and iFR Classification

	Group 1 (FFR >0.80 and iFR >0.89)	Group 2 (FFR >0.80 and iFR ≤0.89)	Group 3 (FFR ≤0.80 and iFR >0.89)	Group 4 (FFR ≤0.80 and iFR ≤0.89)	p Value
Per-vessel analysis (N = 821)	706/821 (86.0)	32/821 (3.9)	40/821 (4.9)	43/821 (5.2)	
Cardiac death	0.9 (6)	3.3 (1)	0.0 (0)	0.0 (0)	0.363
Vessel-related MI	0.9 (5)	0.0 (0)	0.0 (0)	2.3 (1)	0.675
Vessel-related ischemia driven revascularization	1.5 (4)	0.0 (0)	2.5 (1)	11.6 (5)	<0.001
MACE*	2.4 (10)	3.3 (1)	2.5 (1)	11.6 (5)	<0.001

Values are n/N (%) or % (n). The cumulative incidences of clinical outcomes were presented as Kaplan-Meier estimates during the median follow-up of 729.0 (699.0 to 747.0) days. p Values are by log-rank or Breslow p value in survival analysis. *Major adverse cardiovascular events included cardiac death, myocardial infarction, and ischemia-driven revascularization.

Abbreviations as in Tables 1 to 3.

convenience of iFR measurement, there has been insufficient time to generate clinical outcomes data to support an iFR-guided revascularization strategy.

Previous studies have focused on the comparison of diagnostic accuracy of iFR, compared with FFR (3-5), or with other reference standards (6,7) and showed inconsistent results regarding diagnostic accuracy of iFR. Although recent trials showed noninferiority of iFR-guided strategy for 1-year clinical outcomes compared with FFR-guided strategy (9,10), there has been a lack of data on the discrepancy between FFR and iFR and clinical outcomes of deferred lesions with discordant results between the 2 indices. Both the DEFINE-FLAIR and iFR-SWEDEHEART trials adopted exclusive randomization into FFR- or iFR-guided strategy groups and did not permit the simultaneous measurement of both indices in order to avoid bias. In this regard, the current study investigated 2-year clinical outcomes according to FFR and iFR values in deferred lesions.

TABLE 5 Independent Predictors of MACE in the Deferred Lesions

	HR	95% CI	p Value
Group 4 (low FFR and iFR)	6.546	1.933-22.164	0.003
Group 3 discordance (low FFR and high iFR)	2.484	0.367-16.830	0.351
Group 2 discordance (high FFR and low iFR)	3.127	0.497-19.698	0.225
Male	1.894	0.440-8.151	0.391
Hypertension	1.854	0.572-6.006	0.303
Current smoking	3.467	1.147-10.480	0.280
Previous myocardial infarction	1.446	0.236-8.859	0.689
Diabetes mellitus	1.517	0.559-4.120	0.414
SYNTAX score	1.051	0.995-1.111	0.076

Major adverse cardiovascular events included cardiac death, myocardial infarction, and ischemia-driven revascularization. C-index of models was 0.736 (0.618 to 0.854).

CI = confidence interval; HR = hazard ratio; other abbreviations as in Table 2.

ASSOCIATION OF FFR OR iFR WITH FUTURE ADVERSE EVENTS. Like previous studies (11,17), deferred lesions with low FFR showed about 5-fold higher risk of MACE than lesions with high FFR in our study. In addition, FFR showed a significant nonlinear association with the estimated risk of MACE. Previously, the concept of a graded risk continuum of FFR had been validated with the meta-analysis of Johnson et al. (17). Similarly, iFR as continuous values also showed significant association with 2-year MACE rates. Deferred lesions with low iFR possessed about a 5-fold increased risk of MACE than those with high iFR. iFR also showed a significant nonlinear relationship with the estimated risk of MACE.

When comparing discriminant ability between FFR and iFR, both indices showed a comparable c-index. These results imply that decision making based on the current cutoff value of FFR (≤0.80) and iFR (≤0.89) may provide similar clinical outcomes, and these results are in line with the results of recent trials (9,10).

CLINICAL OUTCOME OF LESIONS WITH DISCORDANT RESULTS BETWEEN FFR AND iFR VALUES. In our study, 8.8% of interrogated lesions showed discordant results between FFR and iFR. The lesions with discordant FFR and iFR results (Group 2 or 3) were not associated with increased MACE risk. Furthermore, adding iFR did not show better stratification of patients in the high-FFR subgroup, and the converse was also true for the high-iFR subgroup. In addition, only Group 4 was independently associated with risk of MACE. These results may suggest the importance of comprehensive evaluation rather than choosing only 1 index to properly select optimal target for revascularization.

CLINICAL IMPLICATIONS. The current study strongly supports the current practice of ischemia-

guided revascularization strategy in which lesions with significant results of invasive physiological indices deserves to be revascularized. Regardless of FFR and iFR, deferred lesions with low FFR or low iFR showed about a 5-fold increased event rate during 2-year follow-up. Both FFR and iFR showed significant associations with estimated MACE rates. In comparison of discriminant ability for 2-year MACE rates, both pressure-derived indices showed comparable discriminant ability. It is interesting to note that the lesions with both abnormal results in FFR and iFR showed significantly higher risk of MACE than the other lesions.

STUDY LIMITATIONS. First, although this is the first clinical outcome data on the discrepancy between iFR and FFR, the sample size was relatively small. Second, the small number of events precludes the differentiation of hard endpoints, including death or MI, among the 4 groups. Longer-term follow-up of the current cohort and larger prospective trials are warranted. Third, iFR was calculated off-line in the independent physiology core laboratory.

CONCLUSIONS

Both FFR and iFR showed a significant association with future risk of MACE in deferred lesions. The discordant results between FFR and iFR were not associated with the increased risk of MACE. The risk of MACE was significantly increased only in lesions with abnormal results of both FFR and iFR.

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PERSPECTIVES

WHAT IS KNOWN? Invasive physiological indices, such as FFR or iFR, are used in clinical practice. However, clinical outcomes of deferred lesions with discordant results between FFR and iFR have not been fully investigated.

WHAT IS NEW? We investigated 2-year clinical outcomes according to FFR and iFR values in deferred lesions. Both FFR and iFR showed significant association with 2-year MACE rates, and deferred lesions with low-FFR or low-iFR showed significantly higher risk of MACE than those with high-FFR or high-iFR, respectively. In the 4 groups classified according to FFR and iFR cut-points, the discordant results between FFR and iFR were not associated with increased risk of MACE, and the risk of MACE was significantly increased in deferred lesions with abnormal results in both FFR and iFR.

WHAT IS NEXT? These results may suggest the importance of comprehensive evaluation rather than choosing only 1 index to properly select the optimal target for revascularization. Further study is warranted to investigate the clinical outcomes of those discordant lesions according to treatment strategy (deferral vs. revascularization), compared with concordant abnormal lesions.

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APPENDIX For supplemental figures, please see the online version of this paper.