



# Fractional Flow Reserve and Cardiac Events in Coronary Artery Disease

## Data From a Prospective IRIS-FFR Registry (Interventional Cardiology Research Incooperation Society Fractional Flow Reserve)

Editorial, see p 2252

**BACKGROUND:** We evaluated the prognosis of deferred and revascularized coronary stenoses after fractional flow reserve (FFR) measurement to assess its revascularization threshold in clinical practice.

**METHODS:** The IRIS-FFR registry (Interventional Cardiology Research Incooperation Society Fractional Flow Reserve) prospectively enrolled 5846 patients with  $\geq 1$  coronary lesion with FFR measurement. Revascularization was deferred in 6468 lesions and performed in 2165 lesions after FFR assessment. The primary end point was major adverse cardiac events (cardiac death, myocardial infarction, and repeat revascularization) at a median follow-up of 1.9 years and analyzed on a per-lesion basis. A marginal Cox model accounted for correlated data in patients with multiple lesions, and a model to predict per-lesion outcomes was adjusted for confounding factors.

**RESULTS:** For deferred lesions, the risk of major adverse cardiac events demonstrated a significant, inverse relationship with FFR (adjusted hazard ratio, 1.06; 95% confidence interval, 1.05–1.08;  $P < 0.001$ ). However, this relationship was not observed in revascularized lesions (adjusted hazard ratio, 1.00; 95% confidence interval, 0.98–1.02;  $P = 0.70$ ). For lesions with  $FFR \geq 0.76$ , the risk of major adverse cardiac events was not significantly different between deferred and revascularized lesions. Conversely, in lesions with  $FFR \leq 0.75$ , the risk of major adverse cardiac events was significantly lower in revascularized lesions than in deferred lesions (for  $FFR 0.71\text{--}0.75$ , adjusted hazard ratio, 0.47; 95% confidence interval, 0.24–0.89;  $P = 0.021$ ; for  $FFR \leq 0.70$ , adjusted hazard ratio 0.47; 95% confidence interval, 0.26–0.84;  $P = 0.012$ ).

**CONCLUSIONS:** This large, prospective registry showed that the FFR value was linearly associated with the risk of cardiac events in deferred lesions. In addition, revascularization for coronary artery stenosis with a low FFR ( $\leq 0.75$ ) was associated with better outcomes than the deferral, whereas for a stenosis with a high FFR ( $\geq 0.76$ ), medical treatment would be a reasonable and safe treatment strategy.

**CLINICAL TRIAL REGISTRATION:** URL: <http://www.clinicaltrials.gov>. Unique identifier: NCT01366404.

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Sources of Funding, see page 2250

**Key Words:** coronary disease  
■ coronary stent ■ fractional flow reserve ■ revascularization

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## Clinical Perspective

### What Is New?

- This is the largest prospective, multicenter registry of fractional flow reserve (FFR)-measured patients in daily practice.
- This study showed a risk continuum for FFR in deferred coronary stenoses.
- Independent predictors of clinical events in deferred coronary stenoses were FFR, a thrombus-containing lesion, multivessel coronary artery disease, and percent diameter stenosis.
- The revascularization for coronary artery stenosis with low FFR ( $\leq 0.75$ ) was associated with better outcomes than the deferral, whereas for a stenosis with high FFR ( $\geq 0.76$ ), medical treatment would be a reasonable and safe treatment strategy.

### What Are the Clinical Implications?

- FFR is a useful index for decision making in daily catheter laboratory practice because it stratifies clinical outcomes.
- FFR appeared to be a marker of subsequent outcomes as modulated by treatment (medical therapy versus revascularization) and reinforces the generally accepted guidelines about FFR guidance for revascularization.
- Therefore, FFR could be considered a clinical prognostic index in addition to a physiological quantification for flow-limiting stenosis.

**F**ractional flow reserve (FFR) is considered the invasive standard for identifying flow-limiting coronary artery stenosis.<sup>1</sup> Randomized trials and observational studies demonstrated that FFR safely determined whether a given stenosis required revascularization and showed that FFR-guided percutaneous coronary intervention (PCI) outcome outperformed angiography-guided PCI.<sup>2-7</sup> Therefore, current guidelines appropriately recommend FFR measurement before revascularization unless there is objective evidence of ischemia.<sup>8,9</sup>

However, the dichotomous cutoff value of 0.80 for FFR in decision making was validated in a small study compared with noninvasive functional testing.<sup>1</sup> In addition, there have been concerns in applying the results of previous randomized trials in routine clinical practice because of their strict protocols and selective patient enrollment.<sup>10,11</sup> Recent studies have reported an increased risk of adverse cardiac events in deferred coronary stenoses with borderline FFR values between 0.75 and 0.85 when compared with higher FFR values.<sup>12,13</sup> Moreover, the safety of FFR-guided deferral was compared with PCI using bare metal stents or early generation drug-eluting

stents, which now have been shown to be less safe and effective than currently available second-generation drug-eluting stents.<sup>2,3,14</sup> Therefore, the threshold value for revascularization decision making using FFR should be evaluated in contemporary practice based on large outcome data.

The IRIS-FFR registry (Interventional Cardiology Research In-cooperation Society Fractional Flow Reserve) was designed to prospectively evaluate the natural history of lesions after measurement of FFR in routine clinical practice. The purpose of the current study was to (1) evaluate the prognosis of deferred or revascularized coronary stenoses after FFR measurement, and (2) assess the clinical outcome-derived revascularization threshold of FFR in the era of second-generation drug-eluting stent.

## METHODS

### Study Design

The IRIS-FFR registry was a prospective multicenter study designed to investigate the prognosis of coronary stenoses assessed by FFR. The registry consecutively enrolled all patients who underwent FFR measurement on  $\geq 1$  coronary lesion. Thirty heart centers from South Korea participated in the registry. Exclusion criteria were minimal: (1) a stenosis with a thrombolysis in myocardial infarction flow of  $< 3$ , (2) a graft vessel, (3) overt heart failure, or (4) a stenosis technically unsuitable for FFR evaluation. The study protocol was approved by the institutional review board or ethical committee in each participating center, and all patients provided written informed consent.

### Fractional Flow Measurement and Revascularization

FFR was measured with a commercially available coronary pressure wire after coronary angiography as described previously.<sup>3</sup> After administration of intracoronary nitrates (100 or 200  $\mu\text{g}$ ), the pressure wire was positioned at the distal segment of the target lesion. Intravenous adenosine infusion (140  $\mu\text{g}/\text{kg}/\text{minute}$ ) by a central or large antecubital vein was recommended as the standard method to induce hyperemia. The proximal aortic pressure and distal coronary pressure were measured during sustained hyperemia, and FFR was calculated by mean distal coronary pressure/proximal aortic pressure during hyperemia. Revascularization was generally recommended when FFR was  $< 0.75$  and deferred when FFR was  $> 0.80$ . For FFR values between 0.75 and 0.80, the decision regarding revascularization was left to the operator's discretion. High FFR was defined as  $\geq 0.76$ , and low FFR was defined as  $\leq 0.75$ . Treatment decisions in disagreement with the FFR were retrospectively specified on the basis of the operator's report. All revascularization procedures of PCI or bypass surgery were performed using standard techniques.<sup>15,16</sup> Thereafter, patients received standard medical treatment. During the study period, second-generation drug-eluting stents were used as the default.

## End Points and Definitions

The primary end point was major adverse cardiac events (MACE; a composite of cardiac death, myocardial infarction, and repeat revascularization) arising from FFR-measured lesions. Cardiac death was defined as any death because of a proximate cardiac cause, including cardiac arrest, myocardial infarction, low-output failure, or fatal arrhythmia. Myocardial infarction was defined as follows: (1) within the first 48 hours of the procedure: ischemic symptoms and signs with an elevation of the concentration of creatinine kinase-MB fraction >5 times baseline; (2) ≥48 hours after the procedure: any creatinine kinase-MB or troponin level increase above the upper normal limit accompanied by ischemic symptoms. Repeat revascularization was defined as any PCI or coronary artery bypass surgery of a lesion with an index FFR measurement. All outcomes of interest were confirmed by source documentation collected at each hospital and were centrally adjudicated by an independent clinical events committee. In addition, for the lesion-level analysis, the committee assigned each event to a specific coronary lesion based on the baseline and follow-up data.

## Data and Follow-Up

All baseline clinical, lesion, and outcome data were prospectively collected using a dedicated electronic case report form, which included all coronary stenoses (diameter stenosis by visual estimation >50%) in which FFR was assessed or not. Specialized personnel at each center performed this procedure. Members of the academic coordinating center (Clinical Research Center, Asan Medical Center) periodically performed monitoring and verification of registry data in the participating hospitals. Clinical follow-ups were conducted during hospitalization and at 30 days, 6 months, and 12 months after FFR measurement, as well as every 6 months thereafter. At these visits, the data pertaining to the patient's clinical status, all interventions, and adverse events were recorded.

## Statistical Methods

Continuous variables were expressed as mean±standard deviation; categorical variables were shown as counts and percentages. Continuous variables were compared using unpaired *t* tests or nonparametric Mann-Whitney tests; categorical variables were compared using  $\chi^2$  statistics or Fisher exact test. Time-to-event data are presented as Kaplan–Meier estimates. Baseline variables that were considered clinically relevant or showed a significant univariate relationship with the outcome were entered into multivariable Cox proportional-hazards regression models.<sup>17</sup> Variables for inclusion were carefully chosen given the number of events available to ensure parsimony of the final models. We used a robust estimation for a marginal Cox modeling using the Wei, Lin, and Weissfeld method to account for correlated data in patients with multiple lesions.<sup>18,19</sup> We performed a stepwise model selection by the Akaike information criterion. The proportional hazards assumption was tested using Schoenfeld residuals. Statistical analyses were performed using SAS software version 9.1.3 (SAS Institute) and R software version 3.1.2 (R Foundation for Statistical Computing). All applicable *P* values were 2-sided, and a value of *P*<0.05 was considered statistically significant.

## RESULTS

### Baseline Characteristics

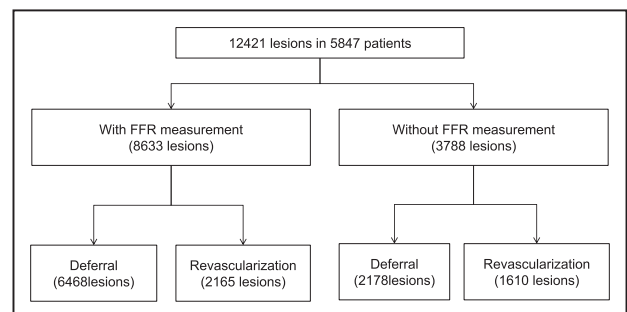
Between August 2009 and August 2015, 5846 patients with 12421 coronary lesions were enrolled in this registry. FFR was assessed in 8633 lesions (Figure 1). The mean age was 64 years, 72% of the patients were male, 76% had stable angina, 31% had diabetes mellitus, and 47% had multivessel coronary artery disease (Table 1).

FFR measurement was frequently performed in the left anterior descending artery and proximal portions of other coronary arteries. Angiographic diameter stenosis ranged between 30% and 70% (Table 2). The mean FFR value was 0.83±0.11. Intravenous adenosine infusion was used in 91% of the patients as the hyperemic stimulant. During FFR measurement, major complications occurred in 0.1% of assessments (Table I in the online-only Data Supplement). After FFR measurement, 6468 stenoses were deferred, and 2165 stenoses were revascularized (Figure 1). PCI with newer generation drug-eluting stents was the most common revascularization strategy (Table II in the online-only Data Supplement). Lesion characteristics with or without FFR assessment are summarized in Table 3 and Table III in the online-only Data Supplement. When compared with coronary lesions that were not assessed physiologically, FFR-assessed lesions were more frequently located in the left anterior descending artery or the proximal portion of a major epicardial coronary artery.

### Outcomes of Deferred and Revascularized Lesions

During a median follow-up of 1.9 years (interquartile range, 1.0–2.9 years), 18 cardiac deaths, 69 myocardial infarctions, 308 repeat revascularizations, and 360 MACE occurred; 77.3% of MACE occurred in FFR-measured lesions (Figure I in the online-only Data Supplement).

One-hundred and seventy-three MACE occurred in deferred lesions after FFR measurement. Figure 2 shows the Kaplan–Meier curve for outcomes of deferred lesions per patient after FFR measurement.



**Figure 1. Lesion treatment strategies.**

FFR indicates fractional flow reserve.

**Table 1. Baseline Patient Characteristics**

Characteristics	N (%)
N	5846
Mean age (SD), y	63.6±9.8
Male	4187 (71.6)
Clinical presentation	
Stable angina	4462 (76.3)
Unstable angina	1050 (18.0)
Non-ST segment elevation myocardial infarction	256 (4.4)
ST segment elevation myocardial infarction	78 (1.3)
Hypertension	3687 (63.1)
Diabetes mellitus	1807 (30.9)
Current smoking	1402 (24.0)
Hyperlipidemia	3507 (60.0)
Multivessel coronary artery disease	2733 (46.7)
Previous myocardial infarction	378 (6.5)
Previous percutaneous coronary intervention	1138 (19.5)
Family history	600 (10.3)
Previous congestive heart failure	70 (1.2)
Previous stroke	345 (5.9)
Peripheral vascular disease	139 (2.4)
Chronic renal failure	119 (2.0)
Chronic obstructive lung disease	125 (2.1)
Discharge medication	
Aspirin	5194 (88.8)
Clopidogrel	3822 (65.4)
Statin	5329 (91.2)
Beta-blocker	3208 (54.9)
Calcium channel blocker	3226 (55.2)
Nitrate	1505 (25.7)

The incidence rates of clinical events were 1.44% (95% confidence interval [CI], 1.15–1.73) lesion-year for MACE and 0.21% (95% CI, 0.10–0.32) lesion-year for the composite of cardiac death or myocardial infarction (Table 4). [Figure II in the online-only Data Supplement](#) shows the incidence rate of MACE and the composite of cardiac death or myocardial infarction in various clinical and lesion subsets. The incidence rate ranged between 0% and 7.93% (95% CI, –1.90 to 17.76) lesion-year for MACE and between 0% and 1.87% (95% CI, –3.06 to 6.80) lesion-year for the composite of cardiac death or myocardial infarction. When excluding 368 deferred lesions despite an FFR of  $\leq 0.75$  (the specified reasons are summarized in [Figure III in the online-only Data Supplement](#)), the incidence rate of clinical events was 1.24% (95% CI, 0.96–1.52) lesion-year for MACE and 0.16% (95% CI, 0.06–0.026) lesion-year for the composite of cardiac death or myocardial infarction.

**Table 2. Lesions Assessed by Fractional Flow Reserve**

Characteristics	N (%)
N	8633
Lesion territory	
Left main	345 (4.1)
Left anterior descending artery	4372 (50.6)
Right coronary artery	2070 (24.0)
Left circumflex artery	1407 (16.3)
Others	430 (5.0)
Lesion location	
Proximal	3862 (44.7)
Mid	2835 (32.8)
Distal	1936 (22.4)
Diameter stenosis, %	
$\geq 70$	1927 (22.3)
50 to 69	4057 (47.0)
30 to 49	2649 (30.7)
AHA/ACC lesion B2C lesion	4819 (55.8)
Long lesion (>20 mm)	3680 (42.6)
Moderate to severe calcified lesion	269 (3.1)
Thrombus-containing lesion	63 (0.7)
Angiographic ulcerated lesion	55 (0.6)

AHA/ACC indicates American Heart Association/American College of Cardiology.

The cumulative incidence of MACE and the composite of cardiac death or myocardial infarction in deferred lesions according to the category of FFR are described in [Figure 3](#) and [Figure IV in the online-only Data Supplement](#). With decreasing FFR categories, the cumulative incidence of MACE increased significantly. The cumulative incidence of the composite of cardiac death or myocardial infarction showed the same trend. After adjustment for covariates, a significant inverse relationship occurred between FFR and the risk of clinical events with respect to MACE, myocardial infarction, and the composite of cardiac death, myocardial infarction, and repeat revascularization (Table 4). Independent predictors of MACE in deferred lesions were FFR (adjusted hazard ratio [aHR] 1.06 per 0.01 U decrease in FFR; 95% CI, 1.05–1.08;  $P < 0.001$ ), thrombus-containing lesion (aHR, 5.46; 95% CI, 1.98–15.0;  $P = 0.001$ ), multivessel coronary artery disease (aHR, 1.66; 95% CI, 1.19–2.33;  $P = 0.003$ ), and diameter stenosis (30% to 49%: aHR 1 [reference], 50% to 69%: aHR 2.20; 95% CI, 1.41–3.44;  $P < 0.001$ ,  $\geq 70$ %: aHR, 2.50; 95% CI 1.41–4.44;  $P = 0.002$ ) ([Table IV in the online-only Data Supplement](#)). A total of 105 MACE occurred in revascularized lesions, and FFR before revascularization was not associated with the risk of clinical events ([Table V in the online-only Data Supplement](#)).

**Table 3. Comparison of Lesion Characteristics of Stenosis Evaluated by Fractional Flow Reserve or Not**

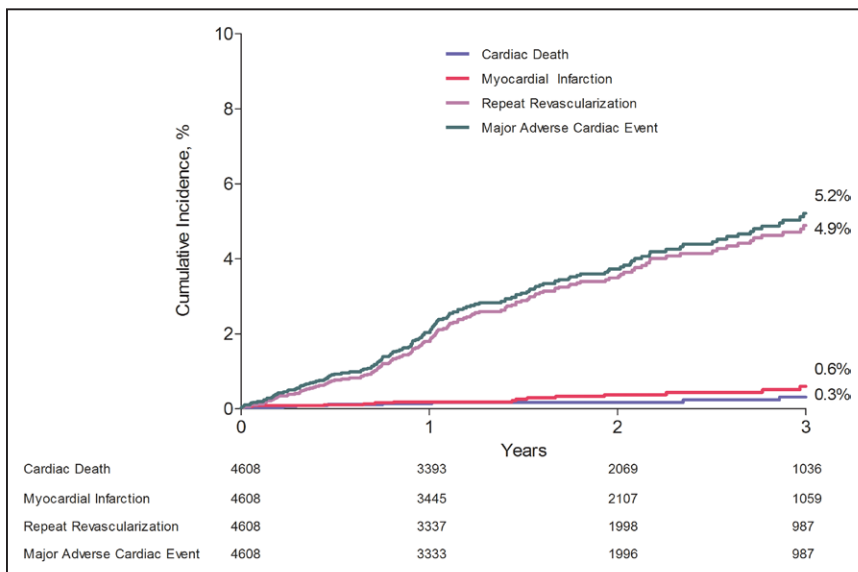
Characteristics	Fractional Flow Reserve Measurement in Deferred Lesion		P Value	Fractional Flow Reserve Measurement in Revascularized Lesion		P Value
	Yes (N=6468)	No (N=2178)		Yes (N=2165)	No (N=1610)	
Lesion territory			<0.001			<0.001
Left main	135 (2.1)	36 (1.7)		219 (10.1)	57 (3.5)	
Left anterior descending artery	3075 (47.5)	370 (17.0)		1297 (59.9)	393 (24.4)	
Right coronary artery	1720 (26.6)	512 (23.5)		350 (16.2)	517 (32.1)	
Left circumflex artery	1186 (18.3)	601 (27.6)		221 (10.2)	433 (26.9)	
Others	352 (5.4)	659 (30.3)		78 (3.6)	210 (13.0)	
Lesion location			<0.001			<0.001
Proximal	2588 (40.0)	596 (27.4)		1274 (58.8)	710 (44.1)	
Mid	2245 (34.7)	309 (14.2)		580 (27.3)	303 (18.8)	
Distal	1635 (25.3)	1273 (58.4)		301 (13.9)	597 (37.1)	
Diameter stenosis, %			<0.001			<0.001
≥70	513 (8.0)	1009 (31.4)		1414 (65.3)	1448 (89.9)	
50 to 69	3321 (51.3)	1028 (47.2)		736 (34.0)	158 (9.8)	
30 to 49	2634 (40.7)	144 (6.5)		15 (0.7)	4 (0.3)	
AHA/ACC lesion B2C lesion	3119 (48.2)	1232 (56.6)	<0.001	1700 (78.5)	1193 (74.1)	0.001
Long lesion (>20 mm)	2315 (35.8)	1202 (55.2)	<0.001	1365 (63.0)	1018 (63.2)	0.91
Moderate to severe calcified lesion	173 (2.7)	42 (1.9)	0.053	96 (4.4)	86 (5.3)	0.20
Thrombus-containing lesion	29 (0.4)	13 (0.6)	0.39	56 (3.5)	34 (1.6)	<0.001
Angiographic ulcerated lesion	8 (0.4)	38 (0.6)	0.22	17 (0.8)	6 (0.4)	0.11

Values indicate N (%). AHA/ACC indicates American Heart Association/American College of Cardiology.

**Revascularization Threshold of FFR**

Observed event rates for MACE in deferred and revascularized lesions were similar in high categories of FFR. In low categories of FFR, revascularized lesions had a lower MACE rate than deferred lesions (Figure 4 and Fig-

ure VB in the online-only Data Supplement). Multivariable Cox proportional-hazards regression models showed that the risk of MACE was similar between deferred and revascularized lesions in categories of FFR ≥0.76, but a significant benefit of revascularization regarding MACE



**Figure 2. Clinical outcomes of deferred patient after fractional flow reserve measurement.**

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**Table 4. Adjusted Risk of Major Adverse Cardiac Events in Deferred Lesions According to the Fractional Flow Reserve**

	Event Number (Incidence Rate)*	Fractional Flow Reserve as Categorical Variable, Hazard Ratio (95% Confidence Interval)						P Value for Trend	Fractional Flow Reserve as a Continuous Variable by Decrease of 0.01, Hazard Ratio (95% Confidence Interval)	P Value
		≤0.70 (N=156)	0.71–0.75 (N=212)	0.76–0.80 (N=596)	0.81–0.85 (N=1510)	0.86–0.90 (N=1665)	0.91–1.00 (N=2329)			
MACE	173 (1.44)	6.66 (3.28–13.5)	5.04 (2.58–9.82)	3.99 (2.26–7.05)	2.48 (1.47–4.20)	1.60 (0.91–2.80)	1 reference	<0.001	1.06 (1.05–1.08)	<0.001
Cardiac death	11 (0.09)	3.03 (0.16–56.8)	5.18 (0.84–31.9)	2.26 (0.37–13.8)	0.44 (0.04–4.35)	0.81 (0.13–5.11)	1 reference	0.19	1.06 (0.99–1.13)	0.12
Myocardial infarction	17 (0.14)	12.0 (0.99–144.1)	22.1 (3.39–143.8)	8.87 (1.56–49.4)	3.43 (0.75–15.7)	0.85 (0.13–5.42)	1 reference	<0.001	1.09 (1.05–1.14)	<0.001
Cardiac death or myocardial infarction	26 (0.21)	5.00 (0.79–31.7)	9.34 (2.40–36.5)	3.48 (0.87–13.85)	1.78 (0.48–6.55)	1.03 (0.26–4.00)	1 reference	<0.001	1.07 (1.04–1.11)	<0.001
Repeat revascularization	161 (1.34)	10.4 (4.52–24.1)	7.73 (3.51–17.0)	5.73 (2.90–11.3)	3.49 (1.88–6.49)	2.07 (1.09–3.91)	1 reference	<0.001	1.07 (1.06–1.09)	<0.001

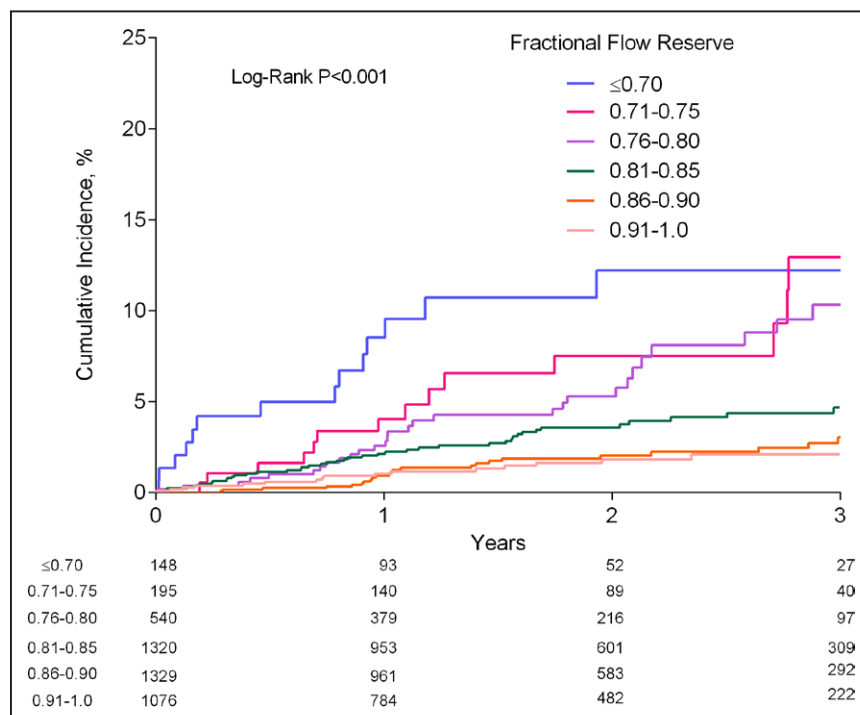
MACE indicates major adverse cardiac events (composite of cardiac death, myocardial infarction, and repeat revascularization).

\*100 lesion-year.

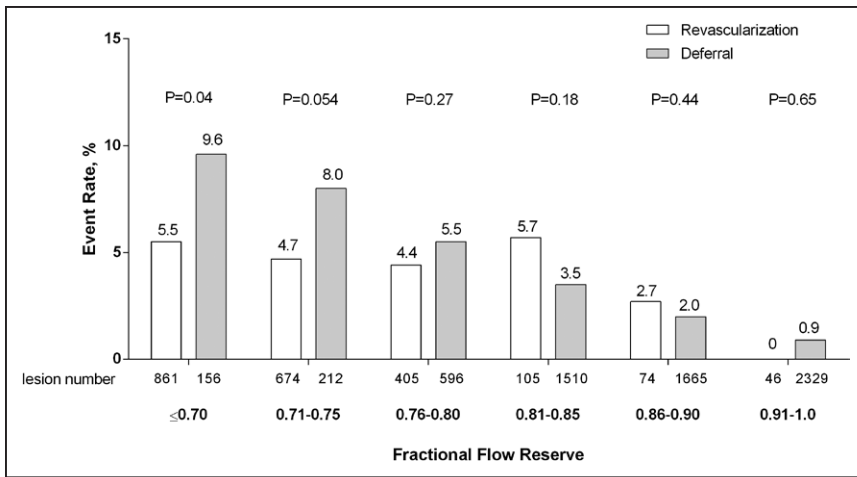
was observed in categories of FFR ≤0.75 (Figure 5). In addition, a significant risk difference of cardiac death or myocardial infarction between the groups was not observed in lesions with an FFR ≤0.80. However, revascularization of lesions with an FFR of 0.81 to 0.85 had

a higher adjusted risk of cardiac death or myocardial infarction (aHR, 7.04; 95% CI, 1.60–30.9; P=0.01) (Figure VIB in the online-only Data Supplement).

To explore the previous findings, we plotted the relationship between FFR and the log of the hazard ratio for



**Figure 3. The incidence of major adverse cardiac events in deferred lesions according to fractional flow reserve categories.** For the per-patient analysis, we selected the lowest fractional flow reserve value as a patient representative value.



**Figure 4.** Observed incidence of major adverse cardiac events over the follow-up period in revascularized versus deferred lesions according to fractional flow reserve categories. P values were derived from a  $\chi^2$  square test.

deferred versus revascularized lesion (Figure 6) based on a multivariable Cox proportional-hazard model predicting MACE; the 2 lines intersected at an FFR value of 0.79. For a composite of cardiac death or myocardial infarction, the 2 lines intersect at an FFR value of 0.64.

### Gray Zone FFR (0.76–0.80)

Tables VI and VII in the online-only Data Supplement provide more information about baseline characteristics in gray zone FFR cases. Revascularization was not associated with a reduced risk of MACE, as seen in Figure 6 (aHR 0.83; 95% CI, 0.46–1.50;  $P=0.53$ ).

## DISCUSSION

In this large, prospective, multicenter registry, we found that the prognosis of coronary artery stenoses after FFR measurement was excellent when lesions were deferred. The incidence rate of MACE and the composite of cardiac death or myocardial infarction were 1.44% and 0.21% lesion-year, respectively. Although the risk of MACE in deferred lesions increased significantly while FFR decreased, the risk of MACE was not significantly different in the range of  $FFR \geq 0.76$  (including gray zone) between deferred and revascularized lesions. Revascularization was associated with better clinical outcomes only for lesions with an  $FFR \leq 0.75$ . Therefore, this study uniquely demonstrated the relationship between clinical outcomes and decision making based on FFR using a 0.75 to 0.80 threshold, which was different from a previous report showing the natural history of deferred coronary artery stenoses.<sup>20</sup>

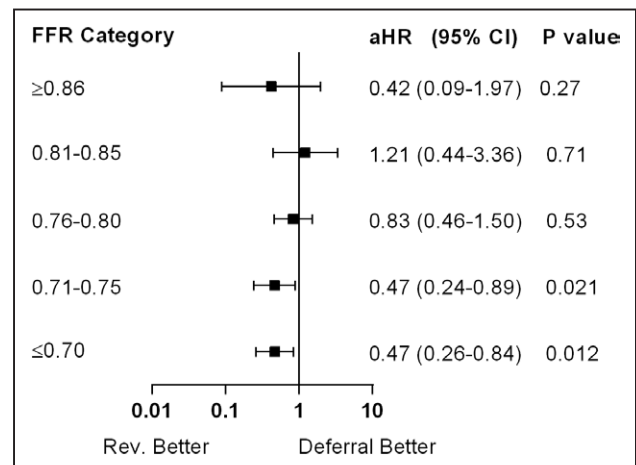
### Outcomes of Deferred Lesions

Our study adds to the robust understanding of the natural history of deferred lesions after FFR assessment based on a large number and broad range of patient and lesion characteristics. Previously, the DEFER study

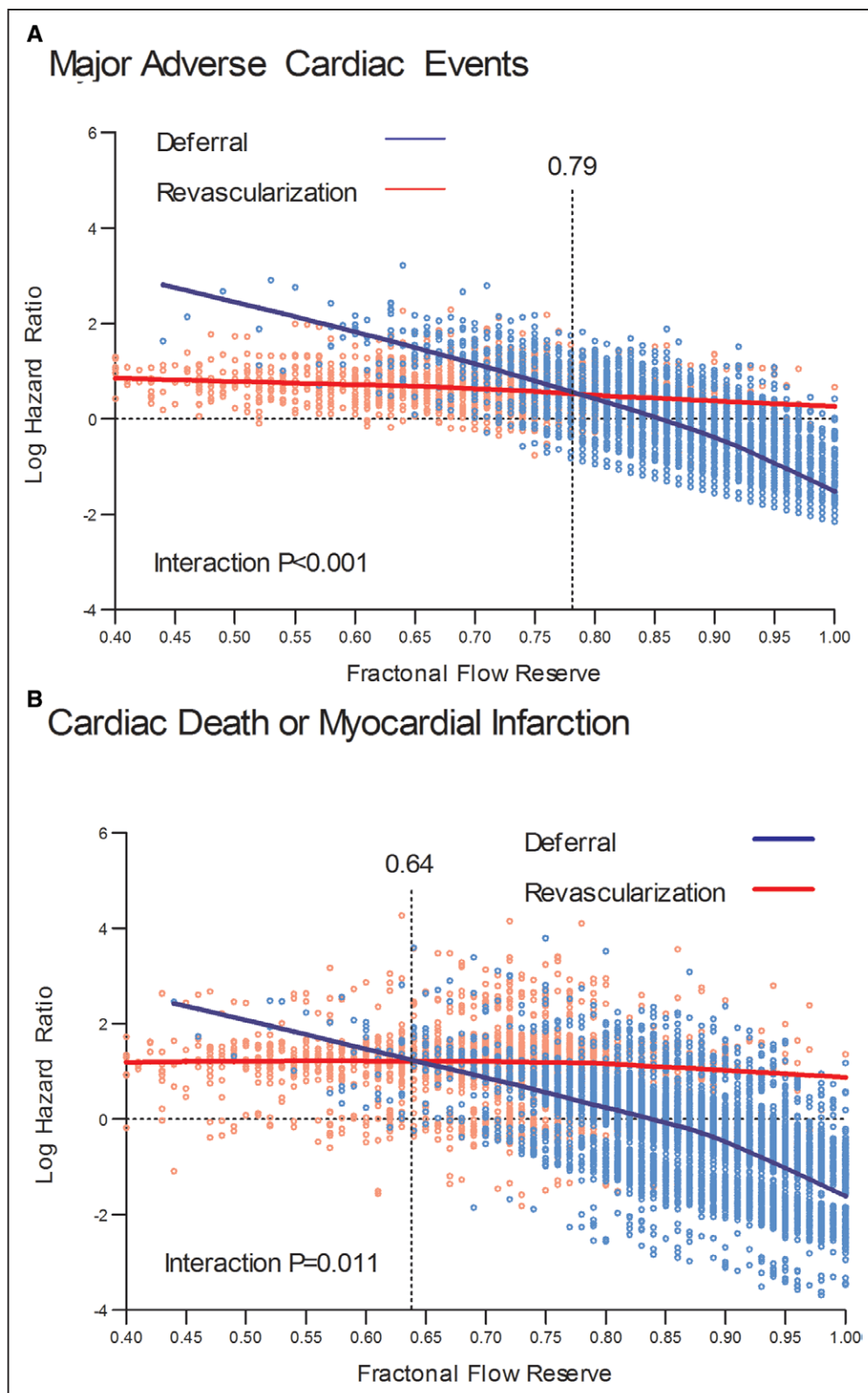
demonstrated that the annual incidence of cardiac death or myocardial infarction in deferred lesion ( $FFR > 0.75$ ) under medical treatment was  $<1\%$  in patients with stable angina and single-vessel disease.<sup>2,21</sup> Subsequent observational studies demonstrated that the annual rate of repeat intervention for deferred lesions ranged between 2.5% and 11% according to different clinical scenarios. Our unselected large population-based observation indicated an incidence rate of 0% to 7.93% lesion-year for MACE and 0% to 1.87% lesion-year for cardiac death and myocardial infarction in various subgroups. These results strongly support the safety of FFR-based deferment of revascularization.

### FFR Risk Continuum

Prognostication by FFR is usually evaluated in a binary fashion. However, recent studies showed that the risk of a clinical event was inversely proportional to the value of the FFR.<sup>12,22</sup> We confirmed that the MACE rate continu-



**Figure 5.** Adjusted hazard ratio (aHR) of major adverse cardiac events between deferred and revascularized lesions according to fractional flow reserve (FFR) categories.



**Figure 6. Revascularization threshold of fractional flow reserve.**

All points represent log hazard ratios of an individual lesion from the final multivariate marginal Cox regression model. Red indicates revascularized lesions, and blue indicates deferred lesions. Two linear lines fitted from individual log hazard ratios intersect at a fractional flow reserve of 0.79 for major adverse cardiac events (A) and 0.64 for cardiac death or myocardial infarction (B). The final models included variables of multivessel coronary artery disease, revascularized lesion (versus deferred lesion), fractional flow reserve as a continuous variable, presentation, hyperlipidemia, previous percutaneous coronary intervention, (Continued)



ously increased as FFR decreased in deferred lesions. This trend was observed even in the nonischemic range of FFR ( $>0.80$ ). Therefore, in native coronary artery disease, FFR appeared to be a physiological biomarker demonstrating a risk continuum. However, the FFR-MACE curve was flat in revascularized lesions, which can be explained by several factors. For low-FFR lesions, relieving the flow limitation reduced the risk of a future event. For high-FFR lesions, the inherent risk of PCI for a functionally insignificant stenosis increased the risk. The exclusive use of second-generation drug-eluting stents with contemporary techniques may have attenuated the effect of the severity of underlying atherosclerosis, which could have contributed to the lack of an association in revascularized lesions.<sup>23</sup>

### Outcome-Derived FFR Threshold for Revascularization

Our study supports the current revascularization threshold of FFR derived from the comparison study with non-invasive functional studies. Regarding MACE, in lesions with an FFR  $\geq 0.76$ , revascularization did not improve the prognosis; in lesions with an FFR  $\leq 0.75$ , a benefit of revascularization over medical treatment was observed. In addition, the 2 lines of log hazard ratio intersected at an FFR value of 0.79, which is within the conventional gray zone (0.75–0.80) of FFR-guided decision making.

Because of the overall low incidence of cardiac death or myocardial infarction in this registry, its risk was not different between deferred and revascularized lesions even when the FFR was  $<0.70$ . However, we observed a significantly increased risk of cardiac death or myocardial infarction in revascularized lesions with an FFR between 0.80 and 0.85 compared with medical treatment, which reinforces contemporary clinical guidelines to prohibit stent implantation for a stenosis without objective evidence of ischemia.<sup>8,9</sup>

### FFR Gray Zone

The treatment strategy of lesions with a gray zone FFR has been debated.<sup>24–26</sup> We showed that the risk of MACE and the composite of cardiac death and myocardial infarction were not significantly different between revascularized and deferred lesions in this range of FFR. Therefore, medical treatment of lesions with a gray zone FFR would be a reasonable strategy. Compared with previous studies, we enrolled a larger number of lesions with an FFR between 0.75 and 0.80 (1001 lesions). Further-

more, our results were derived after vigorous statistical adjustment for baseline patient and lesion characteristics. Nevertheless, our findings should be confirmed or refuted by a future randomized trial, such as the ongoing GzFFR (NCT02425969) study (A Randomised Controlled Trial in Stable Intermediate Coronary Lesions and Grey-zone FFR Values With Evaluation of the Diagnostic Utility of Invasive Coronary Physiological Indices and Quantitative Perfusion MRI).

### Analytic Methods

We performed a per-lesion analysis by accounting for clustering effects of lesions within the same patient using a mixed-effect model. FFR was measured 1.48 times per patient on average because of multivessel disease; also, not all subsequent clinical events result from an FFR-measured stenosis, even in patients with 1 vessel disease. For this reason, the patient-level end point of death was ascribed by default to the lowest FFR lesion. All myocardial infarctions except 3 cases were assigned to specific lesions by an independent committee based on coronary angiography or localizing signs at the time of event (Table VIII in the online-only Data Supplement). Last, 92% of MACE was clearly assigned to a specific lesion, which mitigated the potential limitation of our lesion-level analysis.

### Study Limitations

First, this study is not a randomized trial or a natural history study. The methodology is limited by the fact that the performance of FFR was confounded and a general recommendation was made to perform revascularization in lesions with an FFR  $>0.75$  and to defer revascularization in lesions with an FFR  $<0.8$ . Other factors may have influenced the decision to perform or not perform revascularization. In addition, the FFR value was not blinded to physicians and patients and may have triggered treatment decisions, which in turn may have modulated lesion outcomes. Second, an FFR cutoff value for revascularization was not formally demanded by the protocol. Therefore, 6.9% of lesions were not revascularized despite a low FFR and vice versa. Specific reasons are listed in Figure III in the online-only Data Supplement. Third, as detailed in Table IX in the online-only Data Supplement, 21.6% of deaths were adjudicated as arising from indeterminate causes; however, considering the proportion of cardiac deaths in MACE, this would not have affected the overall findings of our study. Last, FFR measurement is more generally

**Figure 6 Continued.** chronic renal failure, lesion location, thrombus-containing lesion, revascularized lesion (versus deferred lesion)×fractional flow reserve for major adverse cardiac events, and those of revascularized lesion (versus deferred lesion), fractional flow reserve as a continuous variable, revascularized lesion (versus deferred lesion)×fractional flow reserve, age, previous myocardial infarction, previous stroke, chronic renal failure, diameter stenosis, and thrombus-containing lesion for cardiac death or myocardial infarction.

accepted in patients without acute coronary syndrome. Therefore, our population had more favorable clinical characteristics compared with a contemporary PCI population.

## CONCLUSIONS

This large, prospective, multicenter registry demonstrated the value of FFR in decision making in daily catheter laboratory practice, particularly in its stratifying value for clinical outcomes. Revascularization for coronary artery stenosis with a low FFR ( $\leq 0.75$ ) was associated with better outcomes than deferral, whereas for a stenosis with a high FFR ( $\geq 0.76$ ), medical treatment would be a reasonable and safe treatment strategy. Therefore, FFR should be considered a clinical prognostic index in addition to a physiological surrogate to identify flow-limiting stenosis.

## ACKNOWLEDGMENTS

Drs Park and Ahn had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: S.J.P. and J.M.A. Acquisition, analysis, or interpretation of data: S.J.P., J.M.A., and D.W.P. Drafting of the manuscript: J.M.A., D.W.P., and S.J.P. Critical revision of the manuscript for important intellectual content: J.M.A., D.W.P., E.S.S., B.K.K., C.W.M., J.H.D., J.H.K., I.H.C., J.H.Y., S.H.H., K.B.S., W.Y.C., S.S.C., J.B.L., S.W.C., K.I.P., T.J.H., S.Y.L., S.J.K., S.W.L., Y.H.K., C.W.L., and S.W.P. Statistical analysis: S.J.P., J.M.A., D.W.P., and M.K.H. Obtained funding: S.J.P. Administrative, technical, or material support: S.J.P. and J.M.A. Study supervision: S.J.P. and J.M.A.

## SOURCES OF FUNDING

This work was supported by St Jude Medical, DONG-A ST., and the Cardiovascular Research Foundation.

## DISCLOSURES

None.

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## FOOTNOTES

Received July 10, 2016; accepted March 17, 2017.

The online-only Data Supplement is available with this article at <http://circ.ahajournals.org/lookup/suppl/doi:10.1161/CIRCULATIONAHA.116.024433/-/DC1>.

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**Fractional Flow Reserve and Cardiac Events in Coronary Artery Disease: Data From a Prospective IRIS-FFR Registry (Interventional Cardiology Research Incooperation Society Fractional Flow Reserve)**

Jung-Min Ahn, Duk-Woo Park, Eun-Seok Shin, Bon-Kwon Koo, Chang-Wook Nam, Joon-Hyung Doh, Jun Hong Kim, In-Ho Chae, Jung-Han Yoon, Sung-Ho Her, Ki-Bae Seung, Woo-Young Chung, Sang-Yong Yoo, Jin Bae Lee, Si Wan Choi, Kyungil Park, Taek Jong Hong, Sang Yeub Lee, Minkyu Han, Pil Hyung Lee, Soo-Jin Kang, Seung-Whan Lee, Young-Hak Kim, Cheol Whan Lee, Seong-Wook Park and Seung-Jung Park  
On behalf of the IRIS-FFR Investigators

*Circulation*. 2017;135:2241-2251; originally published online March 29, 2017;  
doi: 10.1161/CIRCULATIONAHA.116.024433

*Circulation* is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231  
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:

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## **SUPPLEMENTAL MATERIAL**

This has been provided by the authors to give readers additional information about their work.

Supplement to: Jung-Min Ahn, Duk-Woo Park et al. Fractional Flow Reserve and Cardiac Events in Coronary Artery Disease: Data from a Prospective Registry

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## II. Supplementary Tables

**Supplementary Table 1. Fractional Flow Reserve Characteristics**

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	Lesion Number=8633
Fractional Flow Reserve	
Mean	0.83±0.11
Median (interquartile range)	0.85 (0.77, 0.91)
≤0.75	1903 (22.1%)
0.76-0.80	1001 (11.6%)
≥0.81	5729 (66.3%)
Hyperemic agent	
Adenonsine	8393 (97.2%)
Nicorandil	240 (2.8%)
Route of hyperemic agent	
Intracoronary	752 (8.7%)
Venous	7881 (91.3%)
Serious complication of Fractional Flow Reserve Measurement	
Conduction disturbance requiring treatment	3 (0.03%)
Bronchospasm	2 (0.02%)
Coronary dissection	3 (0.03%)
Ventricular arrhythmia	2 (0.02%)
Thrombus formation	1 (0.01%)

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## Supplementary Table 2. Revascularization Characteristics

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Revascularization during index procedure	3775
Percutaneous coronary intervention	3611 (95.7%)
1 <sup>st</sup> generation drug-eluting stent	113 (3.0%)
New generation drug-eluting stent	3211 (85.1%)
Bare metal stent	22 (0.6%)
Others	265 (7.0%)
Coronary artery bypass graft	164 (4.3%)

---



**Supplementary Table 3. Comparison of Patient and Lesion Characteristics of Stenosis Evaluated by Fractional Flow Reserve or Not**

	Deferral			Revascularization		
	FFR Measurement:	FFR Measurement:	P-value	FFR Measurement:	FFR Measurement:	P-value
	Yes (N=6468)	No (N=2178)		Yes (N=2165)	No (N=1610)	
Age	63.5±9.7	65.2±9.6	<0.001	62.6±9.9	64.1±9.7	<0.001
Gender, male	4543 (70.2%)	1685 (77.4%)	<0.001	1670 (77.1%)	1191 (74.0%)	0.025
Clinical presentation			<0.001			<0.001
Stable angina	5082 (78.6%)	1612 (74.0%)		1513 (69.9%)	1001 (62.2%)	
Unstable angina	1070 (16.5%)	429 (19.7%)		487 (22.5%)	392 (24.3%)	
Non-ST segment elevation myocardial infarction	233 (3.6%)	117 (5.4%)		126 (5.8%)	166 (10.3%)	
ST segment elevation myocardial infarction	83 (1.3%)	20 (0.9%)		39 (1.8%)	51 (3.2%)	
Hypertension	4021 (62.2%)	1539 (70.7%)	<0.001	1397 (64.5%)	1065 (66.1%)	0.30
Diabetes	1997 (30.9%)	788 (36.2%)	<0.001	729 (33.7%)	586 (36.4%)	0.082
Current smoking	1526 (23.6%)	557 (25.6%)	0.06	556 (25.7%)	461 (28.6%)	0.043
Hyperlipidemia	3599 (55.6%)	1512 (69.4%)	<0.001	1405 (64.9%)	1037 (64.4%)	0.76
Multivessel coronary artery disease	3715 (57.4%)	1951 (89.6%)	<0.001	1406 (64.9%)	1432 (88.9%)	<0.001
Previous myocardial infarction	488 (7.5%)	196 (9.0%)	0.030	115 (5.3%)	82 (5.1%)	0.77
Previous percutaneous coronary intervention	1447 (22.4%)	519 (23.8%)	0.16	327 (15.1%)	213 (13.2%)	0.10
Family history	621 (9.6%)	262 (12.0%)	0.001	254 (11.7%)	180 (11.2%)	0.60
Previous congestive heart failure	90 (1.4%)	22 (1.0%)	0.17	16 (0.7%)	10 (0.6%)	0.67
Previous stroke	381 (5.9%)	161 (7.4%)	0.01	136 (6.3%)	101 (6.3%)	0.99
Peripheral vascular disease	136 (2.1%)	63 (2.9%)	0.03	71 (3.3%)	44 (2.7%)	0.33
Chronic renal failure	130 (2.0%)	60 (2.8%)	0.04	47 (2.2%)	31 (1.9%)	0.60
Chronic obstructive lung disease	137 (2.1%)	48 (2.2%)	0.81	51 (2.4%)	29 (1.8%)	0.24
Lesion territory			<0.001			<0.001
Left main	135 (2.1%)	36 (1.7%)		219 (10.1%)	57 (3.5%)	
Left anterior descending artery	3075 (47.5%)	370 (17.0%)		1297 (59.9%)	393 (24.4%)	
Right coronary artery	1720 (26.6%)	512 (23.5%)		350 (16.2%)	517 (32.1%)	
Left circumflex artery	1186 (18.3%)	601 (27.6%)		221 (10.2%)	433 (26.9%)	
Others	352 (5.4%)	659 (30.3%)		78 (3.6%)	210 (13.0%)	
Lesion location			<0.001			<0.001
Proximal	2588 (40.0%)	596 (27.4%)		1274 (58.8%)	710 (44.1%)	

Mid	2245 (34.7%)	309 (14.2%)		580 (27.3%)	303 (18.8%)	
Distal	1635 (25.3%)	1273 (58.4%)		301 (13.9%)	597 (37.1%)	
Diameter stenosis			<0.001			<0.001
≥70%	513 (8.0%)	1009 (31.4%)		1414 (65.3%)	1448 (89.9%)	
50-69%	3321 (51.3%)	1028 (47.2%)		736 (34.0%)	158 (9.8%)	
30-49%	2634 (40.7%)	144 (6.5%)		15 (0.7%)	4 (0.3%)	
AHA/ACC lesion B2C lesion	3119 (48.2%)	1232 (56.6%)	<0.001	1700 (78.5%)	1193 (74.1%)	0.001
Long lesion (>20 mm)	2315 (35.8%)	1202 (55.2%)	<0.001	1365 (63.0%)	1018 (63.2%)	0.91
Moderate to severe calcified lesion	173 (2.7%)	42 (1.9%)	0.053	96 (4.4%)	86 (5.3%)	0.20
Thrombus-containing lesion	29 (0.4%)	13 (0.6%)	0.39	56 (3.5%)	34 (1.6%)	<0.001
Angiographic ulcerated lesion	8 (0.4%)	38 (0.6%)	0.22	17 (0.8%)	6 (0.4%)	0.11

**Supplementary Table 4. Independent Predictors for Major Adverse Cardiac Events in Deferred Lesions**

	Hazard Ratio (95% confidence interval)	P-value
Fractional flow reserve (by increase of 0.01)	0.94 (0.93-0.96)	<0.001
Multivessel coronary artery disease	1.66 (1.19-2.33)	0.003
Thrombus-containing lesion	5.46 (1.98-15.0)	0.001
Diameter stenosis		<0.001
30-50%	1 (reference)	
50-70%	2.20 (1.41-3.44)	<0.001
>70%	2.50 (1.41-4.44)	0.002

**Supplementary Table 5. Adjusted Risk of Major Adverse Cardiac Events in Revascularized Lesions According to the Fractional Flow Reserve**

	Event Number (Incidence Rate)*	FFR as categorical variables					P for trend	FFR as continuous variables	P-value
		≤0.70 (N=861)	0.71-0.75 (N=674)	0.76-0.80 (N=405)	0.81-0.85 (N=105)	0.86-1.00 (N=120)			
MACE†	105 (2.40)	2.68‡ (0.73-9.78)	2.28 (0.61-8.53)	2.28 (0.59-8.81)	3.37 (0.74 –15.4)	1 reference	0.32	1.00 (0.98-1.02)	0.70
Cardiac death or MI	32 (0.71)	1.03 (0.19-5.49)	0.80 (0.14-4.59)	0.97 (0.16-5.99)	1.72 (0.18-16.1)	1 reference	0.86	1.00 (0.98 –1.04)	0.65
Repeat revascularization	81 (1.83)	2.34 (0.64-8.58)	2.03 (0.54-7.69)	1.57 (0.39-6.36)	2.03 (0.40-10.4)	1 reference	0.14	0.99 (0.97-1.01)	0.44

\*100 lesion-year. †MACE denoted the major adverse cardiac event (the composite of cardiac death, myocardial infarction, and repeat revascularization); MI, myocardial infarction. ‡Hazard ratio (95% confidence interval)

**Supplementary Table 6. Baseline Characteristics in Gray Zone FFR**

<b>Patients Characteristics</b>	<b>Revascularization (N=405)</b>	<b>Deferral (N=596)</b>	<b>P-Value</b>
Age	64.0±9.8	64.0±9.7	0.93
Gender (Male)	300 (74.1%)	469 (78.7%)	0.089
Clinical presentation			<0.001
Atypical chest pain	125 (30.9%)	283 (47.5%)	
Typical chest pain	280 (69.1%)	313 (52.5%)	
Hypertension	264 (65.2%)	390 (65.4%)	0.94
Diabetes	132 (32.6%)	197 (33.1%)	0.88
Current smoking	93 (23.0%)	144 (24.2%)	0.66
Hyperlipidemia	259 (64.0%)	339 (56.9%)	0.025
Multivessel disease	252 (62.2)	333 (55.9%)	0.045
Previous myocardial infarction	22 (5.4%)	38 (6.4%)	0.54
Previous PCI	71 (17.5%)	145 (24.3%)	0.010
Family history	43 (10.6%)	58 (9.7%)	0.65
Previous congestive heart failure	4 (1.0%)	3 (0.5%)	0.37
Previous stroke	25 (6.2%)	43 (7.2%)	0.52
Peripheral vascular disease	19 (4.7%)	18 (3.0%)	0.17
Chronic renal failure	7 (1.7%)	77 (1.8%)	0.89
Chronic obstructive lung disease	10 (2.5%)	8 (1.3%)	0.19
<b>Lesion Characteristics</b>			
Lesion territory			<0.001
Left main	29 (7.2%)	19 (3.2%)	
Left anterior descending artery	253 (62.5%)	431 (72.3%)	
Right coronary artery	74 (18.3)	67 (11.2%)	
Left circumflex artery	41 (10.1%)	58 (9.7%)	
Others	8 (2.0%)	21 (3.5%)	
Lesion location			0.002
Proximal	220 (54.3%)	258 (43.3%)	
Mid	129 (31.9%)	226 (37.9%)	
Distal	56 (13.8%)	112 (18.8%)	
Diameter stenosis			<0.001
≥70%	231 (57.1%)	75 (12.5%)	
50-69%	170 (42.0%)	377 (63.3%)	
30-49%	4 (1.0%)	144 (24.2%)	
AHA/ACC lesion B2C lesion	304 (75.1%)	383 (64.3%)	<0.001
Long lesion (>20 mm)	229 (56.5%)	286 (48.0%)	0.008
Moderate to severe calcified lesion	17 (4.2%)	23 (3.9%)	0.79
Thrombus-containing lesion	5 (1.2%)	1 (0.2%)	0.043
Angiographic ulcerated lesion	1 (0.2%)	4 (0.7%)	0.65

AHA/ACC indicates American Heart Association/American College of Cardiology

**Supplementary Table 7. Predictors of MACE in Deferred Lesion with Gray Zone FFR (FFR 0.75-0.80)**

Patients Characteristics	MACE		P Value
	Yes (N=33)	No (N=563)	
Age	65.1±11.8	64.0±9.6	0.59
Gender (Male)	25 (75.8%)	444 (78.9%)	0.67
Clinical presentation			0.017
Atypical chest pain	24 (72.7%)	289 (51.3%)	
Typical chest pain	9 (27.3%)	274 (48.7%)	
Hypertension	24 (72.7%)	366 (65.0%)	0.37
Diabetes	13 (39.4%)	184 (32.7%)	0.43
Current smoking	10 (30.3%)	134 (23.8%)	0.40
Hyperlipidemia	26 (78.8%)	313 (55.6%)	0.009
Multivessel disease	19 (57.6%)	314 (55.8%)	0.84
Previous myocardial infarction	3 (9.1%)	35 (6.2%)	0.46
Previous PCI	13 (39.4%)	132 (23.4%)	0.038
Family history	2 (6.1%)	56 (9.9%)	0.76
Previous congestive heart failure	0	3 (0.5%)	>0.99
Previous stroke	1 (3.0%)	42 (7.5%)	0.50
Peripheral vascular disease	2 (6.1%)	16 (2.8%)	0.26
Chronic renal failure	0	11 (2.0%)	>0.99
Chronic obstructive lung disease	0	8 (1.4%)	>0.99
<b>Lesions Characteristics</b>			
Lesion territory			0.72
Left main	1 (3.0%)	18 (3.2%)	
Left anterior descending artery	21 (63.6%)	410 (72.8%)	
Right coronary artery	6 (18.2%)	61 (10.8%)	
Left circumflex artery	4 (12.1%)	54 (9.6%)	
Others	1 (3.0%)	20 (3.6%)	
Lesion location			0.36
Proximal	18 (54.5%)	240 (45.6%)	
Mid	9 (27.3%)	217 (38.5%)	
Distal	6 (18.2%)	106 (18.8%)	
Diameter stenosis			0.20
≥70%	6 (18.2%)	69 (12.3%)	
50-69%	23 (69.7%)	354 (62.9%)	
30-49%	4 (12.1%)	140 (24.9%)	
AHA/ACC lesion B2C lesion	25 (75.8%)	358 (63.6%)	0.16
Long lesion (>20 mm)	20 (60.6%)	266 (47.2%)	0.15
Moderate to severe calcified lesion	0	23 (4.1%)	0.63
Thrombus-containing lesion	0	1 (0.2%)	>0.99
Angiographic ulcerated lesion	0	4 (0.7%)	>0.99

AHA/ACC indicates American Heart Association/American College of Cardiology

### Supplementary Table 8. No Adjudications of the Event to the Lesion

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Death

Indeterminate cause of death: 21 events

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Myocardial infarction

No adjudicated due to neither coronary angiography nor localization sign: 3 events

Not target lesion events\*: 3 events

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Repeat revascularization

Not target lesion events\*: 32 events

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\* At the time of enrollment, a target lesion was defined as either a lesion with diameter stenosis >50% or a lesion evaluated by FFR

**Supplementary Table 9. Specified Causes of Death**

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	N=97
Cardiac causes	19 (19.6%)
Cardiac arrest	11
Myocardial infarction	4
Fatal arrhythmia	2
Low cardiac output*	2
Vascular causes	9 (9.3%)
Cerebrovascular disease	6
Aortic dissection	1
Other vascular disease	2
Non-cardiovascular causes	48 (49.5%)
Malignancy	24
Infection	9
Accident	1
Pulmonary disease	11
Renal failure	1
Others	2
Indeterminate causes	21 (21.6%)

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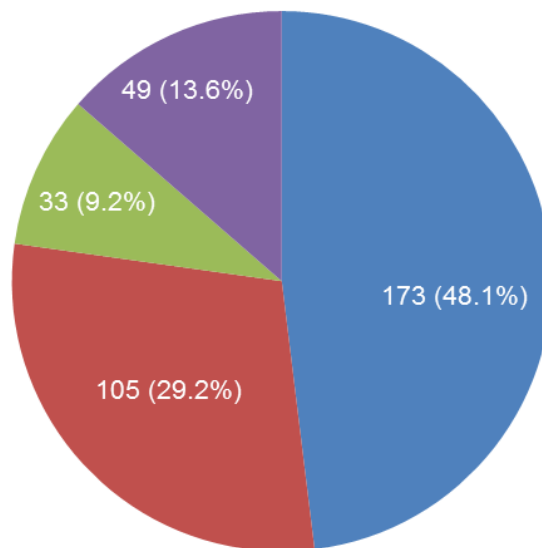
\* One patient who was diagnosed with acute myocarditis was not adjudicated as cardiac death and was censored in the analysis.



## Supplementary Figures

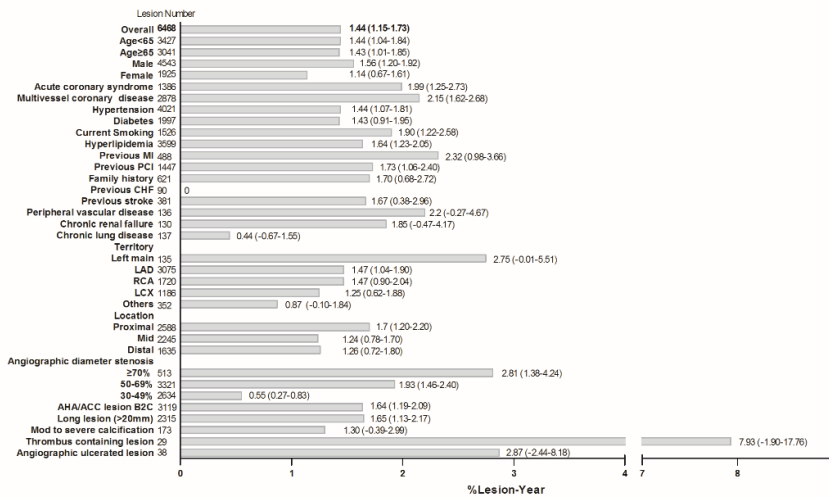
**Supplementary Figure 1. Occurrence of Clinical Outcomes According to the FFR use and Revascularization:** Of a total of 360 major adverse cardiac events, most events occurred in FFR-evaluated lesions, while about 22.8% of events occurred in non-FFR-evaluated lesion

- Deferral With FFR Measurement
- Revascularization With FFR Measurement
- Deferral Without FFR Measurement
- Revascularization Without FFR Measurement

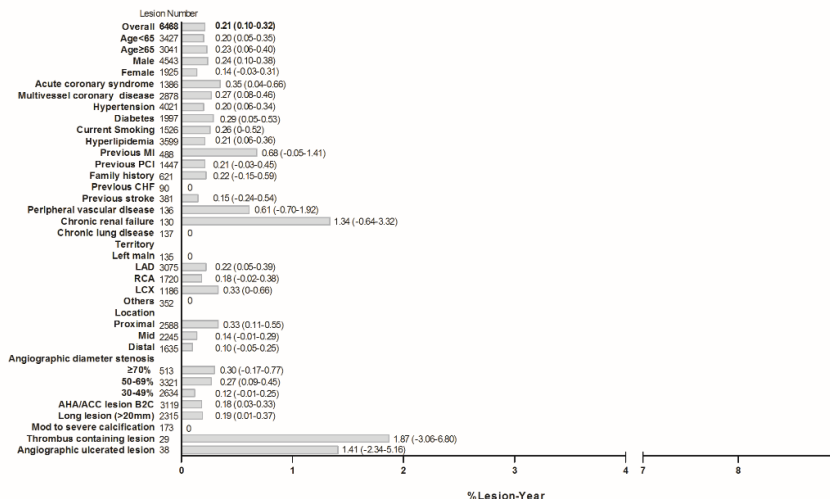


**Supplementary Figure 2. Incidence Rate of Major Adverse Cardiac Events (A) and Cardiac Death and Myocardial Infarction (B) in Deferred Lesions after FFR Measurement in Various Subgroups. MI indicates myocardial infarction; PCI, percutaneous coronary intervention; CHF, congestive heart failure; LAD, left anterior descending artery; RCA, right coronary artery; LCX, left circumflex coronary artery; AHA/ACC, American Heart Association/American College of Cardiology.**

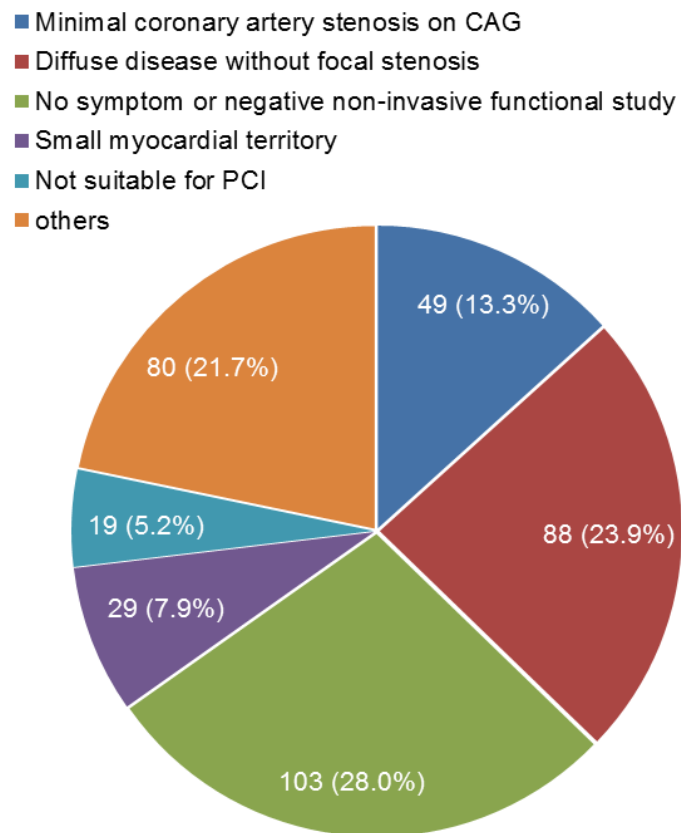
(A) Major Adverse Cardiac Events



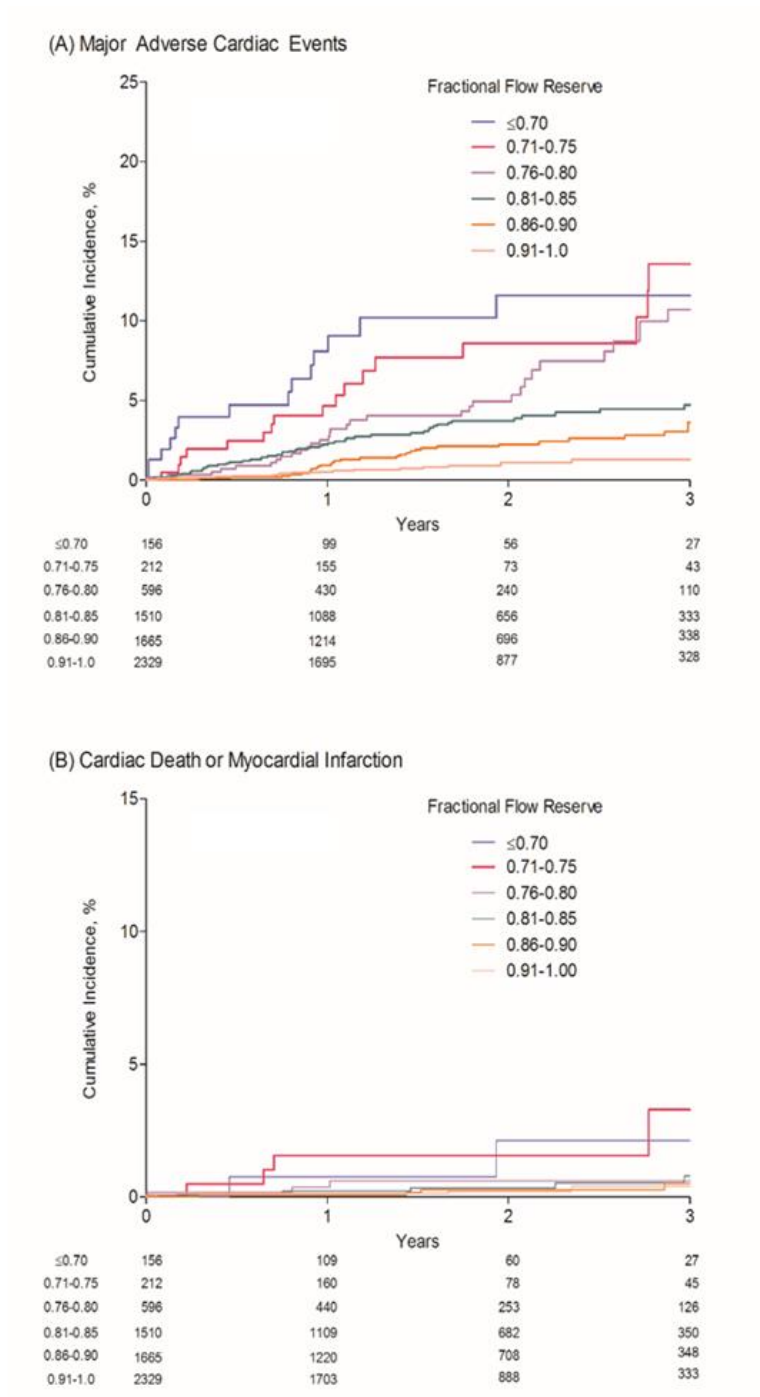
(B) Cardiac Death or Myocardial Infarction



**Supplementary Figure 3. Specified Reasons for Deferred Revascularization despite Low FFR ( $\leq 0.75$ )**

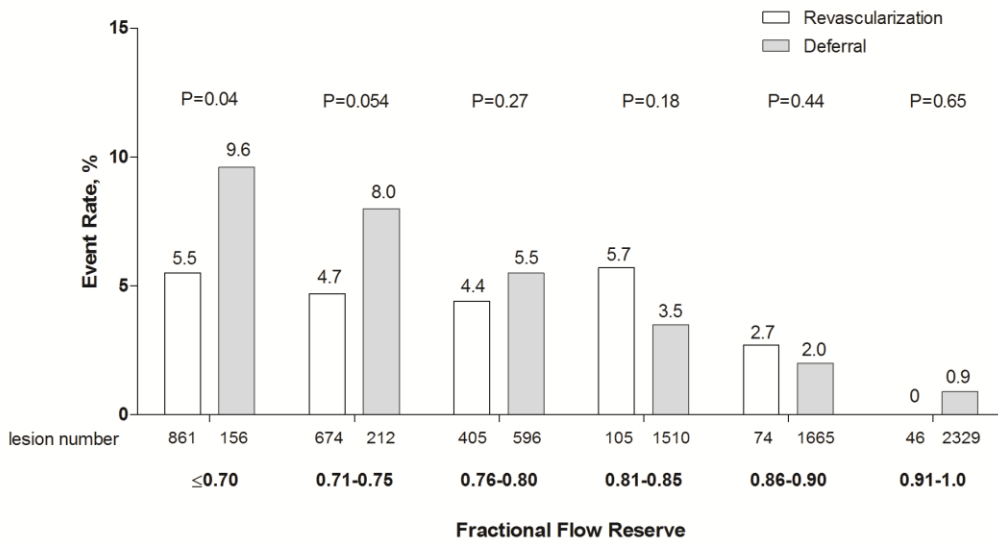


**Supplementary Figure 4. Observed Incidence of Major Adverse Cardiac Events (A) and Cardiac Death and Myocardial Infarction (B) Over the Follow-up Period in Revascularized versus Deferred Lesions According to FFR Categories.**

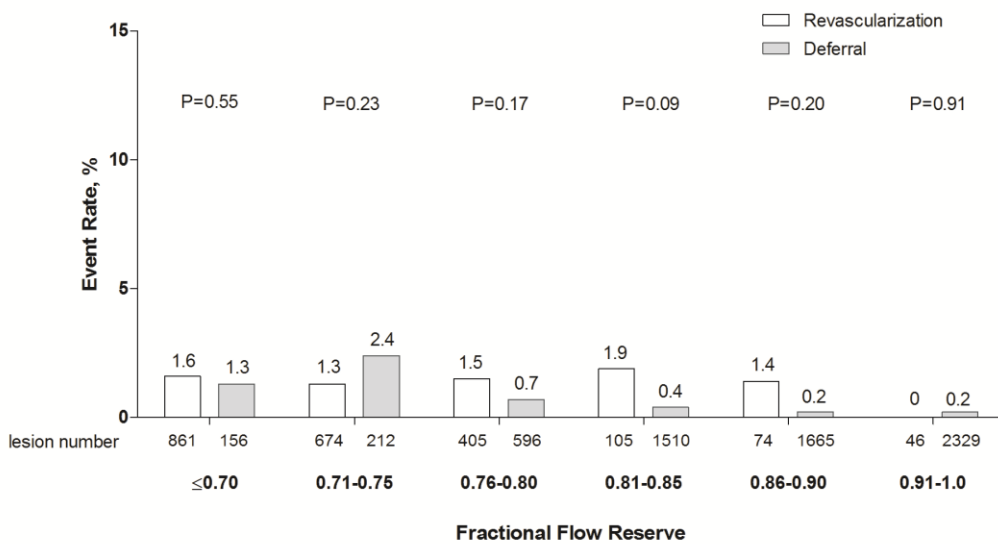


**Supplementary Figure 5. Observed Incidence of Major Adverse Cardiac Events (A) and Cardiac Death and Myocardial Infarction (B) Over the Follow-up Period in Revascularized versus Deferred Lesions According to FFR Categories. P-values were derived from Chi Square test.**

(A) Major Adverse Cardiac Events

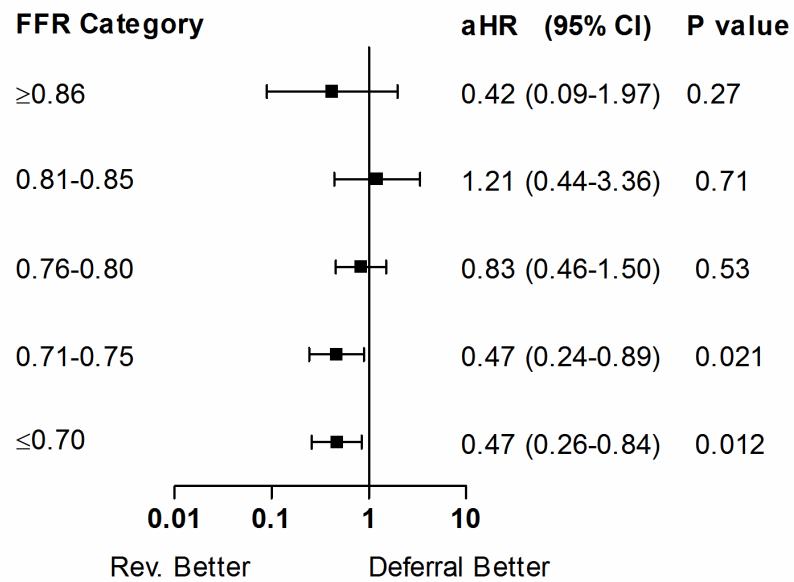


(B) Cardiac Death and Myocardial Infarction



**Supplementary Figure 6. Adjusted Hazard Ratio of Major Adverse Cardiac Events (A) and Cardiac Death and Myocardial Infarction (B) between Deferred and Revascularized Lesions According to FFR Categories.**

**(A) Major Adverse Cardiac Events**



**(B) Cardiac Death or Myocardial Infarction**

