

## Long-Term Clinical Outcomes of Fractional Flow Reserve–Guided Versus Routine Drug-Eluting Stent Implantation in Patients With Intermediate Coronary Stenosis Five-Year Clinical Outcomes of DEFER-DES Trial

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**Background**—We aimed to compare the long-term clinical outcomes between fractional flow reserve (FFR)–guided and routine drug-eluting stent (DES) implantation in patients with an intermediate coronary stenosis.

**Methods and Results**—A total of 229 patients with an angiographically intermediate coronary stenosis were randomly assigned to FFR-guided or Routine-DES implantation group. For FFR-guided group (n=114), treatment strategy was determined according to the target vessel FFR (FFR<0.75: DES implantation [FFR-DES group]; FFR≥0.75: deferral of stenting [FFR-Defer group]). Routine-DES group underwent DES implantation without FFR measurement (n=115). The primary end point was the incidence of major adverse cardiac events, a composite of cardiac death, myocardial infarction, and target lesion revascularization. Of lesions assigned to FFR-guided strategy, only one quarter had functional significance (FFR<0.75). At 2-year follow-up, the cumulative incidence of major adverse cardiac events was 7.9±2.5% in the FFR-guided group and 8.8±2.7% in Routine-DES group ( $P=0.80$ ). At 5-year follow-up, the cumulative incidence of major adverse cardiac events was 11.6±3.0% and 14.2±3.3% for the FFR-guided group and the Routine-DES group ( $P=0.55$ ). There was no difference in major adverse cardiac events rates between the 2 groups ≤5-year follow-up (hazard ratio, 1.25; 95% confidence interval, 0.60–2.60).

**Conclusions**—In lesions with angiographically intermediate stenosis, FFR guidance provides a tailored approach, which is at least as good as an angiography-guided routine-DES implantation strategy and avoids unnecessary DES-stenting in a considerable part of the patients.

**Clinical Trial Registration**—URL: <http://www.clinicaltrials.gov>. Unique identifier: NCT00592228.

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**Key Words:** coronary artery disease ■ coronary stenosis ■ drug-eluting stents ■ myocardial fractional flow reserve ■ percutaneous coronary intervention

Intermediate coronary stenosis is frequently encountered during diagnostic angiography. It is well known that the decision to perform revascularization should be guided by evidence of myocardial ischemia.<sup>1</sup> Fractional flow reserve (FFR) is a lesion-specific physiological index to evaluate the

functional significance of coronary stenosis and can be easily measured in a cardiac catheterization laboratory. Although its benefit has been proven by many clinical studies,<sup>1–6</sup> the use of FFR-guided revascularization is still low and there is still some room to apply FFR in more patients.<sup>7</sup>

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### WHAT IS KNOWN

- Fractional flow reserve (FFR) represents the ratio of the myocardial blood flow to the normal maximal myocardial flow and reflects the functional significance of coronary stenosis.
- FFR-guided revascularization strategy is known to be better than angiography-guided revascularization.
- The DEFER study demonstrated that the revascularization of the lesion with  $\text{FFR} \geq 0.75$  did not improve the clinical outcomes of the patients with intermediate coronary artery stenosis. However, this study was performed in the bare-metal stent era.

### WHAT THE STUDY ADDS

- In patients with intermediate stenosis, FFR-guided drug-eluting stent (DES) implantation had comparable long-term clinical outcomes when compared with routine DES implantation strategy, but with much less use of DES.
- Functionally significant lesions ( $\text{FFR} < 0.75$ ) had the worst clinical outcomes, even after DES implantation. FFR can be helpful to define high-risk groups after DES implantation among patients with intermediate stenosis.

In the Fractional Flow Reserve to Determine the Appropriateness of Angioplasty in Moderate Coronary Stenosis, A Randomized Trial (DEFER trial), patients with intermediate stenosis without definite evidence of myocardial ischemia were randomized to deferral of percutaneous coronary intervention (PCI) and performance of PCI arms.<sup>1</sup> Five-year follow-up data showed that the event-free survival was not different between the defer group and the perform group.<sup>2</sup> However, this study was performed in the bare-metal stent era, and the outcomes of drug-eluting stents (DES) for intermediate stenosis were reported to be excellent.<sup>8</sup> We sought to compare the long-term clinical outcomes between FFR-guided DES implantation and routine DES implantation strategy in patients with intermediate stenosis.

## Methods

### Study Population

Patients with angiographically intermediate stenosis (40%–70% diameter stenosis by visual estimation) in a native coronary artery with a reference diameter  $> 2.5$  mm were included in this study. Included lesions did not have objective proof of ischemia, and noninvasive stress test results were negative, inconclusive, not evaluable for a target lesion, or simply not performed. Patients who had angiographically significant left main disease, cardiogenic shock, chronic kidney disease (serum creatinine  $> 2$  mg/dL), a life expectancy of  $< 2$  years, conduction disturbance more than first-degree AV block or contraindication to adenosine were excluded. The study protocol was approved by the institutional review board of each participating center, and written informed consent was obtained from all patients.

### Study Design

The Proper Fractional Flow Reserve Criteria for Intermediate Lesions in the Era of Drug-Eluting Stent (DEFER-DES) Trial was a

prospective, randomized study conducted in 6 university hospitals in Korea. Eligible patients with an intermediate coronary stenosis were randomly assigned to either FFR-guided or Routine-DES group (Figure 1). For FFR-guided group, treatment strategy was determined according to the target vessel FFR ( $\text{FFR} < 0.75$ : DES implantation [FFR-DES group],  $\text{FFR} \geq 0.75$ : deferral of PCI [FFR-Defer group]). Routine-DES group underwent DES implantation for the target lesion without FFR measurement. This study was designed to include 325 patients with 2-year clinical follow-up as DEFER study,<sup>1</sup> but was prematurely terminated in December 2007 because of the concern of late stent thrombosis after DES implantation. The steering committee decided to stop the enrollment and extend the clinical follow-up out to 5 years.

### Study Procedures

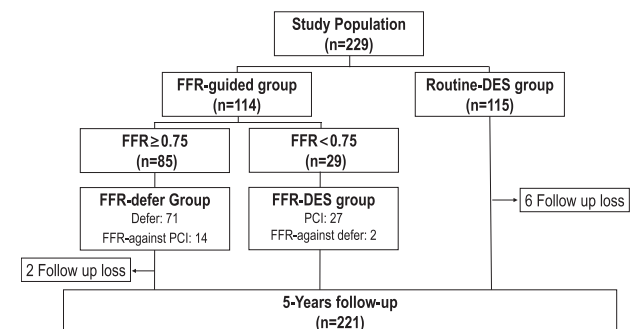
The target vessel was engaged using a guiding catheter of 5F to 7F either by radial or femoral approach. Angiographic images were acquired after intracoronary administration of 100 to 200  $\mu\text{g}$  of nitroglycerin. FFR was measured using a 0.014-inch pressure guidewire (PressureWire; Radi Medical Systems, Uppsala, Sweden) as previously described.<sup>9</sup> Hyperemia was induced with an intracoronary bolus administration (80  $\mu\text{g}$  in left coronary artery and 40  $\mu\text{g}$  in right coronary artery) or intravenous infusion (140  $\mu\text{g}/\text{kg}$  per minute) of adenosine. FFR was calculated as the ratio of the mean distal coronary pressure measured by the pressure wire to the mean aortic pressure measured by the guiding catheter under maximal hyperemia.<sup>10</sup>

### Quantitative Coronary Angiography

Quantitative coronary angiography was performed by an independent core laboratory at Seoul National University Cardiovascular Center. Using the guiding catheter for calibration and an edge detection system (CAAS 5.7; Quantitative Coronary Angiography System; Pie Medical, Maastricht, the Netherlands), the reference diameters, minimum lumen diameter, and lesion length were measured, and the % diameter stenosis was calculated. Lesion location was determined according to the American Heart Association classification.<sup>11</sup>

### End Point and Clinical Follow-Up

The primary end point was the rate of major adverse cardiac events (MACE), and the results at 2 and 5 years were of special interest. MACE was defined as a composite of cardiac death, myocardial infarction (MI), and target lesion revascularization. All deaths were considered cardiac unless there was a clear noncardiac cause. MI was defined as an elevated cardiac enzyme with ischemic symptoms or new pathological Q waves on ECG. Periprocedural MI was not included. Clinical follow-up data were obtained from a Web-based reporting system. Additional information was obtained from hospital records and telephone contact if needed. An independent study monitor verified all information on electronic case report forms. All clinical events were adjudicated by a clinical events committee in a blinded fashion using original source documents and angiographic images.



**Figure 1.** Study flow. DES indicates drug-eluting stent; FFR, fractional flow reserve; and PCI, percutaneous coronary intervention.

**Table 1. Baseline Clinical Characteristics of Study Population**

	FFR-Guided Group (n=114)			Routine-DES Group (n=115)	P Value*
	FFR-Defer (n=85)	FFR-DES (n=29)	All (n=114)		
Age, y	62±10	62±10	62±10	63±10	0.34
Women, n (%)	24 (28)	7 (24)	31 (27)	28 (25)	0.65
Hypertension, n (%)	54 (64)	19 (66)	73 (64)	65 (57)	0.23
Diabetes mellitus, n (%)	22 (26)	8 (28)	30 (26)	39 (34)	0.32
Dyslipidemia, n (%)	60 (71)	20 (69)	80 (70)	78 (68)	0.67
Current smoker, n (%)	20 (24)	10 (35)	30 (26)	38 (33)	0.25
Prior myocardial infarction, n (%)	19 (22)	3 (10)	22 (19)	20 (17)	0.87
Prior PCI, n (%)	16 (19)	6 (21)	22 (19)	20 (17)	0.61
Diagnosis, n (%)					0.79
Stable angina	39 (46)	16 (55)	52 (48)	54 (47)	
Acute coronary syndrome	41 (48)	17 (41)	58 (51)	55 (48)	
One-vessel disease, n (%)	32 (38)	10 (35)	42 (37)	49 (43)	0.64
Two-vessel disease, n (%)	37 (44)	12 (41)	49 (43)	39 (34)	0.36
Triple-vessel disease, n (%)	16 (22)	7 (24)	23 (20)	27 (23)	0.53
Left ventricular EF, %	62±9	62±7	62±9	61±9	0.29

DES indicates drug-eluting stent; EF, ejection fraction; FFR, fractional flow reserve; and PCI, percutaneous coronary intervention.

\*Comparison between FFR-guided group vs Routine-DES group.

### Statistical Analysis

All comparisons were made on an intention-to-treat principle. Categorical variables were expressed as proportions. The  $\chi^2$  test or Fisher exact test was used to compare differences between the groups. Continuous variables are expressed as mean and SD and were compared by Student *t* test or 1-way ANOVA, and Bonferroni correction was used as post hoc analysis. The log-rank test was used to compare hazard rates for the 2 groups. For the comparisons at 2 and 5 years, we directly compared the Kaplan-Meier estimates at these time points using the estimated time-specific SEs

with Bonferroni correction for multiplicity adjustment. A 2-sided  $P < 0.05$  was considered to indicate statistical significance. All statistical analyses were performed using SPSS version 18.0 (SPSS Inc, Chicago, IL).

### Results

From November 2006 to December 2007, a total of 229 patients were enrolled and 114 patients were assigned to the FFR-guided group and 115 patients to the Routine-DES group

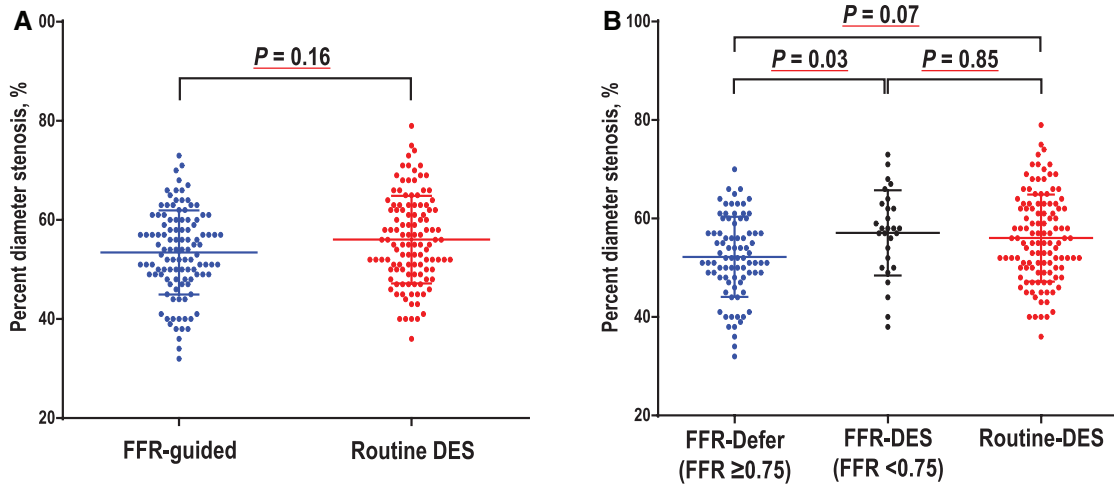
**Table 2. Baseline Lesions Characteristics**

	FFR-Guided Group (n=114)			Routine-DES Group (n=115)	P Value*
	FFR-Defer (n=85)	FFR-DES (n=29)	All (n=114)		
Location of target lesion, %					0.72
Left anterior descending artery	52	66	55	56	
Left circumflex	21	10	21	15	
Right coronary artery	27	24	27	30	
Lesion characteristics					
Proximal reference diameter, mm	3.29±0.50	3.25±0.40	3.28±0.48	3.38±0.48	0.07
Distal reference diameter, mm	3.00±0.45	2.77±0.43	2.94±0.46	3.07±0.51	0.04
% diameter stenosis	53±9	58±10	54±10	56±9	0.13
Minimal lumen diameter, mm	1.46±0.34	1.23±0.33	1.41±0.35	1.41±0.35	0.97
Lesion length, mm	15.6±10.0	29.1±15.9	18.9±13.0	18.4±10.6	0.77
Fractional flow reserve	0.88±0.06	0.68±0.06	0.83±0.10	...	...
Total stent number, n	...	53	...	187	...
First-generation stents, n (%)	...	31 (58)	...	126 (67)	0.25†

DES indicates drug-eluting stent; and FFR, fractional flow reserve.

\*Comparison between FFR-guided group vs Routine-DES group.

†Comparison between FFR-DES group vs Routine-DES group.



**Figure 2.** Angiographic % diameter stenosis. There was no difference in % diameter stenosis between fractional flow reserve (FFR)–guided group and Routine-drug-eluting stent (DES) group (A). However, % diameter stenosis of FFR-Defer group was lower than that of other groups (B).

(Figure 1). FFR was successfully measured in all patients of the FFR-guided group without complication and FFR was <0.75 in only 29 patients. Stents were implanted in nonstudy vessels in 24 patients and 44 patients in the FFR-guided group and the Routine-DES group, respectively.

**Baseline Clinical and Angiographic Characteristics**

Baseline clinical characteristics were similar between the FFR-guided group and the Routine-DES group (Table 1). There was also no difference in patients characteristics between the FFR-Defer and the FFR-DES groups.

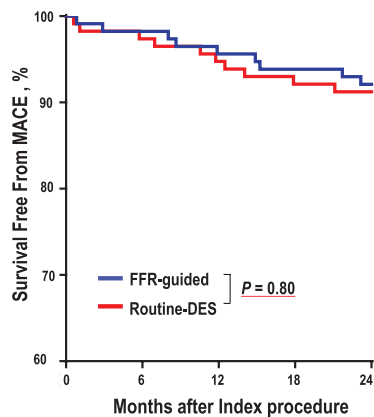
Baseline lesion characteristics are shown in Table 2. Angiographic lesion parameters such as angiographic % diameter, minimal lumen diameter, and lesion length were similar between the 2 groups. Distal reference vessel diameter was larger in the Routine-DES group than in the FFR-guided group (3.07±0.51 versus 2.94±0.46 mm; P=0.04). The post hoc analysis showed that % diameter stenosis of FFR-DES

group was significantly higher than that of the FFR-Defer group (P=0.03). However, there was a wide overlap of angiographic % diameter stenosis among the 3 groups (Figure 2). Furthermore, there was no statistically significant difference in angiographic % diameter stenosis between FFR-Defer and Routine-DES groups (P=0.07). The mean FFR in FFR-Defer and FFR-DES groups were 0.88±0.06 and 0.68±0.06, respectively.

**Clinical Outcomes Between FFR-Guided Group and Routine-DES Group**

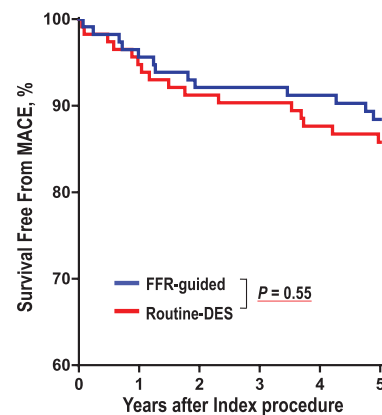
Kaplan–Meier survival curves for MACE by groups at 5-year follow-up are displayed in Figure 3. The incidence of clinical events at 5-year follow-up is shown in Table 3. At 2-year follow-up, the cumulative incidence of MACE (1–Kaplan–Meier estimate) was 7.9±2.5% in the FFR-guided group and 8.8±2.7% in Routine-DES group (P=0.80). At 5-year follow-up, the cumulative incidence of MACE was 11.6±3.0% and 14.2±3.3% for

**A 2-Year Follow-up**



FFR-guided	114	112	109	107	105
Routine DES	115	111	108	104	103

**B 5-Year Follow-up**



FFR-guided	114	109	105	101	99	94
Routine DES	115	108	103	102	96	92

**Figure 3.** Kaplan–Meier survival curve for major adverse cardiac events (MACE). There was no difference in MACE between fractional flow reserve (FFR)–guided group and Routine-drug-eluting stent (DES) group at 2-y follow-up (A) and 5-y follow-up (B).

**Table 3. Five-Year Clinical Outcomes According to Therapeutic Strategy**

	FFR-Guided Group (n=114)			Routine-DES Group (n=115)	P Value*	P Value Among 3 Groups
	FFR-Defer (n=85)	FFR-DES (n=29)	All (n=114)			
Cardiac death or MI	3 (3.5)	1 (3.4)	4 (3.5)	7 (6.1)	0.54	0.66
Target lesion revascularization	4 (4.7)	6 (20.7)	10 (8.8)	9 (7.8)	0.82	0.03
All revascularization	7 (8.2)	8 (27.6)	15 (13.2)	15 (13.0)	1.00	0.03
MACE	6 (7.1)	7 (24.1)	13 (11.4)	16 (13.9)	0.69	0.05

DES indicates drug-eluting stent; FFR, fractional flow reserve; MACE, major adverse cardiac events; and MI, myocardial infarction.  
\*Comparison between FFR-guided group vs Routine-DES group.

the FFR-guided group and the Routine-DES group ( $P=0.55$ ). There was no difference in MACE rates between the 2 groups up to 5-year follow-up (hazard ratio, 1.25; 95% confidence interval, 0.60–2.60). There was also no difference in the incidence of cardiac death, MI, target lesion revascularization, or any repeated revascularization between the 2 groups.

**Clinical Outcomes Among FFR-Defer, FFR-DES, and Routine-DES Groups**

When the clinical outcomes among FFR-Defer, FFR-DES, and Routine-DES groups were compared, there was a difference in MACE rates at 5-year follow-up, which was mainly driven by high target lesion revascularization of FFR-DES group (Figure 4; Table I in the Data Supplement). At 5-year follow-up, the MACE rate was not statistically different between Routine-DES and FFR-Defer groups ( $13.9\pm 3.3\%$  versus  $7.1\pm 2.8\%$ ;  $P=0.13$ ) and between Routine-DES and FFR-DES groups ( $13.9\pm 3.3\%$  versus  $24.1\pm 7.9\%$ ;  $P=0.19$ ). The FFR-DES group had significantly higher rates of MACE ( $7.2\pm 2.8\%$  versus  $24.1\pm 7.9\%$ ;  $P=0.01$ ) than the FFR-Defer group. These results were reproduced by per-protocol analyses.

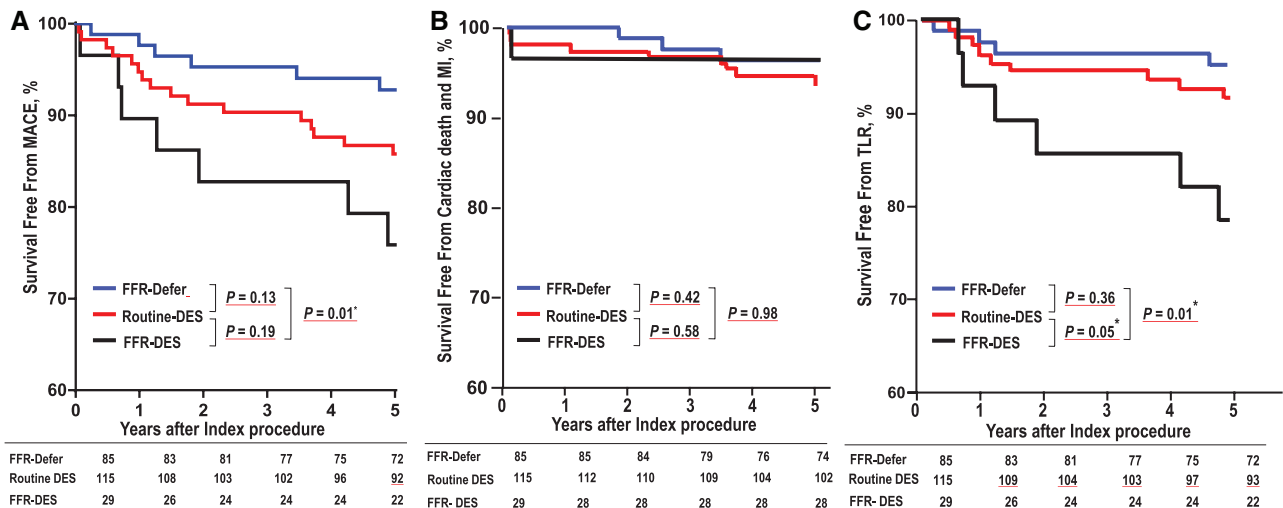
When the incidence of each event was compared, FFR-DES group had the highest incidence of MACE ( $P=0.05$ ), target lesion revascularization ( $P=0.03$ ), and any repeated

revascularization ( $P=0.03$ ). The incidence of cardiac death or MI was not significantly different among the 3 groups (Table 3).

When the DES implanted patients were divided into 2 groups according to angiographic lesion severity (50% diameter stenosis), there was no difference in the rate of MACE at 5-year follow-up between the 2 groups (15.6% in diameter stenosis <50% group, 16.1% in diameter stenosis  $\geq 50\%$  group;  $P=1.00$ ).

**Discussion**

This study investigated the long-term clinical outcomes of FFR-guided revascularization versus routine PCI with DES implantation in patients with intermediate stenosis without objective evidence of ischemia and found that FFR-guided DES implantation had comparable long-term clinical outcomes than routine DES implantation strategy, but with much less use of DES. The present study showed that there was no benefit of routine stent implantation for a functionally insignificant lesion, even if DES was used. The prognosis of lesions with high FFR was excellent with medical treatment, whereas those with low FFR had the worst outcomes even after DES implantation because they had the most severe disease.



**Figure 4.** Kaplan-Meier survival curve for clinical events among 3 groups at 5-y follow-up. The rate of major adverse cardiac events (MACE; **A**) and target lesion revascularization (TLR; **C**) was higher in fractional flow reserve (FFR)-drug-eluting stent (DES) group than in other groups, and no significant difference of cardiac death and myocardial infarction (MI; **B**) rate was observed. FFR-Defer means  $FFR > 0.75$  and FFR-DES means  $FFR < 0.75$ . Routine-DES means no FFR. \* $P < 0.017$  is significant according to Bonferroni correction.



The primary population in our study were patients with intermediate stenosis, which is the preferred indication by clinicians for FFR use. Our study population is different from that in the Fractional Flow Reserve Versus Angiography for Multivessel Evaluation (FAME) study.<sup>4</sup> FAME included patients with multivessel coronary artery disease and more than half of lesions had angiographic stenosis of >70%. Mean FFR in FAME study was 0.71. Mean % diameter stenosis of all studied lesions was 53% in our study, which was similar to that of DEFER study (52%). Mean % diameter stenosis and FFR of defer group were 53% and 0.88 in our study and 48% and 0.87 in the DEFER study,<sup>1</sup> respectively.

In the DEFER study, 325 patients were randomized to deferral of PCI and performance of PCI groups, and then FFR was measured. When FFR was <0.75, PCI was performed in all patients and the randomization was executed only in patients with an FFR  $\geq$ 0.75. This study was performed in the pre-DES era and the PCI performed was balloon angioplasty or bare-metal stent implantation. Our study design was a little bit different from the DEFER study. After introduction of DES into clinical practice, PCI was performed in a wide range of coronary lesions with high success, low complication rate, and excellent long-term patency.<sup>12-14</sup> Therefore, we randomized the patients into FFR-guided DES implantation group and routine DES implantation group to compare the outcomes of 2 different strategies in patients with intermediate stenosis. FFR was measured only in the FFR-guided group in our study, in contrast to the original DEFER study where FFR was available for all patients.

Moses et al<sup>8</sup> reported that DES implantation in patients with intermediate stenosis (% diameter stenosis <50% [mean 44%] by quantitative coronary angiography) resulted in a marked reduction in clinical and angiographic restenosis. Lavi et al<sup>15</sup> investigated the 2-year outcomes of patients with intermediate lesions ( $0.75 \leq \text{FFR} < 0.9$ ) and found that DES implantation resulted in better outcomes than bare-metal stent implantation. Therefore, it is natural to postulate that the results would have been different if DES was used in the DEFER study. In our study, there was no difference in both 2- and 5-year clinical outcomes between the FFR-guided and the Routine-DES groups. There was also no difference in the rate of death or MI. Our study results again confirmed that the use of FFR reduced unnecessary intervention, and PCI even with DES, cannot improve patient outcomes unless ischemia is indicated. In our study, there was no difference in angiographic lesion severity between the 2 groups, and only one quarter of patients in the FFR-guided group had functionally significant stenosis ( $\text{FFR} < 0.75$ ). This finding is important, considering the fact that visual estimation still dominates in the treatment decision for intermediate stenosis and the low penetration rate of FFR.<sup>16</sup>

In the present study, patients with functionally significant lesions had worse clinical outcomes, even after DES implantation. The 5-year event-free survival rate was 75.9% in the FFR-DES group ( $\text{FFR} < 0.75$ ) and 92.9% in the FFR-defer group ( $\text{FFR} \geq 0.75$ ). A similar trend was observed in the DEFER study. Because FFR is determined by several angiographic factors such as lesion length, lesion geometry, and % diameter stenosis, low FFR in patients with intermediate

stenosis might indicate high-risk lesions after PCI. In our study, the lesion length was longer in the FFR-DES group than in the FFR-Defer group ( $29.1 \pm 15.9$  versus  $15.6 \pm 10.0$  mm;  $P < 0.01$ ). Furthermore, when DES implanted patients were divided into 2 groups according to 50% diameter stenosis, there was no difference in clinical outcomes. Although clinical outcome of angiographic intermediate stenosis is generally favorable regardless of treatment strategy, the results of our study and the DEFER study suggest that the lesions with low FFR, despite intermediate degree of stenosis, might need meticulous surveillance for future clinical events.

### Limitations

Our study has several limitations. First, the sample size was small, and the enrollment was interrupted early because of the concern about late stent thrombosis after DES implantation. However, considering the favorable outcomes of intermediate stenosis, regardless of treatment strategy, it may not be easy to perform a study large enough to meet the statistical requirement. Second, the study was not a blinded one. It is possible that the awareness of having an unstented coronary lesion had influenced the decision of the physicians during follow-up. Third, our study was performed in first-generation DES era, and recent reports have shown that second-generation DESs have more favorable clinical outcomes than first-generation DES.<sup>17-19</sup> Fourth, the information on the angina status and antianginal medication was not available in this study. Finally, because this study was designed before FAME studies, PCI indication in the FFR-guided group was  $\text{FFR} < 0.75$ . Recent meta-analysis by Johnson et al<sup>20</sup> found that the lesions with lower FFR were associated with higher risk of clinical events. However, because there was no difference in clinical outcomes between the FFR-guided and Routine-DES groups, the main findings of our study would have not changed significantly, even if the criterion of  $\text{FFR} \leq 0.80$  had been used.

### Conclusions

In lesions with angiographically intermediate stenosis, FFR guidance provides a tailored approach, which is at least as good as an angiography-guided routine DES implantation strategy and avoids unnecessary DES in a considerable part of the patients.

### Disclosures

Dr Koo received the institutional research grant from St Jude Medical. The other authors report no conflicts.

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**Long-Term Clinical Outcomes of Fractional Flow Reserve–Guided Versus Routine Drug-Eluting Stent Implantation in Patients With Intermediate Coronary Stenosis: Five-Year Clinical Outcomes of DEFER-DES Trial**

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Supplement Table 1. Hazard ratio and 95% confidence interval in clinical outcomes among 3 groups

	Hazard ratio	95% CI
5-year MACE		
FFR Defer		
vs. FFR DES	<u>3.67</u>	<u>1.24-10.93</u>
vs. Routine DES	<u>2.05</u>	<u>0.803-5.25</u>
5-year Cardiac death and MI		
FFR Defer		
vs. FFR DES	<u>0.96</u>	<u>0.10-9.23</u>
vs. Routine DES	<u>1.73</u>	<u>0.45-6.69</u>
5-year TLR		
FFR Defer		
vs. FFR DES	<u>4.73</u>	<u>1.34-16.76</u>
vs. Routine DES	<u>1.72</u>	<u>0.53-5.59</u>

CI, confidence interval; MACE, major adverse cardiac events; FFR, fractional flow reserve; DES, drug eluting stent; MI, myocardial infarction; TLR, target lesion revascularization.