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Influence of target vessel on prognostic relevance of fractional flow reserve after coronary stenting

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KEYWORDS

- clinical research
- drug-eluting stent
- fractional flow reserve

Abstract

Aims: We sought to investigate the influence of the target vessel on the prognostic relevance of fractional flow reserve (FFR) after percutaneous coronary intervention (PCI).

Methods and results: A total of 835 patients with available FFR after second-generation drug-eluting stent (DES) implantation were included in this study. The primary outcome was target vessel failure (TVF), including cardiac death, target vessel-related myocardial infarction, and clinically driven target vessel revascularisation. The target vessel was the left anterior descending artery (LAD) in 603 patients (72.2%) and non-LAD in 232 patients (27.8%). The distribution pattern of post-PCI FFR values was different between the LAD and non-LAD ($p<0.001$). The optimal cut-off values of post-PCI FFR for predicting TVF were 0.82 and 0.88 in the LAD and non-LAD, respectively. The cumulative incidence of TVF was significantly higher in patients with lower post-PCI FFR than each cut-off value (10.9% vs 2.5%, hazard ratio [HR] 4.08, 95% confidence interval [CI]: 2.63-6.34, $p<0.001$ in LAD; 8.0% vs 1.9%, HR 6.00, 95% CI: 1.78-20.26, $p=0.004$ in non-LAD).

Conclusions: Higher post-PCI FFR after second-generation DES implantation was associated with better clinical outcomes. Different cut-off values of post-PCI FFR need to be applied according to the target vessel. ClinicalTrials Identifier: NCT01873560

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Abbreviations

AUC	area under the curve
CI	confidence interval
DES	drug-eluting stent
FFR	fractional flow reserve
HR	hazard ratio
IQR	interquartile range
IVUS	intravascular ultrasound
LAD	left anterior descending artery
MI	myocardial infarction
OCT	optical coherence tomography
PCI	percutaneous coronary intervention
QCA	quantitative coronary angiography
TVF	target vessel failure
TVR	target vessel revascularisation

Introduction

The presence of myocardial ischaemia is a key prognostic factor in patients with coronary artery disease. Coronary revascularisation is beneficial only for those with myocardial ischaemia[1]. Fractional flow reserve (FFR) is a standard invasive physiologic index used to define ischaemia-causing coronary artery stenosis[2,3]. In addition to pre-percutaneous coronary intervention (PCI) assessment, previous studies have demonstrated that FFR measured after stent implantation had prognostic implications[4-12]. However, optimal cut-off values of post-PCI FFR ranged widely, from 0.86 to 0.96.

FFR is influenced not only by stenosis severity but also by the amount of perfused myocardium. Therefore, the pressure gradient can be variable according to the supplying myocardium, even in vessels with the same stenosis severity[13]. As the amount of myocardium is significantly larger in the left anterior descending artery (LAD) territory than in the non-LAD territory, the clinical meaning of the same post-PCI FFR value between them can be different. However, the prognostic relevance of post-PCI FFR according to vessel location has not been thoroughly evaluated. We sought to investigate the prognostic relevance of post-PCI FFR and its optimal cut-off value according to the target vessel.

Methods

STUDY POPULATION

This study is based on an international, multicentre, prospective registry to evaluate the prognostic relevance of post-PCI FFR from nine hospitals in Japan and the Republic of Korea. A total of 939 consecutive patients who underwent PCI and post-PCI FFR measurements after angiographically successful stent implantation (residual stenosis <20% by visual estimation) between May 2013 and December 2016 were included in this registry. Exclusion criteria were post-PCI TIMI flow of <3, depressed left ventricular systolic function (ejection fraction <30%), culprit lesion for acute coronary syndrome, graft vessel, collateral feeder, in-stent stenosis, primary myocardial or valvular heart disease, and patients with life expectancy <2 years. Among enrolled patients, 29 had poor FFR data, four patients withdrew from the study, four were lost to follow-up and 67 were treated with bare metal stent or first-generation drug-eluting stent (DES), and were therefore excluded from the current analysis. Finally, a total of 835 patients were included in this study. Among the total study population, 11.4% of patients (95/835) underwent multivessel PCI. In these patients, the target vessel was defined as the vessel with the lowest post-PCI FFR value for the analysis. The study protocol was approved by the ethics committee at each participating centre and was conducted according to the principles of the Declaration of Helsinki (ClinicalTrials.gov Identifier: NCT01873560). All patients provided written informed consent.

INVASIVE CORONARY ANGIOGRAPHY, PCI AND MEASUREMENT OF FFR

Invasive coronary angiography was performed according to standard techniques. During PCI, type of DES, stenting techniques, and the use of additional imaging devices, such as intravascular ultrasound (IVUS) or optical coherence tomography (OCT), were at the operator's discretion.

All angiograms were analysed at a core laboratory (Inje University Ilsan Paik Hospital, Koyang, Republic of Korea) in a blinded fashion. With optimal projections, quantitative coronary angiography (QCA) was performed using a validated software programme (CAAS II; Pie Medical Imaging, Maastricht, the Netherlands).

FFR was measured using a 5-7 Fr guide catheter and a pressure sensor guidewire (St. Jude Medical, St. Paul, MN, USA, or Volcano, San Diego, CA, USA), as previously described[14]. To induce hyperaemia, a continuous infusion of adenosine (140 μg/kg/min) was used in most patients. Intracoronary administration of papaverine, nicorandil or adenosine was used in 189 patients.

DATA COLLECTION, FOLLOW-UP OF PATIENTS, AND STUDY ENDPOINTS

Patient demographic data, cardiovascular risk factors and clinical diagnoses were recorded at the time of index PCI. Clinical follow-up was performed at 1, 6, 12 and 24 months by outpatient clinical visits or telephone contact. The median follow-up duration of the study population was 710 (391-744) days. An external clinical events committee reviewed and adjudicated all relevant medical records for any clinical events.

The primary outcome was target vessel failure (TVF), defined as a composite of cardiac death, target vessel-related myocardial infarction (MI) and clinically driven target vessel revascularisation (TVR) up to two years. All deaths were considered cardiac unless an undisputed non-cardiac cause was present. Periprocedural MI was not counted for clinical outcome. Clinically driven revascularisation was defined as repeat revascularisation in the presence of a diameter stenosis ≥50% with at least one of the following: 1) recurrence of anginal symptoms; 2) positive non-invasive test; 3) positive invasive physiologic test; or 4) presence of diameter stenosis ≥70%, even in the absence of other criteria.

STATISTICAL ANALYSIS

Categorical variables are presented as numbers and relative frequencies. Continuous variables are presented as means and standard deviations or medians with interquartile ranges (IQR) according to their distribution. The Student's t-test and Wilcoxon signed-rank test were performed for comparison of continuous variables according to the distribution of variables. The Kolmogorov-Smirnov test was used to compare the distribution pattern of post-PCI FFR values of the LAD and non-LAD. Linear by linear associations of categorical variables were evaluated using the chi-square test for trends. The optimal cut-off values of post-PCI FFR for predicting clinical outcomes were calculated based on maximising the sum of sensitivity and specificity of each index, using receiver operating characteristic (ROC) curve analysis.

Kaplan-Meier analysis was performed to calculate the cumulative incidence of clinical outcomes and the log-rank test for comparison of group differences. Univariate and multivariate adjusted Cox proportional hazard regression models, stratified by each included centre, were used to calculate the hazard ratio (HR) and 95% confidence interval (CI). The following patient characteristics were included in a multivariate adjusted Cox proportional hazards regression model: age, sex, hypertension, diabetes mellitus, hypercholesterolaemia, chronic kidney disease, previous MI, current smoking, left ventricular dysfunction and clinical diagnosis. The multivariate Cox proportional hazards regression analysis stratified by each included centre was performed to identify the independent predictors of TVF. Covariates that were considered clinically reliable or were associated with TVF (univariate analysis, p-value <0.1) were included in the model. All p-values were two-sided, and p<0.05 was considered statistically significant. The statistical package R, version 3.4.0 (R Foundation for Statistical Computing, Vienna, Austria) was used for statistical analysis.

Results

PATIENT AND LESION CHARACTERISTICS

Baseline characteristics are presented in **Table 1**. Among 835 patients, 651 patients (78.0%) were male and the median age was 64.0 (56.0-72.0) years. A total of 135 patients (16.2%) demonstrated a post-PCI FFR <0.80. Post-PCI FFR values were not significantly different between patients with acute coronary syndrome and those with stable angina (0.85 [0.82-0.90] vs 0.85 [0.81-0.88], p=0.061 in LAD; 0.92 [0.86-0.97] vs 0.91 [0.85-0.96], p=0.298 in non-LAD). Coronary imaging, such as IVUS or OCT, was used in 479 (57.4%) patients for stent optimisation. During post-PCI FFR measurement, four cases (0.5%) of complications occurred (three cases of coronary spasm, and one case of coronary thrombosis).

The target vessel was the LAD in 603 patients (72.2%). Although the angiographic stenosis was more severe in the non-LAD group than in the LAD group (diameter stenosis 70.0% [63.0-77.1] vs 64.0% [57.0-73.0], p<0.001), baseline FFR was higher in the non-LAD group (0.72 [0.63-0.78] in non-LAD vs 0.70 [0.62-0.76] in LAD, p=0.018) **(Table 2)**. After stent implantation, there was no difference in angiographic residual stenosis between the two groups. However, post-PCI FFR was higher in the non-LAD group than in the LAD group (0.92 [0.85-0.96] vs 0.85 [0.81-0.89], p<0.001) **(Table 2)**. The distribution pattern of post-PCI FFR values was significantly different between the LAD and non-LAD groups (p<0.001) **(Figure 1, Table 2)**.

Table 1. Baseline characteristics of study population (N=835).

General characteristics	
Age, years	64.0 (56.0-72.0)
Male	651 (78.0)
Cardiovascular risk factors	
Hypertension	512 (61.3)
Diabetes mellitus	295 (35.3)
Hypercholesterolaemia	422 (50.7)
Current smoker	230 (27.6)
Chronic kidney disease*	68 (8.2)
Previous MI	65 (7.8)
Clinical presentations	
Acute coronary syndrome	383 (45.9)
Stable angina	452 (54.1)
Target vessel	
LAD	603 (72.2)
Proximal	396 (47.4)
LCX	90 (10.8)
RCA	142 (17.0)

Values are median (interquartile ranges, 25th-75th) or n (%). *Chronic kidney disease is defined as previous history of chronic kidney disease or serum creatinine ≥2.0 mg/dL. LAD: left anterior descending artery; LCX: left circumflex artery; MI: myocardial infarction; RCA: right coronary artery

CLINICAL OUTCOMES ACCORDING TO BASELINE AND POST-PCI FFR

There was no association between baseline FFR values and the rates of TVF (p for trend=0.978) **(Figure 2A)**. On the contrary, post-PCI FFR demonstrated a significant association with TVF. The rates of TVF were increased along with a decrease of post-PCI FFR (p for trend <0.001; adjusted HR 1.08 per 0.01, 95% CI: 1.06-1.11, p<0.001) **(Figure 2B)**. Among 10 TVRs in patients with post-PCI FFR below 0.80, four cases occurred in stented segments.

OPTIMAL CUT-OFF VALUE OF POST-PCI FFR

The optimal cut-off values of post-PCI FFR for predicting TVF are presented in **Figure 3**. In all vessels, the optimal cut-off value of post-PCI FFR was 0.84, and sensitivity, specificity and area under the curve (AUC) were 65.1%, 61.3% and 0.696, respectively. The optimal cut-off values of post-PCI FFR in the LAD and non-LAD were different: 0.82 (sensitivity 67.6%, specificity 61.2%, AUC 0.704) and 0.88 (sensitivity 66.1%, specificity 64.5%, AUC 0.721), respectively. The rates of achieving optimal cut-off values according to the target vessel were 65.5% and

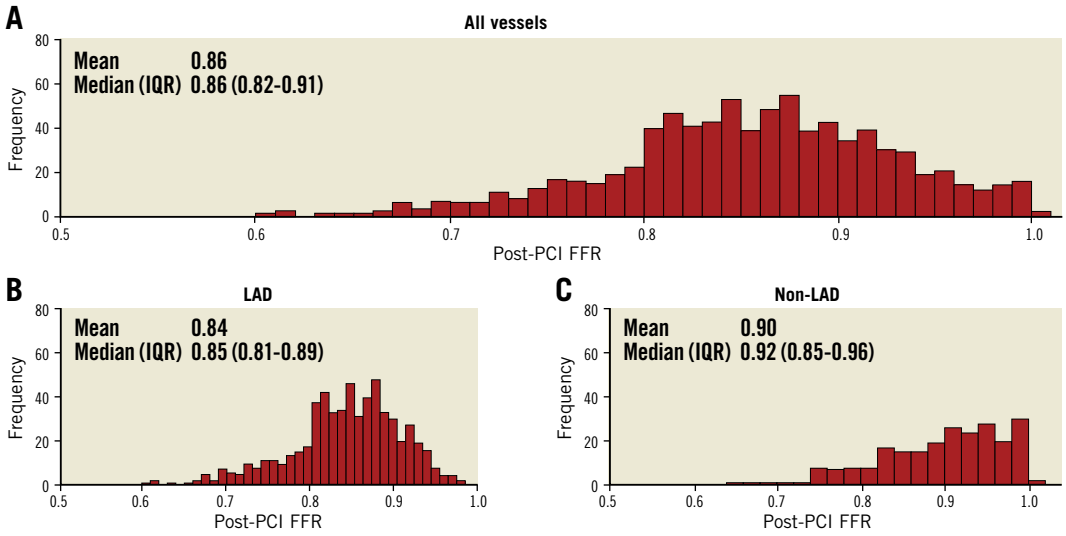

Figure 1. *Distributions of post-PCI FFR. Distributions of post-PCI FFR in all vessels (A), LAD (B) and non-LAD (C) are shown. FFR: fractional flow reserve; IQR: interquartile range; LAD: left anterior descending artery; PCI: percutaneous coronary intervention*

Table 2. Angiographic and functional characteristics.

	All vessels N=835	LAD N=603	Non-LAD N=232	*p*-value*
Fractional flow reserve				
Baseline¶	0.71 (0.62-0.76)	0.70 (0.62-0.76)	0.72 (0.63-0.78)	0.018
Post PCI	0.86 (0.82-0.91)	0.85 (0.81-0.89)	0.92 (0.85-0.96)	<0.001
Quantitative coronary angiography (baseline)				
Reference vessel diameter, mm	2.79 (2.49-3.13)	2.80 (2.49-3.11)	2.76 (2.48-3.17)	0.735
Minimum lumen diameter, mm	0.94 (0.69-1.20)	0.98 (0.75-1.23)	0.82 (0.60-1.10)	<0.001
Diameter stenosis, %	66.0 (58.0-75.0)	64.0 (57.0-73.0)	70.0 (63.0-77.1)	<0.001
Lesion length, mm	21.3 (15.0-28.9)	21.8 (15.0-29.5)	20.0 (14.7-27.9)	0.064
Quantitative coronary angiography (post PCI)				
Reference vessel diameter, mm	2.91 (2.64-3.24)	2.89 (2.62-3.23)	2.96 (2.68-3.25)	0.193
Minimum lumen diameter, mm	2.56 (2.30-2.89)	2.54 (2.30-2.89)	2.57 (2.33-2.90)	0.642
Diameter stenosis, %	11.0 (6.6-16.0)	11.0 (6.9-15.5)	11.1 (6.1-16.0)	0.562
Stent length, mm	25.1 (18.2-32.1)	25.6 (18.4-32.4)	24.1 (18.0-31.7)	0.289

Values are median (interquartile ranges, 25th-75th). **p*-value for comparing LAD and non-LAD. ¶Baseline FFR was available in 645 vessels (499 vessels from LAD and 146 vessels from non-LAD). LAD: left anterior descending artery; PCI: percutaneous coronary intervention

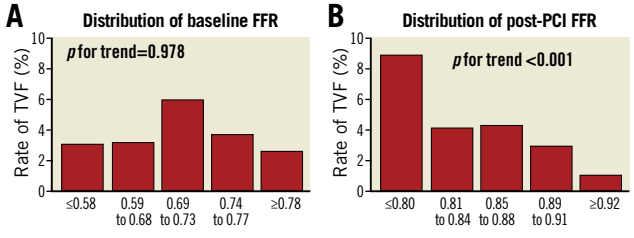

Figure 2. *Clinical outcomes according to baseline and post-PCI FFR. The rates of TVF are shown according to quintiles of baseline FFR (A) and post-PCI FFR (B). FFR: fractional flow reserve; PCI: percutaneous coronary intervention; TVF: target vessel failure*

64.2% in the LAD and non-LAD, respectively. The optimal cut-off values of post-PCI FFR for predicting TVF were not changed after excluding multivessel PCI.

CLINICAL OUTCOMES AND POST-PCI FFR ACCORDING TO THE TARGET VESSEL

With the optimal cut-off value in all vessels, patients with post-PCI FFR ≤0.84 demonstrated significantly higher cumulative incidence of TVF than patients with post-PCI FFR >0.84 (8.3% vs 3.1%; HR 2.51, 95% CI: 1.51-4.16, p<0.001; adjusted HR 2.98, 95% CI: 1.92-4.61, p<0.001) **(Table 3)**. However, when the cut-off value of 0.84 was applied to the non-LAD lesions, there was

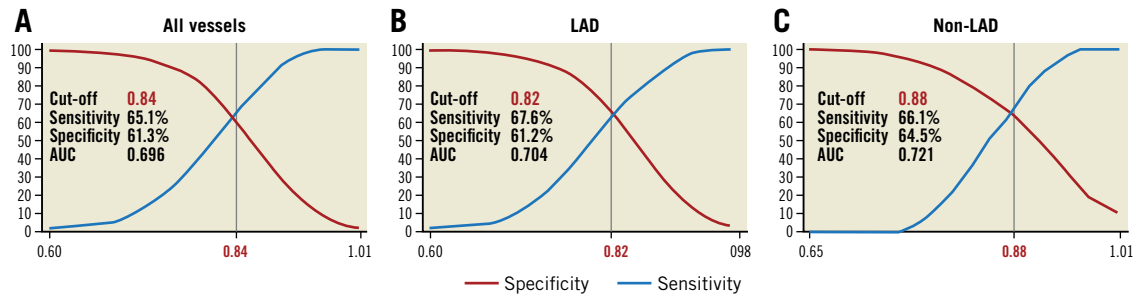

Figure 3. *Optimal cut-off values of post-PCI FFR. Receiver operating characteristic curve analysis was performed to calculate optimal cut-off values of post-PCI FFR in all vessels (A), LAD (B) and non-LAD (C). AUC: area under the curve; FFR: fractional flow reserve; LAD: left anterior descending artery; PCI: percutaneous coronary intervention*

no statistically significant difference in outcomes between the high and low post-PCI FFR groups (HR 2.30, 95% CI: 0.46-11.53, p=0.311; adjusted HR 3.35, 95% CI: 0.62-18.08, p=0.161) **(Supplementary Table 1)**.

When the different cut-off values were used according to the target vessel (LAD 0.82, non-LAD 0.88), the cumulative incidence of TVF was significantly higher in patients with lower post-PCI FFR than each cut-off value (10.9% vs 2.5%, HR 4.08, 95% CI: 2.63-6.34, p<0.001 in LAD; 8.0% vs 1.9%, HR 6.00, 95% CI: 1.78-20.26, p=0.004 in non-LAD) **(Figure 4, Table 3)**. In multivariate analyses, the results were the same as in the unadjusted analyses. These results were not changed after excluding those with multivessel PCI from the analysis **(Supplementary Table 2)**.

The lower post-PCI FFR than each cut-off from the LAD and non-LAD was an independent predictor of TVF (adjusted HR 6.80, 95% CI: 3.33-13.86, p<0.001) **(Supplementary Table 3)**. Neither baseline FFR nor % diameter stenosis before and after PCI was associated with the occurrence of TVF.

Discussion

The current study evaluated the clinical relevance of post-PCI FFR after second-generation DES implantation as well as the influence of the target vessel on the clinical value of post-PCI FFR. The principal findings of this study were as follows. First, both baseline and post-PCI FFR values were higher in the non-LAD group than in the LAD group, and the distribution pattern of post-PCI FFR was different in the LAD and non-LAD. Second, although baseline FFR was not associated with TVF, the rates of TVF increased along with a decrease of post-PCI FFR. Third, optimal cut-off values of post-PCI FFR were different according to the target vessel and were 0.82 and 0.88 in the LAD and non-LAD, respectively. Finally, each cut-off value of post-PCI FFR according to the target vessel was associated with the risk of TVF, and low post-PCI FFR was an independent predictor of TVF.

CURRENT EVIDENCE ON POST-PCI FFR

FFR has been a standard invasive physiologic index used to define the presence of myocardial ischaemia[2,3]. In addition to FFR's role

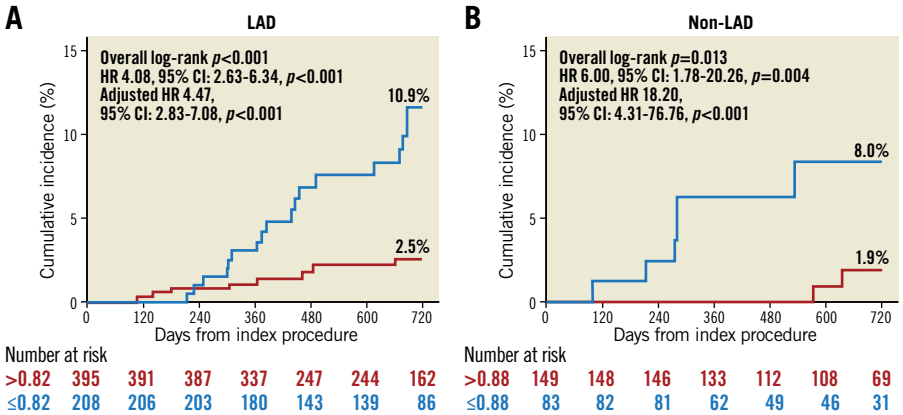

Figure 4. *Cumulative incidence of TVF according to optimal cut-off values of post-PCI FFR. Kaplan-Meier curves of TVF according to the optimal cut-off values of the target vessels are presented. The optimal cut-off values of post-PCI FFR for predicting TVF were 0.82 in the LAD (A) and 0.88 in the non-LAD (B) vessels, respectively. CI: confidence interval; FFR: fractional flow reserve; HR: hazard ratio; LAD: left anterior descending artery; PCI: percutaneous coronary intervention; TVF: target vessel failure*

Table 3. Clinical outcomes according to post-PCI FFR of target vessels.

All vessels	Post-PCI FFR		HR (95% CI)	*p*-value	Adjusted HR (95% CI)	*p*-value
	≤0.84	>0.84				
TVR	15 (6.1%)	13 (3.1%)	1.79 (0.97-3.30)	0.064	1.95 (1.24-3.08)	0.004
MI	1 (0.3%)	0 (0%)	NA	NA	NA	NA
Cardiac death	6 (2.3%)	0 (0%)	NA	NA	NA	NA
TVF	21 (8.3%)	13 (3.1%)	2.51 (1.51-4.16)	<0.001	2.98 (1.92-4.61)	<0.001
LAD	**Post-PCI FFR**		**HR (95% CI)**	***p*-value**	**Adjusted HR (95% CI)**	***p*-value**
	≤0.82	>0.82				
TVR	13 (8.3%)	8 (2.5%)	2.93 (1.81-4.75)	<0.001	3.00 (2.05-4.39)	<0.001
MI	1 (0.5%)	0 (0%)	NA	NA	NA	NA
Cardiac death	5 (2.8%)	0 (0%)	NA	NA	NA	NA
TVF	18 (10.9%)	8 (2.5%)	4.08 (2.63-6.34)	<0.001	4.47 (2.83-7.08)	<0.001
Non-LAD	**Post-PCI FFR**		**HR (95% CI)**	***p*-value**	**Adjusted HR (95% CI)**	***p*-value**
	≤0.88	>0.88				
TVR	5 (6.1%)	2 (1.9%)	4.88 (1.62-14.74)	0.005	13.82 (4.17-45.77)	<0.001
MI	0 (0%)	0 (0%)	NA	NA	NA	NA
Cardiac death	1 (1.9%)	0 (0%)	NA	NA	NA	NA
TVF	6 (8.0%)	2 (1.9%)	6.00 (1.78-20.26)	0.004	18.20 (4.31-76.76)	<0.001

CI: confidence interval; FFR: fractional flow reserve; HR: hazard ratio; LAD: left anterior descending artery; MI: myocardial infarction; NA: not available; PCI: percutaneous coronary intervention; TVF: target vessel failure; TVR: target vessel revascularisation

in pre-PCI treatment decision making, previous studies have also reported the prognostic implications of post-PCI FFR[4-12]. Since Pijls et al reported that post-PCI FFR after bare metal stent implantation was an independent predictor of clinical events at six months[4], many studies, including meta-analyses, have shown that higher post-PCI FFR is associated with better clinical outcomes[4-12]. However, the optimal cut-off value of post-PCI FFR is still controversial, and the proposed values ranged widely, from 0.86 to 0.96[4-12]. This might result from differences in study populations, definition of outcomes, type of stent used, and distribution of included vessels among previous studies.

TARGET VESSEL AND POST-PCI FFR

FFR is a pressure-derived physiologic index influenced not only by lesion severity but also by the amount of coronary flow[15]. Therefore, coronary flow and pressure gradient across the lesion can be greater when the diseased vessel supplies larger myocardium even with the same stenosis severity. In our study, baseline FFR values were lower in the LAD group than in the non-LAD group, despite lower angiographic % diameter stenosis. FFR was still lower in the LAD group than in the non-LAD group after stent implantation with similar residual stenosis. As myocardial mass and coronary flow are greater in the LAD than in the non-LAD, FFR value can be inherently lower in the LAD than in the non-LAD **(Figure 5)**. These results are in line with previous studies which reported that a LAD lesion was an independent predictor of low FFR value[9,10,13,16]. In addition, the distribution pattern of post-PCI FFR was different between the LAD and non-LAD in our study. These results suggest that the clinical meaning of the same post-PCI FFR values between the LAD and non-LAD can be

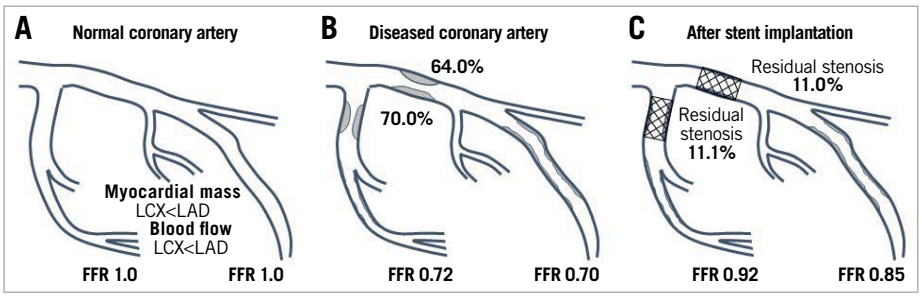

Figure 5. *Stenosis severity and FFR in normal, diseased, and stented vessels. Myocardial mass and coronary blood flow are larger in the LAD territory than in the non-LAD territory (A). Stenosis severity by angiographic diameter stenosis and FFR values from this study, before (B) and after (C) coronary stenting, are presented. FFR: fractional flow reserve; LAD: left anterior descending artery; LCX: left circumflex artery*

different. This may be one of the reasons for various cut-off values of post-PCI FFR in previous studies[4-12]. The current study showed that the optimal cut-off values for predicting TVF could be different in the LAD and in the non-LAD vessels.

CLINICAL RELEVANCE OF POST-PCI FFR ACCORDING TO THE TARGET VESSEL

This study focused on the clinical value of post-PCI FFR according to the target vessel. In our study, the optimal cut-off value of post-PCI FFR derived from all vessels (0.84) could not discriminate the risk of TVF in non-LAD vessels. With different distribution patterns of FFR values according to the target vessel, these results showed the limitations of applying one cut-off value of post-PCI FFR in predicting clinical outcomes after coronary stenting. Recently, Li et al reported the optimal cut-off value of post-PCI FFR in all vessels (0.88) as well as that in the LAD (0.905)[9]. While this report did not describe post-PCI FFR and clinical outcomes according to the target vessel in detail, the optimal cut-off value of post-PCI FFR in all vessels was achieved less frequently in the LAD than in either the left circumflex or right coronary arteries (59.0% vs 85.7%), as in our study. The difference in optimal cut-off values of post-PCI FFR between our study and Li et al's could be because of the difference in study population, lesion and procedural characteristics, and the incidence of clinical events. As the optimal cut-off value of post-PCI FFR is affected by various factors, no single study is able to define the conclusive cut-off value of post-PCI FFR. Taken together, both studies suggest the clinical relevance of applying different post-PCI FFR cut-off values based on different target vessels.

While focusing on the clinical implications of post-PCI FFR according to the target vessel, this study could not explain the influence of interaction between stented and non-stented segments on FFR values and clinical outcomes. However, it is important to understand that there can be complex interactions between stented and non-stented segments for determination of post-PCI FFR and clinical outcomes. A more sophisticated study using pre- and post-PCI FFR and pre- and post-PCI invasive imaging studies in a large number of patients is needed to investigate this relationship clearly. In this context, instantaneous wave-free ratio pullback can be helpful to understand the physiologic contribution of each segment before and after coronary stenting[17].

Limitations

There were several limitations in this study. First, the post-PCI FFR values were not blinded to the physicians. This could be a source of bias as TVR was the main contributor of clinical events. Second, there are inherent limitations of an observational registry study. Third, pullback recordings of post-PCI FFR and intravascular imaging were not mandatory in this study. Therefore, the reasons for suboptimal post-PCI FFR values could not be assessed in all patients. However, as the post-PCI FFR used in this study was measured after clinically and angiographically successful PCI, this study's results provide information on the distribution and clinical relevance of post-PCI FFR in daily practice. Fourth, this study could not provide conclusive optimal cut-off values of post-PCI FFR according to the target vessel due to the relatively small number of patients and events included. Further study is needed to explore the conclusive optimal cut-off values of post-PCI FFR according to the target vessel. Last, the presence of microvascular dysfunction was not systematically assessed. Therefore, this study could not explain the potential influence of microvascular disease on post-PCI FFR.

Conclusions

Higher post-PCI FFR was associated with better clinical outcomes after second-generation DES implantation. Different cut-off values of post-PCI FFR may need to be applied according to the target vessel to optimise clinical outcomes further for patients with coronary artery disease. However, it needs to be emphasised that post-PCI FFR is one of the components that can determine the clinical outcomes in patients with coronary artery disease after stent implantation.

Impact on daily practice

With different distribution patterns of post-PCI FFR values according to the target vessel, optimal cut-off values of post-PCI FFR were different according to the target vessel and were 0.82 and 0.88 in the left anterior descending coronary artery (LAD) and non-LAD, respectively. Each cut-off value of post-PCI FFR according to the target vessel was strongly associated with clinical outcomes. This study suggests the clinical relevance of applying different post-PCI FFR cut-off values based on different target vessels.

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Conflict of interest statement

B-K. Koo and J.M. Lee have received an institutional research grant from St. Jude Medical (Abbott) and Philips Volcano. J-H. Doh has received an institutional research grant from Philips Volcano. J-Y. Hahn has received an institutional research grant from St. Jude Medical (Abbott) and Boston Scientific. The other authors have no conflicts of interest to declare.

References

1. Shaw LJ, Berman DS, Maron DJ, Mancini GB, Hayes SW, Hartigan PM, Weintraub WS, O'Rourke RA, Dada M, Spertus JA, Chaitman BR, Friedman J, Slomka P, Heller GV, Germano G, Gosselin G, Berger P, Kostuk WJ, Schwartz RG, Knudtson M, Veledar E, Bates ER, McCallister B, Teo KK, Boden WE; COURAGE Investigators. Optimal medical therapy with or without percutaneous coronary intervention to reduce ischemic burden: results from

the Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation (COURAGE) trial nuclear substudy. *Circulation.* 2008;117:1283-91.

2. Kim JE, Koo BK. Fractional flow reserve: the past, present and future. *Korean Circ J.* 2012;42:441-6.

3. Neumann FJ, Sousa-Uva M, Ahlsson A, Alfonso F, Banning AP, Benedetto U, Byrne RA, Collet JP, Falk V, Head SJ, Jüni P, Kastrati A, Koller A, Kristensen SD, Niebauer J, Richter DJ, Seferovic PM, Sibbing D, Stefanini GG, Windecker S, Yadav R, Zembala MO; ESC Scientific Document Group. 2018 ESC/EACTS Guidelines on myocardial revascularization. *Eur Heart J.* 2019;40:87-165.

4. Pijls NH, Klauss V, Siebert U, Powers E, Takazawa K, Fearon WF, Escaned J, Tsurumi Y, Akasaka T, Samady H, De Bruyne B; Fractional Flow Reserve (FFR) Post-Stent Registry Investigators. Coronary pressure measurement after stenting predicts adverse events at follow-up: a multicenter registry. *Circulation.* 2002;105:2950-4.

5. Nam CW, Hur SH, Cho YK, Park HS, Yoon HJ, Kim H, Chung IS, Kim YN, Kim KB, Doh JH, Koo BK, Tahk SJ, Fearon WF. Relation of fractional flow reserve after drug-eluting stent implantation to one-year outcomes. *Am J Cardiol.* 2011;107:1763-7.

6. Johnson NP, Toth GG, Lai D, Zhu H, Acar G, Agostoni P, Appelman Y, Arslan F, Barbato E, Chen SL, Di Serafino L, Dominguez-Franco AJ, Dupouy P, Esen AM, Esen OB, Hamilos M, Iwasaki K, Jensen LO, Jimenez-Navarro MF, Katritsis DG, Kocaman SA, Koo BK, Lopez-Palop R, Lorin JD, Miller LH, Muller O, Nam CW, Oud N, Puymirat E, Rieber J, Rioufol G, Rodés-Cabau J, Sedlis SP, Takeishi Y, Tonino PA, Van Belle E, Verna E, Werner GS, Fearon WF, Pijls NH, De Bruyne B, Gould KL. Prognostic value of fractional flow reserve: linking physiologic severity to clinical outcomes. *J Am Coll Cardiol.* 2014;64:1641-54.

7. Doh JH, Nam CW, Koo BK, Lee SY, Choi H, Namgung J, Kwon SU, Kwak JJ, Kim HY, Choi WH, Lee WR. Clinical Relevance of Poststent Fractional Flow Reserve After Drug-Eluting Stent Implantation. *J Invasive Cardiol.* 2015;27:346-51.

8. Agarwal SK, Kasula S, Hacioglu Y, Ahmed Z, Uretsky BF, Hakeem A. Utilizing Post-Intervention Fractional Flow Reserve to Optimize Acute Results and the Relationship to Long-Term Outcomes. *JACC Cardiovasc Interv.* 2016;9:1022-31.

9. Li SJ, Ge Z, Kan J, Zhang JJ, Ye F, Kwan TW, Santoso T, Yang S, Sheiban I, Qian XS, Tian NL, Rab TS, Tao L, Chen SL. Cutoff Value and Long-Term Prediction of Clinical Events by FFR Measured Immediately After Implantation of a Drug-Eluting Stent in Patients With Coronary Artery Disease: 1- to 3-Year Results From the DKCRUSH VII Registry Study. *JACC Cardiovasc Interv.* 2017;10:986-95.

10. Piroth Z, Toth GG, Tonino PAL, Barbato E, Aghlmandi S, Curzen N, Rioufol G, Pijls NHJ, Fearon WF, Jüni P, De Bruyne B. Prognostic Value of Fractional Flow Reserve Measured Immediately After Drug-Eluting Stent Implantation. *Circ Cardiovasc Interv.* 2017 Aug;10(8).

11. Rimac G, Fearon WF, De Bruyne B, Ikeno F, Matsuo H, Piroth Z, Costerousse O, Bertrand OF. Clinical value of post-percutaneous coronary intervention fractional flow reserve value: A systematic review and meta-analysis. *Am Heart J.* 2017;183:1-9.

12. Leesar MA, Satran A, Yalamanchili V, Helmy T, Abdul-Waheed M, Wongpraparut N. The impact of fractional flow reserve measurement on clinical outcomes after transradial coronary stenting. *EuroIntervention.* 2011;7:917-23.

13. Leone AM, De Caterina AR, Basile E, Gardi A, Laezza D, Mazzari MA, Mongiardo R, Kharbanda R, Cuculi F, Porto I, Niccoli G, Burzotta F, Trani C, Banning AP, Rebuzzi AG, Crea F. Influence of the amount of myocardium subtended by a stenosis on fractional flow reserve. *Circ Cardiovasc Interv.* 2013;6:29-36.

14. De Bruyne B, Pijls NH, Kalesan B, Barbato E, Tonino PA, Piroth Z, Jagic N, Mobius-Winkler S, Rioufol G, Witt N, Kala P, MacCarthy P, Engström T, Oldroyd KG, Mavromatis K, Manoharan G, Verlee P, Frobert O, Curzen N, Johnson JB, Jüni P, Fearon WF: FAME 2 Trial Investigators. Fractional flow reserve-guided PCI versus medical therapy in stable coronary disease. *N Engl J Med.* 2012;367:991-1001.

15. De Bruyne B, Sarma J. Fractional flow reserve: a review: invasive imaging. *Heart.* 2008;94:949-59.

16. Park SJ, Kang SJ, Ahn JM, Shim EB, Kim YT, Yun SC, Song H, Lee JY, Kim WJ, Park DW, Lee SW, Kim YH, Lee CW, Mintz GS, Park SW. Visual-functional mismatch between coronary angiography and fractional flow reserve. *JACC Cardiovasc Interv.* 2012;5:1029-36.

17. Kikuta Y, Cook CM, Sharp ASP, Salinas P, Kawase Y, Shiono Y, Giavarini A, Nakayama M, De Rosa S, Sen S, Nijjer SS, Al-Lamee R, Petraco R, Malik IS, Mikhail GW, Kaprielian RR, Wijntjens GWM, Mori S, Hagikura A, Mates M, Mizuno A, Hellig F, Lee K, Janssens L, Horie K, Mohdnazri S, Herrera R, Krackhardt F, Yamawaki M, Davies J, Takebayashi H, Keeble T, Haruta S, Ribichini F, Indolfi C, Mayet J, Francis DP, Piek JJ, Di Mario C, Escaned J, Matsuo H, Davies JE. Pre-Angioplasty Instantaneous Wave-Free Ratio Pullback Predicts Hemodynamic Outcome In Humans With Coronary Artery Disease: Primary Results of the International Multicenter iFR GRADIENT Registry. *JACC Cardiovasc Interv.* 2018;11:757-67.

Supplementary data

Supplementary Table 1. TVF according to cut-off values of post-PCI FFR.

Supplementary Table 2. Clinical outcomes according to post-PCI FFR of target vessels, excluding patients with multivessel PCI.

Supplementary Table 3. Independent predictors of TVF and TLR.

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Supplementary data

Supplementary Table 1. TVF according to cut-off values of post-PCI FFR.

FFR 0.82	**HR (95% CI)**	***p*-value**	**Adjusted HR (95% CI)**	***p*-value**
All vessels	3.96 (2.37-6.63)	<0.001	4.59 (2.93-7.20)	<0.001
LAD	4.08 (2.63-6.34)	<0.001	4.47 (2.83-7.08)	<0.001
Non-LAD	3.86 (0.71-20.96)	0.117	5.90 (0.85-41.08)	0.073
FFR 0.84	**HR (95% CI)**	***p*-value**	**Adjusted HR (95% CI)**	***p*-value**
All vessels	2.51 (1.51-4.16)	<0.001	2.98 (1.92-4.61)	<0.001
LAD	2.55 (1.62-4.00)	<0.001	2.84 (1.93-4.17)	<0.001
Non-LAD	2.30 (0.46-11.53)	0.311	3.35 (0.62-18.08)	0.161
FFR 0.88	**HR (95% CI)**	***p*-value**	**Adjusted HR (95% CI)**	***p*-value**
All vessels	3.55 (2.07-6.09)	<0.001	4.82 (2.78-8.35)	<0.001
LAD	2.73 (1.64-4.56)	<0.001	2.79 (1.91-4.08)	<0.001
Non-LAD	6.00 (1.78-20.26)	0.004	18.20 (4.31-76.76)	<0.001

CI: confidence interval; FFR: fractional flow reserve; HR: hazard ratio; LAD: left anterior descending artery; PCI: percutaneous coronary intervention; TVF: target vessel failure

Supplementary Table 2. Clinical outcomes according to post-PCI FFR of target vessels, excluding patients with multivessel PCI.

All vessels	**Post-PCI FFR**		**HR (95% CI)**	***p*-value**	**Adjusted HR (95% CI)**	***p*-value**
	≤0.84	**>0.84**				
TVR	14 (6.6%)	11 (2.9%)	2.09 (1.18-3.71)	0.012	2.35 (1.68-3.29)	<0.001
MI	1 (0.4%)	0 (0%)	NA	NA	NA	NA
Cardiac death	5 (2.2%)	0 (0%)	NA	NA	NA	NA
TVF	19 (8.7%)	11 (2.9%)	2.85 (1.69-4.82)	<0.001	3.55 (2.24-5.63)	<0.001
LAD	**Post-PCI FFR**		**HR (95% CI)**	***p*-value**	**Adjusted HR (95% CI)**	***p*-value**
	≤0.82	**>0.82**				
TVR	12 (8.8%)	7 (2.6%)	3.18 (2.05-4.92)	<0.001	3.27 (2.17-4.92)	<0.001
MI	1 (0.6%)	0 (0%)	NA	NA	NA	NA
Cardiac death	4 (2.5%)	0 (0%)	NA	NA	NA	NA
TVF	16 (11.1%)	7 (2.6%)	4.27 (2.39-7.63)	<0.001	4.73 (2.65-8.45)	<0.001
Non-LAD	**Post-PCI FFR**		**HR (95% CI)**	***p*-value**	**Adjusted HR (95% CI)**	***p*-value**
	≤0.88	**>0.88**				
TVR	5 (7.8%)	1 (1.0%)	11.57 (1.21-110.70)	0.034	25.72 (2.99-221.20)	0.003
MI	0 (0%)	0 (0%)	NA	NA	NA	NA
Cardiac death	1 (2.4%)	0 (0%)	NA	NA	NA	NA
TVF	6 (10.3%)	1 (1.0%)	14.34 (1.53-134.80)	0.020	32.01 (2.78-368.40)	0.005

CI: confidence interval; FFR: fractional flow reserve; HR: hazard ratio; LAD: left anterior descending artery; MI: myocardial infarction; NA: not available; PCI: percutaneous coronary intervention; TVF: target vessel failure; TVR: target vessel revascularisation

Supplementary Table 3. Independent predictors of TVF and TLR.

Independent predictors of TVF	HR (95% CI)	*p*-value
Age, years	1.04 (1.00-1.08)	0.083
Diabetes mellitus	2.31 (0.98-5.44)	0.054
Hypercholesterolaemia	1.91 (1.12-3.26)	0.017
Chronic kidney disease	2.90 (1.13-7.48)	0.027
LV dysfunction (EF <40%)	6.09 (2.44-15.24)	<0.001
Low post-PCI FFR*	6.80 (3.33-13.86)	<0.001
Independent predictors of TLR	**HR (95% CI)**	***p*-value**
Age, years	1.04 (1.02-1.07)	0.002
Diabetes mellitus	2.61 (0.93-7.27)	0.067
Low post-PCI FFR*	2.95 (1.63-5.35)	<0.001

*Low post-PCI FFR was classified by optimal cut-off values which predict TVF; optimal cut-off values were applied according to vessels in which post-PCI FFR was measured.

Variables included in the prediction model were age, hypertension, diabetes mellitus, hypercholesterolaemia, current smoking, chronic kidney disease, previous myocardial infarction, acute coronary syndrome, LV dysfunction, baseline diameter stenosis, baseline FFR, post-PCI diameter stenosis and post-PCI FFR.

CI: confidence interval; EF: ejection fraction; FFR: fractional flow reserve; HR: hazard ratio; LV: left ventricle; PCI: percutaneous coronary intervention; TLR: target lesion revascularisation; TVF: target vessel failure