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ORIGINAL RESEARCH

Differential Impact of Fractional Flow Reserve Measured After Coronary Stent Implantation by Left Ventricular Dysfunction

Ki Hong Choi, MD, PhD,[a,*] Woochan Kwon, MD,[a,*] Doosup Shin, MD,[b] Seung-Hun Lee, MD, PhD,[c] Doyeon Hwang, MD,[d] Jinlong Zhang, MD, PhD,[e] Chang-Wook Nam, MD, PhD,[f] Eun-Seok Shin, MD, PhD,[g] Joon-Hyung Doh, MD, PhD,[h] Shao-Liang Chen, MD, PhD,[i] Tsunekazu Kakuta, MD, PhD,[j] Gabor G. Toth, MD, PhD,[k] Zsolt Piroth, MD, PhD,[l] Abdul Hakeem, MD,[m] Barry F. Uretsky, MD,[n] Yohei Hokama, MD,[o] Nobuhiro Tanaka, MD, PhD,[p] Hong-Seok Lim, MD, PhD,[q] Tsuyoshi Ito, MD,[r] Akiko Matsuo, MD,[s] Lorenzo Azzalini, MD, PhD, MSc,[t] Massoud A. Leesar, MD,[u] Joost Daemen, MD, PhD,[v] Damien Collison, MB, BCh,[w] Carlos Collet, MD, PhD,[x] Bernard De Bruyne, MD, PhD,[x] Bon-Kwon Koo, MD, PhD,[d] Taek Kyu Park, MD,[a] Jeong Hoon Yang, MD, PhD,[a] Young Bin Song, MD, PhD,[a] Joo-Yong Hahn, MD, PhD,[a] Seung-Hyuk Choi, MD, PhD,[a] Hyeon-Cheol Gwon, MD, PhD,[a] Joo Myung Lee, MD, MPH, PhD[a]

ABSTRACT

BACKGROUND Both left ventricular systolic function and fractional flow reserve (FFR) are prognostic factors after percutaneous coronary intervention (PCI). However, how these prognostic factors are inter-related in risk stratification of patients after PCI remains unclarified.

OBJECTIVES This study evaluated differential prognostic implication of post-PCI FFR according to left ventricular ejection fraction (LVEF).

METHODS A total of 2,965 patients with available LVEF were selected from the POST-PCI FLOW (Prognostic Implications of Physiologic Investigation After Revascularization with Stent) international registry of patients with post-PCI FFR measurement. The primary outcome was a composite of cardiac death or target-vessel myocardial infarction (TVMI) at 2 years. The secondary outcome was target-vessel revascularization (TVR) and target vessel failure, which was a composite of cardiac death, TVMI, or TVR.

RESULTS Post-PCI FFR was independently associated with the risk of target vessel failure (per 0.01 decrease: HR_{adj}: 1.029; 95% CI: 1.009-1.049; $P = 0.005$). Post-PCI FFR was associated with increased risk of cardiac death or TVMI (HR_{adj}: 1.145; 95% CI: 1.025-1.280; $P = 0.017$) among patients with LVEF ≤40%, and with that of TVR in patients with LVEF >40% (HR_{adj}: 1.028; 95% CI: 1.005-1.052; $P = 0.020$). Post-PCI FFR ≤0.80 was associated with increased risk of cardiac death or TVMI in the LVEF ≤40% group and with that of TVR in LVEF >40% group. Prognostic impact of post-PCI FFR for the primary outcome was significantly different according to LVEF ($P_{interaction} = 0.019$).

CONCLUSIONS Post-PCI FFR had differential prognostic impact according to LVEF. Residual ischemia by post-PCI FFR ≤0.80 was a prognostic indicator for cardiac death or TVMI among patients with patients with LVEF ≤40%, and it was associated with TVR among patients with patients with LVEF>40%. (Prognostic Implications of Physiologic Investigation After Revascularization with Stent [POST-PCI FLOW]; NCT04684043) (JACC: Asia 2024;4:229-240)

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ABBREVIATIONS AND ACRONYMS

FFR = fractional flow reserve

LVEF = left ventricular ejection fraction

PCI = percutaneous coronary intervention

TVF = target vessel failure

TVMI = target-vessel myocardial infarction

TVR = target-vessel revascularization

Ischemic heart disease is a common underlying cause of heart failure with reduced left ventricular ejection fraction (LVEF). Previous studies presented that patients with significant coronary artery disease and left ventricular (LV) systolic dysfunction have higher risk of mortality, and LV systolic dysfunction is one of the most significant predictors for adverse cardiac events after percutaneous coronary intervention (PCI).[1] Long-term follow-up results from the STICH (Surgical Treatment for Ischemic Heart Failure) trial demonstrated that surgical revascularization improved long-term survival and angina symptoms more than medical treatment alone in patients with severe LV systolic dysfunction.[2,3] A recent substudy from the ISCHEMIA (International Study of Comparative Health Effectiveness with Medical and Invasive Approaches) trial showed that initial revascularization by PCI or bypass surgery had better event-free survival than conservative strategy among patients with moderate LV systolic dysfunction (LVEF 35%-45%).[4] Furthermore, previous studies consistently identified that FFR-guided decision was associated with lower risks of adverse events compared with angiography-guided decision even in patients with LV systolic dysfunction.[5-7] These results support the importance of ischemia-directed revascularization especially for patients with significant myocardial ischemia and LV systolic dysfunction.

However, it should be noted that ischemia-directed revascularization does not always result in ischemia-resolving revascularization.[8] Previous studies consistently reported that residual ischemia defined by post-PCI fractional flow reserve (FFR) ≤0.80 is common even after angiographically successful PCI, and post-PCI FFR is an independent predictor of adverse cardiac events after PCI.[9-12] Nevertheless, predictability of post-PCI FFR alone was reported to be low,[13,14] and the optimal cutoff values ranged widely according to study population and definition of clinical events.[9-12] This leads to the hypothesis that post-PCI FFR may interact with other clinical factors, and prognostic impact of residual ischemia defined by post-PCI FFR ≤0.80 would be different according to underlying clinical characteristics, especially the presence of LV systolic dysfunction.

In this regard, the current study sought to evaluate the clinically relevant question of whether residual ischemia defined by post-PCI FFR ≤0.80 would have differential prognostic impact according to presence of LV systolic dysfunction.

METHODS

STUDY POPULATION. The POST-PCI FLOW (Prognostic Implications of Physiologic Investigation After Revascularization with Stent) registry is the international patient-level pooled registry of patients who underwent FFR measurement after PCI using drug-

From the [a]Division of Cardiology, Department of Internal Medicine, Heart Vascular Stroke Institute, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea; [b]Division of Cardiology, Department of Internal Medicine, Duke University Medical Center, Durham, North Carolina, USA; [c]Division of Cardiology, Department of Internal Medicine, Heart Center, Chonnam National University Hospital, Chonnam National University Medical School, Gwangju, Korea; [d]Department of Internal Medicine and Cardiovascular Center, Seoul National University Hospital, Seoul, Korea; [e]Department of Cardiology, The Second Affiliated Hospital, School of Medicine, Zhejiang University, Hangzhou, China; [f]Department of Medicine, Keimyung University Dongsan Medical Center, Daegu, Korea; [g]Department of Cardiology, Ulsan University Hospital, University of Ulsan College of Medicine, Ulsan, Korea; [h]Department of Medicine, Inje University Ilsan-Paik Hospital, Goyang, Korea; [i]Division of Cardiology, Nanjing First Hospital, Nanjing Medical University, Nanjing, China; [j]Division of Cardiovascular Medicine, Tsuchiura Kyodo General Hospital, Ibaraki, Japan; [k]University Heart Centre Graz, Medical University Graz, Austria; [l]Gottsegen National Cardiovascular Centre, Budapest, Hungary; [m]Division of Cardiovascular Diseases and Hypertension, Robert Wood Johnson Medical School, Rutgers University, New Brunswick, New Jersey, USA; [n]Central Arkansas VA Health System/University of Arkansas for Medical Sciences, Little Rock, Arkansas, USA; [o]Department of Cardiology, Tokyo Medical University Hachioji Medical Center, Tokyo, Japan; [p]Department of Cardiology, Ajou University School of Medicine, Suwon, Korea; [q]Department of Cardio-Renal Medicine and Hypertension, Nagoya City University Graduate School of Medical Sciences, Nagoya, Japan; [r]Department of Cardiology, Kyoto Second Red Cross Hospital, Kyoto, Japan; [s]Division of Cardiology, Department of Medicine, University of Washington, Seattle, Washington, USA; [t]Division of Cardiovascular Diseases, University of Alabama, Birmingham, Alabama, USA; [u]Department of Interventional Cardiology, Thoraxcenter, Erasmus University Medical Centre, Rotterdam, the Netherlands; [v]West of Scotland Regional Heart and Lung Centre, Golden Jubilee National Hospital, Glasgow, United Kingdom; [w]Cardiovascular Center Aalst, Aalst, Belgium; and the [x]Department of Cardiology, University of Lausanne, Switzerland.
*Drs Ki Hong Choi and Woochan Kwon contributed equally to this work.
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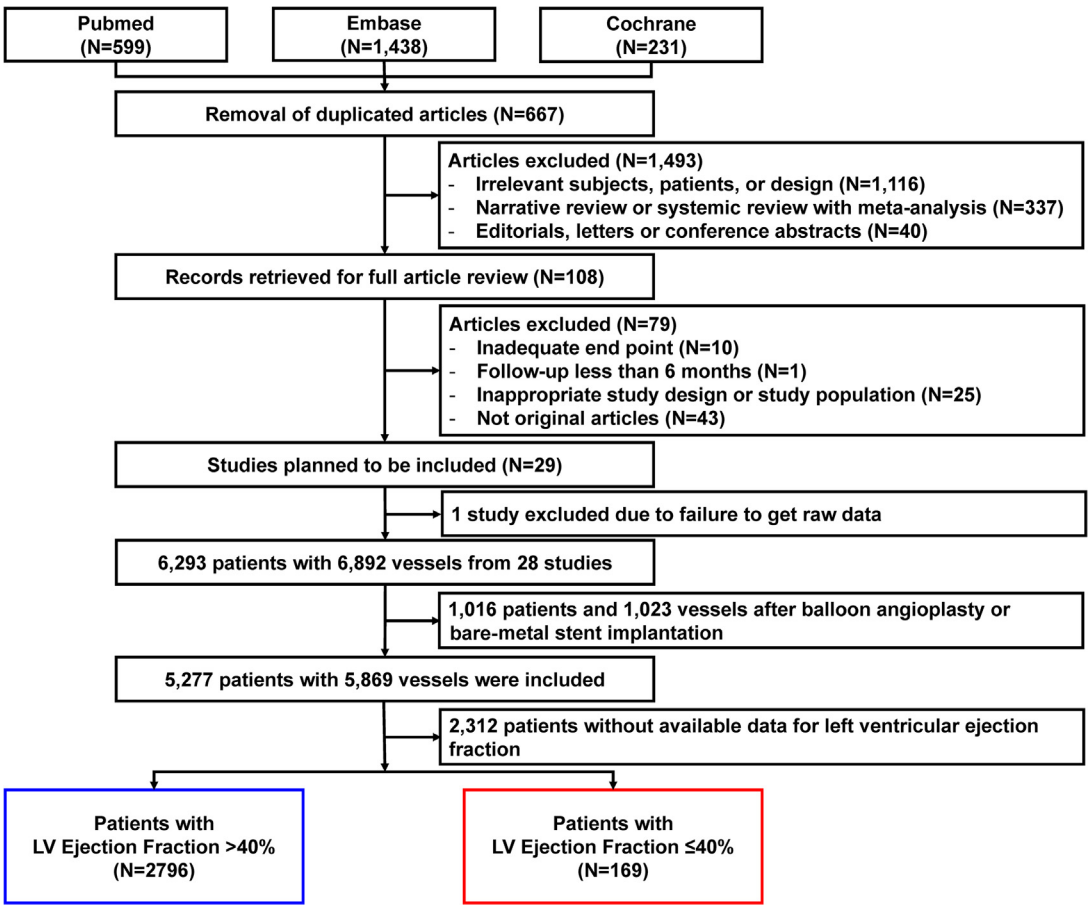
FIGURE 1 Study Flow



Study flow following the guideline of PRISMA-IPD (Preferred Reporting Items for Systematic Review and Meta-analysis of Individual Participant Data). Among the total population of the POST-PCI FLOW (Prognostic Implications of Physiologic Investigation After Revascularization with Stent) registry, 1,424 patients who were not available data for left ventricular (LV) ejection fraction were excluded, and the remaining 2,965 patients were stratified according to the presence of LV systolic dysfunction.

eluting stents. Studies were included if they met the following prespecified criteria: 1) PCI with drug-eluting stents (DES); 2) post-PCI FFR measured with a pressure wire at the end of the procedure; 3) clinical follow-up for at least 6 months; and 4) clinical outcomes data including all-cause death, cardiac death, target vessel myocardial infarction (TVMI), and target vessel revascularization (TVR). Demographics, clinical history and risk factors, and catheterization data (angiographic and physiologic) were aggregated using standardized definitions for variables. Among the studies meeting the inclusion criteria, individual patient-level data were provided from 28 studies from 17 cohorts (Supplemental Table 1). The detailed characteristics of the registry have been previously published.[12] Briefly, a total of 5,277 patients with 6,892 vessels were included, and median follow-up duration of pooled population was 730.0 days (Q1, Q3: 693.0, 760.0 days). Supplemental Table 2 summarizes the detailed profile of included patient cohorts.

The current study was a prespecified substudy of the POST-PCI FLOW registry. For the current analysis, 2,312 patients without available LVEF were additionally excluded, and the remaining 2,965 patients were stratified according to the presence of LV systolic dysfunction, defined by LVEF ≤40% (**Figure 1**). LVEF was obtained from echocardiography and was calculated using the biplane Simpson technique, M-mode, or visual estimation. All processes followed the Preferred Reporting Items for Systematic Review and Meta-analysis of Individual Participant Data

(PRISMA-IPD).[15] The study protocol was approved by the institutional review board at Seoul National University Hospital and conducted under the principles of the Declaration of Helsinki (NCT04684043).

INVASIVE CORONARY ANGIOGRAPHY AND MEASUREMENT OF FFR. Invasive coronary angiography was performed according to standard techniques. Minimal lumen diameter, reference vessel size, lesion length, and percent diameter stenosis (%DS) were analyzed before and after PCI. All coronary physiologic measurements were performed after diagnostic angiography and after completion of the PCI procedure. All measurement were in the native coronary artery. In case of ST-segment elevation myocardial infarction (MI), post-PCI FFR was measured in the noninfarct-related arteries. Hyperemic proximal aortic pressure (Pa) and distal coronary arterial pressure (Pd) were obtained during sustained hyperemia, and FFR was calculated by the mean of Pd/Pa during maximum hyperemia, as previously described.[16] Hyperemia was induced according to standard protocol by preference of participating centers.[16] Post-PCI FFR was measured at the distal segment of a stented vessel. Residual ischemia after PCI was defined by post-PCI FFR ≤0.80.[17]

STUDY OUTCOMES. The primary outcome was a composite of cardiac death or TVMI over 2 years. Secondary outcomes were all-cause death, cardiac death, TVMI, TVR, and target vessel failure (TVF) over 2 years. TVF was defined as a composite of cardiac death, TVMI, and TVR. All clinical outcomes were defined according to the Academic Research Consortium, including the addendum to the definition of MI.[18] All deaths were considered cardiac unless an undisputed noncardiac cause was present. Spontaneous MI was defined as the recurrence of symptoms and the presence of electrocardiographic changes in association with a rise in cardiac biomarker levels above the upper limit of normal, and periprocedural MI was not included as a clinical outcome. TVMI was defined as an MI that occurred by any lesion in the same target vessel. TVR was defined as any unplanned repeat revascularization in the target vessel.

STATISTICAL ANALYSIS. Continuous variables were summarized as mean ± SD, and categorical variables were presented as counts (percentages). Data was analyzed at the patient level. Among patients with multivessel revascularization, the vessel with the lowest post-PCI FFR value was selected as the representative vessel for the patient. The cumulative incidence of clinical outcomes was presented using Kaplan-Meier estimates, and the log-rank test compared group differences. The HR and 95% CI were calculated from a mixed-effects Cox proportional hazard regression model with registry identifiers included as a random effect. Estimated variance of random effects (τ^2) was calculated to assess heterogeneity. The assumption of proportionality was tested using Schoenfeld residuals and log-minus-log plot, and the Cox proportional hazard models for all clinical outcomes satisfied the proportional hazards assumption. For calculating the multivariable-adjusted HR and its 95% CI, the following variables were included in the Cox proportional hazards regression model: age, sex, hypertension, diabetes mellitus, dyslipidemia, previous history of MI, acute coronary syndrome, and post-PCI %DS. In the current study, some patients had missing values in quantitative coronary angiography data. To minimize the sample size loss, the median imputation of the post-PCI %DS for missing value was performed in the multivariable analysis. Stratified analysis was performed on the basis of LVEF (<40% vs ≥40%), and the test for interaction of LVEF and post-PCI FFR for the cardiac death or TVMI was performed using Cox proportional hazard regression model. The association of post-PCI FFR with the risk of cardiac death or TVMI was presented graphically with penalized spline with df = 3. The optimal cutoff value of post-PCI FFR for outcomes stratified by LVEF was calculated based on maximizing the difference of log-rank statistics. All probability values were 2-sided, and *P* values <0.05 were considered statistically significant. Statistical analyses were performed using R Statistical Software version 4.1.2 (R Foundation for Statistical Computing).

RESULTS

BASELINE CHARACTERISTICS OF PATIENTS AND LESIONS. Among the study population, 169 patients (5.7%) had LVEF ≤40% and 385 patients (13.0%) showed post-PCI FFR ≤0.80. The median value of LVEF and post-PCI FFR in the present cohort were 62.0 (Q1, Q3: 56.0, 67.0) and 0.88 (Q1, Q3: 0.84, 0.93), respectively (Supplemental Figure 1). Patients with LVEF ≤40% showed higher prevalence of history of previous MI and cardiovascular risk factors, and lower proportion of acute coronary syndrome at presentation than patients with LVEF >40% (**Table 1**). Pre-PCI angiographic stenosis severity and FFR were not significantly different between the 2 groups. In both groups, PCI resulted in angiographically successful results with minimal residual stenosis; however, post-PCI %DS was significantly higher in the LVEF >40% group than LVEF ≤40% group. Despite

significant difference in post-PCI %DS between the 2 groups, post-PCI FFR value was similar between the 2 groups as well as the proportion of patients with post-PCI FFR ≤0.80 (**Table 1**). Supplemental Table 3 shows baseline characteristics according to the presence of residual ischemia defined by post-PCI FFR ≤0.80. There were no significant differences in the proportion of cardiovascular risk factors and LVEF between the 2 groups classified by post-PCI FFR ≤0.80.

CLINICAL OUTCOMES ACCORDING TO LV SYSTOLIC DYSFUNCTION AND POST-PCI FFR. When comparing clinical outcomes at 2 years, patients with LVEF ≤40% showed significantly higher risk of cardiac death or TVMI than those without LV systolic dysfunction (8.0% vs 1.9%; adjusted HR: 3.462; 95% CI: 1.684-7.117; $P = 0.001$). The difference was mainly driven by significant difference of cardiac death (6.7% vs 0.9%; adjusted HR: 8.949; 95% CI: 3.924-22.41; $P < 0.001$). Conversely, there was no significant difference in the risk of TVR between the 2 groups (6.0% vs 7.1%; adjusted HR: 0.629; 95% CI: 0.302-1.309; $P = 0.210$) (**Figure 2**, **Table 2**). In comparison of clinical outcomes according to post-PCI FFR, patients with post-PCI FFR ≤0.80 showed significantly higher risk of TVF than those with post-PCI FFR >0.80, mainly driven by a higher risk of TVR (Supplemental Table 4). Optimal cutoff values of post-PCI FFR for cardiac death or TVMI were 0.85 in the LVEF >40% group and 0.81 in the LVEF ≤40% group (Supplemental Figure 2).

DIFFERENTIAL PROGNOSTIC IMPACT OF POST-PCI FFR ACCORDING TO LV SYSTOLIC DYSFUNCTION. Post-PCI FFR was independently associated with the risk of TVF, regardless of LVEF (per 0.01 decrease: adjusted HR: 1.029; 95% CI: 1.009-1.049; $P = 0.005$). However, the increased risk of TVF was mainly caused by increased risk of cardiac death or TVMI in patients with LVEF ≤40% (per 0.01 decrease: adjusted HR: 1.145; 95% CI: 1.025-1.280; $P = 0.017$). Conversely, it was mainly caused by the increased risk of TVR in patients with LVEF >40% (per 0.01 decrease: adjusted HR: 1.028; 95% CI: 1.005-1.052; $P = 0.020$). Prognostic impact of post-PCI FFR was significantly different according to LV systolic dysfunction (interaction $P = 0.019$) or LVEF as a continuous value (interaction $P = 0.008$) for the risk of cardiac death or TVMI at 2 years (**Figure 3**, **Table 3**). Similar results were also shown with the presence of residual ischemia defined by post-PCI FFR ≤0.80. Although post-PCI FFR ≤0.80 was significantly associated with increased risk of TVF than post-PCI FFR >0.80 (12.9% vs 7.7%; adjusted HR: 1.855; 95% CI: 1.276-2.695; $P = 0.001$), the increased risk of TVF was mainly driven by an increased risk of cardiac death or TVMI in patients with LVEF ≤40%. Conversely, post-PCI FFR ≤0.80 was mainly associated with an increased risk of TVR in patients with LVEF >40% (**Figure 4**, **Table 4**). In the subgroup of lesions with left anterior descending artery, consistent results were shown (Supplemental Table 5).

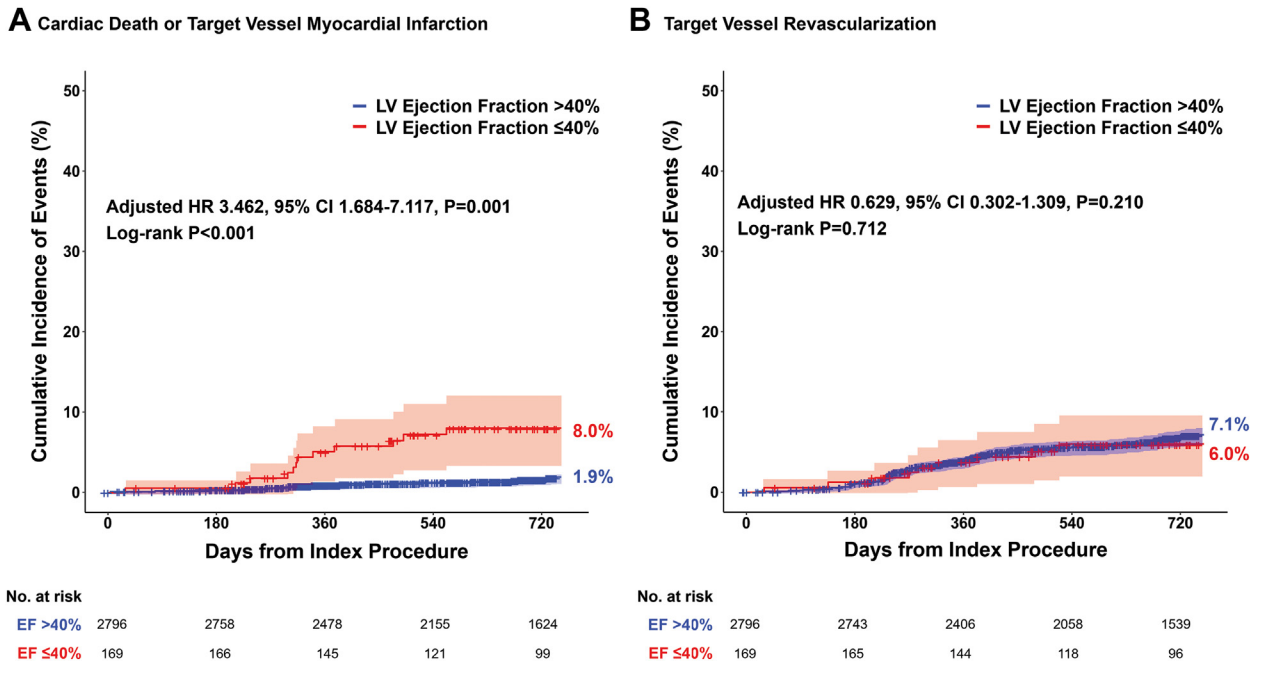
TABLE 1 Baseline Characteristics According to Left Ventricular Dysfunction

	LVEF >40% (n = 2796)	LVEF ≤40% (n = 169)	*P* Value
Demographics			
Age, y	64.3 ± 9.8	65.4 ± 9.5	0.138
Male	2,213 (79.2)	155 (91.7)	<0.001
Cardiovascular risk factors			
Hypertension	2,020 (72.2)	140 (82.8)	0.004
Diabetes mellitus	1,063 (38.0)	83 (49.1)	0.005
Dyslipidemia	1,633 (58.4)	129 (76.3)	<0.001
Current smoking	829 (29.7)	62 (36.7)	0.065
Previous myocardial infarction	378 (13.8)	65 (38.9)	<0.001
Clinical presentation			0.023
Stable ischemic heart disease	1,646 (58.9)	115 (68.0)	
Acute coronary syndrome	1,150 (41.1)	54 (32.0)	
Unstable angina	831 (29.7)	22 (13.0)	
NSTEMI	237 (8.5)	29 (17.2)	
STEMI	82 (2.9)	3 (1.8)	
Left ventricular ejection fraction, %	62.1 ± 7.5	33.2 ± 6.6	<0.001
Location of coronary lesions			<0.001
Left anterior descending artery	1,949 (69.7)	109 (64.5)	
Left circumflex	337 (12.0)	18 (10.7)	
Right coronary artery	499 (17.9)	34 (20.1)	
Unknown	11 (0.4)	8 (4.7)	
Procedural characteristics			
Stents per patient	1.4 ± 0.7	1.4 ± 0.9	0.542
Stent length per patient, mm	33.8 ± 20.7	34.7 ± 21.6	0.603
Use of IVUS or OCT	1,413 (50.5)	53 (31.4)	<0.001
Quantitative coronary angiography, pre-PCI			
Reference diameter, mm	2.89 ± 0.51	2.95 ± 0.52	0.270
Minimum lumen diameter, mm	1.02 ± 0.46	1.20 ± 0.44	0.001
% diameter stenosis	63.7 ± 19.5	65.0 ± 17.8	0.428
Lesion length	22.9 ± 13.6	24.3 ± 14.8	0.241
Quantitative coronary angiography, post-PCI			
Reference diameter, mm	3.02 ± 0.49	3.15 ± 0.48	0.025
Minimum lumen diameter, mm	2.73 ± 0.49	2.83 ± 0.51	0.094
% diameter stenosis	8.3 ± 7.9	5.6 ± 8.2	<0.001
Physiologic Indices			
Pre-PCI FFR	0.69 ± 0.12	0.67 ± 0.13	0.171
Post-PCI FFR	0.88 ± 0.07	0.88 ± 0.07	0.871
Post-PCI FFR ≤0.80	361 (12.9)	24 (14.2)	0.714

Values are mean ± SD or n (%).

FFR = fractional flow reserve; IVUS = intravascular ultrasound; LVEF = left ventricular ejection fraction; NSTEMI = non-ST-segment elevation myocardial infarction; OCT = optical coherence tomography; PCI = percutaneous coronary intervention; STEMI = ST-segment elevation myocardial infarction.

FIGURE 2 Comparison of Clinical Outcomes According to LV Dysfunction



Kaplan-Meier curves and cumulative incidence of (A) cardiac death or target vessel myocardial infarction and (B) target vessel revascularization was compared according to left ventricular (LV) systolic dysfunction.

DISCUSSION

The current study evaluated the differential prognostic impact of post-PCI FFR according to LV systolic dysfunction (Central Illustration). The main findings were as follows. First, the presence of LV systolic dysfunction (LVEF ≤40%) or residual ischemia (post-PCI FFR ≤0.80) were each associated with the increased risk of adverse clinical events after PCI. Second, regardless of the presence of LV systolic dysfunction, post-PCI FFR was independently associated with the risk of TVF. Third, however, the increased risk of TVF was mainly driven by higher risk of cardiac death or TVMI in patients with LV systolic dysfunction. Conversely, it was mainly caused by increased risk of TVR in patients without LV systolic

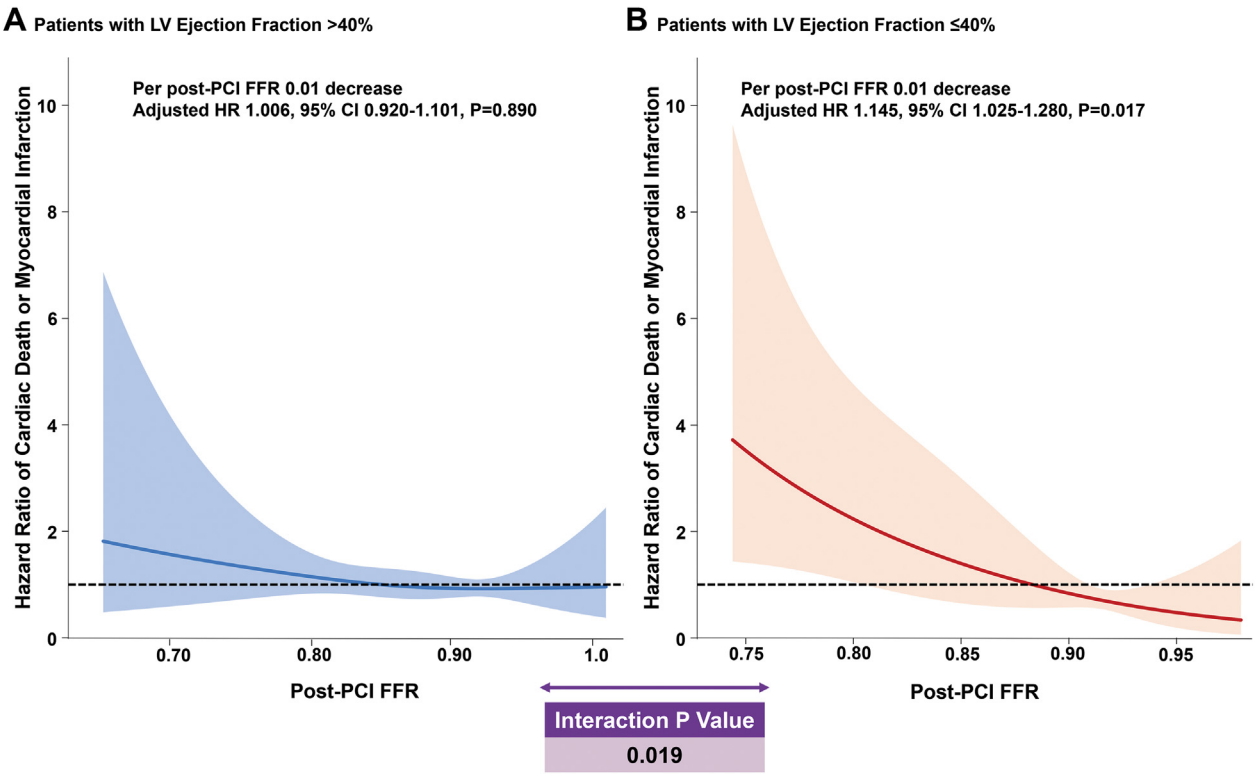
TABLE 2 Clinical Outcomes According to Left Ventricular Dysfunction

	LVEF >40% (n = 2796)	LVEF ≤40% (n = 169)	Univariable HR (95% CI)	*P* Value	τ^2	Multivariable HR[a] (95% CI)	*P* Value	τ^2
Cardiac death or target vessel myocardial infarction	43 (1.9)	12 (8.0)	3.809 (1.659-8.744)	0.002	0.265	3.462 (1.684-7.117)	0.001	0.006
All-cause death	65 (2.8)	17 (11.2)	3.856 (2.055-7.235)	<0.001	0.067	3.537 (1.920-6.155)	<0.001	0.028
Cardiac death	21 (0.9)	10 (6.7)	8.329 (2.290-30.29)	0.001	1.286	8.949 (3.924-20.41)	<0.001	0.036
Target vessel myocardial infarction	24 (1.1)	4 (2.7)	1.862 (0.498-6.955)	0.360	0.861	1.460 (0.367-5.757)	0.590	0.934
Target vessel revascularization	171 (7.1)	9 (6.0)	0.844 (0.374-1.902)	0.680	0.206	0.629 (0.302-1.309)	0.210	0.005
Target vessel failure[b]	195 (8.1)	19 (12.5)	1.591 (0.920-2.753)	0.096	0.088	1.428 (0.843-2.416)	0.185	0.053

The cumulative incidence of clinical outcomes at 2 years is presented as Kaplan-Meier estimates. [a]Adjusted variables for multivariable mixed-effect Cox proportional hazard regression model included age, sex, hypertension, diabetes mellitus, dyslipidemia, previous history of myocardial infarction, and acute coronary syndrome. [b]Target vessel failure was defined as a composite of cardiac death, target vessel myocardial infarction, and target vessel revascularization.

LVEF = left ventricular ejection fraction.

FIGURE 3 Cardiac Death or Target Vessel Myocardial Infarction and Post-PCI FFR According to LV Ejection Fraction



The association of post-PCI fractional flow reserve (FFR) with estimated risk of cardiac death or target vessel myocardial infarction in patients with (A) left ventricular (LV) ejection fraction >40% or (B) LV ejection fraction ≤40%. The estimated risk of clinical events was calculated from multivariable-adjusted, mixed-effects Cox proportional hazards regression, accounting for age, sex, hypertension, diabetes mellitus, dyslipidemia, previous history of myocardial infarction, acute coronary syndrome, and post-PCI percent diameter stenosis. The dotted lines indicate the HR of 1.00. PCI = percutaneous coronary intervention.

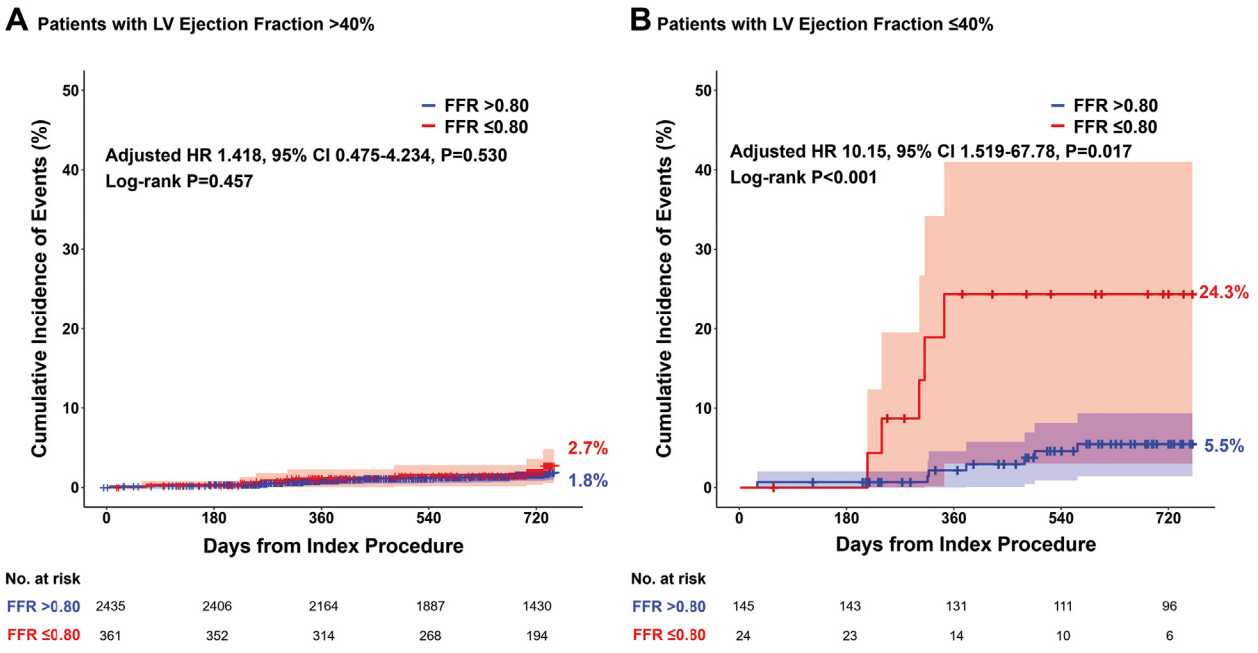
TABLE 3 The Risks of Clinical Events per Post-PCI Fractional Flow Reserve 0.01 Decrease Stratified by Left Ventricular Dysfunction

	Number of Events (%)	Univariable HR (95% CI)	*P* Value	τ^2	Multivariable HR[a] (95% CI)	*P* Value	τ^2
Patients with ejection fraction >40%	n = 2,796						
Cardiac death or target vessel myocardial infarction	43 (1.9)	0.982 (0.923-1.044)	0.560	0.003	1.006 (0.920-1.101)	0.890	0.004
All-cause death	65 (2.8)	1.014 (0.973-1.056)	0.500	<0.001	1.016 (0.977-1.057)	0.420	<0.001
Cardiac death	21 (0.9)	1.017 (0.975-1.060)	0.439	<0.001	1.043 (0.995-1.092)	0.078	<0.001
Target vessel myocardial infarction	24 (1.1)	0.945 (0.866-1.032)	0.210	0.006	0.970 (0.856-1.099)	0.630	0.006
Target vessel revascularization	171 (7.1)	1.026 (1.005-1.048)	0.016	<0.001	1.028 (1.005-1.052)	0.020	<0.001
Target vessel failure[b]	195 (8.1)	1.028 (1.008-1.049)	0.006	<0.001	1.033 (1.011-1.055)	0.003	<0.001
Patients with ejection fraction ≤40%	n = 169						
Cardiac death or target vessel myocardial infarction	12 (8.0)	1.118 (1.021-1.244)	0.016	0.002	1.145 (1.025-1.280)	0.017	<0.001
All-cause death	17 (11.2)	1.121 (1.043-1.204)	0.002	<0.001	1.234 (1.111-1.371)	<0.001	<0.001
Cardiac death	10 (6.7)	1.113 (0.989-1.253)	0.076	0.006	1.186 (0.945-1.488)	0.140	0.009
Target vessel myocardial infarction	4 (2.7)	1.102 (0.980-1.240)	0.100	<0.001	1.038 (0.897-1.201)	0.096	<0.001
Target vessel revascularization	9 (6.0)	1.054 (0.971-1.145)	0.210	<0.001	1.071 (0.951-1.206)	0.260	<0.001
Target vessel failure[b]	19 (12.5)	1.090 (1.024-1.160)	0.007	0.001	1.106 (1.020-1.198)	0.014	<0.001

The cumulative incidence of clinical outcomes at 2 years is presented as Kaplan-Meier estimates. [a]Adjusted variables for multivariable mixed-effect Cox proportional hazard regression model included age, sex, hypertension, diabetes mellitus, dyslipidemia, previous history of myocardial infarction, acute coronary syndrome, and post-percutaneous coronary intervention % diameter stenosis. [b]Target vessel failure was defined as a composite of cardiac death, target vessel myocardial infarction, and target vessel revascularization.

Abbreviation as in Table 1.

FIGURE 4 Cardiac Death or Target Vessel Myocardial Infarction According to Post-PCI FFR and LV Ejection Fraction



Kaplan-Meier curves and cumulative incidence of cardiac death or target vessel myocardial infarction were compared according to binary classification of post-PCI FFR (≤0.80) in patients with (A) LV ejection fraction >40% or (B) LV ejection fraction ≤40%. Abbreviations as in Figure 3.

dysfunction. Fourth, there was significant interaction between post-PCI FFR and LVEF regarding the risk of cardiac death or TVMI after PCI.

CLINICAL RELEVANCE OF POST-PCI FFR AFTER PCI. Over the last decade, ample evidence has shown that post-PCI FFR conveys valuable information regarding the functional results of revascularization, with prognostic implications.[9-12] Although optimal cutoff values for post-PCI FFR vary between 0.86 and 0.96, post-PCI FFR is independently predictive of long-term clinical outcomes, and the inverse relationship between post-PCI FFR and risk of clinical events was consistently observed across studies. In addition, several studies support the role of post-PCI physiologic assessment as a functional optimization tool and gatekeeper to decide further interventional procedures and optimize final results.[19-21] However, it should be noted that the increased risk of adverse clinical events following suboptimal post-PCI FFR was mainly caused by increased risk of repeat revascularization, and positive likelihood ratio of post-PCI FFR alone to predict future adverse clinical events was limited.[13,14] Considering that PCI with stent implantation is a focal treatment while post-PCI FFR reflects total atherosclerotic disease burden in the target vessel, underlying clinical characteristics that determine the total atherosclerotic disease burden may interact with post-PCI FFR. In this regard, the current study evaluated differential prognostic impact of post-PCI FFR according to LV systolic dysfunction, which is one of the major determinants of prognosis after PCI.[22,23]

As with the previous studies, patients with LVEF ≤40% showed significantly higher risk of cardiac death or TVMI than those with LVEF >40%. During 2 years of follow-up, post-PCI FFR was also independently associated with the increased risk of TVF, regardless of the presence of LV systolic dysfunction. However, prognostic impact of post-PCI FFR value or residual ischemia by post-PCI FFR ≤0.80 was different according to the presence of LV systolic dysfunction. Among patients with LVEF ≤40%, increased risk of TVF following lower post-PCI FFR was mainly driven by a higher risk of hard clinical events such as cardiac death or TVMI. Conversely, it was mainly driven by a higher risk of TVR in patients with LVEF >40%. Significant interaction between post-PCI FFR and LVEF for the risk of cardiac death or MI support the study hypothesis regarding the

TABLE 4 Differential Prognostic Impact of Ischemic Post-PCI Fractional Flow Reserve (≤0.80) Stratified by Left Ventricular Dysfunction

	Post-PCI FFR >0.80	Post-PCI FFR ≤0.80	Univariable HR (95% CI)	*P* Value	τ^2	Multivariable HR[a] (95% CI)	*P* Value	τ^2
Patients with ejection fraction >40%	n = 2,435	n = 361						
Cardiac death or target vessel myocardial infarction	36 (1.8)	7 (2.7)	0.709 (0.230-2.188)	0.550	0.247	1.418 (0.475-4.234)	0.530	0.327
All-cause death	59 (2.8)	6 (2.8)	0.808 (0.321-2.033)	0.650	0.114	0.927 (0.376-2.288)	0.870	0.069
Cardiac death	17 (0.8)	4 (1.6)	1.643 (0.553-4.886)	0.370	<0.001	2.317 (0.736-7.290)	0.150	<0.001
Target vessel myocardial infarction	21 (1.1)	3 (1.1)	0.300 (0.042-2.092)	0.220	3.119	1.213 (0.209-7.043)	0.830	0.940
Target vessel revascularization	141 (6.7)	30 (10.0)	1.484 (1.001-2.201)	0.049	0.025	1.593 (1.019-2.489)	0.041	0.011
Target vessel failure[b]	161 (7.6)	34 (11.6)	1.476 (1.020-2.137)	0.039	0.033	1.687 (1.130-2.517)	0.011	0.002
Patients with ejection fraction ≤40%	n = 145	n = 24						
Cardiac death or target vessel myocardial infarction	7 (5.5)	5 (24.3)	8.142 (2.257-29.37)	0.001	0.866	10.15 (1.519-67.78)	0.017	<0.001
All-cause death	13 (9.9)	4 (18.0)	4.567 (1.345-15.51)	0.015	0.009	8.403 (1.991-35.47)	0.004	<0.001
Cardiac death	7 (5.4)	3 (14.5)	6.250 (1.385-28.20)	0.017	0.094	15.46 (2.617-91.29)	0.003	0.009
Target vessel myocardial infarction	2 (1.6)	2 (10.7)	7.626 (1.059-54.93)	0.044	0.003	7.964 (0.953-66.52)	0.055	0.003
Target vessel revascularization	6 (4.5)	3 (17.8)	3.270 (0.746-14.84)	0.120	0.176	2.475 (0.422-14.52)	0.320	<0.001
Target vessel failure[b]	12 (9.1)	7 (35.9)	4.473 (1.581-12.66)	0.005	0.034	5.739 (1.815-18.15)	0.003	0.003

The cumulative incidence of clinical outcomes at 2 years is presented as Kaplan-Meier estimates. [a]Adjusted variables for multivariable mixed-effect Cox proportional hazard regression model included age, sex, hypertension, diabetes mellitus, dyslipidemia, previous history of myocardial infarction, acute coronary syndrome, and post-PCI % diameter stenosis. [b]Target vessel failure was defined as a composite of cardiac death, target vessel myocardial infarction, and target vessel revascularization.

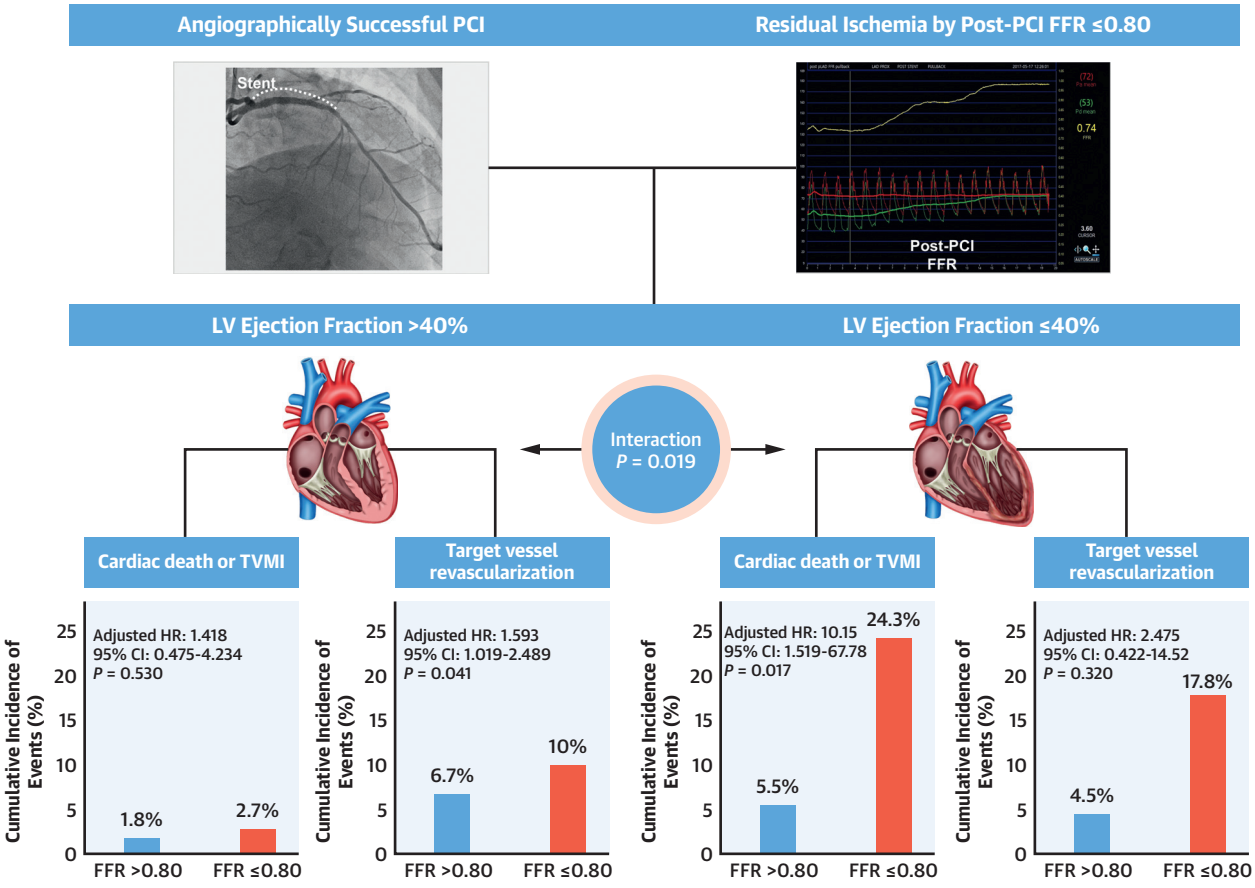
Abbreviation as in Tables 1 and 3.

differential prognostic impact of low post-PCI FFR according to the patient's underlying severity, especially LV systolic dysfunction.

INFLUENCE OF LV SYSTOLIC DYSFUNCTION ON POST-PCI FFR. Differential prognostic impact of post-PCI FFR can be explained by several pathophysiological backgrounds. First, LV systolic dysfunction could be the consequence of previous ischemic insult or long-standing myocardial ischemia with severe ischemic burden. In addition, higher prevalence of cardiovascular risk factors in patients with LV systolic dysfunction indicates the possibility of higher total atherosclerotic disease burden in these patients. Therefore, suboptimal post-PCI FFR would be associated with higher residual myocardial ischemia or residual atherosclerotic disease burden in patients with LV systolic dysfunction than those without LV systolic dysfunction. Second, considering that patients with LV systolic dysfunction might have a smaller viable myocardium supplied by target vessel, post-PCI FFR could underestimate the stenosis severity.[24] Reduced coronary flow reserve in patients with reduced LVEF compared with those with preserved LVEF could be another explanation.[25] Third, interaction between FFR and left ventricular end-diastolic pressure (LVEDP) may also affect post-PCI FFR. Previous studies presented that the elevated LVEDP may impair myocardial blood flow by increased coronary zero flow pressure,[26] and there was positive correlation between LVEDP and FFR values, which was greater in functionally significant stenosis (FFR ≤0.80).[27] In these regards, suboptimal post-PCI FFR in the presence of LV systolic dysfunction indicates a higher degree of functional stenosis than in those without LV systolic dysfunction, which is associated with the increased risk of hard clinical events. These pathophysiological backgrounds imply that suboptimal post-PCI FFR in the presence of LV systolic dysfunction should be regarded as the worst procedural results and evaluation of the possible cause of suboptimal post-PCI FFR and further optimization of stented segment would be more important to improve prognosis after PCI in patients with LV systolic dysfunction.

CLINICAL IMPLICATIONS. Because LV systolic dysfunction is an independent prognostic factor and interacts with post-PCI FFR, it is important to obtain information about the LV function before performing PCI. In the STICH trial, cardiovascular mortality benefits of coronary artery bypass grafting, compared with medical treatment, seem to be only in long-term follow-up period (more than 5 years).[28] Conversely, patients with LV systolic dysfunction and post-PCI FFR ≤0.80 was significantly associated with higher risk of cardiac death or TVMI at 2 years than those with post-PCI FFR >0.80. It should be noted that PCI is a per-lesion local treatment and coronary artery bypass grafting is a per-vessel treatment. Therefore, suboptimal post-PCI FFR could be originated from both residual atherosclerotic disease in the target vessel and suboptimal expansion of the implanted stents. These 2 factors might influence the earlier

CENTRAL ILLUSTRATION **Differential Impact of Fractional Flow Reserve After Percutaneous Coronary Intervention by Left Ventricular Function**



Choi KH, et al. JACC: Asia. 2024;4(3):229-240.

The current study evaluated the differential prognostic impact of post-PCI FFR according to LV systolic dysfunction. Patients with LVEF ≤40% showed increased risk of cardiac death or TVMI compared with patients with LVEF >40%. The increased risk of TVF was mainly caused by increased cardiac death or TVMI in patients with LVEF ≤40%, conversely, it was mainly based on the increased TVR in patients with LVEF >40%. Significant interaction was observed between LVEF and post-PCI FFR for the risk of cardiac death or TVMI. These results imply that prognostic implication of post-PCI FFR should be interpreted based on underlying patients' LV function. FFR = fractional flow reserve; LV = left ventricular; PCI = percutaneous coronary intervention; TVMI = target-vessel myocardial infarction.

separation of survival curve between the 2 groups according to post-PCI FFR values. The current results show that angiographic evaluation of the stented segment would be insufficient to find patients with a higher risk of hard clinical events. When interpreting post-PCI FFR value, the current study suggests that the operator should be aware of the differential prognostic implications of post-PCI FFR according to the presence of LV systolic dysfunction. The recent TARGET-FFR (Trial of Angiography versus pressure-Ratio Guided Enhancement Techniques - Fractional Flow Reserve) study presented post-PCI FFR-guided procedural optimization increases post-PCI FFR value and lower the risk of post-PCI FFR ≤0.80.[21] Therefore, it would be clinically important to evaluate the possible cause of suboptimal post-PCI FFR through intravascular imaging[29] and post-PCI FFR pull back,[14] especially in patients with LV systolic dysfunction. Because suboptimal post-PCI FFR can be from unmodifiable causes, such as diffuse atherosclerotic disease, if no modifiable causes are found, clinicians should take in mind that the patients may follow a relatively unfavorable clinical course and take precautions accordingly.

STUDY LIMITATIONS. First, there is no information about medical treatment after PCI. Second, there was

no mandated poststenting protocol in cases of suboptimal post-PCI FFR. However, post-PCI physiologic evaluation was performed after clinically and angiographically optimal results of PCI. Third, LVEDP was not available in the current registry. Fourth, current results cannot be generalizable to other causes of LV systolic dysfunction such as dilated cardiomyopathy, tachycardia-induced cardiomyopathy, and valvular heart disease. Fifth, the current study cannot present the recovery of LV systolic function after PCI according to post-PCI FFR values. Sixth, some factors that may affect the FFR values could not be standardized, such as the exact position of the pressure wire during the measurement. Seventh, several detailed lesion characteristics, including calcification, in-stent restenosis, and bifurcation, were not collected in the current data set. Eighth, other than TVMI, data for non-TVMI or all MI was not available for analysis. Finally, because stratified analyses were performed in this study, the reliability of the estimates might have declined caused by the reduced sample size and low number of events per group.

CONCLUSIONS

Post-PCI FFR had differential prognostic meaning according to LV systolic function. Residual ischemia defined by post-PCI FFR ≤0.80 was prognostic indicator for cardiac death or TVMI among patients with LVEF ≤40%, while it was associated with TVR among patients with LVEF >40%. Obtaining post-PCI FFR >0.80 by physiologic optimization of PCI when possible is important to reduce the future risk of cardiac death or TVMI among patients with LV systolic dysfunction.

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ADDRESS FOR CORRESPONDENCE: Dr Joo Myung Lee, Division of Cardiology, Department of Medicine, Heart Vascular Stroke Institute, Samsung Medical Center, Sungkyunkwan University School of Medicine, 81 Irwon-ro, Gangnam-gu, Seoul 06351, Republic of Korea. E-mail: drone80@hanmail.net OR joomyung.lee@samsung.com.

PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: We compared the clinical outcomes of patients with ischemic heart disease according to post-PCI FFR and LVEF. Patients with LVEF ≤40% had an increased risk of cardiac death or TVMI compared with patients with preserved LVEF. Regardless of LVEF, post-PCI FFR was independently associated with the risk of TVF. A significant interaction was observed between LVEF and post-PCI FFR for the risk of cardiac death or TVMI.

TRANSLATIONAL OUTLOOK: Physiological optimization to reduce the incidence of residual ischemia may have a role in reducing the future risk of cardiac death or TVMI among patients with LV systolic dysfunction. Further studies are needed to clarify whether post-PCI FFR-guided procedural optimization and resolution of ischemia following PCI reduces future risk of cardiac death or TVMI in patients with LV systolic dysfunction.

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KEY WORDS drug-eluting stent(s), fractional flow reserve, left ventricular ejection fraction, percutaneous coronary intervention, prognosis

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