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Optical Coherence Tomography Fractional Flow Reserve and Cardiovascular Outcomes in Patients With Acute Coronary Syndrome

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ABSTRACT

BACKGROUND Optical coherence tomography–derived fractional flow reserve (OCT-FFR) correlates strongly with wire-based FFR; however, its clinical significance remains uncertain.

OBJECTIVES This study sought to investigate the relationship between post–percutaneous coronary intervention (PCI) OCT-FFR and long-term clinical outcomes in acute coronary syndrome (ACS).

METHODS This retrospective, multicenter, observational cohort study included consecutive patients with ACS who underwent OCT-guided emergency PCI. We analyzed post-PCI OCT images and calculated OCT-FFR to identify independent factors associated with target vessel failure (TVF) after PCI.

RESULTS Among 364 enrolled patients, 54 experienced TVF during a median follow-up of 36 (IQR: 26-48) months. Vessel-level OCT-FFR was significantly lower in the TVF group than in the non-TVF group (0.87 vs 0.94; $P < 0.001$). In the multivariable Cox regression analysis, low vessel-level OCT-FFR (HR per 0.1 increase: 0.38; 95% CI: 0.29-0.49; $P < 0.001$) and thin-cap fibroatheroma in the nonculprit lesion were independently associated with TVF. The TVF rate of vessels with both low vessel-level OCT-FFR (<0.90) and thin-cap fibroatheroma in the nonculprit lesion was 8.1 times higher than that of all other vessels (69.3% vs 12.4%; HR: 8.13; 95% CI: 4.33-15.25; log-rank $P < 0.001$). Furthermore, adding vessel-level OCT-FFR to baseline characteristics and post-PCI OCT findings improved discriminatory and reclassification ability in identifying patients with subsequent TVF.

CONCLUSIONS Vessel-level OCT-FFR was an independent factor associated with TVF after PCI in patients with ACS. Adding the OCT-FFR measurement to post-PCI OCT findings may enable better discrimination of patients with subsequent TVF after PCI for ACS. (Relationship between Intracoronary Optical Coherence Tomography Derived Virtual Fractional Flow Reserve and cardiovascular outcome on Acute coronary syndrome; UMIN000043858)
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The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

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ABBREVIATIONS AND ACRONYMS

ACS = acute coronary syndrome

FFR = fractional flow reserve

LRP = lipid-rich plaque

NCL = nonculprit lesion

OCT = optical coherence tomography

OCT-FFR = optical coherence tomography-derived fractional flow reserve

PCI = percutaneous coronary intervention

TCFA = thin-cap fibroatheroma

TLR = target lesion revascularization

TVF = target vessel failure

TVR = target vessel revascularization

Percutaneous coronary intervention (PCI) is the gold standard treatment for patients with acute coronary syndrome (ACS). However, significant residual ischemia after angiographically successful PCI occurs at a constant rate and is associated with a poor prognosis.[1,2] Although coronary angiography and intravascular imaging are limited in their ability to assess the physiological severity of coronary lesions, the adequacy of PCI results is still largely assessed with these modalities alone without conducting physiological assessments, particularly in ACS.

Optical coherence tomography (OCT) is an intravascular imaging modality that allows for detailed microstructural evaluation during PCI and is increasingly used as an adjunctive imaging technique for PCI. Recent reports indicate that optical coherence tomography-derived fractional flow reserve (OCT-FFR), which was calculated using a basic fluid dynamics equation in the absence of medication, had a significantly stronger correlation with wire-based FFR than conventional measurements such as minimum lumen area or the percentage of area stenosis evaluated using OCT.[3,4] These data suggest that OCT-FFR may provide accessible diagnostic information regarding the presence of functional ischemia both before and after PCI. The relationship between post-PCI OCT-FFR and clinical outcomes after PCI in patients with ACS was investigated in this study.

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METHODS

STUDY DESIGN AND POPULATION. This retrospective, multicenter, and observational cohort study harnessed the Kobe University ACS-OCT registry exploring the relationship between morphological plaque characteristics of ACS culprit lesions and clinical outcomes.[5] Consecutive patients with ACS who underwent OCT-guided PCI at 4 institutions between January 2010 and December 2018 were included. Participating institutions, detailed definitions of ACS, and exclusion criteria are described in the Supplemental Appendix.

This study protocol complied with the Declaration of Helsinki and was approved by the Ethics Committee of Kobe University Hospital. Informed consent was obtained in the form of an opt-out on the website of the Division of Cardiovascular Medicine, Kobe University Graduate School of Medicine.

OCT IMAGE ANALYSIS AND DEFINITIONS

At the end of the procedure, OCT images were acquired using a frequency-domain OCT system (ILUMIEN; Abbott Vascular) with a Dragonfly Optis OCT imaging catheter (Abbott Vascular). The target vessel was divided into the following longitudinal subsegments: 1) stented segment; 2) adjacent reference segments (≤5 mm long); and 3) nonculprit lesion (NCL) (**Figure 1**). An NCL was defined as an untreated coronary segment with >30% diameter stenosis on angiography and at least 5 mm away from the stent. If there were multiple NCLs, the most stenotic lesion was selected for analysis.

Cross-sectional OCT images were analyzed over the entire length scanned using OCT. Stent and lumen areas were measured for every frame (0.1- or 0.2-mm intervals). Qualitative assessment was performed to evaluate in-stent irregular protrusion, thrombus, calcified nodule, malapposition, stent edge dissection, lipid-rich plaque (LRP), thin-cap fibroatheroma (TCFA), and macrophages. We also evaluated the OCT-based suboptimal stent deployment based on the presence of at least 1 of the following OCT findings: 1) stent underexpansion; 2) in-stent plaque or thrombus protrusion ≥500 μm; 3) malapposition >200 μm; and 4) stent edge dissection ≥200 μm.[6] Details are described in the Supplemental Appendix.

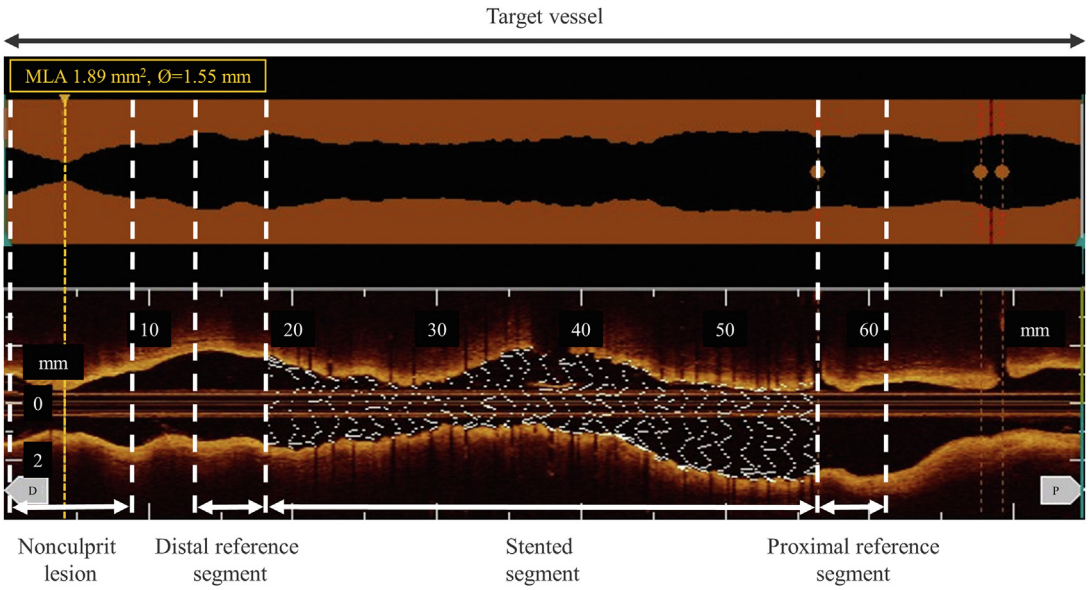
OCT-DERIVED FFR

In the present study, OCT-FFR was calculated from OCT cross-sectional areas with the described algorithm using custom-designed Microsoft Excel-based software.[3] The algorithm was based on the following equation using fluid dynamics: $\Delta P = FV + SV^2$, where V is the flow velocity, F is the coefficient of pressure loss because of viscous friction (Poiseuille resistance), and S is the coefficient of local pressure loss because of abrupt enhancement (flow separation).[3,7]

OCT-FFR was calculated for the target vessel (vessel-level OCT-FFR), stented segment (stent-level OCT-FFR), and NCL (NCL-level OCT-FFR). Because stent-level and NCL-level OCT-FFR could be calculated as independent variables without any interactions with each other, each-level OCT-FFR was calculated assuming that there was no pressure drop in the proximal and distal segments. All residual lesions were categorized as focal, diffuse, or the others, according to the stent-level or NCL-level OCT-FFR and lesion length (Supplemental Appendix).[8]

OUTCOMES. The primary outcome of the study was target vessel failure (TVF), which is a composite of

FIGURE 1 Subsegments Analyzed by Optical Coherence Tomography



The target vessel was divided into the following longitudinal subsegments: 1) stented segment; 2) adjacent reference segments (≤5 mm long); and 3) nonculprit lesion. MLA = minimum lumen area.

cardiac death, target vessel-related myocardial infarction, and ischemia-driven target vessel revascularization (TVR).[9] We further assessed target lesion revascularization (TLR) and non-TLR TVR (NCL-related TVR) to separately evaluate the relationship between stented plus reference segment-related findings and TLR and the relationship between NCL-related findings and non-TLR TVR. All patients were clinically followed up at the primary care institution every 1 to 3 months after discharge, while some patients without symptoms underwent routine angiographic follow-up 8 to 12 months after primary PCI. The decision to perform the angiographic follow-up was left to the physician's discretion (Supplemental Appendix).

STATISTICAL ANALYSES. Continuous variables were expressed as mean ± SD or median (IQR). Student's *t*-test or analysis of variance was performed to evaluate parametric continuous variables. The Mann-Whitney *U* test was performed for nonparametric variables, followed by post hoc testing only if *P* was <0.05. Categorical variables were expressed as frequency and percentage and compared using chi-square or Fisher exact test followed by residual analysis only if *P* was <0.05. The time to clinical outcomes was assessed by Kaplan-Meier analyses, and the log-rank test was performed to compare groups. Cox regression analysis was used to identify independent factors associated with TVF, TLR, and non-TLR TVR, and logistic regression analysis was performed to identify independent factors associated with low vessel-level OCT-FFR. The low vessel-level OCT-FFR was defined as <0.90, which was calculated as the cutoff value for identifying patients with subsequent TVF. To evaluate the additive value of post-PCI OCT findings and vessel-level OCT-FFR to baseline characteristics in identifying patients with subsequent TVF, the improvement in the discriminatory and reclassification ability of the models with post-PCI OCT findings and vessel-level OCT-FFR were compared with those of a model using baseline characteristics only. Similar analyses were conducted on stented plus reference segment and NCL-related findings to identify patients with subsequent TLR and non-TLR TVR, respectively. Further details are described in the Supplemental Appendix.

RESULTS

A total of 511 consecutive patients underwent OCT-guided PCI for ACS during the study period. After excluding 147 patients, 364 patients with 364 vessels were finally enrolled (Supplemental Figure 1). The baseline patient, angiographic, and procedural characteristics are summarized in **Table 1**. Post-PCI OCT-FFR and OCT findings are summarized in **Table 2**. The

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TABLE 1 Baseline Patient, Angiographic, and Procedural Characteristics

	Overall (N = 364)	TVF (n = 54)	Non-TVF (n = 310)	*P* Value
Age, y	69 (61-77)	70 (62-80)	69 (61-76)	0.27
Male	277 (76.1)	41 (75.9)	236 (76.1)	0.97
BMI, kg/m^2	23.2 (21.2-25.3)	23.6 (20.5-25.6)	23.2 (21.3-25.3)	0.71
Comorbidity				
Hypertension	251 (69.0)	38 (70.4)	213 (68.7)	0.81
Dyslipidemia	226 (62.1)	30 (55.6)	196 (63.2)	0.28
Diabetes mellitus	148 (40.7)	21 (38.9)	127 (41.0)	0.77
Smoking	239 (65.7)	34 (63.0)	205 (66.1)	0.65
Family history	62 (17.0)	12 (22.2)	50 (16.1)	0.27
CKD (<60 mL/min/1.73 m^2)	89 (24.5)	15 (27.8)	74 (23.9)	0.54
Regular hemodialysis	9 (2.3)	3 (5.6)	6 (1.9)	0.14
Prior MI	16 (4.4)	2 (3.7)	14 (4.5)	0.57
Prior PCI	25 (6.9)	4 (7.4)	21 (6.8)	0.52
Prior CABG	2 (0.5)	0 (0.0)	2 (0.6)	0.73
Clinical presentation				0.46
STEMI	205 (56.3)	31 (57.4)	174 (56.1)	
Non-STEMI	114 (31.3)	19 (35.2)	95 (30.6)	
Unstable angina	45 (12.4)	4 (7.4)	41 (13.2)	
Laboratory data				
LDL-C, mg/dL	121 (100-148)	108 (94-136)	123 (100-150)	0.097
HDL-C, mg/dL	46 (38-55)	45 (40-55)	46 (37-55)	0.45
TG, mg/dL	110 (69-173)	102 (70-165)	111 (69-174)	0.93
HbA_{1c}, %	6.0 (5.7-6.6)	6.0 (5.7-6.7)	6.0 (5.6-6.6)	0.68
Creatinine, mg/dL	0.80 (0.69-0.94)	0.82 (0.64-0.99)	0.80 (0.69-0.94)	0.90
Peak CK, IU/L	994 (364-2535)	1261 (316-3834)	954 (372-2414)	0.39
Peak CK-MB, IU/L	100 (27-249)	120 (26-294)	98 (32-248)	0.83
LVEF, %	55.0 (46.0-60.0)	50.0 (40.0-57.0)	55.0 (47.0-60.0)	0.006
Medication at hospitalization				
Antiplatelet therapy	53 (14.6)	8 (14.8)	45 (14.5)	0.95
Statin	121 (33.2)	15 (27.8)	106 (34.2)	0.36
ACE inhibitor/ARB	69 (19.0)	10 (18.5)	59 (19.0)	0.93
β-blocker	26 (7.1)	5 (9.3)	21 (6.8)	0.34
Medication at discharge				
Statin	340 (93.4)	44 (81.5)	296 (95.5)	0.001
ACE inhibitor/ARB	281 (77.2)	37 (68.5)	244 (78.7)	0.10
β-blocker	250 (68.7)	33 (61.1)	217 (70.0)	0.19
Lesion location				0.36
LAD	192 (52.7)	33 (61.1)	159 (51.3)	
LCx	50 (13.7)	5 (9.3)	45 (14.5)	
RCA	122 (33.5)	16 (29.6)	106 (34.2)	
Multivessel disease	136 (37.4)	30 (55.6)	106 (34.2)	0.003
Lesion length, mm	22.5 (15.0-28.0)	23.0 (18.0-28.0)	22.0 (15.0-28.0)	0.39
Baseline TIMI flow grade 0 or 1	181 (49.7)	33 (61.1)	148 (47.7)	0.07
Multiple stents	51 (14.0)	9 (16.7)	42 (13.5)	0.54
Stent diameter, mm	3.0 (2.5-3.5)	3.0 (2.5-3.3)	3.0 (2.5-3.5)	0.15
Stent length, mm	23.0 (17.6-31.1)	23.3 (18.4-34.2)	22.9 (17.5-30.6)	0.17
Thrombectomy	197 (54.1)	32 (59.3)	165 (53.2)	0.41
Postdilatation	200 (54.9)	26 (48.1)	174 (56.1)	0.28
Maximum balloon diameter, mm	3.3 (3.0-3.5)	3.0 (2.8-3.5)	3.3 (3.0-3.5)	0.12
Maximum inflation pressure, atm	16 (12-18)	18 (12-20)	16 (12-18)	0.20
PCI for nonculprit vessels	45 (12.4)	9 (16.7)	36 (11.6)	0.30
At the primary PCI	3 (0.8)	1 (1.9)	2 (0.6)	
At a later date in the hospital	42 (11.5)	8 (14.8)	34 (11.0)	

Values are median (IQR) or n (%).

ACE = angiotensin-converting enzyme; ARB = angiotensin II receptor blocker; BMI = body mass index; CABG = coronary artery bypass grafting; CK = creatine kinase; CKD = chronic kidney disease; CK-MB = creatine kinase-myocardial band; HbA_{1c} = glycosylated hemoglobin; HDL-C = high-density lipoprotein cholesterol; LAD = left anterior descending artery; LCx = left circumflex artery; LDL-C = low-density lipoprotein cholesterol; LVEF = left ventricular ejection fraction; MI = myocardial infarction; PCI = percutaneous coronary intervention; RCA = right coronary artery; STEMI = ST-segment elevation myocardial infarction; TG = triglyceride; TIMI = Thrombolysis In Myocardial Infarction; TVF = target vessel failure.

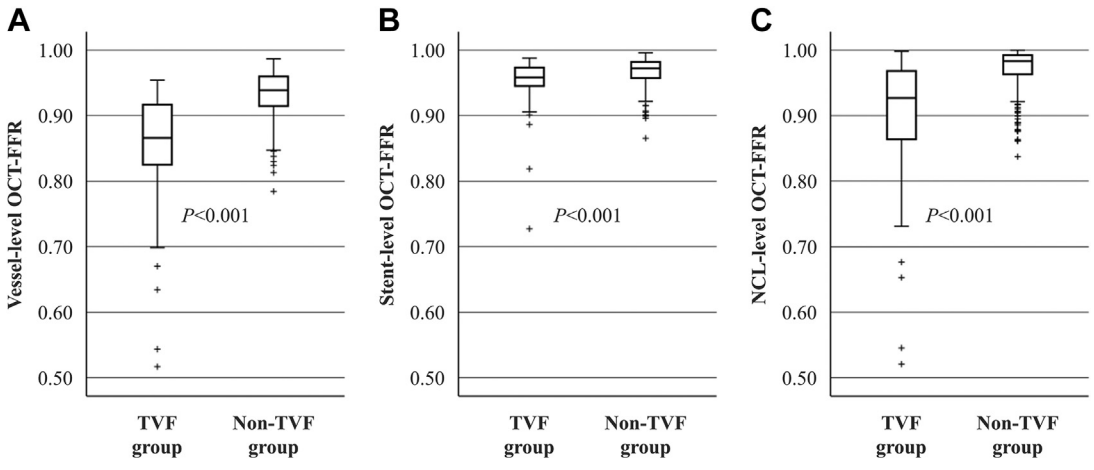
TABLE 2 Post-PCI OCT-FFR and OCT Findings

	Overall (N = 364)	TVF (n = 54)	Non-TVF (n = 310)	*P* Value
Target vessel				
Vessel-level OCT-FFR	0.93 (0.90-0.96)	0.87 (0.83-0.92)	0.94 (0.92-0.96)	<0.001
Length of analyzable images, mm	51.0 (41.8-59.6)	53.9 (45.4-63.4)	50.8 (41.0-59.2)	0.12
Average lumen diameter, mm	2.8 (2.5-3.1)	2.6 (2.4-2.9)	2.9 (2.6-3.2)	<0.001
Average lumen area, mm^2	6.6 (5.3-8.1)	5.4 (4.7-7.1)	6.7 (5.4-8.3)	<0.001
MLA, mm^2	3.5 (2.4-4.8)	2.3 (1.5-3.2)	3.7 (2.6-4.9)	<0.001
Focal or diffuse lesion				<0.001
Focal lesion	76 (20.9)	31 (57.4)	45 (14.5)	
Diffuse lesion	53 (14.6)	7 (13.0)	46 (14.8)	
Others	235 (64.6)	16 (29.6)	219 (70.6)	
Stented segment				
Stent-level OCT-FFR	0.97 (0.96-0.98)	0.96 (0.95-0.97)	0.97 (0.96-0.98)	<0.001
Lumen-related variables				
Average lumen area, mm^2	6.4 (5.3-8.0)	5.9 (4.7-6.9)	6.6 (5.3-8.2)	0.008
In-stent MLA, mm^2	5.0 (3.9-6.4)	4.4 (3.1-5.6)	5.1 (4.0-6.6)	0.004
In-stent MLA <4.5 mm^2	150 (41.2)	27 (50.0)	123 (39.7)	0.16
Stent-related variables				
Average stent area, mm^2	6.3 (5.2-8.1)	5.7 (4.8-7.1)	6.5 (5.2-8.2)	0.011
MSA, mm^2	5.1 (4.0-6.5)	4.7 (3.5-6.0)	5.1 (4.0-6.6)	0.020
Stent underexpansion	114 (31.3)	14 (25.9)	100 (32.3)	0.36
Qualitative findings				
Irregular protrusion	200 (54.9)	38 (70.4)	162 (52.3)	0.014
Thrombus	103 (28.3)	29 (53.7)	74 (23.9)	<0.001
Calcified nodule	19 (5.2)	6 (11.1)	13 (4.2)	0.047
Malapposition	125 (34.3)	19 (35.2)	106 (34.2)	0.89
Suboptimal stent deployment	239 (65.7)	41 (75.9)	198 (63.9)	0.085
Reference segment				
Proximal reference				
Average lumen area, mm^2	7.2 (5.8-9.3)	6.4 (4.7-7.6)	7.3 (6.0-9.6)	0.001
Stent edge dissection	23 (6.3)	9 (16.7)	14 (4.5)	0.003
Thrombus	55 (15.1)	12 (22.2)	43 (13.9)	0.11
LRP	84 (23.1)	21 (38.9)	63 (20.3)	0.003
TCFA	27 (7.4)	8 (14.8)	19 (6.1)	0.032
Calcified nodule	8 (2.2)	2 (3.7)	6 (1.9)	0.34
Macrophage	102 (28.0)	21 (38.9)	81 (26.1)	0.054
Distal reference				
Average lumen area, mm^2	5.4 (4.1-7.4)	4.9 (3.4-6.4)	5.6 (4.1-7.6)	0.011
Stent edge dissection	19 (5.2)	7 (13.0)	12 (3.9)	0.013
Thrombus	33 (9.1)	7 (13.0)	26 (8.4)	0.20
LRP	48 (13.2)	12 (22.2)	36 (11.6)	0.033
TCFA	21 (5.8)	6 (11.1)	15 (4.8)	0.073
Calcified nodule	3 (0.8)	1 (1.9)	2 (0.6)	0.38
Macrophage	91 (25.0)	19 (35.2)	72 (23.2)	0.061
Average reference				
Lumen area, mm^2	6.3 (5.1-8.3)	5.5 (4.6-6.6)	6.5 (5.2-8.4)	0.001
NCL				
NCL-level OCT-FFR	0.98 (0.95-0.99)	0.93 (0.86-0.97)	0.98 (0.96-0.99)	<0.001
Lumen-related variables				
Lesion length, mm	8.3 (6.2-11.2)	10.6 (8.5-12.6)	7.8 (6.0-10.6)	<0.001
MLA, mm^2	4.5 (3.0-6.5)	2.8 (1.6-5.0)	4.8 (3.3-6.7)	<0.001
Qualitative findings				
Thrombus	21 (5.8)	4 (7.4)	17 (5.5)	0.38
LRP	160 (44.0)	32 (59.3)	128 (41.3)	0.014
TCFA	57 (15.7)	21 (38.9)	36 (11.6)	<0.001
Calcified nodule	20 (5.5)	6 (11.1)	14 (4.5)	0.059

Values are median (IQR) or n (%).

LRP = lipid-rich plaque; MLA = minimum lumen area; MSA = minimum stent area; NCL = nonculprit lesion; OCT-FFR = optical coherence tomography–derived fractional flow reserve; TCFA = thin-cap fibroatheroma; other abbreviations as in Table 1.

FIGURE 2 Comparisons of OCT-FFR Between the TVF and Non-TVF Groups in Each Subsegment



(A) Vessel-level optical coherence tomography–derived fractional flow reserve (OCT-FFR). **(B)** Stent-level OCT-FFR. **(C)** Nonculprit lesion (NCL)–level OCT-FFR. The **boxes** represent the IQR, with the median shown as a **horizontal line**. The **whiskers** represent 1.5× IQR on each side. The **plus symbols** represent outliers. TVF = target vessel failure.

median vessel-level OCT-FFR was 0.93 (IQR: 0.90-0.96). Overall, only 3.6% had a value <0.80, while 76.4% had a vessel-level OCT-FFR ≥0.90 (Supplemental Figure 2A).

OUTCOMES. During a median follow-up of 36 (IQR: 26-48) months, TVF occurred in 54 (14.8%) patients. Specifically, the following were observed: cardiac death (16 patients), target vessel-related myocardial infarction (3 patients), and TVR (39 patients). Further details and a representative case with TVR (Supplemental Figure 3) are described in the Supplemental Appendix.

COMPARISONS BETWEEN THE TVF AND NON-TVF GROUPS. The TVF group had a significantly lower left ventricular ejection fraction, less frequent statin use at discharge, and higher incidence of multivessel disease than the non-TVF group (**Table 1**).

The vessel-level OCT-FFR was significantly lower in the TVF group than in the non-TVF group (0.87 [IQR: 0.83-0.92] vs 0.94 [IQR: 0.92-0.96]; $P < 0.001$). The TVF group had a significantly lower stent-level and NCL-level OCT-FFR than the non-TVF group (**Table 2, Figure 2**). In the TVF group, 22.2% of patients had a vessel-level OCT-FFR <0.80, and only 29.6% had a value ≥0.90. Conversely, in the non-TVF group, only 0.3% of patients had a vessel-level OCT-FFR <0.80, and 84.5% had a value ≥0.90 (Supplemental Figure 2B).

The post-PCI OCT findings are presented in **Table 2**. Regarding the target vessel, the TVF group had a significantly smaller average lumen area ($P < 0.001$) and minimum lumen area ($P < 0.001$) than the non-TVF group. The TVF group had a higher prevalence of focal lesions than the non-TVF group.

In-stent minimum lumen area, average stent area, and minimum stent area were significantly smaller in the TVF group than in the non-TVF group. The frequencies of irregular protrusion and thrombus were significantly greater in the TVF group than in the non-TVF group. The OCT-based suboptimal stent deployment tended to be more frequent in the TVF group than in the non-TVF group ($P = 0.085$).

The average reference lumen area was significantly smaller in the TVF group than in the non-TVF group. In both the proximal and distal reference segments, the frequencies of stent edge dissection and LRP were significantly greater in the TVF group than in the non-TVF group.

Regarding the NCL, the TVF group had a significantly longer lesion ($P < 0.001$) and smaller minimum lumen area ($P < 0.001$) than the non-TVF group. The frequencies of LRP and TCFA were significantly greater in the TVF group than in the non-TVF group.

FACTORS ASSOCIATED WITH TVF. The results of the univariable and multivariable Cox regression analyses for TVF are summarized in **Table 3**. The multivariable model showed that low left ventricular ejection fraction, no statin use at discharge, low vessel-level OCT-FFR, the presence of in-stent thrombus, LRP at the proximal reference segment,

small average reference lumen area, and TCFA in the NCL were independently associated with TVF. Multivariable Cox regression analysis focusing on focal or diffuse lesion showed that focal lesion was independently associated with TVF (Supplemental Table 1).

Receiver-operating characteristic curve analysis showed that the cutoff value of the vessel-level OCT-FFR for identifying patients with subsequent TVF was 0.90 (sensitivity: 70.4%; specificity: 84.5%; area under the curve: 0.83; $P < 0.001$; positive predictive value: 44.2%; negative predictive value: 94.2%) (Supplemental Figure 4). The incidence of TVF was 9.9 times higher in vessels with low vessel-level OCT-FFR (<0.90) than in those with high vessel-level OCT-FFR (≥0.90) (log-rank $P < 0.001$). The incidence of cardiac death and TVR was significantly higher in vessels with low vessel-level OCT-FFR (<0.90) than in those with high vessel-level OCT-FFR (≥0.90) (**Figure 3**).

Among the factors independently associated with TVF, low vessel-level OCT-FFR and the presence of TCFA in the NCL were the most powerful factors associated with TVF (**Table 3**). The TVF rate was the highest in vessels with these 2 features, followed by those with 1 of the features and those without both features (**Figure 4A**). The TVF rate of vessels with the 2 features was 8.1 times higher than that of all other vessels (log-rank $P < 0.001$) (**Figure 4B**).

FACTORS ASSOCIATED WITH LOW VESSEL-LEVEL OCT-FFR (<0.90). Multivariable logistic regression analysis showed that left anterior descending artery lesion, small in-stent minimum lumen area, in-stent thrombus, stent edge dissection at the proximal reference segment, long NCL, and small minimum lumen area in the NCL were independently associated with low vessel-level OCT-FFR (<0.90) (**Table 4**). Multivariable logistic regression analysis focusing on focal or diffuse lesion showed that focal lesion was independently associated with low vessel-level OCT-FFR (<0.90) (Supplemental Table 2).

INCREMENTAL VALUE OF VESSEL-LEVEL OCT-FFR IN IDENTIFYING PATIENTS WITH SUBSEQUENT TVF. **Figure 5** shows the C-index, net reclassification index, and relative integrated discrimination improvement values for the 3 models. Compared with model 1 (cardiovascular risk factors, left ventricular ejection fraction, and statin use at discharge), model 2 (model 1 plus post-PCI OCT findings) showed a significantly higher discriminatory ability (C-index: 0.82 vs 0.69; $P = 0.006$) and higher reclassification ability (net reclassification index: 0.87; $P < 0.001$; relative integrated discrimination improvement: 0.13; $P < 0.001$) in identifying patients with subsequent TVF. Compared with model 2, model 3 (model 2 plus vessel-level OCT-FFR) showed further increased discriminatory ability (C-index: 0.92 vs 0.82; $P = 0.005$) and incremental reclassification ability (net reclassification index: 1.07; $P < 0.001$; relative integrated discrimination improvement: 0.24; $P < 0.001$).

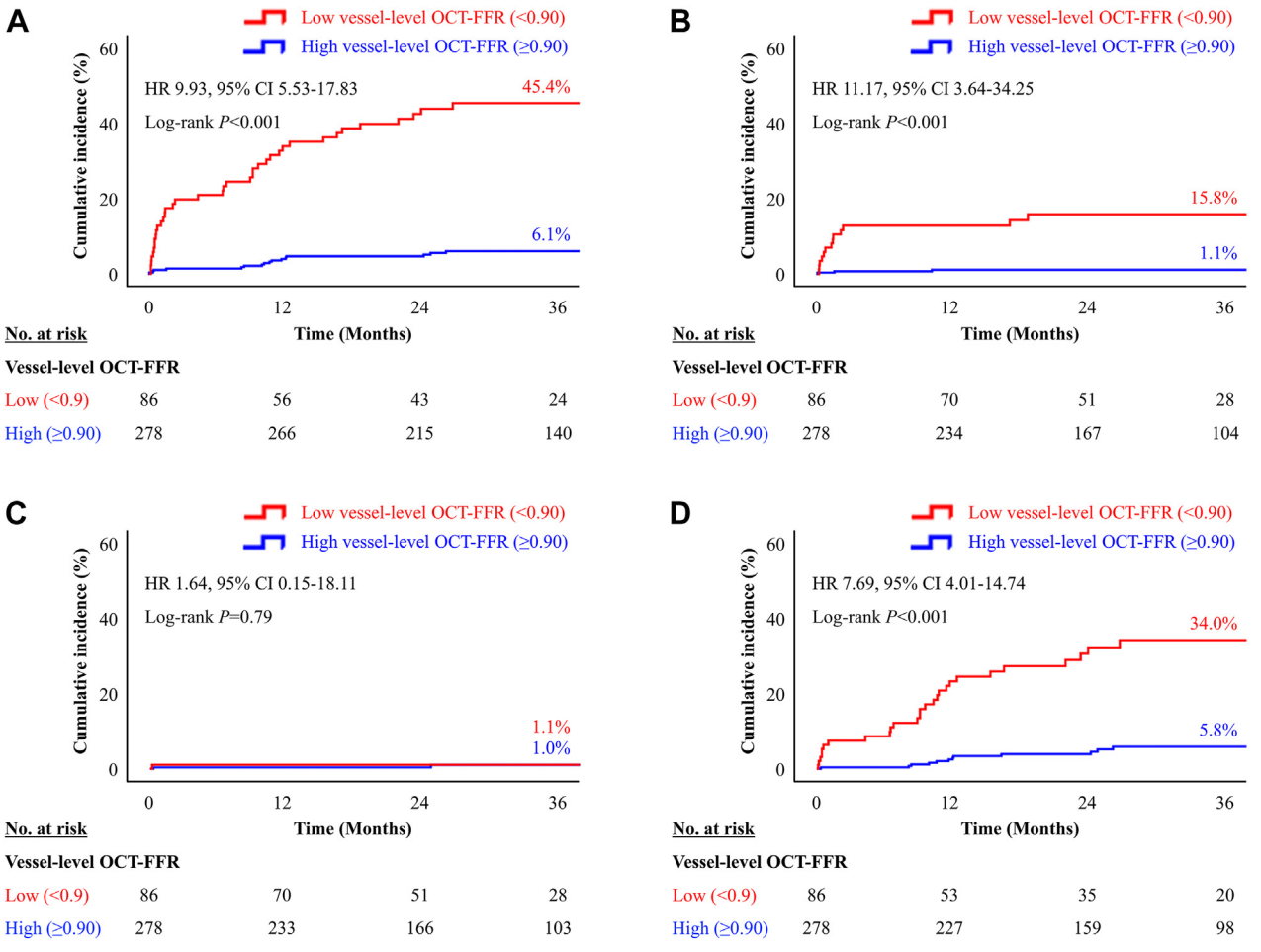
INDIVIDUAL EVALUATION ON STENTED PLUS REFERENCE SEGMENTS AND NCL. Relationship between stented plus reference segment-related findings and TLR. Comparisons between the TLR and non-TLR

TABLE 3 Cox Regression Analyses for Factors Associated With TVF After PCI in Patients With ACS

	Univariable Regression			Multivariable Regression		
	HR	95% CI	*P* Value	HR	95% CI	*P* Value
Traditional cardiovascular risk factors						
Age	1.01	0.99–1.04	0.23			
Male	1.06	0.57–1.99	0.85			
BMI	1.01	0.94–1.09	0.77			
Hypertension	1.07	0.60–1.02	0.83			
Dyslipidemia	0.74	0.43–1.27	0.27			
Diabetes mellitus	0.93	0.54–1.61	0.80			
Smoking	0.84	0.48–1.46	0.54			
LVEF	0.96	0.94–0.98	0.001	0.96	0.93–0.98	<0.001
Statin use at discharge	0.18	0.093–0.35	<0.001	0.33	0.16–0.67	0.002
Multivessel disease	2.18	1.28–3.74	0.004			
Target vessel						
Vessel-level OCT-FFR (per 0.1 increase)	0.40	0.34–0.48	<0.001	0.38	0.29–0.49	<0.001
Average lumen area	0.77	0.66–0.89	0.001			
MLA	0.53	0.42–0.68	<0.001			
Stented segment						
Stent-level OCT-FFR (per 0.1 increase)	0.29	0.18–0.48	<0.001			
Average lumen area	0.81	0.71–0.94	0.005			
Average stent area	0.93	0.72–0.96	0.010			
In-stent MLA	0.83	0.71–0.97	0.016			
MSA	0.83	0.71–0.97	0.016			
Irregular protrusion	2.05	1.14–3.68	0.016			
Thrombus	3.17	1.85–5.41	<0.001	1.86	1.05–3.29	0.033
Calcified nodule	2.42	1.04–5.66	0.041			
Reference segment						
Stent edge dissection at proximal reference	3.32	1.62–6.80	0.001			
Stent edge dissection at distal reference	2.90	1.31–6.42	0.009			
LRP at proximal reference	2.29	1.33–3.96	0.003	1.77	1.01–3.12	0.048
LRP at distal reference	1.96	1.03–3.71	0.041			
TCFA at proximal reference	2.40	1.13–5.08	0.022			
Average reference lumen area	0.80	0.70–0.91	0.001	0.77	0.67–0.89	<0.001
NCL						
NCL-level OCT-FFR (per 0.1 increase)	0.45	0.38–0.54	<0.001			
Lesion length	1.07	1.04–1.11	<0.001			
MLA	0.73	0.64–0.85	<0.001			
LRP	1.89	1.10–3.26	0.021			
TCFA	3.81	2.21–6.59	<0.001	2.56	1.43–4.60	0.002

HR corresponds to an increase of 1 unit for each variable except for OCT-FFR.
ACS = acute coronary syndrome; other abbreviations as in **Tables 1 and 2**.

FIGURE 3 Kaplan-Meier Curves of Each Clinical Outcome According to Vessel-Level OCT-FFR

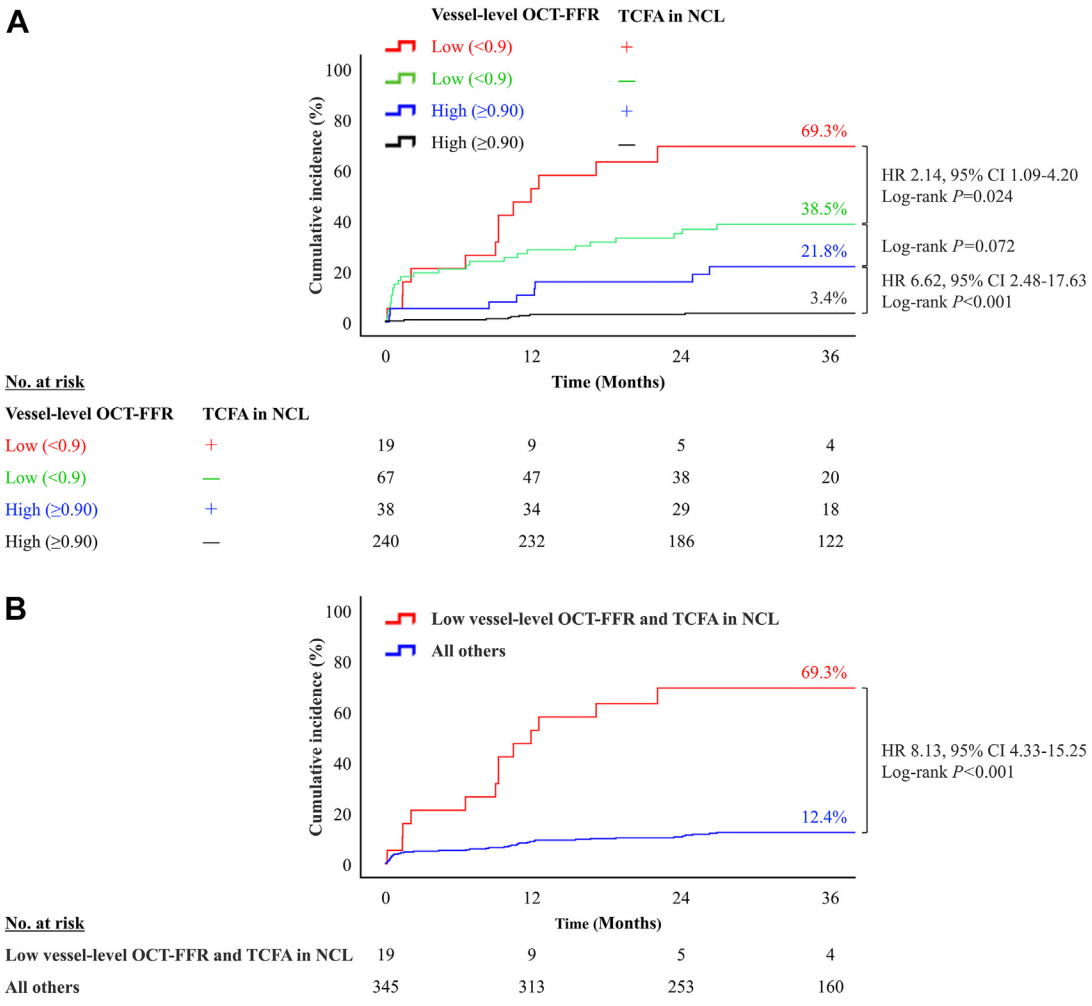


(A) TVF. **(B)** Cardiac death. **(C)** Target vessel-related myocardial infarction. **(D)** Target vessel revascularization (TVR). The incidence of TVF was 9.9 times higher in vessels with low vessel-level OCT-FFR (<0.90) than in those with high vessel-level OCT-FFR (≥0.90). The incidence of cardiac death and TVR was significantly higher in vessels with low vessel-level OCT-FFR (<0.90) than in those with high vessel-level OCT-FFR (≥0.90). Abbreviations as in Figure 2.

groups are presented in Supplemental Tables 3 and 4. The multivariable Cox regression analyses for TLR showed that low stent-level OCT-FFR, multiple stents, in-stent thrombus, stent edge dissection at the distal reference segment, and TCFA at the distal reference segment were independently associated with TLR (Supplemental Table 5). Supplemental Figure 5 shows the C-index, net reclassification index, and relative integrated discrimination improvement values for the 3 models. Compared with model 1 (baseline cardiovascular risk factors and multiple stents), model 2 (model 1 plus post-PCI OCT findings) showed numerically high discriminatory ability (C-index: 0.87 vs 0.72; $P = 0.062$) in identifying patients with subsequent TLR, but this difference was not significant. Conversely, model 3 (model 2 plus stent-level OCT-FFR) showed a significantly higher discriminatory ability (C-index: 0.90 vs 0.72; $P = 0.021$) and reclassification ability (net reclassification index: 0.99; $P < 0.001$; relative integrated discrimination improvement: 0.27; $P < 0.001$) than model 1.

Relationship between NCL-related findings and non-TLR TVR. Comparisons between the non-TLR TVR group and the others are presented in Supplemental Tables 6 and 7. The multivariable Cox regression analyses for non-TLR TVR showed that low NCL-level OCT-FFR and TCFA in NCLs were independently associated with non-TLR TVR (Supplemental Table 8). Among the 3 models, model 3 (model 2 plus NCL-level OCT-FFR) showed the

FIGURE 4 Kaplan-Meier Curves of TVF According to Low Vessel-Level OCT-FFR, the Presence of TCFA in NCL, or Both



(A) The TVF rate was the highest in vessels with both low vessel-level OCT-FFR and thin-cap fibroatheroma (TCFA) in NCL, followed by those with 1 of the features and those without both features. **(B)** The TVF rate of vessels with both low vessel-level OCT-FFR and TCFA in NCL was 8.1 times higher than that of all other vessels. Abbreviations as in Figure 2.

highest discriminatory ability (C-index: 0.88) and highest reclassification ability (net reclassification index: 1.36; relative integrated discrimination improvement: 0.19) in identifying patients with subsequent non-TLR TVR, and the differences were significant (Supplemental Figure 6).

DISCUSSION

This study showed that: 1) despite angiographically satisfactory PCI results, post-PCI OCT-FFR showed a wide variation in patients with ACS who underwent OCT-guided PCI; 2) vessel-level, stent-level, and NCL-level OCT-FFR were significantly lower in the TVF group than in the non-TVF group; 3) in addition to patient characteristics and post-OCT findings, low vessel-level OCT-FFR was independently associated with TVF after PCI in patients with ACS; and 4) the TVF rate of vessels with both low vessel-level OCT-FFR and TCFA in the NCL was 8.1 times higher than that of all other vessels. Finally, we demonstrated the incremental value of vessel-level OCT-FFR in identifying patients with subsequent TVF beyond morphological OCT findings (**Central Illustration**). This study is the first real-world cohort with long-term follow-up clarifying the clinical utility of OCT-FFR

TABLE 4 Logistic Regression Analyses for Factors Associated With Low Vessel-Level OCT-FFR (<0.90)

	Univariable Regression			Multivariable Regression		
	OR	95% CI	*P* Value	OR	95% CI	*P* Value
Age, y	1.03	1.01–1.05	0.015			
Male	0.65	0.38–1.11	0.12			
Lesion location						
LAD	4.27	2.19–8.33	<0.001	4.60	1.84–11.47	0.001
LCx	3.22	1.35–7.68	0.008	2.20	0.70–6.90	0.18
RCA	ref	ref	ref	ref	ref	ref
Lesion length	0.99	0.96–1.01	0.35			
Stent diameter	0.24	0.13–0.44	<0.001			
Stent length	1.02	0.10–1.04	0.081			
Stented segment						
Average lumen area	0.65	0.56–0.76	<0.001			
In-stent MLA	0.61	0.51–0.73	<0.001	0.73	0.57–0.92	0.009
Stent underexpansion	1.16	0.69–1.93	0.58			
Irregular protrusion	1.43	1.87–2.35	0.16			
Thrombus	2.26	1.36–3.76	0.002	2.02	1.01–4.03	0.047
Calcified nodule	1.16	0.41–3.33	0.78			
Reference segment						
Stent edge dissection at proximal reference	3.94	1.67–9.28	0.002	5.51	1.48–20.56	0.011
Stent edge dissection at distal reference	1.96	0.75–5.16	0.17			
Thrombus at proximal reference	1.86	1.02–3.40	0.045			
Thrombus at distal reference	1.24	0.55–2.77	0.61			
Calcified nodule at proximal reference	0.46	0.055–3.76	0.47			
Calcified nodule at distal reference	1.62	0.15–18.13	0.69			
Average reference lumen area	0.64	0.56–0.75	<0.001			
NCL						
Lesion length	1.12	1.06–1.18	<0.001	1.15	1.06–1.25	<0.001
MLA	0.40	0.32–0.50	<0.001	0.46	0.36–0.58	<0.001
Thrombus	3.93	1.61–9.61	0.003			
Calcified nodule	1.08	0.38–3.07	0.88			

OR corresponds to an increase of 1 unit for each variable.
Abbreviations as in Tables 1 and 2.

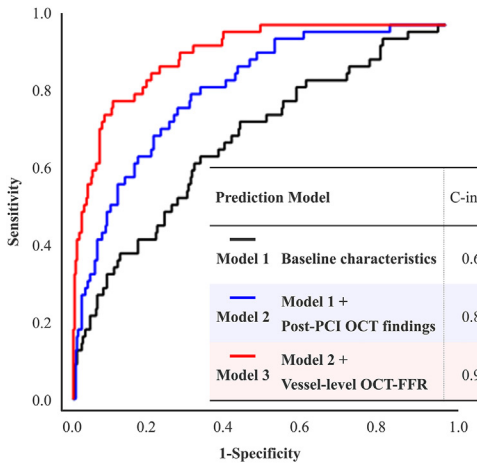
in identifying patients with subsequent TVF in patients with ACS treated with PCI.

ADVANTAGE OF POST-PCI OCT-FFR MEASUREMENT IN PATIENTS WITH ACS. Currently, FFR-guided decision making for PCI is the gold standard for managing patients with coronary artery disease. However, its value in patients with ACS is less well described. Theoretically, microcirculatory vasodilation during hyperemia can be transiently blunted in the acute phase of ACS, owing to myocardial necrosis or microemboli during PCI.[10] Therefore, post-PCI wire-based FFR may underestimate the physiological impact of stenotic lesions in target vessels in the acute phase of ACS. Van der Hoeven et al[11] assessed the reproducibility of wire-based FFR for NCLs after primary PCI for patients with ST-segment elevation myocardial infarction and demonstrated that FFR values during the index procedure were significantly elevated compared with the 30-day follow-up values, and this change was most pronounced in patients with larger infarcts. This suggests that the physiological significance of NCLs may be underestimated with wire-based FFR in the acute setting. Conversely, OCT-FFR uses only quantitative luminal information obtained from conventional OCT images to calculate the virtual FFR. Therefore, OCT-FFR offers a great advantage in evaluating the presence of ischemia in patients with ACS. Particularly in the setting of ACS, in which patients are often hemodynamically unstable, avoiding unnecessary hyperemia introduction can be an important advantage.

Furthermore, OCT can provide detailed information on high-risk vulnerable plaques. Recent reports have suggested that the presence of LRP and TCFA is predictive of future NCL-related major adverse cardiac events.[12] Our results also indicated that the presence of LRP at the proximal reference segment and TCFA in the NCL were associated with TVF independent of low vessel-level OCT-FFR. Furthermore, we found that the approach combining vessel-level OCT-FFR and post-PCI OCT findings significantly increased the discriminatory and reclassification ability in identifying patients with subsequent TVF. Considering that patients with ACS have a higher recurrence rate of ACS events, the combined approach with physiological assessment of the entire target vessel and qualitative nonculprit plaque evaluation could represent an optimal strategy for the management of these patients.

RELATIONSHIP BETWEEN POST-PCI OCT-FFR AND CLINICAL OUTCOMES. Previous studies have suggested a direct relationship between low post-PCI FFR and future adverse cardiac events.[1,2] Although the cutoff value can differ according to the target lesion, vessel, and characteristics of the patients enrolled in each trial, studies consistently suggested that post-PCI FFR >0.9 is an optimal functional endpoint of PCI.[13,14] We also found that the optimal cutoff value of vessel-level OCT-FFR was 0.90, consistent with previous reports. Although we did not measure post-PCI wire-based FFR in this study, Seike et al[3] demonstrated the accuracy of OCT-FFR using invasive wire-based FFR as a reference standard. The similarity among the cutoff values may indirectly support the accuracy of OCT-FFR measured in this study.

FIGURE 5 Discriminatory and Reclassification Ability of Predictive Models for TVF



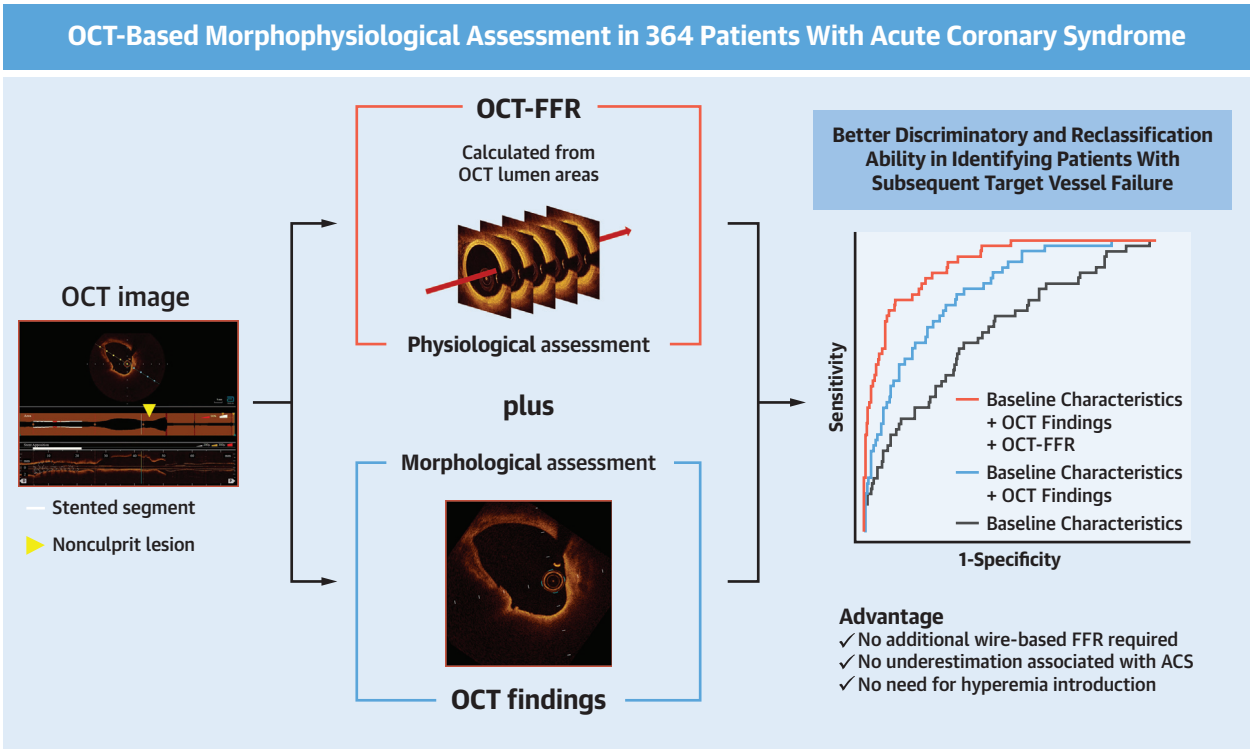
Prediction Model		C-index	*P*-value	NRI	*P*-value	Relative IDI	*P*-value
Model 1	Baseline characteristics	0.69					
Model 2	Model 1 + Post-PCI OCT findings	0.82	vs. Model 1 0.006	0.87	vs. Model 1 <0.001	0.13	vs. Model 1 <0.001
Model 3	Model 2 + Vessel-level OCT-FFR	0.92	vs. Model 2 0.005	1.07	vs. Model 2 <0.001	0.24	vs. Model 2 <0.001

Compared with model 1 (cardiovascular risk factors, left ventricular ejection fraction, and statin use at discharge), model 2 (model 1 plus post-percutaneous coronary intervention [PCI] OCT findings) showed a significantly higher discriminatory ability and higher reclassification ability in identifying patients with subsequent TVF. Compared with model 2, model 3 (model 2 plus vessel-level OCT-FFR) showed further increased discriminatory ability and incremental reclassification ability. IDI = integrated discrimination improvement; NRI = net reclassification index. Abbreviations as in Figure 2

Recent intravascular imaging studies have clarified the detailed mechanisms of unfavorable PCI outcomes within stented segments, and significant improvements in clinical outcomes have been demonstrated with intravascular imaging guidance compared with angiography guidance alone.[6] However, as PCI with stent implantation is a local treatment, intravascular imaging modalities usually focus on the stented segment, failing to consider the entire target vessel. In contrast, post-PCI FFR is a marker of residual epicardial resistance of the entire vessel during maximal microvascular vasodilation. The rationale for post-PCI FFR measurement is to evaluate both the extent of stent optimization and NCL burden, both of which can affect future prognosis. We found that low vessel-level OCT-FFR was a powerful independent factor associated with TVF. Therefore, in addition to stent optimization with intravascular imaging guidance, vessel-level OCT-FFR measurement and consideration of the need for additional PCI strategy may improve clinical outcomes after PCI.

We consider that there are 2 aspects of the potential benefit from measuring OCT-FFR after stenting. First, detection of unrecognized suboptimal stent deployment. In the present study, we found that low vessel-level OCT-FFR (<0.90) was independently associated with suboptimal OCT findings in the stented plus reference segments such as small in-stent minimum lumen area, the presence of in-stent thrombus, and stent edge dissection at the proximal reference segment. Therefore, we recommend that post-balloon dilatation, thrombus aspiration, and new stent placement are considered according to these morphological OCT findings in the stented segment. The separate analysis of stented plus reference segments showed that low stent-level OCT-FFR was independently associated with TLR after stenting, which may support our hypothesis. Importantly, these morphological OCT findings were associated with adverse clinical outcomes after stenting.[6] However, these findings may be missed during busy PCI, particularly for patients with ACS. Therefore, measuring OCT-FFR provides the opportunity to detect morphological findings and improve clinical outcomes in patients with ACS. Second, measuring OCT-FFR may detect overt or occult disease in the remaining part of the coronary artery. We found that a long lesion and small minimum lumen area in the NCL were independently associated with low vessel-level OCT-FFR and recommend considering additional PCI with new stent placement or balloon dilatation followed by drug-coated balloon in these cases. The separate analysis of NCL showed a direct relationship between low NCL-level OCT-FFR and non-TLR TVR, which may support our strategy. Conversely, as the presence of LRP and TCFA was

CENTRAL ILLUSTRATION **Optical Coherence Morphophysiological Assessments**



Kakizaki S, et al. J Am Coll Cardiol Intv. 2022;15(20):2035–2048.

Based on the optical coherence tomography (OCT) image immediately after primary percutaneous coronary intervention (PCI) for acute coronary syndrome (ACS) culprit lesion, we can perform both physiological and morphological assessment for ACS culprit vessels. This novel OCT-based morpho-physiological approach may enable better discrimination of patients with subsequent target vessel failure after PCI for ACS. FFR = fractional flow reserve.

associated with TVF independent of low vessel-level OCT-FFR, we recommend more intensive medical therapy for patients with such vulnerable plaques (eg, intensive statin and eicosapentaenoic acid administration). A prospective study is warranted to validate our hypothesis.

FEATURES OF POST-PCI OCT FINDINGS OF VESSELS WITH LOW VESSEL-LEVEL OCT-FFR. The extent of stent optimization is one of the most important factors affecting post-PCI FFR. Prati et al[6] and our group[15] have reported that suboptimal findings by OCT imaging (eg, in-stent minimum lumen area <4.5 mm^2, stent edge dissection, and in-stent thrombus) frequently occur after optimal angio-guided PCI, particularly in patients with ACS. In this study, an in-stent minimum lumen area <4.5 mm^2 was observed in 41.2% of vessels, stent edge dissection was observed in 11.3%, and in-stent thrombus was observed in 28.3%. Notably, vessels with TVF showed a significantly higher incidence of these findings than those without. Prati et al[6] reported that an in-stent minimum lumen area <4.5 mm^2 and stent edge dissection were independent predictors of major adverse cardiac events. We previously reported that the TLR incidence was significantly higher in patients with in-stent thrombus on OCT images than in those without.[16] Interestingly, our results indicated that the presence of these suboptimal findings translated into low vessel-level OCT-FFR. Small in-stent minimum lumen area, the presence of stent edge dissection at the proximal reference, and in-stent thrombus were independently associated with low vessel-level OCT-FFR. Therefore, low vessel-level OCT-FFR can be used as a sensitive marker to detect important poor prognostic findings in the stented segment. In patients with ACS who are often hemodynamically unstable, PCI does not always result in optimal stent deployment. This study found post-PCI suboptimal stent deployment in 65.7% of cases, with a tendency

toward a higher incidence of subsequent TVF during follow-up. In ACS cases, there is scope for further intervention based on post-PCI OCT-FFR findings to achieve stent optimization. A prospective study evaluating the clinical impact of measuring OCT-FFR in this setting is required.

STUDY LIMITATIONS. First, the study was retrospective; therefore, our results are subject to selection bias. Second, the range of OCT pullback varies with some cases of residual stenotic lesions outside the obtained OCT images. Third, although TVF is a composite outcome whose associated factors may be different in each clinical outcome, we could not separately assess each clinical outcome because of the limited sample size. Fourth, OCT-FFR has not been validated in patients with ACS. However, it may be difficult to evaluate the accuracy of OCT-FFR using wire-based FFR because post-PCI wire-based FFR may underestimate the physiological impact of stenotic lesions in ACS. Fifth, OCT-FFR has not been validated in patients with newly deployed stents. Although Poiseuille's formula and the Borda-Carnot equation were adopted for the calculation of virtual FFR in this study, in principle, these equations should apply to laminar flow (with a Newtonian fluid, fully developed and with steady flow). However, as all PCI procedures were conducted under OCT guidance with current-generation thin-strut drug-eluting stents (<90-μm strut thickness), we consider that the impact of stent struts on our OCT-FFR calculation should be minimal. Finally, although vessel-level OCT-FFR and some OCT findings were clearly associated with worse outcomes, a further prospective study will be warranted to investigate whether an OCT-based morphophysiological approach will improve clinical outcomes.

CONCLUSIONS

This study revealed that vessel-level OCT-FFR was an independent factor associated with TVF after PCI in patients with ACS. Adding the OCT-FFR measurement to post-PCI OCT findings enables better discrimination of patients with subsequent TVF after PCI for ACS. OCT-FFR measurement and consideration of additional PCI strategies may improve clinical outcomes in patients with ACS.

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PERSPECTIVES

WHAT IS KNOWN? Previous studies have suggested a direct relationship between low post-PCI wire-based FFR and future adverse cardiac events, although post-PCI wire-based FFR may underestimate the physiological impact of stenotic lesions in ACS. Conversely, OCT-FFR uses only quantitative luminal information obtained from conventional OCT images, and the accuracy of OCT-FFR has been verified using invasive wire-based FFR as a reference standard.

WHAT IS NEW? The vessel-level OCT-FFR was an independent factor associated with TVF after PCI in patients with ACS, and adding this measurement to post-PCI OCT findings may enable better discrimination of patients with subsequent TVF after PCI for ACS.

WHAT IS NEXT? A prospective study with a larger sample size is needed to further evaluate the clinical impact of measuring OCT-FFR in the setting of ACS.

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KEY WORDS acute coronary syndrome, fractional flow reserve, optical coherence tomography, percutaneous coronary intervention, target vessel failure

APPENDIX For an expanded Methods and References sections and supplemental tables and figures, please see the online version of this paper.