Circulation Journal
Circ J 2023; 87: 1689–1702
doi:10.1253/circj.CJ-22-0837

Comparison of the OPTIVUS-Complex PCI Multivessel Cohort With the Historical CREDO-Kyoto Registry Cohort-3

Ko Yamamoto, MD; Hiroki Shiomi, MD; Takeshi Morimoto, MD; Hiroki Watanabe, MD; Akiyoshi Miyazawa, MD; Kyohei Yamaji, MD; Masanobu Ohya, MD; Sunao Nakamura, MD; Satoru Mitomo, MD; Satoru Suwa, MD; Takenori Domei, MD; Shojiro Tatsushima, MD; Koh Ono, MD; Hiroki Sakamoto, MD; Kiyotaka Shimamura, MD; Masataka Shigetoshi, MD; Ryoji Taniguchi, MD; Yuji Nishimoto, MD; Hideki Okayama, MD; Kensho Matsuda, MD; Kenji Nakatsuma, MD; Yohei Takayama, MD; Jun Kuribara, MD; Hidekuni Kirigaya, MD; Kohei Yoneda, MD; Yuta Imai, MD; Umihiko Kaneko, MD; Hiroshi Ueda, MD; Kota Komiyama, MD; Naotaka Okamoto, MD; Satoru Sasaki, MD; Kengo Tanabe, MD; Mitsuru Abe, MD; Kiyoshi Hibi, MD; Kazushige Kadota, MD; Kenji Ando, MD; Takeshi Kimura, MD on behalf of the OPTIVUS-Complex PCI Investigators

Background: There is a paucity of data on the effect of optimal intravascular ultrasound (IVUS)-guided percutaneous coronary intervention (PCI) compared with standard PCI or coronary artery bypass grafting (CABG) in patients with multivessel disease.

Methods and Results: The OPTIVUS-Complex PCI study multivessel cohort was a prospective multicenter single-arm study enrolling 1,021 patients undergoing multivessel PCI including the left anterior descending coronary artery using IVUS aiming to meet the prespecified criteria for optimal stent expansion. We conducted propensity score matching analyses between the OPTIVUS group and historical PCI or CABG control groups from the CREDO-Kyoto registry cohort-3 (1,565 and 899 patients) fulfilling the inclusion criteria for this study. The primary endpoint was a composite of death, myocardial infarction, stroke, or any coronary revascularization. In the propensity score-matched cohort (OPTIVUS vs. historical PCI control: 926 patients in each group; OPTIVUS vs. historical CABG control: 436 patients in each group), the cumulative 1-year incidence of the primary endpoint was significantly lower in the OPTIVUS group than in the historical PCI control group (10.4% vs. 23.3%; log-rank P<0.001) or the historical CABG control group (11.8% vs. 16.5%; log-rank P=0.02).

Conclusions: IVUS-guided PCI targeting the OPTIVUS criteria combined with contemporary clinical practice was associated with superior clinical outcomes at 1 year compared with not only the historical PCI control, but also the historical CABG control.

Key Words: Drug-eluting stent; Intravascular ultrasound; Percutaneous coronary intervention

The 1-year results of the OPTIVUS-Complex PCI (Optimal Intravascular Ultrasound Guided Complex Percutaneous Coronary Intervention) study multivessel cohort showed that intravascular ultrasound (IVUS)-guided percutaneous coronary intervention (PCI) targeting the prespecified optimal IVUS criteria (OPTIVUS criteria) was associated with significantly and numerically lower rates of the primary cardiovascular composite endpoint compared with the predefined performance goals derived from patients undergoing PCI and coronary artery bypass grafting (CABG), respectively, in the CREDO-Kyoto (Coronary REvascularization Demonstrating Outcome Study in Kyoto) Registry Cohort-2 of patients

Editorial p1703

Received January 4, 2023; revised manuscript received January 29, 2023; accepted February 15, 2023; J-STAGE Advance Publication released online March 11, 2023 Time for primary review: 21 days

Department of Cardiovascular Medicine, Kyoto University Graduate School of Medicine, Kyoto (K. Yamamoto, H. Shiomi, K. Yamaji, K.O., T.K.); Department of Clinical Epidemiology, Hyogo College of Medicine, Nishinomiya (T.M.); Department of Cardiology, Japanese Red Cross Wakayama Medical Center, Wakayama (H.W., S.T.); Cardiocore Japan, Tokyo (A.M.); Department of Cardiology, Kurashiki Central Hospital, Kurashiki (M.O., K. Kadota); Department of Cardiovascular Medicine, New Tokyo Hospital, Matsudo (S.N., S.M.); Department of Cardiology, Juntendo University Shizuoka Hospital, Izunokuni (S. Suwa); Department of Cardiology, Kokura Memorial Hospital, Kitakyushu (T.D., K.A.); Department of Cardiology, Shizuoka General Hospital, Shizuoka (H. Sakamoto, K.S.); Department of Cardiology, National Hospital Organization Okayama Medical Center, Okayama (M.S.); Department of Cardiology, Hyogo Prefectural Amagasaki General Medical Center, Amagasaki (R.T., Y.N.);
(Footnote continued the next page.)

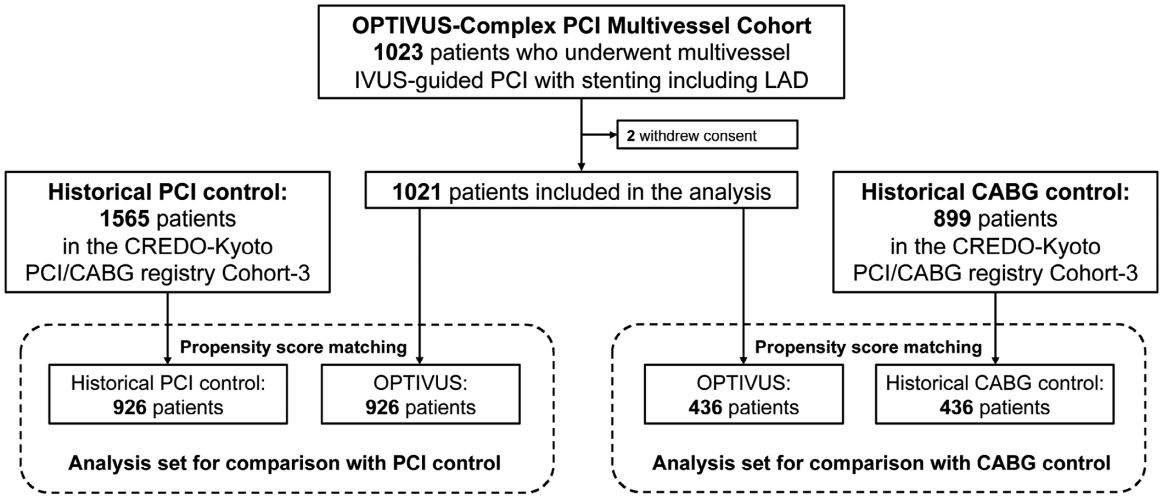


Figure 1. Study flowchart. CABG, coronary artery bypass grafting; CREDO-Kyoto, Coronary REvascularization Demonstrating Outcome Study in Kyoto; IVUS, intravascular ultrasound; LAD, left anterior descending coronary artery; OPTIVUS, OPTimal IntraVascular UltraSound; PCI, percutaneous coronary intervention.

with multivessel disease including the left anterior descending coronary artery (LAD) target.[1] However, the patient population in whom the performance goals were estimated underwent coronary revascularization between 2005 and 2007, a time when clinical practice was much different from contemporary clinical practice in terms of target lesion selection, coronary stent design, interventional and surgical techniques, and pharmacological therapy.[2] In addition, due to lack of IVUS data in the CREDO-Kyoto Registry Cohort-2, we could not assess whether IVUS-guided PCI targeting the prespecified IVUS criteria in OPTIVUS resulted in optimal stent expansion compared with PCI using IVUS without a specific target. To overcome these limitations, we performed a prespecified analysis comparing the IVUS data and clinical outcomes between the OPTIVUS and more recent historical control populations who underwent PCI or CABG in the new-generation drug-eluting stent (DES) era.

Methods

Study Design and Population

The OPTIVUS-Complex PCI study was a prospective multicenter single-arm study that enrolled patients undergoing left main coronary artery (LMCA) PCI or multivessel PCI including a target lesion in the LAD. The PCI operators were mandated to perform optimal IVUS-guided PCI with an intention to meet the prespecified criteria (OPTIVUS criteria) for optimal stent implantation. This paper reports the multivessel cohort; the study design, patient enrollment, and main results at 1 year have been reported in detail previously.[1] Briefly, between March 2019 and April 2021, 1,023 patients who underwent IVUS-guided multivessel PCI including an LAD target in 90 Japanese centers were enrolled. Excluding 2 patients who withdrew consent, 1,021 patients constituted the present study population of the multivessel cohort from the OPTIVUS-Complex PCI study (**Figure 1**). As the historical control groups, we selected the patients in the CREDO-Kyoto PCI/CABG registry cohort-3 (CREDO-Kyoto Registry Cohort-3), which was a multicenter registry enrolling consecutive patients who underwent first coronary revascularization with PCI or isolated CABG at 22 Japanese centers between January 2011 and December 2013.[3] Among 14,927 patients in CREDO-Kyoto Registry Cohort-3, we extracted those patients who fulfilled the inclusion criteria for the OPTIVUS-Complex PCI multivessel cohort (historical PCI control group: n=1,565; historical CABG control group: n=899;

Department of Cardiology, Ehime Prefectural Central Hospital, Matsuyama (H.O., K.M.); Department of Cardiology, Mitsubishi Kyoto Hospital, Kyoto (K.N.); Department of Cardiology, Hamamatsu Medical Center, Hamamatsu (Y.T.); Department of Cardiology, Gunma Prefectural Cardiovascular Center, Maebashi (J.K.); Division of Cardiology, Yokohama City University Medical Center, Yokohama (H.K., K.H.); Department of Cardiology, Tokushima Red Cross Hospital, Tokushima (K. Yoneda); Department of Cardiology, Saiseikai Shiga Hospital, Ritto (Y.I.); Department of Cardiology, Sapporo Heart Center, Sapporo Cardiovascular Clinic, Sapporo (U.K.); Department of Cardiovascular Medicine, Koseikai Takai Hospital, Tenri (H.U.); Division of Cardiology, Mitsui Memorial Hospital, Tokyo (K. Komiyama, K.T.); Division of Cardiology, Osaka Rosai Hospital, Sakai (N.O.); Division of Cardiovascular Medicine, Department of Internal Medicine, Kobe University Graduate School of Medicine, Kobe (S. Sasaki); and Department of Cardiology, National Hospital Organization Kyoto Medical Center, Kyoto (M.A.), Japan

This paper was presented at the 87th Annual Scientific Meeting of the Japanese Circulation Society, Late Breaking Clinical Trials 2-4 (March 11, 2023, Fukuoka, Japan).

Mailing address: Takeshi Kimura, MD, Department of Cardiovascular Medicine, Kyoto University Graduate School of Medicine, 54 Shogoin Kawahara-cho, Sakyo-ku, Kyoto 606-8507, Japan. email: taketaka@kuhp.kyoto-u.ac.jp

ISSN-1346-9843

Figure 1). The extraction process and 5-year clinical outcomes of the historical control groups have been reported in detail previously.[3] This study was performed in accordance with the Declaration of Helsinki.

Study Procedures and OPTIVUS Criteria

Enrolled patients were to undergo PCI using platinum-chromium everolimus-eluting stents (Synergy; Boston Scientific, Marlborough, MA, USA). IVUS-guided PCI was mandatory to optimize stent expansion and apposition according to the OPTIVUS criteria. The most important criteria for stent expansion in lesions other than LMCA were as follows: minimum stent area (MSA) greater than the distal reference lumen area if the stent length was ≥28 mm and MSA greater than 0.8×average reference lumen area if the stent length was <28 mm (average reference lumen area = [proximal reference lumen area + distal reference lumen area]/2). All OPTIVUS criteria are described in the **Supplementary File**. These criteria were selected according to the IVUS-XPL (Impact of IntraVascular UltraSound Guidance on Outcomes of Xience Prime Stents in Long Lesions) trial and the expert consensus document of the European Association of Percutaneous Cardiovascular Interventions.[4,5] Preintervention IVUS was also recommended to help choose the appropriate balloon/stent sizes and the modalities for lesion preparation. Quantitative and qualitative coronary angiography and IVUS analyses were performed by an independent core laboratory (Cardiocore, Tokyo, Japan). Among the 1,021 study patients, coronary angiograms and IVUS images were available for 1,021 (100%) and 1,013 (99.2%) patients, respectively, and were deemed suitable for evaluation by the core laboratory for 1,017 (99.6%), and 982 (96.2%) patients, respectively. In the historical PCI control in the CREDO-Kyoto Registry Cohort-3 (n=1,565), 200 patients were randomly selected for the quantitative and qualitative coronary angiography and IVUS analyses by the same core laboratory. Among these 200 patients, coronary angiograms and IVUS images were available for 160 (80.0%) and 145 (72.5%) patients, respectively, and were deemed suitable for evaluation by the core laboratory for 144 (72.0%) and 133 (66.5%) patients, respectively.

In addition to the IVUS-related recommendations, there were other recommendations to adopt the contemporary clinical, procedural, and pharmacological practice. Target lesions were to be selected based on a stress imaging or physiological assessment (fractional flow reserve [FFR] or instantaneous wave-free ratio [iFR]). Radial access was recommended as the standard approach. PCI for chronic total occlusion (CTO) was to be performed by a dedicated CTO operator. The use of rotational atherectomy was recommended in severely calcified lesions. A proximal optimization technique was recommended in the case of bifurcation lesions. Kissing balloon inflation was recommended if the bifurcation lesions were treated with 2-sent techniques. Scheduled follow-up coronary angiography after PCI was discouraged in asymptomatic patients. Recommended pharmacological management included the use of high-intensity statins therapy with the maximum approved dose of strong statins in Japan, and short-duration (3–6 months) dual antiplatelet therapy (DAPT) after PCI.

Endpoints

The primary endpoint was major cardiac and cerebrovascular events (MACCE), defined as a composite of death from any cause, myocardial infarction, stroke, or any coronary revascularization. Myocardial infarction was adjudicated according to the Academic Research Consortium definition.[6] Stroke was defined as ischemic or hemorrhagic stroke with neurological symptoms lasting >24 h. Scheduled staged coronary revascularization procedures performed within 3 months after the index PCI were not regarded as follow-up events, but included in the index procedure. The definitions of secondary endpoints are provided in the **Supplementary File**. All endpoints were assessed at 1 year (between 335 and 394 days), with censoring on Day 366. All clinical events comprising the primary endpoint were adjudicated based on the source documents by the independent clinical event committee.

Statistical Analysis

Categorical variables are presented as numbers and percentages and were compared using the Chi-squared test. Continuous variables are presented as the mean±SD or as the median with interquartile range and were compared using Student's t-test or the Wilcoxon rank-sum test depending on their distribution. Cumulative incidence was estimated with the Kaplan-Meier method, and differences were assessed with log-rank tests.

Due to the different nature of cohorts between the OPTIVUS group and the historical PCI or CABG control groups in the CREDO-Kyoto registry cohort-3, we used propensity score matching as the main analysis. We used a multivariable logistic regression model to develop a propensity score with 21 clinically relevant variables (age ≥75 years, male sex, body mass index <25 kg/m^2, acute coronary syndrome, hypertension, diabetes, current smoking, heart failure, prior myocardial infarction, prior stroke, peripheral vascular disease, estimated glomerular filtration rate <30 mL/min/1.73 m^2 without hemodialysis, hemodialysis, prior atrial fibrillation, hemoglobin <11.0 g/dL, platelet count <100×10^9/L, malignancy, severe frailty, extent of coronary artery disease, proximal LAD target, CTO target). To create the propensity score-matched cohort, patients in the OPTIVUS group were matched to those in the PCI or CABG groups in the CREDO-Kyoto Registry Cohort-3 using a 1:1 greedy matching technique. We evaluated hazard ratios (HRs) with their 95% confidence intervals (CIs) to assess the risk of the OPTIVUS group relative to the historical PCI or CABG control group for the primary and secondary endpoints. In addition, we conducted a 30-day landmark analysis for the primary endpoint. Moreover, we conducted subgroup analysis stratified by the SYNTAX score for the primary endpoint. As a sensitivity analysis, we constructed multivariable Cox proportional hazard models to assess the risk of the OPTIVUS group relative to the historical PCI or CABG control group in the entire study population before matching. Detailed methods of the multivariable analysis are provided in the **Supplementary File**.

All P values are 2-tailed and P<0.05 was considered statistically significant. All analyses were performed with JMP version 15.2 software (SAS Institute Inc., Cary, NC, USA) and R version 4.1.2 (R Foundation for Statistical Computing, Vienna, Austria).

Results

Baseline Characteristics: OPTIVUS vs. Historical PCI Control

In the entire cohort, patients in the OPTIVUS group were older, more often men, and more often presented as acute

coronary syndrome than those in the historical PCI control group (**Table 1**). Patients in the OPTIVUS group more often had diabetes, but less often had other comorbidities, such as heart failure, mitral regurgitation, history of stroke, and anemia, compared with the historical PCI control group. The prevalence of severe frailty did not differ between the 2 groups. Regarding angiographic and procedural characteristics, invasive FFR or iFR and the radial approach were more often used in patients in the OPTIVUS than historical PCI control group. Compared with the historical PCI control group, patients in the OPTIVUS group less often had complex coronary anatomy, as indicated by a lower SYNTAX score and a lower prevalence of a CTO target. The prevalence of procedural complications was lower in patients in the OPTIVUS than historical PCI control group. In terms of medication at discharge, 44.3% of patients selected prasugrel as a $P2Y_{12}$ inhibitor in the OPTIVUS group, whereas the vast majority of patients in the historical PCI control group selected clopidogrel as the $P2Y_{12}$ inhibitor. The prescription rates of statins, high-intensity statins, β-blockers, and proton pump inhibitors or histamine H_2 receptor blockers were higher in the OPTIVUS than historical PCI control group, whereas the prescription rate of angiotensin converting enzyme inhibitors (ACEI) or angiotensin II receptor blockers (ARB) was higher in the historical PCI control group than in the OPTIVUS group (**Table 1**).

In the propensity score-matched cohort, baseline characteristics were mostly well balanced between the OPTIVUS and historical PCI control groups, except for a lower left ventricular ejection fraction in the OPTIVUS group than in the historical PCI control group (**Table 1**).

Angiographic and Procedural Characteristics: OPTIVUS vs. Historical PCI Control

The mean SYNTAX score was lower in the OPTIVUS than historical PCI control group, which was not balanced even after propensity score matching (**Table 1**). Nevertheless, in the propensity score-matched cohort, there was no imbalance in those factors indicating procedural complex-

Table 1. Baseline Characteristics for the OPTIVUS and CREDO-Kyoto Registry Cohort-3 Historical PCI Control Groups

	Entire cohort			Propensity score-matched cohort		
	OPTIVUS (n=1,021)	PCI historical control (n=1,565)	P value	OPTIVUS (n=926)	PCI historical control (n=926)	P value
Clinical characteristics						
Age (years)	71.2±10.0	70.2±10.3	0.02	71.1±10.0	70.6±10.5	0.28
≥75 years	427 (41.8)	566 (36.2)	0.004	372 (40.2)	375 (40.5)	0.89
Men	803 (78.6)	1,112 (71.1)	<0.001	716 (77.3)	719 (77.6)	0.87
BMI (kg/m^2)	24.1±3.5	24.0±3.7	0.77	24.1±3.6	24.2±3.8	0.60
BMI <25 kg/m^2	666 (65.2)	1,007 (64.3)	0.65	605 (65.3)	577 (62.3)	0.18
Acute coronary syndrome	145 (14.2)	89 (5.7)	<0.001	82 (8.9)	85 (9.2)	0.81
Acute myocardial infarction	68 (6.7)	70 (4.5)	0.02	44 (4.8)	68 (7.3)	0.02
Unstable angina	77 (7.5)	19 (1.2)	<0.001	38 (4.1)	17 (1.8)	0.004
Hypertension	860 (84.2)	1,351 (86.3)	0.14	785 (84.8)	789 (85.2)	0.80
Diabetes	560 (54.8)	740 (47.3)	<0.001	492 (53.1)	492 (53.1)	1.00
On insulin therapy	95 (9.3)	175 (11.2)	0.13	89 (9.6)	111 (12.0)	0.10
Current smoking	176 (17.2)	326 (20.8)	0.02	166 (17.9)	175 (18.9)	0.59
HF	178 (17.4)	334 (21.3)	0.02	171 (18.5)	149 (16.1)	0.18
Prior hospitalization for HF	87 (8.5)	117 (7.5)	0.34	85 (9.2)	55 (5.9)	0.01
Current HF at index hospitalization	133 (13.0)	263 (16.8)	0.01	126 (13.6)	118 (12.7)	0.58
LVEF (%)	57.7±12.3	59.3±13.5	0.002	57.4±12.3	60.3±12.8	<0.001
LVEF <40%	114 (11.2)	157 (11.2)	0.94	108 (11.8)	73 (8.8)	0.04
Mitral regurgitation grade ≥3/4	30 (2.9)	96 (6.8)	<0.001	29 (3.1)	40 (4.8)	0.08
Prior myocardial infarction	180 (17.6)	303 (19.4)	0.27	165 (17.8)	156 (16.8)	0.58
Prior stroke	119 (11.7)	230 (14.7)	0.03	114 (12.3)	123 (13.3)	0.53
Peripheral vascular disease	116 (11.4)	164 (10.5)	0.48	99 (10.7)	105 (11.3)	0.66
eGFR <30 mL/min/1.73 m^2 or hemodialysis	97 (9.5)	139 (8.9)	0.59	86 (9.3)	82 (8.9)	0.75
eGFR <30 mL/min/1.73 m^2 without hemodialysis	38 (3.7)	51 (3.3)	0.53	36 (3.9)	33 (3.6)	0.71
Hemodialysis	59 (5.8)	88 (5.6)	0.87	50 (5.4)	49 (5.3)	0.92
AF	85 (8.3)	129 (8.2)	0.94	80 (8.6)	75 (8.1)	0.68
Anemia (hemoglobin <11.0 g/dL)	96 (9.4)	213 (13.6)	0.001	92 (9.9)	88 (9.5)	0.75
Thrombocytopenia (platelets <100×10^9/L)	10 (1.0)	24 (1.5)	0.23	10 (1.1)	11 (1.2)	0.83
Malignancy	126 (12.3)	179 (11.4)	0.49	117 (12.6)	117 (12.6)	1.00
Severe frailty[A]	39 (3.8)	58 (3.7)	0.88	37 (4.0)	34 (3.7)	0.72
ARC-HBR	539 (52.8)	799 (51.1)	0.39	487 (52.6)	466 (50.3)	0.33

(**Table 1** continued the next page.)

	Entire cohort			Propensity score-matched cohort		
	OPTIVUS (n=1,021)	PCI historical control (n=1,565)	P value	OPTIVUS (n=926)	PCI historical control (n=926)	P value
Procedural characteristics						
Preprocedure tests	215 (21.1)	376 (24.0)	0.08	199 (21.5)	220 (23.8)	0.24
Stress electrocardiogram	104 (10.2)	214 (13.7)		97 (10.5)	131 (14.1)	
SPECT	94 (9.2)	182 (11.6)		86 (9.3)	105 (11.3)	
Cardiac magnetic resonance	9 (0.9)	1 (0.1)		7 (0.8)	0 (0)	
Stress echocardiography	3 (0.3)	10 (0.6)		3 (0.3)	6 (0.6)	
FFR-CT	10 (1.0)	0 (0)		10 (1.1)	0 (0)	
Invasive FFR or iFR	304 (29.8)	139 (8.9)	<0.001	282 (30.5)	89 (9.6)	<0.001
Intracoronary imaging	1,021 (100)	1,355 (86.6)	<0.001	926 (100)	801 (86.5)	<0.001
IVUS	1,021 (100)	1,352 (86.4)		926 (100)	800 (86.4)	
OCT	0 (0)	70 (4.5)		0 (0)	47 (5.1)	
Approach						
Radial artery	893 (87.5)	885 (56.5)	<0.001	811 (87.6)	544 (58.7)	<0.001
Femoral artery	235 (23.0)	674 (43.1)	<0.001	216 (23.3)	378 (40.8)	<0.001
Brachial artery	56 (5.5)	304 (19.4)	<0.001	54 (5.8)	173 (18.7)	<0.001
Extent of coronary artery disease			0.94			0.33
2-vessel disease	813 (79.6)	1,248 (79.7)		744 (80.3)	727 (78.5)	
3-vessel disease	208 (20.4)	317 (20.3)		182 (19.7)	199 (21.5)	
SYNTAX score[B]	18.1±7.2	23.9±8.8	<0.001	18.2±7.3	23.5±8.6	<0.001
Low (<23)	794 (78.5)	395 (46.3)		719 (78.4)	243 (49.1)	
Intermediate (23–32)	173 (17.1)	323 (37.9)	<0.001	154 (16.8)	174 (35.2)	<0.001
High (≥33)	44 (4.4)	135 (15.8)		44 (4.8)	78 (15.8)	
No. target lesions	2.5±0.8	2.5±0.7	0.06	2.5±0.8	2.5±0.7	0.76
Total no. stents	3.0 [2.0–4.0]	3.0 [2.0–4.0]	<0.001	3.0 [2.0–4.0]	3.0 [2.0–4.0]	<0.001
Total stent length (mm)	80.1±37.5	77.5±40.1	0.10	79.8±37.5	78.4±40.8	0.43
Target						
Proximal LAD	1,009 (98.8)	1,508 (96.4)	<0.001	914 (98.7)	916 (98.9)	0.67
Chronic total occlusion	151 (14.8)	359 (22.9)	<0.001	150 (16.2)	162 (17.5)	0.46
Bifurcation	616 (60.3)	941 (60.1)	0.92	558 (60.3)	566 (61.1)	0.70
Bifurcation with 2 stents	22 (2.2)	145 (9.3)	<0.001	19 (2.1)	91 (9.8)	<0.001
New-generation DES	1,021 (100)	1,565 (100)		926 (100)	926 (100)	
Everolimus-eluting stent (SYNERGY™)	851 (83.3)	429 (27.4)	<0.001	769 (83.0)	250 (27.0)	<0.001
Staged PCI	775 (75.9)	1,000 (63.9)	<0.001	702 (75.8)	597 (64.5)	<0.001
PCI procedure success (per patient)[C]	1,021 (100)	1,565 (100)		926 (100)	926 (100)	
Complete success	999 (97.8)	1,487 (95.0)	<0.001	904 (97.6)	883 (95.4)	0.01
Partial success	22 (2.2)	78 (5.0)	<0.001	22 (2.4)	43 (4.6)	0.01
Procedural complications	67 (6.6)	187 (11.9)	<0.001	63 (6.8)	114 (12.3)	<0.001
Side branch occlusion (post TIMI grade ≤2)	22 (2.2)	60 (3.8)		21 (2.3)	39 (4.2)	
Slow flow	32 (3.1)	93 (5.9)		30 (3.2)	61 (6.6)	
Acute occlusion	6 (0.6)	31 (2.0)		6 (0.6)	18 (1.9)	
Perforation	12 (1.2)	25 (1.6)		11 (1.2)	14 (1.5)	
Cardiac tamponade	0 (0)	3 (0.2)		0 (0)	3 (0.3)	
Stent dislodgement	1 (0.1)	4 (0.3)		1 (0.1)	0 (0)	
Stent thrombosis	0 (0)	0 (0)		0 (0)	0 (0)	
No. patients with IVUS evaluation in the core IVUS laboratory[D]	982	133		890	83	
OPTIVUS criteria			0.005			0.17
Met in all stented lesions	394 (40.1)	53 (39.8)		359 (40.3)	31 (37.3)	
Not met in at least 1 lesion	402 (40.9)	40 (30.1)		361 (40.6)	29 (34.9)	
Not met in any lesion	186 (18.9)	40 (30.1)		170 (19.1)	23 (27.7)	

(**Table 1** continued the next page.)

	Entire cohort			Propensity score-matched cohort		
	OPTIVUS (n=1,021)	PCI historical control (n=1,565)	P value	OPTIVUS (n=926)	PCI historical control (n=926)	P value
Baseline medications						
Antiplatelet therapy						
$P2Y_{12}$ inhibitors	1,018 (99.7)	1,561 (99.7)	0.86	923 (99.7)	923 (99.7)	1.00
Ticlopidine	0 (0)	34 (2.2)		0 (0)	19 (2.1)	
Clopidogrel	563 (55.1)	1,521 (97.2)		521 (56.3)	899 (97.1)	
Prasugrel	452 (44.3)	0 (0)		399 (43.1)	0 (0)	
Unknown	0 (0)	6 (0.4)		0 (0.0)	5 (0.5)	
Aspirin	960 (94.0)	1,558 (99.6)	<0.001	869 (93.8)	921 (99.5)	<0.001
Cilostazol	6 (0.6)	45 (2.9)	<0.001	6 (0.6)	28 (3.0)	<0.001
Other medications						
Statins	936 (91.7)	1,206 (77.1)	<0.001	847 (91.5)	714 (77.1)	<0.001
High-intensity statins[E]	374 (36.6)	23 (1.5)	<0.001	348 (37.6)	12 (1.3)	<0.001
β-blockers	454 (44.5)	532 (34.0)	<0.001	414 (44.7)	307 (33.2)	<0.001
ACEI/ARB	584 (57.2)	993 (63.5)	0.001	536 (57.9)	577 (62.3)	0.052
Nitrates	148 (14.5)	387 (24.7)	<0.001	136 (14.7)	226 (24.4)	<0.001
Calcium channel blockers	444 (43.5)	787 (50.3)	0.001	402 (43.4)	471 (50.9)	0.001
Oral anticoagulants	99 (9.7)	130 (8.3)	0.22	93 (10.0)	71 (7.7)	0.07
Warfarin	19 (1.9)	114 (7.3)	<0.001	19 (2.1)	60 (6.5)	<0.001
DOAC	80 (7.8)	16 (1.0)	<0.001	74 (8.0)	11 (1.2)	<0.001
Oral anticoagulants in patients with AF	63/85 (74.1)	83/129 (64.3)	0.13	59/80 (73.8)	50/75 (66.7)	0.34
Warfarin in patients with AF	7/85 (8.2)	69/129 (53.5)	<0.001	7/80 (8.8)	40/75 (53.3)	<0.001
DOAC in patients with AF	56/85 (65.9)	14/129 (10.9)	<0.001	52/80 (65.0)	10/75 (13.3)	<0.001
PPI or histamine H_2 receptor blockers	903 (88.4)	1,126 (71.9)	<0.001	818 (88.3)	660 (71.3)	<0.001
PPI	876 (85.8)	960 (61.3)	<0.001	793 (85.6)	569 (61.4)	<0.001
Histamine H_2 receptor blockers	28 (2.7)	174 (11.1)	<0.001	26 (2.8)	96 (10.4)	<0.001

Categorical variables are presented as numbers and percentages. Continuous variables are presented as the mean ± SD or median [interquartile range]. Body mass index (BMI) was missing for 7 patients in the CREDO-Kyoto registry cohort-3. Left ventricular ejection fraction (LVEF) was missing for 7 patients in OPTIVUS and for 157 patients in the CREDO-Kyoto Registry Cohort-3. Mitral regurgitation was missing for 152 patients in the CREDO-Kyoto Registry Cohort-3. SYNTAX score was missing for 10 patients in OPTIVUS and for 712 patients in the CREDO-Kyoto Registry Cohort-3. [A]Severe frailty was regarded as present when the hospital chart documented an inability to perform usual activities of daily living. [B]The SYNTAX score in the CREDO-Kyoto Registry Cohort-3 was calculated among patients with 3-vessel disease by SYNTAX score committee members and among 144 patients who underwent angiographic analysis in the core laboratory. [C]Clinically successful percutaneous coronary intervention (PCI) was defined as successful dilatation of the target lesion with residual diameter stenosis <50%. [D]In the OPTIVUS study, angiographic and intravascular ultrasound (IVUS) analyses were to be performed in the core laboratory. Coronary angiograms and IVUS images were available and suitable for analysis for 1,017 (99.6%) and 982 (96.2%) patients, respectively. In the CREDO-Kyoto Registry Cohort-3, angiographic and IVUS analyses in the core laboratory were to be performed in 200 randomly selected patients, and coronary angiograms and IVUS images were available and suitable for analysis for 144 (72.0%) and 133 (66.5%) patients, respectively. [E]High-intensity statins therapy was defined as the use of maximum approved doses of strong statins in Japan (e.g., rosuvastatin 10 mg, atorvastatin 20 mg, or pitavastatin 4 mg). ACEI, angiotensin converting enzyme inhibitor; AF, atrial fibrillation; ARB, angiotensin II receptor blocker; ARC-HBR, Academic Research Consortium for High Bleeding Risk; CREDO-Kyoto, Coronary REvascularization Demonstrating Outcome Study in Kyoto; CT, computed tomography; DES, drug-eluting stent; DOAC, direct oral anticoagulant; eGFR, estimated glomerular filtration rate; FFR, fractional flow reserve; HF, heart failure; iFR, instantaneous wave-free ratio; LAD, left anterior descending coronary artery; OPTIVUS, OPTimal IntraVascular UltraSound; PPI, proton pump inhibitors; SPECT, single photon emission computed tomography; TIMI, Thrombolysis in Myocardial Infarction.

ity, such as the number of target lesions and total stent length. Direct stenting was less often performed in lesions in the OPTIVUS than historical PCI control group, whereas post-dilatation was more often performed in lesions in the OPTIVUS than historical PCI control group (**Table 2**). The balloon size for post-dilatation was larger in the OPTIVUS than historical PCI control group. Mean MSA was larger in the OPTIVUS than historical PCI control group (5.7 vs. 5.3 mm^2, respectively; P=0.02). The rate of meeting the OPTIVUS criteria was numerically, but not statistically, higher in the OPTIVUS than historical PCI control group (61.0% vs. 55.2%, respectively; P=0.09). In lesions with stent length ≥28 mm, the rate of meeting the OPTIVUS criteria was higher in the OPTIVUS than historical PCI control group, whereas there was no difference between the 2 groups in the case of lesions with a stent length <28 mm.

DAPT Discontinuation: OPTIVUS vs. Historical PCI Control

The cumulative incidence of DAPT discontinuation at 1 year was significantly higher in the OPTIVUS than historical PCI control group in the entire cohort (68.6% vs. 18.9%, respectively; log-rank P<0.001; **Supplementary Figure 1**). As an antiplatelet monotherapy after stopping DAPT in patients with DAPT discontinuation, $P2Y_{12}$ inhibitors were continued in 60.8% of the patients in the OPTIVUS group, and in 18.3% of the patients in the historical PCI control group (**Supplementary Table 1**). In patients who were on oral anticoagulants at discharge from the index PCI hospitalization, the cumulative incidence of DAPT

Table 2. Angiographic, Procedural, and IVUS Characteristics Evaluated in the Core Angiographic and IVUS Laboratory in the Entire Cohort: OPTIVUS vs. CREDO-Kyoto Registry Cohort-3 Historical PCI Control (Per Lesion Basis)

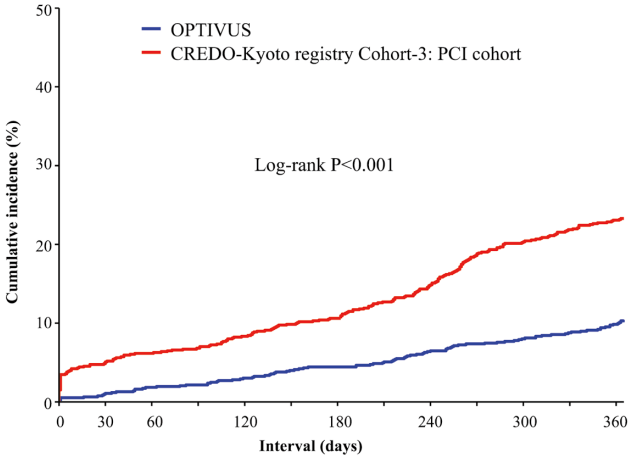
	OPTIVUS	Historical PCI control	P value
No. target lesions	2,595	3,889	
Angiographic and procedural characteristics			
No. lesions with angiographic evaluation in the core angiographic laboratory	2,299	341	
Preprocedure			
Lesion length (mm)	23.5±13.7 (n=2,072)	22.1±14.1 (n=304)	0.09
Reference vessel diameter (mm)	2.6±0.6 (n=2,295)	2.6±0.5 (n=339)	0.24
Minimum lumen diameter (mm)	0.8±0.4 (n=2,296)	0.9±0.4 (n=341)	0.09
% Diameter stenosis	68.7±14.1 (n=2,296)	66.6±14.9 (n=341)	0.01
Thrombus	53/2,297 (2.3)	12/341 (3.5)	0.18
Total occlusion	174/2,297 (7.6)	27/341 (7.9)	0.82
In-stent restenosis	81/2,297 (3.5)	0/341 (0)	<0.001
Bifurcation	1,092/2,297 (47.5)	158/341 (46.3)	0.68
Moderate or severe calcification	722/2,297 (31.4)	94/341 (27.6)	0.15
Index procedure			
Invasive FFR or iFR use	413/2,595 (15.9)	176/3,889 (4.5)	<0.001
IVUS use	2,529/2,595 (97.5)	2,993/3,889 (77.0)	<0.001
Stent use	2,379/2,595 (91.7)	3,703/3,889 (95.2)	<0.001
PCI procedure success	2,571/2,595 (99.1)	3,808/3,889 (97.9)	<0.001
No. stents used per lesion	1.0 [1.0–1.0] (n=2,377)	1.0 [1.0–2.0] (n=3,702)	<0.001
Stent length per lesion (mm)	34.4±18.5 (n=2,377)	32.8±20.6 (n=3,700)	0.002
Minimum stent diameter (mm)	2.5 [2.5–3.0] (n=2,377)	2.75 [2.5–3.0] (n=3,701)	<0.001
Cutting or scoring balloon use	883/2,595 (34.0)	39/3,889 (1.0)	<0.001
Rotational atherectomy use	171/2,595 (6.6)	180/3,889 (4.6)	0.001
Orbital atherectomy use	42/2,595 (1.6)	0/3,889 (0)	<0.001
Direct stenting	183/2,377 (7.7)	396/3,702 (10.7)	<0.001
Post-dilatation	1,838/2,377 (77.3)	2,716/3,702 (73.4)	0.001
Maximum balloon size (mm)	3.2±0.6 (n=1,838)	3.0±0.6 (n=2,713)	<0.001
Post-procedure			
Minimum lumen diameter (mm)			
In-stent	2.5±0.5 (n=2,299)	2.5±0.5 (n=341)	0.61
In-segment	2.2±0.6 (n=2,299)	2.2±0.6 (n=341)	0.99
% Diameter stenosis			
In-stent	14.4±6.7 (n=2,299)	12.9±7.4 (n=341)	<0.001
In-segment	23.7±10.0 (n=2,299)	22.3±10.3 (n=341)	0.01
Acute gain (mm)			
In-stent	1.7±0.5 (n=2,296)	1.7±0.5 (n=341)	0.06
In-segment	1.4±0.6 (n=2,296)	1.3±0.6 (n=341)	0.20
IVUS analysis post-procedure			
No. lesions with IVUS evaluation in the core IVUS laboratory	2,046	230	
Proximal reference vessel area (mm^2)	16.1±5.6 (n=1,684)	15.8±4.5 (n=202)	0.52
Proximal reference lumen area (mm^2)	8.3±3.3 (n=2,046)	7.7±2.8 (n=230)	0.02
Minimum stent area (mm^2)	5.7±2.0 (n=2,046)	5.3±1.9 (n=230)	0.02
Distal reference vessel area (mm^2)	9.8±5.1 (n=1974)	9.5±4.4 (n=225)	0.55
Distal reference lumen area (mm^2)	5.8±2.6 (n=2,046)	5.6±2.2 (n=230)	0.26
Thrombus or protrusion	261/2,046 (12.8)	4/230 (1.7)	<0.001
Incomplete stent apposition	745/2,046 (36.4)	70/230 (30.4)	0.07
Dissection	96/2,046 (4.7)	10/230 (4.3)	0.81
Meeting OPTIVUS criteria	1,246/2,044 (61.0)	127/230 (55.2)	0.09
Stent length ≥28 mm	664/1,228 (54.1)	48/113 (42.5)	0.02
Stent length <28 mm	582/816 (71.3)	79/117 (67.5)	0.40

In the OPTIVUS study, angiographic and IVUS analyses were to be performed in the core laboratory, and coronary angiograms and IVUS images were available and suitable for analysis for 2,299 (96.6%) and 2,046 (86.0%) lesions, respectively. In the CREDO-Kyoto Registry Cohort-3, angiographic and IVUS analyses were to be performed in the core laboratory in 462 stented lesions in 200 randomly selected patients, and coronary angiograms and IVUS images were available and suitable for analysis for 341 (73.8%) and 230 (49.8%) lesions, respectively. Abbreviations as in Table 1.

Table 3. Clinical Outcomes in the Propensity Score-Matched Cohort: OPTIVUS vs. CREDO-Kyoto Registry Cohort-3 Historical PCI Control

Endpoints	No. (%) patients with event[A] (cumulative 1-year incidence)		HR (95% CI)	P value
	OPTIVUS (n=926)	Historical PCI control (n=926)		
Primary endpoint[B]	96 (10.4)	214 (23.3)	0.41 (0.32–0.52)	<0.001
Secondary endpoints				
All-cause death	21 (2.3)	24 (2.6)	0.86 (0.48–1.55)	0.63
Cardiovascular death	8 (0.9)	16 (1.7)	0.49 (0.21–1.15)	0.10
Cardiac death	7 (0.8)	12 (1.3)	0.58 (0.23–1.47)	0.25
Sudden cardiac death	3 (0.3)	7 (0.8)	0.42 (0.11–1.64)	0.21
Non-cardiovascular death	13 (1.4)	8 (0.9)	1.60 (0.66–3.87)	0.29
Myocardial infarction	13 (1.4)	52 (5.6)	0.24 (0.13–0.45)	<0.001
Spontaneous	5 (0.5)	5 (0.5)	0.99 (0.29–3.41)	0.98
Periprocedural	8 (0.9)	47 (5.1)	0.17 (0.08–0.35)	<0.001
Definite stent thrombosis	2 (0.2)	2 (0.2)	0.99 (0.14–7.01)	0.99
Stroke	5 (0.5)	13 (1.4)	0.38 (0.14–1.06)	0.07
Ischemic stroke	3 (0.3)	9 (1.0)	0.33 (0.09–1.22)	0.10
Hemorrhagic stroke	2 (0.2)	5 (0.6)	0.39 (0.08–2.03)	0.27
Major stroke[C]	4 (0.4)	13 (1.4)	0.30 (0.10–0.93)	0.04
Hospitalization for HF	18 (2.0)	35 (3.8)	0.50 (0.29–0.89)	0.02
Major bleeding				
BARC type 3, 4, or 5	30 (3.3)	64 (7.0)	0.45 (0.29–0.70)	<0.001
BARC type 3 or 5	29 (3.2)	64 (7.0)	0.44 (0.28–0.68)	<0.001
BARC type 5	0 (0)	2 (0.2)		
Target-vessel revascularization	55 (6.0)	122 (13.5)	0.43 (0.31–0.59)	<0.001
Clinically driven target-vessel revascularization	55 (6.0)	40 (4.4)	1.36 (0.91–2.04)	0.14
Any coronary revascularization	64 (7.0)	145 (16.1)	0.41 (0.31–0.56)	<0.001
Clinically driven any coronary revascularization	64 (7.0)	51 (5.6)	1.24 (0.86–1.79)	0.25
Composite of death, myocardial infarction, or stroke	39 (4.2)	83 (9.0)	0.45 (0.31–0.66)	<0.001

[A]Percentages are Kaplan-Meier estimates at 365 days. [B]The primary endpoint was a composite of death, myocardial infarction, stroke, or any coronary revascularization. Definitions of the endpoints were provided in the Supplementary File. The hazard ratios (HRs) and 95% confidence intervals (CIs) of OPTIVUS relative to the historical PCI control were calculated using a Cox proportional hazard model. [C]Major stroke was defined as modified Rankin scale ≥2. BARC, Bleeding Academic Research Consortium. Other abbreviations as in Table 1.



Interval (days)	0	30	60	120	180	240	300	365
OPTIVUS								
Number of patients with event		10	17	28	41	60	74	96
Number of patients at risk	926	917	909	897	884	864	848	803
Cumulative incidence (%)		1.1	1.8	3.0	4.4	6.5	8.0	10.4
CREDO-Kyoto registry Cohort-3: PCI cohort								
Number of patients with event		47	57	77	98	137	187	214
Number of patients at risk	926	880	866	844	821	781	729	701
Cumulative incidence (%)		5.1	6.2	8.3	10.6	14.9	20.3	23.3

Figure 2. Kaplan-Meier curves for the primary endpoint in the propensity score-matched cohort: OPTIVUS vs. the historical percutaneous coronary intervention (PCI) control in the CREDO-Kyoto Registry Cohort-3. Time-to-event curves through 1 year after the index PCI for the primary endpoint (a composite of death, myocardial infarction, stroke, or any coronary revascularization) are shown for the propensity score-matched cohorts in the OPTIVUS and historical PCI control. Cumulative incidence was estimated with the Kaplan-Meier method, and differences were assessed with the log-rank test. CREDO-Kyoto, Coronary REvascularization Demonstrating Outcome Study in Kyoto; OPTIVUS, OPTimal IntraVascular UltraSound.

discontinuation at 1 year was significantly higher in the OPTIVUS than historical PCI control group in the entire cohort (97.0% vs. 28.5%, respectively; log-rank P<0.001; **Supplementary Figure 2**).

Follow-up Coronary Angiography: OPTIVUS vs. Historical PCI Control

The cumulative incidence of follow-up coronary angiography at 1 year was significantly lower in the OPTIVUS than historical PCI control group in the entire cohort (18.2% vs. 62.6%, respectively; log-rank P<0.001; **Supplementary Figure 3**).

Clinical Outcomes: OPTIVUS vs. Historical PCI Control

In the propensity score-matched cohort, the cumulative 1-year incidence of the primary endpoint was significantly lower in the OPTIVUS than historical PCI control group (10.4% vs. 23.3%, respectively [log-rank P<0.001]; HR 0.41, 95% CI 0.32–0.52, P<0.001; **Table 3**; **Figure 2**). The differences in the primary endpoint between the OPTIVUS and historical PCI control groups were mainly driven by differences in myocardial infarction and any coronary revascularization (**Table 3**; **Supplementary Figure 4**). The cumulative 1-year incidence of major bleeding (Bleeding Academic Research Consortium [BARC] type 3, 4, or 5) was lower in the OPTIVUS than historical PCI control group (**Table 3**; **Supplementary Figure 4**).

In the 30-day landmark analysis, the cumulative incidence of the primary endpoint was significantly lower in the OPTIVUS than historical PCI control group within and beyond 30 days (**Supplementary Table 2**). In the subgroup analysis stratified by SYNTAX score, there was no significant interaction between the SYNTAX score tertiles and the effect of the OPTIVUS relative to the historical PCI control group (**Supplementary Table 3**).

In the sensitivity analysis, the results in the entire cohort were fully consistent with those in the propensity score-matched cohort (**Supplementary Figure 5**; **Supplementary Table 4**).

Table 4. Baseline Characteristics: OPTIVUS vs. CREDO-Kyoto Registry Cohort-3 Historical CABG Control

	Entire cohort			Propensity score-matched cohort		
	OPTIVUS (n=1,021)	Historical CABG control (n=899)	P value	OPTIVUS (n=436)	Historical CABG control (n=436)	P value
Clinical characteristics						
Age (years)	71.2±10.0	68.6±9.6	<0.001	70.6±10.0	69.4±9.4	0.06
≥75 years	427 (41.8)	266 (29.6)	<0.001	160 (36.7)	153 (35.1)	0.62
Men	803 (78.6)	699 (77.8)	0.64	342 (78.4)	349 (80.0)	0.56
BMI (kg/m^2)	24.1±3.5	23.8±3.5	0.07	24.1±3.8	23.8±3.5	0.20
BMI <25 kg/m^2	666 (65.2)	597 (66.4)	0.59	275 (63.1)	279 (64.0)	0.78
Acute coronary syndrome	145 (14.2)	29 (3.2)	<0.001	21 (4.8)	24 (5.5)	0.65
Acute myocardial infarction	68 (6.7)	18 (2.0)	<0.001	11 (2.5)	15 (3.4)	0.43
Unstable angina	77 (7.5)	11 (1.2)	<0.001	10 (2.3)	9 (2.1)	0.82
Hypertension	860 (84.2)	774 (86.1)	0.25	382 (87.6)	373 (85.6)	0.37
Diabetes	560 (54.8)	478 (53.2)	0.46	239 (54.8)	243 (55.7)	0.79
On insulin therapy	95 (9.3)	189 (21.0)	<0.001	42 (9.6)	92 (21.1)	<0.001
Current smoking	176 (17.2)	159 (17.7)	0.80	71 (16.3)	78 (17.9)	0.53
HF	178 (17.4)	231 (25.7)	<0.001	100 (22.9)	104 (23.9)	0.75
Prior hospitalization for HF	87 (8.5)	167 (18.6)	<0.001	47 (10.8)	73 (16.7)	0.01
Current HF at index hospitalization	133 (13.0)	102 (11.3)	0.26	75 (17.2)	46 (10.6)	0.004
LVEF (%)	57.7±12.3	58.4±14.3	0.22	55.3±12.8	59.6±14.2	<0.001
LVEF <40%	114 (11.2)	111 (12.9)	0.28	63 (14.6)	47 (11.2)	0.14
Mitral regurgitation grade ≥3/4	30 (2.9)	70 (8.1)	<0.001	20 (4.6)	36 (8.6)	0.02
Prior myocardial infarction	180 (17.6)	232 (25.8)	<0.001	91 (20.9)	87 (20.0)	0.74
Prior stroke	119 (11.7)	158 (17.6)	<0.001	64 (14.7)	70 (16.1)	0.57
Peripheral vascular disease	116 (11.4)	128 (14.2)	0.06	43 (9.9)	49 (11.2)	0.51
eGFR <30 mL/min/1.73 m^2 or hemodialysis	97 (9.5)	132 (14.7)	<0.001	53 (12.2)	47 (10.8)	0.52
eGFR <30 mL/min/1.73 m^2 without hemodialysis	38 (3.7)	58 (6.5)	0.01	22 (5.0)	17 (3.9)	0.41
Hemodialysis	59 (5.8)	74 (8.2)	0.04	31 (7.1)	30 (6.9)	0.89
AF	85 (8.3)	69 (7.7)	0.60	41 (9.4)	36 (8.3)	0.55
Anemia (hemoglobin <11.0 g/dL)	96 (9.4)	158 (17.6)	<0.001	55 (12.6)	54 (12.4)	0.92
Thrombocytopenia (platelets <100×10^9/L)	10 (1.0)	24 (2.7)	0.01	9 (2.1)	8 (1.8)	0.81
Malignancy	126 (12.3)	103 (11.5)	0.55	52 (11.9)	53 (12.2)	0.92
Severe frailty[A]	39 (3.8)	14 (1.6)	0.003	11 (2.5)	8 (1.8)	0.49

(**Table 4** continued the next page.)

	Entire cohort			Propensity score-matched cohort		
	OPTIVUS (n=1,021)	Historical CABG control (n=899)	P value	OPTIVUS (n=436)	Historical CABG control (n=436)	P value
Procedural characteristics						
Preprocedure test	215 (21.1)	266 (29.6)	<0.001	101 (23.2)	122 (28.0)	0.10
Stress electrocardiogram	104 (10.2)	123 (13.7)		43 (9.9)	60 (13.8)	
SPECT	94 (9.2)	156 (17.4)		47 (10.8)	66 (15.1)	
Cardiac magnetic resonance	9 (0.9)	1 (0.1)		4 (0.9)	1 (0.2)	
Stress echocardiography	3 (0.3)	6 (0.7)		0 (0)	3 (0.7)	
FFR-CT	10 (1.0)	0 (0)		8 (1.8)	0 (0)	
Extent of coronary artery disease			<0.001			0.50
2-vessel disease	813 (79.6)	277 (30.8)		250 (57.3)	240 (55.0)	
3-vessel disease	208 (20.4)	622 (69.2)		186 (42.7)	196 (45.0)	
SYNTAX score[B]	18.1±7.2	29.1±8.0	<0.001	20.2±7.6	28.2±8.2	<0.001
Low (<23)	794 (78.5)	128 (21.1)		303 (69.7)	66 (26.7)	
Intermediate (23–32)	173 (17.1)	277 (45.6)	<0.001	100 (23.0)	113 (45.7)	<0.001
High (≥33)	44 (4.4)	202 (33.3)		32 (7.4)	68 (27.5)	
No. target lesions or anastomoses	2.5±0.8	3.4±0.9	<0.001	2.8±0.9	3.2±0.9	<0.001
Target						
Proximal LAD	1,009 (98.8)	854 (95.0)	<0.001	427 (97.9)	424 (97.2)	0.51
Chronic total occlusion	151 (14.8)	444 (49.4)	<0.001	139 (31.9)	140 (32.1)	0.94
Internal thoracic artery graft use	–	881 (98.0)		–	429 (98.4)	
Off-pump surgery	–	527 (58.6)		–	255 (58.5)	
Baseline medications						
Antiplatelet therapy						
$P2Y_{12}$ inhibitors	1,018 (99.7)	194 (21.6)	<0.001	433 (99.3)	87 (20.0)	<0.001
Ticlopidine	0 (0)	14 (1.6)		0 (0)	9 (2.1)	
Clopidogrel	563 (55.1)	180 (20.0)		224 (51.4)	78 (17.9)	
Prasugrel	452 (44.3)	0 (0)		207 (47.5)	0 (0)	
Aspirin	960 (94.0)	884 (98.3)	<0.001	405 (92.9)	432 (99.1)	<0.001
Cilostazol	6 (0.6)	27 (3.0)	<0.001	2 (0.5)	13 (3.0)	0.004
Other medications						
Statins	936 (91.7)	586 (65.2)	<0.001	402 (92.2)	277 (63.5)	<0.001
High-intensity statins[C]	374 (36.6)	5 (0.6)	<0.001	166 (38.1)	2 (0.5)	<0.001
β-blockers	454 (44.5)	508 (56.5)	<0.001	231 (53.0)	244 (56.0)	0.38
ACEI/ARB	584 (57.2)	276 (30.7)	<0.001	272 (62.4)	133 (30.5)	<0.001
Nitrates	148 (14.5)	112 (12.5)	0.19	60 (13.8)	54 (12.4)	0.55
Calcium channel blockers	444 (43.5)	340 (37.8)	0.01	191 (43.8)	172 (39.4)	0.19
Oral anticoagulants	99 (9.7)	483 (53.7)	<0.001	52 (11.9)	225 (51.6)	<0.001
Warfarin	19 (1.9)	477 (53.1)	<0.001	11 (2.5)	221 (50.7)	<0.001
DOAC	80 (7.8)	6 (0.7)	<0.001	41 (9.4)	4 (0.9)	<0.001
Oral anticoagulants in patients with AF	63/85 (74.1)	53/69 (76.8)	0.70	31/41 (75.6)	28/36 (77.8)	0.82
Warfarin in patients with AF	7/85 (8.2)	49/69 (71.0)	<0.001	3/41 (7.3)	25/36 (69.4)	<0.001
DOAC in patients with AF	56/85 (65.9)	4/69 (5.8)	<0.001	28/41 (68.3)	3/36 (8.3)	<0.001
PPI or histamine H_2 receptor blockers	903 (88.4)	831 (92.4)	0.003	390 (89.4)	400 (91.7)	0.25
PPI	876 (85.8)	758 (84.3)	0.36	379 (86.9)	362 (83.0)	0.11
Histamine H_2 receptor blockers	28 (2.7)	75 (8.3)	<0.001	11 (2.5)	40 (9.2)	<0.001

Categorical variables were presented as number and percentage. Continuous variables are presented as the mean ± SD or median [interquartile range]. BMI was missing for 1 patient in the CREDO-Kyoto Registry Cohort-3. LVEF was missing for 7 patients in OPTIVUS and for 36 patients in the CREDO-Kyoto Registry Cohort-3. Mitral regurgitation was missing for 35 patients in the CREDO-Kyoto Registry Cohort-3. SYNTAX score was missing for 10 patients in OPTIVUS and for 292 patients in the CREDO-Kyoto Registry Cohort-3. [A]Severe frailty was regarded as present when the hospital chart documented an inability to perform usual activities of daily living. [B]SYNTAX score in the CREDO-Kyoto Registry was calculated among patients with 3-vessel disease by the SYNTAX score committee members, and among patients who were underwent angiographic analysis in the core laboratory. [C]High-intensity statins therapy was defined as the use of maximum approved doses of strong statins in Japan (e.g., rosuvastatin 10 mg, atorvastatin 20 mg, or pitavastatin 4 mg). CABG, coronary artery bypass grafting. Other abbreviations as in Table 1.

Table 5. Clinical Outcomes in the Propensity Score-Matched Cohort: OPTIVUS vs. CREDO-Kyoto Registry Cohort-3 Historical CABG Control

Endpoints	No. (%) patients with event[A] (cumulative 1-year incidence)		HR (95% CI)	P value
	OPTIVUS (n=436)	Historical CABG control (n=436)		
Primary endpoint[B]	51 (11.8)	70 (16.5)	0.66 (0.46–0.95)	0.02
Secondary endpoints				
All-cause death	11 (2.5)	12 (2.9)	0.87 (0.38–1.97)	0.74
Cardiovascular death	4 (0.9)	9 (2.2)	0.42 (0.13–1.37)	0.15
Cardiac death	3 (0.7)	8 (1.9)	0.36 (0.09–1.34)	0.13
Sudden cardiac death	2 (0.5)	5 (1.2)	0.38 (0.07–1.95)	0.24
Non-cardiovascular death	7 (1.6)	3 (0.7)	2.22 (0.57–8.57)	0.25
Myocardial infarction	7 (1.6)	19 (4.4)	0.36 (0.15–0.85)	0.02
Spontaneous	3 (0.7)	2 (0.5)	1.43 (0.24–8.56)	0.70
Periprocedural	4 (0.9)	17 (3.9)	0.23 (0.08–0.69)	0.01
Definite stent thrombosis or symptomatic graft occlusion	1 (0.2)	2 (0.5)	0.48 (0.04–5.29)	0.55
Stroke	2 (0.5)	13 (3.1)	0.15 (0.03–0.65)	0.01
Ischemic stroke	2 (0.5)	11 (2.6)	0.17 (0.04–0.78)	0.02
Hemorrhagic stroke	0 (0)	3 (0.7)		
Major stroke[C]	1 (0.2)	11 (2.6)	0.09 (0.01–0.67)	0.02
Hospitalization for heart failure	12 (2.8)	20 (4.8)	0.56 (0.27–1.15)	0.11
Major bleeding				
BARC type 3, 4, or 5	15 (3.5)	135 (31.2)	0.10 (0.06–0.17)	<0.001
BARC type 3 or 5	15 (3.5)	36 (8.6)	0.39 (0.21–0.71)	0.002
BARC type 5	0 (0)	0 (0)		
Target vessel revascularization	32 (7.5)	31 (7.4)	0.96 (0.59–1.58)	0.88
Ischemia-driven target vessel revascularization	32 (7.5)	16 (3.8)	1.92 (1.05–3.50)	0.03
Any coronary revascularization	34 (7.9)	36 (8.6)	0.88 (0.55–1.40)	0.58
Ischemia-driven any coronary revascularization	34 (7.9)	18 (4.3)	1.81 (1.02–3.20)	0.04
Composite of death, myocardial infarction, or stroke	20 (4.6)	42 (9.9)	0.45 (0.26–0.76)	0.003

[A]Percentages are Kaplan-Meier estimates at 365 days. [B]The primary endpoint was a composite of death, myocardial infarction, stroke, or any coronary revascularization. [C]Major stroke was defined as modified Rankin scale ≥2. Definitions of the endpoints are provided in the Supplementary File. The HRs and 95% CIs of OPTIVUS relative to the historical CABG control were calculated using a Cox proportional hazard model. Abbreviations as in Tables 1,3,4.

Baseline Characteristics: OPTIVUS vs. Historical CABG Control

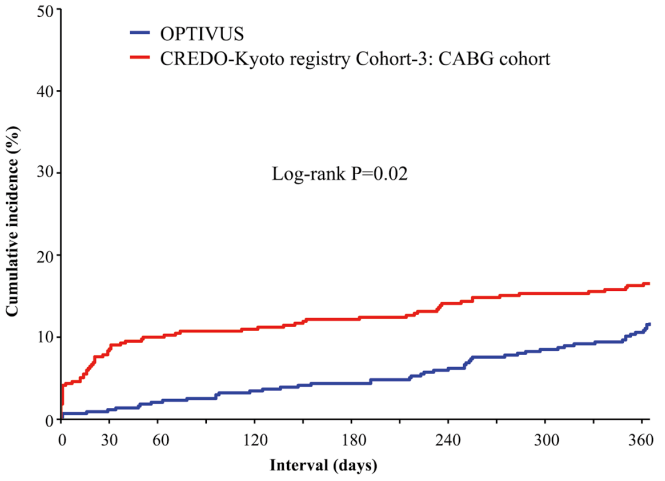
In the entire cohort, patients in the OPTIVUS group were older and more often presented as acute coronary syndrome than those in the historical CABG control group (**Table 4**). Patients in the OPTIVUS group less often had comorbidities such as heart failure, mitral regurgitation, a history of myocardial infarction, stroke, chronic kidney disease, anemia, and thrombocytopenia compared with those in the historical CABG control group. The prevalence of severe frailty was higher in the OPTIVUS than historical CABG control group. Regarding angiographic and procedural characteristics, compared with the historical CABG control group, patients in the OPTIVUS group less often had complex coronary anatomy, as indicated by a lower SYNTAX score and a lower prevalence of 3-vessel disease and CTO target. In terms of medication at discharge, the prescription rates of statins, high-intensity statins, and ACEI or ARB were higher in the OPTIVUS than historical CABG control group, whereas the prescription rates of β-blockers, oral anticoagulants, and proton pump inhibitors or histamine H_2 receptor blockers were higher in the historical CABG control group than in the OPTIVUS group.

In the propensity score-matched cohort, baseline characteristics were mostly well balanced between the OPTIVUS and historical CABG control groups, except for the lower mean SYNTAX score and smaller number of target lesions or anastomoses in the OPTIVUS group. Nevertheless, there was no imbalance in the extent of coronary artery disease, proximal LAD target, and CTO target between the 2 groups.

Clinical Outcomes: OPTIVUS vs. Historical CABG Control

In the propensity score-matched cohort, the cumulative 1-year incidence of the primary endpoint was significantly lower in the OPTIVUS than historical CABG control group (11.8% vs. 16.5%, respectively [log-rank P=0.02]; HR 0.66, 95% CI 0.46–0.95, P=0.02; **Table 5**; **Figure 3**). The differences in the primary endpoint between the OPTIVUS and historical CABG control groups were mainly driven by differences in myocardial infarction and stroke (**Table 5**; **Supplementary Figure 6**). The cumulative 1-year incidence of any coronary revascularization did not differ between the 2 groups (**Table 5**; **Supplementary Figure 6**).

In the 30-day landmark analysis, the cumulative incidence of the primary endpoint was significantly lower in the OPTIVUS than historical CABG control group within 30 days, but not beyond 30 days (**Supplementary Table 5**). In the subgroup analysis stratified by SYNTAX score,



Interval (days)	0	30	60	120	180	240	300	365
OPTIVUS								
Number of patients with event		5	9	15	19	27	37	51
Number of patients at risk	436	431	427	421	417	409	397	374
Cumulative incidence (%)		1.1	2.1	3.4	4.4	6.2	8.5	11.8
CREDO-Kyoto registry Cohort-3: CABG cohort								
Number of patients with event		37	43	47	52	60	65	70
Number of patients at risk	436	386	374	368	363	355	349	344
Cumulative incidence (%)		8.6	10.0	11.0	12.2	14.1	15.3	16.5

Figure 3. Kaplan-Meier curves for the primary endpoint in the propensity score-matched cohort: OPTIVUS vs. the historical coronary artery bypass grafting (CABG) control in the CREDO-Kyoto Registry Cohort-3. Time-to-event curves through 1 year after the index procedure are shown for the primary endpoint (a composite of death, myocardial infarction, stroke, or any coronary revascularization) in the propensity score-matched cohorts in the OPTIVUS and historical CABG control. Cumulative incidence was estimated with the Kaplan-Meier method, and differences were assessed with the log-rank test. CREDO-Kyoto, Coronary REvascularization Demonstrating Outcome Study in Kyoto; OPTIVUS, OPTimal IntraVascular UltraSound.

there was no significant interaction between the SYNTAX score tertiles and the effect of the OPTIVUS relative to the historical CABG control group (**Supplementary Table 6**). Nevertheless, the HR numerically favored the historical CABG control group over the OPTIVUS group for patients with a high SYNTAX score, although the number of patients in this subgroup was very small.

In the sensitivity analysis, the results in the entire cohort were fully consistent with those in the propensity score-matched cohort (**Supplementary Figure 7**; **Supplementary Table 7**).

Discussion

The main findings of the present study were that: (1) mean MSA evaluated at the core laboratory was significantly larger in the OPTIVUS group than in the historical PCI control group; and (2) IVUS-guided PCI targeting the OPTIVUS criteria combined with contemporary clinical practice was associated with superior clinical outcomes at 1 year compared with not both the historical PCI control and the historical CABG control.

In our previous report, the OPTIVUS-Complex PCI study multivessel cohort demonstrated statistically and numerically superior clinical outcomes compared with the predefined PCI and CABG, respectively, performance goals derived from the CREDO-Kyoto Registry Cohort-2 in patients with multivessel disease.[1] However, the patients in the CREDO-Kyoto Registry Cohort-2 were enrolled in the first-generation DES era, when clinical practice was much different from that of contemporary clinical practice. It was reassuring that the results of the OPTIVUS-Complex PCI study were fully consistent with those of the CREDO-Kyoto Registry Cohort-3, a recent real-world study conducted in the new-generation DES era.

Imaging-guided PCI has widely penetrated real-world practice in Japan. In fact, the prevalence of intracoronary imaging use in the CREDO-Kyoto Registry Cohort-3 was very high (86.6%). However, despite the high prevalence of intracoronary imaging use during PCI, PCI compared with CABG had a higher risk of myocardial infarction and any coronary revascularization in patients with multivessel disease in the CREDO-Kyoto Registry Cohort-3.[3,7] We hypothesized that simply using IVUS during PCI may not necessarily be associated with optimal stent expansion, and therefore the long-term outcomes after PCI are still worse than those after CABG. In the OPTIVUS group, the prevalence of direct stenting was lower, the prevalence of post-dilatation was higher, and the maximum balloon size for post-dilatation was larger than in the PCI group in the CREDO-Kyoto Registry Cohort-3 (historical PCI control). The prevalence of the use of a cutting or scoring balloon and rotational or orbital atherectomy was higher in the OPTIVUS than historical PCI control group, although the prevalence of calcified lesions did not differ between the groups. The observed larger MSA in the OPTIVUS than historical PCI control group may have been related to those procedural characteristics under optimal IVUS guidance. MSA is a well-known predictor for better clinical outcomes after coronary stent implantation.[8–11] In addition, the prevalence of procedural complications was lower in the OPTIVUS than historical PCI control group. Optimal IVUS-guided PCI could make it possible to achieve more aggressive but safer stent optimization, which may be one of the reasons why patients enrolled in OPTIVUS had a lower incidence of myocardial infarction and any coronary revascularization than patients in the PCI group in the CREDO-Kyoto Registry Cohort-3. Moreover, patients enrolled in OPTIVUS had a lower incidence of myocardial infarction, and a similar incidence of any coronary revascularization, than patients in the CABG group in the CREDO-Kyoto Registry Cohort-3. Of course, the better outcomes in terms of car-

diovascular events such as myocardial infarction and coronary revascularization in OPTIVUS may be related to factors other than optimal IVUS guidance, such as a higher rate of prescription of high-intensity statins and a lower incidence of follow-up coronary angiography in OPTIVUS than in the CREDO-Kyoto Registry Cohort-3. OPTIVUS, compared with the CREDO-Kyoto Registry Cohort-3, had lower incidence of coronary revascularization, but not clinically driven coronary revascularization, suggesting that the lower incidence of coronary revascularization may be largely driven by the lower incidence of follow-up coronary angiography. Based on these findings, we strongly recommended refraining from scheduled follow-up coronary angiography in asymptomatic patients. This will contribute to avoiding coronary revascularization in asymptomatic patients. The lower incidence of major bleeding in OPTIVUS may be related to the higher prevalence of a radial approach and shorter duration of DAPT in OPTIVUS than in the CREDO-Kyoto Registry Cohort-3. Optimal IVUS-guided PCI together with the evolving contemporary PCI practice are important in improving clinical outcomes after PCI, and could be an alternative to CABG in selected patients with multivessel coronary artery disease.

This study has were several limitations. First, and most importantly, this study was not a randomized trial comparing optimal IVUS-guided PCI with standard PCI or CABG, and there were fundamental differences between the OPTIVUS and historical control groups. The OPTIVUS study population may represent selected patients for a clinical trial and the counterpart was the registry study. Although we conducted a propensity score matching analysis to combine these different cohorts, large differences remained in the selection of patients in the OPTIVUS and historical control groups, especially in terms of coronary anatomy complexity. In addition, patients in the historical PCI or CABG control groups underwent coronary revascularization several years before the enrollment period of the OPTIVUS study. In that time, not only has PCI practice changed, but there have also been improvements in surgical techniques, together with adjunct medical therapy. The propensity score matching and multivariable Cox proportional hazard models could not fully account for the systematic differences between the 2 cohorts. Therefore, we could not evaluate how much the optimal IVUS-guided PCI affected the better results of the OPTIVUS group compared with the historical control groups, which may also have been driven by evolving clinical practice other than IVUS-guided PCI. Second, a 1-year follow-up may be too short to evaluate the effect of IVUS-guided PCI compared with standard PCI or CABG. Follow-up for 5 years in this study is now ongoing. Third, there were no differences in clinical outcomes between patients meeting and those not meeting the OPTIVUS criteria.[1] The OPTIVUS criteria may not be the best IVUS criteria for guiding PCI, although the intention to achieve the OPTIVUS criteria may have contributed to reasonable stent expansion, even if the OPTIVUS criteria could not be achieved in a certain proportion of patients. Fourth, the IVUS data at the core laboratory were available for a very limited proportion of patients in the CREDO-Kyoto Registry Cohort-3, posing a serious limitation in the comparison of the IVUS data between the 2 cohorts. Finally, it is unknown how much of the observed benefits was actually related to the optimal IVUS-guided PCI procedure per se.

Conclusions

IVUS-guided PCI targeting the OPTIVUS criteria combined with contemporary clinical practice was associated with superior clinical outcomes at 1 year compared with both the historical PCI control and the historical CABG control.

Acknowledgments

The authors appreciate the members of the Cardiovascular Clinical Research Promotion Department, Research Institute for Production Development for handling a series of large clinical trials performed by Kyoto University and the co-investigators for enrolling patients, collecting follow-up data, and adjudicating clinical events (**Supplementary Appendix**).

Sources of Funding

This work was supported by Boston Scientific Japan. The study sponsor was not involved in the implementation of the study, data collection, event fixation, or statistical analysis. However, approval of the study sponsor is required for presentation of the data at scientific meetings and for the submission of papers.

Disclosures

K. Yamamoto reports receiving honoraria from Boston Scientific. T.M. reports receiving lecturer fees from AstraZeneca, Bristol-Myers Squibb, Daiichi Sankyo, Japan Lifeline, Kowa, Toray and Tsumura and manuscript fees from Bristol-Myers Squibb and Kowa, as well as sitting on the advisory board for Novartis and Teijin. K.T. reports receiving honoraria from Abbott Medical, Boston Scientific, Japan Lifeline, Medtronic, Orbusneich, and Terumo. T.K. reports receiving research grants from Abbott Medical and Boston Scientific and honoraria from Abbott Medical, Boston Scientific, Daiichi Sankyo, Sanofi, and Terumo, as well as participating in advisory boards for Abbott Medical, Boston Scientific, and Sanofi. K.O. is a member of *Circulation Journal*'s Editorial Team. The other authors have nothing to disclose.

IRB Information

Kyoto University Certified Review Board and Ethics Committee approved OPTIVUS-Complex PCI (Y0011).

Data Availability

The deidentified participant data will not be shared.

References

1. Yamamoto K, Shiomi H, Morimoto T, Watanabe H, Miyazawa A, Yamaji K, et al. Optimal intravascular ultrasound-guided percutaneous coronary intervention in patients with multivessel disease. *JACC Asia* 2023 (in press).
2. Watanabe H, Shiomi H, Morimoto T, Furukawa Y, Nakagawa Y, Ando K, et al. Percutaneous coronary intervention versus coronary arterial bypass grafting in patients with multi-vessel coronary revascularization (from the CREDO-Kyoto PCI/CABG Registry/Cohort-2). *Catheter Cardiovasc Interv* 2020; **96:** 42–51.
3. Watanabe H, Yamamoto K, Shiomi H, Morimoto T, Kato E, Matsumura Y, et al. Percutaneous coronary intervention using new-generation drug-eluting stents versus coronary arterial bypass grafting in stable patients with multi-vessel coronary artery disease: From the CREDO-Kyoto PCI/CABG Registry Cohort-3. *PLoS One* 2022; **17:** e0267906.
4. Hong SJ, Kim BK, Shin DH, Nam CM, Kim JS, Ko YG, et al. Effect of intravascular ultrasound-guided vs angiography-guided everolimus-eluting stent implantation: The IVUS-XPL randomized clinical trial. *JAMA* 2015; **314:** 2155–2163.
5. Räber L, Mintz GS, Koskinas KC, Johnson TW, Holm NR, Onuma Y, et al. Clinical use of intracoronary imaging. Part 1: Guidance and optimization of coronary interventions. An expert consensus document of the European Association of Percutaneous Cardiovascular Interventions. *Eur Heart J* 2018; **39:** 3281–3300.
6. Cutlip DE, Windecker S, Mehran R, Boam A, Cohen DJ, van Es GA, et al. Clinical end points in coronary stent trials: A case for standardized definitions. *Circulation* 2007; **115:** 2344–2351.

7. Matsumura-Nakano Y, Shiomi H, Morimoto T, Yamaji K, Ehara N, Sakamoto H, et al. Comparison of outcomes of percutaneous coronary intervention versus coronary artery bypass grafting among patients with three-vessel coronary artery disease in the new-generation drug-eluting stents era (from CREDO-Kyoto PCI/CABG Registry Cohort-3). *Am J Cardiol* 2021; **145:** 25–36.
8. Sonoda S, Morino Y, Ako J, Terashima M, Hassan AH, Bonneau HN, et al. Impact of final stent dimensions on long-term results following sirolimus-eluting stent implantation: Serial intravascular ultrasound analysis from the SIRIUS trial. *J Am Coll Cardiol* 2004; **43:** 1959–1963.
9. Hong MK, Mintz GS, Lee CW, Park DW, Choi BR, Park KH, et al. Intravascular ultrasound predictors of angiographic restenosis after sirolimus-eluting stent implantation. *Eur Heart J* 2006; **27:** 1305–1310.
10. Song HG, Kang SJ, Ahn JM, Kim WJ, Lee JY, Park DW, et al. Intravascular ultrasound assessment of optimal stent area to prevent in-stent restenosis after zotarolimus-, everolimus-, and sirolimus-eluting stent implantation. *Catheter Cardiovasc Interv* 2014; **83:** 873–878.
11. Katagiri Y, De Maria GL, Kogame N, Chichareon P, Takahashi K, Chang CC, et al. Impact of post-procedural minimal stent area on 2-year clinical outcomes in the SYNTAX II trial. *Catheter Cardiovasc Interv* 2019; **93:** E225–E234.

Supplementary Files

Please find supplementary file(s);
https://doi.org/10.1253/circj.CJ-22-0837