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ORIGINAL RESEARCH

Optimal Intravascular Ultrasound-Guided Percutaneous Coronary Intervention in Patients With Multivessel Disease

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ABSTRACT

BACKGROUND Intravascular ultrasound (IVUS) was only rarely used in landmark trials comparing percutaneous coronary intervention (PCI) with coronary artery bypass grafting (CABG) in patients with multivessel disease.

OBJECTIVES The authors aimed to evaluate clinical outcomes after optimal IVUS-guided PCI in patients undergoing multivessel PCI.

METHODS The OPTIVUS (OPTimal IntraVascular UltraSound)-Complex PCI study multivessel cohort was a prospective multicenter single-arm study enrolling 1,021 patients undergoing multivessel PCI, including left anterior descending coronary artery using IVUS, aiming to meet the prespecified criteria (OPTIVUS criteria: minimum stent area $>$ distal reference lumen area [stent length $\geq$28mm], and minimum stent area $>0.8 \times$ average reference lumen area [stent length $<$28mm]) for optimal stent expansion. The primary endpoint was major adverse cardiac and cerebrovascular events (MACCE) (death/myocardial infarction/stroke/any coronary revascularization). The predefined performance goals were derived from the CREDO-Kyoto (Coronary REvascularization Demonstrating Outcome study in Kyoto) PCI/CABG registry cohort-2 fulfilling the inclusion criteria in this study.

RESULTS In this study, 40.1% of the patients met OPTIVUS criteria in all stented lesions. The cumulative 1-year incidence of the primary endpoint was 10.3% (95% CI: 8.4%-12.2%), which was significantly lower than the predefined PCI performance goal of 27.5% ($P < 0.001$), and which was numerically lower than the predefined CABG performance goal of 13.8%. The cumulative 1-year incidence of the primary endpoint was not significantly different regardless of meeting or not meeting OPTIVUS criteria.

CONCLUSIONS Contemporary PCI practice conducted in the OPTIVUS-Complex PCI study multivessel cohort was associated with a significantly lower MACCE rate than the predefined PCI performance goal, and with a numerically lower MACCE rate than the predefined CABG performance goal at 1 year. (JACC: Asia 2023;3:211-225) © 2023 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

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ABBREVIATIONS AND ACRONYMS

CABG = coronary artery bypass grafting

CTO = chronic total occlusion

DAPT = dual antiplatelet therapy

DES = drug-eluting stent(s)

FFR = fractional flow reserve

IVUS = intravascular ultrasound

LAD = left anterior descending coronary artery

MACCE = major adverse cardiac and cerebrovascular event(s)

MSA = minimum stent area

PCI = percutaneous coronary intervention

RCT = randomized controlled trial

Coronary artery bypass grafting (CABG) is recommended as a standard coronary revascularization modality in patients with multivessel coronary artery disease, although substantial improvements have been reported in the field of percutaneous coronary intervention (PCI).[1,2] A pooled analysis from 11 randomized controlled trials (RCTs) comparing PCI and CABG in patient with multivessel disease showed higher mortality risk of PCI compared with CABG.[3] More recently, the FAME 3 (Fractional Flow Reserve vs Angiography for Multivessel Evaluation) trial reported that fractional flow reserve (FFR)-guided PCI relative to CABG was associated with worse outcomes in patients with 3-vessel disease.[4] However, intracoronary imaging such as intravascular ultrasound (IVUS) was only rarely used in these landmark RCTs comparing PCI with CABG.[3-7] The benefit of IVUS in reducing ischemic events after PCI was well established in previous RCTs, and patients with optimal stent expansion were reported to have better outcomes when compared with patients with suboptimal stent expansion.[8,9] Nevertheless, there is a scarcity of data on clinical outcomes after optimal IVUS-guided PCI in patients undergoing multivessel PCI. In our previous observational study, compared with CABG, PCI remained associated with a higher long-term risk for myocardial infarction and any coronary revascularization in patients with 3-vessel disease despite a high prevalence of IVUS use during PCI.[10] We hypothesized that simply using IVUS during PCI may not necessarily lead to optimal stent expansion, which could explain why PCI was still worse than CABG. In the present study, 1-year clinical outcomes in patients undergoing multivessel IVUS-guided PCI aim to meet the prespecified optimal IVUS criteria were assessed and compared with the predefined performance goals derived from our previous observational study.[11]

METHODS

STUDY DESIGN AND POPULATION. The OPTIVUS-Complex PCI (Optimal Intravascular Ultrasound Guided Complex Percutaneous Coronary Intervention) 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 left anterior descending coronary artery (LAD). The participating centers were encouraged to enroll consecutive patients who were planned to undergo IVUS-guided PCI for LMCA or multivessel disease including LAD target. The PCI operators were mandated to perform optimal IVUS-guided PCI with a target for the prespecified criteria (OPTIVUS criteria) for optimal stent implantation. The exclusion criteria were those patients with ST-segment elevation myocardial infarction, cardiogenic shock, and previous history of CABG. The study protocol was approved by the central review board, Kyoto University Certified Review Board, based on the enforcement of the Clinical Trials Act in Japan.[12] Written informed consent was provided from all enrolled patients.

In this paper, we report 1-year clinical outcomes in the multivessel cohort. Between March 2019 and April 2021, 1,134 patients were screened and planned to undergo multivessel PCI including a target lesion in LAD (**Figure 1**). Of those, 1,023 patients actually underwent IVUS-guided multivessel PCI including LAD target in 90 Japanese centers. Excluding 2 patients who withdrew consent, the current study population consisted of 1,021 patients.

STUDY PROCEDURES AND OPTIVUS CRITERIA. Enrolled patients were to undergo PCI using

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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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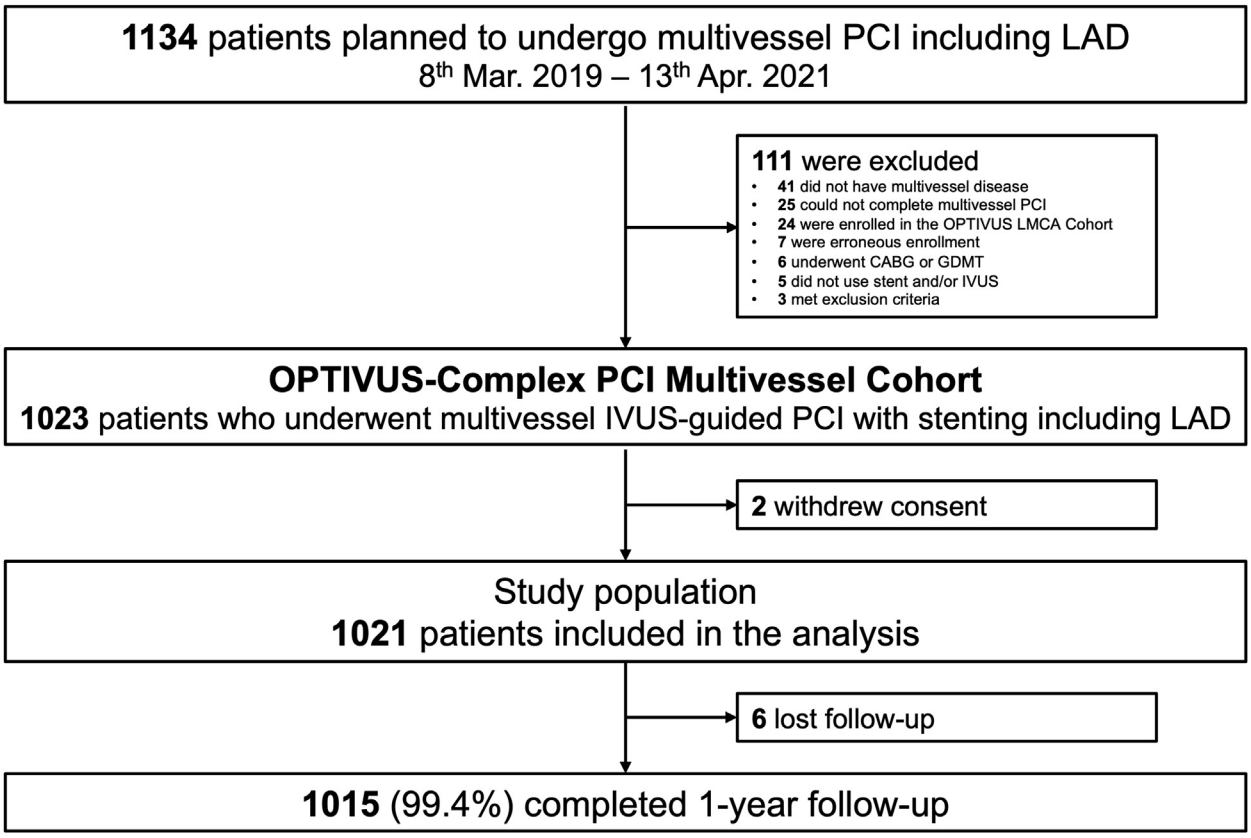
FIGURE 1 Study Flow



Between March 2019 and April 2021, 1,134 patients were screened and planned to undergo multivessel percutaneous coronary intervention (PCI) including a target lesion in the left anterior descending coronary artery (LAD). Of those, 1,023 patients actually underwent intravascular ultrasound (IVUS)-guided multivessel PCI including LAD target. Excluding 2 patients who withdrew consent, the current study population consisted of 1,021 patients. CABG = coronary artery bypass grafting; GDMT = guideline-directed medical therapy; LMCA = left main coronary artery; OPTIVUS = OPTimal IntraVascular UltraSound.

platinum-chromium everolimus-eluting stents (Synergy, Boston Scientific). 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 defined as follows: minimum stent area (MSA) > the distal reference lumen area if the stent length ≥28 mm, and MSA >0.8 × average reference lumen area if the stent length <28 mm (average reference lumen area = [proximal reference lumen area + distal reference lumen area]/2). All of the OPTIVUS criteria were described in the Supplemental Materials. These criteria were determined 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.[8,13] Preintervention IVUS was also recommended to help choose the appropriate balloon/stent sizes and the modalities for lesion preparation. Quantitative and qualitative coronary angiography analysis was to be performed in all target lesions, and IVUS analysis was to be performed in all target lesions with stenting by an independent core laboratory (Cardiocore). Among 1,021 study patients, coronary angiograms and IVUS images were available in 1,021 patients (100%) and 1,013 patients (99.2%), respectively, and were deemed suitable for evaluation by the core laboratory in 1,017 patients (99.6%) and 982 patients (96.2%), 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

(FFR or instantaneous wave-free ratio). Radial access was recommended as the standard approach. PCI for chronic total occlusion (CTO) was to be performed by a dedicated CTO operator. Use of rotational atherectomy was recommended in severely calcified lesions. Proximal optimization technique was recommended in bifurcation lesions. Kissing balloon inflation was recommended if bifurcation lesions were treated with 2-sent techniques. Scheduled follow-up coronary angiography after PCI was discouraged in asymptomatic patients. Recommended pharmacological management included use of high-intensity statins therapy with the maximum approved dose of strong statins in Japan, and short duration (3-6 months) of dual antiplatelet therapy (DAPT) after PCI.

ENDPOINTS. The primary endpoint was a major adverse 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.[14] Stroke was defined as ischemic or hemorrhagic stroke with neurological symptoms lasting >24 hours. Scheduled staged coronary revascularization procedures performed within 3 months after the index PCI were not regarded as follow-up events but were included in the index procedure. The definitions of secondary endpoints are described in the Supplemental Appendix. 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 an independent clinical event committee.

STATISTICAL ANALYSIS. The event rate for the primary endpoint in this single-arm study was compared against the predefined performance goals. To define the performance goals in this study, we used data from 945 and 1,248 patients in the PCI and CABG groups, respectively, from the CREDO-Kyoto (Coronary REvascularization Demonstrating Outcome Study in Kyoto) PCI/CABG registry cohort-2 who fulfilled the inclusion criteria for the multivessel cohort in the OPTIVUS-Complex PCI study.[11] IVUS was used during the PCI procedure in 60.3% of patients in the CREDO-Kyoto registry cohort-2. The rate of MACCE in the registry was 27.5% (95% CI: 24.7%-30.4%) and 13.8% (95% CI: 11.9%-15.8%) at 1 year and 51.2% (95% CI: 48.0%-54.4%) and 32.5% (95% CI: 29.8%-35.0%) at 5 years in the PCI and CABG groups, respectively, which were regarded as the performance goals in the present study. Based on the protocol of this present study, superiority analysis is to be performed for the performance goal derived from the PCI patients, whereas noninferiority analysis is to be performed for the performance goal at 5 years derived from the CABG patients. The sample size of the multivessel cohort was calculated based on the performance goal at 1 year derived from the PCI patients. Assuming a 15% relative risk reduction, a sample size of 892 patients would provide a power of 80% with 1-sided alpha of 2.5%. We decided to enroll 1,000 patients considering the possible dropouts. The sample size of 1,000 patients would provide 96% power for the noninferiority analysis relative to the performance goal at 5 years derived from the CABG patients with a noninferiority margin of 1.38 on the HR scale.

Categorical variables were presented as number and percentage and were compared with the chi-square test. Continuous variables were expressed as mean ± SD or median (IQR) and were compared using the Student's *t*-test or Wilcoxon rank-sum test depending on their distributions. The cumulative incidence was estimated with the Kaplan-Meier method. We used the 1-sample binominal test to compare the 1-year incidence of the primary endpoint in this study with the performance goal of 27.5% derived from the PCI patients. In addition, we estimated the 1-year incidence of the primary endpoint in this study with the reference of the performance goal of 13.8% derived from the CABG patients.

The cumulative 1-year incidences of the primary and secondary endpoints were assessed between patients meeting and not meeting OPTIVUS criteria (meeting in all stented lesion, not meeting in some lesion[s], and not meeting in any lesion).

All *P* values were 2-sided, and *P* values <0.05 were considered statistically significant except for the assessment to fulfill the performance goal, where 1-sided *P* values <0.025 were considered statistically significant. All analyses were performed with JMP version 15.2 software (SAS Institute Inc) and R version 4.1.2 (R Foundation for Statistical Computing).

RESULTS

BASELINE CHARACTERISTICS. The mean age of the OPTIVUS study population was 71.2 years, 78.6% of the patients were men, and 14.2% of the patients presented with acute coronary syndrome (**Table 1**). The prevalence of diabetes and academic research consortium-high bleeding risk were 54.8% and 52.8%, respectively. Regarding the angiographic and procedural characteristics, a noninvasive test for ischemia and FFR or instantaneous wave-free ratio were performed in 21.1% and 29.8% of the patients, respectively. The prevalence of radial approach was

TABLE 1 Baseline and Procedural Characteristics of the OPTIVUS Study Population (per Patient Basis) (N = 1,021)

Clinical characteristics	
Age, y	71.2 ± 10.0
≥75 y	427 (41.8)
Men	803 (78.6)
Body mass index, kg/m^2	24.1 ± 3.5
<25.0 kg/m^2	666 (65.2)
Acute coronary syndrome	145 (14.2)
Acute myocardial infarction	68 (6.7)
Unstable angina	77 (7.5)
Hypertension	860 (84.2)
Diabetes mellitus	560 (54.8)
on insulin therapy	95 (9.3)
Current smoking	176 (17.2)
Heart failure	178 (17.4)
Prior hospitalization for heart failure	87 (8.5)
Current heart failure at index hospitalization	133 (13.0)
Left ventricular ejection fraction, %	57.7 ± 12.3
<40%	114 (11.2)
Mitral regurgitation grade ≥3/4	30 (2.9)
Prior myocardial infarction	180 (17.6)
Prior stroke	119 (11.7)
Peripheral vascular disease	116 (11.4)
eGFR <30 mL/min/1.73 m^2 or hemodialysis	97 (9.5)
eGFR <30 mL/min/1.73 m^2, without hemodialysis	38 (3.7)
Hemodialysis	59 (5.8)
Atrial fibrillation	85 (8.3)
Anemia (hemoglobin <11.0 g/dL)	96 (9.4)
Thrombocytopenia (platelet <100 × 10^9/L)	10 (1.0)
Malignancy	126 (12.3)
Severe frailty[a]	39 (3.8)
ARC-HBR	539 (52.8)
Procedural characteristics	
Preprocedure noninvasive test	215 (21.1)
Stress electrocardiogram	104 (10.2)
SPECT	94 (9.2)
Cardiac magnetic resonance	9 (0.9)
Stress echocardiography	3 (0.3)
FFR-CT	10 (1.0)
Invasive FFR or iFR use	304 (29.8)
IVUS use	1,021 (100.0)
Radial artery approach	893 (87.5)
Femoral artery approach	235 (23.0)
Brachial artery approach	56 (5.5)
Number of patients with angiographic evaluation in the core angiographic laboratory	1,017 (99.6)
Extent of coronary artery disease	
2-vessel disease	813 (79.6)
3-vessel disease	208 (20.4)
SYNTAX score[b]	18.1 ± 7.2
Low <23	794 (78.5)
Intermediate 23-32	173 (17.1)
High ≥33	44 (4.4)
Number of target lesions	2.5 ± 0.8
Total number of stents	3.0 (2.0-4.0)
Total stent length, mm	80.1 ± 37.5
Target of proximal LAD	1,009 (98.8)
Target of chronic total occlusion	151 (14.8)
Target of bifurcation	616 (60.3)
Bifurcation with 2 stents	22 (2.2)

Continued in the next column

TABLE 1 Continued

New-generation DES use	1,021 (100.0)
Everolimus-eluting stent (SYNERGY) use	851 (83.3)
Staged PCI	775 (75.9)
PCI procedure success (per patient)[c]	1,021 (100.0)
Complete success	999 (97.8)
Partial success	22 (2.2)
Procedural complications	67 (6.6)
Side branch occlusion (post-TIMI flow grade ≤2)	22 (2.2)
Slow flow	32 (3.1)
Acute occlusion	6 (0.6)
Perforation	12 (1.2)
Cardiac tamponade	0 (0)
Stent dislodgement	1 (0.1)
Stent thrombosis	0 (0)
Number of patients with IVUS evaluation in the core IVUS laboratory	982 (96.2)
OPTIVUS criteria	
Meeting in all stented lesions	394 (40.1)
Not meeting in at least one lesion	402 (40.9)
Not meeting in any lesion	186 (18.9)
Baseline medications	
Antiplatelet therapy	
$P2Y_{12}$ inhibitors	1,018 (99.7)
Clopidogrel	563 (55.1)
Prasugrel	452 (44.3)
Aspirin	960 (94.0)
Cilostazol	6 (0.6)
Other medications	
Statins	936 (91.7)
High-intensity statins[d]	374 (36.6)
Beta-blockers	454 (44.5)
ACE-I/ARB	584 (57.2)
Nitrates	148 (14.5)
Calcium-channel blockers	444 (43.5)
Oral anticoagulants	99 (9.7)
Warfarin	19 (1.9)
DOAC	80 (7.8)
Oral anticoagulants in patients with atrial fibrillation (n = 85)	63 (74.1)
Warfarin in patients with atrial fibrillation (n = 85)	7 (8.2)
DOAC in patients with atrial fibrillation (n = 85)	56 (65.9)
Proton pump inhibitors or histamine type-2 receptor blockers	903 (88.4)
Proton pump inhibitors	876 (85.8)
Histamine type-2 receptor blockers	28 (2.7)

Values are mean ± SD, n (%), or median (IQR). Left ventricular ejection fraction was missing in 7 patients. SYNTAX (Synergy Between Percutaneous Coronary Intervention With Taxus and Cardiac Surgery) score was missing in 10 patients. [a]Severe frailty was regarded as present when the hospital chart documented the inability to perform usual activities of daily living. [b]SYNTAX score was evaluated in the core angiographic laboratory. [c]Percutaneous coronary intervention (PCI) procedure success was defined as successful dilatation of target lesion with residual diameter stenosis <50%. [d]High-intensity statin therapy was defined as the use of maximum approved doses of strong statins in Japan (eg, rosuvastatin 10 mg, atorvastatin 20 mg, or pitavastatin 4 mg).

ACE-I = angiotensin converting enzyme inhibitors; ARB = angiotensin II receptor blockers; ARC-HBR = academic research consortium for high bleeding risk; DES = drug-eluting stent; DOAC = direct oral anticoagulant; eGFR = estimated glomerular filtration rate; FFR = fractional flow reserve; FFR-CT = fractional flow reserve-computed tomography; iFR = instantaneous wave-free ratio; IVUS = intravascular ultrasound; LAD = left anterior descending coronary artery; OPTIVUS = OPTimal IntraVascular UltraSound; SPECT = stress single photon emission computed tomography; TIMI = Thrombolysis In Myocardial Infarction.

TABLE 2 Angiographic, Procedural, and IVUS Characteristics in the Core Angiographic and IVUS Laboratory in the OPTIVUS Study (per Lesion Basis, Number of Target Lesions = 2,595)

Angiographic and procedural characteristics	
Number of lesions with angiographic evaluation in the core angiographic laboratory	2,299
Preprocedure	
Lesion length, mm	23.5 ± 13.7 (n = 2,072)
Reference vessel diameter, mm	2.6 ± 0.6 (n = 2,295)
Minimum lumen diameter, mm	0.8 ± 0.4 (n = 2,296)
Percent diameter stenosis, %	68.7 ± 14.1 (n = 2,296)
Thrombus	53/2,297 (2.3)
Total occlusion	174/2,297 (7.6)
In-stent restenosis	81/2,297 (3.5)
Bifurcation	1,092/2,297 (47.5)
Moderate or severe calcification	722/2,297 (31.4)
Index procedure	
Invasive FFR or iFR use	413/2,595 (15.9)
IVUS use	2,529/2,595 (97.5)
Stent use	2,379/2,595 (91.7)
PCI procedure success[a]	2,571/2,595 (99.1)
Number of stents used per lesion	1.0 (1.0-1.0) (n = 2,377)
Stent length per lesion, mm	34.4 ± 18.5 (n = 2,377)
Minimum stent diameter, mm	2.5 (2.5-3.0) (n = 2,377)
Cutting or scoring balloon use	883/2,595 (34.0)
Rotational atherectomy use	171/2,595 (6.6)
Orbital atherectomy use	42/2,595 (1.6)
Direct stenting	183/2,377 (7.7)
Maximum stent inflation pressure, atm	12.7 ± 3.1 (n = 2,372)
Post-dilatation	1,838/2,377 (77.3)
Maximum balloon size, mm	3.2 ± 0.6 (n = 1,838)
Maximum balloon inflation pressure, atm	18.0 ± 4.3 (n = 1,834)
Postprocedure	
Minimum lumen diameter, mm	
In-stent	2.5 ± 0.5 (n = 2,299)
In-segment	2.2 ± 0.6 (n = 2,299)
Percent diameter stenosis, %	
In-stent	14.4 ± 6.7 (n = 2,299)
In-segment	23.7 ± 10.0 (n = 2,299)
Acute gain, mm	
In-stent	1.7 ± 0.5 (n = 2,296)
In-segment	1.4 ± 0.6 (n = 2,296)

Continued on the next page

87.5%. The prevalence of patients who had 3-vessel disease was 20.4%, and the mean SYNTAX (SYNergy between percutaneous coronary intervention with TAXus and cardiac surgery) score was 18.1, with 78.5% of patients <23. In patients with IVUS evaluation at the core laboratory, 40.1% of the patients met the OPTIVUS criteria in all stented lesions, and 40.9% of the patients did not meet OPTIVUS criteria in at least 1 lesion, while 18.9% of the patients failed to meet OPTIVUS criteria in all lesions. In terms of medications at discharge, the selected $P2Y_{12}$ inhibitors were clopidogrel in 55.1% and reduced dose (20 mg loading and 3.75 mg maintenance) prasugrel in 44.3%. The prescription rates of statins and high-intensity statins were 91.7% and 36.6%, respectively (Table 1).

Baseline characteristics were not different between patients meeting and not meeting OPTIVUS criteria except for a few aspects (Supplemental Table 1).

ANGIOGRAPHIC, IVUS, AND PROCEDURAL CHARACTERISTICS. On angiography, the mean lesion length was 23.5 mm, and the mean reference vessel diameter was 2.6 mm (Table 2). Among 2,595 lesions, 2,379 lesions (91.7%) were treated with stents. The prevalence of direct stenting and post-dilatation were 7.7% and 77.3%, respectively. In the IVUS analysis in stented lesions after index procedure, the proximal reference lumen area, MSA, and distal reference lumen area were 8.3, 5.7, and 5.8 mm^2, respectively. The rate of meeting OPTIVUS criteria was 61.0% in all lesions, 54.1% in lesions with stent length ≥28 mm, and 71.3% in lesions with stent length <28 mm (Figure 2).

The lesions not meeting OPTIVUS criteria more often had complex lesions such as long lesions, bifurcation lesions, and calcified lesions compared with the lesions meeting OPTIVUS criteria (Supplemental Table 2). Postdilatation with a larger balloon size was more often performed in the lesions not meeting OPTIVUS criteria than in the lesions meeting OPTIVUS criteria (Supplemental Table 2). In the IVUS analysis after index procedure, MSA was greater in the lesions meeting OPTIVUS criteria than in those not meeting OPTIVUS criteria, and proximal and distal reference lumen area were smaller in the lesions meeting OPTIVUS criteria than in those not meeting OPTIVUS criteria (Table 3).

The prevalence of procedural complications was acceptably low (Tables 1 and 2). The rates of side branch occlusion and slow flow were higher in patients not meeting OPTIVUS criteria in any lesion than in those meeting OPTIVUS criteria in all stented lesions and in those not meeting OPTIVUS criteria in at least 1 lesion (Supplemental Table 1).

CHANGING PCI STRATEGY BASED ON THE PREINTERVENTION AND POSTINTERVENTION IVUS EVALUATION. Among lesions evaluated by preintervention IVUS, PCI strategy was changed based on the IVUS findings in 41.2% of the lesions (Supplemental Table 3). Among lesions evaluated by postintervention IVUS, PCI strategy was changed based on the IVUS findings in 39.6% of the lesions (Supplemental Table 4).

DAPT DISCONTINUATION. The cumulative incidences of DAPT discontinuation at 60 days, 180 days, and 1 year were 17.3%, 37.4%, and 68.6%, respectively (Supplemental Figure 1). As an

antiplatelet monotherapy after stopping DAPT in patients with DAPT discontinuation, 60.8% of the patients continued $P2Y_{12}$ inhibitors (Supplemental Table 5). In patients who were on oral anticoagulants at discharge from the index PCI hospitalization, the cumulative incidences of DAPT discontinuation at 60 days, 180 days, and 1 year were 82.8%, 93.9%, and 97.0%, respectively (Supplemental Figure 2).

FOLLOW-UP CORONARY ANGIOGRAPHY. The cumulative incidence of follow-up coronary angiography at 1 year was 18.2% (Supplemental Figure 3). The cumulative incidence of clinically driven coronary angiography at 1 year was 4.8%, whereas that of scheduled coronary angiography at 1 year was 12.7% (Supplemental Figure 4).

CLINICAL OUTCOMES. Complete 1-year clinical follow-up was achieved in 1,015 patients (99.4%) (**Figure 1**). The cumulative 1-year incidence of the primary endpoint was 10.3% (95% CI: 8.4%-12.2%), which was significantly lower than the predefined PCI performance goal of 27.5% ($P < 0.001$) and was numerically lower than the predefined CABG performance goal of 13.8% (**Figure 3**). The results for the secondary endpoints were shown in **Table 3**.

When comparing patients who met OPTIVUS criteria to those who did not, the cumulative 1-year incidence of the primary endpoint was similar among the groups (criteria met in all stented lesions and criteria not met in at least 1 lesion: 12.0% and 9.7%; log-rank $P = 0.26$ [**Figure 4A**]; criteria met in all stented lesions, criteria not met in at least 1 lesion, and criteria not met in any lesion: 12.0%, 9.0%, and 11.4%; log-rank $P = 0.36$ [**Figure 4B**]) (**Table 4**).

MSA and distal reference lumen area were not different in lesions between patients with and without the primary endpoint, whereas proximal reference lumen was smaller in lesions in patients with the primary endpoint than in lesions in patients without (Supplemental Table 6).

TABLE 2 Continued

Procedural complications	75/2,595 (2.9)
Side branch occlusion (post TIMI flow grade ≤2)	23/2,595 (0.9)
Slow flow	36/2,595 (1.4)
Acute occlusion	6/2,595 (0.2)
Perforation	13/2,595 (0.5)
Cardiac tamponade	0/2,595 (0)
Stent dislodgement	1/2,595 (0)
Stent thrombosis	0/2,595 (0)
IVUS analysis postprocedure[b]	
Number of lesions with IVUS evaluation in the core IVUS laboratory	2,046
Proximal reference vessel area, mm^2	16.1 ± 5.6 (n = 1,684)
Proximal reference lumen area, mm^2	8.3 ± 3.3 (n = 2,046)
Minimum stent area, mm^2	5.7 ± 2.0 (n = 2,046)
Distal reference vessel area, mm^2	9.8 ± 5.1 (n = 1,974)
Distal reference lumen area, mm^2	5.8 ± 2.6 (n = 2,046)
Thrombus or protrusion	261/2,046 (12.8)
Incomplete stent apposition[c]	745/2,046 (36.4)
Dissection	96/2,046 (4.7)
Meeting OPTIVUS criteria	1,246/2,044 (61.0)
Stent length ≥28 mm	664/1,228 (54.1)
Stent length <28 mm	582/816 (71.3)

Values are mean ± SD, n/N (%), or median (IQR). [a]PCI procedure success was defined as successful dilatation of target lesion with residual diameter stenosis <50%. [b]IVUS analyses were to be performed in all target lesions with stenting. [c]Incomplete stent apposition was defined as the presence of blood flow between stent struts and vessel wall.

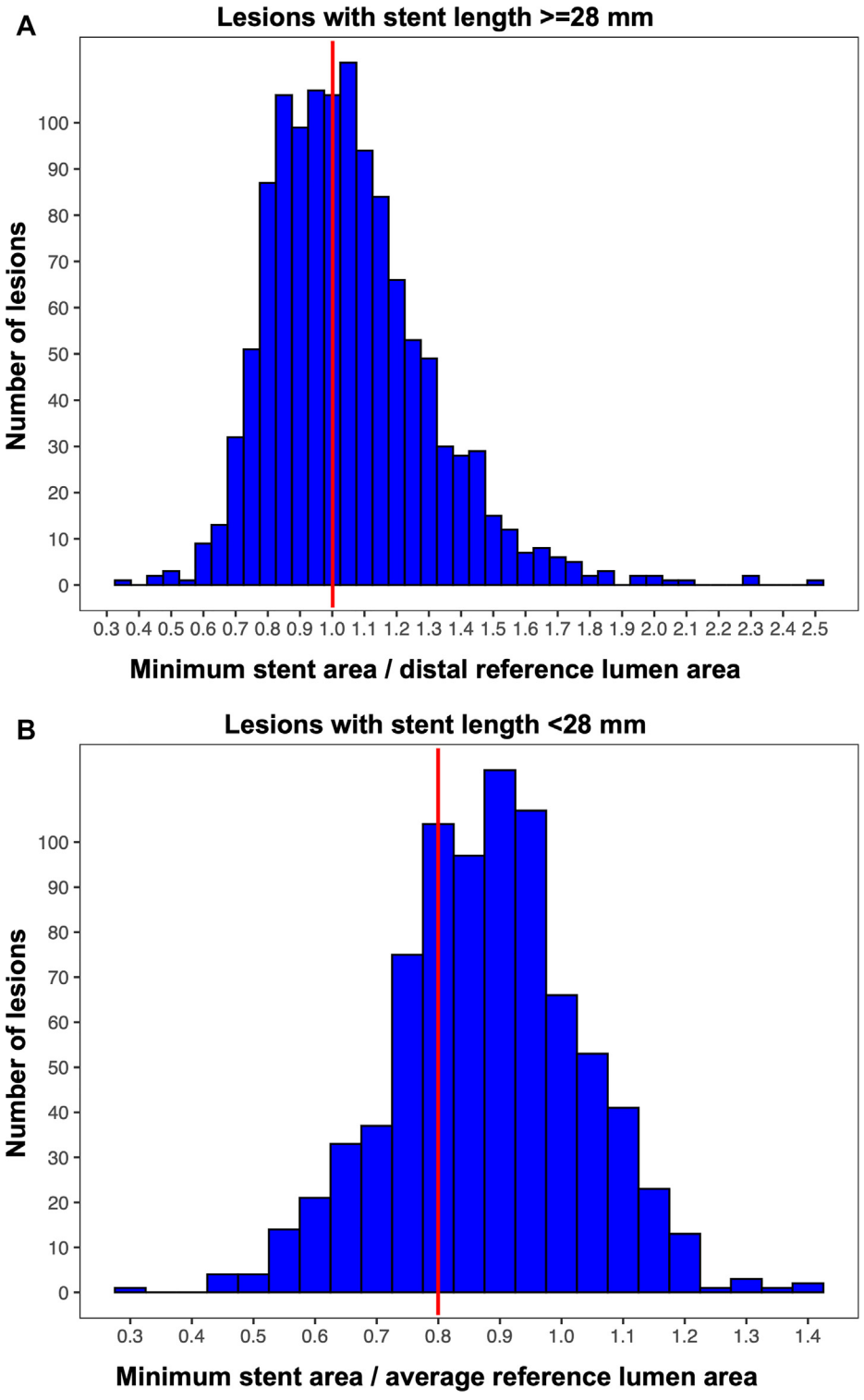
Abbreviations as in **Table 1**.

DISCUSSION

The main findings of this prospective study were the following: 1) IVUS-guided multivessel PCI targeting the OPTIVUS criteria combined with contemporary clinical practice was associated with a significantly lower MACCE rate than the predefined PCI performance goal, and a numerically lower MACCE rate than the predefined CABG performance goal at 1 year; and 2) the rate of the primary endpoint at 1 year was not different between patients who met or did not meet the prespecified OPTIVUS criteria (**Central Illustration**).

The SYNTAX II study demonstrated that PCI using SYNTAX II strategy in patients with 3-vessel disease improved 5-year clinical outcomes compared with PCI in the original SYNTAX trial, and resulted in comparable 5-year clinical outcomes compared with CABG in the original SYNTAX trial.[15] SYNTAX II strategy included heart team decision making, physiology-guided PCI, implantation of new-generation drug-eluting stents (DES), IVUS-guided PCI, contemporary CTO revascularization technique, and guideline-directed medical therapy. The basic concept and study design of the present OPTIVUS-Complex PCI study were similar to those of the SYNTAX II study but more focused on IVUS guidance. Consistent with the results of the SYNTAX II study, the OPTIVUS-Complex PCI study demonstrated that IVUS-guided PCI combined with contemporary clinical practice in patients with multivessel disease was associated with superior clinical outcomes at 1 year compared with the predefined PCI performance goal derived from the CREDO-Kyoto registry cohort-2, which was a real-world registry conducted in the first-generation DES era when the original SYNTAX trial was also conducted. The 1-year incidences of the MACCE in this study were consistent with the other studies which

FIGURE 2 **The Distribution of Minimum Stent Area After Percutaneous Coronary Intervention**



The histogram for **(A)** minimum stent area/distal reference lumen area in lesions with stent length ≥28 mm, and **(B)** minimum stent area/average reference lumen area in lesions with stent length <28 mm. Average reference lumen area was defined as the mean of proximal and distal reference lumen area. The red line represents the cutoff point of OPTIVUS criteria.

TABLE 3 IVUS Findings in Lesions Meeting vs Not Meeting OPTIVUS Criteria (per Lesion Basis)

	OPTIVUS Criteria		
	Meeting	Not Meeting	*P* Value
Entire study population	(n = 1,246)	(n = 798)	
Proximal reference vessel area, mm^2	15.5 ± 5.3 (n = 1,041)	16.9 ± 5.9 (n = 641)	<0.001
Proximal reference lumen area, mm^2	7.9 ± 3.1	8.8 ± 3.5	<0.001
Minimum stent area, mm^2	5.7 ± 2.0	5.5 ± 2.1	0.03
Distal reference vessel area, mm^2	9.3 ± 4.7 (n = 1,203)	10.4 ± 5.6 (n = 769)	<0.001
Distal reference lumen area, mm^2	5.2 ± 2.2	6.7 ± 2.9	<0.001
Thrombus or protrusion	158 (12.7)	102 (12.8)	0.95
Incomplete stent apposition[a]	389 (31.2)	354 (44.4)	<0.001
Dissection	68 (5.5)	28 (3.5)	0.04
Stent length ≥28 mm	(n = 664)	(n = 564)	
Proximal reference vessel area, mm^2	16.9 ± 5.3 (n = 523)	17.1 ± 5.6 (n = 443)	0.59
Proximal reference lumen area, mm^2	8.6 ± 3.4	8.7 ± 3.3	0.91
Minimum stent area, mm^2	5.4 ± 1.8	5.5 ± 2.0	0.32
Distal reference vessel area, mm^2	8.3 ± 4.1 (n = 645)	10.0 ± 5.1 (n = 545)	<0.001
Distal reference lumen area, mm^2	4.5 ± 1.7	6.6 ± 2.6	<0.001
Thrombus or protrusion	92 (13.9)	83 (14.7)	0.67
Incomplete stent apposition[a]	251 (37.8)	246 (43.6)	0.04
Dissection	39 (5.9)	22 (3.9)	0.11
Stent length <28 mm	(n = 582)	(n = 234)	
Proximal reference vessel area, mm^2	14.2 ± 5.0 (n = 518)	16.5 ± 6.7 (n = 198)	<0.001
Proximal reference lumen area, mm^2	7.1 ± 2.6	9.2 ± 3.9	<0.001
Minimum stent area, mm^2	6.1 ± 2.2	5.6 ± 2.3	0.003
Distal reference vessel area, mm^2	10.5 ± 5.0 (n = 558)	11.4 ± 6.6 (n = 224)	0.03
Distal reference lumen area, mm^2	5.9 ± 2.5	6.9 ± 3.5	<0.001
Thrombus or protrusion	66 (11.3)	19 (8.1)	0.17
Incomplete stent apposition[a]	138 (23.7)	108 (46.2)	<0.001
Dissection	29 (5.0)	6 (2.6)	0.12

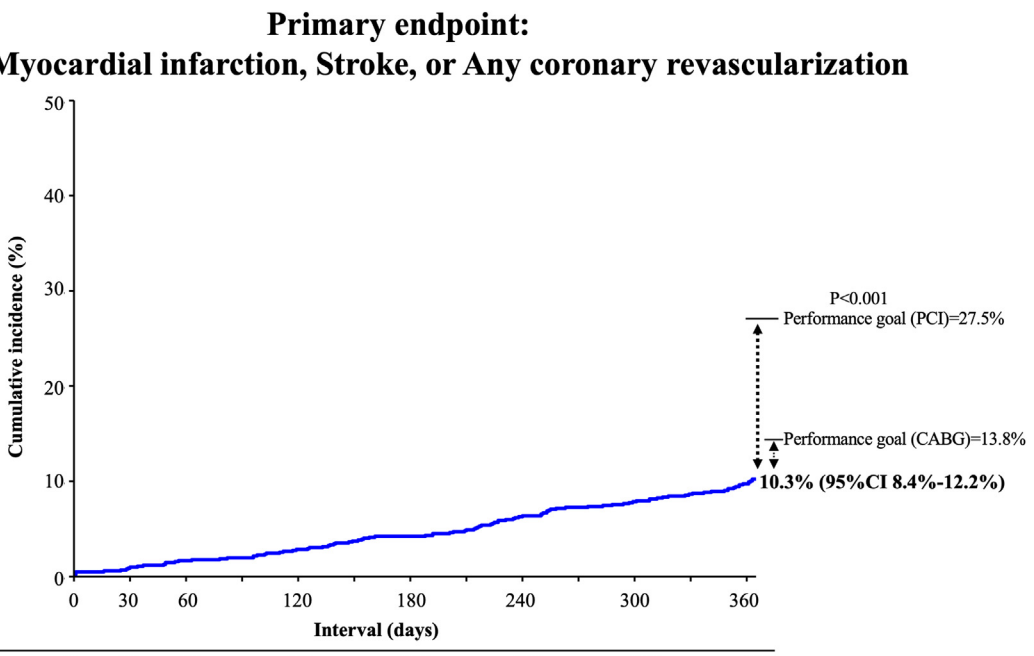
Values are mean ± SD. Categorical variables are presented as number and percentage. [a]Incomplete stent apposition was defined as the presence of blood flow between stent struts and vessel wall.

Abbreviations as in Table 1.

evaluated contemporary clinical practice after multivessel PCI such as the SYNTAX II study and the FAME 3 (Fractional Flow reserve versus Angiography for Multivessel Evaluation) trial (OPTIVUS-Complex PCI: 10.3%, SYNTAX II: 10.6%, and PCI arm in FAME 3: 10.6%), despite the higher prevalence of advanced age and comorbidities in this study compared with the SYNTAX II study and FAME 3 trial.[4,15] This study showed clinical outcomes at 1 year not only superior to the predefined PCI performance goal, but also numerically better than the predefined CABG performance goal. The better outcome in this study compared with the predefined CABG performance goal should be interpreted with caution, because the incidence of MACCE after contemporary multivessel CABG was very low (CABG arm in FAME 3: 6.9%).[4]

In the SYNTAX II study, IVUS was not used in all patients (84.1% of the patients/76.4% of the lesions), and further optimization after IVUS evaluation was performed in only 30.2% of the stented lesions.[15] In the OPTIVUS-Complex PCI study, IVUS was used in all patients with an intension to achieve the optimal IVUS criteria. In the previous RCTs, IVUS-guided PCI demonstrated a significant reduction in ischemic events compared with angiography-guided PCI.[8,9] The mechanisms of the benefit in IVUS-guided PCI over angiography-guided PCI might include adequate evaluation of plaque morphology, selection of appropriate diameter and length of the stents and balloons, detection for complications, and poststent optimization. In this study, PCI strategy was changed in 41.2% of the lesions based on the preintervention IVUS evaluation. IVUS before stenting would lead to selection of accurate stent size and length and more appropriate lesion modification or preparation, especially in complex lesions with heavily calcified or lipid-rich plaques. In addition, PCI strategy was changed in 39.6% of the lesions based on the postintervention IVUS evaluation. IVUS after stenting would have led to more aggressive, but safe stent postdilatation intended to achieve optimal stent expansion and detection of complications such as

FIGURE 3 Kaplan-Meier Curve for the Primary Endpoint



Interval (days)	0	30	60	120	180	240	300	365
Number of patients with event		10	17	29	43	65	80	105
Number of patients at risk	1021	1011	1003	990	976	953	936	886
Cumulative incidence (%)		1.0	1.7	2.8	4.2	6.4	7.9	10.3

The time-to-event curve through 1 year after index percutaneous coronary intervention (PCI) for the primary endpoint (a composite of death, myocardial infarction, stroke, or any coronary revascularization) in patients enrolled in the OPTIVUS (OPTimal IntraVascular UltraSound)-Complex PCI study multivessel cohort. The cumulative incidence was estimated with the Kaplan-Meier method. One-sample binominal test was used to compare the incidence of primary endpoint with the predefined performance goals of 27.5% derived from the PCI patients in the CREDO-Kyoto (Coronary REvascularization Demonstrating Outcome study in Kyoto) registry Cohort-2. CABG = coronary artery bypass grafting.

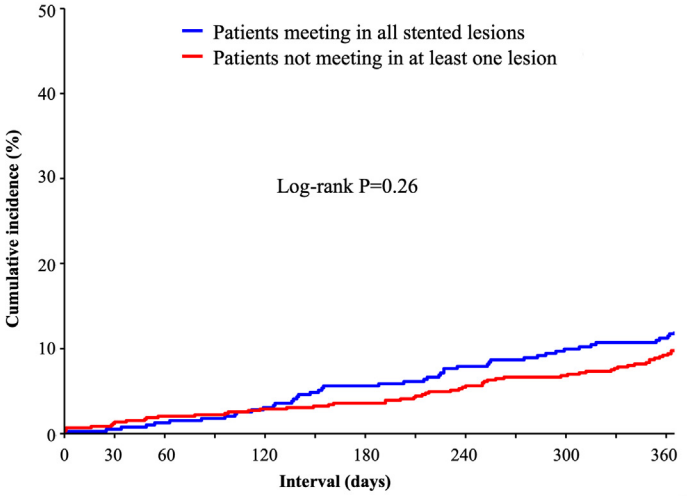
stent edge dissections. The achievement rate of OPTIVUS criteria was 61.0%, which was not much different compared with the previous studies.[8,9] However, clinical outcomes were not different between patients with and without meeting OPTIVUS criteria. Several reasons might be suggested to explain why patients who did not meet the OPTIVUS criteria did not have worse clinical outcomes compared with patients who met the OPTIVUS criteria. First, the OPTIVUS criteria might not be the appropriate criteria for stent expansion to predict clinical outcomes. A study from the ADAPT-DES (Assessment of Dual Antiplatelet Therapy With Drug-Eluting Stents) registry evaluated various stent expansion indexes to determine the best predictor of clinical outcomes.[16] Conventional stent expansion criteria in which MSA was compared with reference lumen area such as IVUX-XPL criteria could not predict clinical events, and only MSA/vessel area at the MSA site could predict clinical outcomes.[16] Reference lumen area might not be appropriate when stent length is long, when a lesion has diffuse disease, and when stent edge is located at a bifurcation. Moreover, MSA/vessel area at the MSA site could strongly predict clinical outcomes if the MSA is small (MSA <4.5 mm^2), but not if the MSA is large.[16] In the OPTIVUS-Complex PCI study, the lesions which did not meet the OPTIVUS criteria had large reference lumen area, and their MSA was relatively large (mean MSA $= 5.5$ mm^2). Relative stent expansion criteria only might work if MSA is small. Further studies will be needed to explore the optimal stent expansion criteria predicting the clinical outcomes that could be used as a guide during PCI.

Improved clinical outcomes in the OPTIVUS-Complex PCI might be caused not only by the IVUS-guided PCI, but also by the adoption of contemporary clinical practice. First, the patients in this study exclusively used new-generation DES. The superiority of new-generation DES compared with

FIGURE 4 Kaplan-Meier Curves: Patients Meeting vs Not Meeting OPTIVUS Criteria

A

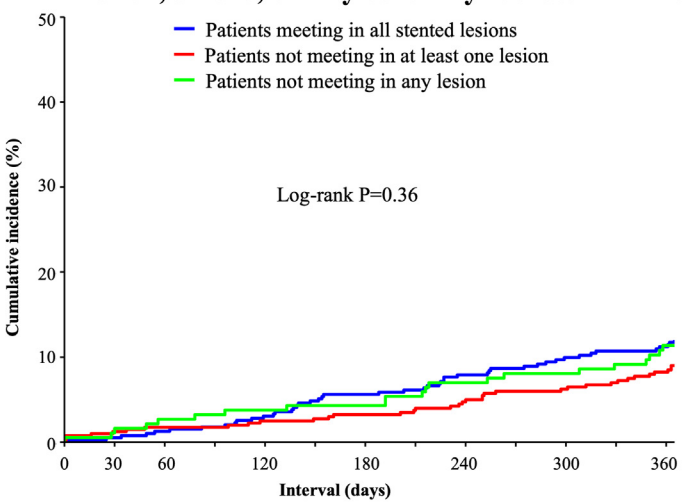
Primary endpoint:
Death, Myocardial infarction, Stroke, or Any coronary revascularization



Interval (days)	0	30	60	120	180	240	300	365
Patients meeting in all stented lesions								
Number of patients with event		2	5	12	22	31	39	47
Number of patients at risk	394	391	388	380	370	361	353	341
Cumulative incidence (%)		0.5	1.3	3.1	5.6	7.9	9.9	12.0
Patients not meeting in at least one lesion								
Number of patients with event		8	12	17	21	33	40	57
Number of patients at risk	588	581	576	571	567	554	545	507
Cumulative incidence (%)		1.4	2.0	2.9	3.6	5.6	6.8	9.7

B

Primary endpoint:
Death, Myocardial infarction, Stroke, or Any coronary revascularization



Interval (days)	0	30	60	120	180	240	300	365
Patients meeting in all stented lesions								
Number of patients with event		2	5	12	22	31	39	47
Number of patients at risk	394	391	388	380	370	361	353	341
Cumulative incidence (%)		0.5	1.3	3.1	5.6	7.9	9.9	12.0
Patients not meeting in at least one lesion								
Number of patients with event		5	7	10	13	20	25	36
Number of patients at risk	402	397	395	392	389	381	375	353
Cumulative incidence (%)		1.2	1.7	2.5	3.2	5.0	6.2	9.0
Patients not meeting in any lesion								
Number of patients with event		3	5	7	8	13	15	21
Number of patients at risk	186	184	181	179	178	173	170	154
Cumulative incidence (%)		1.6	2.7	3.8	4.3	7.0	8.1	11.4

Continued on the next page

TABLE 4 Clinical Outcomes

Endpoints	OPTIVUS Entire Study Population (N = 1,021)	OPTIVUS Criteria			Log-Rank *P* Value
		Meeting in All Stented Lesions (n = 394)	Not Meeting in at Least 1 Lesion (n = 402)	Not Meeting in Any Lesion (n = 186)	
	Patients With Event (Cumulative 1-y Incidence)	Patients With Event (Cumulative 1-y Incidence)			
Primary endpoint					
A composite of death, myocardial infarction, stroke, or any coronary revascularization	105 (10.3)	47 (12.0)	36 (9.0)	21 (11.4)	0.36
Secondary endpoints					
All-cause death	22 (2.2)	10 (2.6)	8 (2.0)	4 (2.2)	0.87
Cardiovascular death	9 (0.9)	5 (1.3)	2 (0.5)	2 (1.1)	0.51
Cardiac death	7 (0.7)	3 (0.8)	2 (0.5)	2 (1.1)	0.73
Sudden cardiac death	3 (0.3)	0 (0)	2 (0.5)	1 (0.5)	0.37
Non-cardiovascular death	13 (1.3)	5 (1.3)	6 (1.5)	2 (1.1)	0.91
Myocardial infarction	13 (1.3)	5 (1.3)	6 (1.5)	2 (1.1)	0.91
Spontaneous	5 (0.5)	3 (0.8)	2 (0.5)	0 (0)	0.48
Periprocedural	8 (0.8)	2 (0.5)	4 (1.0)	2 (1.1)	0.68
Definite stent thrombosis	2 (0.2)	1 (0.3)	1 (0.3)	0 (0)	0.79
Stroke	6 (0.6)	3 (0.8)	1 (0.3)	2 (1.1)	0.43
Ischemic stroke	4 (0.4)	3 (0.8)	0 (0)	1 (0.5)	0.23
Hemorrhagic stroke	2 (0.2)	0 (0)	1 (0.3)	1 (0.5)	0.39
Major stroke[a]	5 (0.5)	3 (0.8)	1 (0.3)	1 (0.5)	0.59
Hospitalization for heart failure	18 (1.8)	8 (2.1)	5 (1.3)	5 (2.7)	0.45
Major bleeding					
BARC type 3, 4, or 5	36 (3.6)	13 (3.3)	13 (3.3)	8 (4.3)	0.77
BARC type 3 or 5	35 (3.5)	12 (3.1)	13 (3.3)	8 (4.3)	0.71
BARC type 5	0 (0)	0 (0)	0 (0)	0 (0)	
GUSTO moderate or severe	31 (3.1)	13 (3.3)	9 (2.3)	7 (3.8)	0.51
GUSTO severe	17 (1.7)	5 (1.3)	7 (1.8)	3 (1.6)	0.86
Target-lesion revascularization	44 (4.4)	20 (5.2)	14 (3.6)	10 (5.5)	0.43
Clinically driven target-lesion revascularization	43 (4.3)	19 (4.9)	14 (3.6)	10 (5.5)	0.48
Target-vessel revascularization	61 (6.1)	27 (7.0)	20 (5.1)	13 (7.1)	0.45
Clinically driven target-vessel revascularization	60 (6.0)	26 (6.7)	20 (5.1)	13 (7.1)	0.50
Any coronary revascularization	71 (7.1)	33 (8.5)	24 (6.1)	13 (7.1)	0.39
Clinically driven any coronary revascularization	70 (7.0)	32 (8.2)	24 (6.1)	13 (7.1)	0.47
A composite of death, myocardial infarction, or stroke	41 (4.0)	18 (4.6)	15 (3.7)	8 (4.3)	0.84

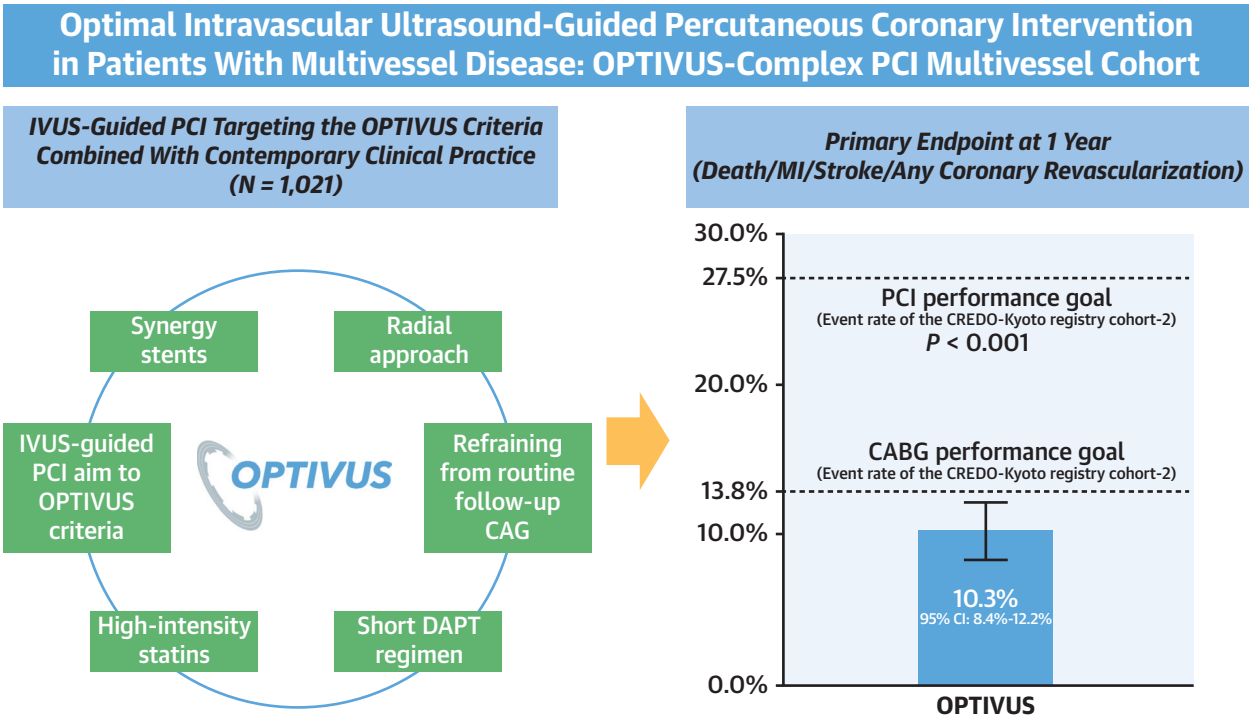
Values are n (%). Cumulative 1-year incidence was estimated with Kaplan-Meier method. Definitions of the endpoints were described in the Supplemental Materials.
[a]Major stroke was defined as modified Rankin scale ≥2.
BARC = Bleeding Academic Research Consortium.

first-generation DES for clinical outcomes has been well established in a meta-analysis.[17] Second, radial artery approach was used in 87.5% of the patients in this study. In a meta-analysis, the radial approach compared with femoral approach reduced not only major bleeding and vascular complications, but also mortality and major adverse cardiovascular events.[18] Third, the prescription rate of statins was 91.7% in this study, which was much higher compared with the patients in the CREDO-Kyoto registry cohort-2 (PCI:

FIGURE 4 Continued

The time-to-event curves through 1 year after index percutaneous coronary intervention (PCI) for the primary endpoint (a composite of death, myocardial infarction, stroke, or any coronary revascularization) in patients with or without meeting OPTIVUS (OPTimal IntraVascular UltraSound) criteria. **(A)** Comparison between patients meeting in all stented lesion and patients not meeting in at least 1 lesion. **(B)** Comparison among patients meeting in all stented lesions, patients not meeting in some lesion(s), and patients not meeting in any lesion. The cumulative incidence was estimated with the Kaplan-Meier method, and the differences were compared with the log-rank test.

CENTRAL ILLUSTRATION **OPTIVUS-Complex PCI Study Multivessel Cohort**



Yamamoto K, et al. JACC: Asia. 2023;3(2):211–225.

Contemporary percutaneous coronary intervention (PCI) practice conducted in the OPTIVUS (OPTimal IntraVascular UltraSound)-Complex PCI study was associated with a significantly lower major adverse cardiac and cerebrovascular event (MACCE) rate than the predefined PCI performance goal, and with a numerically lower MACCE rate than the predefined coronary artery bypass grafting (CABG) performance goal at 1 year. DAPT = dual antiplatelet therapy; IVUS = intravascular ultrasound; MI = myocardial infarction.

56%, and CABG: 31%). Moreover, high-intensity statin therapy was prescribed in 36.6% of the patients, which was almost never used in the CREDO-Kyoto registry cohort-2.[19] Fourth, the discontinuation rates of DAPT at 180 days and at 1 year were 37.4% and 68.6%, and the dominant antiplatelet monotherapy after stopping DAPT was $P2Y_{12}$ inhibitors in this study. A meta-analysis reported the efficacy and safety of $P2Y_{12}$ inhibitors monotherapy after very short DAPT compared with standard 12-month DAPT.[20] Fifth, the incidence of follow-up coronary angiography at 1 year was only 18.2% in this study, because we strongly recommended refraining from scheduled follow-up coronary angiography in asymptomatic patients. In the CREDO-Kyoto registry cohort-2, scheduled follow-up coronary angiography after PCI was a common clinical practice, which undoubtedly increased coronary revascularization by the so-called "oculostenotic reflex."[21] These contemporary clinical practices may have contributed to the observed better clinical outcomes in this study.

STUDY LIMITATIONS. Most importantly, this study was not a randomized trial comparing the optimal IVUS-guided PCI with standard PCI or CABG. In addition, 1-year follow-up might be too short to evaluate the effect of IVUS-guided PCI compared with standard PCI or CABG. Second, the study for calculating the performance goal of PCI or CABG was conducted over a decade ago. Not only the PCI practice, but also the surgical techniques have improved together with adjunctive medical therapy. In addition, the coronary anatomic complexity such as SYNTAX score, and the prevalence of 3-vessel disease or chronic total occlusion target was lower in this study than in the CREDO-Kyoto registry cohort-2.[11] Therefore, there were various differences in clinical practice between the present study population and the population for calculating the performance goal.[11] Moreover, the present study population might

represent selected patients for a clinical trial. The patient and lesion characteristics might be different between the present study and the real-world registry enrolling consecutive patients. Third, clinical outcomes were not different between patients with and without meeting OPTIVUS criteria, although we defined OPTIVUS criteria based on the previous studies. In addition to possible selected patient enrollment, OPTIVUS criteria might not be the best IVUS criteria for guiding PCI, although the intention to achieve the OPTIVUS criteria might have contributed to obtain reasonable stent expansion, even if we could not achieve the OPTIVUS criteria in certain proportion of patients. Finally, we could not evaluate any IVUS analysis in target lesions without stenting.

CONCLUSIONS

Contemporary PCI practice conducted in the OPTIVUS-Complex PCI study was associated with a significantly lower MACCE rate than the predefined PCI performance goal, and with a numerically lower MACCE rate than the predefined CABG performance goal at 1 year.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: IVUS-guided multivessel PCI targeting the prespecified IVUS criteria (OPTIVUS criteria) combined with contemporary clinical practice was associated with a significantly lower MACCE rate than the predefined PCI performance goal, and with a numerically lower MACCE rate than the predefined CABG performance goal at 1 year. The cumulative 1-year incidence of the primary endpoint was not significantly different regardless of meeting or not meeting OPTIVUS criteria.

TRANSLATIONAL OUTLOOK: Further studies will be needed to explore the optimal stent expansion criteria predicting the clinical outcomes that could be used as a guide during PCI.

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