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ORIGINAL ARTICLE
Imaging

Dual Antiplatelet Therapy Duration After Multivessel Optimal Intravascular Ultrasound-Guided Percutaneous Coronary Intervention

Ko Yamamoto, MD; Hiroki Shiomi, MD; Takeshi Morimoto, MD, MPH; Akiyoshi Miyazawa, MD; Hiroki Watanabe, MD; Sunao Nakamura, MD; Satoru Suwa, MD; Takenori Domei, MD; Koh Ono, MD; Hiroki Sakamoto, MD; Masataka Shigetoshi, MD; Ryoji Taniguchi, MD; Hideki Okayama, MD; Takafumi Yokomatsu, MD; Masahiro Muto, MD; Ren Kawaguchi, MD; Koichi Kishi, MD; Mitsuyoshi Hadase, MD; Tsutomu Fujita, MD; Yasunori Nishida, MD; Masami Nishino, MD; Hiromasa Otake, MD; Masahiro Natsuaki, MD; Hirotoshi Watanabe, MD; Nobuhiro Suematsu, 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 scarcity of data evaluating contemporary real-world dual antiplatelet therapy (DAPT) strategies after percutaneous coronary intervention (PCI).

Methods and Results: In the OPTIVUS-Complex PCI study multivessel cohort enrolling 982 patients undergoing multivessel PCI, including left anterior descending coronary artery using intravascular ultrasound (IVUS), we conducted 90-day landmark analyses to compare shorter and longer DAPT. DAPT discontinuation was defined as withdrawal of $P2Y_{12}$ inhibitors or aspirin for at least 2 months. The prevalence of acute coronary syndrome and high bleeding risk by the Bleeding Academic Research Consortium were 14.2% and 52.5%, respectively. The cumulative incidence of DAPT discontinuation was 22.6% at 90 days, and 68.8% at 1 year. In the 90-day landmark analyses, there were no differences in the incidences of a composite of death, myocardial infarction, stroke, or any coronary revascularization (5.9% vs. 9.2%, log-rank P=0.12; adjusted hazard ratio, 0.59; 95% confidence interval, 0.32–1.08; P=0.09) and BARC type 3 or 5 bleeding (1.4% vs. 1.9%, log-rank P=0.62) between the off- and on-DAPT groups at 90 days.

Conclusions: The adoption of short DAPT duration was still low in this trial conducted after the release of the STOPDAPT-2 trial results. The 1-year incidence of cardiovascular events was not different between the shorter and longer DAPT groups, suggesting no apparent benefit of prolonged DAPT in reducing cardiovascular events even in patients who undergo multivessel PCI.

Key Words: Coronary stent; Dual antiplatelet therapy; Intravascular ultrasound; Percutaneous coronary intervention

Several randomized controlled trials have suggested that the strategy of shorter duration of dual antiplatelet therapy (DAPT) followed by $P2Y_{12}$ inhibitors monotherapy reduces major bleeding without increasing cardiovascular events after percutaneous coronary intervention (PCI).[1–6] However, actual DAPT durations have not been adequately reported in real clinical practice after these clinical trials. Moreover, the majority of patients enrolled in the clinical trials evaluating short DAPT had relatively low coronary anatomic complexity, and the prevalence of complex lesions such as multivessel disease was low.[1–6] There is a scarcity of data evaluating contemporary

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Department of Cardiovascular Medicine, Kyoto University Graduate School of Medicine, Kyoto (K.Y., H. Shiomi, K.O., Hirotoshi Watanabe, T.K.); Department of Clinical Epidemiology, Hyogo College of Medicine, Nishinomiya (T.M.); Cardiocore Japan, Tokyo (A.M.); Department of Cardiology Japanese Red Cross Wakayama Medical Center, Wakayama (Hiroki Watanabe); Department of Cardiovascular Medicine, New Tokyo Hospital, Matsudo (S.N.); Department of Cardiology, Juntendo University Shizuoka Hospital, Izunokuni (S.S.); Department of Cardiology, Kokura Memorial Hospital, Kitakyushu (T.D., K.A.); Department of Cardiology, Shizuoka General Hospital, Shizuoka (H. Sakamoto); Department of Cardiology, National Hospital Organization Okayama Medical Center, Okayama (M.S.); Department of Cardiology, Hyogo Prefectural Amagasaki General Medical Center, Amagasaki (R.T.); Department of Cardiology, Ehime Prefectural Central Hospital, Matsuyama (H. Okayama); Department of Cardiology, Mitsubishi Kyoto Hospital, Kyoto (T.Y.); Department of Cardiology, Hamamatsu Medical Center, Hamamatsu (M.M.); Department of Cardiology, Gunma Prefectural Cardiovascular Center, Maebashi (R.K.); Department of Cardiology, Tokushima Red Cross Hospital, Tokushima (K. Kishi); Department of Cardiology, Saiseikai Shiga Hospital, Ritto (M.H.);
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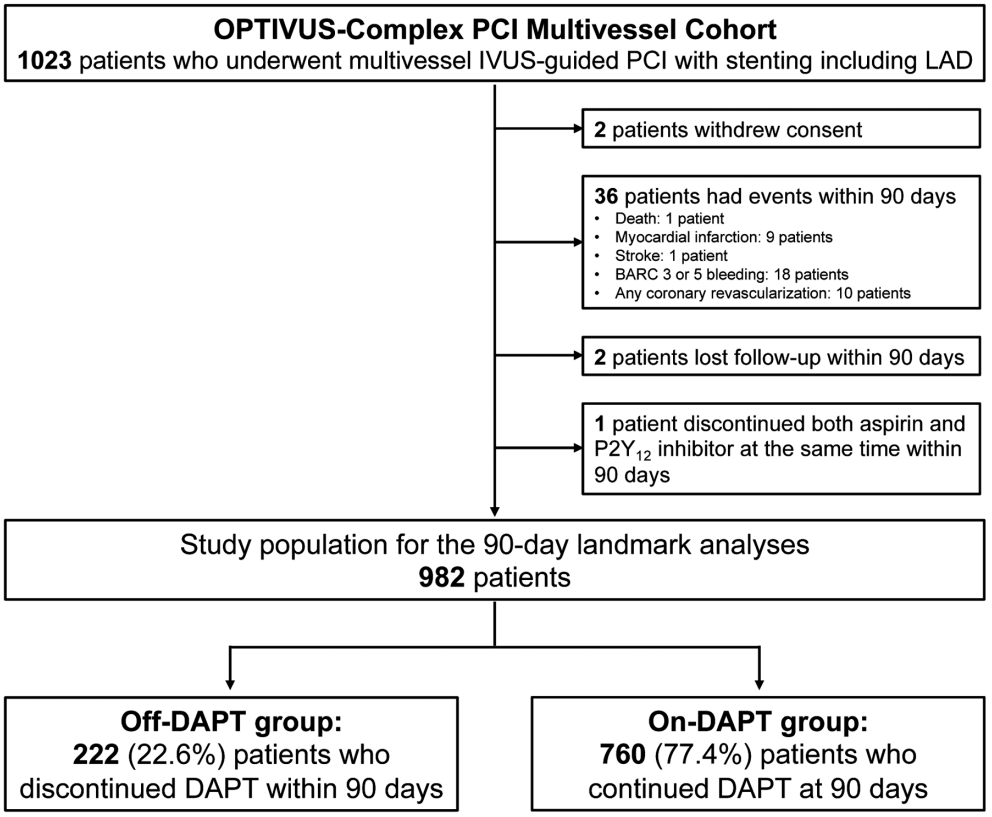

Figure 1. Study flowchart. BARC, Bleeding Academic Research Consortium; DAPT, dual antiplatelet therapy; IVUS, intravascular ultrasound; LAD, left anterior descending coronary artery; OPTIVUS, OPTimal IntraVascular UltraSound; PCI, percutaneous coronary intervention.

real-world DAPT strategies and the effect of shorter DAPT relative to longer DAPT after multivessel PCI. The OPTIVUS-Complex PCI (Optimal Intravascular Ultrasound Guided Complex Percutaneous Coronary Intervention) multivessel cohort was a prospective multicenter single-arm study enrolling patients who underwent IVUS-guided multivessel PCI with a target of prespecified criteria for optimal stent implantation.[6] In this study, we evaluated DAPT duration and the effect of shorter DAPT relative to longer DAPT after multivessel IVUS-guided PCI in this cohort.

Methods

Study Population

The OPTIVUS-Complex PCI study multivessel cohort enrolled patients who underwent IVUS-guided multivessel PCI including a target lesion in left anterior descending coronary artery (LAD). Patients who underwent left main PCI were enrolled in the "OPTIVUS-Complex PCI study left main cohort". Therefore, the present study population (OPTIVUS-Complex PCI study multivessel cohort) did not include patients who underwent left main and multivessel PCI. The exclusion criteria were ST-segment-elevation myocardial infarction, cardiogenic shock, and previous history of coronary artery bypass grafting. The PCI operators were mandated to perform optimal IVUS-guided PCI with a target of prespecified criteria (OPTIVUS criteria) for optimal stent implantation. The design, patient enrollment, and main results at 1 year were previously reported in detail.[7,8] Written informed consent was provided from

Department of Cardiology, Sapporo Heart Center, Sappro Cardio Vascular Clinic, Sapporo (T.F.); Department of Cardiovascular Medicine, Koseikai Takai Hospital, Tenri (Y.N.); Division of Cardiology, Osaka Rosai Hospital, Sakai (M. Nishino); Division of Cardiovascular Medicine, Department of Internal Medicine, Kobe University Graduate School of Medicine, Kobe (H. Otake); Department of Cardiovascular Medicine, Saga University, Saga (M. Natsuaki); Division of Cardiology, Saiseikai Fukuoka General Hospital, Fukuoka (N.S.); Division of Cardiology, Mitsui Memorial Hospital, Tokyo (K.T.); Department of Cardiology, National Hospital Organization Kyoto Medical Center, Kyoto (M.A.); Division of Cardiology, Yokohama City University Medical Center, Yokohama (K.H.); and Department of Cardiology, Kurashiki Central Hospital, Kurashiki (K. Kadota), 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

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all enrolled patients. This study was in accordance with the Declaration of Helsinki.

Between March 2019 and April 2021, 1,023 patients who underwent IVUS-guided multivessel PCI including LAD target were enrolled in 90 Japanese centers. To explore the effect of shorter DAPT relative to longer DAPT in this cohort, we conducted 90-day landmark analyses. After excluding 2 patients who withdrew consent, 36 patients who had clinical events within 90 days, 2 patients who were lost to follow-up within 90 days, and 1 patient who discontinued both $P2Y_{12}$ inhibitor and aspirin at the same time within 90 days, the current study population for the 90-day landmark analyses consisted of 982 patients (**Figure 1**). The study population was divided into 2 groups: off-DAPT group and on-DAPT group at 90 days. The off-DAPT group was defined as patients who discontinued either $P2Y_{12}$ inhibitors or aspirin within 90 days after the index PCI, and the on-DAPT group was defined as patients who had maintained DAPT with $P2Y_{12}$ inhibitors and aspirin at 90 days after the index PCI.

Antiplatelet Therapy

In this study, short DAPT of 1–6 months duration was recommended, but the actual management of antiplatelet therapy was left to the discretion of each attending physician. Data on the status of $P2Y_{12}$ inhibitors and aspirin were collected throughout follow-up. DAPT discontinuation was defined as withdrawal of $P2Y_{12}$ inhibitors or aspirin for at least 2 months, consistent with our previous studies.[7,8]

Study Procedures and OPTIVUS Criteria

The PCI operators were mandated to perform optimal IVUS-guided PCI with a target of prespecified criteria (OPTIVUS criteria) for optimal stent implantation. The details of the OPTIVUS criteria are provided in the **Supplementary File**. In addition to IVUS-related recommendations, there were other recommendations to adopt for contemporary clinical, procedural, and pharmacologic practice. Target lesions were to be selected by stress imaging or physiological assessment (fractional flow reserve [FFR] or instantaneous wave-free ratio [iFR]), although the actual indication of PCI was left to the discretion of each attending physician. Enrolled patients were to undergo PCI using platinum-chromium everolimus-eluting stents (Synergy; Boston Scientific, Marlborough, MA, USA). Radial access was recommended as the standard approach. Scheduled follow-up coronary angiography (CAG) after PCI was discouraged in asymptomatic patients. Use of high-intensity statin therapy was recommended with the maximum approved dose of strong statins in Japan. All recommendations are described in the **Supplementary File**. Quantitative and qualitative CAG (QCA) analyses were to be performed for all target lesions, and IVUS analysis was to be performed for all target lesions with stenting by an independent core laboratory (Cardiocore, Tokyo, Japan).

Endpoints

The primary endpoint was a major adverse cardiac and cerebrovascular event defined as a composite of death from any cause, myocardial infarction (MI), stroke, or any coronary revascularization. MI was adjudicated according to the Academic Research Consortium definition.[9] Stroke was defined as ischemic or hemorrhagic stroke with neurological symptoms lasting >24 h. Bleeding was defined according to the Bleeding Academic Research Consortium (BARC) classification.[10] The definitions of secondary endpoints are given in the **Supplementary File**. All endpoints were assessed at 1 year (between 335 and 394 days), with censoring on day 366. All clinical events were adjudicated based on the source documents by an independent clinical events committee.

Statistical Analysis

Categorical variables are presented as number and percentage and were compared with chi-square test. Continuous variables are expressed as mean±standard deviation or median with interquartile range (IQR) and were compared using Student's t-test or Wilcoxon rank-sum test depending on their distribution. The cumulative 1-year incidence of DAPT discontinuation was estimated with the Kaplan-Meier method.

Regarding the clinical outcomes, we conducted 90-day landmark analyses to compare the off-DAPT and on-DAPT groups as described previously. The cumulative 1-year incidences of the primary endpoint and BARC type 3 or 5 bleeding were estimated with the Kaplan-Meier method, and the differences were compared with the log-rank test. The effect of off-DAPT relative to on-DAPT for the primary and secondary endpoints were expressed as hazard ratio (HR) and 95% confidence intervals (CIs) estimated by a Cox proportional hazard model. Because the secondary endpoints occurred infrequently, we did not adjust the HRs of secondary endpoints, but we constructed a multivariable Cox proportional hazard model to assess the effect of off-DAPT relative to on-DAPT for the primary endpoint at 1 year. The risk-adjusting variables were 12 clinically relevant factors listed in **Table 1**. We also conducted subgroup analyses stratified by the Academic Research Consortium for High Bleeding Risk (ARC-HBR) for the primary endpoint, major bleeding, and a composite of death, MI, or stroke. Furthermore, we conducted additional analyses for the primary endpoint, major bleeding, and a composite of death or MI after excluding patients who were on oral anticoagulants at discharge from the index PCI hospitalization. We did not adjust the subgroup or additional analyses due to the small number of events.

All P values were two-sided and $P<0.05$ was considered statistically significant. All analyses were performed with R version 4.1.2 (R Foundation for Statistical Computing, Vienna, Austria).

Results

Antiplatelet Therapy and DAPT Discontinuation

In the entire study population, the cumulative incidence of DAPT discontinuation was 22.6% at 90 days, and 68.8% at 1 year (**Figure 2A**). The cumulative incidence of DAPT discontinuation was 90.2% at 90 days and 96.7% at 1 year in patients taking oral anticoagulants, and was 15.6% at 90 days and 65.9% at 1 year in patients not taking oral anticoagulants (**Supplementary Figure 1**). In the off-DAPT group, the cumulative incidence of DAPT discontinuation was 39.6% at 30 days, 74.8% at 60 days, and 100% at 90 days (**Figure 2B**), and the median interval from the index PCI to DAPT discontinuation was 36 (IQR: 0–61) days (**Table 1**). In the on-DAPT group, the cumulative incidence of DAPT discontinuation was 18.7% at 180 days, and 59.6% at 1 year (**Figure 2B**), and the median interval from the index PCI to DAPT discontinuation was 211

Table 1. Baseline Clinical Characteristics (per Patient Basis)

	Entire study population (n=982)	Off-DAPT at 90 days (n=222)	On-DAPT at 90 days (n=760)	P value
(A) Antiplatelet therapy				
Antiplatelet therapy at discharge				
$P2Y_{12}$ inhibitor	979 (99.7)	219 (98.6)	760 (100)	
Clopidogrel	545 (55.5)	146 (65.8)	399 (52.5)	
Prasugrel	432 (44.0)	72 (32.4)	360 (47.4)	
Aspirin	927 (94.4)	167 (75.2)	760 (100)	
DAPT discontinuation within 1 year	672 (68.4)	222 (100)	450 (59.2)	
Interval from index PCI to DAPT discontinuation (days)	156 (61–229)	36 (0–61)	211 (156–264)	
Antiplatelet monotherapy after DAPT discontinuation†				
$P2Y_{12}$ inhibitors	398 (60.1)	174 (78.4)	224 (50.9)	
Aspirin	264 (39.9)	48 (21.6)	216 (49.1)	
(B) Clinical characteristics				
Age (years)	71.1±10.0	72.6±10.2	70.7±9.9	0.01
≥75*	409 (41.6)	104 (46.8)	305 (40.1)	0.07
Men*	775 (78.9)	174 (78.4)	601 (79.1)	0.82
Body mass index (kg/m^2)	24.1±3.6	24.1±3.8	24.1±3.5	0.80
<25.0	637 (64.9)	145 (65.3)	492 (64.7)	0.87
Acute coronary syndrome*	139 (14.2)	33 (14.9)	106 (13.9)	0.73
Acute MI	64 (6.5)	11 (5.0)	53 (7.0)	0.28
Unstable angina	75 (7.6)	22 (9.9)	53 (7.0)	0.15
Hypertension	826 (84.1)	184 (82.9)	642 (84.5)	0.57
Diabetes mellitus*	541 (55.1)	125 (56.3)	416 (54.7)	0.68
On insulin therapy	93 (9.5)	17 (7.7)	76 (10.0)	0.29
Dyslipidemia	909 (92.6)	199 (89.6)	710 (93.4)	0.06
On statin therapy	665 (67.7)	149 (67.1)	516 (67.9)	0.83
Total cholesterol (mg/dL)	176.1±42.3	173.6±41.3	176.8±42.6	0.35
HDL cholesterol (mg/dL)	49.4±13.6	48.7±12.7	49.6±13.8	0.39
Triglycerides (mg/dL)	122 (88–182)	118 (84–183)	123 (90–182)	0.46
LDL cholesterol (mg/dL)	99.4±36.7	98.7±36.3	99.6±36.9	0.74
Current smoking	171 (17.4)	29 (13.1)	142 (18.7)	0.052
HF*	169 (17.2)	57 (25.7)	112 (14.7)	<0.001
Prior hospitalization for HF	82 (8.4)	23 (10.4)	59 (7.8)	0.22
Current HF at index hospitalization	125 (12.7)	44 (19.8)	81 (10.7)	<0.001
LVEF (%)	57.8±12.3	57.3±13.3	57.9±12.0	0.52
<40%	109 (11.2)	34 (15.5)	75 (9.9)	0.02
Mitral regurgitation grade ≥3/4	29 (3.0)	8 (3.6)	21 (2.8)	0.52
Prior MI*	175 (17.8)	39 (17.6)	136 (17.9)	0.91
Prior stroke*	115 (11.7)	27 (12.2)	88 (11.6)	0.81
Peripheral vascular disease	111 (11.3)	28 (12.6)	83 (10.9)	0.48
eGFR <30 mL/min/1.73 m^2 or hemodialysis*	93 (9.5)	27 (12.2)	66 (8.7)	0.12
eGFR <30 mL/min/1.73 m^2 without hemodialysis	36 (3.7)	14 (6.3)	22 (2.9)	0.02
Hemodialysis	57 (5.8)	13 (5.9)	44 (5.8)	0.97
Atrial fibrillation	79 (8.0)	56 (25.2)	23 (3.0)	<0.001
Anemia (hemoglobin <11.0 g/dL)	89 (9.1)	27 (12.2)	62 (8.2)	0.07
Thrombocytopenia (platelets <100×10^9/L)	10 (1.0)	4 (1.8)	6 (0.8)	0.19
Malignancy	123 (12.5)	30 (13.5)	93 (12.2)	0.61
Severe frailty	36 (3.7)	11 (5.0)	25 (3.3)	0.25
ARC-HBR*	516 (52.5)	151 (68.0)	365 (48.0)	<0.001
J-HBR	621 (63.2)	163 (73.4)	458 (60.3)	<0.001
CREDO-Kyoto thrombotic risk score	2 (1–3)	2 (1–4)	1 (1–2)	<0.001
Low (0–1)	469 (47.8)	80 (36.0)	389 (51.2)	
Intermediate (2–3)	340 (34.6)	80 (36.0)	260 (34.2)	<0.001
High (≥4)	173 (17.6)	62 (27.9)	111 (14.6)	

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

	Entire study population (n=982)	Off-DAPT at 90 days (n=222)	On-DAPT at 90 days (n=760)	P value
CREDO-Kyoto bleeding risk score	1 (0–2)	1 (0–3)	0 (0–2)	<0.001
Low (0)	469 (47.8)	82 (36.9)	387 (50.9)	
Intermediate (1–2)	348 (35.4)	79 (35.6)	269 (35.4)	<0.001
High (≥3)	165 (16.8)	61 (27.5)	104 (13.7)	
(C) Procedural characteristics				
Pre-procedure noninvasive test	206 (21.0)	46 (20.7)	160 (21.1)	0.92
Stress ECG	101 (10.3)	21 (9.5)	80 (10.5)	
SPECT	88 (9.0)	21 (9.5)	67 (8.8)	
Cardiac magnetic resonance	9 (0.9)	1 (0.5)	8 (1.1)	
Stress echocardiography	3 (0.3)	1 (0.5)	2 (0.3)	
FFR-CT	10 (1.0)	2 (0.9)	8 (1.1)	
Invasive FFR or iFR use	296 (30.1)	72 (32.4)	224 (29.5)	0.40
IVUS use	982 (100)	222 (100)	760 (100)	–
Radial artery approach	857 (87.3)	195 (87.8)	662 (87.1)	0.77
Femoral artery approach	224 (22.8)	43 (19.4)	181 (23.8)	0.17
Brachial artery approach	54 (5.5)	13 (5.9)	41 (5.4)	0.79
Extent of coronary artery disease*				
2-vessel	781 (79.5)	186 (83.8)	595 (78.3)	0.07
3-vessel	201 (20.5)	36 (16.2)	165 (21.7)	
SYNTAX score	17.9±7.1	16.9±6.8	18.2±7.1	0.02
Low <23	769 (79.1)	181 (81.9)	588 (78.3)	
Intermediate 23–32	161 (16.6)	36 (16.3)	125 (16.6)	0.11
High ≥33	42 (4.3)	4 (1.8)	38 (5.1)	
No. of target lesions	2.5±0.8	2.5±0.8	2.6±0.8	0.47
Total no. of stents	3.0±1.2	2.9±1.1	3.0±1.3	0.18
Total stent length (mm)	79.7±37.1	75.8±33.7	80.8±37.9	0.08
Target of proximal LAD*	970 (98.8)	217 (97.7)	753 (99.1)	0.11
Target of chronic total occlusion*	141 (14.4)	24 (10.8)	117 (15.4)	0.09
Target of bifurcation	591 (60.2)	132 (59.5)	459 (60.4)	0.80
Bifurcation with 2 stents	22 (2.2)	7 (3.2)	15 (2.0)	0.30
New-generation DES use	982 (100)	222 (100)	760 (100)	–
Staged PCI	745 (75.9)	148 (66.7)	597 (78.6)	<0.001
PCI procedure success (per patient)				0.35
Complete success	963 (98.1)	216 (97.3)	747 (98.3)	
Partial success	19 (1.9)	6 (2.7)	13 (1.7)	
Procedural complications	58 (5.9)	11 (5.0)	47 (6.2)	0.49
Side branch occlusion (post TIMI grade ≤2)	19 (1.9)	4 (1.8)	15 (2.0)	
Slow flow	28 (2.9)	5 (2.3)	23 (3.0)	
Acute occlusion	6 (0.6)	2 (0.9)	4 (0.5)	
Perforation	8 (0.8)	1 (0.5)	7 (0.9)	
Cardiac tamponade	0 (0)	0 (0)	0 (0)	
Stent dislodgement	1 (0.1)	1 (0.5)	0 (0)	
Stent thrombosis	0 (0)	0 (0)	0 (0)	
OPTIVUS criteria				0.96
Met in all stented lesions	380 (40.2)	88 (40.4)	292 (40.2)	
Not met in some lesion(s)	390 (41.3)	91 (41.7)	299 (41.1)	
Not met in any lesion	175 (18.5)	39 (17.9)	136 (18.7)	
(D) Medications at discharge				
Cilostazol	6 (0.6)	4 (1.8)	2 (0.3)	0.01
Statins	905 (92.2)	202 (91.0)	703 (92.5)	0.46
High-intensity statins‡	363 (37.0)	89 (40.1)	274 (36.1)	0.27
β-blockers	437 (44.5)	103 (46.4)	334 (43.9)	0.52
ACE-I/ARB	560 (57.0)	124 (55.9)	436 (57.4)	0.69
Nitrates	146 (14.9)	35 (15.8)	111 (14.6)	0.67
Calcium-channel blockers	426 (43.4)	98 (44.1)	328 (43.2)	0.79

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

	Entire study population (n=982)	Off-DAPT at 90 days (n=222)	On-DAPT at 90 days (n=760)	P value
Oral anticoagulants	92 (9.4)	83 (37.4)	9 (1.2)	<0.001
Warfarin	17 (1.7)	16 (7.2)	1 (0.1)	<0.001
DOAC	75 (7.6)	67 (30.2)	8 (1.1)	<0.001
Proton pump inhibitors or histamine type-2 receptor blockers	869 (88.5)	195 (87.8)	674 (88.7)	0.73
Proton pump inhibitors	842 (85.7)	187 (84.2)	655 (86.2)	0.47
Histamine type-2 receptor blockers	28 (2.9)	8 (3.6)	20 (2.6)	0.44

Categorical variables are presented as number and percentage. Continuous variables are presented as mean±standard deviation. Data on total cholesterol were missing for 68 patients, HDL cholesterol for 23 patients, triglycerides for 20 patients, LDL cholesterol for 17 patients, and LVEF for 7 patients. *Risk-adjusting variables selected for the Cox proportional hazard model. †10patients who discontinued $P2Y_{12}$ inhibitors and aspirin at the same time in the on-DAPT group were excluded. ‡High-intensity statin 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). ACE-I, angiotensin converting enzyme inhibitor; ARB, angiotensin II receptor blocker; ARC-HBR, Academic Research Consortium for High Bleeding Risk; DAPT, dual antiplatelet therapy; DES, drug-eluting stent; DOAC, direct oral anticoagulant; eGFR, estimated glomerular filtration rate; FFR, fractional flow reserve; FFR-CT, fractional flow reserve-computed tomography; HDL, high-density lipoprotein; HF, heart failure; iFR, instantaneous wave-free ratio; IVUS, intravascular ultrasound; J-HBR, Japanese version high bleeding risk; LAD, left anterior descending coronary artery; LDL, low-density lipoprotein; LVEF, left ventricular ejection fraction; MI, myocardial infarction; OPTIVUS, OPTimal IntraVascular UltraSound; PCI, percutaneous coronary intervention; SPECT, stress single photon emission computed tomography; SYNTAX, synergy between percutaneous coronary intervention with taxus and cardiac surgery; TIMI, Thrombolysis in Myocardial Infarction.

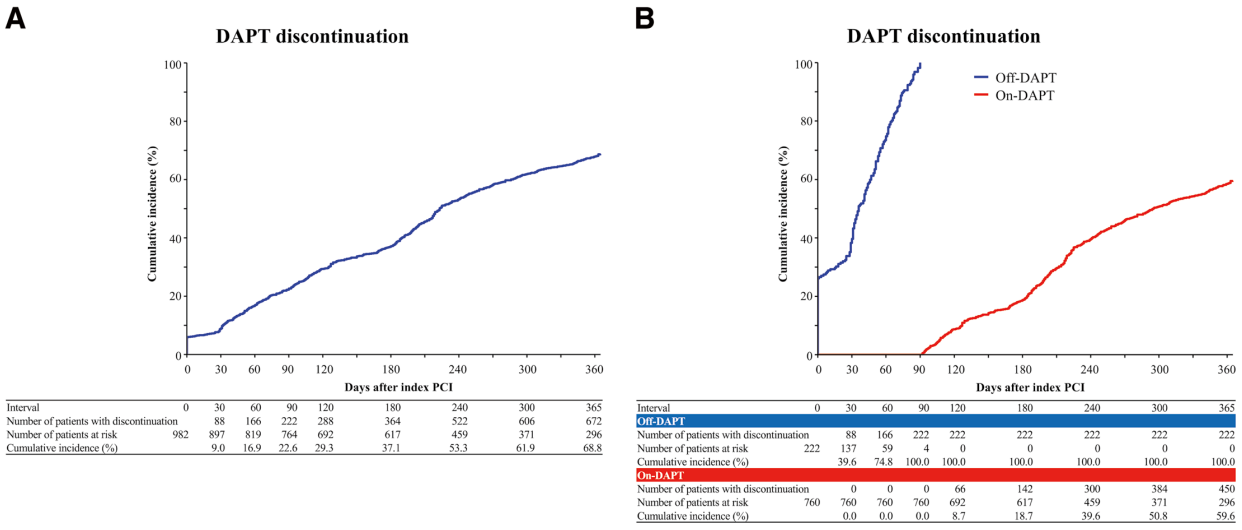


Figure 2. Kaplan-Meier curve for DAPT discontinuation (**A**) in the entire study population, and (**B**) in the off- and on-DAPT groups at 90 days. The cumulative incidence was estimated with the Kaplan-Meier method. DAPT discontinuation was defined as withdrawal of $P2Y_{12}$ inhibitor or aspirin for at least 2 months. DAPT, dual antiplatelet therapy; PCI, percutaneous coronary intervention.

(IQR: 156–264) days (**Table 1**). At discharge from the index hospitalization for PCI, clopidogrel was more often selected as the $P2Y_{12}$ inhibitor in the off-DAPT group than in the on-DAPT group (65.8% vs. 52.5%) (**Table 1**). In terms of the type of antiplatelet monotherapy after DAPT discontinuation, $P2Y_{12}$ inhibitors were more often selected in the off-DAPT group than in the on-DAPT group (78.4% vs. 50.9%).

Baseline Characteristics

The mean age was 71.1 years, and 14.2% of the patients presented as acute coronary syndrome (**Table 1**). The prevalence of ARC-HBR and Japanese version HBR (J-HBR) was 52.5% and 63.2%, respectively. Patients in the off-DAPT group were older and more often had comorbidities such as heart failure, systolic left ventricular dysfunction, chronic kidney disease, and atrial fibrillation compared with the on-DAPT group (**Table 1**). The prevalence of ARC-HBR and J-HBR was higher in the off-DAPT group than in the on-DAPT group (68.0% vs. 48.0%, P<0.001 and 73.4% vs. 60.3%, P<0.001, respectively). Regarding the angiographic and procedural characteristics, the SYNTAX score was higher in the on-DAPT group than in the off-DAPT group (**Table 1**). Staged PCI was more often performed in the on-DAPT group than in the off-DAPT group. In terms of the medications at discharge, prescription rates of cilostazol and oral anticoagulants were higher in the off-DAPT group than in the on-DAPT group (**Table 1**).

Angiographic, IVUS and Procedural Characteristics (per Lesion)

On angiography, patients in the on-DAPT group more often had complex lesions such as long or bifurcation lesions compared with the off-DAPT group (**Table 2**). The prevalence of in-stent restenosis was higher in the off-DAPT group than in the on-DAPT group. Rotational atherectomy device was more often used in the on-DAPT group than in the off-DAPT group.

In the IVUS analysis for the stented lesions after index procedure, the proximal reference lumen area, minimum stent area, distal reference lumen area, and the rate of

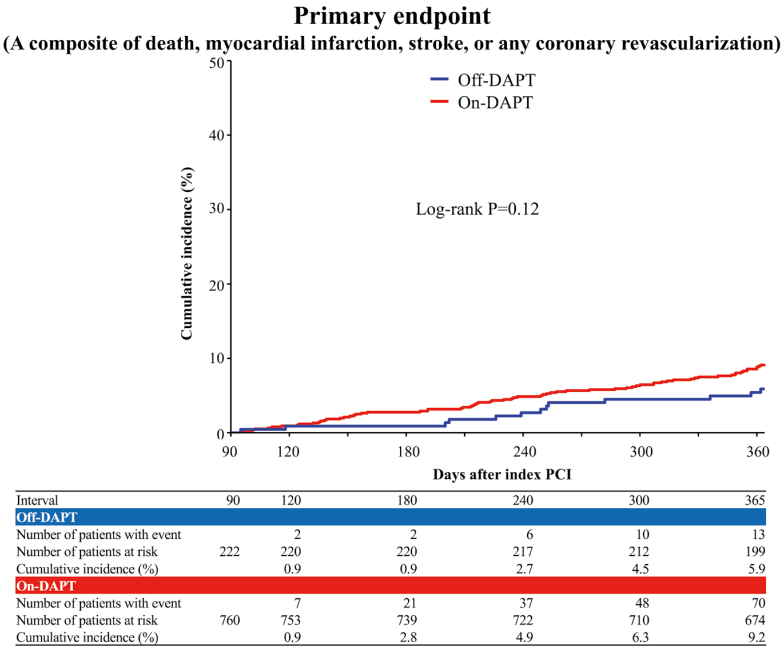
Table 2. Angiographic, Procedural, and IVUS Characteristics in the Core Angiographic and IVUS Laboratory (per Lesion Basis)

	Off-DAPT at 90 days (No. of target lesions=556)	On-DAPT at 90 days (No. of target lesions=1,936)	P value
(A) Angiographic and procedural characteristics			
No. of lesions with angiographic evaluation in the core angiographic laboratory	511	1,706	
Pre-procedure			
Lesion length (mm)	21.7±12.4 (n=470)	23.9±13.9 (n=1,531)	0.002
Reference vessel diameter (mm)	2.6±0.6 (n=508)	2.6±0.5 (n=1,705)	0.81
Minimum lumen diameter (mm)	0.8±0.4 (n=509)	0.8±0.4 (n=1,705)	0.14
Percent diameter stenosis (%)	67.7±13.0 (n=509)	69.0±14.3 (n=1,705)	0.06
Thrombus	12/509 (2.4)	40/1,706 (2.3)	0.99
Total occlusion	33/509 (6.5)	134/1,706 (7.9)	0.30
In-stent restenosis	32/509 (6.3)	49/1,706 (2.9)	<0.001
Bifurcation	210/509 (41.3)	845/1,706 (49.5)	0.001
Moderate or severe calcification	143/509 (28.1)	543/1,706 (31.8)	0.11
Index procedure			
Invasive FFR or iFR use	97 (17.4)	306 (15.8)	0.36
IVUS use	541 (97.3)	1,890 (97.6)	0.67
Stent use	520 (93.5)	1,770 (91.4)	0.11
PCI procedure success*	549 (98.7)	1,922 (99.3)	0.22
No. of stents used per lesion	1.2±0.5 (n=518)	1.3±0.5 (n=1,770)	0.04
Stent length per lesion (mm)	32.5±17.3 (n=518)	34.7±18.6 (n=1,770)	0.02
Minimum stent diameter (mm)	2.75 (2.5–3.0) (n=518)	2.75 (2.5–3.0) (n=1,770)	0.95
Cutting or scoring balloon use	185 (33.3)	665 (34.3)	0.64
Rotational atherectomy use	25 (4.5)	134 (6.9)	0.04
Orbital atherectomy use	10 (1.8)	31 (1.6)	0.75
Direct stenting	56/518 (10.8)	120/1,770 (6.8)	0.002
Maximum stent inflation pressure (atm)	12.7±3.0 (n=516)	12.7±3.2 (n=1,767)	0.96
Post-dilatation	391/518 (75.5)	1,384/1,770 (78.2)	0.19
Maximum balloon size (mm)	3.3±0.6 (n=391)	3.2±0.6 (n=1,384)	0.41
Maximum balloon inflation pressure (atm)	18.0±4.3 (n=388)	18.0±4.3 (n=1,383)	1.00
Post-procedure			
Minimum lumen diameter (mm)			
In-stent	2.5±0.5 (n=511)	2.5±0.5 (n=1,706)	0.66
In-segment	2.2±0.5 (n=511)	2.2±0.6 (n=1,706)	0.81
Percent diameter stenosis (%)			
In-stent	14.1±6.6 (n=511)	14.5±6.5 (n=1,706)	0.25
In-segment	23.5±9.9 (n=511)	23.7±9.8 (n=1,706)	0.76
Acute gain (mm)			
In-stent	1.7±0.5 (n=509)	1.7±0.5 (n=1,705)	0.11
In-segment	1.4±0.5 (n=509)	1.4±0.6 (n=1,705)	0.19
Procedural complications	13 (2.3)	52 (2.7)	0.65
Side branch occlusion (post TIMI grade ≤2)	4 (0.7)	16 (0.8)	
Slow flow	6 (1.1)	25 (1.3)	
Acute occlusion	2 (0.4)	4 (0.2)	
Perforation	1 (0.2)	8 (0.4)	
Cardiac tamponade	0 (0)	0 (0)	
Stent dislodgement	1 (0.2)	0 (0)	
Stent thrombosis	0 (0)	0 (0)	

(**Table 2** continued the next page.)

	Off-DAPT at 90 days (No. of target lesions=556)	On-DAPT at 90 days (No. of target lesions=1,936)	P value
(B) IVUS analysis post-procedure†			
No. of lesions with IVUS evaluation in the core IVUS laboratory	458	1,519	
Proximal reference vessel area (mm²)	15.9±5.7 (n=383)	16.1±5.6 (n=1,242)	0.39
Proximal reference lumen area (mm²)	8.3±3.5 (n=458)	8.3±3.3 (n=1,519)	0.77
Minimum stent area (mm²)	5.8±2.2 (n=458)	5.6±2.0 (n=1,519)	0.08
Distal reference vessel area (mm²)	10.1±5.5 (n=442)	9.7±5.0 (n=1,467)	0.17
Distal reference lumen area (mm²)	5.9±2.8 (n=458)	5.7±2.6 (n=1,519)	0.11
Incomplete stent apposition‡	174/458 (38.0)	548/1,519 (36.1)	0.46
Dissection	26/458 (5.7)	68/1,519 (4.5)	0.29
Meeting OPTIVUS criteria	281/457 (61.5)	928/1,518 (61.1)	0.89
Stent length ≥28 mm	130/254 (51.2)	512/928 (55.2)	0.26
Stent length <28 mm	151/203 (74.4)	416/590 (70.5)	0.29

Categorical variables are presented as number and percentage. Continuous variables are presented as mean±standard deviation or median with interquartile range. *PCI procedural success defined as successful dilatation of target lesion with residual diameter stenosis <50%. †IVUS analyses performed in all target lesions with stenting. ‡Incomplete stent apposition defined as the presence of blood flow between the stent struts and vessel wall. Abbreviatiopns as in Table 1.



Interval	90	120	180	240	300	365
Off-DAPT						
Number of patients with event		2	2	6	10	13
Number of patients at risk	222	220	220	217	212	199
Cumulative incidence (%)		0.9	0.9	2.7	4.5	5.9
On-DAPT						
Number of patients with event		7	21	37	48	70
Number of patients at risk	760	753	739	722	710	674
Cumulative incidence (%)		0.9	2.8	4.9	6.3	9.2

Figure 3. Kaplan-Meier curve for the primary endpoint. The cumulative 1-year incidence was estimated with the Kaplan-Meier method, and the difference was assessed with the log-rank test. DAPT, dual antiplatelet therapy; PCI, percutaneous coronary intervention.

meeting OPTIVUS criteria were not different between groups (**Table 2**).

Follow-up CAG

The cumulative incidence of follow-up CAG at 1 year was lower in the off-DAPT group than in the on-DAPT group (8.7% vs. 20.3%, log-rank P<0.001) (**Supplementary Figure 2**). The cumulative incidence of clinically-driven follow-up CAG at 1 year was not different between groups (2.3% vs. 4.8%, log-rank P=0.11) (**Supplementary Figure 3**), but that of scheduled follow-up CAG at 1 year was lower in the off-DAPT group than in the on-DAPT group (5.5% vs. 15.0%, log-rank P<0.001) (**Supplementary Figure 4**).

Clinical Outcomes

The cumulative 1-year incidence of the primary endpoint was not different between the off- and on-DAPT groups (5.9% vs. 9.2%, log-rank P=0.12) (**Figure 3**). After adjusting confounders, the effect of off-DAPT relative to on-DAPT was not significant for the primary endpoint (HR, 0.59; 95% CI, 0.32–1.08; P=0.09) (**Table 3**). The cumulative 1-year incidence of BARC type 3 or 5 bleeding was not different between groups (1.4% vs. 1.9%, log-rank P=0.62) (**Figure 4**). The cumulative 1-year incidences of target vessel and any coronary revascularization were lower in the off-DAPT group than in the on-DAPT group, but there were no differences in other secondary endpoints between groups (**Table 3**).

Table 3. Clinical Outcomes

	Off-DAPT at 90 days (n=222)	On-DAPT at 90 days (n=760)	Crude HR (95% CI)	P value	Adjusted HR (95% CI)	P value
	No. of patients with event (cumulative 1-year incidence)					
Primary endpoint						
Composite of death, MI, stroke, or any coronary revascularization	13 (5.9%)	70 (9.2%)	0.62 (0.35–1.13)	0.12	0.59 (0.32–1.08)	0.09
Secondary endpoints						
All-cause death	6 (2.7%)	14 (1.9%)	1.48 (0.57–3.84)	0.43		
Cardiovascular death	3 (1.4%)	5 (0.7%)	2.06 (0.49–8.62)	0.32		
Cardiac death	3 (1.4%)	4 (0.5%)	2.58 (0.58–11.52)	0.22		
Sudden cardiac death	1 (0.5%)	2 (0.3%)	1.72 (0.16–18.92)	0.66		
Noncardiovascular death	3 (1.4%)	9 (1.2%)	1.15 (0.31–4.24)	0.84		
MI	1 (0.5%)	3 (0.4%)	1.15 (0.12–11.02)	0.91		
Spontaneous	1 (0.5%)	3 (0.4%)	1.15 (0.12–11.02)	0.91		
Periprocedural	0 (0%)	0 (0%)	NA			
Definite stent thrombosis	0 (0%)	2 (0.3%)	NA			
Stroke	0 (0%)	5 (0.7%)	NA			
Ischemic stroke	0 (0%)	3 (0.4%)	NA			
Hemorrhagic stroke	0 (0%)	2 (0.3%)	NA			
Major stroke*	0 (0%)	4 (0.5%)	NA			
Major bleeding						
BARC type 3, 4, or 5	3 (1.4%)	15 (2.0%)	0.68 (0.20–2.36)	0.55		
BARC type 3 or 5	3 (1.4%)	14 (1.9%)	0.73 (0.21–2.55)	0.62		
BARC type 5	0 (0%)	0 (0%)	NA			
Target lesion revascularization	4 (1.8%)	32 (4.3%)	0.43 (0.15–1.20)	0.11		
Clinically driven	4 (1.8%)	31 (4.1%)	0.44 (0.15–1.24)	0.12		
Target vessel revascularization	5 (2.3%)	45 (6.0%)	0.37 (0.15–0.94)	0.04		
Clinically driven	5 (2.3%)	44 (5.9%)	0.38 (0.15–0.97)	0.04		
Any coronary revascularization	7 (3.2%)	53 (7.1%)	0.45 (0.20–0.98)	0.04		
Clinically driven	7 (3.2%)	52 (6.9%)	0.45 (0.21–0.999)	0.049		
Composite of death, MI, or stroke	7 (3.2%)	22 (2.9%)	1.09 (0.47–2.56)	0.84		

Cumulative 1-year incidence was estimated with the Kaplan-Meier method. The effects of off-DAPT relative to on-DAPT for the primary and secondary endpoints expressed as hazard ratio (HR) and their 95% confidence intervals (CIs) estimated by the Cox proportional hazard model. We constructed the multivariable Cox proportional hazard model to assess the effect of off-DAPT relative to on-DAPT for the primary endpoint. The risk-adjusting variables were 12 clinically relevant factors listed in Table 1. Definitions of the endpoints are described in the Supplementary File. *Major stroke defined as modified Rankin scale ≥2. BARC, Bleeding Academic Research Consortium; DAPT, dual antiplatelet therapy; MI, myocardial infarction.

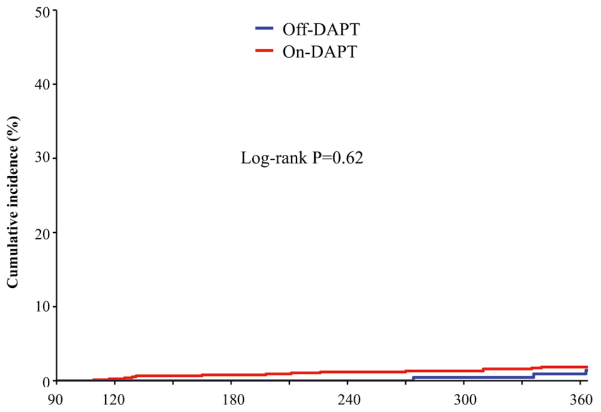
In the subgroup analysis stratified by ARC-HBR, the results were consistent with those in the main analysis (**Supplementary Table 1**).

In the analyses after excluding patients who were on oral anticoagulants at discharge, the cumulative 1-year incidences of the primary endpoint and BARC type 3 or 5 bleeding were not different between groups (5.1% vs. 9.2%; HR, 0.54; 95% CI, 0.25–1.17; P=0.12; and 1.4% vs. 2.9%; HR, 0.49; 95% CI, 0.11–2.08; P=0.33) (**Supplementary Table 2**).

Discussion

The main findings of this study enrolling patients who underwent IVUS-guided multivessel PCI were: (1) only 22.6% of the patients discontinued DAPT at 90 days after PCI despite 52.5% prevalence of patients with ARC-HBR, and (2) the 90-day landmark analyses showed no differences between the shorter and longer DAPT groups for the cumulative 1-year incidences of cardiovascular and bleeding endpoints.

The cumulative incidence of DAPT discontinuation was only 22.6% at 90 days and 68.8% at 1 year, although these were much higher than in the CREDO-Kyoto registry cohort-3, which was a real-world observational study conducted between 2011 and 2013 (3.3% at 90 days, and 18.9% at 1 year).[8] The enrollment into the present study started in March 2019, when the STOPDAPT-2 trial results were released suggesting the safety and efficacy of 1-month DAPT followed by clopidogrel monotherapy after PCI using drug-eluting stents.[2] The Japanese guideline on antithrombotic therapy after PCI was revised in March 2020 to recommend 1–3 months of DAPT after PCI in patients with HBR or low thrombotic risk.[11] Given the 85% of patients with chronic coronary syndrome and 53% of



Interval	90	120	180	240	300	365
Off-DAPT						
Number of patients with event		0	0	0	1	3
Number of patients at risk	222	221	221	220	216	203
Cumulative incidence (%)		0.0	0.0	0.0	0.5	1.4
On-DAPT						
Number of patients with event		2	6	9	10	14
Number of patients at risk	760	755	750	746	740	716
Cumulative incidence (%)		0.3	0.8	1.2	1.3	1.9

Figure 4. Kaplan-Meier curve for BARC type 3 or 5 bleeding. The cumulative 1-year incidence was estimated with the Kaplan-Meier method, and the difference was assessed with the log-rank test. BARC, Bleeding Academic Research Consortium; DAPT, dual antiplatelet therapy; PCI, percutaneous coronary intervention.

patients with HBR in this study, the duration of DAPT might still have been too long, revealing slow penetration of the clinical trial results into clinical practice. Many physicians might still be reluctant to choose short DAPT in patients with multivessel disease.

The 1-year incidence of the primary cardiovascular endpoint was numerically lower in the shorter DAPT group than in the longer DAPT group, which was driven by the lower incidence of any coronary revascularization. The lower incidence of follow-up CAG would have been the reason for the lower incidence of any coronary revascularization in the shorter DAPT group. The present study protocol discouraged follow-up CAG in asymptomatic patients based on the recent clinical trial result in Japan.[12] The site investigators who chose shorter DAPT duration might have been more willing to adopt the clinical trial results in their own clinical practice than those who chose longer DAPT duration. Another reason for the lower incidence of any coronary revascularization in the shorter DAPT group than in the longer DAPT group might be the lesser coronary anatomic complexity as indicated by the lower SYNTAX scores in the former than in the latter. The rate of meeting the OPTIVUS criteria was not different between the shorter and longer DAPT groups, suggesting that physicians did not select duration of DAPT based on whether or not they were meeting the OPTIVUS criteria. The incidence of a composite of death, MI, or stroke was low and not significantly different between groups, suggesting no apparent benefit of prolonged DAPT in reducing hard cardiovascular events even in patients who underwent multivessel PCI.

The incidence of bleeding events was also low and not significantly different between the shorter and longer DAPT groups, but was numerically lower in the shorter DAPT group than in the longer DAPT group, particularly in patients not treated with oral anticoagulants, consistent with previous randomized controlled trials.[1–6]

Study Limitations

First, the observational study design precluded any definitive conclusions, because of selection bias, especially for the decision of the period of DAPT. Second, the number of enrolled patients was relatively small, and the incidence of both cardiovascular and bleeding events was very low. Therefore, this study was obviously underpowered to evaluate the effect of shorter DAPT vs. longer DAPT, as well as the potential risk for unadjusted confounders. Third, the study population might represent selected low-risk patients for a clinical trial compared with real-world populations. Approximately 80% of the patients had a low SYNTAX score, and the study results should be interpreted with caution when applying them to patients with moderate or high SYNTAX score. Fourth, the prevalence of acute coronary syndrome was only 14.2%. Caution is needed in applying apply these study results to patients with acute coronary syndrome. Fifth, the study population did not include any cases of left main disease, so the results cannot be extrapolated to patients with left main disease.

Conclusions

The adoption of short DAPT duration was still low in this trial conducted after the release of the STOPDAPT-2 trial results. The 1-year incidence of cardiovascular events was not different between the shorter and longer DAPT groups in patients who underwent multivessel PCI.

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Disclosures

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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.

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Supplementary Files

Please find supplementary file(s);
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