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ORIGINAL ARTICLE

Very Short Dual Antiplatelet Therapy After Drug-Eluting Stent Implantation in Patients Who Underwent Complex Percutaneous Coronary Intervention

Insight From the STOPDAPT-2 Trial

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BACKGROUND: Safety and efficacy of clopidogrel monotherapy after very short dual antiplatelet therapy (DAPT) is uncertain in patients undergoing complex percutaneous coronary intervention (PCI).

METHODS: We conducted a post hoc subgroup analysis based on the complexity of PCI in the STOPDAPT-2 trial (Short and Optimal Duration of Dual Antiplatelet Therapy-2), which randomly compared 1-month DAPT followed by clopidogrel monotherapy with 12-month DAPT after cobalt-chromium everolimus-eluting stent implantation. Complex PCI was defined as any of the following: 3 vessels treated, ≥3 stents implanted, ≥3 lesions treated, bifurcation with 2 stents, >60 mm total stent lengths, and target of chronic total occlusion. The primary end point was the composite of cardiovascular (cardiovascular death/myocardial infarction/definite stent thrombosis/stroke) and bleeding (TIMI [Thrombolysis in Myocardial Infarction] major/minor) end points. The major secondary end points were the cardiovascular and bleeding end points.

RESULTS: Among the 3009 study patients, there were 509 patients (16.9%) with complex PCI (1-month DAPT: N=245, and 12-month DAPT: N=264) and 2500 patients (83.1%) without complex PCI (1-month DAPT: N=1255, and 12-month DAPT: N=1245). There were no significant interactions between the complexity of PCI and the effects of 1-month DAPT versus 12-month DAPT on the primary end point (complex PCI: 1.67% versus 5.32%, hazard ratio, 0.30 [95% CI, 0.10–0.92], P=0.04, and noncomplex PCI: 2.50% versus 3.35%, hazard ratio, 0.75 [95% CI, 0.47–1.20], P=0.23; $P_{interaction}$=0.14), and on the major secondary cardiovascular end point (complex PCI: 1.67% versus 3.04%, hazard ratio, 0.54 [95% CI, 0.16–1.79], P=0.31, and noncomplex PCI: 2.02% versus 2.39%, hazard ratio, 0.86 [95% CI, 0.50–1.47], P=0.58; $P_{interaction}$=0.49). The cumulative 1-year incidence of the major secondary bleeding end point was significantly lower in the 1-month DAPT group than in the 12-month DAPT group regardless of the complexity of PCI (complex PCI: 0% versus 2.29%, log-rank P=0.02, and noncomplex PCI: 0.48% versus 1.38%, log-rank P=0.02).

CONCLUSIONS: The effects of clopidogrel monotherapy after 1-month DAPT relative to 12-month DAPT for the primary and major secondary end points were comparable in complex PCI and noncomplex PCI without significant interactions.

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Key Words: clopidogrel ■ drug-eluting stent ■ percutaneous coronary intervention ■ stent ■ thrombosis

See Editorial by Briguori

WHAT IS KNOWN

- The optimal antithrombotic management after complex percutaneous coronary intervention (PCI) has not been yet well established.
- In the subgroup analyses of patients who underwent complex PCI from the GLOBAL LEADERS (A Clinical Study Comparing Two Forms of Anti-Platelet Therapy After Stent Implantation) and TWILIGHT (Ticagrelor With Aspirin or Alone in High-Risk Patients After Coronary Intervention) trials, the efficacy of ticagrelor monotherapy after very short (1-3 months) DAPT was suggested.
- However, no previous study has addressed the safety and efficacy of clopidogrel monotherapy after 1-month DAPT in patients who underwent complex PCI.

WHAT THE STUDY ADDS

- In this subgroup analysis of the STOPDAPT-2 trial (Short and Optimal Duration of Dual Antiplatelet Therapy-2), the effects of clopidogrel monotherapy after 1-month DAPT relative to 12-month DAPT for the primary and major secondary end points were comparable in complex PCI and noncomplex PCI without significant interactions.
- There was no signal of increased ischemic risk with clopidogrel monotherapy following 1-month DAPT compared with 12-month DAPT after complex PCI.

Nonstandard Abbreviations and Acronyms

DAPT	dual antiplatelet therapy
GLOBAL LEADERS	A Clinical Study Comparing Two Forms of Anti-Platelet Therapy After Stent Implantation
HBR	high bleeding risk
MI	myocardial infarction
PCI	percutaneous coronary intervention
PRECISE-DAPT	Predicting Bleeding Complication in Patients Undergoing Stent Implantation and Subsequent Dual Antiplatelet Therapy
RCT	randomized controlled trial
SMART-CHOICE	Comparison Between P2Y12 Antagonist Monotherapy and Dual Antiplatelet Therapy in Patients Undergoing Implantation of Coronary Drug-Eluting Stents
STOPDAPT-2	Short and Optimal Duration of Dual Antiplatelet Therapy-2
TICO	Ticagrelor Monotherapy After 3 Months in the Patients Treated With New Generation Sirolimus Stent for Acute Coronary Syndrome
TIMI	Thrombolysis in Myocardial Infarction
TWILIGHT	Ticagrelor With Aspirin or Alone in High-Risk Patients After Coronary Intervention

Recent randomized controlled trials (RCTs) have suggested that the strategy of shorter duration of dual antiplatelet therapy (DAPT) followed by $P2Y_{12}$ inhibitors monotherapy reduces major bleeding events without increasing cardiovascular events after percutaneous coronary intervention (PCI).[1–5] However, the procedural complexity of PCI has been acknowledged as a determinant for ischemic events, and prolonged DAPT has been reported to reduce the risk of ischemic events after PCI.[6] In the real-world clinical practice, physicians might still be reluctant to choose very short DAPT even in patients with high bleeding risk (HBR), if they had undergone complex PCI procedures, mainly due to concerns on their higher risk for stent thrombosis. Recently, 2 studies have suggested efficacy of ticagrelor monotherapy after very short DAPT in preventing cardiovascular events. In the subgroup analysis of patients who underwent complex PCI from the GLOBAL LEADERS trial (A Clinical Study Comparing Two Forms of Anti-Platelet Therapy After Stent Implantation), 23-month ticagrelor monotherapy following 1-month DAPT was superior to 12-month aspirin monotherapy following 12-month DAPT for a composite of all-cause death or new Q-wave myocardial infarction (MI).[7] In the subgroup analysis of patients who underwent complex PCI from the TWILIGHT (Ticagrelor With Aspirin or Alone in High-Risk Patients After Coronary Intervention) trial,

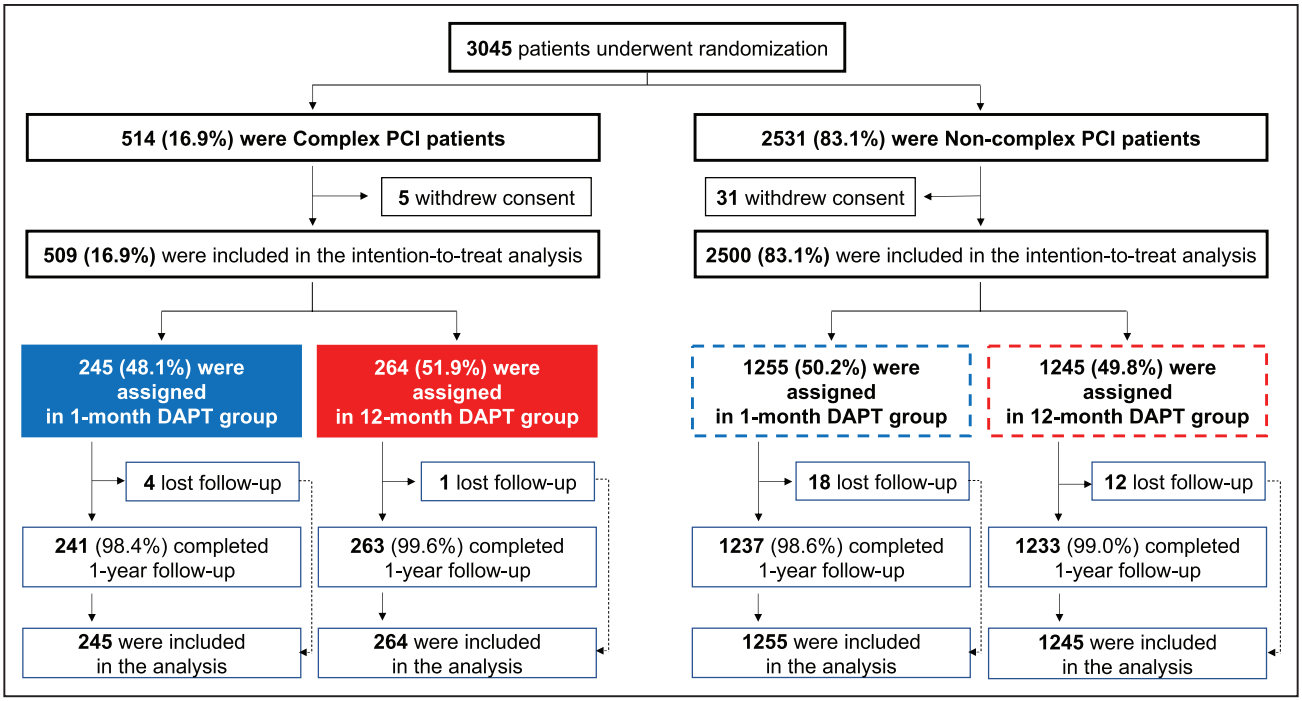


Figure 1. Study flow.
DAPT indicates dual antiplatelet therapy; and PCI, percutaneous coronary intervention.

there were no significant differences in death, MI, or stroke between the 2 groups receiving ticagrelor with and without aspirin following 3-month DAPT.[8] However, no previous study has addressed the safety and efficacy of clopidogrel monotherapy after 1-month DAPT in patients who underwent complex PCI. Therefore, we conducted a post hoc subgroup analysis of the STOPDAPT-2 trial (Short and Optimal Duration of Dual Antiplatelet Therapy-2) based on the complex PCI criteria.

METHODS

Study Population

STOPDAPT-2 is a physician-initiated, prospective, multicenter, open-label, adjudicator blinded randomized clinical trial in Japan, which was designed to assess the noninferiority of 1 month of DAPT followed by clopidogrel monotherapy compared to 12 months of DAPT with aspirin and clopidogrel after cobalt-chromium everolimus-eluting stent implantation as for the composite of cardiovascular and bleeding outcome. The design, patient enrollment, and main results at 1-year follow-up of the STOPDAPT-2 were previously reported in detail.[1] In brief, a total of 3045 patients with successful cobalt-chromium everolimus-eluting stent implantation without in-hospital major complications (MI, stroke, and major bleeding) were enrolled and randomized in a 1-to-1 ratio either to the 1-month DAPT group or 12-month DAPT group. After exclusion of 36 participants who withdrew consent, the final analysis set included 3009 patients comprising 1500 patients in the 1-month DAPT group and 1509 patients in the 12-month DAPT group (Figure 1). The ethical committees in all the participating centers approved the study protocol, and written informed consent were obtained from all patients. The authors declare that all supporting data are available within the article.

In the original analysis of STOPDAPT-2, the index PCI procedure was defined as the procedure just before enrollment and randomization. Therefore, in case the patients had undergone staged PCI, the lesions treated at the staged procedure(s) preceding the index PCI procedure were not included as the target lesions. However, in this subgroup analysis of complex PCI, the lesions treated at the staged procedure(s) preceding the index PCI procedure were included as the target lesions.

Table 1. Prevalence of Complex PCI and Its Criteria in the STOPDAPT-2 Participants

	Overall	1-mo DAPT group	12-mo DAPT group
	N=3009	N=1500	N=1509
Complex PCI	509 (16.9)	245 (16.3)	264 (17.5)
Criteria for complex PCI			
Target of 3 vessels	86 (2.9)	38 (2.5)	48 (3.2)
≥3 stents implanted	273 (9.1)	131 (8.7)	142 (9.4)
≥3 lesions treated	150 (5.0)	65 (4.3)	85 (5.6)
Bifurcation with 2 stents	17 (0.6)	9 (0.6)	8 (0.5)
Total stent length >60 mm	380 (12.6)	185 (12.3)	195 (12.9)
Target of CTO	137 (4.6)	62 (4.1)	75 (5.0)

Values are n (%). CTO indicates chronic total occlusion, DAPT, dual antiplatelet therapy, PCI, percutaneous coronary intervention; and STOPDAPT-2, Short and Optimal Duration of Dual Antiplatelet Therapy-2.

Table 2. Clinical and Procedural Characteristics and Medications at Discharge: Complex PCI Versus Noncomplex PCI

	Complex PCI	Noncomplex PCI	
	N=509	N=2500	*P* value
Demographics			
Age, y	69.5±10.1	68.5±10.8	0.0498
≥75 y	164 (32.2)	783 (31.3)	0.69
Men	408 (80.2)	1929 (77.2)	0.14
BMI, kg/m^2	24.5±3.4	24.3±3.6	0.33
<25 kg/m^2	297 (58.4)	1518 (60.7)	0.32
Presentation			
Acute coronary syndrome	164 (32.2)	984 (39.4)	0.003
STEMI	87 (17.1)	474 (19.0)	0.32
NSTEMI	27 (5.3)	153 (6.1)	0.48
Unstable angina	50 (9.8)	357 (14.3)	0.007
Stable coronary artery disease	345 (67.8)	1516 (60.6)	0.003
Past history			
Prior PCI	118 (23.2)	628 (25.1)	0.36
Prior first-generation DES	17 (3.3)	95 (3.8)	0.62
Prior CABG	13 (2.6)	46 (1.8)	0.29
Prior myocardial infarction	90 (17.7)	316 (12.6)	0.002
Prior ischemic or hemorrhagic stroke	35 (6.9)	151 (6.0)	0.48
Prior bleeding	10 (2.0)	37 (1.5)	0.42
Heart failure	58 (11.4)	164 (6.6)	<0.001
Atrial fibrillation	13 (2.6)	44 (1.8)	0.23
Severe anemia	59 (11.6)	204 (8.2)	0.01
Thrombocytopenia	10 (2.0)	21 (0.8)	0.02
COPD	15 (2.9)	69 (2.8)	0.82
Liver cirrhosis	1 (0.2)	9 (0.4)	0.56
Malignancy	44 (8.6)	212 (8.5)	0.9
Peripheral artery disease	38 (7.5)	158 (6.3)	0.34
Moderate CKD	188 (36.9)	861 (34.4)	0.28
Severe CKD	34 (6.7)	132 (5.3)	0.21
eGFR <30 and not on dialysis	17 (3.3)	47 (1.9)	0.04
Dialysis	17 (3.3)	85 (3.4)	0.95
Hypertension	388 (76.2)	1833 (73.3)	0.17
Dyslipidemia	403 (79.2)	1841 (73.6)	0.009
Diabetes	243 (47.7)	916 (36.6)	<0.001
Insulin-treated	48 (9.4)	154 (6.2)	0.007
Current smoking	111 (21.8)	599 (24.0)	0.3
Left ventricular ejection fraction	57.7±11.4	60.2±10.1	<0.001
<40%	35 (7.4)	80 (3.5)	<0.001
Mitral regurgitation with grade 3/4	25 (4.9)	50 (2.0)	<0.001
PARIS thrombotic risk score	3.3±1.8	2.5±1.6	<0.001
Low	181 (35.6)	1306 (52.2)	<0.001
Intermediate	183 (36.0)	913 (36.5)	
High	145 (28.5)	281 (11.2)	
PARIS bleeding risk score	5.4±2.7	5.2±2.6	0.04
Low	141 (27.7)	717 (28.7)	0.03
Intermediate	246 (48.3)	1312 (52.5)	
High	122 (24.0)	471 (18.8)	
CREDO-Kyoto thrombotic risk score	1.7±1.5	1.2±1.4	<0.001
Low	279 (54.8)	1819 (72.8)	<0.001
Intermediate	174 (34.2)	502 (20.1)	
High	56 (11.0)	179 (7.2)	
CREDO-Kyoto bleeding risk score	0.8±1.2	0.6±1.1	<0.001
Low	293 (57.6)	1699 (68.0)	<0.001
Intermediate	164 (32.2)	635 (25.4)	
High	52 (10.2)	166 (6.6)	
ARC-HBR	203 (39.9)	851 (34.0)	0.01
Procedural background			
Invasive FFR	80 (15.7)	335 (13.4)	0.17
Radial approach	418 (82.1)	2115 (84.6)	0.16
Brachial approach	44 (8.6)	130 (5.2)	0.002
Femoral approach	140 (27.5)	286 (11.4)	<0.001
No. of target lesions	2.08±0.94	1.11±0.31	<0.001
≥3	150 (29.5)	0 (0)	<0.001
Total number of stents	2.71±1.11	1.17±0.38	<0.001
≥3	273 (53.6)	0 (0)	<0.001
Minimal stent diameter, mm	2.64±0.38	3.01±0.48	<0.001
<3.0 mm	368 (72.3)	939 (37.6)	<0.001
Total stent length, mm	73.3±31.5	26.9±11.1	<0.001
≥28 mm	483 (94.9)	1160 (46.4)	<0.001
>60 mm	380 (74.7)	0 (0)	<0.001
Target vessel			
LMCA	41 (8.1)	46 (1.8)	<0.001
LAD	368 (72.3)	1440 (57.6)	<0.001
CX	204 (40.1)	467 (18.7)	<0.001
RCA	289 (56.8)	706 (28.2)	<0.001
Graft	1 (0.2)	6 (0.2)	0.85
Target of CTO	137 (26.9)	0 (0)	<0.001
Target of bifurcation	236 (46.4)	583 (23.3)	<0.001
Bifurcation with 2 stents	17 (3.3)	0 (0)	<0.001
Target of 2 vessels or more	321 (63.1)	200 (8.0)	<0.001
Target of 3 vessels	86 (16.9)	0 (0)	<0.001
Use of intravascular ultrasound	480 (94.3)	2094 (83.8)	<0.001
Use of optical coherence tomography	55 (10.8)	406 (16.2)	0.002
Staged PCI	243 (47.7)	99 (4.0)	<0.001
Medication at discharge			
Aspirin	508 (99.8)	2948 (99.9)	0.45
$P2Y_{12}$ receptor blockers	509 (100)	2498 (99.9)	0.52

(*Continued*)

Table 2. Continued

	Complex PCI	Noncomplex PCI	
	N=509	N=2500	*P* value
Clopidogrel	312 (61.3)	1540 (61.6)	0.9
Prasugrel	195 (38.3)	956 (38.2)	0.98
Ticlopidine	2 (0.4)	2 (0.1)	0.08
Cilostazol	0 (0)	6 (0.2)	0.27
Oral anticoagulants	3 (0.6)	10 (0.4)	0.55
Beta blockers	251 (49.3)	1064 (42.6)	0.005
ACE inhibitors or ARB	330 (64.8)	1543 (61.7)	0.19
Statins	447 (87.8)	2188 (87.5)	0.85
Proton pump inhibitors	411 (80.8)	1972 (78.9)	0.34

Values are means±SD or n (%). The lesions treated at the staged procedure(s) preceding the index PCI procedure were included as the target lesions. Staged procedures were defined as scheduled PCI procedures performed within 3 mo of the first procedure. ACE indicates angiotensin-converting enzyme; ARB, angiotensin 2 receptor blockers; ARC-HRB, Academic Research Consortium for HBR; BMI, body mass index; CABG, coronary artery bypass grafting; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; CREDO-Kyoto, Coronary Revascularization Demonstrating Outcome study in Kyoto; CTO, chronic total occlusion; CX, left circumflex coronary artery; DES, drug-eluting stents; eGFR, estimated glomerular filtration rate; FFR, fractional flow reserve; HBR, high bleeding risk; LAD, left anterior descending coronary artery; LMCA, left main coronary artery; NSTEMI, non–ST-segment–elevation myocardial infarction; PARIS, Patterns of Non-Adherence to Anti-Platelet Regimen in Stented Patients; PCI, percutaneous coronary intervention; RCA, right coronary artery; and STEMI, ST-segment–elevation myocardial infarction.

Staged procedures were defined as scheduled PCI procedures performed within 3 months of the first procedure. Therefore, the baseline lesion and procedural characteristics and the outcome measures related to the target lesions were redefined and were different from those reported in the previous publication (Methods in the Data Supplement).

Application of Complex PCI Criteria

In the present analysis, patients were divided into the 2 subgroups based on the complex PCI criteria.[6] Giustino et al[6] have proposed procedural complexity criteria, called complex PCI, and the criteria were endorsed by the clinical guidelines of the European Society of Cardiology and Japanese Circulation Society[9,10]; complex PCI was defined as a procedure with at least one of the following procedural criteria: 3 vessels treated, ≥3 stents implanted, ≥3 lesions treated, bifurcation with 2 stents implanted, total stent length >60 mm, or chronic total occlusion as the target lesion.

Outcome Measures

The primary end point of the STOPDAPT-2 was a composite of cardiovascular and bleeding outcomes that is a composite of death from cardiovascular cause, MI, definite stent thrombosis, ischemic or hemorrhagic stroke, and bleeding defined as TIMI (Thrombolysis in Myocardial Infarction) major or minor criteria.[11] The major secondary cardiovascular end point was a composite of death from cardiovascular cause, MI, definite stent thrombosis, and ischemic or hemorrhagic stroke, whereas the major secondary bleeding end point was the bleeding defined as TIMI major or minor bleeding. Other definitions of the end points were described in the Methods in the Data Supplement.

Statistical Analysis

Categorical variables were presented as number and percentage and were compared with χ^2 test. Continuous variables were expressed as mean±SD or median with interquartile range and were compared using the Student *t* test or Wilcoxon rank-sum test depending on their distributions. The cumulative incidence was estimated with the Kaplan-Meier method and the differences between 1-month and 12-month DAPT were compared with log-rank test. Absolute difference of incidence rate was calculated as the event rate in the 1-month DAPT group minus the event rate in the 12-month DAPT group. The hazard ratios (HR) of 1-month DAPT relative to 12-month DAPT for the end point events were calculated by the Cox proportional hazard model with 95% CI calculated from Wald statistics. In addition, we also assessed the cumulative incidences of the primary and major secondary cardiovascular end points in the categories derived from the individual component of complex PCI criteria. Furthermore, the main analysis was conducted in the subgroup stratified by the Academic Research Consortium for HBR criteria.[12,13]

Because the present study was post hoc subgroup analysis, we did not make any power calculation for the primary and major secondary end points, and all reported *P* values were superiority basis and 2 tailed. $P<0.05$ were considered statistically significant. All analysis was performed with JMP version 14.0 software (SAS Institute, Inc, Cary, NC).

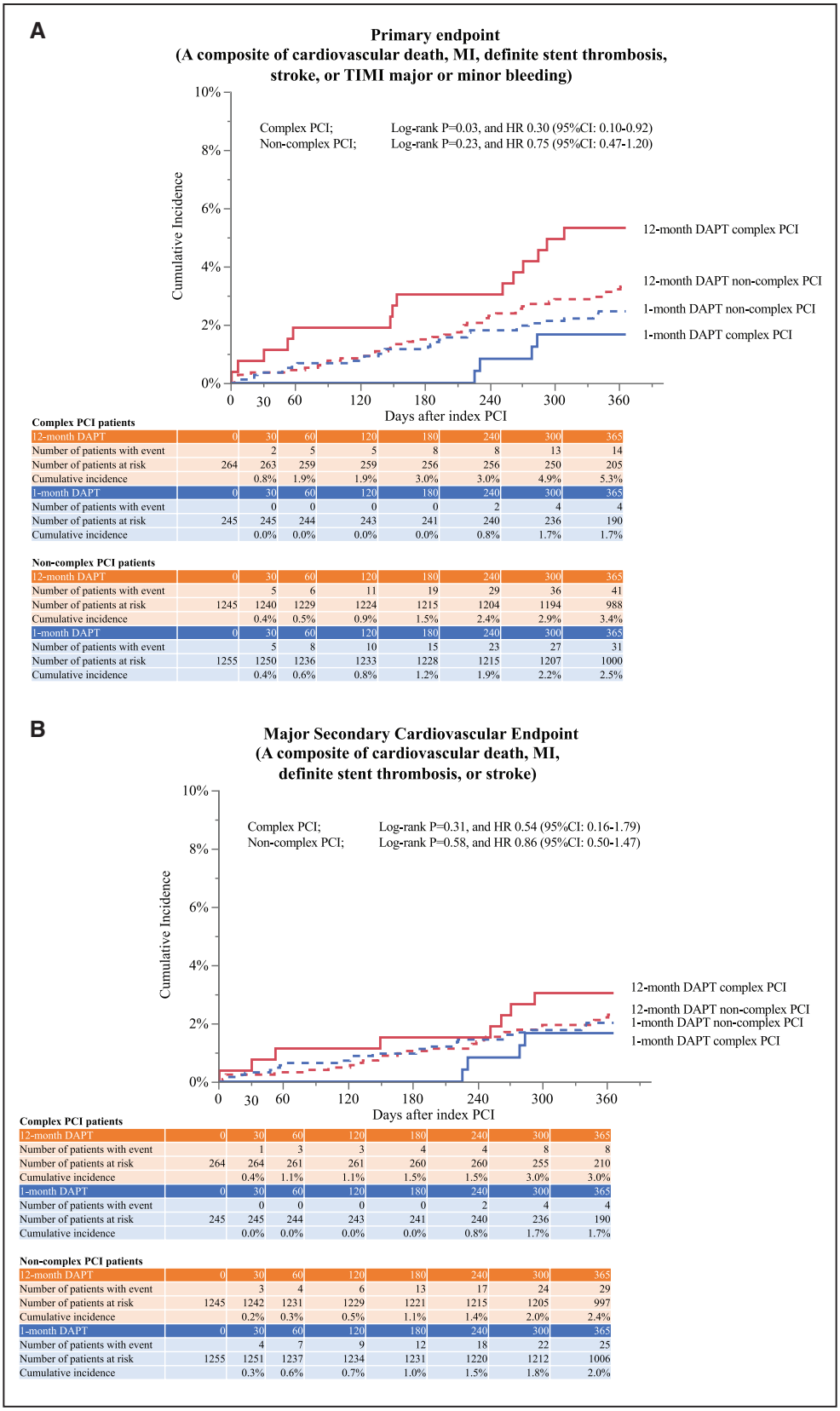
RESULTS

Study Population

Among the 3009 study patients, there were 509 patients (16.9%) with complex PCI (1-month DAPT group: N=245, and 12-month DAPT group: N=264) and 2500 patients (83.1%) without complex PCI (1-month DAPT group: N=1255, and 12-month DAPT group: N=1245; Figure 1). Among the criteria for complex PCI, >60 mm total stent length (12.6%), and ≥3 stents implanted (9.1%) were more prevalent than the other criteria, whereas bifurcation with 2 stents (0.6%) was less prevalent than the other criteria (Table 1).

Baseline Characteristics

Patients with complex PCI more often presented as stable coronary artery disease and more often had comorbidities, such as heart failure, anemia, thrombocytopenia, chronic kidney disease, dyslipidemia, diabetes, left ventricular dysfunction, and mitral regurgitation than those without. Procedural characteristics were totally different between patients with complex PCI and those without (Table 2). Baseline characteristics and medications were well balanced between the 1-month DAPT and 12-month DAPT groups (Table I in the Data Supplement).



Complex PCI patients

12-month DAPT	0	30	60	120	180	240	300	365
Number of patients with event		2	5	5	8	8	13	14
Number of patients at risk	264	263	259	259	256	256	250	205
Cumulative incidence		0.8%	1.9%	1.9%	3.0%	3.0%	4.9%	5.3%
1-month DAPT	0	30	60	120	180	240	300	365
Number of patients with event		0	0	0	0	2	4	4
Number of patients at risk	245	245	244	243	241	240	236	190
Cumulative incidence		0.0%	0.0%	0.0%	0.0%	0.8%	1.7%	1.7%

Non-complex PCI patients

12-month DAPT	0	30	60	120	180	240	300	365
Number of patients with event		5	6	11	19	29	36	41
Number of patients at risk	1245	1240	1229	1224	1215	1204	1194	988
Cumulative incidence		0.4%	0.5%	0.9%	1.5%	2.4%	2.9%	3.4%
1-month DAPT	0	30	60	120	180	240	300	365
Number of patients with event		5	8	10	15	23	27	31
Number of patients at risk	1255	1250	1236	1233	1228	1215	1207	1000
Cumulative incidence		0.4%	0.6%	0.8%	1.2%	1.9%	2.2%	2.5%

Complex PCI patients

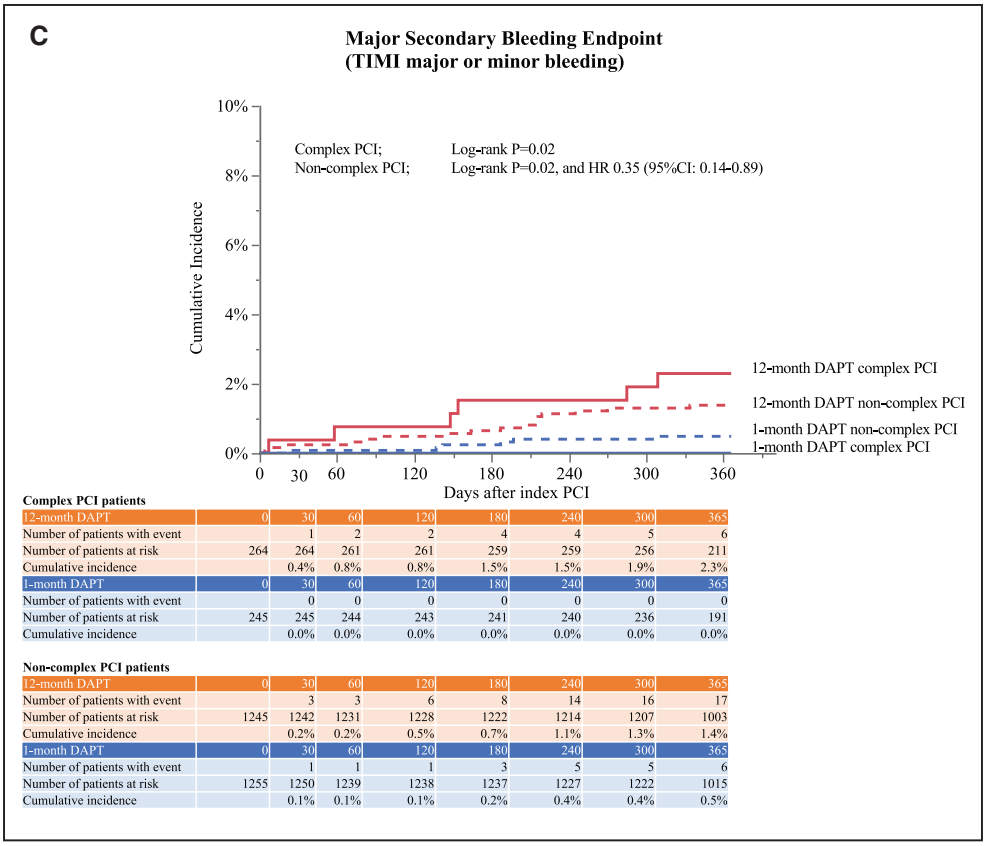
12-month DAPT	0	30	60	120	180	240	300	365
Number of patients with event		1	3	3	4	4	8	8
Number of patients at risk	264	264	261	261	260	260	255	210
Cumulative incidence		0.4%	1.1%	1.1%	1.5%	1.5%	3.0%	3.0%
1-month DAPT	0	30	60	120	180	240	300	365
Number of patients with event		0	0	0	0	2	4	4
Number of patients at risk	245	245	244	243	241	240	236	190
Cumulative incidence		0.0%	0.0%	0.0%	0.0%	0.8%	1.7%	1.7%

Non-complex PCI patients

12-month DAPT	0	30	60	120	180	240	300	365
Number of patients with event		3	4	6	13	17	24	29
Number of patients at risk	1245	1242	1231	1229	1221	1215	1205	997
Cumulative incidence		0.2%	0.3%	0.5%	1.1%	1.4%	2.0%	2.4%
1-month DAPT	0	30	60	120	180	240	300	365
Number of patients with event		4	7	9	12	18	22	25
Number of patients at risk	1255	1251	1237	1234	1231	1220	1212	1006
Cumulative incidence		0.3%	0.6%	0.7%	1.0%	1.5%	1.8%	2.0%

Figure 2. Clinical outcomes at 1-y stratified by complex percutaneous coronary intervention (PCI) and noncomplex PCI: 1-mo vs 12-mo dual antiplatelet therapy (DAPT).

Time-to-event curves up to 1 y for (**A**) the primary end point, (**B**) the major secondary cardiovascular end point, and (**C**) the major secondary bleeding end point stratified by complex PCI and noncomplex PCI. HR indicates hazard ratio; MI, myocardial infarction; and TIMI, Thrombolysis in Myocardial Infarction. (*Continued*)



Complex PCI patients

12-month DAPT	0	30	60	120	180	240	300	365
Number of patients with event		1	2	2	4	4	5	6
Number of patients at risk	264	264	261	261	259	259	256	211
Cumulative incidence		0.4%	0.8%	0.8%	1.5%	1.5%	1.9%	2.3%
1-month DAPT	0	30	60	120	180	240	300	365
Number of patients with event		0	0	0	0	0	0	0
Number of patients at risk	245	245	244	243	241	240	236	191
Cumulative incidence		0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%

Non-complex PCI patients

12-month DAPT	0	30	60	120	180	240	300	365
Number of patients with event		3	3	6	8	14	16	17
Number of patients at risk	1245	1242	1231	1228	1222	1214	1207	1003
Cumulative incidence		0.2%	0.2%	0.5%	0.7%	1.1%	1.3%	1.4%
1-month DAPT	0	30	60	120	180	240	300	365
Number of patients with event		1	1	1	3	5	5	6
Number of patients at risk	1255	1250	1239	1238	1237	1227	1222	1015
Cumulative incidence		0.1%	0.1%	0.1%	0.2%	0.4%	0.4%	0.5%

Figure 2 Continued.

As we previously reported, the vast majority of the study patients received the assigned antiplatelet therapy according to the study protocol.[1] The patterns of DAPT discontinuation were similar and not significantly different between those patients with and without complex PCI (Figure I in the Data Supplement).

Clinical Outcomes

In patients with complex PCI, the primary end point occurred in 4 patients (1.67%) in the 1-month DAPT group and in 14 patients (5.32%) in the 12-month DAPT (HR, 0.30 [95% CI, 0.10–0.92], *P*=0.04), whereas in patients without complex PCI, it occurred in 31 patients (2.50%) in the 1-month DAPT group and in 41 patients (3.35%) in the 12-month DAPT group (HR, 0.75 [95% CI, 0.47–1.20], *P*=0.23; Figures 2A and 3 and Table II in the Data Supplement). There was no significant interaction between the complexity of PCI and the effect of 1-month DAPT relative to 12-month DAPT on the primary end point ($P_{interaction}$=0.14; Figure 3).

The major secondary cardiovascular end point occurred in 4 patients (1.67%) in the 1-month DAPT group and in 8 patients (3.04%) in the 12-month DAPT group in patients with complex PCI (HR, 0.54 [95% CI, 0.16–1.79], *P*=0.31), whereas in patients without complex PCI, it occurred in 25 patients (2.02%) in the 1-month DAPT group and in 29 patients (2.39%) in the 12-month DAPT group (HR, 0.86 [95% CI, 0.50–1.47], *P*=0.58; Figures 2B and 3, and Table II in the Data Supplement). There was no significant interaction between the complexity of PCI and the effect of 1-month DAPT relative to 12-month DAPT on the major secondary cardiovascular end point ($P_{interaction}$=0.49; Figure 3).

In patients with complex PCI, the secondary bleeding end point did not occur in the 1-month DAPT group, but occurred in 6 patients (2.29%) in the 12-month group (log-rank *P*=0.02), whereas in patients without complex PCI, it occurred in 6 patients (0.48%) in the 1-month DAPT group and in 17 patients (1.38%) in the 12-month DAPT group (HR, 0.35 [95% CI, 0.14–0.89], *P*=0.03; Figures 2C and 3, and Table II in the Data Supplement).

In patients with complex PCI, there was no definite or probable stent thrombosis in both the 1- and 12-month DAPT groups, whereas in patients without complex PCI, it occurred in 4 patients (0.32%) in the 1-month DAPT group and in 1 patient (0.08%) in the 12-month DAPT group (HR, 3.98 [95% CI, 0.44–35.58], *P*=0.22; Table II in the Data Supplement). Results for the other secondary end points were presented in Table II in the Data Supplement.

The 1-month DAPT group compared with the 12-month DAPT group had numerically lower incidences of the primary and major secondary cardiovascular end points in all the categories derived from the individual component of the complex PCI criteria (Figure 4).

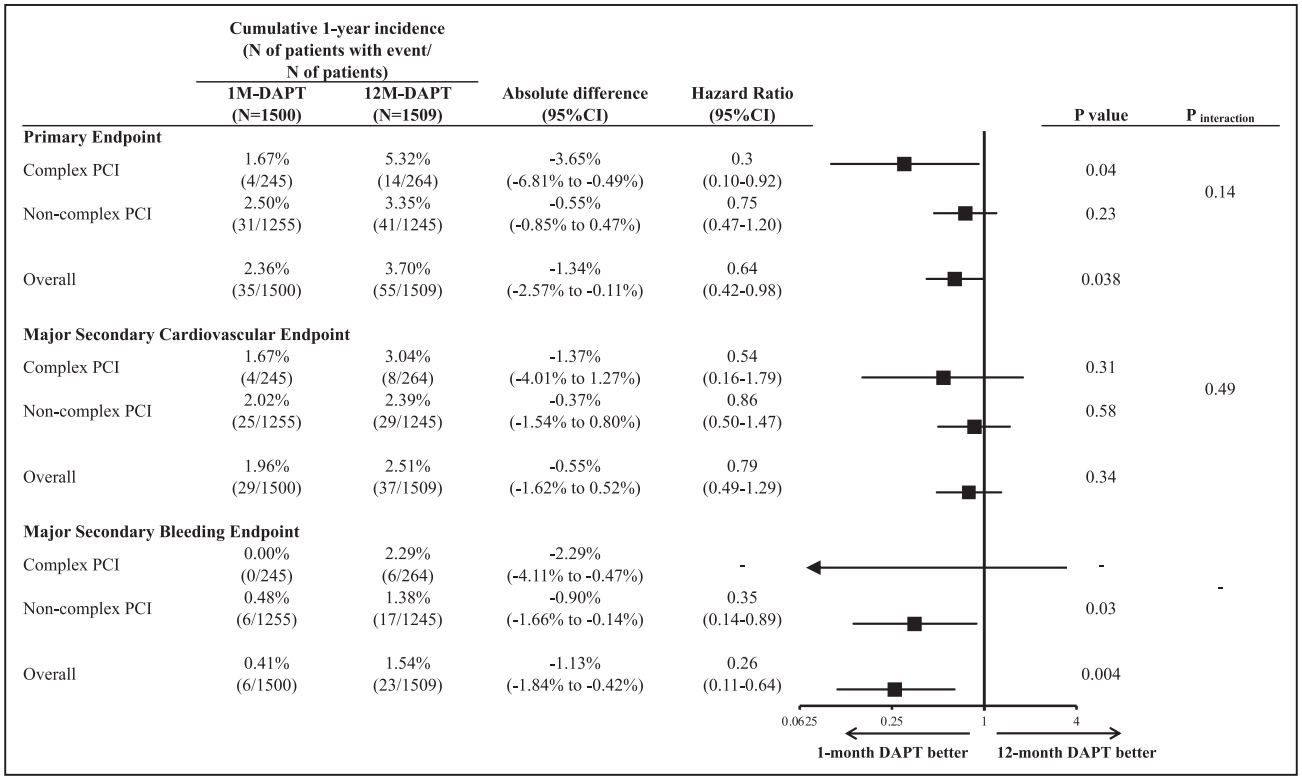


Figure 3. Forest plots for the effect of 1-mo relative to 12-mo dual antiplatelet therapy (DAPT) for the primary and major secondary end points in the complex percutaneous coronary intervention (PCI) and noncomplex PCI subgroups.

In the stratified analysis by Academic Research Consortium for HBR criteria, the results were consistent with the main results (Figure II in the Data Supplement).

DISCUSSION

The main findings of the present subgroup analysis of the STOPDAPT-2 trial based on the complex PCI criteria were the following (1) the effects of 1-month DAPT relative to 12-month DAPT for the primary and major secondary end points were consistent in complex PCI and noncomplex PCI without significant interactions; (2) there was no signal of increased ischemic risk with clopidogrel monotherapy following 1-month DAPT compared with 12-month DAPT after complex PCI.

European Society of Cardiology and Japanese Circulation Society guidelines have suggested that complex PCI is a risk factor of stent-driven recurrent ischemic events.[9,10] After introduction of drug-eluting stent, patients undergoing complex PCI were often managed with prolonged DAPT, even if they were at HBR.[14] Recently, very short (1-3 months) DAPT with subsequent $P2Y_{12}$ inhibitors monotherapy as compared to standard (12–15 months) DAPT was reported to be associated with reduction in bleeding events without increase in cardiovascular events in several RCTs including STOPDAPT-2, GLOBAL LEADERS, SMART-CHOICE (Comparison Between P2Y12 Antagonist Monotherapy and Dual Antiplatelet Therapy in Patients Undergoing Implantation of Coronary Drug-Eluting Stents), TWILIGHT, and TICO (Ticagrelor Monotherapy After 3 Months in the Patients Treated With New Generation Sirolimus Stent for Acute Coronary Syndrome) trials.[1–5] However, physicians might still be reluctant to choose very short DAPT in patients undergoing complex PCI, mainly due to concerns about stent thrombosis and other ischemic events. The prevalence of patients receiving complex PCI was consistently low in previous RCTs (18% in the Giustino et al's[6] study of a pooled analysis of 6 RCTs, 21% in the PRECISE-DAPT study (Predicting Bleeding Complication in Patients Undergoing Stent Implantation and Subsequent Dual Antiplatelet Therapy), 28% in the GLOBAL LEADERS trial, and 33% in the TWILIGHT trial), and it was 17% in the STOPDAPT-2 trial, although there were minor differences in the criteria of complex PCI among the studies.[6–8,15] The optimal antithrombotic management after complex PCI has not been yet well established. Giustino et al[6] reported that prolonged (12–24 months) DAPT reduced major adverse cardiac events and coronary thrombotic events compared with short (3-6 months) DAPT after complex PCI in the pooled analysis of 6 RCTs.[6] On the other hand, in the subgroup analyses of the GLOBAL LEADERS and TWILIGHT trials, very short (1–3 months) DAPT followed by ticagrelor monotherapy compared with standard (12 months) DAPT was not associated with increased risk of ischemic events in patients receiving complex PCI.[7,8] In the present study, clopidogrel monotherapy after 1-month DAPT was also not associated with increased risk of

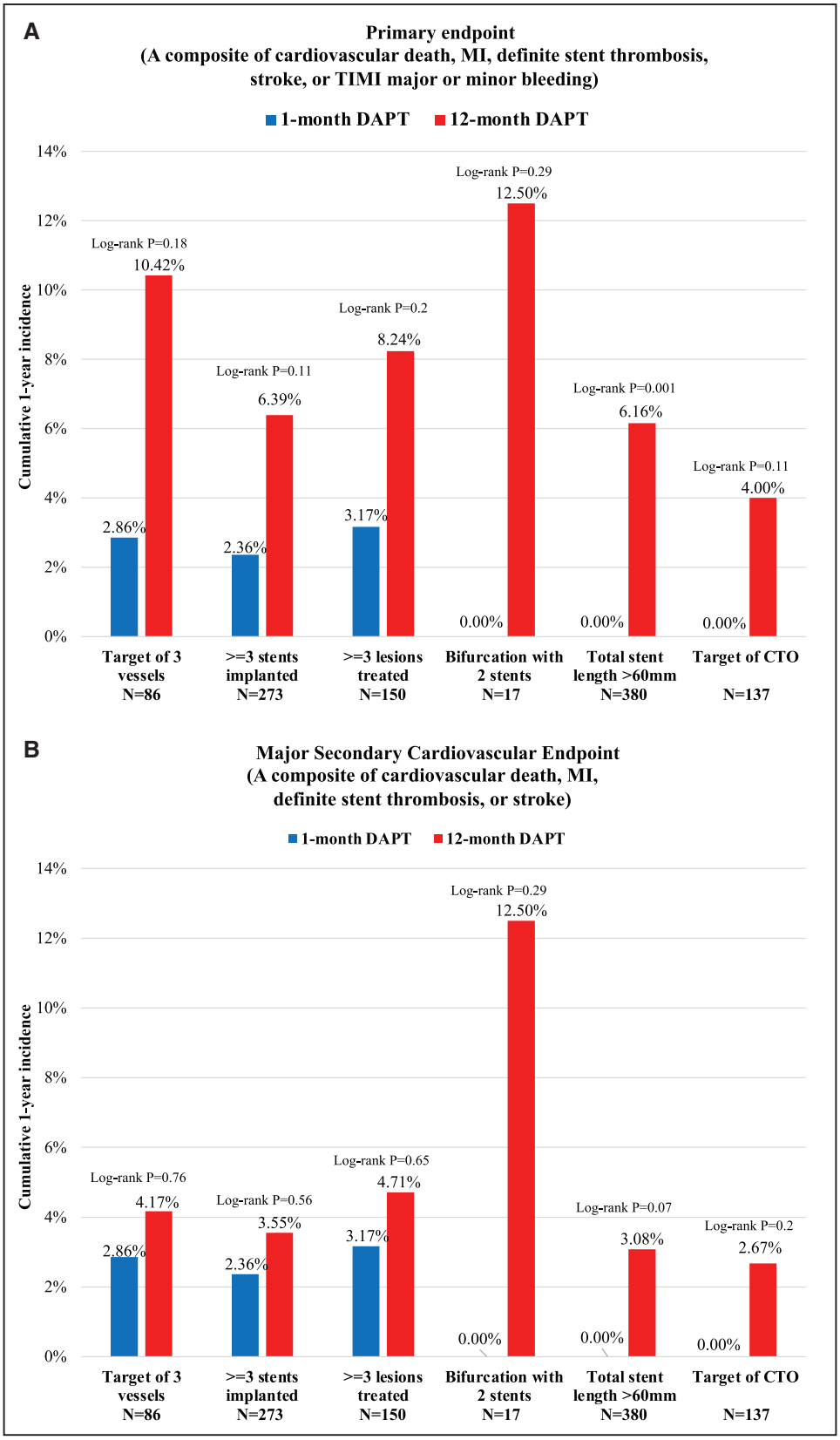


Figure 4. Clinical outcomes at 1-y according to the individual component of complex percutaneous coronary intervention (PCI) criteria.

Cumulative 1-y incidence for (**A**) the primary end point and (**B**) the major secondary cardiovascular end points were estimated in the categories derived from the individual component of complex PCI criteria. CTO indicates chronic total occlusion; DAPI, dual antiplatelet therapy; MI, myocardial infarction; and TIMI, Thrombolysis in Myocardial Infarction.

ischemic events, but associated with decreased risk of major bleeding in patients undergoing complex PCI. The discrepancy between the previous meta-analysis and the later clinical trials might be explained by the choice of $P2Y_{12}$ receptor blocker monotherapy after DAPT in the later studies rather than aspirin in the previous meta-analysis. However, further research would be important to evaluate the safety of very short DAPT and define the optimal antiplatelet monotherapy after stopping DAPT in patients undergoing complex PCI.

It has been reported that patients with complex PCI were also associated with higher bleeding risk as compared with those without.[6–8] Indeed, the rate of major bleeding with 12-month DAPT was numerically higher in patients with complex PCI than those without in the present study. In patients with complex PCI, 1-month DAPT compared with 12-month DAPT was associated with significantly lower risk for major bleeding while maintaining a similar risk of ischemic event. As a result, the net clinical benefit of 1-month DAPT over 12-month DAPT was numerically greater in patients with complex PCI than in those without. The net clinical benefit of very short DAPT in patients with complex PCI was consistently seen in the subgroup analyses of the GLOBAL LEADERS and TWILIGHT trials.[7,8] Therefore, very short DAPT and subsequent $P2Y_{12}$ receptor blockers monotherapy would be an attractive antiplatelet regimen in patients undergoing complex PCI, particularly in patients with concomitant HBR characteristics.

There are several important limitations in current analysis, in addition to the original trial design including using a composite of cardiovascular and bleeding end points as the primary end point and relatively small sample size.[1] First, the prevalence of complex PCI was low, and thus, the present post hoc subgroup analysis was underpowered and exploratory. Especially, the prevalence of bifurcation with 2 stents, which was reported as the strongest risk factor for ischemic events, was much lower than in the previous reports.[6] In addition, the majority of patients enrolled in the STOPDAPT-2 trial had low or intermediate ischemic risk, and the patients who experienced in-hospital major complications other than periprocedural MI were excluded. Indeed, the incidence of adverse events in patients with complex PCI was low as compared with previous study.[14] Furthermore, a considerable number of patients eligible for the study were not enrolled because of physician's choice or patient refusal despite the all-comer study design, who were reported to have higher risk for both cardiovascular and bleeding event than those actually enrolled.[16] Therefore, the favorable results of 1-month DAPT in patients with complex PCI should be regarded as hypothesis-generating, and the safety and efficacy of clopidogrel monotherapy after very short DAPT in patients with complex PCI should be confirmed in larger studies. Second, we set 90 days as the time period for screening the staged PCI. We could not rule out the possibility that some patients might have had staged PCI procedures with time interval longer than 90 days. Third, it is well known that Japanese patients with coronary artery disease had lower ischemic risk as compared with US/European patients.[17] Moreover, the vast majority of the study patients underwent PCI guided by intracoronary imaging devices, which was quite different from the practice in United States and Europe. Therefore, we should be cautious about extrapolating these study results outside Japan.

CONCLUSIONS

In this subgroup analysis of the STOPDAPT-2 trial, the effects of clopidogrel monotherapy after 1-month DAPT relative to 12-month DAPT for the primary and major secondary end points were comparable in complex PCI and noncomplex PCI without significant interactions. There was no signal of increased ischemic risk with clopidogrel monotherapy following 1-month DAPT compared with 12-month DAPT after complex PCI. However, the results of this post hoc analysis should be considered as hypothesis-generating.

ARTICLE INFORMATION

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Disclosures

Dr Watanabe reports honoraria from Abbott, Daiichi Sankyo, Otsuka, Kowa, Bayer, Pfizer, Ono Pharmaceutical, and Boehringer Ingelheim. Dr Morimoto reports hono-

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Supplemental Materials

Expanded Methods
Tables I–II
Figures I–II
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