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ORIGINAL RESEARCH

Clopidogrel Monotherapy After 1-Month DAPT in Patients With High Bleeding Risk or Complex PCI

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ABSTRACT

BACKGROUND High bleeding risk (HBR) and complex percutaneous coronary intervention (PCI) are major determinants for dual antiplatelet therapy (DAPT) duration.

OBJECTIVES The aim of this study was to evaluate the effects of HBR and complex PCI on short vs standard DAPT.

METHODS Subgroup analyses were conducted on the basis of Academic Research Consortium–defined HBR and complex PCI in the STOPDAPT-2 (Short and Optimal Duration of Dual Antiplatelet Therapy After Verulam's-Eluting Cobalt-Chromium Stent–2) Total Cohort, which randomly compared clopidogrel monotherapy after 1-month DAPT with 12-month DAPT with aspirin and clopidogrel after PCI. The primary endpoint was the composite of cardiovascular (cardiovascular death, myocardial infarction, definite stent thrombosis, or stroke) or bleeding (Thrombolysis In Myocardial Infarction [TIMI] major or minor) endpoints at 1 year.

RESULTS Regardless of HBR (n = 1,893 [31.6%]) and complex PCI (n = 999 [16.7%]), the risk of 1-month DAPT relative to 12-month DAPT was not significant for the primary endpoint (HBR, 5.01% vs 5.14%; non-HBR, 1.90% vs 2.02%; $P_{interaction}$ = 0.95) (complex PCI, 3.15% vs 4.07%; noncomplex PCI, 2.78% vs 2.82%; $P_{interaction}$ = 0.48) and for the cardiovascular endpoint (HBR, 4.35% vs 3.52%; and non-HBR, 1.56% vs 1.22%; $P_{interaction}$ = 0.90) (complex PCI, 2.53% vs 2.52%; noncomplex PCI, 2.38% vs 1.86%; $P_{interaction}$ = 0.53), while it was lower for the bleeding endpoint (HBR, 0.66% vs 2.27%; non-HBR, 0.43% vs 0.85%; $P_{interaction}$ = 0.36) (complex PCI, 0.63% vs 1.75%; noncomplex PCI, 0.48% vs 1.22%; $P_{interaction}$ = 0.90). The absolute difference in the bleeding between 1- and 12-month DAPT was numerically greater in patients with HBR than in those without HBR (−1.61% vs −0.42%).

CONCLUSIONS The effects of 1-month DAPT relative to 12-month DAPT were consistent regardless of HBR and complex PCI. The absolute benefit of 1-month DAPT over 12-month DAPT in reducing major bleeding was numerically greater in patients with HBR than in those without HBR. Complex PCI might not be an appropriate determinant for DAPT durations after PCI. (Short and Optimal Duration of Dual Antiplatelet Therapy After Everolimus-Eluting Cobalt-Chromium Stent–2 [STOPDAPT-2], NCT02619760; Short and Optimal Duration of Dual Antiplatelet Therapy After Everolimus-Eluting Cobalt-Chromium Stent–2 for the Patients With ACS [STOPDAPT-2 ACS], NCT03462498) (JACC: Asia 2023;3:31–46) © 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

ARC = Academic Research Consortium

DAPT = dual antiplatelet therapy

HBR = high bleeding risk

PCI = percutaneous coronary intervention

Recently, several randomized controlled trials have suggested that the strategy of shorter duration of dual antiplatelet therapy (DAPT) followed by $P2Y_{12}$ inhibitor monotherapy reduces major bleeding events without increasing cardiovascular events after percutaneous coronary intervention (PCI).[1-5] In real clinical practice, high bleeding risk (HBR) and complex PCI are the major determinants of whether shorter or longer DAPT duration is adopted. Shorter DAPT duration is preferred in patients with HBR because of concerns surrounding the higher rates of major bleeding events with prolonged DAPT.[6-12] In contrast, longer DAPT duration is preferred in patients who undergo complex PCI, because the procedural complexity of PCI has been acknowledged as a determinant of higher risk for ischemic events, and prolonged DAPT has been reported to reduce the risk for ischemic events after PCI.[13] However, the influence of HBR and complex PCI on the effects of short vs prolonged DAPT for ischemic and bleeding events after PCI has not been fully addressed and remains controversial. We previously reported subgroup analyses on the basis of HBR and complex PCI from the STOPDAPT-2 (Short and Optimal Duration of Dual Antiplatelet Therapy After Everolimus-Eluting Cobalt-Chromium Stent-2) trial, but these post hoc subgroup analyses were totally underpowered.[6-7,14] Therefore, we sought to evaluate the effects of Academic Research Consortium (ARC)-defined HBR and complex PCI on the safety and efficacy of clopidogrel monotherapy after 1-month DAPT relative to 12-month DAPT using a pooled population of STOPDAPT-2 and STOPDAPT-2 ACS (Short and Optimal Duration of Dual Antiplatelet Therapy After Everolimus-Eluting Cobalt-Chromium Stent-2 for the Patients With ACS) trials (STOPDAPT-2 Total Cohort).[15]

METHODS

STUDY POPULATION. STOPDAPT-2 (December 2015 to December 2017, 90 centers; NCT02619760) and STOPDAPT-2 ACS (March 2018 to June 2020, 74 centers; NCT03462498) are physician-initiated, prospective, multicenter, open-label, adjudicator-blinded randomized clinical trials in Japan in which we compared an experimental strategy of 1-month DAPT followed by clopidogrel monotherapy with the standard strategy of 12-month DAPT with aspirin and clopidogrel after PCI using cobalt-chromium everolimus-eluting stent (Abbott Vascular) implantation.[2,16] In both STOPDAPT-2 and STOPDAPT-2 ACS, patients without in-hospital major complications were enrolled and randomized in a 1-to-1 ratio to either the 1-month DAPT group or the 12-month DAPT group. During the initial 1-month period (30-59 days), all patients were to receive DAPT with aspirin 81 to 200 mg/d and a $P2Y_{12}$ inhibitor (clopidogrel 75 mg/d or prasugrel 3.75 mg/d at the discretion of the attending physician). In the 1-month DAPT group, antiplatelet therapy was switched to clopidogrel monotherapy at 1 month, while in the

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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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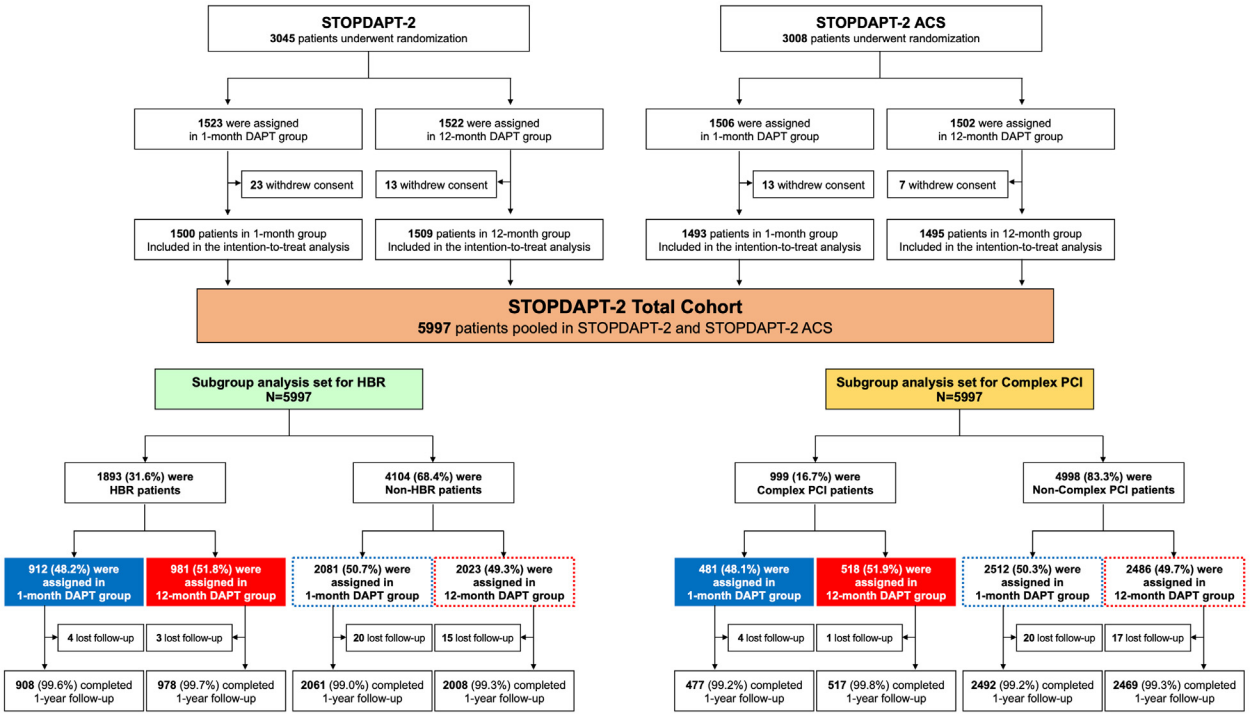
FIGURE 1 **Study Flow for the Academic Research Consortium-Defined HBR and Complex PCI Subgroup Analyses**



High bleeding risk (HBR) is defined by the Academic Research Consortium definition.[13] Complex percutaneous coronary intervention (PCI) was defined as a procedure with at least 1 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 according to the previous reports.[11,12] DAPT = dual antiplatelet therapy; STOPDAPT-2 = Short and Optimal Duration of Dual Antiplatelet Therapy After Everolimus-Eluting Cobalt-Chromium Stent-2; STOPDAPT-2 ACS = Short and Optimal Duration of Dual Antiplatelet Therapy After Everolimus-Eluting Cobalt-Chromium Stent-2 for the Patients With ACS.

12-month DAPT group, patients were to receive DAPT with aspirin and clopidogrel up to 12 months. We obtained the prespecified final analytical population of 5,997 patients as the STOPDAPT-2 Total Cohort (3,009 patients from STOPDAPT-2 and 2,988 patients from STOPDAPT-2 ACS) (**Figure 1**).[17] The ethics committees at all participating centers approved the study protocol, and written informed consent was obtained from all patients.

APPLICATION OF ARC-DEFINED HBR AND COMPLEX PCI CRITERIA. In the present study, we constructed the 2-subgroup analysis sets on the basis of ARC-defined HBR and complex PCI (**Figure 1**).

As the first analysis set for ARC-defined HBR, 5,997 patients in the STOPDAPT-2 Total Cohort were divided into 2 subgroups on the basis of the ARC definitions of HBR.[15] Patients were regarded as at HBR if they had at least 1 major criterion or 2 minor criteria of ARC-defined HBR. We modified the ARC definitions of HBR, because some criteria of ARC-defined HBR were not exactly captured in the STOPDAPT-2 trial. The detailed modification is described in the Supplemental Methods and was consistent with the previous subgroup analysis on the basis of ARC-defined HBR in STOPDAPT-2.[6,7]

As the second analysis set for complex PCI, the same 5,997 patients were divided into 2 subgroups on the basis of the criteria for complex PCI. Giustino et al[13] 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.[18,19] Complex PCI was defined as a procedure with at least 1 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. The definition was also consistent with the previous subgroup analysis on the basis of complex PCI in STOPDAPT-2.[13]

TABLE 1 Baseline Characteristics and Medications: HBR vs Non-HBR

	HBR (n = 1,893)	Non-HBR (n = 4,104)	*P* Value
Patient demographics			
Age, y	76.4 ± 8.7	63.8 ± 10.2	<0.001
≥75 y	1,332 (70.4)	500 (12.2)	<0.001
Men	1,303 (68.8)	3,400 (82.8)	<0.001
Body mass index, kg/m^2	23.3 ± 3.5	24.7 ± 3.6	<0.001
<25 kg/m^2	1,365 (72.1)	2,345 (57.1)	<0.001
Clinical presentation			
Acute coronary syndrome	1,149 (60.7)	2,987 (72.8)	<0.001
STEMI	633 (55.1)	1,691 (56.6)	0.61
NSTEMI	231 (20.1)	595 (19.9)	
Unstable angina	285 (24.8)	701 (23.5)	
Medical history and comorbidities			
Prior percutaneous coronary intervention	466 (24.6)	568 (13.8)	<0.001
Prior first-generation drug-eluting stent	81 (4.3)	75 (1.8)	<0.001
Prior coronary artery bypass grafting	47 (2.5)	30 (0.7)	<0.001
Prior myocardial infarction	231 (12.2)	349 (8.5)	<0.001
Prior stroke	249 (13.2)	73 (1.8)	<0.001
Prior ischemic stroke	234 (12.4)	73 (1.8)	<0.001
Prior hemorrhagic stroke	15 (0.8)	0 (0)	<0.001
Prior bleeding events	58 (3.1)	11 (0.3)	<0.001
Heart failure	250 (13.2)	218 (5.3)	<0.001
Atrial fibrillation	52 (2.7)	45 (1.1)	<0.001
Moderate anemia	793 (41.9)	326 (7.9)	<0.001
Severe anemia	428 (22.6)	0 (0)	<0.001
Thrombocytopenia	42 (2.2)	0 (0)	<0.001
Chronic obstructive pulmonary disease	67 (3.5)	80 (1.9)	<0.001
Liver cirrhosis	16 (0.8)	0 (0)	<0.001
Cancer	257 (13.6)	197 (4.8)	<0.001
Peripheral artery disease	155 (8.2)	88 (2.1)	<0.001
Moderate chronic kidney disease	1,113 (58.8)	579 (14.1)	<0.001
Severe chronic kidney disease	271 (14.3)	0 (0)	<0.001
Estimated glomerular filtration rate < 30 mL/min/1.73 m^2 not on dialysis	133 (7.0)	0 (0)	<0.001
Dialysis	138 (7.3)	0 (0)	<0.001
Hypertension	1,482 (78.3)	2,747 (66.9)	<0.001
Hyperlipidemia	1,316 (69.5)	2,929 (71.4)	0.14
Diabetes	731 (38.6)	1,299 (31.7)	<0.001
Diabetes with insulin	127 (6.7)	160 (3.9)	<0.001
Current smoking	313 (16.5)	1,450 (35.3)	<0.001
Left ventricular ejection fraction, %	56.9 ± 11.1	58.6 ± 10.5	<0.001
<40%	112 (6.4)	136 (3.6)	<0.001
Procedural characteristics			
Radial approach	1,519 (80.2)	3,750 (91.4)	<0.001
Invasive fractional flow reserve	188 (9.9)	320 (7.8)	0.007
Staged procedure	306 (16.2)	483 (11.8)	<0.001
Number of procedures	1.18 ± 0.44	1.13 ± 0.37	<0.001
Number of target lesions	1.34 ± 0.65	1.25 ± 0.57	<0.001
≥3	111 (5.9)	191 (4.7)	0.049

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OUTCOME MEASURES AND DEFINITIONS. Clinical outcomes were assessed at 1 year after index PCI. The primary and major secondary endpoints in the present study were identical to those adopted in STOPDAPT-2 and STOPDAPT-2 ACS. The primary endpoint was a composite of cardiovascular and bleeding outcomes, which is a composite of cardiovascular (death of cardiovascular cause, myocardial infarction, definite stent thrombosis, or any stroke) or bleeding (TIMI [Thrombolysis In Myocardial Infarction] major or minor bleeding) events.[20] The major secondary cardiovascular and bleeding endpoints were the cardiovascular and bleeding components of the primary endpoint, respectively. The definitions of myocardial infarction and stent thrombosis were derived from the ARC, and stroke was adjudicated as neurologic dysfunction lasting longer than 24 hours with confirmation by imaging examinations.[21] Other secondary endpoints are described in the Supplemental Appendix. An independent clinical event committee adjudicated clinical events blinded to group assignment.

STATISTICAL ANALYSIS. Categorical variables are presented as number (percentage) and were compared using the chi-square test. Continuous variables are expressed as mean ± SD or as median (IQR) and were compared using Student's *t*-test or the Wilcoxon rank sum test depending on their distributions. The cumulative incidence was estimated using the Kaplan-Meier method, and the differences between the 1- and 12-month DAPT groups were compared using the log-rank test. Absolute differences were calculated as the cumulative incidence rate at 1 year in the 1-month DAPT group minus that in the 12-month DAPT group. The effects of 1-month DAPT relative to 12-month DAPT for the endpoint events are expressed as HRs with their 95% CIs. The original studies were randomized clinical trials, but HRs were estimated using Cox proportional hazards models adjusting for clinical presentation (acute coronary syndrome vs chronic coronary syndrome) and study (STOPDAPT-2 vs STOPDAPT-2 ACS). The differences in the effects of 1-month DAPT relative to 12-month DAPT in the subgroups (HBR vs non-HBR and complex PCI vs noncomplex PCI) were evaluated using the interaction terms in the models.

We did not make any power calculation for the primary and major secondary endpoints in this pooled analytical population, and all reported *P* values were superiority based and 2-tailed. Values $P < 0.05$ were considered to indicate statistical significance. All analyses were performed using JMP version 15.2 (SAS Institute).

RESULTS

STUDY POPULATION IN THE ARC-DEFINED HBR SUBGROUPS. Among the 5,997 study patients, there

were 1,893 patients (31.6%) with HBR (1-month DAPT group, n = 912; 12-month DAPT group, n = 981) and 4,104 patients (68.4%) without HBR (1-month DAPT group, n = 2,081; 12-month DAPT group, n = 2,023) (**Figure 1**). ARC-defined HBR major criteria were not prevalent in this study population, except for the small proportion of patients with severe anemia (7.1%) and severe chronic kidney disease (4.5%), while ARC-defined HBR minor criteria were much more prevalent, including age ≥75 years (30.5%), moderate chronic kidney disease (28.2%), and moderate anemia (18.7%) (Supplemental Table 1).

BASELINE CHARACTERISTICS AND MEDICATIONS IN THE ARC-DEFINED HBR SUBGROUPS. Patient characteristics were different between patients with HBR and those without (**Table 1**). Patients with HBR were older, were more often women, more often had low body weight, and less often presented with acute coronary syndrome than those without. Besides comorbidities included in the ARC-defined HBR criteria, patients with HBR more often had prior myocardial infarction, heart failure, atrial fibrillation, chronic obstructive pulmonary disease, hypertension, diabetes, and left ventricular dysfunction than those without. Regarding procedural characteristics, patients with HBR more often underwent complex PCI than those without (19.8% vs 15.2%; $P < 0.001$). Intracoronary imaging devices were used during PCI in more than 97% of patients regardless of HBR. In terms of medications at discharge, patients with HBR more often received clopidogrel as a $P2Y_{12}$ inhibitor within 1 month than those without. Statins and proton pump inhibitors were less often prescribed in patients with HBR than in those without. Baseline characteristics were well balanced between the 1- and 12-month DAPT groups (Supplemental Table 2).

The vast majority of study patients received the assigned antiplatelet therapy according to the study protocol in both groups of patients with and without HBR. The patterns of DAPT discontinuation were similar and not significantly different between patients with and without HBR (Supplemental Figure 1).

CLINICAL OUTCOMES IN THE HBR SUBGROUPS. The median duration of follow-up was 365 days (IQR: 365-365 days) in patients with and without HBR. Regardless of HBR, there was no significant excess risk of 1-month DAPT relative to 12-month DAPT for the primary endpoint (HBR, 5.01% vs 5.14% [HR: 0.97; 95% CI: 0.65-1.45]; non-HBR, 1.90% vs 2.02% [HR: 0.95; 95% CI: 0.61-1.48]; *P* for interaction = 0.95) and for the cardiovascular endpoint (HBR, 4.35% vs 3.52% [HR: 1.24; 95% CI: 0.78-1.97]; non-HBR, 1.56% vs

TABLE 1 Continued

	HBR (n = 1,893)	Non-HBR (n = 4,104)	*P* Value
Target lesion location			
Left main coronary artery	93 (4.9)	86 (2.1)	<0.001
Left anterior descending coronary artery	1,069 (56.5)	2,535 (61.8)	<0.001
Left circumflex coronary artery	415 (21.9)	840 (20.5)	0.20
Right coronary artery	767 (40.5)	1,320 (32.2)	<0.001
Bypass graft	5 (0.3)	4 (0.1)	0.15
Chronic total occlusion	80 (4.2)	157 (3.8)	0.46
Bifurcation lesion	551 (29.1)	1,079 (26.3)	0.02
Final 2 stents implantation	17 (0.9)	17 (0.4)	0.03
Target of 2 vessels or more	430 (22.7)	641 (15.6)	<0.001
Target of 3 vessels	84 (4.4)	103 (2.5)	<0.001
Use of intravascular imaging	1,850 (97.7)	3,999 (97.4)	0.50
Use of intravascular ultrasound	1,675 (88.5)	3,491 (85.1)	<0.001
Use of optical coherence tomography	238 (12.6)	669 (16.3)	<0.001
Number of implanted stents	1.51 ± 0.89	1.38 ± 0.75	<0.001
≥3	215 (11.4)	314 (7.7)	<0.001
Minimal stent diameter, mm	2.93 ± 0.49	3.01 ± 0.51	<0.001
<3.0	873 (46.1)	1,607 (39.2)	<0.001
Total stent length, mm	37.8 ± 26.7	33.6 ± 22.3	<0.001
≥28	1,115 (58.9)	2,179 (53.1)	<0.001
>60	299 (15.8)	457 (11.1)	<0.001
Complex PCI	374 (19.8)	625 (15.2)	<0.001
Medication at discharge			
Aspirin	1,886 (99.6)	4,104 (100)	<0.001
200 mg/d	4 (0.2)	3 (0.1)	0.0499
100 mg/d	1,840 (97.6)	4,040 (98.4)	
81 mg/d	42 (2.2)	61 (1.5)	
$P2Y_{12}$ inhibitors	1,889 (99.8)	4,103 (100)	0.03
Clopidogrel	1,193 (63.0)	2,237 (54.5)	<0.001
Prasugrel	694 (36.7)	1,865 (45.4)	<0.001
Anticoagulant agents	29 (1.5)	0 (0)	<0.001
ACE inhibitors/ARBs	1,301 (68.7)	2,861 (69.7)	0.44
Beta-blockers	963 (50.9)	2,154 (52.5)	0.25
Statins	1,655 (87.4)	3,901 (95.1)	<0.001
High-intensity statin therapy	432 (22.8)	1,056 (25.7)	0.01
Proton pump inhibitors	1,605 (84.8)	3,568 (86.9)	0.03
Study			
STOPDAPT-2	1,054 (55.7)	1,955 (47.6)	<0.001
STOPDAPT-2 ACS	839 (44.3)	2,149 (52.4)	

Values are mean ± SD or n (%). Moderate anemia was defined as a preprocedural hemoglobin level <13 and ≥11 g/dL in men and <12 and ≥11 g/dL in women. Severe anemia was defined as a preprocedural hemoglobin level <11 g/dL. Hemoglobin values were missing for 9 patients, who were included in the no-anemia group. Thrombocytopenia was defined as a preprocedural platelet count <100 × 10^9/L. Platelet counts were missing for 23 patients, who were included in the no-thrombocytopenia group. Moderate and severe chronic kidney disease were defined as a preprocedural estimated glomerular filtration rate <60 and <30 mL/min/1.73 m^2, respectively, or maintenance dialysis therapy. Preprocedural creatinine values were missing for 18 patients. Three of these patients on dialysis were included in the severe chronic kidney disease group, while the remaining 15 patients were regarded as having neither moderate nor severe chronic kidney disease. Left ventricular ejection fraction was missing for 474 patients. 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 = angiotensin-converting enzyme; ARB = angiotensin 2 receptor blocker; HBR = high bleeding risk; NSTEMI = non–ST-segment elevation myocardial infarction; PCI = percutaneous coronary intervention; STEMI = ST-segment elevation myocardial infarction; STOPDAPT-2 = Short and Optimal Duration of Dual Antiplatelet Therapy After Everolimus-Eluting Cobalt-Chromium Stent-2; STOPDAPT-2 ACS = Short and Optimal Duration of Dual Antiplatelet Therapy After Everolimus-Eluting Cobalt-Chromium Stent-2 for the Patients With ACS.

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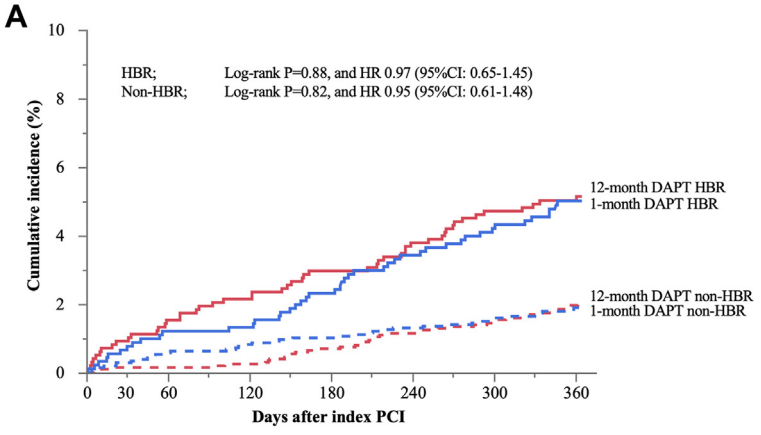
FEBRUARY 2023:31–46

FIGURE 2 Primary and Major Secondary Endpoints Stratified by HBR

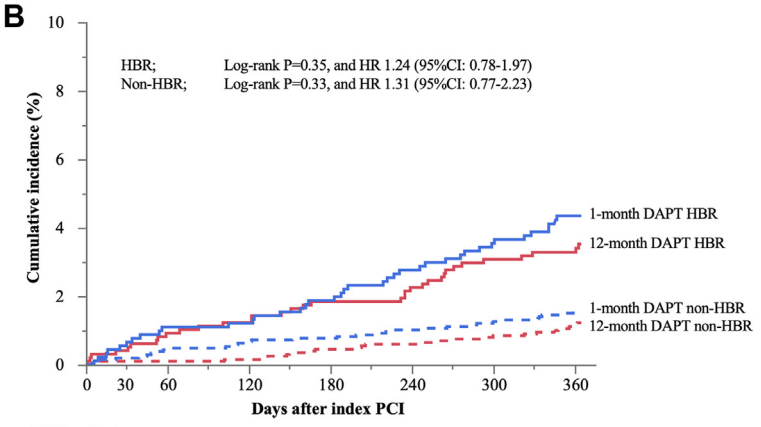


HBR patients

1-month DAPT	0	30	60	120	180	240	300	365
Number of patients with event		7	11	12	21	31	38	45
Number of patients at risk	912	905	897	892	881	868	856	704
Cumulative incidence (%)		0.77	1.21	1.32	2.31	3.43	4.21	5.01
12-month DAPT	0	30	60	120	180	240	300	365
Number of patients with event		9	15	21	29	37	46	50
Number of patients at risk	981	972	961	955	946	937	926	762
Cumulative incidence (%)		0.92	1.53	2.15	2.97	3.79	4.71	5.14

Non-HBR patients

1-month DAPT	0	30	60	120	180	240	300	365
Number of patients with event		6	12	17	21	27	32	39
Number of patients at risk	2081	2075	2059	2054	2047	2037	2029	1653
Cumulative incidence (%)		0.29	0.58	0.82	1.01	1.30	1.55	1.90
12-month DAPT	0	30	60	120	180	240	300	365
Number of patients with event		3	3	5	14	23	31	40
Number of patients at risk	2023	2019	2009	2004	1995	1985	1976	1565
Cumulative incidence (%)		0.15	0.15	0.25	0.70	1.14	1.54	2.02



HBR patients

1-month DAPT	0	30	60	120	180	240	300	365
Number of patients with event		6	10	11	17	25	32	39
Number of patients at risk	912	906	898	893	885	874	862	709
Cumulative incidence (%)		0.66	1.10	1.21	1.87	2.76	3.54	4.35
12-month DAPT	0	30	60	120	180	240	300	365
Number of patients with event		4	9	12	18	22	30	34
Number of patients at risk	981	977	967	964	957	951	941	773
Cumulative incidence (%)		0.41	0.92	1.23	1.84	2.25	3.08	3.52

Non-HBR patients

1-month DAPT	0	30	60	120	180	240	300	365
Number of patients with event		4	9	14	16	21	26	32
Number of patients at risk	2081	2077	2062	2057	2052	2043	2035	1660
Cumulative incidence (%)		0.19	0.43	0.67	0.77	1.01	1.26	1.56
12-month DAPT	0	30	60	120	180	240	300	365
Number of patients with event		2	2	3	9	12	17	24
Number of patients at risk	2023	2020	2010	2006	2000	1996	1989	1579
Cumulative incidence (%)		0.10	0.10	0.15	0.45	0.60	0.85	1.22

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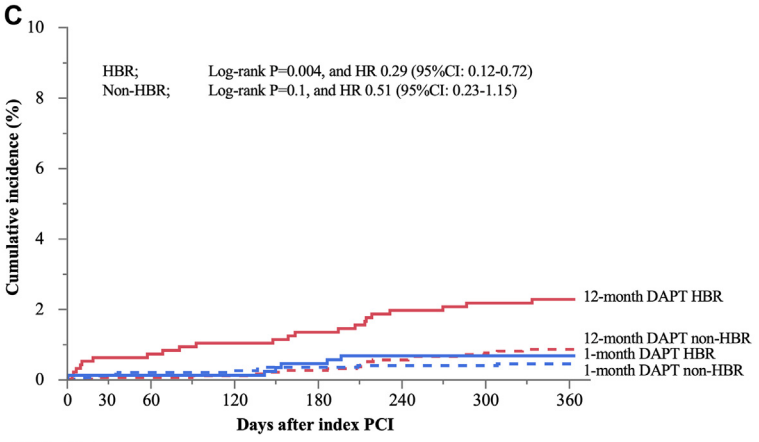
FIGURE 2 Continued



HBR patients

1-month DAPT	0	30	60	120	180	240	300	365
Number of patients with event		1	1	1	4	6	6	6
Number of patients at risk	912	909	906	902	897	889	882	727
Cumulative incidence (%)		0.11	0.11	0.11	0.44	0.66	0.66	0.66
12-month DAPT	0	30	60	120	180	240	300	365
Number of patients with event		6	7	10	13	19	21	22
Number of patients at risk	981	974	966	961	954	946	940	777
Cumulative incidence (%)		0.61	0.71	1.02	1.33	1.95	2.16	2.27

Non-HBR patients

1-month DAPT	0	30	60	120	180	240	300	365
Number of patients with event		2	4	5	7	8	8	9
Number of patients at risk	2081	2076	2064	2063	2058	2052	2045	1673
Cumulative incidence (%)		0.10	0.19	0.24	0.34	0.39	0.39	0.43
12-month DAPT	0	30	60	120	180	240	300	365
Number of patients with event		1	1	2	5	11	15	17
Number of patients at risk	2023	2021	2011	2007	2003	1995	1989	1583
Cumulative incidence (%)		0.05	0.05	0.10	0.25	0.55	0.75	0.85

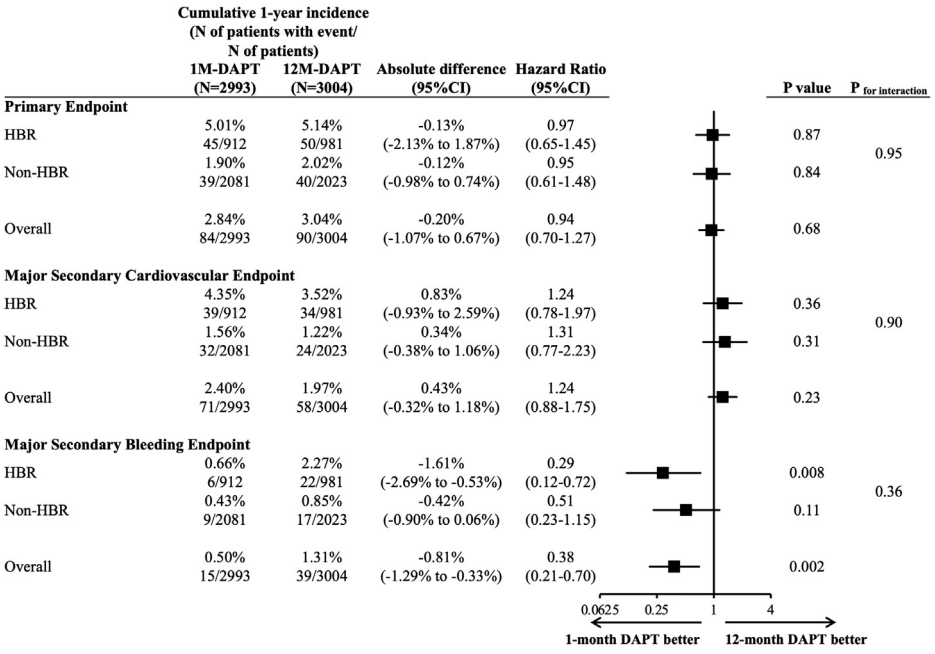
Time-to-event curves during 1 year after index PCI: **(A)** for the primary endpoint (a composite of cardiovascular death, myocardial infarction, definite stent thrombosis, any stroke, or TIMI (Thrombolysis In Myocardial Infarction) major or minor bleeding), **(B)** for the major secondary cardiovascular endpoint (a composite of cardiovascular death, myocardial infarction, definite stent thrombosis, or any stroke), and **(C)** for the major secondary bleeding endpoint (TIMI major or minor bleeding) stratified by HBR and non-HBR. The cumulative incidence was estimated using the Kaplan-Meier method, and the differences between 1- and 12-month DAPT were compared using the log-rank test. The HRs of 1-month DAPT relative to 12-month DAPT for the endpoint events were calculated using a Cox proportional hazards model with 95% CIs adjusting for acute coronary syndrome and study. Abbreviations as in Figure 1.

1.22% [HR: 1.31; 95% CI: 0.77-2.23]; *P* for interaction = 0.90). There was lower risk of 1-month DAPT relative to 12-month DAPT for the bleeding endpoint regardless of HBR (HBR, 0.66% vs 2.27% [HR: 0.29; 95% CI: 0.12-0.72] non-HBR, 0.43% vs 0.85% [HR: 0.51; 95% CI: 0.23-1.15]; *P* for interaction = 0.36). Nevertheless, because of the higher rate of major bleeding in patients with HBR, the absolute difference in the rate of bleeding between the 1- and 12-month DAPT groups was numerically greater in the HBR subgroup (−1.61%; 95% CI: −2.69% to −0.53%) than in the non-HBR subgroup (−0.42%; 95% CI: −0.90% to 0.06%) (Figures 2 and 3).

Other secondary endpoints in patients with and without HBR are presented in Supplemental Table 3. The incidences of ischemic outcomes such as myocardial infarction, any coronary revascularization, and major adverse cardiac events was numerically higher in the 1-month DAPT group than in the 12-month DAPT group regardless of HBR (Supplemental Table 3).

STUDY POPULATION IN THE COMPLEX PCI SUBGROUPS. Among the 5,997 study patients, there were 999 patients (16.7%) with complex PCI (1-month DAPT group, n = 481; 12-month DAPT group, n = 518) and 4,998 patients (83.3%) with noncomplex PCI (1-month DAPT group, n = 2,512; 12-month DAPT

FIGURE 3 Forest Plots Stratified by HBR and Non-HBR



The cumulative incidence was estimated using the Kaplan-Meier method. The HRs of 1-month DAPT relative to 12-month DAPT for the endpoint events were calculated using a Cox proportional hazards model with 95% CIs adjusting for acute coronary syndrome and study. Abbreviations as in Figure 1.

group, n = 2,486) (Figure 1). Among the criteria for complex PCI, >60-mm total stent length (12.6%), and ≥3 stents implanted (8.8%) were more prevalent than other criteria, while bifurcation with 2 stents (0.6%) was less prevalent than other criteria (Supplemental Table 4).

BASELINE CHARACTERISTICS AND MEDICATIONS IN THE COMPLEX PCI SUBGROUPS. Patients with complex PCI were older, less often presented with acute coronary syndrome, and more often had comorbidities such as prior myocardial infarction and stroke, heart failure, anemia, chronic kidney disease, hyperlipidemia, diabetes, and left ventricular dysfunction than those without (Table 2). Patients with complex PCI more often had HBR on the basis of the ARC definition than those without (37.4% vs 30.4%; $P < 0.001$). Procedural characteristics were totally different between patients with complex PCI and those without. Intracoronary imaging devices were used during PCI in more than 97% of patients regardless of complex PCI. Regarding medications at discharge, beta-blockers and high-intensity statins were more often prescribed in patients with complex PCI than those without. Baseline characteristics were well balanced between the 1- and 12-month DAPT groups (Supplemental Table 5).

The vast majority of the study patients received the assigned antiplatelet therapy according to the study protocol in both groups of patients with and without complex PCI. The patterns of DAPT discontinuation were similar and not significantly different between patients with and without complex PCI (Supplemental Figure 2).

CLINICAL OUTCOMES IN THE COMPLEX PCI SUBGROUPS. The median duration of follow-up was 365 days (IQR: 365-365 days) in patients with and without complex PCI. Regardless of complex PCI, there was no significant excess risk of 1-month DAPT relative to 12-month DAPT for the primary endpoint (complex PCI, 3.15% vs 4.07% [HR: 0.76; 95% CI: 0.39-1.48]; noncomplex PCI, 2.78% vs 2.82% [HR: 0.99; 95% CI: 0.71-1.39]; P for interaction = 0.48) and for the cardiovascular

endpoint (complex PCI, 2.53% vs 2.52% [HR: 0.99; 95% CI: 0.45-2.17]; noncomplex PCI, 2.38% vs 1.86% [HR: 1.31; 95% CI: 0.89-1.93]; *P* for interaction = 0.53). There was lower risk of 1-month DAPT relative to 12-month DAPT for the bleeding endpoint regardless of complex PCI (complex PCI, 0.63% vs 1.75% [HR: 0.35; 95% CI: 0.10-1.30]; noncomplex PCI, 0.48% vs 1.22% [HR: 0.39; 95% CI: 0.20-0.77]; *P* for interaction = 0.90) (**Figures 4 and 5**).

In patients with complex PCI, definite or probable stent thrombosis occurred in 2 patients (0.42%) in the 1-month DAPT group and 1 patient (0.19%) in the 12-month DAPT group, while in patient with noncomplex PCI, it occurred in 9 patients (0.37%) in the 1-month DAPT group and in 3 patients (0.13%) in the 12-month DAPT group (Supplemental Table 6). Other secondary endpoints in patients with and without complex PCI are presented in Supplemental Table 6. The incidence of the ischemic outcomes such as myocardial infarction, any coronary revascularization, and major adverse cardiac events was numerically higher in the 1-month DAPT group than in the 12-month DAPT group regardless of complex PCI (Supplemental Table 6).

DISCUSSION

The main findings of the present analyses in the STOPDAPT-2 Total Cohort were as follows. First, the risk of 1-month DAPT followed by clopidogrel monotherapy relative to 12-month DAPT with aspirin and clopidogrel was not significant for the primary and major secondary cardiovascular endpoints but was significantly lower for the major secondary bleeding endpoint, which was consistent regardless of HBR or non-HBR subgroups and complex PCI or noncomplex PCI subgroups without significant interaction. Second, the absolute benefit of 1-month DAPT relative to 12-month DAPT in reducing major bleeding was greater in patients with HBR than in those without HBR because of the higher rate of major bleeding in patients with HBR (**Central Illustration**).

Recently, more and more concerns have been raised regarding the increase in bleeding events associated with prolonged DAPT. In real-world practice, approximately 40% of patients receiving PCI had HBR on the basis of the ARC definition, and the incidence of major bleeding was unacceptably high in patients with HBR.[22-24] Moreover, in several previous studies, very short DAPT compared with prolonged DAPT was reported to be associated with substantial reduction in major bleeding.[6-12] Therefore, the current European, American, and Japanese guidelines have prioritized HBR as the determinant of DAPT duration after PCI.[18,19,25] In the present study, the magnitude of relative risk reduction for major bleeding with 1-month DAPT relative to 12-

TABLE 2 Baseline Characteristics and Medications: Complex PCI vs Noncomplex PCI

	Complex PCI (n = 999)	Noncomplex PCI (n = 4,998)	*P* Value
Patient demographics			
Age, y	69.1 ± 11.1	67.5 ± 11.4	<0.001
≥75	342 (34.2)	1,490 (29.8)	0.006
Men	798 (79.9)	3,905 (78.1)	0.22
Body mass index, kg/m^2	24.1 ± 3.5	24.2 ± 3.6	0.41
<25	628 (62.9)	3,082 (61.7)	0.48
Clinical presentation			
Acute coronary syndrome	654 (65.5)	3,482 (69.7)	0.009
STEMI	387 (59.2)	1,937 (55.6)	<0.001
NSTEMI	153 (23.4)	673 (19.3)	
Unstable angina	114 (17.4)	872 (25.0)	
Medical history and comorbidities			
Prior percutaneous coronary intervention	174 (17.4)	860 (17.2)	0.87
Prior first-generation drug-eluting stent	31 (3.1)	125 (2.5)	0.29
Prior coronary artery bypass grafting	19 (1.9)	58 (1.2)	0.07
Prior myocardial infarction	127 (12.7)	453 (9.1)	0.001
Prior stroke	69 (6.9)	253 (5.1)	0.02
Prior ischemic stroke	67 (6.7)	240 (4.8)	0.02
Prior hemorrhagic stroke	2 (0.2)	13 (0.3)	1.00
Prior bleeding events	12 (1.2)	57 (1.1)	0.87
Heart failure	106 (10.6)	362 (7.2)	0.001
Atrial fibrillation	20 (2.0)	77 (1.5)	0.31
Moderate anemia	225 (22.5)	894 (17.9)	0.001
Severe anemia	95 (9.5)	333 (6.7)	0.002
Thrombocytopenia	10 (1.0)	32 (0.6)	0.23
Chronic obstructive pulmonary disease	27 (2.7)	120 (2.4)	0.58
Liver cirrhosis	2 (0.2)	14 (0.3)	0.64
Cancer	78 (7.8)	376 (7.5)	0.76
Peripheral artery disease	48 (4.8)	195 (3.9)	0.20
Moderate chronic kidney disease	306 (30.6)	1,386 (27.7)	0.06
Severe chronic kidney disease	57 (5.7)	214 (4.3)	0.06
Estimated glomerular filtration rate < 30 mL/min/1.73 m^2 not on dialysis	32 (3.2)	101 (2.0)	0.03
Dialysis	25 (2.5)	113 (2.3)	0.65
Hypertension	724 (72.5)	3,505 (70.1)	0.14
Hyperlipidemia	736 (73.7)	3,509 (70.2)	0.03
Diabetes	421 (42.1)	1,609 (32.2)	<0.001
Diabetes with insulin	66 (6.6)	221 (4.4)	0.005
Current smoking	279 (27.9)	1,484 (29.7)	0.26
Left ventricular ejection fraction, %	55.9 ± 11.4	58.5 ± 10.6	<0.001
<40%	70 (7.6)	178 (3.9)	<0.001
ARC-defined HBR	374 (37.4)	1,519 (30.4)	<0.001
Procedural characteristics			
Radial approach	878 (87.9)	4,391 (87.9)	0.98
Invasive fractional flow reserve	114 (11.4)	394 (7.9)	<0.001
Staged procedure	543 (54.4)	246 (4.9)	<0.001
Number of procedures	1.63 ± 0.64	1.05 ± 0.22	<0.001
Number of target lesions	2.10 ± 0.90	1.11 ± 0.31	<0.001
≥3	302 (30.2)	0 (0)	<0.001

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TABLE 2 Continued

	Complex PCI (n = 999)	Noncomplex PCI (n = 4,998)	*P* Value
Target lesion location			
Left main coronary artery	102 (10.2)	77 (1.5)	<0.001
Left anterior descending coronary artery	726 (72.7)	2,878 (57.6)	<0.001
Left circumflex coronary artery	385 (38.5)	870 (17.4)	<0.001
Right coronary artery	592 (59.3)	1,495 (29.9)	<0.001
Bypass graft	2 (0.2)	7 (0.1)	0.65
Chronic total occlusion	237 (23.7)	0 (0)	<0.001
Bifurcation lesion	460 (46.0)	1,170 (23.4)	<0.001
Final 2 stents implantation	34 (3.4)	0 (0)	<0.001
Target of 2 vessels or more	676 (67.7)	395 (7.9)	<0.001
Target of 3 vessels	187 (18.7)	0 (0)	<0.001
Use of intravascular imaging	991 (99.2)	4,858 (97.2)	<0.001
Use of intravascular ultrasound	930 (93.1)	4,236 (84.8)	<0.001
Use of optical coherence tomography	150 (15.0)	757 (15.1)	0.92
Number of implanted stents	2.70 ± 1.09	1.16 ± 0.37	<0.001
≥3	529 (53.0)	0 (0)	<0.001
Minimal stent diameter, mm	2.65 ± 0.39	3.05 ± 0.49	<0.001
<3.0	723 (72.4)	1,757 (35.2)	<0.001
Total stent length, mm	73.8 ± 31.4	27.1 ± 11.0	<0.001
≥28	944 (94.5)	2,350 (47.0)	<0.001
>60	756 (75.7)	0 (0)	<0.001
Medication at discharge			
Aspirin	997 (99.8)	4,993 (99.9)	0.33
200 mg/d	2 (0.2)	5 (0.1)	0.70
100 mg/d	979 (98.2)	4,901 (98.2)	
81 mg/d	16 (1.6)	87 (1.7)	
$P2Y_{12}$ inhibitors	999 (100)	4,993 (99.9)	0.60
Clopidogrel	568 (56.9)	2,862 (57.3)	0.81
Prasugrel	429 (42.9)	2,130 (42.6)	0.85
Anticoagulant agents	4 (0.4)	25 (0.5)	0.67
ACE inhibitors/ARBs	717 (71.8)	3,445 (68.9)	0.07
Beta-blockers	548 (54.9)	2,569 (51.4)	0.046
Statins	924 (92.5)	4,632 (92.7)	0.84
High-intensity statin therapy	295 (29.5)	1,193 (23.9)	<0.001
Proton pump inhibitors	875 (87.6)	4,298 (86.0)	0.18
Study			
STOPDAPT-2	509 (51.0)	2,500 (50.0)	0.59
STOPDAPT-2 ACS	490 (49.0)	2,498 (50.0)	

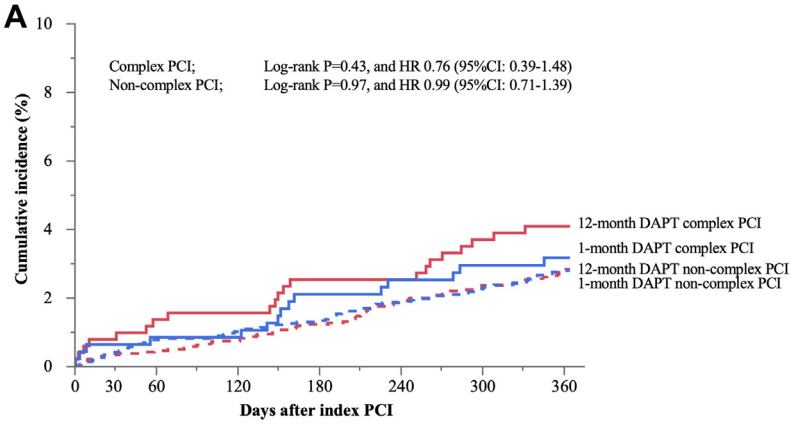
Values are mean ± SD or n (%). Moderate anemia was defined as a preprocedural hemoglobin level <13 and ≥11 g/dL in men and <12 and ≥11 g/dL in women. Severe anemia was defined as a preprocedural hemoglobin level <11 g/dL. Hemoglobin values were missing for 9 patients, who were included in the no-anemia group. Thrombocytopenia was defined as a preprocedural platelet count $<100 \times 10^9$/L. Platelet counts were missing for 23 patients, who were included in the no-thrombocytopenia group. Moderate and severe chronic kidney disease were defined as a preprocedural estimated glomerular filtration rate <60 and <30 mL/min/1.73 m^2, respectively, or maintenance dialysis therapy. Preprocedural creatinine values were missing for 18 patients. Three of these patients on dialysis were included in the severe chronic kidney disease group, while the remaining 15 patients were regarded as having neither moderate nor severe chronic kidney disease. Left ventricular ejection fraction was missing for 474 patients. 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).

Abbreviations as in Table 1.

month DAPT was consistent regardless of HBR or non-HBR subgroup. However, the absolute benefit of 1-month DAPT relative to 12-month DAPT in reducing major bleeding was greater in patients with HBR than in those without HBR. Therefore, 1-month DAPT would be an attractive antithrombotic regimen, particularly in patients with HBR. In the meantime, it is well known that patients with HBR also have high risk for cardiovascular events.[22-24] When adopting very short DAPT in patients with HBR, physicians might have concerns regarding a possible increase in cardiovascular events with very short DAPT. Indeed, in the present study, the rate of cardiovascular events was much higher in patients with HBR than in those without HBR. However, the excess risk of 1-month DAPT relative to 12-month DAPT was not significant for cardiovascular events regardless of HBR or non-HBR subgroup. Furthermore, in the MASTER DAPT (Management of High Bleeding Risk Patients Post Bioresorbable Polymer Coated Stent Implantation With an Abbreviated Versus Standard DAPT Regimen) trial, an abbreviated DAPT regimen compared with a standard DAPT regimen reduced clinically relevant bleeding events without an increase in cardiovascular events in patients with HBR.[10] Moreover, in a pooled analysis of 6 randomized controlled trials, $P2Y_{12}$ inhibitor monotherapy after very short DAPT was associated with a numerically lower incidence of death, myocardial infarction, or stroke compared with standard DAPT in patients with HBR.[9] These data would support the current guideline recommendation of very short DAPT in patients with HBR, although the effects of 1-month DAPT relative to 12-month DAPT for cardiovascular and bleeding events were consistent regardless of HBR. Further studies are warranted to establish the optimal antithrombotic monotherapy after stopping DAPT in patients with HBR.

Complex PCI is reported to be a risk factor of stent-driven recurrent ischemic events.[13] In real clinical practice, patients who undergo complex PCI are often managed with prolonged DAPT, even if they are at HBR.[26,27] Physicians might still be reluctant to choose very short DAPT in patients who undergo complex PCI, mainly because of concerns regarding stent thrombosis and other stent-driven recurrent ischemic events. Giustino et al[13] 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 a pooled analysis of 6 randomized controlled trials, in which aspirin was mainly used after stopping DAPT.[13] More recently, Valgimigli et al[9] suggested that $P2Y_{12}$ inhibitor monotherapy after short DAPT compared with standard DAPT was not associated with increased risk for ischemic events in patients

FIGURE 4 **The Primary and Major Secondary Endpoints Stratified by Complex PCI**

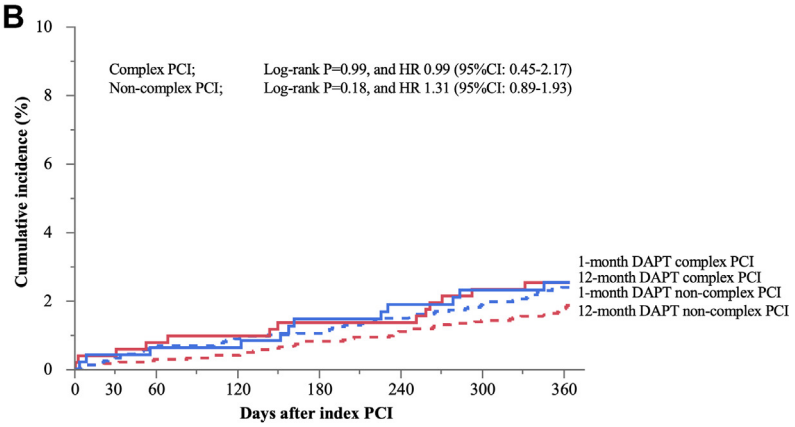


Complex PCI patients

1-month DAPT	0	30	60	120	180	240	300	365
Number of patients with event		3	4	4	10	12	14	15
Number of patients at risk	481	478	476	475	466	464	458	383
Cumulative incidence (%)		0.62	0.83	0.83	2.09	2.51	2.93	3.15
12-month DAPT	0	30	60	120	180	240	300	365
Number of patients with event		4	7	8	13	13	19	21
Number of patients at risk	518	514	509	507	502	502	495	392
Cumulative incidence (%)		0.77	1.35	1.55	2.52	2.52	3.68	4.07

Non-complex PCI patients

1-month DAPT	0	30	60	120	180	240	300	365
Number of patients with event		10	19	25	32	46	56	69
Number of patients at risk	2512	2502	2480	2471	2462	2441	2427	1974
Cumulative incidence (%)		0.40	0.76	1.00	1.28	1.84	2.24	2.78
12-month DAPT	0	30	60	120	180	240	300	365
Number of patients with event		8	11	18	30	47	58	69
Number of patients at risk	2486	2477	2461	2452	2439	2420	2407	1935
Cumulative incidence (%)		0.32	0.44	0.73	1.21	1.90	2.35	2.82



Complex PCI patients

1-month DAPT	0	30	60	120	180	240	300	365
Number of patients with event		2	3	3	7	9	11	12
Number of patients at risk	481	479	477	476	469	467	461	385
Cumulative incidence (%)		0.42	0.62	0.62	1.46	1.88	2.31	2.53
12-month DAPT	0	30	60	120	180	240	300	365
Number of patients with event		2	4	5	7	7	12	13
Number of patients at risk	518	516	512	510	508	508	502	398
Cumulative incidence (%)		0.39	0.77	0.97	1.36	1.36	2.33	2.52

Non-complex PCI patients

1-month DAPT	0	30	60	120	180	240	300	365
Number of patients with event		8	16	22	26	37	47	59
Number of patients at risk	2512	2504	2483	2474	2468	2450	2436	1984
Cumulative incidence (%)		0.32	0.64	0.88	1.04	1.48	1.88	2.38
12-month DAPT	0	30	60	120	180	240	300	365
Number of patients with event		4	7	10	20	27	35	45
Number of patients at risk	2486	2481	2465	2460	2449	2439	2428	1954
Cumulative incidence (%)		0.16	0.28	0.40	0.81	1.09	1.42	1.86

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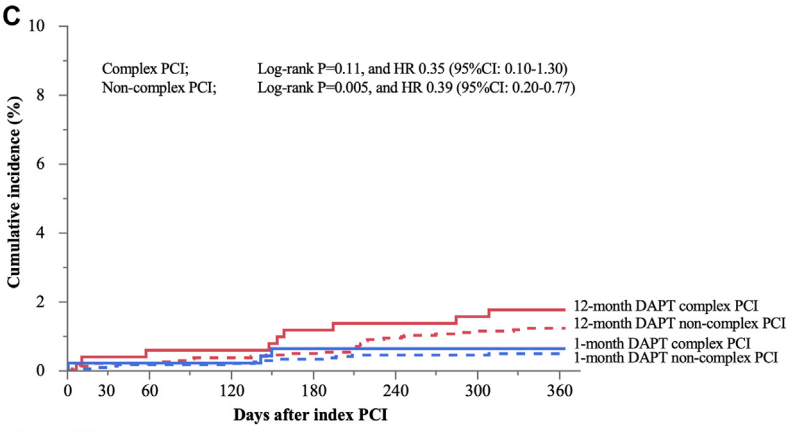
FIGURE 4 Continued



Complex PCI patients

1-month DAPT	0	30	60	120	180	240	300	365
Number of patients with event		1	1	1	3	3	3	3
Number of patients at risk	481	480	479	478	473	472	466	390
Cumulative incidence (%)		0.21	0.21	0.21	0.63	0.63	0.63	0.63
12-month DAPT	0	30	60	120	180	240	300	365
Number of patients with event		2	3	3	6	7	8	9
Number of patients at risk	518	516	512	511	507	506	503	401
Cumulative incidence (%)		0.39	0.58	0.58	1.17	1.36	1.56	1.75

Non-complex PCI patients

1-month DAPT	0	30	60	120	180	240	300	365
Number of patients with event		2	4	5	8	11	11	12
Number of patients at risk	2512	2505	2491	2487	2482	2469	2461	2010
Cumulative incidence (%)		0.08	0.16	0.20	0.32	0.44	0.44	0.48
12-month DAPT	0	30	60	120	180	240	300	365
Number of patients with event		5	5	9	12	23	28	30
Number of patients at risk	2486	2479	2465	2457	2450	2435	2426	1959
Cumulative incidence (%)		0.20	0.20	0.36	0.49	0.93	1.14	1.22

Time-to-event curves during 1 year after index PCI: **(A)** for the primary endpoint (a composite of cardiovascular death, myocardial infarction, definite stent thrombosis, any stroke, or TIMI major or minor bleeding, **(B)** for the major secondary cardiovascular endpoint (a composite of cardiovascular death, myocardial infarction, definite stent thrombosis, or any stroke), and **(C)** for the major secondary bleeding endpoint (TIMI major or minor bleeding) stratified by complex PCI and noncomplex PCI. The cumulative incidence was estimated using the Kaplan-Meier method, and the differences between 1- and 12-month DAPT were compared using the log-rank test. The HRs of 1-month DAPT relative to 12-month DAPT for the endpoint events were calculated using a Cox proportional hazards model with 95% CIs adjusting for acute coronary syndrome and study. Abbreviations as in Figures 1 and 2.

undergoing complex PCI in a pooled analysis of 6 randomized controlled trials. In the present study, clopidogrel monotherapy after 1-month DAPT was also not associated with increased risk for cardiovascular events compared with 12-month DAPT with aspirin and clopidogrel in patients who underwent complex PCI. Moreover, there was no interaction between the subgroup factor of complex PCI and the effect of 1-month DAPT relative to 12-month DAPT for cardiovascular events. Therefore, complex PCI would not be an appropriate determinant for DAPT durations after PCI.

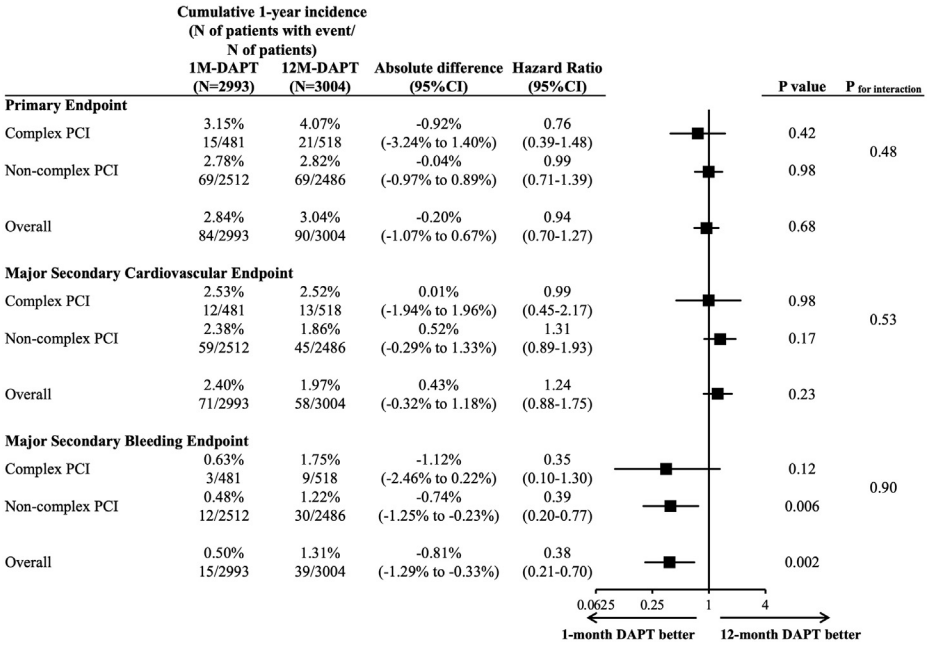
STUDY LIMITATIONS. The individual STOPDAPT-2 and STOPDAPT-2 ACS trials pooled in the STOPDAPT-2 Total Cohort had limitations, such as open-label design, use of net clinical benefit for the primary endpoint, timing of randomization (at baseline but not at 1 month, when the study medications were changed), and representation of lower risk patients than those in real clinical practice.[28]

There are other important limitations in the present study. First, any subgroup analysis could be underpowered and thus should be interpreted as exploratory, although we pooled 2 large clinical trials as an analytical population.

Second, we pooled patients from the 2 trials conducted in different periods, and there may have been some heterogeneity in this pooled population, although the protocols of the 2 trials were almost same, and we included the enrolled study as a risk-adjusting factor.

Third, the exclusion criteria in the original studies included patients receiving oral anticoagulant agents.

FIGURE 5 **Forest Plots Stratified by Complex PCI and Noncomplex PCI**



The cumulative incidence was estimated using the Kaplan-Meier method. The HRs of 1-month DAPT relative to 12-month DAPT for the endpoint events were calculated using a Cox proportional hazards model with 95% CIs adjusting for acute coronary syndrome and study. Abbreviations as in **Figure 1**.

We could not apply this HBR subgroup analysis to patients receiving oral anticoagulant agents. In addition, there were few patients with ARC-defined HBR major criteria. Therefore, patients with HBR in this study might represent a somewhat lower risk population than those encountered in real clinical practice.

Fourth, the prevalence of complex PCI was low. In particular, the prevalence of bifurcation with 2 stents, which was reported as the strongest risk factor for ischemic events, was much lower than in previous studies.[13,26] In addition, the STOPDAPT-2 and STOPDAPT-2 ACS trials excluded patients who experienced in-hospital major complications, so the event rates of ischemic outcomes were very low. Patients with complex PCI in this study might also represent a somewhat lower risk population than that encountered in real clinical practice.

Fifth, it is well known that Japanese patients with coronary artery disease have lower ischemic risk compared with U.S. and European patients.[29] In addition, the vast majority of the study patients underwent PCI guided by intracoronary imaging devices, which is quite different from the practice in United States and Europe. Moreover, there are differences between Japan and the United States or Europe in terms of the types and doses of standard antithrombotic therapy. Ticagrelor and the standard dose of prasugrel are not available in Japan, although these medications are recommended in patients with acute coronary syndrome in U.S. and European guidelines.[18,19,25] Therefore, one should be cautious in extrapolating the present study results outside Japan.

CONCLUSIONS

The effects of clopidogrel monotherapy after 1-month DAPT relative to 12-month DAPT with aspirin and clopidogrel for cardiovascular and bleeding outcomes were consistent regardless of HBR and complex PCI. The absolute benefit of 1-month DAPT in reducing major bleeding was numerically greater in patients with HBR than in those without HBR. Complex PCI might not be an appropriate determinant of DAPT duration after PCI.

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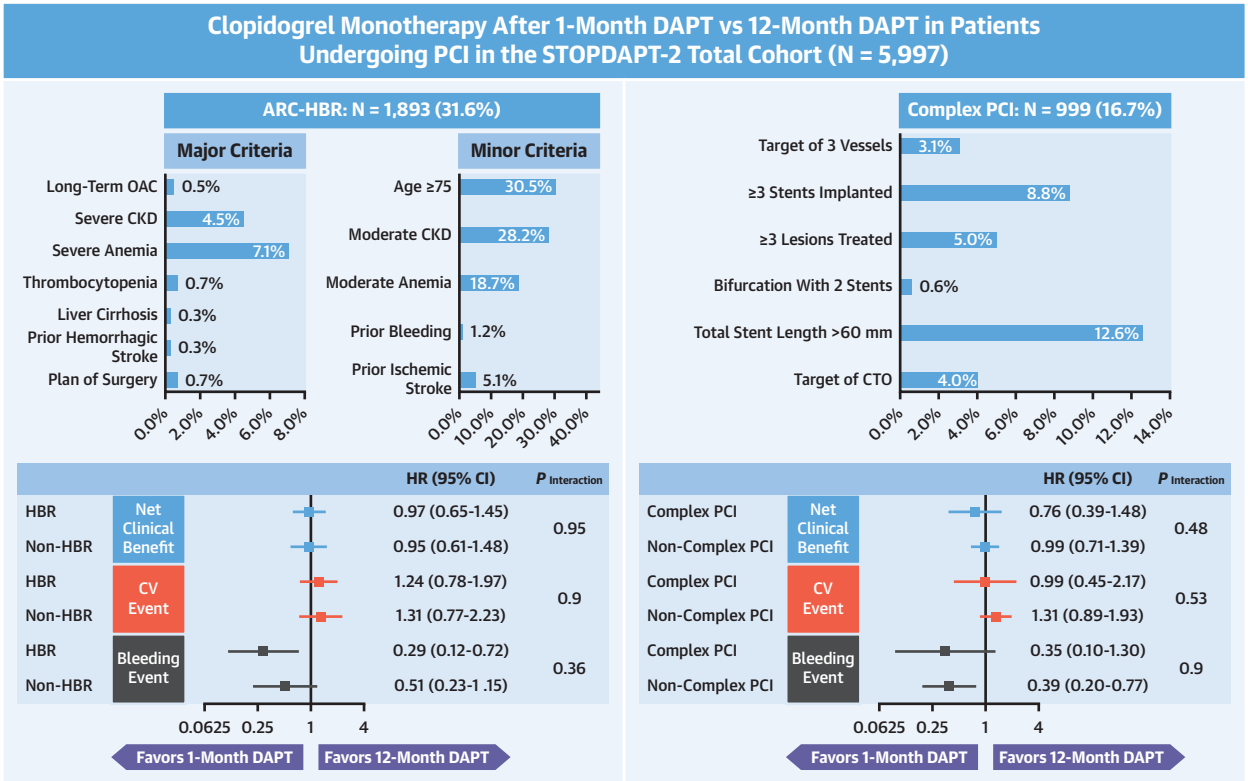
CENTRAL ILLUSTRATION **Clopidogrel Monotherapy After 1-Month DAPT in Patients With HBR or Complex PCI**



Yamamoto K, et al. JACC: Asia. 2023;3(1):31–46.

The risk of clopidogrel monotherapy after 1-month dual antiplatelet therapy (DAPT) relative to 12-month DAPT with aspirin and clopidogrel was not significant for the primary and major secondary cardiovascular endpoints but was significantly lower for the major secondary bleeding endpoint, which was consistent regardless of high bleeding risk (HBR) or non-HBR subgroup and complex percutaneous coronary intervention (PCI) or noncomplex PCI subgroup, without a significant interaction. ARC = Academic Research Consortium; CKD = chronic kidney disease; CTO = chronic total occlusion; CV = cardiovascular; OAC = oral anticoagulation; STOPDAPT-2 = Short and Optimal Duration of Dual Antiplatelet Therapy After Everolimus-Eluting Cobalt-Chromium Stent–2.

trials performed at Kyoto University and the co-investigators enrolling patients, collecting follow-up data, or adjudicating clinical events.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: The risk of 1-month DAPT followed by clopidogrel monotherapy relative to 12-month DAPT with aspirin and clopidogrel was not significant for cardiovascular events but was significantly lower for bleeding events, which were consistent regardless of HBR or non-HBR subgroup and complex PCI or noncomplex PCI subgroup, without a significant interaction. The absolute benefit of 1-month DAPT relative to 12-month DAPT in reducing major bleeding was greater in patients with HBR than in those without HBR because of the higher rate of major bleeding in patients with HBR. Complex PCI might not be an appropriate determinant of DAPT duration after PCI.

TRANSLATIONAL OUTLOOK: Further studies are warranted to establish the optimal antithrombotic monotherapy after stopping DAPT in patients with HBR.

REFERENCES

1. Vranckx P, Valgimigli M, Juni P, et al. Ticagrelor plus aspirin for 1 month, followed by ticagrelor monotherapy for 23 months vs aspirin plus clopidogrel or ticagrelor for 12 months, followed by aspirin monotherapy for 12 months after implantation of a drug-eluting stent: a multicentre, open-label, randomised superiority trial. *Lancet*. 2018;392:940–949.

2. Watanabe H, Domei T, Morimoto T, et al. Effect of 1-month dual antiplatelet therapy followed by clopidogrel vs 12-month dual antiplatelet therapy on cardiovascular and bleeding events in patients receiving PCI: the STOPDAPT-2 randomized clinical trial. *JAMA*. 2019;321:2414–2427.

3. Hahn JY, Bin Song Y, Oh JH, et al. Effect of $P2Y_{12}$ inhibitor monotherapy vs dual antiplatelet therapy on cardiovascular events in patients undergoing percutaneous coronary intervention: the SMART-CHOICE randomized clinical trial. *JAMA*. 2019;321:2428–2437.

4. Mehran R, Baber U, Sharma SK, et al. Ticagrelor with or without aspirin in high-risk patients after PCI. *N Engl J Med*. 2019;381:2032–2042.

5. Kim BK, Hong SJ, Cho YH, et al. Effect of ticagrelor monotherapy vs ticagrelor with aspirin on major bleeding and cardiovascular events in patients with acute coronary syndrome: the TICO randomized clinical trial. *JAMA*. 2020;323:2407–2416.

6. Watanabe H, Domei T, Morimoto T, et al. Very short dual antiplatelet therapy after drug-eluting stent implantation in patients with high bleeding risk insight from the STOPDAPT-2 trial. *Circulation*. 2019;140:1957–1959.

7. Watanabe H, Domei T, Morimoto T, et al. Details on the effect of very short dual antiplatelet therapy after drug-eluting stent implantation in patients with high bleeding risk: insight from the STOPDAPT-2 trial. *Cardiovasc Interv Ther*. 2021;36:91–103.

8. Valgimigli M, Mehran R, Franzone A, et al. Ticagrelor monotherapy versus dual-antiplatelet therapy after PCI: an individual patient-level meta-analysis. *J Am Coll Cardiol Intv*. 2021;14:444–456.

9. Valgimigli M, Gragnano F, Branca M, et al. $P2Y_{12}$ inhibitor monotherapy or dual antiplatelet therapy after coronary revascularisation: individual patient level meta-analysis of randomised controlled trials. *BMJ*. 2021;373:n1332.

10. Valgimigli M, Frigoli E, Heg D, et al. Dual antiplatelet therapy after PCI in patients at high bleeding risk. *N Engl J Med*. 2021;385:1643–1655.

11. Mehran R, Cao D, Angiolillo DJ, et al. 3- or 1-Month DAPT in patients at high bleeding risk undergoing everolimus-eluting stent implantation. *J Am Coll Cardiol Intv*. 2021;14:1870–1883.

12. Escaned J, Cao D, Baber U, et al. Ticagrelor monotherapy in patients at high bleeding risk undergoing percutaneous coronary intervention: TWILIGHT-HBR. *Eur Heart J*. 2021;42(45):4624–4634.

13. Giustino G, Chieffo A, Palmerini T, et al. Efficacy and safety of dual antiplatelet therapy after complex PCI. *J Am Coll Cardiol*. 2016;68:1851–1864.

14. Yamamoto K, Watanabe H, Morimoto T, et al. Very short dual antiplatelet therapy after drug-eluting stent implantation in patients who underwent complex percutaneous coronary intervention: insight from the STOPDAPT-2 trial. *Circ Cardiovasc Interv*. 2021;14:e010384.

15. Urban P, Mehran R, Colleran R, et al. Defining high bleeding risk in patients undergoing percutaneous coronary intervention: a consensus document from the Academic Research Consortium for High Bleeding Risk. *Eur Heart J*. 2019;40:2632–2653.

16. Watanabe H, Morimoto T, Natsuaki M, et al. Clopidogrel monotherapy after 1-2 month dual antiplatelet therapy in acute coronary syndrome: the STOPDAPT-2 ACS randomized clinical trial. *JAMA Cardiol*. 2022;7:407–417.

17. Obayashi Y, Watanabe H, Morimoto T, et al. Clopidogrel monotherapy after 1-month dual antiplatelet therapy in percutaneous coronary intervention: from the STOPDAPT-2 total cohort. *Circ Cardiovasc Interv*. 2022;15(8):e012004.

18. Collet JP, Thiele H, Barbato E, et al. 2020 ESC guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation. *Eur Heart J*. 2021;42:1289–1367.

19. Nakamura M, Kimura K, Kimura T, et al. JCS 2020 guideline focused update on antithrombotic therapy in patients with coronary artery disease. *Circ J*. 2020;84:831–865.

20. Rao AK, Pratt C, Berke A, et al. Thrombolysis In Myocardial Infarction (TIMI) trial-phase I: hemorrhagic manifestations and changes in plasma fibrinogen and the fibrinolytic system in patients treated with recombinant tissue plasminogen activator and streptokinase. *J Am Coll Cardiol*. 1988;11:1–11.

21. Cutlip DE, Windecker S, Mehran R, et al. Clinical end points in coronary stent trials: a case for standardized definitions. *Circulation*. 2007;115:2344–2351.

22. Natsuaki M, Morimoto T, Shiomi H, et al. Application of the academic research consortium high bleeding risk criteria in an all-comers registry of percutaneous coronary intervention. *Circ Cardiovasc Interv*. 2019;12:e008307.

23. Natsuaki M, Morimoto T, Shiomi H, et al. Effects of acute coronary syndrome and stable coronary artery disease on bleeding and ischemic risk after percutaneous coronary intervention. *Circ J*. 2021;85:1928–1941.

24. Cao D, Mehran R, Dangas G, et al. Validation of the Academic Research Consortium high bleeding risk definition in contemporary PCI patients. *J Am Coll Cardiol*. 2020;75:2711–2722.

25. Lawton JS, Tamis-Holland JE, Bangalore S, et al. 2021 ACC/AHA/SCAI guideline for coronary artery revascularization: a report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. *J Am Coll Cardiol*. 2022;79(2):e21–e129.

JACC: ASIA, VOL. 3, NO. 1, 2023
FEBRUARY 2023:31–46

26. Yamamoto K, Shiomi H, Morimoto T, et al. Ischemic and bleeding risk after complex percutaneous coronary intervention in patients with or without high bleeding risk. *Catheter Cardiovasc Interv*. 2021;97:E758–E770.

27. Wang HY, Dou KF, Yin D, et al. Risk/benefit tradeoff of prolonging dual antiplatelet therapy more than 12 months in TWILIGHT-like high-risk patients after complex percutaneous coronary intervention. *Am J Cardiol*. 2020;133:61–70.

28. Kanenawa K, Yamaji K, Tashiro H, et al. Patient selection and clinical outcomes in the STOPDAPT-2 trial: an all-comer single-center registry during the enrollment period of the STOPDAPT-2 randomized controlled trial. *Circ Cardiovasc Interv*. 2021;14:e010007.

29. Levine GN, Jeong YH, Goto S, et al. Expert consensus document: World Heart Federation expert consensus statement on antiplatelet therapy in East Asian patients with ACS or undergoing PCI. *Nat Rev Cardiol*. 2014;11:597–606.

KEY WORDS antiplatelet therapy, complexity, coronary stent, high bleeding risk, percutaneous coronary intervention

APPENDIX For definitions of clinical outcomes as well as a supplemental Methods section, tables, figures, please see the online version of this paper.