Monotherapy With Prasugrel After Dual-Antiplatelet Therapy for Japanese Percutaneous Coronary Intervention Patients With High Bleeding Risk
— A Prospective Cohort Study (PENDULUM mono Study) —

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Background: The risks of bleeding and cardiovascular events in high bleeding risk (HBR) Japanese patients undergoing percutaneous coronary intervention (PCI) while receiving single-antiplatelet therapy (SAPT) remains unknown. We aimed to evaluate the frequency of bleeding and cardiovascular events associated with prasugrel monotherapy after short-term dual-antiplatelet therapy (DAPT) in Japanese HBR patients after PCI.

Methods and Results: The PENDULUM mono study was a multicenter, non-interventional, prospective registry (n=1,173). The primary endpoint was the cumulative incidence of clinically relevant bleeding (CRB; Bleeding Academic Research Consortium types 2, 3, and 5) from 1 to 12 months after PCI. Secondary endpoints included major adverse cardiac and cerebrovascular events (MACCE). The proportion of patients who received prasugrel monotherapy at 12 months after PCI was 79.7%, and no cases of stent thrombosis were observed among these patients. The cumulative incidence of CRB was 3.2% from 1 to 12 months after PCI; that of MACCE was 3.8%. Severe anemia, chronic kidney disease, oral anticoagulant use at discharge, and heart failure were significantly associated with CRB.

Conclusions: Among HBR patients undergoing PCI who were not suitable for concomitant aspirin and were scheduled for prasugrel monotherapy, most patients were on prasugrel monotherapy after DAPT. Cumulative incidences of CRB and MACCE after periprocedural period were 3.2% and 3.8%, respectively, and no cases of stent thrombosis were reported. SAPT might be a suitable alternative to DAPT.

Key Words: Bleeding risk; Japan; Percutaneous coronary intervention; Prasugrel; Single-antiplatelet therapy

In patients who undergo percutaneous coronary intervention (PCI), treatment strategies that favor optimal medical therapy have been shown to be comparable to treatment strategies that favor revascularization.[1] Antiplatelet therapy is one of the key treatments for optimal medical therapy; however, a recent study suggested that bleeding complications worsen prognosis leading to subsequent fatal events.[2] Bleeding management is essential to improve the prognosis after PCI, especially with the introduction of potent antiplatelet drugs and a new generation

of drug-eluting stents (DES).

Several approaches to bleeding management have been investigated, with each approach aimed at eliminating the risk of adverse events while maintaining antiplatelet efficacy. One such approach is risk assessment, which helps determine the optimal duration of dual-antiplatelet therapy (DAPT).[3,4] Many efforts have been made to establish risk models,[5–7] and recent guidelines recommended the use of a risk score to determine the optimal DAPT duration in daily practice.[8] Another approach is escalation or de-escalation of antiplatelet therapy guided by platelet aggregability or CYP2C19 genotype.[9] An extensively investigated approach is the so-called aspirin-free strategy (single-antiplatelet therapy [SAPT] with a $P2Y_{12}$ antagonist after shortening the DAPT duration); this may be of benefit because aspirin at discharge increases the risk of cerebral hemorrhage and gastrointestinal hemorrhage.[10] For example, in both the STOPDAPT-2 and TWILIGHT studies, which compared a $P2Y_{12}$ antagonist (prasugrel or clopidogrel, and ticagrelor, respectively) with or without aspirin, the aspirin-free groups had reduced bleeding events without increased thrombotic events compared with the groups receiving continuous DAPT.[2,11] Prasugrel is a $P2Y_{12}$ inhibitor that is less affected by genetic polymorphisms,[12] but evidence for monotherapy after DAPT is scarce.

Recently, the Academic Research Consortium (ARC) defined high bleeding risk (HBR) and proposed clinical factors associated with HBR.[13] However, information regarding the clinical utility of the ARC-HBR criteria remains limited. Furthermore, bleeding events can vary widely in severity depending on DAPT duration. Our previous research focused on HBR patients specifically on long-term DAPT (12 months);[14] hence, gaining knowledge of the risk of bleeding in patients on short-term DAPT would be of value.

The PrasugrEl moNotherapy after DrUg eLUting stent deployMent as a Management Of patients who are uNsuitable for lOng-term dual antiplatelet therapy (PENDULUM mono study) aims to evaluate the frequency of bleeding events and cardiovascular events associated with SAPT with prasugrel in Japanese HBR patients after PCI, particularly among patients receiving short-term DAPT (<6 months) in an effort to ameliorate the risk of adverse events associated with long-term DAPT.

Methods

Study Design
The PENDULUM mono study is a multicenter, non-interventional, prospective registry survey that started on July 2017 and is planned to be completed in December 2020. The registration period was from July 2017 to December 2018. Registered patients will be followed for 24 months. Clinical cases were collected by electronic data capture, and events were assessed by independent event evaluation committees. The study protocol was approved by the institutional review board or independent ethics committee at each participating center, and the study was performed in accordance with the principles of the Declaration of Helsinki and the International Council for Harmonisation Good Clinical Practice Guidelines. All patients provided written informed consent prior to participation. This study was registered at UMIN-CTR Clinical Trial under the identifier number UMIN000028023.

Patients
The present study included patients indicated for PCI with DES and who were not considered appropriate for long-term combination treatment with aspirin because of their HBR status. Specifically, patients were included in the study if all of the following criteria were met: given written informed consent; age ≥20 years at informed consent; planned to receive prasugrel for ≥12 months after PCI; met at least one of the following criteria and were not considered appropriate for long-term combination treatment with aspirin[15–19] (peptic ulcer complication; history of bleeding [e.g., intracranial, lung bleeding, gastrointestinal bleeding, and fundus bleeding]; bleeding tendency [e.g., anemia or hemoglobin <11 g/dL before PCI]; impaired renal function [e.g., renal failure, renal dialysis, or estimated glomerular filtration rate <60 mL/min/1.73 m^2 before PCI]; requiring continuous nonsteroidal anti-inflammatory drugs [other than aspirin] after PCI; requiring continuous oral anticoagulants after PCI; age ≥75 years at informed consent; body weight ≤50 kg; and other bleeding risks as judged by the attending physician).

Patients were excluded if they met any of the following criteria: might require ≥6 months of DAPT because of high thrombotic risk; with a current bleeding event (e.g., hemophilia, intracranial hemorrhage, gastrointestinal hemorrhage, urinary tract hemorrhage, hemoptysis, and vitreous hemorrhage); with a PCI lesion at the venous graft; participating or planning to participate in other clinical studies before the completion of the follow-up period of this study; and participating in the PENDULUM registry (UMIN000020332).

Among the enrolled patients, those who received prasugrel within 1 day after PCI were analyzed. Moreover, for the duration of the study, patients who were not considered appropriate for continued treatment with prasugrel alone were allowed to change to other antiplatelet treatments as judged by the attending physician.

The approved dosages of aspirin and prasugrel in Japan are as follows: aspirin 100 mg administered once daily, and

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Figure 1. Patient disposition. [a]Includes 33 patients who died. [b]Some patients met more than 1 exclusion criteria. DES, drug-eluting stent; PCI, percutaneous coronary intervention.
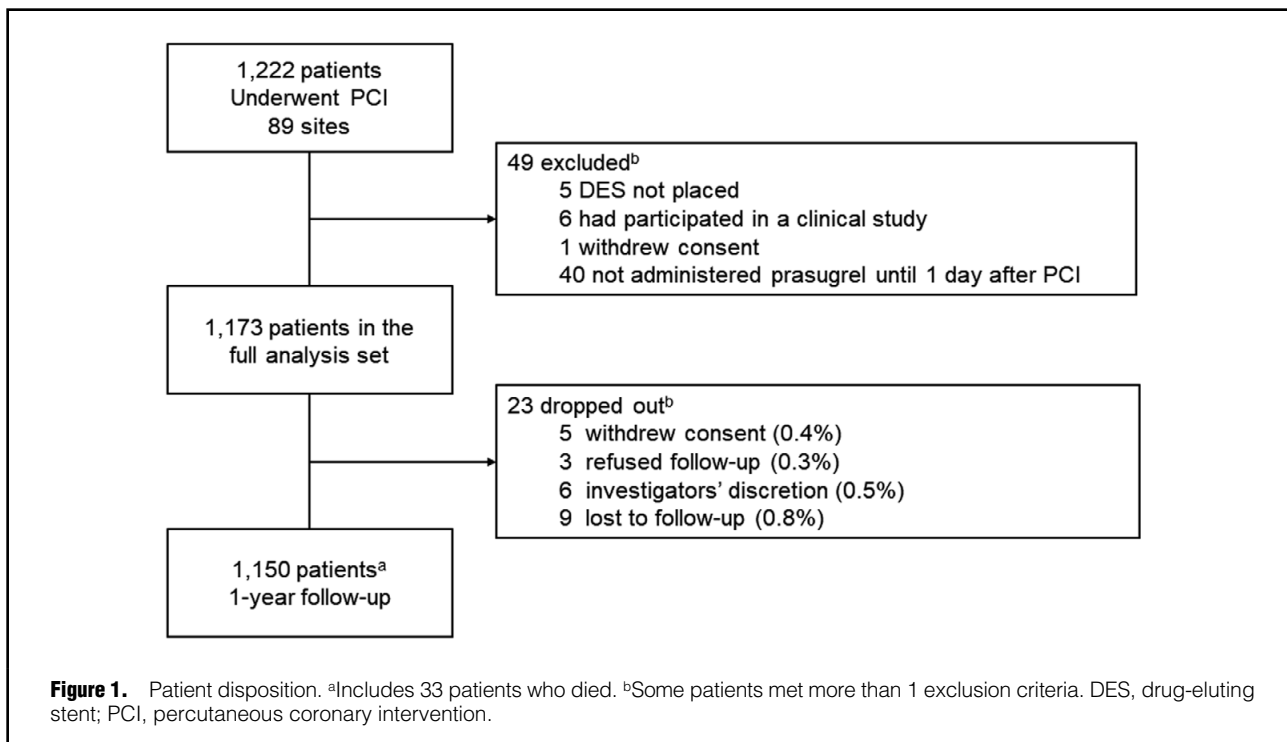
the dose can be increased up to 300 mg once daily; prasugrel 20 mg administered once as a loading dose, followed by 3.75 mg once daily as the maintenance dose. As the risk of bleeding may increase in patients with low body weight (≤50 kg), the maintenance dose of prasugrel can be reduced to 2.5 mg once daily, if necessary.

Outcomes

The primary endpoint was the cumulative incidence of clinically relevant bleeding (CRB: Bleeding Academic Research Consortium [BARC] types 2, 3, and 5)[20] from 1 to 12 months after PCI (time point A). The secondary endpoints were the cumulative incidence of CRB from PCI to 12 months (time point B); the cumulative incidence of major bleeding events, defined as BARC types 3 and 5, from 1 month to 12 months after PCI and from PCI to 12 months; cumulative incidence of major adverse cardiac and cerebrovascular events (MACCE: all-cause death, non-fatal myocardial infarction [MI], non-fatal stroke, and stent thrombosis [ST]) and thrombotic events (all-cause death, cardiovascular death, non-fatal MI, non-fatal stroke, non-fatal cerebral infarction, revascularization, transient ischemic attack, and ST) recorded at time points A and B; and the event rate of each bleeding event (each BARC criterion and Thrombolysis in Myocardial Infarction [TIMI] major/minor bleeding criterion) recorded at time points A and B.

Sample Size

This prospective cohort sample size was planned as follows: the cumulative incidence of CRB (BARC types 2, 3, and 5) from 1 to 12 months after PCI was assumed to be 4%, based on the results of a previous clinical trial,[21] and considering the bleeding risk in Japanese PCI patients,[22] it was estimated that 1,025 cases would be required to have an accuracy within ±1.2% of the 95% confidence interval

(CI) of cumulative incidence. Assuming a dropout rate of about 10% in this study, we estimated the sample size to be 1,100 patients.

Statistical Analysis

Descriptive statistics were used for baseline demographic and clinical characteristics, with n (%) for categorical variables and mean±standard deviation for continuous variables. For time to event outcomes, the cumulative incidence and 95% CIs at 12 months were calculated from 1 month after PCI by the Kaplan-Meier method. For a landmark analysis from 1 to 12 months, patients whose events occurred during the period from PCI to 1 month after PCI were treated as dropouts. The stratification for ARC-HBR criteria was conducted in accordance with the literature previously reported by Nakamura et al.[14] Hazard ratios (HR) and 95% CIs were calculated by Cox regression model. For multivariate analysis, variables were selected based on prior studies and clinical importance; sex, body weight (≤/>50 kg), diabetes mellitus, acute coronary syndrome (ACS), and ARC-HBR score (calculated as 1 point for ARC-HBR major criterion and 0.5 point for ARC-HBR minor criterion) were used as covariates for CRB; age (</≥75 years), diabetes mellitus, cigarette smoking, prior PCI or coronary artery bypass graft, ACS, and estimated glomerular filtration rate (</≥30 mL/min/1.73 m^2) were used as covariates for MACCE. In the subgroup analysis, patients were stratified and the frequency of CRB and MACCE from 1 to 12 months after PCI was analyzed. The factors used for stratification were ARC-HBR criteria and other clinically important factors such as heart failure, low body weight, and history of peripheral artery disease (PAD), puncture site, sex, and ACS. The clinically important factors were selected with reference to the Japanese guideline.[23] The software used for the statistical analysis was SAS Release 9.4 (SAS Institute, Cary, NC, USA).

Table 1. Patient Baseline Demographic and Clinical Characteristics

	Total (n=1,173)
Age, years	76.3±8.7
≥75	801 (68.3)
Sex, male	825 (70.3)
Body weight, kg	59.9±11.5
≤50	248 (21.1)
Body mass index, kg/m²	23.6±3.6
Hypertension	989 (84.3)
Hyperlipidemia	876 (74.7)
Diabetes mellitus	460 (39.2)
Cigarette smoking, current	168 (14.3)
Congestive heart failure	177 (15.1)
Peripheral artery disease	53 (4.5)
Atrial fibrillation	197 (16.8)
Malignancy	86 (7.3)
History of MI	207 (17.6)
History of PCI	436 (37.2)
History of CABG	37 (3.2)
History of ischemic stroke	114 (9.7)
History of transient ischemic attack	17 (1.4)
History of cerebral hemorrhage	33 (2.8)
History of gastrointestinal bleeding	77 (6.6)
ARC-HBR score	1.47±0.86
≥1	923 (78.7)
Clinical presentation	
Non-ACS	792 (67.5)
ACS	381 (32.5)
Unstable angina	134 (11.4)
Non-STEMI	87 (7.4)
STEMI	160 (13.6)
Baseline laboratory parameters	
Hemoglobin, g/dL	n=1,145
Mean±SD	12.8±1.8
<11	190 (16.2)
Male: ≥11 to <13	
Female: ≥11 to <12	329 (28.0)
eGFR, mL/min/1.73m²	n=1,157
Mean±SD	54.1±20.8
<30	128 (10.9)
≥30 to <60	586 (50.0)
White blood cell count, ×10³/μL	n=1,145
Mean±SD	6.50±2.16
Platelet count, ×10⁴/μL	n=1,145
Mean±SD	20.7±6.5
<10	23 (2.0)
Angiographic features	
No. of diseased vessels	
1	655 (55.8)
2	333 (28.4)
3	162 (13.8)
Left main coronary trunk	42 (3.6)
Procedural data	
Puncture site	
Femoral	202 (17.2)
Brachial	33 (2.8)
Radial	938 (80.0)

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

	Total (n=1,173)
Imaging guidance	
IVUS or OCT/OFDI	1,127 (96.1)
Complex PCI	
All	231 (19.7)
≥3 stents	64 (5.5)
No. of treated lesions ≥3	91 (7.8)
Bifurcation with 2 stents	17 (1.4)
Total stent length >60mm	122 (10.4)
Chronic total occlusion lesion	81 (6.9)
Medication status at discharge	
Prasugrel	1,169 (99.7)
3.75mg	1,112 (94.8)
2.5mg	55 (4.7)
Clopidogrel	0 (0.0)
Aspirin	1,103 (94.0)
Anticoagulant	257 (21.9)
DOAC	204 (17.4)
Warfarin	53 (4.5)
Proton-pump inhibitor	1,036 (88.3)
NSAIDs except aspirin	75 (6.4)
Steroids	41 (3.5)

Data are presented as n (%) or mean±SD. ACS, acute coronary syndrome; ARC, Academic Research Consortium; CABG, coronary artery bypass graft; DOAC, direct oral anticoagulant; eGFR, estimated glomerular filtration rate; HBR, high bleeding risk; IVUS, intravascular ultrasound; MI, myocardial infarction; NSAIDs, nonsteroidal anti-inflammatory drugs; OCT, optical coherence tomography; OFDI, Optical frequency domain imaging; PCI, percutaneous coronary intervention; SD, standard deviation; STEMI, ST elevation myocardial infarction.
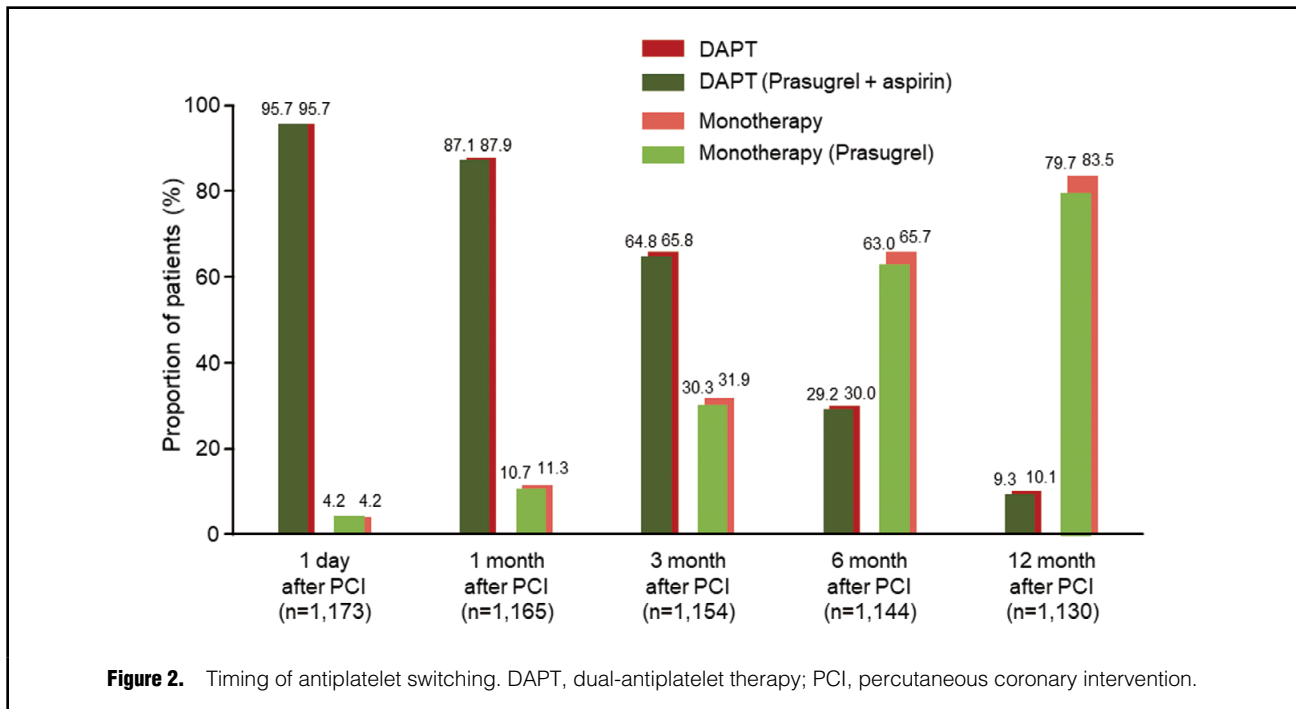
Results

Patients

A total of 1,222 patients were enrolled in our study (**Figure 1**). Of them, 49 were excluded for the following reasons: DES not placed (n=5), had participated in a clinical study (n=6), withdrew consent (n=1), and not administered prasugrel until 1 day after PCI (n=40); thus, 1,173 patients were evaluated. A total of 1,150 (98.0%) patients were evaluated for the 12-month follow-up analysis. The mean follow-up duration was 13.2±4.9 months.

Patient baseline demographic and clinical characteristics are shown in **Table 1**. Mean age was 76.3 years, 825 (70.3%) patients were male, and 381 (32.5%) had ACS. The proportions of patients with atrial fibrillation and congestive heart failure were 16.8% and 15.1%, respectively. The proportion of patients who received nonsteroidal anti-inflammatory drugs or steroids was 8.7%. The majority of patients (923 [78.7%]) met the ARC-HBR criteria. The prevalence of each ARC-HBR criterion is shown in **Supplementary Table 1**.

Status of Antiplatelet Therapy at 12 Months

The proportions of patients who switched to SAPT were 4.2% at 1 day, 11.3% at 1 month, 31.9% at 3 months, 65.7% at 6 months, and 83.5% at 12 months after PCI (**Figure 2**). Monotherapy at 12 months after PCI was mainly prasugrel (79.7%). The remaining patients were treated with aspirin (2.9%) or clopidogrel (0.8%) (**Supplementary Table 2**).

Figure 2. Timing of antiplatelet switching. DAPT, dual-antiplatelet therapy; PCI, percutaneous coronary intervention.

Outcomes

The cumulative incidence of CRB (BARC types 2, 3, and 5) from 1 to 12 months after PCI (primary endpoint) was 3.2% (95% CI, 2.3–4.5) (**Figure 3A**). The cumulative incidence of CRB from PCI to 12 months was 4.4% (95% CI, 3.3–5.8) (**Figure 3A**). The cumulative incidence of major bleeding events (BARC types 3 and 5) was 2.6% (95% CI, 1.8–3.8) from 1 to 12 months after PCI (**Figure 3A**), and 3.3% (95% CI, 2.4–4.6) from PCI to 12 months.

The cumulative incidence of MACCE was 3.8% (95% CI, 2.9–5.2) from 1 to 12 months after PCI (**Figure 3B**), and 4.8% (95% CI, 3.7–6.3) from PCI to 12 months. The event rate breakdown for the components of MACCE was as follows: all-cause death at 2.5%, non-fatal MI at 0.4%, and non-fatal stroke at 0.9%. To date, no cases of ST have been documented. **Table 2** shows bleeding event rates from 1 to 12 months after PCI and 12 months after PCI.

Multivariate Analysis The results of multiple Cox regression analysis for CRB and MACCE from 1 to 12 months after PCI are shown in **Table 3** and **Table 4**. The ARC-HBR score was independently associated with CRB, while ACS and severe chronic kidney disease (CKD) were significantly associated with MACCE.

Risk of CRB in Patients With ARC-HBR The cumulative incidence of CRB (BARC types 2, 3, and 5) from 1 to 12 months after PCI was numerically higher in ARC-HBR patients than non-ARC-HBR patients (3.7% vs. 1.5%; HR, 2.88 [95% CI, 0.88–9.41]; P=0.081) (**Supplementary Figure**).

Subgroup Analysis Patients were stratified into prespecified subgroups and the HRs for the CRB and MACCE are shown in **Figure 4**. Anticoagulant use at discharge and history of gastrointestinal bleeding were significantly associated with CRB, and malignancy, history of PAD, and ACS were significantly associated with MACCE. Severe CKD, severe anemia, and heart failure were significantly associated with both CRB and MACCE. Event rates of CRB and MACCE stratified by risk factors are shown in

Supplementary Table 3. Among patients receiving anticoagulants at discharge, the event rates of CRB and MACCE from 1 to 12 months after PCI were 5.1% (13/253) and 4.7% (12/254), respectively.

Discussion

This is the first prospective study to investigate bleeding and ischemic events in HBR Japanese patients, of whom approximately 80% fulfilled the ARC-HBR criteria and were treated with prasugrel monotherapy following a relatively short administration of DAPT after PCI. Of note, a high proportion of patients received monotherapy with prasugrel (79.7%) at 12 months after PCI. The main findings of this study were: (1) BARC type 2, 3, or 5 bleeding occurred in 3.2% of patients between 1 and 12 months after PCI; (2) MACCE occurred in 3.8% but no cases of ST were observed; (3) multivariate analysis showed that the ARC-HBR score was independently associated with CRB, and the subgroup analysis revealed that severe anemia, severe CKD, and heart failure were significantly associated with both ischemic and bleeding events, and anticoagulant use and history of gastrointestinal bleeding were significantly associated with CRB in this cohort.

Patients enrolled in this study were not considered well suited for long-term administration of aspirin as per their HBR status. Although the study protocol for this study was developed prior to the simultaneous release of the ARC-HBR criteria for Europe and the USA, the inclusion criteria for this study were similar to the ARC-HBR criteria.[13] Of note, approximately 80% of patients in this cohort fulfilled the ARC-HBR criteria. Although patients in this cohort were unsuitable for treatment with aspirin, many patients in the HBR category may be good candidates for monotherapy with P2Y12 inhibitors. The applicability of the ARC-HBR criteria to Japanese patients was confirmed by Natsuaki et al;[24] however, their reported analysis is
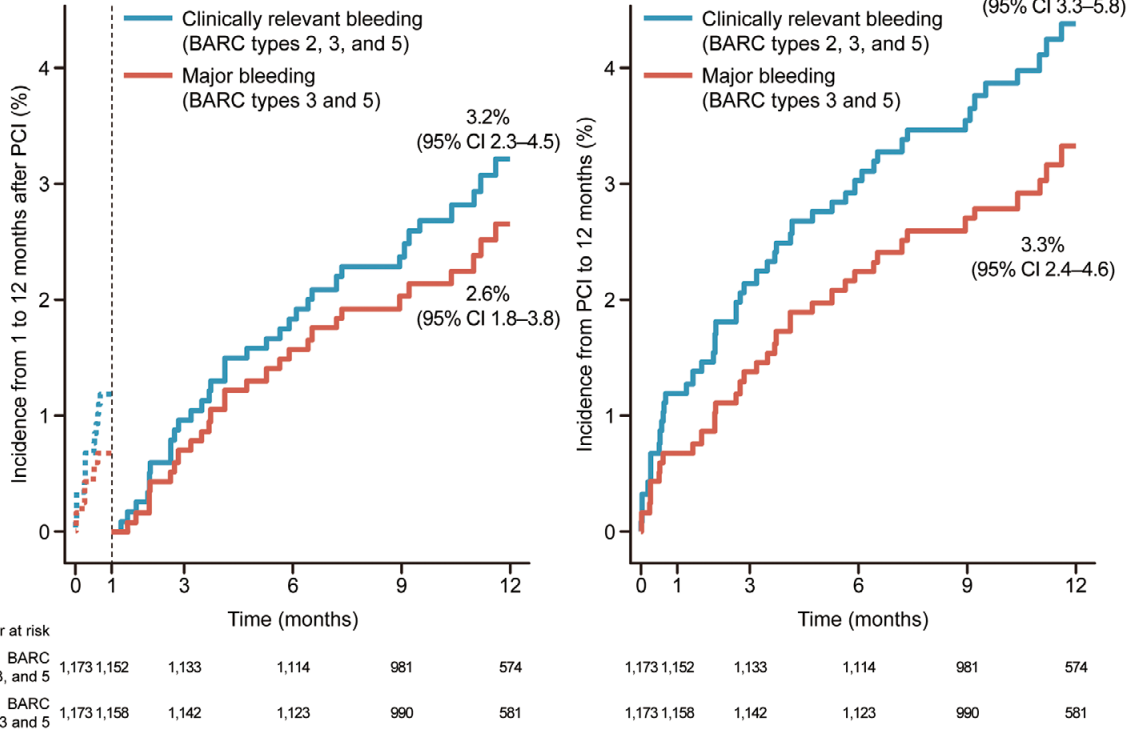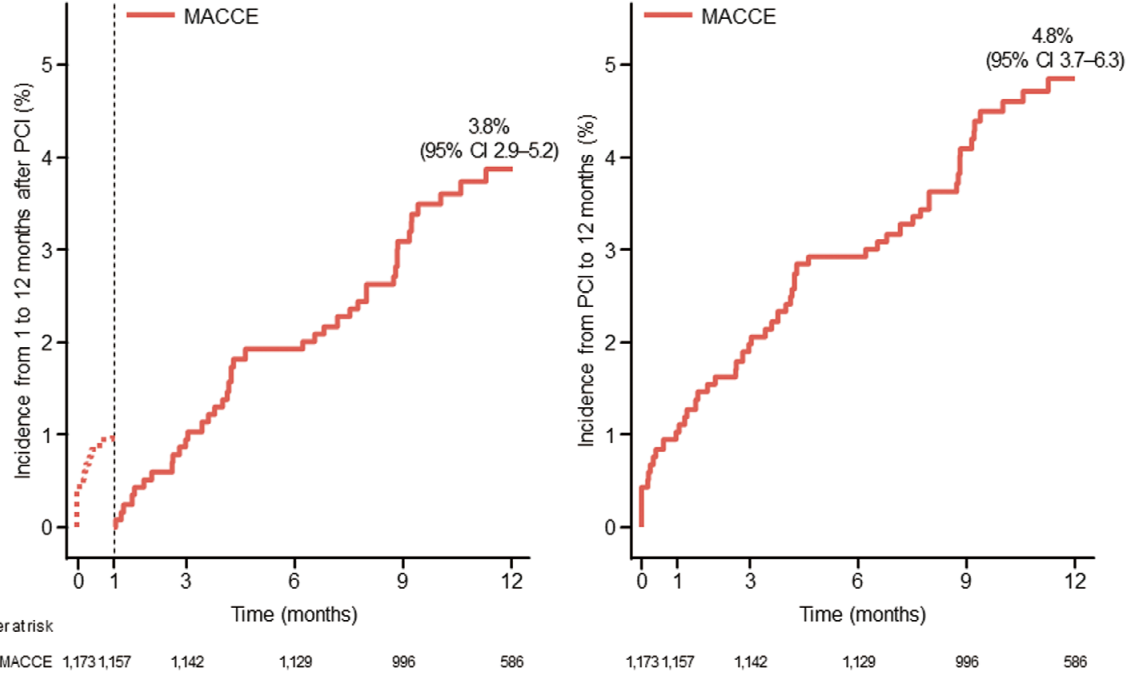
Figure 3. (**A**) Time to event and event rate Kaplan-Meier curves of clinically relevant bleeding (BARC types 2, 3, and 5) and major bleeding (BARC types 3 and 5) from 1 to 12 months after PCI (**Left**) and from PCI to 12 months (**Right**). (**B**) Time to event and event rate Kaplan-Meier curves of MACCE (all-cause death, non-fatal MI, non-fatal stroke, and stent thrombosis) from 1 month to 12 months after PCI (**Left**) and from PCI to 12 months (**Right**). BARC, Bleeding Academic Research Consortium; CI, confidence interval; MACCE, major adverse cardiac and cerebrovascular events; PCI, percutaneous coronary intervention.

Table 2. Bleeding Event Rates From 1 to 12 Months After PCI and 12 Months After PCI

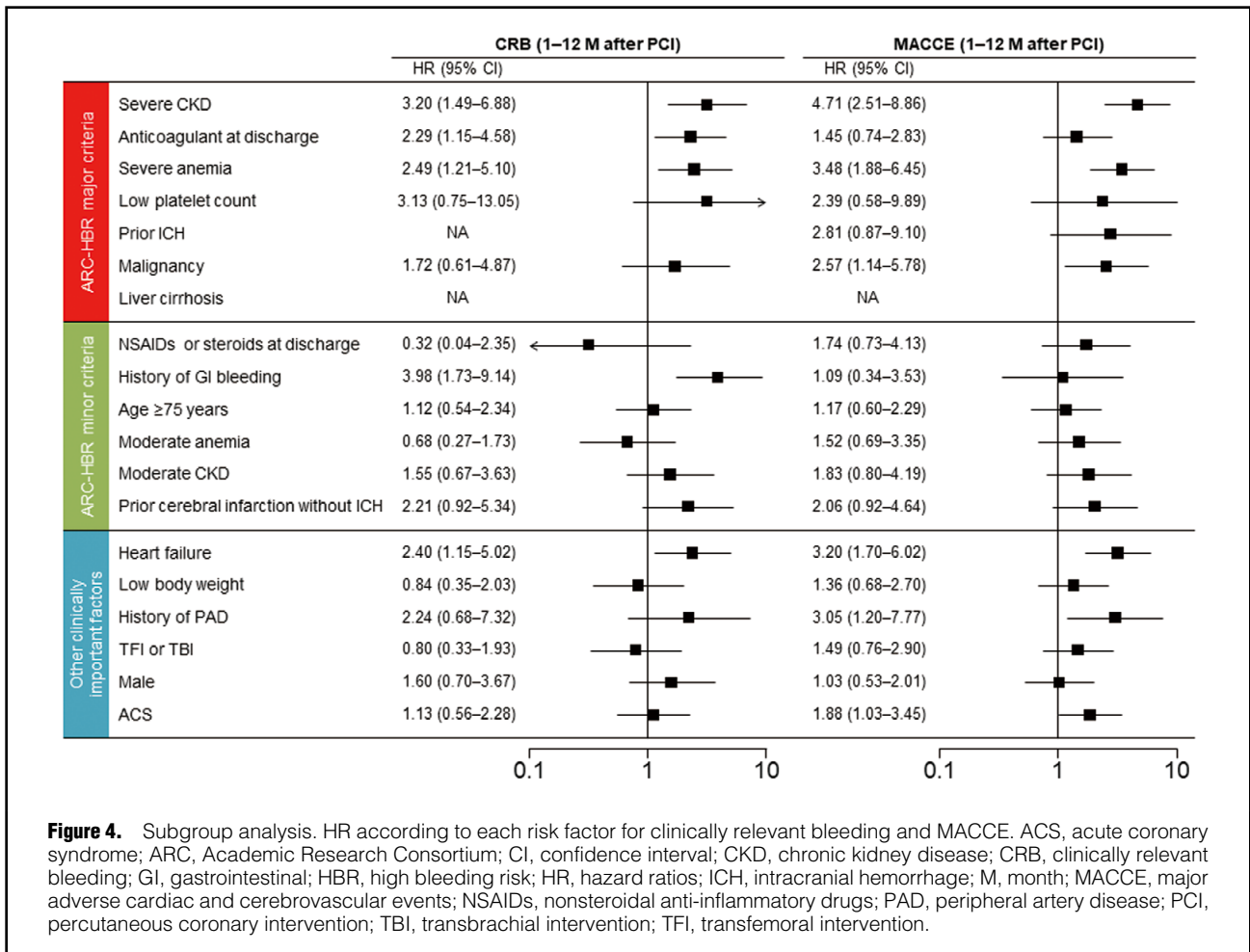|	Event rate (n=1,173)	
	1–12 months (Primary)	12 months after PCI
Clinically relevant bleeding (BARC types 2, 3, and 5)	34 (3.0)	48 (4.1)
Major bleeding (BARC types 3 and 5)	28 (2.4)	36 (3.1)
All bleeding events (BARC types 1–5)	61 (5.4)	99 (8.4)
BARC 1	30 (2.6)	56 (4.8)
BARC 2	6 (0.5)	12 (1.0)
BARC 3	26 (2.2)	33 (2.8)
BARC 4	0 (0.0)	0 (0.0)
BARC 5	2 (0.2)	3 (0.3)
TIMI major bleeding	20 (1.7)	25 (2.1)
TIMI minor bleeding	8 (0.7)	11 (0.9)
MACCE[a]	42 (3.6)	54 (4.6)
All-cause death	29 (2.5)	33 (2.8)
Cardiovascular death	18 (1.5)	21 (1.8)
Non-fatal MI	5 (0.4)	9 (0.8)
Non-fatal stroke	11 (0.9)	16 (1.4)
Non-fatal ischemic stroke	8 (0.7)	12 (1.0)
Stent thrombosis	0 (0.0)	0 (0.0)
NACE[b]	64 (5.6)	83 (7.1)
Revascularization	53 (4.6)	54 (4.6)
Peripheral artery occlusion	2 (0.2)	2 (0.2)

Data are presented as n (%). [a]Composite of all-cause death, non-fatal MI, non-fatal stroke, and stent thrombosis. [b]Composite of MACCE and major bleeding (BARC types 3 and 5). BARC, Bleeding Academic Research Consortium; MACCE, major adverse cardiac and cerebrovascular events; MI, myocardial infarction; NACE, net adverse clinical events; PCI, percutaneous coronary intervention; TIMI, Thrombolysis in Myocardial Infarction.

Table 3. Multivariate Regression Analysis of Clinically Relevant Bleeding From 1 to 12 Months After PCI

Variable	Events (%)	Multivariate	
		HR	95% CI
Sex: male	27 (3.3) vs. 7 (2.1)	1.43	0.58–3.50
Body weight, kg: ≤50	6 (2.5) vs. 28 (3.1)	0.91	0.35–2.35
Diabetes mellitus	17 (3.7) vs. 17 (2.4)	1.41	0.71–2.80
ACS	12 (3.2) vs. 22 (2.8)	1.32	0.65–2.68
ARC-HBR score	NA	1.92	1.38–2.67

CI, confidence interval; HR, hazard ratio; NA, not applicable. Other abbreviations as in Table 1.

Table 4. Multivariate Regression Analysis of MACCE From 1 to 12 Months After PCI

Variable	Events (%)	Multivariate	
		HR	95% CI
Age, years: ≥75	30 (3.8) vs. 12 (3.2)	1.69	0.80–3.54
Diabetes mellitus	20 (4.4) vs. 22 (3.1)	1.15	0.60–2.18
Cigarette smoking	10 (4.5) vs. 30 (3.5)	1.35	0.63–2.92
History of PCI or CABG	15 (3.3) vs. 27 (3.9)	0.96	0.50–1.85
Acute coronary syndrome	20 (5.3) vs. 22 (2.8)	2.24	1.18–4.22
eGFR, mL/min/1.73 m^2: <30	15 (12.0) vs. 27 (2.7)	5.84	2.97–11.48

Abbreviations as in Tables 1 and 3.

Figure 4. Subgroup analysis. HR according to each risk factor for clinically relevant bleeding and MACCE. ACS, acute coronary syndrome; ARC, Academic Research Consortium; CI, confidence interval; CKD, chronic kidney disease; CRB, clinically relevant bleeding; GI, gastrointestinal; HBR, high bleeding risk; HR, hazard ratios; ICH, intracranial hemorrhage; M, month; MACCE, major adverse cardiac and cerebrovascular events; NSAIDs, nonsteroidal anti-inflammatory drugs; PAD, peripheral artery disease; PCI, percutaneous coronary intervention; TBI, transbrachial intervention; TFI, transfemoral intervention.

	CRB (1–12 M after PCI) HR (95% CI)	MACCE (1–12 M after PCI) HR (95% CI)
ARC-HBR major criteria		
Severe CKD	3.20 (1.49–6.88)	4.71 (2.51–8.86)
Anticoagulant at discharge	2.29 (1.15–4.58)	1.45 (0.74–2.83)
Severe anemia	2.49 (1.21–5.10)	3.48 (1.88–6.45)
Low platelet count	3.13 (0.75–13.05)	2.39 (0.58–9.89)
Prior ICH	NA	2.81 (0.87–9.10)
Malignancy	1.72 (0.61–4.87)	2.57 (1.14–5.78)
Liver cirrhosis	NA	NA
ARC-HBR minor criteria		
NSAIDs or steroids at discharge	0.32 (0.04–2.35)	1.74 (0.73–4.13)
History of GI bleeding	3.98 (1.73–9.14)	1.09 (0.34–3.53)
Age ≥75 years	1.12 (0.54–2.34)	1.17 (0.60–2.29)
Moderate anemia	0.68 (0.27–1.73)	1.52 (0.69–3.35)
Moderate CKD	1.55 (0.67–3.63)	1.83 (0.80–4.19)
Prior cerebral infarction without ICH	2.21 (0.92–5.34)	2.06 (0.92–4.64)
Other clinically important factors		
Heart failure	2.40 (1.15–5.02)	3.20 (1.70–6.02)
Low body weight	0.84 (0.35–2.03)	1.36 (0.68–2.70)
History of PAD	2.24 (0.68–7.32)	3.05 (1.20–7.77)
TFI or TBI	0.80 (0.33–1.93)	1.49 (0.76–2.90)
Male	1.60 (0.70–3.67)	1.03 (0.53–2.01)
ACS	1.13 (0.56–2.28)	1.88 (1.03–3.45)

limited by its retrospective study design. Therefore, this prospective study provides important information about the applicability of the HBR concept in Japan and enhances our knowledge about HBR in this patient population. Our results showed that the cumulative incidence of CRB (BARC types 2, 3, and 5) was 3.2% from 1 to 12 months after PCI in Japanese HBR patients who were treated with short-term DAPT and prasugrel monotherapy. Additionally, the incidence of BARC type 3 and 5 bleeding for 12 months after PCI was <4%, and the HBR group was not associated with statistically significantly higher CRB compared with non-HBR patients (3.7% vs. 1.5%, P=0.081). In part, these findings suggest the potential benefit of monotherapy after short-term DAPT in Japanese HBR patients. Further, the present results support the findings of a *post hoc* subgroup analysis of the STOPDAPT-2 trial,[25] which showed not only that very short (1 month) DAPT was associated with low bleeding risk for HBR patients, but that shorter DAPT may be beneficial for HBR patients.

The cumulative incidence of CRB of 3.2% in our study was slightly lower than expected. However, as we reported for the PENDULUM registry,[26] the incidence of bleeding events after PCI may be decreasing because of advances in treatment strategies, such as the use of proton-pump inhibitors and a radial approach during PCI. Indeed, when compared with the PENDULUM registry including HBR and non-HBR patients, there was no numerical difference in the incidence of BARC type 3 or 5 at 1 month after PCI (0.7%). Of note, there were no cases of ST during the study period. The potential explanation for the lower-than-expected incidence of ST with prasugrel monotherapy may be that most patients underwent intravascular ultrasound- or optical coherence tomography-guided PCI,[27,28] as this is common practice in Japan.

The observed incidence of major bleeding was 3.3% and that of MACCE was 4.8% from PCI to 12 months. Although a direct comparison of the present results with those of other studies is difficult, a real-world analysis by Ueki et al showed that in HBR patients, a combined device-oriented endpoint of cardiac death, target-vessel MI, and target lesion revascularization was 12.5% compared with 6.4% for major bleeding at 1 year.[29] In the CREDO-Kyoto registry cohort,[24] the incidence of ischemic events (death, MI, stroke) in HBR patients was 39.9% over 5 years and that of major bleeding was 18.9%. Cao et al recently reported that patients with HBR also experienced higher all-cause death (4.7% vs. 0.6%; P<0.001) and MI (4.2% vs. 2.0%; P<0.001) at 1 year compared with non-HBR patients.[30] Thus, compared with these previous reports, the ratio of MACCE to bleeding was likely to be lower in the present study, which suggests the efficacy of P2Y12 mono-therapy. Considering that the Japanese guidelines recommended SAPT with a P2Y12 inhibitor after short-term

DAPT for HBR patients, the present findings suggest that P2Y$_{12}$ monotherapy with prasugrel after short-term DAPT may be a suitable treatment option.[23]

Multivariate analysis revealed that the ARC-HBR score was an independent risk factor for CRB even in patients who received P2Y$_{12}$ inhibitor monotherapy. The Kaplan-Meier curve revealed that among patients who were unsuitable for long-term DAPT therapy, those with ARC-HBR had a higher risk of CRB (**Supplementary Figure**). Furthermore, subgroup analysis showed that among the ARC-HBR criteria, severe CKD, anticoagulant use at discharge, severe anemia, and history of gastrointestinal bleeding were significantly associated with CRB, and heart failure was also significantly associated with CRB as a non-ARC-HBR criterion. In addition, severe CKD and severe anemia were common risk factors for both CRB and MACCE. From the clinical point of view, the current findings may provide valuable information for determining the optimal duration of DAPT. Oral anticoagulant use and gastrointestinal bleeding were associated with bleeding events but not with MACCE. Therefore, special attention to bleeding may be required for patients receiving oral anticoagulants and with a history of gastrointestinal bleeding. Although that factor is an ARC-HBR major criterion, we have to consider that overlapping of the ARC-HBR categories independently enhanced the chance of bleeding. In the PENDULUM registry, many patients had overlapping ARC-HBR criteria. As more criteria were met, the risk of CRB also increased.[14] Similar trends were observed in the CREDO-Kyoto study, in which the 5-year incidence of the primary bleeding endpoint increased with increasing number of ARC-HBR criteria.[24] Conversely, in patients with ACS, prior PAD, and malignancy, it might be better to consider the balance between the risk and benefits of de-escalation of antiplatelet therapy. In addition, this study confirmed that severe CKD, severe anemia, and heart failure are associated with both ischemic and bleeding events, which is consistent with previous studies in which CKD, anemia, and heart failure, among other factors, were found to be common predictors of both thrombotic and bleeding events.[5,7,31] Based on current evidence, the presence of anemia is associated with increased adverse events, hospitalization rates, and death among patients with CKD and heart failure.[32–34] There is a complex interaction among the pathogenesis of these 3 disease states, and the most appropriate treatment regimens for these coexisting conditions remain to be defined. Thus, further study of the antiplatelet management in this subset of patients is warranted.

Study Limitations
First, because this was a single-arm study, it is difficult to state the superiority of this strategy compared with long-term DAPT. However, in general, shorter DAPT is a more promising strategy for PCI patients with HBR. Second, all patients were Japanese and the proportion of patients with ACS was relatively low, which means generalizability of our findings beyond East Asia is unclear. Third, because of the nature of the observational study design, the findings should be interpreted with caution. Additionally, selection bias was inevitable. Fourth, monotherapy was limited to prasugrel. Whether studies of other antiplatelet agents, such as clopidogrel and ticagrelor, will replicate the findings, or whether prasugrel is the best option for SAPT remains unclear. However, the data obtained in the present study is the first large-scale data set for patients treated with prasugrel as SAPT, and may provide important clinical insights. Finally, enrolled patients were characterized by not being suitable for treatment with aspirin, which reflects HBR, but it is unclear if this finding could be generalized in all patients classified as having HBR.

In conclusion, the cumulative incidence of CRB after the periprocedural period (1–12 months after PCI) was 3.2% in Japanese patients who were not considered appropriate for long-term combination treatment with aspirin because of their HBR status and who were scheduled to receive SAPT with prasugrel. The cumulative incidence of MACCE was 3.8%. A total of 721 (63.0%) and 901 (79.7%) patients received SAPT with prasugrel at 6 and 12 months after PCI, respectively, and in these patients, no cases of ST occurred. SAPT might be a suitable alternative to DAPT after PCI.

Data Availability
The deidentified participant data and the study protocol will be shared on a request basis for up to 36 months after the publication of this article. Researchers who make the request should include a methodologically sound proposal on how the data will be used; the proposal may be reviewed by the responsible personnel at Daiichi Sankyo Co. Ltd., and the data requestors will need to sign a data access agreement. Please directly contact the corresponding author to request data sharing.

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IRB Information
The study protocol and associated documents were approved by the Ethics Committee at Toho University Ohashi Medical Center on 31 May 2017 (reference code: H17006).

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Supplementary Files