Journal of the American Heart Association

ORIGINAL RESEARCH

Relationship Between Platelet Reactivity and Ischemic and Bleeding Events After Percutaneous Coronary Intervention in East Asian Patients: 1-Year Results of the PENDULUM Registry

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BACKGROUND: The balance between ischemic and bleeding events and their association with platelet reactivity in patients receiving antiplatelet therapy after percutaneous coronary intervention (PCI), which differs among regions, is not fully evaluated for East Asians. We examined ischemic/bleeding events and platelet reactivity in Japanese patients undergoing PCI and determined associations between high/low platelet reactivity and clinical outcomes.

METHODS AND RESULTS: PENDULUM (Platelet Reactivity in Patients with Drug Eluting Stent and Balancing Risk of Bleeding and Ischemic Event) is a prospective, multicenter registry of Japanese patients with PCI. Primary end points were incidence of first major adverse cardiac and cerebrovascular events (MACCE) and first major bleeding events at 12 months post-PCI. Platelet reactivity ($P2Y_{12}$ reaction unit [PRU] value) was measured at 12 to 48 hours post-PCI; patients were grouped as having high PRU (>208), optimal PRU (>85 to ≤208), and low PRU (≤85). MACCE and major bleeding occurred in 4.4% and 2.8% of 6267 patients, respectively. The mean±SD PRU value was 182.1±77.1. MACCE was significantly higher in the high PRU (5.7%; n=2227) versus the optimal PRU group (3.6%; n=3002). The hazard ratio (HR) for high PRU versus optimal PRU level was significantly higher for MACCE (adjusted HR, 1.53; 95% CI, 1.14–2.06 [*P*=0.004]); stent thrombosis followed the same trend. Incidence of major bleeding did not differ significantly between groups. A high PRU level was significantly associated with MACCE in both patients with and patients without acute coronary syndrome.

CONCLUSIONS: These real-world data suggest an association between high platelet reactivity and cardiovascular events in Japanese patients undergoing PCI. The trend was the same in both patients with and patients without acute coronary syndrome.

REGISTRATION: URL: https://www.umin.ac.jp/ctr. Unique identifier: UMIN 000020332.

Key Words: antiplatelet therapy ■ bleeding ■ ischemic ■ $P2Y_{12}$ ■ percutaneous coronary intervention

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Supplementary Materials for this article are available at https://www.ahajournals.org/doi/suppl/10.1161/JAHA.119.015439

*A complete list of the PENDULUM Registry Investigators can be found in Appendix S1.

For Sources of Funding and Disclosures see page 12.

JAHA is available at: www.ahajournals.org/journal/jaha

CLINICAL PERSPECTIVE

What Is New?

- Data regarding the relationship between the clinical events after percutaneous coronary intervention and platelet reactivity have been reported for non–East Asian patients but not for East Asian patients.
- To date, this is the largest registry to elucidate the role of high platelet reactivity for patients with acute coronary syndrome and stable coronary artery disease.

What Are the Clinical Implications?

- These real-world data demonstrating the association of high platelet reactivity with ischemic events in Japanese patients undergoing percutaneous coronary intervention will aid in the management of antiplatelet treatment in the East Asian population.

Nonstandard Abbreviations and Acronyms

ACS	acute coronary syndrome
ADAPT-DES	Assessment of Dual Antiplatelet Therapy With Drug Eluting Stents
BARC	Bleeding Academic Research Consortium
DES	drug-eluting stent
HPR	high $P2Y_{12}$ reaction unit
HR	hazard ratio
LPR	low $P2Y_{12}$ reaction unit
MACCE	major adverse cardiac and cerebrovascular events
MI	myocardial infarction
OPR	optimal $P2Y_{12}$ reaction unit
PARIS	Patterns of Non-adherence to Antiplatelet Regimens in Stented Patients
PCI	percutaneous coronary intervention
PENDULUM	Platelet Reactivity in Patients with Drug Eluting Stent and Balancing Risk of Bleeding and Ischemic Event
PHILO	Phase the International Study of Ticagrelor and Clinical Outcomes in Asian ACS Patients
PRU	$P2Y_{12}$ reaction unit
PLATO	Study of Platelet Inhibition and Patient Outcomes
SENIOR	Synergy II Everolimus Eluting Stent in Patients Older Than 75 Years Undergoing Coronary Revascularisation Associated With a Short Dual Antiplatelet Therapy
ST	stent thrombosis
UMIN	University hospital Medical Information Network

High platelet reactivity after percutaneous coronary intervention (PCI) has been reported to be significantly associated with ischemic complications. In addition, low platelet reactivity has been reported to be associated with bleeding complications. It has been shown that the balance between the incidence of ischemic and bleeding complications after PCI is a critical factor in deciding optimal antiplatelet treatment.[1–4]

In recently published consensus documents, the possibility of a differential ischemic/bleeding tradeoff in East Asians and non–East Asians was highlighted.[5,6] However, there are not enough data from East Asian patients regarding ischemic/bleeding events and their association with platelet reactivity after PCI in daily practice. This study aimed to examine the most recent available data of ischemic/bleeding events and platelet reactivity in Japanese patients undergoing PCI, and to elucidate the association between high and low platelet reactivity, compared with optimal platelet reactivity, and clinical outcomes.

METHODS

Data Sharing Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Study Design, Setting, and Participants

The PENDULUM (Platelet Reactivity in Patients with Drug Eluting Stent and Balancing Risk of Bleeding and Ischemic Event) registry was a prospective, multicenter study of Japanese patients who underwent PCI. The enrollment of patients was conducted in 67 institutions nationwide between December 2015 and June 2017. Patients were aged 20 years and older, indicated for PCI with drug-eluting stents (DES), and administered antiplatelet drugs. Full inclusion and exclusion criteria are listed in Table S1.

The 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 Ethical Guidelines for Medical and Health Research Involving Human Subjects. Written informed consent was given by all patients before participation. This trial was registered in the University hospital Medical Information Network (UMIN) Clinical Trial Registry (UMIN 000020332).

Procedures

Dual antiplatelet therapy (DAPT) was based on the standard of care. Drug type, dosage, and treatment duration were selected at the discretion of the attending physician. The approved dosages of aspirin, clopidogrel, and prasugrel in Japan are as follows: aspirin, 100 mg is administered once daily and the dosage can be increased up to 300 mg once daily; clopidogrel, 300 mg is administered once as a loading dose on the treatment start day, followed by 75 mg once daily as a maintenance dosage; and prasugrel, 20 mg is administered once as a loading dose, followed by 3.75 mg once daily as a maintenance dosage. In Japan, both clopidogrel and prasugrel have been approved for the treatment of acute coronary syndrome (ACS) and stable angina, and in patients who previously experienced old myocardial infarction (MI) and were planning to undergo PCI. The standard duration of DAPT according to the Japanese treatment guidelines is a minimum of 6 months for patients without ACS and a minimum of 12 months for patients with ACS.[7,8]

Data were aggregated for a period up to 12 months after the index PCI procedure. Study outcomes were assessed at 30 days, 12 months, 24 months, and 30 months after the index PCI. Patients underwent follow-up as part of routine clinical practice. Patients were expected to visit the hospital whenever possible but could be questioned by telephone or letter if visits were difficult. The following data were collected: drug administration status (type [eg, antiplatelet, anticoagulant], dosage, administration period, and interruption period), thrombotic events, hemorrhagic events, and other adverse events. Reasons for treatment interruption or discontinuation were confirmed. Thrombotic and hemorrhagic events were evaluated by independent assessment committees.

End Points

Primary end points were the incidence of first major adverse cardiac and cerebrovascular events (MACCE; all-cause death, nonfatal MI, nonfatal stroke, and stent thrombosis [ST]) and first major bleeding (Bleeding Academic Research Consortium [BARC][9] type 3 and 5) 12 months after index PCI. Nonfatal MI was defined as a new acute MI or reinfarction after a diagnosis of index PCI following ischemic chest pain and the presence of a myocardial injury marker (myocardial prolapse enzyme: creatine phosphokinase, creatine kinase-MB, troponin T, or troponin I) or an ECG. Nonfatal stroke was defined as a new neurological sign or symptom with a responsible lesion confirmed by computed tomography or magnetic resonance imaging examination. Stroke was classified into ischemic stroke (cerebral infarction) and nonischemic stroke (eg, cerebral hemorrhage and subarachnoid hemorrhage). Ischemic stroke was defined as a new neurological sign or symptom with a new associated infarct that was confirmed by computed tomography or magnetic resonance imaging examination, regardless of whether neurological signs or symptoms persisted for more than 24 hours. ST was classified as definite, probable, or possible according to Academic Research Consortium definitions. Detailed definitions of efficacy events are listed in Data S1.

The main secondary end points were the incidence of each component of MACCE, cardiovascular death, target vessel revascularization, and bleeding events based on all categories of BARC criteria, and Thrombolysis in Myocardial Infarction criteria.[9,10]

Platelet reactivity was measured as $P2Y_{12}$ reaction unit (PRU) values using the VerifyNow system (Instrumentation Laboratory) and results were reported in PRU. The measurement between 12 and 48 hours after the index PCI was mandatory. Measurements immediately after PCI, 12 months after the index, and the earliest visit after ischemic/bleeding events were optional and collected whenever possible.

The relationship between platelet reactivity and each primary end point was examined. Patients were stratified into 3 groups, high PRU (HPR [high P2Y12 reaction unit]: >208), optimal PRU (OPR [optimal P2Y12 reaction unit]: >85 to ≤208), and low PRU (LPR [low P2Y12 reaction unit]: ≤85) based on the PRU values, according to the recent consensus document for platelet function and genetic testing to guide the use of $P2Y_{12}$ antagonists.[6]

Statistical Analysis

The required sample size for the registry was calculated based on both the incidence of MACCE and major bleeding at 12 months after index PCI. From the literature review, we found that the incidences of MACCE and major bleeding were 3%[11–18] and 4%,[19,20] respectively, in the Japanese population. Using this information, we set the incidence of the primary end points at 3%. We applied precision-based sample size calculation and the precision was set as ±0.5% within the range of the 95% CI. Allowing for a withdrawal rate of 10% during the first 12 months of the study, the required number of patients was calculated as 4969 (rounded up to 5000 patients).

The frequencies of patients experiencing any of the primary outcome events (each first event of MACCE and major bleeding events) for 12 months after the index PCI were calculated. To compare the 2 groups, the chi-square test or Fisher's test was used for binary variables, and the Student's *t* test was used for continuous variables. Kaplan–Meier curves were used to describe the incidences of events through to 12 months after the index PCI. If a patient had multiple events of the same outcome, the first event was selected as an end point. Patients who discontinued the study and those alive at the end of the observation period were handled as censored data. The 3 levels, HPR, OPR, and LPR, were used in Cox regression models to calculate the

hazard ratios (HRs), 95% CIs, and *P* values for clinical events; OPR was used as the reference level. For adjustment of covariates, the following clinically relevant factors were selected: sex, age, body weight, smoking, ACS/non-ACS, and a composite of prior MI, prior PCI, and prior coronary artery bypass graft surgery for MACCE, all-cause death, nonfatal MI, and nonfatal stroke; age, smoking, ACS/non-ACS, and a composite of prior MI, prior PCI, and prior coronary artery bypass graft surgery for ST; and sex, age, body weight, smoking, ACS/non-ACS, and a composite of history of cerebral hemorrhage and gastrointestinal hemorrhage for bleeding events. For the primary outcomes, summary statistics for PRU values at 12 to 48 hours after index PCI were calculated for patients with or without the events. Subgroup analyses for ACS and non-ACS, and $P2Y_{12}$ inhibitors were performed by analyzing each category separately. Statistical analyses were conducted using SAS release 9.4 (SAS Institute Inc). All tests were 2-sided with a 5% level of significance.

RESULTS

Between December 2015 and June 2017, 6422 patients were registered from 67 institutions. A total of 6267 patients were included in the full analysis set; 155 patients were excluded. Of the patients in the full analysis set, 6147 (98.1%) patients were evaluated for 1-year follow-up analysis (Figure 1).

Study Population

The mean age of patients was 70.0 years; 4909 (78.3%) were men and 2015 (32.2%) had ACS. Image-guided PCI was performed in 5918 patients (94.4%), a transradial approach was used in 4516 patients (72.1%), and a proton pump inhibitor was used at discharge in 5295 patients (84.5%) (Table 1). Antiplatelet therapy at discharge was aspirin in 6143 patients (98.0%), clopidogrel in 2213 patients (35.3%), and prasugrel in 3921 patients (62.6%). Baseline characteristics stratified by PRU level are also shown in Table 1.

Clinical Outcomes

At 1 year, the cumulative incidence of MACCE was 4.4% (95% CI, 3.9–5.0) and that of major bleeding was 2.8% (95% CI, 2.4–3.3) (Figure 2). The cumulative incidence of all-cause death, nonfatal MI, nonfatal stoke, and ST at 1 year was 2.7% (95% CI, 2.3–3.1), 1.0% (95% CI, 0.8–1.3), 0.9% (95% CI, 0.7–1.1), and 0.3% (95% CI, 0.2–0.5), respectively, and all bleeding was observed in 7.1% (95% CI, 6.5–7.8) of patients (Table S2).

Relationship Between Primary Outcomes and PRU

We obtained valid PRU measurements in 5906 (94.2%) patients at a mean time of 21.6±5.5 hours after index PCI (the distribution of PRU is shown in Figure 3 and measurement time is shown in Figure S1). The mean±SD

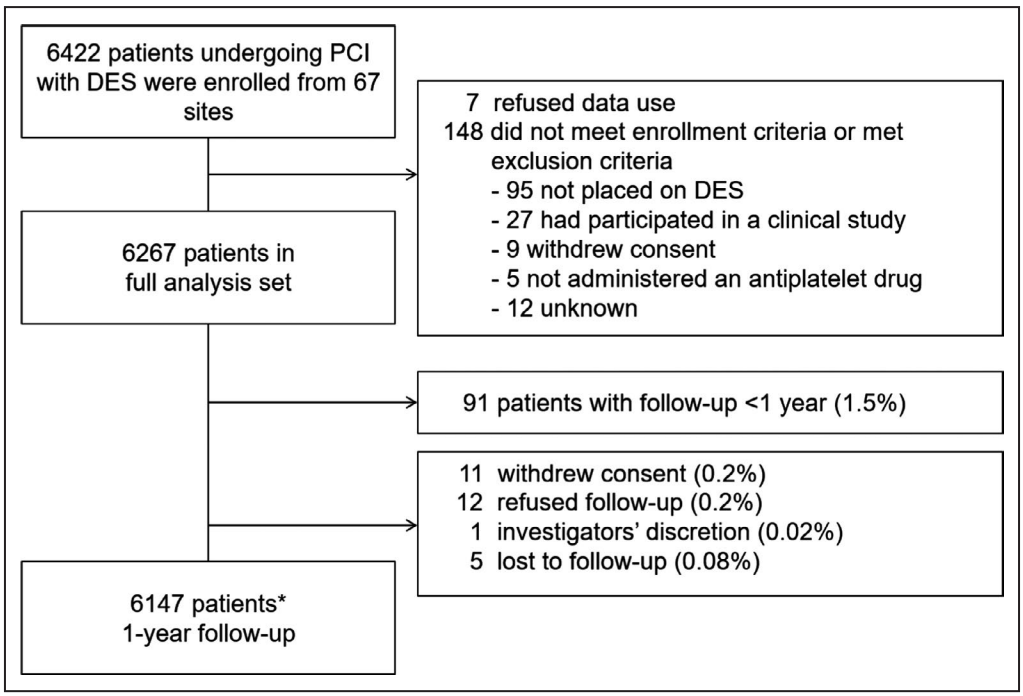

Figure 1. Patient flow diagram at 1-year follow-up.
*Includes 156 patients who died. DES indicates drug-eluting stent, and PCI, percutaneous coronary intervention.

Table 1. Baseline Patient Characteristics

	Total (N=6267)	LPR (n=677)	OPR (n=3002)	HPR (n=2227)
Age, y	70.0 (10.7)	68.5 (11.8)	69.1 (10.7)	71.8 (10.2)
≥75	2324 (37.1%)	227 (33.5%)	979 (32.6%)	989 (44.4%)
Men	4909 (78.3%)	528 (78.0%)	2451 (81.6%)	1650 (74.1%)
Body weight, kg	64.0 (12.6)	62.4 (12.7)	65.2 (12.7)	62.9 (12.3)
≤50 kg	794 (12.7%)	111 (16.4%)	314 (10.5%)	320 (14.4%)
Body mass index, kg/m^2	24.2 (3.6)	23.5 (3.5)	24.5 (3.6)	24.1 (3.6)
Hypertension	5186 (82.8%)	525 (77.5%)	2462 (82.0%)	1905 (85.5%)
Hyperlipidemia	4919 (78.5%)	503 (74.3%)	2340 (77.9%)	1795 (80.6%)
Diabetes mellitus	2767 (44.2%)	232 (34.3%)	1306 (43.5%)	1075 (48.3%)
Cigarette smoking, current	1327 (21.2%)	159 (23.5%)	667 (22.2%)	409 (18.4%)
Anemia	1161 (18.5%)	84 (12.4%)	360 (12.0%)	638 (28.6%)
Heart failure	850 (13.6%)	79 (11.7%)	353 (11.8%)	371 (16.7%)
Peripheral arterial disease	421 (6.7%)	35 (5.2%)	152 (5.1%)	212 (9.5%)
Atrial fibrillation	538 (8.6%)	55 (8.1%)	233 (7.8%)	227 (10.2%)
Malignancy	367 (5.9%)	39 (5.8%)	151 (5.0%)	160 (7.2%)
Previous MI	1575 (25.1%)	129 (19.1%)	750 (25.0%)	619 (27.8%)
Previous PCI	2567 (41.0%)	177 (26.1%)	1214 (40.4%)	1043 (46.8%)
Previous CABG	265 (4.2%)	33 (4.9%)	121 (4.0%)	100 (4.5%)
History of ischemic stroke	655 (10.5%)	51 (7.5%)	273 (9.1%)	302 (13.6%)
History of cerebral hemorrhage	124 (2.0%)	16 (2.4%)	48 (1.6%)	54 (2.4%)
History of renal insufficiency	1103 (17.6%)	78 (11.5%)	454 (15.1%)	500 (22.5%)
Clinical presentation				
Non-ACS	4252 (67.8%)	380 (56.1%)	2060 (68.6%)	1607 (72.2%)
ACS	2015 (32.2%)	297 (43.9%)	942 (31.4%)	620 (27.8%)
Unstable angina	790 (12.6%)	156 (23.0%)	354 (11.8%)	225 (10.1%)
Non-STEMI	323 (5.2%)	54 (8.0%)	146 (4.9%)	98 (4.4%)
STEMI	908 (14.5%)	90 (13.3%)	443 (14.8%)	298 (13.4%)
Baseline laboratory parameters				
Hemoglobin, g/dL	13.3 (2.0)	13.9 (2.5)	13.7 (1.8)	12.5 (1.9)
Creatinine clearance, mL/min	68.2 (35.5)	72.9 (42.6)	72.3 (34.7)	61.3 (33.0)
White blood cell count, ×10^3/μL	6.94 (2.82)	7.20 (4.21)	6.94 (2.52)	6.80 (2.59)
Angiographic features				
No. of diseased vessels				
1	3165 (50.5%)	345 (51.0%)	1539 (51.3%)	1097 (49.3%)
2	1865 (29.8%)	201 (29.7%)	889 (29.6%)	666 (29.9%)
3	1151 (18.4%)	122 (18.0%)	535 (17.8%)	429 (19.3%)
Left main disease	349 (5.6%)	36 (5.3%)	155 (5.2%)	143 (6.4%)
LVEF, %	56.7 (12.9)	55.7 (13.7)	56.6 (12.6)	57.3 (13.3)
Procedural data				
Puncture site				
Femoral access	1632 (26.0%)	142 (21.0%)	720 (24.0%)	659 (29.6%)
Brachial access	270 (4.3%)	25 (3.7%)	119 (4.0%)	109 (4.9%)
Radial access	4516 (72.1%)	525 (77.5%)	2233 (74.4%)	1514 (68.0%)
Imaging guided	5918 (94.4%)	639 (94.4%)	2848 (94.9%)	2095 (94.1%)
PCI for chronic total occlusion	429 (6.8%)	32 (4.7%)	221 (7.4%)	151 (6.8%)
Second-generation DES	6267 (100%)	677 (100%)	3002 (100%)	2227 (100%)

(*Continued*)

Table 1. Continued

	Total (N=6267)	LPR (n=677)	OPR (n=3002)	HPR (n=2227)
Medication status at discharge				
Aspirin	6143 (98.0%)	664 (98.1%)	2946 (98.1%)	2181 (97.9%)
$P2Y_{12}$ inhibitor	6195 (98.9%)	673 (99.4%)	2984 (99.4%)	2183 (98.0%)
PRU*	182.1 (77.1)			
Clopidogrel	2213 (35.3%)	95 (14.0%)	855 (28.5%)	1141 (51.2%)
PRU*	212.9 (71.1)			
Prasugrel	3921 (62.6%)	578 (85.4%)	2100 (70.0%)	1012 (45.4%)
PRU*	163.5 (74.5)			
DOAC	610 (9.7%)	59 (8.7%)	283 (9.4%)	250 (11.2%)
Proton pump inhibitor	5295 (84.5%)	574 (84.8%)	2504 (83.4%)	1910 (85.8%)
NSAIDs except aspirin	334 (5.3%)	38 (5.6%)	147 (4.9%)	131 (5.9%)
Steroids	250 (4.0%)	29 (4.3%)	117 (3.9%)	91 (4.1%)

Data are expressed as number of patients (percentage) or mean (SD). ACS indicates acute coronary syndrome; CABG, coronary artery bypass graft surgery; DES, drug-eluting stent; DOAC, direct oral anticoagulant; HPR, high $P2Y_{12}$ reaction unit; LPR, low $P2Y_{12}$ reaction unit; LVEF, left ventricular ejection fraction; MI, myocardial infarction; OPR, optimal $P2Y_{12}$ reaction unit; and STEMI, ST-segment–elevation myocardial infarction.

*The $P2Y_{12}$ reaction unit (PRU) of $P2Y_{12}$ inhibitor (n=5906), clopidogrel (n=2091), and prasugrel (n=3690) was measured at 12 to 48 hours after percutaneous coronary intervention (PCI).

PRU was 182.1±77.1, and the mean±SD PRU with clopidogrel and prasugrel treatment were 212.9±71.1 and 163.5±74.5, respectively. The numbers of patients in the HPR, OPR, and LPR groups were 2227 (37.7%), 3002 (50.8%), and 677 (11.5%), respectively (Table 1). The PRU value at 12 to 48 hours after index PCI was strongly associated with the incidence of MACCE at 1 year (3.0% for LPR, 3.6% for OPR, and 5.7% for HPR), with the incidence of MACCE in the HPR group being significantly higher than that in the OPR group (unadjusted HR, 1.55; 95% CI, 1.19–2.02 [*P*=0.001]) (Figure 4A and Table 2). In contrast, the PRU value at 12 to 48 hours after index PCI was not associated with the incidence of major bleeding at 1 year (Figure 4B).

Relationship Between PRU and Each Component of MACCE and All Bleeding

HPR was associated with a significantly higher incidence of each component of MACCE except for nonfatal stroke, and LPR was not associated with all bleeding events (Figures S2A through S2E). However, results from Kaplan–Meier curve of all bleeding showed numerically higher bleeding events immediately after index PCI for the LPR group.

Adjusted HPR and LPR Hazard Risk for Events

The risk of MACCE and ST was significantly higher in the group with HPR than in the OPR group even after adjusted analysis (adjusted HR for MACCE, 1.53; 95% CI, 1.14–2.06 [*P*=0.004]; adjusted HR for ST, 4.06; 95% CI, 1.27–13.00 [*P*=0.018]) (Table 2). In contrast, the risks of major bleeding and all bleeding events were not different between LPR and OPR in either unadjusted or adjusted analyses (adjusted HR for major bleeding, 1.26; 95% CI, 0.72–2.21 [*P*=0.417]; adjusted HR for all bleeding, 1.27; 95% CI, 0.90–1.80 [*P*=0.167]) (Table 2).

Subgroup Analysis of ACS and Non-ACS Groups

In the subgroup analysis, the respective 1-year cumulative incidences of MACCE and major bleeding were 5.5% (95% CI, 4.6–6.6) and 3.0% (95% CI, 2.3–3.9) in the ACS group, and 3.9% (95% CI, 3.4–4.6) and 2.7% (95% CI, 2.3–3.3) in the non-ACS group (Figure S3A and S3B). The PRU value at 12 to 48 hours after index PCI was strongly associated with the incidence of MACCE at 1 year in both the ACS (Figure 5A) and non-ACS groups (Figure 5B); the incidence of MACCE in the HPR group was significantly higher than that in the OPR group for patients in both the ACS and non-ACS groups (unadjusted HR, 1.61; 95% CI, 1.06–2.46 [*P*=0.027] in ACS; unadjusted HR, 1.55; 95% CI, 1.11–2.18 [*P*=0.011] in non-ACS) (Table 3). In contrast, the PRU value at 12 to 48 hours after index PCI was not associated with the incidence of major bleeding at 1 year (Figure 5B, Table 3). Even after adjustment, HPR was an independent risk factor for MACCE in both ACS (adjusted HR, 1.72; 95% CI, 1.05–2.82 [*P*=0.031]) and non-ACS (adjusted HR, 1.45; 95% CI, 1.00–2.09 [*P*=0.048]) groups (Table 3).

Subgroup Analysis of $P2Y_{12}$ Inhibitors

The cumulative incidence of MACCE in patients with HPR was significantly higher than that in patients with OPR, irrespective of the prescribed type of drug before adjustment (clopidogrel: unadjusted HR, 1.61

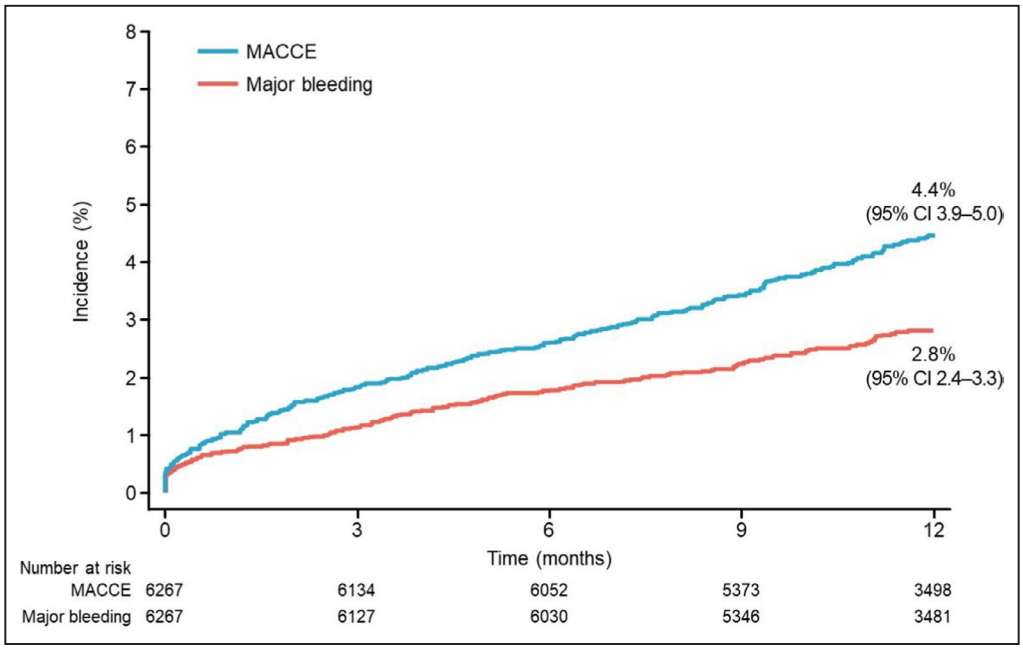

Figure 2. Time-to-event curves of major adverse cardiac and cerebrovascular events (MACCE) (all-cause death, nonfatal myocardial infarction [MI], nonfatal stroke, and stent thrombosis) and major bleeding from baseline to year 1.

[*P*=0.042]; prasugrel: unadjusted HR, 1.50 [*P*=0.028]). However, after adjustment, the trend remained significant only for the prasugrel subgroup (clopidogrel: adjusted HR, 1.50 [*P*=0.102]; prasugrel: adjusted HR, 1.54 [*P*=0.033]) (Figure S4A and S4B).

DISCUSSION

Our prospective study was the largest registry study to date to include PRU measurements of East Asian patients who underwent PCI. We found the following:

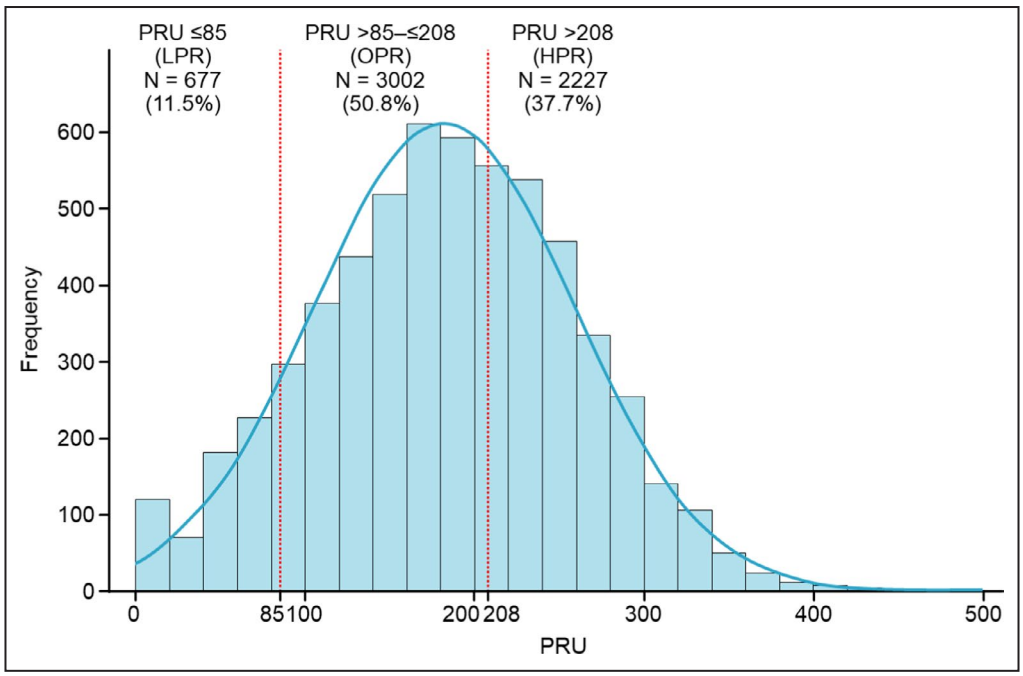

Figure 3. Distribution of $P2Y_{12}$ reaction unit (PRU) value at 12 to 48 hours after index percutaneous coronary intervention.
HPR indicates high $P2Y_{12}$ reaction unit; LPR, low $P2Y_{12}$ reaction unit; and OPR, optimal $P2Y_{12}$ reaction unit.

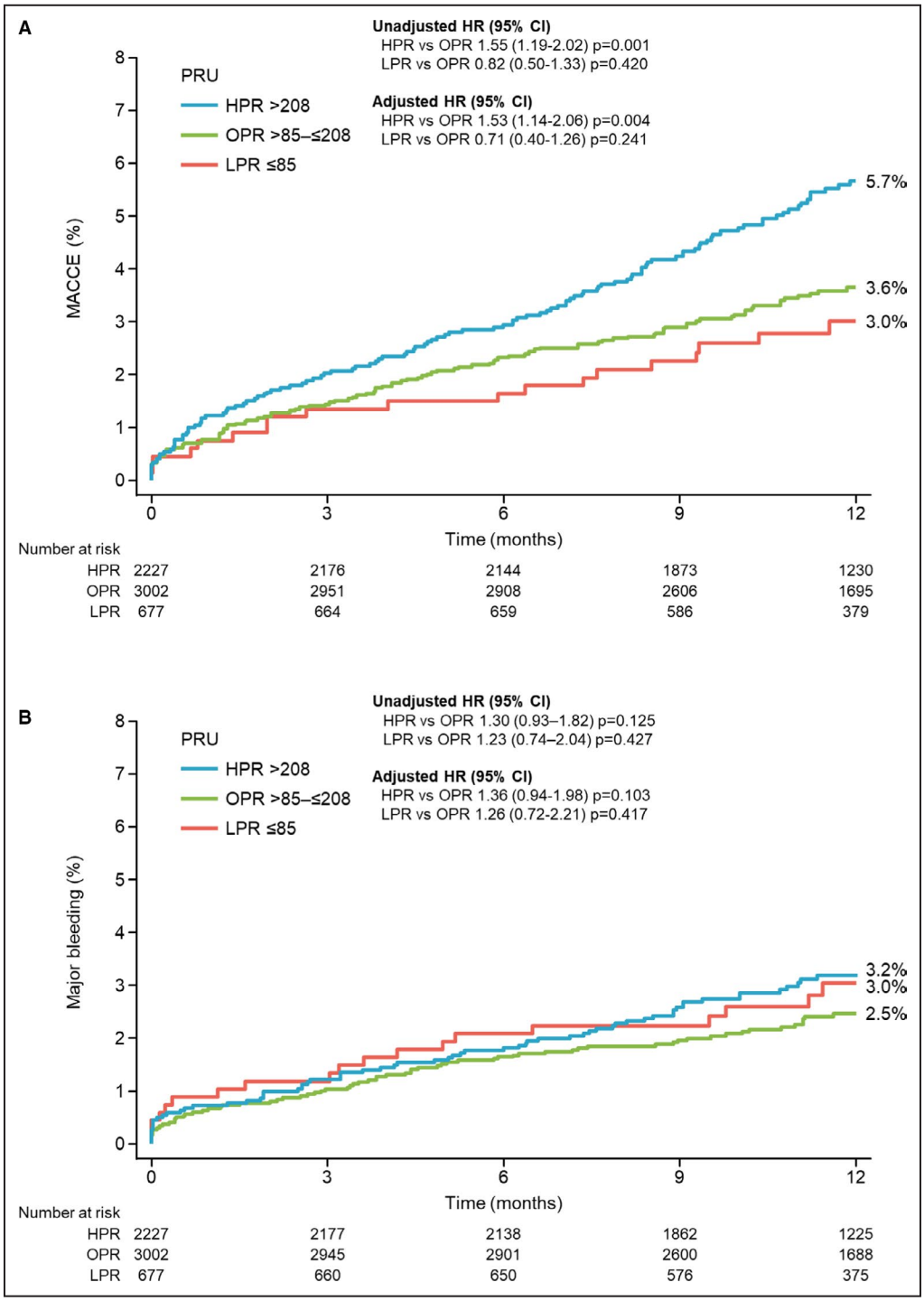

Figure 4. Time-to-event curves from baseline to 1 year according to platelet reactivity.
A, Major adverse cardiac and cerebrovascular events (MACCE) (all-cause death, nonfatal MI, nonfatal stroke, and stent thrombosis); (**B**) major bleeding. HPR indicates high $P2Y_{12}$ reaction unit; HR, hazard ratio; LPR, low $P2Y_{12}$ reaction unit; MI, myocardial infarction; OPR, optimal $P2Y_{12}$ reaction unit; and PRU, $P2Y_{12}$ reaction unit.

(1) high platelet reactivity was an independent risk factor for the occurrence of MACCE and ST, one of the components of MACCE; and (2) high platelet reactivity was associated with MACCE in both patients with and patients without ACS; the association was stronger in patients with compared with patients without ACS.

East Asian patients are believed to be more susceptible to bleeding events than patients from Europe or the United States but are relatively resistant to

Table 2. Risk of PRU for Ischemic Events (PRU=208) and Bleeding Events (PRU=85) Through 1-Year Follow-Up

	Event Rates at 1 y			LPR vs OPR				HPR vs OPR			
	LPR (n=677)	OPR (n=3002)	HPR (n=2227)	Unadjusted HR (95% CI)	*P* Value	Adjusted HR (95% CI)	*P* Value	Unadjusted HR (95% CI)	*P* Value	Adjusted HR (95% CI)	*P* Value
MACCE*	2.8% (19)	3.4% (103)	5.3% (117)	0.82 (0.50–1.33)	0.420	0.71 (0.40–1.26)	0.241	1.55 (1.19–2.02)	0.001	1.53 (1.14–2.06)	0.004
All-cause death*	1.8% (12)	2.0% (60)	3.1% (70)	0.89 (0.48–1.65)	0.710	0.71 (0.34–1.51)	0.377	1.58 (1.12–2.24)	0.009	1.44 (0.98–2.12)	0.064
Nonfatal MI*	0.3% (2)	0.8% (24)	1.4% (32)	0.37 (0.09–1.57)	0.177	0.39 (0.09–1.64)	0.198	1.81 (1.07–3.08)	0.028	1.66 (0.95–2.89)	0.075
Nonfatal stroke*	0.6% (4)	0.8% (23)	0.9% (20)	0.77 (0.27–2.24)	0.637	0.72 (0.21–2.46)	0.596	1.18 (0.65–2.15)	0.583	1.46 (0.74–2.89)	0.276
ST†	0.1% (1)	0.1% (4)	0.4% (10)	1.11 (0.12–9.93)	0.926	0.93 (0.10–8.35)	0.948	3.37 (1.06–10.75)	0.040	4.06 (1.27–13.00)	0.018
Major bleeding‡	2.8% (19)	2.3% (69)	3.0% (66)	1.23 (0.74–2.04)	0.427	1.26 (0.72–2.21)	0.417	1.30 (0.93–1.82)	0.125	1.36 (0.94–1.98)	0.103
All bleeding‡	7.4% (50)	6.3% (188)	7.1% (158)	1.19 (0.87–1.63)	0.270	1.27 (0.90–1.80)	0.167	1.15 (0.93–1.42)	0.207	1.22 (0.97–1.54)	0.094

HPR indicates high $P2Y_{12}$ reaction unit; HR, hazard ratio; LPR, low $P2Y_{12}$ reaction unit; MACCE, major adverse cardiac and cerebrovascular events; OPR, optimal $P2Y_{12}$ reaction unit; PRU, $P2Y_{12}$ reaction unit; and ST, stent thrombosis.

*Variables entered in this model include sex, age, body weight, smoking, acute coronary syndrome (ACS)/non-ACS, and composite of prior myocardial infarction (MI), prior percutaneous coronary intervention, and prior coronary artery bypass graft surgery.

†Variables entered in this model include age and ACS/non-ACS.

‡Variables entered in this model include sex, age, body weight, smoking, ACS/non-ACS, and composite of history of cerebral hemorrhage and gastrointestinal hemorrhage.

thromboembolic events. However, differences in genetic polymorphisms result in higher incidences of reduced response to $P2Y_{12}$ inhibitors in East Asian patients,[21–23] leading to the East Asian paradox. A recent randomized controlled study comparing standard doses of ticagrelor and clopidogrel in Korean patients with ACS strongly supported and facilitated this theory of regional differences in ischemic and bleeding risks. Consistent with the PHILO (Phase the International Study of Ticagrelor and Clinical Outcomes in Asian ACS Patients) study, which included Japanese patients in majority,[19] and in contrast to the PLATO (Study of Platelet Inhibition and Patient Outcomes) trial conducted mainly in Western countries,[20] Korean patients with ACS have a statistically higher incidence of bleeding events and numerically higher incidence of ischemic events under standard-dose ticagrelor treatment.[24] The precise reason for the East Asian paradox has not been completely elucidated, but differences in body mass index, pharmacokinetic and pharmacodynamic profiles of $P2Y_{12}$ inhibitors, intrinsic thrombogenicity, genetic polymorphisms, hemostatic factor, and the like have been proposed. These findings suggest a higher bleeding risk in East Asian patients and endorse the strategy of optimizing antiplatelet drug dosage to minimize ischemic and bleeding event risks. This might be essential for managing thrombotic and bleeding risks after PCI in East Asian patients. Lower doses of antithrombotic drugs have been recommended in Japan based on a pivotal study conducted in Japan.[25,26] The present study provided an opportunity to elucidate current practice in Japanese patients undergoing PCI from the perspective of platelet reactivity.

In the present study, the 1-year cumulative incidence of MACCE was 4.4%, which was comparable to the expected rate in the planning stage of this study and that reported in previously published registry studies such as the PARIS (Patterns of Non-adherence to Anti-platelet Regimens in Stented Patients)[27] and ADAPT-DES (Assessment of Dual Antiplatelet Therapy With Drug Eluting Stents)[28] registries; however, the incidence of ST was low (0.3%) compared with the PARIS (1.1%) and ADAPT-DES (0.8%) registry studies.

HPR was independently associated with MACCE and ST, even after adjustment. Notably, even though the incidence of ST was 0.3%, patients with HPR had an occurrence rate of ST that was 4 times the rate of that in patients with OPR. The low ST rate probably reflects the routine use of imaging-guided DES deployment (94.4%). These procedural characteristics may have mitigated the risk of ST after DES deployment in the present study. This explanation is supported by the recent subanalysis of ADAPT-DES in which Maehara et al[29] showed that high platelet reactivity and intravascular ultrasound guidance were both independent

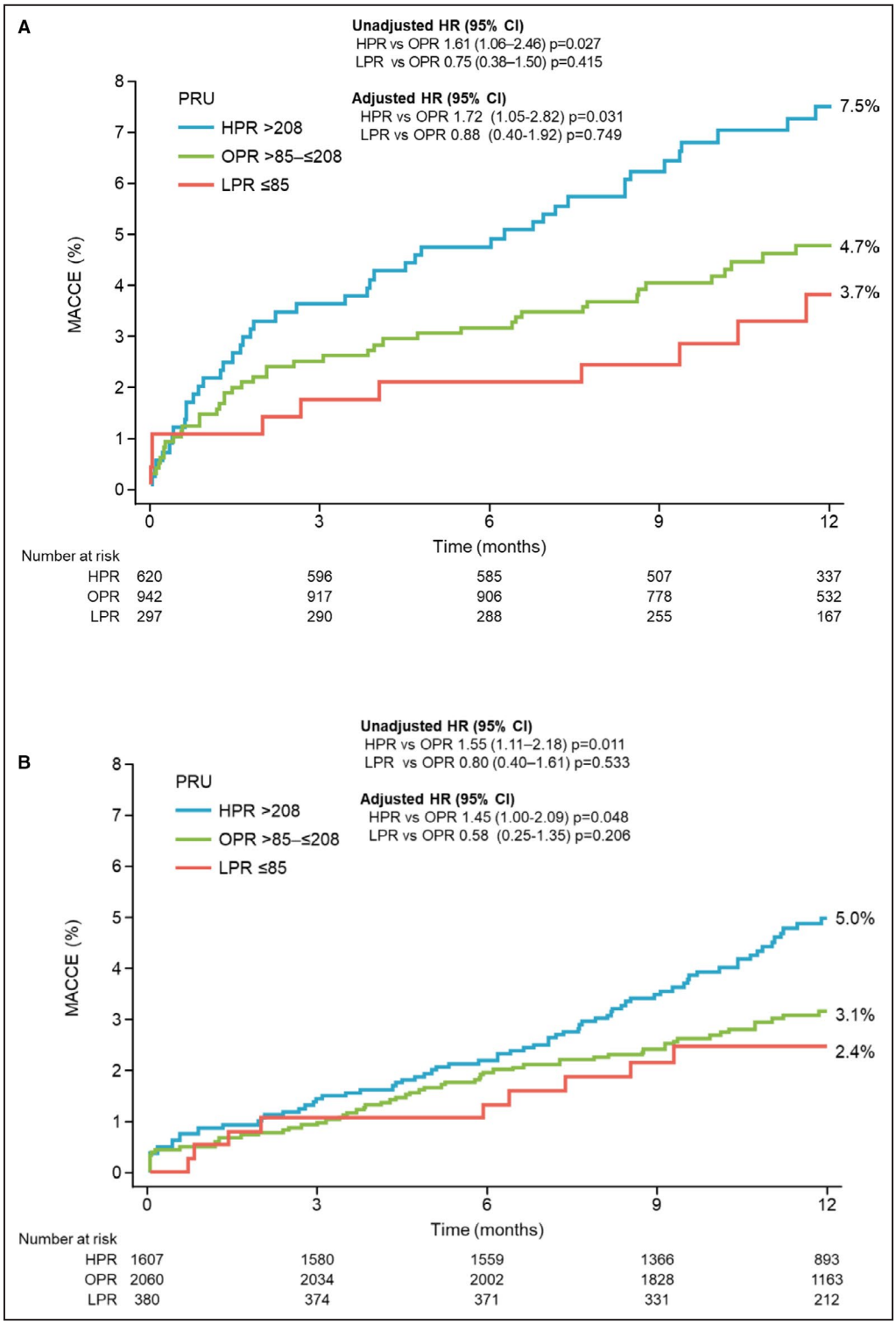

Figure 5. Time-to-event curves of major adverse cardiac and cerebrovascular events (MACCE) from baseline to 1 year according to platelet reactivity.
A, Patients with acute coronary syndrome (ACS); (**B**) patients without ACS. HPR indicates high $P2Y_{12}$ reaction unit; LPR, low $P2Y_{12}$ reaction unit; OPR, optimal $P2Y_{12}$ reaction unit; and PRU, $P2Y_{12}$ reaction unit.

predictors of ST. Furthermore, early improvement in clinical events after DES implantation with intravascular ultrasound guidance was increased with longer-term (2-year) follow-up. This finding highlights the role of platelet reactivity in ST even in an era of imaging-guided DES deployment.

Table 3. Risk of PRU for MACCE (PRU=208) and Major Bleeding Events (PRU=85) Through 1-Year Follow-Up According to ACS or Non-ACS

	Event Rates at 1 y			LPR vs OPR			HPR vs OPR			
	LPR	OPR	HPR	Unadjusted HR (95% CI)	*P* Value	Adjusted HR (95% CI)	P Value	Unadjusted HR (95% CI)	*P* Value	Adjusted HR (95% CI)	*P* Value
MACCE*											
ACS	3.4% (10/297)	4.5% (42/942)	7.1% (44/620)	0.75 (0.38–1.50)	0.415	0.88 (0.40–1.92)	0.749	1.61 (1.06–2.46)	0.027	1.72 (1.05–2.82)	0.031
Non-ACS	2.4% (9/380)	3.0% (61/2060)	4.5% (73/1607)	0.80 (0.40–1.61)	0.533	0.58 (0.25–1.35)	0.206	1.55 (1.11–2.18)	0.011	1.45 (1.00–2.09)	0.048
Major bleeding†											
ACS	2.4% (7/297)	2.8% (26/942)	3.2% (20/620)	0.85 (0.37–1.95)	0.698	0.90 (0.33–2.43)	0.836	1.17 (0.65–2.10)	0.594	1.55 (0.81–2.96)	0.188
Non-ACS	3.2% (12/380)	2.1% (43/2060)	2.9% (46/1607)	1.54 (0.81–2.91)	0.190	1.61 (0.82–3.17)	0.166	1.39 (0.92–2.11)	0.120	1.31 (0.83–2.07)	0.251

ACS indicates acute coronary syndrome; HPR, high $P2Y_{12}$ reaction unit; HR, hazard ratio; LPR, low $P2Y_{12}$ reaction unit; MACCE, major adverse cardiac and cerebrovascular events; OPR, optimal $P2Y_{12}$ reaction unit; and PRU, $P2Y_{12}$ reaction unit.

*Variables entered in this model include sex, age, body weight, smoking, and composite of prior myocardial infarction, prior percutaneous coronary intervention, and prior coronary artery bypass graft surgery.

†Variables entered in this model include sex, age, body weight, smoking, and composite of history of cerebral hemorrhage and gastrointestinal hemorrhage.

Although it has been proposed that East Asian patients have a high risk of complicated bleeding events, major bleeding events according at BARC 3 and 5 were lower than expected (4.0%), occurring in 2.8% of patients. This observation might be attributable to the high frequency of use of the transradial approach.[30] A similar low bleeding rate was observed in the recent SENIOR (Synergy II Everolimus Eluting Stent in Patients Older Than 75 Years Undergoing Coronary Revascularisation Associated With a Short Dual Antiplatelet) trial,[31] which used the transradial approach in 80% of cases. The high prevalence of proton pump inhibitor treatment (84.5%) and *Helicobacter pylori* eradication might contribute to the lower incidence of gastrointestinal bleeding, which is known as a main cause of major bleeding.[32]

Contrary to the ischemic event findings, bleeding events were not associated with LPR. It has been reported that LPR is a strong independent predictor of bleeding events during antiplatelet therapy.[33] Part of the reason for this resides in the findings of the low prevalence of LPR (11.5%), which may not be enough to evaluate the relationship between bleeding events and LPR. Thus, this study might be underpowered to detect any difference in bleeding events. According to a recent report, the incidence of bleeding events after PCI in Japanese patients has decreased[34] compared with the known incidence in the period when the present study was planned. However, the numerically higher periprocedural bleeding events in the LPR group strongly suggests the importance of procedure-related management (Figure S2E). In fact, the periprocedural bleeding events in the LPR group were mainly related to components of the PCI procedure (ie, puncture related and urethral catheterization).

In the present study, 2 types of antiplatelet drugs, clopidogrel and prasugrel, were used. In contrast, clopidogrel was the only antiplatelet drug used in the ADAPT-DES study.[28] It is possible that the relationship between HPR and ischemic events observed in this study could be attributed to the type of drug administered, as the PRU may vary depending on which of the 2 types of drugs were administered (clopidogrel: 212.9±71.1; prasugrel: 163.5±74.5). However, the cumulative incidence of MACCE in patients with HPR was significantly higher than that in patients with OPR, irrespective of the prescribed type of drug before adjustment. However, in the clopidogrel group, the adjusted HR is not statistically significant, but it is reasonable to believe that this was caused by the small sample size in each stratified subgroup. Based on the HRs between the 2 drugs, the clinical significance should be considered as similar regardless of the drug. Taken together, the results of the present study suggest that the association of HPR and high

ischemic event rate was also present in East Asian populations. While a PRU of 208 might also be applicable to Japanese patients, additional exploration of the optimal PRU thresholds for the efficacy of antiplatelet drugs is required.

The observation described above was consistent with patients with ACS, in whom HPR was associated with a higher risk of ischemic events, and is likely to be in line with the finding that potent $P2Y_{12}$ inhibitors improve clinical outcomes in ACS.[20,35] Notably, a similar trend was observed in patients without ACS even after adjustment. To the best of our knowledge, this is the first study to show an association between ischemic events and high platelet reactivity in patients without ACS. Although the clinical usefulness of a point-of-care approach using the platelet function test has not been proven beneficial in previously reported randomized controlled trials, which indicates that hypothesis-generated studies to address this are essential, the present study suggests the importance of avoiding HPR, regardless of ACS status, for preventing ischemic events.

STUDY LIMITATIONS

There are several important limitations in this study. First, given the nature of observational studies, the findings should be interpreted with caution. Selection bias was inevitable because not all patients undergoing PCI at each institution could be enrolled in the study. Reasons for lack of enrollment included enrollment in other randomized controlled trials, difficulty in obtaining informed consent because of a high level of urgency with PCI procedures, and refusal of some patients to give informed consent. Second, all patients were Japanese and the proportion of patients with ACS was relatively low. The generalizability of our findings beyond East Asia is unclear. However, the relationship between HPR and ischemic events seems consistent with the findings of the ADAPT-DES study. Third, although HPR was an independent risk factor for MACCE and ST, there are known (eg, chronic kidney disease, diabetes mellitus, and anemia) and unknown confounding factors that were not used for adjustment. Fourth, it was mandatory to assess platelet reactivity at one point between 12 to 48 hours after index PCI. The timing of PRU measurements was set based on the ADAPT-DES study, the only registry that measured the PRU of a sample size equivalent to the present study. The PRU measurement at 12 to 48 hours was presumed to be earlier than the time-to-maximum drug efficacy of clopidogrel with its loading dose. Almost all of clopidogrel was already prescribed during the preprocedural period. Furthermore, the clinical implications of HPR were similar, regardless of antiplatelet drugs used. Fifth, the investigators were not blinded from the PRU values and thus were able to access this information. Despite this, there were few cases (<2%) of switching between the 2 $P2Y_{12}$ inhibitors through to the time of discharge. Finally, PRU was the only measure of platelet reactivity used in this study, although it is the most widely applied and investigated method.[34,36,37]

CONCLUSIONS

In real-world patients undergoing PCI in Japan, HPR was independently associated with MACCE. The same trend was observed in both patients with and patients without ACS.

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Received January 16, 2020; accepted April 8, 2020.

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Acknowledgments

We appreciate the support and collaboration of the coinvestigators participating in the PENDULUM registry. The authors wish to thank Keyra Martinez Dunn, MD, and David Murdoch, BSc (Hons), of Edanz Medical Writing for providing medical writing assistance, which was funded by Daiichi Sankyo Co., Ltd.

Author contributions: Masato Nakamura conceived of the article. Yoshitaka Murakami verified analytical methods. All authors discussed the results and contributed to the final article.

Sources of Funding

This work was supported by Daiichi Sankyo Co., Ltd.

Disclosures

Nakamura has received research funding from Daiichi Sankyo Co., Ltd. and Sanofi K.K., and personal fees from Daiichi Sankyo Co., Ltd., Sanofi K.K., and Terumo Corporation. Iijima has received personal fees from Daiichi Sankyo Co., Ltd. Kadota received personal fees from Daiichi Sankyo Co., Ltd., during the conduct of the study, and personal fees from Sanofi, outside the submitted work. Kanda has received personal fees from Daiichi Sankyo Co., Ltd. Anzai has received personal fees from Daiichi Sankyo Co., Ltd. Yasaka has received personal fees from Daiichi Sankyo Co., Ltd., outside the submitted work. Yamaguchi has received personal fees from Daiichi Sankyo Co., Ltd., during the conduct of the study; and grants from Abbott Vascular, Boston Scientific, Medtronic, and TERUMO, as well as personal fees from Daiichi Sankyo Co., Ltd., outside the submitted work. Ishii has received personal fees from Daiichi Sankyo Co., Ltd. Takahashi has received personal fees from Daiichi Sankyo Co., Ltd. Shibata has received personal fees from Daiichi Sankyo Co., Ltd.

Takamisawa has received personal fees from Daiichi Sankyo Co., Ltd., outside the submitted work. Harada and Motohashi are employees of Daiichi Sankyo Co., Ltd. Uemura has received research funding from Daiichi Sankyo Co., Ltd., and scholarship grants from Astellas Pharma Inc., Abbot Vascular Japan Co., Ltd., Sanofi K.K., Daiichi Sankyo Co., Ltd., Terumo Corporation, Nippon Boehringer Ingelheim Co., Ltd., Goodman Co., Ltd., Bayer Yakuhin Ltd., Shionogi and Co., Ltd., Sumitomo Dainippon Pharma Co., Ltd., Boston Scientific Japan K.K., Amgen Astellas BioPharma Co., Ltd., Kaken Pharmaceutical Co., Ltd., Takeda Pharmaceutical Co., Ltd., Taisho Pharmaceutical Co., Ltd., Mitsubishi Tanabe Pharmaceutical Co., Ltd., Japan Lifeline Co., Ltd., MSD K.K., Nipro Corporation, Actelion Pharmaceuticals Japan Ltd., and Pfizer Japan Inc. Murakami has received personal fees from Daiichi Sankyo Co., Ltd., SRD, and Sanofi K.K. Takeda has no disclosures to report.

Supplementary Materials

Appendix S1
Data S1
Tables S1–S2
Figures S1–S4

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Supplemental Material

Appendix

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Toho University Ohashi Medical Center	282
Sakurakai Takahashi Hospital	265
Asahi General Hospital	253
Ota Memorial Hospital	218
Miyazaki Medical Association Hospital	202
Ogikubo Hospital	202
Hyogo Brain and Heart Center	157
Kawasaki Medical School	153
Sakakibara Heart Institute	150
Rinku General Medical Center	146
Tokyo Women's Medical University	146
Kansai Rosai Hospital Cardiovascular Center	143
Tokyo Medical University Hachioji Medical Center	143
Juntendo University Shizuoka Hospital	139
Chikamori Hospital	130
Tokyo Women's Medical University Yachiyo Medical Center	124
Ageo Central General Hospital	115
Tokyo Kamata Hospital	114
Fujisawa City Hospital	108
Tokushima Prefectural Central Hospital	102
Hiroshima Prefectural Hospital	100
Saiseikai Utsunomiya Hospital	100

Sakurabashi Watanabe Hospital	100
Shin-Koga Hospital	100
Tokushima Red Cross Hospital	100
Tokushima University Hospital	100
Wakayama Medical University	100
Showa University School of Medicine	97
Yokohama City University Medical Center	97
Japanese Red Cross Okayama Hospital	92
National Hospital Organization Osaka National Hospital	89
Mitsui Memorial Hospital	88
Edogawa Hospital	86
Funabashi Municipal Medical Center Heart and Vascular Institute	86
Nihon University School of Medicine	82
Kurume University Hospital	75
Osaka Police Hospital	74
Showa University Northern Yokohama Hospital	74
Shiga General Hospital	73
Fukui Cardiovascular Center	71
Tenri Hospital	71
Saiseikai Nakatsu Hospital	64
Tokyo Rosai Hospital	63
Matsusaka Central Hospital	56
Kobe City Medical Center General Hospital	54
Yokohama Sakae Kyosai Hospital	53
Tokyo Medical University	52
Fukuoka Sanno Hospital	51

Saiseikai Kawaguchi General Hospital	50
Tokyo Metropolitan Tama Medical Center	45
Fujita Health University Hospital	44
Nagoya University Graduate School of Medicine	43
Hyogo Prefectural Awaji Medical Center	41
University of Occupational and Environmental Health	39
Ogaki Municipal Hospital	36
The Jikei University School of Medicine	35
Saiseikai Kumamoto Hospital	30
St. Luke's International Hospital	29
Kobe University Graduate School of Medicine	28
Odawara Cardiovascular Hospital	28
Dokkyo Medical University	25
Nagoya Kyoritsu Hospital	15
Teikyo University School of Medicine	14
Yokohama City University Hospital	14
Osaka University Graduate School of Medicine	13
Juntendo University Graduate School of Medicine	4

Data S1. Definitions used in this study

Definition of the efficacy events

(1) Death
All deaths from any cause. All-cause death: All deaths are applicable regardless of the cause. Cardiovascular death: Deaths resulting from damage to the cardiac vessels.
(2) Non-fatal myocardial infarction
Non-fatal myocardial infarction is defined as myocardial infarction that is nonfatal based on diagnosis by markers for cardiomyopathy (cardiac enzymes) or electrocardiogram* etc. in the presence of symptoms suggestive of a new onset of acute myocardial infarction or reinfarction after index percutaneous coronary intervention (PCI) or coronary artery bypass graft surgery (CABG). *An ST change of $\geq \pm 1$ mm (0.1 mV) (new onset or recurrence) or a new Q wave abnormality is observed.
(3) Non-fatal stroke
A patient has cerebral stroke when neurologic symptoms or signs newly develop and when the culprit lesion is detected by computed tomography (CT) or magnetic resonance imaging (MRI) scans. Cerebral stroke is divided into two major subtypes:

ischemic stroke (cerebral infarction) and nonischemic stroke (e.g., cerebral hemorrhage, subarachnoid hemorrhage). Ischemic stroke (cerebral infarction): A new onset of neurological signs or symptoms with a new infarct lesion related to the neurological signs or symptoms, which is confirmed by CT or MRI scans, regardless of whether the neurological signs or symptoms last at least 24 hours or not. Nonischemic stroke: Cerebral hemorrhage, subarachnoid hemorrhage, etc.
(4) Revascularization
Revascularization is defined as unscheduled (emergent) PCI, CABG, or intracoronary thrombolysis introduced after index PCI or CABG. · Target Lesion Revascularization Repeat PCI or CABG for the target lesion (proximal and distal 5-mm-long segments from the edge of the implanted stent) due to restenosis of the target lesion or other complications. · Target Vessel Revascularization Repeat PCI or CABG for the target vessel due to restenosis of the target vessel or other complications.
(5) Transient ischemic attack (TIA)

TIA is defined as transient episodes of neurologic dysfunction caused by focal cerebral, spinal cord, and retinal ischemia. CT and MRI scans reveal no evidence of acute infarction.
(6) Stent thrombosis
Stent thrombosis is defined as definite, probable, or possible stent thrombosis by the Academic Research Consortium classification.
(7) Peripheral arterial occlusive disease
Peripheral arterial occlusive disease internally or surgically treated due to acute ischemia

Table S1. Study criteria

Inclusion criteria
Patients who met all the following criteria were included in this study: 1. Patients aged ≥20 years when consent was obtained 2. Patients with coronary artery lesions that were visually confirmed by coronary angiography and for which PCI was indicated by drug-eluting stent placement (as judged with reference to the package insert) 3. Patients administered antiplatelet drugs 4. Patients providing written consent after receiving an explanation of the contents of this clinical research (in case of an emergency, consent could be obtained from a designated representative)
Exclusion criteria
Patients who were participating or planning to participate in a clinical study that consisted of a clinical trial or intervention before the follow-up of this study was complete.

Patients who had acute coronary syndrome or coronary artery disease requiring elective intracoronary stenting and who had undergone PCI with DES implantation were eligible for the study. DES = drug-eluting stent, PCI = percutaneous coronary intervention.

Table S2. One-year cumulative incidence of primary and secondary endpoints

	Number of events	Incidence (%)
MACCE	261	4.4
All cause death	156	2.7
Non-fatal myocardial infarction	62	1.0
Non-fatal stroke	51	0.9
Stent thrombosis	17	0.3
Major bleeding (BARC type 3 and 5)	165	2.8
All bleedings	419	7.1

BARC = Bleeding Academic Research Consortium; MACCE = major adverse cardiac and cerebrovascular events.

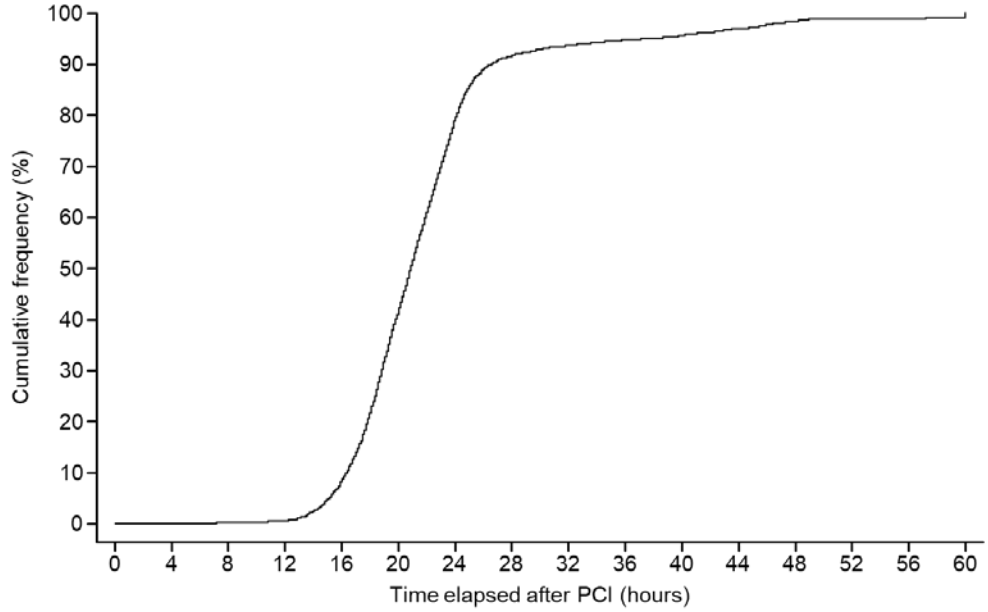

Figure S1. Time to measurement of PRU 12–48 h after PCI

PCI = percutaneous coronary intervention; PRU = $P2Y_{12}$ reaction units.

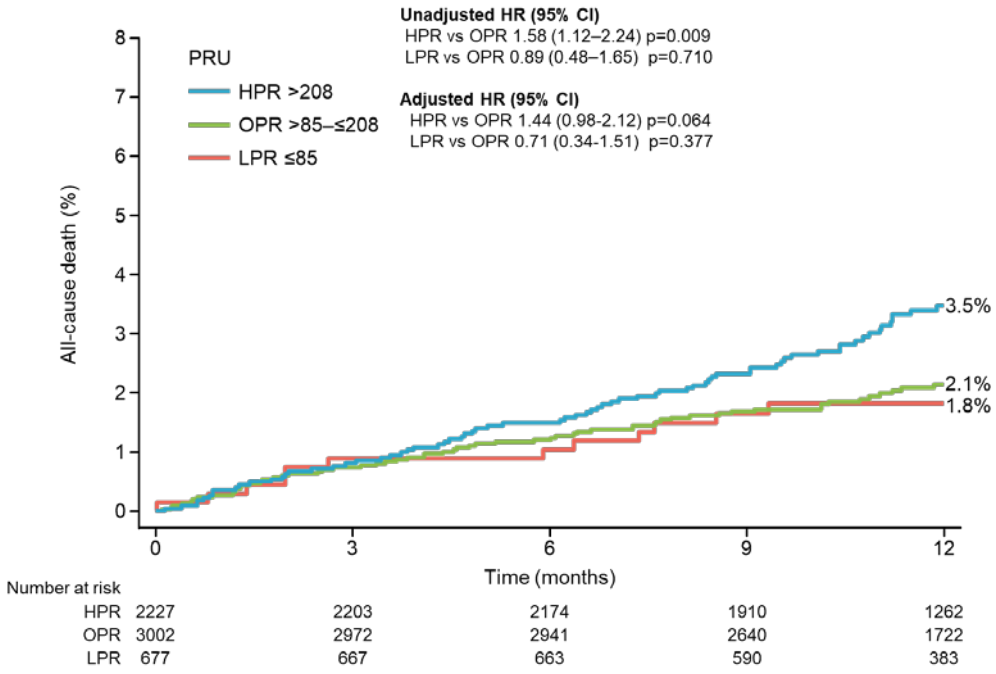

Figure S2A. Time–to–event curves through 1 year for all–cause death according to platelet reactivity

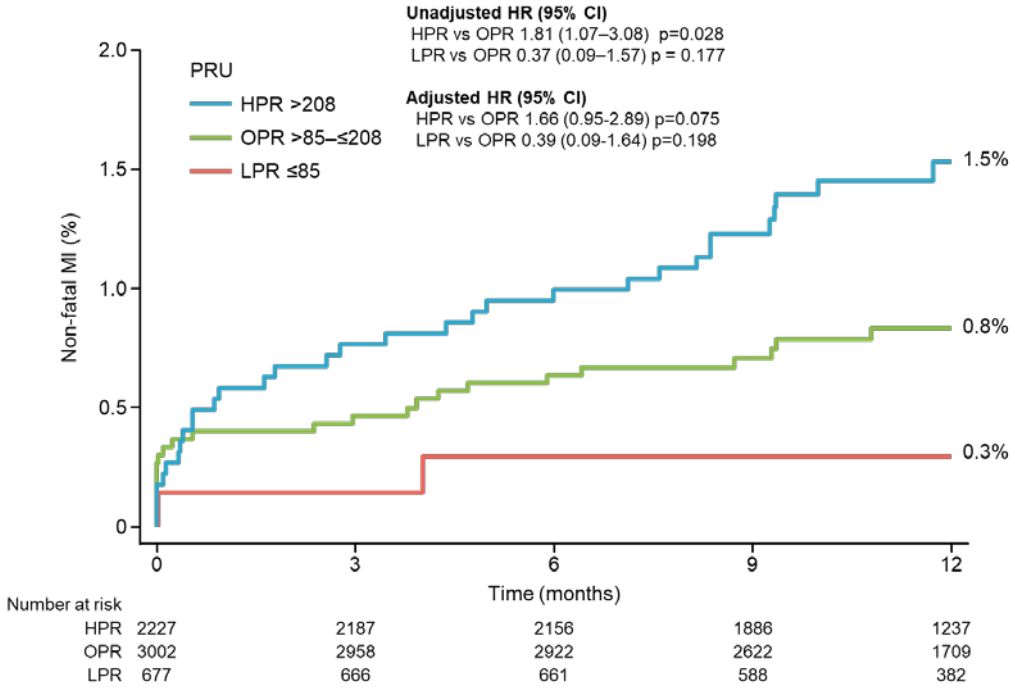

Figure S2B. Time–to–event curves through 1 year for non–fatal MI according to platelet reactivity

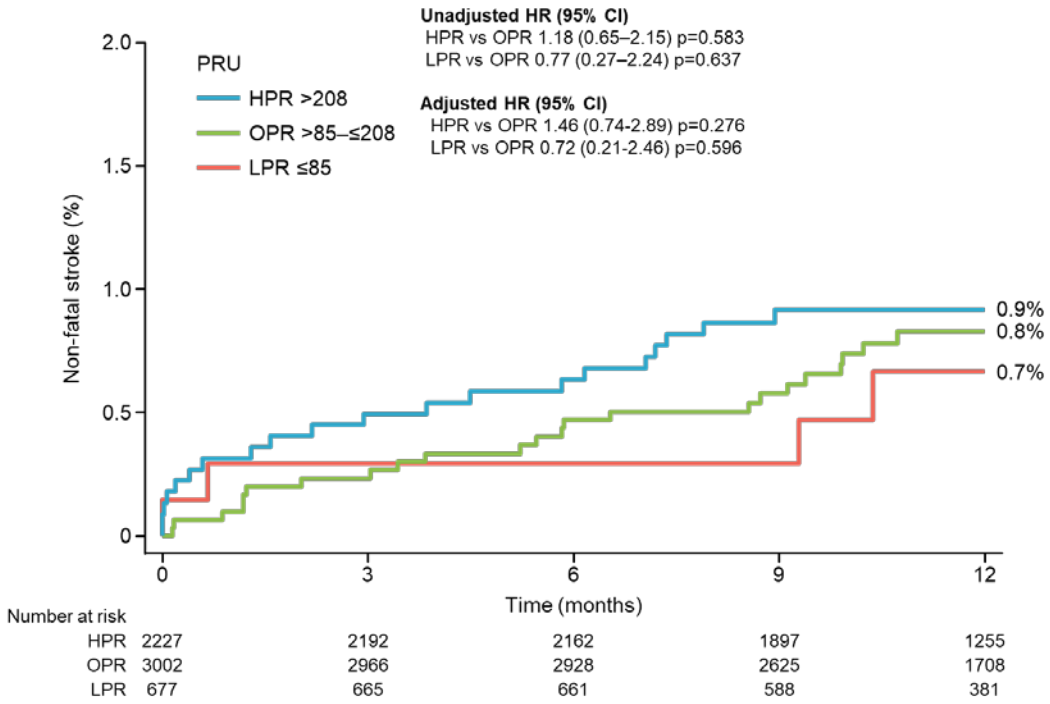

Figure S2C. Time–to–event curves through 1 year for non–fatal stroke according to platelet reactivity

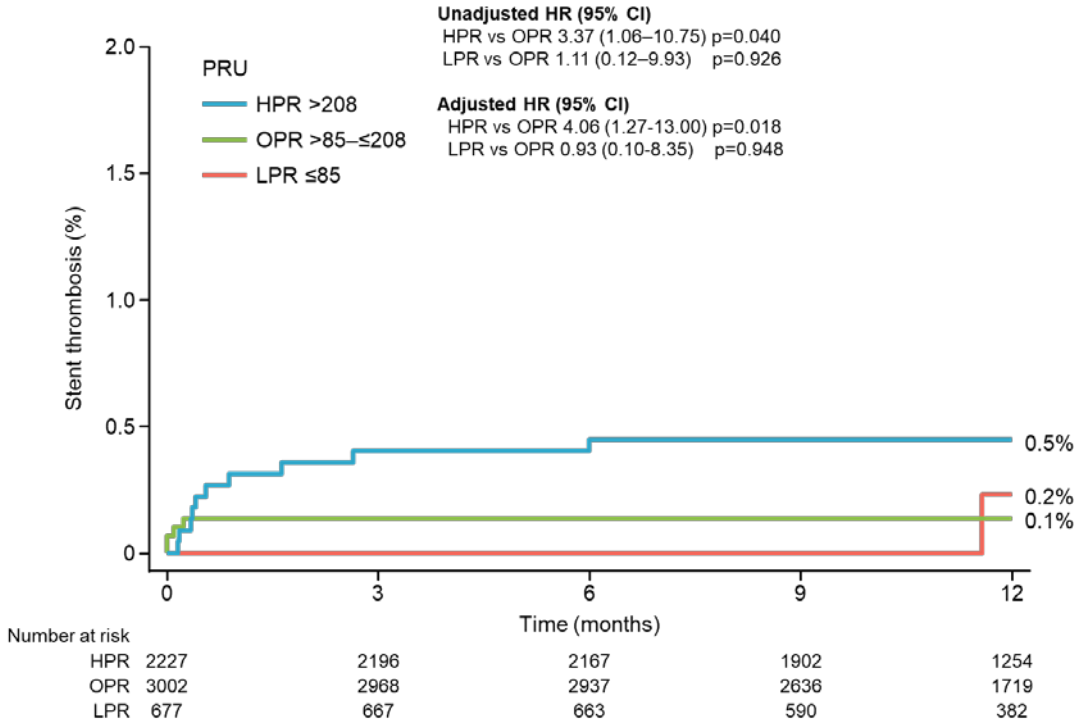

Figure S2D. Time–to–event curves through 1 year for stent thrombosis according to platelet reactivity

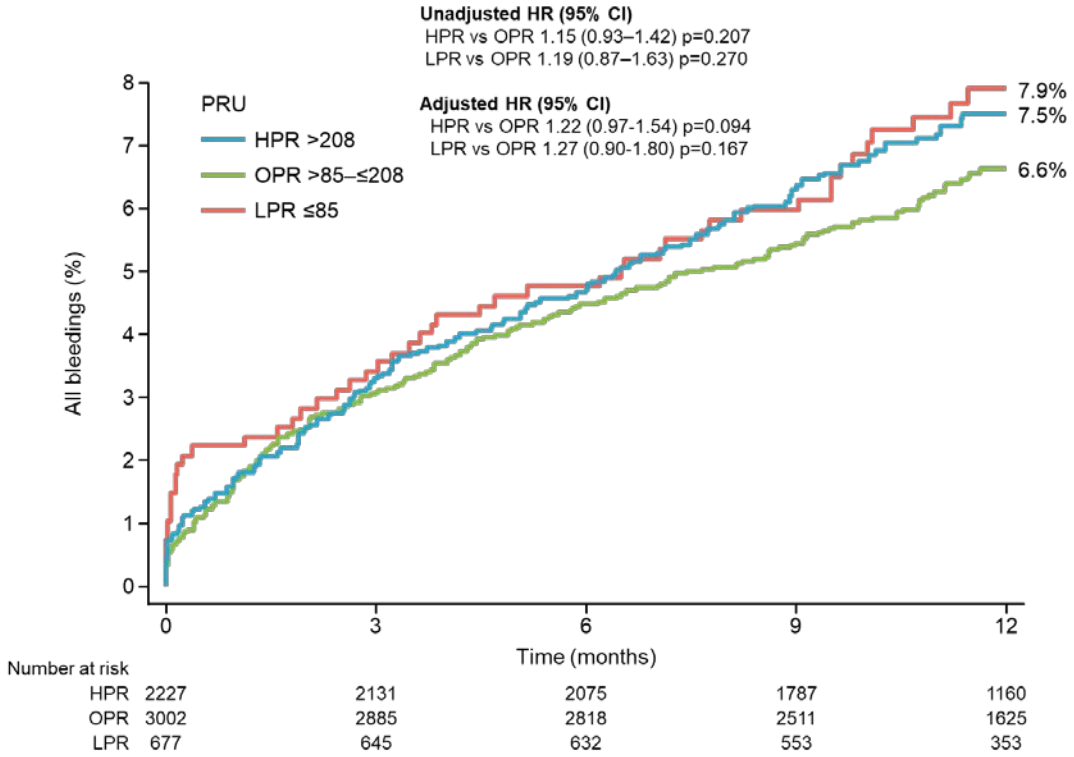

Figure S2E. Time–to–event curves through 1 year for all bleeding according to platelet reactivity

HPR = high $P2Y_{12}$ reaction units; LPR = low $P2Y_{12}$ reaction units; MI = myocardial infarction; OPR = optimal $P2Y_{12}$ reaction units; PRU = $P2Y_{12}$ reaction units.

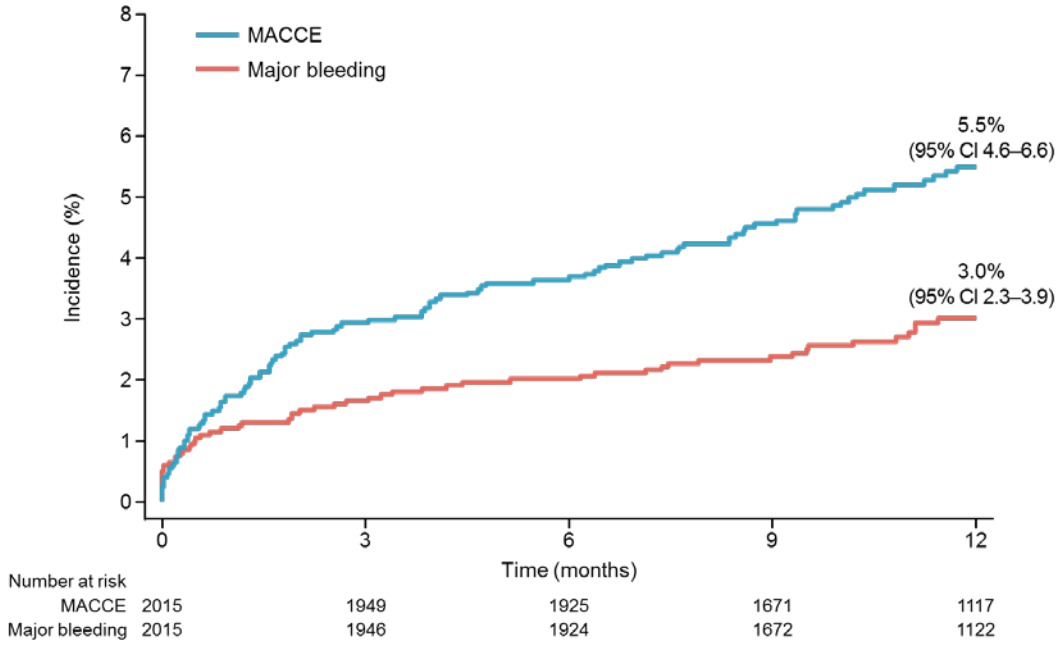

Figure S3A. Time to event curves of ACS and non-ACS groups through 1 year (ACS patients)

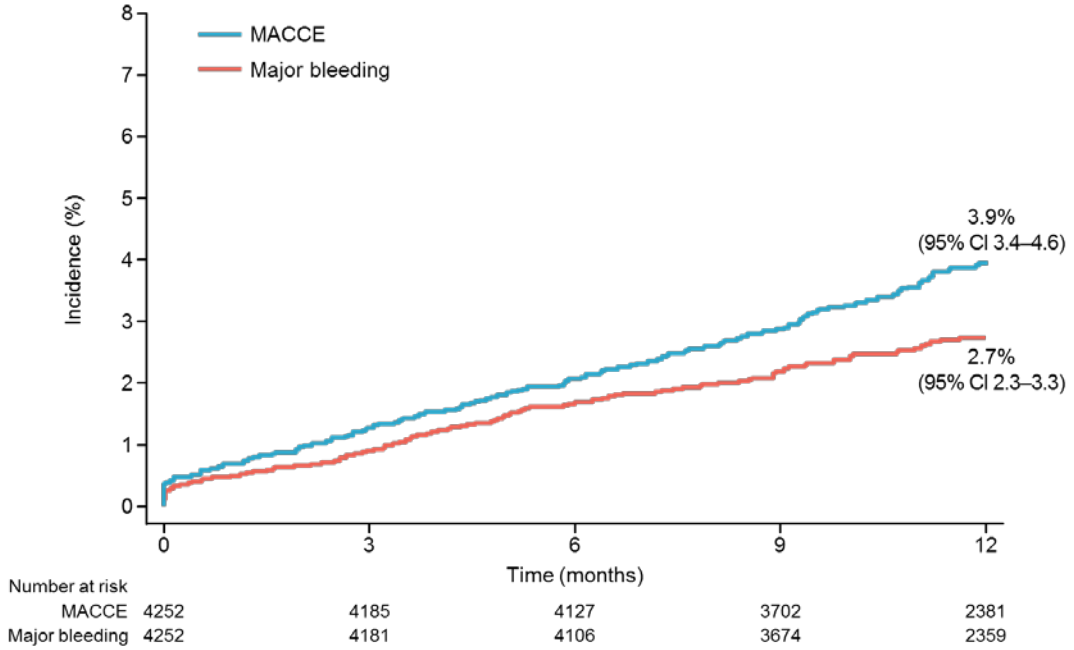

Figure S3B. Time to event curves of ACS and non-ACS groups through 1 year (non-ACS patients)

ACS = acute coronary syndrome; CI = confidence interval; MACCE = major adverse cardiac and cerebrovascular events.

	All			Prasugrel			Clopidogrel		
	LPR	OPR	HPR	LPR	OPR	HPR	LPR	OPR	HPR
N	677	3002	2227	578	2100	1012	95	855	1141
Number of events	19	103	117	16	70	50	2	27	57
Cumulative incidence (%)	3.0	3.6	5.7	3.0	3.6	5.3	2.3	3.3	5.4
Unadjusted HR on OPR	0.82	-	1.55	0.83	-	1.50	0.67	-	1.61
P value	0.420	-	0.001	0.492	-	0.028	0.589	-	0.042
Adjusted HR on OPR	0.71	-	1.53	0.82	-	1.54	0.34	-	1.50
P value	0.241	-	0.004	0.508	-	0.033	0.352	-	0.102

Figure S4A. One-year cumulative incidence of MACCE according to platelet reactivity by P2Y12 inhibitor at discharge

	All			Prasugrel			Clopidogrel		
	LPR	OPR	HPR	LPR	OPR	HPR	LPR	OPR	HPR
N	677	3002	2227	578	2100	1012	95	855	1141
Number of events	19	69	66	13	47	34	5	20	28
Cumulative incidence (%)	3.0	2.5	3.2	2.5	2.4	3.6	5.6	2.5	2.6
Unadjusted HR on OPR	1.23	-	1.30	1.01	-	1.52	2.33	-	1.06
P value	0.427	-	0.125	0.988	-	0.062	0.090	-	0.840
Adjusted HR on OPR	1.26	-	1.36	1.16	-	1.71	2.09	-	0.93
P value	0.417	-	0.103	0.665	-	0.031	0.182	-	0.810

Figure S4B. One-year cumulative incidence of major bleeding according to platelet reactivity by $P2Y_{12}$ inhibitor at discharge

HPR = high $P2Y_{12}$ reaction units; HR = hazard ratio; LPR = low $P2Y_{12}$ reaction units; MACCE = major adverse cardiac and cerebrovascular events; OPR = optimal $P2Y_{12}$ reaction units; PRU = $P2Y_{12}$ reaction units.