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Original Article

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Association between High Platelet Reactivity Following Dual Antiplatelet Therapy and Ischemic Events in Japanese Patients with Coronary Artery Disease Undergoing Stent Implantation

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Aim: Although high on-treatment platelet reactivity (HTPR) with dual antiplatelet therapy (DAPT) correlates with long-term adverse outcomes in patients undergoing percutaneous coronary intervention, the correlation in Japanese patients remains unclear. Therefore, we examined the relationship between platelet reactivity during DAPT with aspirin and clopidogrel and 1-year clinical outcomes following successful coronary stent implantation.

Methods: A prospective, multicenter registry study (j-CHIPS) was conducted in patients undergoing coronary stenting and receiving aspirin and clopidogrel at 16 hospitals in Japan. A VerifyNow point-of-care assay was used to assess platelet reactivity, and a cutoff value to define HTPR was established.

Results: Between February 2011 and May 2013, 1047 patients were prospectively enrolled, of which 854 patients with platelet function evaluation at 12–24 h after PCI were included in the final analysis. After 1 year of follow-up, the incidence of the primary endpoint (a composite of all-cause mortality, myocardial infarction, stent thrombosis, and ischemic stroke) was significantly higher in patients with HTPR than in those without (5.9% vs. 1.5%, $p=0.008$), and HTPR showed a modest ability to discriminate between patients who did and did not experience major adverse cardiac and cerebrovascular events (area under the curve, 0.60; 95% confidence interval, 0.511–0.688, $p=0.039$). HTPR status did not identify patients at risk for major or minor bleeding events.

Conclusion: HTPR was significantly associated with adverse ischemic outcomes at 1 year after PCI in Japanese patients receiving maintenance DAPT, indicating its potential as a prognostic indicator of clinical outcomes in this high-risk patient population.

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Key words: Dual antiplatelet therapy, High on-treatment platelet reactivity, Coronary stent implantation

Introduction

Dual antiplatelet therapy (DAPT) with aspirin and a P2Y12 receptor antagonist such as clopidogrel is the most commonly used antiplatelet strategy to prevent stent thrombosis in patients with coronary artery

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disease (CAD) undergoing percutaneous coronary intervention (PCI)[1, 2], for reasons that include its safety profile following long-term use[3]. However, in spite of the use of DAPT, many patients go on to develop adverse ischemic events after PCI[4]. Clopidogrel, a prodrug, is absorbed from the small intestine and, subsequently, metabolized by CYP2C19 to its activated form[5, 6]. A large variability in response to clopidogrel has been reported, ranging from high on-treatment platelet reactivity (HTPR) in patients designated as low responders, to low on-treatment platelet reactivity[7-12]. HTPR is associated with a higher risk of ischemic events, such as death from cardiovascular causes, nonfatal myocardial infarction, stent thrombosis, and ischemic stroke[7-12], highlighting the importance of optimal platelet inhibition in patients with CAD undergoing PCI. VerifyNow-P2Y12 (Accumetrics, San Diego, California) is a point-of-care platelet reactivity assay for determining a patient's response to antiplatelet therapy that has been used to demonstrate an association between HTPR and ischemic events[7, 8-12]. Previous studies have reported optimal cutoff values for HTPR of 208–230 IU of the P2Y12 reaction unit (PRU)[8-12]. Several mechanisms of HTPR have been described, including genetics such as CYP2C19 loss-of-function gene polymorphism (*2 and *3 variants) and cellular and clinical factors[13-17]. Although Japanese patients appear to have a higher rate of CYP2C19 loss-of-function gene alleles compared with Caucasian patients, and typically receive a lower loading dose of clopidogrel[18], the incidence of adverse cardiovascular events, especially stent thrombosis, has been reported as low in this population[19]. This may partly be attributable to recent developments in stent technology and the routine use of intravascular ultrasound or optical coherence tomography to verify adequate deployment of the stent within the coronary artery. Low on-treatment platelet reactivity seems to be associated with a higher risk of bleeding[7, 14], and present evidence for a bleeding threshold appears insufficient[20], with bleeding likely related to heterogeneous underlying diseases. Therefore, in Japanese patients receiving current PCI, it is necessary to establish the HTPR cutoff values to minimize both ischemic events and bleeding.

Aim

We sought to determine the optimal HTPR cutoff value for predicting cardiovascular events in Japanese patients undergoing PCI with a 1-year follow-up. Additionally, we investigated the relationship between on-treatment platelet reactivity and thrombosis in myocardial infarction (TIMI) major/minor bleeding.

Methods

Patient Population and Study Design

A prospective multicenter observational study, Japanese Clopidogrel Hyporesponsiveness with CAD after Undergoing Stent Implantation Study (j-CHIPS), was conducted from Feb 2011 to May 2013 in Japan. The study protocol was initially approved by the ethics committee of Mie University Hospital (approval no. 2196), and subsequently by the institutional review boards at all other participating hospitals in accordance with the Declaration of Helsinki. All patients provided written informed consent prior to participation. This study is registered with the UMIN Clinical Trials Registry (000005375).

Patients with CAD requiring PCI, including acute coronary syndrome (unstable angina and myocardial infarction), and with no known allergy to aspirin or clopidogrel were eligible for participation. In patients receiving DAPT loading, 300 mg clopidogrel and 100 mg aspirin were orally administered 12–24 hours before stent implantation, whereas non-loading patients received 75 mg clopidogrel and 100 mg aspirin per day for 14 days prior to stent implantation. After the procedure, patients were prescribed a maintenance dose of 100 mg of aspirin and 75 mg of clopidogrel per day for 1 year.

The majority of patients received either a bare metal stent or a drug-eluting stent. During the procedure, all patients underwent intravascular ultrasound or optical coherence tomography to verify adequate deployment of the stent within the coronary artery. Patients with confirmed active bleeding disease or cerebral infarction with embolization from the heart, or those taking anticoagulation agents before the procedure such as warfarin and other antiplatelet agents, with the exception of aspirin and clopidogrel, were excluded from the study. Patients considered unsuitable for participation according to the investigator's judgment were also excluded. Laboratory-based inclusion criteria were as follows: hematocrit, 33%–52%; platelet count, 119,000–502,000/mm^3; total cholesterol, 98–316 mg/dL; triglyceride, 41–824 mg/dL; and fibrinogen, 171–599 mg/dL. Diabetes mellitus (DM) was defined as HbA_{1c} level $>6.5\%$ or receipt of insulin or hypoglycemic medication. Chronic kidney disease was defined as eGFR <60 mL/min/1.73 m^2 present for at least 3 months. In cases of early death and early stent thrombosis among non-loading patients, platelet function data from immediately prior to PCI were used.

The efficacy endpoint in j-CHIPS was the rate of major adverse cardiac and cerebral events (MACCE), consisting of death, nonfatal myocardial infarction,

stent thrombosis, and ischemic stroke. Death was defined as unequivocal cardiovascular death and non-cardiovascular death that could be confirmed. Myocardial infarction was defined according to the criteria of the American College of Cardiology[1] as elevated serum troponin I or increased creatine kinase-myocardial band isoenzyme to at least twice the upper normal limit, accompanied by at least one of the following: acute onset of prolonged (≥ 20 min) typical ischemic chest pain; ECG changes comprising ST-segment elevation of at least 1 mm in two or more contiguous electrocardiographic leads or ST-segment depression ≥ 0.5 mm in more than two contiguous leads; or T-wave inversion ≥ 1 mm in leads with predominant R waves. Stent thrombosis was defined as "definite" or "probable" according to definitions established by the Academic Research Consortium[21]. Safety outcomes included non-coronary artery bypass graft-related bleeding events that occurred during 1 year. The following types of bleeding events were assessed: TIMI major bleeding (intracranial bleeding or bleeding leading to a decrease in hemoglobin of ≥ 5 g/dl), TIMI minor bleeding (bleeding leading to a decrease in hemoglobin of 3–< 5 g/dl), and TIMI minimal bleeding (any clinically overt sign of bleeding leading to a decrease in hemoglobin of < 3 g/dl)[22].

Platelet Function Assays

Blood samples for platelet function analysis were collected by atraumatic venipuncture of the antecubital vein via a 21-gage needle. To avoid measuring platelet activation induced by needle puncture, the initial blood sample drawn was used for blood chemistry analysis. Blood was collected into a Venoject® (Terumo, Tokyo, Japan) containing 3.8% trisodium citrate, a Vacuette® (Greiner Bio-One International, Kremsmünster, Austria) containing 3.2% sodium citrate, and a Neotube® (Nipro, Osaka, Japan) containing ACD-A and EDTA-2Na. Platelet function testing was performed within 2 h after blood sampling. Blood sampling points for the assessment of platelet function were (1) immediately prior to PCI, (2) at 12–24 h post PCI, (3) at 14–56 days post PCI, and (4) at 5–7 months post PCI. Patients with no blood sampling data at 14–56 days after stenting were not included in the final analysis, as these data were required to determine the periprocedural events (stent thrombosis, MI, and bleeding). VerifyNow-P2Y12 platelet reaction units were measured using a turbidimetric method (Accumetrics Inc., San Diego, CA, USA)[17]. The test cartridge contained a lyophilized preparation of human fibrinogen-coated beads, platelet agonist, preservative, and buffer. ADP (20 μM) was used to maximize platelet activation by binding to the P2Y1 and P2Y12 platelet receptors, while prostaglandin E1 was used to suppress the ADP-induced P2Y1-mediated increase in intracellular calcium levels, thereby reducing the activation contributed by P2Y1 and increasing assay sensitivity.

Statistical Analysis

Continuous variables are presented as means ± SD. Categorical variables are presented as frequencies (percentage) and were compared using Fisher's exact test and the χ^2 test. Values of $p < 0.05$ were considered statistically significant. To evaluate the ability of the VerifyNow P2Y12 assay to distinguish between patients who did and did not meet the primary end point by the 1-year follow-up, a receiver operating characteristic (ROC) curve analysis was calculated for each test. The optimal cutoff level was calculated by determining the smallest distance between the ROC curve and the upper left corner of the graph. Patients above the optimal cutoff level were considered to exhibit HTPR. A survival analysis for patients determined to exhibit HTPR or not (no-HTPR) was performed using the Kaplan–Meier method, and the differences between groups were assessed by the log-rank test, with calculation of odds ratios (OR) and 95% confidence intervals (CI) associated with the 1-year rates of outcomes of interest. After assessment of the proportional hazard assumption, the Cox regression model for multivariate analysis was used to identify risk factors for outcome and adjust for potential confounders associated with endpoints upon univariate analysis (age, sex, DM, chronic kidney disease, C-reactive protein level of 3 mg/L, AMI setting, HTPR, reduced left ventricular ejection fraction, multi-vessel disease, total length of stent, and bifurcation lesions). A second ROC curve analysis was performed based on the 1-year primary safety endpoint, combining TIMI major/minor/minimal bleeding. SPSS version 18.0 for Windows (SPSS Institute, Chicago, IL, USA) was used to perform statistical analysis.

Results

Patients

Between February 2011 and May 2013, 1047 patients were enrolled at 16 hospitals in Japan. Of these, 34 patients were subsequently excluded in accordance with the protocol inclusion/exclusion criteria, or for withdrawal of consent. A further 159 patients with missing platelet aggregation data from 12–24 h after PCR were excluded from the final analysis. Therefore, the final study population for evaluation of the primary endpoint consisted of 854 patients (**Fig. 1**).

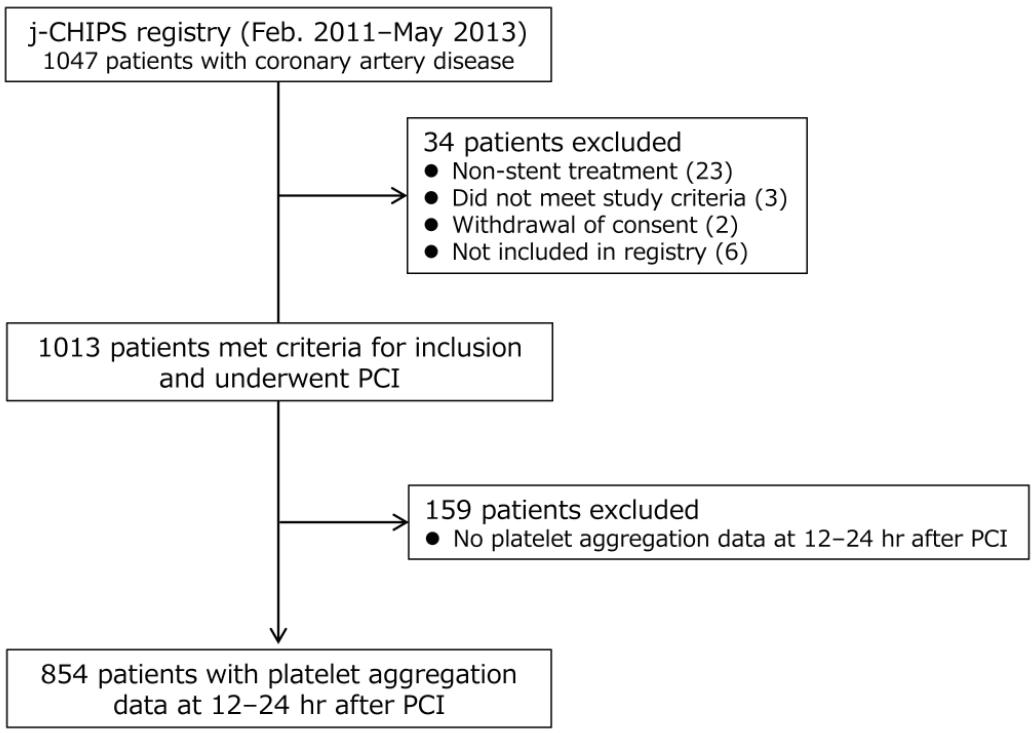


Fig. 1. Study flow diagram of the j-CHIPS registry

Table 1 shows patient clinical characteristics. All patients received clopidogrel pretreatment: 58.2% received a maintenance dose of 75 mg daily therapy for more than 14 days before PCI, while 41.8% received a loading dose of 300 mg for at least 24 hours before PCI. Adherence to clopidogrel was 99% after 1 year. **Table 2** shows the clinical outcomes for all patients at 1 year: 1.1% (9 cases) of patients had died of any cause (7 cases of cardiovascular death [6 cases of fatal myocardial infarction and 1 case of cardiac tamponade] and 2 from sepsis and pneumonia), 2.6% (22 cases) had reported a myocardial infarction, 0.5% (4 cases) had reported stent thrombosis, 0.5% (4 cases) had reported ischemic stroke, and 4.3% (37 cases) had undergone revascularization. Nineteen cases (2.2%) presented with bleeding: 10 TIMI major (7 gastrointestinal, 2 intracranial, and 1 cardiac tamponade), two TIMI minor bleeding (both gastrointestinal), and seven TIMI minimal bleeding (3 gastrointestinal, 2 urogenital, 1 nasal, and 1 ocular bleeding). The cardiac tamponade was a life-threatening bleeding event at 5 days after PCI.

Platelet Reactivity and ROC Curve Analyses

Platelet reactivity data were obtained for 405 patients before PCI, 854 patients at 12–24 h post PCI, 1006 patients at 14–56 days post PCI, and 587 patients at 5–7 months post PCI. Platelet reactivity (PRU values) at 12–24 h post PCI were significantly higher than those at 14–56 days or at 5–7 months post PCI (**Fig. 2A** and **2B**). Higher mean on-treatment platelet reactivity at 12–24 h post PCI was observed in patients with acute coronary syndrome (ACS) versus those with stable CAD (273.1±76.3 PRU vs. 247.4±79.3 PRU, $p<0.001$) (**Fig. 2A**). There was no difference in platelet reactivity before PCI and post PCI in clopidogrel loading versus non-loading patients (**Fig. 2B**). However, platelet reactivity at 12–24 hours after PCI was higher in patients with composite ischemic events at the 1-year follow-up than in patients with no events, although the difference was not statistically significant (281.3±63.2 PRU vs. 260.0±79.7 PRU, $p=0.051$). ROC curve analysis of platelet reactivity at 12–24 h post PCI in 854 patients demonstrated that a PRU value of 221 (AUC=0.613, 95% CI: 0.532–0.695, $p=0.023$) represented a cutoff for HTPR that provided sensitivity of 91.4% and specificity of 31.9%. The cutoff value of platelet reactivity in 1006 patients at 14–56 days post PCI was estimated as 231 PRU (AUC=0.591, 95% CI: 0.501–0.681, $p=0.09$, sensitivity 66.7%, specificity 54.3%), so the PRU value of 221 was selected as the optimal cutoff value. **Table 1** summarizes baseline clinical and procedural characteristics by

Table 1. Baseline clinical and procedural characteristics of study patients by HTPR status

	All patients, $n=854$	No-HTPR, $n=264$	HTPR, $n=590$	P-value
Demographics				
Age, years	67.7 (10.0)	66.0 (10.4)	68.5 (9.7)	0.001
≥ 75 years	221 (25.9%)	55 (6.4%)	166 (19.4%)	0.024
Male	663 (77.6%)	232 (27.2%)	431 (50.5%)	<0.001
Height*, cm	161.7 (9.0)	164.0 (8.6)	160.7 (9.0)	<0.001
Weight*, kg	63.8 (12.2)	66.1 (12.3)	62.8 (12.0)	<0.001
≤ 60 kg*	345 (40.5%)	82 (9.6%)	263 (30.9%)	<0.001
Body mass index*, kg/m^2	24.3 (3.4)	24.4 (3.2)	24.2 (3.5)	0.476
≥ 25 kg/m^2*	339 (39.8%)	111 (13.0%)	228 (26.8%)	0.345
Risk factors				
Current smoker	205 (24.0%)	82 (9.6%)	123 (14.4%)	0.001
Smoking history	531 (62.2%)	184 (21.5%)	347 (40.6%)	0.002
Diabetes mellitus	370 (43.3%)	115 (13.5%)	255 (29.9%)	0.926
Dyslipidemia	664 (77.8%)	194 (22.7%)	470 (55.0%)	0.045
Hypertension	681 (79.7%)	215 (25.2%)	466 (54.6%)	0.409
eGFR <60 mL/min/1.73 m^2	358 (41.9%)	106 (12.4%)	252 (29.5%)	0.483
PCI	260 (30.4%)	94 (11.0%)	166 (19.4%)	0.028
CABG	14 (1.6%)	6 (0.7%)	8 (0.9%)	0.383
MI	178 (20.8%)	59 (6.9%)	119 (13.9%)	0.469
AP	288 (33.7%)	100 (11.7%)	188 (22.0%)	0.086
PAD	89 (10.4%)	33 (3.9%)	56 (6.6%)	0.184
Ischemic stroke	76 (8.9%)	29 (3.4%)	47 (5.5%)	0.152
HF	16 (1.9%)	2 (0.2%)	14 (1.6%)	0.170
Medication				
Calcium channel blocker	378 (44.3%)	110 (12.9%)	268 (31.4%)	0.307
ACE inhibitor	181 (21.2%)	57 (6.7%)	124 (14.5%)	0.850
ARB	432 (50.6%)	133 (15.6%)	299 (35.0%)	0.936
Beta blocker	334 (39.1%)	101 (11.8%)	233 (27.3%)	0.733
Statin	592 (69.3%)	174 (20.4%)	418 (48.9%)	0.148
Cilostazol	80 (9.4%)	33 (3.9%)	47 (5.5%)	0.036
Proton pump inhibitor	503 (58.9%)	137 (16.0%)	366 (42.9%)	0.005
Presentation and treatment				
Stable CAD	532 (62.3%)	188 (22.0%)	344 (40.3%)	<0.001
ACS	322 (37.7%)	76 (8.9%)	246 (28.8%)	<0.001
Unstable angina	123 (14.4%)	35 (4.1%)	88 (10.3%)	0.598
Non-ST elevation MI	26 (3.0%)	7 (0.8%)	19 (2.2%)	0.830
ST elevation MI	173 (20.3%)	34 (4.0%)	139 (16.3%)	<0.001
Number of diseased vessels				
1	715 (83.7%)	218 (25.5%)	497 (58.2%)	0.548
2	117 (13.7%)	37 (4.3%)	80 (9.4%)	0.914
3	22 (2.6%)	9 (1.1%)	13 (1.5%)	0.350
Diseased vessel				
RCA	280 (32.8%)	85 (10.0%)	195 (22.8%)	0.806
LAD	476 (55.7%)	148 (17.3%)	328 (38.4%)	0.899
LCX	199 (23.3%)	68 (8.0%)	131 (15.3%)	0.256
LMT	55 (6.4%)	16 (1.9%)	39 (4.6%)	0.762
HL	5 (0.6%)	2 (0.2%)	3 (0.4%)	0.647
Bifurcation diseased vessel	383 (44.8%)	113 (13.2%)	270 (31.6%)	0.422

(Cont Table 1)

	All patients, $n=854$	No-HTPR, $n=264$	HTPR, $n=590$	*P*-value
Stent type				
Bare metal stent	84 (9.8%)	24 (2.8%)	60 (7.0%)	0.625
Drug eluting stent	775 (90.7%)	244 (28.6%)	531 (62.2%)	0.258
EES	556 (65.1%)	171 (20.0%)	385 (45.1%)	0.891
PES	24 (2.8%)	5 (0.6%)	19 (2.2%)	0.278
SES	1 (0.1%)	0 (0.0%)	1 (0.1%)	1.000
ZES	21 (2.5%)	5 (0.6%)	16 (1.9%)	0.476
BES	189 (22.1%)	67 (7.8%)	122 (14.3%)	0.126
Clopidogrel				
Loading (300 mg)	357 (41.8%)	96 (11.2%)	261 (30.6%)	0.031
Non-loading	497 (58.2%)	168 (19.7%)	329 (38.5%)	0.031

Values are either mean (SD) or *n* (%)
*examined in 851 patients (263 patients in No-HTPR and 588 patients in HTPR).
HPTR: high on-treatment platelet reactivity, eGFR: estimated glomerular filtration rate, PCI: percutaneous coronary intervention, CABG: coronary artery bypass grafting, MI: myocardial infarction, AP: angina pectoris, PAD: peripheral arterial disease, HF: heart failure, ACE: angiotensin converting enzyme, ARB: angiotensin II receptor blocker, CAD: coronary artery disease, ACS: acute coronary syndrome, MI: myocardial infarction, RCA: right coronary artery, LAD: left anterior descending coronary artery, LCX: left circumflex coronary artery, LMT: left main trunk, HL: high lateral branch, EES: everolimus-eluting stent, PES: paclitaxel-eluting stent, SES: sirolimus-eluting stent, ZES: zotarolimus-eluting stent, BES: biolimus-eluting stent.

Table 2. One-year outcome rates by platelet reactivity

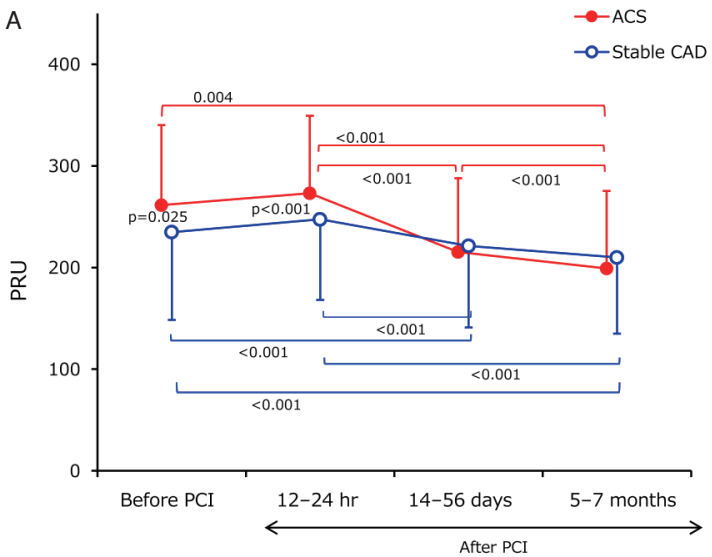
	Overall, $n=854$ *n* (%)	No-HTPR, $n=264$ *n* (%)	HTPR, $n=590$ *n* (%)	OR	95% CI		*P*-value
					lower	upper	
MACCE	39 (4.1%)	4 (1.5%)	35 (5.9%)	4.099	1.442	11.654	0.008
Death, all-cause	9 (1.1%)	0 (0.0%)	9 (1.5%)				
Cardiovascular death	7 (0.8%)	0 (0.0%)	7 (1.2%)				
Stent thrombosis	4 (0.5%)	0 (0.0%)	4 (0.7%)				
Non-fatal myocardial infarction	22 (2.6%)	3 (1.1%)	19 (3.2%)				
Ischemic stroke	4 (0.5%)	1 (0.4%)	3 (0.5%)				
Revascularization	37 (4.3%)	8 (3.0%)	29 (4.9%)	1.654	0.746	3.669	0.216
Bleeding	18 (2.1%)	5 (1.9%)	13 (2.2%)	1.167	0.412	3.308	0.771
TIMI scale							
Major	9 (1.1%)	5 (1.9%)	4 (0.7%)				
Minor	2 (0.2%)	0 (0.0%)	2 (0.3%)				
Minimal	7 (0.8%)	0 (0.0%)	7 (1.2%)				

HTPR: high on-treatment platelet reactivity, CI: confidence interval, MACCE: major adverse cardiac and cerebral events, TIMI: Thrombosis in Myocardial Infarction

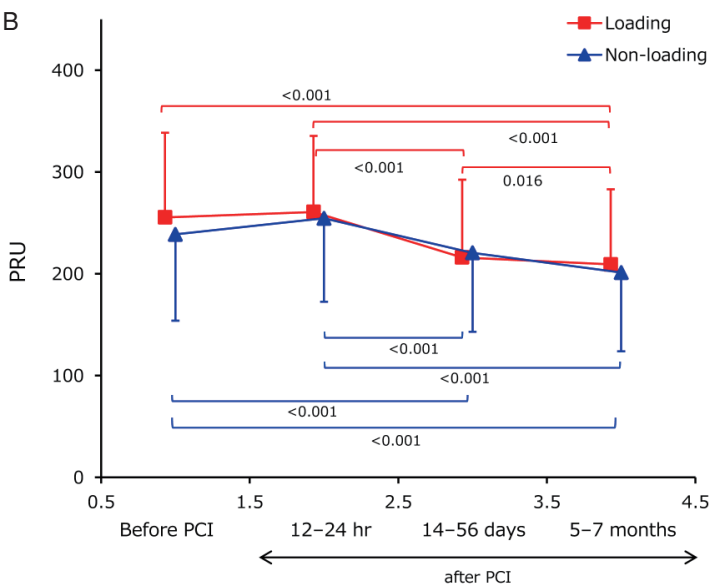
HTPR status. In the overall population, the incidence of HTPR was 69.1%. Patients with HTPR were older (68.5 ± 9.7 years vs. 66.0 ± 10.4 years, $p=0.001$) and more likely to be male (50.0% vs 27.2%, $p<0.001$). More patients were current smokers (14.4% vs. 9.6%, $p=0.001$) among the HTPR population. The presence of dyslipidemia, having undergone PCI previously, and clopidogrel loading or non-loading treatment were associated with HTPR. The prevalence of concurrent use of medications between the two groups was similar, except for cilostazol and proton pump inhibitors (both of which were taken more frequently by patients with HTPR).

Outcome at 1 Year by HTPR Status

Clinical follow-up at 1 year was completed by all



	Before PCI			After PCI, 12-24 hr			After PCI, 14-56 days			After PCI, 5-7 months		
	n	mean	(SD)	*n*	mean	(SD)	*n*	mean	(SD)	*n*	mean	(SD)
All	405	243.1	(83.4)	854	257.1	(79.1)	1006	220.2	(77.7)	587	203.3	(74.4)
ACS	151	264.2	(83.4)	322	273.1	(76.3)	427	217.4	(72.2)	255	199.2	(74.7)
Stable CAD	254	235.6	(86.2)	532	247.4	(79.3)	579	221.8	(80.9)	332	206.5	(74.2)



	Before PCI			After PCI, 12-24 hr			After PCI, 14-56 days			After PCI, 5-7 months		
	n	mean	(SD)	*n*	mean	(SD)	*n*	mean	(SD)	*n*	mean	(SD)
All	405	243.1	(86.3)	854	257.1	(79.1)	1006	220.2	(77.7)	587	203.3	(74.4)
Loading	146	255.6	(89.4)	357	260.7	(74.8)	427	218.0	(77.5)	296	209.0	(73.1)
Non-loading	259	237.4	(84.3)	497	254.5	(82.0)	579	221.7	(77.9)	291	197.5	(75.5)

Fig. 2. Platelet reactivity before and after PCI

A: Platelet reactivity in patients with ACS (●) or with stable CAD (○).
B: Platelet reactivity in patients treated with loading (■) or non-loading (▲) doses of clopidogrel.

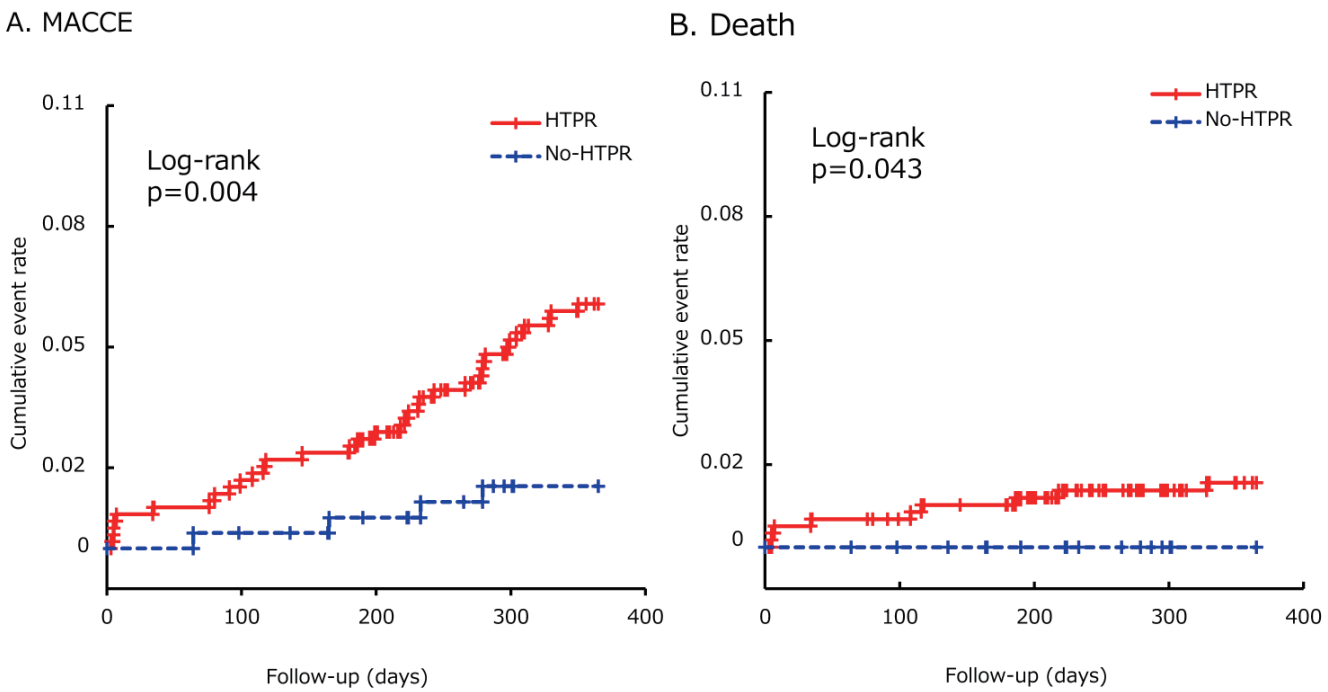


Fig. 3. Kaplan–Meier analysis of 1-year MACCE (A) and all-cause death (B) in patients with and without HTPR
HTPR ( ), No-HTPR ( )

patients. The ischemic cutoff value (221 PRU) that we established was capable of distinguishing between patients with and without MACCE and death at the 1-year follow-up (**Fig. 3**). However, ROC analysis of bleeding events demonstrated that the VerifyNow test could not discriminate between patients with or without TIMI major/minor/minimal bleeding. **Table 2** shows observed clinical outcomes according to HTPR status. At the 1-year follow-up, the MACCE rate was higher among patients with HTPR compared with those without HTPR. All-cause death and cardiovascular death also occurred more frequently in patients with HTPR. We analyzed the OR according to platelet reactivity in patients with stable CAD and ACS (**Table 3**). HTPR (>221 PRU) was not associated with the increased rate of MACCE both in stable CAD and ACS, although there was a trend toward a higher rate of MACCE in patients with ACS (p=0.067).

When we applied an alternative definition of HTPR (>208 PRU), as used in the ADAPT-DES study[12], HTPR was significantly associated with an increased rate of MACCE (OR: 4.086, 95% CI: 1.245–13.407, p=0.02), indicating that analogous results to those using >221 PRU were obtained. However, the incidence of HTPR >208 PRU was 75.4% (644/854) in our study compared with 42.8% (3,610/8,449) in the ADAPT-DES study.

Multivariate Cox regression analysis of ischemic clinical events showed that HTPR (>221 PRU) was associated with a significantly higher risk of MACCE at 1-year (HR: 4.168, 95% CI: 1.469–11.827, p=0.007) after adjusting for potential confounders associated with endpoints on univariate Cox regression analysis (age, sex, body mass index [BMI], DM, chronic kidney disease, C-reactive protein level of 3 mg/L, ACS presentation, and multi-vessel disease). HTPR, three-vessel disease, eGFR <15 mL/min/1.73 m^2, ACS presentation, and BMI (kg/m^2) were independent predictors for 1-year composite ischemic events. Statin treatment was significantly associated with a reduced risk of composite ischemic events (**Table 4**).

Multivariate Cox regression analysis of TIMI major/minor/minimal bleeding events showed that age ≥ 75 years and eGFR <15 mL/min/1.73 m^2 were associated with a significantly higher risk of bleeding events at 1 year (age ≥ 75 years HR: 4.212, 95% CI: 1.764–10.056, p=0.001; eGFR <15 mL/min/1.73 m^2 HR: 3.733, 95% CI: 1.087–12.817, p=0.036) after adjusting for potential confounders associated with endpoints on univariate Cox regression analysis (age ≥ 75 years, body weight ≤ 45 kg, sex, and eGFR < 15 mL/min/1.73 m^2).

Table 3. Outcome rates according to platelet reactivity in patients with stable CAD and ACS

	Stable-CAD, *n* = 532					ACS, *n* = 322				
	n (%)	No-HTPR, *n* = 188, *n* (%)	HTPR, *n* = 344, *n* (%)	OR (95% CI)	*p*	*n* (%)	No-HTPR, *n* = 76, *n* (%)	HTPR, *n* = 246, *n* (%)	OR (95% CI)	*p*
MACCE	18 (3.4%)	3 (1.6%)	15 (4.4%)	2.812 (0.803–9.839)	0.106	21 (6.5%)	1 (1.3%)	20 (8.1%)	6.637 (0.876–50.298)	0.067
Death, all-cause	2 (0.4%)	0 (0.0%)	2 (0.6%)	-		7 (2.2%)	0 (0.0%)	7 (2.8%)	-	
Cardiovascular death	1 (0.2%)	0 (0.0%)	1 (0.3%)	-		6 (1.9%)	0 (0.0%)	6 (2.4%)	-	
Stent thrombosis	3 (0.6%)	0 (0.0%)	3 (0.9%)	-		1 (0.3%)	0 (0.0%)	1 (0.4%)	-	
Non-fatal myocardial infraction	11 (2.1%)	3 (1.6%)	8 (2.3%)	1.468 (0.385–5.602)	0.574	11 (3.4%)	0 (0.0%)	11 (4.5%)	-	
Ischemia stroke	2 (0.4%)	0 (0.0%)	2 (0.6%)	-		2 (0.6%)	1 (1.3%)	1 (0.4%)	0.306 (0.019–4.953)	0.405
Revascularization	20 (3.8%)	7 (3.7%)	13 (3.8%)	0.437 (0.105–1.817)	0.255	17 (5.3%)	1 (1.3%)	16 (6.5%)	1.143 (0.065–20.018)	0.927
Bleeding	9 (1.9%)	2 (1.14%)	7 (2.0%)	1.932 (0.397–9.394)	0.415	10 (3.1%)	3 (3.9%)	7 (2.2%)	0.713 (0.180–2.826)	0.713
TIMI Major	4 (0.8%)	2 (1.1%)	2 (06%)	0.544 (0.076–3.892)	0.544	6 (1.6%)	3 (3.9%)	3 (1.2%)	0.300 (0.059–1.520)	0.146
TIMI Minor	1 (0.2%)	0 (0.0%)	1 (0.3%)	-		1 (0.3%)	0 (0.0%)	1 (0.4%)	-	
TIMI Minimal	7 (0.8%)	0 (0.0%)	1 (0.3%)	-		3 (0.9%)	0 (0.0%)	3 (1.2%)	-	

HTPR: high on-treatment platelet reactivity, OR: odds ratio, CI: confidence interval, MACCE: major adverse cardiac and cerebral events, TIMI: Thrombosis in Myocardial Infarction

Table 4. Predictors of MACCE by multivariate Cox hazard analysis

	HR	95% CI	*P*
HTPR >221 PRU	4.168	1.469–11.827	0.007
Three-vessel disease	4.138	1.194–14.344	0.025
eGFR <15 mL/min/1.73 m^2	2.667	1.065–6.681	0.036
ACS	1.58	0.824–3.031	0.169
BMI, kg/m^2	1.119	1.023–1.223	0.014
Statin treatment	0.341	0.174–0.666	0.002

HR: hazard ratio, CI: confidence interval, PRU: P2Y12 reaction unit, HTPR: high on-treatment platelet reactivity, eGFR: estimated glomerular filtration rate, ACS: acute coronary syndrome, BMI: body mass index.

Discussion

HTPR in patients receiving DAPT after coronary intervention has been associated with an increased risk for ischemic events, although the relationship has been less characterized in Japanese patients. The primary finding of this prospective observational study was that the presence of HTPR (>221 PRU) at 12–24 h after

PCI was significantly and independently associated with an increased risk for ischemic events (death, stent thrombosis, myocardial infarction, and ischemic stroke) and mortality. Of note, patients with ACS (37.7%) or stable CAD (62.3%) were included in the study population at proportions similar to those included in a recent meta-analysis (ACS, 41.5%; stable CAD, 58.5%) and, thus, were considered representative of the actual clinical population[23]. Platelet reactivity at 12–24 hours post PCI in patients with ACS was higher than in those with stable CAD, although platelet reactivity following clopidogrel loading was similar to that without loading. The cutoff value of 221 PRU determined using the VerifyNow-P2Y12 assay had relatively high sensitivity but low specificity for the prognostic risk of MACCE. Given that the majority of evaluated patients showed HTPR (>221 PRU), the prognostic value of platelet reactivity alone might be limited.

Multivariate Cox hazard analysis revealed that three-vessel disease, HTPR (>221 PRU), eGFR <15 mL/min/1.73 m^2, and BMI (kg/m^2) were independent predictive factors for MACCE, but that statin treatment was a negative risk factor. These data support the possibility that statin treatment may lead to fewer cardiovascular events owning to the LDL-cholesterol lowering effect as well as several pleotropic protective effects against the progression of atherosclerosis, although the extent of attainment of LDL-cholesterol guideline-recommended levels in post-PCI patients is unclear in this study.

In the present study in Japanese patients, the incidence of HTPR was markedly higher at 69.1% than that reported in previous studies in patients in Europe and the US[10-12], in which the incidence of HTPR was approximately 40%. A similar high prevalence (61.8%) of HTPR (>235 PRU) has also been reported among patients in Korea[24], while a post hoc analysis of the PRASFIT-ACS study in Japanese patients undergoing PCI also reported a high prevalence (69.6%) of HTPR (>262 PRU) among patients receiving clopidogrel[25]. Several reports have indicated ethnic differences in genetic polymorphisms for CYP2C19, clopidogrel treatment, OCT/IVUS usage, HTPR incidence, use of intravascular ultrasound/optical coherence tomography, and rate of clinical outcomes[7, 14]. Furthermore, platelet response can vary over time, and some studies have reported intra-individual variability in the P2Y12-ADP receptor blockade during maintenance therapy[26]. Although the acute effects of P2Y12-ADP receptor antagonist loading are well known, less has been reported on the long-term effects of loading doses, particularly in Japanese patients. It is of clinical relevance to determine these effects because optimized antiplatelet therapy during the maintenance phase after PCI can clearly determine the clinical outcome. Furthermore, a large proportion of patients with ACS require an additional PCI during the maintenance phase as a result of multi-vessel disease, and few studies to date have examined the optimal use of P2Y12-ADP receptor antagonists in this high-risk patient population[27].

The present study indicated that the TIMI major/minor/minimal bleeding cutoff point was not captured by the VerifyNow assay, consistent with the findings of the TRIAGE study[28]. The present study included more patients than the TRIAGE study; however, the results are comparable. Our findings also indicate that platelet function testing does not provide the necessary prognostic information to identify patients with higher bleeding risk, as, overall, few patients reported TIMI major/minor bleeding. Multivariate Cox hazard analysis revealed that age ≥ 75 years and eGFR <15 mL/min/1.73 m^2 were independent predictive factors for TIMI major/minor/minimal bleeding in the present study. Therefore, unlike the relationship of HTPR with thrombotic events, we found that on-treatment platelet reactivity appeared to have no association with TIMI major/minor bleeding events. Further studies in a larger population may be required to identify such a relationship.

By using prasugrel, which is not affected by the CYP2C19 polymorphism[29], instead of clopidogrel, it may be possible to overcome the effects of HTPR which may have implications for the prognostic utility of the VerifyNow P2Y12 assay and the identification of clinically effective strategies for P2Y12 antagonist therapy in Japanese PCI patients.

This study had several limitations. First, a relatively small number of patients were included, meaning that the study may have been underpowered to assess clinical outcome. Second, we measured platelet reactivity only using the VerifyNow P2Y12 assay, and different outcomes may have been obtained using other platelet function tests such as the vasodilator-stimulated phosphoprotein assay. Third, bleeding endpoints were assessed by TIMI criteria, such as the occurrence of the composite of TIMI major or minor bleeding. Fourth, we did not collect data regarding PCI access sites. The frequency of bleeding complications was too low, however, to determine clinical or laboratory predictors of hemorrhagic events. Finally, genetic testing, particularly for the CYP2C19 polymorphism, was not performed. The response to clopidogrel treatment is closely linked to the CYP2C19 polymorphism, and Japanese patients appear to have a higher rate of CYP2C19 loss-of-function gene alleles compared with Caucasian patients[18]. A high prevalence of the CYP2C19 polymorphism in our study population might have confounded the results of our study.

Conclusion

HTPR was significantly associated with adverse ischemic outcomes at 1 year after PCI in Japanese patients receiving maintenance DAPT, indicating its potential as a prognostic indicator of clinical outcomes in this high-risk patient population.

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Conflict of Interest

M Nishikawa has received honoraria from Daiichi Sankyo and clinical research funding from Daiichi Sankyo and Otsuka Pharmaceutical. K Kimura has received honoraria from AstraZeneca and Daiichi Sankyo, clinical research funding from Daiichi Sankyo, and a scholarship grant from Daiichi Sankyo. T Takayama has received clinical research funding from Daiichi Sankyo and Tanabe Mitsubishi. A Hirayama has received honoraria from TOA EIYO, Boehringer Ingelheim Japan, Sanofi, Astellas Pharma, Sumitomo Dainippon Pharma, Bristol-Myers Squibb, Amgen Astellas Biopharma, AstraZeneca, Daiichi Sankyo and Bayer Yakuhin, and teaches courses endowed by Boston Scientific Japan, Otsuka Pharmaceutical, Fukuda Denshi, St. Jude Medical Japan, Medtronic Japan, and Japan Lifeline. T Isshiki has received patent royalties from Nipro, honoraria from Sanofi and Daiichi Sankyo, and clinical research funding from Daiichi Sankyo. H Yokoi has received honoraria from Daiichi Sankyo, Sanofi, Bayer Yakuhin, Terumo, and a scholarship grant from Daiichi Sankyo. The other authors have no conflicts of interest to declare.

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