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, 0.51–0.688, *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
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\(^(*2\text{ and } *3\text{ variants})\) 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.
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 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. 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).

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 Vacutette® (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 assay to distinguish between 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 χ² 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 endpoint 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 founders 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).
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, \( p = 0.051 \)) (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, \( p = 0.051 \)).

**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

| Demographics | All patients, n = 854 | No-HTPR, n = 264 | HTPR, n = 590 | P-value |
|--------------|-----------------------|------------------|---------------|---------|
| 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/m² | 24.3 (3.4)     | 24.4 (3.2)       | 24.2 (3.5)    | 0.476   |
| ≥ 25 kg/m²*  | 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 m² | 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   |
ment 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

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

|                | All patients, n = 854 | No-HTPR, n = 264 | HTPR, n = 590 | OR  | 95% CI lower | 95% CI upper | P-value |
|----------------|-----------------------|------------------|--------------|-----|--------------|--------------|---------|
| MACCE          |                       |                  |              |     |              |              |         |
| Death, all-cause| 39 (4.1%)             | 4 (1.5%)         | 35 (5.9%)    | 4.099| 1.442        | 11.654       | 0.008   |
| 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%)     |     |              |              |         |

Values are either mean (SD) or n (%)
*examined in 851 patients (263 patients in No-HTPR and 588 patients in HTPR).

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).
**Platelet Reactivity in Coronary Stenting**

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.
Multivariate Cox regression analysis of ischemic clinical events showed that HTPR (\(\geq 221\) 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 \(\leq 15\) 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 \(\geq 75\) years and eGFR <15 mL/min/1.73 m\(^2\) were associated with a significantly higher risk of bleeding events 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).

When we applied an alternative definition of HTPR (\(\geq 208\) 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.
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.

**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. 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 m², and BMI (kg/m²) 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 m² 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, Agen Astellas Biopharma, AstraZeneca, Daiichi Sankyo and Bayer Yakuhin, and teaches courses endowed by Boston Scientific Japan, 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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