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Platelet Reactivity and Clinical Outcomes After Drug-Eluting Stent Implantation

Results From the PTRG-DES Consortium

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on behalf of the PTRG Investigators

ABSTRACT

BACKGROUND The long-term prognostic implication of platelet reactivity after percutaneous coronary intervention (PCI) is not clearly known.

OBJECTIVES The impacts of platelet reactivity from the PTRG-DES consortium were assessed.

METHODS The primary endpoint was the major adverse cardiac and cerebrovascular events (MACCE) including all-cause death, myocardial infarction, stent thrombosis, or stroke. Key secondary endpoints were all-cause mortality, major bleeding, and net adverse clinical events (NACE), including MACCE and bleeding.

RESULTS Between 2003 and 2018, a total of 11,714 patients were enrolled and grouped into tertiles according to $P2Y_{12}$ reaction units (PRUs): high PRUs (≥253), intermediate PRUs (188-252), and low PRUs (<188). The Kaplan-Meier (KM) estimates of the primary outcome were significantly different across the groups; the high-PRU group showed the highest MACCE rate at 5 years (12.9%, 11.1%, and 7.0% in high-, intermediate-, and low-PRU groups, respectively; $P < 0.001$), as well as at 1 year ($P < 0.001$). The high-PRU group had the greatest KM estimates of all-cause death (8.2%, 5.9%, and 3.7%, respectively; $P < 0.001$) at 5 years without significant differences of major bleeding, and resultant of a higher KM estimates of NACE (15.7%, 13.6%, and 9.7%, respectively; $P < 0.001$). A PRU ≥252, the best cutoff value, was strongly related to MACCE (HR: 1.39; 95% CI: 1.11-1.74; $P = 0.003$) and all-cause death at 5 years after PCI (HR: 1.42; 95% CI: 1.04-1.94; $P = 0.026$). The optimal cutoff value of aspirin reaction units predicting the MACCE occurrence was ≥414 and was significantly associated with 5-year MACCE occurrence or all-cause death ($P < 0.001$).

CONCLUSIONS In this large-scale cohort, high PRU was significantly associated with occurrence of MACCE, all-death death, and NACE at 5 years, as well as 1 year after PCI. (PTRG-DES Consortium [PTRG]; NCT04734028)
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High platelet reactivity (HPR) has been recognized as a strong predictor of ischemic events after percutaneous coronary intervention (PCI).[1] Dual antiplatelet therapy (DAPT) with aspirin and a $P2Y_{12}$ inhibitor is the standard of care for patients with drug-eluting stent (DES) implantation. Thus, understanding clinical impact of antiplatelet effect in patients on DAPT is

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ABBREVIATIONS AND ACRONYMS

ANOVA = analysis of variance

ARU = aspirin reaction unit

DAPT = dual antiplatelet therapy

DES = drug-eluting stent(s)

HPR = high platelet reactivity

MACCE = major adverse cardiac and cerebrovascular event(s)

MI = myocardial infarction

NACE = net adverse clinical event(s)

PCI = percutaneous coronary intervention

PFT = platelet function test

PRU = $P2Y_{12}$ reaction unit

ST = stent thrombosis

of great clinical importance. In addition, due to the coexisting risks of bleeding and ischemia after DES implantation, it is important to identify an optimal therapeutic window for platelet inhibition that can effectively suppress ischemic events while minimizing the risks of bleeding.[2] By taking the advantage of platelet function assessment, numerous studies on utilizing HPR after DES implantation have been conducted.[3,4]

SEE PAGE 2266

However, individual pharmacodynamic responses to antiplatelet agents are quite heterogeneous according to genetic predisposition and environmental modifications.[5] Indeed, platelet reactivity is recognized to be significantly affected by biodemographic factors such as gender and ethnicity, as well as by clinical risk factors including diabetes mellitus and chronic kidney disease.[5] Additionally, an accumulating body of evidence supports that the East Asian population has unique ischemic and bleeding risk ratios that are distinct from that of Western populations, indicating different optimal therapeutic windows of platelet inhibiton.[6,7] However, prognostic implications of on-treatment platelet reactivity after PCI in East Asian patients are not clearly demonstrated.[8] Thus, we sought to investigate the long-term effects of platelet reactivity on the occurrence of clinical events after DES implantation in the Korean population by using a large-scale, nationwide, multicenter cohorts.

METHODS

STUDY POPULATION. The multicenter PTRG-DES (Platelet function and genoType-Related long-term proGnosis in Drug-Eluting Stent-treated patients with coronary artery disease) consortium is a multicenter, real-world registry of patients who underwent PCI with DES and received DAPT of aspirin and clopidogrel in South Korea (NCT04734028).[9] An organizing committee of the PTRG-DES investigators was established to define their scientific goals. The organizing committee invited the lead investigators of clopidogrel-related prospective clinical registries published on ClinicalTrials.gov as of January 2018 to participate. Finally, 9 prospective registries from 32 Korean academic centers have joined the PTRG-DES consortium. The Institutional Review Board of each participating center approved the registry and waived the requirement for written informed consent for access to an institutional registry. The study was performed in accordance with the Good Clinical Practice Guidelines and the principles of the Declaration of Helsinki.

Consecutive patients at each center were successfully treated with 1 or more DES approved by the U.S. Food and Drug Administration or CE mark, and those who were adequately loaded with aspirin and clopidogrel were eligible for enrollment, regardless of patient or lesion complexity. The exclusion criteria were the occurrence of a major complication during the procedures, PCI strategies other than DES (balloon angioplasty only or use of bare-metal stents), use of any $P2Y_{12}$ inhibitor other than clopidogrel, or oral anticoagulants. The study flow of this study is provided in the Supplemental Figure 1.

PROCEDURES AND PLATELET FUNCTION TEST. All PCI procedures were performed according to the standard techniques.[10] Following procedures, patients were administered with 100 mg aspirin and 75 mg clopidogrel per day. Patients were recommended with aspirin indefinitely and clopidogrel for at least 1 year, and all other treatments were per standard of care. Acute coronary syndrome patients treated with ticagrelor or prasugrel were not included in this study. Clinical outcomes were evaluated until the last outpatient visit.

A platelet function test (PFT) for measuring the platelet reactivity was conducted after an adequate period to ensure the full antiplatelet effect, using the VerifyNow assay (Accriva). Aspirin was given as either: 1) a coated oral dose of 300 mg for at least 6

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hours; or 2) a dose of 100 mg at least 5 days before PCI. Clopidogrel was given as: 1) a dose of 600 mg for at least 6 hours; 2) a dose of 300 mg for at least 12 hours; or 3) a dose of 75 mg for at least 5 days before PCI. No patients receiving abciximab were enrolled because of a long washout period. A VerifyNow Aspirin test for measuring the aspirin reaction units (ARUs) were performed in 7,162 patients. The VerifyNow assay is a whole-blood, point-of-care, turbidimetric optical detection assay designed to measure agonist-induced platelet aggregation. Blood samples were collected in 3.2% citrate Vacuette tubes (Greiner Bio-One Vacuette North America). The measurement protocol followed the manufacturer's recommendation, and the details are described elsewhere.[1] Data from the PFT were collected as continuous measures: VerifyNow $P2Y_{12}$ reaction units (PRUs) and ARUs.

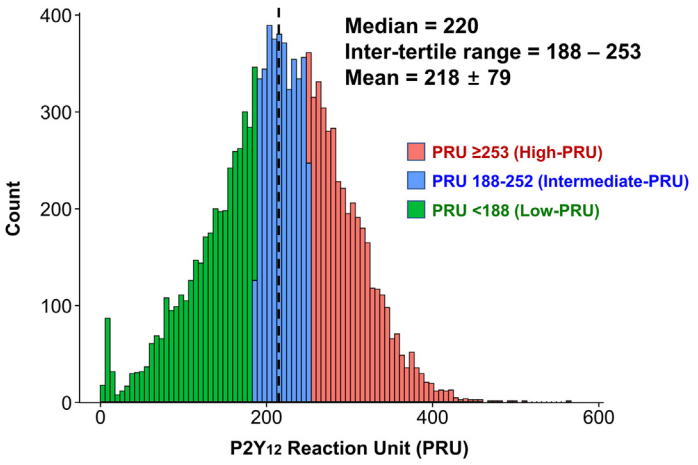
OUTCOME DEFINITIONS. The primary endpoint was the occurrence of major adverse cardiac and cerebrovascular events (MACCE) including all-cause death, myocardial infarction (MI), stent thrombosis (ST), or stroke for 5 years after PCI. Key secondary endpoints were all-cause death, major bleeding (Bleeding Academic Research Consortium type 3-5),[11] and net adverse clinical events (NACE), including MACCE and major bleeding. Other secondary endpoints included the composite of cardiovascular death, MI, and ST, and other individual events (cardiovascular death, MI, ST, any revascularization, or stroke).

MI after discharge was defined as the presence of clinical symptoms, electrocardiographic changes, or abnormal imaging findings associated with MI combined with an increase in creatine kinase-myocardial band above the upper normal limit or troponin T/I greater than the 99th percentile of the upper limit of normal, unrelated to an interventional procedure.[12] ST was defined as definite ST according to the Academic Research Consortium criteria.[13] Cardiovascular death was defined as: 1) death due to MI, cardiac perforation, or pericardial tamponade; arrhythmia or conduction abnormality; or stroke within 30 days of the procedure or related to the procedure; 2) death due to procedural complication; or 3) any case of death in which a cardiac cause could not be excluded. Stroke included any new embolic, thrombotic, or hemorrhagic stroke events with neurologic deficits that persisted for at least 24 hours. Any revascularization included PCI or bypass surgery on either target or nontarget vessels. Fatal bleeding was defined as any death occurring within 10 days of a major bleeding episode.

STATISTICAL ANALYSIS. Continuous variables are reported as the mean ± SD. One-way analysis of variance or Kruskal-Wallis test was used to compare the 3 independent groups according to PRU value, followed by Holm's sequential Bonferroni post hoc analysis. Student's *t*-test or the Mann-Whitney *U* test was used to compare between 2 groups according to the cutoff value of PRUs. Categorical variables are presented as number and percentage and compared using the chi-square test or Fisher exact test. Event rates were compared using the Kaplan-Meier survival analysis and compared using the log-rank test. HRs with 95% CIs were computed using a Cox regression analysis. The relationship between HPR and subsequent clinical outcomes using standard receiver-operating characteristic curve analyses was assessed.

To identify independent predictors of each clinical outcome, univariate and multivariate Cox regression analyses were conducted by formulating 2 regression models: model 1 included only the variables with $P < 0.10$ in the univariate analyses and PRU value, and model 2 included major clinical or procedural risk factors along with the variables included in model 1. Based on a previous study that identified a best cutoff value of PRU for ischemic events in Korea,[14] HPR on clopidogrel was defined as a PRU value of 252 or higher that predicted the occurrence of MACCE at 5 years with an area under the curve of 0.56, a sensitivity of 0.46, and a specificity of 0.66 ($P < 0.001$). After adjustment for contributing variables such as age, sex, body mass index, chronic kidney disease, and diabetes, the area under the curve of a PRU ≥252 for prediction of MACCE was 0.67. To examine the relationship between PRUs (as the continuous variable) and MACCE, restricted cubic spline curve was plotted to explore a potential nonlinear relationship.[15] Sensitivity analyses were conducted to assess the robustness of primary finding in the entire population according to: 1) clinical presentation (chronic coronary syndrome vs acute coronary syndrome); 2) year of PCI (2003-2010 vs 2011-2018); 3) type of DES (second-generation DES vs first-generation DES). Propensity score matchings were also conducted to according to the cutoff value of PRUs and ARUs by including variables such as age, sex, diabetes, chronic kidney disease, body mass index, hemoglobin level, multivessel disease, and heart failure for calculation of propensity score. All data were processed using SAS version 9.2 (SAS Institute).

FIGURE 1 Distribution of PRUs



Enrolled patients were assigned to 1 of 3 groups according to $P2Y_{12}$ reaction unit (PRU) tertile values (intertertile range: 188-253): high-PRU **(red)**, intermediate-PRU **(blue)**, and low-PRU **(green)** groups. The **dotted line** indicates the median PRU value. Values are mean ± SD.

All tests were 2-sided, and *P* values of <0.05 were considered statistically significant.

RESULTS

Among the 13,160 DES-treated patients between July 2003 and August 2018, a total of 11,714 patients conducting the PFT using the VerifyNow $P2Y_{12}$ assay were finally enrolled for this study (Supplemental Figure 1).

PRU VALUE AND CLINICAL CHARACTERISTICS. The distribution of PRU values among enrolled patients is provided in **Figure 1**. The median PRU value was 220 (intertertile range: 188-253). Patients were classified into the 3 groups according to PRU distribution: 1) a PRU value of ≥253 (high-PRU group), n = 3,881 (33.0%); 2) PRU value of 188-252 (intermediate-PRU group), n = 3,921 (33.0%); and 3) a PRU value <188 (low-PRU group), n = 3,912 (33.0%). The high-PRU group was more likely to be older and have female sex, with higher prevalence of cardiovascular comorbidities (eg, diabetes mellitus, hypertension, chronic kidney disease) and multivessel disease; by contrast, the low-PRU group was more likely to be a current smoker (**Table 1**). A significant difference in index presentation as acute MI was identified among the groups. The high-PRU group had lower baseline levels of hemoglobin, white blood cells, and platelets than the low-PRU group. The prevalence of prolonged DAPT administration (duration >12 months) was not significantly different among the groups. Information on the prescribed antiplatelet agent after cessation of DAPT is presented in Supplemental Table 1.

PRU VALUE AND CLINICAL OUTCOME. The median duration of follow-up was 551 (IQR: 365-1,752) days. The occurrence and Kaplan-Meier estimates fort the primary and secondary outcomes at 1 or 5 years after PCI are presented in **Table 2** according to the tertile distribution of PRUs. At 5 years after DES implantation, the Kaplan-Meier estimates for the primary endpoint of MACCE were 12.9% in the high-PRU group, 11.1%, intermediate-PRU group, and 7.0%, low-PRU group (HR for high-PRU group vs low-PRU group: 1.93; 95% CI: 1.59-2.34; $P < 0.001$; HR for high-PRU group vs intermediate-PRU group: 1.23; 95% CI: 1.04-1.45; $P = 0.018$) (**Central Illustration**), as well as at 1 year after PCI ($P < 0.001$ by analysis of variance [ANOVA]).

Furthermore, all-cause mortality was significantly greater in the high-PRU group than in the intermediate-PRU and the low-PRU groups at 1 and 5 years after PCI (all $P < 0.001$ by ANOVA) (**Table 2, Central Illustration**). However, no significant difference in the incidence of major bleeding or fatal bleeding was found among the groups (**Table 2, Figure 2A**). Consequently, the risk of NACE including both MACCE and major bleeding at 5 years after PCI was significantly greater in the high-PRU group than in the intermediate-PRU (10.2% vs 8.0%; HR: 1.50; 95% CI: 1.19-1.88; $P < 0.001$) and the low-PRU (10.2% vs 5.9%; HR: 2.23; 95% CI: 1.72-2.89; $P < 0.001$) groups (**Figure 2B**), as well as at 1 year after PCI ($P < 0.001$ by ANOVA). For the occurrence of other secondary outcomes at 5 years after PCI, the high-PRU group (3.7%) compared with the low-PRU group (1.9%) showed a significantly higher rate of the composite endpoint of cardiovascular death, MI, and ST (HR: 2.00; 95% CI: 1.50-2.66; $P < 0.001$) (**Table 2**). On the individual event, cardiac death (HR: 2.22; 95% CI: 1.47-3.34; $P < 0.001$) or ST (HR: 3.95; 95% CI: 1.89-8.22; $P < 0.001$) was more frequently observed in the high-PRU group as compared with the low-PRU group at 1 and 5 years after PCI.

ASSOCIATION BETWEEN HPR AND CLINICAL EVENTS. The PRU value was linearly correlated with risk of MACCE at 5 years after PCI (**Figure 3A**). The cutoff PRU value (252) significantly separated patients at higher and lower risk for ischemic events; a PRU value ≥252 was associated with greater risk of MACCE occurrence at 5 years after PCI (unadjusted HR: 1.52; 95% CI: 1.31-1.76; $P < 0.001$) (**Figure 3B**). After adjustment for the covariates that were significant in the univariate analysis (model 1) or well-

TABLE 1 Baseline Characteristics

	High PRU (≥253; n = 3,881)	Intermediate PRU (188-252; n = 3,921)	Low PRU (<188; n = 3,912)	*P* Value
Age, y	67.1 ± 10.3	64.4 ± 10.7	61.7 ± 11.0	<0.001
Women	1,705 (43.9)	1,185 (30.2)	873 (22.3)	<0.001
Body mass index, kg/m^2	24.4 ± 3.2	24.7 ± 3.1	24.6 ± 3.1	0.001
Diabetes mellitus	1,495 (38.5)	1,381 (35.2)	1,181 (30.2)	<0.001
Hypertension	2,514 (64.8)	2,373 (60.5)	2,162 (55.3)	<0.001
Peripheral artery disease	561 (14.5)	817 (20.8)	443 (11.3)	<0.001
Chronic kidney disease	1,049 (27.0)	449 (11.5)	634 (16.2)	<0.001
Current smoker	826 (21.3)	749 (19.1)	1,351 (34.5)	<0.001
Prior percutaneous coronary intervention	528 (13.6)	530 (13.5)	510 (13.0)	0.730
Prior stroke	290 (7.5)	257 (6.6)	266 (6.8)	0.256
Presentation as acute myocardial infarction	1,145 (29.5)	1,020 (26.0)	1,173 (30.0)	<0.001
2- or 3-vessel disease	1,600 (41.2)	1,463 (37.3)	1,481 (37.9)	0.001
Left-main PCI	191 (4.9)	180 (4.6)	201 (5.1)	0.527
Laboratory tests				
Hemoglobin, g/dL	12.8 ± 1.7	13.7 ± 1.7	14.2 ± 1.8	<0.001
White blood cell count, ×10^3 cells/mm^3	7.7 ± 2.9	7.7 ± 2.8	8.1 ± 3.2	<0.001
Platelet count, ×10^3 cells/mm^3	233.3 ± 73.6	230.8 ± 69.5	236.8 ± 73.9	0.001
Discharge medication				
Beta-blocker	2,238 (57.7)	2,235 (57.0)	2,196 (56.1)	0.392
Angiotensin-converting enzyme or angiotensin receptor blocker	2,371 (61.1)	2,318 (59.1)	2,238 (57.2)	0.002
Calcium-channel blocker	956 (24.6)	879 (22.4)	982 (25.1)	0.012
DAPT duration				
<3 mo	291 (7.5)	252 (6.4)	256 (6.5)	0.122
>12 mo	1,766 (45.5)	1,772 (45.2)	1,804 (46.1)	0.312
≤12 mo	2,115 (54.5)	2,149 (54.8)	2,108 (53.9)	
>24 mo	1,102 (28.4)	1,082 (27.6)	1,072 (27.4)	0.432

Values are mean ± SD or n (%).
DAPT = dual antiplatelet therapy; PCI = percutaneous coronary intervention; PRU = P2Y$_{12}$ reaction unit.

established risk factors for ischemic events after PCI, as well as the significant covariates in the univariate regression (model 2), the incidences of 1-year and 5-year MACCE after DES implantation were significantly higher in patients with a PRU ≥252, compared with than those with a PRU <252 (**Table 3, Figure 3B,** Supplemental Table 2). In addition, a PRU ≥252 was significantly associated with increased risks of all-cause death and NACE at 1 and 5 years. The risk of major bleeding was not significantly different between these 2 groups. Sensitivity analyses revealed a consistent association of high PRU (≥252) with the risk of MACCE, all-cause death, or NACE, regardless of clinical presentation (Supplemental Table 3), year of PCI (Supplemental Table 4), or type of DES (Supplemental Table 5), and in a propensity score-matched population (Supplemental Tables 6 and 7).

ARU VALUE AND CLINICAL OUTCOME. From the PTRG-PFT cohort, a total of 7,162 (61.1%) patients had available results of the VerifyNow Aspirin test. The optimal cutoff value of ARUs that best predicted the occurrence of MACCE was 414, with an area under the curve of 0.55, a sensitivity of 0.62, and a specificity of 0.48 ($P < 0.001$). At 5 years after PCI, an ARU ≥414 (n = 4,350 [61.0%]) was significantly associated with the occurrence of MACCE, all-cause death, or NACE (all $P < 0.01$), while not being related to major bleeding compared with those with an ARU <414 (n = 2,812 [39.0%]) (**Table 4**). Consistent findings were observed in a propensity-matched population (Supplemental Tables 8 and 9). Depending on the cutoff values of PRU and ARU, 4 groups were classified; the rates of MACCE and all-cause death were significantly different among the groups (Supplemental Figure 2). Patients with a PRU ≥252 and ARU ≥414 showed the highest risk of MACCE and all-cause mortality at 1 and 5 years after PCI ($P < 0.001$).

COMPARISON WITH THE ADAPT-DES REGISTRY. The mean PRU value in the PTRG-DES cohort registry was significantly higher than that of the Assessment of Dual Antiplatelet Therapy With Drug-Eluting

TABLE 2 Occurrence and the Kaplan-Meier Estimates of Primary and Secondary Outcomes After Percutaneous Coronary Intervention per Tertile Value of PRU

	Follow-Up	High PRU (≥253; n = 3,881)	Intermediate PRU (188-252; n = 3,921)	Low PRU (<188; n = 3,912)	*P* Value[a]
Primary and key secondary outcomes					
MACCE	1 y	154 (4.1)	109 (2.8)	70 (1.8)	<0.001
	5 y	310 (12.9)	240 (11.1)	155 (7.0)	<0.001
All-cause death	1 y	84 (2.3)	48 (1.2)	36 (0.9)	<0.001
	5 y	189 (8.2)	119 (5.9)	81 (3.7)	<0.001
Major bleeding	1 y	83 (2.2)	70 (1.9)	67 (1.8)	0.886
	5 y	120 (4.2)	107 (4.3)	97 (3.7)	0.844
Net adverse cardiac events	1 y	219 (5.8)	170 (4.4)	126 (3.3)	<0.001
	5 y	397 (15.7)	314 (13.6)	230 (9.7)	<0.001
Other secondary outcomes					
Cardiovascular death, myocardial infarction, or stent thrombosis	1 y	84 (2.3)	51 (1.3)	34 (0.9)	<0.001
	5 y	142 (5.5)	97 (4.0)	73 (3.2)	<0.001
Cardiovascular death	1 y	46 (1.2)	25 (0.6)	19 (0.5)	<0.001
	5 y	74 (2.8)	36 (1.3)	34 (1.4)	<0.001
Myocardial infarction	1 y	35 (1.0)	18 (0.7)	9 (0.5)	0.042
	5 y	70 (3.0)	60 (2.7)	42 (2.0)	0.036
Stent thrombosis	1 y	35 (0.9)	18 (0.5)	9 (0.2)	<0.001
	5 y	35 (0.9)	18 (0.5)	9 (0.2)	<0.001
Stroke	5 y	67 (3.0)	70 (3.1)	42 (1.7)	0.017
Any revascularization	5 y	229 (8.8)	273 (9.5)	242 (9.5)	0.602
Fatal bleeding	5 y	31 (0.8)	26 (0.7)	19 (0.5)	0.226

Values are n (%). [a]*P* values adjusted by age, female sex, chronic kidney disease, and acute myocardial infarction.
MACCE = major adverse cardiac and cerebrovascular event(s); PRU = $P2Y_{12}$ reaction unit.

Stents (ADAPT-DES) registry (218 ± 79 vs 188 ± 97; $P < 0.001$),[1] resulting in a greater incidence of patients with a PRU >208 (cutoff value of ADAPT-DES registry: 56% vs 43%; $P < 0.001$). Likewise, the mean value of ARUs (444 ± 69 vs 419 ± 55; $P < 0.001$) and those with an ARU >550 (cutoff value of ADAPT-DES registry: 11% vs 6%; $P < 0.001$) was greater in the PTRG-DES cohort. Compared with the event rates of the ADAPT-DES registry, the PTRG-DES cohort showed significantly lower incidence rates of ST (0.5% vs 0.8%; $P = 0.013$), MI (0.7% vs 3.1%; $P < 0.001$), and all-cause death (1.4% vs 1.8%; $P = 0.022$) at 1 year after PCI.

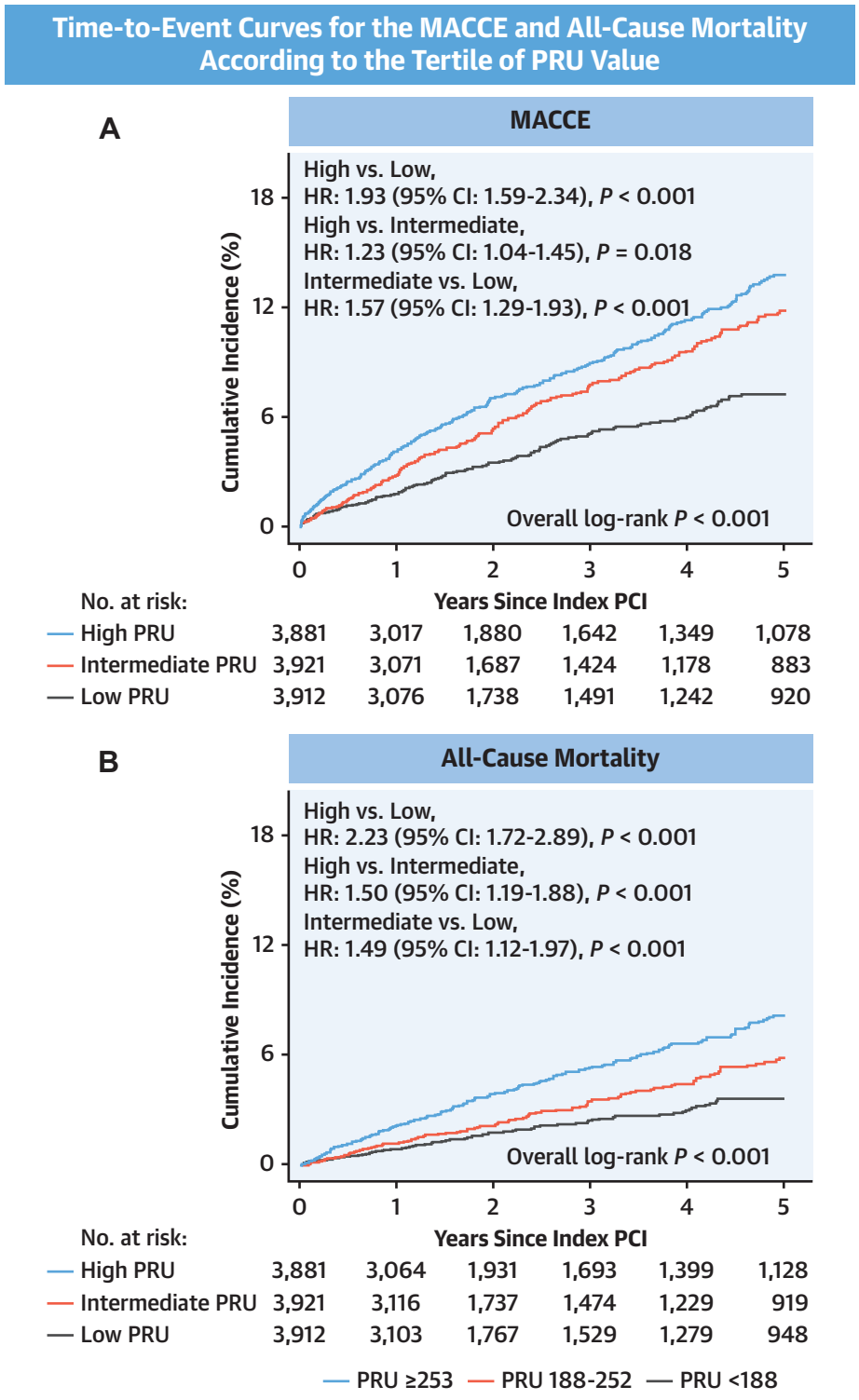
DISCUSSION

The principal findings from the nationwide, multicenter, PTRG-DES consortium are as follows: 1) to the best of our knowledge, the PTRG-DES consortium is the largest nationwide cohort that has investigated the long-term effect of platelet reactivity on ischemic and bleeding outcomes after DES implantation, particularly in East Asian patients; 2) HPR on clopidogrel is significantly associated with the increased risks for MACCE and mortality; 3) the optimal cutoff value of PRU for predicting MACCE occurrence in East Asian patients was 252, which is distinctly different than the values reported by Western patients (PRU >208)[1]; and 4) HPRs to clopidogrel and aspirin were particularly associated with the increased risk of ischemic outcomes including mortality.

DAPT with aspirin and clopidogrel is the mainstay of treatment in patients with stable coronary artery diseases undergoing DES implantation in contemporary practice.[16] For high-bleeding-risk patients having the diverse spectrums, clopidogrel-based DAPT is still preferred, even in the era of potent $P2Y_{12}$ inhibitors, for acute coronary syndrome.[17,18] In addition, $P2Y_{12}$ inhibitor monotherapy is gaining much attention as a maintenance therapy after cessation of DAPT.[2,19,20] However, the highly heterogeneous antiplatelet effect of clopidogrel could be the primary obstacle for the wide and safe extension of antiplatelet therapy using clopidogrel. Thus, the evaluation of platelet reactivity under antiplatelet therapy would be essential for predicting and optimizing future ischemic and bleeding risks after DES implantation.

Previously, by analyzing the ADAPT-DES registry, which investigated 1-year clinical outcomes after DES implantation in 8,583 Western patients, Stone et al[1] reported that HPR on clopidogrel was strongly associated with the risk of MI and ST but inversely related to the occurrence of major bleeding without any significant relationship with mortality. However, no established data exist regarding the exact definition of HPR and the effects of HPR on clinical outcomes including both ischemic and bleeding outcomes, particularly in non-Western ethnicities. In the current PTRG-DES consortium of East-Asian patients who underwent PFT after DES implantation (n = 11,714), high PRU was significantly associated with the increased risks for MACCE at short- and long-term follow-up after PCI. Of note, even after adjusting for major clinical and procedural risk factors related to occurrence of ischemic events after PCI, HPR on clopidogrel was significantly associated with all-cause mortality. These findings are the first evidence to reveal a significant association between HPR and mortality after DES implantation from the long-term, clinically followed, largest-scale cohort investigating the roles of PFT after DES implantation. In contrast to the lower bleeding risk of the patients with high PRU reported from the ADAPT-DES registry, those with a high PRU value in the present PTRG-DES consortium demonstrated no significant bleeding risk as

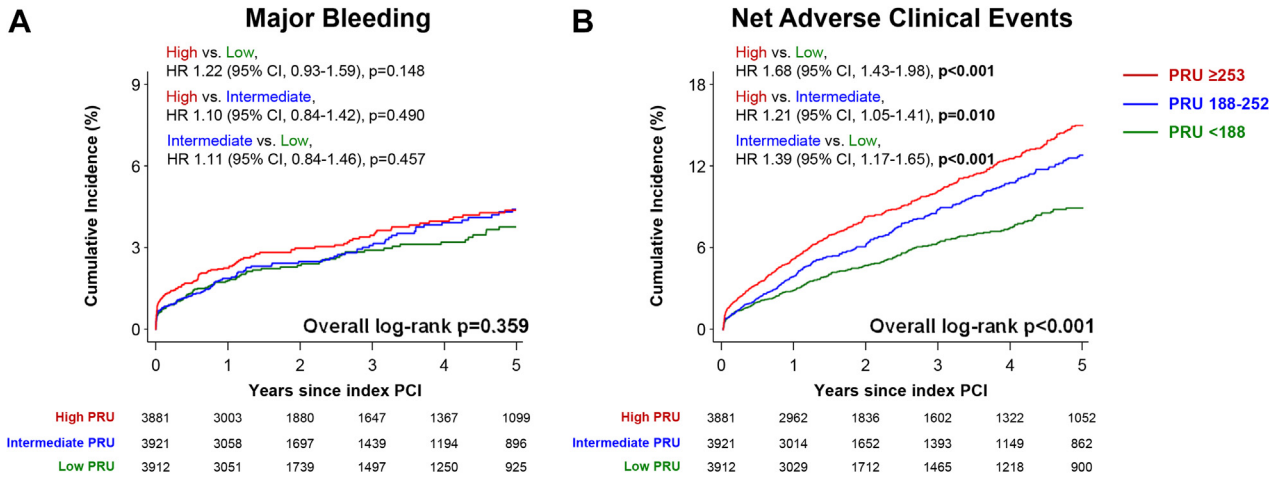
CENTRAL ILLUSTRATION **Platelet Reactivity and Outcomes Following PCI According to the Tertile of the PRU Value**



Lee S-J, et al. J Am Coll Cardiol Intv. 2022;15(22):2253–2265.

Time-to-event curves for **(A)** the primary outcome and **(B)** all-cause mortality according to $P2Y_{12}$ reaction unit (PRU) tertile. Kaplan-Meier estimates were conducted among tertile groups according to PRU values. Bonferroni correction was applied for multiple comparisons between the 2 groups. MACCE = major adverse cardiac and cerebrovascular event(s); PCI = percutaneous coronary intervention.

FIGURE 2 Secondary Outcomes According to PRU

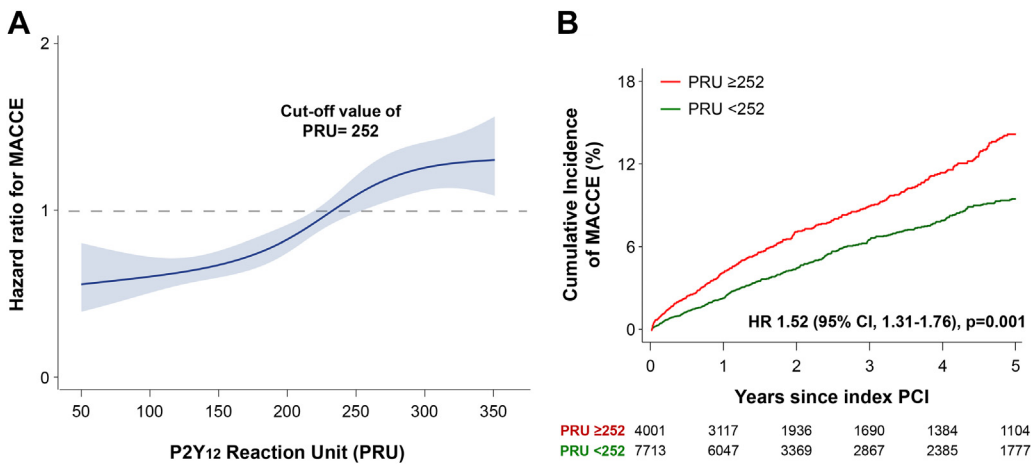


Time-to-event curves for **(A)** major bleeding and **(B)** net adverse clinical events according to $P2Y_{12}$ reaction unit (PRU) tertile. Kaplan-Meier estimates were conducted among tertile groups according to the PRU value. Bonferroni correction was applied for multiple comparisons between the 2 groups. PCI = percutaneous coronary intervention.

compared with those with a low PRU value. Consequently, when considering the risk of ischemic and bleeding outcomes simultaneously, patients with a high PRU value showed worse NACE than patients with a low PRU value.

As for the phenotypic distribution of the PFT across the ethnicities, the East-Asian population included in the present PTRG-DES consortium exhibited a higher mean PRU value and a higher cutoff PRU value predicting MACCE than the Western population in the ADAPT-DES study (PRU >208 in ADAPT-DES registry vs ≥252 in the PTRG-DES consortium). Meanwhile, despite the higher average value of PRUs, the incidence of ST or MI was relatively lower in the PTRG-

FIGURE 3 The Association Between High Platelet Reactivity (PRU ≥252) and the Risk of MACCE



(A) Spline curve depicting the association between PRU values (as a continuous variable) and the HR of major adverse cardiac and cerebrovascular events (MACCE) **(blue line)** (presented with 95% CI **[shaded area]**). **(B)** Kaplan-Meier estimates between the patients with a PRU ≥252 and a PRU <252. Abbreviations as in Figure 2.

TABLE 3 Incidence and Relative Risk of Primary and Key Secondary Outcomes After Percutaneous Coronary Intervention According to Cutoff Value of PRU (252)

Primary and Key Secondary Outcomes	Follow-Up	PRU ≥252 (n = 4,001)	PRU <252 (n = 7,713)	Adjusted HR (95% CI) (Model 1)[a]	Adjusted HR (95% CI) (Model 2)[b]
MACCE	1 y	155 (3.9)	171 (2.2)	1.39 (1.11-1.74)	1.36 (1.09-1.71)
	5 y	320 (8.0)	385 (5.0)	1.29 (1.11-1.50)	1.23 (1.06-1.44)
All-cause death	1 y	85 (2.1)	81 (1.1)	1.42 (1.04-1.94)	1.40 (1.03-1.90)
	5 y	194 (4.8)	195 (2.5)	1.41 (1.15-1.73)	1.30 (1.06-1.60)
Major bleeding	1 y	86 (2.1)	134 (1.7)	1.02 (0.77-1.34)	0.86 (0.65-1.14)
	5 y	125 (3.1)	199 (2.6)	1.02 (0.80-1.31)	0.86 (0.68-1.08)
Net adverse cardiac events	1 y	223 (5.6)	285 (3.7)	1.23 (1.03-1.47)	1.20 (1.01-1.43)
	5 y	412 (10.3)	529 (6.9)	1.22 (1.07-1.39)	1.17 (1.02-1.33)

Values are n (%), unless otherwise indicated. [a]Variables included age, female sex, chronic kidney disease, and acute myocardial infarction. [b]Variables included age, female sex, chronic kidney disease, acute myocardial infarction, body mass index ≥25 kg/m^2, hypertension, dyslipidemia, smoking, diabetes mellitus, current smoker, heart failure, prior percutaneous coronary intervention, prior stroke, multivessel disease, left main percutaneous coronary intervention, beta-blocker prescription at discharge, and angiotensin-converting enzyme inhibitor or receptor blocker prescription at discharge.

Abbreviations as in Table 2.

DES consortium. As the first plausible explanations for these differences, there was a significant difference in follow-up duration between the 2 studies, as well as in the design of cohort, which may have caused a differential impact of PRU on ischemic and bleeding outcomes. However, at 1-year after DES implantation, high PRU was not associated with the occurrence of major bleeding in the PTRG-DES consortium, whereas it showed significant inverse correlation in the ADAPT-DES registry, suggesting the ethnicity-specific response to HPR to clopidogrel as the second possible explanation for this difference between the cohorts. Supporting our findings, a Japanese cohort also found that a low PRU value was not associated with increased risk of bleeding, whereas a high PRU value was significantly correlated with the risk of ischemic events.[21] Taken together, these findings suggest that the effect of PRUs on ischemic outcomes could be universal irrespective of ethnic difference, although the response to HPR might be diverse, resulting in different cutoff values, and the impact of high PRU on mortality or NACE including bleeding outcomes could be different according to racial or anthropologic differences. Indeed, the genetic polymorphism of *CYP2C19*, a major clopidogrel-metabolizing enzyme, significantly differs among races, demonstrating greater prevalence of loss-of-function genotype of *CYP2C19* in East Asian populations than in Western populations (~65% vs ~30%) and resulting in reduced clopidogrel metabolism and HPR on clopidogrel.[22]

In addition to the genetic variations related to clopidogrel metabolism, individual patients' characteristics such as age, body mass index, chronic kidney disease, or diabetes are known to be significantly related to platelet reactivity,[5] in accordance with our finding. In this regard, as compared with genetic testing for *CYP2C19* loss-of-function alleles, the PFT has its advantage of being able to comprehensively reflect the effects of various comorbidities and individual characteristics of patients as well as readily provide the information in a point-of-care setting.[23] Furthermore, prediction of a clopidogrel nonresponder based on clinical parameters with genotypes has been known to be effective in identifying the high-risk population after PCI.[24] Therefore, together

TABLE 4 Incidences and Risks of Primary and Secondary Outcomes According to Cutoff Value of ARUs (414)

	Follow-Up	ARU ≥414 (n = 4,350)	ARU <414 (n = 2,812)	Adjusted HR (95% CI)[a]	*P* Value
Primary and key secondary outcomes					
MACCE	1 y	140 (3.2)	53 (1.9)	1.59 (1.16-2.18)	0.004
	5 y	240 (5.5)	100 (3.6)	1.44 (1.14-1.82)	0.002
All-cause death	1 y	64 (1.5)	20 (0.7)	1.84 (1.11-3.04)	0.018
	5 y	117 (2.7)	39 (1.4)	1.75 (1.22-2.52)	0.002
Major bleeding	1 y	112 (2.6)	52 (1.8)	1.29 (0.93-1.80)	0.128
	5 y	147 (3.4)	66 (2.3)	1.34 (0.94-1.80)	0.094
Net adverse cardiac events	1 y	230 (5.3)	98 (3.5)	1.41 (1.12-1.79)	0.004
	5 y	349 (8.0)	147 (5.2)	1.43 (1.18-1.73)	<0.001
Other secondary outcomes					
Cardiovascular death, myocardial infarction, or stent thrombosis	5 y	126 (2.9)	46 (1.6)	1.67 (1.19-2.34)	0.003
Stent thrombosis	5 y	23 (0.5)	5 (0.2)	3.11 (1.18-8.20)	0.021
Myocardial infarction	5 y	72 (1.7)	30 (1.1)	1.48 (0.96-2.27)	0.072
Cardiovascular death	5 y	48 (1.3)	23 (0.7)	1.75 (1.06-2.88)	0.028
Any revascularization	5 y	290 (6.7)	185 (6.6)	1.00 (0.83-1.21)	0.985
Stroke	5 y	61 (1.4)	35 (1.2)	1.04 (0.69-1.58)	0.853

Values are n (%), unless otherwise indicated. [a]Variables included age, female sex, chronic kidney disease, and acute myocardial infarction.

ARU = aspirin reaction unit; MACCE = major adverse cardiac and cerebrovascular event(s).

with consideration of ethnic difference, comprehensive estimation of individual patients' ischemic or bleeding risk according to platelet reactivity by integrating with clinical variables or genotype could contribute to establishment of patient-tailored antiplatelet therapy.

Despite the indispensable role of aspirin as a lifelong maintenance therapy after the mandatory DAPT period post-PCI, prior studies found no significant correlation between HPR on aspirin and clinical outcomes.[1,25] Meanwhile, the present study, which conducted long-term follow-up in the largest-scale cohort with PFT, revealed that HPR on aspirin had a significant correlation with the occurrence of ischemic outcome or all-cause death after PCI. Similar to the result of PRU, there was no significant association between the value of ARU and occurrence of bleeding. Consequently, HPR on aspirin (ARU ≥414) was significantly related the risk of NACE. As a possible explanation for this difference in the clinical impact of HPR on aspirin, a strategy for determining the cutoff value of ARU for MACCE could be considered; while the ADAPT-DES registry adopted the cutoff value of ARUs (550) derived from the laboratory assessment,[26] which classified only 5.6% of patients as HPR on aspirin, the PTRG-DES consortium acquired the clinically significant cutoff value of ARUs (414) that strongly predicted the occurrence of MACCE and all-cause death. These findings together indicate the distinct risk-benefit profile according to platelet inhibition in East Asian population, supporting the theory of the East Asian paradox.[8]

Numerous attempts have been made to utilize on-treatment platelet reactivity for determining the optimal antiplatelet treatment strategy in post-PCI patients.[27-29] In the GRAVITAS (Gauging Responsiveness With a VerifyNow P2Y12 Assay: Impact on Thrombosis and Safety) trial, a PRU <208 after PCI was significantly associated with a lower risk of cardiovascular events, but the risk was not alleviated by treatment with high-dose clopidogrel DAPT (150 mg daily).[27,30] The TRIGGER-PCI (Testing Platelet Reactivity in Patients Undergoing Elective Stent Placement on Clopidogrel To Guide Alternative Therapy With Prasugrel) trial that aimed to overcome clopidogrel nonresponder (PRU >208) by switching to prasugrel 10 mg in stable CAD patients after PCI was prematurely stopped due to lower-than-expected event rate.[31] Consequently, these trials had provided limited evidence on the benefit of antiplatelet escalation strategy in patients with high on-treatment platelet reactivity as compared with unguided standard DAPT strategy.[32] In the Assessment by a ARCTIC (Double Randomization of a Conventional Antiplatelet Strategy versus a Monitoring-guided Strategy for Drug-Eluting Stent Implantation and of Treatment Interruption versus Continuation One Year after Stenting) trial, no significant improvements in clinical outcomes were found with platelet function monitoring and treatment adjustment during and after PCI.[33] However, this study adopted a cutoff value for HPR (PRU ≥235) different from previous trials and applied a double-dose clopidogrel (150 mg daily) strategy in clopidogrel nonresponders, which was considered to be not effective. In the TROPICAL-ACS (Testing Responsiveness To Platelet Inhibition On Chronic Antiplatelet Treatment For Acute Coronary Syndromes) trial, the platelet function-guided de-escalation strategy in ACS patients was not superior over the continuous use of more potent $P2Y_{12}$ inhibitors.[29] Taken together, cumulative evidence from clinical studies support the role of high PRUs as the risk factor for ischemic outcomes after DES implantation, but a lack of strong evidence regarding the effective PRU modulation strategy still exits. Considering that HPR patients have an unpredictable response to clopidogrel, there is a fundamental limitation in overcoming the risk of ischemic events in HPR patients by increasing the dose or extending the duration of clopidogrel administration. In this regard, the use of a potent $P2Y_{12}$ inhibitor could be a promising strategy to overcome the unmet needs of clopidogrel, but the increased bleeding risks by these would be the primary limitation in HPR patients. Indeed, recently reported real-world data have shown that treatment with potent $P2Y_{12}$ inhibitor vs clopidogrel was significantly associated with a lower risk of ischemic events after PCI in patients with *CYP2C19* loss-of-function alleles.[34] Furthermore, a network meta-analysis that included 61,898 patients from 15 randomized controlled trials presented a guided DAPT approach as the only treatment strategy associated with reduced ischemic outcome without increasing bleeding.[35] Furthermore, in another recent meta-analysis that analyzed 20,743 patients who were treated with either guided or standard antiplatelet therapy, the guided selection of antiplatelet therapy was associated significant reductions in cardiovascular death, ischemic events, and minor bleeding.[36] Future randomized trials should aim to optimize antiplatelet treatment strategy by considering the unique pharmacodynamic character of East Asian populations and ischemic/bleeding risks according to platelet reactivity.

STUDY LIMITATIONS. First, this was a nonrandomized, observational study; thus, inherent selection bias and the possibility of residual confounding even after multivariable adjustment or propensity score matching cannot be excluded. Because patients using any $P2Y_{12}$ inhibitors other than clopidogrel were not included in this study, there remains the possibility of selection bias in patients with acute coronary syndrome, and the role of platelet reactivity in patients with acute coronary syndrome treated with potent $P2Y_{12}$ inhibitors such as prasugrel or ticagrelor should be reinvestigated. In addition, the detailed reason for noncardiac death, which was also higher in patients with high PRUs, was not available. Therefore, the results presented are for hypothesis generation, and thus care should be taken in understanding and expanding on our results. Second, although the association of on-treatment platelet reactivity and long-term clinical outcome was investigated in the present study, no data were available regarding the platelet reactivity at the time of clinical events or during the follow-up. Third, no data were available regarding the association between the exact duration of DAPT or type of mono antiplatelet therapy after DAPT and the PRU level. Additionally, information on the vascular access site, which could be significantly related to bleeding or ischemic outcome, was also not available. Fourth, VerifyNow was the only method of platelet function measurement in this study, not including other tools such as adenosine diphosphate-indued light transmittance aggregometry. Furthermore, because all patients with oral anticoagulation therapy were excluded from this study, the results of our analyses should be confined to patients not requiring anticoagulation. Last, the effects of the genetic variation in clopidogrel metabolism-related genes were not fully considered in this study.

CONCLUSIONS

In this large-scale East Asian cohort treated with DES with long-term clinical follow-up, high on-treatment platelet reactivity was significantly associated with the occurrence of MACCE, all-cause death, and NACE at 5 years after PCI.

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PERSPECTIVES

WHAT IS KNOWN? The clinical significance of the HPR on clopidogrel treatment after PCI in the Western population has been clearly clarified.

WHAT IS NEW? This large-scale, nationwide consortium consisted of multicenter cohorts in South Korea clearly showed that HPR on clopidogrel was significantly associated with all-cause mortality, as well as with the occurrent of MACCE at 5 years after PCI. On the other hand, unlike the study results in Western patients, HPR did not show a significant association with bleeding in the East-Asian population. As a result, HPR was significantly associated with risk of NACE.

WHAT IS NEXT? Randomized controlled trials aiming to optimize antiplatelet treatment strategy by considering the individual patients' ischemic/bleeding risks according to platelet reactivity should be conducted.

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KEY WORDS drug-eluting stent(s), percutaneous coronary intervention, platelet function tests, stent thrombosis

APPENDIX For supplemental tables and figures, please see the online version of this paper.