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ORIGINAL RESEARCH

Association of Age- and Body Mass Index-Stratified High On-Treatment Platelet Reactivity With Coronary Intervention Outcomes in East Asian Patients

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BACKGROUND: Although age and body mass index (BMI) significantly affect platelet reactivity units and clinical outcomes after percutaneous coronary intervention, there are limited data on the relationship between high on-treatment platelet reactivity (HPR) and clinical outcomes on age and BMI differences. Thus, we investigated the association of HPR with clinical outcomes according to age and BMI.

METHODS AND RESULTS: The study analyzed 11 714 patients who underwent platelet function tests after percutaneous coronary intervention. The primary end point was the occurrence of major adverse cardiac and cerebrovascular events (MACCEs), whereas the secondary end point was major bleeding. HPR was defined as platelet reactivity units ≥252. Patients were categorized by age (<67 years of age or ≥67 years of age) and BMI (≤22.6 kg/m^2 or >22.6 kg/m^2). Patients <67 years of age with HPR had increases in both MACCEs (adjusted hazard ratio [HR], 1.436 [95% CI, 1.106–1.867]; *P*=0.007) and major bleeding (adjusted HR, 1.584 [95% CI, 1.095–2.290]; *P*=0.015) compared with the those with non-HPR, respectively. In patients ≥67 years of age with HPR, there were no differences in MACCEs, but there was a decrease in major bleeding (adjusted HR, 0.721 [95% CI, 0.542–0.959]; *P*=0.024). Meanwhile, patients with HPR with BMI >22.6 kg/m^2 had increases in MACCEs (adjusted HR, 1.387 [95% CI, 1.140–1.688]; *P*=0.001). No differences were shown in major bleeding.

CONCLUSIONS: HPR was linked to an increase in MACCEs or a decrease in major bleeding in patients after percutaneous coronary intervention, depending on age and BMI. This study is the first to observe that clinical outcomes in patients with HPR after percutaneous coronary intervention may vary based on age and BMI. Because the study is observational, the results should be viewed as hypothesis generating and emphasize the need for randomized clinical trials.

Key Words: age ■ body mass index ■ clinical outcomes ■ P2Y12 inhibitors ■ percutaneous coronary intervention ■ platelet reactivity

Although high on-treatment platelet reactivity (HPR) has been reported to be a predictor of adverse ischemic events after percutaneous coronary intervention (PCI) in numerous studies,[1–3] the platelet reactivity unit (PRU) is affected not only by different kinds of drugs, but also the patient's characteristics, including

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CLINICAL PERSPECTIVE

What Is New?

- The largest population registry on platelet reactivity unit levels after percutaneous coronary intervention found that high on-treatment platelet reactivity is associated with higher risk of ischemic adverse events and lower rates of major bleeding events, which are influenced by age and body mass index.

What Are the Clinical Implications?

- Although age and body mass index are established risk factors for cardiovascular disease, no association with high on-treatment platelet reactivity according to age and body mass index is identified.
- This study is the first to suggest that the impact of high on-treatment platelet reactivity on post-percutaneous coronary intervention clinical outcomes may differ according to the patient's age and body mass index, highlighting the need for personalized patient management.

Nonstandard Abbreviations and Acronyms

DAPT	dual antiplatelet therapy
HPR	high on-treatment platelet reactivity
MACCE	major adverse cardiac and cerebrovascular event
PRU	platelet reactivity units

age, body mass index (BMI), and other comorbidities.[4–6] Age and BMI are well-known risk factors for cardiovascular disease.[7,8] Numerous studies have reported that aging is strongly associated with an increased incidence of ischemic and bleeding events.[9,10] Moreover, because PRU continuously increases with age, HPR in older patients may translate into an increased risk of ischemic events.[4,9,10] Meanwhile, although BMI is associated with adverse clinical outcomes in patients after PCI and low response to clopidogrel, in other words, increased PRU,[8,11,12] few studies have reported an association between BMI and PRU in terms of adverse ischemic outcomes. Moreover, there are little data on the association between age or BMI and PRU on major bleeding. Thus, current guidelines provide no specific recommendations on dual antiplatelet therapy (DAPT) for patients after PCI according to age or BMI.

Because PRU is affected by age and BMI, the association of HPR and clinical outcome may differ according to age and BMI. To address this gap in understanding, we conducted a nationwide, multicenter, large-scale analysis of the impact of HPR on clinical outcomes, with a focus on stratifying the data by age and BMI in patients who have undergone DAPT following an index PCI.

METHODS

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

Study Population

The PTRG-DES (Platelet Function and Genotype-Related Long-Term Prognosis in DES-Treated Patients) consortium is a retrospective, multicenter, real-world registry of patients who underwent PCI between January 2006 and December 2018 in South Korea (NCT04734028).[13] Briefly, data from 32 academic centers in Korea were used for study at the individual patient level. All clinical events were assessed by an independent clinical events committee that was unaware of the platelet function test and genotyping data. The committee made their assessments based on the original source materials. The assessment of clinical outcomes was conducted until the final outpatient visit. Following the validation of the PTRG-DES central database, in the event of significant concerns, individual data were transmitted to the main investigator of the corresponding registry for the purpose of data confirmation, rectification, and supplementation. A total of 13 160 patients were included from the PTRG-DES registry. Among 13 160 patients, the present study evaluated platelet function in 11 714 patients after index PCI. The inclusion criteria were as follows: enrolled patients who underwent drug-eluting stent (DES) implantation and were administered adequate loading and maintenance doses of clopidogrel for DAPT. The exclusion criteria were as follows: (1) presence of major complications before the platelet function test, (2) plan to undergo bypass surgery after index PCI, and (3) use of oral anticoagulants or P2Y12 inhibitors other than clopidogrel. The institutional review board of each participating center approved the study, and the requirement for written and informed consent was waived owing to the retrospective nature of the study. The study was performed in accordance with the Good Clinical Practice Guidelines and principles of the Declaration of Helsinki.

Procedures

All patients were assessed for the need for loading doses of DAPT at the time of the index PCI. If required, aspirin (300 mg) and clopidogrel (300–600 mg) were administered. The recommended, but not mandatory, duration of

DAPT after index PCI was 12 months. Subsequently, DAPT was discontinued at the physician's discretion. The on-treatment PRU value was measured using a VerifyNow P2Y12 device (Accumetrics, San Diego, CA).

Outcome Definitions

The primary end point was major adverse cardiac and cerebrovascular events (MACCEs), defined as a composite of all-cause death, myocardial infarction (MI), stent thrombosis, and cerebrovascular accident within 5 years after PCI. The secondary end point was major bleeding (Bleeding Academic Research Consortium grade ≥3). 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 the creatine kinase-myocardial band above the upper normal limit or troponin T/I >99th percentile of the upper normal limit unrelated to an interventional procedure.[14] Stent thrombosis was defined as definite stent thrombosis according to the Bleeding Academic Research Consortium criteria.[15] Cerebrovascular accidents included any new embolic, thrombotic, or hemorrhagic stroke event with neurological deficits that persisted for at least 24 hours.

Statistical Analysis

The baseline characteristics analysis stratified by age and BMI, using 67 years of age and 22.6 kg/m^2 as cut-off points, respectively (Figure 1). Continuous variables are reported as means and SDs. Discrete variables were described through frequencies and percentages. Categorical variables are presented as numbers with percentages and were compared using the χ^2 test or Fisher exact test. Event rates were compared using the Kaplan-Meier survival analysis with the log-rank test. Hazard ratios (HRs) with 95% CIs were computed using the Cox regression analysis. The HPR, defined as an augmented platelet response to agonists, leading to enhanced platelet aggregation despite the administration of antiplatelet medications, was PRU ≥252 based on a previous study.[16] Briefly, a linear correlation existed between the PRU value and the risk of MACCEs after PCI. In addition, the use of clopidogrel by patients with HPR was strongly related to MACCEs (HR, 1.39 [95% CI, 1.11–1.74]; P=0.003).[16] Receiver operating curve analysis was conducted to find the cut-off value for age and BMI that are most effective at predicting the occurrence of MACCEs (Figure 1). These values were selected because they offer the best combination of sensitivity and specificity. In this large-scale registry analysis with a long-term follow-up, PRU 252 (defined as HPR, PRU ≥252), age of 67 years, and BMI 22.6 kg/m^2 were the cutoff values for predicting MACCEs.

Multivariable Cox regression analysis was conducted to identify independent predictors of clinical outcomes. In addition, comparisons of the primary and secondary outcomes of HPR according to age and BMI were performed, and the interactions among PRU, age, and BMI were assessed using a Cox regression model. The multivariable analysis included only those baseline variables that exhibited a P value of <0.1 in the univariate analysis. Moreover, by incorporating significant clinical and procedural risk factors from previous studies,[16] the present study included variables of clinical relevance in the multivariable model to identify independent predictors of MACCEs. Thus, the final Cox proportional hazards model for MACCEs was conducted using a range of variables, such as age of 67 years, BMI 22.6 kg/m^2, hypertension, diabetes, chronic kidney disease, acute MI presentation, anemia, peripheral artery disease, heart failure, prior cerebrovascular accident, and HPR (Tables S1 and S2). Also, the final Cox proportional hazards model for major bleeding was conducted by incorporating variables such as age of 67 years, BMI 22.6 kg/m^2, hypertension, dyslipidemia, chronic kidney disease, peripheral artery disease, prior MI, chronic total occlusion, and HPR (Tables S3 and S4). All statistical analyses were performed using SPSS (version 25.0; IBM, Armonk, NY). All tests were 2-sided, and statistical significance was set at P<0.05.

RESULTS

The distributions of age and BMI values are shown in Figure 1. For age, the optimal cutoff value for predicting MACCE occurrence within 5 years after PCI in this registry was 67 years (Figure 1A). As for BMI, the optimal cutoff value for predicting MACCE occurrence within 5 years after PCI in this registry was 22.6 kg/m^2 (Figure 1B).

Baseline Characteristics According to Age

Compared with patients <67 years of age, patients ≥67 years of age were more likely to be women, have a lower BMI, and have a higher prevalence of cardiovascular comorbidities (eg, hypertension, diabetes, chronic kidney disease, anemia, peripheral artery disease, and heart failure). Additionally, significant differences were observed between the groups with respect to the presence of multivessel disease, bifurcation lesions, and the proportional use of a second DES. Angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, calcium channel blockers, and proton pump inhibitors were more frequently used in patients ≥67 years of age. Conversely, statins were used less frequently in this group of patients. Additionally, patients ≥67 years of age had a higher PRU level (≥67 versus <67 years of age, 232.8±78.7

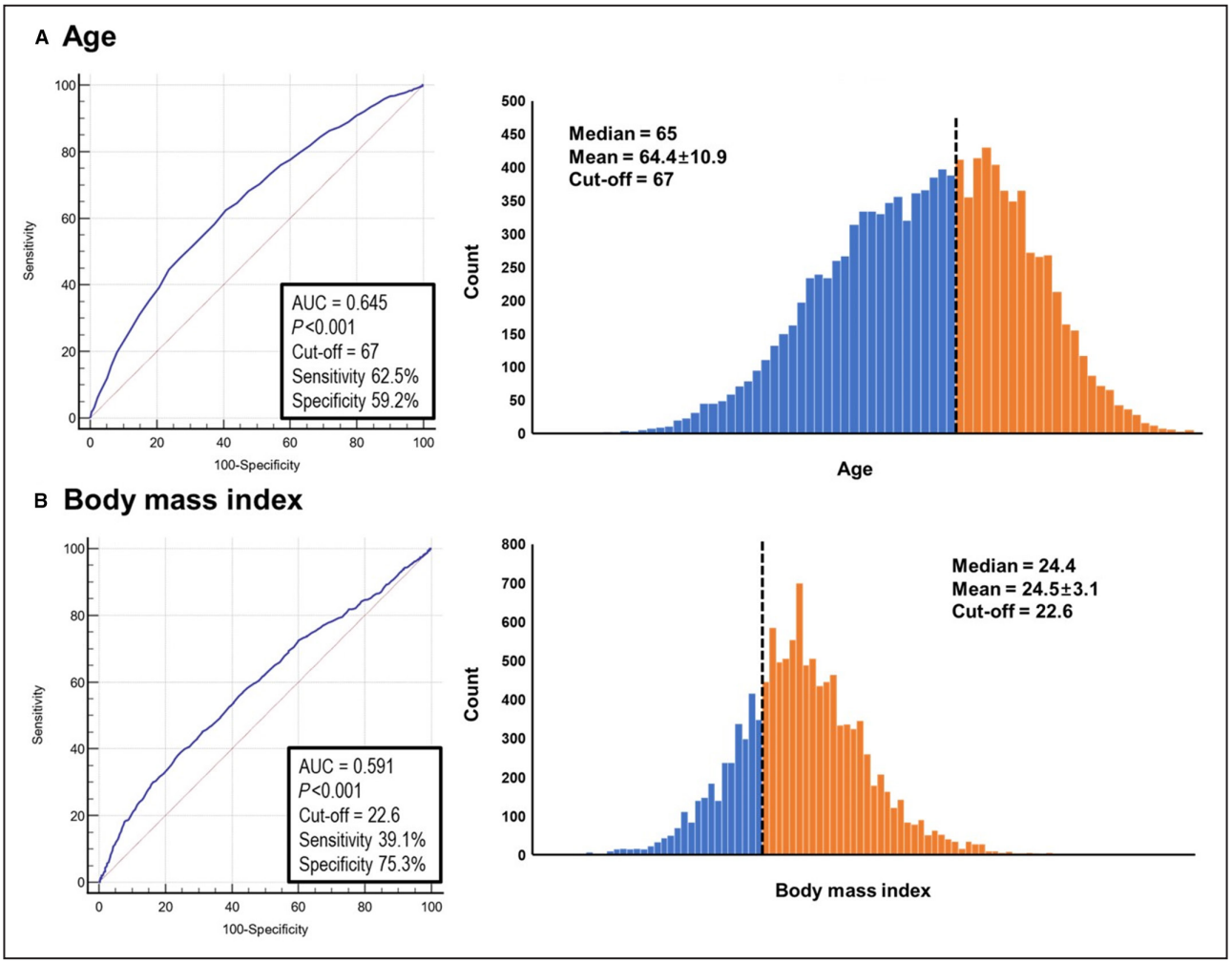


Figure 1. Distribution and receiver operating characteristic analysis to determine the optimal cutoff value for major adverse cardiac and cerebrovascular events.
A, Age. **B**, Body mass index. AUC indicates area under the curve.

versus 205.2±76.5, *P*<0.001) and higher prevalence of HPR than patients <67 years of age (42.4% versus 27.3%, *P*<0.001) (Table 1).

Baseline Characteristics According to BMI

Compared with patients with a BMI >22.6 kg/m^2, those who presented with a BMI ≤22.6 kg/m^2 were more likely to be women, older, have a lower prevalence of cardiovascular comorbidities (eg, hypertension, diabetes, and dyslipidemia), and have a higher prevalence of anemia, peripheral artery disease, and cerebrovascular accident. In addition, significant differences were observed in clinical presentations among the groups, including acute MI, left ventricular ejection fraction, and proportional use of a second DES. Angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, and calcium channel blockers were used less frequently in patients with a BMI ≤22.6 kg/m^2, whereas proton pump inhibitors were used more frequently in patients with a BMI >22.6 kg/m^2. Although there was no significant correlation between BMI and PRU, the prevalence of HPR was higher in patients with a BMI ≤22.6 kg/m^2 than in those with a BMI >22.6 kg/m^2 (Table 2).

Clinical Outcomes of HPR on Age Difference

The median follow-up duration was 551 days (interquartile range, 365–1752 days). With respect to the primary outcome at 5 years after DES implantation according to age stratification, the patients <67 years of age with HPR had a higher incidence of MACCEs than those without HPR (6.0% versus 3.2%, log-rank *P*<0.001). However, the patients ≥67 years of age had no differences in rates of MACCEs with respect to HPR (9.7%

Table 1. Baseline and Lesion Characteristics With Respect to Age

Characteristic	Total (N=11 714)	Age <67 y (N=6393)	Age ≥67 y (N=5321)	*P* value
Male sex	7951 (67.9%)	4937 (77.2%)	3014 (56.6%)	<0.001
Age, y	64.4±10.9	56.3±7.2	74.0±5.2	<0.001
BMI, kg/m^2	24.5±3.1	25.0±3.0	24.0±3.1	<0.001
<23	3441 (29.4%)	464 (20.3%)	818 (24.6%)	
23–25	3332 (28.4%)	584 (25.6%)	1007 (30.2%)	
25–30	4397 (37.5%)	1059 (46.4%)	1363 (40.9%)	
≥30	544 (4.6%)	175 (7.7%)	141 (4.2%)	
Hypertension	7049 (60.2%)	3399 (53.2%)	3650 (68.6%)	<0.001
Diabetes	4057 (34.6%)	2052 (32.1%)	2005 (37.7%)	<0.001
Dyslipidemia	7555 (64.5%)	4256 (66.6%)	3299 (62.0%)	<0.001
Chronic kidney disease	2432 (20.8%)	856 (13.4%)	1576 (29.6%)	<0.001
Current smoking	3285 (28.0%)	2363 (37.0%)	922 (17.3%)	<0.001
AMI presentation	3338 (28.5%)	1802 (28.2%)	1536 (28.9%)	0.429
Anemia	2921 (24.9%)	970 (15.2%)	1951 (36.7%)	<0.001
Peripheral artery disease	1453 (12.4%)	628 (9.8%)	8,25 (15.5%)	<0.001
Heart failure	880 (7.5%)	422 (6.6%)	458 (8.6%)	<0.001
Left ventricular ejection fraction	58.8±10.6	59.2±10.0	58.3±11.2	<0.001
Prior myocardial infarction	839 (7.2%)	460 (7.2%)	379 (7.1%)	0.908
Prior PCI	1568 (13.4%)	776 (12.1%)	792 (14.9%)	<0.001
Prior cerebrovascular accident	813 (6.9%)	314 (4.9%)	499 (9.4%)	<0.001
Multivessel diseases	4544 (38.8%)	2339 (36.6%)	2205 (41.4%)	<0.001
Bifurcation lesion	1363 (11.6%)	692 (10.8%)	671 (12.6%)	0.003
CTO	821 (7.0%)	472 (7.4%)	349 (6.6%)	0.089
Multivessel PCI	2917 (24.9%)	1516 (23.7%)	1401 (26.3%)	0.001
New-generation DES implanted	10 770 (91.9%)	5819 (91.0%)	4951 (93.0%)	<0.001
No. of stents	1.6±0.8	1.6±0.8	1.6±0.8	<0.001
Length of stent, mm	35.9±22.5	35.3±22.5	36.5±22.5	0.004
Discharge medication				
β-Blocker	6669 (56.9%)	3664 (57.3%)	3005 (56.5%)	0.372
ACEi or ARB	6927 (59.1%)	3703 (57.9%)	3224 (60.6%)	0.004
Calcium channel blocker	2817 (24.0%)	1466 (22.9%)	1351 (25.4%)	0.002
Statin	10 379 (88.6%)	5708 (89.3%)	4671 (87.8%)	0.012
Proton pump inhibitor	1991 (17.0%)	965 (15.1%)	1026 (19.3%)	<0.001
Duration of DAPT, d, median	381	381	382	0.240
Platelet reactivity unit	217.8±78.7	205.2±76.5	232.8±78.7	<0.001
High platelet unit, PRU ≥252	4001 (34.2%)	1743 (27.3%)	2258 (42.4%)	<0.001

ACEi indicates angiotensin-converting enzyme inhibitor; AMI, acute myocardial infarction; ARB, angiotensin II receptor blocker; BMI, body mass index; CTO, chronic total occlusion; DAPT, dual antiplatelet therapy; DES, drug-eluting stent; PCI, percutaneous coronary intervention; and PRU, platelet reactivity unit.

versus 7.8%, log-rank *P*=0.065) (Figure 2A). Additionally, the patients <67 years of age with HPR had a significantly higher risk of MACCEs than those ≥67 years of age, with a significant interaction (adjusted HR, 1.437 [95% CI, 1.106–1.866]; *P*=0.007) (*P* interaction=0.033) (Figure S1). On the secondary outcome, the patients <67 years of age with HPR had a higher incidence of major bleeding than those without HPR (2.8% versus 1.5%, log-rank *P*=0.004; adjusted HR, 1.584 [95% CI, 1.095–2.290]; *P*=0.015). Conversely, the patients ≥67 years of age with HPR had numerically decreased rates of major bleeding than those without HPR (3.4% versus 4.1%, log-rank *P*=0.126) (Figure 2B). In addition, the patients ≥67 years of age with HPR had a lower risk of major bleeding (adjusted HR, 0.721 [95% CI, 0.542–0.959]; *P*=0.024), with significant interaction in

Table 2. Baseline and Lesion Characteristics With Respect to BMI

Characteristic	Total (N=11 714)	BMI ≤22.6 (N=2995)	BMI >22.6 (N=8719)	*P* value
Male sex	7951 (67.9%)	1940 (64.8%)	6011 (68.9%)	<0.001
Age, y	64.4±10.9	67.5±10.7	63.3±10.7	<0.001
<55	2282 (19.5%)	464 (13.5%)	584 (17.5%)	
55–65	3329 (28.4%)	818 (23.8%)	1007 (30.2%)	
65–75	3899 (33.3%)	1197 (34.8%)	1162 (34.9%)	
≥75	2204 (18.8%)	962 (28.0%)	579 (17.4%)	
BMI, kg/m^2	24.5±3.1	20.8±1.6	25.8±2.4	<0.001
Hypertension	7049 (60.2%)	1607 (53.7%)	5442 (62.4%)	<0.001
Diabetes	4057 (34.6%)	959 (32.0%)	3098 (35.5%)	0.001
Dyslipidemia	7555 (64.5%)	1695 (56.6%)	5860 (67.2%)	<0.001
Chronic kidney disease	2432 (20.8%)	639 (21.3%)	1793 (20.6%)	0.383
Current smoking	3285 (28.0%)	847 (28.3%)	2438 (28.0%)	0.756
AMI presentation	3338 (28.5%)	1091 (36.4%)	2247 (25.8%)	<0.001
Anemia	2921 (24.9%)	1115 (37.2%)	1806 (20.7%)	<0.001
Peripheral artery disease	1453 (12.4%)	444 (14.8%)	1009 (11.6%)	<0.001
Heart failure	880 (7.5%)	252 (8.4%)	628 (7.2%)	0.033
Left ventricular ejection fraction	58.8±10.6	57.2±11.4	59.3±10.2	<0.001
Prior myocardial infarction	839 (7.2%)	214 (7.1%)	625 (7.2%)	0.999
Prior PCI	1568 (13.4%)	355 (11.9%)	1213 (13.9%)	0.005
Prior cerebrovascular accident	813 (6.9%)	262 (8.7%)	551 (6.3%)	<0.001
Multivessel diseases	4544 (38.8%)	1206 (40.3%)	3338 (38.3%)	0.057
Bifurcation lesion	1363 (11.6%)	346 (11.6%)	1017 (11.7%)	0.896
CTO	821 (7.0%)	188 (6.3%)	633 (7.3%)	0.076
Multivessel PCI	2917 (24.9%)	733 (24.5%)	2184 (25.0%)	0.547
New-generation DES implanted	10 770 (91.9%)	3213 (93.4%)	3027 (90.8%)	0.002
No. of stents	1.6±0.8	1.6±0.8	1.6±0.8	0.561
Length of stent, mm	35.9±22.5	35.8±22.3	35.9±22.6	0.888
Discharge medication				
β-Blocker	6669 (56.9%)	1708 (57.0%)	4961 (56.9%)	0.919
ACEi or ARB	6927 (59.1%)	1711 (57.1%)	5216 (59.8%)	0.010
Calcium channel blocker	2817 (24.0%)	644 (21.5%)	2173 (24.9%)	<0.001
Statin	10 379 (88.6%)	2644 (88.3%)	7735 (88.7%)	0.541
Proton pump inhibitor	1991 (17.0%)	604 (20.2%)	1387 (15.9%)	<0.001
Duration of DAPT, d, median	381	381	382	0.432
Platelet reactivity unit	217.8±78.7	219.3±83.6	217.2±77.0	0.227
High platelet unit, PRU ≥252	4001 (34.2%)	1093 (36.5%)	2908 (33.4%)	0.002

ACEi indicates angiotensin-converting enzyme inhibitor; AMI, acute myocardial infarction; ARB, angiotensin II receptor blocker; BMI, body mass index; CTO, chronic total occlusion; DAPT, dual antiplatelet therapy; DES, drug-eluting stent; PCI, percutaneous coronary intervention; and PRU, platelet reactivity unit.

multivariable analysis (*P* interaction=0.001) (Figure S2). The 1-year incidence of the primary and secondary outcomes is described in Table S5.

Clinical Outcomes of HPR on BMI Difference

In the BMI >22.6 kg/m^2 group, patients with HPR had a higher incidence of MACCEs than those without HPR (7.1% versus 3.9%, log-rank *P*<0.001), whereas those with a BMI ≤22.6 kg/m^2 had no differences in rates of MACCEs with respect to HPR (10.5% versus 8.5%, log-rank *P*=0.289) (Figure 3A). Additionally, among the patients with BMI >22.6 kg/m^2, HPR was an independent predictor of MACCEs (adjusted HR, 1.387 [95% CI, 1.140–1.688]; *P*=0.001), with a significant interaction (*P* interaction=0.005) (Figure S3). For major bleeding, no differences were found between BMI and HPR with

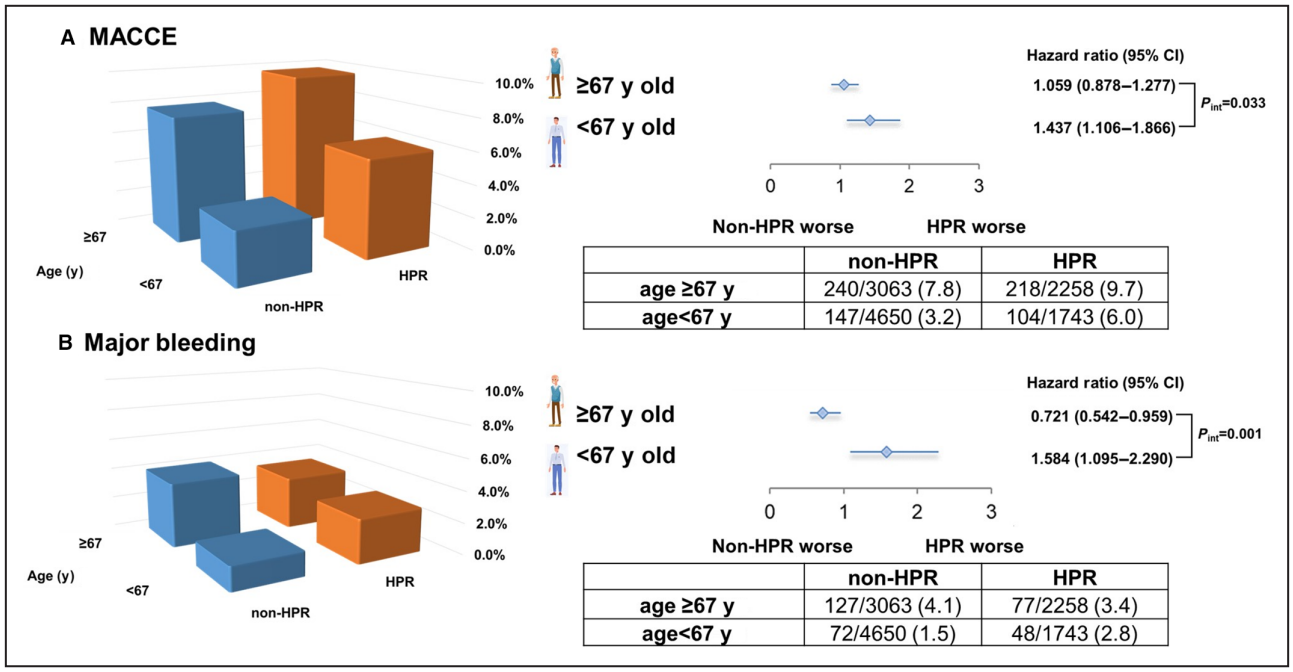


Figure 2. Age-stratified HPR on clinical outcomes.
A, MACCE. **B**, Major bleeding. HPR indicates high on-treatment platelet reactivity; and MACCE, major adverse cardiac and cerebrovascular event.

respect to incidence and association (Figure 3B). The 1-year incidence of the primary and secondary outcomes is described in Table S6.

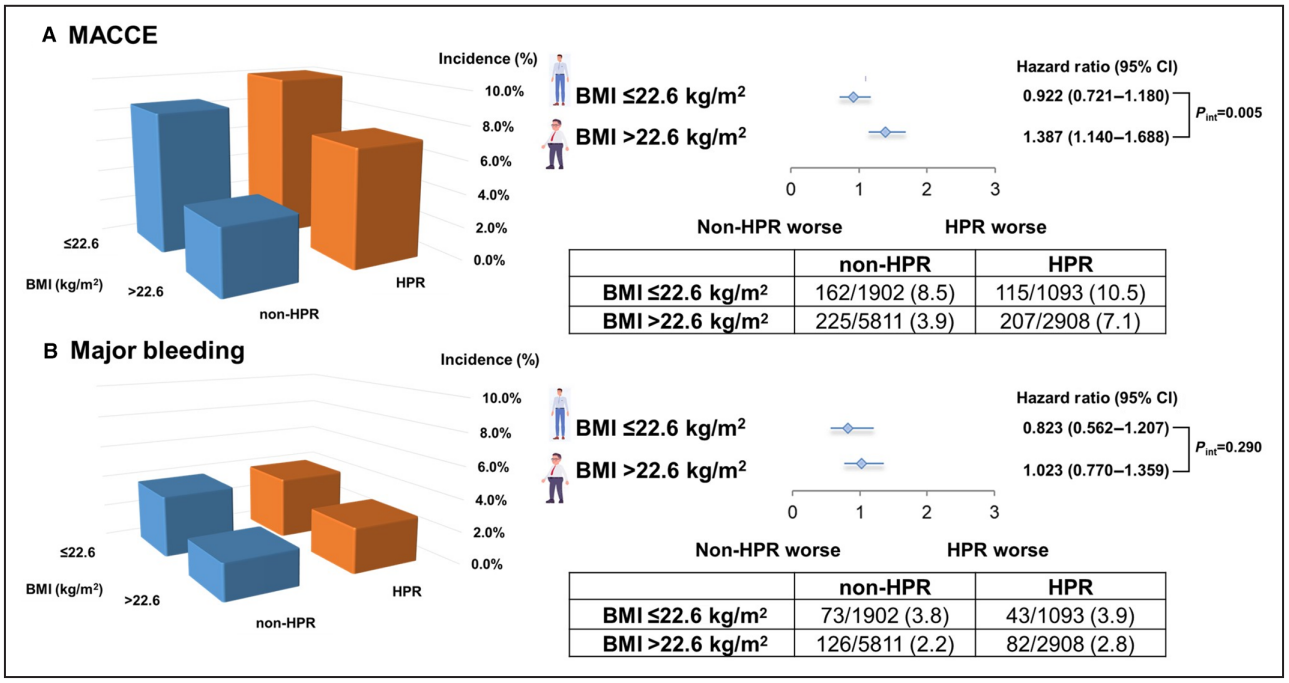
Clinical Outcomes of HPR on Age and BMI Difference

In patients <67 years of age, those with HPR in both the BMI >22.6 kg/m^2 (5.3% versus 3.8%, log-rank P<0.001) and BMI ≤22.6 kg/m^2 groups (8.5% versus 4.7%, log-rank P<0.001) had a higher incidence of MACCEs than those without HPR. In patients ≥67 years of age, those with HPR had a higher incidence of MACCEs than those without HPR in the BMI >22.6 kg/m^2 group (8.8% versus 5.8%, log-rank P=0.002), whereas those in the BMI ≤22.6 kg/m^2 group had no difference in rates of MACCEs with respect to HPR (11.5% versus 12.0%). However, HPR on age and BMI difference showed no significant interaction. The 1-year incidence of MACCEs is described on Table S7. For major bleeding, in patients <67 years of age, those with HPR in both the BMI >22.6 kg/m^2 (2.3% versus 1.4%, log-rank P=0.050) and BMI ≤22.6 kg/m^2 groups (4.4% versus 2.0%, log-rank P=0.026) had a higher incidence of major bleeding than those without HPR, respectively. Conversely, in patients ≥67 years of age, those with HPR in both the BMI >22.6 kg/m^2 (3.3% versus 3.5%, log-rank P=0.684) and BMI ≤22.6 kg/m^2 groups (3.7% versus 5.6%, log-rank P=0.053) had a numerically lower incidence of major bleeding than those without HPR, respectively. However, there were no significant interactions with respect to HPR on age and BMI differences. The incidence of major bleeding is described in Table S8.

DISCUSSION

The present study investigated the association of HPR with coronary intervention outcomes based on 11 714 patients after successful DES implantation on age and BMI differences. The main findings were as follows: (1) In the patients <67 years of age, patients with HPR had an increased risk of MACCEs with significant interaction. In the patients with BMI >22.6 kg/m^2, HPR was also associated with an increased risk of MACCEs with significant interaction. However, HPR on both age and BMI difference showed no significant interaction. (2) In the patients <67 years of age group, patients with HPR had an increased risk of major bleeding, whereas in the ≥67 years of age group, patients with HPR had a decreased risk of major bleeding. No significant difference was shown in terms of BMI 22.6 kg/m^2. To the best of our knowledge, this is the first observational study where the impact of HPR on clinical outcomes in patients after PCI may differ depending on the age and BMI status.

Previous large-scale analyses have reported an increased risk of adverse ischemic outcomes with increasing age and BMI.[8,9,12] Although previous studies



	non-HPR	HPR
BMI ≤22.6 kg/m²	162/1902 (8.5)	115/1093 (10.5)
BMI >22.6 kg/m²	225/5811 (3.9)	207/2908 (7.1)

	non-HPR	HPR
BMI ≤22.6 kg/m²	73/1902 (3.8)	43/1093 (3.9)
BMI >22.6 kg/m²	126/5811 (2.2)	82/2908 (2.8)

Figure 3. BMI-stratified HPR on clinical outcomes.
A, MACCE. **B**, Major bleeding. BMI indicates body mass index; HPR, high on-treatment platelet reactivity; and MACCE, major adverse cardiac and cerebrovascular event.

have reported no correlation between elevated PRU and mortality,[3] the present PTRG-DES registry showed a significant correlation based on a large-scale analysis of nearly 12 000 patients.[16] Hence, PRU may contribute to mortality risk and other factors, such as diabetes, chronic kidney disease, and heart failure. Moreover, in agreement with previous findings of increased risk of adverse ischemic outcomes with increased PRU, the same trends were observed in our study in the analyses of age and BMI.[8,9,12]

The association between HPR and adverse ischemic outcomes, including MI and stent thrombosis, has been reported in numerous real-world registries of patients after PCI.[3,17,18] In addition, older patients had an increased frequency of high on-treatment PRU compared with younger patients, which is consequently associated with an increased risk of ischemic events.[19] Despite this, there are only a few reports on the correlation between clinical outcomes and HPR with respect to age. A generally accepted explanation for the worse clinical outcomes of older patients after PCI is fragility.[7] However, the present study showed that the clinical outcomes of older patients may differ from that of younger patients depending on another factor, such as BMI status.

Although obesity is a major risk factor for coronary artery disease,[20] previous studies have reported that it may be independently associated with better clinical outcomes in patients after PCI.[21,22] The present study found a direct and independent association between BMI and MACCEs, and this is consistent with the results of various large-scale studies demonstrating increased adverse ischemic outcomes in patients with lower BMI after PCI.[8,12,19,22,23] However, although numerous studies have investigated the association between BMI and clinical outcomes in patients after PCI, no large-scale study has reported a correlation between clinical outcomes and HPR with respect to BMI status. In context, the present study showed the first observation that HPR may be associated with clinical outcomes in patients after PCI.

The above analyses led us to investigate the association between HPR on age and BMI differences and clinical outcomes. Biologically, changes in platelet reactivity associated with age or BMI may alter the effectiveness and metabolic processing of antiplatelet therapy, which can lead to varied responses among patients with HPR. For example, older patients may exhibit increased platelet reactivity due to coexisting conditions and a propensity for thrombosis, potentially influencing the effect of HPR on the likelihood of MACCEs. The results of the present study were impressive observations of denying the obesity paradox[22]; in other words, obesity had worse clinical outcomes in patients with HPR after PCI. Interestingly, in the ≥67 years of age group, patients with HPR had decreased rates of major bleeding than those without HPR. These observations are consistent with those of a previous study.[24]

The present study has several limitations. First, data were collected from a nonrandomized and

observational cohort registry. Despite adjustments to minimize bias through multivariable analysis, inherent selection bias and the possibility of residual confounding variables, including genetic variations and non-Asian populations, cannot be ruled out. However, the PTRG-DES registry is the largest population-based registry, with long-term clinical follow-up data on platelet reactivity. Thus, this study suggests that PRU, age, and BMI may affect clinical outcomes of patients after PCI; however, the results should be interpreted with caution. Second, although we investigated the impact of HPR on long-term clinical outcomes according to age and BMI stratification, the present analyses did not provide any mechanistic insight into the modified platelet function measurements in clopidogrel-treated patients caused by genetic variability in the CYP450-isozymes involved in clopidogrel metabolism, because no pharmacogenetics data were available. In addition, all groups were divided based on PRU on DAPT during the index procedure, and no additional data on PRU were available during the follow-up period. Third, this study defined subgroups using cutoff values for age and BMI determined by receiver operating characteristic analysis. Consequently, the results should be interpreted distinctly within the separate contexts of age and BMI. Moreover, it is important to recognize the study's susceptibility to issues related to multiple comparisons and post hoc data-derived findings, factors that can significantly complicate the interpretation of the results. Finally, it remains unclear how these specific findings apply to patients treated with other antiplatelet agents, such as ticagrelor and prasugrel. Therefore, these results should be considered for hypothesis generation, and further randomized clinical trials are needed to confirm our findings.

CONCLUSIONS

HPR was associated with an increase in MACCEs or a decrease in major bleeding in patients after PCI, depending on age and BMI.

ARTICLE INFORMATION

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Disclosures

None.

Supplemental Material

Tables S1–S8
Figures S1–S3

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