
















ORIGINAL RESEARCH

# Sex Differences in Midterm Prognostic Implications of High Platelet Reactivity After Percutaneous Coronary Intervention With Drug-Eluting Stents in East Asian Patients: Results From the PTRG-DES (Platelet Function and Genotype-Related Long-Term Prognosis in Drug-Eluting Stent-Treated Patients With Coronary Artery Disease) Consortium

Soo-Jin Kim , MD, PhD; Ae-Young Her , MD, PhD; Young-Hoon Jeong , MD, PhD; Byeong-Keuk Kim , MD, PhD; Hyung Joon Joo , MD, PhD; Yongwhi Park , MD, PhD; Kiyuk Chang , MD, PhD; Young Bin Song , MD, PhD; Sung Gyun Ahn , MD, PhD; Jung-Won Suh , MD, PhD; Sang Yeub Lee , MD, PhD; Jung Rae Cho, MD, PhD; Hyo-Soo Kim , MD, PhD; Moo Hyun Kim , MD, PhD; Do-Sun Lim , MD, PhD; Eun-Seok Shin , MD, PhD; on behalf of PTRG-DES Consortium Investigators

**BACKGROUND:** Although high platelet reactivity (HPR) on clopidogrel is associated with higher ischemic events and lower bleeding events in patients who have undergone percutaneous coronary intervention with drug-eluting stents, the differential risk of HPR in East Asian women versus men is unknown.

**METHODS AND RESULTS:** We compared 11 714 patients enrolled in the PTRG-DES (Platelet Function and Genotype-Related Long-Term Prognosis in Drug-Eluting Stent-Treated Patients With Coronary Artery Disease) Consortium according to sex and the presence/absence of HPR on clopidogrel (defined as  $\geq 252$  P2Y12 reactivity units). The primary study end point was major adverse cardiac and cerebrovascular events (MACCEs; comprising all-cause mortality, myocardial infarction, cerebrovascular accident, and stent thrombosis). HPR was more common in women (46.7%) than in men (28.1%). In propensity-adjusted models, HPR was an independent predictor of MACCEs (men with HPR: hazard ratio [HR], 1.60 [95% CI, 1.20–2.12]; women with HPR: HR, 0.99 [95% CI, 0.69–1.42]) and all-cause mortality (men with HPR: HR, 1.61 [95% CI, 1.07–2.44]; women with HPR: HR, 0.92 [95% CI, 0.57–1.50]) in men, although those associations were insignificant among women. In addition, a significant interaction between sex was noted in the associations between HPR and MACCE ( $P_{\text{interaction}}=0.013$ ) or all-cause mortality ( $P_{\text{interaction}}=0.025$ ).

**CONCLUSIONS:** In this study, HPR was a differential risk factor for 1-year MACCEs and all-cause mortality in women and men. And it was an independent predictor of 1-year MACCEs and all-cause mortality in men but not in women.

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Correspondence to: Eun-Seok Shin, MD, PhD, 877 Bangeojinsunhwan-doro, Dong-gu, Dong-gu, Ulsan, 44033, South Korea. Email: [sesim1989@gmail.com](mailto:sesim1989@gmail.com)

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**Key Words:** coronary artery disease ■ drug-eluting stent ■ female ■ platelet function ■ sex

## CLINICAL PERSPECTIVE

### What Is New?

- High platelet reactivity on clopidogrel was associated with a significantly higher risk of major adverse cardiac and cerebrovascular events and all-cause death only in the male population.
- The incremental risk of major adverse cardiac and cerebrovascular events and all-cause mortality showed significant sex disparities.

### What Are the Clinical Implications?

- The impact of high platelet reactivity as a prognostic factor is significant in men, but not in women, of East Asian descent.

## Nonstandard Abbreviations and Acronyms

<b>ADAPT-DES</b>	Assessment of Dual Antiplatelet Therapy With Drug-Eluting Stents
<b>DAPT</b>	dual-antiplatelet therapy
<b>DES</b>	drug-eluting stent
<b>HPR</b>	high platelet reactivity
<b>MACCE</b>	major adverse cardiac and cerebrovascular event
<b>PRU</b>	P2Y12 reaction unit
<b>PTRG-DES</b>	Platelet Function and Genotype-Related Long-Term Prognosis in Drug-Eluting Stent-Treated Patients With Coronary Artery Disease

Previous studies have reported that high platelet reactivity (HPR) to clopidogrel has higher ischemic events in patients who have undergone percutaneous coronary intervention (PCI) with drug-eluting stents (DES), whereas low platelet reactivity is related to bleeding events.<sup>1-5</sup> The differential risk/benefit ratio of HPR in women versus men remains unknown. In a post hoc analysis of the ADAPT-DES (Assessment of Dual Antiplatelet Therapy With Drug-Eluting Stents) study, the associated risk of HPR for stent thrombosis (ST) was similar in men and women, whereas HPR was associated with significantly reduced bleeding events among women only during 1 year after DES implantation.<sup>6</sup>

However, East Asian people are known to have a lower risk of thrombotic and atherosclerotic events and a higher risk of severe bleeding than Westerners. In addition, East Asian people have a low response to

clopidogrel, and their optimal potency and achieved risk/benefit ratio during antithrombotic treatment would be relatively different from that of the Western population.<sup>7</sup> Studies on the association between platelet reactivity and clinical outcomes according to sex have been conducted<sup>6</sup> but are still lacking, especially in East Asian women. Therefore, this study aimed to examine the differences in characteristics by sex and compare the clinical implications of HPR in East Asian women and men who underwent PCI for coronary artery disease.

## METHODS

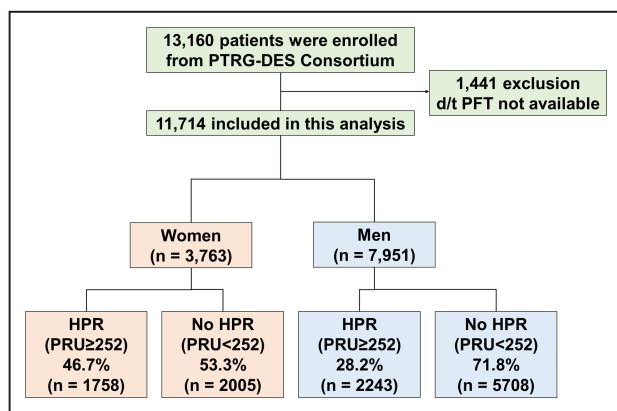
The data that support the findings of this study are available from the corresponding author on reasonable request.

### Study Population

The PTRG-DES (Platelet Function and Genotype-Related Long-Term Prognosis in Drug-Eluting Stent-Treated Patients With Coronary Artery Disease) Consortium was a prospective multicenter registry ([ClinicalTrials.gov](https://clinicaltrials.gov) identifier: NCT04734028) into which 13 160 patients who successfully underwent PCI for significant coronary artery disease at 9 PCI registries in Korea between July 2003 and August 2018 were recruited (Table S1). The patients underwent successful PCI with at least 1 DES and received dual-antiplatelet therapy (DAPT) with clopidogrel and/or aspirin. Among the PTRG-DES cohort, 11 714 patients underwent the VerifyNow P2Y12 test during clopidogrel treatment (PTRG-PFT cohort). Clinical follow-up was performed via a visit to the outpatient clinic or by a telephone interview with the patient at the end of the first month and every 3 or 6 months after the PCI procedure.<sup>8</sup> The institutional review board of each participating center approved the registry and waived the requirement for written informed consent for access to institutional registries. The study was performed in accordance with the Good Clinical Practice Guidelines and the principles of the Declaration of Helsinki. We assessed baseline characteristics and 1-year outcomes according to sex and the presence of HPR (Figure 1).

### Platelet Function Test and Definition of HPR

If the patients were not taking aspirin or clopidogrel at the time of PCI, loading doses of aspirin, 300 mg, and clopidogrel, 300 to 600 mg, were administered before PCI. After PCI, DAPT with aspirin and clopidogrel for



**Figure 1. Study flow.**

HPR indicates high platelet reactivity; PFT, platelet function test; PRU, P2Y12 reaction unit; and PTRG-DES, Platelet Function and Genotype-Related Long-Term Prognosis in Drug-Eluting Stent-Treated Patients With Coronary Artery Disease.

12 months was recommended, but the discontinuation of DAPT was left to each physician's discretion. Baseline and on-treatment (clopidogrel) platelet reactivity was measured using VerifyNow P2Y12 point-of-care assay (Accumetrics, San Diego, CA). Details are in the previous study design article.<sup>8</sup>

The platelet function test results are presented as VerifyNow P2Y12 reaction units (PRUs). According to a previous report, HPR was defined as the cutoff value of 252 PRUs for the 1-year clinical outcome.<sup>9</sup> We defined HPR on clopidogrel as PRUs  $\geq 252$ , the highest tertile that corresponds well with those in the previous literature involving East Asian people.<sup>10</sup>

## Study End Points

The study end point was 1-year clinical outcome, and 1-year outcome information came from all patients without follow-up loss. The primary end point was major adverse cardiac and cerebrovascular events (MACCEs), a composite of all-cause mortality, recurrent myocardial infarction (MI), ST, and cerebrovascular accident. The secondary end points included all-cause mortality, recurrent MI, ST, and major bleeding. MI was defined as the presence of clinical symptoms, electrocardiographic changes, or abnormal imaging findings associated with MI combined with an increase in creatine kinase-MB above the upper normal limit or troponin T/I >99th percentile of the upper normal limit, unrelated to an interventional procedure.<sup>11</sup> ST was defined as definite ST according to the Academic Research Consortium criteria.<sup>12</sup> Cerebrovascular accident included any new embolic, thrombotic, or hemorrhagic stroke events with neurologic deficits that persisted for at least 24 hours. Major bleeding events were defined as Bleeding Academic Research Consortium types 3 and 5.<sup>13</sup>

## Statistical Analysis

Categorical variables are presented as percentages and were compared using the  $\chi^2$  or Fisher exact test. Continuous variables are presented as mean  $\pm$  SD or median and interquartile range (IQR) and were compared using Student *t*-test or the Wilcoxon rank-sum test for medians. Time-to-event data are presented as Kaplan-Meier estimates and were compared using the log-rank test. Hazard ratios (HRs) and 95% CIs were generated using Cox proportional hazard regression models. In the subgroup analysis, the association of HPR versus no HPR and clinical outcomes was examined using Cox regression. Considering that this study is a registry study, propensity scores were used to correct for associations between HPR and events in each female and male subgroup, and the propensity score was calculated by modeling the baseline variables with HPR as a dependent variable in a logistic regression model. After considering control variables, the selected variables were controlled, and the baseline variables included age, acute MI presentation, body mass index, hypertension, hyperlipidemia, smoking, chronic kidney disease, anemia, peripheral artery disease, previous MI, previous PCI, previous cerebrovascular accident, white blood cell count, total cholesterol level, multivessel coronary artery disease, chronic total occlusion, use of second-generation DES, concomitant medications (aspirin, clopidogrel, cilostazol,  $\beta$ -blockers, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, calcium channel blockers, statins, and proton pump inhibitors).

The propensity score model showed proper discrimination in both women and men (C statistics of 0.618 and 0.668, respectively). Cox proportional hazards regression stratified by propensity score was used to adjust the HRs associated with the events of interest. In addition, to examine the relationship between sex and HPR for the end points, formal interaction testing was conducted. All tests were 2-sided, and  $P < 0.05$  was considered statistically significant. Analyses were performed using SAS version 9.2 (SAS Institute Inc, Cary, NC) and R-statistics version 3.6.1.

## RESULTS

Of the PTRG-PFT cohort ( $n=11\,714$ ), 3763 (32.1%) were women and 7951 (67.9%) were men (Figure 1). Women showed a higher level of platelet reactivity ( $240 \pm 80$  PRUs) than men ( $207 \pm 76$  PRUs) (Figure S1). HPR was more common in women ( $n=1758$  [46.7%]) than in men ( $n=2243$  [28.2]; Table S2).

## Baseline Characteristics by Group

The median age of the women was 69.0 years, higher than that of the men (63.0 years). The prevalence of

hypertension, diabetes, chronic kidney disease, and anemia was higher in women than in men; a previous MI history and current smoking status were more common in men. Angiographic findings showed that left anterior descending artery lesions and multivessel disease were more common in women than in men (Table S3).

Overall, HPR showed similar baseline characteristics in women and men. Both sexes in HPR group were older, had a higher prevalence of hypertension, diabetes, anemia, and peripheral artery disease, and were less likely to be smokers than no HPR group. Acute MI presentation and multivessel disease were more frequently noted in men with HPR than in those without HPR but not in women (Table).

### Clinical Outcomes and HPR

The occurrence of 1-year MACCEs was 334 (2.85%) in the total population, and it showed an insignificant difference between the sexes (women versus men: 123

[3.3%] versus 211 [2.7%]; HR, 1.23 [95% CI, 0.99–1.54];  $P=0.066$ ). The median follow-up duration was 717 (IQR, 365–1942) days in women and 470 (IQR, 365–1758) days in men.

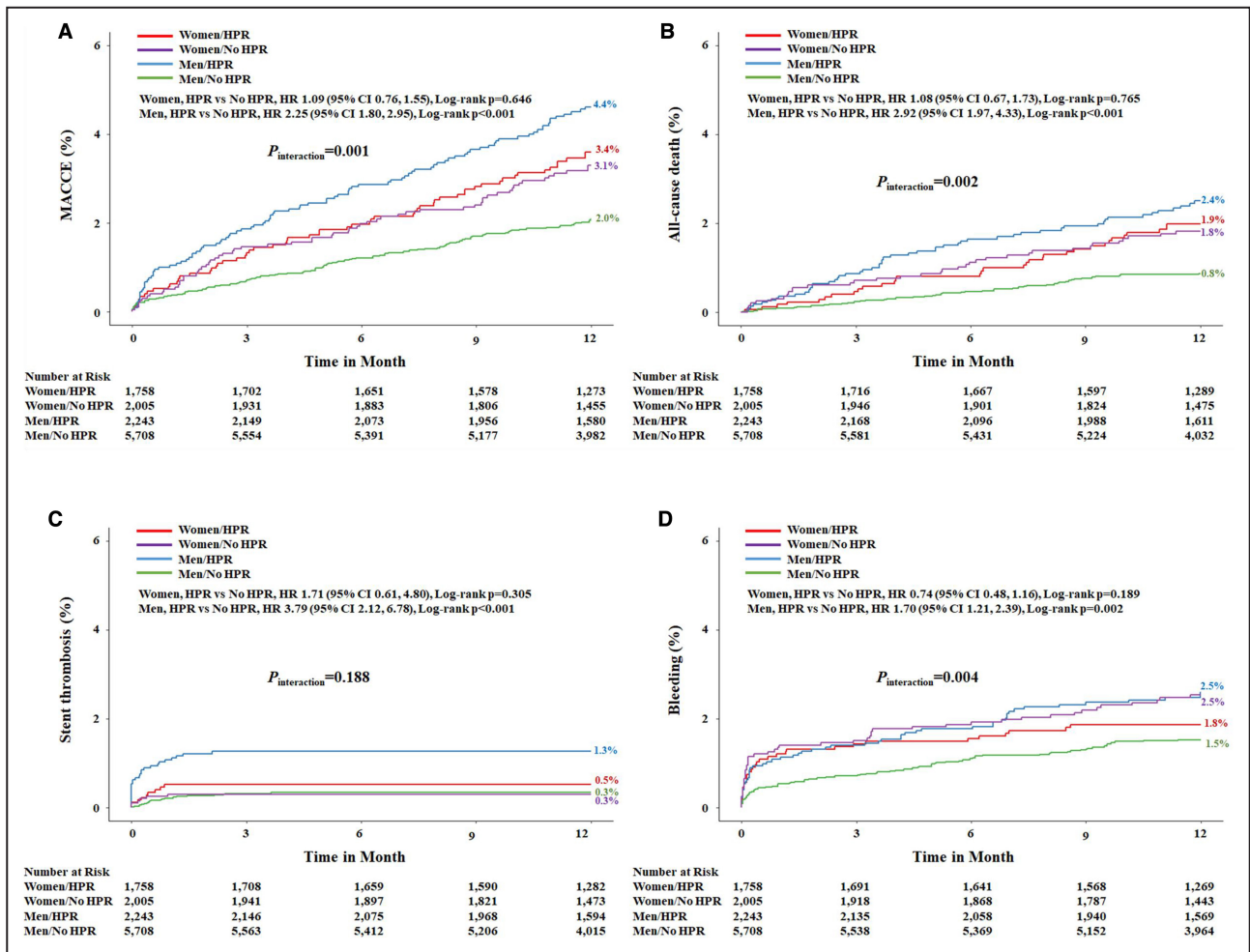
MACCEs occurred in 3.4% of women with HPR, 3.1% of women with no HPR, 4.4% of men with HPR, and 2.0% of men with no HPR. Among women, HPR was not associated with the risk of MACCEs (HR, 1.09 [95% CI, 0.76–1.55];  $P=0.646$ ) (Figure 2A), which was constant after multivariate adjustment (adjusted HR, 0.99 [95% CI, 0.69–1.42];  $P=0.940$ ) (Figure 3). Conversely, in the male population, HPR was an independent predictor of MACCE occurrence (adjusted HR, 1.60 [95% CI, 1.20–2.12];  $P=0.001$ ); the sex difference in HPR for MACCEs was observed in formal interaction test ( $P=0.013$ ) (Figure 3).

Similarly, HPR in women was not associated with all-cause mortality (Figure 2B), a finding that was consistent with the adjusted results (Figure 3). HPR in men was an independent predictor of all-cause mortality,

**Table. Baseline Characteristics**

Characteristic	Women (n=3763)		P value	Men (n=7951)		P value
	HPR (n=1758)	No HPR (n=2005)		HPR (n=2243)	No HPR (n=5708)	
Age, y	70.0 (64.0–76.0)	68.0 (60.0–75.0)	<0.001	66.0 (58.0–73.0)	61.0 (54.0–70.0)	<0.001
Body mass index, kg/m <sup>2</sup>	24.4 (22.4–26.7)	24.2 (22.2–26.3)	0.058	24.2 (22.4–26.1)	24.6 (22.8–26.4)	<0.001
Medical history, n (%)						
Hypertension	1236 (70.3)	1304 (65.0)	0.001	1351 (60.2)	3158 (55.3)	<0.001
Diabetes	729 (41.5)	710 (35.4)	<0.001	858 (38.3)	1852 (32.5)	<0.001
Dyslipidemia	1085 (61.7)	1294 (64.5)	0.073	1448 (64.6)	3728 (65.3)	0.525
Current smoker	103 (5.9)	193 (9.6)	<0.001	758 (33.8)	2231 (39.1)	<0.001
Chronic kidney disease	564 (32.1)	615 (30.7)	0.353	506 (22.6)	747 (13.1)	<0.001
Peripheral artery disease	221 (12.6)	225 (11.2)	0.201	355 (15.8)	652 (11.4)	<0.001
Previous PCI	230 (13.1)	299 (14.9)	0.107	311 (13.9)	728 (12.8)	0.186
Previous CVA	127 (7.2)	145 (7.2)	0.993	170 (7.6)	371 (6.5)	0.085
Presentation as acute myocardial infarction	466 (26.5)	521 (26.0)	0.716	701 (31.3)	1650 (28.9)	0.039
Multivessel disease, n (%)	735 (41.8)	795 (39.7)	0.179	904 (40.3)	2110 (37.0)	0.006
LAD lesion, n (%)	1102 (62.7)	1268 (63.2)	0.724	1252 (55.8)	3338 (58.5)	0.031
Laboratory measurements						
WBC count, ×10 <sup>3</sup> /mm <sup>3</sup>	6.9 (5.7–8.7)	7.1 (5.8–8.9)	0.061	7.1 (5.8–9.0)	7.3 (6.0–9.3)	0.029
Hemoglobin, g/dL	12.4 (11.4–13.3)	13.0 (12.0–13.9)	<0.001	13.4 (12.2–14.4)	14.5 (13.5–15.5)	<0.001
Platelet, ×10 <sup>3</sup> /mm <sup>3</sup>	234.0 (195.0–281.0)	234.0 (195.0–282.0)	0.868	216.0 (179.0–256.0)	220.0 (184.0–262.0)	0.009
PRU	299.0 (274.0–330.0)	197.0 (151.0–225.0)	<0.001	287.0 (268.0–317.0)	183.0 (139.0–215.0)	<0.001
Discharge medications, n (%)						
β-blocker	1006 (57.2)	1092 (54.5)	0.089	1291 (57.6)	3280 (57.5)	0.939
Angiotensin blockade	1083 (61.6)	1085 (54.1)	<0.001	1361 (60.7)	3398 (59.5)	0.348
Calcium channel blocker	439 (25.0)	537 (26.8)	0.206	542 (24.2)	1299 (22.8)	0.181
Statin	1525 (86.8)	1658 (82.7)	0.001	1998 (89.1)	5198 (91.1)	0.007

Continuous variables are expressed in median (interquartile range) as indicated. CVA indicates cerebrovascular accident; HPR, high platelet reactivity; LAD, left anterior descending artery; PCI, percutaneous coronary intervention; PRU, P2Y12 reaction unit; and WBC, white blood cell.



**Figure 2. Kaplan-Meier curve according to sex and high platelet reactivity (HPR) for clinical outcomes.** Kaplan-Meier curves according to sex and HPR showing major adverse cardiac and cerebrovascular events (MACCEs) (A), all-cause mortality (B), stent thrombosis (C), and major bleeding (D). HR indicates hazard ratio.

with sex differences in formal interaction ( $P=0.025$ ) (Figure 3).

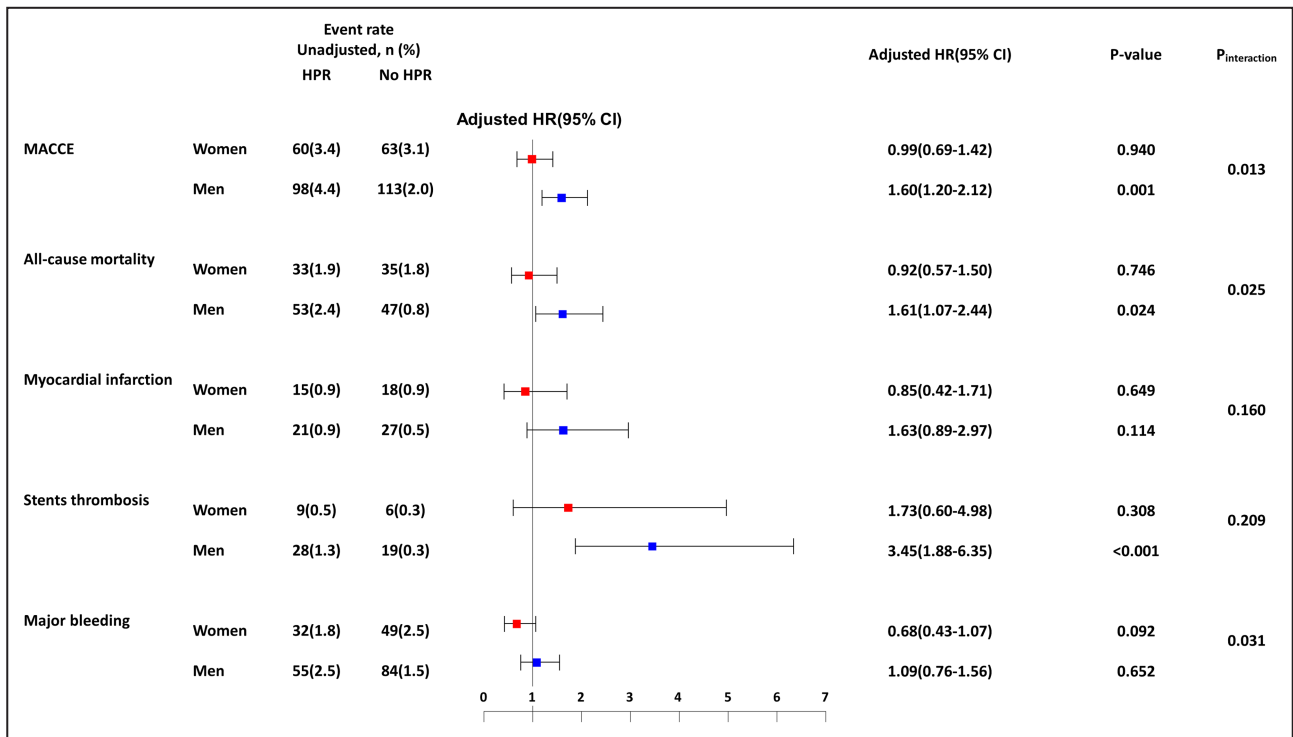
The association between HPR and MI was insignificant in women but significantly higher in men (HR, 2.01 [95% CI, 1.14–3.56];  $P=0.014$ ). After multivariate adjustment, the higher risk of MI did not remain statistically significant in either sex (Figure 3). HPR was associated with a higher incidence of ST (1.7-fold in women and 3.8-fold in men), but this difference was not statistically significant among women (Figure 2C). Propensity-adjusted multivariate models also showed significantly higher risk among men but not women. Formal interaction testing was not significant ( $P_{interaction}=0.209$ ) (Figure 3).

In the unadjusted analysis of the association between HPR and major bleeding events, HPR showed an insignificant association in women but higher bleeding events in men (Figure 2D). However, this trend disappeared after the multivariate adjustment. However, the sex interaction was observed even after adjustment ( $P=0.031$ ) (Figure 3).

## DISCUSSION

In this post hoc analysis of the nationwide large-scale multicenter PTRG-DES Consortium of East Asian patients, we found the following: (1) HPR was more common in women than in men; (2) HPR had a different prognostic implication in women than in men; (3) HPR phenotype showed significantly higher risk of 1-year MACCEs, all-cause mortality, and ST in men only; and (4) the association between HPR and major bleeding events was not significant in women or men.

As in previous studies of sex differences, in the present study, women were older and had more cardiovascular risk factors than men.<sup>14–17</sup> The HPR rate was higher in women than in men, a finding that is consistent with the results of previous studies.<sup>18–20</sup> Numerous factors that can influence platelet function (eg, inflammatory markers, platelet count, platelet surface receptor, vessel wall biology, sex hormones, and age) can be related to this sex difference, but this



**Figure 3. Association between sex, high platelet reactivity (HPR), and clinical outcomes.** HR indicates hazard ratio; and MACCE, major adverse cardiac and cerebrovascular event.

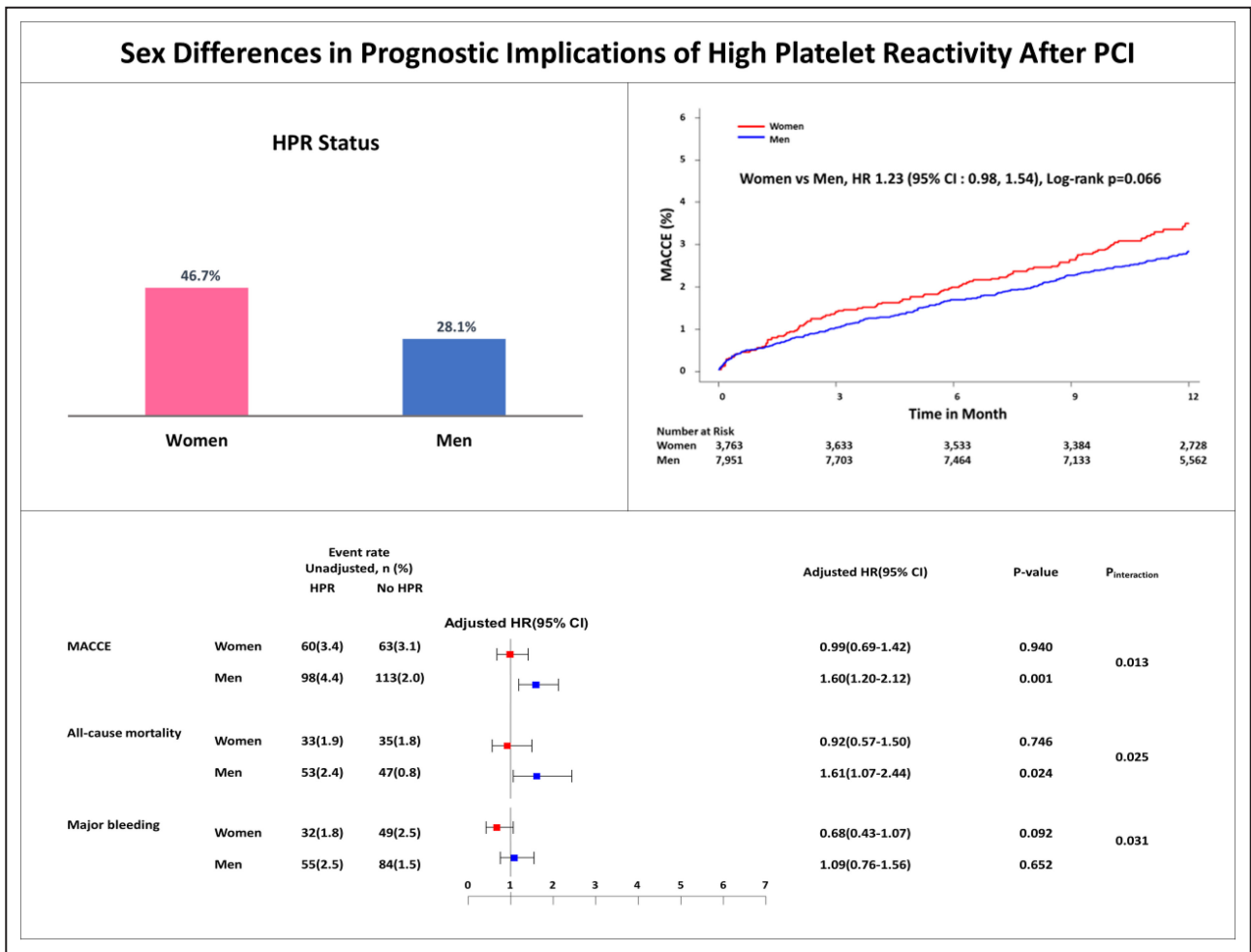
was inconclusive.<sup>21–25</sup> Previous reports suggested that there are no sex differences in the genes involved in clopidogrel metabolism.<sup>26</sup> Considering the higher baseline platelet reactivity (VerifyNow BASE) in women versus men from the results of the present study, the higher prevalence of HPR may be attributable to higher baseline (off-clopidogrel) platelet reactivity in women (Table S2).<sup>18</sup>

The “East Asian paradox” suggested in 2012 indicated the low response to clopidogrel in East Asian versus Western populations (mainly related to different frequencies of the cytochrome P450 2C19 loss-of-function allele) and the unique risk/benefit ratio according to platelet reactivity in East Asian patients.<sup>7,27</sup> These observations could be related to the different cutoffs of HPR between the races for determining the risk of ischemic and bleeding events ( $\geq 252$  PRUs from PTRG-DES [Koreans] versus  $>208$  PRUs from ADAPT-DES study [Westerners]).<sup>6</sup> In both studies, the frequency of HPR was higher in women than in men (1.7-fold in PTRG-DES and 1.3-fold in ADAPT-DES study). In the ADAPT-DES study, HPR was statistically significant as a predictor for 1-year ST, MI, and MACCEs in the male population, but the formal interaction test between women and men was insignificant.

In this study, HPR in men was a statistically significant predictive factor for 1-year MACCEs, all-cause mortality, and ST. Adjusted interaction test among sexes was insignificant in the relationship between

HPR and ST, but there was a statistically significant association between HPR and MACCEs and all-cause mortality (Table S4). The association between HPR and ischemic events was prominent in men, and the effect was less in women. In addition, in this analysis of East Asian patients, the differences between the sexes in MACCEs and all-cause mortality were more pronounced than those of Westerners. Moreover, detailed studies on the differences in platelet function and clinical relevance between Western and East Asian women are needed.

Previous studies demonstrated that female sex is an independent predictor of bleeding events during hospitalization and long-term follow-up after PCI.<sup>17,28–31</sup> In this analysis, women showed more major bleeding events (Bleeding Academic Research Consortium 3 or 5) within 30 days after PCI (1.30% versus 0.69%; log-rank,  $P=0.001$ ), and major bleeding events during 1 year was 2.18% in women and 1.76% in men (log-rank,  $P=0.120$ ). The association between HPR and major bleeding showed a sex disparity during 1-year follow-up ( $P_{\text{interaction}}=0.031$  between women: HR, 0.68 [95% CI, 0.43–1.07];  $P=0.092$  versus men: HR, 1.09 [95% CI, 0.76–1.56];  $P=0.652$ ), but a disparity was not observed during 30 days ( $P_{\text{interaction}}=0.122$  between women: HR, 0.81 [95% CI, 0.45–1.44];  $P=0.471$  versus men: HR, 1.09 [95% CI, 0.62–1.92];  $P=0.765$ ) after multivariate adjustment. The ADAPT-DES study reported that the association between bleeding and HPR showed a sex



**Figure 4. Sex differences in prognostic implications of high platelet reactivity (HPR) after percutaneous coronary intervention (PCI).**

HPR was more common in women than men (left upper). There was no statistically significant difference between women and men in 1-year major adverse cardiac and cerebrovascular events (MACCEs) (right upper). Compared with women, HPR is important as an independent predictor of 1-year MACCEs and 1-year mortality in men (lower). HR indicates hazard ratio.

disparity and that HPR contributed to fewer bleeding events only in women population.<sup>6</sup> In the ADAPT-DES study, bleeding (including minor bleeding events) was used as an end point, but in this study, major bleeding events was the end point and the association between HPR and major bleeding was insignificant.

This study compared sex differences in the association of HPR with clinical outcomes in East Asian patients. In women, HPR was not predictive of MACCEs and, in detail, did not predict all-cause mortality, MI, ST, or major bleeding. However, MACCEs, all-cause mortality, and ST were predictable in men. Although the proportion of HPR was higher in women, the association with clinical events was insignificant. Bleeding time is longer in women than in men compared with platelet function tests and platelet count,<sup>32,33</sup> but there may be factors we are unaware of, and the influence of various clinical factors may be greater. In the future, a more in-depth study of sex and racial differences in

platelet function and factors that can predict clinical events in East Asian women will be needed.

**Limitations**

This study had several limitations. First, it was a post hoc analysis of prospective observational registries and has limitations because it was not a randomized controlled trial comparing the clinical outcomes of men and women. Information on previous drug use or adherence to medications that could affect platelet function tests was lacking, and this was not a randomized study in women and men. Second, we assessed platelet reactivity at only one time point. As some have suggested that platelet responsiveness varies over time, serial platelet function tests might have provided an incremental prognosis.<sup>34,35</sup> An appropriate time point for platelet function tests should be recommended through future studies on platelet function tests. Third, we did not consider the hormonal

influences (menopausal status) in our women, which may have affected the results. Fourth, physicians tried to administer dual-antiplatelet and antiplatelet therapy according to guidelines, but the drug use in the bleeding status was up to the physician's discretion in a case-by-case basis, and detailed information was not collected. DAPT duration was 389 (IQR, 389–1101) days versus 378 (IQR, 328–825) days in female and male group in this study. Not all patients have taken full DAPT medication for 1 year, and information on the use of glycoprotein IIb/IIIa inhibitors was lacking. Finally, the baseline characteristics differed between the 2 groups. For a fair comparison between sexes, many influencing factors were corrected using the Cox proportional hazard model with the propensity score, but the possibility of residual confounding factors could not be excluded.

## CONCLUSIONS

In East Asian patients treated with DES implantation, HPR served as a predictor of MACCEs, all-cause mortality, and ST in men only, and the prognostic implication of HPR on MACCEs, all-cause mortality, and major bleeding during 1 year showed sex-based disparities (Figure 4).

## ARTICLE INFORMATION

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### Affiliations

Division of Cardiology, Department of Internal Medicine, Kosin University College of Medicine, Busan, South Korea (S-J.K.); Division of Cardiology, Department of Internal Medicine, Kangwon National University School of Medicine, Chuncheon, South Korea (A-Y.H.); Chung-Ang University Thrombosis Center, Gwangmyeong Chung-Ang University Medical Center, Gwangmyeong, South Korea (Y-H.J.); Severance Cardiovascular Hospital, Yonsei University College of Medicine, Seoul, South Korea (B-K.K.); Department of Cardiology, Cardiovascular Center, Korea University Anam Hospital, Korea University College of Medicine, Seoul, South Korea (H-J.J., D-S.L.); Department of Internal Medicine, Gyeongsang National University School of Medicine and Cardiovascular Center, Gyeongsang National University Changwon Hospital, Changwon, South Korea (Y.P.); Division of Cardiology, Department of Internal Medicine, College of Medicine, Catholic University of Korea, Seoul, South Korea (K.C.); Division of Cardiology, Department of Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, South Korea (Y.B.S.); Department of Cardiology, Yonsei University Wonju Severance Christian Hospital, Wonju, South Korea (S.G.A.); Department of Internal Medicine, Seoul National University College of Medicine and Department of Cardiology, Seoul National University Bundang Hospital, Seongnam, South Korea (J-W.S.); Division of Cardiology, Department of Internal Medicine, Chungbuk National University, College of Medicine, Cheongju, South Korea (S.Y.L.); Cardiology Division, Department of Internal Medicine, Kangnam Sacred Heart Hospital, Hallym University College of Medicine, Seoul, South Korea (J.R.C.); Department of Internal Medicine and Cardiovascular Center, Seoul National University Hospital, Seoul, South Korea (H-S.K.); Department of Cardiology, Dong-A University Hospital, Busan, South Korea (M.H.K.); and Department of Cardiology, Ulsan University Hospital, University of Ulsan College of Medicine, Ulsan, South Korea (E-S.S.).

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### Disclosures

Dr Jeong has received honoraria for lectures from AstraZeneca, Daiichi Sankyo, Sanofi-Aventis, Han-mi Pharmaceuticals, and Yuhan Pharmaceuticals, and research grants or support from Yuhan Pharmaceuticals and U&I Corporation; Dr Song has received honoraria for lectures from AstraZeneca, Daiichi Sankyo, Sanofi-Aventis, Bayer Korea, and Samjin Pharmaceutical; Dr Joo has received honoraria for lectures from AstraZeneca, Hanmi, Samjin, Dong-A, HK inno.N Pharmaceuticals, and DIO Medical Ltd.

### Supplemental Material

Data S1  
Tables S1–S4  
Figure S1

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## **SUPPLEMENTAL MATERIAL**

## **Data S1. PTRG-DES Consortium Investigators**

### ***Principal Investigators***

Do-Sun Lim (Department of Cardiology, Cardiovascular Center, Anam Hospital, Seoul, South Korea); Yangsoo Jang (Division of Cardiology, Severance Cardiovascular Hospital, Yonsei University College of Medicine, Seoul, South Korea); Won Yong Shin (Division of Cardiology, Department of Internal Medicine, Soonchunyang University Cheonam Hospital, Cheonam, South Korea); JungHan Yoon (Division of Cardiology, Department of Internal Medicine, Wonju Severance Christian Hospital, Yonsei University Wonju College of Medicine, Wonju, South Korea); Yong Hoon Kim (Division of Cardiology, Department of Internal Medicine, Kangwon National University School of Medicine, Chuncheon, South Korea); Yun-Hyeong Cho (Department of Internal Medicine, Seonam University, Myongji Hospital, Goyang, South Korea); Woong Chol Kang (Department of Cardiology, Gachon University Gil Medical Center, Incheon, South Korea); Weon Kim (Department of Internal Medicine, Division of Cardiology, Kyung Hee University Hospital, Kyung Hee University School of Medicine, Seoul, South Korea); Young-Hyo Lim (Division of Cardiology, Department of Internal Medicine, Hanyang University College of Medicine, Seoul, South Korea); Hyeon-Cheol Gwon (Division of Cardiology, Department of Internal Medicine, Samsung medical center, Sungkyunkwan University School of Medicine, Seoul, South Korea); WoongGil Choi (Division of Cardiology, Department of Internal Medicine, Konkuk University College of Medicine, Chungju, South Korea); Seok-Yeon Kim (Department of Cardiology, Seoul Medical Center, Seoul, South Korea); YoungKeun Ahn (Department of Cardiology, Chonnam National University Hospital, Gwangju, South Korea); JaeWoong Choi (Department of Cardiology, Eulji General Hospital, Eulji University College of Medicine, Seoul, South Korea); Young Won Yoon (Department of Internal Medicine, Gangnam Severance Hospital, Yonsei College of Medicine, Seoul, South

Korea); Myoung-Ho Yoon (Department of Cardiology, Ajou University School of Medicine, Suwon, South Korea); DongHun Yang (Division of Cardiology, Department of Internal Medicine, Kyungpook National University School of Medicine, Daegu, South Korea); Jae-Bin Seo (Department of Internal Medicine, Seoul Metropolitan Government Seoul National University Borame Medical Center, Seoul, South Korea); SeungMin Choi (Department of Internal Medicine, Cardiovascular Center, National Medical Center, Seoul, South Korea); JongSeon Park (Division of Cardiology, Department of Internal Medicine, Yeungnam University Medical Center, Daegu, South Korea); Jae-Gook Shin (Department of Clinical pharmacology, Inje University Busan Paik Hospital, Busan, South Korea); Kiyuk Chang, Ki-Bae Seung (Cardiovascular Center and Cardiology Division, Seoul St. Mary's Hospital, College of Medicine, The Catholic University of Korea, Seoul, South Korea); Yoon-Seok Koh (Department of Cardiology, Uijeongbu St. Mary's Hospital, The Catholic University of Korea, Uijeongbu, South Korea); Mahn-Won Park (Department of Cardiology, Daejeon St. Mary's Hospital, The Catholic University of Korea, Daejeon, South Korea); Yun Seok Choi (Department of Cardiology, Yeouido St. Mary's Hospital, The Catholic University of Korea, Seoul, South Korea); Young-Hoon Jeong (Cardiovascular Center, Gyeongsang National University Changwon Hospital, Changwon, South Korea); Jin-Yong Hwang (Division of Cardiology, Department of Medicine, Cardiovascular Center, Gyeongsang National University Hospital, Jinju, South Korea); Young Bin Song (Division of Cardiology, Department of Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, South Korea); Sung Gyun Ahn (Division of Cardiology, Department of Internal Medicine, Wonju Severance Christian Hospital, Yonsei University Wonju College of Medicine, Wonju, South Korea); Jung-Won Suh (Cardiovascular Center, Seoul National University Bundang Hospital, Seungnam, Gyeonggi-do, South Korea); Hyo-Soo Kim (Cardiovascular Center,

Department of Internal Medicine, Seoul National University Hospital, Seoul, South Korea); Moo Hyun Kim (Department of Cardiology, Dong-A University Hospital, Busan, South Korea); Sang Yeub Lee (Division of Cardiology, Department of Internal Medicine, Chungbuk National University College of Medicine, Cheongju, South Korea); Jung Rae Cho (Division of Cardiology, Department of Internal Medicine, Hallym University Kangnam Sacred Heart Hospital, Seoul, South Korea).

***Investigators***

Myeong-Ki Hong, Young-Guk Ko, Jung-Sun Kim, Chul-Min Ahn, Sung-Jin Hong, Donghoon Choi, Seung-Jun Lee (Severance Cardiovascular Hospital, Seoul, South Korea); Ki-Hyun Jeon, Jeehoon Kang, Kyung Woo Park, In-Ho Chae (Seoul National University College of Medicine and Department of Cardiology, South Korea); Myung Ho Jeong, Seung Hun Lee (Chonnam National University Hospital, Gwangju, South Korea); Seung-Hyuck Choi, Joo-Yong Hahn, Taek Kyu Park, Joo Myung Lee, Ki Hong Choi, David Hong (Samsung Medical Center, Seoul, South Korea); Young Jin Youn, Jun-Won Lee, Jung-Hee Lee, Ho-Sung Jeon, Se-Eun Kim (Yonsei University Wonju Severance Christian Hospital, Wonju, South Korea).

**Table S1. List of Participating Registries**

Name of registry	Participating centers	Principal investigator
GENIUS (n=4155, 20 centers)	Department of Cardiology, Cardiovascular Center, Anam Hospital, Seoul, South Korea	Do-Sun Lim
	Division of Cardiology, Severance Cardiovascular Hospital, Yonsei University College of Medicine, Seoul, South Korea	Yangsoo Jang
	Division of Cardiology, Department of Internal Medicine, Soonchunyang Univeristy Cheonan Hospital, Cheonan, South Korea	Won Yong Shin
	Division of Cardiology, Department of Internal Medicine, Wonju Severance Christian Hospital, Yonsei University Wonju College of Medicine, Wonju, South Korea	JungHan Yoon
	Division of Cardiology, Department of Internal Medicine, Kangwon National University School of Medicine, Chuncheon, South Korea	Yong Hoon Kim
	Department of Internal Medicine, Seonam University, Myongji Hospital, Goyang, South Korea	Yun-Hyeong Cho
	Department of Cardiology, Gachon University Gil Medical Center, Incheon, South Korea	Woong Chol Kang
	Department of Internal Medicine, Division of Cardiology, Kyung Hee University Hospital, Kyung Hee University School of Medicine, Seoul, South Korea	Weon Kim
	Division of Cardiology, Department of Internal Medicine, Hanyang University College of Medicine, Seoul, South Korea	Young-Hyo Lim
	Division of Cardiology, Department of Internal Medicine, Samsung medical center, Sungkyumkwan University School of Medicine, Seoul, South Korea	Hyeon-Cheol Gwon
	Division of Cardiology, Department of Internal Medicine, Konkuk University College of Medicine, Chungju, South Korea	WoongGil Choi
	Department of Cardiology, Seoul Medical Center, Seoul, South Korea	Seok-Yeon Kim
	Department of Cardiology, Chonnam National University Hospital, Gwangju, South Korea	YoungKeun Ahn
	Department of Cardiology, Eulji General Hospital, Eulji University College of Medicine, Seoul, South Korea	JaeWoong Choi
	Department of Internal Medicine, Gangnam Severance Hospital, Yonsei College of Medicine, Seoul, South Korea	YoungWon Yoon
	Department of Cardiology, Ajou University School of Medicine, Suwon, South Korea	Myoung-Ho Yoon
	Division of Cardiology, Department of Internal Medicine, Kyungpook National University School of Medicine, Daegu, South Korea	DongHun Yang
	Department of Internal Medicine, Seoul Metropolitan Government Seoul National University Borame Medical Center, Seoul, South Korea	Jae-Bin Seo
	Department of Internal Medicine, Cardiovascular Center, National Medical Center, Seoul, South Korea	SeungMin Choi
	Division of Cardiology, Department of Internal Medicine, Yeungnam University Medical Center, Daegu, South Korea	JongSeon Park
Catholic (n=1823, 5 centers)	Department of Clinical pharmacology, Inje University Busan Paik Hospital, Busan, South Korea	Jae-Gook Shin
	Cardiovascular Center and Cardiology Division, Seoul St. Mary's Hospital, College of Medicine, The Catholic University of Korea, Seoul, South Korea	Kiyuk Chang, Ki-Bae Seung
	Department of Cardiology, Uijeongbu St. Mary's Hospital, The Catholic University of Korea, Uijeongbu, South Korea	Yoon-Seok Koh
	Department of Cardiology, Daejeon St. Mary's Hospital, The Catholic University of Korea, Daejeon, South Korea	Mahn-Won Park
	Department of Cardiology, Yeouido St. Mary's Hospital, The Catholic University of Korea, Seoul, South Korea	Yun Seok Choi
GNUH (n=1778, 2 centers)	Cardiovascular Center, Gyeongsang National University Changwon Hospital, Changwon, South Korea	Young-Hoon Jeong
	Division of Cardiology, Department of Medicine, Cardiovascular Center, Gyeongsang National University Hospital, Jinju, South Korea	Jin-Yong Hwang
SMC (n=1328, 1 center)	Division of Cardiology, Department of Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, South Korea	Young Bin Song
WSC (n=1288, 1 center)	Division of Cardiology, Department of Internal Medicine, Wonju Severance Christian Hospital, Yonsei University Wonju College of Medicine, Wonju, South Korea	Sung Gyun Ahn
SNU (n=1147, 2 centers)	Cardiovascular Center, Seoul National University Bundang Hospital, Seungnam, Gyeonggi-do, South Korea	Jung-Won Suh
	Cardiovascular Center, Department of Internal Medicine, Seoul National University Hospital, Seoul, South Korea	Hyo-Soo Kim
Dong-A (n=838, 1 center)	Department of Cardiology, Dong-A University Hospital, Busan, South Korea	Moo Hyun Kim
CNU (n=475, 1 center)	Division of Cardiology, Department of Internal Medicine, Chungbuk National University College of Medicine, Cheongju, South Korea	Sang Yeub Lee
KSH (n=328, 1 center)	Division of Cardiology, Department of Internal Medicine, Hallym University Kangnam Sacred Heart Hospital, Seoul, South Korea	Jung Rae Cho

**Table S2. Platelet function test**

	<b>Women</b>	<b>Men</b>	<b>p-value</b>
<b>VerifyNow P2Y12 assay</b>	<b>(n=3763)</b>	<b>(n=7951)</b>	
PRU	239.8 ± 79.7	207.3 ± 76.1	<0.001
PRU≥252	1758 (46.7%)	2243 (28.2%)	<0.001
BASE	321.6 ± 57.4	287.1 ± 56.6	<0.001
% inhibition	25.5 ± 21.6	27.7 ± 22.6	<0.001
<b>VerifyNow Aspirin assay</b>	<b>(n=2324)</b>	<b>(n=4838)</b>	
ARU	442.9 ± 68.1	444 ± 70.0	<0.001

Continuous variables were expressed in mean ± SD.

Abbreviations: ARU, aspirin reaction units; PRU, P2Y12 reaction unit.

**Table S3. Baseline characteristics of the study population**

Variables	Women (n=3,763)	Men (n=7,951)	p-value
Age, years	69.0 (62.0-75.0)	63.0 (55.0-71.0)	<0.001
Body mass index, kg/m <sup>2</sup>	24.5 ± 3.3	24.6 ± 3.0	0.119
Medical history, n (%)			
Hypertension	2540 (67.5%)	4509 (56.7%)	<0.001
Diabetes mellitus	1439 (38.2%)	2712 (34.1%)	<0.001
Dyslipidemia	2379 (63.2%)	5176 (65.1%)	0.047
Current smoker	296 (7.9%)	2989 (37.6%)	<0.001
Chronic kidney disease	1179 (31.3%)	1253 (15.8%)	<0.001
Peripheral artery disease	446 (11.9%)	1007 (12.7%)	0.213
Congestive heart failure	281 (7.5%)	599 (7.5%)	0.899
Previous PCI	529 (14.1%)	1039 (13.1%)	0.142
Previous CVA	272 (7.2%)	541 (6.8%)	0.399
Presentation as acute myocardial infarction	987 (26.2%)	2351 (29.6%)	<0.001
Multivessel disease, n (%)	1530 (40.7%)	3014 (37.9%)	0.004
LAD lesion, n (%)	2370 (63.0%)	4590 (57.7%)	<0.001
Laboratory measurements			
WBC, x10 <sup>3</sup> /mm <sup>3</sup>	7.0 (5.8-8.8)	7.3 (5.9-9.2)	<0.001
Hemoglobin, g/dL	12.7 (11.7-13.6)	14.2 (13.1-15.2)	<0.001
Platelet, x10 <sup>3</sup> /mm <sup>3</sup>	234.0 (195.0-282.0)	219.0 (182.0-260.0)	<0.001
Discharge medications, n (%)			
Beta blocker	2098 (55.8%)	4571 (57.5%)	0.076
Angiotensin blockade	2168 (57.6%)	4759 (59.9%)	0.021
Calcium channel blocker	976 (25.9%)	1841 (23.2%)	0.001
Statin	3183 (84.6%)	7196 (90.5%)	<0.001

Continuous variables were expressed in mean ± SD or median (IQR) as indicated.

Abbreviations: CVA, cerebrovascular accident; HPR, high platelet reactivity; PCI, percutaneous coronary intervention; WBC, white blood cell.



**Table S4. HPR & ischemic clinical outcomes**

ADAPT-DES					PTRG-DES				
		Adjusted HR (95% CI)	P- value	P <sub>interaction</sub>			Adjusted HR (95% CI)	P- value	P <sub>interaction</sub>
ST	Women	2.28 (0.86-6.05)	0.10	0.99	ST	Women	1.73 (0.60-4.98)	0.31	0.21
	men	1.97 (1.05-3.72)	0.04			men	3.45 (1.88-6.35)	<0.01	
All-Cause Death	Women	0.99 (0.50-1.96)	0.99	0.18	All-Cause Death	Women	0.92 (0.57-1.50)	0.75	0.03
	men	1.37 (0.92-2.04)	0.12			men	1.61 (1.07-2.44)	0.02	
MI	Women	1.23 (0.77-1.98)	0.39	0.44	MI	Women	0.85 (0.42-1.71)	0.65	0.16
	men	1.52 (1.11-2.10)	0.01			men	1.63 (0.89-2.97)	0.11	
MACE	Women	1.12 (0.79-1.58)	0.52	0.32	MACCE	Women	0.99 (0.69-1.42)	0.94	0.01
	men	1.23 (1.0-1.53)	0.06			men	1.60 (1.20-2.12)	<0.01	

Abbreviations: MACE, major adverse cardiac event, a composite of cardiac death, myocardial infarction, or target lesion revascularization for ischemia/symptoms; MACCE, major adverse cardiac and cerebrovascular event; MI, myocardial infarction; CI, confidence interval; HR, hazard ratio; ST, stent thrombosis.

Figure S1. Platelet function test

