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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

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**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 ≥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 ($P_{interaction}$=0.013) or all-cause mortality ($P_{interaction}$=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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**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

| | |
|---|---|
| **ADAPT-DES** | Assessment of Dual Antiplatelet Therapy With Drug-Eluting Stents |
| **DAPT** | dual-antiplatelet therapy |
| **DES** | drug-eluting stent |
| **HPR** | high platelet reactivity |
| **MACCE** | major adverse cardiac and cerebrovascular event |
| **PRU** | P2Y12 reaction unit |
| **PTRG-DES** | 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.[1–5] 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.[6]

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.[7] Studies on the association between platelet reactivity and clinical outcomes according to sex have been conducted[6] 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 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.[8] 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

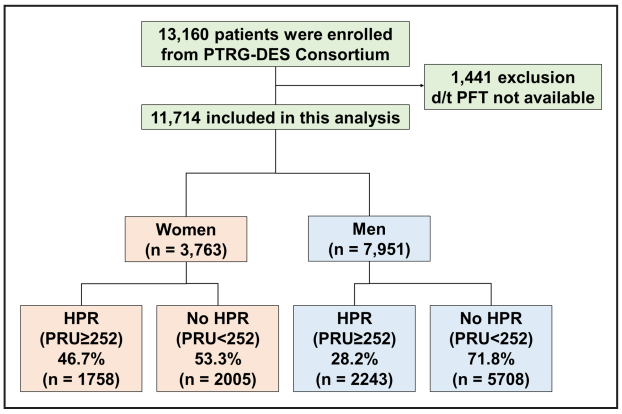


**Figure 1. Study flow.**
HPR indicates high platelet reactivity; PFT, platelet function test; PRU, P2Y12 reaction unit; and PTRG-DES, Platelet Function and Genotype-Related Long-Term Prognosis in Drug-Eluting Stent–Treated Patients With Coronary Artery Disease.

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.[8]

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.[9] We defined HPR on clopidogrel as PRUs ≥252, the highest tertile that corresponds well with those in the previous literature involving East Asian people.[10]

## 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.[11] ST was defined as definite ST according to the Academic Research Consortium criteria.[12] 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.[13]

## 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±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, β-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±80 PRUs) than men (207±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) | | | Men (n=7951) | | |
|---|---|---|---|---|---|---|
| | HPR (n=1758) | No HPR (n=2005) | *P* value | HPR (n=2243) | No HPR (n=5708) | *P* value |
| 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$^2$ | 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$^3$/mm$^3$ | 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$^3$/mm$^3$ | 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.

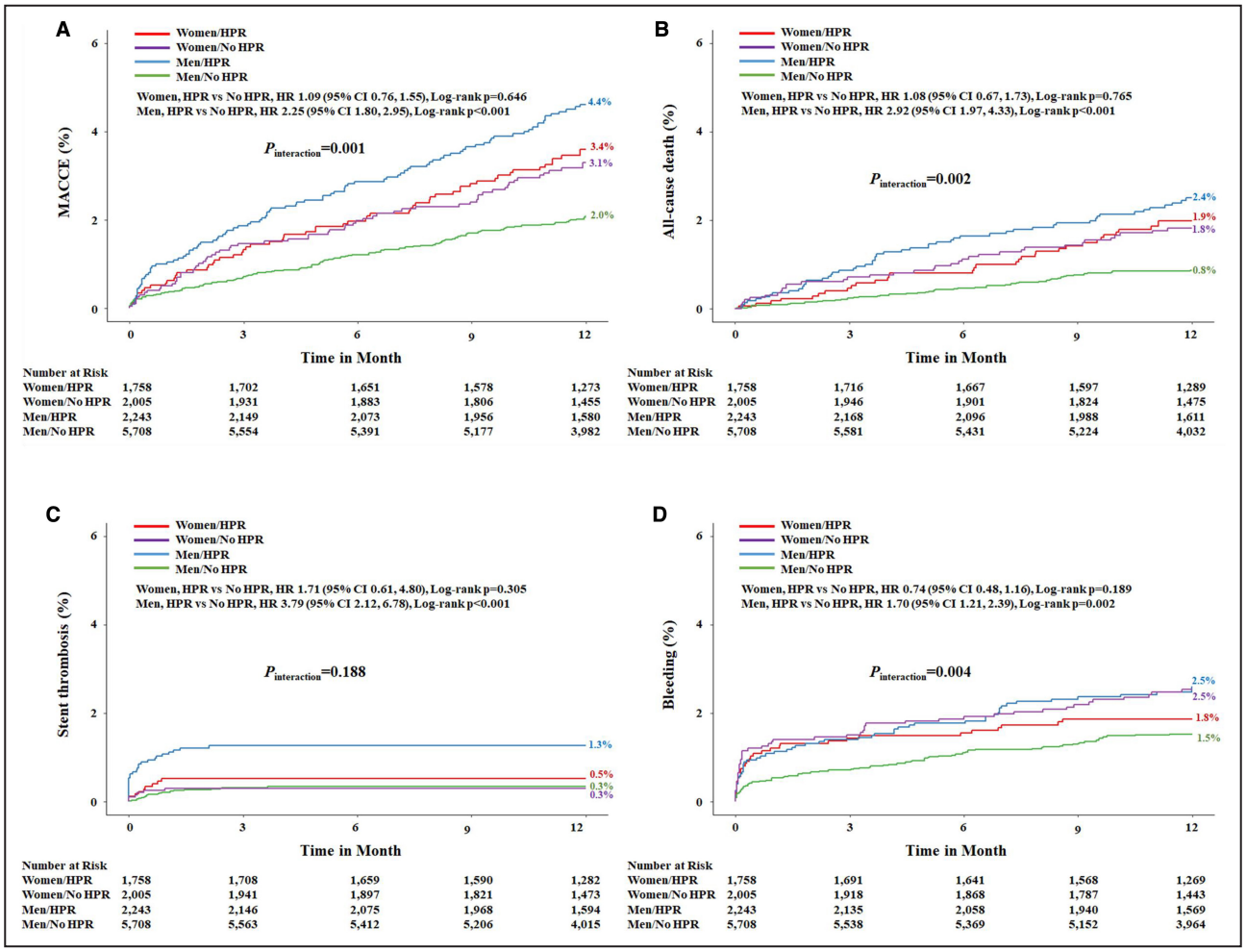


**Figure 2. Kaplan-Meier curve according to sex and high platelet reactivity (HPR) for clinical outcomes.**
Kaplan-Meier curves according to sex and HPR showing major adverse cardiac and cerebrovascular events (MACCEs) (**A**), all-cause mortality (**B**), stent thrombosis (**C**), and major bleeding (**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.[14–17] The HPR rate was higher in women than in men, a finding that is consistent with the results of previous studies.[18–20] 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

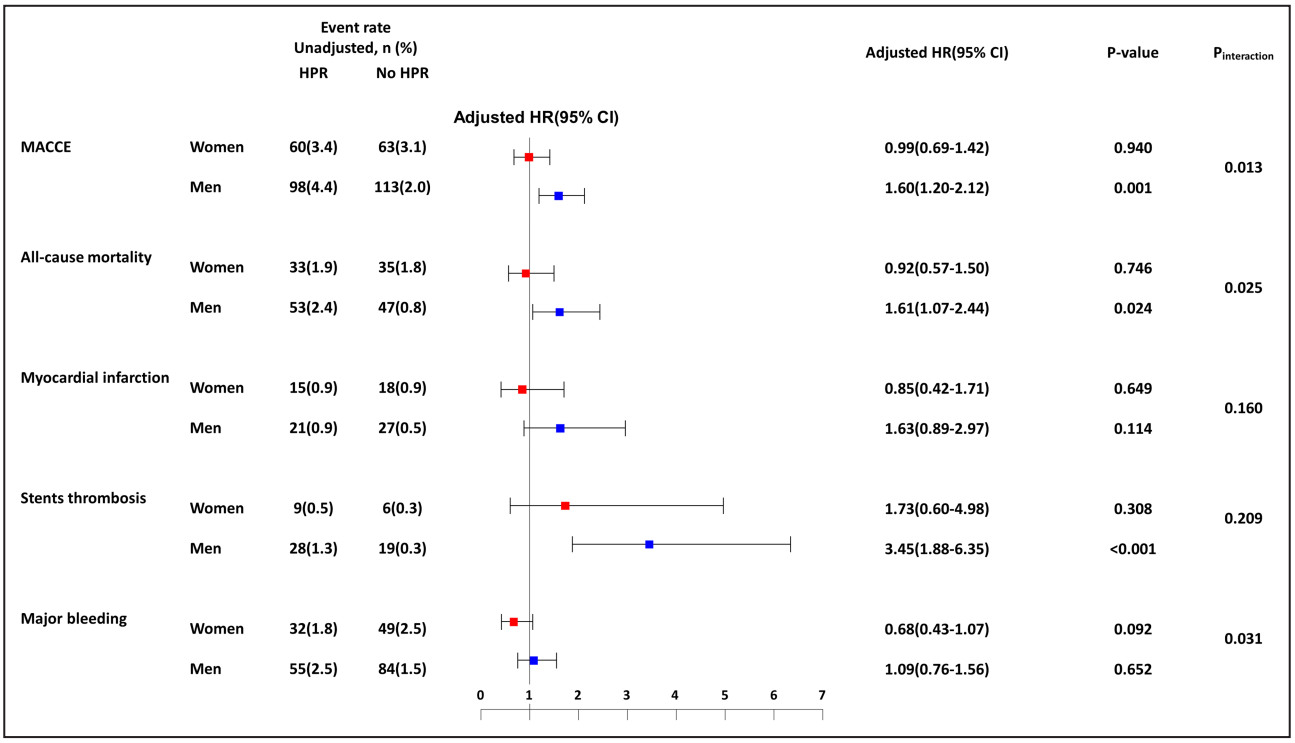


**Figure 3. Association between sex, high platelet reactivity (HPR), and clinical outcomes.**
HR indicates hazard ratio; and MACCE, major adverse cardiac and cerebrovascular event.

was inconclusive.[21–25] Previous reports suggested that there are no sex differences in the genes involved in clopidogrel metabolism.[26] 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).[18]

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.[7,27] These observations could be related to the different cutoffs of HPR between the races for determining the risk of ischemic and bleeding events (≥252 PRUs from PTRG-DES [Koreans] versus >208 PRUs from ADAPT-DES study [Westerners]).[6] 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.[17,28–31] 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 ($P_{interaction}$=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 ($P_{interaction}$=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

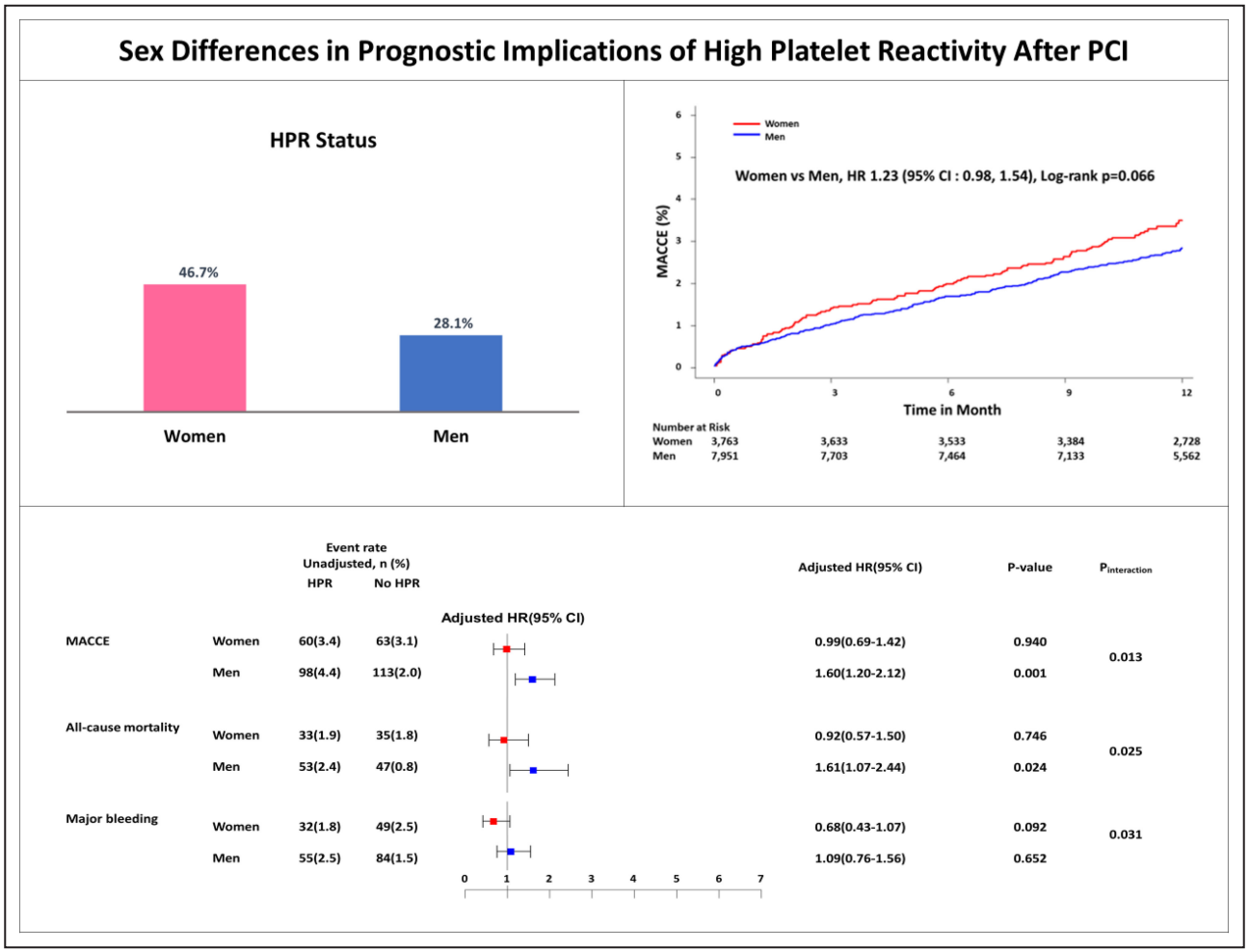


**Figure 4. Sex differences in prognostic implications of high platelet reactivity (HPR) after percutaneous coronary intervention (PCI).**
HPR was more common in women than men (left upper). There was no statistically significant difference between women and men in 1-year major adverse cardiac and cerebrovascular 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.[6] 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,[32,33] 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.[34,35] 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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### 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

## REFERENCES

1. Aradi D, Kirtane A, Bonello L, Gurbel PA, Tantry US, Huber K, Freynhofer MK, ten Berg J, Janssen P, Angiolillo DJ, et al. Bleeding and stent thrombosis on P2Y12-inhibitors: collaborative analysis on the role of platelet reactivity for risk stratification after percutaneous coronary intervention. *Eur Heart J.* 2015;36:1762–1771. doi: 10.1093/eurheartj/ehv104
2. Stone GW, Witzenbichler B, Weisz G, Rinaldi MJ, Neumann F-J, Metzger DC, Henry TD, Cox DA, Duffy PL, Mazzaferri E, et al. Platelet reactivity and clinical outcomes after coronary artery implantation of drug-eluting stents (ADAPT-DES): a prospective multicentre registry study. *Lancet.* 2013;382:614–623. doi: 10.1016/S0140-6736(13)61170-8
3. Sibbing D, Aradi D, Alexopoulos D, Ten Berg J, Bhatt DL, Bonello L, Collet JP, Cuisset T, Franchi F, Gross L, et al. Updated expert consensus statement on platelet function and genetic testing for guiding P2Y12 receptor inhibitor treatment in percutaneous coronary intervention. *JACC Cardiovasc Interv.* 2019;12:1521–1537. doi: 10.1016/j.jcin.2019.03.034
4. Tantry US, Bonello L, Aradi D, Price MJ, Jeong Y-H, Angiolillo DJ, Stone GW, Curzen N, Geisler T, Ten Berg J, et al. Consensus and update on the definition of on-treatment platelet reactivity to adenosine diphosphate associated with ischemia and bleeding. *J Am Coll Cardiol.* 2013;62:2261–2273. doi: 10.1016/j.jacc.2013.07.101
5. Price MJ, Endemann S, Gollapudi RR, Valencia R, Stinis CT, Levisay JP, Ernst A, Sawhney NS, Schatz RA, Teirstein PS, et al. Prognostic significance of post-clopidogrel platelet reactivity assessed by a point-of-care assay on thrombotic events after drug-eluting stent implantation. *Eur Heart J.* 2008;29:992–1000. doi: 10.1093/eurheartj/ehn046
6. Yu J, Mehran R, Baber U, Ooi S-Y, Witzenbichler B, Weisz G, Rinaldi MJ, Neumann FJ, Metzger DC, Henry TD, et al. Sex differences in the clinical impact of high platelet reactivity after percutaneous coronary intervention with drug-eluting stents: results from the ADAPT-DES study (Assessment of Dual Antiplatelet Therapy With Drug-Eluting Stents). *Circ Cardiovasc Interv.* 2017;10:e003577. doi: 10.1161/CIRCINTERVENTIONS.116.003577
7. Kim HK, Tantry US, Smith SC Jr, Jeong MH, Park S-J, Kim MH, Lim DS, Shin ES, Park DW, Huo Y, et al. The East Asian paradox: an updated position statement on the challenges to the current antithrombotic strategy in patients with cardiovascular disease. *Thromb Haemost.* 2021;121:422–432. doi: 10.1055/s-0040-1718729
8. Her AY, Jeong YH, Kim BK, Joo HJ, Chang K, Park Y, Song YB, Ahn SG, Suh JW, Lee SY, et al. Platelet function and genotype after DES implantation in East Asian patients: rationale and characteristics of the PTRG-DES consortium. *Yonsei Med J.* 2022;63:413–421. doi: 10.3349/ymj.2022.63.5.413
9. Lee SJ, Cha JJ, Jeong YH, Hong SJ, Ahn CM, Kim JS, Ko YG, Choi D, Hong MK, Jang Y, et al. Platelet reactivity and clinical outcomes after drug-eluting stent implantation: results from the PTRG-DES consortium. *JACC Cardiovasc Interv.* 2022;15:2253–2265. doi: 10.1016/j.jcin.2022.09.007
10. Suh JW, Lee SP, Park KW, Lee HY, Kang HJ, Koo BK, Cho YS, Youn TJ, Chae IH, Choi DJ, et al. Multicenter randomized trial evaluating the efficacy of cilostazol on ischemic vascular complications after drug-eluting stent implantation for coronary heart disease: results of the

CILON-T (influence of CILostazol-based triple antiplatelet therapy ON ischemic complication after drug-eluting stenT implantation) trial. *J Am Coll Cardiol.* 2011;57:280–289. doi: 10.1016/j.jacc.2010.08.631
11. Moussa ID, Klein LW, Shah B, Mehran R, Mack MJ, Brilakis ES, Reilly JP, Zoghbi G, Holper E, Stone GW. Consideration of a new definition of clinically relevant myocardial infarction after coronary revascularization: an expert consensus document from the Society for Cardiovascular Angiography and Interventions (SCAI). *J Am Coll Cardiol.* 2013;62:1563–1570. doi: 10.1016/j.jacc.2013.08.720
12. Garcia-Garcia HM, McFadden EP, Farb A, Mehran R, Stone GW, Spertus J, Onuma Y, Morel MA, van Es GA, Zuckerman B, et al. Standardized end point definitions for coronary intervention trials: the Academic Research Consortium-2 consensus document. *Eur Heart J.* 2018;39:2192–2207. doi: 10.1093/eurheartj/ehy223
13. Mehran R, Rao SV, Bhatt DL, Gibson CM, Caixeta A, Eikelboom J, Kaul S, Wiviott SD, Menon V, Nikolsky E, et al. Standardized bleeding definitions for cardiovascular clinical trials: a consensus report from the Bleeding Academic Research Consortium. *Circulation.* 2011;123:2736–2747. doi: 10.1161/CIRCULATIONAHA.110.009449
14. Lansky AJ, Mehran R, Cristea E, Parise H, Feit F, Ohman EM, White HD, Alexander KP, Bertrand ME, Desmet W, et al. Impact of gender and antithrombin strategy on early and late clinical outcomes in patients with non–ST-elevation acute coronary syndromes (from the ACUITY trial). *Am J Cardiol.* 2009;103:1196–1203. doi: 10.1016/j.amjcard.2009.01.030
15. Kovacic JC, Mehran R, Karajgikar R, Baber U, Suleman J, Kim MC, Krishnan P, Dangas G, Sharma SK, Kini A. Female gender and mortality after percutaneous coronary intervention: results from a large registry. *Catheter Cardiovasc Interv.* 2012;80:514–521. doi: 10.1002/ccd.23338
16. Lansky AJ, Pietras C, Costa RA, Tsuchiya Y, Brodie BR, Cox DA, Aymong ED, Stuckey TD, Garcia E, Tcheng JE. Gender differences in outcomes after primary angioplasty versus primary stenting with and without abciximab for acute myocardial infarction: results of the Controlled Abciximab and Device Investigation to Lower Late Angioplasty Complications (CADILLAC) trial. *Circulation.* 2005;111:1611–1618. doi: 10.1161/01.CIR.0000160362.55803.40
17. Yu J, Mehran R, Grinfeld L, Xu K, Nikolsky E, Brodie BR, Witzenbichler B, Kornowski R, Dangas GD, Lansky AJ. Sex-based differences in bleeding and long term adverse events after percutaneous coronary intervention for acute myocardial infarction: three year results from the HORIZONS-AMI trial. *Catheter Cardiovasc Interv.* 2015;85:359–368. doi: 10.1002/ccd.25630
18. Breet N, Sluman M, Van Berkel M, Van Werkum J, Bouman H, Harmsze A, Kelder JC, Zijlstra F, Hackeng CM, Ten Berg JM. Effect of gender difference on platelet reactivity. *Neth Heart J.* 2011;19:451–457. doi: 10.1007/s12471-011-0189-y
19. Staritz P, Kurz K, Stoll M, Giannitsis E, Katus HA, Ivandic BT. Platelet reactivity and clopidogrel resistance are associated with the H2 haplotype of the P2Y12-ADP receptor gene. *Int J Cardiol.* 2009;133:341–345. doi: 10.1016/j.ijcard.2007.12.118
20. Price MJ, Nayak KR, Barker CM, Kandzari DE, Teirstein PS. Predictors of heightened platelet reactivity despite dual-antiplatelet therapy in patients undergoing percutaneous coronary intervention. *Am J Cardiol.* 2009;103:1339–1343. doi: 10.1016/j.amjcard.2009.01.341
21. Jastrzebska M, Marcinowska Z, Oledzki S, Chelstowski K, Siennicka A, Klysz M, Clark JS. Variable gender-dependent platelet responses to combined antiplatelet therapy in patients with stable coronary-artery disease. *J Physiol Pharmacol.* 2018;69:595–605. doi: 10.26402/jpp.2018.4.10
22. Hobson AR, Qureshi Z, Banks P, Curzen N. Gender and responses to aspirin and clopidogrel: insights using short thrombelastography. *Cardiovascular Therapeutics.* 2009;27:246–252. doi: 10.1111/j.1755-5922.2009.00106.x
23. Patti G, De Caterina R, Abbate R, Andreotti F, Biasucci LM, Calabrò P, Cioni G, Davì G, Di Sciascio G, Golia E, et al. Platelet function and long-term antiplatelet therapy in women: is there a gender-specificity? A 'state-of-the-art' paper. *Eur Heart J.* 2014;35:2213–2223. doi: 10.1093/eurheartj/ehu279
24. Haque SF, Matsubayashi H, Izumi S, Sugi T, Arai T, Kondo A, Makino T. Sex difference in platelet aggregation detected by new aggregometry using light scattering. *Endocr J.* 2001;48:33–41. doi: 10.1507/endocrj.48.33
25. Wang TY, Angiolillo DJ, Cushman M, Sabatine MS, Bray PF, Smyth SS, Dauerman HL, French PA, Becker RC. Platelet biology and response to antiplatelet therapy in women: implications for the development and use of antiplatelet pharmacotherapies for cardiovascular disease. *J Am Coll Cardiol.* 2012;59:891–900. doi: 10.1016/j.jacc.2011.09.075
26. Jochmann N, Stangl K, Garbe E, Baumann G, Stangl V. Female-specific aspects in the pharmacotherapy of chronic cardiovascular diseases. *Eur Heart J.* 2005;26:1585–1595. doi: 10.1093/eurheartj/ehi397
27. Levine GN, Jeong YH, Goto S, Anderson JL, Huo Y, Mega JL, Taubert K, Smith SC Jr. Expert consensus document: World Heart Federation expert consensus statement on antiplatelet therapy in East Asian patients with ACS or undergoing PCI. *Nat Rev Cardiol.* 2014;11:597–606. doi: 10.1038/nrcardio.2014.104
28. Moscucci M, Fox KA, Cannon CP, Klein W, López-Sendón J, Montalescot G, White K, Goldberg RJ. Predictors of major bleeding in acute coronary syndromes: the Global Registry of Acute Coronary Events (GRACE). *Eur Heart J.* 2003;24:1815–1823. doi: 10.1016/S0195-668X(03)00485-8
29. Subherwal S, Bach RG, Chen AY, Gage BF, Rao SV, Newby LK, Wang TY, Gibler WB, Ohman EM, Roe MT. Baseline risk of major bleeding in non-st-segment-elevation myocardial infarction: the CRUSADE (Can Rapid risk stratification of Unstable angina patients Suppress ADverse outcomes with Early implementation of the ACC/AHA guidelines) bleeding score. *Circulation.* 2009;119:1873–1882. doi: 10.1161/CIRCULATIONAHA.108.828541
30. Rao SV, McCoy LA, Spertus JA, Krone RJ, Singh M, Fitzgerald S, Peterson ED. An updated bleeding model to predict the risk of post-procedure bleeding among patients undergoing percutaneous coronary intervention: a report using an expanded bleeding definition from the National Cardiovascular Data Registry CathPCI registry. *JACC Cardiovasc Interv.* 2013;6:897–904. doi: 10.1016/j.jcin.2013.04.016
31. Mehran R, Pocock SJ, Nikolsky E, Clayton T, Dangas GD, Kirtane AJ, Parise H, Fahy M, Manoukian SV, Feit F, et al. A risk score to predict bleeding in patients with acute coronary syndromes. *J Am Coll Cardiol.* 2010;55:2556–2566. doi: 10.1016/j.jacc.2009.09.076
32. Bain B, Forster T. A sex difference in the bleeding time. *Thromb Haemost.* 1980;43:131–132. doi: 10.1055/s-0038-1650033
33. O'Brien JR. The bleeding time in normal and abnormal subjects. *J Clin Pathol.* 1951;4:272–285. doi: 10.1136/jcp.4.3.272
34. Price MJ, Angiolillo DJ, Teirstein PS, Lillie E, Manoukian SV, Berger PB, Tanguay JF, Cannon CP, Topol EJ. Platelet reactivity and cardiovascular outcomes after percutaneous coronary intervention: a time-dependent analysis of the Gauging Responsiveness with a Verify Now P2Y12 assay: Impact on Thrombosis and Safety (GRAVITAS) trial. *Circulation.* 2011;124:1132–1137. doi: 10.1161/CIRCULATIONAHA.111.029165
35. Jaitner J, Stegherr J, Morath T, Braun S, Bernlochner I, Schömig A, Kastrati A, Sibbing D. Stability of the high on-treatment platelet reactivity phenotype over time in clopidogrel-treated patients. *Thromb Haemost.* 2011;105:107–112. doi: 10.1160/TH10-07-0440

# SUPPLEMENTAL MATERIAL

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

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## Table S1. List of Participating Registries

| Name of registry | Participating centers | Principal investigator |
|---|---|---|
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| | Division of Cardiology, Department of Internal Medicine, Hanyang University College of Medicine, Seoul, South Korea | Young-Hyo Lim |
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| | Division of Cardiology, Department of Internal Medicine, Yeungnam University Medical Center, Daegu, South Korea | JongSeon Park |
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| 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 |
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| 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

| | Women | Men | p-value |
|---|---|---|---|
| **VerifyNow P2Y12 assay** | **(n=3763)** | **(n=7951)** | |
| 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 |
| **VerifyNow Aspirin assay** | **(n=2324)** | **(n=4838)** | |
| 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$^2$ | 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, x103/mm3 | 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, x103/mm3 | 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 | $P_{interaction}$ | | | Adjusted HR (95% CI) | P-value | $P_{interaction}$ |
| 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**