

## 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)

Jennifer Yu, MBBS; Roxana Mehran, MD; Usman Baber, MD, MS; Sze-Yuan Ooi, MBBS; Bernhard Witzenbichler, MD; Giora Weisz, MD; Michael J. Rinaldi, MD; Franz-Josef Neumann, MD; D. Christopher Metzger, MD; Timothy D. Henry, MD; David A. Cox, MD; Peter L. Duffy, MD, MMM; Ernest L. Mazzaferri, Jr, MD; Bruce R. Brodie, MD; Thomas D. Stuckey, MD; Akiko Maehara, MD; Ke Xu, PhD; Ori Ben-Yehuda, MD; Ajay J. Kirtane, MD, SM; Gregg W. Stone, MD

**Background**—Sex differences in the outcomes after percutaneous coronary intervention with drug-eluting stents and in the response to clopidogrel therapy have been reported; however, the differential risk of high platelet reactivity (HPR) on clopidogrel in women versus men is unknown.

**Methods and Results**—We compared 8448 patients enrolled in the ADAPT-DES study (Assessment of Dual Antiplatelet Therapy With Drug-Eluting Stents) according to sex and the presence/absence of HPR on clopidogrel (defined as P2Y12 reactivity units >208). Study end points were definite and probable stent thrombosis (ST), clinically relevant bleeding, all-cause mortality, myocardial infarction, and major adverse cardiac events (comprising mortality, myocardial infarction, and target lesion revascularization). HPR was more common among women (1118/2163, 51.7%) than men (2491/6285, 39.6%). HPR was associated with a roughly double risk of 1-year ST in both women and men (women with versus without HPR: 1.4% versus 0.7%; hazard ratio [HR], 2.02; 95% confidence interval [CI], 0.82–4.95;  $P=0.12$ ; and men: 1.2% versus 0.5%; HR, 2.42; 95% CI, 1.36–4.30;  $P=0.002$ ;  $P_{\text{interaction}}=0.73$ ). HPR was associated with almost half the rate of clinically relevant bleeding in women (women: HPR versus no HPR, 5.3% versus 9.8%; HR, 0.54; 95% CI, 0.40–0.74;  $P<0.001$ ), whereas men had similar rates of bleeding regardless of HPR status (men: HPR versus no HPR, 5.7% versus 5.9%; HR, 0.96; 95% CI, 0.78–1.18;  $P=0.70$ ;  $P_{\text{interaction}}=0.003$ ). In propensity-adjusted models, HPR was an independent predictor of ST and myocardial infarction in men; although both associations were nonsignificant among women, no interaction was observed in the associations between HPR and either ST or myocardial infarction. Conversely, HPR was an independent predictor of reduced bleeding only in women (women: adjusted HR, 0.58; 95% CI, 0.41–0.82;  $P=0.002$ ; and men: adjusted HR, 0.83; 95% CI, 0.65–1.04;  $P=0.11$ ;  $P_{\text{interaction}}=0.01$ ).

**Conclusions**—In the current analysis, the associated risk of HPR for ST was similar in both sexes. However, HPR was associated with significantly reduced bleeding only among women.

**Clinical Trial Registration**—URL: <http://www.clinicaltrials.gov>. Unique identifier: NCT00638794.

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**Key Words:** drug-eluting stents ■ female ■ hemorrhage ■ myocardial infarction ■ sex

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From The Zena and Michael A. Wiener Cardiovascular Institute, Icahn School of Medicine at Mount Sinai, New York, NY (J.Y., R.M., U.B.); Prince of Wales Clinical School, University of NSW, Australia (J.Y., S.-Y.O.); Clinical Trials Center, Cardiovascular Research Foundation, New York, NY (R.M., G.W., A.M., K.X., O.B.-Y., A.J.K., G.W.S.); Department of Cardiology and Pneumology, Helios Amper-Klinikum, Dachau, Germany (B.W.); Els & Charles Bendheim Department of Cardiology, Shaare Zedek Medical Center, Jerusalem, Israel (G.W.); Center for Interventional Vascular Therapy, Division of Cardiology, Columbia University Medical Center, New York, NY (G.W., A.M., O.B.-Y., A.J.K., G.W.S.); Sanger Heart and Vascular Institute/Carolinas HealthCare System, Charlotte, NC (M.J.R.); Heart Center, University of Freiburg, Bad Krozingen, Germany (F.-J.N.); Wellmont CVA Heart Institute, Kingsport, TN (D.C.M.); Minneapolis Heart Institute Foundation at Abbott Northwestern Hospital, MN (T.D.H.); Cedars-Sinai Heart Institute, Los Angeles, CA (T.D.H.); Lehigh Valley Health Network, Allentown, PA (D.A.C.); Reid Heart Center, FirstHealth of the Carolinas, Pinehurst, NC (P.L.D.); The Ohio State University Wexner Medical Center, Columbus (E.L.M.); and LeBauer Cardiovascular Research Foundation/Cone Health, Greensboro, NC (B.R.B., T.D.S.).

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Correspondence to Gregg W. Stone, MD, Cardiovascular Research Foundation, 111 E 59th St, 11th Floor, New York, NY 10022. E-mail [gs2184@columbia.edu](mailto:gs2184@columbia.edu)

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### WHAT IS KNOWN

- Among patients undergoing percutaneous coronary intervention, women are older with more comorbidities and are at greater risk for worse outcomes compared with men.
- Sex differences in the impact of clopidogrel in terms of the clinical benefit and the platelet reactivity have also been reported.
- The ADAPT-DES study (Assessment of Dual Antiplatelet Therapy With Drug-Eluting Stents) demonstrated an association between high platelet reactivity (HPR) on clopidogrel treatment and ischemic outcomes, albeit offset by a reduction in bleeding complications.

### WHAT THE STUDY ADDS

- In this study, the first study to examine the impact of HPR specifically by sex, the associated risk of HPR for stent thrombosis was similar in both sexes, but HPR was associated with significantly reduced bleeding only among women.

Previous studies have found significant differences in women and men undergoing percutaneous coronary intervention (PCI), with women being older with more comorbidities at the time of PCI,<sup>1-3</sup> and at greater risk for subsequent ischemic events and overall mortality.<sup>1,3-5</sup> Although attention to the prevention of ischemic events is, therefore, necessary, women have also been shown to be at a greater risk of bleeding complications.<sup>6-8</sup> Sex differences in the benefit derived from clopidogrel therapy and the platelet response to clopidogrel as measured by P2Y12 reactivity units (PRU) have also been reported.<sup>9-11</sup> Therefore, finding the optimal balance of ischemic protection without incurring excessive bleeding risk may, in some respects, be even more relevant in women compared with men.

### See Editorial by Sarma and O'Donoghue

The ADAPT-DES study (Assessment of Dual Antiplatelet Therapy With Drug-Eluting Stents) demonstrated an association between high platelet reactivity (HPR) on clopidogrel and ischemic outcomes, albeit offset by a reduction in bleeding complications.<sup>12</sup> In this analysis, we sought to characterize and compare the clinical impact of HPR in women and men after PCI with DES.

### Methods

ADAPT-DES was a prospective, multicentre registry that enrolled 8665 patients from the United States and Germany who underwent PCI between January 2008 and September 2010. The study methods have been described.<sup>12</sup> In brief, patients were eligible if they had successful PCI with at least 1 DES and received both aspirin and clopidogrel loading doses. After PCI and an adequate duration post-antiplatelet loading, patients were tested with the VerifyNow Aspirin, P2Y12, and Iib/IIIa assays (Accumetrics, San Diego, CA). The timing of VerifyNow testing was variable depending on whether the patient was already on maintenance clopidogrel or the loading dose given as follows: (1) patients on maintenance clopidogrel—at least 5

days before testing, (2) after 300-mg loading dose—at least 12 hours before testing, and (3) after 600-mg loading dose—at least 6 hours before testing. Treating physicians were not informed on these results, and patients continued dual antiplatelet therapy with aspirin and clopidogrel (the former indefinitely and the latter for a recommended duration of at least 1 year). Patients were followed for 2 years with visits at 30 days, 1 year, and 2 years. The study was approved by the institutional review board at every participating center.

### Study End Points

The definitions of the study end points have been published.<sup>12</sup> The primary end point was definite and probable stent thrombosis (ST) according to the Academic Research Consortium definition.<sup>13</sup> Secondary end points included clinically relevant bleeding, all-cause mortality, myocardial infarction (MI), and major adverse cardiac events (MACE), a composite of cardiac death, MI, or target lesion revascularization for ischemia/symptoms. Clinically relevant bleeding included Thrombolysis in Myocardial Infarction major or minor bleeding, any GUSTO (Global Use of Strategies to Open Occluded Arteries) bleeding, ACUITY (Acute Catheterization and Urgent Intervention Triage Strategy) major bleeding, and bleeding requiring medical attention post-discharge.<sup>14-16</sup> MI was defined using the ACUITY criteria.<sup>17</sup> All death, MI, and ST events were adjudicated by an independent clinical events committee which was blinded to the platelet reactivity results.

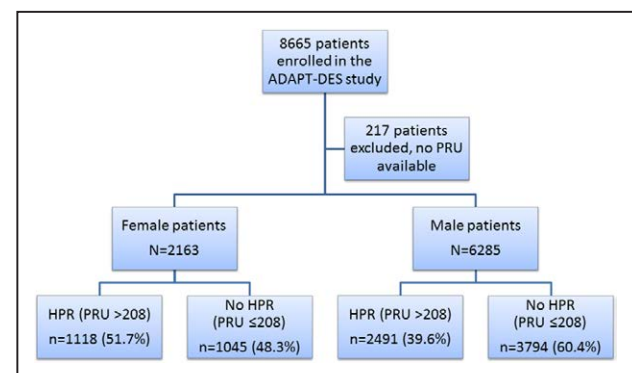
### Current Analysis

We examined baseline characteristics and 1-year outcomes according to sex and the presence/absence of HPR. We included the 8448 patients who had VerifyNow P2Y12 testing (Figure 1) on clopidogrel treatment. HPR was defined as PRU >208 based on the available evidence and published consensus.<sup>18-20</sup>

### Statistical Analysis

Categorical variables are presented as percentages and compared using the  $\chi^2$  or Fisher exact tests. Continuous variables are presented as median and interquartile range and were compared by Wilcoxon rank-sum test for medians. Time-to-event data were presented as Kaplan–Meier estimates and compared using the log-rank test.

A propensity score model was constructed as part of the original analysis by modeling HPR status in a logistic regression model with 87 variables to assess the independent association between HPR and outcomes.<sup>12</sup> Discrimination was good in both women and men with C statistics of 0.714 and 0.759, respectively. Model variables and baseline characteristics in the propensity score quintiles are shown in Table I in the [Data Supplement](#). Cox proportional hazards regression stratified by the propensity score was used to fully adjust HPR-specific hazard ratios (HRs) associated with events of interest. Known risk factors of study end points were included as covariates: covariates for ST models included previous MI, dialysis, ST-segment–elevation MI or non-ST-segment–elevation MI presentation, hemoglobin, creatinine clearance,



**Figure 1.** Study flow chart. ADAPT-DES indicates Assessment of Dual Antiplatelet Therapy With Drug-Eluting Stents; HPR, high platelet reactivity; and PRU, P2Y12 reactivity units.

white cell count, and platelet count. Additional covariates for the other assessed end points included age, diabetes, chronic kidney disease, hypertension, hyperlipidemia, current smoking, and number of vessels treated. As a secondary analysis, we repeated the analysis using PRU adjusted for hematocrit using published methods,<sup>21</sup> and with body mass index, bivalirudin use and aspirin discharge dose as additional covariates in the multivariable model for bleeding. Formal interaction testing was undertaken to examine the association between sex, HPR, and 1-year outcomes. All *P* values are 2-tailed. All statistical analyses were performed using SAS version 9.2 (SAS Institute Inc, Cary, NC).

## Results

Among 8448 patients who had VerifyNow P2Y12 testing in the ADAPT-DES study, 2163 patients were female (25.6%), and 6285 patients were male (74.4%). The median PRU was higher in women (214.0; interquartile range, 132.0–288.0 versus 181.0; interquartile range 108.0–249.0; *P*<0.001). As such, HPR as defined by PRU >208 was more common among women than men (51.7% versus 39.6%; *P*<0.0001; Figure 1).

### Baseline and Treatment Characteristics

In general, HPR was associated with similar baseline characteristics in women and men. Patients with HPR had greater

body mass index and prevalence of diabetes mellitus and were less likely to be White or smokers (Table 1). New York Heart Association class IV heart failure and anemia were more common in women with HPR compared with women with no HPR. Men with HPR were significantly older and more likely to have a history of previous coronary artery bypass surgery, peripheral artery disease, hypertension, heart failure, renal insufficiency, and dialysis and to present with acute coronary syndrome, New York Heart Association class III or IV heart failure, and creatinine clearance <60 mL/min than men without HPR.

Among women, HPR was associated with bivalirudin use (Table 2). Among men, HPR was associated with triple vessel disease, baseline Thrombolysis in Myocardial Infarction flow 0/1, and the use of bivalirudin and glycoprotein IIb/IIIa inhibitors. There were multiple differences in women and men with no HPR (Table II in the [Data Supplement](#)).

### Clinical Outcomes

HPR was associated with almost a 2-fold increase in the rate of ST in women and men, but this difference did not reach

**Table 1. Baseline Characteristics**

	Women		<i>P</i> Value	Men		<i>P</i> Value
	PRU >208 (n=1118)	PRU ≤208 (n=1045)		PRU >208 (n=2491)	PRU ≤208 (n=3794)	
Age, y	66.0 (58.0, 74.0)	67.0 (59.0, 74.0)	0.28	65.0 (57.0, 72.0)	62.0 (54.0, 70.0)	<0.001
Weight, kg	79.1 (69.0, 93.0)	72.0 (63.0, 84.0)	<0.001	91.0 (81.0, 104.0)	86.9 (78.0, 98.0)	<0.001
Body mass index	30.1 (26.2, 35.1)	27.5 (24.0, 32.0)	<0.001	29.4 (26.5, 33.0)	28.0 (25.5, 31.1)	<0.001
White	82.4% (921/1118)	86.3% (902/1045)	0.01	89.2% (2222/2491)	91.0% (3451/3794)	0.02
Diabetes mellitus	44.7% (500/1118)	28.9% (302/1045)	<0.001	39.8% (991/2491)	24.6% (933/3794)	<0.001
Hypertension	83.1% (929/1118)	81.6% (853/1045)	0.37	80.9% (2016/2491)	77.2% (2928/3794)	<0.001
Dyslipidemia	75.0% (839/1118)	73.0% (763/1045)	0.28	75.2% (1872/2491)	74.2% (2815/3794)	0.40
Current smoker	20.4% (228/1118)	24.0% (251/1045)	0.04	19.3% (481/2491)	25.4% (964/3794)	<0.001
Previous MI	20.8% (232/1118)	20.9% (218/1045)	0.95	27.4% (683/2491)	26.2% (995/3794)	0.30
History of CHF	9.1% (102/1118)	8.2% (86/1045)	0.46	9.6% (240/2491)	6.8% (259/3794)	<0.001
Previous PCI	36.5% (408/1118)	40.5% (423/1045)	0.06	44.6% (1110/2491)	44.2% (1678/3794)	0.80
Previous CABG	13.0% (145/1118)	13.0% (136/1045)	0.98	20.0% (498/2491)	17.4% (659/3794)	0.009
Peripheral artery disease	9.3% (104/1118)	12.1% (126/1045)	0.04	11.5% (287/2491)	9.1% (344/3794)	0.002
Renal insufficiency	8.0% (89/1118)	6.5% (68/1045)	0.19	10.1% (252/2491)	6.3% (238/3794)	<0.001
Dialysis	1.7% (19/1118)	1.8% (19/1045)	0.83	2.1% (52/2491)	1.1% (43/3794)	0.002
Time from PCI to VerifyNow, h	18.9 (16.0, 21.7)	18.8 (16.3, 21.7)	0.83	18.8 (16.2, 21.6)	19.1 (16.5, 21.9)	0.007
Acute coronary syndrome	55.5% (621/1118)	52.5% (549/1045)	0.16	54.4% (1356/2491)	47.9% (1819/3794)	<0.001
NYHA class III heart failure	25.1% (281/1118)	25.5% (266/1045)	0.86	25.5% (634/2491)	22.1% (838/3794)	0.002
NYHA class IV heart failure	22.2% (248/1118)	16.8% (176/1045)	0.002	17.9% (445/2491)	15.0% (569/3794)	0.003
Baseline hemoglobin, g/dL	12.9 (12.0, 13.7)	13.3 (12.4, 14.2)	<0.001	13.9 (12.9, 14.8)	14.6 (13.8, 15.5)	<0.001
Anemia*	25.1% (279/1113)	17.1% (177/1038)	<0.001	31.5% (780/2480)	15.3% (580/3782)	<0.001
CrCl <60 mL/min	26.8% (298/1111)	30.1% (312/1038)	0.10	15.0% (372/2481)	10.2% (385/3780)	<0.001
Platelet count, K/mm <sup>3</sup>	237 (202, 283)	242 (202, 290)	0.13	209.0 (175, 249)	212 (180, 253)	0.002

Values are percentage (n/N) or median (first quartile, third quartile). CABG indicates coronary artery bypass graft surgery; CHF, congestive heart failure; CrCl, creatinine clearance; MI, myocardial infarction; NYHA, New York Heart Association; PCI, percutaneous coronary intervention; and PRU, P2Y12 reaction units.

\*Defined as hematocrit <36 in females and <39 in males.

**Table 2. Procedural Characteristics**

	Women		P Value	Men		P Value
	PRU >208 (n=1118)	PRU ≤208 (n=1045)		PRU >208 (n=2491)	PRU ≤208 (n=3794)	
Three vessel disease	23.9% (267/1118)	25.7% (269/1045)	0.32	31.7% (790/2491)	29.2% (1108/3794)	0.03
Left main >50%	2.3% (26/1118)	2.1% (22/1045)	0.73	3.4% (85/2491)	3.2% (121/3794)	0.63
Ejection fraction <40%	24.4% (273/1118)	28.6% (299/1045)	0.03	30.6% (763/2491)	31.7% (1204/3794)	0.36
LVEDP, mm Hg	18.0 (12.0, 23.0)	15.0 (10.0, 21.0)	<0.001	16.0 (11.0, 23.0)	14.0 (9.0, 20.0)	<0.001
No. of lesions treated	1.0 (1.0, 2.0)	1.0 (1.0, 2.0)	0.53	1.0 (1.0, 2.0)	1.0 (1.0, 2.0)	0.83
No. of stents implanted	1.0 (1.0, 2.0)	1.0 (1.0, 2.0)	0.34	1.0 (1.0, 2.0)	1.0 (1.0, 2.0)	0.53
TIMI 0/1 flow pre-PCI	7.2% (81/1118)	6.8% (71/1045)	0.68	11.6% (288/2491)	9.1% (344/3794)	0.001
TIMI 0/1 flow post-PCI	0.1% (1/1118)	0.1% (1/1045)	>0.99	0.1% (2/2491)	0.1% (5/3794)	0.71
Femoral access	93.9% (1050/1118)	94.7% (990/1045)	0.41	95.8% (2386/2491)	95.7% (3629/3794)	0.80
Mechanical closure device	58.9% (659/1118)	57.8% (604/1045)	0.59	62.2% (1549/2491)	60.5% (2297/3794)	0.19
Bivalirudin	66.6% (745/1118)	56.3% (588/1045)	<0.001	61.3% (1526/2491)	52.5% (1992/3794)	<0.001
GPI	2.6% (29/1118)	3.0% (31/1045)	0.60	4.0% (100/2491)	2.9% (109/3794)	0.01
Cardiac enzymes post-procedure						
Peak, ×ULN	1.0 (0.5, 6.7)	0.9 (0.4, 2.8)	0.003	1.2 (0.6, 12.3)	0.9 (0.5, 4.0)	<0.001
In patients with normal baseline value, ×ULN	0.6 (0.3, 1.4)	0.6 (0.3, 1.1)	0.45	0.7 (0.4, 1.5)	0.6 (0.4, 1.3)	0.07

Values are percentage (n/N) or median (first quartile, third quartile). GPI indicates glycoprotein IIb/IIIa inhibitor; LVEDP, left ventricular end-diastolic pressure; PCI, percutaneous coronary intervention; PRU, P2Y<sub>12</sub> reaction units; TIMI, Thrombolysis in Myocardial Infarction; and ULN, upper limit of normal.

statistical significance among women probably because of the limited sample size (Figure 2A). In propensity-adjusted multivariable models, the magnitude of increased risk associated with HPR for ST was similar in women and men (Figure 3), and formal interaction testing (using adjusted HR) was not significant ( $P_{\text{interaction}}=0.99$ ). Results were consistent when only definite ST was considered.

Among women, 1-year mortality, MI, and MACE were similar irrespective of HPR status before and after multivariable adjustment (Figure 3). In the unadjusted analysis, HPR was associated with significantly increased rates of MI (HR, 1.54; 95% confidence interval, 1.15–2.05;  $P=0.003$ ) and MACE (HR, 1.37; 95% confidence interval, 1.13–1.66;  $P=0.001$ ) in men. After multivariable adjustment, the increased risk of MI but not MACE remained statistically significant; however, formal interaction testing was not significant. The study findings were consistent when 2-year data were used (Figures I through III in the Data Supplement) and when HPR was defined using PRU adjusted for the hematocrit (data not shown).

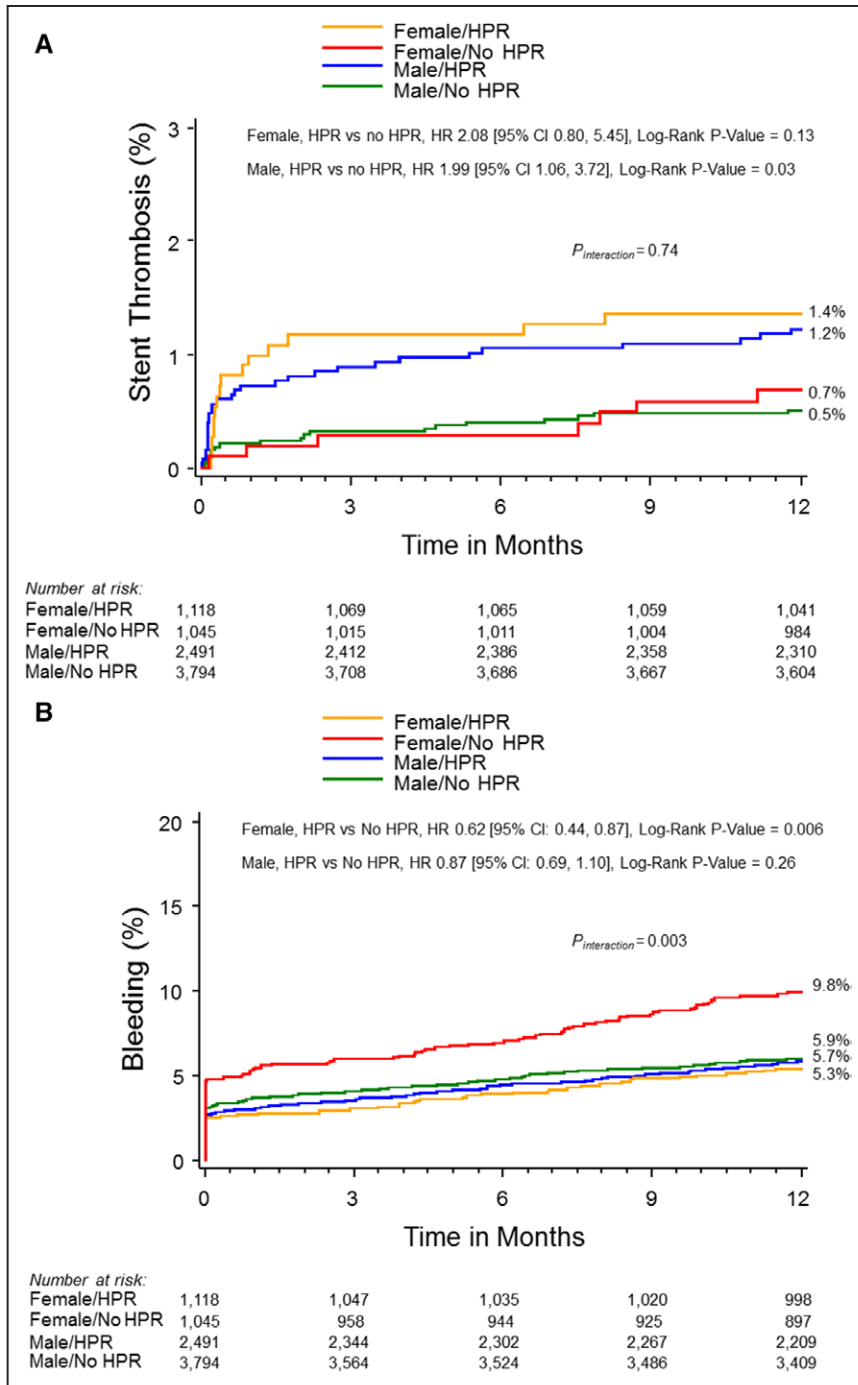
In contrast, women with HPR had almost half the rate of clinically relevant bleeding as women with no HPR in the unadjusted analysis, whereas men had similar rates of bleeding regardless of HPR status (Figure 2B). The reduced rate of bleeding among women with HPR comprised decreases in both early and late bleeding events (Figure 4), whereas HPR and no HPR men had similar rates of both early and late bleeds. The difference in in-hospital bleeding was driven by minor bleeding events, that is, GUSTO mild bleeds (Table III in the Data Supplement). There was no difference in the rate of blood transfusions. Out-of-hospital bleeding events were not classified by severity in

this study, but ≈50% of these events required transfusion of blood products, and the overall result comprised differences in both access site-related and gastrointestinal bleeding events. This association between HPR and reduced bleeding in women persisted after multivariable adjustment, and formal interaction testing (using adjusted HR) remained significant ( $P_{\text{interaction}}=0.01$ ; Figure 3). All interaction coefficients are shown in Table IV in the Data Supplement. The result was essentially unchanged when body mass index, bivalirudin use, and aspirin dose at discharge were added to the Cox model (data not shown) and when a sensitivity analysis was performed, excluding any patients who had clopidogrel cessation in the first year after PCI (data not shown). Figure IV in the Data Supplement shows 1-year bleeding in women and men with no HPR.

## Discussion

In this post hoc analysis from the large, prospective ADAPT-DES study, we found that (1) HPR was more common in women than in men, (2) HPR was associated with nearly doubled risk of ST at 1 year in both women and men, (3) HPR was associated with significantly increased rates of MI and MACE only in men, but formal interaction testing was not significant, and (4) HPR was associated with almost half the rate of both early (30 days) and late (30 days to 1 year) clinically relevant bleeding events in women but not in men; formal interaction testing was significant.

Our finding that women are more likely to have HPR than men is consistent with several smaller studies.<sup>10,22,23</sup> Although the rate of clopidogrel metabolism to its active form has been shown to be similar in women and men,<sup>24</sup> women have higher baseline platelet reactivity to adenosine diphosphate (ie, off

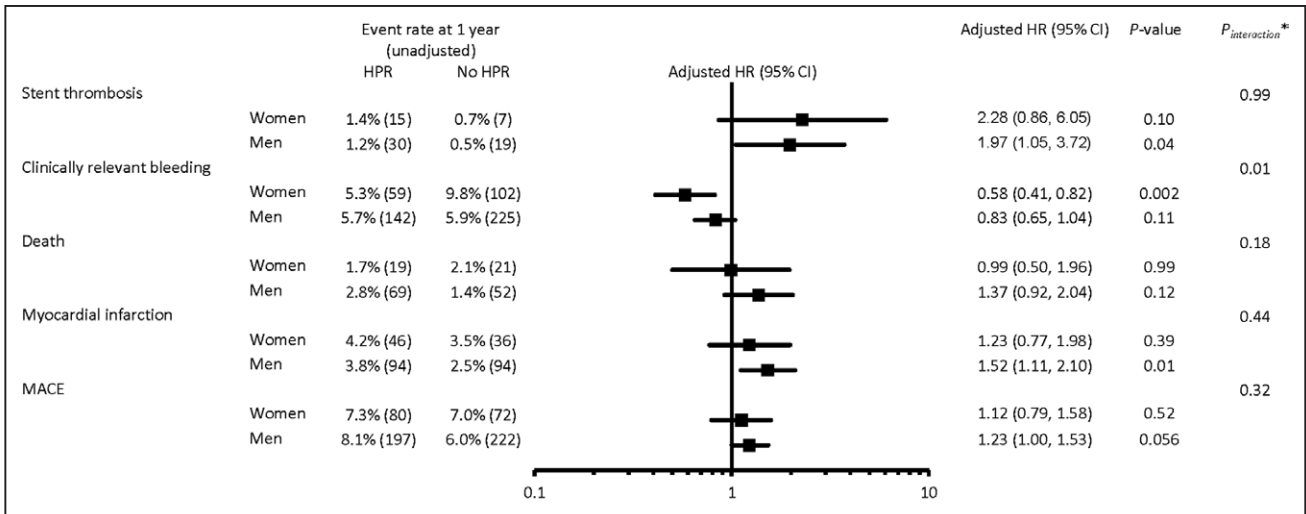


**Figure 2.** Time-to-event curves according to sex and high platelet reactivity (HPR). **A**, Definite or probable stent thrombosis. **B**, Clinically relevant bleeding. CI indicates confidence interval; and HR, hazard ratio.

antiplatelet therapy) than men.<sup>25</sup> This raises the question whether the observed difference in on-treatment platelet reactivity reflects the increased baseline platelet reactivity rather than a decreased effect of the active clopidogrel metabolite in women compared with men. Unfortunately, we were not able to examine this in the current analysis in the absence of baseline (off treatment) PRU.

Previous studies have shown that female sex is an independent predictor of bleeding events in hospital (or periprocedural),<sup>26–28</sup> at 30 days,<sup>2,6–8,29</sup> and longer term after PCI.<sup>8,30</sup> To our knowledge, the current analysis represents the first to examine whether HPR contributes to this sex disparity in bleeding, an

important end point in light of increasing evidence that not only major but also minor bleeding events contribute to worse prognosis, including long-term survival.<sup>12,31–33</sup> In this study, consistent with previous reports, women had higher overall rates of clinically relevant bleeding compared with men. Notably, however, our study showed that this difference was entirely driven by the higher bleeding rate among women without HPR (ie, women responsive to clopidogrel), with similar bleeding rates among women with HPR and men (irrespective of HPR). Previous examinations of the relationship of PRU to bleeding events have been contradictory, with several studies showing a positive association between low HPR and



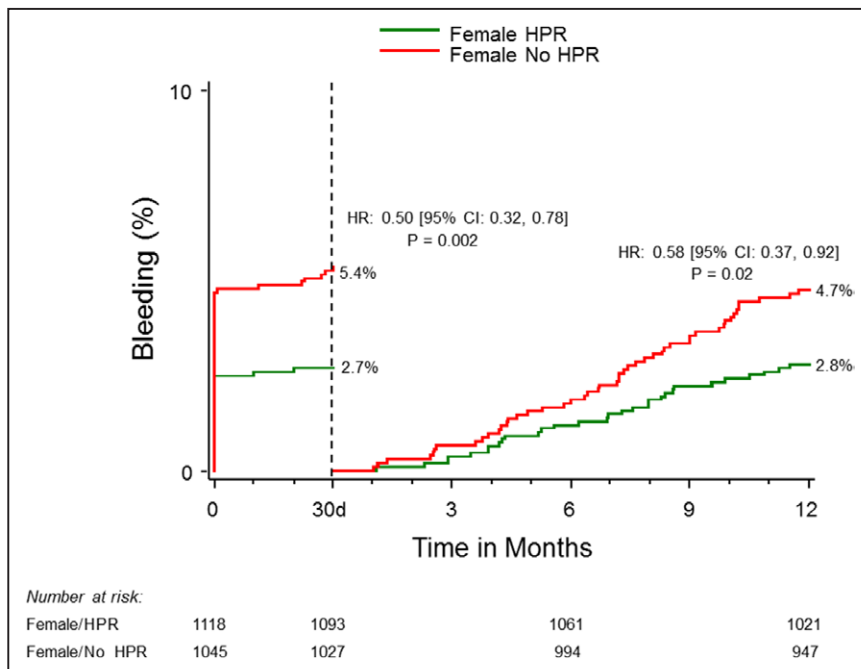
**Figure 3.** Association between sex, high platelet reactivity (HPR), and clinical events. Event rates are Kaplan–Meier estimates at 1 year (number of events). CI indicates confidence interval; and MACE, major adverse cardiac events. \* $P_{interaction}$  performed using adjusted hazard ratios (HRs).

increased bleeding after PCI<sup>12,34–37</sup> and others finding no such association.<sup>38–40</sup> A sex disparity in the association between HPR and bleeding, as suggested by this study, may help to account for these conflicting results to date, with differences in the absolute number and percentage of women included in these studies being contributory. Additional confounding factors may include differences in the bleeding definition used, varying durations of follow-up, the indication for PCI, and the baseline bleeding risk profiles of enrolled patients.

These results are also contrary to the hypothesis that a relative overdose of clopidogrel may be responsible for the increased rates of bleeding among women after PCI (given the smaller weight and differences in renal function in women and the lack of weight adjustment of clopidogrel).<sup>8,41,42</sup> Our results confirm that women are, in fact, more likely to have higher, not lower, PRU. Also, previous studies have shown

that despite increased baseline platelet reactivity, women have longer bleeding times compared with men.<sup>41,43</sup> In this study, we found that compared with very low PRU (<95), intermediate PRU (95–208) was associated with similar bleeding rates in women and reduced bleeding rates in men. These data raise the hypothesis that women may require a higher level of platelet reactivity than men to achieve hemostasis.

Finally, given the low absolute rates of ST in this contemporary population of patients treated with aspirin and clopidogrel after PCI with DES, and that the increased ST events associated with HPR mainly occurred in the first 30 days, our data suggest that women may derive less net benefit in the longer term from clopidogrel responsiveness compared with men. Increased bleeding in women (versus men) with clopidogrel responsiveness may help, in part, to explain the findings from a large meta-analysis of 23 000 women and 56 000 men which found



**Figure 4.** Clinically relevant bleeding among women according to high platelet reactivity (HPR) with landmark at 30 d. CI indicates confidence interval; and HR, hazard ratio.

that although clopidogrel conferred cardiovascular protection in both men and women, the number needed to treat was far higher in women with respect to mortality (women versus men, 909 versus 192) and that the inverse was true with respect to number needed to harm and major bleeding (196 versus 455).<sup>11</sup>

### Limitations

As a post hoc analysis, the study findings should be considered exploratory. HPR was defined using an isolated PRU measurement assessed after index PCI. Previous studies have shown that serial measurements can show significant differences, although the clinical significance of this finding is not known.<sup>44</sup> Few patients had PCI via the radial approach, which may have impacted the rate of in-hospital bleeding complications in women and men. Data on out-of-hospital events are subject to recall bias and potential under-reporting. This may have particular relevance for events occurring after 30-day follow-up and for minor bleeding events. Out-of-hospital bleeding events were not adjudicated according to the existing definitions such as the Bleeding Academic Research Consortium, Thrombolysis in Myocardial Infarction, or GUSTO classifications, which limits comparisons with other trials. The number of female patients was significantly smaller than the number of male patients, reducing the power of our statistical comparisons. The menopause status was not collected in the case report forms, and its impact on platelet reactivity was outside the scope of this study. Finally, there were numerous differences in the baseline and treatment characteristics of our study groups, and while we attempted to adjust for these with multivariable models, residual confounding cannot be excluded.

### Conclusions

In the current analysis, HPR was more common in women than men. Although the associated risk of HPR for ST was similar in men and women, HPR was associated with significantly reduced bleeding events among women only. Our results emphasize the need for sex-specific analyses in trials comparing novel antiplatelet therapy to clopidogrel.

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**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)**

Jennifer Yu, Roxana Mehran, Usman Baber, Sze-Yuan Ooi, Bernhard Witzenbichler, Giora Weisz, Michael J. Rinaldi, Franz-Josef Neumann, D. Christopher Metzger, Timothy D. Henry, David A. Cox, Peter L. Duffy, Ernest L. Mazzaferri, Jr, Bruce R. Brodie, Thomas D. Stuckey, Akiko Maehara, Ke Xu, Ori Ben-Yehuda, Ajay J. Kirtane and Gregg W. Stone

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