Differential prognostic impact of high on-treatment platelet reactivity among patients with acute coronary syndromes versus stable coronary artery disease undergoing percutaneous coronary intervention

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Background High on-treatment platelet reactivity (HTPR) after clopidogrel is associated with a higher risk of cardiovascular events after percutaneous coronary intervention (PCI). However, it remains unclear whether HTPR is of similar prognostic value for different clinical presentations.

Methods We compared the prognostic impact of HTPR, measured by the VerifyNow P2Y12 assay (Accumetrics, San Diego, CA), on outcomes between 1,095 patients with acute coronary syndromes (ACS) and 1,329 patients with stable coronary artery disease (CAD) who were treated with PCI. Before PCI, patients received optimal clopidogrel treatment (75 mg daily for at least 5 days or if <5 days, 300-600 mg loading), and platelet reactivity was measured at 24 to 48 hours after PCI. The primary end point was a composite of death, myocardial infarction, stent thrombosis, or stroke.

Results During follow-up (median, 22.0 months), HTPR was independently associated with higher risks of the primary end point (hazard ratio [HR] 2.03, 95% CI 1.30-3.18, $P = .002$) and mortality (HR 3.46, 95% CI 1.18-10.18, $P = .02$) in patients with ACS. By contrast, for patients with stable CAD, HTPR was not associated with adjusted risks of the primary end point (HR 1.00, 95% CI 0.71-1.39, $P = .98$) or mortality (HR 0.74, 95% CI 0.36-1.51, $P = .41$). Significant interactions were present between HTPR status and clinical presentations for the primary end point ($P = .02$) and mortality ($P = .04$).

Conclusion There was a substantial interaction between platelet reactivity on clopidogrel and clinical presentations on cardiovascular events after PCI. High on-treatment platelet reactivity was significantly associated with higher risks of cardiovascular events in ACS patients, whereas this association was absent in stable CAD patients. (Am Heart J 2013;165:34-42.e1.)

Although dual antiplatelet therapy with aspirin and clopidogrel has significantly reduced atherothrombotic events among patients with acute coronary syndrome (ACS) or receiving percutaneous coronary intervention(PCI), a wide interindividual variability to clopidogrel has been observed and a lower degree of platelet inhibition is associated with worse outcomes.[1]

Currently, several point-of-care platelet function assays were tested, and high on-treatment platelet reactivity (HTPR) was associated with a higher risk of major cardiovascular events in patients undergoing PCI.[2,3] However, several important questions are still unresolved, such that HTPR after PCI can be uniformly applied to predict adverse outcomes across the broad spectrums of patients and so the routine platelet function testing in clinical practice remains controversial. Especially, there are limited data regarding whether prognostic implications of HTPR status would be same or not according to different clinical presentations; ACS versus stable coronary artery disease (CAD). We, therefore, evaluate that there are differential outcomes and its interaction according to HTPR status in patients presented with ACS or stable CAD.

Methods

Study population and platelet function testing

Consecutive patients with chronic, stable CAD who were eligible for elective PCI or ACS who were eligible for emergent or urgent PCI were enrolled in the study. Patients were enrolled as the part of the Asan-Verify Registry, which is a single-center, prospective observational registry designed to evaluate the

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Table I. Baseline characteristics according to platelet reactivity in patients with ACS and stable CAD

	ACS (n = 1095)			Stable CAD (n = 1329)		
Variable	**HTPR (n = 682)**	**No HTPR (n = 413)**	***P***	**HTPR (n = 816)**	**No HTPR (n = 513)**	***P***
Characteristics						
Age	62.1 ± 10.2	60.2 ± 10.4	.004	63.3 ± 9.1	59.5 ± 8.9	<.001
Male sex	477 (69.9)	319 (77.2)	.009	540 (66.2)	415 (80.9)	<.001
Body mass index	24.9 ± 3.1	24.9 ± 3.1	.87	25.1 ± 2.9	25.1 ± 2.74	.82
Diabetes	182 (26.7)	99 (24.0)	.32	229 (28.1)	143 (27.9)	.94
Hypertension	411 (60.3)	229 (55.4)	.12	500 (61.3)	290 (56.5)	.09
Current smoking	200 (29.3)	126 (30.5)	.68	172 (21.1)	137 (26.7)	.02
Hypercholesterolemia	390 (57.2)	243 (58.8)	.59	525 (64.3)	314 (61.2)	.25
Previous MI	39 (5.7)	22 (5.3)	.78	28 (3.4)	24 (4.7)	.25
Renal insufficiency	12 (1.8)	6 (1.5)	.70	16 (2.0)	8 (1.6)	.59
Ejection fraction	57.6 ± 8.0	58.4 ± 7.7	.13	59.4 ± 6.3	59.6 ± 6.3	.48
Loading dose of clopidogrel			.78			.07
75 mg/d for >5 d	168 (24.6)	109 (26.4)		259 (31.7)	194 (37.8)	
300 mg	455 (66.7)	267 (64.6)		540 (66.2)	311 (60.6)	
600 mg	59 (8.7)	37 (9.0)		17 (2.1)	8 (1.6)	
Medications at admission						
ACE inhibitor	193 (28.3)	102 (24.7)	.19	239 (29.3)	130 (25.3)	.12
β-Blocker	488 (71.6)	287 (69.5)	.47	550 (67.4)	341 (66.5)	.73
Calcium-channel blocker	572 (83.9)	355 (86.0)	.35	720 (88.2)	459 (89.5)	.49
Statin	547 (80.2)	330 (79.9)	.90	666 (81.6)	417 (81.3)	.88
Proton pump inhibitor	19 (2.8)	12 (2.9)	.91	27 (3.3)	7 (1.4)	.03
Warfarin	5 (0.7)	5 (1.2)	.52	5 (0.6)	2 (0.4)	.71
Multivessel disease	330 (48.4)	189 (45.8)	.40	404 (49.5)	241 (47.0)	.37
Left anterior descending artery	473 (69.4)	297 (71.9)	.37	590 (72.3)	377 (73.5)	.64
Left main disease	51 (7.5)	39 (9.4)	.25	71 (8.7)	45 (8.8)	.96
Bifurcation lesion	220 (32.3)	124 (30.0)	.44	290 (35.5)	158 (30.8)	.08
No. of stents implanted	1.8 ± 1.1	1.7 ± 1.0	.04	1.9 ± 1.1	1.9 ± 1.1	.76
Total stent length, mm	44.9 ± 28.9	41.8 ± 27.7	.08	48.2 ± 29.5	47.6 ± 31.1	.75
Type of stent			.58			.06
Drug-eluting stent	669 (98.1)	407 (98.5)		779 (95.5)	500 (97.5)	
Bare-metal stent	13 (1.9)	6 (1.5)		37 (4.5)	13 (2.5)	

Data are shown as mean (SD) or numbers (percentage). Abbreviation: *ACE*, Angiotensin-converting enzyme.

prognostic value of on-treatment platelet reactivity measured by VerifyNow assay (Accumetrics, San Diego, CA) in the routine PCI practice.[4] *Acute coronary syndrome* was defined as the group of clinical symptoms, electrocardiographic changes, or elevation of cardiac biomarkers that is compatible with acute myocardial ischemia and encompasses an acute myocardial infarction (MI) (ST-segment elevation and non–ST-segment elevation MI) as well as unstable angina.[5] Patients were excluded if they were presented with cardiogenic shock, had use of glycoprotein IIb/IIIa inhibitors or cilostazol, had a known platelet function disorder or thrombocytopenia (platelet count $<80 \times 10^3$ μL), and had contraindication to aspirin or clopidogrel. This study was approved by the Institutional Review Board of the Asan Medical Center, and all patients provided written informed consent. This study was partly funded by the Cardiovascular Research Foundation and the Korea Health 21 R&D Project, Ministry of Health & Welfare, Korea (A090264).

All interventions were performed according to current standard guidelines, and the type of stent implanted was at the discretion of the operator. Before PCI, all patients received optimal clopidogrel treatment (defined as 75 mg daily for at least 5 days or if <5 days, 300-600 mg loading). After the procedure, all patients were prescribed with aspirin (100-200 mg once daily) indefinitely and with 75 mg/d of clopidogrel for at least 12 months. Higher maintenance doses were not used.

Platelet function was measured with the Verify Now P2Y12 test 24 to 48 hours after PCI immediately before discharge. This test is a whole blood cartridge-based method to determine the magnitude of ADP-induced platelet agglutination using 20 μmol/L adenosine diphosphate (ADP) to induce platelet activation and 22 nmol/L prostaglandin E1 to decrease the contribution of P2Y1 receptor stimulation by ADP to platelet aggregation.[2] Platelet reactivity was reported as value of the P2Y12 reaction units (PRUs). All platelet function testing was performed by personnel blinded to patient information and study objectives.

According to the expert consensus of the American College of Cardiology,[6] *HTPR status* was defined as PRU value of ≥235. Secondarily, post hoc cutoff of 208 PRU was also examined based on results from the GRAVITAS trial.[7]

End points and follow-up

The primary end point of the study was a composite of all-cause death, nonfatal MI, stent thrombosis, or stroke. Key

Table II. Outcome rates according to platelet reactivity in patients with ACS and stable CAD

	ACS (n = 1095)						Stable CAD (n = 1329)						
	At 1 y		At 2 y				At 1 y		At 2 y				
Outcome	HTPR	No HTPR	HTPR	No HTPR	HR (95% CI)*	P	HTPR	No HTPR	HTPR	No HTPR	HR (95% CI)*	P	Int. P
	% (no. of events)						% (no. of events)						
Primary end point													
Death, MI, stent thrombosis, or stroke	10.0 (68)	5.6 (23)	11.9 (77)	6.0 (24)	2.17 (1.40-3.37)	.001	10.9 (89)	10.2 (52)	12.5 (97)	12.1 (58)	1.09 (0.79-1.49)	.61	.01
Secondary end points													
Death	0.8 (5)	0.3 (1)	2.7 (14)	0.6 (2)	3.92 (1.35-11.39)	.01	0.7 (6)	1.2 (6)	2.3 (14)	3.1 (12)	0.91 (0.47-1.79)	.79	.02
MI	9.1 (62)	5.6 (23)	9.1 (62)	5.6 (23)	1.68 (1.04-2.70)	.03	10.0 (82)	9.2 (47)	10.2 (83)	9.2 (47)	1.11 (0.78-1.59)	.57	.18
Death or MI	9.3 (63)	5.6 (23)	11.2 (72)	6.0 (24)	1.99 (1.28-3.10)	.002	10.6 (86)	10.0 (51)	12.1 (94)	11.9 (57)	1.07 (0.78-1.48)	.67	.03
Stent thrombosis	0	0	0	0	...†	...†	0.2 (2)	0.4 (2)	0.2 (2)	0.4 (2)	0.63 (0.09-4.46)	.64	...†
Stroke	1.1 (7)	0.2 (1)	1.1 (7)	0.2 (1)	5.76 (0.73-45.55)	.10	0.5 (4)	0.2 (1)	0.7 (5)	0.6 (2)	2.05 (0.41-10.24)	.38	.40
Repeat revascularization	5.5 (35)	4.8 (19)	6.0 (39)	6.1 (23)	1.05 (0.65-1.70)	.84	4.3 (34)	5.2 (25)	5.8 (41)	6.8 (30)	0.84 (0.54-1.30)	.43	.50
Bleeding													
Major	1.2 (8)	0.2 (1)	1.6 (10)	0.2 (1)	6.09 (0.78-47.59)	.09	0.4 (3)	0.2 (1)	0.5 (4)	0.2 (1)	2.49 (0.28-22.32)	.41	.56
All type	3.3 (22)	2.2 (9)	4.1 (26)	2.8 (11)	1.74 (0.89-3.38)	.10	1.7 (14)	1.6 (8)	2.0 (16)	2.4 (11)	0.88 (0.43-1.80)	.73	.19

Cumulative rates of the event from Kaplan-Meier estimates. Abbreviation: *Int. P*, interaction *P*.
*Hazard ratios are for patients with HTPR, as compared with those without HTPR.
†Could not be estimated.

secondary end points were the individual components of the primary end point, composite of death or MI, repeat revascularization, and bleeding.

Death was defined as death resulting from any cause. The occurrence of MI was assessed according to the universal definition of MI.[8] Periprocedural MI was also included because of reported associations with HTPR in several studies and biologic plausibility.[9,10] Stent thrombosis was defined according to the Academic Research Consortium definitions, and the definite/probable event was assessed. Stroke, as detected by the occurrence of a new neurologic deficit, was confirmed by a neurologist and on imaging. *Repeat revascularization* was defined as any percutaneous or surgical revascularization of the target or nontarget vessel. Major and all types (major, minor, or minimal) of bleedings were assessed in accordance with the thrombolysis in myocardial infarction criteria.[11] All study end points were confirmed based on source documentations and were adjudicated by an independent group of clinicians.

Baseline and outcome data were collected prospectively by independent research personnel and entered into a central database. Clinical follow-up was performed via office visit or telephone contact at 1, 6, and 12 months and then every 6 months thereafter. Adherence to antiplatelet medication was routinely assessed by outpatient visits at each time of follow-up and also verified by pharmacy refill data. For validation of complete follow-up data, information about vital status was obtained from the National Population Registry of the Korea National Statistical Office with the use of a unique personal identification number.

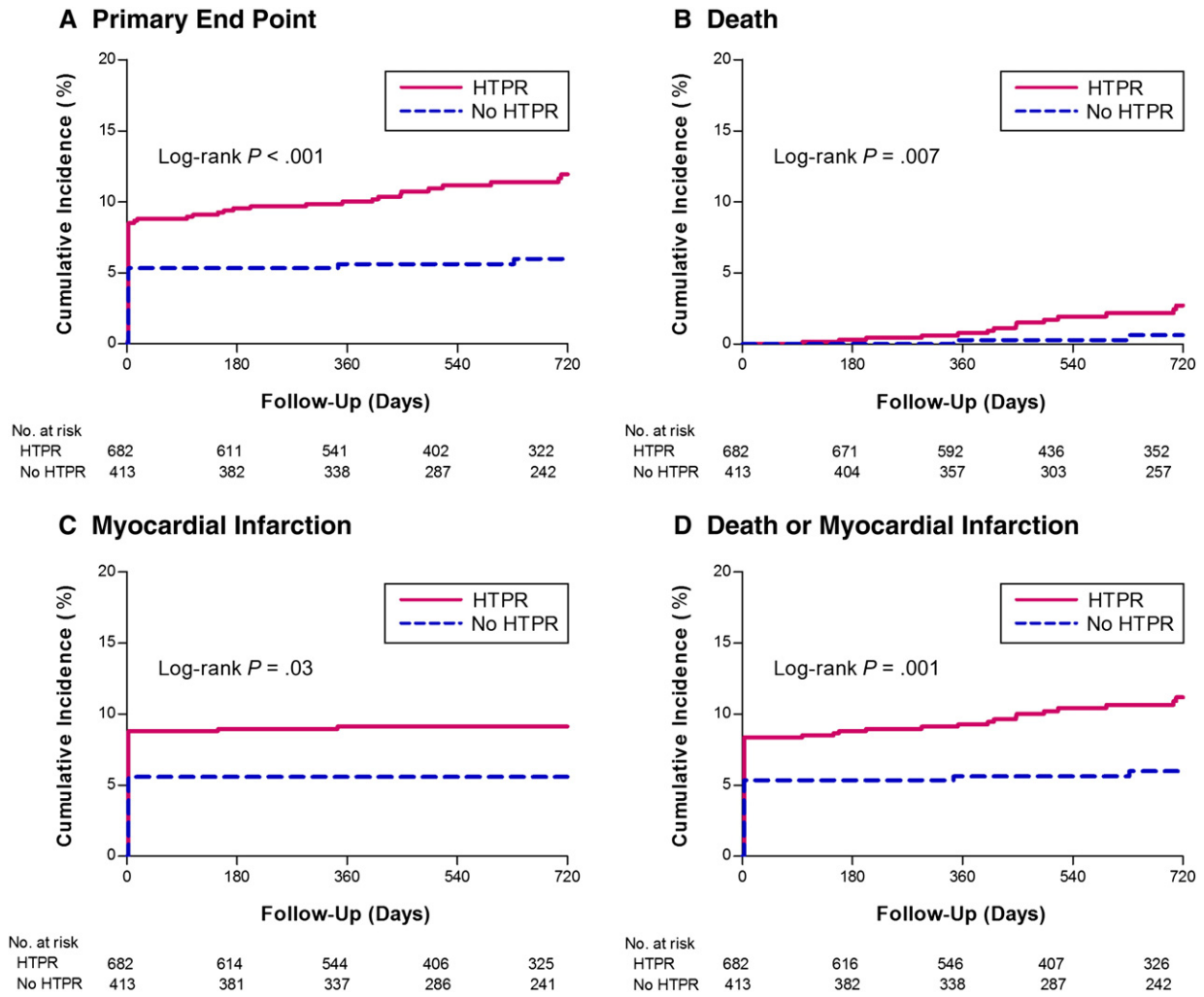
Statistical methods

Continuous variables are presented as mean (±SD) and were compared with the *t* test or Mann-Whitney *U* tests. Categorical variables are reported as frequencies (percentages) and were compared with the χ^2 statistics or Fisher exact test, as appropriate. Cumulative probability and survival curves were constructed from Kaplan-Meier estimates and compared by use of the log-rank test.

Cox proportional hazards regression was used to evaluate crude and adjusted association between HTPR status and clinical outcomes in patients with ACS and stable CAD. Then, we tested for interactions of the presence of HTPR with clinical presentations by use of multivariable, stratified Cox models that included HTPR status, clinical presentation (ACS and stable CAD), and their interaction.

To determine independent association of HTPR with clinical events, we performed multivariable Cox regression analyses adjusting for conventional clinical and procedural characteristics associated with outcome in each cohort of ACS and stable

Figure 1



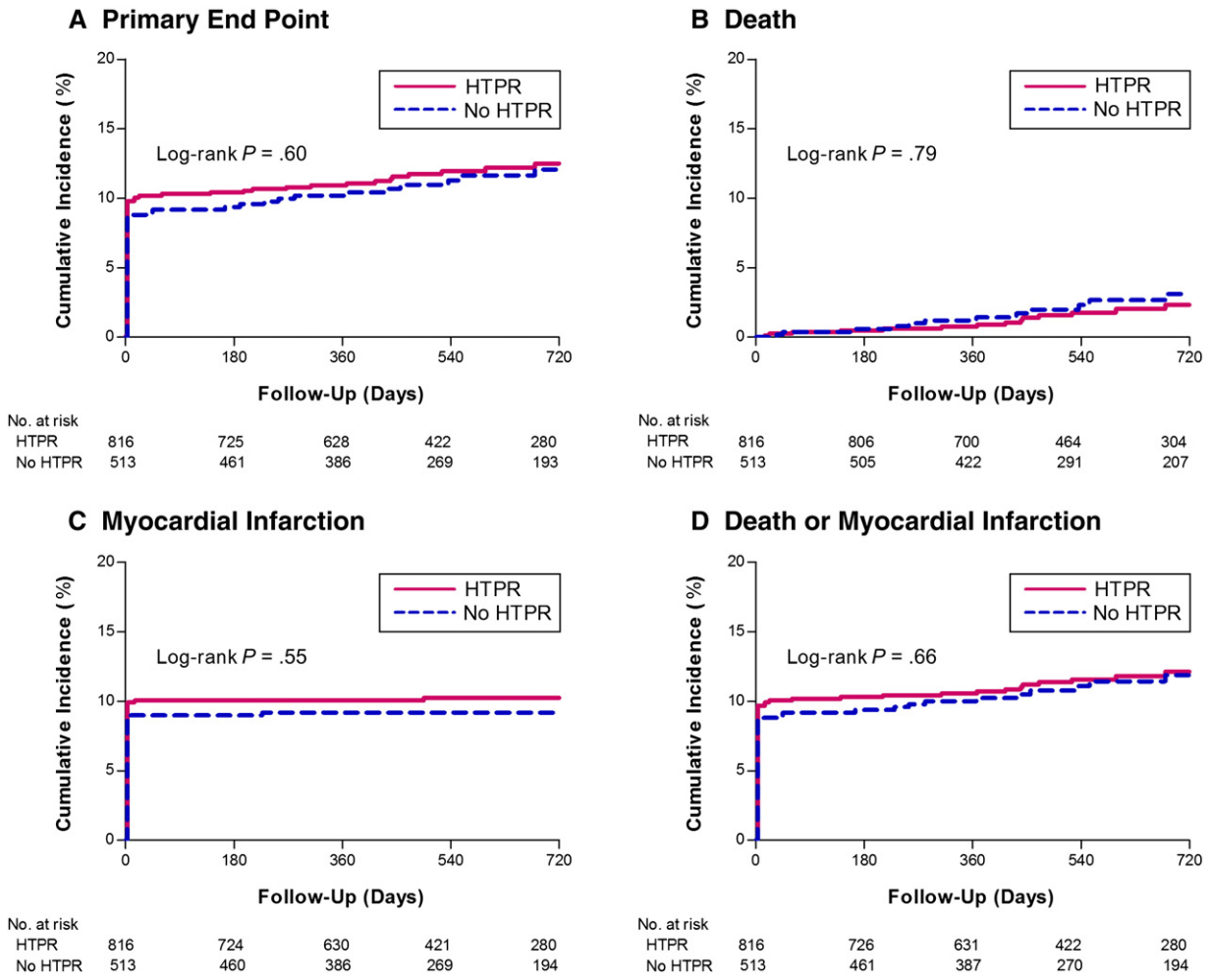
Cumulative incidence of the primary end point and selected secondary end points, according to platelet reactivity in patients with acute coronary syndrome. Cumulative incidence curves are shown for the primary end point (panel A), all-cause death (panel B), MI (panel C), and the composite of death or MI (panel D).

CAD. The following candidate predictors were assessed: age, gender, body mass index, history of diabetes, hypertension, current smoking or hyperlipidemia, prior MI, renal insufficiency, ejection fraction, periprocedural clopidogrel regimen, concomitant medications, multivessel PCI, lesions of left anterior descending artery, left main, or bifurcation, number of stents, total stent length, and type of stent. Covariates that were associated with outcome at an $\alpha = .05$ level of significance were included as fixed covariates in the multivariate model. In addition, to enable an even more rigorous adjustment for a significant difference inpatients' characteristics according to HTPR status and to avoid model overfitting based on few events in secondary end points, we performed the weighted Cox proportional hazards models using inverse-probability-of-treatment weighting.[12] A propensity score analysis was performed with a logistic regression model from which the probability for HTPR was calculated for each patient. In weighted Cox multivariable model with inverse-probability-of-treatment weighting methods, the weights for patients with HTPR were the inverse of (1-propensity score), and weights for patients without HTPR were the inverse of the propensity score. We also tested the significance of interactions between HTPR and clinical presentation on outcomes in these models.

All reported P values are 2 sided, and $P < .05$ was considered to indicate statistical significance. SAS software, version 9.1 (SAS Institute, Cary, NC), was used for statistical analysis.

The authors are solely responsible for the design and conduct of this study, all study analyses, the drafting and editing of the manuscript, and its final contents.

Figure 2



Cumulative incidence of the primary end point and selected secondary end points, according to platelet reactivity in patients with stable CAD. Cumulative incidence curves are shown for the primary end point (panel A), all-cause death (panel B), MI (panel C), and the composite of death or MI (panel D).

Results

Patient characteristics

From January 2006 through January 2010, 2,424 patients were enrolled in the study; 1,095 (45.2%) patients were presented with ACS, and 1,329 (54.8%) were admitted for stable CAD. In the whole population, the mean PRU value was 261 ± 80, and the incidence of HTPR was 61.8%. The rate of HTPR was not different according to clinical presentation (62.3% in ACS and 61.4% in stable CAD; P = .66). Baseline characteristics according to clinical presentations and HTPR status are shown in Table I. In ACS population, patients with HTPR were older and female gender and had higher number of stents than those without HTPR. In stable CAD population, patients with HTPR were older and female gender, had a lower incidence of current smoking, and had higher use of proton pump inhibitor that those without HTPR. Most of patients received drug-eluting stents.

Clinical outcomes according to clinical presentation and HTPR status

The median follow-up duration was 22.0 months (interquartile range 14.5-38.6 months). Complete follow-up data for major clinical events were obtained in 97.2% and 97.4% (P = .76) in patients with and without HTPR, respectively. During follow-up, the status of dual antiplatelet therapy at different time intervals did not differ between patients with and without HTPR (92.1% vs 91.5% at 1 year, P = .63, and 71.4% vs 70.3% at 2 years,; P = .70).

Table III. Adjusted hazard ratios of HTPR for the clinical outcomes in patients with ACS and stable CAD

	Adjusted for conventional risk factors					Adjusted for all covariates using inverse-probability-of-treatment weights				
	ACS (n = 1095)		Stable CAD (n = 1329)		Int.	ACS (n = 1095)		Stable CAD (n = 1329)		Int.
Outcomes	**HR (95% CI)**	***P***	**HR (95% CI)**	***P***	***P***	**HR (95% CI)**	***P***	**HR (95% CI)**	***P***	***P***
Primary end point										
Death, MI, stent thrombosis, or stroke	1.94 (1.24-3.01)	.003	0.98 (0.71-1.36)	.91	.01	2.03 (1.30-3.18)	.002	1.00 (0.71-1.39)	.98	.02
Secondary end points										
Death	3.53 (1.20-10.39)	.02	0.65 (0.32-1.29)	.22	.006	3.46 (1.18-10.18)	.02	0.74 (0.36-1.51)	.41	.04
MI	1.52 (0.94-2.47)	.09	1.05 (0.73-1.52)	.78	.22	1.57 (0.97-2.56)	.07	1.06 (0.73-1.55)	.76	.29
Death or MI	1.76 (1.13-2.75)	.01	0.97 (0.70-1.34)	.84	.03	1.86 (1.18-2.92)	.007	0.99 (0.71-1.39)	.95	.05
Stent thrombosis	...*	...*	...*	...*	...*	...*	...*	0.43 (0.6-3.15)	.41	...*
Stroke	5.70 (0.71-45.09)	.10	1.22 (0.23-6.44)	.82	.27	4.27 (0.53-34.36)	.17	1.18 (0.22-6.44)	.85	.42
Repeat revascularization	1.04 (064-1.68)	.89	0.84 (0.53-1.31)	.44	.48	1.15 (0.71-1.87)	.58	0.85 (0.54-1.36)	.51	.31
Bleeding										
Major	6.77 (0.86-53.38)	.07	1.89 (0.20-17.57)	.58	.50	6.68 (0.60-36.65)	.14	1.03 (0.12-9.16)	.98	.50
All type	1.59 (0.81-3.11)	.18	0.68 (0.33-1.42)	.30	.11	1.43 (0.71-2.87)	.32	0.68 (0.32-1.42)	.30	.26

Hazard ratios are for patients with HTPR, as compared with those without HTPR.
*Could not be estimated.

During the entire study period, 278 primary composite events occurred, including 61 deaths, 216 MIs, 4 stent thromboses, and 18 stroke. Observed clinical outcomes according to HTPR status in patients with ACS versus stable CAD are shown in Table II, Figure 1, and Figure 2. Among patients with ACS, those with HTPR had significantly a higher incidence of primary end point than those without HTPR; in particular, early difference was driven by periprocedural MI, and late difference was driven by mortality. According to subtypes of ACS (unstable angina, non–ST-segment elevation or ST-segment elevation MI), a directionally consistent hazard for primary end point (range, 2.1-3.1) was observed. As the secondary end points, HTPR status was significantly associated with increased risks of death, MI, and the composite of death or MI. By contrast, among patients with stable CAD, incidences of primary or any secondary end points did not differ among patients with and without HTPR. A significant interaction was present between HTPR status and clinical presentations for the risk of primary end point (P = .01), death (P = .02), and the composite of death or MI (P = .03).

After adjustments of clinical covariates, these findings were consistent (Table III). In the ACS population, the adjusted risks for the primary end point, death, and the composite of death or MI were significantly higher in patients with HTPR than in those without HTPR. However, in patients with stable CAD, the adjusted risks for primary and any secondary end points were not significantly different according to HTPR status. There are statistically significant interactions between HTPR status and clinical presentation for covariate-adjusted risks of primary end point (P = .02), death (P = .04), and the composite of death or MI (P = .05).

In landmark analyses according to timing of events, HTPR was consistently (but not always statistically significantly) associated with higher risks of early, intermediate, and late occurrence of primary outcome among patients with ACS (Figure 3). However, in patients with stable CAD, there was no association of HTPR with primary outcome irrespective of timing of events.

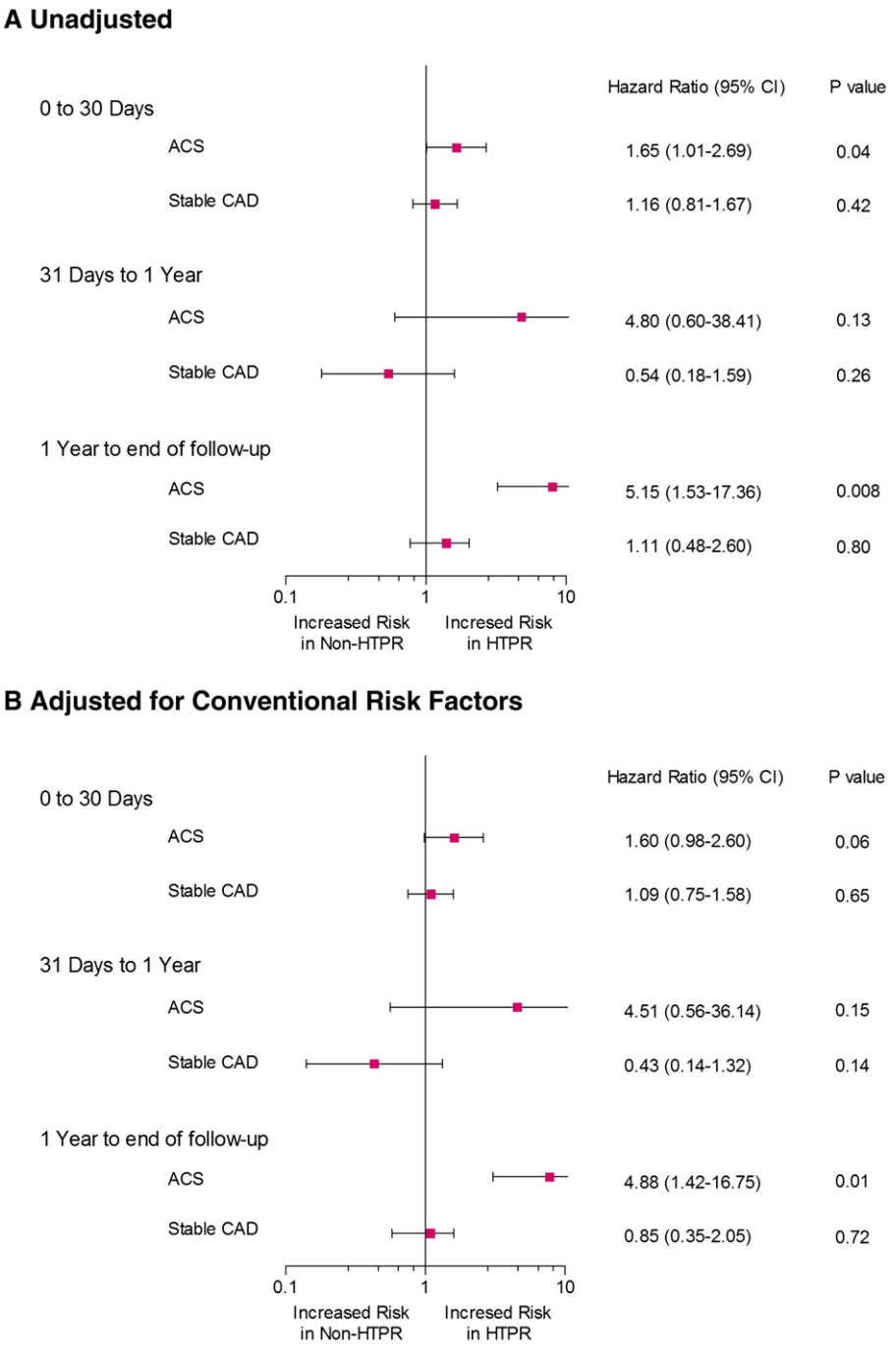
In addition, when analyses were confined to patients who were treated with dual antiplatelet therapy to end of follow-up, overall findings were consistent; HTPR was independently associated with a higher risk of primary end point in ACS patients (hazard ratio [HR] 1.78, 95% CI 1.13-2.80, P = .01), whereas HTPR was not associated with primary end point in stable CAD patients (HR 1.02, 95% CI 0.73-1.42, P = .92) (P for interaction = .03).

However, when we used the alternative definition of high platelet reactivity (PRU ≥208), high reactivity was not significantly associated with increased rates of clinical events both in ACS and stable angina, although there was a trend toward a higher risk of primary outcome in patients with ACS (P = .07) (Appendix Table I).

Discussion

The major findings of this study are (1) that inpatients undergoing PCI for ACS, HTPR on clopidogrel was independently associated with increased risks of cardiovascular events, whereas inpatients with stable CAD, HTPR did not significantly affect clinical outcomes, and (2) that a significant interaction was present between status of HTPR status and clinical presentations on the adjusted risks of the primary end point, mortality, and the composite of death or MI.

Figure 3



Crude and adjusted risk for primary end point according to timing of events. Hazard ratios (patients with HTPR versus those without HTPR) are shown for the primary end point.

Previous studies suggested a strong relationship of HTPR with ischemic events in "high-risk" ACS patients.[13,14] By contrast, there is controversy of prognostic implications of these testing in "low-risk" or "stable" population,[2,4,15,16] such as the negative results of recent clinical trials: GRAVITAS and TRIGGER-PCI. Consistent with previous findings, our study suggested that there was a strong association of HTPR with cardiovascular

events in ACS patients, but no association of HTPR with outcomes in stable CAD. Similarly, large-sized registry also suggested that clopidogrel responsiveness was useful to predict early stent thrombosis in ACS patients, but it was less useful in stable CAD.[17] Coinciding with platelet function assays, several genetic polymorphisms on clopidogrel metabolism have been linked to increased risks of cardiovascular events in "high-risk" ACS patients[18,19] but not in a relatively low-risk population.[20] Therefore, further research is required to determine "selected" population who benefit from platelet function testing or genetic screen.

Apart from the relationship of HTPR with ischemic events, we found that the HTPR status was not associated with bleeding events irrespective of clinical syndromes. However, there are still debates regarding this association.[10,15,21] Further studies with larger population adopting more specific bleeding criteria would be required to define this relationship.

In our study, unexpectedly lower incidence of periprocedural MI in patients with ACS than in those with stable CAD might largely be explained by the universal definition of MI (type 4a).[8] The current MI definition could have penalized the ACS population, especially having elevated baseline cardiac enzyme (ie, non–ST-segment elevation MI or ST-segment elevation MI) because subsequent MI is adjudicated with documentation of falling, nadir, or normal enzyme on serial measurements. In addition, in our study, the rate of mortality and clinical outcomes in patients with ACS was relatively lower than expected, for reasons that extremely "high-risk" subsets in ACS patients, such as those presenting with cardiogenic shock or requiring use of glycoprotein IIb/IIIa inhibitors, were excluded by our study criteria.

In the current study, the prevalence of HTPR was much higher at 60%, in contrast to GRAVITAS and prior studies, where the prevalence of HTPR was 40%. Recently, several data suggest that there may be ethnic differences in genetic polymorphisms for CYP2C19, clopidogrel response, HTPR prevalence, and clinical outcomes.[4,18,22,23] In addition, contrary to the consistent association between the CYP2C19 genotype and clinical outcomes among Western population, there are inconsistent linkage between genetic polymorphisms, antiplatelet effect, and cardiovascular events in Asian population. These discrepancies among different ethnic groups warrant further investigations.

Limitations

First, our study evaluated nonrandomized, observational data. As in any observational cohort study, residual confounding is of concern. Second, the results should be considered hypothesis generating, and therefore, current findings should be confirmed or through larger clinical trials. Third, in our study, there were no serial measurements of residual platelet reactivity, which might be variable over time during follow-up. Finally, the study does not address the clinical value of tailored antiplatelet therapy, and thus, current findings should not be construed as implying a direct benefit of reducing platelet reactivity after PCI without further clinical evidences.

Conclusions

High on-treatment platelet reactivity, as measured by the VerifyNow P2Y12 assay, was significantly associated with cardiovascular events in patients with ACS undergoing PCI, whereas HTPR was not associated with a higher risk of events in patients with stable CAD. The present study suggests that measuring platelet reactivity in every patient would not be useful in routine PCI practice, and further research should be performed to identify "high-risk" patients who would benefit from selective testing and personalizing medical therapy.

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Appendix

This appendix has been provided by the authors to give readers additional information about their work.

Supplement to: Park et al "Differential Prognostic Impact of High On-Treatment Platelet Reactivity Among Patients With Acute Coronary Syndromes Versus Stable Coronary Artery Disease Undergoing Percutaneous Coronary Intervention"

Contents

The alternative defined high platelet reactivity, defined post hoc, was defined as PRU value of 208. For multivariable analysis, the following candidate variables were assessed (age, gender, body mass index, history of diabetes, hypertension, current smoking or hyperlipidemia, prior MI, renal insufficiency, ejection fraction, periprocedural clopidogrel regimen, concomitant medications, multivessel PCI, lesions of left anterior descending artery, left main, or bifurcation, number of stents implanted, total stent length, and type of stent). Among these variables, covariates that were associated with outcome at an $\alpha = .05$ level of significance (age, renal insufficiency, use of proton pump inhibitor, bifurcation lesion, and total stent length) were included as fixed covariates in the final multivariate model.

Appendix Table I. Hazard ratios of alternatively defined high platelet reactivity for the clinical outcomes in patients with ACS and stable CAD

	Unadjusted					Adjusted for conventional risk factors				
	ACS (n = 1095)		Stable CAD (n = 1329)			ACS (n = 1095)		Stable CAD (n = 1329)		
Outcomes	**HR (95% CI)**	***P***	**HR (95% CI)**	***P***	**Int. *P***	**HR (95% CI)**	***P***	**HR (95% CI)**	***P***	**Int. *P***
Primary end point										
Death, MI, stent thrombosis, or stroke	1.59 (0.96-2.62)	.07	1.15 (0.79-1.68)	.47	.32	1.44 (0.86-2.38)	.16	1.04 (0.71-1.52)	.85	.28
Secondary end points										
Death	1.69 (0.58-4.89)	.34	0.67 (0.33-1.37)	.27	.16	1.64 (0.55-4.85)	.37	0.52 (0.25-1.09)	.08	.06
MI	1.39 (0.80-2.42)	.25	1.32 (0.85-2.05)	.22	.89	1.31 (0.75-2.30)	.35	1.21 (0.78-1.89)	.40	.83
Death or MI	1.47 (0.88-2.43)	.14	1.16 (0.79-1.70)	.45	.47	1.33 (0.80-2.21)	.28	1.04 (0.71-1.53)	.84	.42
Stent thrombosis	…*	…*-	0.30 (0.04-2.11)	.23	…*	…*	…*	…*	…*	…*
Stroke	2.67 (0.34-21.07)	.35	0.91 (0.18-4.52)	.91	.41	2.92 (0.37-23.10)	.31	0.66 (0.13-3.38)	.62	.29
Repeat revascularization	0.87 (0.51-1.48)	.60	0.75 (0.47-1.22)	.25	.70	0.87 (0.51-1.48)	.60	0.74 (0.45-1.20)	.22	.66
Bleeding										
Major	2.93 (0.38-22.88)	.31	…*	…*	…*	3.87 (0.47-31.69)	.21	…*	…*	…*
All type	1.88 (0.80-4.45)	.15	1.03 (0.45-2.40)	.94	.33	1.80 (0.76-4.28)	.18	0.89 (0.38-2.10)	.80	.25

Hazard ratios are for patients with HTPR, as compared with those without HTPR. Abbreviation: *Int. P*, interaction *P*.
*Could not be estimated.