Impact of Point-of-Care Platelet Function Testing Among Patients With and Without Acute Coronary Syndromes Undergoing Percutaneous Coronary Intervention With Drug-Eluting Stents (from the ADAPT-DES Study)

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We sought to examine if the risk conferred by high on-treatment platelet reactivity (HPR) varies based upon clinical presentation. We examined the relation between HPR (P2Y12 reaction units >208) and adverse ischemic and bleeding events among patients with and without acute coronary syndromes (ACS) from ADAPT-DES; 51.7% of patients had ACS. After clopidogrel loading, ACS patients had higher P2Y12 reaction units and a greater prevalence of HPR based on VerifyNow P2Y12 assay. Of 92 definite or probable stent thrombosis (ST) events at 2 years, 65.2% occurred among patients with ACS. HPR was independently associated with ST in ACS patients (adjusted hazard ratio 2.29, 95% confidence interval 1.32 to 3.98) but not with clinically relevant bleeding. Although no statistical interactions between ACS status and these associations were observed, non-ACS patients exhibited an attenuated association between HPR and ST, and an inverse association between HPR and clinically relevant bleeding. HPR was similarly associated with myocardial infarction, but not with overall mortality in ACS and non-ACS patients. In conclusion, the majority of ST events in the 2 years after drug-eluting stent placement occurred in ACS patients; HPR was strongly associated with ST in these patients. These data support current recommendations for using more potent antiplatelet therapies in ACS patients. **(Am J Cardiol 2019;123:549−557)**

Dual antiplatelet therapy with aspirin plus a P2Y12 receptor antagonist following stent implantation is the gold standard for protection against stent thrombosis (ST).[1] However, the response to the most commonly used P2Y12 antagonist clopidogrel is variable, and is affected by both genetic and nongenetic factors.[2] The on-clopidogrel platelet reactivity following percutaneous coronary intervention (PCI) is independently associated with increased risk of adverse clinical events.[3−7] Residual platelet reactivity as well as the risk ST and other adverse ischemic events are higher among patients with versus without acute coronary syndrome (ACS). More potent P2Y12 receptor antagonists than clopidogrel, such as prasugrel and ticagrelor, were superior to clopidogrel in large-scale randomized trials of patients with ACS,[8−10] but there are less data supporting the use of more potent P2Y12 antagonists in patients without ACS,[11−14] and the risks of high on-treatment platelet reactivity (HPR) on subsequent adverse outcomes in the non-ACS population are less well described. We sought to examine the relation between HPR and adverse ischemic events among patients with and without ACS to examine whether the risk conferred by HPR varied based upon clinical presentation.

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See page 556 for disclosure information.

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Methods

The study design, protocol, and primary results of ADAPT-DES have been previously described in detail.[6] In brief, ADAPT-DES was a large, prospective, multicenter registry specifically designed to determine the relation between P2Y12 reaction units (PRU) and subsequent clinical events in patients treated with aspirin and clopidogrel who underwent successful coronary drug-eluting stent (DES) implantation. A total of 8,582 patients who underwent PCI with at least 1 DES who were adequately loaded with aspirin and clopidogrel were enrolled at 11 hospitals in the United States and Germany, and were followed clinically for 2 years.

Adenosine diphosphate (ADP) receptor platelet function testing was performed using the VerifyNow P2Y12 assay (Accumetrics, San Diego, California), with the results expressed in PRU. Clopidogrel was given as either (1) 600 mg at least 6 hours before VerifyNow testing, (2) 300 mg at least 12 hours before VerifyNow testing, or (3) 75 mg or more for at least 5 days before VerifyNow testing. Aspirin was given as either (1) a non−enteric-coated oral dose of 300 mg or more at least 6 hours before PCI, or (2) a chewed dose of 324 mg or intravenous dose of 250 mg or more at least 30 minutes before PCI. If eptifibatide or tirofiban were used during PCI, a 24-hour washout period was required before VerifyNow testing. A 10-day washout period was required if abciximab was used, and thus no patients receiving abciximab were enrolled. Patients were treated with aspirin indefinitely and with clopidogrel for at least 1 year following PCI. Treating physicians were blinded to VerifyNow results.

Patients were followed for 2 years with visits at 30 days, 1 year, and 2 years. For the purposes of the present analysis, patients were stratified based upon clinical presentation (ACS vs non-ACS) as captured on the enrollment case report form. The definitions of the study end points have been published.[6] The primary end point was definite or probable ST, according to the Academic Research Consortium definition.[15] Secondary end points included myocardial infarction (MI), all-cause death, clinically relevant bleeding, and major adverse cardiac events (MACE) that was a composite of cardiac death, MI, and target lesion revascularization for ischemia or symptoms. Bleeding was deemed to be clinically relevant if it met criteria for thrombolysis in MI major or minor bleeding, any GUSTO bleeding, ACUITY major bleeding, or if it required medical attention after discharge.[9,16,17] MI was defined using the ACUITY criteria, with an enzyme threshold of >3× the upper limit of normal following PCI.[16] All death, MI, and ST events were adjudicated by an independent clinical events committee that was blinded to platelet reactivity results.

Categorical variables were compared using the chi-square test, and continuous variables using the *t* test. Cumulative event rates were compared using Kaplan-Meier methodology and the log-rank test. The unadjusted and adjusted association between ACS and clinical outcomes was assessed using uni- and multivariable Cox proportional hazards regression, using a stepwise selection of relevant confounder variables. An interaction term between ACS and HPR was included to assess whether the association between HPR and outcomes was different for patients with versus without ACS.

Results

Of the 8,582 patients included in the analyses, 4,433 patients had a presentation consistent with ACS (51.7%; Table 1). Among ACS patients, the presenting clinical syndrome was unstable angina in 53.5%, non-ST segment elevation MI in 28.2%, and ST-elevation MI in 18.4% of patients. VerifyNow measurements for P2Y12 reactivity were obtained in 8,448 patients (98%) and were significantly higher in the ACS cohort (193.8 ± 96.3 vs 181.8 ± 96.9, $p < 0.001$). Accordingly, the proportion of patients with HPR (defined as PRU >208) was greater for ACS compared with non-ACS patients (45.5% vs 39.8%, $p < 0.001$; Table 2).

Patients in the ACS cohort were younger, more often female, and more often current smokers but had a lower prevalence of other cardiovascular risk factors compared with patients in the non-ACS cohort. ACS patients presented with less-complex coronary artery disease, having significantly fewer diseased vessels and less left main disease (Table 1). The PCI procedure was also less extensive for ACS patients, with significantly fewer lesions treated per patient in fewer vessels per patient than for the non-ACS cohort. In addition, the ACS cohort had significantly fewer stents implanted per patient, and these stents were of shorter length.

Definite or probable ST events occurred in 92 patients within 2 years (730 days) of their index PCI procedure (of note, successful PCI without complication was a prerequisite for enrollment in ADAPT-DES). Of these events, 72 patients had STs adjudicated as definite ST and the remaining 20 had STs adjudicated as probable. Among the 92 patients with ST, 60 were from the ACS cohort and 32 were from the non-ACS cohort (1.4% vs 0.8%, $p = 0.008$).

Overall, patients with ST had higher PRU values than non-ST patients (222.9 ± 99.2 vs 187.6 ± 96.7, $p < 0.001$) and ST patients more commonly had HPR (59.3% vs 42.5%, $p = 0.001$). A greater proportion of ACS patients with ST event had HPR (67.8% vs 45.2% for non-ST, $p < 0.001$), but no difference was detected in the frequency of HPR between ST and non-ST groups within the non-ACS cohort (43.8% for ST vs 39.7% for non-ST, $p = 0.65$; Table 3).

In unadjusted analyses, HPR was associated with ST through 2 years (hazard ratio [HR] 1.92; 95% confidence interval [CI] 1.27 to 2.93, $p = 0.002$). Notably, the absolute difference in ST incidence between HPR and non-HPR groups was greater in the ACS cohort as compared with the non-ACS cohort (Figure 1). For ACS patients, there was an absolute 1.2% difference in ST incidence between HPR and non-HPR groups; in non-ACS patients, this difference was only 0.1%. In adjusted analyses, HPR was independently associated with ST through 2 years in the full cohort (HR 1.76, 95% CI 1.15 to 2.70, $p = 0.009$) and within the ACS cohort (HR 2.29, 95% CI 1.32 to 3.98, $p = 0.003$), but not within the non-ACS cohort (HR 1.13, 95% CI 0.56 to 2.29, $p = 0.73$).

MI occurred within 2 years of the index procedure in 228 ACS patients (5.1%) compared with 163 non-ACS patients (3.9%; $p = 0.006$). Overall, patients with MI had higher PRU

Table 1
Baseline characteristics and presenting clinical syndromes

Variable	Acute coronary syndromes		p value
	Yes (n = 4,433)	No (n = 4,149)	
Age (years)	62.5 ± 11.3	64.8 ± 10.2	<0.001
Women	27.3%	24.4%	0.002
Unstable angina pectoris	2370 (53.5%)	—	<0.001
Non-ST segment elevation MI	1249 (28.2%)	—	
ST-segment elevation MI	814 (18.4%)	—	
Hypertension*	73.5%	86.1%	<0.001
Hyperlipidemia†	64.2%	85.2%	<0.001
Diabetes mellitus	30.0%	35.0%	<0.001
Insulin-treated	10.4%	12.9%	<0.001
Prior myocardial infarction	23.8%	26.7%	0.002
History of renal insufficiency‡	7.2%	8.3%	0.052
Current dialysis	1.8%	1.4%	0.25
Current cigarette smoker	28.7%	16.1%	<0.001
Body mass index (kg/m^2)	29.6 ± 5.9	29.3 ± 5.5	0.005
Number of diseased vessels			
1	1808 (40.8%)	1475 (35.6%)	<0.001
2	1496 (33.7%)	1339 (32.3%)	
3	1129 (25.5%)	1335 (32.2%)	
Left main	107 (2.4%)	150 (3.6%)	0.002
Left ventricular ejection fraction (%)	53.8 ± 12.2	56.3 ± 12.6	<0.001
Left ventricular end-diastolic pressure (mm Hg)	17.4 ± 9.0	15.4 ± 9.6	<0.001

MI = myocardial infarction.

* Currently on antihypertensive pharmacologic therapy or a documented history of hypertension diagnosed and treated with medication or blood pressure >140 mm Hg systolic or >90 mm Hg diastolic on at least 2 occasions.

† Currently on a statin and either admission cholesterol >200 mg/dl or documented history of total cholesterol >200 mg/dl or LDL ≥130 mg/dl or HDL <30 mg/dl.

‡ Documented history of renal insufficiency or creatinine >2.0 mg/dl.

Table 2
Baseline procedural details

Procedural details	Acute coronary syndromes		p value
	Yes (n = 4,433)	No (n = 4,149)	
Number of coronary arteries treated per patient	1.15 ± 0.39	1.21 ± 0.46	<0.001
Number of narrowings per patient	1.45 ± 0.73	1.56 ± 0.84	<0.001
Number of stents per patient	1.65 ± 0.93	1.79 ± 1.10	<0.001
Total stent length (mm)	31.1 ± 20.2	33.9 ± 24.4	<0.001
Coronary vessels treated			
Left main	2.9%	4.6%	<0.001
Left circumflex	29.7%	32.3%	0.009
Left anterior descending	44.8%	47.4%	0.016
Right	37.5%	36.7%	0.41
Bypass graft	5.4%	4.6%	0.10
Drug-eluting stent type*			
XIENCE/PROMUS	65.5%	63.5%	0.062
TAXUS	18.3%	14.6%	<0.001
Cypher	10.3%	16.8%	<0.001
Endeavor	7.2%	5.2%	<0.001
Resolute	1.6%	2.8%	<0.001
Other	0.0%	0.5%	<0.001
VerifyNow measurements			
Platelet reactivity units	193.8 ± 96.3	181.8 ± 96.9	<0.001
HPR (platelet reactivity units >208)	45.5%	39.8%	<0.001

HPR = high platelet reactivity.

* Some patients had >1 stent type implanted.

Table 3
Stent thrombosis events at 2 years

Cohort	Stent thrombosis (n)		PRU (mean ± SD)	p value	PRU >208 n (%)	p value	Unadjusted (univariable) hazard ratio (95% CI)	p value	Adjusted (univariable) hazard ratio (95% CI)]	p value
Full	Yes	91*	222.9 ± 99.2	<0.001	54 (59.3%)	0.001	1.92 (1.27-2.93)	0.002	1.76 (1.15-2.70)	0.009
	No	8357	187.6 ± 96.7		3555 (42.5%)					
ACS	Yes	59*	227.8 ± 93.0	0.006	40 (67.8%)	<0.001	2.55 (1.48-4.41)	<0.001	2.29 (1.32-3.98)	0.003
	No	4285	193.3 ± 96.3		1937 (45.2%)					
Non-ACS	Yes	32	213.8 ± 110.6	0.060	14 (43.8%)	0.65	1.19 (0.59-2.40)	0.62	1.13 (0.56-2.29)	0.73
	No	4071	181.5 ± 96.8		1618 (39.7%)					

ACS = acute coronary syndromes; CI = confidence interval; PRU = P2Y12 reaction units; SD = standard deviation.
* One additional patient in the ACS cohort experienced an ST, but no VerifyNow (PRU) data were available for this patient.

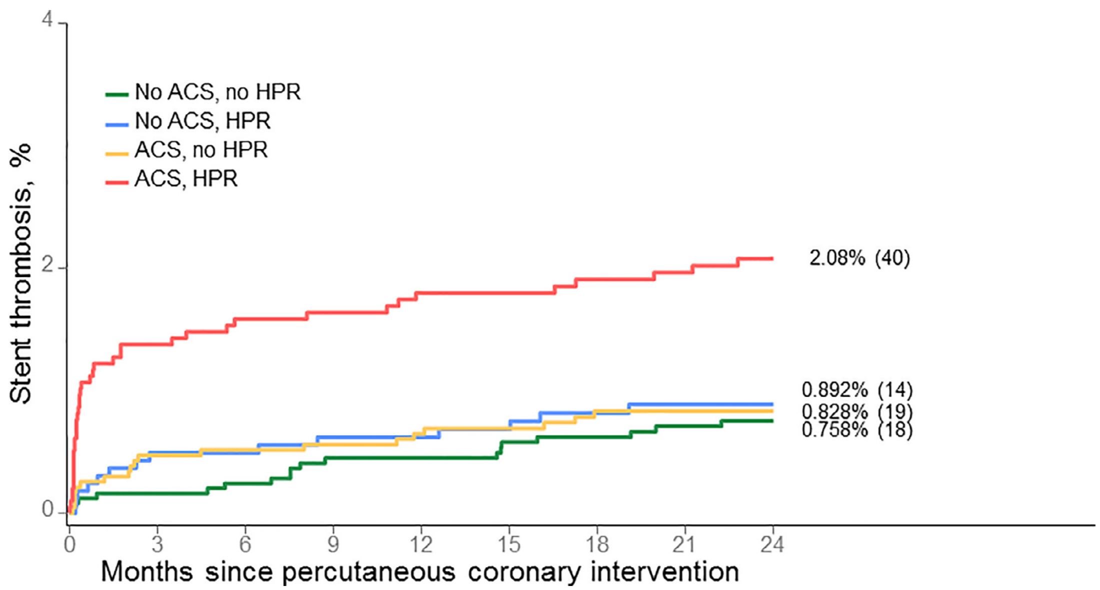

Figure 1. Kaplan-Meier curves of stent thrombosis over 2 years by ACS and HPR status, which shows a higher ST frequency at 2 years (730 days) in the ACS cohort of patients with HPR and demonstrates that these differences at 2 years appear to be primarily due to differences in ST occurrences within the first 30 days after index PCI.

values than non-MI patients (207.3 ± 104.8 vs 187.0 ± 96.3, p <0.001) and a higher prevalence of HPR (51.2% vs 42.3%, p <0.001). The proportion of patients with HPR was significantly higher among patients with versus without an MI event for both ACS (53.4% vs 45.1%, p = 0.016) and non-ACS patients (48.1% vs 39.4%, p = 0.026; Table 4).

In unadjusted analyses, HPR was associated with MI through 2 years (HR 1.41, 95% CI 1.15 to 1.72, p <0.001). The absolute difference in MI incidence between HPR and non-HPR groups was only slightly greater in the HPR group for both the ACS and non-ACS cohorts (Figure 2). In adjusted analyses, HPR was independently associated with MI through 2 years within the full cohort (HR 1.31, 95% CI 1.07 to 1.61, p = 0.009) and trended toward independent association within both the ACS (HR 1.29, 95% CI 0.98 to .68, p = 0.067) and the non-ACS cohorts (HR 1.35, 95% CI 0.99 to 1.84, p = 0.057).

Clinically relevant bleeding occurred within 2 years of their index PCI procedure in 323 ACS patients (7.3%) compared with 416 non-ACS patients (10.0%; p <0.001). Overall, patients with clinically relevant bleeding had lower PRU values than patients with no clinically relevant bleeding (181.0 ± 103.2 vs 188.6 ± 96.1, p = 0.045); however, the prevalence of HPR was not significantly different between patients with and without clinically relevant bleeding (40.6% vs 42.9%, p = 0.24). These results were consistent with those found for the non-ACS cohort (PRU: 172.6 ± 103.8 vs 182.8 ± 96.1, p = 0.043; and HPR: 36.6% vs 40.1%, p = 0.16); however, neither PRU values nor percentage of patients with HPR were significantly different for ACS patients with and without clinically relevant bleeding (PRU: 192.3 ± 101.6 vs 193.9 ± 95.9, p = 0.79, and HPR: 46.1% vs 45.5%, p = 0.83; Table 5).

In unadjusted analyses, HPR was not associated with clinically relevant bleeding through 2 years (HR 0.89, 95% CI 0.75 to 1.04). Notably, the absolute difference in clinically relevant bleeding incidence was higher in the non-HPR group for both the ACS and non-ACS cohorts

Table 4
Myocardial infarction events at 2 years

Cohort	Myocardial infarction (n)		PRU (mean ± SD)	p value	PRU >208 n (%)	p value	Unadjusted (univariate) hazard ratio (95% CI)	p value	Adjusted (univariate) hazard ratio (95% CI)	p value
Full	Yes	383*	207.3 ± 104.8	<0.001	196 (51.2%)	<0.001	1.41 (1.15-1.72)	<0.001	1.31 (1.07-1.61)	0.009
	No	8065	187.0 ± 96.3		3413 (42.3%)					
ACS	Yes	221*	209.5 ± 103.5	0.013	118 (53.4%)	0.016	1.39 (1.07-1.81)	0.014	1.29 (0.98-1.68)	0.067
	No	4124	192.9 ± 95.8		1859 (45.1%)					
Non-ACS	Yes	162*	204.2 ± 106.7	0.003	78 (48.1%)	0.026	1.43 (1.05-1.95)	0.023	1.35 (0.99-1.84)	0.057
	No	3941	180.9 ± 96.4		1554 (39.4%)					

ACS = acute coronary syndromes; CI = confidence interval; PRU = P2Y12 reaction units; SD = standard deviation.
* Eight additional patients (7 in the ACS cohort and 1 in the non-ACS cohort) experienced an MI, but no VerifyNow (PRU) data were available for these patients.

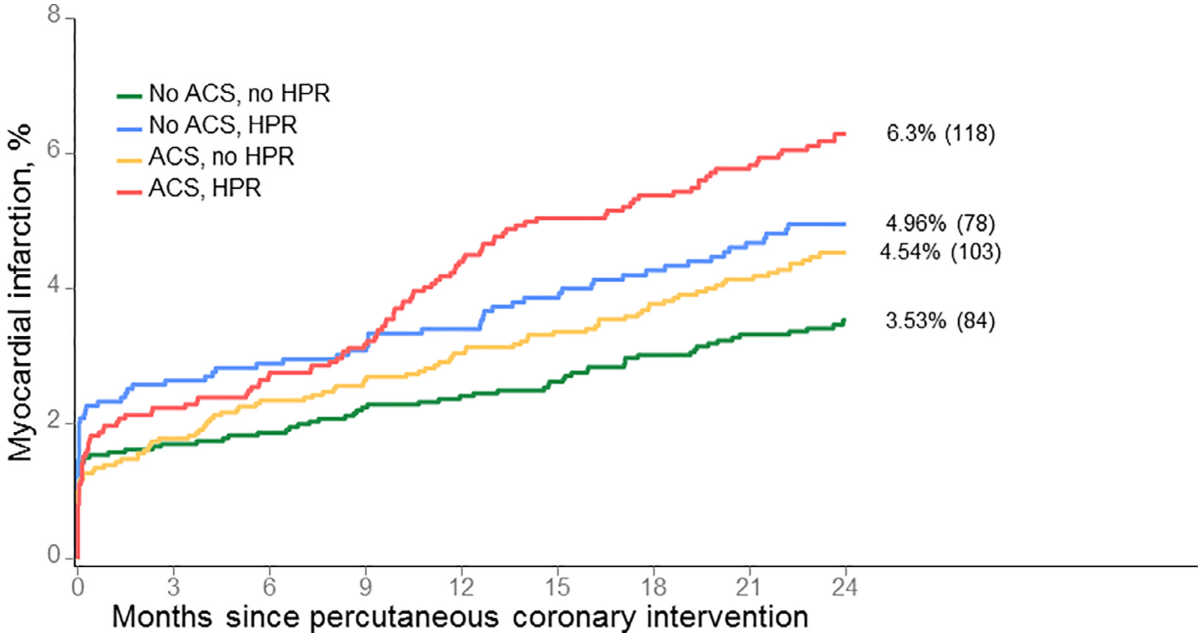

Figure 2. Kaplan-Meier curves of myocardial infarction over 2 years by ACS and HPR status, which demonstrates a higher MI frequency at 2 years (730 days) in the ACS and non-ACS cohorts of patients with HPR. It also shows in the ACS cohort that this difference appears to be primarily due to differences in MI frequency between 9 and 15 months post-PCI, whereas in the non-ACS cohort a difference in MI frequency appears almost immediately post-PCI and increases minimally through 2 years.

(Figure 3), but neither difference was significant. In adjusted analyses, HPR was independently inversely associated with clinically relevant bleeding through 2 years in the full cohort (HR 0.85, 95% CI 0.72 to 1.00, p = 0.049) and in the non-ACS cohort (HR 0.81, 95% CI 0.66 to 1.00, p = 0.051), but this association was attenuated in the ACS cohort (HR 0.90, 95% CI 0.70 to 1.15, p = 0.39).

Death occurred in 164 ACS patients (3.7%) compared with 152 non-ACS patients (3.7%) patients within 2 years of their index PCI procedure (p = 0.84). Overall, patients who died had higher PRU values than patients who did not die (211.0 ± 101.0 vs 187.1 ± 96.5, p <0.001) and had a greater prevalence of HPR (53.9% vs 42.3%, p <0.001). These differences between patients who did versus did not die were slightly more pronounced among patients with ACS (PRU: 220.9 ± 98.4 vs 192.7 ± 96.1, p <0.001; and HPR: 59.6% vs 45.0%, p <0.001) than those without ACS (PRU: 200.6 ± 102.8 vs 181.1 ± 96.6, p = 0.015; and HPR: 48.0% vs 39.5%, p = 0.036; Table 6).

In unadjusted analyses, HPR was associated with subsequent all-cause death through 2 years (HR 1.60, 95% CI 1.28 to 2.00, p <0.001). Notably, the absolute difference in all-cause death incidence between HPR and non-HPR groups was greater in the HPR group for both the ACS and non-ACS cohorts (Figure 4). For ACS patients, there was an absolute 2.2% difference in all-cause death incidence between the HPR and non-HPR groups; in non-ACS patients, this difference was 1.3%. In adjusted analyses, the HPR association with death through 2 years only approached significance in the full cohort (HR 1.24, 95%

Table 5
Clinically relevant bleeding events at 2 years

Cohort	Clinically relevant bleeding (n)		PRU (mean ± SD)	p value	P2Y12 PRU >208 % patients	p value	Unadjusted (univariate) hazard ratio (95% CI)	p value	Adjusted (univariate) hazard ratio (95% CI)	p value
Full	Yes	721*	181.0 ± 103.2	0.045	293 (40.6%)	0.24	0.89 (0.75-1.04)	0.14	0.85 (0.72-1.00)	0.049
	No	7727	188.6 ± 96.1		3316 (42.9%)					
ACS	Yes	308*	192.3 ± 101.6	0.79	142 (46.1%)	0.83	0.95 (0.75-1.21)	0.69	0.90 (0.70-1.15)	0.39
	No	4037	193.9 ± 95.9		1835 (45.5%)					
Non-ACS	Yes	413*	172.6 ± 103.8	0.04	151 (36.6%)	0.16	0.84 (0.69-1.03)	0.10	0.81 (0.66-1.00)	0.051
	No	3690	182.8 ± 96.1		1481 (40.1%)					

ACS = acute coronary syndromes; CI = confidence interval; PRU = P2Y12 reaction units; SD = standard deviation.
* Eighteen additional patients (15 in the ACS cohort and 3 in the non-ACS cohort experienced clinical relevant bleeding.

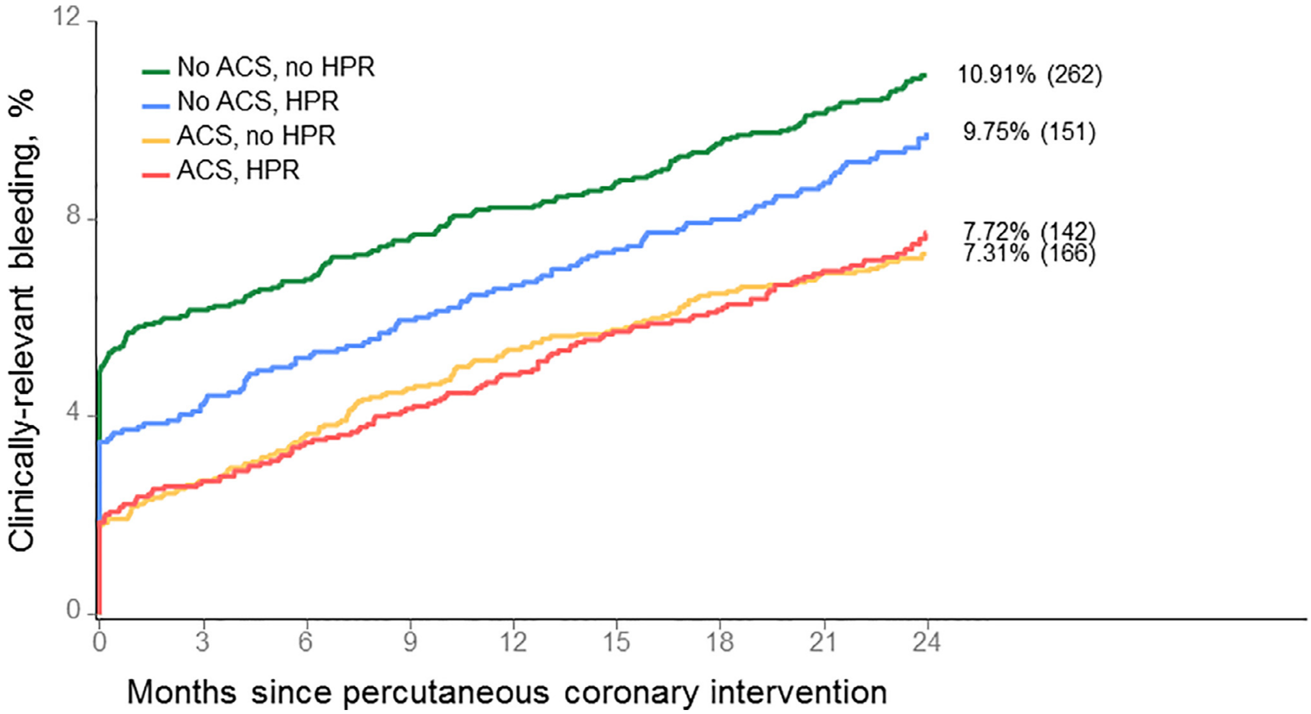

Figure 3. Kaplan-Meier curves of all-cause death over 2 years by ACS and HPR status, which shows a higher frequency of death at 2 years (730 days) in the ACS and non-ACS cohorts of patients with HPR. It also shows in the ACS cohort that differences begin to appear around 30 days after index PCI and consistently increase through 2 years, whereas in the non-ACS cohort the differences appear to begin around 4 months post-PCI and then consistently increase through 2 years.

CI 0.98 to 1.56, p = 0.072) and in the ACS cohort (HR 1.33, 95% CI 0.96 to 1.85, p = 0.084), but this association was attenuated within the non-ACS cohort (HR 1.15, 95% CI 0.83 to 1.58, p = 0.41).

Discussion

The principal findings of this substudy of the ADAPT-DES study are as follows: (1) HPR was more frequently observed among ACS compared with non-ACS patients, and ACS patients were at higher risk for ischemic events compared with non-ACS patients; (2) HPR was an independent predictor of ischemic events (particularly ST) at 2 years. This relation was most pronounced among ACS patients for both ST and MI, whereas it was attenuated (especially on an absolute scale) in the non-ACS population. (3) Inversely, HPR appeared to be protective of clinically relevant bleeding particularly in the non-ACS cohort compared with the ACS cohort.

In ADAPT-DES, ACS patients more frequently had HPR compared with non-ACS patients, a finding consistent with other smaller studies. Although this finding may be partially attributable to differences in baseline demographic characteristics and co-morbidities among ACS and non-ACS patients, it is also consistent with a heightened prothrombotic state that is the hallmark of ACS. In conjunction with a greater prevalence of HPR, ACS patients had an increased risk of ST and MI events. The rate of ST events appeared to be greatest among ACS patients with HPR, whereas patients with ACS without HPR had similar rates of ST as compared with non-ACS patients both with and

Table 6
All-cause death at 2 years

Cohort	All-cause death (n)		PRU (mean ± SD)	p value	PRU >208 n (%)	p value	Unadjusted (univariate) hazard ratio (95% CI)	p value	Adjusted (univariate) hazard ratio (95% CI)	p value
Full	Yes	306*	211.0 ± 101.0	<0.001	165 (53.9%)	<0.001	1.60 (1.28-2.00)	<0.001	1.24 (0.98-1.56)	0.072
	No	8142	187.1 ± 96.5		3444 (42.3%)					
ACS	Yes	156*	220.9 ± 98.4	<0.001	93 (59.6%)	<0.001	1.79 (1.30-2.46)	<0.001	1.33 (0.96-1.85)	0.084
	No	4189	192.7 ± 96.1		1884 (45.0%)					
Non-ACS	Yes	150*	200.6 ± 102.8	0.015	72 (48.0%)	0.036	1.43 (1.04-1.97)	0.030	1.15 (0.83-1.58)	0.41
	No	3953	181.1 ± 96.6		1560 (39.5%)					

ACS = acute coronary syndromes; CI = confidence interval; PRU = P2Y12 reaction units; SD = standard deviation.
* Ten additional patients (8 in the ACS cohort and 2 in the non-ACS cohort) died, but no VerifyNow (PRU) data were available for these patients.

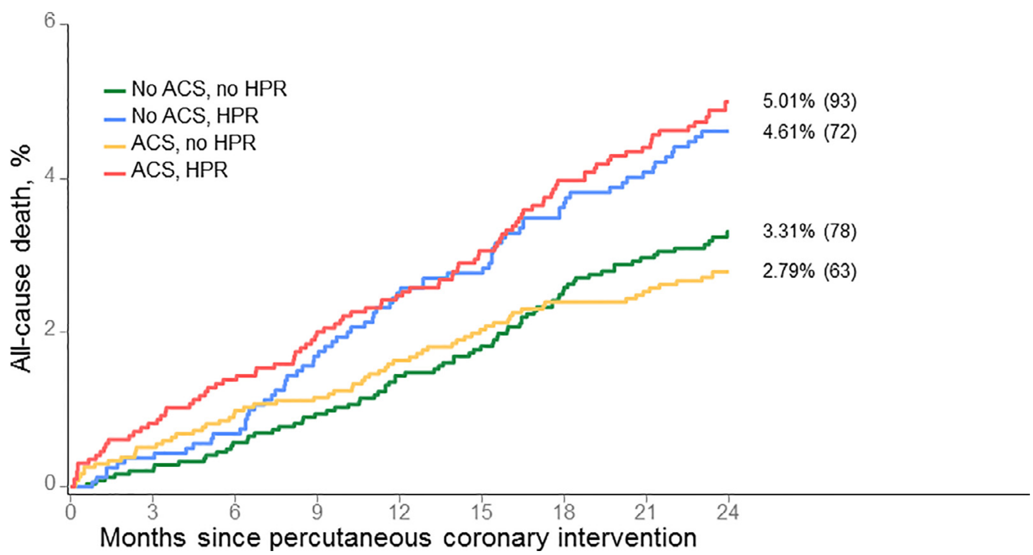

Figure 4. Kaplan-Meier curves of clinically relevant bleeding over 2 years by ACS and HPR status, which clearly shows less-frequent bleeding at 2 years (730 days) in the ACS cohort than in the non-ACS cohort. This difference is evident in both the HPR and non-HPR patients, but appears to be less pronounced in the HPR patients. Also evident is that all differences appear almost immediately post-PCI and remain relatively constant through 2 years.

without HPR (Figure 1). In adjusted analyses, the independent association between HPR and ST was only evident among ACS patients, although the limited number of ST events (even among a cohort of >4,000 patients) limits the power to demonstrate associations between HPR and ST in the group of non-ACS patients.

These findings may explain the negative results of 3 randomized trials in predominately stable patients testing the effect of tailoring antiplatelet therapies based on platelet reactivity.[11−14] Conversely, these data also support using more potent P2Y12 inhibitors in ACS patients who underwent PCI.[8−10] Although it is now known whether clopidogrel is associated with similar ST outcomes as other potent P2Y12 inhibitors in ACS patients without HPR, the TROPICAL-ACS study[18] may have provided the answer. In this study, 2,610 patients who underwent PCI for ACS were randomly assigned to usual care with prasugrel or prasugrel for 1 month followed by de-escalation to clopidogrel and platelet function testing. Patients with HPR (39%) were switched back to prasugrel and the remainder continued clopidogrel. At 1 year, de-escalation was found to be noninferior to standard therapy with no difference in MACE, ST, or bleeding events.

In contrast to ST, HPR tended to be independently associated with a greater frequency of MI in both the ACS and non-ACS cohorts. This finding may be partially explained by a greater frequency of MI events relative to ST, and therefore greater power to detect differences attributable to HPR. Speculatively, it is also possible that the impact of overall thrombogenicity on nonstent (compared with stent-specific) events may be different. In ADAPT-DES, the rates of death were similar among the ACS and non-ACS cohorts (3.9% vs 3.8%, respectively), and HPR was not independently associated with death either in aggregate or within the ACS or non-ACS cohorts. Clinically relevant bleeding events occurred more frequently in the non-ACS cohort (10.0% vs 7.3%), and HPR was independently inversely associated with the bleeding. This association may suggest that HPR is protective of clinically relevant bleeding, particularly in the non-ACS cohort compared with the ACS cohort, where the association is attenuated.

The modest sensitivity and specificity of platelet function testing, coupled with the low prevalence of ST, implies that platelet function testing is unlikely to provide useful information to guide clinical decision-making for the prevention of ST in most individual patients, including those with ACS. Nonetheless, tailoring antiplatelet pharmacotherapy to platelet reactivity may clinically benefit certain patient subsets at highest risk for ST and bleeding events, although further trials in this population are necessary.[19] This tailored approach is likely most applicable to the ACS population where a relation between HPR and outcomes is clearer. Given that the highest concentration of both thrombotic and bleeding events occurs within the first 30 days, such a tailored approach would have the most impact early with diminishing relevance over time. As HPR is not strongly associated with thrombotic events in non-ACS patients but appears to be protective of bleeding, a tailored approach might be best targeted toward the ACS population.

HPR is affected by both genetic and nongenetic factors. Pharmacogenetic post hoc analyses of the PLATO and TRITON-TIMI 38 studies suggest that in ACS, clopidogrel responsive noncarriers of the CYP2C19 loss-of-function allele have similar thrombotic outcomes as carriers treated with the more potent agents.[8,20] A randomized trial comparing clopidogrel to the more potent agents in the STEMI population with CYP2C19 loss-of-function noncarriers is planned.[21] Numerous patient-specific factors are involved in the risks and benefits of more potent antiplatelet agents. Appropriate duration of DAPT also remains an issue for patients following DES implantation. Long-term administration of dual antiplatelet therapy has been shown in the DAPT trial to reduce the incidence of ST but increase the risk of bleeding and mortality including in patients with and without MI.[22] Although platelet testing appears to have little role in the non-ACS population, HPR was highly predictive in the ACS population. A prediction model has been developed that can identify patients more likely to benefit from extended DAPT, and it is possible that the platelet function testing could further augment the predictive capacity of such a model in the ACS population.[23] Thus platelet testing might have utility not just in selection of an antiplatelet regimen but also in duration of administration; however, whether a tailored approach to antiplatelet therapy in this population can be of benefit remains controversial and requires further study. The randomized ANTARCTIC trial evaluated platelet function testing for a tailored approach to antiplatelet therapy in ACS patients over age of 75 years. Although 39% of patients were switched to clopidogrel for PRU <85 and 3% were switched to prasugrel 10 mg/day over conventional therapy of prasugrel 5 mg/day, no difference was found in MACE including ST or bleeding at 1 year. These findings again challenge the hypothesis that platelet function testing is beneficial in routine patient care and support the downgrading of platelet function testing in patients who underwent coronary revascularization from a class IIa to a class IIb recommendation.[24] In contrast, although routine platelet testing does not appear to provide clinical benefit, platelet testing may allow for de-escalation from potent antiplatelet therapy in ACS patients to clopidogrel in responsive patients, which may provide an economic benefit.

This study is a post hoc analysis of the data collected in the ADAPT-DES prospective, multicenter, observational study of unselected patients who underwent successful DES implantation. ADAPT-DES was conducted almost 10 years ago and approximately one-third of the patients received first- rather than second-generation DESs.[6] PRU was measured at baseline only, and we therefore could not account for changes over time in PRU. Patients were not preselected into the study as ACS or non-ACS, nor was the parent ADAPT-DES study powered for the analyses performed in this ACS substudy. The relatively small number of ST events precludes detailed assessment of the association HPR and ST for patients with ACS versus stable CAD across different time-periods. In addition, the relatively small number of non-ACS patients experiencing an ST may have minimized the statistical significance of the ST results in the non-ACS cohort. The multivariate analysis model used in this study adjusted for available confounders; however, the possible presence of residual or unmeasured confounders cannot be excluded, which may add some degree of imprecision to the final models. The ST, MI, and death events underwent independent adjudication by a blinded clinical events committee; however, the bleeding events underwent no such independent adjudication, introducing the potential for reporting bias of these events. Due to these limitations, the results of this study should not be regarded as definitive, but rather as suggestive requiring further study.

Disclosures

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