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Is There an Ideal Level of Platelet $P2Y_{12}$-Receptor Inhibition in Patients Undergoing Percutaneous Coronary Intervention?

"Window" Analysis From the ADAPT-DES Study (Assessment of Dual AntiPlatelet Therapy With Drug-Eluting Stents)

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ABSTRACT

OBJECTIVES This study sought to determine whether there is an ideal level of platelet reactivity (PR) to optimize safety and efficacy within the large multicenter ADAPT-DES (Assessment of Dual AntiPlatelet Therapy With Drug-Eluting Stents) study of 8,582 patients receiving successful drug-eluting stent implantation.

BACKGROUND Patients with high PR on clopidogrel have a greater incidence of adverse ischemic events after stent implantation, whereas low PR may increase bleeding. Due to limited sample size, previous studies have not been able to adjust for differences in baseline characteristics that may confound the relationship of PR and outcomes.

METHODS In the ADAPT-DES study, routine platelet function testing (VerifyNow) was performed following clopidogrel loading. To characterize the independent association between PR and clinical events, patients were stratified into quintiles of $P2Y_{12}$ reaction units (PRU).

RESULTS The PRU medians of the 5 quintiles were 57, 130, 187, 244, and 317 (most to least inhibited). There was a monotonic association between successively higher PRU quintiles and stent thrombosis, whereas for clinically relevant bleeding, the greatest risk occurred in the lowest PRU quintile, with similar risks across the 4 higher quintiles. These relationships remained significant in fully adjusted multivariable analyses (adjusted hazard ratio [HR] for stent thrombosis in Q5 versus Q1: 2.32; 95% confidence interval [CI]: 1.17 to 4.59; $p = 0.02$; adjusted HR for clinically relevant bleeding in Q5 versus Q1: 0.61; 95% CI: 0.47 to 0.77; $p < 0.001$). However, there were no significant independent associations between the level of PRU and mortality.

CONCLUSIONS In this large observational study, increasing PRU was associated with a monotonic increase in stent thrombosis, whereas bleeding risk was confined to the lowest PRU quintile, suggesting an optimal therapeutic window of platelet inhibition at moderately inhibited PRU. However, there was no demonstrable threshold effect for PRU and mortality in adjusted analyses, perhaps due to the offsetting impact of bleeding and ischemia across the spectrum of platelet inhibition. (Assessment of Dual AntiPlatelet Therapy With Drug-Eluting Stents [ADAPT-DES]; NCT00638794) (J Am Coll Cardiol Intv 2015;8:1978–87) © 2015 by the American College of Cardiology Foundation.

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Dual antiplatelet therapy with both aspirin and a $P2Y_{12}$ receptor antagonist is the cornerstone of antithrombotic therapy to prevent ischemic cardiovascular events in patients who undergo percutaneous coronary intervention (PCI) and those with acute coronary syndromes (ACS). The availability of point-of-care platelet function assays assessing platelet reactivity (PR) has permitted the real-time assessment of antiplatelet effects, and high platelet reactivity (HPR) on clopidogrel has been associated with adverse ischemic

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events in numerous previous studies (1–6). Although ischemic events such as stent thrombosis (ST) and myocardial infarction (MI) have been strongly associated with subsequent mortality, the association between HPR and overall mortality has been weaker, perhaps due to more frequent major hemorrhagic complications with effective $P2Y_{12}$ receptor inhibition (7–10). In recognition of these counterbalancing effects, the concept of a "therapeutic window" has been proposed, representing the optimal level of platelet inhibition to suppress ischemic complications without causing excessive bleeding, as described from unadjusted analyses from small- to modest-sized observational studies (8–11). These studies did not, however, adjust for differences in baseline demographic, laboratory, and angiographic characteristics that may confound the interpretation of relative event rates between PR strata.

The ADAPT-DES (Assessment of Dual AntiPlatelet Therapy With Drug-Eluting Stents) study was a prospective, 8,582-patient, multicenter study of patients undergoing routine PR testing following clopidogrel loading after drug-eluting stent (DES) implantation. Therefore, this study represents an ideal population in which to potentially explore the concept of an optimal range of PR. We sought to characterize the relationships among ST, clinically relevant bleeding, and mortality according to quintiles (Q) of $P2Y_{12}$ reaction units (PRU) in order to examine both the unadjusted as well as the independent associations of PRU with clinical outcomes.

ABBREVIATIONS AND ACRONYMS

ACS = acute coronary syndrome(s)
CI = confidence interval
DES = drug-eluting stent(s)
HPR = high platelet reactivity
HR = hazard ratio
MI = myocardial infarction
PCI = percutaneous coronary intervention
PR = platelet reactivity
PRU = $P2Y_{12}$ reaction units
Q = quintile(s)
ST = stent thrombosis
TIMI = Thrombolysis In Myocardial Infarction

METHODS

The study design, protocol, and primary results of the ADAPT-DES study have been previously described in detail (7). In brief, ADAPT-DES was a large, prospective, multicenter registry specifically designed to determine the relationships among PRU and subsequent clinical events in patients treated with aspirin and clopidogrel undergoing successful coronary DES implantation. A total of 8,582 patients undergoing 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 receptor platelet function testing was performed using the VerifyNow P2Y12

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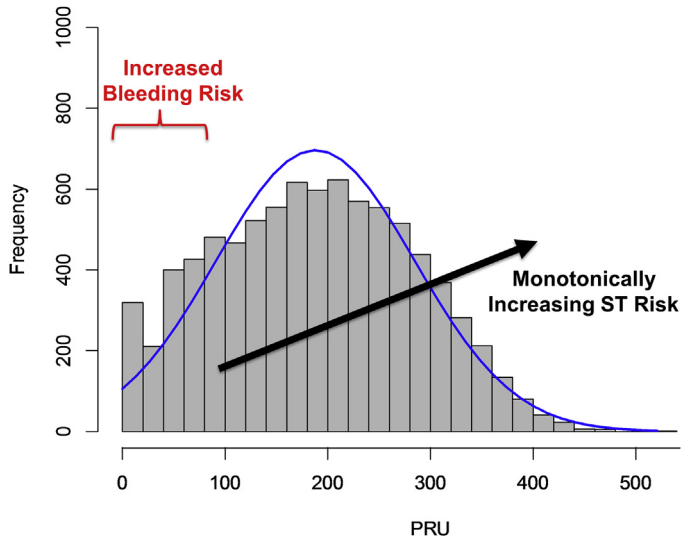
assay (Accumetrics, San Diego, California), with the results expressed in PRU. Clopidogrel was given as one of the following: 1) a dose of 600 mg at least 6 h before VerifyNow testing; 2) a dose of 300 mg at least 12 h before VerifyNow testing; or 3) a dosage of 75 mg or more for at least 5 days before VerifyNow testing. Aspirin was given as either: 1) a nonenteric coated oral dose of 300 mg or more at least 6 h before PCI; or 2) a chewed dose of 324 mg or intravenous dose of 250 mg or more at least 30 min before PCI. If eptifibatide or tirofiban were used during PCI, a 24-h 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.

The primary endpoint for which the original study size was calculated was definite or probable ST, defined according to the Academic Research Consortium definitions (12). Additional endpoints included all-cause mortality and MI as previously defined (7); clinically relevant bleeding was defined as the occurrence of any of the following: a TIMI (Thrombolysis In Myocardial Infarction) major or minor bleed, a GUSTO (Global Utilization of Streptokinase and TPA for Occluded Arteries) bleed, an ACUITY (Acute Catheterization and Urgent Intervention Triage Strategy) major bleed, or any post-discharge bleeding event requiring medical attention. All death, MI, and ST events were adjudicated by an independent clinical events committee that was unaware of the VerifyNow results; bleeding outcomes were site-reported.

FIGURE 1 Distribution of PRU in the ADAPT-DES Population



Distribution of PRU levels in the ADAPT-DES population. The annotations illustrate how increasing PR on clopidogrel was associated with increasing rates of ST in a monotonic fashion, whereas bleeding risk was confined to patients in the lowest PR group. ADAPT-DES = Assessment of Dual AntiPlatelet Therapy With Drug-Eluting Stent(s); PR = platelet reactivity; PRU = $P2Y_{12}$ reaction units; ST = stent thrombosis.

STATISTICAL ANALYSIS. The present study was confined to 8,448 patients with stent implantation for whom VerifyNow P2Y12 testing was performed. These results were categorized into quintiles of lowest to highest PRU (i.e., most to least inhibited). Categorical variables are presented as percentages and were compared with the chi-square test. Continuous variables are presented as mean ± SD and were compared across quintile categories with analysis of variance. The rates of clinical outcomes at 2 years are presented as Kaplan-Meier estimates in order to account for loss to follow-up.

Numerous clinical, laboratory, and angiographic variables that may affect clinical outcomes have also been strongly correlated with PRU (7). Thus, in order to identify the independent associations between PRU quintiles and clinical outcomes, the PRU quintile plus other baseline variables identified as clinically relevant from previous studies (see footnotes in **Table 4** and Online Table 1) were entered into multivariable Cox proportional hazards regression models for ST, clinically relevant bleeding, and all-cause mortality at 2 years. Multivariable models were built by stepwise variable selection with entry and exit criteria set at the $p = 0.10$ level. For multivariable analyses assessing the independent association of PR with outcomes, the first (lowest) quintile of PRU was used as the referent category. In sensitivity analyses, the second quintile of PRU (PRU 95 to 159) was used as the referent category to examine whether there was an optimal "window" of antiplatelet effect. All p values are 2-tailed; a p value <0.05 was considered statistically significant. Statistical analyses were performed using SAS (version 9.1.3, SAS Institute, Cary, North Carolina).

RESULTS

The mean PRU was 188 ± 97 (**Figure 1**). When the 8,448 patients were categorized into quintiles of lowest to highest PRU (most to least inhibited), the PRU cutoff values defining the quintiles were <95, 95 to 159, 160 to 215, 216 to 275, and >275, and the median PRU of these 5 quintiles were 57, 130, 187, 244, and 317, respectively.

TABLE 1 Baseline Characteristics and Clinical Presentation

	Quintile 1 PRU <95 (n = 1,690)	Quintile 2 PRU 95-159 (n = 1,669)	Quintile 3 PRU 160-215 (n = 1,691)	Quintile 4 PRU 216-275 (n = 1,706)	Quintile 5 PRU >275 (n = 1,692)	p Value
Age, yrs	62.2 ± 10.8	63.2 ± 10.7	63.1 ± 10.8	64.2 ± 10.8	65.3 ± 10.8	<0.001
Male	1,332 (78.8)	1,313 (78.7)	1,314 (77.7)	1,260 (73.9)	1,066 (63.0)	<0.001
Body mass index, kg/m^2	27.8 ± 4.7	28.8 ± 5.0	29.5 ± 5.6	30.2 ± 6.0	30.9 ± 6.5	<0.001
Diabetes mellitus	355 (21.0)	426 (25.5)	527 (31.2)	644 (37.8)	774 (45.7)	<0.001
Insulin-treated	124 (7.3)	133 (8.0)	186 (11.0)	234 (13.7)	302 (17.9)	<0.001
History of peripheral arterial disease	178 (10.5)	157 (9.4)	151 (8.9)	176 (10.3)	199 (11.8)	0.065
History of congestive heart failure	119 (7.0)	112 (6.7)	126 (7.5)	145 (8.5)	185 (10.9)	<0.001
Previous myocardial infarction	433 (25.6)	408 (24.5)	427 (25.3)	424 (24.9)	436 (25.8)	0.90
Previous coronary artery bypass graft surgery	270 (16.0)	254 (15.2)	307 (18.2)	289 (16.9)	318 (18.8)	0.03
Previous percutaneous coronary intervention	784 (46.4)	704 (42.2)	697 (41.2)	724 (42.4)	710 (42.0)	0.02
History of renal insufficiency	110 (6.5)	91 (5.5)	115 (6.8)	136 (8.0)	195 (11.5)	<0.001
History of dialysis	14 (0.8)	26 (1.6)	22 (1.3)	29 (1.7)	42 (2.5)	0.003
Hypertension	1,330 (78.7)	1,286 (77.1)	1,332 (78.8)	1,381 (81.0)	1,397 (82.6)	0.001
Hyperlipidemia	1,284 (76.0)	1,212 (72.6)	1,233 (72.9)	1,278 (74.9)	1,282 (75.8)	0.07
Cigarette smoking, current	471 (27.9)	408 (24.5)	382 (22.6)	378 (22.2)	285 (16.8)	<0.001
Presenting clinical syndrome						
Acute coronary syndrome	796 (47.1)	821 (49.2)	865 (51.2)	925 (54.2)	938 (55.4)	<0.001
Unstable angina	458 (27.1)	456 (27.3)	453 (26.8)	470 (27.6)	475 (28.1)	0.94
Non-ST-segment elevation	234 (13.9)	211 (12.6)	242 (14.3)	266 (15.6)	271 (16.0)	0.04
ST-segment elevation	104 (6.2)	154 (9.2)	170 (10.1)	189 (11.1)	192 (11.4)	<0.001
Stable angina	565 (33.4)	525 (31.5)	485 (28.7)	464 (27.2)	429 (25.4)	<0.001
Baseline laboratory parameters						
Hemoglobin, g/dl	14.4 ± 1.5	14.3 ± 1.5	14.2 ± 1.5	13.9 ± 1.4	13.1 ± 1.4	<0.001
Creatinine clearance, ml/min/1.73 m^2	92.0 ± 33.0	95.6 ± 34.8	96.7 ± 38.5	95.3 ± 39.1	91.2 ± 40.4	<0.001
White blood cell count, ×10^6/ml	8.0 ± 3.5	7.9 ± 4.0	7.9 ± 2.9	8.1 ± 2.9	7.9 ± 2.6	0.61
Platelet count, ×10^6/mm^3	234.9 ± 67.1	222.4 ± 62.6	224.4 ± 59.8	224.5 ± 61.8	226.8 ± 62.3	<0.001

Values are mean ± SD or n (%).
PRU = $P2Y_{12}$ reaction units.

Patients with higher PRU were older, more likely to be female, and had higher body mass indices (Table 1). Patients with higher PRU had a greater prevalence of comorbidities, including diabetes mellitus, hypertension, congestive heart failure, previous revascularization, and renal insufficiency. However, current smoking was less likely as PRU increased. Clinical presentation with ACS was also more prevalent with greater PRU. Baseline hemoglobin levels were lower among patients in the highest PRU quintiles, as was creatinine clearance. Platelet counts were highest among patients with the lowest PRU and relatively similar across the other PRU quintiles.

Angiographic and procedural characteristics were mostly similar across the PRU quintiles with the exception of lower left ventricular ejection fraction (and higher left ventricular end-diastolic pressure) as well as slightly fewer stents (and lower total stent length) among patients in the higher PRU quintiles (Table 2).

UNADJUSTED CLINICAL OUTCOMES. There was a monotonic increase in the incidence of definite/probable ST from 0.7% to 1.8% across quintiles of PRU (p = 0.025) (Table 3, Figure 2A). The incidence of MI was similar in the lower 3 quintiles, and increasingly higher in the 2 highest PRU quintiles (p = 0.001) (Table 3). Conversely, the rate of clinically relevant bleeding was highest among patients in the lowest PRU quintile (11.2%), and relatively constant across the 4 higher PRU quintiles (p = 0.006) (Table 3, Figure 2B). This finding was consistently observed for both in-hospital and out-of-hospital bleeding. Finally, in this unadjusted analysis, all-cause mortality monotonically increased with higher PRU quintiles and was highest in the highest PRU quintile (p = 0.006) (Table 3, Figure 2C).

MULTIVARIABLE ANALYSIS. After multivariable adjustment for differences in baseline demographic, laboratory, angiographic, and procedural characteristics among the PRU quintiles, higher PRU remained independently associated with 2-year definite/probable ST, with a stepwise reduction in ST risk from Q5 to Q1 (hazard ratio [HR] for ST in Q5 vs. Q1 as referent: 2.32; 95% confidence interval [CI]: 1.17 to 4.59; p = 0.02) (Table 4).

TABLE 2 Angiographic and Procedural Characteristics

	Quintile 1 PRU <95 (n = 1,690)	Quintile 2 PRU 95-159 (n = 1,669)	Quintile 3 PRU 160-215 (n = 1,691)	Quintile 4 PRU 216-275 (n = 1,706)	Quintile 5 PRU >275 (n = 1,692)	p Value
Angiographic characteristics						
Number of vessels diseased						
1	619 (36.6)	677 (40.6)	650 (38.4)	652 (38.2)	633 (37.4)	0.19
2	585 (34.6)	512 (30.7)	575 (34.0)	544 (31.9)	567 (33.5)	0.09
3	486 (28.8)	480 (28.8)	466 (27.6)	510 (29.9)	492 (29.1)	0.67
Left main >50%	52 (3.1)	48 (2.9)	50 (3.0)	56 (3.3)	48 (2.8)	0.95
Ejection fraction, %	56.2 ± 12.3	55.1 ± 11.9	54.6 ± 12.3	55.1 ± 12.5	53.5 ± 12.8	<0.001
Left ventricular end-diastolic pressure, mm Hg	15.0 ± 8.5	15.5 ± 9.2	16.4 ± 9.2	17.7 ± 10.5	18.2 ± 8.3	<0.001
Procedural characteristics						
Vascular access site						
Femoral	1,604 (94.9)	1,597 (95.7)	1,617 (95.6)	1,628 (95.4)	1,609 (95.1)	0.79
Brachial	5 (0.3)	2 (0.1)	2 (0.1)	5 (0.3)	4 (0.2)	0.65
Radial	81 (4.8)	70 (4.2)	72 (4.3)	73 (4.3)	79 (4.7)	0.88
Lesions treated per patient	1.5 ± 0.8	1.5 ± 0.8	1.5 ± 0.8	1.5 ± 0.8	1.5 ± 0.7	0.11
Stents implanted per patient	1.8 ± 1.0	1.7 ± 1.0	1.8 ± 1.0	1.7 ± 1.1	1.7 ± 1.0	0.04
Total stent length, mm	33.4 ± 23.7	31.5 ± 21.6	32.9 ± 22.4	33.2 ± 23.2	31.4 ± 21.0	0.02
Maximum vessel diameter, mm	3.1 ± 0.7	3.1 ± 0.7	3.1 ± 0.7	3.1 ± 0.8	3.1 ± 0.7	0.51

Values are n (%) or mean ± SD.
PRU = $P2Y_{12}$ reaction units.

In multivariable analyses, compared with PRU within the first quintile, higher PRU within Q2, Q3, Q4, and Q5 remained associated with a lower hazard of clinically relevant bleeding (Table 4). When compared with patients within the highest PRU quintile, the lowest PRU quintile was independently associated with a >60% relative increase in clinically relevant bleeding (HR for clinically relevant bleeding in Q1 vs. Q5 as referent: 1.64; 95% CI: 1.31 to 2.06; p < 0.001). Even compared with the next higher quintile of PRU (Q2: PRU 95 to 159), the lowest quintile PRU was independently associated with a 34% increase in clinically relevant bleeding (HR for Q1 vs. Q2: 1.34; 95% CI: 1.07 to 1.68; p = 0.001) (Figure 3A).

In a multivariable model assessing the relationship between PRU quintiles and mortality, neither high nor low PR, as defined by the highest (or lowest) PRU quintile, was independently associated with all-cause mortality (HR for Q5 vs. Q1 as referent: 1.08; 95% CI:

TABLE 3 Clinical Outcomes at 2 Years

	Quintile 1 PRU <95 (n = 1,690)	Quintile 2 PRU 95-159 (n = 1,669)	Quintile 3 PRU 160-215 (n = 1,691)	Quintile 4 PRU 216-275 (n = 1,706)	Quintile 5 PRU >275 (n = 1,692)	p Value
Death, all-cause	47 (2.9)	47 (2.9)	62 (3.9)	69 (4.3)	81 (5.0)	0.006
Cardiovascular	29 (1.8)	27 (1.7)	39 (2.5)	41 (2.6)	53 (3.3)	0.02
Noncardiovascular	18 (1.1)	20 (1.3)	23 (1.5)	28 (1.7)	28 (1.8)	0.46
Myocardial infarction	69 (4.3)	59 (3.7)	70 (4.3)	79 (4.9)	106 (6.5)	0.001
Q-wave	9 (0.6)	5 (0.3)	7 (0.4)	13 (0.8)	19 (1.2)	0.02
Non-Q-wave	60 (3.7)	54 (3.4)	66 (4.1)	67 (4.1)	88 (5.4)	0.04
Target vessel failure	239 (14.7)	202 (12.6)	256 (15.7)	270 (16.5)	284 (17.5)	0.001
Stent thrombosis						
Definite or probable	12 (0.7)	13 (0.8)	16 (1.0)	21 (1.3)	29 (1.8)	0.025
Definite	9 (0.6)	10 (0.6)	13 (0.8)	17 (1.0)	23 (1.4)	0.055
Clinically relevant bleeding	182 (11.2)	134 (8.3)	133 (8.1)	129 (8.0)	143 (9.1)	0.006
In-hospital bleeding	76 (4.5)	49 (2.9)	47 (2.8)	46 (2.7)	41 (2.4)	0.004
Out-of-hospital bleeding	144 (8.9)	114 (7.1)	110 (6.8)	101 (6.3)	127 (8.1)	0.03

Values are n (%).
PRU = $P2Y_{12}$ reaction units.

0.72 to 1.60; p = 0.72). These findings were mirrored when the sample was restricted to patients with ACS (Online Table 1). Although the second quintile of PR appeared to optimize the balance between both bleeding and ST risk (**Figure 3A**), in sensitivity analyses, the hazards of overall mortality were consistent (and not significantly different from unity) across all PRU quintiles when compared with Q2 as the referent group (**Figure 3B**).

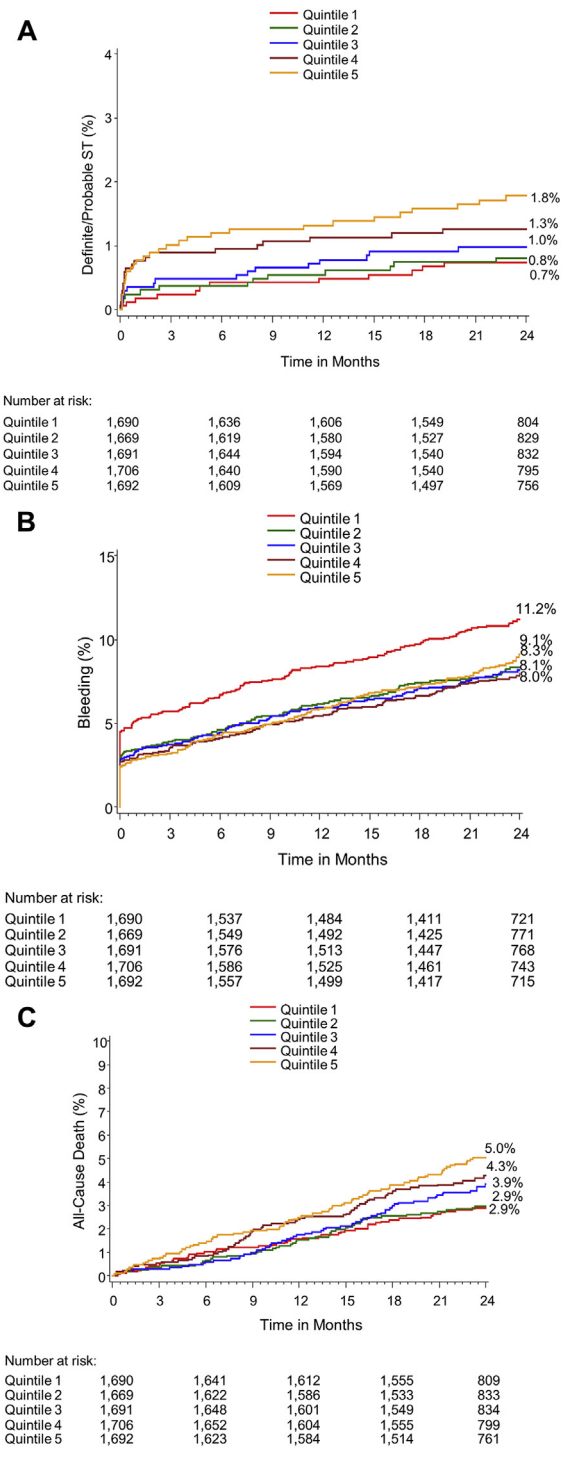
DISCUSSION

The principal findings from the present analysis of 8,448 patients with routine measurement of on-treatment PRU using VerifyNow following successful DES implantation are the following: 1) PRU was associated with the occurrence of ST through 2-year follow-up in a monotonically increasing relationship, and in multivariable analyses, PRU within the highest quintile was independently associated with a >2-fold increase in ST; 2) the lowest PRU quintile was associated with the greatest rate of clinically relevant bleeding in both univariable and multivariable analyses, with similar rates of bleeding at higher PRU levels; and 3) whereas higher PRU was associated with greater all-cause mortality in unadjusted analyses, there was no association between PRU and mortality after multivariable adjustment for baseline differences, with a similar overall hazard for mortality in each PRU quintile.

The finding of high on-treatment PRU has been associated with adverse ischemic outcomes in numerous previous observational studies of both ACS as well as in patients after stent implantation (1-6). Nonetheless, the contributors to HPR can be multifactorial (13). Whether measured HPR is simply a marker or deterministic in the pathogenesis of adverse ischemic events following stent implantation has been controversial. This controversy has been fueled by the observation that most patients exhibiting HPR remain event-free, and by the failure of several clinical trials that sought to demonstrate the utility of intensifying antiplatelet therapy in PCI patients with HPR (14-16).

The present findings of an increasing and independent association between greater levels of PRU and ST within the ADAPT-DES study demonstrate the potential utility of PRU as a risk factor for adverse ischemic events after DES and are consistent with the results of randomized trials demonstrating reductions in ST with greater $P2Y_{12}$ receptor inhibition among high-risk patients (17,18). In the present analysis, however, a relationship between increasing PRU and mortality was observed only in unadjusted

FIGURE 2 Association of PRU Quintiles With Definite/Probable ST, Clinically Relevant Bleeding, and Mortality



Kaplan-Meier curves depicting the association of PRU quintiles with the definite/probable ST **(A)**, clinically relevant bleeding **(B)**, and mortality **(C)**. Analyses are unadjusted and do not account for differences in baseline and procedural characteristics between groups. Abbreviations as in **Figure 1**.

TABLE 4 Multivariable Cox Regression Models of PRU Quintiles With Clinical Outcomes

	Hazard Ratio	95% Confidence Interval	p Value
Stent thrombosis, definite or probable*			
PRU Q1, referent	1.00	–	–
PRU Q2 vs. Q1	1.13	0.51–2.48	0.76
PRU Q3 vs. Q1	1.37	0.64–2.90	0.41
PRU Q4 vs. Q1	1.71	0.84–3.49	0.14
PRU Q5 vs. Q1	2.32	1.17–4.59	0.02
Clinically relevant bleeding†			
PRU Q1, referent	1.00	–	–
PRU Q2 vs. Q1	0.74	0.60–0.93	0.010
PRU Q3 vs. Q1	0.71	0.57–0.89	0.003
PRU Q4 vs. Q1	0.63	0.50–0.79	<0.001
PRU Q5 vs. Q1	0.61	0.47–0.77	<0.001
All-cause mortality‡			
PRU Q1, referent	1.00	–	–
PRU Q2 vs. Q1	0.90	0.58–1.40	0.64
PRU Q3 vs. Q1	1.22	0.82–1.84	0.33
PRU Q4 vs. Q1	1.17	0.78–1.73	0.45
PRU Q5 vs. Q1	1.08	0.72–1.60	0.72

*Model includes PR quintile, clopidogrel usage (time dependent), insulin treatment, previous MI, history of dialysis, ST-segment elevation MI, baseline white blood cell count, baseline platelet count. †Model includes PR quintile, clopidogrel usage (time dependent), age, history of renal insufficiency, history of hypertension, current smoking status, number of vessels treated per patient, baseline hemoglobin, baseline white blood cell count. ‡Model includes PR quintile, clopidogrel usage (time dependent), age, male sex, history of diabetes, previous MI, history of renal insufficiency, current smoking status, ST-segment elevation MI, non-ST-segment elevation MI, baseline hemoglobin, creatinine clearance, white blood cell count.

MI = myocardial infarction; PR = platelet reactivity; PRU = P2Y$_{12}$ reaction units; Q = quintile(s).

analyses and not after multivariable adjustment for differences in baseline and procedural characteristics between patients with high versus low PR. There are several possible explanations for this discordance. Although the lack of a significant correlation between PRU and mortality admittedly could be due to lack of power, with nearly 8,500 studied patients, the absence of even a trend toward an increase in the hazard of mortality across quintiles of PRU (**Table 4**) suggests that there are other influences upon overall mortality than PRU alone. For example, comorbidities that correlate with elevated PRU (e.g., diabetes, ACS, and greater extent of atherosclerosis) are likely stronger contributors to mortality risk than is PRU alone.

Another possible explanation for the lack of an independent relationship between PRU and mortality in the present study is the offsetting effects of bleeding and ischemia. In addition to reducing ST and MI, randomized trials have shown that greater inhibition of the platelet P2Y$_{12}$ receptor also results in increased hemorrhagic complications (17–19). The present and previous studies have now clearly documented an association between profound inhibition of PRU and bleeding events (7,9,20,21), which in numerous studies have also been found to strongly correlate with subsequent mortality (22–24).

These observations have led to the desire to search for an optimal "therapeutic window" of antiplatelet effect—one in which PR is low enough to prevent ischemic events, but not so low as to predispose to bleeding (8–11). In the present study, after multivariable adjustment for differences in baseline and procedural risk, patients in the lowest quintile of PR (those with PRU <95) were at the greatest risk for both in-hospital as well as out-of-hospital bleeding events following DES implantation, but at the least risk for ST. However, whereas ST rates steadily increased with increasing PRU, the hazard of bleeding within the 4 higher PRU quintiles was similar. As a result, these adjusted observations potentially identify an optimal therapeutic window of effect at levels of moderately inhibited PRU (Q2) to minimize ST without inordinately increasing clinically relevant bleeding. Previous groups have identified potentially different PRU cutoffs for the optimal window of antiplatelet effect (11). Variability in the identification of an optimal window of antiplatelet effect could be due to study-specific differences including the analytic plan to assess cutpoints (receiver-operating curve-based analyses vs. quantile analyses), overall sample size, and adjunctive pharmacotherapies administered at the time of PCI, among other factors. Admittedly, some of the bleeding risk observed at the lowest values of PRU within ADAPT-DES could additionally be mitigated by the more assiduous use of bleeding avoidance strategies (e.g., the use of transradial access). However, the present data are entirely consistent with previous observations with potent platelet receptor blockers in which bleeding times were greatly increased only at the highest levels of platelet inhibition (e.g., with >90% receptor blockade). Thus, whether specific bleeding avoidance strategies could facilitate further downward titration of platelet reactivity to minimize ischemic complications without incurring excessive bleeding risk is an area of active interest.

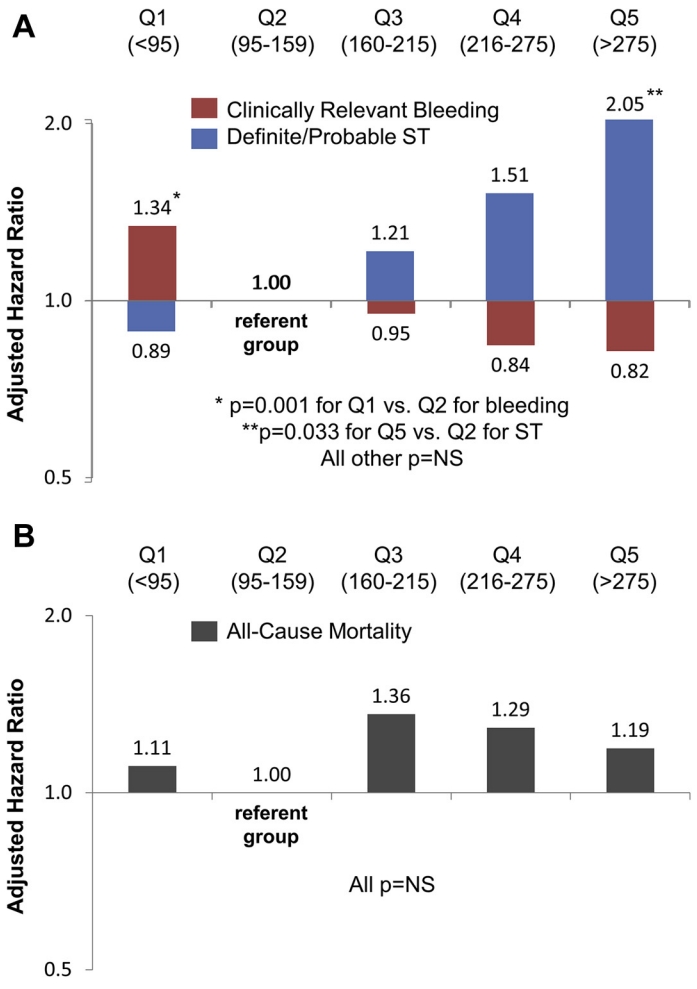
Conversely, whether targeting platelet inhibition to a pre-specified level or window of inhibition results in improved net clinical benefits in terms of overall patient outcomes remains to be proven in an adequately powered randomized trial. Even within the present cohort, the definition of net clinical benefit can be problematic. By simply combining the incidence of ischemic and bleeding outcomes, especially in the case of a significant discrepancy in the number of each event (e.g., bleeding events were 8-fold more common than ST events), pooling of events simply results in the greater frequency event

"dominating" the analyses. In multivariable analyses from the current dataset in which ST and bleeding were combined as a composite endpoint, the results largely mirror the models in which bleeding is the sole endpoint. Moreover, simply pooling event counts does not take into account the fact that the events themselves may be of differing clinical significance (e.g., an ST event may be worse for the patient than an access site bleed, depending upon the bleeding definition used). Thus, without being able to adequately "weigh" the (relative) offsetting risks of ST and bleeding, simply pooling the events can be misleading.

In this regard, the present study, which failed to demonstrate an independent relationship between PRU quintiles and all-cause mortality, suggests that such PRU targeting has a limited ability to impact overall survival even in a large cohort of studied patients. However, more subtle benefits may accrue from such a strategy, which may be particularly useful in patients at differential risks for ischemic and bleeding complications. For example, several precedent studies have demonstrated that PR monitoring may have utility to minimize bleeding risk for clopidogrel-treated patients scheduled to undergo surgery (25). Additionally, preliminary data from 300 ACS patients treated with prasugrel who were switched to clopidogrel if on-treatment PR was indeed too low demonstrated a lower rate of minor bleeding following the down-titration of antiplatelet therapy without an apparent increase in ischemic events (26). It is possible that titration of antiplatelet effect to a "therapeutic window" using platelet function testing to ensure that platelets are adequately inhibited to prevent ischemic complications but not overinhibited so as to predispose to excessive bleeding may be clinically useful. Further studies are required to demonstrate whether a broader implementation of this strategy will result in superior patient outcomes (and is time- and cost-effective) compared with standard "one size fits all" dosing.

ADAPT-DES is the first study large enough to apply multivariable modeling across PR subgroups and thus affords novel insights into not only the optimal PRU range to maximize the difference between ischemia and bleeding, but also to the expected net benefit on overall patient outcomes. In this regard, the present analysis is also notable in highlighting the differences in findings from unadjusted versus adjusted analyses. The fact that univariable analyses demonstrated greater mortality with increasing PRU suggests that this readily available test may be used as a biomarker to predict future risk (similar to more traditional risk factors such as advanced age and diabetes). However, the absence of an independent relationship between PRU and mortality suggests that currently available potent antiplatelet therapies capable of lowering PR would not be expected to reduce all-cause mortality, despite a potentially favorable effect on ST (notwithstanding non-platelet-related "off-target" effects of some of these agents) (18).

FIGURE 3 Adjusted HR of the 2-Year Rates of Definite/Probable ST, Clinically Relevant Bleeding, and Mortality Across PRU Quintiles



Multivariable adjusted hazard ratios (HR) of the 2-year rates of **(A)** definite/probable ST and clinically relevant bleeding, and **(B)** all-cause mortality across PRU quintiles, with the second quintile of PRU (PRU 95 to 159) as the referent category. Abbreviations as in Figure 1.

STUDY LIMITATIONS. Despite multivariable adjustment, it is possible that unmeasured confounders could explain some of the observed findings from the present nonrandomized study. Although ADAPT-DES

represents the largest series of patients examined with routine on-treatment PR testing and was powered to assess differences in low-frequency endpoints such as ST, the present analysis—in stratifying patients by quintiles of PRU to examine window effects—has less power to assess the relationship between PRU and clinical outcomes than either a continuous or dichotomous categorization of PR. Conversely, the use of discrete quantiles can be useful because it avoids assumptions of monotonicity or homogeneity of effect.

Additionally, because ADAPT-DES enrolled patients following successful PCI procedures, patients with PCI-related complications or unsuccessful stent procedures were not enrolled, resulting in lower event rates than had a truly unselected PCI population been studied. As with any secondary analysis, the results of this analysis need to be contextualized within individual patient scenarios. In a sense, it is likely too simplistic to think that a single best range of antiplatelet effect exists for all patients independent of individualized ischemic and bleeding risks. The present study additionally only assessed PR using a single assay; as such, it remains unclear how these specific findings may apply to other devices, or to patients treated with other (newer) antiplatelet agents. Finally, platelet reactivity has been shown to be a dynamic process over time, and the differential ability of baseline PRU (compared with change in PRU over time) to predict subsequent events is an area of active investigation.

CONCLUSIONS

In this large, prospective observational study of DES-treated patients, increasing PR on clopidogrel was associated with increasing 2-year rates of ST in a monotonic fashion, whereas bleeding risk was confined to patients in the lowest PR quintile (PRU <95). This observation suggests that suppression of ST while minimizing the risk of bleeding with greater $P2Y_{12}$ receptor platelet inhibition may be optimized in DES-treated patients within a therapeutic VerifyNow PRU window of moderately inhibited PRU. However, there was no demonstrable threshold effect of PRU for all-cause mortality in adjusted analyses, suggesting that targeting PR to a specific window would not be expected to substantially affect the overall rates of death.

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PERSPECTIVES

WHAT IS KNOWN? HPR has been associated with adverse ischemic events among patients undergoing PCI.

WHAT IS NEW? In this large multicenter registry study of 8,582 patients, HPR remained associated with adverse ischemic events among PCI patients, but low PR was associated with increased bleeding events, lending credence to the concept of an optimal therapeutic window of antiplatelet effect.

WHAT IS NEXT? Whether personalizing antiplatelet effects to balance the offsetting risks of ischemic and bleeding events can optimize overall outcomes for PCI patients remains to be shown prospectively, but there has been a renewed interest in this approach with the more widespread availability of more potent oral antiplatelet therapies, particularly in the context of the increasing complexity of current day PCI.

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KEY WORDS hemorrhage, platelets, stent(s), thrombosis

APPENDIX For a supplemental table, please see the online version of this article.