Stent Thrombosis Risk Over Time on the Basis of Clinical Presentation and Platelet Reactivity

Analysis From ADAPT-DES

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ABSTRACT

OBJECTIVES The aim of this study was to determine the risk period for increased stent thrombosis (ST) after percutaneous coronary intervention (PCI) in patients with acute coronary syndromes (ACS) and whether this increased risk is related to high platelet reactivity (HPR).

BACKGROUND ST risk after PCI is higher among patients with ACS than those with stable ischemic heart disease. When ST risk is highest in patients with ACS and how that is affected by HPR is unknown.

METHODS Using the ADAPT-DES (Assessment of Dual Antiplatelet Therapy With Drug-Eluting Stents) registry, ST rates during 2-year follow-up post-PCI with drug-eluting stents were compared among patients presenting with ACS (myocardial infarction [MI] or unstable angina) or stable ischemic heart disease (non-ACS). Landmark analyses were done at 30 days and 1 year post-PCI. Platelet reactivity on aspirin and clopidogrel post-PCI was assessed using VerifyNow assays.

RESULTS Of 8,582 patients, 2,063 presented with MI, 2,370 with unstable angina, and 4,149 with non-ACS. Incidence rates of HPR were 48.0%, 43.3%, and 39.8%, respectively (p < 0.001). Within the first 30 days post-PCI, patients presenting with MI had increased ST risk compared with patients with non-ACS (hazard ratio [HR]: 4.52; 95% confidence interval [CI]: 2.01 to 10.14; p < 0.001). After 30 days, relative ST risks were progressively lower and no longer significant between groups (31 days to 1 year post-PCI: HR: 1.97; 95% CI: 0.80 to 4.85; >1 year post-PCI: HR: 0.89; 95% CI: 0.27 to 2.92). The elevated ST risk in patients with MI within 30 days was largely confined to those with HPR on clopidogrel (HR: 5.77; 95% CI: 2.13 to 15.63; p < 0.001).

CONCLUSIONS Among patients undergoing PCI, rates of ST during 2-year follow-up were highest in those with MI and lowest in those with non-ACS. Increased ST risk in patients with MI was greatest in the first 30 days post-PCI and was observed predominantly among those with increased HPR on clopidogrel. These findings emphasize the importance of adequate P2Y$_{12}$ inhibition after MI, especially within the first 30 days after stent implantation. (J Am Coll Cardiol Intv 2021;■:■−■) © 2021 by the American College of Cardiology Foundation.

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ABBREVIATIONS AND ACRONYMS

ACS = acute coronary syndrome(s)

ARU = aspirin reaction units

DAPT = dual-antiplatelet therapy

DES = drug-eluting stent(s)

HPR = high platelet reactivity

MI = myocardial infarction

NSTEMI = non–ST-segment elevation myocardial infarction

PCI = percutaneous coronary intervention

PRU = P2Y$_{12}$ reaction units

ST = stent thrombosis

STEMI = ST-segment elevation myocardial infarction

UA = unstable angina

Stent thrombosis (ST) is an infrequent but clinically important complication of percutaneous coronary intervention (PCI) that is associated with high rates of myocardial infarction (MI) and death [1]. Patients presenting with acute coronary syndromes (ACS) have an increased risk for ST after PCI with drug-eluting stents (DES) compared with patients presenting with stable ischemic heart disease, with 30-day rates ranging from about 1% to 3% in patients with ACS compared with about 0.3% to 0.5% in those with stable ischemic heart disease [2-5]. The higher ST rates observed among patients with ACS are thought to be due at least in part to a more acute prothrombotic state, and previous studies have shown a correlation between high platelet reactivity (HPR) and ST [6-8].

Heightened platelet reactivity is frequently present in patients with ACS and in part underlies the rationale for the use of more potent antiplatelet therapies (and for a longer duration) in such patients [9,10]. Current guidelines recommend dual-antiplatelet therapy (DAPT) with a potent P2Y$_{12}$ receptor inhibitor and aspirin for 1 year post-PCI in patients presenting with ACS [11]; however, whether the increase in the risk for ST after PCI in patients presenting with ACS continues throughout this period is uncertain. In this regard potent platelet inhibitors can increase hemorrhagic complications, and post-PCI bleeding has been strongly associated with increased mortality [12-14]. Thus potent platelet inhibitors may be most useful when used in the period of highest ischemic risk.

In the present study we sought to determine the temporal risk for ST in patients with and without ACS during 2-year follow-up after PCI from the large, prospective, multicenter ADAPT-DES (Assessment of Dual Antiplatelet Therapy With Drug-Eluting Stents) registry. In addition to assessing ST risk over time on the basis of clinical presentation, we also sought to correlate ST risk with platelet reactivity in patients treated with aspirin and clopidogrel.

METHODS

The study design of ADAPT-DES has been described previously [8]. The study was approved by the Institutional Review Board of each participating center, and all patients enrolled provided written informed consent.

Briefly, ADAPT-DES was an international, large-scale, multicenter registry designed to assess platelet reactivity after successful PCI with DES in prospectively enrolled patients treated with aspirin and clopidogrel. A total of 11 centers in the United States and Germany participated in enrollment. Inclusion criteria were broad, consisting of successful treatment with at least 1 DES approved by the U.S. Food and Drug Administration and adequate loading with aspirin and clopidogrel. There were no clinical or anatomic exclusion criteria. The only major exclusion criteria were the occurrence of a major complication during the procedure or before platelet function testing and if bypass surgery was planned after PCI. All patients were treated with aspirin indefinitely, and clopidogrel was recommended for at least 1 year post-PCI. Clinical follow-up occurred at 30 days, 1 year, and 2 years.

The present study is a post hoc analysis, and patients were divided into 3 groups on the basis of initial clinical presentation: ACS with MI (ST-segment elevation MI [STEMI] or non–ST-segment elevation MI [NSTEMI]), ACS without MI (unstable angina [UA]), and non-ACS (stable ischemic heart disease). Further stratification of patients presenting with MI into those with STEMI versus NSTEMI was performed for sensitivity analyses. The primary endpoint was definite or probable ST according to the Academic Research Consortium definitions [15]. Timing of ST was defined as early (≤30 days after PCI), late (31 days to 1 year after PCI), or very late (>1 year after PCI).

PROCEDURES. Platelet reactivity was assessed in all patients post-PCI using the VerifyNow aspirin and P2Y$_{12}$ assays (Accumetrics, San Diego, California). Aspirin was given as either a non-enteric-coated oral dose of 300 mg or more at least 6 hours prior to PCI or a chewed dose of 324 mg or intravenous dose of

TABLE 1 Baseline Patient Characteristics Categorized by Clinical Presentation

	Myocardial Infarction (n = 2,063)	Unstable Angina (n = 2,370)	Non-ACS (n = 4,149)	p Value
Age, yrs	61.6 ± 11.7	63.3 ± 11.0	64.8 ± 10.2	<0.001
Female	547 (26.5)	666 (28.1)	1,012 (24.4)	0.02
Body mass index, kg/m^2	29.3 ± 5.8	29.9 ± 5.9	29.3 ± 5.5	<0.001
Hypertension	1,304 (63.2)	1,943 (82.5)	3,572 (86.1)	<0.001
Hyperlipidemia	992 (48.1)	1,856 (78.3)	3,535 (85.2)	<0.001
Smoking	1,273 (61.7)	1,375 (58.0)	2,182 (52.6)	<0.001
Diabetes mellitus	538 (26.1)	789 (33.3)	1,452 (35.0)	<0.001
History of peripheral arterial disease	163 (7.9)	242 (10.2)	473 (11.4)	<0.001
History of congestive heart failure	124 (6.0)	168 (7.1)	407 (9.8)	<0.001
Prior myocardial infarction (>7 days)	380 (18.4)	675 (28.5)	1,108 (26.7)	<0.001
Prior coronary artery bypass grafting	223 (10.8)	512 (21.6)	734 (17.7)	<0.001
Prior PCI	483 (23.4)	1,185 (50.0)	2,012 (48.5)	<0.001
History of renal insufficiency	159 (7.7)	159 (6.7)	344 (8.3)	0.22
LVEF, %	52.1 ± 13.3	55.5 ± 10.7	56.3 ± 12.6	<0.001

Values are mean ± SD or n (%).

ACS = acute coronary syndromes; LVEF = left ventricular ejection fraction; PCI = percutaneous coronary intervention.

250 mg or more at least 30 min prior to PCI. Clopidogrel was given as a dose of 600 mg at least 6 hours before VerifyNow testing, a dose of 300 mg at least 12 hours before VerifyNow testing, or a dose of 75 mg or more for at least 5 days before VerifyNow testing. HPR on clopidogrel was defined as >208 $P2Y_{12}$ reaction units (PRU) [16-19]. HPR on aspirin was defined as ≥550 aspirin reaction units (ARU) [20]. Research coordinators performed the VerifyNow testing, and results were entered into a computerized database without informing the treating physicians or affecting management decisions. An independent clinical events committee masked to VerifyNow results adjudicated all clinical events.

FIGURE 1 Incidence of 2-Year Stent Thrombosis Stratified by Clinical Presentation
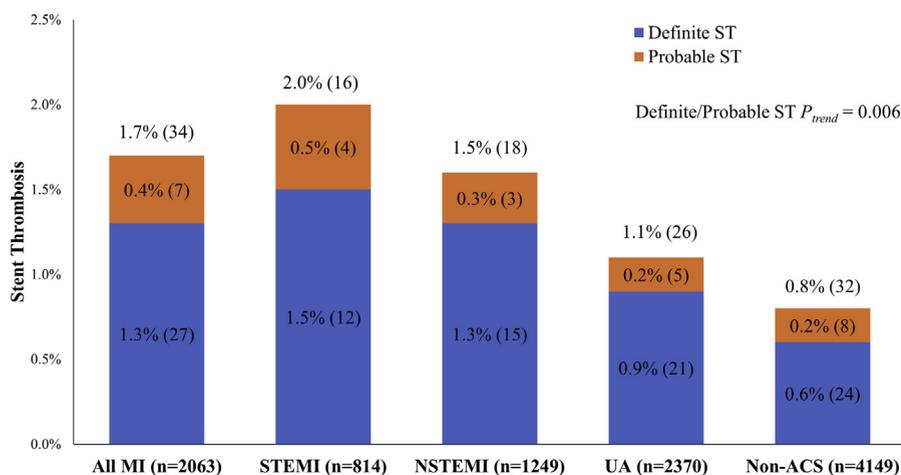
Patients presenting with acute coronary syndromes (ACS) had a significantly higher incidence of stent thrombosis (ST) than those presenting with stable ischemic heart disease (non-ACS). Patients presenting with myocardial infarction (MI), in particular ST-segment elevation MI (STEMI), had the highest incidence of ST. Event rates are Kaplan-Meier estimates (percentage [number of events]). NSTEMI = non–ST-segment elevation myocardial infarction; UA = unstable angina.

TABLE 2 Risk for Stent Thrombosis Categorized by Clinical Presentation and Timing of Events

	Event Rate		Univariate Model		Multivariate Model	
Group 1 vs. Group 2	Group 1	Group 2	HR (95% CI)	p Value	HR (95% CI)	p Value
All stent thrombosis (0–2 yrs)						
MI vs. non-ACS	1.7 (34)	0.8 (32)	2.17 (1.34–3.51)	0.002	2.38 (1.43–3.94)	<0.001
UA vs. non-ACS	1.1 (26)	0.8 (32)	1.42 (0.85–2.39)	0.18	1.33 (0.79–2.25)	0.28
Early stent thrombosis (0–30 days)						
MI versus non-ACS	1.0 (20)	0.2 (9)	4.50 (2.05–9.87)	<0.001	4.52 (2.01–10.14)	<0.001
UA versus non-ACS	0.4 (10)	0.2 (9)	1.95 (0.79–4.79)	0.15	1.95 (0.79–4.83)	0.15
Late stent thrombosis (31 days to 1 year)						
MI versus non-ACS	0.5 (10)	0.3 (12)	1.70 (0.73–3.93)	0.22	1.97 (0.80–4.85)	0.14
UA versus non-ACS	0.5 (11)	0.3 (12)	1.61 (0.71–3.64)	0.26	1.40 (0.61–3.2)	0.42
Very late stent thrombosis (1–2 years)						
MI versus non-ACS	0.2 (4)	0.3 (11)	0.74 (0.24–2.33)	0.61	0.89 (0.27–2.92)	0.85
UA versus non-ACS	0.2 (5)	0.3 (11)	0.80 (0.28–2.29)	0.67	0.70 (0.24–2.03)	0.51

Event rates are Kaplan-Meier estimated % (n).
ACS = acute coronary syndromes; CI = confidence interval; HR = hazard ratio; MI = myocardial infarction; UA = unstable angina.

STATISTICAL ANALYSIS. Categorical variables were compared between groups using the chi-square or Fisher exact test as appropriate. Continuous variables are presented as mean ± SD and were compared between groups using Student's *t*-test or analysis of variance. Time-to-event data are presented as Kaplan-Meier estimates and were compared between groups using the log-rank test or as hazard ratios derived from univariate and multivariate Cox proportional hazards regression models. Landmark analyses were used to determine time-to-event rates from 0 to 30 days, 30 days to 1 year, and 1 year to 2 years after PCI. Multivariate models were adjusted for the following covariates: age, diabetes mellitus, cigarette smoking status, history of previous PCI, history of previous surgical coronary artery bypass grafting, generation of DES implanted, number of stents implanted, and total stent length.

Whether HPR modified the effect of clinical presentation on ST risk was examined by conducting separate analyses in patients with and without HPR with the inclusion of an interaction term between clinical presentation and HPR in the multivariate models. The extent to which HPR was associated with ST risk according to MI presentation was explored by comparing the estimated effect sizes for MI and UA versus non-ACS in 2 separate multivariable Cox models, one without HPR as a covariate (total effect of clinical presentation) and one with HPR as a covariate (effect of clinical presentation after accounting for HPR). The p values for trend for categorical variables were compared using the chi-square test or Fisher exact test and for continuous variables were compared using the linear regression test for trend. Time-to-event data were compared using the log-rank test for trend. A p value of <0.05 was considered to indicate statistical significance. Statistical analyses were performed using SAS version 9.1.3 (SAS Institute, Cary, North Carolina).

RESULTS

PATIENT AND PROCEDURAL CHARACTERISTICS. A total of 8,665 patients were prospectively enrolled after successful DES placement between January 7, 2008, and September 16, 2010. After excluding 82 patients who underwent platelet function testing prior to the protocol-required glycoprotein IIb/IIIa inhibitor washout period and 1 patient who was inadvertently enrolled twice, the final study cohort consisted of 8,582 patients. Of these, 2,063 patients (24.0%) presented with MI (including 814 [9.5%] with STEMI and 1,249 [14.6%] with NSTEMI), 2,370 patients (27.6%) presented with UA, and 4,149 patients (48.3%) presented with non-ACS. Median follow-up time was 729 days (interquartile range: 703 to 742 days) (Supplemental Table 1).

The mean patient age was 63.6 ± 10.9 years, and 25.9% of patients were women. When grouped by clinical presentation, patients presenting with ACS (MI or UA) tended to be younger, were more likely to be female, tended to have fewer comorbidities, and had lower baseline left ventricular ejection fractions than patients with non-ACS presentations. Patients presenting with MI were also less likely to have prior MI, coronary artery bypass grafting, or PCI (Table 1).

FIGURE 2 **Risk of Stent Thrombosis Stratified by Clinical Presentation Over Time**

Landmark analysis was done at 30 days and 1 year after percutaneous coronary intervention (PCI). Within the first 30 days post-PCI, patients presenting with MI had a higher risk for ST than patients presenting with UA, and patients presenting with stable ischemic heart disease (non-ACS) had the lowest risk for ST. Beyond 30 days, no significant difference in ST risk was observed between the different clinical presentation groups. P values were obtained using the log-rank test. Abbreviations as in **Figure 1**.

The majority of patients had 1 coronary vessel treated with a stent, and more than 70% of patients received second-generation DES (the majority of which were everolimus-eluting stents) (Supplemental Table 2). Patients presenting with MI or UA tended to have fewer lesions and vessels treated and fewer stents placed.

INCIDENCE AND TIMING OF ST. A total of 92 patients (1.1%) had definite or probable ST within 2 years, including 39 (0.5%) with early ST, 33 (0.4%) with late ST, and 20 (0.2%) with very late ST. As shown in **Figure 1**, patients presenting with MI had the highest 2-year rates of ST (1.7%); ST rates were intermediate (1.1%) in those with UA and lowest (0.8%) in those with non-ACS. Among those with MI, ST within 2 years occurred in 2.0% with STEMI and 1.5% with NSTEMI.

Table 2 shows rates of ST stratified by clinical syndrome and timing of event. By multivariate analysis, patients presenting with MI had a 2.38-fold increase in risk for ST during the 2-year post-PCI follow-up period compared with patients presenting with non-ACS. This increase in ST risk was largely confined to the first 30 days after PCI (adjusted hazard ratio: 4.52). The rates of ST within the first 30 days were particularly high in patients with STEMI (Supplemental Table 3). After the first 30 days, the differences in ST risk between the groups were

attenuated (**Figure 2**). There were no significant differences in ST risk between UA and non-ACS in any time period.

ASSOCIATION BETWEEN HPR AND RISK FOR ST. Mean PRU levels and rates of HPR on clopidogrel were highest in patients with MI and lowest in those with non-ACS (**Table 3**). Conversely, ARU levels were independent of presenting clinical syndrome, and HPR on aspirin was infrequent in all groups.

Among patients with HPR on clopidogrel, those presenting with MI had an increased 2-year risk for ST compared with patients with non-ACS (Supplemental Table 3). The greatest risk for ST was observed among patients with both HPR and MI (**Central Illustration**). A

TABLE 3 **Platelet Reactivity Categorized by Clinical Presentation**

	Myocardial Infarction (n = 2,063)	Unstable Angina (n = 2,370)	Non-ACS (n = 4,149)	p Value for Trend
Platelet reactivity to clopidogrel				
PRU	198.8 ± 95.4	189.3 ± 96.9	181.8 ± 96.9	<0.001
HPR (PRU >208)	990 (48.0)	1,026 (43.3)	1,651 (39.8)	<0.001
Platelet reactivity to aspirin				
ARU	418.6 ± 51.9	420.3 ± 56.3	418.9 ± 56.3	0.98
HPR (ARU ≥550)	91 (4.4)	149 (6.3)	241 (5.8)	0.02

Values are mean ± SD or n (%).

ACS = acute coronary syndromes; ARU = aspirin reaction units; HPR = high platelet reactivity; PRU = $P2Y_{12}$ reaction units.

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CENTRAL ILLUSTRATION Stent Thrombosis Risk in Patients With and Without High Platelet Reactivity Stratified by the Presence of Myocardial Infarction

A ADAPT-DES Stent Thrombosis Over Time, N = 8,582
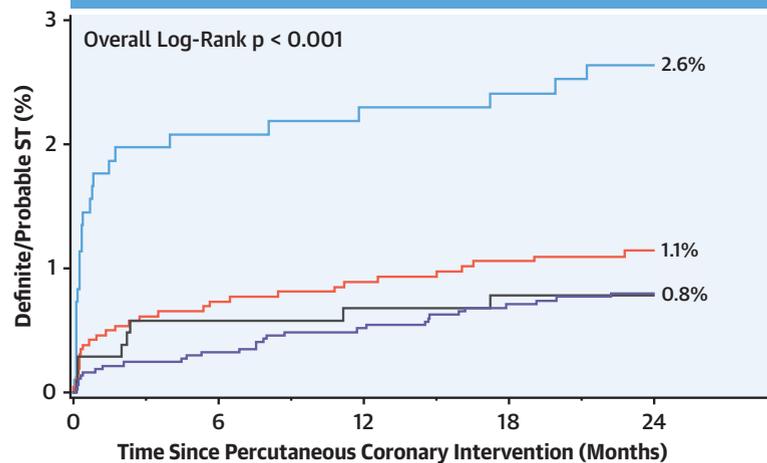
No. at risk:					
HPR/MI	975	917	893	864	396
HPR/No MI	2,634	2,534	2,458	2,354	1,244
No HPR/MI	1,058	1,016	983	955	475
No HPR/No MI	3,781	3,681	3,605	3,480	1,901

B ADAPT-DES Stent Thrombosis Over Time, N = 8,582
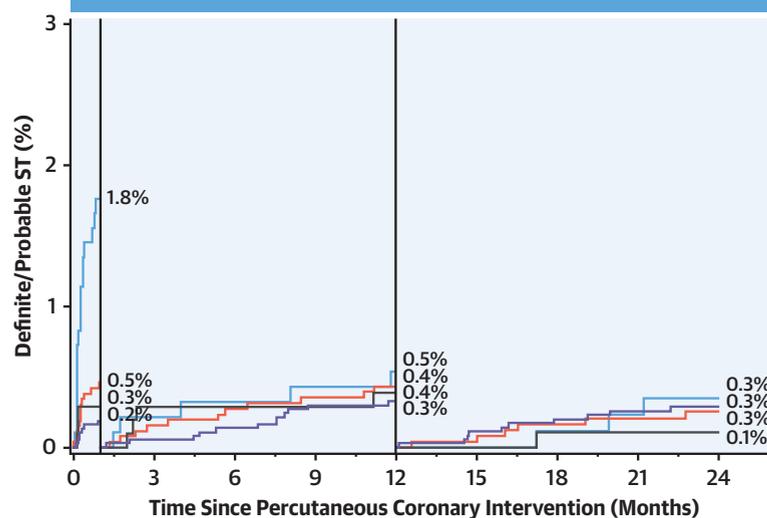
No. at risk:					
HPR/MI	3,781	3,683	3,617	3,491	1,907
HPR/No MI	1,058	1,018	984	959	477
No HPR/MI	2,634	2,542	2,473	2,370	1,249
No HPR/No MI	975	928	908	879	397

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(A) Patients with high platelet reactivity (HPR) and presenting with myocardial infarction (MI) had a higher risk for stent thrombosis (ST) than patients with HPR with non-MI presentations and patients without HPR. **(B)** Landmark analyses done at 30 days and 1 year after percutaneous coronary intervention (PCI) showed that within the first 30 days post-PCI, patients with HPR presenting with MI had a higher risk for ST than patients with HPR with non-MI presentations and patients without HPR (log-rank p < 0.001). Beyond 30 days, no significant difference in ST risk was observed between patients with or without HPR regardless of MI presentation (log-rank p [31 days to 1 year] = 0.79, log-rank p [1 to 2 years] = 0.75).

FIGURE 3 Stent Thrombosis Risk in Patients With and Without High Platelet Reactivity According to Clinical Presentation
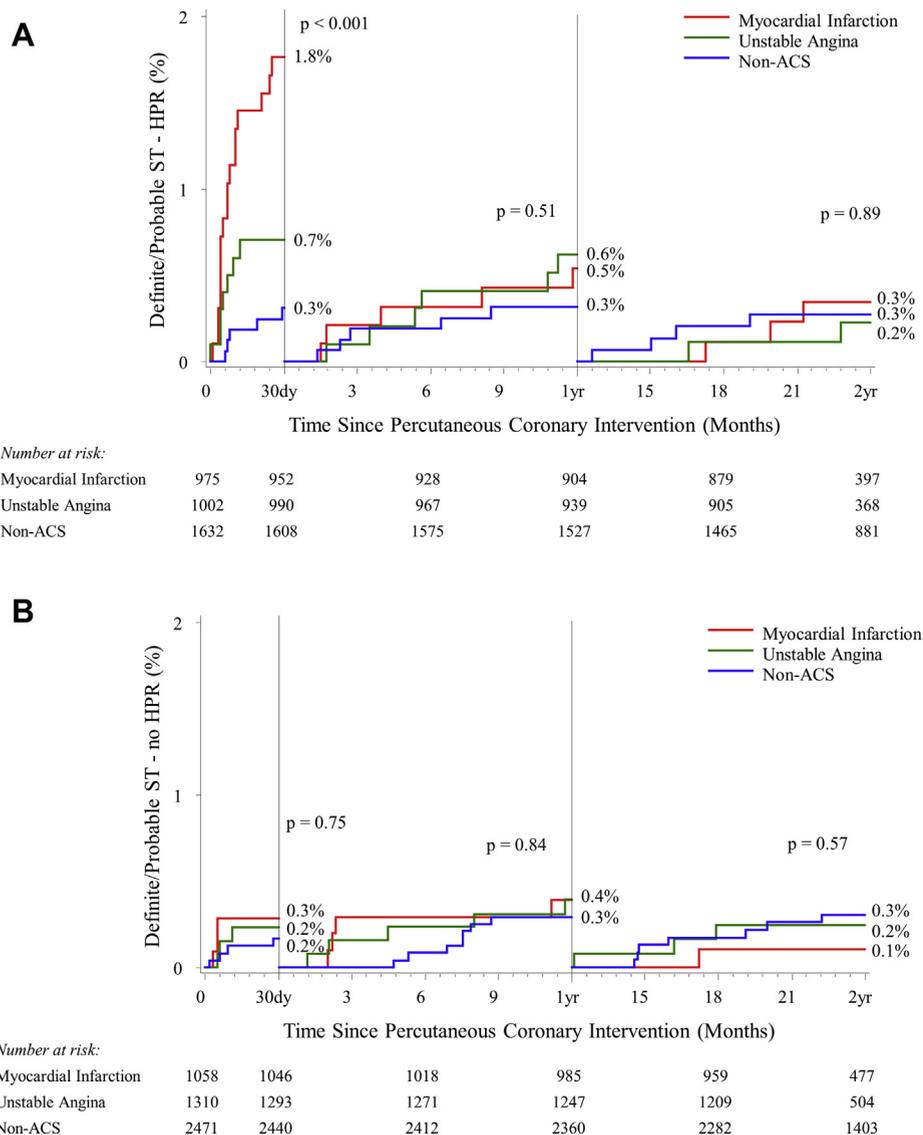
Landmark analyses were done at 30 days and 1 year post-PCI in patients with and without high platelet reactivity (HPR). **(A)** In patients with HPR, patients presenting with MI had a higher 30-day risk for ST than patients presenting with UA, and patients presenting with stable ischemic heart disease (non-ACS) had the lowest 30-day risk for stent thrombosis (ST). Beyond 30 days, no significant difference in ST risk was observed between the different clinical presentation groups. **(B)** In patients without HPR, no significant differences in ST risk were found between the different clinical presentation groups for any time period. The p values were obtained using the log-rank test. Abbreviations as in **Figure 1 and 2**.

significant interaction was present between clinical presentation and HPR status for the 2-year risk fir ST risk (Supplemental Figure 1). However, the increased ST risk in patients with MI was confined largely to the first 30 days after PCI (Central Illustration), with no differences in ST risk between the different groups present after 30 days (Figure 3A). In patients without HPR, no significant differences in ST risk were

present between the groups in any time period (Figure 3B, Supplemental Table 4).

DISCUSSION

To our knowledge the present study is the first to examine the risk for ST after PCI in different time periods as a function of HPR and acuity of

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presentation. The principal findings of this study are as follows: 1) a gradient of ST risk during 2-year follow-up after PCI was present according to the initial acuity of clinical presentation, ranging from STEMI (highest ST risk) to NSTEMI to UA to non-ACS (lowest ST risk); 2) the increased risk for ST in patients with ACS was greatest in the first 30 days after PCI; and 3) this increased risk for early ST was confined largely to patients with increased HPR on clopidogrel. Notably, among patients without HPR, there was no significant association between clinical presentation and ST risk in any period.

PLATELET REACTIVITY AND P2Y$_{12}$ INHIBITOR THERAPY. In the large-scale, prospective, all-comers ADAPT-DES study, patients with higher acuity clinical presentations were more likely to have HPR on clopidogrel on the basis of VerifyNow PRU testing. ST rates during 2-year follow-up after PCI were also higher in patients with ACS (particularly those with MI) compared with non-ACS, a risk that was confined largely to those patients with MI who also had HPR on clopidogrel. Finally, the incremental ST risks of MI presentation and HPR on clopidogrel were limited to the first 30 days after stent implantation. These findings, in particular our finding pertaining to the time period of highest ST risk, extend the results of previous studies examining the rates and implications of HPR after PCI (8,21-24). The present results provide mechanistic support for large-scale trials that have shown the potent P2Y$_{12}$ inhibitors prasugrel and ticagrelor to be superior to clopidogrel in reducing ST and ischemic complications for up to 1 year in patients with ACS (9,10). However, in the present all-comers study, the heightened risk for ST in patients with ACS was most evident within the first 30 days after PCI, especially among patients with HPR, suggesting that this is the greatest period of need to ensure adequate platelet P2Y$_{12}$ receptor inhibition. Conversely, no difference in early or late ST risk according to clinical presentation was found for patients with HPR on aspirin on the basis of VerifyNow ARU testing, which is also consistent with prior data (8,16-19,25).

Prior studies have examined the use of platelet reactivity testing to guide DAPT use, particularly for patients with increased risk for ST or bleeding. In the TROPICAL-ACS (Testing Responsiveness to Platelet Inhibition on Chronic Antiplatelet Treatment for Acute Coronary Syndromes Trial) trial, initial prasugrel use followed by deescalation to clopidogrel in patients without HPR on platelet function testing was noninferior to standard 12-month prasugrel therapy after PCI in patients with ACS (26). Other randomized trials, however, have not shown benefits of using platelet reactivity to guide pharmacotherapy (27-29). It should be noted, though, that these trials enrolled predominantly patients presenting without ACS. There are numerous factors that contribute to HPR, both genetic and nongenetic, and platelet reactivity changes over time, further complicating the application of HPR data in clinical decision making (30-32). The POPular Genetics trial found that the use of CYP2C19 genotype-guided testing to select P2Y$_{12}$ inhibitor therapy was noninferior to standard treatment with ticagrelor or prasugrel at 12 months with respect to ST and was superior with respect to bleeding events (33). A risk score that incorporates both clinical and genotype characteristics was developed to predict HPR status in patients on clopidogrel and was also found to correlate with adverse outcomes (34). In the TAILOR-PCI (Tailored Antiplatelet Therapy Following PCI) trial, the largest randomized trial to date to test a genotype-guided antiplatelet agent section strategy (n = 5,302 patients), use of ticagrelor in patients with CYPC219 *2 or *3 loss-of-function alleles compared with continuing clopidogrel did not reduce the primary composite ischemic endpoint, of death, MI, stroke, ST, or recurrent ischemia at 12 months, although a reduction in recurrent events was observed (hazard ratio: 0.60; p = 0.011) (35). Consistent with our findings, a post hoc analysis from TAILOR-PCI revealed that the greatest reduction of adverse events with CYP2C19 status–guided therapy was present within the first 3 months.

TIMING OF INCREASED ST RISK. The monotonic increase in ST risk from non-ACS to UA to NSTEMI to STEMI in the present study is striking and is concordant with lower levels of platelet inhibition to clopidogrel along this continuum of risk. In addition, the finding that the increased ST risk was evident primarily within the first 30 days after PCI is notable, further emphasizing the therapeutic importance of higher potency P2Y$_{12}$ inhibition in the subacute phase after PCI in ACS. The potential for safely reducing the intensity of DAPT beyond this initial high-risk period (as might be inferred from the present study) is consistent with recent reports (36-43). Furthermore, data from trials enrolling patients at high bleeding risk have suggested that shorter durations (1 or 3 months) of DAPT may be safe (39,43). Our data are mechanistically supportive of recent trends in deescalating the duration or intensity of DAPT after 30 days, particularly in those without MI, but also support large-scale randomized trials examining the safety and effectiveness of this practice in MI (37,40).

STUDY LIMITATIONS. The present study was a post hoc analysis testing multiple comparisons. As such our findings should be considered hypothesis generating. In addition, only patients with successful and uncomplicated PCI and DES placement were included in ADAPT-DES. The risk for ST and reliance on potent DAPT across the spectrum of clinical presentations may be greater in patients with procedural complications. Although multivariate and interaction analyses confirmed that the heightened ST risk on the basis of clinical presentation within the first 30 days was modified by the presence of HPR, given the modest number of events, we cannot exclude increased ST risk after 30 days in patients with HPR on clopidogrel. Also, it is recommended that patients presenting with ACS be treated with more potent $P2Y_{12}$ inhibitors, such as ticagrelor and prasugrel. Thus large-scale, adequately powered randomized trials are required to determine whether a deescalation strategy of potent $P2Y_{12}$ inhibition after 30 days has a favorable risk-benefit profile. In this regard, ticagrelor therapy was associated with a reduction in cardiac death between 30 days and 1 year compared with clopidogrel in patients with ACS (10). Finally, PRU was measured at baseline only; we therefore could not account for changes in PRU over time.

CONCLUSIONS

Among patients undergoing successful DES implantation, the 2-year risk for ST progressively increases according to the presenting clinical syndrome acuity. The increased ST risk in patients with ACS was greatest within the first 30 days post-PCI and was confined largely to patients with HPR on clopidogrel. These findings are consistent with the importance of ensuring adequate $P2Y_{12}$ inhibition within the first 30 days after DES treatment in patients with MI (either with the use of potent $P2Y_{12}$ inhibitors or possibly clopidogrel with platelet function or genotype testing) and are thought provoking for deescalating DAPT therapy thereafter.

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PERSPECTIVES

WHAT IS KNOWN? ST risk after PCI is higher among patients with ACS than those with stable ischemic heart disease. When ST risk is highest in patients with ACS and how that is affected by HPR, however, are unknown.

WHAT IS NEW? A gradient of ST risk during 2-year follow-up after PCI was present according to the initial acuity of clinical presentation, from STEMI (highest ST risk) to NSTEMI to UA to non-ACS (lowest ST risk).

Increased ST risk in patients with MI was greatest in the first 30 days post-PCI and was observed predominantly among those with increased HPR on clopidogrel.

WHAT IS NEXT? These findings emphasize the importance of adequate $P2Y_{12}$ inhibition after MI, especially within the first 30 days after stent implantation, and are thought provoking for deescalating DAPT therapy.

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KEY WORDS acute coronary syndromes, antiplatelet therapy, platelet reactivity, stent thrombosis

APPENDIX For supplemental tables and a figure, please see the online version of this paper.