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Impact of Aspirin and Clopidogrel Hyporesponsiveness in Patients Treated With Drug-Eluting Stents

2-Year Results of a Prospective, Multicenter Registry Study

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ABSTRACT

OBJECTIVES In this analysis of 2-year outcomes in the ADAPT-DES (Assessment of Dual AntiPlatelet Therapy with Drug-Eluting Stents) study, the authors sought to examine the independent associations between platelet reactivity to both aspirin and clopidogrel and subsequent outcomes.

BACKGROUND The relationship between platelet reactivity and long-term adverse events following implantation of drug-eluting stents (DES) has been incompletely characterized.

METHODS The ADAPT-DES study was a multicenter registry of patients undergoing routine platelet function testing following percutaneous coronary intervention with DES. The primary study endpoint was definite or probable stent thrombosis (ST); other endpoints were all-cause mortality, myocardial infarction, and clinically relevant bleeding.

RESULTS A total of 8,582 patients were enrolled between 2008 and 2010; 46.3% of patients were on dual antiplatelet therapy at 2 years without discontinuation. At 2 years, definite or probable ST occurred in 92 patients (1.07%). In patients treated with dual antiplatelet therapy continuously for 2 years, high platelet reactivity on clopidogrel was independently associated with definite or probable ST (adjusted hazard ratio [HR]: 2.16; 95% confidence interval [CI]: 1.27 to 3.67; p = 0.003), myocardial infarction (adjusted HR: 1.35; 95% CI: 1.05 to 1.74; p = 0.02), freedom from clinically relevant bleeding (adjusted HR: 0.74; 95% CI: 0.62 to 0.90; p = 0.002), and all-cause mortality (adjusted HR: 1.36; 95% CI: 1.01 to 1.85; p = 0.04). Between years 1 and 2, high platelet reactivity was not associated with the very late ST and in patients on aspirin monotherapy, aspirin hyporesponsiveness was not associated with adverse outcomes.

CONCLUSIONS The present study confirms the strong relationship of high platelet reactivity on clopidogrel to 2-year ischemic and bleeding outcomes after DES. The majority of stent-related events occurred within the first year.
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ABBREVIATIONS AND ACRONYMS

ADP = adenosine diphosphate

ARU = aspirin reaction units

ASA = aspirin

CI = confidence interval

DAPT = dual antiplatelet therapy

DES = drug-eluting stent(s)

HPR = high platelet reactivity

HR = hazard ratio

MI = myocardial infarction

PCI = percutaneous coronary intervention

PRU = $P2Y_{12}$ reaction units

ST = stent thrombosis

Stent thrombosis (ST) occurring after percutaneous coronary intervention (PCI) with drug-eluting stents (DES) is associated with high rates of myocardial infarction (MI) and death (1). Dual antiplatelet therapy (DAPT) with aspirin (ASA) and an adenosine diphosphate (ADP) receptor inhibitor is currently recommended for 6 months to 1 year in patients at low risk for bleeding, with indefinite continuation of ASA alone (2,3). Although second-generation DES have reduced the risk of early, late, and very late ST, an ongoing risk of very late ST in certain patient subsets is present which may prompt long-term DAPT usage in selected patients (4–6). The role of chronic DAPT beyond 1 year remains controversial, with reductions in ischemic risk needing to be weighed against increases in bleeding (6–12).

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Whether ASA resistance is importantly related to ischemic events, particularly in patients treated with ASA as monotherapy beyond 1 year, remains incompletely characterized (13–16). Moreover, whereas residual high platelet reactivity (HPR) on clopidogrel has been clearly demonstrated to be a significant risk factor for short-term adverse outcomes after DES (17–20), whether HPR contributes to adverse outcomes beyond 1 year has not been examined. In this regard the highly variable pharmacologic response to clopidogrel due to a variety of genetic and clinical factors that themselves may be independent prognostic predictors introduces the need to control for confounding variables. We previously reported from the large-scale, prospective, multicenter ADAPT-DES (Assessment of Dual Anti-Platelet Therapy with Drug-Eluting Stents) study that HPR on clopidogrel was strongly related to ST and MI and inversely related to bleeding at 1 year after successful PCI with DES (20). In the ADAPT-DES study, patients were additionally followed to 2 years with the aim of testing whether ASA hyporesponsiveness during a phase of planned clopidogrel discontinuation (ASA monotherapy phase) between years 1 and 2 would be associated with ST or other adverse outcomes. In addition, because many patients remain on DAPT between years 1 and 2, we sought to further examine the impact of clopidogrel hyporesponsiveness measured at the time of PCI and outcomes during this time period among patients remaining on DAPT.

METHODS

The ADAPT-DES study was a prospective, multicenter registry designed to determine the relationship between platelet reactivity and subsequent clinical

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events in patients with coronary artery disease treated with ASA and clopidogrel after successful DES implantation. The study design, procedures, statistical analysis, and 1-year results have been previously reported (20). To summarize, 8,582 consecutive patients who were successfully treated with 1 or more approved DES at 9 U.S. and 2 German sites and who were adequately loaded with ASA and clopidogrel were enrolled in the study. Consecutive patients were enrolled regardless of clinical risk or angiographic complexity. The only exclusion criteria were unsuccessful stenting, a major complication either during the procedure or before platelet testing, planned bypass surgery after stenting, or significant anemia preventing accurate measurement of platelet reactivity. Platelet reactivity was assessed after successful PCI and after an adequate wash-in period to ensure full antiplatelet effect (20) using the VerifyNow Aspirin, $P2Y_{12}$, and IIb/IIIa assays (Accumetrics, San Diego, California). Following PCI, ASA was recommended indefinitely, and clopidogrel for at least 1 year. Decisions regarding continuation of DAPT were at the discretion of the primary treating physicians. Clinical follow-up was scheduled at 30 days, 1 year, and 2 years. We defined HPR for this study using previously defined and widely accepted cutpoints (for the $P2Y_{12}$ assay: $P2Y_{12}$ reaction units [PRU] >208; for the ASA assay: aspirin reaction units [ARU] >550).

DEFINITIONS AND ENDPOINTS. Detailed endpoint definitions have been previously reported (20). The primary endpoint was definite or probable ST according to the Academic Research Consortium criteria. Death was classified as cardiac or noncardiac as specified by Academic Research Consortium criteria. MI was defined as the presence of clinical or electrocardiographic changes consistent with MI in the setting of elevated cardiac biomarkers. Major adverse cardiac events (MACE) were classified as cumulative incidence of cardiac death, MI, or definite or probable ST. An independent clinical events committee adjudicated all deaths, MI, and ST events using original source documents. Clinically relevant bleeding was defined as the occurrence of any of the following: a Thrombosis In Myocardial Infarction major or minor bleed, a Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries bleed, an ACUITY (Acute Catheterization and Urgent Intervention Triage Strategy) trial bleed, or any post-discharge bleeding event requiring medical attention.

STATISTICAL METHODS. Statistical comparisons of categorical variables were performed with the chi-square or Fisher exact test, as appropriate. Continuous variables were compared using the Student *t* test and are presented as mean ± SD. Time-to-event data were compared with log-rank tests and are presented as Kaplan-Meier estimates. Landmark analyses were performed for events occurring between years 1 and 2 in 2 patient cohorts, those who remained event free at 1 year and were on ASA alone as monotherapy and those who remained on DAPT between 1 and 2 years or until an event occurred. To avoid confounding by intermittent usage of antiplatelet agents, patients in both landmark cohorts consisted only of patients who remained on ASA or DAPT daily without discontinuation (or until an event occurred). Patients who had an event between years 1 and 2 were defined by the therapy they were on at the time of the event; for example, if DAPT was discontinued between years 1 and 2 and a patient remained on ASA alone until the time an event occurred, after which DAPT was reinstituted, the patient was included in the ASA monotherapy cohort.

To identify independent predictors of outcomes, HPR plus other baseline variables deemed clinically relevant from prior studies were entered into multivariable Cox proportional hazards regression models for every event type and then further adjusted for the propensity for HPR. All p values were 2-tailed, and a p value of 0.05 was considered to be significant. Statistical analyses were performed using SAS version 9.2 (SAS Institute, Cary, North Carolina).

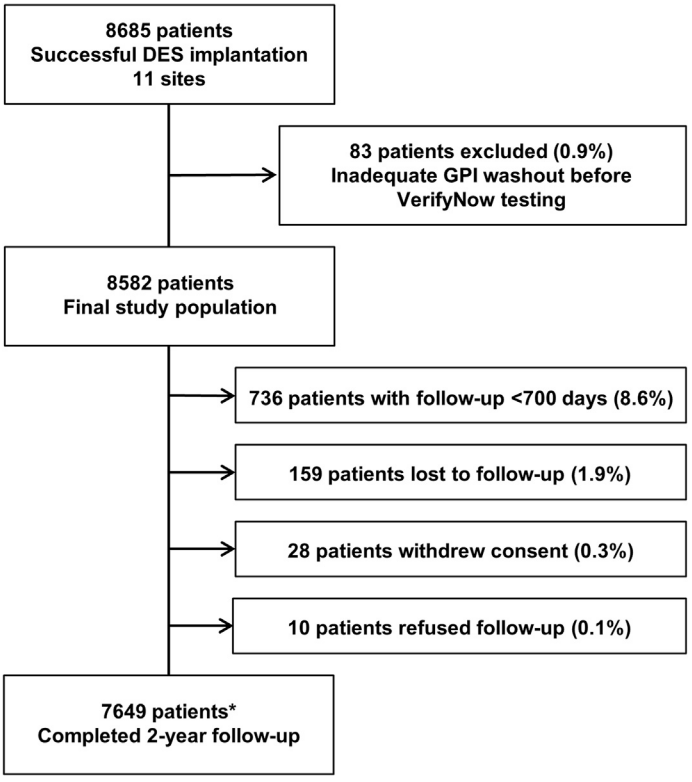
RESULTS

PATIENTS, PLATELET FUNCTION, AND ANTIPLATELET AGENT ADHERENCE. Between January 7, 2008, and September 16, 2010, 8,582 patients were prospectively enrolled at 11 hospitals in the United States and Germany. Valid measurements were obtained in 8,526 (99.3%) patients for VerifyNow Aspirin and 8,448 (98.4%) patients for VerifyNow $P2Y_{12}$. The mean ARU was 419 ± 55 and the mean PRU was 188 ± 97. A total of 478 (5.6%) patients had HPR on ASA according to the pre-specified cutoff of ARU >550, and a total of 3,609 (42.7%) patients had HPR to clopidogrel according to the pre-specified cutoff of PRU >208.

The study flow diagram to 2-year follow-up is shown in **Figure 1**. Follow-up was complete at 2 years in 89.1% of enrolled patients (7,649 of 8,582), including 316 patients who died (3.7%). An additional 8.6% (736 of 8,582) had early follow-up (<700 days) and are included in the 2-year analysis. A total of 1.9% patients (159 of 8,582) were lost to follow-up, and the remainder (0.4%, 38 of 8,582) withdrew consent or refused further follow-up.

Antiplatelet administration throughout 2 years is shown in **Table 1**. ASA was prescribed at discharge in

FIGURE 1 Study Flow Diagram



All-comers patients consecutively enrolled and successfully treated with one or more approved drug-eluting stents and who were adequately loaded with aspirin and clopidogrel. *Includes 316 patients who died (3.7%). DES = drug-eluting stent(s); GPI = glycoprotein IIb/IIIa inhibitor.

99.2% of patients; at 2 years 93.4% remained on ASA, and 87.7% of patients took ASA daily for 2 years without discontinuation. A thienopyridine was prescribed in 99.7% of patients at discharge; at 2 years 56.9% were taking a thienopyridine, and 49.6% of patients took a thienopyridine daily for 2 years without discontinuation. Among patients taking a thienopyridine, clopidogrel was used in 99.7% at discharge. Ticagrelor was not used during this study. Clopidogrel was used by 55.5% and DAPT was used by 53.9% of patients at 2 years, and 46.4% of patients took DAPT for 2 years without discontinuation at any time.

TABLE 1 Antiplatelet Agent Use Throughout the Study Duration

	Aspirin	Thienopyridine	DAPT
Pre-admission	7,041/8,582 (82.0)	3,681/8,582 (42.9)	3,437/8,582 (40.0)
Loading dose pre-percutaneous coronary intervention	7,584/8,582 (88.4)	6,515/8,582 (75.9)	6,122/8,582 (71.3)
Discharge	8,508/8,576 (99.2)	8,550/8,576 (99.7)	8,491/8,582 (98.9)
Daily through 1 yr without any discontinuation	7,599/8,279 (91.8)	6,536/8,293 (78.8)	6,241/8,293 (75.3)
Daily through 2 yrs without any discontinuation	6,930/7,905 (87.7)	3,923/7,905 (49.6)	3,668/7,905 (46.4)
Taking at 1 yr	7,893/8,279 (95.3)	6,972/8,315 (83.8)	6,715/8,315 (80.8)
Taking at 2 yrs	7,383/7,905 (93.4)	4,499/7,905 (56.9)	4,257/7,905 (53.9)

Values are n/N (%).
DAPT = dual antiplatelet therapy.

The baseline characteristics of the patients enrolled in the ADAPT-DES study are shown in Table 2. The study population was a high-risk cohort, with a large proportion of patients having diabetes, multivessel disease, and prior MI. Just over one-half of the patients presented with an acute coronary syndrome (ACS), and nearly two-thirds had implantation of an everolimus-eluting stent.

2-YEAR OUTCOMES IN THE ENTIRE STUDY POPULATION. Definite or probable ST within 2 years occurred in 92 of 8,582 patients (1.07%) (Figure 2). ST occurred in 20 patients (0.23%) between years 1 and 2; of these events, 6 (30%) occurred on DAPT, 8 (40%) occurred on ASA alone, and 6 (30%) occurred on no antiplatelet therapy. Within 2 years MI, clinically relevant bleeding and all-cause mortality occurred in 391 (4.8%), 739 (8.6%) and 316 (3.9%) patients, respectively.

The unadjusted and propensity-adjusted risks for 2-year adverse events in the entire patient cohort are shown in Table 3. Similar to the 1-year findings, HPR on clopidogrel was strongly correlated with the 2-year occurrence of definite or probable ST and MI, and inversely associated with clinically relevant bleeding, with a strong trend toward an association with increased all-cause mortality. In contrast, HPR on ASA was not significantly associated with any of the major outcome events through 2 years.

OUTCOMES TO 2 YEARS IN PATIENTS REMAINING ON DAPT THROUGH 2 YEARS. Table 4 shows the relationship of ST to ARU and PRU in patients who were on DAPT at the end of year 1 and remained on DAPT continuously to 2 years or until an event occurred, including those with temporary interruption (12%). As in the total population, HPR on ASA in this cohort was infrequent (277 of 4,179, 6.6%), and mean ARU was similar in patients with and without ST. The frequency of HPR on ASA was also similar in those with and without ST. In contrast, mean PRU was significantly higher among patients with ST, as was the frequency of HPR.

In unadjusted analyses, HPR on clopidogrel at the time of the procedure in patients remaining on DAPT through 2 years was significantly associated with the 2-year rate of definite or probable ST, MI, all-cause death, and MACE, and inversely related to clinically relevant bleeding (Figure 3, Table 5). MI due to ST and MI

unrelated to ST both occurred more commonly in patients with HPR. Clinically relevant bleeding to 2 years was less frequent in patients with HPR. In the propensity-adjusted multivariable model, HPR on clopidogrel was independently associated with definite or probable ST (adjusted hazard ratio [HR]: 2.16; 95% confidence interval [CI]: 1.27 to 3.67; p = 0.003), MI (adjusted HR: 1.35; 95% CI: 1.05 to 1.74; p = 0.02), freedom from clinically relevant bleeding (adjusted HR: 0.74; 95% CI: 0.62 to 0.90; p = 0.002), all-cause mortality (adjusted HR: 1.36; 95% CI: 1.01 to 1.85; p = 0.04), and MACE (HR: 1.31; 95% CI: 1.06 to 1.63; p = 0.01) (Table 5).

LANDMARK POPULATIONS AFTER 1 YEAR. The baseline and procedural characteristics of patients who were event free at 1 year and then remained on ASA alone continuously or DAPT continuously through 2 years (unless an event occurred before 2 years) are shown in Online Table 1. Compared to ASA alone, patients remaining on DAPT through 2 years were higher risk overall: they were more likely to have diabetes, hyperlipidemia, and prior cardiac disease. They were also more likely to present with an ACS, and there were differences between groups in the type of stent implanted.

Outcomes of patients on ASA alone after 1 year. The outcomes of patients who did not experience an ischemic event by 1 year and who remained on ASA monotherapy (without an ADP antagonist) continuously without interruption until 2 years or until an event occurred are shown in Table 6 stratified by ARU. The overall rate of definite or probable ST between years 1 and 2 in this cohort was low at 0.3%, and none of the cases occurred in patients with HPR to ASA. Similarly, in this group there was no relationship between ASA hyporesponsiveness and MI, clinically relevant bleeding, or all-cause mortality.

Outcomes of patients on DAPT continuously to 2 years. As shown in Table 7, definite or probable ST was uncommon between years 1 and 2 in patients event free at 1 year who were continuously maintained on DAPT through 2 years without interruption, and was not significantly related to HPR on clopidogrel. Similarly, both MI and clinically relevant bleeding were unrelated to HPR during this period. In patients with baseline HPR on clopidogrel in this cohort, an increase in all-cause mortality after 1 year was present in unadjusted analysis, but statistical significance was no longer present after multivariable adjustment.

TABLE 2 Baseline Characteristics (N = 8,582)

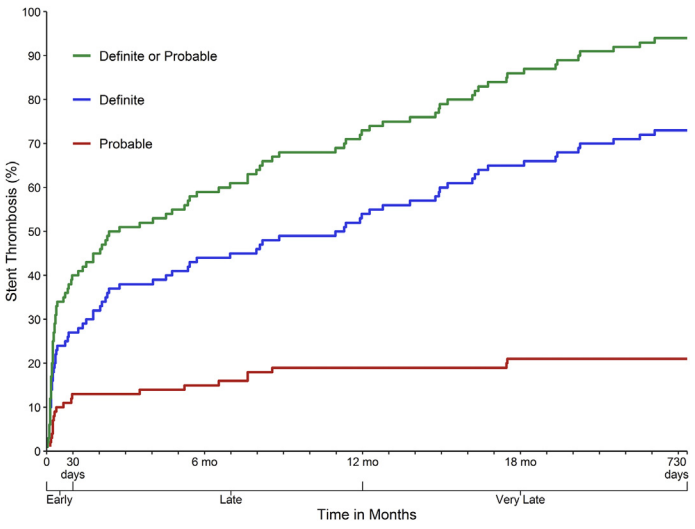
Age, yrs	64 ± 11
Male	6,357 (74.1)
Race	
Caucasian	7,605 (88.6)
Asian	51 (0.6)
Black	457 (5.3)
Other	469 (5.5)
Hypertension	6,833 (79.6)
Hyperlipidemia	6,380 (74.3)
Diabetes mellitus	2,783 (32.4)
Insulin treated	998 (11.6)
Current smoker	4,829 (56.3)
Previous myocardial infarction	2,164 (25.2)
Previous percutaneous coronary intervention	3,618 (42.9)
Previous coronary artery bypass surgery	1,468 (17.1)
History of peripheral arterial disease	876 (10.2)
History of renal insufficiency	660 (7.7)
Body mass index, kg/m^2	30.0 ± 5.7
Presenting clinical syndrome	
Stable coronary artery disease	4,149 (48.3)
Acute coronary syndrome	4,433 (51.7)
Unstable angina	2,370 (27.6)
Non-ST-segment elevation myocardial infarction	1,249 (14.6)
ST-segment elevation myocardial infarction	814 (9.5)
Angiographic features	
Number of diseased vessels	
1	3,283 (38.3)
2	2,835 (33.0)
3	2,464 (28.7)
Left main disease	257 (3.0)
Procedural data	
Lesions treated per patient	1.5 ± 0.8
Stents implanted per patient	1.7 ± 1.0
Total stent length per patient, mm	32.0 ± 22.4
Maximum vessel diameter, mm	3.1 ± 0.7
Maximum diameter stenosis pre-intervention, %	84.7 ± 11.9
Maximum diameter stenosis post-intervention, %	1.2 ± 5.5
Drug-eluting stent type	
Everolimus eluting	5,538 (64.5)
Paclitaxel eluting	1,414 (16.5)
Sirolimus eluting	1,155 (13.5)
Zotarolimus eluting, fast release	535 (6.2)
Zotarolimus eluting, slow release	187 (2.2)
Other	5 (0.1)

Values are mean ± SD or n (%).

DISCUSSION

With follow-up to 1 year (20), the large-scale, prospective APAPT-DES study demonstrated a strong relationship between HPR on clopidogrel and both ST and MI after successful DES implantation. Also observed was an inverse relationship between HPR on clopidogrel to clinically relevant bleeding, with no significant overall association with all-cause mortality. HPR on ASA was unrelated to the occurrence of any major ischemic or bleeding endpoint. With follow-up to 2 years, the present report extends these earlier findings and provides novel new insights between platelet reactivity at the time of PCI and

FIGURE 2 Time to First Stent Thrombosis to 2 Years



Kaplan-Meier curves for the primary endpoint (definite or probable stent thrombosis according to the Academic Research Consortium Criteria) in patients followed to 2 years.

long-term outcomes as follows: 1) HPR on ASA tested at the time DES implantation was not associated with ST through 2 years, including in lower-risk patients treated with ASA monotherapy after ADP antagonist discontinuation in patients who were event free at 1 year; 2) HPR on clopidogrel measured after successful DES implantation remained associated with ST, MI, and reduced bleeding at 2 years, with a borderline association with increased all-cause mortality not observed in the 1-year analysis. The same held true in a higher-risk cohort of patients who continued on DAPT per physician preference through 2 years; 3) nonetheless, the majority of adverse events in patients on continuous DAPT through 2 years occurred in the first year, and ST, MI, clinically relevant bleeding, and death between years 1 and 2 were not significantly associated with HPR on clopidogrel.

Recent studies have demonstrated that patients treated with second-generation DES who were event free at 1 year and thereafter maintained on ASA alone have a low subsequent rate of ST, and data from the present study confirm these findings (14,21,22). Our data also reinforce the observations from the PARIS (Patterns of Non-adherence to Anti-platelet Regimens in Stented Patients) registry that planned DAPT discontinuation often occurs in patients with a lesser extent of disease, and is associated with a low overall event rate (5). Specifically, despite the largely unrestricted and high-risk nature of patients enrolled in the present study, very late ST between 1 and 2 years occurred in only 0.23% of patients, in part due to use of second-generation DES in the majority of patients (principally everolimus eluting), which are safer than their first generation counterparts (8–10). Low rates of very late ST were also noted after DAPT discontinuation in everolimus-eluting stent-treated patients in the DAPT randomized trial and in a broad patient population randomized to zotarolimus- or everolimus-eluting stents in the TWENTE (The real-World Endeavor Resolute versus Xience V drug-eluting steNt study in TwentE) study (0.3%) (6,21).

HPR on ASA in patients maintained on ASA monotherapy implies the virtual absence of any antiplatelet effect. The impact of this phenomenon in patients developing very late ST after planned thienopyridine discontinuation has been uncertain

TABLE 3 Unadjusted and Propensity-Adjusted Multivariable Risk of High Platelet Reactivity for Adverse Events Through 2-Year Follow-Up in the Entire Patient Population

	PRU				ARU			
	Event Rates at 2 Years (Unadjusted)				Event Rates at 2 Years (Unadjusted)			
	PRU >208 (n = 3,609)	PRU ≤208 (n = 4,839)	Adjusted HR (95% CI)	p Value	ARU >550 (n = 478)	ARU ≤550 (n = 8,048)	Adjusted HR (95% CI)	p Value
Stent thrombosis								
Definite/probable	1.5 (54)	0.8 (37)	1.87 (1.18–2.96)	0.007	1.1 (5)	1.1 (86)	1.03 (0.41–2.55)	0.95
Definite	1.2 (43)	0.6 (29)	2.11 (1.27–3.52)	0.004	0.9 (4)	0.9 (67)	1.12 (0.40–3.10)	0.83
Myocardial infarction	5.7 (196)	4.0 (187)	1.33 (1.06–1.66)	0.01	4.6 (20)	4.8 (367)	0.82 (0.51–1.31)	0.40
Clinically relevant bleeding	8.6 (293)	9.2 (428)	0.79 (0.67–0.93)	0.005	8.9 (39)	9.0 (694)	0.75 (0.54–1.06)	0.10
Death, all cause	4.8 (165)	3.1 (141)	1.22 (0.96–1.57)	0.11	5.0 (23)	3.8 (288)	0.98 (0.63–1.54)	0.94

Values are % (n) unless otherwise specified.

ARU = aspirin reaction units; CI = confidence interval; HR = hazard ratio; PRU = $P2Y_{12}$ reaction units.

TABLE 4 Relationship Between Platelet Reactivity and Subsequent Definite or Probable ST in Patients on DAPT Through 2-Year Follow-Up

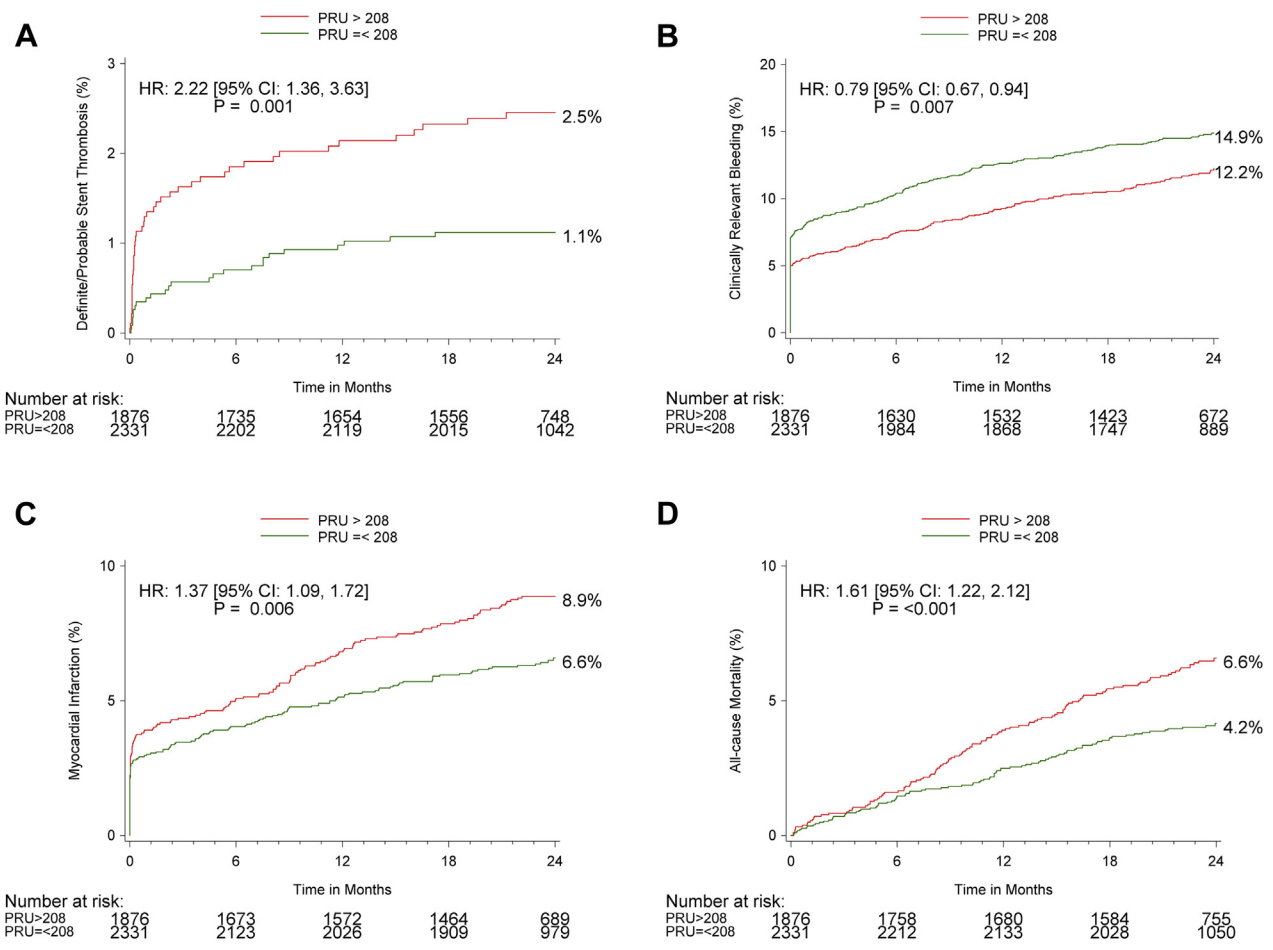
	ST (n = 69)	No ST (n = 4,138)	HR (95% CI)	p Value
ARU	420 ± 52	423 ± 58	—	0.62
>550	3/68 (4.4)	274/4,138 (6.7)	0.66 (0.21–2.10)	0.48
PRU	224 ± 101	192 ± 95	—	0.01
>208	44/69 (63.8)	1,832/4,138 (44.3)	2.22 (1.36–3.63)	0.001

Values are mean ± SD or n/N (%).
ST = stent thrombosis; other abbreviations as in Tables 1 and 3.

(15,16), and the present study is the largest to address this question. Although some prior studies have suggested that ASA resistance may have a role in adverse outcomes after PCI (12–15), our data suggest that HPR on ASA is infrequent, and is not associated with 2-year ischemic or bleeding events. Moreover, very late ST occurring in a lower-risk group of patients remaining on ASA monotherapy was not attributable to HPR on ASA. Further studies are warranted to determine whether thromboxane-mediated platelet activation is not an important pathway contributing to ST, or whether a different assay might be able to detect a relationship between HPR on ASA and adverse ischemic events after DES.

Current guidelines recommend that most patients receiving DES be treated with 6 or 12 months of DAPT (according to whether the initial presentation is stable coronary artery disease or an ACS (2,3). Nonetheless, the optimal duration of DAPT continues to be debated. In the DAPT trial, event-free patients

FIGURE 3 Time-to-Event Curves Through 2 Years According to Platelet Reactivity in Patients on Dual Antiplatelet Therapy Unless an Event Occurred



(A) Definite or probable stent thrombosis, **(B)** myocardial infarction, **(C)** clinically relevant bleeding, **(D)** and all-cause mortality. CI = confidence interval; HR = hazard ratio; PRU = $P2Y_{12}$ reaction units.

TABLE 5 Unadjusted and Propensity-Adjusted Multivariable Risk of High Platelet Reactivity on Clopidogrel for Subsequent 2-Year Events in Patients Maintained on Dual Antiplatelet Therapy for 2 Years

	Event Rates at 2 Years (Unadjusted)				
	PRU >208 (n = 1,876)	PRU ≤208 (n = 2,331)	p Value	Adjusted HR (95% CI)	p Value
ST (definite/probable)	44 (2.5)	25 (1.1)	0.001	2.16 (1.27–3.67)	0.003
Very late (year 1–2)	5 (0.31)	3 (0.14)	0.29	3.44 (0.71–16.78)	0.13
Myocardial infarction	157 (8.9)	145 (6.6)	0.006	1.35 (1.05–1.74)	0.02
ST related	29 (1.6)	13 (0.6)	0.001	2.96 (1.47–5.96)	0.002
Non-ST related	74 (4.4)	66 (3.1)	0.03	1.06 (0.74–1.53)	0.74
Very late (year 1–2)	41 (2.6)	32 (1.6)	0.03	1.43 (0.85–2.39)	0.17
ST related	5 (0.3)	2 (0.1)	0.14	4.53 (0.77–26.68)	0.09
Clinically relevant bleeding	214 (12.3)	333 (14.9)	0.007	0.74 (0.62–0.90)	0.002
In hospital	94 (5.0)	167 (7.2)	0.004	0.76 (0.57–1.02)*	0.06
After discharge	127 (7.6)	180 (8.3)	0.29	0.74 (0.58–0.95)	0.02
Very late (year 1–2)	55 (3.7)	58 (2.9)	0.29	0.94 (0.63–1.41)	0.78
Death, all-cause	114 (6.6)	90 (4.2)	<0.001	1.36 (1.01–1.85)	0.04
Very late (year 1–2)	44 (2.8)	34 (1.7)	0.03	1.58 (0.97–2.59)	0.07
MACE (cardiac death/MI/ST [definite/probable])	211 (11.9)	190 (8.6)	<0.001	1.31 (1.06–1.63)	0.01
Very late (year 1–2)	63 (4.0)	49 (2.5)	0.01	1.38 (0.91–2.09)	0.13

Values are n (%) unless otherwise indicated. *Odds ratio.
MACE = major adverse cardiac events; MI = myocardial infarction; other abbreviations as in Tables 4 and 5.

randomized to an additional 18 months of DAPT versus ASA alone after 12 months had reduced rates of ST and MI at the cost of increased bleeding and possibly mortality (6). Notably, the absolute reduction in very late ST in the DAPT trial with extended DAPT use was ~1.4% with first-generation DES versus 0.4% with second generation everolimus-eluting stents, although a reduction in MI not related to ST (and thus stent generation independent) accounted for 55% of the treatment benefit (23). The benefits of long-term DAPT in the DAPT trial were also most evident in patients presenting with MI (24). Similarly, the PEGASUS-TIMI 54 (Prevention of Cardiovascular Events in Patients with Prior Heart Attack Using Ticagrelor Compared to Placebo on a Background of Aspirin-Thrombolysis In Myocardial Infarction 54) trial demonstrated that in high-risk patients with prior MI more than 1 year previously, the addition of the potent antiplatelet agent ticagrelor in doses of 60 and 90 mg twice daily to ASA lowered the subsequent 3-year rates of MI and cardiac death, although with an increased risk of major bleeding and a neutral effect on all-cause mortality (25).

TABLE 6 Events Between Years 1 and 2 in Patients Who Were Event Free at 1 Year and Were Maintained on Aspirin Monotherapy Continuously After 1 Year, According to ARU

		Event Rates Between 1 and 2 Years (Unadjusted)				
	Events	ARU >550 (n = 119)	ARU ≤550 (n = 2,876)	p Value	Adjusted HR (95% CI)	p Value
Stent thrombosis (definite/probable)	8 (0.3)	0 (0.0)	8 (0.3)	0.99	0	1.00
Myocardial infarction	35 (1.2)	1 (0.9)	34 (1.2)	0.73	1.68 (0.50–5.64)	0.40
Clinically relevant bleeding	61 (2.1)	4 (3.4)	59 (2.1)	0.30	1.49 (0.53–4.22)	0.45
Death, all cause	28 (1.0)	1 (0.9)	27 (1.0)	0.91	0.71 (0.09–5.48)	0.74

Values are n (%) unless otherwise indicated.
Abbreviations as in Table 3.

The ADAPT-DES study is the largest available study evaluating 2-year outcomes in patients whose treatment between years 1 and 2 reflects an individualized provider strategy, thus adding an important perspective to the results from prior randomized trials. In the present study, patients remaining on DAPT to 2 years were a higher-risk group, with greater frequency of ACS presentation, prior documented coronary disease, diabetes, first-generation stents implanted, and complex anatomy. Nonetheless, the absolute rate of very late ST in patients was low on DAPT with clopidogrel, consistent with the DAPT trial. In the ADAPT-DES study, HPR on clopidogrel, tested at the time of the original procedure was not associated with an increased rate of ST or MI between years 1 and 2, nor was it associated with a reduction in major bleeding. However, the point estimates for all ischemic events were higher and type II error due to the low frequency of events after 1 year cannot be excluded. In contrast to the 1 year data, in which HPR on clopidogrel was not independently associated with all-cause mortality, possibly due to the offsetting effects of ischemia and bleeding reduction, HPR at 2 years was weakly predictive with a widening trend over time. This suggests a potential optimization of the risk-benefit balance between ischemic and bleeding events with reduction potentially related to individualized patient selection for DAPT continuation. Discriminate patient selection in the use of continued DAPT beyond 1 year for patients with high residual risk (and avoidance in high bleeding risk) could modify favorably the offsetting effects of ischemic risk and bleeding. A recent pooled analysis of 6 randomized trials of long term DAPT suggested significant reduction in MACE in those with complex versus noncomplex disease (26). Similarly, an externally validated risk score derived for DAPT continuation from the DAPT trial also suggested greater reduction in ischemic events as well as less bleeding in high-risk groups (27). Nonetheless, the impact of clopidogrel continuation on overall mortality in randomized trials has not suggested a difference (including the recent Food and Drug Administration

analysis), but the impact of patient risk assessment for DAPT continuation beyond 1 year has yet to be tested in prospective clinical trials (28). In this regard, the ADAPT-DES study is unique in giving providers unstructured latitude in choice of DAPT continuation, allowing for incorporation of personalized variables potentially influencing both ischemia and bleeding, and thus outcome. Based on the 2 year findings in the ADAPT study, use of clopidogrel with platelet function testing combined with externally validated risk scores for patient selection for continued DAPT beyond 1 year might be useful to fine-tune antiplatelet potency in high-risk patients, such as elderly patients with ACS, although the small randomized ANTARCTIC (Assessment of a Normal Versus Tailored Dose of Prasugrel After Stenting in Patients Aged >75 Years to Reduce the Composite of Bleeding, Stent Thrombosis, and Ischemic Complications) trial did not demonstrate the benefits of such an approach (27,29,30). Patients responsive to clopidogrel may stay on this agent, with the expected benefit of a low rate of ischemic events, lower cost, and potentially lower bleeding risk compared with prasugrel or ticagrelor (31,32). Given the association of bleeding events to overall mortality after PCI (33,34), this approach might maximize net clinical benefit.

The fact that baseline HPR on clopidogrel was predictive of ischemic events and mortality and inversely related to clinically relevant bleeding through 2 years of follow-up after successful DES implantation is notable, although the majority of probable or definite ST occurred within the first year, and adverse events were most frequent among patients with ACS. The overall low positive predictive value of the test (20) suggests that measuring PRU routinely would be of limited clinical value, supporting the class III guideline recommendations against routine platelet function testing (3,35–37). Finally, it should be noted that platelet reactivity may change over time from the index event, independent of genetic status, possibly due to changing clinical and biologic patient profiles over time (e.g., changes in cigarette smoking and diabetes). In a study by Campo et al. (17), 83 of 300 patients (28%) undergoing PCI changed their responder status in 1 month, with the majority converting from nonresponders to responders. In contrast, in a 102 serial platelet function testing substudy from the ADAPT-DES study, HPR to clopidogrel was present in 35% of patients on day 1, in 43% at 1 month, and in 46% at 6 months after PCI; 38.2% of patients changed clopidogrel responder status at least once within 6 months (37). These data suggest that later testing might be most useful for long term DAPT decision making. Nonetheless, in the ADAPT-DES study assessment of platelet reactivity on clopidogrel immediately after PCI, the most clinically convenient time for its assessment provided prognostic utility through 2-year follow-up.

TABLE 7 Events Between Years 1 and 2 in Patients Who Were Event Free at 1 Year and Were Maintained on DAPT Continuously After 1 Year, According to PRU

		Event Rates Between 1 and 2 Years (Unadjusted)				
	Events	PRU >208 (n = 1,439)	PRU ≤208 (n = 1,808)	p Value	Adjusted HR (95% CI)	p Value
Stent thrombosis (definite/probable)	6 (0.3)	4 (0.3)	2 (0.1)	0.27	4.69 (0.73–30.1)	0.10
Myocardial infarction	56 (1.9)	31 (2.3)	25 (1.6)	0.09	1.19 (0.66–2.12)	0.57
Clinically relevant bleeding	41 (1.3)	22 (1.7)	19 (1.1)	0.21	1.13 (0.57–2.27)	0.72
Death, all cause	58 (1.9)	34 (2.5)	24 (1.5)	0.03	1.67 (0.94–2.98)	0.08

Values are n (%) unless otherwise indicated.
Abbreviations as in Table 3.

STUDY LIMITATIONS. The decision to discontinue or remain on DAPT after 1 year was made at the discretion of the patient's physician (and possibly influenced by the patient), introducing selection bias into the specific substudy cohorts that might have affected event rates. The frequency of ASA and clopidogrel resistance may also vary depending on the measuring technique (36,38). Finally, despite the large size of the present registry, the number of adverse events occurring after 1 year was modest, and follow-up was truncated at 2 years. We thus cannot exclude some relationship between HPR on clopidogrel and ischemic events after 1 year in patients chronically treated with DAPT.

CONCLUSIONS

In the large-scale, prospective, multicenter ADAPT-DES study registry, HPR on ASA as measured by VerifyNow testing was infrequent and was not associated with early, late, or very late ST or other ischemic or bleeding events in the entire study population, as well as in lower-risk patients treated with ASA monotherapy after 1 year. In contrast, the present data demonstrates a strong relationship of HPR on clopidogrel measured by VerifyNow testing after successful DES implantation with increased 2-year rates of ST and MI, and reduced bleeding, although relatively few events occurred after 1 year.

Further studies are required to establish whether a long-term relationship exists between HPR on clopidogrel, individualized patient selection for DAPT, and all-cause mortality, and whether further information might be provided by repeat platelet function testing at 1 year. The overall low rate of events between years 1 and 2 in this large-scale registry in which long-term DAPT decisions were made based on clinical risk features and other real-world variables supports an individualized strategy to long-term DAPT decision making.

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PERSPECTIVES

WHAT IS KNOWN? Continuation of DAPT beyond 1 year in patients following successful stenting is associated with ischemic event reduction and bleeding.

WHAT IS NEW? ASA hyporesponsiveness in low-risk patients maintained on ASA monotherapy beyond 1 year did not predict late events. HPR in high-risk patients maintained on dual antiplatelet therapy was independently associated with outcomes to 2 years.

WHAT IS NEXT? Future studies evaluating the long-term use of ADP inhibition should incorporate individualized patient selection to optimize the tradeoff between ischemic event reduction and bleeding.

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KEY WORDS coronary artery disease, drug-eluting stent(s), platelet reactivity, stent thrombosis

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