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Platelet Reactivity and Risk of Ischemic Stroke After Coronary Drug-Eluting Stent Implantation

From the ADAPT-DES Study

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ABSTRACT

OBJECTIVES The authors sought to investigate the association between $P2Y_{12}$ reaction units (PRU) and the risk of ischemic stroke (IS) after successful coronary drug-eluting stents (DES) implantation.

BACKGROUND The association between platelet reactivity on clopidogrel and the risk for ischemic cerebrovascular events remains unclear.

METHODS Incidence, predictors, and prognostic impact of IS were evaluated among patients enrolled in the multicenter, prospective ADAPT-DES (Assessment of Dual AntiPlatelet Therapy With Drug Eluting Stents) study. By protocol, patients were maintained on aspirin for 2 years and clopidogrel for at least 1 year. Baseline platelet reactivity on clopidogrel and aspirin were assessed by means of VerifyNow point-of-care assay after successful DES implantation.

RESULTS Among 8,582 patients enrolled, 68 (0.8%) had an IS during 2-year follow-up. Across the spectrum of PRU, rates of IS were progressively greater as patients transitioned from the lowest quintile of PRU (more $P2Y_{12}$ receptor inhibition; 2-year rate of 0.51%) to the highest quintile of PRU (less $P2Y_{12}$ receptor inhibition; 2-year rate of 1.34%; adjusted $p = 0.04$). PRU >208 was independently associated with higher risk of IS at 2 years (adjusted hazard ratio 1.81; 95% confidence interval 1.08 to 3.04; $p = 0.03$). The association between higher PRU and risk for IS was also consistent in patients with versus without high CHA_2DS_2-VASc score ($p_{interaction} = 0.30$) and in those on or off oral anticoagulation at discharge ($p_{interaction} = 0.99$). Occurrence of IS was strongly associated with increased risk of all-cause mortality at 2 years (adjusted HR: 4.16; 95% CI: 1.95 to 8.87; $p < 0.0001$).

CONCLUSIONS Higher PRU was associated with increased risk of IS after coronary DES implantation. Ensuring adequate platelet $P2Y_{12}$ receptor inhibition may reduce the risk of IS in this patient population. (Assessment of Dual AntiPlatelet Therapy With Drug Eluting Stents [ADAPT-DES]; NCT00638794) (J Am Coll Cardiol Intv 2018;11:1277–86)

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ABBREVIATIONS AND ACRONYMS

ARU = aspirin reaction unit(s)

CI = confidence interval

DAPT = dual antiplatelet therapy

DES = drug-eluting stent(s)

HR = hazard ratio

HS = hemorrhagic stroke

IS = ischemic stroke

PCI = percutaneous coronary intervention

PRU = $P2Y_{12}$ reaction unit(s)

ST = stent thrombosis

After percutaneous coronary intervention (PCI) with drug-eluting stents (DES), a period of dual antiplatelet therapy (DAPT) combining a $P2Y_{12}$ receptor inhibitor and aspirin is recommended to prevent the occurrence of stent-related thrombotic complications (1). The pathobiological rationale of DAPT post-PCI is predicated on the need to protect the stented vascular segment while vascular healing and stent strut endothelialization are ongoing (1,2). Additionally, platelet inhibition may prevent the development of atherothrombosis arising from atherosclerosis progression and acute plaque changes occurring outside the stented vascular segment, within the coronary vasculature, and possibly throughout the systemic arterial system (3,4). A significant interindividual variability in platelet response to clopidogrel has been described and has been attributed to genetic and epigenetic factors that influence pharmacokinetic and pharmacodynamic properties of clopidogrel (5,6). As such, high on-clopidogrel platelet reactivity has been widely described as a strong independent predictor of increased risk of stent thrombosis (ST) and myocardial infarction after PCI (5,6).

Stroke is a devastating clinical event associated with substantial morbidity and mortality (7). Patients with coronary artery disease are also at an increased risk of ischemic stroke (IS) due to concomitant atherosclerotic disease within the extra- and intracranial arterial system or due to cardiogenic embolism (7–9). Whether the degree of residual $P2Y_{12}$ receptor inhibition influences the risk of IS in a PCI population, in which the primary indication of DAPT is the prevention of coronary-related events, remains unclear. Therefore, in the largescale ADAPT-DES (Assessment of Dual Antiplatelet Therapy with Drug-Eluting Stents) study, we sought to investigate the association between platelet reactivity on clopidogrel and aspirin and the risk of IS in patients with coronary artery disease who underwent successful DES-PCI.

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METHODS

STUDY DESIGN AND OBJECTIVES. The ADAPT-DES study was a prospective, multicenter registry specifically designed to determine the association between platelet reactivity and ST after DES implantation. The design and major outcomes of the ADAPT-DES study have been previously described (6). In brief, a total of 8,582 all-comers patients were prospectively enrolled

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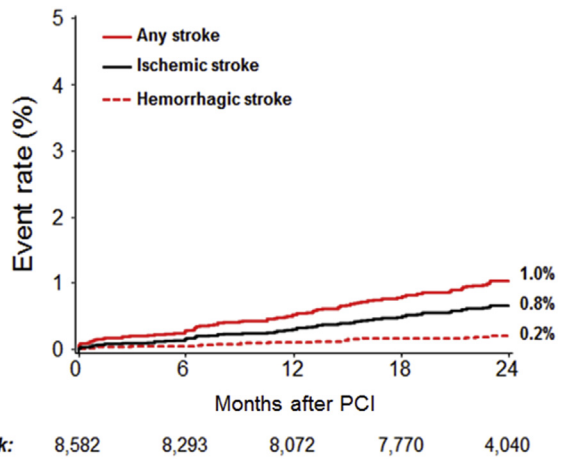
at 11 sites in the United States and Germany. All patients who were successfully treated with 1 or more DES and who were adequately loaded with aspirin and clopidogrel were eligible for enrollment, regardless of clinical presentation (51.7% had an acute coronary syndrome) or procedural complexity. The only major exclusion criteria were the occurrence of a major complication during the procedure or before platelet function testing, or if bypass surgery was planned after PCI. Additionally, patients with hemoglobin <10 mg/dl and platelet count <100,000/mm^3 were excluded from the study cohort. Platelet reactivity on aspirin and clopidogrel was assessed after an adequate loading period to ensure full antiplatelet effect using the VerifyNow Aspirin, P2Y$_{12}$, and IIb/IIIa assays (Accumetrics, San Diego, California) (6). After PCI, patients were treated with aspirin indefinitely, and clopidogrel was recommended for at least 1 year. All other treatments were as per standard of care. Clinical follow-up was scheduled at 30 days, 1 year,

FIGURE 1 Rates of Stroke at 2 Years After PCI With DES



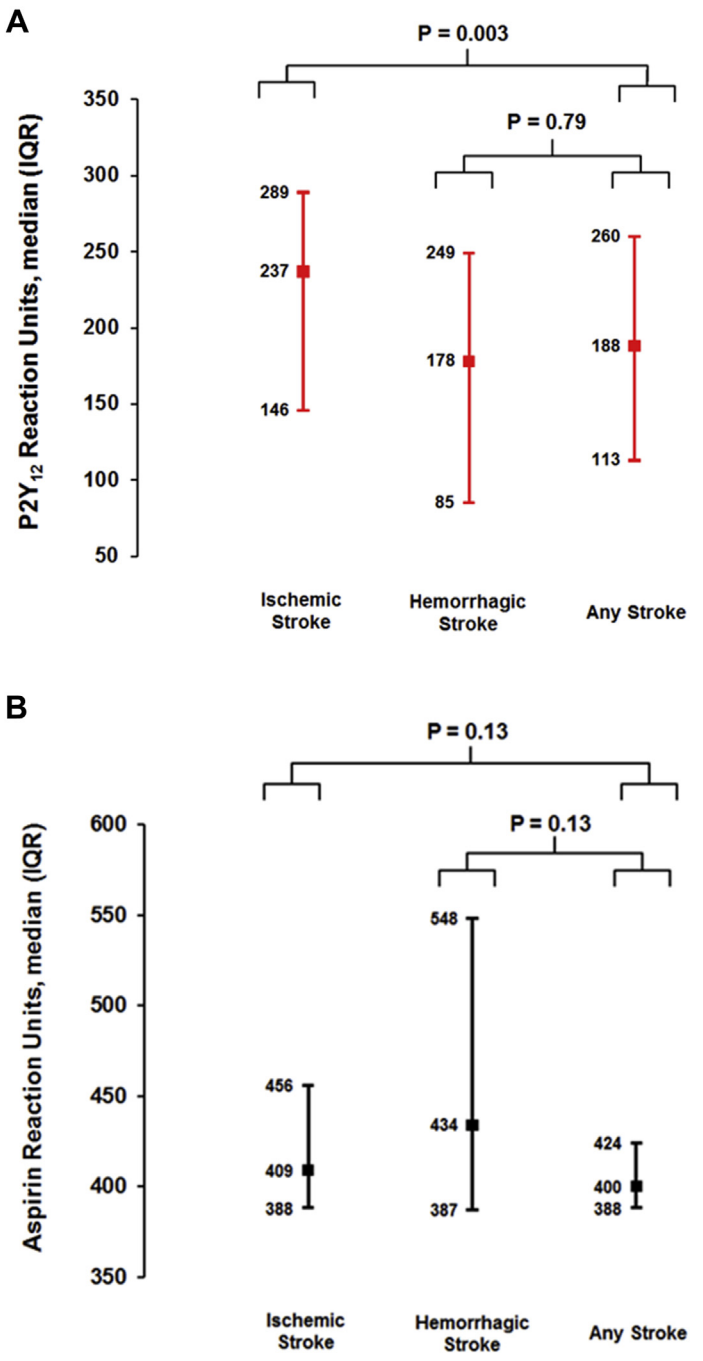
Kaplan-Meier curves for any stroke, ischemic stroke, and hemorrhagic stroke at 2-year follow-up. DES = drug-eluting stent(s); PCI = percutaneous coronary intervention.

TABLE 1 Baseline Clinical Characteristics in Patients With IS, HS, and No Stroke at 2-Year Follow-Up

	Ischemic Stroke (n = 68)	Hemorrhagic Stroke (n = 14)	No Stroke (n = 8,500)	p Value*	p Value†
Age, yrs	67.1 ± 10.0	69.1 ± 11.1	63.6 ± 10.9	0.006	0.04
Male	60.3 (41/68)	50.0 (7/14)	74.2 (6,309/8,500)	0.005	0.06
Race				0.55	0.39
Caucasian	91.2 (62/68)	100.0 (14/14)	88.6 (7,529/8,500)		
Non-Caucasian	8.8 (6/68)	0.0 (0/14)	11.4 (971/8,500)		
Body mass index, kg/m^2	30.2 ± 5.6	26.9 ± 4.3	29.5 ± 5.7	0.36	0.07
Diabetes mellitus	47.1 (32/68)	28.6 (4/14)	32.3 (2,747/8,500)	0.02	1.00
Insulin-treated	44.1 (30/68)	28.6 (4/14)	28.2 (2,395/8,500)	0.005	1.00
Peripheral artery disease	25.0 (17/68)	7.1 (1/14)	10.1 (858/8,500)	<0.0001	1.00
Congestive heart failure	14.7 (10/68)	7.1 (1/14)	8.1 (688/8,500)	0.04	1.00
Prior myocardial infarction	35.3 (24/68)	28.6 (4/14)	25.1 (2,136/8,500)	0.12	0.13
Prior coronary artery bypass grafting	27.9 (19/68)	21.4 (3/14)	17.0 (1,446/8,500)	0.03	0.72
Prior percutaneous coronary intervention	48.5 (33/68)	50.0 (7/14)	42.8 (3,638/8,500)	0.35	0.58
Arterial hypertension	88.2 (60/68)	85.7 (12/14)	79.5 (6,761/8,500)	0.09	0.13
Chronic kidney disease‡	22.7 (15/68)	42.9 (6/14)	16.3 (1,381/8,461)	0.16	0.02
Hyperlipidemia	83.8 (57/68)	92.9 (13/14)	74.2 (6,310/8,500)	0.09	0.12
Cigarette smoking	60.3 (41/68)	35.7 (5/14)	56.3 (4,783/8,500)	0.47	0.12
Current smoker	19.1 (13/68)	0.0 (0/14)	22.7 (1,927/8,500)	0.56	0.05
Previous smoker	41.2 (28/68)	35.7 (5/14)	33.6 (2,856/8,500)	0.21	1.00
Clinical presentation					
Asymptomatic coronary artery disease	8.8 (6/68)	7.1 (1/14)	12.4 (1,057/8,500)	0.41	1.00
Stable angina	69.1 (47/68)	78.6 (11/14)	71.2 (6,050/8,500)	0.03	0.77
Unstable angina	17.6 (12/68)	21.4 (3/14)	27.7 (2,355/8,500)	0.05	0.77
Non-STEMI	16.2 (11/68)	21.4 (3/14)	14.5 (1,235/8,500)	0.62	0.44
STEMI	11.8 (8/68)	7.1 (1/14)	9.5 (805/8,500)	0.46	1.00
NYHA functional class II–IV	64.7 (44/68)	78.6 (11/14)	67.5 (5,741/8,500)	0.50	0.57
Ejection fraction, %	55.53 ± 12.80	54.30 ± 5.31	54.88 ± 12.42	0.76	0.73
Laboratory data					
Hemoglobin, g/dl	13.5 ± 1.5	13.6 ± 1.8	14.0 ± 1.5	0.004	0.34
Hematocrit, %	39.7 ± 4.4	40.1 ± 5.1	41.0 ± 4.3	0.02	0.45
White blood cells, ×1,000/ml	8.28 ± 2.42	7.54 ± 2.65	7.95 ± 3.20	0.32	0.63
Platelet count, ×1,000/mm^3	225.1 ± 73.2	196.6 ± 52.2	226.8 ± 63.0	0.80	0.07

Values are mean ± SD or % (n/N). *Hemorrhagic stroke versus no stroke. †creatinine clearance <60 ml/min calculated by Cockcroft-Gault formula. ‡ischemic stroke versus no stroke.
HS = hemorrhagic stroke; IS ischemic stroke; NYHA = New York Heart Association; STEMI = ST-segment elevation myocardial infarction.

FIGURE 2 VerifyNow-Assessed PRU and ARU According to the Type of Stroke at 2 Years



$P2Y_{12}$ reaction units (PRU) **(A)** and aspirin reaction units (ARU) **(B)** in patients with ischemic, hemorrhagic, and any stroke at 2-year follow-up. IQR = interquartile range.

and 2 years. An independent clinical events committee blinded to platelet function testing results adjudicated all death, myocardial infarction, and stent thrombosis events using original source documents. The institutional review board at each participating center approved the study, and all eligible patients signed written informed consent before enrollment.

The present post hoc analysis from the ADAPT-DES study has the following objectives: 1) to investigate the association between $P2Y_{12}$ reaction units (PRU) and aspirin reaction units (ARU) and risk of IS after successful DES-PCI; 2) to assess the association between PRU and ARU and IS adjusting by CHA_2DS_2-VASc score, which is an established risk prediction tool for stroke; and 3) to estimate the adjusted impact of IS on mortality in a successful DES-PCI population. The incidence and univariate correlates of hemorrhagic stroke (HS) were also investigated.

STUDY DEFINITIONS. IS was defined according to guidelines criteria as an episode of neurological dysfunction caused by focal cerebral, spinal, or retinal infarction (the latter defined as a brain, spinal cord, or retinal cell death attributable to ischemia based on clinical [≥24 h], imaging, or pathological evidence). HS was defined as a rapidly developing clinical signs of neurological dysfunction attributable to a focal collection of blood within the brain parenchyma or ventricular system. All stroke events were site-reported events not adjudicated by a clinical events committee blinded to platelet function testing. Sites were asked to determine stroke on the basis of guideline-recommended clinical criteria with imaging and local neurologist confirmation.

STATISTICAL ANALYSIS. Descriptive statistics are presented as mean ± SD and were compared with the Student's *t*-test; categorical variables are reported as percentages and were tested with the chi-square test. Incidence of IS and HS were estimated with the Kaplan-Meier method. Adjusted hazard ratio (HR) to evaluate the association between PRU, ARU, and IS was obtained with multivariable Cox regression modeling including the following covariates: age, sex, congestive heart failure, diabetes, hypertension, peripheral arterial disease, smoking, anemia, renal insufficiency, and warfarin pre-PCI.

The study population was categorized according to the CHA_2DS_2-VASc score in 3 categories: low risk (score = 1), intermediate risk (score = 2 or 3), and high risk (score ≥4). The CHA_2DS_2-VASc score was calculated as reported previously, with the exception that "history of prior stroke" was empirically set to zero, because this variable was lacking at the time of study enrollment based upon the ADAPT-DES case report form. All patients in the dataset were given a score of 1 by default, given that all of them had coronary artery disease. The predictive value of the

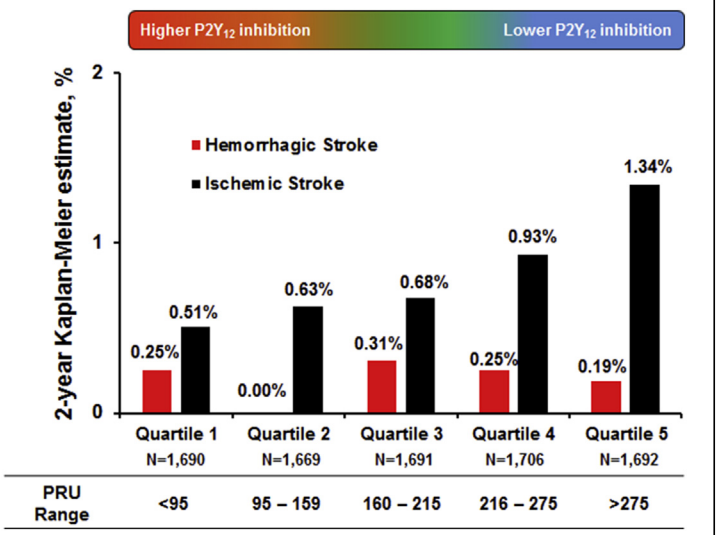
CHA_2DS_2-VASc score (tested as a linear scale) was assessed in Cox regression models, with receiver-operating characteristics, area under the curve, and C-statistic to assess discrimination, and with the Hosmer-Lemeshow statistic to evaluate calibration.

The impact of IS on all-cause mortality was evaluated by including IS as a time-dependent covariate in a multivariable Cox regression model together with the following covariates: age, sex, history of congestive heart failure, diabetes mellitus, hypertension, peripheral vascular disease, PRU, and ARU. Due to the rarity of the events, only univariate associations between clinical variables and HS, and HS and all-cause mortality, are provided. Statistical analyses were performed with SAS version 9.4 (SAS Institute, Cary, North Carolina). A 2-sided $p < 0.05$ was deemed statistically significant.

RESULTS

PLATELET REACTIVITY AND RISK OF STROKE. Among 8,582 patients enrolled in the ADAPT-DES study, the median follow-up time was 729 (interquartile range: 703 to 742) days: of these, 316 died (at a median time to death of 352 [interquartile range: 183 to 502] days). Two years of follow-up was completed in 7,649 patients; among the remainders, 159 patients were lost at follow-up, 10 refused 2-year follow-up, 28 patients withdrew consent, whereas 736 had <700 days of follow-up. At 2 years of follow-up, stroke occurred in 82 patients (1.0%) (Figure 1); an incidence roughly comparable to that of definite or probable ST (1.1% at 2 years). Of these, 68 (0.8%) (Figure 1) had an IS, and 14 (0.2%) (Figure 1) had an HS. The overall rate of 2-year IS was comparable to that of definite or probable ST at 2 years (1.1%). Baseline clinical and procedural characteristics of patients with IS, HS, and no stroke are reported in Table 1 and Online Table 1. Compared with patients without IS, those who had an IS were older and more commonly female, with a higher prevalence of diabetes and other cardiovascular comorbidities. Patients with IS had higher levels of PRU as assessed with the VerifyNow assay (Figure 2A). By contrast, there were no differences in PRU between patients with versus without HS. ARU was similar among patients with and without stroke (Figure 2B). Medication use through 2 years is reported in Online Table 2. Although there were no significant differences in prescription of warfarin at discharge, at 2 years, patients who had an IS were more likely to be on warfarin compared with patients who did not have an IS. There were no significant differences in $P2Y_{12}$ receptor inhibitor and DAPT use through 2 years between patients with versus without IS.

FIGURE 3 Kaplan-Meier Estimates of IS and HS at 2 Years Across Levels of $P2Y_{12}$ Receptor Inhibition

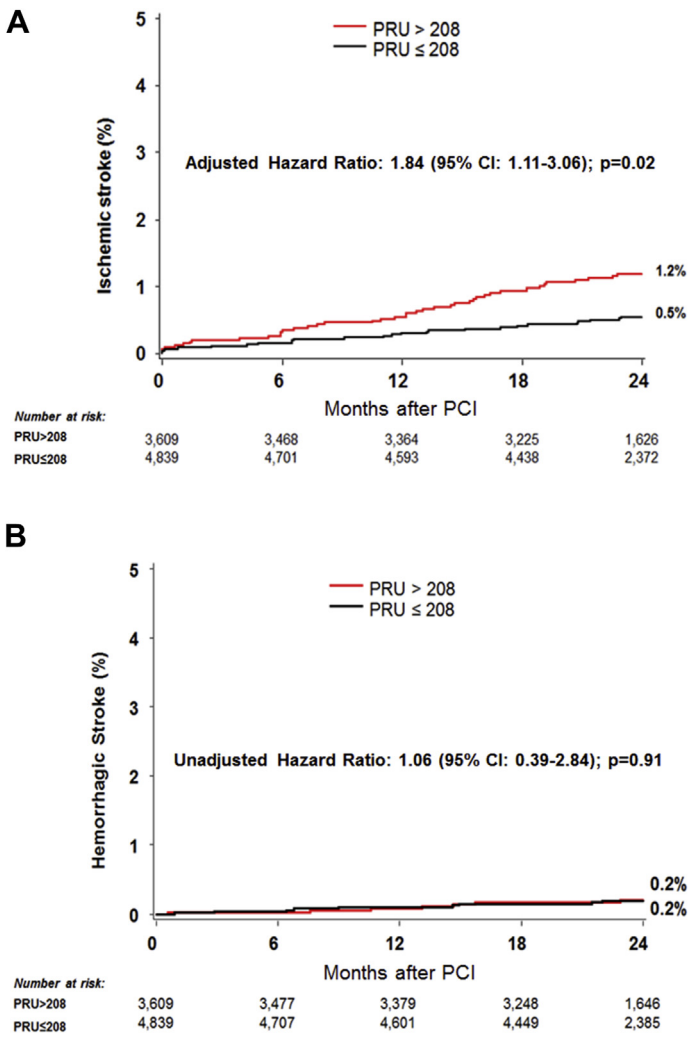


Results are reported across quintiles of $P2Y_{12}$ reaction units, from the lowest quintile (more $P2Y_{12}$ receptor inhibition) to the highest quintile (less $P2Y_{12}$ receptor inhibition). HS = hemorrhagic stroke; IS = ischemic stroke; PRU = $P2Y_{12}$ reaction units.

Kaplan-Meier estimates of IS and HS across the quintiles of PRU are illustrated in Figure 3. A greater risk of IS was observed as patients transitioned from the first quintile of PRU (more $P2Y_{12}$ inhibition) toward the fifth quintile of PRU (less $P2Y_{12}$ inhibition); conversely no significant differences were observed in the rates of HS across quintiles. Patients with PRU >208 had higher risk of IS at 2 years (Figure 4A) (1.2% vs. 0.5%; univariate HR: 2.18; 95% confidence interval [CI]: 1.32 to 3.60; $p = 0.01$); an association that persisted following multivariable adjustment (Figure 5) (adjusted HR: 1.84; 95% CI: 1.11 to 3.06; $p = 0.02$). Conversely, there were no differences in HS in patients with versus without PRU >208 (Figure 4B) (0.2% vs. 0.2%; univariate HR: 1.06; 95% CI: 0.39 to 2.84; $p = 0.91$). Independent correlates of IS are illustrated in Table 2. In addition to PRU, peripheral artery disease emerged as the strongest correlate of IS (adjusted HR: 2.44; 95% CI: 1.37 to 4.34; $p = 0.003$). ARU was not independently associated with increased risk of IS when modeled as a continuous metric or when a cutoff at ARU >550 was used to classify patients as aspirin resistant (Figure 5).

Crude rates of IS were highest among patients that had high ARU as well as high PRU (Online Figure 1),

FIGURE 4 Kaplan-Meier Curves for IS and HS in Patients With Versus Without PRU >208



Kaplan-Meier curves for ischemic stroke **(A)** and hemorrhagic stroke **(B)**. CI = confidence interval; other abbreviations as in Figures 1 and 2.

but there was no statistical interaction between greater PRU and greater ARU ($p_{interaction}$ = 0.19). There was also no interaction between greater PRU and peripheral artery disease (Online Figure 2) ($p_{interaction}$ = 0.45). The effect of greater PRU was also uniform between patients discharged with (per 50-U increase, adjusted HR: 1.15; 95% CI: 0.63 to 1.20) or without (adjusted HR: 1.15; 95% CI: 1.00 to 1.32) oral anticoagulation ($p_{interaction}$ = 0.99).

ASSOCIATION BETWEEN STROKE AND MORTALITY. By modeling IS as a time-dependent covariate and by adjusting for baseline confounders, IS was strongly associated with 2-year all-cause mortality (adjusted HR: 4.16; 95% CI: 1.95 to 8.87; p < 0.0001) and cardiovascular mortality (adjusted HR: 4.57, 95% CI: 1.86 to 11.24; p = 0.0009).

CHA_2DS_2-VASc SCORE, PLATELET REACTIVITY, AND RISK OF STROKE. Distribution and the predicted risk for 2-year IS across CHA_2DS_2-VASc score categories in the ADAPT-DES population is illustrated in Online Figure 3. IS rates across the low-risk, intermediate-risk, and high-risk groups are illustrated in Figure 6A. The area under the curve for the CHA_2DS_2-VASc score was of 0.64 (95% CI: 0.58 to 0.70) with good calibration, as assessed by the Hosmer-Lemeshow test (p = 0.55). Harrel's C-statistic for a model containing CHA_2DS_2-VASc was modest (0.65). Two-year rates of IS per high PRU (PRU >208) and CHA_2DS_2-VASc score >2 are illustrated in Figure 6B. After adjustment for the CHA_2DS_2-VASc score, PRU, but not ARU, was independently associated with IS (adjusted HR: 1.18 per 50-PRU increase, 95% CI: 1.03 to 1.34; p = 0.016 vs. adjusted HR: 1.24 per 100-ARU increase, 95% CI: 0.82 to 1.88; p = 0.30). There was no evidence of interaction between CHA_2DS_2-VASc score and high PRU ($p_{interaction}$ = 0.30).

DISCUSSION

The main findings of this largescale study investigating the association between on-clopidogrel and aspirin platelet reactivity and risk for stroke after successful DES-PCI in more than 8,000 patients are as follows: 1) After successful DES-PCI, the 2-year incidence of IS was comparable to that of ST; 2) PRU is independently associated with risk of IS at 2 years, which was consistent after adjusting for baseline stroke risk; of note, the observed risk of IS was progressively greater across the spectrum of residual $P2Y_{12}$ receptor inhibition with the lowest risk in patients in the lowest quintile of PRU (more $P2Y_{12}$ receptor inhibition) and the greatest risk in those in the highest quintile of PRU (less $P2Y_{12}$ receptor inhibition); and 3) ARU was not associated with increased risk of IS or HS.

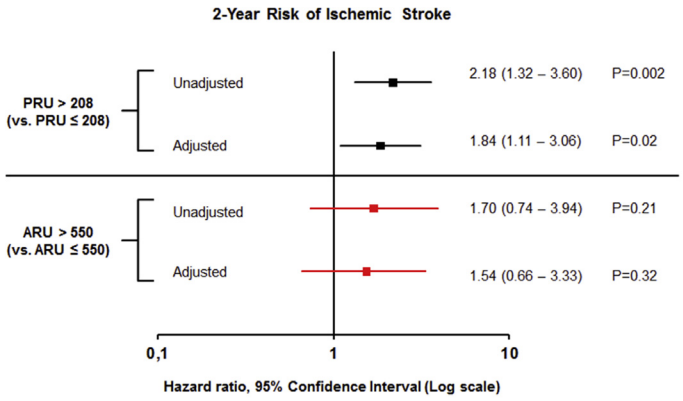
Atherosclerosis affects the coronary, cerebral, and systemic vasculature in a continuum (10). Atherothrombosis, which can be defined as an atherosclerotic lesion disruption with superimposed thrombus formation, is a major cause of acute coronary syndromes, cardiac death, and stroke (9). Stroke is the leading cause of long-term disability and among the top 5 causes of death in the United States (11). Because stroke often causes irreversible sequelae, early recognition of patients at risk and application of

appropriate preventive measures remain at the cornerstone of patient care (11). Approximately 90% of strokes are IS, and most of these are related to atherothrombosis and/or cardioembolism (12-15). In the current post hoc analysis from the largescale ADAPT-DES study, we investigated the incidence, correlates, and impact of IS in a patient population with coronary artery disease that was treated with successful DES-PCI and antiplatelet therapies. The ADAPT-DES study was designed to investigate the association between PRU and the 1-year risk of DES thrombosis, an event considered to be particularly important to prevent after PCI (6). Interestingly, our study shows that the observed rates of IS (0.8% at 2 years) were roughly comparable to that of definite or probable ST (1.1% at 2 years). Furthermore, the strength of the association was comparable for PRU and IS as it was for PRU and ST, with similar discrimination (6). Because the effect on morbidity and mortality of IS is at least of comparable magnitude to that of ST, our findings imply that the risk of IS should be taken into consideration when risk-stratifying patients and selecting antiplatelet regimens after PCI.

Less $P2Y_{12}$ receptor inhibition was associated with greater risk of IS in both unadjusted and adjusted analyses. Conversely, in contrast to PRU, ARU was not significantly associated with IS risk, although a trend toward greater risk for IS with increasing ARU was observed. Although we did not observe a multiplicative interaction between PRU and ARU on the risk of IS, patients with high PRU in combination with high ARU had incrementally higher risk of IS (Online Figure 1) (+1.4% on an absolute scale and 3.9-fold on a relative scale compared with patients with none of these conditions). When interpreted in the context of available data, our study suggests that ensuring adequate platelet inhibition through the $P2Y_{12}$ receptor and the COX pathways can reduce the risk of IS after PCI. Thus, because the incidence of IS after PCI appears to be similar to that of definite or probable ST, and because IS may have a greater impact on morbidity and mortality than that of an ST event, further attention should be payed to mitigating IS risk.

Our results must be put into perspective with previous trials investigating the association between antiplatelet therapy and risk for stroke. Compared with placebo, aspirin therapy demonstrated a reduction in the risk of IS by ≈15% in primary prevention trials and ≈25% in secondary prevention trials in patients at high risk for cardiovascular events (16). However, in a recent substudy of the SOCRATES (Acute Stroke or Transient Ischaemic Attack Treated With Aspirin or Ticagrelor and Patient Outcomes) trial, $P2Y_{12}$ inhibition with the more potent agent ticagrelor versus COX inhibition with aspirin significantly reduced the risk of ischemic stroke by 27% in the subset of patients with acute IS or transient ischemic attack of atherosclerotic origin (17). In terms of DAPT, in the randomized, double-blinded, placebo-controlled CHANCE (Clopidogrel in High-Risk Patients With Acute Non-Disabling Cerebrovascular Events) trial, the combination of aspirin and clopidogrel for 21 days was superior to aspirin alone in reducing the risk for stroke at 90 days after the onset of minor IS or high-risk transient ischemic attack (18). In addition, compared with aspirin alone, more intense

FIGURE 5 Unadjusted and Adjusted Association Between High Platelet Reactivity on Clopidogrel and on Aspirin With the Risk of IS at 2 Years



Abbreviations as in Figures 2 and 3.

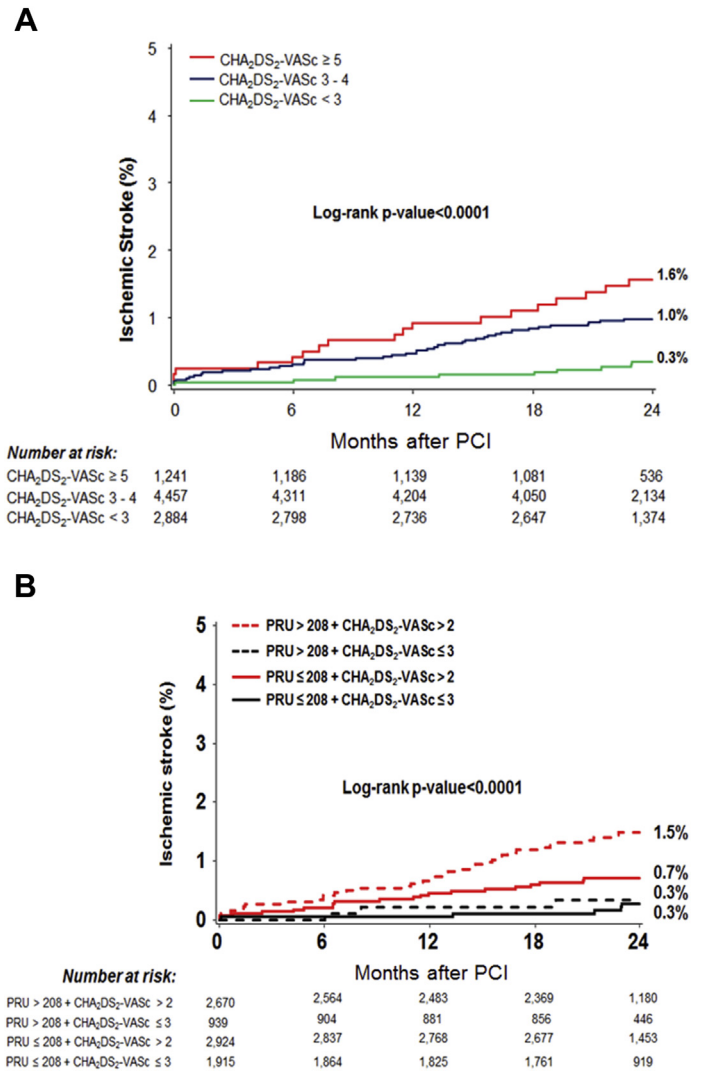
TABLE 2 Independent Correlates of Stroke at 2 Years

	Adjusted HR (95% CI)	p Value
Any stroke		
Peripheral artery disease	2.07 (1.20–3.58)	0.009
Sex, female	1.79 (1.12–2.86)	0.01
Aspirin reaction units, per 100-U increase	1.39 (0.97–1.98)	0.07
Ischemic stroke		
Peripheral artery disease	2.44 (1.37–4.34)	0.003
$P2Y_{12}$ reaction units, per 50-U increase	1.15 (1.01–1.31)	0.04
Sex, female	1.61 (0.95–2.71)	0.07

Candidate covariates included: age, sex, $P2Y_{12}$ reaction units >208, diabetes mellitus, peripheral artery disease, congestive heart failure, and arterial hypertension.

CI = confidence interval; HR = hazard ratio.

FIGURE 6 Kaplan-Meier Curves for IS According to the CHA_2DS_2-VASc Score and PRU



Kaplan-Meier curves for ischemic stroke according to CHA_2DS_2-VASc score categories **(A)** and Kaplan-Meier curves for ischemic stroke according to CHA_2DS_2-VASc score categories and $P2Y_{12}$ reaction units **(B)**. Abbreviations as in Figures 2 and 3.

platelet inhibition by combining aspirin with a $P2Y_{12}$ receptor inhibitor or thrombin receptor antagonists demonstrated a reduction in the risk of both ischemic and all-cause stroke in a population at high risk for atherothrombosis (34% and 28% relative risk reduction, respectively) (12). However, it should also be noted that in patients with history of lacunar infarcts, the combination of aspirin plus clopidogrel versus aspirin alone and the combination of clopidogrel plus aspirin versus clopidogrel alone were both associated with increased risk of major bleeding in absence of significant ischemic benefit, as observed in the SPS3 (Secondary Prevention of Small Subcortical Strokes) and the MATCH (Management of Atherothrombosis with Clopidogrel in High-risk patients) trials, respectively (19,20).

Because the role of measurement of pharmacological responsiveness to guide antiplatelet therapies in clinical practice remains controversial (21), we evaluated the association between PRU and ARU (which remain valid surrogates of the degree of platelet inhibition) with risk for IS after adjustment for established clinical risk factors of IS. First, we observed that the CHA_2DS_2-VASc score, which was developed to guide anticoagulation therapy in patients with atrial fibrillation (22), predicted IS in the ADAPT-DES population with a C-statistic surprisingly comparable to that observed in cohorts of patients with atrial fibrillation (23). Of interest, the association between PRU and risk for IS persisted after adjustment with the CHA_2DS_2-VASc score, further reinforcing that ensuring adequate platelet inhibition may be of value even in the context of established clinical risk factors for IS.

Current guidelines recommend at least 6 months and at least 12 months of DAPT therapy after PCI with DES in patients with stable coronary artery disease and acute coronary syndromes, respectively (24). After this guideline-recommended mandatory period, extension of DAPT may be considered if the risk-benefit ratio of prolonging versus stopping DAPT is deemed to be favorable. Our study suggests that the individual risk of IS should be taken into account at the time of clinical decision making for secondary prevention with antiplatelet therapies.

STUDY LIMITATIONS. First, because this is a post hoc analysis from a prospective cohort study, our results have to be considered hypothesis-generating. Second, most of the patients in the ADAPT-DES study received clopidogrel as the $P2Y_{12}$ receptor inhibitor; therefore, generalizability to novel high-potency antiplatelet drugs remains limited. Third, history of prior stroke was not captured in the dataset, and therefore, it could not be computed in the calculation of CHA_2DS_2-VASc score for individual patients. Fourth, history of atrial fibrillation or flutter was not captured; however, the effect of PRU on risk of IS was similar in patients discharged with or without oral anticoagulation, for which atrial fibrillation is the most common indication in this patient population. Fifth, in the ADAPT-DES study, stroke was a site-reported event with no blinded clinical event committee adjudication. Details on type of IS (atherothrombotic vs. cardioembolic),

infarct location, and neurological sequelae were also not captured. Finally, due to the low number of events, we were unable to assess the independent association between PRU and ARU with HS.

CONCLUSIONS

In an all-comers population treated with successful DES-PCI and DAPT, the risk for IS was similar to that of ST and was strongly associated with 2-year mortality. High on-clopidogrel platelet reactivity was independently associated with increased risk for IS at 2 years. The magnitude of increase in risk of IS was greater per lesser degrees of $P2Y_{12}$ receptor inhibition. The results of the present investigation suggest that ensuring optimal platelet inhibition may reduce the risk for IS in this patient population.

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PERSPECTIVES

WHAT IS KNOWN? Patients with coronary artery disease are at an increased risk of IS due to atherothrombosis within the extra- or intracranial arterial vasculature or due to cardiac embolism. Dual antiplatelet therapy, with aspirin and clopidogrel, reduces the risk of stent-related thrombotic events after PCI. Whether platelet reactivity on clopidogrel influences the risk for IS remains unclear.

WHAT IS NEW? In patients with coronary artery disease treated with PCI and dual antiplatelet therapy, high on-clopidogrel platelet reactivity is associated with increased risk of IS. Of note, the observed risk of IS was progressively greater across the spectrum of residual platelet inhibition, from the lowest (more platelet inhibition) to the highest (less platelet inhibition) quintiles of $P2Y_{12}$ reaction units.

WHAT IS NEXT? Further research is warranted to understand whether or not optimal platelet inhibition reduces the risk for IS in patients with atherosclerotic cardiovascular disease.

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KEY WORDS drug-eluting stent(s), percutaneous coronary intervention, platelet reactivity, stroke

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