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Impact of High On-Aspirin Platelet Reactivity on Outcomes Following Successful Percutaneous Coronary Intervention with Drug-Eluting Stents

Brief title: Aspirin Resistance and DES

Christine J. Chung, MD,[a] Ajay J. Kirtane, MD, SM,[a,b] Yiran Zhang, MS,[b] Bernhard Witzenbichler, MD,[c] Giora Weisz, MD,[b,d] Thomas D. Stuckey, MD,[e] Bruce R. Brodie,[e] MD, Michael J. Rinaldi, MD,[f] Franz-Josef Neumann, MD,[g] D. Christopher Metzger, MD,[h] Timothy D. Henry, MD,[I,j] David A. Cox, MD,[k] Peter L. Duffy, MD, MMM,[l] Ernest L. Mazzaferri Jr., MD,[m] Roxana Mehran, MD,[n] Gregg W. Stone, MD [a,b]

[a]NewYork-Presbyterian Hospital/Columbia University Medical Center, New York, NY

[b]Clinical Trials Center, Cardiovascular Research Foundation, New York, NY;

[c]Department of Cardiology and Pneumology, Helios Amper-Klinikum, Dachau, Germany

[d]Montefiore Medical Center, Bronx, NY

[e]LeBauer-Brodie Center for Cardiovascular Research and Education/Cone Health, Greensboro, NC

[f]Sanger Heart & Vascular Institute/Carolinas HealthCare System, Charlotte, NC

[g]Division of Cardiology and Angiology II, Heart Center University of Freiburg, Bad Krozingen, Germany

[h]Wellmont CVA Heart Institute, Kingsport, TN

[i]Minneapolis Heart Institute Foundation at Abbott Northwestern Hospital, Minneapolis, MN

[j]Cedars-Sinai Heart Institute, Los Angeles, CA

[k]Lehigh Valley Health Network, Allentown, PA

lReid Heart Center, FirstHealth of the Carolinas, Pinehurst, NC

[m]The Ohio State University Wexner Medical Center, Columbus, OH

[n]The Zena and Michael A. Wiener Cardiovascular Institute, Icahn School of Medicine at Mount Sinai, New York, NY

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Address for correspondence
Gregg W. Stone, MD
Columbia University Medical Center
Cardiovascular Research Foundation
1700 Broadway, 9th Floor
New York, NY 10019
Tel: (646) 434-4134
Fax: (646) 434-4715
gs2184@columbia.edu

ABSTRACT

Background: Whether high on-aspirin platelet reactivity (HAPR) confers an increased risk of adverse outcomes after percutaneous coronary intervention (PCI) remains unclear. We sought to examine the specific relationship between HAPR and clinical outcomes in ADAPT-DES.

Methods: A total of 8526 "all-comer" patients in the ADAPT-DES registry who underwent placement of drug-eluting stents and were treated with aspirin and clopidogrel were assessed to measure platelet reactivity. HAPR was characterized as ≥550 aspirin reaction units and high on-clopidogrel platelet reactivity (HCPR) as >208 P2Y12 reaction units. Univariable and propensity-adjusted multivariable analyses were used to assess the relationship between HAPR and clinical outcomes.

Results: HAPR was present in 478 (5.6%) patients. Patients with HAPR were older, had more comorbid illnesses, and had more complex coronary anatomy. During 2-year follow-up, HAPR was not associated with increased rates of major adverse cardiac events (MACE), stent thrombosis, myocardial infarction, or all-cause mortality. In propensity-adjusted multivariable analyses, HAPR was not an independent predictor of MACE after successful PCI (multivariable adjusted hazard ratio [HR]: 1.04; 95% confidence interval [CI] 0.64-1.69, p=0.87). Nor was HAPR associated with reduced bleeding. Even among patients with concomitant HCPR, HAPR was not associated with worse ischemic outcomes (adjusted HR for 2-year MACE: 1.06; 95% CI 0.55-2.00, p=0.87).

Conclusions: HAPR was infrequently present in a large registry of patients undergoing PCI. There was no clear relationship between HAPR and 2-year clinical outcomes. Investigation of antiplatelet regimens without aspirin after DES implantation are ongoing and should inform future management of patients undergoing PCI.

Keywords: High platelet reactivity, aspirin, major adverse cardiac events, percutaneous coronary intervention, drug-eluting stents

Platelet activation and aggregation are strongly related to the occurrence of major adverse cardiac events (MACE) after percutaneous coronary intervention (PCI).[1] When administered together, aspirin and clopidogrel reduce ischemic MACE in patients with acute coronary syndromes but often at the cost of increased bleeding.[2, 3] Because aspirin and P2Y12 antagonists such as clopidogrel inhibit platelet function through different pathways, their antiplatelet properties have long been considered additive. However, there is increasing evidence that their effects intersect. For instance, a high level of P2Y12 receptor inhibition has been shown to reduce platelet responsiveness to thromboxane A_2 as well as decrease platelet production of further thromboxane A_2,[4] thereby lessening the downstream impact of aspirin therapy.

Prior to binding to the platelet P2Y12 adenosine diphosphate receptor, clopidogrel requires conversion to an active metabolite through a process regulated by the cytochrome P450 complex,[5] which is susceptible to genetic polymorphisms, resulting in wide variability in the extent of platelet inhibition.[6] We previously explored the relationship between HCPR and ischemic outcomes and bleeding at 1 year in the large-scale Assessment of Dual AntiPlatelet Therapy with Drug-Eluting Stents (ADAPT-DES) registry, the largest prospective cohort of patients in whom point-of-care platelet reactivity testing was performed at the time of drug-eluting stent (DES) implantation. In those with HCPR, we found significantly greater risk of definite or probable stent thrombosis and myocardial infarction (MI),[7] findings consistent with smaller prior studies.[8-10] We recently showed that HCPR continues to predict adverse outcomes including all-cause mortality at 2 years in patients treated with dual antiplatelet therapy (DAPT).[11]

In contrast, the impact of HAPR on MACE, particularly after implantation of newer-generation DES in the DAPT era, remains unclear. Early studies of the association between aspirin resistance and ischemic events enrolled patients with stable coronary artery disease treated without intervention, and were thus primarily examinations of the effects of aspirin monotherapy.[12, 13] Prior studies investigating the role of HAPR on outcomes after PCI in patients treated with DES have been limited by small cohorts and

reported conflicting results.[14-17] In the present study we sought to examine the specific relationship between HAPR and clinical outcomes in the ADAPT-DES registry in an effort to elucidate the role of aspirin in preventing ischemic complications after DES implantation.

METHODS

Patient selection and platelet function testing. ADAPT-DES was a prospective, multicenter registry of patients enrolled between January 2008 and September 2010 at 11 hospitals in the United States and Germany who underwent successful implantation of one or more DES and were treated with aspirin and clopidogrel. The inclusion criteria were broad, and meant to include a near "all-comers" population. 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. Aspirin was administered as either a non-enteric coated oral dose of 300 mg or more at least 6 hours before PCI, or as a chewed dose of 324 mg or intravenous dose of 250 mg or more at least 30 minutes before PCI. Clopidogrel was administered as either 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. A total of 8526 patients were assessed with VerifyNow (Accriva Diagnostics, Piscataway, NJ) point-of-care assays to measure platelet reactivity after successful PCI. Full details of study procedures have been published previously.[7] Clinical follow-up was performed at 30 days, 1 year, and 2 years after DES implantation. Aspirin resistance was prospectively defined as ≥550 aspirin reaction units (ARU) and clopidogrel resistance was prospectively defined as ≥208 P2Y12 reaction units (PRU). These pre-specified cut-offs have been validated and utilized in prior studies.[9, 18-21] Patients were classified as having discontinued clopidogrel if they were prescribed clopidogrel at the time of hospital discharge and did not take it continuously throughout the 2-year follow-up period.

Definition of endpoints and statistical analyses. The primary endpoints were definite or probable stent thrombosis, MI, and all-cause mortality, as well as the composite outcome of MACE (cardiac death, MI, or stent thrombosis). The secondary endpoint was clinically-relevant bleeding, defined as any of the following: Thrombolysis in Myocardial Infarction (TIMI) major or minor bleed, Global Use of Strategies to Open Occluded Arteries (GUSTO) bleed, Acute Catheterization and Urgent Intervention Triage Strategy (ACUITY) major bleed, or any post-discharge bleeding event requiring medical attention (i.e. similar to the Bleeding Academic Research Consortium 2-5 criteria).[22] An independent committee masked to VerifyNow results adjudicated all stent thrombosis, MI, and death events using original source documents. No extramural funding was used to support this work, and the authors are solely responsible for the design and conduct of this study, all study analyses, the drafting and editing of the paper and its final contents.

Categorical baseline characteristics were presented as percentages and compared using χ^2 or the Fisher exact tests. Continuous characteristics were reported as mean ± standard deviation and compared using the Student *t* test or the Wilcoxon rank-sum test for non-normally distributed data. Clinical outcomes were summarized as time-to-event variables using the Kaplan-Meier method and were compared using the log-rank test.

Univariable and propensity-adjusted Cox multivariable analyses were performed to characterize the relationship between HAPR and adverse clinical outcomes after PCI. The following pre-specified covariates were used to create the propensity score: age, BMI, hypertension, hyperlipidemia, insulin-dependent diabetes mellitus (defined as Type I diabetes mellitus and Type II diabetes mellitus requiring insulin therapy), renal insufficiency, current smoking, angina, positive stress test, history of CAD, history of congestive heart failure (CHF), history of peripheral arterial disease (PAD), prior MI, STEMI, and prior CABG. Proportional hazard assumptions were verified by including time-dependent covariates in the Cox models. In addition to the principal analyses performed in the entire study population, the impact

of HAPR was evaluated in the subgroup of patients also demonstrating high residual platelet activity on clopidogrel.

RESULTS

Baseline patient and procedural characteristics, and aspirin compliance.

Baseline clinical characteristics are shown in Table I. HAPR was detected in 478 (5.6%) patients. Patients with HAPR were significantly older, with 25.7% >75 years of age. They had lower body mass index and a higher prevalence of comorbid conditions such as congestive heart failure and chronic kidney disease. Those with HAPR were more likely to have undergone prior PCI or coronary artery bypass grafting.

Patients with HAPR were just as likely as their counterparts without HAPR to present with an acute coronary syndrome (Table II); however, they were less likely to present with an ST-segment elevation MI (STEMI). They were more likely to have complex coronary artery disease. No difference was found in the number of coronary lesions treated per patient or the average length of stent implanted in those with aspirin resistance compared with those without it. There was slightly greater utilization of a first-generation DES in the aspirin resistant group, but overall approximately two-thirds of all patients in the study received a newer-generation stent.

Among 8526 patients, 6993 (82.0%) were taking aspirin prior to enrollment in the study. During the index hospitalization after undergoing PCI, 8410 (98.6%) patients were treated with aspirin. Aspirin was prescribed at discharge in 8453 (99.2%) patients and was taken for a mean of 649±175 days over 2 years of follow-up, with 6861 (80.5%) of patients reporting daily use without any discontinuation. There was no significant difference in the incidence of patients receiving a loading dose of aspirin at any time prior to or during PCI between those with and without HAPR (Table III). Patients with HAPR were more likely to be discharged on low-dose aspirin (i.e. 81 mg daily) than those without HAPR; however, the majority of patients were discharged on full-dose aspirin (i.e. 325 mg daily). There was no significant

difference in rates of discontinuation of the drug, with approximately 80% of all patients reporting daily use of aspirin through two years of follow-up.

Clinical outcomes in patients with high on-aspirin platelet reactivity. By univariable analysis, HAPR was not associated with stent thrombosis, MI, MACE, or all-cause mortality over 2 years of follow-up (Figure 1). Additionally, HAPR was not associated with decreased rates of clinically-relevant bleeding (Figure 2). Given the significant demographic and clinical differences between patients with and without HAPR, propensity-adjusted multivariable analysis was performed. After adjustment for age, body mass index, history of prior PCI or coronary artery bypass grafting, MI, congestive heart failure, chronic kidney disease, hyperlipidemia, presentation with a STEMI, positive stress test, and current or prior history of smoking, HAPR was not significantly associated with adverse cardiac events after DES implantation [Table IV]).

Impact of concurrent high on-clopidogrel platelet reactivity. A total of 3593 (42.1%) patients had HCPR, 213 (5.9%) of whom also had HAPR. Examination of the impact of high residual platelet reactivity to both aspirin and clopidogrel demonstrated that HCPR (but not HAPR) was associated with adverse outcomes. Even among patients with HCPR, HAPR was not associated with worse outcomes (multivariable adjusted hazard ratio for MACE 1.06 [95% confidence interval 0.55, 2.00], p=0.87). Patients with HCPR had the highest rates of MACE regardless of whether or not they had HAPR (8.3% in those with HCPR and HAPR versus 9.8% in those with HCPR but not HAPR, p=0.51). The rate of MACE was 6.5% in patients without high residual platelet reactivity to either antiplatelet agent, which was not significantly different than that in those with HAPR alone (Figure 3). Moreover, in propensity-adjusted multivariable analyses conducted in patients with HCPR, HAPR was not independently associated with stent thrombosis, MI, MACE, clinically-relevant bleeding, or mortality over 2 years of follow-up (Table V). Finally, among patients who discontinued clopidogrel during the follow-up period, there was no association between HAPR and clinical outcomes at 2 years (Table VI).

DISCUSSION

The principal findings of this study are: (i) HAPR, as defined by VerifyNow ARU ≥550, was infrequently present in a large, prospective, multicenter all-comers registry of 8526 patients undergoing PCI; (ii) patients with HAPR were older, had more comorbid illnesses, and had more complex coronary artery disease; (iii) no relationship was present between HAPR and adverse clinical outcomes after DES implantation by either univariable or propensity-adjusted multivariable analyses; and (iv) HAPR was not associated with increased rates of ischemic complications or a decreased risk of clinically-relevant bleeding even in patients with concomitant HCPR.

Why HAPR may not correlate with ischemic complications after PCI is unknown. In contrast to the mechanism of in situ atherothrombosis of a native coronary artery, the pathophysiology of stent thrombosis is more complex, involving stent-, procedure-, and patient-related factors, as well as different mechanisms of thrombus formation at various time points after stent deployment.[HOLMES] While prior studies in the pre-PCI era suggested that aspirin may be beneficial for secondary prevention,[23] the platelet pathways that aspirin inhibits may be less involved in the prevention of stent-related adverse events. It is also possible that *in vitro* assessment of residual platelet reactivity after drug treatment does not fully reflect *in vivo* inhibition of atherothrombotic activity. The wide variation in the prevalence of HAPR reported in the literature[24] reflects the significant heterogeneity of available testing modalities and subsequent definitions of HAPR utilized. The development of standardized diagnostic criteria for HAPR will facilitate ongoing research on its potential clinical implications.

Head-to-head comparisons of methods of platelet function testing have demonstrated substantial differences in prevalence of HAPR and its impact on outcomes.[25-27] The POPular study was a prospective, observational study of patients with stable coronary artery disease undergoing elective PCI with DES implantation treated with clopidogrel and low-dose aspirin in whom several platelet function tests were performed to determine their ability to predict adverse outcomes. In a small cohort of 422 patients, ROC

curve analysis determined that a cut-off of 454 ARU, but not 550 ARU, discriminated between patients who did and did not experience the primary endpoint of all-cause mortality, non-fatal MI, stent thrombosis and ischemic stroke at one year. However, this finding was driven by marginally higher rates of stent thrombosis (2 events in those with HAPR compared to 1 event in those without HAPR) and stroke (3 events in those with HAPR compared to 2 events in those without HAPR), highlighting the limitations of using a small sample to study rates of infrequent events.

The results of this study are in contrast to those of the Intracoronary Stenting and Antithrombotic Regimen-Aspirin and Platelet Inhibition (ISAR-ASPI) registry, in which 7090 patients undergoing DES implantation were tested for platelet reactivity to aspirin prior to PCI. In that study, HAPR was an independent predictor of stent thrombosis or mortality at 1 year (adjusted hazard ratio 1.46, 95% CI 1.12, 1.89; p=0.005).[28] These discordant results may be explained by use of different platelet function assays and cutoff values to define HAPR. The ISAR-ASPI study utilized multiple electrode aggregometry, in which the addition of arachidonic acid to whole blood triggers platelet attachment to electrode sensors, thereby resulting in a change in impedance over time. High platelet reactivity to aspirin was then defined as the upper quintile of platelet aggregation measurements, resulting in a much larger cohort of 1414 patients with HAPR. Defining HAPR in this manner raises the possibility that the cohort encompassed a significant proportion of patients whose measurements were on the high end of the normal bell curve. The VerifyNow assay used in the present study consists of a cartridge containing fibrinogen-coated beads and arachidonic acid. After the addition of whole blood, activated platelets bind to fibrinogen, causing the beads to agglutinate and light transmission to increase.[29] The ARU cutoff value of 550 has been correlated to HAPR as determined by epinephrine-induced optical aggregometry.[30]

Alternative explanations for the varying study results between ADAPT-DES and ISAR-ASPI may relate to differences between patients in the two studies, with variability in thromboxane A_2-mediated vs. ADP-mediated pathways of platelet activation and aggregation. Other soluble products such as GAS6, serotonin, and cytokines with pro-aggregation effects are present in the local milieu of an

actively propagating thrombus,[31] the presence of which may depend on the proportion and type of patients with ACS enrolled. Finally, non-compliance with aspirin confound true HAPR,[32, 33] and it is possible there were different rates of medication adherence between the two (drug compliance was not assessed in the ISAR-ASPI study).

Major limitations of many prior studies of the impact of HAPR on outcomes after PCI has been small sample size. The results of the current large-scale study thus enhance our understanding of aspirin's role in the contemporary management of patients after DES implantation. In the effort to optimize protection against ischemic complications while minimizing the risk of bleeding after implantation of newer-generation DES, many prior studies have focused on determining the ideal duration of DAPT rather than challenging the necessity of DAPT itself. In a meta-analysis of 11 randomized controlled trials enrolling a total of 33,051 patients, there was no significant difference in rates of stent thrombosis, MI, major hemorrhage, or death in those treated with DAPT for 3 to 6 months compared with 12 months.[34] As a result, the most recent American College of Cardiology/American Heart Association guidelines recommend that patients with stable ischemic heart disease treated with DAPT therapy after undergoing DES implantation receive clopidogrel for a minimum of 6 months (and at least 12 months after ACS) but that aspirin should be continued indefinitely.[35]

Evidence from studies of patients with atrial fibrillation suggests it may be safe to omit aspirin in patients at the highest risk of bleeding complications — those with indications for both DAPT and anticoagulant therapy. The WOEST trial showed that aspirin may be safely omitted in patients requiring a vitamin K antagonist and taking clopidogrel after PCI, reducing bleeding without an increase in MI or stent thrombosis.[36] The GEMINI-ACS-1 trial omitted aspirin in patients after an ACS event, the majority of whom underwent PCI with DES implantation. The combination of low-dose rivaroxaban plus a P2Y12 inhibitor resulted in similar rates of bleeding and stent thrombosis as a standard DAPT regimen.[37]

Consistent findings were reported from the PIONEER AF-PCI[38] and Re-Dual PCI[39] trials with rivaroxaban and dabigatran, respectively. The ongoing AUGUSTUS trial (NCT02415400) will elucidate whether similar outcomes can be achieved when patients with atrial fibrillation and ACS who undergo PCI with stent implantation are treated with apixaban and a P2Y12 inhibitor alone. Though the findings from these studies are encouraging, there are significant differences in the patient characteristics and background medical therapy of the cohorts enrolled in these trials of atrial fibrillation management and that of ADAPT-DES, thus limiting their generalizability to patients with ACS.

The results of the current study support further investigation of P2Y12 inhibitor monotherapy, without aspirin, following DES implantation. Two ongoing randomized controlled trials will provide a strong evidence base for clinicians striving to balance the risk of ischemic complications with that of bleeding for their patients after PCI in whom chronic oral anticoagulation is not required. The GLOBAL LEADERS trial (NCT01813435) is comparing ticagrelor monotherapy vs. 1 year of DAPT with ticagrelor and aspirin followed by 1 year of aspirin monotherapy after DES.[40] The Ticagrelor with Aspirin or Alone in High-Risk Patients after Coronary Intervention (TWILIGHT) study (NCT02270242) is comparing ticagrelor alone vs. aspirin plus ticagrelor for a 1-year period.[41] These trials will more definitively answer the question of whether it is safe to forego DAPT in favor of monotherapy with a P2Y12 inhibitor.

Limitations. Despite a large all-comers cohort representing a high-risk population of elderly patients, the proportion with HAPR as defined in the current study was low, resulting in wide confidence intervals for many of the results. The small number of patients with HAPR precluded meaningful subgroup analysis; it remains possible that certain high-risk characteristics, such as diabetes or chronic kidney disease, confer susceptibility to potential adverse effects of aspirin resistance. However, the fact that HAPR did not contribute to adverse events even in patients with concomitant HCPR (i.e. representing minimal platelet inhibition through any pathway) suggests that this condition does not contribute to stent-related adverse events, at least during 2-year follow-up. Nonetheless, despite adjusting for numerous baseline demographic, clinical and procedural variables that impact platelet reactivity, there may still be

unmeasured confounders that could have influenced the study findings. Furthermore, HAPR was assessed at a single point in time. Although it is possible that a patient's response to aspirin may vary over time, a single point-of-care assessment of platelet reactivity at the time of PCI has the greatest relevance for informing clinical decision-making and has been the standard in prior studies.[14, 16, 18, 29]

Conclusions. HAPR was infrequently detected in a large multicenter registry of patients undergoing PCI. No significant relationship between HAPR and adverse clinical outcomes within 2 years after DES implantation was observed. Investigation of antiplatelet regimens without aspirin after DES implantation are ongoing and should inform future management of patients undergoing PCI.

DISCLOSURES

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FIGURE LEGENDS

Figure 1. Time-to-Event Curves Over 2 Years of Follow-up for Major Adverse Events According to Aspirin Resistance.

ARU = aspirin reaction units; MACE = major adverse cardiac events; MI = myocardial infarction.

Figure 2. Time-to-Event Curves Over 2 Years of Follow-up for Clinically-Relevant Bleeding According to Aspirin Resistance.

ARU = aspirin reaction units.

Figure 3. Impact of Concurrent Aspirin and Clopidogrel Resistance on Outcomes after Percutaneous Coronary Intervention.

Group 1 vs Group 2: p=0.90; Group 1 vs Group 3: p=0.51; Group 1 vs Group 4: p=0.28; Group 2 vs Group 3: p=0.38; Group 2 vs Group 4: p=0.33; Group 3 vs Group 4: p<0.0001. ARU = aspirin reaction units; MACE = major adverse cardiac events; PRU = P2Y12 reaction units.

Figure 1

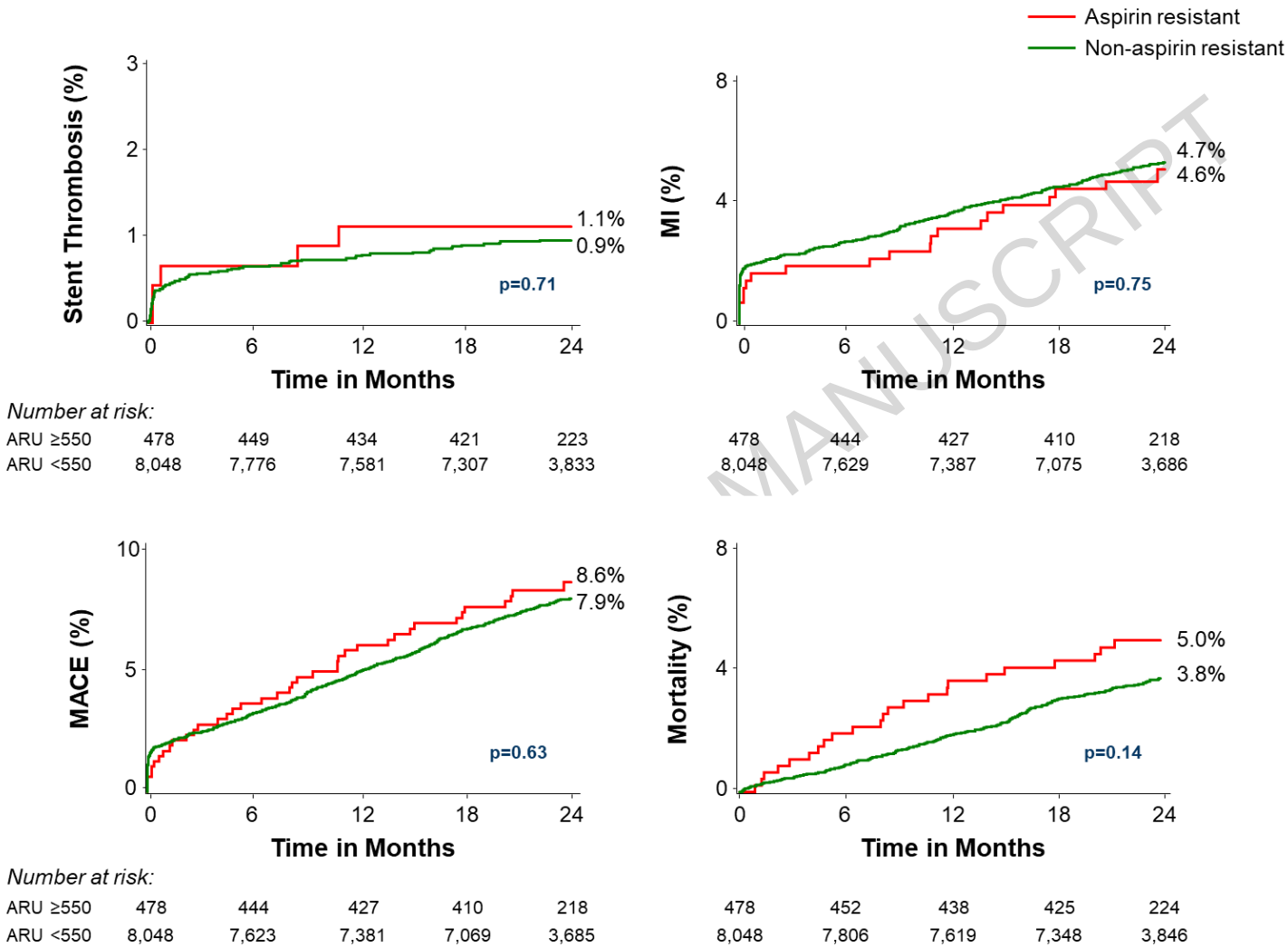
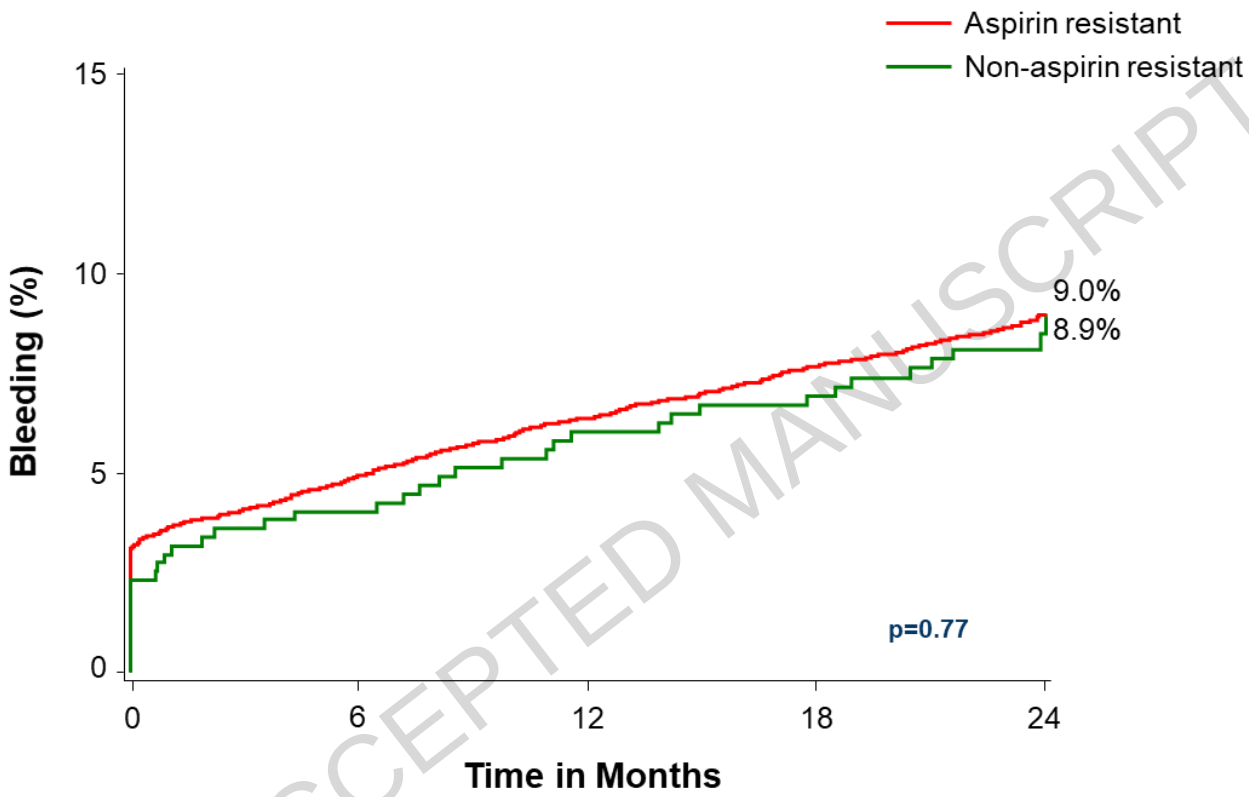


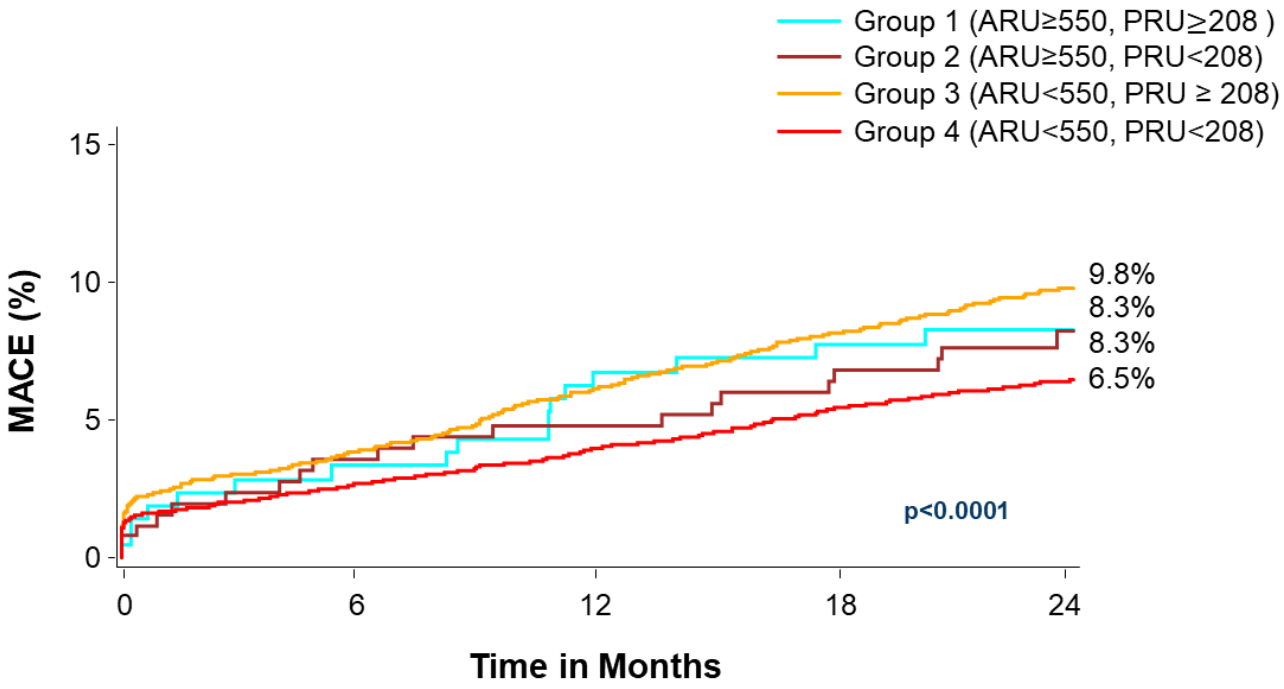
Figure 2



Number at risk:

ARU≥550	8,048	7,434	7,161	6,820	3,540
ARU<550	478	437	417	401	209

Figure 3



Number at risk:

Group 1	213	198	188	182	97
Group 2	259	241	236	225	120
Group 3	3,380	3,169	3,053	2,907	1,470
Group 4	4,549	4,343	4,222	4,063	2,172

Table I. Baseline Characteristics

	Aspirin Reaction Units		
	≥550	**<550**	**p Value**
	(n = 478)	**(n = 8048)**	
Age	67 ± 11	63 ± 11	<0.0001
≥75	123 (25.7)	1313 (16.3)	<0.0001
Male	358 (74.9)	5961 (74.1)	0.69
White	398 (83.3)	7158 (88.9)	0.0001
Body mass index	28.9 ±5.6	29.5 ± 5.7	0.04
Congestive heart failure	54 (11.3)	641 (8)	0.001
Peripheral arterial disease	60 (12.6)	810 (10.1)	0.08
Diabetes mellitus	160 (33.5)	2601 (32.3)	0.60
Hypertension	396 (82.8)	6397 (79.5)	0.08
Hyperlipidemia	383 (80.1)	5960 (74.1)	0.003
Chronic kidney disease	63 (13.2)	591 (7.3)	<0.0001
Current smoking	68 (14.2)	1862 (23.1)	<0.0001
Prior myocardial infarction	137 (28.7)	2018 (25.1)	0.08
Prior percutaneous coronary intervention	232 (48.5)	3426 (42.6)	0.01
Prior coronary artery bypass grafting	148 (31)	1307 (16.2)	<0.0001

Values are mean ± standard deviation or n (%).

Table II. Initial Presentation and Procedural Characteristics

	Aspirin Reaction Units		
	≥550 (n = 478)	**<550 (n = 8048)**	**p Value**
Presentation at hospital admission			
Asymptomatic coronary artery disease	73 (15.3)	984 (12.2)	0.05
Positive stress test	175 (36.6)	2233 (27.7)	<0.0001
Stable coronary artery disease	241 (50.4)	3887 (48.3)	0.37
Acute coronary syndromes	237 (49.6)	4161 (51.7)	0.37
Unstable angina	147 (30.8)	2203 (27.4)	0.11
Non–ST-segment elevation myocardial infarction	69 (14.4)	1170 (14.5)	0.95
ST-segment elevation myocardial infarction	21 (4.4)	788 (9.8)	<0.0001
Procedural characteristics			
1 diseased vessel	183 (38.3)	3076 (38.2)	0.10
2 diseased vessels	138 (28.9)	2678 (33.3)	0.05
3 diseased vessels	157 (32.8)	2294 (28.5)	0.04
Left main coronary artery disease	25 (5.2)	228 (2.8)	0.003
Glycoprotein IIb/IIIa inhibitor use	13 (2.7)	257 (3.2)	0.57
Lesions treated per patient	1.55 ± 0.82	1.50 ± 0.78	0.19
Total stent length, mm	33.6 ± 23.5	32.4 ± 22.3	0.29
Second-generation drug-eluting stent*	286 (59.8)	5122 (63.6)	0.09
First-generation drug-eluting stent†	147 (30.8)	2136 (26.5)	0.04

Values are mean ± standard deviation or n (%). *Everolimus-eluting or zotarolimus-eluting; †paclitaxel-eluting or sirolimus-eluting.

Table III. Aspirin Dosing and Compliance at 30 Days, 1 Year and 2 Years of Follow-Up

	Aspirin Reaction Units		p
	ARU ≥550 (n = 478)	**ARU <550 (n = 8048)**	**Value**
Aspirin use			
Before hospital admission	86.8% (415/478)	81.7% (6578/8048)	0.005
Loading dose anytime through procedure	91.0% (435/478)	88.6% (7129/8048)	0.10
Aspirin Prescribed at discharge			
None	0.4% (2/478)	0.8% (65/8042)	0.59
81 mg	18.3% (87/476)	13.5% (1077/7976)	0.003
≤100 mg	38.4% (183/47)	42.7% (3407/7976)	0.07
>100 mg	61.6% (293/476)	57.3% (4569/7976)	0.07
325 mg	60.5% (288/476)	56.2% (4484/7976)	0.07
Any dose	99.6% (476/478)	99.2% (7977/8042)	0.59
Aspirin compliance through 30 days			
Daily without discontinuation	95.4% (456/478)	93.8% (7553/8048)	0.17
None/discontinued	4.6% (22/478)	6.2% (495/8048)	0.17
Aspirin compliance through 1 year			
Daily without discontinuation	87.4% (418/478)	87.1% (7008/8048)	0.81
None/discontinued	12.6% (60/478)	12.9% (1040/8048)	0.81
Aspirin compliance through 2 years			
Daily without discontinuation	79.7% (381/478)	80.5% (6480/8048)	0.66
None/discontinued	20.3% (97/478)	19.5% (1568/8048)	0.66
Total days of aspirin use			
Median [IQR]	720.0 [696.0, 731.0]	722.0 [701.0, 731.0]	0.10
Mean ± SD	633.2 ± 194.7	650.1 ± 173.7	0.06

Table IV. Univariable and Propensity-Adjusted Multivariable Analysis of the Impact of Aspirin Resistance on Outcomes 2 Years after Drug-Eluting Stent Implantation

	Event Rate at 2 Years		Crude Hazard Ratio [95% Confidence Interval]	p Value	Multivariable Adjusted Hazard Ratio [95% Confidence Interval]	p Value
	ARU ≥550 (n = 478)	ARU <550 (n = 8048)				
Stent thrombosis	1.08% (5)	0.9% (72)	1.19 [0.48, 2.94]	0.71	1.00 [0.24, 4.21]	1.00
Myocardial infarction	4.57% (20)	4.74% (367)	0.93 [0.59, 1.46]	0.75	1.00 [0.52, 1.91]	1.00
Clinically-relevant bleeding	8.93% (39)	9.01% (694)	0.95 [0.69, 1.32]	0.77	1.30 [0.74, 2.28]	0.36
Major adverse cardiac events	8.62% (39)	7.93% (616)	1.08 [0.78, 1.50]	0.63	1.04 [0.64, 1.69]	0.87
All-cause mortality	5.04% (23)	3.77% (288)	1.38 [0.90, 2.11]	0.14	1.25 [0.67, 2.33]	0.48

Rates are Kaplan-Meier estimates at 2 years (number of events). p values correspond to the crude (unadjusted) and multivariable adjusted hazard ratio [95% confidence interval].
ARU = aspirin reaction units.

Table V. Impact of Aspirin Resistance on Outcomes 2 Years after Drug-Eluting Stent Implantation in Patients with Clopidogrel Resistance

	Event Rate at 2 Years		Crude Hazard Ratio	p Value	Multivariable Adjusted	p Value
	ARU ≥550 PRU ≥208 (n = 213)	ARU <550 PRU ≥208 (n = 3380)	[95% Confidence Interval]		Hazard Ratio [95% CI]	
Stent thrombosis	2.42% (5)	1.34% (44)	1.82 [0.72, 4.60]	0.20	1.45 [0.33, 6.31]	0.62
Myocardial infarction	4.94% (10)	5.72% (185)	0.86 [0.46, 1.63]	0.65	0.99 [0.67, 1.45]	0.94
Clinically-relevant bleeding	8.95% (17)	8.59% (274)	0.99 [0.61, 1.62]	0.98	1.17 [0.56, 2.41]	0.68
Major adverse cardiac events	8.30% (17)	9.80% (319)	0.85 [0.52, 1.39]	0.51	1.06 [0.55, 2.00]	0.87
All-cause mortality	4.43% (9)	4.83% (155)	0.94 [0.48, 1.83]	0.84	0.93 [0.37, 2.34]	0.88

Rates are Kaplan-Meier estimates at 2 years (number of events). p values correspond to the crude (unadjusted) and multivariable adjusted hazard ratio [95% confidence interval]. ARU = aspirin reaction units; PRU = P2Y12 reaction units.

Table VI. Impact of Aspirin Resistance on Outcomes 2 Years after Drug-Eluting Stent Implantation in Patients Who Discontinued Clopidogrel

	Event Rate at 2 Years		Crude Hazard Ratio [95% Confidence Interval]	p Value	Multivariable Adjusted Hazard Ratio [95% Confidence Interval]	p Value
	ARU ≥550 (n = 202)	ARU <550 (n = 4127)				
Stent thrombosis	1.00% (2)	0.82% (34)	1.24 [0.30, 5.15]	0.77	—	—
Myocardial infarction	4.56% (9)	4.88% (203)	0.82 [0.48, 1.81]	0.82	0.61 [0.18, 1.93]	0.40
Clinically-relevant bleeding	12.99% (26)	12.28% (510)	1.07 [0.72, 1.59]	0.73	0.72 [0.36, 1.41]	0.34
Major adverse cardiac events	7.93% (16)	7.19% (300)	1.11 [0.67, 1.84]	0.67	1.01 [0.49, 2.07]	0.98
All-cause mortality	4.46% (9)	2.68% (111)	1.71 [0.87, 3.37]	0.12	1.71 [0.73, 4.02]	0.21

Rates are Kaplan-Meier estimates at 2 years (number of events). p values correspond to the crude (unadjusted) and multivariable adjusted HR [95% CI]. ARU = aspirin reaction units; PRU = P2Y12 reaction units.

HIGHLIGHTS

- High on-aspirin platelet reactivity (HAPR) was infrequently present in a large registry of patients undergoing PCI.
- There was no clear relationship between HAPR and 2-year clinical outcomes in patients undergoing DES implantation.
- Even among patients with concomitant high on-clopidogrel platelet reactivity, HAPR was not associated with worse ischemic outcomes (adjusted HR for 2-year MACE: 1.06; 95% CI 0.55-2.00, p=0.87).