Aspirin Treatment and Outcomes After Percutaneous Coronary Intervention

Results of the ISAR-ASPI Registry

Katharina Mayer, MD,* Isabell Bernlochner, MD,† Siegmund Braun, MD,* Stefanie Schulz, MD,*
Martin Orban, MD,‡ Tanja Morath, MD,* Lisena Cala, MS,* Petra Hoppmann, MD,†
Heribert Schunkert, MD,*§ Karl-Ludwig Laugwitz, MD,†§ Adnan Kastrati, MD,*§ Dirk Sibbing, MD‡§

ABSTRACT

BACKGROUND Aspirin administration, as part of a dual antiplatelet treatment regimen, is essential for patients undergoing percutaneous coronary intervention (PCI). Although the correlation between high on-clopidogrel treatment platelet reactivity (HCPR) and clinical outcome is well established, data for high on-aspirin treatment platelet reactivity (HAPR) are conflicting.

OBJECTIVES The aim of the ISAR-ASPI (Intracoronary Stenting and Antithrombotic Regimen—ASpirin and Platelet Inhibition) registry was to assess the value of HAPR as a possible prognostic biomarker in PCI-treated patients with regard to clinical outcome.

METHODS From February 2007 to May 2013, we identified 7,090 consecutive PCI-treated patients with measured on-aspirin treatment platelet aggregation values directly before PCI. Platelet function was assessed with a Multiplate analyzer. The primary endpoint was death or stent thrombosis (ST) at 1 year.

RESULTS The upper quintile of patients (n = 1,414), according to Multiplate measurements, was defined as the HAPR cohort. Compared with non-HAPR patients (n = 5,676), HAPR patients showed a significantly higher risk of death or ST at 1 year (6.2% vs. 3.7%, respectively; odds ratio [OR]: 1.78; 95% confidence interval [CI]: 1.39 to 2.27; p < 0.0001). HAPR was found to be an independent predictor of the primary outcome (adjusted hazard ratio [HR_{adj}]: 1.46; 95% CI: 1.12 to 1.89; p = 0.005).

CONCLUSIONS HAPR, measured at the time point of the PCI, is associated with a higher risk for death or ST during the first year after PCI. Present data are in support of the addition of HAPR to a panel of prognostic biomarkers in PCI-treated patients. (J Am Coll Cardiol 2014;64:863-71) © 2014 by the American College of Cardiology Foundation.

A dual antiplatelet therapy consisting of aspirin and an adenosine diphosphate (ADP) receptor inhibitor represents the standard of care in patients with an acute coronary syndrome and in patients undergoing percutaneous coronary intervention (PCI). Although the phenomenon of inter-individual drug response variability is well described for the ADP receptor inhibitor clopidogrel and a high on-clopidogrel treatment platelet reactivity (HCPR) has been linked to a higher risk for ischemic events after PCI (1), data are conflicting with regard to aspirin treatment and a possible association with high on-aspirin treatment platelet reactivity (HAPR) and clinical outcome.

Early studies reported an association between HAPR and a higher risk for ischemic events in patients with cardiovascular disease (2-5), as well as an increased risk for the occurrence of stent thrombosis (ST) (6-8). Meta-analyses investigating the issue of HAPR and clinical outcome arrived at the same result: there were more cardiovascular events in patients displaying HAPR (9-11). In contrast, the recently published results of the large-scale ADAPT-DES (Assessment of Dual AntiPlatelet Therapy With Drug Eluting Stents) trial did not find a link between HAPR and the risk for ischemic events including ST, myocardial infarction (MI), or death (12). In contrast to HCPR (1), the term HAPR and the phenomenon of "aspirin resistance" are poorly defined in published reports, and its prevalence varies widely (13-16).

In this study, we measured periprocedural on-aspirin treatment platelet reactivity to further stratify PCI-treated patients with regard to their risk for ischemic events, and the aim of the ISAR-ASPI (Intracoronary Stenting and Antithrombotic Regimen—ASpirin and Platelet Inhibition) registry was to assess the prognostic value of HAPR in PCI-treated patients.

METHODS

STUDY POPULATIONS. For the registry, patients undergoing PCI (all Caucasian) in 2 participating centers (Deutsches Herzzentrum München and I. Medizinische Klinik, Klinikum rechts der Isar, Technische Universität München, Munich, Germany) were investigated.

Clinical and outcome data from all patients who were enrolled in this registry were prospectively collected. Between February 2007 and May 2013, a total of 7,090 consecutive patients who were pretreated with aspirin were analyzed with regard to platelet aggregation data and their clinical outcome (ischemic and bleeding events). All patients received an intravenous (IV) dose of 500 mg of aspirin and pretreatment with an ADP receptor antagonist in preparation for the PCI procedure. Aspirin, 100 mg twice daily, was recommended for an indefinite period. All other treatments, such as a dual antiplatelet treatment regimen including aspirin, were recommended per standard of care.

The availability of a platelet function assessment for the on-aspirin treatment platelet reactivity obtained immediately before PCI was part of the inclusionary criteria. Patients were included in our registry with all clinical presentations, including stable angina, unstable angina, and ST-segment elevation myocardial infarction (STEMI) or non–ST-segment elevation myocardial infarction (NSTEMI). Patients with cardiogenic shock or ST at their index PCI were excluded from this registry.

BLOOD SAMPLING AND PLATELET FUNCTION TESTING. Whole blood for platelet function testing was collected from all patients in 4.5-ml plastic tubes containing the anticoagulant lepirudin (25 μg/ml) (Refludan; Dynabyte, Munich, Germany). Along with the index PCI, blood samples for platelet function testing were obtained from the arterial sheath of patients immediately before PCI and after the administration of 500 mg of aspirin (IV) that was given a few minutes before PCI. Evidence that a few minutes' duration from administration of IV aspirin to measurement of platelet function is sufficient was provided earlier by our group (17) and others (18,19), by showing complete and immediate platelet inhibition across the thromboxane pathway within 5 min of IV aspirin administration.

Quantitative determination of platelet function triggered by arachidonic acid (AA) was assessed with impedance aggregometry, using the Multiplate analyzer (Roche Diagnostics, Basel, Switzerland), as recently described (20). Each Multiplate test cell incorporates 2 independent sensor units. One unit consists of 2 silver-coated highly conductive copper wires with a length of 3.2 mm. After dilution (1:2 with 0.9% NaCl solution) of lepirudin-anticoagulated whole blood and stirring for 3 min in the test cuvettes at 37°C, a final concentration of AA (0.5 mmol/l) was added. The increase of impedance due to the attachment of platelets to the electrodes is continuously recorded for each sensor unit separately and transformed to aggregation units (AU) that are plotted against time. Measurement time is 6 min. Aggregation measured with multiple electrode aggregometry is quantified as area under the curve of AU (AU × min). All materials used, including AA, were obtained from the manufacturer (Roche Diagnostics).

We defined HAPR by setting a cut-off point at the upper quintile (20%) of platelet aggregation measurements. The primary ischemic outcome measure was the composite of death from any cause or ST (definite or probable ST) at 1 year. Early outcome data (at 30 days) are presented here as well. We also assessed the incidence of cardiovascular death and MI. Cardiovascular death and definite and probable ST were defined according to Academic Research Consortium criteria (21). Hypercholesterolemia, arterial hypertension, and diabetes mellitus were defined according to World Health Organization guidelines

(Online Table S1). The troponin value shown in the baseline characteristics in **Table 1** was the pre-catheter value within the shortest interval to catheterization. With regard to bleeding, we assessed the incidence of in-hospital major and minor bleeding events, defined according to Thrombolysis In Myocardial Infarction (TIMI) criteria. Patients were expected to stay in the hospital for at least 2 days after PCI. Discharged patients were interviewed by telephone after 30 ± 7 days and after 1 year. Those patients with cardiac complaints were seen in the outpatient clinic for complete clinical, electrocardiographic, and laboratory check-up. ISAR study center personnel collected patient data and prospectively entered them into a computer database. All possible information from referring physicians, relatives, and hospital readmissions were entered. Source documents were checked to ensure high-quality data.

STATISTICAL ANALYSIS. Variables are mean $\pm$ SD, counts (percentages), and median with interquartile range. Kolmogorov-Smirnov test was used to test for normal distribution of continuous data. Platelet function data were not normally distributed, and dependent data were compared with 2-sided Wilcoxon test. Categorical variables were compared using chi-square test, and normally distributed variables were compared using the 2-sided Student *t* test. Survival analyses were performed by using the Kaplan-Meier method, and the differences between groups were assessed by the log-rank test and the calculation of odds ratios (ORs) (95% confidence intervals [CIs]) associated with the 30-day and 1-year rates of outcome of interest. For 1-year outcome data, a Cox proportional hazards model was used to assess the independent association between HAPR and death or ST by calculating adjusted hazard ratios (HR) with 95% CI. All variables in **Table 1** were entered into the Cox model together with HAPR. Propensity score matching analysis was used to select an equal number of non-HAPR patients (n = 1,414) who matched the HAPR patient cohort with regard to variables shown in Online Table S2. The discriminatory power of the model regarding death or ST risk with and without inclusion of HAPR was assessed by calculating the c-statistics as well as the integrated discrimination improvement (IDI) and the net reclassification improvement (NRI) according to Pencina et al. (22). For both c-statistic and NRI, the R software library "Hmisc" of Harrell (without categories) was used (23,24).

For all statistical analyses, a p value of <0.05 was considered significant. All analyses were performed using R software package (R Statistical Software, Foundation for Statistical Computing, Vienna, Austria).
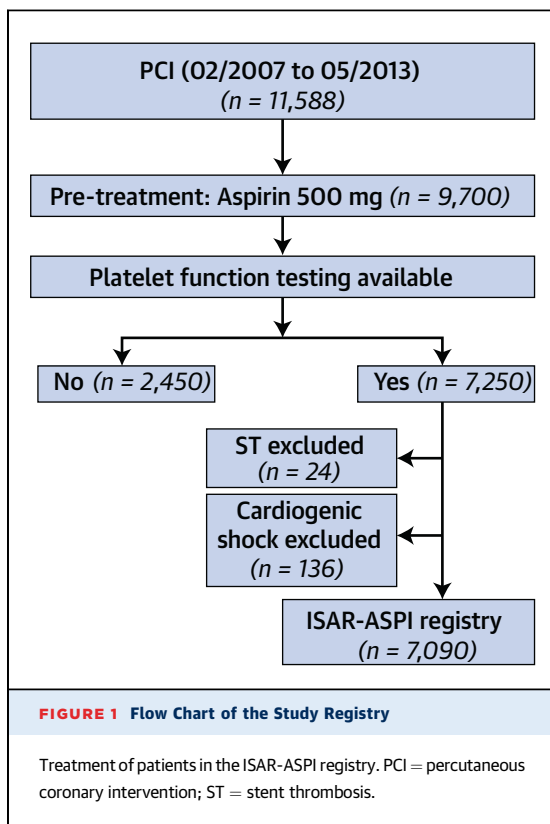
TABLE 1 Baseline Characteristics of the Patients			
	ASPI >203 (5th Quintile) (n = 1,414)	ASPI ≤203 (1st-4th Quintile) (n = 5,676)	p Value
Age, yrs	68.6 ± 11.3	68.0 ± 10.9	0.08
Female	283 (20)	1,399 (24.6)	0.0002
Body mass index, kg/m²	27.3 ± 4.4	27.6 ± 4.5	0.03
Patients with diabetes mellitus	380 (26.9)	1,608 (28.3)	0.28
Patients with arterial hypertension	818 (57.9)	3302 (58.2)	0.83
Systolic blood pressure, mm Hg	144.8 ± 25.7	148.2 ± 25.4	<0.0001
Active smokers	220 (15.6)	962 (16.9)	0.21
Patients with hypercholesterolemia	1,000 (70.7)	4,256 (74.9)	0.001
LDL cholesterol, mg/dl	105.7 ± 39.2	108.3 ± 41.2	0.03
HDL cholesterol, mg/dl	49.4 ± 15.9	49.9 ± 15.3	0.28
Troponin T, ng/ml	0.17 ± 0.65	0.12 ± 0.63	0.009
Creatinine, mg/dl	1.1 ± 0.4	1.1 ± 0.6	0.85
ADP (AU × min)	371.2 ± 277.3	281 ± 241.8	<0.0001
Taking aspirin at admission	1,290 (91.2)	5,323 (93.8)	0.0006
Taking ADP receptor blocker at admission	943 (66.7)	4,042 (71.2)	0.001
Taking ADP receptor blocker at discharge			0.21
None	6 (0.4)	14 (0.2)	
Clopidogrel	1,340 (94.8)	5,396 (95.1)	
Prasugrel	61 (4.3)	248 (4.4)	
Ticagrelor	6 (0.4)	17 (0.3)	
Ticlopidin	1 (0.07)	1 (0.02)	
Patients with previous MI	357 (25.3)	1,428 (25.2)	0.95
Patients with previous bypass surgery	197 (13.9)	786 (13.9)	0.93
Patients with coronary artery disease			0.68
1-vessel disease	258 (18.3)	994 (17.5)	
2-vessel disease	379 (26.8)	1,493 (26.3)	
3-vessel disease	777 (54.9)	3,189 (56.2)	
Patients with CAD presentation			<0.0001
STEMI	140 (9.9)	523 (9.2)	
NSTEMI	137 (9.7)	419 (7.4)	
Unstable angina	291 (20.6)	1,453 (25.6)	
Stable angina	846 (59.8)	3,281 (57.8)	

Values are mean ± SD or n (%).

ADP = adenosine diphosphate; ASPI = arachidonic-acid-induced platelet aggregation value on the Multiplate Analyzer (ASPItest); AU = aggregation unit; CAD = coronary artery disease; HDL = high-density lipoprotein; LDL = low-density lipoprotein; MI = myocardial infarction; NSTEMI = non–ST-segment elevation myocardial infarction; STEMI = ST-segment elevation myocardial infarction.

RESULTS

Figure 1 provides an overview of patients included in the ISAR-ASPI registry. The baseline characteristics of the HAPR and non-HAPR cohorts are shown in **Table 1**. The 2 cohorts differed with regard to a number of baseline characteristics (**Table 1**). Patients with HAPR were more often men and showed hypercholesterolemia less often; had lower body mass index, low-density lipoprotein cholesterol concentrations, and systolic blood pressure, as well as higher troponin and ADP values at admission than non-HAPR patients. Additionally, non-HAPR patients more often had aspirin and ADP receptor blocker in their medication regimens at admission. The percentage of aspirin at admission was 91.2% in HAPR

FIGURE 1   Flow Chart of the Study Registry

Treatment of patients in the ISAR-ASPI registry. PCI = percutaneous coronary intervention; ST = stent thrombosis.

patients compared to 93.8% in non-HAPR patients (p = 0.0006). The percentage of ADP receptor blocker at admission was 66.7% in HAPR patients compared to 71.2% in non-HAPR patients (p = 0.001). Further details about the type of ADP receptor blocker

administered at discharge are provided in **Table 1**. Of note, the proportion of patients with STEMI and NSTEMI at presentation was higher in patients with HAPR than in non-HAPR patients, whereas the proportion of patients with stable and unstable angina was higher in non-HAPR patients. Detailed information for angiographic and procedural characteristics of both study cohorts is shown in **Table 2**. The distribution of these characteristics was well balanced between the 2 cohorts. The majority of lesions (94%) were treated with a drug-eluting stent (DES) during the index procedure.

According to propensity matching analysis, 1,414 HAPR patients and 1,414 non-HAPR patients matched for variables displayed in Online Table S2 were identified. Baseline characteristics of propensity score-matched cohorts are shown in Online Table S2.

ON-ASPIRIN TREATMENT PLATELET AGGREGATION.
The median (interquartile range) AA-induced platelet aggregation of patients in the ISAR-ASPI registry was 115 (52 to 179) AU × min. The upper quintile of platelet aggregation values was defined as HAPR, corresponding to a cut-off value of 203 AU × min. Patients with an AA-induced platelet aggregation value of ≤203 AU × min are referred to as non-HAPR (n = 5,676) patients, and those with values >203 are referred to as HAPR patients (n = 1,414). **Figure 2** shows the distribution of platelet reactivity measurements observed after stimulation with AA, following loading with a single high-loading dose of 500 mg aspirin.

CLINICAL OUTCOME. The incidence of in-hospital bleeding events (TIMI major and minor) in the HAPR patients was not significantly different from that in the non-HAPR cohort (95 bleeding events [6.7%] in the HAPR cohort vs. 324 bleeding events [5.7%] in the non-HAPR cohort; p = 0.15). The 30-day outcome data for all ischemic endpoints under investigation are shown in **Table 3**.

The incidence of the primary outcome (incidence of 1-year death or ST) was significantly higher in the HAPR cohort than in the non-HAPR cohort (88 events [6.2%] vs. 208 events [3.7%]; OR: 1.78, 95% CI: 1.39 to 2.27; p < 0.0001). **Figure 3** shows a comparison between the cumulative incidence of the primary outcome during 1-year follow-up in the HAPR versus that in the non-HAPR cohort. The risk for 1-year ST (definite or probable) was significantly higher in the HAPR than in the non-HAPR cohort of patients (16 STs [1.1%] vs. 35 STs [0.6%]; OR: 1.88; 95% CI: 1.05 to 3.37; p = 0.03) (**Figure 4**). The incidence of cardiovascular death was 4.2% in HAPR versus 1.9% in non-HAPR patients (OR: 2.27; 95% CI: 1.67 to 3.09; p < 0.0001). **Table 4** shows a comparison between the entire

TABLE 2 Angiographic and Procedural Characteristics			
	ASPI >203 (5th Quintile) (n = 2,509)	ASPI ≤203 (1st–4th Quintile) (n = 9,990)	p Value
Target vessels			0.59
Left main coronary artery	118 (4.7)	485 (4.9)	
Left anterior descending coronary artery	1,047 (41.7)	4,111 (41.2)	
Left circumflex coronary artery	630 (25.1)	2,444 (24.5)	
Right coronary artery	671 (26.7)	2,734 (27.4)	
Venous bypass graft	43 (1.7)	216 (2.2)	
Complex (type B2 or C) lesions	1,941 (77.4)	7,690 (76.9)	0.68
Chronic occlusions	168 (6.7)	689 (6.9)	0.72
Ostial lesions	619 (24.7)	2,404 (24.1)	0.53
Bifurcation lesions	784 (31.2)	3,048 (30.5)	0.47
Type of intervention			0.06
Placement of drug-eluting stent	2,368 (94.4)	9,377 (93.9)	
Placement of bare-metal stent	26 (1.0)	71 (0.7)	
Balloon angioplasty	115 (4.6)	542 (5.4)	

Values are n (%). Lesion-related angiographic and procedural characteristics of the patients are shown.

clinical outcome data for HAPR versus those for non-HAPR patients at 1 year.

After we performed propensity-score matching, the incidence of in-hospital bleeding events (TIMI major and minor) differed significantly between cohorts (95 bleeding events [6.7%] in the HAPR cohort vs. 67 bleeding events [4.7%] in the non-HAPR cohort; p = 0.023). According to propensity matching analysis, the incidence of the primary outcome (incidence of 1-year death or stent thrombosis) was significantly higher in the HAPR than in the non-HAPR cohort (88 [6.2%] vs. 63 [4.5%] events, respectively; HR: 1.44; 95% CI: 1.04 to 1.99; p = 0.027). Detailed results are provided in Online Table S3.

MULTIVARIATE ANALYSES. In a Cox proportional hazards model with the primary endpoint as the dependent variable and HAPR and all variables listed in Table 1 (including troponin) as independent variables, HAPR was found to be an independent predictor of the primary outcome (adjusted HR [HR_{adj}]: 1.46; 95% CI: 1.12 to 1.89; p = 0.005).

For the primary endpoint of death or ST, the c-statistic of the model without inclusion of HAPR was 0.796. Adding HAPR to the model increased the c-statistic to 0.797 (p = 0.002). The IDI for the primary endpoint was calculated, and inclusion of HAPR in the model was associated with a significant improvement of the discriminatory power of the model regarding the prediction of death or ST at 1 year (absolute IDI = 0.0038; relative IDI = 3.8%; p = 0.018). The NRI improved significantly and was 19.1% after inclusion of HAPR (95% CI: 7.5% to 30.7%; p < 0.001).

DISCUSSION

In the present ISAR-ASPI registry, we investigated the prognostic value of on-aspirin treatment platelet aggregation measurements and specifically that of HAPR in PCI-treated patients. There are 3 key findings from our study. First, the risk of death or ST is significantly higher in HAPR than in non-HAPR patients; second, HAPR is an independent predictor for ischemic event occurrence in PCI-treated patients receiving aspirin; and third, knowledge of the presence or absence of HAPR can be used to further stratify PCI-treated patients regarding their risk for death or stent thrombosis. In fact, performance measure with regard to association (ORs and HRs), discrimination (c-statistics, IDI), and reclassification (NRI) were positive for the biomarker (HAPR) under investigation.

With our registry data, we provide evidence for a possible role of HAPR as a clinically useful biomarker that could be added to the well-established biomarkers in coronary artery disease (CAD) patients.
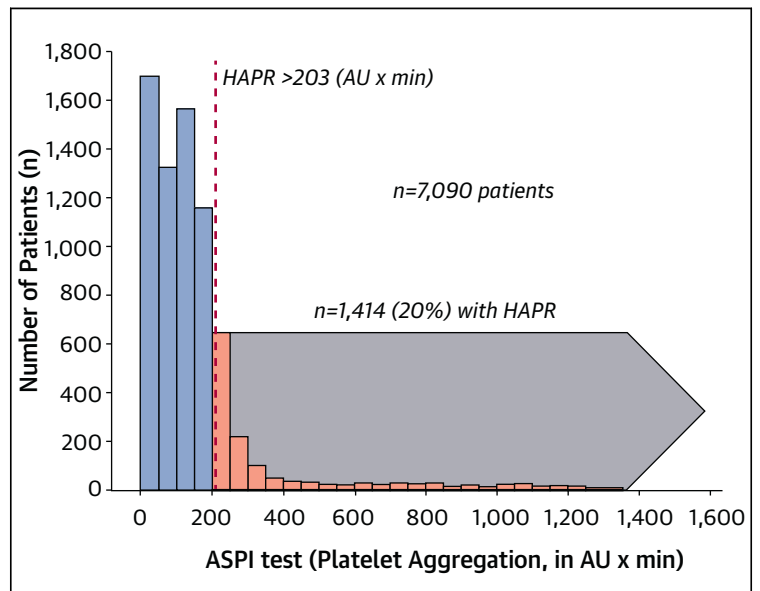

FIGURE 2   Distribution of On-Aspirin Treatment Platelet Reactivity Measurements

Distribution of platelet function measurements in the ISAR-ASPI registry of PCI-treated patients following loading with 500 mg of aspirin. Values obtained with the Multiplate analyzer assay are shown as AU × min. The **dotted line** indicates the cut-off value for HAPR. The **gray arrow** illustrates the proportion of patients with HAPR. AU = aggregation unit; HAPR = high on-aspirin platelet reactivity; PCI = percutaneous coronary intervention.

Of note, information on the presence or absence of HAPR increased the discriminatory power of our multivariate Cox model, including troponin, for death or ST prediction. Thus, knowledge of the presence of HAPR in a PCI-treated patient receiving aspirin and obtained at the time point of the intervention offers prognostic information that is independent of or even supplementary to that provided by well-established

TABLE 3   Clinical Outcome at 30 Days

Event	ASPI >203 (5th Quintile) (n = 1,414)	ASPI ≤203 (1st–4th Quintile) (n = 5,676)	OR (95% CI)	p Value
Primary endpoint				
Death or ST definite or ST probable	35 (2.5)	63 (1.1)	2.24 (1.50–3.36)	<0.0001
Secondary endpoints				
ST definite or probable	12 (0.8)	20 (0.4)	2.42 (1.21–4.84)	0.012
ST definite	9 (0.6)	17 (0.3)	2.14 (0.97–4.70)	0.06
ST probable	3 (0.2)	3 (0.05)	4.05 (0.92–17.7)	0.06
All-cause death	30 (2.1)	50 (0.9)	2.43 (1.56–3.76)	<0.0001
Cardiovascular death	24 (1.7)	37 (0.7)	2.62 (1.59–4.29)	0.0001
Myocardial infarction	38 (2.7)	121 (2.1)	1.26 (0.88–1.82)	0.21
Death or MI	59 (4.2)	157 (2.8)	1.51 (1.13–2.04)	0.006

Values are n (%). Ischemic clinical outcome data in the HAPR (ASPI >203) and non-HAPR (ASPI ≤203) cohorts at 30 days are shown.

CI = confidence interval; HAPR = high on-aspirin treatment platelet reactivity; MI = myocardial infarction; OR = odds ratio; ST = stent thrombosis.
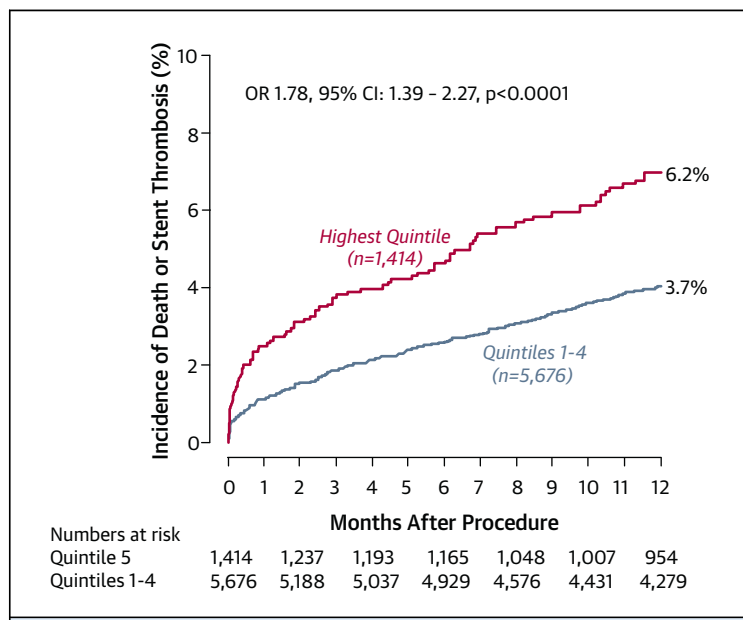
FIGURE 3 1-Year Incidence of Death or Stent Thrombosis

Kaplan-Meier curves show the incidence of the primary endpoint (death or stent thrombosis) during the 1-year follow-up period according to platelet reactivity on-aspirin treatment in HAPR patients **(red line)** versus non-HAPR patients **(slate line)**. CI = confidence interval; HAPR = high on-aspirin treatment platelet reactivity; OR = odds ratio.
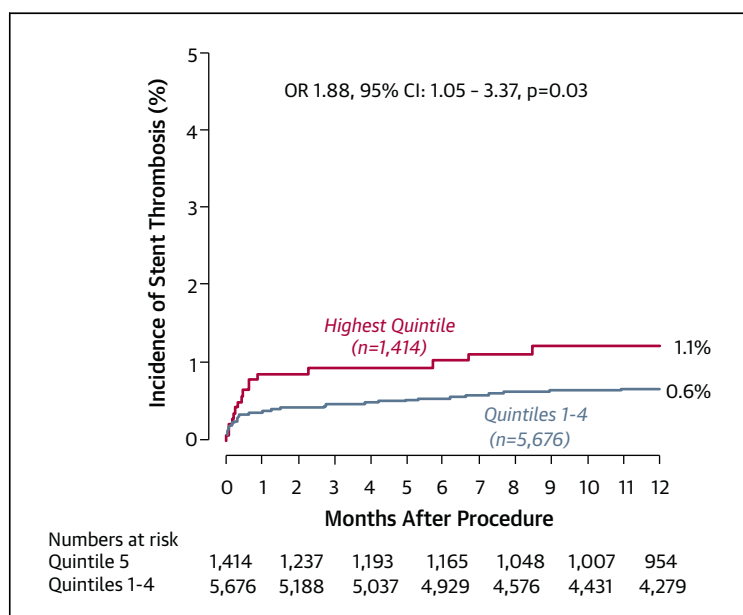

FIGURE 4 1-Year Incidence of Stent Thrombosis

Kaplan-Meier curves show the incidence of stent thrombosis (probable or definite) during the 1-year follow-up period according to platelet reactivity on-aspirin treatment in HAPR patients **(red line)** versus non-HAPR patients **(slate line)**. Abbreviations as in **Figure 3**.

cardiovascular risk factors such as troponin level, diabetes or other relevant comorbidities, and clinical variables (**Central Illustration**). From a statistical point of view and with regard to the performance of HAPR as a prognostic biomarker, with the different metrics applied (c-statistics, IDI, NRI) to assess the additive value of HAPR in addition to clinical variables provided, statistically significant results support the usefulness of HAPR as a biomarker in CAD patients. The NRI based on platelet function testing in our study performed well in comparison to the values of other biomarkers such as HCPR, coronary calcification, and intima media thickness that have been used to improve cardiovascular risk stratification (25-28).

We assessed platelet reactivity in a large cohort of 7,090 PCI-treated patients who had received a dual antiplatelet treatment regimen consisting of aspirin and an ADP receptor blocker. Our findings concur with those from previous, smaller studies and from meta-analyses investigating HAPR and its role in clinical outcome prediction (2-6,11-14,31). In contrast to our findings, the recently published results of the ADAPT-DES trial (12) showed no significant association between HAPR and ischemic events, including death or ST. Although both our study, with 7,090 subjects, and the ADAPT-DES trial, with 8,665 subjects, investigated a large cohort of PCI-treated patients including the largest population cohorts that have been studied thus far to assess the prognostic value of platelet function testing, the exact reason for the discrepancy in results remains unclear. Possible explanations include differences in study design, which are a different time point of blood sampling and platelet function testing (during PCI in our cohort vs. day 1 post-PCI in ADAPT-DES), a different testing device used (Multiplate analyzer in our cohort vs. VerifyNow assay [Accumetrics, San Diego, California] in ADAPT-DES), each with a distinct cut-off value to define HAPR. By using different devices with distinct HAPR cut-off values, the composition and size for the populations at risk for cardiovascular events varies widely between these 2 studies (20% in our cohort vs. 5.6% in ADAPT-DES) (12), which may in part explain the different results observed in the 2 studies.

General issues surrounding the testing for on-aspirin treatment platelet reactivity include the lack of clearly defined and established cut-off values to define this phenomenon. This is in contrast to testing the responsiveness to ADP receptor antagonists, where consensus cut-off values are established for the most commonly used devices for testing (1,29). Lacking such a clear definition of HAPR, the reported proportion of HAPR varies widely from 0.4% to 83.3% between test methods (13-16). We chose the upper

quintile of patients for defining a "population at-risk" with regard to on-aspirin treatment platelet reactivity. Fixing a cut-off point at the upper quintile of patients for HAPR was analogous to our early investigations with regard to HCPR in clopidogrel-treated patients undergoing PCI (30). Conflating present results and results of our previous investigations in clopidogrel-treated patients (30), it can be stated that the upper quintile of patients must be considered a high-risk cohort for the occurrence of ischemic events with regard to both ADP- and AA-mediated platelet reactivity testing results for the respective antiplatelet agents (clopidogrel and aspirin) under investigation. However, further studies are needed to corroborate present results and to fix HAPR cut-off values for the different devices used for testing.

Of note, the most important factor leading to the phenomenon of aspirin resistance or HAPR in previous studies was postulated to be simply noncompliance to aspirin treatment (31,32). However, the issue of noncompliance is overcome by the design of our registry, as we assessed the on-aspirin treatment platelet aggregation values after monitored IV treatment with 500 mg of aspirin, and HAPR was assessed at 1 time point directly before PCI. It is important to emphasize in this context that the value we measured cannot be considered simply as a response marker for aspirin treatment, because baseline (off-treatment values) are missing here, and the determined on-treatment value is a result of the baseline platelet reactivity level of the individual patient and the individual response to the administered aspirin treatment. Numerous clinical variables and a certain inflammatory status are likely to have an impact on this determined aggregation value.

We investigated the prognostic value of HAPR as a new biomarker. In multivariate analyses, we identified HAPR in our registry as an independent predictor of primary outcome (death or ST) at 1 year after PCI. Thus, for the individual patient undergoing PCI, HAPR, assessed at a single time point at PCI, offers prognostic information in addition to well-established risk factors to further stratify PCI-treated patients receiving aspirin regarding their risk for death or ST. This leaves room for improved clinical decision making based on HAPR assessment. The role of HAPR testing for guidance of treatment remains unclear and cannot be answered by our data. The question remains whether there is a high-risk group of patients who might benefit from a tailored antiplatelet therapy based on HAPR testing. Recent attempts to assess the impact of an intensified aspirin treatment on clinical outcome provide divergent
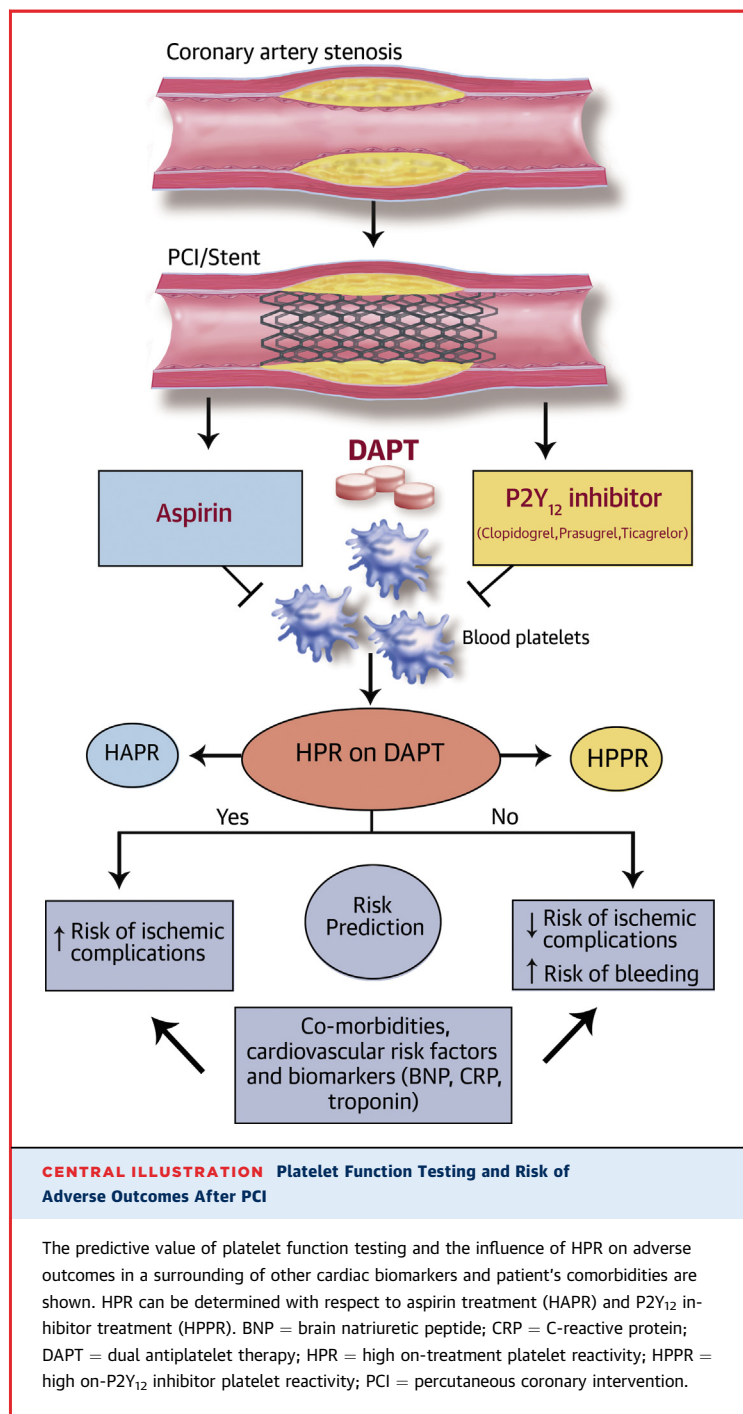
TABLE 4	Clinical Outcome at 1 Year			
Event at 1 Year	ASPI >203 (5th Quintile) (n = 1,414)	ASPI ≤203 (1st–4th Quintile) (n = 5,676)	OR (95% CI)	p Value
Primary endpoint				
Death or ST definite or ST probable	88 (6.2)	208 (3.7)	1.78 (1.39–2.27)	<0.0001
Secondary endpoints				
ST definite or probable	16 (1.1)	35 (0.6)	1.88 (1.05–3.37)	0.03
ST definite	11 (0.8)	27 (0.5)	1.67 (0.84–3.34)	0.15
ST probable	5 (0.4)	8 (0.1)	2.61 (0.89–7.66)	0.08
All-cause death	84 (5.9)	189 (3.3)	1.87 (1.45–2.41)	<0.0001
Cardiovascular death	59 (4.2)	109 (1.9)	2.27 (1.67–3.09)	<0.0001
Myocardial infarction	48 (3.4)	153 (2.7)	1.28 (0.92–1.77)	0.14
Death or MI	117 (8.3)	316 (5.6)	1.54 (1.25–1.90)	<0.0001

Values are n (%). Ischemic clinical outcome data in the HAPR (ASPI >203) and non-HAPR (ASPI ≤203) cohorts at 1 year are shown.

Abbreviations as in **Table 3**.

results. Although there is evidence implicating the fact that HAPR can be overcome by higher doses of aspirin (33), a large meta-analysis in 2002 saw no advantage of medium or high doses compared to low doses of aspirin for clinical outcome (34). Another meta-analysis in 2012 comparing high- and low-dose aspirin in patients with acute coronary syndrome found no difference in ischemic event rates (35). In the large-scale ARCTIC (Assessment by a Double Randomization of a Conventional Antiplatelet Strategy Versus a Monitoring-Guided Strategy for Drug-Eluting Stent Implantation and of Treatment Interruption Versus Continuation One Year After Stenting) trial, designed to assess the impact of tailored antiplatelet therapy, in case of HAPR, an additional bolus of IV aspirin was administered without any clinical benefit (36). Another approach was described by Frelinger et al. (37), who demonstrated that there are ADP-dependent but cyclooxygenase-1– and cyclooxygenase-2–independent pathways in patients with residual HAPR. This suggests that, at least in part, residual HAPR might be overcome by additional administration (or even prolongation) of ADP receptor antagonist treatment (37).

Research and a better characterization of novel biomarkers in CAD patients may improve ischemic risk prediction and may thereby improve the outcome of PCI-treated patients. In clinical practice, a panel of biomarkers is used to improve individual risk assessment (38). Testing for HAPR as a new biomarker for PCI-treated patients under treatment with aspirin can help to refine the predictive accuracy of such risk prediction panels in these patients. However, further studies are needed to investigate

CENTRAL ILLUSTRATION Platelet Function Testing and Risk of Adverse Outcomes After PCI

The predictive value of platelet function testing and the influence of HPR on adverse outcomes in a surrounding of other cardiac biomarkers and patient's comorbidities are shown. HPR can be determined with respect to aspirin treatment (HAPR) and $P2Y_{12}$ inhibitor treatment (HPPR). BNP = brain natriuretic peptide; CRP = C-reactive protein; DAPT = dual antiplatelet therapy; HPR = high on-treatment platelet reactivity; HPPR = high on-$P2Y_{12}$ inhibitor platelet reactivity; PCI = percutaneous coronary intervention.

the role of HAPR and HCPR alone and in concert with regard to their predictive value and with regard to their roles as possible modifiable cardiovascular risk factors that can be altered by a tailored antiplatelet treatment in patients undergoing PCI.

STUDY LIMITATIONS. First, present data are observational, with all the inherent limitations of a retrospective analysis. We did not perform an assessment of aspirin response because baseline (off-treatment values) data were missing in addition to on-treatment testing. Here, we only used 1 device (Multiplate analyzer) for platelet function testing, and it is unknown how our findings should be extrapolated to other platelet function assays and clinical scenarios. Platelet reactivity on aspirin was measured only at a single time point in the acute phase after acute administration. These results cannot substitute for chronic on-treatment platelet reactivity data. For this study, drug compliance, including compliance with antiplatelet treatment, was not recorded on an individual basis, and we cannot exclude the possibility that this may have influenced the results. However, both early outcome data at 30 days, when a high compliance rate can be assumed, as well as 1-year outcome data provided uniform results with regard to the predictive value of on-aspirin treatment platelet aggregation measurements.

CONCLUSIONS

HAPR, measured at a single time point before PCI is associated with a higher risk for death or ST during the first year post-PCI. Present data support the addition of HAPR to a panel of prognostic biomarkers in PCI-treated patients.

REPRINT REQUESTS AND CORRESPONDENCE: Dr. Katharina Mayer, Deutsches Herzzentrum München, Lazarettstrasse 36, 80636 Munich, Germany. E-mail: katharina.mayer.mt@gmx.de.

PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: Although a relationship between platelet reactivity and clinical outcomes has been established for therapy with clopidogrel in patients undergoing PCI, correlative data regarding the clinical implications of platelet reactivity on aspirin have been inconsistent. This study found high platelet reactivity in patients on aspirin at the time of PCI associated with a greater risk of death or stent thrombosis during the first year after PCI.

TRANSLATIONAL OUTLOOK: Additional studies are needed to investigate the utility of measuring platelet reactivity in response to both aspirin and clopidogrel in patients undergoing PCI to facilitate individualized antiplatelet treatment regimens.

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KEY WORDS aspirin, biomarker, high platelet reactivity, stent thrombosis

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