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Original Article

High on-aspirin platelet reactivity predicts cardiac death in acute coronary syndrome patients undergoing PCI

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ABSTRACT

Objective: To evaluate the possible role of high on-aspirin platelet reactivity (HaPR) in a prospective cohort of acute coronary syndrome (ACS) patients undergoing percutaneous coronary intervention (PCI).
Background: Several studies documented that high on-clopidogrel platelet reactivity (HcPR) is associated with increased risk of ischemic events in ACS patients undergoing PCI. On the contrary, conflicting data are available on HaPR and clinical outcome.
Methods: Platelet reactivity was assessed by light transmittance aggregometry using arachidonic acid as an agonist in 1789 ACS patients undergoing PCI.
Results: HaPR was found in 20.3% of patients. These patients were significantly older, with a higher prevalence of hypertension, diabetes and reduced ejection fraction. Patients with non ST-segment elevation ACS, 3-vessel disease and multivessel PCI had a significantly higher prevalence of HaPR. In addition, stent number and length, and use of drug-eluting stents were significantly higher in HaPR patients. At 24-month follow-up the prevalence of cardiac death was 9.7% in HaPR and 3.8% in non-HaPR [HR2.63(1.72–4.02), $p < 0.0001$], that of stent thrombosis 6.1% in HaPR and 2.6% in non-HaPR [HR2.4(1.42–4.07), $p < 0.001$], with no significant differences in other clinical end-points. At multivariate analysis, HaPR was confirmed as an independent risk factor for cardiac death [HR1.88(1.21–2.93), $p = 0.005$] and stent thrombosis [HR1.91(1.12–3.28), $p = 0.018$]. The addition of HaPR to a model including clinical and procedural risk factors and HcPR led to a significant improvement in the prediction of cardiac death (NRI 39 ± 10%, $p = 0.0003$) and stent thrombosis (NRI 34.7 ± 13.2%, $p = 0.009$).
Conclusion: HaPR was found to be an independent risk factor for cardiac death and stent thrombosis in ACS patients undergoing PCI.

1. Introduction

Several studies showed that high on clopidogrel platelet reactivity (HcPR) is associated with a high risk for major cardiovascular events in patients with acute coronary syndromes (ACS) undergoing percutaneous coronary intervention (PCI) [1,2]; on the contrary, fewer and conflicting data are available with regard to a possible correlation between high on aspirin platelet reactivity (HaPR) and clinical outcome. Indeed, in contrast to HcPR, the phenomenon of "aspirin resistance" is less well defined, and its prevalence varies widely among published reports [3–5]. Some studies found a higher risk for ischemic events and stent thrombosis in patients with HaPR [6–9], and recently, the results of the large-scale ISAR–ASPI (Intracoronary Stenting and Antithrombotic Regimen–Aspirin and Platelet Inhibition) registry showed that HaPR is associated with a higher risk for death or stent thrombosis during the first year after PCI [10]. In contrast, in the prospective multicenter ADAPT-DES (Assessment of Dual AntiPlatelet Therapy with Drug Eluting Stents) registry no association was found between HaPR and ischemic events [11].

The aim of our study was to evaluate the possible role of HaPR in the population of RECLOSE 2 (Responsiveness to Clopidogrel and Stent Thrombosis 2)–ACS study, in which we demonstrated that HcPR is

Abbreviations: HcPR, High on clopidogrel platelet reactivity; ACS, Acute coronary syndromes; PCI, Percutaneous coronary intervention; HaPR, High on aspirin platelet reactivity; STEMI, ST-segment elevation myocardial infarction; NSTEMI, Non-STEMI; UA, Unstable angina; AA, Arachidonic acid; DES, Drug eluting stents; ADP, Adenosine diphosphate.

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associated with increased risk of ischemic events at short and long term follow-up [2].

2. Methods

2.1. Study design and patient population

The RECLOSE 2–ACS study was a prospective, observational, single-center cohort study of consecutive patients with ACS undergoing an invasive procedure in which platelet reactivity after PCI was prospectively assessed [2]. The study enrolled consecutive patients undergoing coronary stent implantation for ACS from April 2005 to April 2009 at the Division of Cardiology of Careggi Hospital, Florence, Italy. ACS included ST-segment elevation myocardial infarction (STEMI), non-STEMI (NSTEMI), and unstable angina (UA) with ST segment changes. All patients were considered eligible for the study irrespective of clinical presentation of ACS or coronary anatomy. Thus, patients with multivessel disease requiring multivessel intervention in the same procedure or in a staged procedure were included. The exclusion criteria were in-hospital death that was not due to stent thrombosis, and anticipated non-adherence to dual antiplatelet treatment for at least 6 months, which was assessed through the evaluation of potential side effects of antiplatelet administration, such as hypersensitivity and active pathological bleeding (i.e. peptic ulcer, intracranial hemorrhage). Furthermore, we excluded patients with life-expectancy lower than 6 months. The study was approved by the local Ethics Committee. All patients gave written informed consent.

2.2. PCI and antiplatelet management

All interventions were performed according to current standards [12], and the type of stent implanted and the use of glycoprotein IIb/IIIa inhibitors were at the discretion of the operator. All STEMI patients received 500 mg of aspirin intravenously (I.V.), and a loading dose of 600 mg of clopidogrel per os (p.o.). NSTEMI/UA patients received 325 mg aspirin p.o., and a loading dose of 600 mg of clopidogrel p.o. Aspirin, 100–325 mg once daily, was recommended for an indefinite period; clopidogrel 75 mg once daily for at least 12 months.

2.3. Platelet reactivity assessment

Platelet reactivity assessment was made by light transmittance aggregometry (APACT4, Helena Laboratories, Milan, Italy) using arachidonic acid (AA) as an agonist. Blood samples anticoagulated with 0.109 M sodium citrate (ratio, 9:1) were obtained 12–18 h from PCI. Platelet rich plasma, obtained by centrifuging whole blood for 10 min at 200 g, was stimulated with 1 mM AA. HaPR by AA test was defined as platelet aggregation of 20% or greater [13].

2.4. Follow-up and end-points

All patients had scheduled examinations at 1, 6, and 12 months, and annually thereafter. Adherence to antiplatelet treatment was assessed during scheduled or unscheduled examinations. All other possible information derived from hospital readmission or by the referring physician, relatives, or municipality live registries were entered into the prospective database.

All deaths were considered cardiac unless an unequivocal noncardiac cause could be documented. Myocardial infarction definition included the following criteria: electrocardiographic changes consistent with myocardial infarction or cardiac biomarker elevation (creatine kinase-MB or troponin I 3 times higher than the upper normal limit on 2 measurements) or cardiac biomarker re-elevation in patients with pre-PCI values higher than the upper normal limits (at least 50% higher than the previous nadir, with documentation that cardiac biomarkers were decreasing before PCI). Urgent coronary revascularization included intervention due to the recurrence of ACS. Stent thrombosis was defined according to the Academic Research Consortium criteria [14].

All events were adjudicated by an event adjudication committee whose members (R.M., P.B., and R.A.) were blinded for platelet function data.

2.5. Statistical analysis

Statistical analysis was performed using the software package SPSS 20 (SPSS Inc., Chicago, Illinois, USA). Discrete data were summarized as frequencies, and continuous data were expressed as means and standard deviations or medians and interquartile ranges (IQRs), as appropriate. The χ^2 test was used for comparison of categorical variables, and the unpaired 2-tailed Student t test or Mann–Whitney rank sum test were used to test the differences among continuous variables. Survival curves were generated with the use of the Kaplan–Meier method, and the difference between groups was assessed by log-rank test. A multivariable Cox proportional hazard model was performed to evaluate the independent contribution of clinical, angiographic, and procedural variables to the clinical end-points. Variables known to be related with prognostic outcome or variables with a p value < 0.05 at univariate Cox analysis were forced into the final multivariate model. To quantify how much the addition of a new biomarker correctly increases (upward movements) or decreases (downward movements) the risk predicted by the model for events and non-events, we assessed category-free Net Reclassification Improvement (NRI) according to Xanthakis et al. [15] by using Stata 13.0 (Lakeway Dr. College Station, TX, USA). All tests were two-sided, and a p value < 0.05 was considered significant.

3. Results

Baseline characteristics of the study population are reported in Table 1. HaPR was found in 20.3% of patients (364/1789). The patients with HaPR were significantly older, and had a significantly higher prevalence of hypertension, diabetes and reduced ejection fraction.

Table 1
Baseline characteristics of study population.

Characteristics	Total ($n = 1789$)	No HaPR ($n = 1425$)	HaPR ($n = 364$)	p value
Age, median (IQ), years	69.8 (61.2–78.0)	69.0 (60.3–76.8)	74.1 (65.5–80.2)	<0.001
Aged ≥ 75 years, *n* (%)	664 (37)	479 (34)	185 (51)	<0.001
Male gender, *n* (%)	1423 (80)	1143 (80)	280 (77)	0.16
BMI, median (IQ), kg/m^2	25.9 (23.7–28.4)	26.0 (23.8–28.7)	25.9 (23.7–27.8)	0.22
BMI ≥ 30 kg/m^2, *n* (%)	295 (16)	240 (17)	55 (15)	0.43
Smokers, *n* (%)	437 (24)	359 (25)	78 (21)	0.14
Hypertension, *n* (%)	1021 (57)	792 (56)	229 (63)	0.01
Diabetes mellitus, *n* (%)	355 (20)	256 (18)	99 (27)	<0.001
Hypercholesterolemia, *n* (%)	801 (45)	630 (44)	171 (47)	0.34
Previous MI, *n* (%)	324 (18)	231 (16)	93 (25)	<0.001
Previous PCI, *n* (%)	273 (15)	209 (15)	64 (18)	0.17
Previous CABG, *n* (%)	91 (5)	67 (5)	24 (6)	0.14
STEMI, *n* (%)	829 (46)	724 (51)	105 (29)	<0.001
NSTEMI/UA, *n* (%)	960 (54)	701 (49)	259 (71)	
Creatinine >1.5 mg/dl	188 (10)	146 (10)	42 (11)	0.47
LVEF, median (IQ), %	45 (40–55)	46 (40–55)	45 (35–55)	0.02
LVEF ≤ 40%, *n* (%)	552 (31)	415 (29)	137 (38)	0.002
Killip class III–IV, *n* (%)	104 (6)	77 (5)	27 (7)	0.14
1 mM AA-LTA, median (IQ), %	12 (7–18)	10 (7–13)	34 (23–72)	<0.001
10uM ADP-LTA, median (IQ), %	46 (27–71)	41 (23–55)	66 (51–75)	<0.001

HaPR, high on-aspirin platelet reactivity; IQ, interquartile range; BMI, body mass index; MI, myocardial infarction; PCI, percutaneous coronary intervention; CABG, coronary artery bypass graft; STEMI, ST-segment elevation MI; NSTEMI, non-STEMI; UA, unstable angina; LVEF, left ventricular ejection fraction; AA-LTA, arachidonic acid light transmittance aggregometry; ADP-LTA, adenosine diphosphate LTA.