



LETTER TO THE EDITOR

Prevalence of high on-treatment platelet reactivity in patients after percutaneous coronary intervention

**KEYWORDS**

platelet reactivity;
coronary artery disease;
major adverse
cardiovascular event

Acetylsalicylic acid (ASA) represents a standard part of dual antiplatelet treatment with clopidogrel in patients with coronary artery disease (CAD) undergoing percutaneous coronary intervention (PCI) with stent placement.¹ In certain patients, high residual platelet reactivity is highly correlated with aspirin resistance. Therefore, our study was focused on the prevalence of high on-treatment platelet reactivity, due to aspirin resistance in patients with coronary artery disease after PCI with stent placement, and evaluation of any difference in prevalence by the presence of metabolic syndrome and/or type 2 diabetes mellitus.²

The study was conducted in Belgrade at the Cardiology Clinic, Clinical Center of Serbia. We enrolled 90 adult patients (62 male, 28 female; mean age 63 ± 12 years) with CAD who underwent PCI with stent placement (BMS, DES or BMS + DES). All patients signed a written informed consent to participate in the study, according to the study protocols approved by the institutional commission for postgraduate studies of the University of Belgrade, School of Medicine. The first patient was enrolled in August 2010, and the last patient was enrolled in December 2012. All patients were already on aspirin treatment (100 mg/day) prior to PCI and continued with the same dosing after successful PCI. Clopidogrel was administered in a 600 mg loading dose prior to PCI and continued in a 75 mg daily dose after successful PCI according to standard dual antiplatelet treatment guidelines. Patients with stable coronary artery disease were included, and 69 patients (77%) had a history of previous myocardial infarction. All patients were enrolled in a

prospective consecutive manner, until the minimum estimated number for statistical power of the study of 30 subjects in the control group and 60 subjects in the cardiometabolic risk group was reached. Patients were then divided into three groups based on: absence (control group) or presence of metabolic syndrome (MetSy) and type 2 diabetes mellitus as follows: group 1 included 30 patients without MetSy and without type 2 diabetes mellitus; group 2 included 33 patients with MetSy, and no type 2 diabetes mellitus; group 3 included 27 patients with MetSy and type 2 diabetes mellitus. The diagnosis of MetSy was set according to NHLBI Adult Treatment Panel III (ATP III)³ and type 2 diabetes mellitus was diagnosed in patients with morning blood glucose level ≥ 7.0 mmol/l or patients on active DM therapy.

We evaluated platelet reactivity with a whole blood impedance aggregometer, by testing responsiveness to aspirin using ASPI-test (aspirin-test with arachidonic acid as activating agent). For responsiveness to clopidogrel, aggregation was measured using a high-sensitivity ADPtest (combination of ADP and prostaglandin E1). This combination is used to enhance sensitivity to the effects of clopidogrel on ADP-induced platelet activation. PGE1 reduces intracellular calcium mobilization, and therefore platelet activation, thus acting synergistically with the clopidogrel effect. Multielectrode platelet analyzer is a widely used point-of-care test for the estimation of platelet reactivity.⁴ All subjects reported ingestion of an ASA tablet in the morning on the day of the intervention (4 to 7 hours before intervention). Approximately 30 minutes after successful PCI with stent(s) implanted, 5 mL of whole blood from antecubital vein was sampled in a vacutainer tube. After a 30-min sample homogenization period, and 3-min stirring with saline solution pre-warmed to 37°C, the reactivity measurement was performed in a single-use test cell with two pairs of electrodes (two separate impedance sensors) over 6 minutes. Analyzer's software transforms data into aggregatory units, plotting values as two separate aggregation curves against time, for each pair of electrodes. The result for each sample tested was expressed as AUC (area under the curve), representing AU*min (aggregatory units per minute). Aspirin resistance was defined as a test result

Peer review under responsibility of Hellenic Cardiological Society.

<http://dx.doi.org/10.1016/j.hjc.2016.05.006>

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value above 600 AUC.⁵ Clopidogrel resistance was defined as a test result value equal to and above 468 AUC.⁶ The mean duration of follow-up period was 11 months (SD = 3). Major adverse cardiovascular event (MACE) was defined as: clinically manifested myocardial infarction (MI), revascularization procedure in same vessel, cerebrovascular insult (CVI), and MACE-related death. Discrete data were summarized as frequencies and continuous data were summarized as the mean \pm SD. The chi-square test was used for comparison of categorical variables, and the two-tailed

Student's *t* test was used to test differences among continuous variables. Dichotomous platelet reactivity variables, according to aspirin resistance criteria were used. A value of $p < 0.05$ was considered to be significant. All statistical analyses were performed using SPSS software, version 17.0 (SPSS Inc., Chicago, Illinois, USA). There were no significant differences between groups regarding age, gender, previous myocardial infarction, previous interventions or current pharmacological treatment. Data on baseline clinical characteristics of the patients and major

Table 1 Participants' clinical characteristics.

| | All | Group 1 | Group 2 | Group 3 | p-value | |
|--------------------------------------|-----------------------|-----------|-----------|------------|-----------|--------|
| n/(%) | 90 | 30 | 33 | 27 | | |
| Age (years) | 63 | 64 | 62 | 63 | .256 | |
| Male | 62 (68.9) | 23 (76.7) | 21 (63.6) | 18 (66.7) | .513 | |
| Female | 28 (31.1) | 7 (23.3) | 12 (36.4) | 9 (33.3) | | |
| Body weight in kg | 81.4 | 78.6 | 80.6 | 85.5 | .431 | |
| Body mass Index in kg/m ² | 27.1 | 25.1 | 27.3 | 28.1 | .032 | |
| Waist circumference in cm | 98.9 | 93.6 | 101.3 | 101.8 | <0.001 | |
| Triglycerides mmol/l | 1.89 | 1.53 | 1.85 | 2.19 | .120 | |
| HDL mmol/l | 1.16 | 1.26 | 1.13 | 1.14 | .392 | |
| Blood glucose mmol/l | 6.52 | 5.44 | 5.38 | 8.42 | .030 | |
| Blood pressure mmHg | systolic | 131.4 | 134.3 | 126.5 | 133.4 | .263 |
| | diastolic | 81.4 | 84.5 | 79.0 | 80.5 | .045 |
| Ejection fraction (EF%) | 54.2 | 52.0 | 54.8 | 55.5 | .368 | |
| mean AUC | aspirin | 251 | 276 | 269 | 201.6 | .378 |
| | clopidogrel | 371 | 343 | 392 | 375.5 | .351 |
| aspirin resistance | | 6 (6.7) | 0 | 4 (12.1) | 2 (7.4) | .154 |
| | | | | 6 (10.0) | | .065 |
| clopidogrel resistance | 34 (37.8) | 12 (40.0) | 14 (42.4) | 8 (29.6) | .569 | |
| Previous myocardial infarction | 69 (76.7) | 24 (80.0) | 26 (78.8) | 19 (70.4) | .574 | |
| Previous intervention | PCI | 22 (24.4) | 7 (23.3) | 10 (30.3) | 5 (18.5) | .655 |
| | CABG | 2 (2.2) | 0 | 1 (3.0) | 1 (3.7) | |
| | Pacemaker | 1 (1.1) | 1 (3.3) | 0 | 0 | |
| Abdominal obesity | 53 (58.9) | 6 (20.0) | 26 (78.8) | 21 (77.8) | <0.001 | |
| Hypertension | 79 (87.8) | 20 (66.7) | 32 (97.0) | 27 (100.0) | <0.001 | |
| Hyperlipidemia | 70 (77.8) | 18 (60.0) | 30 (90.9) | 22 (81.5) | 0.011 | |
| Diabetes mellitus | 27 (30.0) | 0 | 0 | 27 (100.0) | <0.001 | |
| Current medication | statin | 57 (63.3) | 17 (56.7) | 22 (66.7) | 18 (66.7) | .650 |
| | β -blocker | 37 (41.1) | 9 (30.0) | 13 (39.4) | 15 (55.6) | .142 |
| | ACE inhibitor/ARB | 47 (52.2) | 15 (50.0) | 16 (48.5) | 16 (59.3) | .677 |
| | Ca-antagonists | 9 (10.0) | 3 (10.0) | 5 (15.2) | 1 (3.7) | .339 |
| | nitrates | 42 (46.7) | 12 (40.0) | 18 (54.5) | 12 (44.4) | .494 |
| | diuretics | 14 (15.6) | 2 (6.7) | 6 (18.2) | 6 (22.2) | .236 |
| | IPP/H2-antagonist | 23 (25.6) | 8 (26.7) | 7 (21.2) | 8 (29.6) | .747 |
| | oral antidiabetic | 24 (26.7) | 0 (0.0) | 0 (0.0) | 24 (88.9) | <0.001 |
| | Smoking | 39 (43.3) | 13 (43.3) | 10 (30.3) | 16 (59.3) | .116 |
| | Non smoker | 23 (25.6) | 8 (26.7) | 8 (24.2) | 7 (25.9) | |
| | Active smoker | 28 (31.1) | 9 (30.0) | 15 (45.5) | 4 (14.8) | |
| Stent type | BMS | 51 (56.7) | 15 (50.0) | 21 (63.6) | 15 (55.6) | .814 |
| | DES | 34 (37.8) | 13 (43.3) | 10 (30.3) | 11 (40.7) | |
| | BMS + DES | 5 (5.6) | 2 (6.7) | 2 (6.1) | 1 (3.7) | |
| Follow-up | Myocardial infarction | 12 (13.3) | 4 (13.3) | 5 (15.2) | 3 (11.1) | .900 |
| | Revascularization | 19 (21.1) | 5 (16.7) | 7 (21.2) | 7 (25.9) | .694 |
| | CVI | 0 | 0 | 0 | 0 | — |
| | Cardiac death | 2 (2.2) | 1 (3.3) | 1 (3.0) | 0 | .570 |
| | MACE | 33 (36.7) | 10 (33.3) | 13 (39.4) | 10 (37.0) | .570 |

n/(%) stands for numbers in columns/ parentheses.

Clinically significant differences are represented in italics.

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