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LETTER TO THE EDITOR

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

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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 $\geq$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

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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 ± 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	Non smoker	39 (43.3)	13 (43.3)	10 (30.3)	16 (59.3)	.116
	Ex-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.

Table 2 Cardiovascular risk factors, aspirin resistance and clopidogrel resistance.

Cardiovascular risk factor presence		Aspirin resistance		*p*-value
		No n(%)	Yes n(%)	
Arterial hypertension	No	11 (12.2)	0 (0)	.344
	Yes	73 (81.1)	6 (6.7)	
Lipid disorder	No	20 (22.2)	0 (0)	.175
	Yes	64 (71.1)	6 (6.7)	
Glycemia disorder	No	59 (65.6)	4 (4.4)	.154
	Yes	25 (27.8)	2 (2.2)	
Abdominal obesity	No	37 (41.1)	0 (0)	*.034*
	Yes	47 (52.2)	6 (6.7)	
Tobacco smoking	Non-smoker	36 (40.0)	3 (3.3)	.872
	Ex-smoker	22 (24.4)	1 (1.1)	
	Active smoker	26 (28.9)	2 (2.2)	
Clopidogrel resistance	No	54 (60.0)	2 (2.2)	.131
	Yes	30 (33.3)	4 (4.4)	

Clinically significant differences are represented in italics.

adverse cardiovascular events during follow-up are summarized in Table 1. The three groups of subjects significantly differed by the presence of MetSy and/or T2DM ($p < 0.005$). We investigated the relationship between cardiovascular risk factors and aspirin resistance. Abdominal obesity was the only risk factor significantly ($p = .034$) associated with a positive finding of aspirin resistance (Table 2).

High residual platelet reactivity related to aspirin resistance was a more frequent finding in patients with coexisting cardiovascular risk factors, such as MetSy, with or without T2DM. Although the more frequent finding of aspirin resistance in our study coincides with the shorter MACE-free survival period in some groups of patients, we did not find aspirin resistance to be the single predicting factor for MACE(s) during the follow-up period; a finding recently reported by others.[7,8] Patients with metabolic syndrome and diabetes mellitus demonstrated a higher rate of MACE, particularly revascularization after stent placement. A weak platelet response to aspirin treatment could be expected in subjects with several known, coexisting cardiovascular risk factors, due to the load of platelet aggregation stimuli in the circulating blood of patients with T2DM, or patients with coronary blood vessel pathology. These results imply that the coexistence of several cardiovascular risk factors (elevated blood pressure, elevated blood lipid levels, elevated blood sugar levels and abdominal obesity) can lead to the presence of high platelet reactivity after standard aspirin dosing, and a shorter MACE-free survival period after PCI. These findings from our study may indicate a possible interaction between circulating proinflammatory agents, the presence of metabolically active abdominal fat deposits, and ingested aspirin, causing low responsiveness to treatment. Clopidogrel resistance was registered more frequently; 37.8% overall in subjects, but with no significant between-group differences ($p = .569$). Although four out of the six non-responders to aspirin were concomitantly non-responders to clopidogrel therapy, this relationship was not significant ($p = .131$), nor was there an increase in MACE documented for these patients. Several studies have shown the health implications of excessive fat tissue deposit localization, especially abdominal (visceral) fat, in contrast to subcutaneous, demonstrating a significant relationship with the increased risk of various disease development.[9] Waist circumference, one of the most comfortable ways to estimate increased abdominal fat deposits, can be routinely measured during regular check-ups as a vital parameter, similar to arterial blood pressure measurement or body mass index estimation.[10]

High residual platelet reactivity, despite dual antiplatelet therapy, is a more prevalent finding in patients with prominent cardiometabolic risk profiles. In such patients, cardiovascular risk evaluation and an individualized approach to antiplatelet treatment should be considered to be options after successful coronary intervention.

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