VIA MEDICA

ORIGINAL ARTICLE

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The impact of metabolic syndrome on the antiplatelet effect of clopidogrel and aspirin in patients with acute coronary syndrome

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Folia Medica Copernicana 2014;
Volume 2, Number 2, 66–72

ISSN 2300–5432

ABSTRACT

Aim. The aim of this study was to evaluate the impact of metabolic syndrome and features clustering in this syndrome on the antiplatelet effect of clopidogrel and aspirin in patients with myocardial infarction.

Material and methods. The study population comprised 186 consecutive patients treated with primary percutaneous coronary intervention for acute myocardial infarction. Measurements of ADP induced platelet aggregation (ADP-PA) and arachidonic acid induced platelet aggregation (AA-PA) were performed using impedance aggregometry with a Multiplate Analyser. The following factors were analysed as potential determinants of responsiveness to clopidogrel and to aspirin: diagnosed metabolic syndrome, diabetes, hypertension, abdominal obesity, body mass index (BMI), and serum concentrations of triglycerides, HDL-cholesterol and high sensitivity C-reactive protein (hsCRP).

Results. The ADP-PA was significantly higher in patients with metabolic syndrome and with diabetes. The AA-PA was significantly higher in subjects with increased levels of hsCRP and in subjects with BMI > 25 kg/m^2. The hsCRP was found to be the only independent factor influencing APD-PA ($p=0.034$). Serum concentrations of hsCRP, HDL-cholesterol and abdominal obesity were independent factors influencing AA-PA ($p=0.000004$).

Conclusion. Metabolic syndrome, diabetes mellitus, obesity and increased hsCRP are determinants of low responsiveness to aspirin and clopidogrel in patients with ACS treated with PCI.

Key words: clopidogrel, aspirin, metabolic syndrome, acute coronary syndrome, PCI

Folia Medica Copernicana 2014; 2 (2): 66–72

Introduction

A dual antiplatelet therapy with clopidogrel and aspirin has been shown to reduce the risk of major adverse cardiovascular events after percutaneous coronary intervention. However, a substantial proportion of patients do not respond to such therapy sufficiently [1–4]. Several factors behind this poor response to treatment in patients with acute coronary syndromes (ACS), including drug-drug interactions, diabetes, genetic factors and other biological factors, such as inflammation and platelet activation due to plaque rupture, should be taken into account [3, 5–9]. Patients with diabetes as well as those with metabolic syndrome are characterised by a prothrombotic state that includes increased platelet reactivity [10–12]. Antiplatelet therapy in these pathological conditions is still a matter of intense debate, especially because of the high prevalence of resistance to these drugs.

The aim of this study was to evaluate the impact of metabolic syndrome and features clustering in this syndrome on the antiplatelet effect of clopidogrel and aspirin in patients with myocardial infarction.

Methods

Study design and patients characteristics

This was a prospective, observational, single-centre study. The study population comprised 186 consecutive patients treated with primary percutaneous coronary intervention (pPCI) for acute ACS. Exclusion criteria were defined as follows: the need for prolonged use of heparin or fondaparinux, oral anticoagulant therapy, bleeding disorders (including thrombocytopenia $<100 \times 10^3/\mu l$), anaemia with haemoglobin (HGB) < 10.0 g/dL, active inflammation, congestive heart failure (CHF) in NYHA classes III and IV, and life expectancy < 1 year. In-hospital management and discharge treatment recommendations strictly adhered to the European Society of Cardiology guidelines. Patients received a 600 mg loading dose and 75 mg maintenance dose of clopidogrel in combination with aspirin doses of 300 mg and 75 mg, respectively. To avoid additional confounding factors, concomitant therapy was standardised and included bisoprolol, perindopril and simvastatin if no contraindications were present. When therapy with proton pump inhibitor was indicated, only pantoprazole was allowed. In case of a necessity to use additional medication, drugs with known or potential drug–drug interaction with clopidogrel were avoided. Study population characteristics are set out in Table 1.

The following factors were analysed as potential determinants of responsiveness to clopidogrel and to aspirin: diagnosed metabolic syndrome, diabetes, hypertension, abdominal obesity, body mass index (BMI kg/m^2), serum concentrations of triglycerides, high-density lipoprotein cholesterol (HDL-C), and high sensitivity C-reactive protein (hsCRP). The International Diabetes Federation definition of metabolic syndrome was applied: central obesity (waist size more than 94 cm in males or more than 80 cm in females) and any two of the following: raised triglycerides: > 150 mg/dL or specific treatment for this lipid abnormality; reduced HDL cholesterol: < 40 mg/dL in males, < 50 mg/dL in females or specific treatment for this lipid abnormality; raised blood pressure (BP): systolic BP > 130 or diastolic BP > 85 mm Hg or treatment of previously diagnosed hypertension; raised fasting plasma glucose (FPG): > 100 mg/dL or previously diagnosed type 2 diabetes. Measurements of biochemical parameters were performed in the Department of Laboratory Medicine, University Hospital, CM, NCU.

The study protocol has been approved by The Ethical Committee of Nicolaus Copernicus University.

Platelet function assessment

Blood samples were collected into hirudin-containing tubes (Dynabyte Medical, Munich, Germany) at 10.00 a.m. on the 4th day of hospitalisation. Measurements of ADP induced platelet aggregation (ADP-PA) and arachidonic acid induced platelet aggregation (AA-PA) were performed using impedance aggregometry. Whole blood was tested with a Multiplate Analyser (Medical Cyclotron, Munich, Germany). One Multiplate test cell incorporates two independent sensor units, each consisting of two silver-coated highly conductive wires. When activated platelets adhere onto the sensor wires, the electrical resistance between the wires rises, which is continuously registered. The instrument detects the impedance change of each sensor separately and transforms it into arbitrary aggregation units (AU) that are plotted against time. The area under the aggregation curve (AUC) is an estimator of platelet aggregation, and as such was evaluated in our study. It is affected by the total height of the AUC as well as by its slope, and is best suited to express overall platelet activity. Aggregation, quantified as the area under the curve, is displayed in arbitrary units [U].

Table 1. Characteristics of study population according to median (upper quartile–lower quartile) or number (percent)

Feature	Whole population (n = 186)
Age (years)	60.0 (53.0–67.0)
Gender (male)	138 (74.2%)
STEMI	158 (84.9%)
NSTEMI	28 (15.1%)
Metabolic syndrome	76 (40.9%)
Abdominal obesity	121 (65.1%)
BMI [kg/m^2]	27.7 (24.9–30.8)
Arterial hypertension	104 (55.9%)
Diabetes	64 (34.4%)
Total cholesterol [mg/dL]	213.0 (177.0–240.0)
LDL-C [mg/dL]	139.0 (115.0–170.0)
HDL-C [mg/dL]	40.0 (34.5–47.5)
TG [mg/dL]	100.5 (70.5–152.5)
hsCRP [mg/l]	10.8 (4.9–31.5)
ADP-PA [U]	25.0 (17.0–37.0)
AA-PA [U]	12.5 (7.0–20.0)
BT [min]	5.0 (4.0–6.5)

STEMI — ST elevation myocardial infarction; NSTEMI — non-ST elevation myocardial infarction; BMI — body mass index; LDL-C — low-density lipoprotein-cholesterol; HDL-C — high-density lipoprotein-cholesterol; TG — triglycerides; hsCRP — high-sensitivity C-reactive protein; ADP-PA — ADP induced platelet aggregation; AA-PA — arachidonic acid induced platelet aggregation; BT — bleeding time

Table 2. ADP–PA, AA–PA and BT values with regard to analysed factors

Factor	ADP-PA	AA-PA	BT
Metabolic syndrome (+) n = 76	**28.5 (19.5–40.0)**	13.5 (9.0–22.0)	5.0 (3.75–6.5)
Metabolic syndrome (–) n = 110	**23.0 (15.0–36.0)**	12.0 (6.0–20.0)	5.0 (4.0–7.0)
Abdominal obesity (+) n = 121	27.0 (18.0–38.0)	13.0 (7.0–21.0)	5.0 (4.0–6.5)
Abdominal obesity (–) n = 65	22.0 (16.0–35.0)	12.0 (7.0–20.0)	5.0 (3.5–7.0)
BMI > 25 kg/m^2 n = 136	27.0 (18.0–37.0)	**14.0 (8.0–21.0)**	5.0 (3.75–6.0)
BMI ≤ 25 kg/m^2 n = 50	21.0 (14.0–41.0)	**10.0 (5.0–17.0)**	5.5 (4.5–7.0)
Arterial hypertension (+) n = 104	27.0 (18.5–37.5)	12.5 (8.0–19.0)	5.0 (4.0–6.0)
Arterial hypertension (–) n = 82	23.0 (14.0–37.0)	12.5 (6.0–21.0)	5.0 (3.5–7.0)
Diabetes (+) n = 64	**30.0 (19.0–41.0)**	14.5 (9.0–22,0)	5.0 (3.5–6.5)
Diabetes (–) n = 122	**24.0 (16.0–34.0)**	12.0 (7.0–19.0)	5.0 (4.0–6.5)
HDL-C<50mg/dl (F);<40mg/dL (M) n = 107	25.0 (17.0–37.0)	13.0 (6.0–20.0)	5.0 (4.0–6.5)
HDL-C≥50mg/dl (F);≥40mg/dL (M) n = 78	24.5 (17.0–37.0)	12.0 (8.0–20.0)	4.5 (3.5–6.5)
TG ≥ 150 mg/dL n = 53	30.0 (18.0–41.0)	13.0 (8.0–22.0)	4.5 (3.5–6.0)
TG < 150 mg/dL n = 133	24.0 (16.0–35.0)	12.0 (7.0–20.0)	5.5 (4.0–7.0)
hsCRP > 3.0 mg/L n = 157	26.0 (17.0–40.0)	**13.0 (8.0–21.0)**	8.0 (3.0–16.0)
hsCRP ≤ 3.0 mg/L n = 25	23.0 (16.0–31.0)	**8.0 (3.0–16.0)**	4.5 (4.0–6.5)

$p < 0.05$; $p \geq 0.05$

ADP-PA — ADP induced platelet aggregation; AA-PA — arachidonic acid induced platelet aggregation; BT — bleeding time; BMI — body mass index; HDL-C — high-density lipoprotein-cholesterol; TG — triglycerides; hsCRP — high-sensitivity C-reactive protein

Bleeding time (BT) measurements

For the measurements of bleeding time, the patients were seated with arm supine on a steady support with the volar surface exposed. Incision site was located on the muscular area of the forearm distal to the antecubital fossa. The skin was cleansed with alcohol and allowed to dry for at least 30 seconds. The sphygmomanometer cuff was placed on the arm and inflated to 40 mm Hg to cause a venous stasis. The puncture was performed using a Medlance® incision device with 21G needle and 2.4 mm penetration depth. After the incision was made, the timer was started. The flow was gently blotted with filter paper every 30 seconds until blood no longer stained the paper. The time from when the incision was made until the bleeding stopped was recorded. If the incision continued to bleed for more than ten minutes, the measurement was stopped and the result was recorded as > 10 minutes.

Statistical analysis

According to the Shapiro-Wilk test, the investigated continuous variables were non-normally distributed, therefore they were reported as medians and interquartile ranges (IR). For comparisons between two and three groups, the Mann-Whitney unpaired rank sum test and the Kruskal–Wallis one-way analysis of variance were used, respectively. Categorical variables were expressed as a number of patients presenting the given feature and a percentage of patients in the analysed group. Categorical variables were compared using the χ^2 test with the Yates' correction if required. The Cochran–Armitage test was used to assess the presence of a linear trend among categorical variables. Differences were considered significant at $p < 0.05$. The statistical analysis was carried out using the Statistica 10.0 package (StatSoft, Tulsa, OK, USA). Univariate and multivariate logistic regression models were used. Variables with a p-value of ≤ 0.1 in the univariate analysis were introduced into the multivariate logistic regression model. Subsequently, variables with no significant impact on the prevalence of the efficacy end-points ($p \geq 0.05$) were one by one removed from the multivariate model according to their decreasing p-values.

Results

Comparative analysis of ADP-PA, AA-PA and BT values with regard to metabolic syndrome, abdominal obesity, BMI, arterial hypertension, diabetes, serum concentration of HDL-cholesterol, triglycerides and hsCRP was performed (Tab. 2). The ADP-PA was significantly higher in patients with metabolic syndrome (Fig. 1), as well as in individuals with diabetes (Fig. 2), while AA-PA was significantly higher with increased levels of hsCRP (Fig. 3) and in subjects with BMI > 25 kg/m^2 (Fig. 4).

The ADP-PA weakly correlated with hsCRP and with BMI (Tab. 3). Average correlation between AA-PA and hsCRP was found. Moreover, AA-PA weakly correlat-

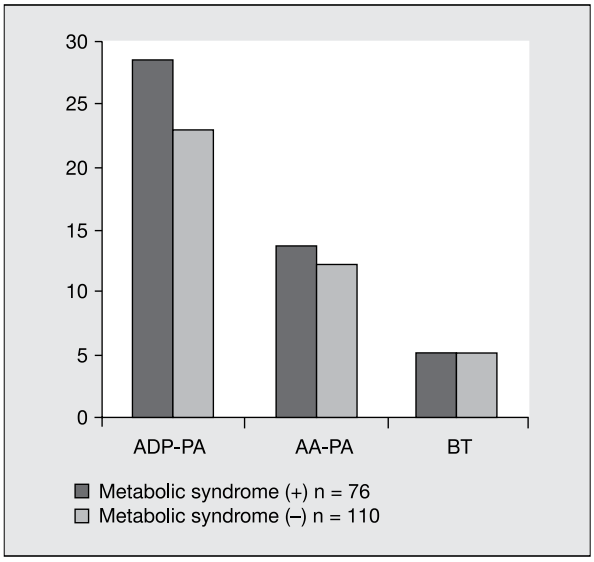

Figure 1. Comparison of ADP-PA, AA-PA and BT values in patients with and without metabolic syndrome. ADP-PA — ADP induced platelet aggregation; AA-PA — arachidonic acid induced platelet aggregation; BT — bleeding time

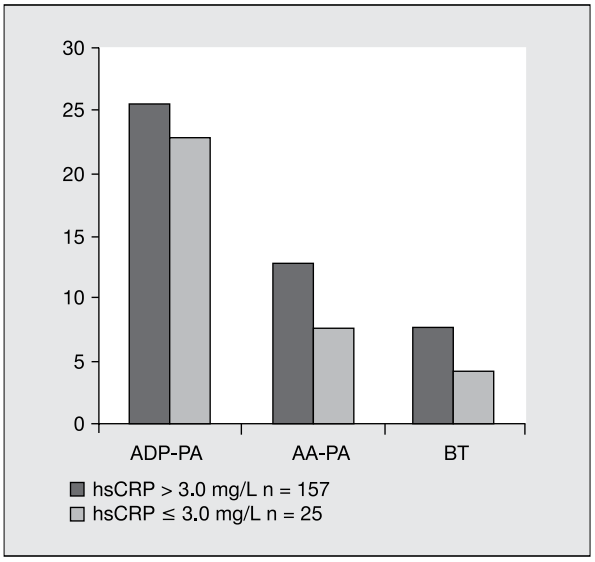

Figure 3. Comparison of ADP-PA, AA-PA and BT values in patients with hsCRP > 3.0 mg/L versus hsCRP ≤ 3.0 mg/L. ADP-PA — ADP induced platelet aggregation; AA-PA — arachidonic acid induced platelet aggregation; BT — bleeding time; hsCRP — high-sensitivity C-reactive protein

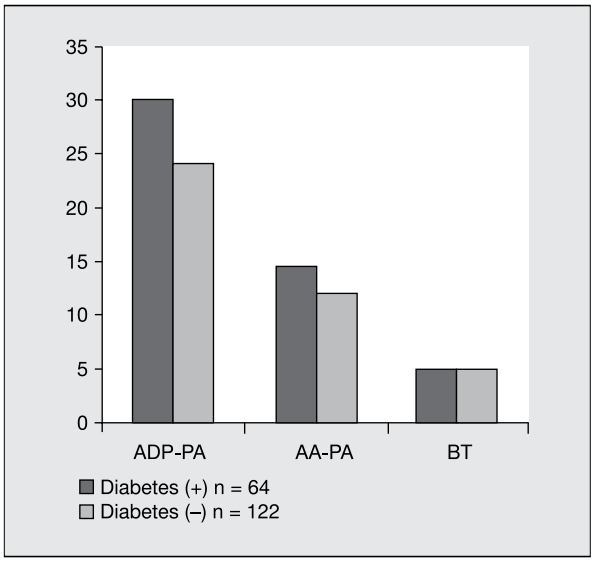

Figure 2. Comparison of ADP-PA, AA-PA and BT values in patients with and without diabetes. ADP-PA — ADP induced platelet aggregation; AA-PA — arachidonic acid induced platelet aggregation;BT — bleeding time

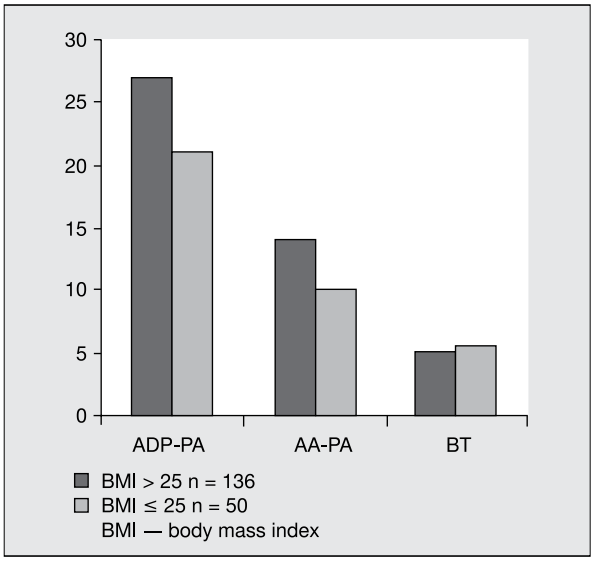

Figure 4. Comparison of ADP-PA, AA-PA and BT values in patients with BMI > 25 kg/m^2 versus BMI ≤ 25 kg/m^2. ADP-PA — ADP induced platelet aggregation; AA-PA — arachidonic acid induced platelet aggregation; BT — bleeding time; BMI — body mass index

ed with BMI (Tab. 4). The hsCRP was the only factor correlated with BT (inverse, weak correlation) (Tab. 5).

The hsCRP was found to be the only independent factor influencing APD-PA according to multivariate analysis (p = 0.034). It explains only 2.5% of the variability in the platelet response to clopidogrel. We found serum concentrations of hsCRP, HDL-cholesterol and abdominal obesity to be independent factors influencing AA-PA (p = 0.000004). The regression model explains 15.6% of the variability in the platelet response to aspirin.

Table 3. Correlations between ADP-PA and continuous variables

Variable	R Spearman's rank correlation coefficient	p
TG	0.0559	0.449
HDL-C	–0.0294	0.690
hsCRP	**0.1886**	**0.011**
BMI	**0.1542**	**0.036**

ADP-PA — ADP induced platelet aggregation; TG — triglycerides; HDL-C — high-density lipoprotein-cholesterol; hsCRP — high-sensitivity C-reactive protein; BMI — body mass index

Table 4. Correlations between AA-PA and continuous variables

Variable	R Spearman's rank correlation coefficient	p
TG	–0.0170	0.818
HDL-C	0.0070	0.924
hsCRP	**0.3329**	**0.000004**
BMI	**0.1699**	**0.020**

AA-PA — arachidonic acid induced platelet aggregation; TG — triglycerides; HDL-C — high-density lipoprotein-cholesterol; hsCRP — high-sensitivity C-reactive protein; BMI — body mass index

Table 5. Correlations between BT and continuous variables

Variable	R Spearman's rank correlation coefficient	P
TG	–0.0804	0.275
HDL-C	–0.0084	0.908
hsCRP	**–0.1511**	**0.042**
BMI	–0.0973	0.186

BT — bleeding time; TG — triglycerides; HDL-C — high-density lipoprotein-cholesterol; hsCRP — high-sensitivity C-reactive protein; BMI — body mass index

Discussion

Platelets in patients affected by metabolic syndrome and diabetes mellitus show an enhanced activation state, mirrored by an increased expression of membrane activation markers. These abnormalities are responsible for a pro-thrombotic condition, contributing to a high cardiovascular risk [13].

Moreover, features clustering in metabolic syndrome are responsible for the lower-than-expected response to antiplatelet agents. Cağirci et al. [14] postulated that a significant proportion of patients with metabolic syndrome do not benefit from aspirin use due to high aspirin resistance. The prevalence of aspirin resistance achieved 46.9% compared to 20% in the control group ($p = 0.033$). According to multivariate logistic regression analysis, hsCRP concentration also significantly affected aspirin resistance [14]. This observation is in line with our own results showing significantly higher AA-PA in patients with increased levels of hsCRP and in subjects with BMI > 25 kg/m^2 and confirmed by corresponding positive correlations and by multivariate analysis. Correlation of aspirin resistance with prothrombotic (fibrinogen) and proinflammatory (hsCRP) factors was also found in another study [15]. However, hsCRP levels correlated with aspirin resistance only in patients with metabolic syndrome [15]. Kahraman et al. [16] observed aspirin resistance in 21.9% of patients with metabolic syndrome. The frequency of aspirin resistance in patients with metabolic syndrome was more common in patients with higher hs-CRP levels [16].

Possible explanations for this phenomenon, besides underdosing of the drug and/or its reduced bioavailability subsequent to excess of adipose tissue, include enhanced platelet turnover, leading to unacetylated COX-1 and COX-2 in newly formed platelets as a source of aspirin-escaping thromboxane formation; extraplatelet sources of thromboxane, driven by inflammatory triggers; and enhanced lipid peroxidation, activating platelets with a mechanism bypassing COX-1 acetylation or limiting COX-isozyme acetylation by aspirin [17].

On the other hand, Mao et al. [18] demonstrated that regulators of G protein signalling transcripts (according to mRNA levels) are elevated in aspirin-resistant platelets from patients with metabolic syndrome. Regulators of G protein signalling, which accelerate the deactivation of G protein signalling, are expressed in platelets. G protein-coupled receptor signalling plays a crucial role in platelet activation [18]. The P2Y12 receptor inhibited by clopidogrel also belongs to the group of G protein-coupled receptors. Nevertheless, according to Erlinge et al. [19], the mechanism of incomplete platelet inhibition in clopidogrel poor-responders and in diabetic patients is lower plasma levels of its active metabolite and not differences in platelet P2Y(12) receptor function. Interestingly, Pankert et al. [20] observed the impaired response to clopidogrel only in obese patients with metabolic syndrome, while obese patients without metabolic syndrome had no significant difference in platelet reactivity compared to non-obese patients [20].

In our study, the ADP-PA was significantly higher in patients with metabolic syndrome and in individuals with diabetes. Moreover, the hsCRP was found to be the only independent factor associated with high platelet reactivity in patients on clopidogrel.

Platelets mediate and amplify the inflammatory response to ACS through adhesive interactions with leukocytes [21]. On the other hand, depressed responsiveness to aspirin and clopidogrel, due to antiplatelet resistance caused by systemic inflammation, may be observed in inflammatory diseases [22]. According to Malek et al., impaired antiplatelet response to clopidogrel, but not to aspirin, may contribute to weaker anti-inflammatory response as assessed by hs-CRP in patients with ST-elevation MI [10]. In a study published by Osmancik et al. [23], multivariate logistic regression revealed a higher body weight, apart from other factors, to be associated with an increased risk for being a non-responder to clopidogrel. More pronounced inflammation, as expressed by plasma concentration of CRP, was also observed by Ge et al. [24] in patients with clopidogrel resistance compared to those with normal responsiveness. Furthermore, they revealed that diabetes mellitus was an independent predictor for unresponsiveness to clopidogrel after stent implantation according to multivariate analyses. In another study, elevated levels of CRP, WBC count and fibrinogen were associated with high platelet reactivity in patients on chronic clopidogrel treatment [25]. The correlation between ADP-PA and WBC count suggests platelets-leukocytes functional interaction, while the expression of the P2Y12 receptors on leukocytes suggests that clopidogrel may act directly on these cells and not only on platelets. Clopidogrel treatment may reduce the influence of leukocytes on platelets and result in decreased leukocyte activation [26]. Grdinic et al. [27] revealed significantly elevated levels of inflammatory markers in non-responders to clopidogrel. Dual non-responders to clopidogrel and aspirin had a higher platelet count, LDL-cholesterol, and CRP, and lower HDL-cholesterol.

Obesity, the pivotal factor in metabolic syndrome, is strongly associated with glucose metabolism disorders and inflammation. Thus, the results of our research, indicating relationships between these factors and the extent of platelet inhibition with aspirin and clopidogrel in patients with ACS, are not surprising. Further studies are required to elucidate mechanisms of our observations and to define strategies to overcome shortcomings of investigated treatment in patients with metabolic syndrome.

Conclusion

Metabolic syndrome, diabetes mellitus, obesity and increased hsCRP are determinants of low responsiveness to aspirin and clopidogrel in patients with ACS treated with PCI.

Acknowledgement

This study was supported by a scientific grant from Nicolaus Copernicus University (No. 202). All authors declare no conflict of interest regarding this article.

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