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Factors responsible for "aspirin resistance" — can we identify them?

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Abstract

Background: Aspirin (ASA) is an effective antiplatelet drug that reduces the risk of myocardial infarction, stroke, or death by approximately 25% in patients who are at increased risk of cardiovascular events. However, many patients with cardiovascular disease do not respond to ASA treatment and are deemed ASA resistant. The term "ASA resistance" has been used to describe not only the lack of expected pharmacologic effects of ASA on platelets but also poor clinical outcomes, such as recurrent vascular events, in patients treated with ASA.

Aim: In this prospective observation of patients with stable coronary artery disease (CAD) who received ASA for secondary prevention, we investigated factors responsible for ASA resistance by determining ASA response using the PFA-100 analyser and evaluating relation of ASA resistance to various studied parameters.

Methods: Platelet function tests with the PFA-100 point-of-care system were performed in 92 patients with CAD (mean age 68 ± 8 years, 36 females) who had been taking 75–150 mg of ASA daily for secondary prevention for at least 3 months. Each patient had an angiographically documented CAD with stable angina. ASA resistance was defined as a normal collagen/epinephrine closure time (CEPI-CT) on the PFA-100 (≤ 150 s). Patients with CT ≥ 250 s were defined as ASA responders and patients with CT between 150 and 250 s as semi-responders.

Results: Using a collagen/epinephrine-coated cartridge on the PFA-100, the prevalence of platelet inhibition failure was 29%, while 30% of patients were semi-responders. In our study population, adequate response to ASA was found in 40% of patients. In multivariate logistic regression analysis, parameters independently related to platelet inhibition failure included compliance to ASA therapy [odds ratio (OR) 0.8, 95% confidence interval (CI) 0.20–0.35, p = 0.001], total cholesterol/HDL cholesterol level ratio > 2.99 (OR 0.19, 95% CI 0.05–0.81, p = 0.02), and heart rate > 69 bpm (OR 4.44, 95% CI 1.37–14.38, p = 0.01).

Conclusions: In patients with stable CAD, about one third of the subjects were ASA resistant by PFA-100. Our study shows that non-compliance could be one of the most important risk factors responsible for high residual platelet activity in patients with stable CAD taking ASA. Thus, non-compliant patients should be carefully educated about the mechanism of action of this drug to understand the necessity and long-term benefits of treatment with ASA.

Key words: aspirin resistance, platelets, PFA-100, stable coronary artery disease

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INTRODUCTION

Platelet activation is a crucial event in the pathophysiology of acute coronary syndromes (ACS). Antiplatelet therapy, primarily using acetylsalicylic acid (ASA), is considered a necessary component of both primary and secondary prevention of acute thrombotic cardiovascular events. Chronic use of antiplatelet therapy in patients with stable coronary artery disease (CAD) leads to a 30% reduction of major cardiovascular events including cardiac deaths and nonfatal myocardial infarction (MI) and stroke. Among patients with unstable

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angina, risk reduction with antiplatelet therapy is as high as 46%, and the treatment effects seem to be independent from age, gender, and concomitant conditions [1]. However, the rate of adverse cardiovascular outcomes in these patients continues to be high despite intensive treatment. One proposed mechanism of the limited effectiveness of drug therapy is inadequate response to ASA or even frank drug resistance. Emerging data in the literature suggest an association between increased rate of cardiovascular events and inadequate platelet inhibition by ASA [2, 3]. Numerous hypotheses have been proposed to explain these observations. Potential mechanisms of inadequate antiplatelet action of ASA include an adverse effect of smoking, leading to increased platelet aggregation, concomitant use of nonsteroidal antiinflammatory drugs, sympathetic nervous system activation, metabolic abnormalities (dyslipidemia, hyperglycemia), alternative pathways of platelet activation, increased platelet turnover, and genetic variation in the population [2–8].

The aim of this study was to perform a laboratory evaluation of the response to antiplatelet drug therapy in a group of patients with stable CAD treated with ASA and to analyse risk factors related to inadequate platelet inhibition.

METHODS

We performed an open, prospective, multicenter study in a population of patients with stable CAD following previous MI and/or coronary revascularisation with percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG) who remained under outpatient specialist cardiological care in four administrative areas of Warsaw (Ochota, Mokotów, Żoliborz and Praga Południe). We included patients aged 18 to 80 years following ACS or coronary revascularisation (PCI or CABG) who were receiving chronic therapy with ASA (≥ 75 mg/day) as a secondary prevention for at least 3 months.

The exclusion criteria included ACS or coronary revascularisation (PCI or CABG) within previous 3 months, stroke within previous 3 months, documented ASA intolerance, active peptic ulcer disease, treatment with other antiplatelet drugs including thienopyridines (clopidogrel, ticlopidine) or anticoagulant drugs (unfractionated or low-molecular-weight heparin) within last 24 hours before biochemical testing, chronic use of oral anticoagulants (acenocoumarol or warfarin), history of bleeding diathesis, platelet count of < 150,000/μL, hemoglobin level of < 8 g/dL, chronic kidney disease requiring dialysis therapy, documented history of *heparin-induced thrombocytopenia*, a history of myeloproliferative disorder, surgical procedures within previous month, malignant paraproteinemia, and other advanced systemic disease.

From November 2006 to March 2007, all patients fulfilling the inclusion criteria who came for a follow-up visit to a study center were referred to the coordinating center for initial selection. Based on available medical records, physical examination, and detailed history using a questionnaire developed for the purpose of this study, we evaluated CAD risk factors, previous clinical course of the disease and its treatment, concomitant conditions, previous acute coronary events, and other medications used in the secondary prevention or as symptomatic treatment. In addition, the questionnaire included information about established risk factors of ASA resistance including tobacco use, diabetes, hyperlipidemia, hypertension, heart failure, and dose, timing and adherence to treatment with ASA. Current severity of angina and/or heart failure symptoms were categorised using Canadian Cardiovascular Society (CCS) and New York Heart Association (NYHA) classifications. After written informed consent was given, a blood sample for biochemical testing was taken from each patient. The patients were included in the study after considering potential exclusion criteria based on the results of biochemical testing.

The study was approved by the local ethics committee at the Medical University of Warsaw. Each patient was given written detailed study description including its goals and conduct, and gave written informed consent for the participation in the study.

Whole blood parameters

Blood samples were taken 2–12 hours after the last ASA dose and placed in test tubes containing 3.2% buffered sodium citrate solution. All biologic material in this study was collected by a single person. After 30 minutes to 2 hours from blood collection, platelet activity was measured using the PFA-100 platelet function analyser and collagen-epinephrine (CEPI) and collagen/ADP (CADP) cartridges. On the same day, the following blood parameters were evaluated: C-reactive protein (CRP), fibrinogen, complete blood count, serum lipoprotein profile, coagulation tests, fasting plasma glucose, and plasma creatinine level.

PFA-100 platelet function analyser

The PFA-100 analyser is a point-of-care system to test *in vitro* platelet adhesion and aggregation induced by blood vessel damage. PFA-100 measures the ability of platelets, present in whole blood samples taken from patients, to occlude a microaperture membrane covered with various platelet agonists, such as 2 μg of collagen type I and 10 μg of epinephrine (CEPI) or 2 μg of collagen type I and 50 μg of ADP (CADP). Platelet activity is measured by time necessary for flow cessation due to aperture closure by a platelet plug (closure time, CT). According to the manufacturer data and results of previous studies, CEPI-CT values above 250 s are consistent with non-closure of the aperture. Complete inhibition of platelet activity is indicated by non-closure of the CEPI cartridge in the presence of ASA [8, 9].

Similarly to other studies, the cutoff CEPI-CT value suggesting lack of response to ASA was defined as ≤ 150 s [10].

Depending on the obtained CEPI-CT values, patients with CEPI-CT ≥ 250 s were classified as ASA responders (ASA-R), patients with CEPI-CT > 150 s but < 250 s as partial ASA responders (semiresponders, ASA-SR), and patients with CEPI-CT ≤ 150 s as ASA non-responders (ASA-NR). At the same time, we measured CT with PFA-100 using CADP cartridges (CADP-CT).

Statistical analysis

Results are presented as mean values and standard deviations for continuous variables or numbers and percentages for categorical variables. Multivariable logistic regression model was used to assess the effects of selected parameters on ASA resistance. Stepwise elimination was used to determine parameters that remained significant at the 0.1 level ($p < 0.05$). Fitting of logistic regression models was tested using the Homer-Lemeshow analysis. The PFA-100 CADP-CT values were compared between various groups of ASA resistance using the Kruskal-Wallis test, with the level of significance set at $p < 0.05$. Pairwise comparisons were performed for any statistically significant values ($p = 0.017$ according to the Bonferroni correction). All statistical analyses were performed using Stata v. 9.0 software (Stata Statistical Software: Release 9.0., College Station, TX, Stata Corporation).

RESULTS

Out of the whole study group of 300 patients with CAD, platelet function tests were performed in 92 patients aged 68.02 ± 8.35 years (39% of women) with stable CAD who were taking 75–150 mg of ASA daily (mean 87.5 ± 25.5 mg/d) for secondary prevention for at least 3 months and fulfilled all inclusion criteria. The clinical, demographic and biochemical characteristics of the study group is shown in Table 1.

Evaluation of platelet activity

Based on PFA-100 measurements (mean CEPI-CT 208.2 ± ± 77.17 s, range 82–300 s), our study population of 92 patients was divided into three groups. As specified above, non--response to ASA was found in 27 patients (29%; mean CEPI-CT 119.33 ± 20.36 s, range 82–150 s), partial response to ASA in 28 patients (30%; mean CEPI-CT 181.86 ± 30.55 s, range 151–247 s), and adequate response to ASA in 37 patients (40%; mean CEPI-CT 292.0 ± 14.31 s, range 255–300 s). The clinical and biochemical characteristics of the ASA-R, ASA-SR, and ASA-NR groups are shown in Tables 2 and 3. We also measured CADP-CT in all subjects (mean CADP-CT 99.94 ± 36.28 s, range 46–275 s). No results were obtained in four cases due to flow obstruction. CADP-CT was significantly lower in the ASA-NR group (mean CADP-CT 86.18 ± ± 19.71 s, range 57–148 s) compared to the ASA-R group (mean CADP-CT 111.4 ± 45.08 s, range 52–275 s; p = = 0.007). Measured CADP-CT values did not discriminate between the ASA-SR group (mean CADP-CT 98.81 ± 31.97 s, range 46–178 s) and either ASA-NR group ($p = 0.12$) or ASA-R group ($p = 0.28$). Overall, the difference between the three groups was significant ($p = 0.02$).

Predictors of response to ASA

Out of clinical factors, the only variables significantly related to non-response to ASA were compliance to ASA therapy [odds ratio (OR) 0.8, 95% confidence interval (CI) 0.20–0.35, $p = 0.001$] and heart rate above the median value, ie. 69 bpm (OR 4.44, 95% CI 1.37–14.38, $p = 0.01$). Out of biochemical parameters, the only variable significantly related to non-response to ASA was total cholesterol/HDL cholesterol level ratio above the median value, ie. 2.99 (OR 0.19, 95% CI 0.05–0.81, $p = 0.02$). Borderline significance was found for red blood cell count above the median value, ie. 4.61×10^9/mL (OR 3.5, 95% CI 0.99–12.37, $p = 0.05$) (Table 4).

DISCUSSION

In the recent years, increasing attention has been paid to inter-individual variability of platelet inhibition in response to ASA. In the previous studies, the prevalence of laboratory non-response to ASA as evaluated using various methods in patients with cardiovascular disease ranged from 0.4 to 83% [2–8]. A systematic review on ASA resistance included 22 studies with the use of the PFA-100 system to measure platelet activity in patients taking ASA. Overall, the prevalence of ASA resistance as measured using PFA-100 was 29.0% (95% CI 2.1–34.8) [5]. In the PROSPECTAR study, the rate of ASA resistance measured using PFA-100 in 234 patients with stable CAD was 22% [11]. Thus, it seems that the rate of ASA resistance seen in our population of stable CAD patients receiving ASA for secondary prevention corresponds well to the actual scope of this problem.

Determination of CADP-CT was an additional approach to differentiate patients based on platelet function inhibition by PFA-100. Measured CADP-CT values were significantly lower in the ASA-NR group compared to the ASA-R group. It has been proposed that in CAD patients with impaired platelet response to ASA, platelets may be more reactive to other platelet-activating substances [12–14]. In a study involving 700 patients, Frelinger et al. [15] have shown that platelet activation induced by arachidonic acid in patients receiving ASA was partially inhibited by clopidogrel acting through P2Y12 ADP receptor. These complex interactions between various pathways of platelet activation may in part explain the additive effect of clopidogrel co-administered with ASA. However, increased responsiveness to ADP in ASA resistant patients does not provide any clear explanation of mechanisms that might be responsible for inappropriate response to ASA.

In our group of CAD patients receiving ASA for secondary prevention, drug compliance was one of the most important predictive factors of appropriate response to the antiplatelet therapy. The most commonly given reasons for non-

Table 1. Clinical, demographic and biochemical characteristics of the study population

Variable	Mean ± SD	Range
Age [years]	68.02 ± 8.35	(48–80)
Body mass [kg]	77.46 ± 13.24	(49–125)
Body mass index [kg/m^2]	27.64 ± 4.29	(19.88–43.03)
ASA dose [mg/kg]	1.10 ± 0.28	(0.60–2.31)
Duration of ASA treatment [years]	4.61 ± 4.03	(0.25–21)
Mean ASA dose [mg]	87.5 ± 25.5	(75–150)
SBP [mm Hg]	139.59 ± 19.39	(90–190)
DBP [mm Hg]	81.42 ± 10.27	(56–100)
Heart rate [bpm]	68.75 ± 8.68	(49–100)
	Number of patients	**Percentage**
Women	36	39
ASA 75 mg/d	70	76.08
ASA 100 mg/d	10	10.86
ASA 150 mg/d	12	13.04
Hypertension	79	85.86
Diabetes	14	15.21
Heart failure	42	45.65
Compliance to ASA therapy	66	71.74
History of PCI	37	40.2
History of CABG	35	38
History of tobacco use	56	60.87
Current tobacco use	6	6.5
Medications	**Number of patients**	**Percentage**
Beta-blocker	88	95.6
ACE inhibitor	80	86.9
Statin	86	93.5
Calcium antagonist	25	27.2
Nitrate	14	15.2
NSAID	17	18.5
Biochemical parameters	**Mean ± SD**	**Range**
Glucose [mg/dL]	111.41 ± 44.31	(79.00–384.00)
RBC [× 10^9/mL]	4.84 ± 0.44	(3.88–6.68)
HBG [g/dL]	14.44 ± 1.62	(10.40–17.7)
HCT [%]	43.02 ± 3.71	(34.30–52.60)
PLT [× 10^3/μL]	247.14 ± 100.27	(150.00–449.00)
MPV [μm^3]	8.27 ± 1.33	(2.8–10.8)
Leukocytes [× 10^3/μL]	7.65 ± 2.45	(3.85–22.70)
Cholesterol [mg/dL]	179.15 ± 38.53	(90.00–288.00)
HDL-C [mg/dL]	50.88 ± 11.57	(27.00–77.00)
LDL-C [mg/dL]	101.25 ± 33.93	(29.00–182.00)
TG [mg/dL]	129.15 ± 58.60	(45.00–419.00)
Creatinine [mg/dL]	1.00 ± 0.27	(0.53–1.99)
Uric acid [mg/dL]	6.1 ± 1.62	(3.20–10.60)
Fibrinogen [mg/dL]	400.34 ± 93.15	(233.00–746.00)
CRP [mg/L]	3.67 ± 5.92	(0.20–52.60)
CEPI-CT [s]	208.2 ± 77.17	(82.00–300.00)
CADP-CT [s]	96.41 ± 29.56	(63.00–300.00)

ASA — acetylsalicylic acid; SBP — systolic blood pressure; DBP — diastolic blood pressure; PCI — percutaneous coronary intervention; CABG — coronary artery bypass grafting; ACE — angiotensin-converting enzyme; NSAID — non-steroidal anti-inflammatory drug; RBC — red blood cell count; HBG — hemoglobin; HCT — hematocrit; PLT — platelets; MPV — mean platelet volume; HDL-C — high-density lipoprotein cholesterol; LDL-C — low-density lipoprotein cholesterol; TG — triglycerides, CRP — C-reactive protein; CEPI-CT — collagen-epinephrine occlusion time; CADP-CT — collagen-ADP occlusion time

Table 2. Clinical characteristics of patients in various ASA response groups

	ASA-NR (n = 27)	ASA-SR (n = 28)	ASA-R (n = 37)
Females	33.3% (9 pts)	39.3% (11 pts)	43.2% (16 pts)
Males	66.7% (18 pts)	60.7% (17 pts)	56.8% (21 pts)
Age [years]	67.81 ± 8.26	68.0 ± 8.62	68.19 ± 8.44
Age < 70 years	48.15% (13 pts)	46.43% (13 pts)	45.95% (17 pts)
Body mass index [kg/m^2]	28.01 ± 3.83	26.77 ± 3.85	28.24 ± 5.13
Heart rate [bpm]	71.7 ± 8.05	70.96 ± 13.28	67.84 ± 10.96
SBP [mm Hg]	143 ± 20.97	145 ± 16.73	145.49 ± 26.98
DBP [mm Hg]	86.55 ± 10.32	85.39 ± 9.25	83.27 ± 19.72
SBP ≥ 140 [mm Hg]	51.85% (14 pts)	46.43% (13 pts)	45.95% (17 pts)
DBP ≥ 90 [mm Hg]	22.22% (6 pts)	17.86% (5 pts)	18.92% (7 pts)
Hypertension duration [years]	9.21 ± 8.26	11.48 ± 10.67	8.82 ± 10.45
ASA dose [mg/kg]	1.03 ± 0.27	1.16 ± 0.34	1.10 ± 0.31
Duration of ASA treatment [years]	6.14 ± 4.13	4.68 ± 2.88	5.79 ± 4.69
Morning ASA dose	70.37% (19 pts)	82.14 % (23 pts)	67.57% (25 pts)
ASA compliance	51.85% (14 pts)	75.00% (21 pts)	83.78% (31 pts)
FBG [mg/dL]	121.59 ± 71.54	102.93 ± 21.53	102.86 ± 23.37
Diabetes	14.81% (4 pts)	14.29% (4 pts)	16.22% (6 pts)

FBG — fasting blood glucose; ASA-NR — patients not responding to ASA; ASA-SR — patients partially responding to ASA; ASA-R — patients responding to ASA. Other abbreviations as in Table 1

Table 3. Biochemical characteristics of patients in various ASA response groups

	ASA-NR (n = 27)	ASA-SR (n = 28)	ASA-R (n = 37)
CEPI-CT [s]	119.33 ± 20.36	181.86 ± 30.55	292.97 ± 14.31
CADP-CT [s]	86.18 ± 19.71	98.81 ± 31.97	111.4 ± 45.08
RBC [× 10^9/mL]	4.71 ± 0.37	4.60 ± 0.32	4.55 ± 0.40
HBG [g/dL]	14.42 ± 0.94	14.05 ± 0.95	13.68 ± 2.45
HCT (%)	42.24 ± 2.70	40.67 ± 2.50	40.40 ± 3.08
PLT [× 10^3/μl]	201.81 ± 52.54	204 ± 42.75	242.73 ± 168.07
MPV [μm^3]	10.22 ± 1.21	10.5 ± 1.13	10.30 ± 1.21
Leukocytes [× 10^3/μl]	7.29 ± 1.89	7.70 ± 3.56	8.41 ± 8.19
Cholesterol [mg/dL]	178.48 ± 45.08	164.43 ± 28.72	163.78 ± 30.61
HDL-C [mg/dL]	55.52 ± 10.74	54.78 ± 12.63	52.76 ± 10.82
LDL-C [mg/dL]	98.30 ± 43.01	88.44 ± 24.77	87.53 ± 29.62
LDL-C < 100 mg/dL	59.25% (16 pts)	67.85% (19 pts)	64.86% (24 pts)
TG [mg/dL]	121.78 ± 44.24	120.89 ± 56.90	121.16 ± 55.96
TG < 150 mg/dL	77.78% (21 pts)	82.14% (23 pts)	81.08% (30 pts)
Cholesterol/HDL-C	3.30 ± 1.02	3.11 ± 0.72	3.23 ± 0.89
Creatinine [mg/dL]	0.92 ± 0.26	1.07 ± 0.34	0.96 ± 0.27
Uric acid [mg/dL]	5.44 ± 1.57	6.33 ± 1.31	6.03 ± 1.58
Fibrinogen [mg/dL]	413.90 ± 98.95	411.21 ± 81.70	419.81 ± 108.84
CRP [mg/L]	3.45 ± 4.79	3.41 ± 3.31	3.46 ± 6.49

Abbreviations as in Table 1

Table 4. Factors independently related to ASA resistance in multivariate analysis

Variable	Odds ratio (95%CI)	P
Compliance with ASA therapy	0.8 (0.2–0.35)	0.001
Erythrocytes > 4.61 × 10^9/mL	3.5 (0.99–12.37)	0.051
Cholesterol/HDL-cholesterol > 2.99	0.19 (0.046–0.81)	0.024
Heart rate > 69 bpm	4.44 (1.37–14.38]	0.013

-compliance included forgetting about the need to take the medication, inadequate motivation for therapy, distrust in appropriate physician choice of the therapy, lack of knowledge about the mechanism of the action of the drug, medication adverse effects, and a complex therapeutic regimen [16]. Suboptimal compliance with ASA therapy is often cited as one on the major factors responsible for observed laboratory non-response to ASA. In our study group, self-reported adequate compliance with ASA therapy was noted in approximately 75% of patients, which is consistent with other published data regarding medication compliance in patients receiving antiplatelet drugs for secondary prevention of cardiovascular events. Observational data suggest that ASA resistance is rare in CAD patients who are compliant to ASA therapy [17–19]. Thus, it seems that in every case of suspected inappropriate response to ASA, compliance with this therapy should be evaluated and patients should be carefully educated about long-term benefits of aintiplatelet therapy [7].

Another strong predictor of ASA resistance in our study population was an increased heart rate (above the median value). According to our knowledge, such an observation has not been previously published, but an association between increased platelet activation and aggregation and increased sympathetic activity has been often discussed in the literature [20–23].

Multivariate analysis in our study also showed a relation between erythrocyte count and ASA resistance of borderline statistical significance. One postulated mechanism associated with platelet activation is an interaction between platelets and other blood morphotic elements. Previous studies showed incomplete platelet inhibition by ASA in the presence of erythrocytes in nearly two thirds of patients with atherosclerotic lesions despite complete inhibition of thromboxane A2 synthesis [24, 25].

Limitations of the study

A limitation of our study was a small number of studied patients that restricted possible statistical analyses. In addition, platelet function was evaluated with only one analytical method.

CONCLUSIONS

Laboratory non-response to ASA that is associated with increased risk of cardiovascular events, as shown in the published meta-analyses, is present in about one third of patients with CAD taking ASA for secondary prevention. Our study shows that non-compliance could be one of the most important risk factors responsible for ASA resistance by PFA-100. Thus, in addition to control of modifiable risk factors of ASA resistance, patients should be carefully educated about long-term benefits of treatment with ASA and compliance with this therapy should be evaluated during each follow-up visit.

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Czynniki warunkujące antyagregacyjną odpowiedź na kwas acetylosalicylowy w prewencji wtórnej — czy potrafimy je przewidzieć?

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Streszczenie

Wstęp: Kwas acetylosalicylowy (ASA) od lat należy do najczęściej przepisywanych leków. Jego zastosowanie w ramach prewencji wtórnej ostrych zespołów wieńcowych opiera się na wynikach wielu opublikowanych dotychczas badań. Istnieje wiele przyczyn związanych z brakiem całkowitej skuteczności prewencji zdarzeń sercowo-naczyniowych. Jedną z postulowanych przyczyn jest oporność na przeciwpłytkowy efekt po podaniu ASA. Dysponujemy kilkoma testami biochemicznymi, które pozwalają na ocenę aspirynooporności. PFA-100 jest analizatorem, który służy do oceny adhezji i agregacji płytek, a także jest coraz częściej wykorzystywany do analizy zaburzeń hemostazy.

Cel: Laboratoryjna ocena odpowiedzi na leczenie przeciwpłytkowe w populacji osób ze stabilną postacią choroby niedokrwiennej serca przyjmujących ASA w ramach prewencji wtórnej, z uwzględnieniem oceny czynników ryzyka występowania nieprawidłowego zahamowania aktywności płytek krwi.

Metody: Spośród 300 pacjentów do otwartego, prospektywnego i wieloośrodkowego badania włączono 92 osoby ze stabilną chorobą wieńcową, które w czasie ostatnich 3 miesięcy w ramach prewencji wtórnej przyjmowały przewlekle ASA w dawce dobowej 75–150 mg. Populację badaną rekrutowano spośród pacjentów z udokumentowaną angiograficznie stabilną postacią choroby niedokrwiennej serca po przebytym zawale serca i/lub zabiegu angioplastyki wieńcowej i/lub zabiegu pomostowania aortalno-wieńcowego pozostających pod opieką specjalistycznych poradni kardiologicznych. Oznaczenie aktywności płytek krwi wykonano u wszystkich uczestników badania przy użyciu analizatora funkcji płytek PFA-100 za pomocą kaset pomiarowych kolagen/epinefryna (CEPI) oraz kaset pomiarowych kolagen/ADP (CADP) systemu PFA-100. W zależności od wartości czasu okluzji wyrażonego w sekundach (CT) z zastosowaniem kaset testowych zawierających kolagen/epinefrynę (CEPI) wyróżniono grupę pacjentów wrażliwych na ASA (CEPI-CT $\geq$ 250 s) — ASA-R, grupę pacjentów pośrednio wrażliwych na ASA (CEPI-CT > 150 s < 250 s) — ASA-SR oraz grupę pacjentów opornych na ASA (CEPI-CT $\leq$ 150 s) — ASA-NR. Jednocześnie oznaczono wybrane parametry stanu zapalnego (CRP, fibrynogen), glikemię na czczo i osoczowe stężenie kreatyniny oraz wykonano morfologię krwi obwodowej, lipidogram i koagulogram.

Wyniki: Zgodnie z przyjętymi kryteriami brak odpowiedzi na ASA stwierdzono u 29,35% uczestników badania (27 osób), pośrednią wrażliwość na ASA — wyjściowo u 30,43% pacjentów (28 osób), natomiast prawidłową odpowiedź na ASA — u 40,2% badanych (37 osób). W przeprowadzonym modelu wieloczynnikowej analizy regresji logitowej, uwzględniając wpływ wszystkich ocenianych dla badanej grupy parametrów na występowanie braku odpowiedzi na ASA na początku prowadzonej obserwacji, istotność statystyczną stwierdzono odnośnie do regularnego przyjmowania ASA (OR 0,8; 95% CI: 0,20–0,35, p = 0,001) oraz częstotliwości rytmu serca powyżej mediany (tętno > 69 uderzeń/min) (OR 4,44; 95% CI: 1,37–14,38,

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p = 0,01). Wśród parametrów biochemicznych poziom istotności statystycznej osiągnął jedynie stosunek stężenia cholesterolu całkowitego do cholesterolu frakcji HDL powyżej mediany (cholesterol całkowity/HDL > 2,99; OR 0,19; 95% CI: 0,05–0,81, p = 0,02). Z kolei graniczny poziom istotności statystycznej osiągnęła liczba erytrocytów (RBC) powyżej mediany (RBC > > 4,61 mln/ml; OR 3,5; 95% CI: 0,99–12,37, p = 0,05).

Wnioski: Laboratoryjna oporność na ASA, która jak wynika z dostępnych metaanaliz zwiększa ryzyko wystąpienia zdarzeń sercowo-naczyniowych, występuje u około 1/3 populacji pacjentów z chorobą wieńcową otrzymujących ASA w ramach prewencji wtórnej. W przeprowadzonym badaniu na podstawie oznaczeń PFA-100 stwierdzono, że jednym z ważniejszych czynników odpowiedzialnych za brak odpowiedzi na ASA jest nieprzestrzeganie zaleceń lekarskich. Uwzględniając te obserwacje, poza kontrolą modyfikowalnych czynników ryzyka oporności na ASA, należy odpowiednio edukować chorych i podczas każdej wizyty oceniać przestrzeganie zaleceń lekarskich.

Słowa kluczowe: aspirynooporność, płytki krwi, PFA-100, stabilna choroba niedokrwienna serca

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