Prevalence and Features of Aspirin Resistance in Patients with Coronary Artery Disease

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Abstracts: Purpose. To determine the frequency of development of aspirin resistance in patients with coronary heart disease and to identify risk factors for the development of resistance to acetylsalicylic acid (ASA) in patients with coronary heart disease. Material and Methods: 96 patients were enrolled in this study with stable forms of ischemic heart disease who received a standard dose of aspirin 75 mg/day for a long time. Patients were divided into 4 groups according to the prescription of ASA. Group 1 consisted of patients who did not receive aspirin, the second group consisted of patients taking aspirin up to 1 year, the third group consisted of patients taking aspirin from 1 year to 5 years, and the fourth group included patients taking aspirin for more than 5 years. An addition, according to the results of determining aspirin resistance, the patients were divided into 2 groups. Platelet aggregation was measured using a laser analyzer: adenosine diphosphate (ADP) with 1.0 and 5.0 μmol was used. Resistance criterion: ADP ≥72% at 5.0 μmol.

Results: 17.7% of patients who took aspirin in a standard dose of 75 mg/day were resistant to aspirin, and a third of them took aspirin for more than 5 years. According to the results of a study of platelet aggregation activity, the average degree of platelet aggregation with 5.0 μmol of ADP was 82.4% in patients with no reaction to aspirin. An inadequate response to aspirin was reliably often observed in women and the elderly (58.8% and 70.5%). When analyzing the results of routine laboratory studies in patients with aspirin resistance, there was a tendency to higher levels of cholesterol and glucose (p<0.05). Possible risk factors for the development of ASA resistance are hypercholesterolemia and hyperglycemia, since aspirin resistance was more common in patients with diabetes mellitus and obesity (13 out of 17) and obesity (11 out of 17). Conclusion: High rates of ADP-induced platelet aggregation were obtained in ¼ patients with coronary heart disease. Aspirin resistance was observed more in women over 65 years old and in patients taking aspirin over 5 years old. Possible risk factors for the development of resistance to ASA are hypercholesterolemia and hyperglycemia, since aspirin resistance was more common in patients with diabetes mellitus and obesity.

Keywords: acetylsalicylic acid; aspirin resistance; cardiac ischemia; platelet aggregation.

INTRODUCTION

Despite advances in medical science and prevention, cardiovascular disease (CVD) is the main cause of morbidity and mortality in economically developed countries (Alyavi, A., & Uzokov, J. 2017).

Among the main etiopathogenetic factors of coronary heart disease (CHD), coronary atherosclerotic thrombosis is considered as the main factor in the progression of the disease, the development of acute coronary syndrome (ACS), as well as sudden cardiac events (Alyavi, A.L. et al., 2018; Radjabova, D. I. et al., 2018; Маматкулов, Х. А. et al.). It was shown that atherosclerotic and inflammatory lesions of the intima of the coronary vessels with a violation of its integrity occupy a leading place in the mechanism of atherothrombosis (UZOKOV, J. et al., 2019). Hypercoagulation, a slowdown in blood flow, and a decrease in the process of fibrinolysis can also lead to the formation of a blood clot (Cucumbers, P.P. et al., 2012; Uzokov, J. 2015, June).

Platelets play a central role in the pathophysiology of coronary heart disease (CHD):
platelet activation and aggregation is one of the key mechanisms of blood clot formation. Platelets are known to be the first to respond to rupture of an atherosclerotic plaque and form the basis for the formation of an arterial thrombus (Calkin, A. C. et al., 2009; Alyavi, A. L., & Uzokov, J. K. 2016; Alyavi, Bax., & Uzokov, J. 2018).

The prevalence of coronary heart disease, its role as a cause of disability, and a decrease in the quality of life of a significant part of the population determined the continuous improvement of treatment methods for various forms of this pathology. Given the relationship between the activation of the hemostatic system and the main risk factors, as well as its leading role in the development and progression of atherosclerosis and its complications, it seems pathogenically justified to prescribe antithrombotic drugs not only for treatment, but also for the prevention of cardiovascular diseases. Their use reduces the risk of development burden associated with thrombosis, or to improve the prognosis of patients with already developed thrombosis (Geisler, T. et al., 2010; Uzokov, J., et al., 2016; Anis, J.U., & Alyavi, B.A. 2016; Alyavi, A. L. et al., 2017).

The appointment of antiplatelet agents reduces the functional activity of platelets, thereby preventing their response to aggregation-inducing effects of pathophysiological processes of post-infarction remodeling of the cardiovascular system. From the standpoint of evidence-based medicine, the appointment of antiplatelet drugs for primary and secondary prophylaxis of acute cardiovascular events is an obligatory component of the pharmacotherapy of coronary heart disease and is included in the clinical recommendations at different levels (Vadász, D. et al., 2013; Alyavi, A. L. et al., 2017; Alyavi, B., & Uzokov, J. 2017; Abdullaev, A. X. Et. al., 2018; Alyavi, B. A., et al., 2018; Uzokov, J. et al., 2018).

To date, the only antiplatelet which clinical effectiveness has been proven by numerous clinical studies is acetylsalicylic acid (aspirin). The effectiveness of the use of acetylsalicylic acid for primary and secondary prevention of fatal complications of lesions of arteries in the various vascular pools has been confirmed by a large number of controlled clinical trials (Garabedian, T., & Alam, S. 2013; Abdullaev, A. Kh., et al., 2018; Alyavi, B. A., et al., 2018; Alyavi, B., & Uzokov, J. 2018; You, J. J. et al., 2012; Alyavi, A. et al., 2018).

According to a meta-analysis of 287 studies, including 212,000 patients at high risk for cardiovascular complications, conducted by an ATT Collaboration expert group (Antithrombotic Trialists' Collaboration), prolonged intake of aspirin (75–325 mg per day) reduces the total incidence of myocardial infarction, stroke and cardiovascular death by 23%. In accordance with the recommendations of the American Heart Association, the appointment of aspirin, in the absence of contraindications, is advisable for all patients with coronary artery disease. Acetylsalicylic acid (ACA) or aspirin has been widely used in cardiology since the 80s of the XX century as an antiplatelet drug. Aspirin blocks type 1 cyclooxygenase (COX 1) in platelets, inhibiting the synthesis of a powerful platelet aggregation (AT) inducer - thromboxane A2 (TXA2). As a result, irreversible suppression of antibodies occurs.

Despite the widespread use of ASA for the prevention of cardiovascular complications in patients with coronary heart disease, ischemic events still occur in some patients receiving regular antithrombotic therapy, which is regarded as manifestations of resistance, i.e., resistance, to ASA. The causes of this phenomenon are not fully understood (Friend, M. et al., 2003; Radjabova, D. I. et al., 2018; Alyavi, B.A., et al., 2019).

In the literature, there is a different prevalence of aspirin resistance - from 5.5% to 43% and largely depends on the applied diagnostic tests and studies of categories of patients. Recently, there has been increasing evidence that individuals showing a poor response to conventional antiplatelet agents have an increased risk of atherothrombosis. Moreover, such patients appear to have a poorer prognosis than patients with clear, ASA-dependent inhibition of platelet function (Fleg, J. et al., 2013; ABDULLAEV, A. Kh., et al., 2019; Alyavi, B.A., et al., 2019).

Aspirin resistance is defined as: the inability of aspirin to protect the patient from thrombotic complications; lengthen bleeding time; inhibit the biosynthesis of TXA2; inhibit platelet function in one or more in vitro tests. Aspirin resistance is divided into clinical and laboratory. The clinical type of resistance is indicated when, despite taking aspirin, thrombotic complications occur. The laboratory type of aspirin resistance is diagnosed based on an in vitro determination of platelet function while taking ASA.

The problem of resistance to antiplatelet drugs is fundamental in its significance, since it creates the prerequisites for the individualization of preventive therapy and the formation of more effective methods of preventing the disease (Uzokov, J. 2019; Xu, X. R. et al., 2016). In this regard, the question arises about the use of methods for assessing the effectiveness of antiplatelet therapy over the next months and years. The frequency variability of resistance to antiplatelet agents depends on the test system used, therefore, to date, the determination of individual sensitivity and change of antiplatelet in connection with its laboratory resistance are limited only by the scope of scientific research.
The “Gold Standard” in assessing the effect of ASA on platelet reactivity is the optical aggregatometry method, also called light transmission aggregometry (LTA) (You, J. J. et al., 2012; Staessen, J. A. et al., 2016). The effectiveness and safety of ongoing antiplatelet therapy in the early and long term after a vascular event can be evaluated as a clinical analysis and as laboratory methods, which include the study of spontaneous platelet aggregation (Geisler, T. et al., 2010; Park, J. B. 2016; Perk, J. et al., 2012).

Spontaneous aggregation is the formation of microaggregates, initiated by stirring a suspension of platelets without the addition of exogenous inducers. It is known that spontaneous aggregation is sometimes detected in healthy individuals, increased in patients with cardiovascular diseases and, according to some studies, may be a risk factor for thrombotic events.

Most of the methods for studying spontaneous platelet aggregation can be divided according to the principle of their implementation into two main groups:

- optical (measuring the optical density of a platelet suspension);
- visual (direct morphological assessment of aggregated platelets or a change in their number).

According to Usacheva E.V., et al., (Uzokov, J. et al., 2016; Deedwani, P. C. 2003; Uzokov, J. et al., 2016; Craft, R. M. et al., 2004), indicators of spontaneous platelet aggregation in 58.4% of patients with coronary heart disease, despite the ongoing antiplatelet therapy, are higher than the reference values. Since among patients with coronary atherosclerosis receiving ASA, 76.2% of patients have signs of hyperaggregation during spontaneous platelet aggregation. Platelet hyperaggregation during spontaneous aggregation in patients with coronary atherosclerosis receiving ASA may underlie the development of repeated vascular events, which requires further study of this issue with a comparison of the results with clinical data and indicators of induced platelet aggregation.

In a meta-analysis of the results of 6 studies, including 3059 patients (Uzokov, J. et al., 2016; Brar, S. S. et al., 2011; Uzokov, J. et al., 2016; Tanashyan, M. M. et al., 2016; Alyavi, A., & Uzokov, J. 2016, September). it was found that the residual platelet aggregation activity determined using the Verify Now method P2Y12 ≥ 230 units was associated with a higher incidence of the combined endpoint [Odds ratio (OR) 2.10; 95% confidence interval (CI) 1.62–2.73; p <0.0001], including individual deaths (OR 1.66; 95% CI 1.04–2.68; p = 0.04), myocardial infarction (OR: 2.04; 95% CI 1.51–2.76; p<0.001) and stent thrombosis (OR 3.11; 95% CI 1.50–6.46; p=0.001). Using a combined ROC (combined receiver operator curve) analysis, cut-off points were determined (> 46% aggregation at 5 μmol ADP and> 59% for 20 μmol ADP), which were associated with a high risk of ischemic events (58% and 54%, respectively, depending on the dose ADP) (Alyavi, A. L., et al., 2017; Alyavi, A. et al., 2017; Usacheva, E.V., et al., 2013).

Patients with chronic coronary heart disease take aspirin for years without knowing the effectiveness of the drug (Alyavi, A. L., et al., 2017). Determining the effectiveness of antiplatelet agents using laboratory tests do not always carried out.

**Purpose of this study was to investigate the prevalence of aspirin resistance, and factors affecting to the aspirin resistance in patients with coronary heart disease who have been taking aspirin for a long time.**

**Materials and Methods**

The study included 96 patients aged >18 years with a diagnosis of stable angina pectoris (SAP) of II-III functional classes (FC). Patients were admitted to the cardiology department of the Republican Specialized Scientific and Practical Medical Center for Therapy and Medical Rehabilitation. The diagnosis of coronary heart disease in the form of clinical forms of stable angina pectoris I-III FC was established in accordance with European recommendations (Alyavi, B. et al., 2018). The diagnosis was made on the basis of anginal pain or chest discomfort arising in exertion or emotional stress lasting no more than 15 minutes and stopping on their own or after taking nitrates.

Exclusion criteria: SAP IV FC; MI with and without ST segment elevation on the ECG; CHF IV FC by NYHA; other congenital and acquired diseases of the heart and blood vessels; concomitant diseases in the acute stage; a history of stenting and CABG in coronary arteries; intolerance to aspirin; prehospital administration of thrombolytic drugs and/or unfractionated heparin; taking medications that could affect the results of the study: long-term use of oral anticoagulants, antacids, proton pump inhibitors, systemic glucocorticosteroids, immunosuppressants, cardiac glycosides.

All patients received standard therapy: antiplatelet, antihypertensive, antianginal drugs and statins. As an antiplatelet agent, ASA (enteric-coated tablets) was prescribed at a dose of 75 mg.

Patients with SAP were divided into 4 groups according to the prescription of ASA. Group 1 consisted of patients who did not receive aspirin, the second group consisted of patients taking aspirin up to 1 year, the third group consisted of patients taking aspirin from 1 year to 5 years, and the fourth group included patients taking aspirin for more than 5 years.
Furthermore, patients were divided into 2 groups according to the presence of aspirin resistance.

All patients underwent physical examination, laboratory tests (general blood test, biochemical blood test, blood lipid spectrum and coagulogram), platelet aggregation study and functional diagnostics (ECG, EchoCG). The platelet aggregation in platelet-rich citrate plasma was studied using the Born and O’Brien method using a two-channel laser platelet aggregation analyzer Alat-2 Biola (produced by NPI BIOLA (Russia), with computer processing using the AGGR program and adenophosphate solutions were used as adenosine diphosphate solutions), (ADP) with final concentrations of 0.1, 1.0, and 5 μg/ml. The normal activity limits of the platelet aggregation process with the addition of 5.0 μmol of ADP are 25-72%. Call level of spontaneous aggregation >1.5 RLU level and platelet aggregation induced with ADP 5.0 mmol >72%.

Below are examples of normal and elevated curves of the degree of spontaneous aggregation and 5.0 μmol of ADP-induced platelet aggregation (Fig. 1-4).

![Fig. 1. Spontaneous aggregation.](image1)

![Fig. 2. ADP 5 μmol-induced aggregation.](image2)

Statistical processing of the research data was carried out using SPSS 18.0 software taking into account the type of variables and the normality of the distribution. A probability value (p) of less than 0.05 (two-sided significance test) demonstrated statistical significance.

**RESULTS**

The study included 96 patients (49 men and 50 women), the mean age was 64.5 (56.4-72.7) years. The number of patients with post infarction cardiosclerosis was 82 (85%), with CHF 39 (40.6%). Of the concomitant pathologies, hypertension — 82 (85.4%), type 2 diabetes mellitus — 58 (60.4%), and atrial fibrillation — 12 (12.5%) were most often noted.

Table 1 presents the characteristics of patients with coronary artery disease.
Table 1. Clinical and anamnestic characteristic of patients with CHD.

<table>
<thead>
<tr>
<th>Parameters</th>
<th>n(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHD</td>
<td>96</td>
</tr>
<tr>
<td>Age, years</td>
<td>64.5 ±9.3</td>
</tr>
<tr>
<td>Male, number</td>
<td>46 (47%)</td>
</tr>
<tr>
<td>Female number</td>
<td>50 (53%)</td>
</tr>
<tr>
<td>Obese (BMI&gt;30)</td>
<td>49 (51%)</td>
</tr>
<tr>
<td>Smoking</td>
<td>33 (34%)</td>
</tr>
<tr>
<td>Alcohol</td>
<td>26 (27%)</td>
</tr>
<tr>
<td>Stable angina II functional class</td>
<td>69 (72%)</td>
</tr>
<tr>
<td>Stable angina III functional class</td>
<td>27 (28%)</td>
</tr>
<tr>
<td>Postinfarction cardiосclerosis</td>
<td>36 (37%)</td>
</tr>
<tr>
<td>Atherosclerosis</td>
<td>41 (42%)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>82 (85%)</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>12 (12%)</td>
</tr>
<tr>
<td>CHF</td>
<td>39 (40%)</td>
</tr>
<tr>
<td>Type 2 diabetes mellitus</td>
<td>58 (60%)</td>
</tr>
</tbody>
</table>

The average degree of induced platelet aggregation with the addition of an ADP inducer of 5.0 μMol in the first group was 58.2%, in the second group was 33.2%, in the third group was 42.2%, and in the fourth group was 68.8%. According to the results of the platelet aggregation activity, 17 (17.7%) patients with no reaction to aspirin (i.e., patients with aspirin resistance) were identified in which the average degree of induced platelet aggregation with 5.0 μmol ADP was 82.4%, moreover, the vast majority of resistant patients - 11 out of 17, were in the 4th group. In this regard, it was precisely that group of patients was analyzed in more detail.

The results of the study are presented in table.

Table 2. Indices of spontaneous and ADP-induced platelet aggregation in patients with coronary heart disease who have been taking aspirin for a long time

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Patients not taking aspirin</th>
<th>Patients taking aspirin up to 1 year</th>
<th>Patients taking aspirin from 1 year to 5 years</th>
<th>Patients taking aspirin more than 5 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spontaneous</td>
<td>2.03</td>
<td>1.08</td>
<td>1.6</td>
<td>2.24*</td>
</tr>
<tr>
<td>0.1 μmoll ADP</td>
<td>6.4</td>
<td>3.4</td>
<td>5.4</td>
<td>7.8</td>
</tr>
<tr>
<td>1.0 μmoll ADP</td>
<td>15.7</td>
<td>6.5</td>
<td>12.8</td>
<td>31.8</td>
</tr>
<tr>
<td>5.0 μmoll ADP</td>
<td>58.2%</td>
<td>43.2%</td>
<td>52.2%</td>
<td>68.8%*</td>
</tr>
</tbody>
</table>

* P<0.05 compared with baseline

Given the close relationship between lipid metabolism disorders and platelet functional state, we analyzed the possibility of developing ASA resistance depending on the lipid spectrum. The most significant negative correlation between platelet aggregation index was determined in relation to cholesterol level (r = −0.41) and triglycerides (r = −0.43).

In addition, the possibility of a systemic compensatory decrease in the sensitivity to aspirin of all cells, including platelets, whose main functions are due to the metabolism of arachidonic acid and the synthesis of prostaglandins, is not ruled out. The effect of platelet count on the development of aggregation aspirin resistance may indicate a lack of antiplatelet administration. According to our studies, a comparison of platelet concentrations in groups of patients with aggregation aspirin sensitivity (control group) and aspirin resistance did not reveal statistically significant differences between the groups (see Table 3).
An inadequate response to aspirin was reliably often observed in women and the elderly (58.8% and 70.5%). In the aspirin-resistant group, there were more patients suffering from multifocal atherosclerosis, arterial hypertension, however, these differences did not reach significance. Aspirin-resistant patients were significantly more likely to have patients with diabetes mellitus (DM) (13 of 17 and 76.4%, respectively) than patients with a normal platelet response to ASA (p = 0.04), as well as patients with obesity (respectively 11 out of 17 and 64.7%) (p = 0.05).

**DISCUSSION**

The problem of aspirin resistance has attracted the attention of a wide range of doctors and patients, since aspirin is probably the most used drug in the world. According to P. Ogurtsov et al., (Susлина, Z.A. et al., 2011; Uzokov, J. et al., 2018; Babaev, M. et al., 2018.), the increase in the number of aspirin-resistant patients increased linearly with the increase in the duration of aspirin administration with a high approximation confidence value (R2 = 0.9063). The predicted number of aspirin-resistant patients after 2 years of taking aspirin is 70%. In our study, 17.7% of patients who took aspirin in a standard dose of 75 mg/day were resistant to aspirin, and a third of them took aspirin for more than 5 years (Uzokov, J., & Alyavi, B. 2018).

In recent studies, the term “high residual platelet reactivity” (HRPA) is used to objectively evaluate platelet function (platelet activity), which is an increase in platelet activity relative to a known range, which is determined after taking the recommended dose of antiplatelet drug (Alyavi, B. et al., 2018; Ryabukha, V.V. et al., 2006). Various prediction models have been proposed. Thus, when observing 1092 patients with coronary artery disease and percutaneous coronary interventions (PCI), the most powerful predictors of HRPA were: age> 65 years, type 2 diabetes mellitus, decreased left ventricular function, serum creatinine>1.5 mg/dL and ACS.

Among the factors that have the greatest influence on the effectiveness of antithrombotic therapy for secondary prevention of coronary heart disease, the state of lipid metabolism is important. The work describes not only an increase in platelet aggregation activity, but also its interaction with cholesterol levels of atherogenic lipoproteins with the effectiveness of taking antiplatelets, in particular, ASA. Up to 69% of patients with hyperlipidemia have signs of aspirin resistance (Alyavi, A. et al., 2018; Alyavi, B. A., et al., 2019). A close association of a decrease in sensitivity to ASA with lipid metabolism disorders was also noted: in patients with aspirin resistance, higher levels of triglycerides and cholesterol of low-density lipoproteins were more often observed (Ishhakov, S. et al., 2019). The studies revealed that hypercholesterolemia, observed in both II_A and II_B types of dyslipidemias.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Resistant group (n=17)</th>
<th>Sensitive group (n=79)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>TC (mmol/L) (M±σ)</td>
<td>8,6±1,32</td>
<td>5,1±1,22</td>
<td>0,04*</td>
</tr>
<tr>
<td>TG (mmol/L) (M±σ)</td>
<td>2,51±1,6</td>
<td>1,97±1,7</td>
<td>0,04*</td>
</tr>
<tr>
<td>LDL-C (mmol/L) (M±σ)</td>
<td>4,76±1,4</td>
<td>4,12±1,5</td>
<td>0,46</td>
</tr>
<tr>
<td>VLDL-C (mmol/L) (M±σ)</td>
<td>0,95±1,6</td>
<td>0,88±1,2</td>
<td>0,72</td>
</tr>
<tr>
<td>HDL-C (mmol/L) (M±σ)</td>
<td>0,84±1,0</td>
<td>0,96±1,4</td>
<td>0,74</td>
</tr>
<tr>
<td>RBC (mln/μL)</td>
<td>4,73±0,44</td>
<td>4,84±0,49</td>
<td>0,88</td>
</tr>
<tr>
<td>Platelet (thousand/μL)</td>
<td>261,9±61,6</td>
<td>279,9±67,3</td>
<td>0,82</td>
</tr>
<tr>
<td>Blood glucose</td>
<td>8,7±3,6</td>
<td>5,6±4,3</td>
<td>0,05*</td>
</tr>
</tbody>
</table>

*P<0,05 – to compare with controls

Statistically significant differences were revealed in a number of laboratory and clinical parameters in patients with and without aspirin resistance (see table 4).

**Table 4.** Indicators with a statistically significant difference in the presence of aspirin resistance in patients with coronary heart disease

<table>
<thead>
<tr>
<th>Parameter</th>
<th>CHD+H (n=17)</th>
<th>CHD-H (n=79)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duration of CHD, years</td>
<td>8,65†</td>
<td>4,23</td>
<td>0,02</td>
</tr>
<tr>
<td>Angina pectoris more than 5 years</td>
<td>11 (64,7%)†</td>
<td>6 (7,5%)</td>
<td>0,001</td>
</tr>
<tr>
<td>Female</td>
<td>10 (58,8%)†</td>
<td>34 (43,0%)</td>
<td>0,05</td>
</tr>
<tr>
<td>Elderly patients &gt;65 years</td>
<td>12 (70,5%)†</td>
<td>43 (54,4%)</td>
<td>0,04</td>
</tr>
<tr>
<td>Obesity</td>
<td>11 (64,7%)†</td>
<td>38 (48,1%)</td>
<td>0,03</td>
</tr>
<tr>
<td>Concomitant type 2 diabetes mellitus</td>
<td>13 (76,4%)†</td>
<td>45 (56,9%)</td>
<td>0,04</td>
</tr>
<tr>
<td>CHF</td>
<td>9 (52,9%)†</td>
<td>30 (37,9%)</td>
<td>0,04</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>8 (47,0%)†</td>
<td>25 (31,6%)</td>
<td>0,04</td>
</tr>
</tbody>
</table>

† - the value is higher than in the comparison group
are accompanied by the least sensitivity to ASA (Lutfullayevich, A. A. et al., 2017). In our study, the most significant negative correlation between platelet aggregation index was determined in relation to cholesterol level (r = −0.41) and triglycerides (r = −0.43). The percentage of obesity was 64.7% among aspirin-resistant patients with coronary artery disease (p = 0.05).

One of the possible reasons for the development of aspirin resistance against the background of chronic hyperglycemia is the intensification of glycation of platelet proteins and coagulation factors, which can interfere with acetylation processes and, thus, lead to an inadequate anti-aggregation effect of aspirin (Saydaliev, R.S., et al., 2015; Usarov, M., et al., 2016). It is assumed that in patients with metabolic syndrome, hypercholesterolemia leads to an increase in the “rigidity” of the platelet membrane and a deterioration in the sensitivity of glycoprotein receptors, one of the manifestations of which may be a decrease in sensitivity to aspirin (Lutfullayevich, A. A. et al., 2017).

Diabetes patients are always at high risk for the development of cardiovascular complications. Manifestations of atherothrombosis are a direct cause of death in 80% of patients with diabetes mellitus, of which three quarters of cases are associated with coronary heart disease (Mukhamedova, M. et al., 2019). According to the results of our research, in the aspirin-resistant group there were more patients suffering from multifocal atherosclerosis, arterial hypertension, however, these differences did not reach significance. Patients with diabetes mellitus (diabetes) were significantly more likely to be resistant to aspirin (13 of 17 and 76.4%, respectively) than with a normal platelet response to ASA (p = 0.04). It should be emphasized that in conditions associated with the infectious process and inflammation, non-platelet sources (monocytes, macrophages and endothelial cells) activate the COX-2 enzyme, resulting in increased formation of thromboxane A2 (TXA2) and increased levels of F2-isoprostanes (Ahmedov, I. et al., 2016; Habib, G. et al., 2019). These mechanisms, independent of COX-1, play a special role in patients with diabetes mellitus, hyperlipidemia, heart failure, and tobacco dependence. So, all these diseases are accompanied by increased peroxidation of lipids and arachidonic acid and, as a result, isotropin production by products. Standard doses of aspirin in such situations cannot completely inhibit TXA2 (Babaev, M. et al., 2018; Dobrovolsky, A.B. 2015). These data indicate the need to take into account aspirin resistance, primarily in patients with diabetes mellitus and with dyslipidemia, in order to resolve the issue of alternative ways of correcting platelet function. The results of the study evaluating platelet aggregation activity in patients with coronary heart disease suggest that:

1. Aggregate aspirin resistance was more common in ¼ patients with coronary heart disease taking aspirin for more than 5 years, in elderly and women.
2. Aggregated aspirin resistance may be due to chronic hypoxia and endogenous intoxication due to the presence of concomitant diseases such as hypertension, diabetes mellitus and obesity.
3. A relationship was found between sensitivity to ASA and lipid metabolism: negative correlation with levels of total cholesterol, TG.
4. Optimally selected antiplatelet therapy with acetylsalicylic acid is characterized by a decrease in platelet aggregation activity due to blocking the release phase along the curves of the average 5.0 μg/ml dose of ADP-induced platelet aggregation.

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