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# THE PREVENTION OF CARDIOVASCULAR COMPLICATIONS AFTER CORONARY STENTING IN PATIENTS WITH UNSTABLE ANGINA AND RESISTANCE TO ANTIPLATELET AGENTS

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**SUMMARY**

**Objective:** the aim of the study was evaluation of the clinical significance of high residual platelet reactivity in patients with unstable angina and coronary arteries stenting in the inpatient and outpatient monitoring and development of optimal ways of correction of this condition.

**Material and Methods:** the study included 131 patients with unstable angina after coronary stenting. The main group represented 78 patients (UA) underwent dynamic observation of platelet aggregation (Multiplate aggregometer) on the inpatient and outpatient observations (7 day, 1 month, 6 months, 12 months, 18 months) to identify primary and secondary resistance to antiplatelet agents with subsequent correction of antiplatelet therapy. The control group consisted of 53 patients with standard therapy with antiplatelet agents without control of platelet aggregation. All patients were performed: general blood analysis, biochemical blood analysis with determination of the level of TnI, C-reactive protein, myeloperoxidase, von Willebrand factor, and fibrinogen; the test of thrombin generation, also ECG, EchoCG, 24-hour ECG monitoring, coronary angiography.

**Results:** the results of our study showed a reduction in sensitivity to clopidogrel at 24,4% of patients with UA and stenting of the coronary arteries, of which the original clopidogrel in 7,7% of patients, generic clopidogrel 16,7% pts. Reduced sensitivity to acetylsalicylic acid was detected in 17,9% of individuals with UA. Laboratory resistance to ASA and/or clopidogrel increased the relative risk of recurrent cardiovascular events more than 4 times [CI 2,9; 5,6] during the 18 months of observation in comparison with a group of pts with no signs of resistance to antiplatelet agents.

**Conclusions:** execution of aggregatogram to patients with unstable angina and stenting of the coronary arteries allows to identify patients with high residual platelet reactivity, to correct of antiplatelet therapy and to reduce the number of repeat cardiovascular events in patients with signs of laboratory resistance to antiplatelet agents.

**Keywords:** *unstable angina, resistance to antiplatelet agents, agregatogramm, stenting of coronary arteries.*

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## INTRODUCTION

In recent years, there has been an increase in the frequency of percutaneous coronary intervention (PCI) with stenting in patients with acute coronary syndrome, therefore increasing attention is paid to the solution of problems related to thrombosis and restenosis inside stents. The in-stent thrombosis is observed in approximately 0,87-2,2% of cases and usually develops within the first year after stent placement [1,2].

In order to prevent thrombosis, patients are prescribed dual disaggregant therapy and anticoagulants. Clinical data indicate that neither acetylsalicylic acid nor clopidogrel in standard doses with no monitoring of antiplatelet activity can fully guarantee the effectiveness of disaggregant therapy, aimed to reduce the risk of repeated acute vascular events [2,3]. Besides, it is possible the development of atherothrombotic complications in other arteries, even in those that were not involved in the operation. A new generation of blockers P2Y12 receptor – prasugrel and ticagrelor – allows to improve the prognosis after acute coronary syndrome (ACS). However, clopidogrel remains the most commonly used blocker of P2Y12-receptor of platelets due to the high cost of new drugs and availability on the market less expensive reproduced antiplatelet medicines (generics) [2,3,4,5]. To avoid the consequences of insensitivity to acetylsalicylic acid (ASA) and clopidogrel is possible by regular monitoring of the level of platelet aggregation activity [6,7]. When assessing the functional activity of platelets by the method of multichannel aggregometry (Multiplate), the patient can be considered resistant to clopidogrel when AUC ADP test more than 46 U and he can be considered resistant to acetylsalicylic acid when AUC ASPI-test more than 40 U [2,6,7]. The above threshold values were obtained in patients with coronary artery disease, which had both stable and unstable forms of it and different methods of treatment. It should be noted that the terms of detection of high residual platelet reactivity (WORTH) is not so much for the purpose to define a remote risk for patients, but also for the possibility to correct the therapy [8,9,10]. The problem of individual selection of antiplatelet therapy is currently undergoing clinical studies. The most common options for correction of antiplatelet therapy in patients with persistently high platelet aggregation are: increasing the dose of the drug (e.g., clopidogrel), clopidogrel replacement for new inhibitors of P2Y12 receptors (prasugrel, ticagrelor) [8,9,10,11].

There is still no clear algorithm of examination of patients to identify risk factors for high reactivity of platelets, recommendations on tactics of antiplatelet therapy based on controlled laboratory studies. In this regard, it is extremely important to conduct further studies on the clinical consequences of laboratory resistance to antiplatelet drugs and also to improve methods of primary and secondary prevention of cardiovascular events.

**Objective**: to evaluate the clinical value of high residual platelet reactivity in patients with unstable angina and performed coronary arteries stenting during the inpatient and outpatient observation and to develop the best ways of correction of this condition.

## MATERIAL AND METHODS

In the present study, there are 131 patients included with unstable angina after coronary stenting. Randomization of patients to main study and control groups was conducted by random sampling. The main group represented 78 patients (HC) undergoing dynamic observation of platelet aggregation in the inpatient and outpatient stages of follow-up (7 day, 1 month., 6 months, 12 months, 18 months), that helped to identify primary and secondary resistance to antiplatelet agents with subsequent correction of antiplatelet therapy. The control group consisted of 53 patients with standard therapy with antiplatelet agents in the inpatient and outpatient stages of observation without control of platelet aggregation.

The observation period was 2±1,4 years. The criteria for inclusion into the study: new-onset or progressive angina associated with ECG signs indicating acute myocardial ischemia (ST segment elevation, depression of ST segment, inversion of T wave), with a duration of no more than 4 weeks from the acute condition, with a use of invasive endovascular treatment strategy.

Exclusion criteria: 1) persons with coronary artery disease and have heart failure II B and above (by Strazhesko-Vasilenko); 2) lesions of the valves of the heart, requiring surgical correction; 3) acute myocardial infarction; 4) acute violation of brain blood circulation; 5) pulmonary embolism; 6) thrombophlebitis of the lower limbs; 7) other acute inflammatory diseases of various organs and systems; 8) diseases of the blood.

Stenting was performed on 3,2±1,6 days of admission. There were used stents with drug coating: Xience V stent (manufacturer, Abbott, USA) coated with everolimus and the Biomatrix stent (Biosensors manufacturer company, Switzerland), coated with Biolimus A9 drug. All patients with unstable angina at admission were prescribed anticoagulants: a synthetic selective inhibitor of activated factor X (Xa): fondaparinux (Arixtra) 2,5 mg/d n/a or enoxaparin (Clexan) at the rate of 1 mg/kg of body weight every 12 hours subcutaneously. The average duration of anticoagulant therapy was 6,8±1,1 days. In addition to treatment with anticoagulants patients with unstable angina were prescribed double desegregate therapy, including clopidogrel at the dose of 75 mg 1 time per day and acetylsalicylic acid (ASA) 75 mg 1 time per day; loading doses of clopidogrel (600 mg) before stenting of the coronary arteries, 300 mg of acetylsalicylic acid. The duration of dual antiplatelet therapy was 12 months.

On clinical and anamnestic data and the main instrumental characteristics, the patients of main group and the control group were comparable, which is presented in table 1.

The study examined the risk of occurrence of the following endpoints: death, acute myocardial infarction, recurrent unstable angina, life-threatening heart rhythm and conduction disorders of ischemic origin. All patients got: common blood test using siteprotect method on automatic geoanalyzer Micros 60 (France), biochemical blood analysis with determination of the lipid spectrum, level of troponin I, high sensitive C-reactive protein; levels of myeloperoxidase (MPO). Evaluation of coagulation-plasma hemostasis was done with the performance of the thrombin generation test, determination of fibrinogen, von Willebrand factor. Aggregatogram for patients of the main group was performed on the analyzer Multiplat with the definition of ASPI-test (inducer – arachidonic acid) and ADP test (inductor ADF). Patients were considered resistant to clopidogrel when the value of area under the curve were AUC ADP test >46 U, characterizing high residual platelet reactivity (WORTH), and resistant to ASA – at AUC ASPI-test >40 U. All patients had ECG, echocardiography, coronary angiography performed.

**Statistical analysis.** Depending on the compliance or noncompliance of the type of distribution of the analyzed characteristics of the normal distribution, the calculations used parametric or nonparametric methods. To identify the strength and direction of relationships between the studied variables was used correlation analysis with the calculation of the parametric Pearson

**Table 1. Clinical-anamnestic and instrumental characteristics of the patients with unstable angina**

| Index | Main group | Control group |
|---|---|---|
| The number of patients, n | 78 | 53 |
| The average age (number of years) | 61,2±7,3 | 58±3,6 |
| Body mass index >30 kg/m$^2$, n (%) | 24 (30,7%) | 17 (32%) |
| Men, n (%) | 52 (66,7%) | 39 (73,6%) |
| Diabetes mellitus, n (%) | 27 (34,6%) | 16 (30,2%) |
| Arterial hypertension, n (%) | 59 (75,6%) | 42 (79,2%) |
| Myocardial infarction in anamnesis, n (%) | 19 (24,4%) | 11 (20,7%) |
| Stenting of coronary arteries in anamnesis, n (%) | 11 (14,1%) | 7 (13,2%) |
| LV ejection fraction (b-mode), % | 54,1±6,1 | 52,7±4,2 |
| Critical failure of 1 coronary artery, n (%) | 49 (62,8%) | 37 (69,8%) |
| Critical failure of 2 coronary arteries, n (%) | 29 (37,2%) | 16 (30,2%) |
| Hypercholesterolemia, n (%) | 58 (74,4%) | 41 (77,4%) |

correlation coefficient and the nonparametric Spearman correlation coefficient. Analysis of the results of research was carried out on the basis of the biostatistical methods of MSEXCELXP program, MedCalcStatisticalSoftware.

## RESULTS

Of the 78 patients in the main group included in the study, on the 7th day of the appointment of antiplatelet agents we saw a reduction in sensitivity to acetylsalicylic acid (ASA) in the standard dose in 14 (17,9 percent) individuals; to clopidogrel – in 19 (24,4%) individuals (including the original clopidogrel in 6 (7,7%) patients; to generic clopidogrel in 13 (16,7%) of individuals). Thus, a high residual platelet reactivity were detected in 33 patients (42,3 percent).

The aggregatogram results showed that the area under curve of AUC ADP test became 70,6±7,7 U after 7 days of treatment with clopidogrel (table 2).

Taking into account the previously identified prognostic relationship of repeated coronary events with hyper aggregating of platelets and disruption of the cardiovascular plasma hemostasis [12], patients with WORTH, who were receiving clopidogrel, also got therapy by low molecular weight heparins and fondaparinux until discharge from hospital (10-12 days) with the control of aggregatogram at discharge. The need for long-term administration of anticoagulants was confirmed by the fact that all patients of this group had an increased level of thrombin, which indicates the activation of plasma hemostasis and high risk of atherothrombosis. The peak concentration of thrombin in patients with WORTH and AUC ADP test more than 46 U was 322,5±17,4 nm (norm 220-280 nm), the level of high-sensitivity CRP of 5,9±0,5 g/l (norm up to 3,35 mg/l), myeloperoxidase 337±21 pmol/l (normal 200 pmol/l).

Given the possibility of drug-drug interaction, for individuals with identified resistance to clopidogrel and increased ADP test (AUC) >46 U the assignment of proton pump inhibitors (PPIS) were carried out only at the risk of gastrointestinal bleeding. It is known that the proton pump inhibitors (omeprazole, pantoprazole, lansazol, etc.) inhibit the CYP2C19 enzyme, responsible for the conversion of clopidogrel to the active metabolite. Thus, the reduced activity of clopidogrel was happening not only when it was administered simultaneously with omeprazole, but also at intervals of 12 hours. Therefore, if necessary, patients were administered pantoprazole, which is a weak inhibitor of CYP2C19.

When monitoring platelet function in 1 month after discharge, during outpatient observation, normoaggregation was registered in 9 of the 13 resistant patients (69,2%), who were receiving generic clopidogrel, which has been achieved by assigning the original clopidogrel and cancellation of proton pump inhibitors. In 1 month, the AUC ADP test in these patients was 45 U (38 U to 47 U). In the remaining four patients, AUC ADP test after 1 month was 67,9±4,7 U, which is much higher than normal levels, and so within a year these individuals developed repeated coronary events.

Of the 6 patients with WORTH, while taking clopidogrel original, the two individuals managed to reach normoaggregetaion by prescribing a ticagrelor in dose of 90 mg 2 times a day. During laboratory control after 3 and 6 months from the beginning of the disease, because of the prescribed ticagrelor, AUC ADP test was less than 40 U, and there was a significant reduction in the levels of thrombin, and the downward trend in the level of MPO and CRP. The remaining four patients continued to take clopidogrel original (not being able to acquire ticagrelor), and in a month it was a decrease in the value of area under the curve AUC ADP test to 56 U (U 51 – 60 U), but the optimal values of AUC ADP test was not received, that eventually led to the development of repeated coronary events in these patients.

Thus, after correction of therapy, WORTH was registered in 8 out of 78 patients (10,3%) after 1 month of observation. It should be noted, that these patients had not only activation of platelet hemostasis, but also vascular and plasma links of hemostasis, which was confirmed by a high level of thrombin, myeloperoxidase, CRP and indicated a high risk of repeated cardiovascular events.

For patients sensitive to clopidogrel, AUC ADP test on day 7 was 40±9,4 U, and in 6 and 12 months it was 38±5,3 U and 40,1±8,9 U respectively. While controlling the aggregatogram during outpatient stage of people who are sensitive to clopidogrel, 8 (13,6 percent) out of the 59 noted the appearance of reduced sensitivity to the drug, which is associated with the replacement of the original clopidogrel to generic during 6 to 8 months after stenting. We didn't have any cases of independent drug cancellation for the entire period of observation. In connection with the identified violations, a correction of desagregants therapy was performed and the original clopidogrel was prescribed, which allowed, eventually, to reduce residual platelet reactivity and to improve indicators of vascular-platelet and plasma hemostasis.

According to imbedance aggregatogram, when you run ASPI-test with arachidonic acid and after 5-7 days of ingestion of acetylsalicylic acid after stenting, 14 individuals showed a reduction in sensitivity to ASA (17,9 percent), when the value of AUC ASPI-test became 61,6±6,8 U (table 3).

**Table 2.Dynamics of indicators of AUC ADP test in individuals with unstable angina , sensitive and resistant to clopidogrel (the main group)**

| Index | AUC ADP-test on 7th day | AUC ADP-test – 1 month | AUC ADP-test – 6 months | AUC ADP-test – 12 months |
|---|---|---|---|---|
| Sensitive to clopidogrel patients, n=59 (75,6 %) | 38±7,4 | 38±5,3 | 46,2±13,9 | 45,1±7,9 |
| Clopidogrel-resistant patients, n=19 (24,4%) | 70,6±7,7 | 49,7±5,1 | 47,3±6,4 | 46,3±4,2 |

In case of WORTH, while taking acetylsalicylic acid, it was recommended to receive "uncovered" acetylsalicylic acid at a dose of 75 mg per day.

Whith monitoring the impedance aggregatometry in 1 month and the quantitative values of AUC ASPI-test >40 U, the dose of acetylsalicylic acid was increased to 100 mg per day with the further repeated control of ASPI-test in 1 month after increasing the dose. With the continuing hyper aggregation, the dose of acetylsalicylic acid was increased to 150 mg daily with subsequent control of ASPI-test in 1 month after increasing the dose.

By receiving uncovered acetylsalicylic acid at a dose of 75 mg per day and correction of therapy , and was possible to reduce residual platelet reactivity after 1 month of observation in 7 individuals out of 14 (50%) with signs of laboratory resistance to acetylsalicylic acid detected at the stationary stage of treatment. Acetylsalicylic acid at a dose of 100 mg was received by 6 patients (42,9%) and at a dose of 150 mg – 1patient out of 14 (7,1%). By 3 months of monitoring, indicators of AUC ASPI-test in the above-mentioned individuals were 52,3±8,1 U, in 6 and 12 months – 40,3±7,4 U and 42,8±9,1 U, respectively, which exceeds the normal value. When monitoring the aggregatogram in 18 months (due to cancellation of clopidogrel), 7 patients that were taken 100-150 mg of acetylsalicylic acid again started to have an increase of the value of area under the curve ASPI-test. On average, the results of AUC ASPI-test of these individuals were 72,9±6,3 U, which is much higher than normal levels and indicates a high risk of repeated coronary events.

64 patients out of 78 (82%) were sensitive to acetylsalicylic acid and received standard dual antiplatelet therapy. In the subgroup of patients, sensitive to acetylsalicylic acid, the level of platelet aggregation after 7 days of treatment was 29,4±9,4 U ($p<0.01$), after 6 months of observation – 26,1±5,3 U and increased to 38,6±13,9 U in 12 months and 46,7±8,7 U in 18 months of control.

A gradual increase in the AUC ASPI-test is due to the fact that out of the 64 patients, sensitive to acetylsalicylic acid, 10 (15,6%) individuals who had control of aggregatogram in 6 months, started to have a reduced sensitivity to acetylsalicylic acid (secondary resistance), which required changing the dosage with the subsequent control of platelet aggregation. Also, indicators of lipid metabolism played an important role. Correlation was found between sensitivity to acetylsalicylic acid and lipid metabolism: the levels of total cholesterol (r=-0,56), triglycerides (r=-0,49), low density lipoprotein (r=-0,51) and cholesterol of high density lipoproteins (r=0,46).

Monitoring of patients with a history of unstable angina and laboratory signs of resistance to acetylsalicylic acid (ASPI-test) showed that because of the correction of antiplatelet therapy (dose change of acetylsalicylic acid) and concomitant therapy (increase doses of statins, inhibitors of the proton pump) it was possible to reduce the reactivity of platelets and reduce the magnitude of the AUC ASPI-test below 40 U in 100% of cases within 6 months of observation, but in 12-18 months this result was significantly less than that which is associated with the cancellation of clopidogrel and the lack of its influence on acetylsalicylic acid and also because of prescription of "covered" forms of acetylsalicylic acid in patients not initially sensitive to this form of medication.

In the main group, during the first year of observation, repeated cardiovascular complications developed in 11 patients (14,1%), including 8 patients with signs of WORTH, mainly with resistance to clopidogrel and the inability to replace original clopidogrel or ticagrelor. The stent thrombosis with myocardial infarction developed in 3 patients (3,8%) in the long term period (in 5-7 months after implantation of stents with antiproliferative coating) and was confirmed by coronary angiography, it was observed in patients with high residual platelet reactivity during outpatient observation and the inability to replace generic clopidogrel to original or ticagrelor prescription. Early thrombosis of the stent (up to 1 month) in the main group was not registered, which is probably connected with the timely correction of antiplatelet and anticoagulant therapy in identifying WORTH. Recurrent angina with rehospitalization was registered in 6 individuals (7,7 per cent), while in 4 cases there was restenosis of the zone of stenting in a period of 1 to 3 months after the procedure, and two patients had no pathological changes in the zone of stenting, while the coronary angiogram recorded lesions in other coronary arteries (atherosclerotic plaques 50-60%). One patient (1,3%) had paroxysms of ventricular tachycardia on the background of WORTH, and according to coronary angiography, it was noted the smaller diameter of the stented coronary artery (about 2,5 mm) and extended stenosis, that increased the risk of stent thrombosis. One patient died suddenly in his sleep from acute coronary insufficiency (1,3%) and he belonged to the group of individuals with WORTH, and according to coronary angiography (in addition to the stented right interventricular branch) was characterized by the presence of critical atherosclerotic plaques (30-60%) in the coronary arteries (right coronary artery, circumflex branch, diagonal branch) (table 4).

**Table 3. Dynamics of indicators of AUC ASPI – test in individuals with unstable angina from the general group, sensitive and resistant to acetylsalicylic acid**

| Index | AUC ASPI-test on 7th day. | AUC ASPI test – 1 month | AUC ASPI-test – 6 months | AUC ASPI-test – 12 months |
|---|---|---|---|---|
| The ASA sensitive patients n=64 (82%) | 29,4±9,4 | 26,1±5,3 | 38,6±13,9 | 42,7±8,7 |
| The ASA sensitive patients, n=14 (17,9%) | 61,6±6,8 | 52,3±8,1 | 44,3±7,4 | 46,8±9,1 |

**Table 4. Clinical outcomes in individuals of the main group who have suffered unstable angina and stenting of the coronary arteries over 2 years of observation**

| Complications | 1 year | | 2 year | |
|---|---|---|---|---|
| | Sensitivity, n=45 | Resistense, n=33 | Sensitivity, n=45 | Resistence, n=3 |
| Recurrent unstable angina, number of cases | 2 (4,4%) | 4 (12,1%) | - | 2 (6%) |
| Myocardial infarction, number of cases | 1 (2,2%) | 2 (6%) | - | - |
| Life-threatening arrhythmias, the number of cases | - | 1 (3%) | - | 1(3%) |
| ADCC, TIA, number of cases | - | - | - | 4 (12,1%) |
| Mortality, number of cases | - | 1 (3%) | - | - |

In the main group during the second year of monitoring (due to cessation of clopidogrel) complications occurred in 7 (10,3%) patients, 5 of them were individuals with signs of laboratory resistance to acetylsalicylic acid. At this stage, an acute cerebrovascular accident (CVA) and transient ischemic attack (TIA) dominated in 4 patients (12,1%), recurrent angina in 2 patients (6%) with angiographic signs of restenosis.

In General, during the first year of monitoring, cardiovascular complications occurred in 8 individuals (24,2 per cent) with the original laboratory signs of WORTH, and in 3 patients with normal sensitivity to antiplatelet agents (6,7%).

During the second year of monitoring, recurrent coronary events developed only in patients with high residual platelet reactivity, while receiving acetylsalicylic acid – 7 (21,2%) patients. It is not excluded that one of the reasons for adverse outcomes after coronary stenting in patients with unstable angina was ineffective desegregate therapy. According to our data, the presence of laboratory resistance to acetylsalicylic acid and/or clopidogrel increases the relative risk (RR) of ischemic complications in the future (death, life-threatening arrhythmias, recurrent angina) is more than 4 times [CI 2,9; 5,6] during the 18 months of observation in comparison with a group of people with no signs of resistance to antiplatelet agents.

In the cardiogram during the first year of monitoring, recurrent cardiovascular complications occurred in 14 patients (26.4 per cent). Myocardial infarction due to stent thrombosis occurred in 3 patients (5.7 percent), 2 patients had it in 1 month after stenting and in 1 case in happened in the average period (3 months) and was confirmed by coronary angiography, and it was observed in patients, receiving generic clopidogrel. One patient died from acute coronary insufficiency in 2 weeks after stenting, with autopsy signs of reocclusions stent thrombosis (in patients receiving generic clopidogrel). Recurrent angina with rehospitalization was registered in 8 persons (13,2%), of which in 4 cases there was restenosis of stenting zones and four patients had no pathological changes in stenting zones, but the coronary angiogram recorded lesions in other coronary arteries (atherosclerotic plaques 50-60%). The paroxysm of ventricular tachycardia was registered in 2 patients (3,8%).

In the cardiogram during the second year of monitoring, complications occurred in 6 (11,3%) patients. At this stage, recurrent angina was in 4 patients (7,5%) with angiographic signs of restenosis, stroke and TIA in 2 patients (3,8%).

Thus, it should be noted, that the overwhelming number of repeated cardiovascular events in patients with unstable angina and stenting of the coronary arteries is registered within the first year of observation, despite ongoing dual antiplatelet therapy.

The relative risk of complications in patients with unstable angina and stenting of the coronary arteries without monitoring platelet function is 1,8 times higher, than for patients with performance of aggregatogram and identifying the WORTH with the subsequent correction of antiplatelet therapy.

**DISCUSSION**

It is known that antiplatelet therapy is an important component in the treatment of unstable angina, but it's also important in treatment of other forms of acute coronary syndrome regardless of the treatment strategy. The clinical efficacy of dual antiplatelet therapy with aspirin and clopidogrel was proved by the large number of international studies, but some patients with double antiplatelet therapy re-occur ischemic events, which may be due to insufficient sensitivity of patients to their activity [2,3,12]. The results of our study showed that 24.4% of patients with unstable angina after coronary stenting had a reduction in sensitivity to clopidogrel (to the original clopidogrel – 7,7% of patients, to generic clopidogrel – 16,7% of individuals). Reduced sensitivity to acetylsalicylic acid were detected in 17,9% of individuals with unstable angina.

In our study, during the first year of monitoring, cardiovascular complications occurred in 24,2% of patients who had the original laboratory signs of WORTH and 6,7% of patients with normal sensitivity to antiplatelet agents. The existence of laboratory resistance to acetylsalicylic acid and/or clopidogrel increases the relative risk of repeated cardiovascular events more than in 4 times [CI 2,9; 5,6] during the 18 months of observation in comparison with a group of people with no signs of resistance to antiplatelet agents.

It should be noted that the sense of identifying the WORTH is not so much to define a remote risk patients, but for the correction of therapy [10,11]. The problem of individual selection of antiplatelet therapy is currently undergoing clinical studies. The most common correction options of antiplatelet therapy in patients with persistently high platelet aggregation are: increasing the dose of the drug (for example, clopidogrel), clopidogrel replacement for new inhibitors of P2Y12 receptors (prasugrel, ticagrelor) [2,10,11].

Correction of therapy in our study was carried out as follows: 1) while detecting the clopidogrel resistance and if it was a generic drug it was prescribed the original clopidogrel. For individuals with WORTH and elevated levels of thrombin anticoagulants (low molecular weight heparins) were administered in long-term (8-10 days). When monitoring platelet function in a month we saw that it was not sufficient to reduce the amplitude of AUC ADP test, we changed the drug to ticagrelor; 2) if the resistance to acetylsalicylic acid was detected, it was recommended to receive "uncovered" acetylsalicylic acid at a dose of 75 mg per day. When monitoring the impedance of aggregatometry in 1 month and if the quantitative values of AUC ASPI-test >40 U, the dose of acetylsalicylic acid was increased to 100 mg per day with the further re-control of ASPI-test in 1 month after increasing the dose. With the continuing hyper aggregation, the dose of acetylsalicylic acid was increased to 150 mg daily with further subsequent control of ASPI-test in a month after increasing the dose. Medical schemes with a gradual increase of dosage of "uncovered" acetylsalicylic acid (75-150 mg) and correction of the concomitant therapy (hypercholesterolemia, dyslipidemia, cancellation NSAIDs) allow to overcome laboratory resistance to acetylsalicylic acid that happened to be because of inadequate doses of the drug or its interaction with other medications.

Aggregatogram execution and dynamic monitoring of platelet aggregation in individuals with unstable angina and stenting of the coronary arteries allows to detect high residual platelet reactivity in patients receiving antiplatelet agents and to conduct correction of the treatment, reducing the relative risk of repeated cardiovascular events in 1,8 times for 1 year of control.

When assessing the effectiveness of therapy we also need to control the regularity of receiving antiplatelet drugs and their combinations with existing competitive drugs (e.g., aspirin, ibuprofen, or clopidogrel and omeprazole) that may significantly affect the end results of platelet aggregation. In addition, it is necessary to adjust the dosage of statins, and to evaluate the lipid-lowering effect, particularly in individuals with dyslipidemia. In our study, the application of these schemes of treatment has allowed to reduce the number of patients with signs of laboratory resistance to antiplatelet agents and to reduce the number of repeated cardiovascular events. However, because of the small number of observations, it is necessary to continue research in this direction.

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