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Research article

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Laboratory Evaluation of the Platelet Component of Hemostasis in acute Coronary Syndrome With ST Segment Elevation

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RELEVANCE Acute coronary syndrome (ACS) is one of the most common cardiovascular diseases associated with increased mortality and disability of patients. Regarding the factor of genetic resistance to antiplatelet therapy, and we get an even more serious problem faced by cardiologists around the world. The study of antiplatelet therapy and resistance to it is a pressing issue in modern cardiology. This is important not only for determining the effectiveness of treatment for each patient, but also for personalizing therapy based on genetic characteristics. This allows improving the effectiveness of treatment and preventing recurrent cardiovascular complications. As a result, the study of antiplatelet therapy and resistance to it is an important aspect in the treatment of ACS. This helps prevent recurrent cardiovascular complications, improve the effectiveness of treatment and develop new methods of therapy.

AIM OF THE STUDY ST-segment elevation ACS (STEMI) based on a personalized approach to antiplatelet therapy and modification of the program to predict the course and outcome. To study the possibilities of various laboratory diagnostic methods for assessing the platelet component of hemostasis in patients with STEMI depending on (1) the combination of antiplatelet drugs used (aspirin + clopidogrel; aspirin + ticagrelor); (2) the presence of factors of genetic resistance to antiplatelet agents.

MATERIAL AND METHODS The study included patients with STEMI who underwent percutaneous coronary intervention in the infarct-related artery territory, a total of 46 patients (13 women, 33 men) aged 35 to 83 years, average age 61.7 years. Patients were divided into groups according to the received combination of dual antiplatelet therapy (DAPT) aspirin + clopidogrel (23 patients), aspirin + ticagrelor (23 patients), groups with and without genetic determination (GD) were assessed. The platelet component of hemostasis was assessed in three different ways: standard coagulogram, aggregometry, rotation thromboelastometry. The following pharmacogenetic markers were determined in all patients: CYP2C19*17, CYP2C19*2, CYP2C19*3, SLCO1B1, CYP3A5*3. LOF alleles were detected in 32 patients (67%). Among them, in the group taking aspirin in combination with clopidogrel, three subgroups of patients were distinguished: 7 patients in the slow metabolizer (SM) subgroup, 8 patients in the general rapid metabolizer subgroup, and 8 patients without LOF alleles were designated as normal metabolizers. In the group taking aspirin in combination with ticagrelor, 9 patients with intermediate metabolism were identified. Seven patients in the SM group. Seven patients without LOF alleles were classified as NM group. The course of the disease and its outcomes were assessed.

RESULTS Against the background of the use of antiplatelet agents, at research points 2 and 3, the values of the CT-EXTEM parameter statistically significantly increased compared to research point 1 and went beyond the reference values, reflecting drug-induced hypocoagulation of the platelet hemostasis link (66.1±2 and 96.3±14.3 s, respectively, p=0.02). It was especially important that in the group with GR, the CT-EXTEM parameter did not change either by research point 2 or by research point 3, reflecting platelet normal or hypercoagulation.

CONCLUSION Aggregometry parameters do not allow adequate assessment of the state of the platelet hemostasis link and its response to antiplatelet therapy in patients with acute coronary syndrome with ST segment elevation. Among the studied traditional and viscoelastic hemostatic parameters, the only parameter that should be used to assess the state of the platelet hemostasis link and its response to antiplatelet therapy is the CT-EXTEM test.

Keywords: acute coronary syndrome with ST segment elevation, dual antiplatelet therapy, genetic resistance, ROTEM, agregometry, Ticagrelor, Clopidogrel, platelet hemostasis

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A10 — clot density obtained after 10 minutes
ACS — acute coronary syndrome
APTT — activated partial thromboplastin time
BMI — body mass index
CAG — coronary angiography
CFT — Clot formation time
CT — Coagulation Time
DAPT — dual antiplatelet therapy
DNA — deoxyribonucleic acid
ECG — electrocardiogram
GD — genetic determination
GR — genetic resistance
GRA — genetic resistance to antiplatelet agents
IHD — ischemic heart disease
LOF — Loss of Function, reduced function
MCF — Maximum clot firmness, maximum clot density
PCI — percutaneous coronary intervention
PCR — polymerase chain reaction
PCSamp — difference in clot density between external activation and functional fibrinogen test
RI — reference interval
ROTEM — rotational thromboelastometry
ST —segment elevation acute coronary syndrome
STEMI — ST-elevation myocardial infarction

INTRODUCTION

Acute coronary syndrome (ACS) with ST segment elevation (ST- segment elevation ACS) is one of the most common forms of coronary heart disease (CHD) and the leading cause of mortality and disability both in Russia and in other countries [1]. The main method of treating patients with ST- segment elevation ACS is myocardial revascularization [2]. The latter is achieved using either endovascular techniques of angioplasty and stenting of infarction-related coronary arteries — percutaneous coronary intervention (PCI), or direct cardiac surgery with coronary artery bypass grafting [3].

The second fundamentally important direction of treatment of patients with STEMI, leading to a statistically significant improvement in the outcome of the disease, is antithrombotic therapy, the standard of which is currently dual antiplatelet therapy (DAPT) [4]. A combination of aspirin and a drug from the thienopyridine group (clopidogrel , prasugrel or ticagrelor) is routinely used in the vast majority of patients as DAPT [5]. The use of DAPT leads to a statistically significant reduction in the risk of developing recurrent STEMIdue to the development of coronary artery thrombosis or an installed stent [6]. At the same time, there is a problem of genetic resistance (GR) to antiplatelet (GRA) drugs, which, according to various authors, has a fairly high prevalence [7]. The incidence of GR to aspirin is 5–45%, to clopidogrel – 16–45%, to ticagrelor – 6–12%, to both of these antiplatelet drugs – 6–8% [8].

Evaluation of the platelet component of hemostasis is important for the prevention of the development of recurrent ACS and/or its recurrent course, as well as for assessing the effectiveness of DAPT [9]. Currently, the laboratory "gold standard" in the study of the platelet component of hemostasis is aggregometry [10]. In the last decade, viscoelastic methods for assessing hemostasis, in particular, rotational thromboelastometry (ROTEM) [11], have become widespread. However, to date there are no data on the significance of aggregometry and the results of using ROTEM to assess the platelet component of hemostasis in patients with STEMI. In this regard, the presented study was planned.

The aim of the study was to investigate the possibility of various laboratory diagnostic methods for assessing the platelet component of hemostasis in patients with STEMI depending on (1) the duration of the disease and, accordingly, the duration of use of antiplatelet agents; (2) the combination of antiplatelet drugs used (aspirin + clopidogrel; aspirin + ticagrelor); (3) the presence of GRA factors.

MATERIAL AND METHODS

The study was conducted at the N.V. Sklifosovsky Research Institute for Emergency Medicine of the Moscow Health Department in the period from 2019 to 2023. Determination of genetic polymorphism and levels of concentration of antiplatelet drugs in plasma was carried out at the Russian Medical - Academy of Continuous Professional Education of the Ministry of Health of the Russian Federation.

Inclusion criteria: acute phase of STEMI, age 18–75 years.

Exclusion criteria: contraindications to DAPT, thrombolysis, congenital or acquired thrombocytopenia, thrombocytopathy, taking antiplatelet agents before the development of ACS, sepsis, organ dysfunction that existed before the development of ACS.

In accordance with the inclusion criteria, 46 patients (13 women and 33 men) aged 35 to 83 years (61.7±1.9 years) were included in the study. All patients included in the study gave written informed consent to participate in it.

The study design involved three research points. Before coronary angiography (CAG) and PCI, blood samples were taken from the cubital vein to assess hemostasis and ROTEM parameters (research point 1). Then, blood samples with the necessary laboratory tests were taken 72 hours and on the 6th day after the onset of the disease (research points 2 and 3).

In accordance with the purpose and objectives of the study, it included two parts. The first part of the study was devoted to the study of the effect of GRA on clinical and laboratory parameters and outcomes in STEMI. The second part of the study was devoted to the search for laboratory parameters that would statistically significantly assess the state of platelet hemostasis and its response to antiplatelet therapy in patients with STEMI, including taking into account the presence of GRA in patients. Verification of GRA was based on the detection of LOF alleles in a patient, determining slow and intermediate metabolism of antiplatelet agents. Detection of normal metabolism of antiplatelet agents or LOF alleles causing fast metabolism suggested the absence of GRA.

At the time of admission, the patient's complaints were collected in detail, the general condition was assessed: level of consciousness, constitution, body temperature, skin and visible mucous membranes, vascular changes, moisture and turgor of the skin, edema, and soreness. Electrocardiography (ECG) was routinely performed upon admission, after PCI, on the 3rd and 6th day after the operation, as well as before discharge from the hospital and each time the patient's condition worsened. At each stage of the study, clinical and biochemical blood tests were performed, and the hemostasis system was examined.

Traditional coagulation tests included activated partial thromboplastin time (APTT) (reference interval (RI): 25–31.3 s), D-dimer (RI: 0.05–0.5 mg/L), thrombin time (RI: 14–21 s), international normalized ratio (RI: 0.8–1.2), and fibrinogen level (RI: 1.8–3.5 g/L). These tests were performed on an ACL TOP 700 analyzer (IL Werfen , USA). The platelet component of hemostasis was assessed using aggregometry on an optical aggregometer (Chrono-log, USA) and ROTEM (ROTEM delta with accessories from Tem Innovations GmbH, Germany). All - hemostasis tests were performed in the laboratory of the N.V. Sklifosovsky Research Institute for Emergency Medicine, Department of Health of the City of Moscow.

Aggregometry was performed using the Borne photometric method [12]. Adenosine diphosphate was used as an inducer of platelet activation. The aggregometry parameters included an assessment of Antithrombin III, the main plasma protein in the mechanism of thrombin inactivation (RI: 75–125), and platelet aggregation, the rate of platelet aggregation (RI: 25–75%).

The ROTEM parameters that evaluate the platelet link of hemostasis are: MCF-EXTEM — maximum clot density in external activation mode (RI: 50–72 mm), CFT-EXTEM — clot compaction time in external activation mode (RI: 34–159 s), A 10-EXTEM — clot density obtained after 10 minutes in external activation mode (RI: 43–65 mm), CT-EXTEM — time to clot formation in external activation mode (RI: 38–79 s), PCSamp — difference in clot density between external activation and functional fibrinogen test (RI: ≈ 43 mm), MCF-

INTEM — maximum clot density in internal activation mode (RI: 50–72 mm), CFT-INTEM — clot compaction time in internal activation mode (RI: 30–110 s), A 10- INTEM — clot density, obtained after 10 minutes, in the internal activation mode (RI: 44–66 mm) and CT-INTEM — the time until the onset of clot formation in the internal activation mode (RI: 100–240 s) [13].

The platelet component of clot strength is expressed as the difference in clot strength between EXTEM and FIBTEM tests, for platelet inhibitors GP II b /III a MCEplatelet = MCF-EXTEM – MCF-FIBTEM. The MCE values for EXTEM and FIBTEM tests were used to calculate the platelet component, PCSamp = MCF-EXTEM – MCF-FIBTEM — the difference in amplitude between the EXTEM and FIBTEM test values is considered an indicator of the platelet contribution to clot strength, and PCSel = MCF-EXTEM – MCF-FIBTEM. Normal ranges are 54–72 mm for MCF-EXTEM and 9–25 mm for MCF-FIBTEM. Accordingly, MCE values range from 117 to 257 for EXTEM and from 9.9 to 33 for FIBTEM [14].

At the second research point, blood was additionally taken for genetic studies. Pharmacogenetic studies were performed at the Research Institute of Molecular and Personalized Medicine of the Russian Medical Academy of Postgraduate Education of the Ministry of Health of the Russian Federation. The biological material for the extraction of genomic DNA (deoxyribonucleic acid) was 4–6 ml of venous blood, which was taken from the cubital vein into a VACUETTE® vacuum tube (GreinerBio-One, Austria) containing EDTA-K2 or EDTA-K3. The samples were stored at –80°C until the moment of DNA extraction. DNA was isolated using the MagNa Pure Compact Nucleic Acid Isolation reagent kit. Kit I for the extraction of genomic DNA from whole blood (Roche, Switzerland) on the automated MagNa Pure Compact system (Roche, Switzerland). In patients receiving clopidogrel, the carriage of polymorphic markers CYP2C19*2 (681 G>A, rs 4244285) and CYP2C19*3 (636G>A, rs 4986893) was determined using commercial reagent kits for determining the corresponding polymorphisms (OOO Sintol, Russia).

Single nucleotide genetic polymorphisms were determined by allele-specific PCR (polymerase chain reaction) in real time on a CFX 96 Touch Real Time System with CFX Manager version 3.0 software (BioRad, USA). The carriage of the polymorphic marker CYP2C19*17 (C-806 T, rs 12248560) was determined using commercial TaqMan®SNP Genotyping Assays and TaqMan Universal Master Mix II, no UNG kits (Applied Biosystems, USA).

In patients receiving ticagrelor, the carriage of polymorphic markers of the SLCO1B1 (T521C, rs4149056) and CYP3A5*3 (A>G, rs 776746) genes was determined using commercial reagent kits for determining the corresponding polymorphisms (Synthol LLC, Russia) [15]. Determination of single-nucleotide genetic polymorphisms was performed by allele-specific PCR in real time on a CFX 96 Touch Real Time System with CFX Manager version 3.0 software (BioRad, USA).

Despite the large number of identified genetic markers, only the CYP2C19 gene polymorphism has a sufficient evidence base and clinical significance. The CYP2C19 gene has about 34 allelic variants. Eight allelic variants have been identified that predict intermediary metabolism. With regard to the pharmacodynamics of clopidogrel, CYP2C19 loss-of-function alleles are inherited as autosomal codominant traits, heterozygotes (e.g., *1/*2, *1/*3) have platelet sensitivity to clopidogrel and are between the wild-type homozygous types (i.e., *1/*1) and loss-of-function allelic homozygotes or compound heterozygotes (e.g., *2/*2, *2/*3) [16]. Thus, based on the identified CYP2C19 genotypes, individuals are typically classified as normal (e.g., *1/*1), intermediate (e.g., *1/*2, *1/*3), or poor (e.g., *2/*2, *2/*3) metabolizers. The frequency of CYP2C19 intermediate metabolizers is ~ 2–5% among Caucasians and Africans and ~15% in Asians [17]. The most common CYP2C19 loss- of - function allele is *2 (c.681 G>A; rs 4244285), with an allele frequency of ~15% in Caucasians and Africans. In contrast, the common CYP2C allele 19 *17 (c-806C>T; rs 12248560) results in increased activity due to enhanced transcription, with an average prevalence of ~3–21%. Thus, individuals carrying this allele can be classified as ultrarapid metabolizers (e.g., *17/*17). Some studies suggest that this allele results in increased platelet inhibition and hence an increased risk of bleeding. However, it is worth noting that the gain-of-function allele *17 always occurs on a haplotype that also contains the wild-type G ' allele *2, so the observed effect of the gain-of-function allele *17 may actually be partly due to the absence of the loss-of-function allele *2, given these data, *17 is not able to fully compensate for the loss-of-function allele *2, and their compound

heterozygotes *2/*17 should be classified as intermediate metabolizers [18].

CYP2C19 1 metabolizers are characterized by the presence of two alleles of normal function (eg, CYP2C19*1/*1).

CYP2C19 intermediate metabolizers are characterized by the presence of one normally functional allele and one non-functional allele (e.g., CYP2C19*1/*2). Limited data suggest that the gain-of-function allele CYP2C19*17 may not compensate for no- function alleles such as CYP2C19 *2, and thus diplotypes containing one no-function allele and one gain-of-function allele (e.g., CYP2C19 * 2/*17) are also defined as intermediate metabolizers.

3. Rapid metabolizers CYP2C19 diplotypes, characterized by one allele of normal function and one allele of increased function (i.e. CYP2C19*1/*17), also include the category of ultra-rapid metabolizers (i.e. CYP2C19*17/*17) [19].

In the ticagrelor group, we also identified all major groups with the presence of LOF alleles [15].

To achieve the set goal, the dynamics were analyzed and a comparative analysis of the platelet hemostasis parameters was performed at three research points, and a comparison of the platelet hemostasis parameters was performed depending on the combination of antiplatelet drugs used (aspirin + clopidogrel and aspirin + ticagrelor), and depending on the presence or absence of GR factors to antiplatelet agents (the presence of GR factors and the absence of GR factors or the presence of alleles that enhance the pharmacodynamic effects of antiplatelet agents).

All intensive care patients received therapy in strict accordance with Russian and international recommendations for providing care to patients with ACS.

The data obtained during the study were archived using a personal computer in a Windows environment using the Microsoft Excel program. Statistical processing was performed using parametric (Student's t -test, Pearson's chi-square test) and nonparametric statistics (Mann-Whitney, Wilcoxon, Fisher's test) using the Biostat, Statistica 6.0 statistical software packages. Sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) were calculated using generally accepted formulas. The Shapiro-Wilk test was used to assess the normality of distribution.

To assess differences in the compared groups, the Kruskal–Wallis test for independent samples was used. To determine the correlation dependence, the Spearman test (r) was used. Differences were considered statistically significant at a level of $p < 0.05$.

Demographic data and patient characteristics are shown in Table 1.

Table 1

Demographic data and patient characteristics upon admission to the intensive care unit

Indicator	Meanings
Number of patients	46
Men/women, n	13/33
Age, years (avg. ± st. error avg.)	61.7±1.9
Single-vessel coronary artery disease, n (%)	15 (29.5)
Two-vessel coronary artery disease, n (%)	10 (19.6)
Multivessel coronary artery disease, n (%)	21 (41.2)
Weight, kg (avg. ± st. error avg.)	88.9±3.1
Body mass index (mean±s.m. error)	30±0.8
Time from onset of disease to hospitalization, min (mean ± standard error mean)	475.8±84.1
Time from hospitalization to coronary angiography, min (mean ± standard error of mean)	67.9±10.5

Notes: avg.±st. error avg. — mean ± standard error of the mean

LOF alleles were detected in 32 patients (69.6%). Among them, in the group taking aspirin in combination with clopidogrel, three subgroups of patients were identified, including 7 patients with heterozygous alleles (CYP2C19*1/*2, CYP2C19*2/*17) — responsible for intermediate metabolism, and this group included 1 patient with the presence of alleles — CYP2C19 *2/*3, responsible for slow metabolism. A patient with homozygous CYP2C19*17/*17 alleles, which are classified as ultrafast metabolites, was combined with a group of carriers of heterozygous CYP2C19*1/*17 gene alleles, under the general group of fast metabolizers, and 8 patients without LOF alleles, designated as patients with normal metabolism.

In the group receiving aspirin in combination with ticagrelor, 9 patients with a heterozygous variant of the SLCO1B1c.52 T>C allele responsible for intermediate metabolism were identified. 3 patients with a homozygous variant of SLCO1B1c.521T>C and 4 patients with the presence of CYP3A4*1G and CYP3A5*3 polymorphism,

causing a decrease in metabolism and thereby the action of the drug, were distributed into the slow metabolism group. Patients without LOF alleles were allocated to the normal metabolism group.

The groups did not differ in the severity of the condition, in the time from the moment of hospitalization to the performance of CAG and the beginning of antiplatelet therapy. However, in the group using the combination of aspirin and ticagrelor, patients were statistically significantly younger, and their weight was statistically significantly higher than in the group using the combination of aspirin and clopidogrel (Table 2).

In the group of patients taking ticagrelor, there was a statistically significant difference in the time to hospitalization between the groups, the longest waiting time was in the group with normal metabolism, however, the data did not have a statistically significant difference (Table 3).

Table 2

Patients in the clopidogrel group

Indicator	Metabolizer group (mean±standard error mean)			r
	Normal (n = 8)	Intermediate (n = 7)	Fast (n = 8)	
Age, years	73.5±3.5	60±6.1	63.5±4.6	0.1
Weight, kg	85.6±7.4	79.4±5.3	80.9±5.6	0.85
Body mass index	29.9±2.4	28.3±2.7	28.6±1.9	0.82
Time from onset of disease to hospitalization, min	443.9±163.8	468.6±313.9	243.3±129.2	0.24
Time from hospitalization to coronary angiography	65.1±13.5	75.9±24	48.4±9.1	0.67

Notes: avg.±standard error of the mean

Table 3

Patients in the ticagrelor group

Indicator	Metabolizer group (mean±standard error mean)			r
	Normal (n = 7)	Intermediate (n = 9)	Slow (n = 7)	
Age, years	58.3±3.1	54.78±3.9	60.28±4.6	0.58
Weight, kg	109.9±12.8	91.2±5.5	87.14±4.7	0.24
Body mass index	33.6±1.5	30.58±1.9	29.3±1.03	0.1
Period from onset of disease to hospitalization, min	820±264.5	294.4±119.4	674.3±231.1	0.09
Time from hospitalization to coronary angiography	57.7±14.1	84.3±42.2	74.6±33.2	0.85

Notes: avg.±standard error of the mean

RESULTS

The dynamics of traditional (platelet level) and advanced (aggregometry, ROTEM) indicators reflecting the state of the platelet link of hemostasis in patients with STEMI included in the study are presented in Table 4.

As can be seen from Table 4, aggregometry demonstrated a general suppression of platelet activity; however, platelet aggregation indices remained below reference values throughout the study period. This circumstance seriously limits the possibility of using aggregometry as a reliable tool for assessing the effect of antiplatelet agents on the platelet component of hemostasis in this group of patients. The obtained results suggest that aggregometry in its standard form may not be sensitive enough to detect changes in platelet function induced by antiplatelet agents in the conditions of STEMI.

Table 4

Indicators of laboratory tests assessing the state of the platelet link of hemostasis, depending on the duration of use of antiplatelet drugs

Indicator	RI	Research point (avg.±st. error avg.)			r		
		1	2	3	(1–2)	(2–3)	(1–3)
Platelet count	150–370	237.6±9.1	233.4±15.9	249.1±32.5	0.7	0.68	0.37
Platelet aggregation, %	69–88	**25.8±3.9**	**21.5±2.1**	**19.9±2.7**	0.28	0.58	0.12
PCSel	3–50	45.6±0.9	41.6±1.5	41.7±1.7	**0.02**	0.76	**0.01**
ST-I NTEM , with	100–240	214.4±13.6	194.6±7.5	207±10.5	0.35	0.13	0.85
CT-EXTEM, with	38–79	76.7±3.8	**83.5±6.2**	**82.6±3.8**	0.65	0.46	**0.048**
MCF-EXTEM, mm	50–72	65.6±0.9	67.5±1	69.1±0.8	**0.003**	0.1	**0.001**

Notes: — mean±standard error of the mean; RI — reference interval

Data analysis revealed statistically significant differences in the blood clotting time determined by thromboelastometry (CT-EXTEM). This suggests that the CT-EXTEM test may serve as the only available indicator for assessing the efficacy of antiplatelet therapy aimed at modulating the platelet component of hemostasis within the framework of this study. At the first study point (reflecting the initial state of the platelet component before the onset of the pharmacodynamic action of antiplatelet agents), the CT-EXTEM indicator was within the reference values. At the second and third study points, corresponding to the period of exposure to antiplatelet agents, an increase in CT-EXTEM values was observed. Statistically significant differences were found between the first and third study points ($p < 0.048$), indicating the effect of antiplatelet therapy on this indicator.

In contrast to the CT-EXTEM data, platelet aggregation indices remained reduced at all three study points and no statistically significant differences were found between them. PCSel and MCF-EXTEM indices differed statistically significantly between study points, but they remained within the reference values throughout the study. Platelet count and CT-INTEM indices did not change statistically significantly throughout the study, remaining within the reference values. The MCF-EXTEM index of maximum clot density assessment is noteworthy: despite its values remaining within the normal range, a statistically significant increase in maximum clot density was noted by day 3, which is reflected in the results of comparing the first study point with the second ($p < 0.003$) and with the third ($p < 0.01$). This fact may indicate complex clot remodeling processes occurring under the influence of antiplatelet agents and requires further study.

Table 5 presents data from laboratory tests assessing the state of the platelet component of hemostasis depending on the regimen of antiplatelet drugs used.

As can be seen from Table 5, despite the data on significant inhibition of the platelet component of hemostasis obtained using aggregometry, it is worth noting that the platelet aggregation indices in both groups remained below the reference values throughout the entire observation period. This fact significantly limits the applicability of the aggregometry method for adequately assessing the effect of the antiplatelet agents used on platelet function in patients with STEMI in this study.

A statistically significant difference between the groups was found only for one parameter - blood clotting time, determined by thromboelastometry (CT-EXTEM) on the first day of the study ($p = 0.03$). However, it is important to consider that at the time of blood sampling for hemostasis tests at the first point of the study, antiplatelet agents probably had not yet had time to fully demonstrate their pharmacodynamic effects.

Table 5

Diagnostic significance of laboratory tests assessing the state of the platelet component of hemostasis, depending on the antiplatelet drug regimen used

Indicator	RI	Aspirin+ticagrelor (n =23) avg.±st. error avg.	Aspirin+clopidogrel (n =23) avg.±st. error avg.	r
1st day (research point 1)				
CT- INTEM, with	100-240	214.4±13.6	223.6±18.8	0.54
CT- EXTEM, with	38–79	67.7±2.9	**86.6±6.6**	**0.03**
MCF- EXTEM, mm	50–72	66.3±1.4	64.8±1.2	0.3
PCSel	3–50	45.6±0.8	44.7±1.4	0.4
Platelet aggregation, %	69–88	**24.2±4.7**	**28.9±7.6**	0.64
Platelets	150–370	239.6±9.3	235.8±15.4	0.3
Day 3 (research point 2)				
CT- INTEM, with	100–240	194.6±7.5	212.2±9	0.13
CT- EXTEM, with	38–79	79.4±7.6	**88.1±10.2**	0.35
MCF- EXTEM, mm	50–72	68.6±0.9	66.3±1.9	0.29
PCSel	3–50	41.6±1.5	45.3±0.9	0.11
Platelets	150–370	217.2±17.9	249.5±26.3	0.36
Platelet aggregation, %	69–88	**17±1.9**	**29.6±3.9**	**0.01**
Day 6 (research point 3)				
CT- INTEM, with	100–240	207±10.5	212.6±8.7	0.89
CT- EXTEM, with	38–79	**82.5±5.4**	**82.7±5.5**	1
MCF- EXTEM, mm	50–72	69.5±1.3	68.6±1.2	0.46
PCSel	3–50	41.7±1.7	46.3±1.2	0.07
Platelet aggregation, %	69–88	**15.5±2.3**	**26.7±5.3**	0.56
Platelets	150–370	217.6±17.7	288.5±69.8	0.11

Notes: mean±standard error of the mean; RI — reference interval

It is noteworthy that CT-EXTEM values in the group receiving aspirin + clopidogrel remained above reference values throughout the study, while in the aspirin + ticagrelor group, an excess of CT-EXTEM reference values was noted only at the third study point - by the 6th day from the start of therapy.

Overall, the results obtained indicate that the standard laboratory tests used in this study were insufficiently sensitive to adequately assess the impact of various DAPT regimens on the state of the platelet component of hemostasis in patients with STEMI. This emphasizes the need to search for and implement more advanced methods for monitoring antiplatelet therapy.

Table 6 presents the results of the assessment of the parameters characterizing the platelet link of hemostasis, depending on the presence of genetic factors in patients that affect the metabolism of antiplatelet agents.

Table 6

Parameters of laboratory tests assessing the state of the platelet link of hemostasis, depending on the presence of alleles responsible for the metabolism of antiplatelet drugs

Indicator	RI	Metabolizer group (mean±standard error mean)			
		Intermediate	Slow	Fast	Normal
1st day (research point 1)					
CT- INTEM, with	100–240	252.14±22.7	184.1±10	219.9±37	199.5±10.7
CT- EXTEM, with	38–79	78.9±6.8	66.1±2	**96.3±14.3**	68.9±2.4
MCF- EXTEM, mm	50–72	65.6±1.7	65.1±2.3	65.3±1.5	66±1.8
PCSel	3–50	44.7±1	47.1±2	44.8±2.8	44.8±1.1
Platelets	150–370	240.9±11.2	225.1±12.2	244.6±22.5	236.4±22.6
Platelet aggregation, %	69–88	**24.1±5.9**	**30±11.53**	**33±25**	**24±6.4**
Day 3 (research point 2)					
CT- INTEM, with	100–240	205.5±10.7	200.9±10.8	207.9±19	199.1±10.1
CT- EXTEM, with	38–79	**106.4±15.2**	71.3±3.1	78.9±15.3	69.1±3.9
MCF- EXTEM, mm	50–72	65.3±2.4	67.9±1.6	68.9±1.2	68.9±1.5
PCSel	3–50	41.2±2.2	45.8±1.8	43±3	43.1±1.4
Platelets	150–370	229.6±17.3	261.5±30.8	196.6±16.7	252.3±58.3
Platelet aggregation, %	69–88	**17.7±2.9**	**27±10.4**	**19.4±3.2**	**25.4±4.2**
Day 6 (research point 3)					
CT- INTEM, with	100–240	225.9±8.6	208.8±17.6	190±29	202.5±8.2
CT- EXTEM, with	38–79	**93.2±5.7**	69.5±2.9	**87.7±16.5**	75.2±4.1
MCF- EXTEM, mm	50–72	68.9±1.4	66.7±2.1	69.2±2.3	70.3±1.5
PCSel	3–50	42.6±2.7	44.6±1.7	44.8±2.3	42.7±2.4
Platelets	150–370	235±22.3	**373.5±120.5**	216.5±3.5	178.5±9.5
Platelet aggregation, %	69–88	**21.2±4.9**	**16±2.9**	**19.3±7.6**	**21±5.4**

Notes: mean ± standard error of the mean; RI— reference interval

Table 7 shows the statistical results of comparison of patient groups (p values), according to data and characteristics of metabolism, depending on the presence of LOF alleles responsible for the metabolism of antiplatelet drugs.

The analysis of the data presented in Table 7 revealed a statistically significant difference between the groups of patients with different combinations of genetic alleles only for one parameter: blood clotting time determined by thromboelastometry (CT-EXTEM). It is noteworthy that this parameter exceeded the reference values. In patients with slow metabolism, the CT-EXTEM value was statistically significantly lower than in patients with fast metabolism already at the first point of the study (66.1±2 and 96.3±14.3 sec, respectively, p = 0.02), indicating accelerated blood clotting in the slow metabolism group.

Table 7

Groups of patients with different alleles responsible for the metabolism of antiplatelet agents according to hemostasis parameters reflecting the platelet link of hemostasis

Indicator	RI	P1–P2	P1–P3	P1–P4	P2–P3	P2–P4	P3–P4
1st day (research point 1)							
CT- INTEM, with	100–240	0.13	0.74	0.07	0.54	0.24	0.21
CT- EXTEM, with	38–79	0.46	0.49	0.36	**0.02**	0.48	**0.026**
MCF- EXTEM, mm	50–72	0.86	0.9	0.86	0.78	0.84	0.7
PCSel	3–50	0.95	1	0.15	0.83	0.2	0.5
Platelet aggregation, %	69–88	1	1	1	0.9	1	0.8
Platelets	150–370	0.48	0.8	0.4	0.53	0.7	0.87
Day 3 (research point 2)							
CT- INTEM, with	100–240	0.67	1	0.97	0.8	0.86	0.62
CT- EXTEM, with	38–79	**0.019**	0.056	0.13	0.5	1	0.8
MCF- EXTEM, mm	50–72	0.38	0.4	0.64	1	0.74	0.8
PCSel	3–50	0.35	0.13	0.27	0.38	0.53	0.64
Platelet aggregation, %	69–88	0.18	0.46	0.44	0.86	0.44	0.79
Platelets	150–370	0.9	0.28	0.22	0.76	0.43	0.19
Day 6 (research point 3)							
CT- INTEM, with	100–240	0.05	0.28	0.24	0.6	0.96	0.7
CT- EXTEM, with	38–79	**0.026**	**0.002**	0.1	0.2	0.96	1
MCF- EXTEM, mm	50–72	0.47	0.83	0.9	0.8	0.2	0.4
PCSel	3–50	0.67	0.6	0.6	0.85	0.56	1
Platelet aggregation, %	69–88	0.86	0.4	1	0.3	0.9	0.88
Platelets	150–370	0.2	0.48	1	1	0.33	0.3

Notes: P1 — intermediate metabolizers, P2 — slow metabolizers; P3 - rapid metabolizers; P4 - normal metabolizers; RI—reference interval

The fast and intermediate metabolizer groups tended to have higher CT-EXTEM values (statistically significant in some comparisons, not in others) compared to the normal and slow metabolizer groups at various points in the study (see Tables 6 and 7). This suggests a potential link between genetic factors underlying the fast and intermediate metabolizer groups and the slower coagulation process.

It is important to note that, according to other hemostasiological parameters characterizing the state of the platelet link of hemostasis, no significant differences were found between the groups of patients divided based on the presence or absence of specific genetic alleles.

DISCUSSION OF RESULTS

Antiplatelet therapy is the standard treatment for patients with ACS, stroke, lower limb ischemia, and other atherosclerosis-related diseases [21]. In addition, antiplatelet agents are widely used for primary and secondary prevention of a wide range of different ischemic events [22]. Thus, millions of people worldwide receive therapy with various antiplatelet drugs.

Despite the widespread use of antiplatelet drugs, there are currently no generally accepted laboratory tests that would allow adequate assessment of the state of the platelet component of hemostasis and the effects of antiplatelet therapy [23]. The most commonly used method for assessing platelet function in clinical practice is aggregometry using various inducers of their aggregation [24]. However, aggregometry involves isolated activation of platelets, which entails a number of methodological limitations in interpreting the hemostasis situation [25]. Our study demonstrated that aggregometry cannot be used to assess the state of the platelet component of hemostasis and the response to therapy with antiplatelet drugs in patients with STEMI. The obtained results indicate that the aggregometry indices are below the reference values at all study points and with different patient division options (in the general group of patients, when the effect of the duration of antiplatelet therapy on the parameters of the platelet hemostasis link was studied; in groups divided according to the principle of the used antiplatelet therapy regimen - aspirin + clopidogrel, aspirin + ticagrelor; in groups divided according to the principle of the presence or absence of genetic alleles). Obviously, the use of a parameter for assessing platelet function, which has values that are outside the reference values, is inappropriate. This is due to the impossibility of correctly interpreting the obtained results and formulating adequate therapeutic tactics for conducting antiplatelet therapy [26].

Platelet hemostasis, caused by the interaction of platelets, fibrinogen, von Willebrand factor and factor XIII, is a complex cascade and multi-level process [27]. This should explain the failure of aggregometry as a test capable of assessing the function of the platelet component of hemostasis and its response to antiplatelet therapy in the studied category of patients, revealed in our study.

According to the literature, the state of the platelet hemostasis link can be assessed using ROTEM [28]. The following parameters can be used for this purpose: CT-INTEM, CT-EXTEM, MCF-EXTEM, PCSel [29]. Our study demonstrated that the only one of the above parameters that statistically significantly reflects the state of the platelet hemostasis link and the effect of antiplatelet drugs on it is the CT-EXTEM indicator. This indicator was within the reference values in the general population of examined patients at the first research point, reflecting the state of the platelet hemostasis link before the onset of the pharmacodynamic effects of antiplatelet agents, and increased at the second and third research points against the background of the effect of antiplatelet agents on the platelet hemostasis link.

This result seems to be extremely important, since monitoring the CT-EXTEM level can allow interpreting the adequacy of the choice of an antiplatelet agent and (or) its dose to assess the achievement of the antiplatelet effect of the therapy. In other words, as a result of our study, the CT-EXTEM indicator can be recommended as the main laboratory marker for assessing the effectiveness of antiplatelet therapy by analogy with the APTT indicator, routinely used to assess the effectiveness of heparin therapy. Thus, the obtained results can be considered as a basis for introducing into clinical practice a new criterion for the effectiveness of antiplatelet therapy, which should be considered effective when the CT-EXTEM level is reached more than 79 s after the start of using antiplatelet agents. Further studies are certainly needed to test the validity of this criterion.

The study showed that the aspirin and clopidogrel antiplatelet therapy regimen is not inferior in laboratory efficacy to the aspirin and ticagrelor regimen. Moreover, the CT-EXTEM level in the aspirin and ticagrelor group of patients increased only by the 6th day of antiplatelet therapy, unlike the aspirin and clopidogrel group of patients, in whom this parameter increased already at the beginning of the study.

An extremely interesting and important result of the study was that we were able to identify a statistically significant relationship between the CT-EXTEM level and genetic features of antiplatelet drug metabolism. Patients with rapid and intermediate metabolism quickly achieved an increased CT-EXTEM level. While patients with normal or slow metabolism achieved an increased (target) CT-EXTEM level with a delay or did not achieve it at all. Thus, the study allowed us not only to find a hemostasis parameter that should be used as a guide when assessing the effectiveness of antiplatelet therapy, but also to justify the proposed tactics for correcting the therapy.

Failure to achieve the target CT-EXTEM level during antiplatelet therapy for 24–48 hours allows us to interpret the results as probable carriage of gene alleles that cause genetic refractoriness to

antiplatelet therapy. According to the literature, the proportion of such patients with respect to aspirin is 5–45%, clopidogrel – 16–45%, ticagrelor – 6–8% [8, 30]. These statistics determine the high relevance of the problem of genetic refractoriness to antiplatelet drugs, especially in the population of such patients as patients with ST-ACS.

CONCLUSION

The conducted study revealed that the only hemostatic parameter that statistically significantly reflects the state of the platelet link of hemostasis, the influence of antiplatelet drugs and genetic refractoriness factors on it, is the rotational thromboelastometry indicator - CT-EXTEM.

Based on our data, it can be assumed that the absence of an increase in the CT-EXTEM level against the background of antiplatelet therapy for 24-48 hours can be considered as an indication for genetic studies. In the case of normal metabolism of antiplatelet agents, the issue of increasing the dose of the antiplatelet agents used should be considered, and in the presence of slow metabolism or other genetic features that can be interpreted as the presence of genetic refractoriness to the antiplatelet agents used, antiplatelet therapy should be adjusted. Further studies are certainly necessary to assess the correctness of the proposed tactics.

FINDINGS

1. The only hemostatic parameter that statistically significantly reflects the state of the platelet link of hemostasis, the effect of antiplatelet drugs and factors of genetic resistance to antiplatelet agents on it in patients with acute coronary syndrome with ST segment elevation at the resuscitation stage of treatment is the rotational thromboelastometry indicator - CT-EXTEM ($p = 0.02$). In patients with slow metabolism, the CT-EXTEM indicator was statistically significantly lower compared to the fast metabolism group already at the first research point (66.1 ± 2 and 96.3 ± 14.3 sec, respectively, $p = 0.02$). In groups with fast and intermediate metabolism, the CT-EXTEM indicator was higher (in some comparisons statistically significantly, insignificantly in some) compared to the normal and slow metabolism groups at different research points.

2. The target level of the CT-EXTEM indicator, reflecting the response of the platelet component of hemostasis to the antiplatelet therapy, is its value above 79 seconds. A possible reason for the absence of an increase in the CT-EXTEM level above 79 seconds against the background of antiplatelet therapy conducted for 24–48 hours is the presence of genetic refractoriness to the therapy in the patient ($p = 0.048$).

3. The rate of metabolism, determined by the metabolic enzymes involved in the bioactivation of clopidogrel and ticagrelor, especially CYP 2 C 19, plays a key role in the effectiveness of antiplatelet therapy.

4. The high prevalence of the combination of alleles responsible for slow metabolism of clopidogrel and ticagrelor in combination with aspirin emphasizes the importance of genetic factors in an individual approach to antiplatelet therapy.

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