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NECESSITY OF SCREENING PATIENTS WITH STENTING FOR ACUTE CORONARY SYNDROME BY *CYP2C19* POLYMORPHISM

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ABSTRACT

The *relevance* of this article is due to the fact that cardiovascular diseases are currently the leading cause of death and disability worldwide. The leading role in the structure of mortality from cardiovascular diseases belongs to coronary heart disease. Ischemic heart disease (IHD) is a chronic disease that develops with insufficient oxygen supply to the myocardium. The main cause (more than 90% of cases) of insufficient intake of oxygen is the formation of atherosclerotic plaques in the lumen of the coronary arteries, the arteries of the blood supplying the heart muscle (myocardium).

One of the main drugs for antiplatelet therapy in cardiology is clopidogrel, the use of which can reduce the incidence of thrombotic complications. Clopidogrel is the most famous member of the thienopyridine group. Clopidogrel remains the main drug for antiplatelet therapy in patients who received stenting of the coronary vessels for acute coronary syndrome. The rationale and design of the observational study aimed at testing the hypothesis that the high frequency of the genetic polymorphism of cytochrome CYP2C19*2 is associated with coronary stent thrombosis is presented.

Keywords: Clopidogrel, coronary stenting, the acute coronary syndrome, personalized therapy, clopidogrel resistance, paradoxical response, genetic polymorphisms.

The relevance of this article is due to the fact that cardiovascular diseases are currently the leading cause of death and disability worldwide. The leading role in the structure of mortality from cardiovascular diseases belongs to coronary heart disease. Ischemic heart disease (IHD) is a chronic disease that develops with insufficient oxygen supply to the myocardium. The main cause (more than 90% of cases) of insufficient intake of oxygen is the formation of atherosclerotic plaques in the lumen of the coronary arteries, the arteries of the blood supplying the heart muscle (myocardium).

According to the World Health Organization (WHO), mortality from cardiovascular disease is 31% and is the most common cause of death worldwide. In the territory of the Russian Federation, this figure is 57.1%, of which the share of CHD falls more than half of all cases (28.9%), which in absolute terms is 385.6 people per 100 thousand people per year. For comparison, mortality from the same cause in the European Union is 95.9 people per 100 thousand people a year, which is 4 times less than in our country. The incidence of IHD increases dramatically with age: in women from 0.1-1% at the age of 45-54 to 10-15% at the age of 65-74 years, and in men with 2-5% at the age of 45-54 years to 10 -20% at the age of 65-74 years. Despite the multiply increased possibilities of modern conservative therapy of the above pathology, in the absence of effect, surgical methods of treatment are performed:

1. Percutaneous coronary intervention - balloon angioplasty with the installation of a stent (a metal frame that preserves the restored lumen of the vessel);
2. Coronary bypass - the imposition of shunts around the affected areas of the coronary arteries. As a shunt, one uses his own veins (usually the subcutaneous vein of the thigh) or the internal thoracic artery of the patient.

Percutaneous coronary intervention (PCI) is one of the widely used methods for treating patients with acute coronary syndrome. In the Russian Federation, in 2012 the number of PCI increased by 13,049 procedures or 20.9%, compared to 2011, and amounted to 75,378 procedures. The average for Russia, indicator of the frequency of PCI performance per 1 million population in 2012 was 531 [3]. It is important to note that, despite the obvious success of the use of PCI, this method has certain complications. Thus, among patients who underwent coronary stenting, the frequency of such a

life-threatening complication as acute or subacute stent thrombosis, according to international literature, reaches 1-3% [2]. In this case, the frequency of repeated interventions on a stented coronary vessel can reach 17% (especially when implanting a stent without drug coating) [3]. In order to reduce the risk of developing cardiovascular disasters, the patient needs to use antiplatelet drugs after performing PCI and stenting of the coronary vessels.

One of the main drugs for antiplatelet therapy in cardiology is clopidogrel, the use of which can reduce the incidence of thrombotic complications. Clopidogrel is the most famous member of the thienopyridine group. It like ticlopidine and prasugrel, refers to prodrugs. The drug has a complex metabolism. Its absorption in the intestine and entry into the blood is associated with the P-glycoprotein encoded by the MDR1 gene (ABCB1). 85% of the dose is converted into an inactive carboxyl derivative due to the action of esterase plasma. The remaining 15% of the dose undergoes two-stage oxidation under the action of cytochrome P450 isoforms, first turning into 2-oxo-clopidogrel, and then into the active thiol derivative. In turn of it irreversibly inhibits the binding of ADP to the P2Y12-receptor platelets. Further, inhibition of fibrinogen binding to the GP IIb / IIIa receptor and reduction of aggregation occurs. Clopidogrel is used in patients with acute coronary syndrome (ACS), including those who underwent coronary artery stenting (SCS) with percutaneous coronary intervention (PCI) [4]. The standard route of administration of clopidogrel provides a loading dose of 300 mg and then a maintenance dose of 75 mg daily; the increased dosage includes the administration of 600 mg in a loading dose, then 150 mg for 6 days and thereafter 75 mg per day [23] or a maintenance dose of 150 mg per day for 6 months. [25]. Double antiplatelet therapy is often used, involving the simultaneous use of clopidogrel and acetylsalicylic acid preparations, both for long-term treatment and for short periods (1 month after PCI with stenting) [25], although it has now been shown that the use of clopidogrel without combination with aspirin is associated with a significant reduction in hemorrhagic complications without an increase in the frequency of thrombotic events [26].

In recent years, significant progress has been made in the development of new inhibitors of the receptor for ADP P2Y12 (prasugrel, ticagrelor) with a faster onset of action, more pronounced platelet inhibition, and possibly a better efficacy profile than clopidogrel used in the standard dosage, but clopidogrel remains the first-line drug due to significant differences in the availability of innovative P2Y12 inhibitors in European countries. Antiplatelet therapy to optimize the results of SCS should provide a balance between the minimized risk of stent thrombosis and the risk of bleeding [17].

At the present time, it has become evident that the systems of conveyors and biotransformation have genetic polymorphism, characterized by the presence of enzyme isoforms with high and low activity. Accordingly, there are genetic characteristics that affect the pharmacological response in a particular patient. Depending on the status of this gene, three groups of individuals are distinguished: homozygotes (without mutations), heterozygotes (mutation in the 1st allele), persons with a mutant genotype (mutations in two alleles). Based on the genotype CYP2C19, three main phenotypes of the metabolizer *CYP2C19* can be distinguished: *1/*1 - "fast" with normal functional activity of the enzyme, *1 /*2 - "slowed" with reduced enzyme activity, *2/*2 - " slow "- significantly reduced by the functional activity of the enzyme or its absence. The so-called wild type of the *CYP2C19* gene (*1st allele) is characterized by normal enzymatic activity of *CYP2C19*. The most common allelic variant of *CYP2C19* with loss of function is the allele *2. The frequency of genotypes according to *CYP2C19*, corresponding to slow metabolizers in the Russian population, is 11.4%, which is comparable to European ethnic groups. However, in Russian patients with ischemic heart disease (IHD), *CYP2C19* genotypes associated with slow metabolism can occur at a frequency of up to 27.3% [6]. Cytochrome CYP2C19 is a member of the cytochrome P450 family of enzymes and is an S-mefenitonine hydroxylase enzyme. Low enzyme activity is associated with a risk of developing myocardial infarction or ischemic stroke - in patients with decreased enzyme activity, the risk of death from cardiovascular events increased by 53%. The gene encoding cytochrome CYP2C19 is located in 10 chromosomes, locus 10q24. This locus is part of a large cluster containing the genes *CYP2C19, CYP2C18, CYP2C19, CYP2C9, CYP2C8*, and associated with a reduced response to clopidogrel based on the results of a full-genome assay of associations [7].

The allelic variant *CYP2C19*2* (rs4244285) refers to prothrombogenic variants of cytochrome *CYP2C19*. Replacement G <A (Gly681Ala) is associated with high residual platelet aggregation after taking clopidogrel, increased thrombogenesis and a general deterioration in the prognosis in patients with cardiovascular pathology, especially after stent placement. This applies to homozygotes A/A (*2/*2), carriers of this genotype belong to the group of slow metabolizers, but patients with heterozygotes G/A (*1/*2) are also characterized by a reduced rate of clopidogrel metabolism. Currently, the possibility of administering large doses of clopidogrel to such patients is being discussed, but no unambiguous recommendations have yet been developed.

After the introduction of PCI with stenting from the 1980s, the rate of restenosis was 24%, then after improving the intervention procedures and introducing more advanced stent models, the incidence of restenosis decreased to 1-2%. However, according to Russian studies, in our country this situation remains disappointing, since the recurrence of ACS due to stent thrombosis develops on average in 8% of patients. In connection with the development and massive introduction of these high-tech methods of treatment of cardiovascular diseases in our country and in our region, the question of increasing the number of patients with genetically determined resistance to the so-called "standard scheme" of disaggregant therapy: aspirin (75 mg) + clopidogrel (75 mg) due to the polymorphism of *CYP2C19*, an increase in the complications in the form of restorations of implanted stents. It has been demonstrated that the addition of clopidogrel to ASA provides additional benefit in patients with MI, especially with coronary artery stenting. At the same time, in a number of studies, a wide interindividual variability of the antiplatelet effect of clopidogrel has been demonstrated. Pharmacodynamic and clinical studies have demonstrated that the polymorphism of the *CYP2C19* gene (CYP2C19*2 allele) is associated with a decreased antiplatelet effect of clopidogrel and an increase in the incidence of severe cardiovascular complications [8]. Evidence of a thorough analysis of the effectiveness of clopidogrel is published in the leading cardiological journals of the world, debates in European and American cardiology forums. Various components of the effectiveness of clopidogrel - compliance, dosages, duration of two-component antiplatelet therapy, the effect of concomitant treatment with statins, proton pump inhibitors, and the effects of other factors (smoking) are discussed.

The contribution of the polymorphism of the *CYP2C19* gene to the formation of the phenomenon of resistance to clopidogrel has been confirmed by numerous studies. Thus, a randomized ISAR study refers to carriage of the *2 CYP2C19

allele with an independent predictor of stent thrombosis within 30 days. A triple increase in the risk of stent thrombosis in patients with acute coronary syndrome (ACS) and the presence of the CYP2C19 *2 allele was also shown by the TRITON-TIMI study [25]. A study performed on a Chinese population found an increased risk of occurrence of cardiovascular complications within 1 year after PCI of 3.65-fold in the carrier group of at least one mutant CYP2C19 allele (* 2 or *3) compared to the wild-type genotype [22]. A meta-analysis of nine studies, which included 9685 patients, showed a statistically significantly higher risk of death for cardiac and vascular reasons, as well as stent thrombosis in patients who are "slow metabolizers" compared to individuals who do not have alleles with a reduced functional activity [20]. In the PAPI (Pharmacogenomics of Antiplatelet Intervention) study, clopidogrel was administered within 7 days to 429 healthy individuals; the response was determined by the method of aggregometry. Genotyping of 2C19 * 2 was performed. Data obtained from healthy individuals were compared with the data of 227 patients undergoing stenting of the coronary arteries. We studied the relationship between platelet function, genotyping and cardiovascular outcomes. It was found that the response to clopidogrel was highly dependent on heredity (p <0.001): 13 single-nucleotide polymorphisms in the chromosome 10q24 in the *CYP2C18-CYP2C19-CYP2C9-CYP2C8* cluster were significantly associated with a reduced response to clopidogrel. Patients with the CYP2C19*2 allele had more MTB or fatal outcomes during the year (20.9% versus 10.0%, risk ratio 2.42, p = 0.02) [24].

In a meta-analysis conducted by M.V.Holmes, with the inclusion of 32 studies totaling 42,000 respondents, the genotype influenced only the incidence of stent thrombosis, in connection with other cardiovascular outcomes not demonstrated [15].

At the same time, the results of a large randomized PLATO study revealed the association of various polymorphic *CYP2C19* markers with the incidence of cardiovascular events in patients with ACS only in the early stages of the disease, after a year of observation, the differences were not significant. The results of large studies [16, 18, 20] confirmed the prognostic value of the polymorphism of the gene *CYP2C19* in patients taking clopidogrel. In a meta-analysis of 9 pharmacogenetic studies of clopidogrel that included 9685 patients, a reliable association was found between homo- or heterozygotes for a mutant allele with a decreased function of *CYP2C19* and an increased risk of cardiovascular death, myocardial infarction, or cerebral stroke [11].

A domestic study conducted in 2015 also confirmed the association between the carriage of COR2C19*2 in patients after PCI and the risk of developing resistance (due to high residual platelet activity) [5].

The accumulated knowledge served as the basis for introducing in 2010 the instructions on the use of original clopidogrel information on the effect of the mutant gene *CYP2C19* on the effectiveness of therapy. The American Heart Association and the American Society of Cardiology, the European Society of Cardiology, note the need for genotyping for *CYP2C19* to detect alleles of "slow metabolizers" and recommend it for some groups of patients at high risk of thrombotic complications, mainly with ACS and planned PCI. The carrier frequency of the CYP2C19*2 allele in the Russian population is about 13.3%, and in the IHD patients this is slightly higher (the incidence of genotypes with reduced metabolic activity may reach 27.3%) [13].

In our country, there is also growing interest in this issue, in connection with which in various clinics, patient studies are conducted. So in 2013, a study was conducted at the National Medical Science Centre of Cardiovascular surgery named after A.N.Bakulev with the participation of 72 patients (50 men and 22 women) who took clopidogrel after the operation of planned myocardial revascularization performed a genetic study on the carriage of allelic variants of cytochrome P-450 and CYP2C19*1 and *2 isoenzymes. As a result, it was concluded that the carriage of allelic variants of the CYP2C192* gene according to different authors is found in the population with a frequency of up to 40% (confirmed by the results of the study) and is one of the risk factors for low laboratory response to clopidogrel therapy [4]. Carrying out the genetic test for carriage of *CYP2C19*2* to all patients before stenting can help optimize the appointment of antiplatelet therapy, which in turn could prevent the potential complications associated with insufficient effectiveness of clopidogrel.

Summing up, there is a need for further larger-scale research in this area, the purpose of which will be to develop new clinical guidelines for the treatment of cardiovascular patients, which ultimately aims to increase life expectancy.

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EXPERIENCE EXCHANGE

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HOSPITAL MORBIDITY RATES AS A FACTOR IN THE SELECTION OF PATHOLOGY TO DEVELOP PERSONALIZED PREVENTION AND TREATMENT METHODS

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ABSTRACT

Indicators of the hospitalized incidence of adult population according to YSC CMP Hospital during 2015-2017 are presented in article. The characteristic of dynamics and structure of the cases demanding performing treatment in stationary conditions is given. Growth of cases of hospitalization of patients with metabolic disorders, including diabetes 2 types and diseases of cardiovascular system is established. The obtained data served as the basis for conducting research and developing molecular genetic methods of diagnosis in relation to this pathology.

Keywords: hospital morbidity, structure and dynamics of incidence, methods of personalized medicine, molecular diagnostics.

Introduction. Diseases with the inheritance of predispositions today are widespread and are determined by a factor called the genetic load. It is the high prevalence of polymorphic variants of genes predisposing to the development of multifactorial diseases that determines the spectrum of somatic pathology with a characteristic for a specific population structure. In addition, the polymorphism of variants of predisposing genes affects not only the structure, but also the characteristics of the formation and course of diseases, the development of complications, as well as the susceptibility, resistance and tolerance of drug therapy [4].

Today, molecular technologies allow the formation of risk groups taking into account the genetic characteristics of patients and carrying out preventive measures in them at the stage of preclinical manifestations of the disease in order to prevent the development of the disease itself and its complications. Personalized medicine methods are highly effective and contribute to improving the quality and increasing the life expectancy of the population. In turn, the use of such expensive and highly specific technologies requires an informed approach to the choice of both the spectrum of diseases and genetic markers that predispose to the development of pathology.

To determine the significance of a particular pathology helps a comprehensive assessment of public health, which is carried out using indicators of general and primary morbidity recorded by attendance, as well as using data on morbidity with temporary and permanent disability, morbidity from the results of medical examinations and hospitalization activity of the population [3].

As a factor in the selection of pathology by degree of importance, such an indicator of medical statistics as hospitalized morbidity is often used, which gives an idea of the most severe pathology requiring attention and treatment in inpatient conditions, as a rule, in specialized departments. This indicator is very informative, since it characterizes neglect and severity of pathology, which in turn contributes to the formation of a chronic process and disability, which ultimately leads to a decrease in the patient's quality of life [1].

The unit of accounting for hospitalized morbidity is the case of hospitalization of the patient in the hospital, and the accounting document is the "Statistical map of the out-of-hospital" (f. 066 / u). The "statistical card of the discharged from the hospital" is compiled on the basis of the "Medical card of the inpatient patient" (f. 003 / u) and is a statistical document containing information about the disused, discharged from the hospital (discharged, dead). The card is compiled simultaneously with the recording of the epicrisis in the "Medical card of the inpatient" by the attending physician on all those who left the hospital (written out or died). The card reflects the basic information: about the duration of treatment of the patient in the hospital, the diagnosis of the main and concomitant diseases, the duration, nature and effectiveness of surgical care, the outcome of the disease, etc. from which the patient has left. In cases where two or more diagnoses of diseases are indicated in the map, the patient refers to each of these diseases in the report, which was the main cause of hospitalization. This document provides the most rational development of information for the preparation of the relevant sections of the report [3,5].Thus, the **purpose** of this study is to study the dynamics and structure of the hospitalized morbidity of the adult population of the RS (Ya) according to the data of the YSC CMP Hospital as a factor in selecting the most significant pathology for determining the priority directions of molecular genetics research in the development of diagnostic test systems for multifactorial diseases.

Materials and methods. The base of the study was the Yakut Science Centre CMP (Yakutsk), the object being the adult population from 18 to 80 years old, hospitalized in the hospital in 2015–2017. The material for analyzing the dynamics and structure of the hospitalized morbidity was the data from the statistical reports of the inpatient units of the Hospital of the Yakutsk Scientific Medical Center. The statistical data processing was carried out using descriptive statistics methods.

Results and discussion. In its structure, the Hospital of the YSC CMP has 110 beds of which 44 are therapeutic, 41 are cardiological and 25 are gynecological. To identify current trends in the dynamics of hospital morbidity, a preliminary analysis of the organization of inpatient care was carried out. Accord-