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PHARMACOGENETICS OF CLOPIDOGREL AND ITS SIGNIFICANCE FOR THE CLINIC

The purpose of a brief review for the pharmacogenetics of clopidogrel and its significance for the clinic. The results of some studies conducted on the basis of pharmacogenetic testing are presented. Bedside aggregatometry can be recommended for patients on dual antiplatelet therapy *in order to reduce the risk of fatal complications – thrombosis and bleeding, identify cases of resistance and compliance problems, which will significantly improve the quality of medical care, allow to personalize the antiplatelet therapy, reduce the cost of treatment, the number and duration of hospitalizations. In the treatment of patients, the results of pharmacogenetic studies should be considered, taking into account the populations of different nationalities, for the doctors to be confident in the safety and efficacy of drugs.*
Keywords*: clopidogrel, pharmacogenetics, CYP2C19, pharmacogenetic test. antiplatelet therapy, aggregatometry*

The problem of effective and safe pharmacotherapy in the world is actualized in connection with the growth of the number of drugs (D).
At the present time, the clinicians still face the problems of patients treatment, choice of the most safe and effective D, adjustment of drug dosage taking into consideration their compatibility and interaction with other D, prevention of adverse events and correction when they occur.
We cannot but recognize the development of standards and clinical guidelines for patients' treatment, based on the principles of evidence-based medicine and the results of clinical studies as the achievements of the past century. But in the course of this approach the individual features of patients that influence the outcome of the drug therapy were not taken into account. [1].
The results of foreign scientific studies [2,3,4,5,6,7] showed that patients have different pharmacological responses to the standard drug dose. Some patients have too high concentration of MA in blood, which leads to the development of side reactions; others have too low concentration and the treatment becomes ineffective. The third group of patients has a paradoxical response, which can lead to fatal outcome. According to the data of the World Health Organization (2009), the effectiveness of patients' treatment is, on average, only 60%. In the United States, up to 100,000 people die from inappropriate use of drugs, which occupies the 6th place among the causes of death. More than 2 million adverse drug reactions (ADR) are recorded. The economic damage increased from 76.6 (1997) to 177.4 billion dollars (2001) [7].
The results of pharmacogenetic studies differ in different national affiliations of people. For example, the work of Professor Yu.N. Chernov shows that the frequencies of clinically significant allelic variants of the biotransformation system genes of Russians are comparable to those of other European countries. But among the Chukchi living in the Far North, these frequencies are higher. Genetic characteristics of a person affecting the pharmacological response are determined during pharmacogenetic testing [8, 9].
Genetically determined features of the enzymes and receptors of patients, non-compliance with the drug regimen by patients, presence of current inflammatory processes, obesity, diabetes and smoking are causes of clopidogrel resistance.
For overcoming resistance some authors (B. Aleil and coauthors) suggest increasing the dose of clopidogrel or replacing it with another antiplatelet agent. In this connection, after increasing the dose of clopidogrel from 75 mg / day to 150 mg / day the number of resistant patients with percutaneous coronary intervention decreased from 33% to 12% without an increase in the number of bleeding [10].
The data from a systematic review of 15 studies indicate that according to laboratory testing 25% of patients have clopidogrel resistance [8].
Studies of CAPRIE (Clopidogrel versus Aspirin in Patients at Risk of Ischemic Events), CURE (Clopidogrel in Unstable angina of Recurrent Events), CREDO (Clopidogrel for the Reduction of Events during Observation) report an unambiguously positive effect of clopidogrel on the reduction of total mortality from heart diseases. [11-13].
It is also known that during these studies from 5 to 44% of patients with coronary heart disease show insufficient effectiveness for clopidogrel application, which is "resistance" [14–15].
The prescription of P2Y12 inhibitors of receptors and acetylsalicylic acid as a dual anti-thrombocytic therapy is an integral part of the treatment of patients with acute coronary syndrome (ACS). However, depending on a variety of genetic, clinical, demographic, laboratory, and other factors, the patients' response to clopidogrel may vary considerably. Clopidogrel is an inactive prodrug and for the formation of an active metabolite, its oxidation by cytochrome P-450 (CYP) enzymes is required. There are variants of this gene that encode the formation of an enzyme with reduced or absent function. Polymorphisms contributing to the loss of enzyme function are defined as CYP2C19 * 2 and CYP2C19 * 3, while ordinary polymorphism is defined as CYP2C19 * 1. CYP2C19 * 2 and CYP2C19 * 3 alleles do not have an effective metabolism of clopidogrel [18]. These two alleles are responsible for the majority of alleles with reduced platelet function among patients of Asian (99%) and Caucasoid (85%) origin [19]. According to numerous studies on patients' clopidogrel resistance with a homozygous mutation by CYP2C19 * 2 (G681A) allele [20] ticagrelor should be prescribed instead of clopidogrel. There are significant ethnic and racial differences in the frequency of the CUR2C19 * 2 allele. It is established that the frequency of occurrence of carriers of the CUR2C19 * 2 (G681A) allele is about 15% among Caucasians and Africans and 29-35% among Asians. It follows that up to 35% of Asians have a high risk of thrombotic complications after PCI. Based on the identified SUR2C19 genotypes, people are classified as fast metabolisers (EMs; * 1 / * 1), intermediate metabolisers (IMs; * 1 / * 2 and * 1 / * 3) and poor metabolisers (PMs, * 2 / * 2 and * 2 / * 3). The frequencies of SUR2S19 PMs are ~ 2–5% among Caucasians and Africans and ~ 15% among Asians [21]. Among patients carriers of a genetic variant with loss of function of the CYP2C19 * 2 enzyme (* 2 / * 2) during the treatment with clopidogrel the risk of stent thrombosis is 3-6 times higher. Taking into account the data of numerous studies on clopidogrel resistance, patients with a homozygous mutation by the CYP2C19 * 2 (G681A) allele or poor metabolisers, should be prescribed ticagrelor instead of clopidogrel [20]. In a study conducted by W.P.Zhong and others, new variants in the genes (SLC14A2, ABCA1, N6AMT1) that affect clopidogrel's antiplatelet response were identified among Chinese patients. These new variants have significantly improved the predictability of the variability of the residual platelet reactivity (ORT) to 37.7%. In addition, the association of the above mentioned genetic variants with the development of the main adverse cardiovascular events after PCI was identified.
From recommendations of the European Society of Cardiology (ESC) and the European Association of Cardiothoracic Surgeons (EACTS) on myocardial revascularization of 2014, platelet function testing or genetic testing can be considered in high-risk situations. Today, genetic testing in routine practice is not recommended because there are insufficient prospective data [22]. However, genetic characteristics are the cause from 20 to 95% of all adverse responses of the human body, the attribute of which is their constancy throughout life. Availability of various oral inhibitors P2Y12 allowed physicians to consider the possibility of switching therapy depending on the specific clinical situations. This decision can be facilitated by many factors: the patient's clinical characteristics, concomitant therapy, social problems, development of side effects, adherence to treatment, and patient and / or physician preference. Therefore, if necessary, the P2Y12 inhibitor can be replaced [16].
According to A.I. Akhmetov's study of pharmacogenetic testing of patients with ACS was a significant predictor of antiplatelet therapy correction. The correction included the replacement of clopidogrel with ticagrelor or an increase in the maintenance dose of clopidogrel up to 150 mg / day, which did not affect the significant clinical outcomes [17].
Pharmacogenetic testing of CYP2C19 gene polymorphisms is described in the thesis research by D.A. Mansurov. In the study of 101 patients after percutaneous coronary intervention, genotyping was performed by the allelic variants of CYP2C19 * 2 (G681A) and CYP2C19 * 3

(Trp212Ter). The average age of all patients was 58.5 (+10.2), minimum 36 and maximum 87. 77 of them were men (76.2%) and 24 women (23.8%). By nationality 75 (74.3%) were Kazakhs and 26 (25.7%) were Caucasians.
As a result of genetic analysis by the CYP2C19 * 2 allele (G681A) the following distribution was received:
- 44 (43.6%) patients had normal CYP2C19 * 1 / * 1 genotype, 32 of them (41.6%) were men and 12 (50%) were women (p = 0.757); 32 (42.7%) were of Kazakh nationality and 12 (46.2%) were of the Caucasian race (p = 0.466);
-51 (50.5%) patients were heterozygous carriers of CYP2C19 * 1 / * 2, 39 (50.6%) of them were men and 12 (50%) were women (p = 0.953); 38 (50.7%) were of Kazakh nationality and 13 (50%) were of the Caucasian race (p = 0.956);
- 6 (5.9%) men (7,8%) (p=0,331) were homozygous carriers of CYP2C19 * 2 / * 2 (mutant homozygote); 5 (6.7%) were of Kazakh nationality and 1 (3.8%) was of the Caucasian race (p = 0.600).
By the allelic variant of CYP2C19 * 3 (Trp212Ter), the studied patients were distributed as follows:
- 94 (93.1%) patients had the normal genotype CYP2C19 * 1 / * 1; 72 (93.5%) of them were men and 22 (91.7%) were women (p = 0.669); by their nationality 69 (92%) were Kazakhs and 25 (96.2%) were Caucasians (p = 0.674);
- 7 (6.9%) patients were heterozygous carriers of CYP2C19 * 1 / * 3, 5 (6.4%) of them were men and 2 (8.3%) were women (p = 0.669); by nationality - 6 (7.9%) were Kazakhs and 1 (3.8%) were Caucasians (p = 0.472);
- patients with homozygous carriage of CYP2C19 * 2 / * 3, * 3 / * 3 were not defined.
Thus, as a result of genotyping of the CYP2C19 polymorphism * 2, there were defined 43.6% of patients with normal genotype CYP2C19 * 1 / * 1, 50.5% with heterozygous CYP2C19 * 1 / * 2 and 5.9% with homozygous CYP2C19 * 2 / * 2 carriership. By the CYP2C19 * 3 allele: 6, 9% of patients were heterozygous carriers of CYP2C19 * 1 / * 3, patients with homozygous carrier of CYP2C19 * 2 / * 3, * 3 / * 3 were not identified. The carriership rate for CYP2C19 * 2 is 49.5% higher than that for CYP2C19 * 3 [23].
The thesis of K. B. Mirzaeva gives a profound interpretation of the pharmacogenetic testing and recommendations on the tactics of patients management. Depending on the catalytic activity of the CYP2C19 isoenzyme, the following phenotypes are distinguished in the human population (Figure 1):
"Extensive metabolisers" (EM; carriers of CYP2C19 * 1 / * 1 genotype),
“Intermediate metabolisers” (IM; carriers of CYP2C19 * 1 / * 2, * 1 / * 3, * 2 / * 17, * 3 / * 17), “slow metabolizers” (PM; carriers of CYP2C19 * 2 / * 2 genotypes, * 2 / * 3, * 3 / * 3) and "ultrafast metabolisers" (UM; carriers of CYP2C19 * 1 / * 17, * 17 / * 17 genotypes) (http://www.pharmgkb.org/). Individuals with PM and IM phenotypes produce CYP2C19 with reduced enzymatic activity, which leads to an increase in the concentration of drugs in the plasma (the transformation of drugs into an inactive metabolite slows down), despite the delivery of therapy in the standard dose. If the medicinal agent is a prodrug and it requires bioactivation in humans, then patients with PM and IM phenotypes show insufficient effectiveness of pharmacotherapy (slowing in formation of the active metabolite).
It is observed that patients with UM phenotype produce CYP2C19 with an increased enzymatic activity and, as a consequence, there is a decrease in the pharmacological effect of drugs taken in the standard dose (in the case of prodrugs, the risk of undesirable drug reactions, on the contrary, increases).

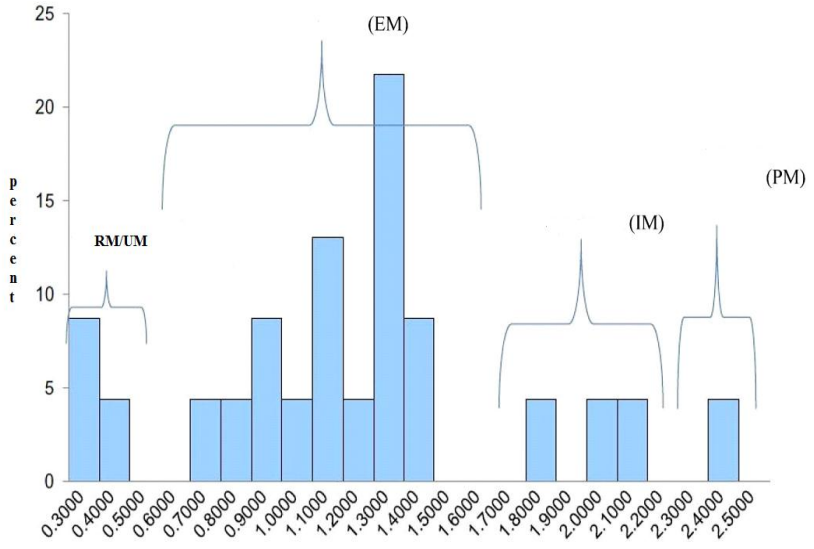

Figure 1 - Patient groups according to the metabolic ratio of the concentration of omeprazole to 5-OH-omeprazole 4 hours after 20 mg of omeprazole, metabolized by CYP2C19 isoenzyme. (Adapted from: Scott SA, 51 Sangkuhl K, Stein CM, et al; Clinical Pharmacogenetics

Implementation Consortium. Clinical Pharmacogenetics Implementation Guide for CYP2C19 genotype and clopidogrel therapy: 2013 update. Clin Pharmacol 2013 2013; 94 (3): 317-323).
In 2010 US Food and Drug Administration (FDA) amended the instructions for medical use of the original drug, with a warning that the drug may be ineffective for carriers of functionally defective alleys of the CYP2C19 gene. In 2011, the Guidelines of the European Society of Cardiology (ESC) for the treatment of patients with ACS included the possibility of pharmacogenetic testing in order to select an antiaggregant drug for certain categories of patients (level of evidence IIB). According to the recommendations of the American Heart Association (AHA) / American College of Cardiology (ACC), pharmacogenetic testing is justified only for patients from the risk group of developing stent thrombosis (level of evidence IIIC). According to the recommendations of the International Consortium on the introduction of pharmacogenetics into clinical practice, and the European Society of Cardiology, when detecting slow allelic variants of the CYP2C19 gene, it is recommended to choose an antiplatelet drug not metabolizable (ticagrelor) or less metabolizable (prasugrel) by this isozyme (Scott, 2013) (Figure 2).

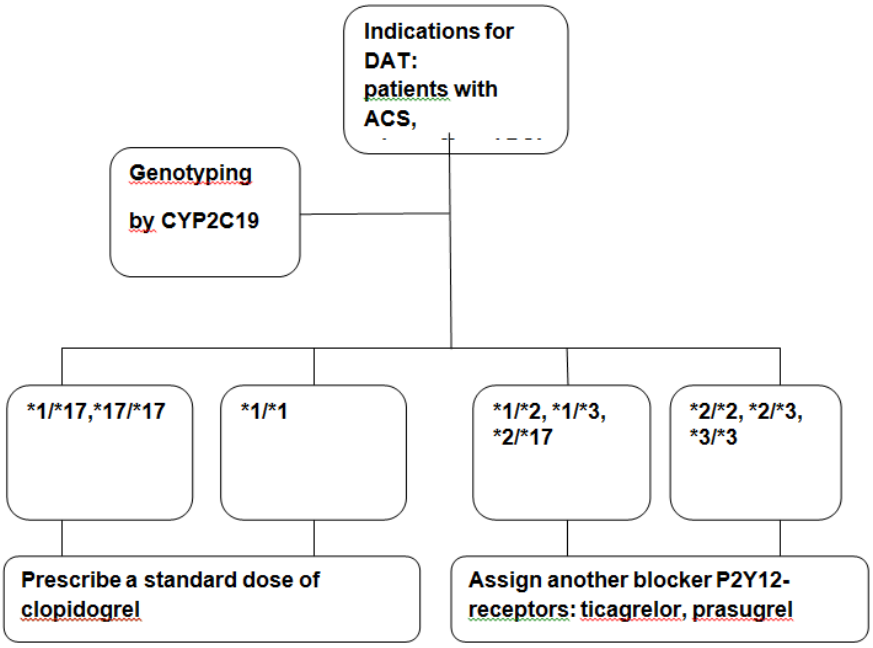

Figure 2 - Recommendations on the tactics of patients management with ACS and PCI according to the results of pharmacogenetic testing. (Adapted from: Scott SA, Sangkuhl K, Stein CM, et al; Clinical Pharmacogenetics Implementation Consortium. Clinical Pharmacogenetics

Implementation Guide for CYP2C19 genotype and clopidogrelotherapy: 2013 update. Clin Pharmacol 2013; 94 (3): 317- 323).
Indications for pharmacogenetic for CYP2C19 testing for prediction of clopidogrel resistance.
Clinical situations in which it is desirable to conduct pharmacogenetic testing for CYP2C19 (AHA 2012: class IIb, level of evidence C. ESC 2011: class IIb, level of evidence B)
• intervention on an unprotected LCA trunk (AHA 2012),
• bifurcation stenosis of the left coronary artery trunk (AHA 2012),
• stenosis of the only passable coronary artery (AHA 2012),
• repeated PCI (AHA 2012),
• history of stent thrombosis (CPIC 2013),
• clinical high risk factors (ACS, diabetes, chronic renal failure) (CPIC 2013)
The problem of predicting the antiplatelet effect of clopidogrel, considering genetic polymorphism and catalytic activity of isoenzymes, clinical, laboratory and demographic features of the patient remains relevant at the present time.
A promising direction for solving this problem is the development of complex algorithms with the integration of the results of genotyping, phenotyping, patient's individual characteristics, which makes it possible to take a step towards a more complete adaptation and personalization of antiplatelet therapy compared to the traditional practice of isolated assessment of factors affecting the pharmacological response to clopidogrel. Currently, there is an active development of such forecasting algorithms and the study of the possibility of their use by patients of different ethnic groups and race. The factor stimulating the development of various algorithms for predicting antiplatelet activity is also gaining more and more evidence the concept of a "therapeutic window" for the use of P2Y12 receptor blockers (Malhotra N, 2015)) [24].
High residual platelet reactivity is a proven factor of increasing the risk of adverse cardiovascular events, while low platelet reactivity is associated with the risk of bleeding. According to the results of clinical studies, numerous domestic and foreign standards and clinical guidelines determine the indications for aggregometry. Testing platelets function may be recommended for patients on a dual antiplatelet therapy in the following clinical situations:
1. High risk of stent thrombosis in the following cases: repeated ACS, non-cardioembolic strokes, episodes of acute lower limb ischemia; stent thrombosis in history; the patient underwent multiple stenting; a lesion of the left main coronary artery or a lesion of the only remaining vessel supplying the myocardium was diagnosed;
2. High risk of bleeding;
3. Suspected resistance to one of the components of DAT (including the identification of genotypes, the carriership of which is associated with clopidogrel resistance);
4. Suspected adherence to treatment problems;
5. Preparation for conducting CABG or other, including non-cardiac surgical intervention;
6. Prescription of reproduced (generic) clopidogrel, replacing clopidogrel from one manufacturer with clopidogrel from another manufacturer, replacing ticagrelor or prosugrel with clopidogrel to evaluate the effect of drug withdrawal.
From the existing methods of aggregatometry, the "point of care" or "bedside" method seems to be the best, Verify now, which meets the challenges facing clinicians and all the requirements of modern aggregometry. Thus, bedside aggregatometry can be recommended for patients on DAT in order to reduce the risk of fatal complications such as thrombosis and bleeding, detect the cases of resistance and problems with compliance, which will significantly improve the quality of medical care, allow to personalize the ongoing antiplatelet therapy, reduce the cost of treatment, the number and duration of hospitalizations [25].
The main goal of platelet function assessment is to identify a patient with high residual platelet reactivity in the course of the treatment with clopidogrel and to be able to adjust therapy to reduce the risk of cardiovascular accidents such as myocardial infarction and stent and / or shunt thrombosis. Genotyping, in turn, allows us to determine who is at risk of high residual reactivity of platelets during therapy, but does not replace the assessment of platelet function. Genotyping in combination with an assessment of platelet function may help determine the best strategy, mainly in the case of homozygous carriage of CYP2C19 * 2 for patients at high risk of developing complications after percutaneous coronary intervention. Further prospective studies should determine whether these strategies can lead to an optimal risk-benefit ratio and be cost-effective in the overall population or in certain groups of patients at high risk of adverse events [26].
Thus, while treating patients, doctors should take into account the results of pharmacogenetic studies, considering different national populations, in order to be sure that the drugs are safe and effective. Application of drugs on the basis of a pharmacogenetic test for the individualization of its dosing regimen, i.e. personalized pharmacotherapy [1] is the future of medicine [1].

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КЛОПИДОГРЕЛ ФАРМАКОГЕНЕТИКАСЫ МЕН ОНЫҢ КЛИНИКАЛЫҚ МАҢЫЗЫ

Түйін: Қысқаша шолу мақсаты клопидогрел фармакогенетикасы мен оның клиникалық маңызына арналады. Фармакогенетикалық тест негізінде кейбір зерттеу жұмыстарының нәтижелері мысал ретінде келтірілген. Төсек жанындағы агрегатометрия - қос антитромбоцитарлық терапияны алушылардың фаталдық асқынулары мен қан кету қаупін төмендету, резистенттік жағдайларды және комплаенттілік проблемаларын анықтау мақсатында ұсынылуы мүмкін, бұл көрсетілетін медициналық көмектің сапасын айтарлықтай жақсартып, жүргізілетін тромбоцитарлық терапияны дербестендіруге, емдеуге жұмсалатын шығындарды, емделушілер саны мен емделу ұзақтығын төмендетуге мүмкіндік береді. Науқастарды емдеу барысында әртүрлі популцияларды ескере отырып, дәрігерлердің дәрілердің қауіпсіздігі мен тиімділігіне деген сенімі үшін фармакогенетикалық зерттеулердің нәтижелері ескерілуі керек.
Түйінді сөздер: клопидрогел, фармакогенетика, CYP2C19, фармакогенетикалық тест, антитромбоцитарлы терапия, агрегатометрия.

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ФАРМАКОГЕНЕТИКА КЛОПИДОГРЕЛА И ЕЕ ЗНАЧЕНИЕ ДЛЯ КЛИНИКИ

Резюме: Предназначение краткого обзора для фармакогенетике клопидогреля и ее значению для клиники. Приведены результаты некоторых исследовании проведенных на основе фармакогенетического тестирования. Прикроватная агрегатометрия может быть рекомендована для пациентов на двойной антитромбоцитарной терапии с целью снижения риска фатальных осложнений – тромбозов и кровотечений, выявления случаев резистентности и проблем с комплаентностью, что существенно улучшит качество оказываемой медицинской помощи, позволит персонализировать проводимую антитромбоцитарную терапию, снизить затраты на лечение, количество и продолжительность госпитализаций. При лечении больных должны учитываться результаты фармакогенетических исследований с учетом различных по национальной принадлежности популяций, для уверенности врачей в безопасности и эффективности лекарств.
Ключевые слова: клопидогрель, фармакогенетика, CYP2C19, фармакогенетический тест, антитромбоцитарная терапия, агрегатометрия